An appraisal of developments in surgical and catheter-based cardiovascular therapy

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AN APPRAISAL OF DEVELOPMENTS IN SURGICAL AND CATHETER-BASED CARDIOVASCULAR THERAPY

Een evaluatie van ontwikkelingen in chirurgisch
en cathetergebonden cardiovasculaire behandelingen

Thesis

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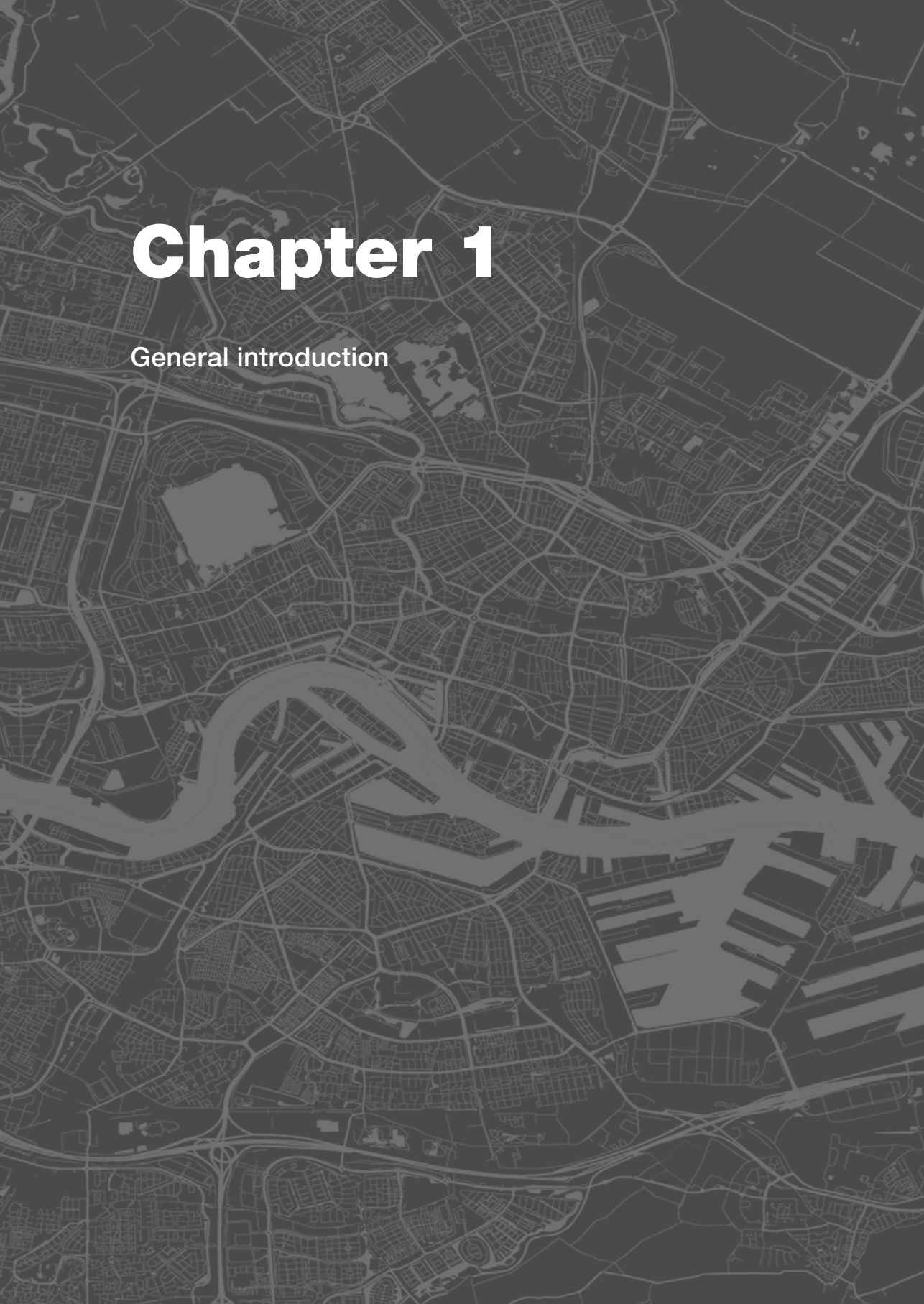

Chapter 1

General introduction

A BRIEF HISTORY OF CARDIAC SURGERY

After a few decades of limited experience in treating congenital heart defects, the introduction of cardiopulmonary bypass in 1954 provided the opportunity to advance cardiac surgery into an adult patient population.[1, 2] In the 1960s this resulted in the first aortic and mitral valve procedures to treat patients with valvular stenosis and/or regurgitation. Evolving from ball-caged valves to stentless porcine bioprosthetic valves,[3] tens of millions of patients have undergone aortic, mitral, or combined valve replacements with excellent short- and long-term valve durability and survival, even with the earliest generation of mechanical valves.[4, 5]

Ischemic heart disease was the leading cause of death in the general population (Figure 1), and the only treatment available at that time -- medical therapy -- fell short to reduce early mortality. Despite the pioneering work of Arthur M. Vineberg to induce coronary anastomosis of an internal mammary artery graft by burrowing it in the myocardium,[6] surgical revascularization did not take off until in the mid-1960s when coronary artery bypass grafting (CABG) through surgical anastomosis was introduced.[7,8] Its wide-spread adoption caused CABG to rapidly evolve as the standard of care for patients suffering from coronary artery disease.[9]

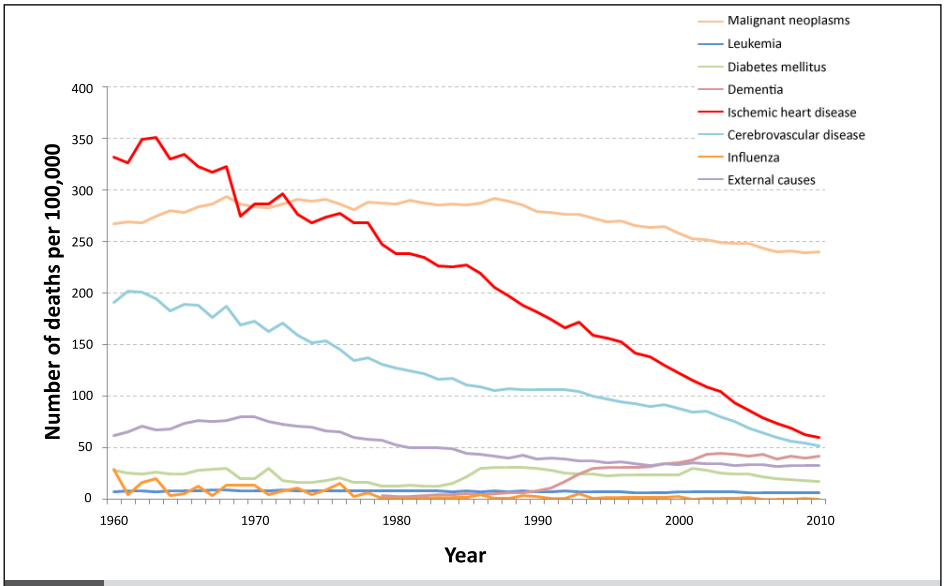

Figure 1 **Trends in causes of death in the Netherlands through 1960-2010**

A BRIEF HISTORY OF INTERVENTIONAL CARDIOLOGY

Compared with cardiac surgery, interventional cardiology is a young specialty. Cardiac catheterization procedures were introduced in the early 1940s.[10] Further developments of aortography with contrast finally --by accident-- led to the first coronary catheterization in 1958.[11, 12] After almost two decades, Andreas Grüntzig pioneered percutaneous transluminal coronary angioplasty by reopening the coronary stenosis with a balloon-tipped catheter.[13] The subsequent development of bare-metal and drug-eluting stents further improved outcomes with percutaneous coronary intervention (PCI).

The introduction of transcatheter heart valves marked a new era. Interventional cardiologists were no longer only able to treat coronary artery disease, but indications expanded to valvular disease as well. Transcatheter aortic interventions were initially described in 1965 and the development of balloon aortic valvuloplasty in 1986 was a huge leap forward.[14, 15]However, it was not until the first transcatheter aortic valve implantation (TAVI) in 2002 that there was a definitive catheter-based treatment for aortic stenosis.[16]

COMPARATIVE EFFECTIVENESS

The introduction of new treatment strategies --being either an operative technique or the launch of innovative technology --should be paralleled by rigorous evaluation compared with the standard therapy. Usually this occurs in the setting of a dedicated randomized controlled trial (RCT), the highest level of evidence originating from clinical research. Such randomized evaluation against standard therapy is needed, as innovation may not always be beneficial. A systematic assessment of 205 RCTs identified 72 (35%) trials to have non-significant results.[17] If not evaluated, a significant number of patients would have been subject to new but suboptimal therapy.

In case a new therapy seems to be efficient it might be tempting to implement it without substantial evidence. This poses the risk of letting such therapies 'run its course' without proper evaluation. At least observational studies should be performed to assess the safety and effectiveness, before a situation is reached where there is no turning back:[18]

"Accompanying this widespread optimism [regarding CABG], however, is a growing uneasiness that by simple common consent, rather than by rational analysis of data, we may be adopting for general use a form of treatment that has yet to prove itself. Some fear that even though the long-term effectiveness of direct revascularization has not yet been demonstrated, we may be propelled into a position in which it will be considered poor medical practice to withhold this form of therapy from almost any patient with coronary artery disease…"

Eugene Braunwald, 1976

Although data from observational studies may be positive, subsequent data coming from RCTs may be necessary to amplify the body of evidence. Results should be weighted proportionally, considering the quality of research.[19]

METHODOLOGY

Methodological issues are important to consider when interpreting the results of RCTs and observational studies. Frequently study results are translated as monochrome outcomes, which may result in unsubstantiated treatment recommendations and may jeopardize quality of care. Important flaws in reporting of trial results have been identified,[20, 21] and it might therefore be difficult to draw the correct conclusion from trials.[17] This results in a need to critically evaluate cardiovascular research and methodology to enhance understanding and interpretation of study results.

SURGERY OR CATHETER-BASED INTERVENTIONS?

Since the introduction of catheter-based interventions, cardiac surgeons and interventional cardiologists have been treating similar patient populations. Due to significant developments in percutaneous technology, it has become inevitable that an increasing percentage of patients is treated through lesser invasive interventions. However, even though safety and efficacy of both surgical and catheter-based interventions has increased, it remains difficult to define which patients benefit from a specific treatment strategy.

Risk models can be helpful tools to determine the patient population with optimal safety and efficacy of therapies. Many physicians rely on risk models for decision-making purposes, and models are often used by policy makers and health care organizations for benchmarking and/or benefit-risk analyses. However, risk models are only useful in specific patient populations, for certain procedures, and for a particular outcome;[22] there remains a need for improved risk models.

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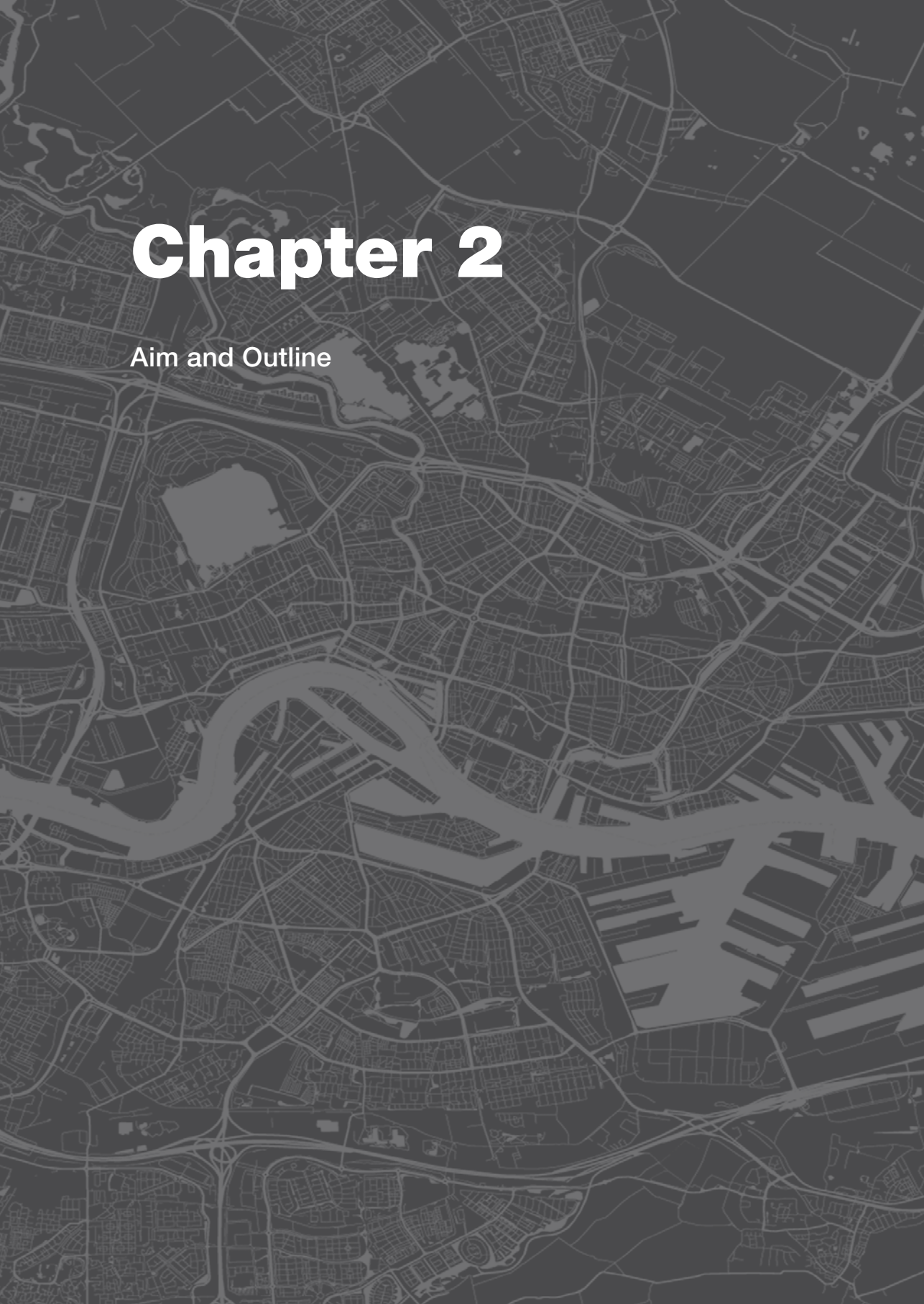

Chapter 2

Aim and Outline

AIM

The goal of this thesis is to appraise the methodological quality of the current evidence, provide recommendations to improve methodology, and produce risk-benefit analyses of new developments to substantiate evidence-based guidelines.

OUTLINE

Part 1 of this thesis highlights the current status of patient selection and decision-making. Two different aspects are discussed. First, how risk stratification in cardiac surgery can be improved. Secondly, how risk stratification can help decision-making in selecting the most appropriate surgical or catheter-based intervention for individual patients.

The different strategies for the treatment of aortic stenosis are discussed in **part 2**. It evaluates the outcomes of surgical aortic valve replacement and transcatheter aortic valve implantation, and provides a comparison between both treatments.

Part 3 aims to evaluate the most optimal treatment for complex coronary artery disease. It will focus on the comparison between percutaneous and surgical revascularization with regard to patients with diabetes, the incidence and outcomes of stroke, and the impact of incomplete revascularization. It describes how the outcomes of revascularization can be further improved.

A thoughtful evaluation of study methodology is presented in **part 4**. A specific analysis of non-inferiority trial designs is performed, focusing on lessons from recent cardiovascular trials. It furthermore emphasizes the need for a critical appraisal of analyses from randomized trials and observational studies.

Part 5 addresses harmonization of clinical endpoints, aiming to improve comparability of studies evaluating aortic valve interventions.

Part 1

Patient selection and decision-making


London

Chapter 3

The new EuroSCORE II does not improve prediction of mortality in high-risk patients undergoing cardiac surgery: a collaborative analysis of 2 European centers

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ABSTRACT

Objectives

Prediction of operative risk in adult patients undergoing cardiac surgery remains a challenge, particularly in high-risk patients. In Europe, the EuroSCORE is the most commonly used risk prediction model, but is no longer accurately calibrated to be used in contemporary practice. The new EuroSCORE II was recently published in an attempt to improve risk prediction. We sought to assess the improvement in predictive value of EuroSCORE II in high-risk patients.

Methods

Patients who underwent surgery between 01-04-2006 and 31-03-2011 with a preoperative logistic EuroSCORE ≥10 were identified from prospective databases. Additional variables included in EuroSCORE II but not in the original EuroSCORE were collected through patient chart review. The c-statistic to predict in-hospital mortality was calculated for the additive EuroSCORE, logistic EuroSCORE, and EuroSCORE II models. The Hosmer-Lemeshow test was used to assess model calibration by comparing observed and expected mortality in a number of risk strata. The fit of the models was compared using Aikike's Information Criterion (AIC).

Results

A total of 933 patients were identified; the median additive EuroSCORE was 10 (interquartile range 9-11), median logistic EuroSCORE was 15.3 (IQR 12.0-24.1), and the median EuroSCORE II was 9.3 (5.8-15.6). There were 90 (9.7%) in-hospital deaths. None of the EuroSCORE models performed well with a c-statistic of 0.67 for the additive EuroSCORE and EuroSCORE II, and 0.66 for the logistic EuroSCORE. Model fit was poor for the EuroSCORE II (chi-square 16.5; p=0.035). Both the additive EuroSCORE and logistic EuroSCORE had better model fit, the additive EuroSCORE significantly so (difference in was -5.66; p=0.017).

Conclusions

The new EuroSCORE II does not improve risk prediction in high-risk patients undergoing adult cardiac surgery as compared with original additive and logistic EuroSCOREs. The key problem of risk stratification in high-risk patients has not been addressed by this new model. Future iterations of the score should explore more advanced statistical methods and focus on developing procedure-specific algorithms. In addition, models that predict complications in addition to mortality may prove of increasing value.

INTRODUCTION

Accurate risk stratification is critical for delivering cardiac surgical clinical practice. It has helped inform surgeons of the probable risks of surgery allowing them to aid patients in making informed choices, particularly when alternative treatments are available it has been useful to select those patients that have the most chance of benefiting from surgery.[1] Furthermore, it has helped drive improvements in outcome through national audits and it has facilitated benchmarking of clinical results between institutions. Recently risk stratification has come to clinical prominence in its role of deciding which patients should be offered experimental therapeutic interventions, such as trans-catheter aortic valve implantation.[2]

Within Europe the EuroSCORE and its Logistical variant are the most frequently used risk stratification models.[3, 4] Developed in 1999 from a relatively small database of 20,000 patients, its predictive power was good. However, the predictive power of any risk stratification algorithms can drift over time due to changes in practice and populations, and in recent years a decline in the predictive power of the EuroSCORE has been observed especially for procedures such as aortic valve replacement.[5, 6] This drift may in part be due to a combination of the change in risk profile observed in cardiac surgery with older patients with multiple co-morbidities being considered for more complex procedures,[7] and the progress seen in improved cardiac surgical outcomes in recent years. The "high-risk" group has been shown to be a predictive challenge and the original EuroSCORE fails to provide an accurate estimation of risk.[5, 6, 8, 9] Outcome prediction in this group of patients is particularly important, as often there may be alternative therapeutic strategies available if conventional surgery is considered too risky. In light of these developments the EuroSCORE was considered to be outdated and due for updating; recently the new EuroSCORE II was published.[10]

The aim of this study was to compare the original additive and logistic EuroSCOREs with the new EuroSCORE II to assess whether the latter provides improved risk prediction in patients at high-risk for mortality following cardiac surgery.

METHODS

Data from 2 European centers in the Netherlands (Erasmus MC, Rotterdam) and the United Kingdom (University Hospital NHS Foundation Trust, Birmingham) were pooled. At both centers, prospective collected data were analysed retrospectively to identify patients that underwent cardiac surgery from April 2006 – March 2011 and were predicted to be at increased risk as defined by a logistic EuroSCORE ≥10.[5] Patients were grouped as per EuroSCORE II definitions into those that had undergone isolated CABG, isolated valve or a combined procedure.[11]

Although this model was proposed as a generic risk stratification tool we excluded patients undergoing aortic surgery, those undergoing procedures for adult congenital heart disease, thoracic organ transplantation or post-infarction VSD repair to focus specifically on patients undergoing conventional high-risk surgery and to avoid the bias that patients undergoing these specific procedures may have introduced into the analysis. Patient data was initially obtained from the departmental database. The EuroSCORE II model, however, also requires a number of variables not previously used. These variables were obtained through retrospective patient notes review. The EuroSCORE II was calculated using the online calculator available at www.euroscore.com.

Statistical analyses

Continuous variables are expressed as mean (interquartile range (IQR)) and categorical data as proportions. Generalised linear models with a logit link and binomial error were developed for each version of the EuroSCORE, with patient status at discharge from the hospital (in-hospital mortality as end point) as the response variable. We assessed the discriminating ability of the risk models by using the c-statistic methodology. We assessed model calibration by portioning the cohort into 6 risk strata of similar size and comparing the difference between the observed and expected number of events, using calibration plots and the Hosmer Lemeshow test, as suggested by Collins and Altman.[11] Finally, model fit between the EuroSCORE II and the original additive and logistic EuroSCORE was compared using the Aikiake Information Criterion (AIC). Analyses were performed using SAS 9.2.

RESULTS

Patient characteristics

A total of 933 patients were identified that fulfilled the study criteria. Median age was 74.3 years old (IQR 68 - 78.4), and 57.5% were male (Table 1). Isolated CABG was performed in 271 patients, and 185 patients underwent isolated single valve procedures. A combined procedure was performed in 477 patients (CABG + valve), of which 173 patients underwent 3 procedures as defined by EuroSCORE II. The high-risk nature of these patients is well demonstrated by the high prevalence of previous cardiac surgery (19.4%), urgent surgery (50.2%), severe renal impairment or dialysis (41.8%), and patients in NYHA class III/IV (70.2%).

Prediction of in-hospital mortality

The observed in-hospital mortality was 9.7% (90 deaths). The m edian predicted in-hospital mortality was 10% (IQR 9-11) by additive EuroSCORE, 15.3% (IQR 12.0-24.1) by logistic EuroSCORE, and 9.3% (IQR 5.8-15.6) by EuroSCORE II, The c-statistic was similar for the 3

Table 1 Patient demographics by EuroSCORE II variable

	Number of patients (%)
Age, median (IQR)	74.3 (68 - 78.4)
Renal impairment	
Dialysis	21 (2.3)
Severe	369 (39.5)
Moderate	439 (47.1)
Normal	104 (11.1)
Extra cardiac arteriopathy	243 (26)
Poor mobility	67 (7.2)
Previous cardiac surgery	181 (19.4)
Chronic lung disease	260 (27.9)
Active endocarditis	58 (6.2)
Critical pre-operative state	221 (23.7)
Diabetic on insulin	84 (9)
NYHA III	333 (35.7)
NYHA IV	322 (34.5)
CCS IV	255 (27.3)
LV function	
Good	390 (41.8)
Moderate	412 (44.2)
Poor	104 (11.1)
Very poor	27 (2.9)
Recent MI	313 (33.5)
Pulmonary hypertension	
Severe	183 (19.6)
Moderate	151 (16.2)
Normal	599 (64.2)
Urgency	
Elective	376 (40.3)
Urgent	468 (50.2)
Emergency	86 (9.2)
Salvage	3 (0.3)
Weight of the intervention	
Isolated CABG	271 (29)
Single non-CABG	185 (19.8)
2 procedures	304 (32.6)
3 procedures	173 (18.5)
Additive EuroSCORE, median (IQR)	10 (9 - 11)
Logistic EuroSCORE, median (IQR)	15.26 (12.0 - 24.1)
EuroSCORE II, median (IQR)	9.15 (5.7 - 15.5)

models (0.67 for both the additive EuroSCORE and EuroSCORE II, and 0.66 for the logistic EuroSCORE).

The observed versus expected deaths for all three models are described in Figure 1. The Hosmer-Lemeshow statistic was compared to a Chi-squared distribution and the p value calculated. Model prediction was poor across risk strata for the EuroSCORE II; for the

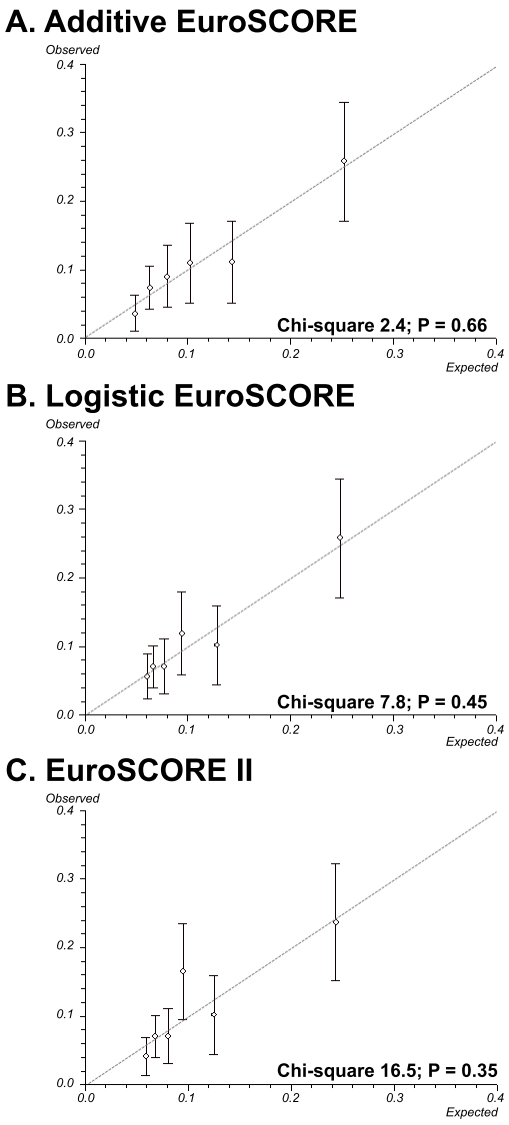

Figure 1 **Observed versus expected risk of mortality (± 95% CI) for risk strata of the additive EuroSCORE (A), the logistic EuroSCORE (B), and the EuroSCORE II (C)**

additive EuroSCORE χ^2 was 2.40 (p=0.66), for the logistic EuroSCORE χ^2 was 7.81 (p=0.45), and for EuroSCORE II χ^2 was16.55 (p=0.040). Model fit was significantly worse for the Comparing the EuroSCORE II compared with the additive EuroSCORE - difference in AIC of -5.66 (p=0.017). Between the logistic EuroSCORE and EuroSCORE II there was no evidence of a real difference in model fit - AIC = -1.00 (p=0.32).

DISCUSSION

The main finding of this study is that EuroSCORE risk stratification models have poor predictability in high-risk patients and the EuroSCORE II did not improve risk stratification when compared to the additive and logistic EuroSCORE. Furthermore, the EuroSCORE II exhibited worse calibration than the additive EuroSCORE in our data set.

We chose to assess the prediction models in a population of patients with multiple comorbidities and or advanced age, as these are known to be at higher risk for conventional cardiac surgery. It is in this group that it is important to have a reliable tool to predict outcome, as often in these patients there are also alternative therapeutic strategies. Patients considered for high-risk procedures will be discussed in a multi-disciplinary setting. For these patients it is important to consider surgical and percutaneous options available for both aortic valve disease [2] and coronary artery disease [12] and it is therefore important to have an accurate assessment of operative risk so that recommendations can be justified,[13] and patients fully informed. The accurate assessment of risk is now also important for the benchmarking of results as part of the current quality improvement agenda.

The risk prediction of all EuroSCORE systems is based on early operative mortality. The operative mortality of routine cardiac surgery has been significantly reduced over the last decades, which may complicate the longevity of risk models because they no longer represent contemporary practice. Such reductions could furthermore produce a paradigm shift in which mortality may no longer be the key outcome to evaluate. In the United Kingdom the in-hospital mortality for non emergency isolated first time CABG is now <1%, and in these patients it is equally important to develop tools to predict significant complications and or long-term survival. The EuroSCORE II adopted a pragmatic approach to encompass a wide spectrum of surgical procedures and risk, and overall its predictability appears to have improved over previous iterations of the model. However, when a new risk stratification scoring system is introduced, there is also the potential disadvantage that a wealth of data from previous systems is no longer useful particularly for contemporaneous benchmarking and quality control. This needs to be offset by a significant improvement in the new prediction model, particularly in the areas where the previous EuroSCOREs have shown to have a problem. The original EuroSCORE could have been re-calibrated. This approach was initially used in the United Kingdom when mortality for first time CABG was benchmarked

against the logistic EuroSCORE and divided by a correction factor calculated from the drift of predictability with time. This has the advantages of allowing benchmarking against previously collected data and allows the use of current data capture systems for future work. Another option is to design contemporary bespoke models for procedure-specific prediction; the approach adopted by the Society of Thoracic Surgeons (STS). The STS approach has the advantage of utilising procedure-specific risk data, but to do so an entirely new dataset needs to be constructed in a prospective manner, and it then becomes impossible to benchmark results against existing datasets. The EuroSCORE investigators have taken a 'half-way house' approach. They have retained the majority of the pre-specified variables, but have added further fields such as estimated glomerular filtration, which has previously been shown to be an independent predictor of risk in addition to the EuroSCORE.[14]

In this study we have tested the EuroSCORE II, in a selected high risk group of patients and it is not surprising that a model designed for a range of procedures and risk would not necessarily perform well in such a subset. There might be several reasons for this phenomenon.[15]

The EuroSCORE II dataset has been based upon data from a multitude of centres throughout Europe in whom there are differences in outcomes. This phenomenon is demonstrated by the fact that while EuroSCORE II seems to be accurate for high risk CABG patients in Finland,[16] in the UK national database it has shown to have a 30% calibration drift by over-estimating predicted mortality.[17] The original EuroSCORE model was based on data from 128 surgical centres in 8 European countries.[18] Patients from these countries showed major differences in risk profile and model discrimination ranged from 0.74 in Spain to 0.87 in Finland.[19] For EuroSCORE II a total of 154 centres from 43 European (n=27) and non-European (n=16, such as Argentina, India, Saudi Arabia, South Africa, Sudan, Taiwan) participated, which is an even more heterogenic patient cohort and represents very different practices.

The new model is quite simple and did not for example explore the value of using interaction terms between variables, which is important especially in high-risk patients with multiple co-morbidities. The cumulative risk of these factors may cause significant over-estimation of the risk of mortality if no interaction terms are used. The STS model does take into account interactions (e.g., age x reoperation),[20, 21] which allows for a more continuous increase of risk that correspond better with observed mortality rates in high-risk patients (Figure 2).[5, 6] In our cohort of 933 patients, a large number of patients were high-risk because they had multiple co-morbidities and/or underwent ≥2 procedures and/or required urgent intervention. Their risk would probably have been more accurate if interaction terms were used.

Similar to interactions between risk factors, procedure-specific models can be developed based on interaction terms between risk factors and the type of procedure.[20, 21] The use of procedure-specific models, or at least procedure-related coefficients with interaction terms,

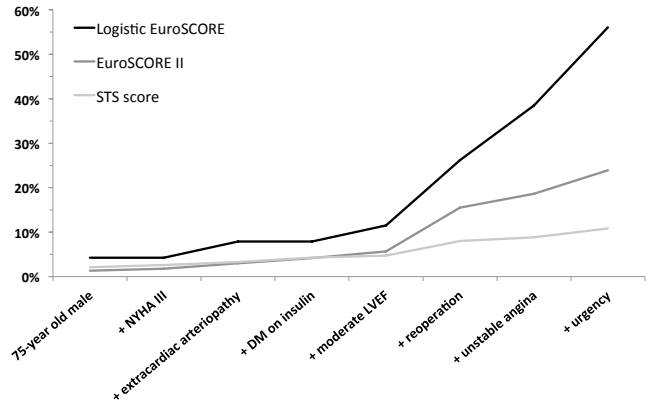

Figure 2 **The effect of risk factors on the EuroSCORE II and STS score in a patient undergoing AVR + CABG for aortic stenosis and three-vessel disease**

DM = diabetes mellitus; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association classification

is clearly one solution to more accurate risk estimation if designing tools with a specific aim towards high risk groups.

While the EuroSCORE II model did include several variables that were not in the original EuroSCORE (e.g., NYHA classification), there are still some predictive variables that were not included. Studies have shown that frailty is an important predictor in patients undergoing cardiac surgery, particularly in patients with advanced age,[22] and a recent report showed that the addition of frailty to existing STS and EuroSCORE models increased model discrimination.[23]

Finally, the trade-off between number of variables to include in any model and its resulting accuracy, remains unclear. Some simple, user-friendly models with limited number of variables (e.g. ACEF score) have shown to be very predictive,[24] while inclusion of a great number of variables may cause inaccuracies by differently interpreting definitions or calculation errors.[15, 25]

Limitations

The addition of the new variables in EuroSCORE II has meant that we had to retrospectively collect a number of variables. Some patients may therefore be misclassified as having a risk factor and the EuroSCORE II might be slightly different. Nevertheless, all included patients were already labelled as high-risk by the logistic EuroSCORE.

The current dataset was too small to perform procedure-specific analyses, which would have provided additional insights with regard to the development of procedure-specific models. Future, larger studies should focus on whether the EuroSCORE II performs equally well in CABG, valve, or combined surgery. The additive EuroSCORE was not intended for

cohort studies, nevertheless it has been used widely in clinical practice ,and for this reason we included it in study design. Our analysis allows relative comparison of EuroSCORE 2 with the additive and its logistic iteration.

CONCLUSIONS

The new EuroSCORE II does not improve risk prediction in high-risk patients undergoing adult cardiac surgery as compared with the original additive or logistic EuroSCORE. Future iterations of the score should explore more advanced statistical methods and focus on developing procedure-specific algorithms. In addition, the possibility of predicting procedure-related complications (e.g., stroke) would add significant value to the EuroSCORE model.

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Rotterdam

Chapter 4

Predicting prognosis in cardiac surgery: a prophecy?

Kappetein AP, **Head SJ**

Eur J Cardiothorac Surg 2012;41:732-733

COMMENT:

Physicians need to make predictions on the prognosis of a treatment that helps them in the choice of therapy. Medicine used to be much more subjective than in the current evidence-based era. Shared decision-making, where physicians and patients both participate in deciding on choices for therapy, is also more common.[1] Clinical prediction models like EuroSCORE may provide the evidence-based input for shared decision-making by providing an estimate of the operative risk of patients undergoing cardiac surgery. An ideal clinical model would be something simple dividing the patients into 'good' and 'bad' without further specification of the survival chances. The original EuroSCORE was a compromise between the 'statistical ideal' and the 'clinical ideal'. It was developed from a large multi-national European population and was a model predicting mortality based on 17 variables, either from a logistic regression equation or from an additive model. Numerous institutions throughout the world have tested and validated EuroSCORE.

Loss of calibration with the additive and logistic EuroSCORE has been observed by many investigators and an update of the EuroSCORE was warranted. One possible reason for the poor calibration of the original EuroSCORE score is that the score was developed from patients undergoing surgery almost 20 years ago. As surgical and perioperative care evolves and the impact of clinical variables change, prediction models therefore require revision. These factors may also vary between institutions and it is well known that the quality of care and comorbidities of patients differs between countries. The original EuroSCORE already identified major differences in the risk profile of national samples.[2] This is therefore one of the major concerns with EuroSCORE II: 154 hospitals from 43 countries participated, of which many were outside Europe.[3] One may, therefore, question whether the term EuroSCORE is still valid or another name should be used that reflects the fact that so many countries outside Europe participated. With this in mind, it becomes even more important that, as indicated by the authors, units and surgeons calculate their own risk-adjusted mortality ratio. The model is probably more reliable in the prediction of death over a wide range of risk groups rather than the prediction of the vital status of an individual patient.

Another reason for the poor calibration in the original EuroSCORE might be that a large number of risk factors in the model are highly correlated. It is important to recognize correlation between predicting variables, as the additional risk contribution of certain variables can in some part be explained by the effect of other variables. Some predicting variables may also be more important for some types of operations then for others. The large number of risk factors with potential interaction may overestimate risk in certain categories of patients (e.g. intermediate risk or extreme risk). It is therefore a pity that the authors have not explored possible interaction terms in the new EuroSCORE II, something the Society of Thoracic Surgeons score has taken into account.

For the analysis, the authors chose to drop cases with missing data. Besides inefficient use of available data, bias may arise due to systematic differences between subjects with complete data and subjects with missing data. An estimated regression coefficient for a predictor might be influenced if the missing data are associated in some way with the outcome.[4] They could have chosen to use some form of imputation to preserve those cases. In general, the quality of those centres with missing data or those unable to provide specific outcome data may be questioned.

One of the major concerns with EuroSCORE II is that the primary outcome was mortality at the base hospital. In current practice, however, it is common that patients are transferred to referring hospitals at different points in time after the operation. There is significant geographic and hospital variance with regard to the day of transfer. For example, the length of stay in coronary bypass patients in the SYNTAX trial ranged from a mean of 5–20 days. A fixed point in time in a mortality prediction model has advantages over the current model, as it provides the ability to compare centres. Current guidelines and clinical trial practices mandate mortality assessment at 30, 60 or 90 days.[5, 6]The number of centres that provided 30- or 90-day mortality was disappointing.

The authors are to be admired for the amount of work they have put into the new model and for their energy in starting already on a EuroSCORE III project. We have to be careful, however, not to add prognostic factors all the time. Models with only a few parameters are quite stable and estimating a few calibration parameters might be enough.[7] 'Garbage in, garbage out' is a well-known problem inherent to risk models, causing inaccurate risk prediction. The inclusion of a greater number of variables increases the risk of errors that can be caused by differences in the interpretation of definitions, typing errors or conflicting chart information.[8]

It took many years to learn the advantages and shortcomings of EuroSCORE I. Many institutions have adopted the EuroSCORE in their quality control programmes. Implementing EuroSCORE II and learning the benefits will also take some time. There is currently more need for models that not only focus on mortality but also on postoperative complications and the development of procedure-specific models. As clinicians are confronted with more elderly patients, it might also be useful to focus on specific subsets of patients. A prognostic model is only useful if its predictions are at least as accurate as those of the doctors who would use it. We have to be thankful to the initiators of the EuroSCORE project for their great contribution to our profession.

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London

Chapter 5

The SURTAVI model: proposal for a pragmatic risk stratification for patients with severe aortic stenosis

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EuroIntervention 2012;8:258-266

ABSTRACT

Transcatheter aortic valve implantation (TAVI) is a less invasive alternative to surgical aortic valve replacement (SAVR) for patients with symptomatic severe aortic stenosis (AS) and a high operative risk. Risk stratification plays a decisive role in the optimal selection of therapeutic strategies for AS patients. The accuracy of contemporary surgical risk algorithms for AS patients has spurred considerable debate especially in the higher risk patient population. Future trials will explore TAVI in patients at intermediate operative risk. During the design of the SURgical replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial, a novel concept of risk stratification was proposed based upon age in combination with a fixed number of predefined risk factors, which are relatively prevalent, easy to capture and with a reasonable impact on operative mortality. Retrospective application of this algorithm to a contemporary academic practice dealing with clinically significant AS patients allocates about one-fourth of these patients as being at intermediate operative risk. Further testing is required for validation of this new paradigm in risk stratification. Finally, the Heart Team, consisting of at least an interventional cardiologist and cardiothoracic surgeon, should have the decisive role in determining whether a patient could be treated with TAVI or SAVR.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is rapidly emerging as a viable and less invasive alternative to surgical aortic valve replacement (SAVR) for high-risk patients with symptomatic severe aortic valve stenosis (AS).[1-4] In spite of the ever improving outcome with SAVR, especially in higher risk cohorts, the EURO Heart survey suggested that a considerable number of AS patients are denied surgery for various reasons including age, left ventricular (LV) dysfunction and comorbidities.[5] By precluding sternotomy and cardiopulmonary bypass, TAVI provides the potential for off-pump and beating heart valve implantation, which may translate into faster recovery, shorter hospitalisation and more rapid improvement in quality of life. Risk stratification plays a decisive role in the optimal selection of therapeutic strategies among AS patients.

Various national and multicentre TAVI registries, and single centre experiences have reported favourable short- and mid-term clinical outcomes.[1-7] Cohort B of the randomised Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated an important improvement in 1-year mortality and quality of life with TAVI as compared to optimal medical therapy and/or isolated balloon aortic valvuloplasty in prohibitive surgical risk patients.[8] The PARTNER Cohort A demonstrated similar 1-year survival rates among high-risk patients randomly assigned to either TAVI or SAVR. Vascular complications and neurological events, however, were higher in the TAVI cohort, whereas atrial fibrillation and major bleeding were more frequent in the SAVR cohort.[9] From a European perspective, the PARTNER trial has to be critically commented on in regard to the fact that a) patients were selected, thus not all-comers were treated and, b) patients were on a waiting list, both of which may lead to improved outcomes.

The applicability of contemporary surgical risk algorithms for AS patients has spurred considerable debate in both cardiac surgery and cardiology communities.[10-14] The STS Predicted Risk of Mortality (PROM) and the logistic EuroSCORE have been widely applied to determine the operative mortality risk of AS patients undergoing SAVR. Both scoring models, however, are fraught with shortcomings, especially in higher-risk patient populations currently undergoing TAVI. These risk models in isolation may not provide a satisfactory risk assessment. Even though the combination of different risk scores may improve their predictive value, combining risk models to determine a predictive value has not been validated and raises practical concerns. It is axiomatic that a risk-scoring model should be relatively simple, reliable and reproducible.

The SURgical replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial is a multicentre randomised trial to assess the optimal treatment strategy for patients with symptomatic, severe AS at intermediate risk by randomising patients to either SAVR or TAVI with the Medtronic CoreValve System™ (Medtronic, Minneapolis, MN, USA).

Our aim was to illustrate the process of conceptualising a randomised trial with TAVI and SAVR in patients with symptomatic severe AS at intermediate operative risk with respect to the current knowledge of risk stratification. We briefly underscore the inconsistencies and shortcomings of the two widely used risk models (STS PROM and Logistic EuroSCORE). In accordance with the body of contemporary published literature, we suggest that the concept of risk stratification could be based upon age in combination with a fixed number of predefined risk factors. It should be emphasised that, in all scenarios, the Heart Team, consisting of at least an interventional cardiologist and cardiothoracic surgeon, has a decisive role in determining whether a patient could be treated with TAVI or SAVR.[15]

INCONCISTENCIES IN THE LOGISTIC EUROSCORE AND STS PROM

Models for predicting surgical outcomes on the basis of preoperative patient characteristics are valuable tools for research, quality improvement and clinical practice and may even be used for patient counselling about an individual's operative risk.

The STS PROM and Logistic EuroSCORE are widely used risk models to assess the operative risk of AS patients.[16-19] However, inaccurate risk estimation for surgical AVR is more the rule than the exception, and inconsiderate use of these algorithms for benchmark performance testing could lead to inappropriate enthusiasm for technologic innovations like TAVI.[10, 13] Recent data suggest that a risk model containing only three variables (age, EF and creatinine) might have at least as good accuracy and calibration as the more complex risk models.[20] An Italian multicentre study analysing 29,659 consecutive patients who underwent cardiac surgery demonstrated that this same simple model led to overestimation of short-term operative mortality risk in patients at very-low risk and, conversely, underestimation in patients at very-high risk.[21]

RATIONALE FOR THE ALGORITHM OF 10 RISK FACTORS

With the established shortcomings of currently used risk models in mind we moved to a novel concept of risk stratification, the so-called SURTAVI model. Clearly, according to established risk models like the STS PROM and Logistic EuroSCORE, an increasing number of risk factors will augment an individual patient's risk. This begs the question of whether a patient's operative risk will be based on age and the number of risk factors present (Figure 1). Analysis of the impact of different risk variables and their combination in different age cohorts in the STS score and Logistic EuroSCORE suggests risk variables can accommodate for age resulting in similaroverall risk profiles. An arbitrarily defined intermediate risk with STS score <10 and/or Logistic EuroSCORE <20 is reached by either the combination of an

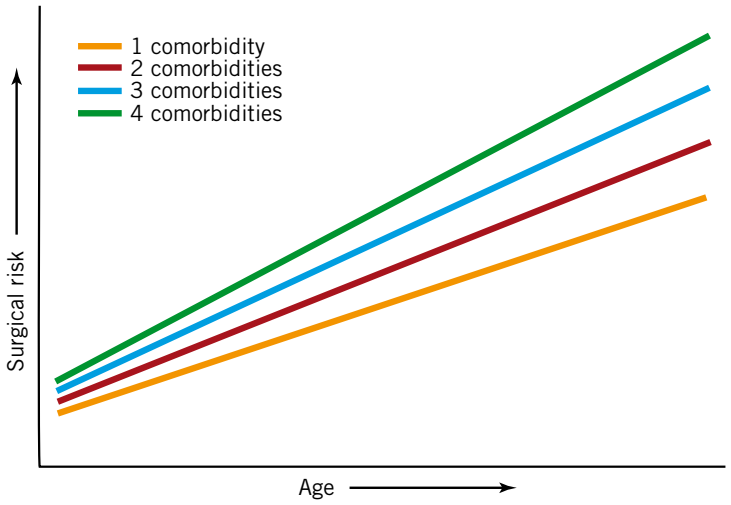

Figure 1 **Concept of risk models: impact of age and comorbidities on operative risk**

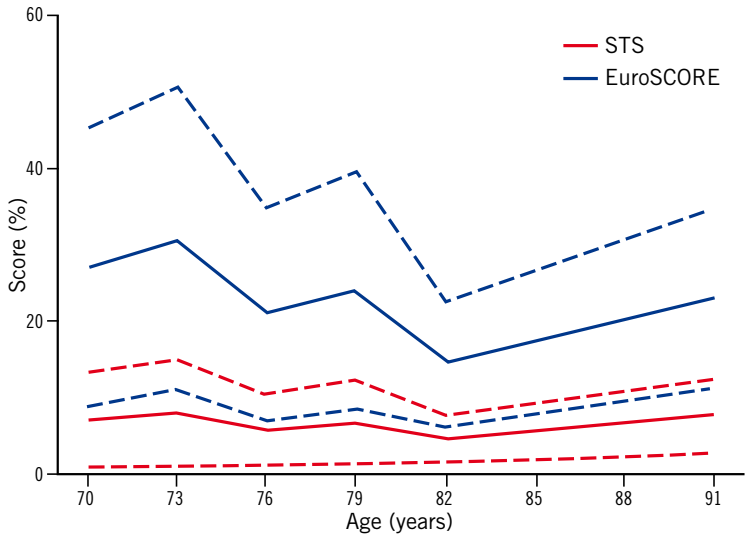

Figure 2 **Range of STS score and Logistic EuroSCORE in intermediate risk patients according to the SURTAVI model**

The SURTAVI model is a combination of age 70-75 years and 2 or 3 comorbidities, age 75-79 and 1 or 2 comorbidities and age ≥80 and 0 or 1 comorbidities.

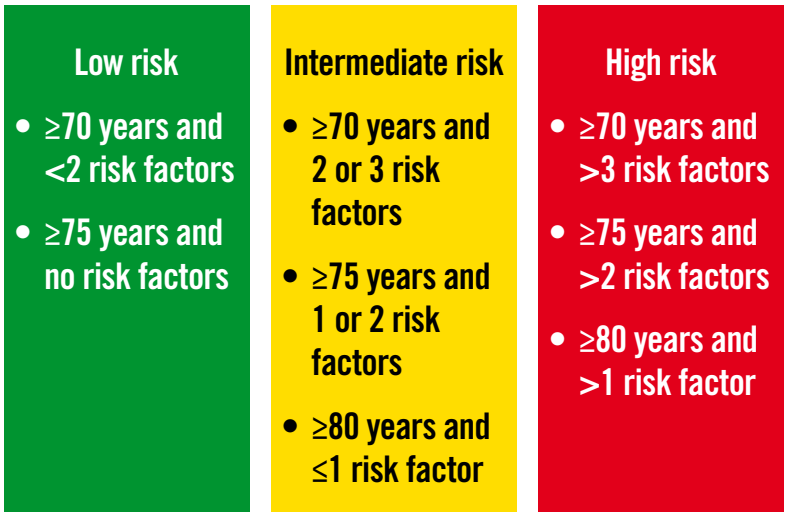

Figure 3 **Principles of the SURTAVI model**

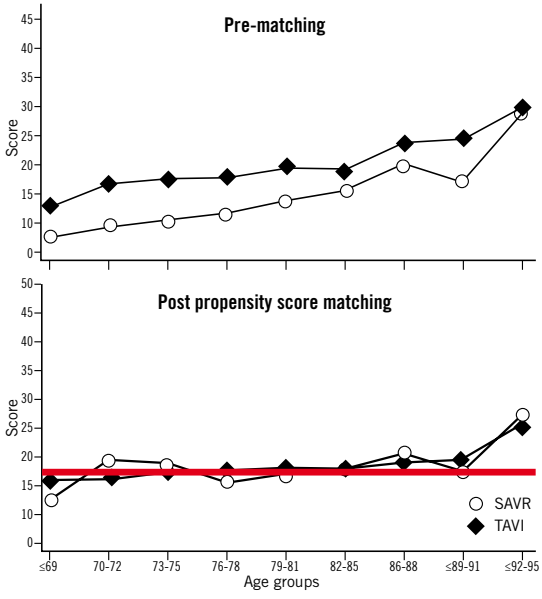

Figure 4 **BERMUDA initiative**

Upper panel: Logistic EuroSCORE in different age groups for TAVI and SAVR. *Lower Panel:* propensity score matched analysis in which the comparable Logistic EuroSCORE across age groups suggests that lower age groups have more comorbidities.

age of 70-74 years with two or three comorbidities, or an age of 75-79 with one or two comorbidities or an age ≥80 and one or no comorbidities (Figure 2). The SURTAVI model 1) emphasises the pivotal importance of the independent "age" variable and 2) allows the identification of an intermediate risk group across different age cohorts based on the number of predefined risk variables. A younger patient with more risk factors may have a similar risk profile as that of an older patient who has less risk factors. Accordingly, the SURTAVI algorithm defines a low-risk, intermediate and high-risk cohort (Figure 3).

Data from the Bern-Munich-Rotterdam (BERMUDA) initiative illustrated the concept of age and comorbidities in a pooled dataset of 2,884 SAVR and 782 TAVI patients. The estimated logistic EuroSCORE increased with age, while each age group of TAVI patients had a higher logistic EuroSCORE than SAVR patients (Figure 4). Propensity score matching analysis identified a patient cohort of 784 patients (392 in each group) and demonstrated 1) both TAVI and SAVR cohorts had similar estimated operative risks according to the Logistic EuroSCORE and 2) the risk profile was similar across all age groups (Figure 4). The latter illustrates that younger patients had more comorbidities than their older counterparts, which therefore counterbalanced the risk related to age in this study. Figure 5 demonstrates that neither the STS score nor Logistic EuroSCORE can uniformly discriminate between

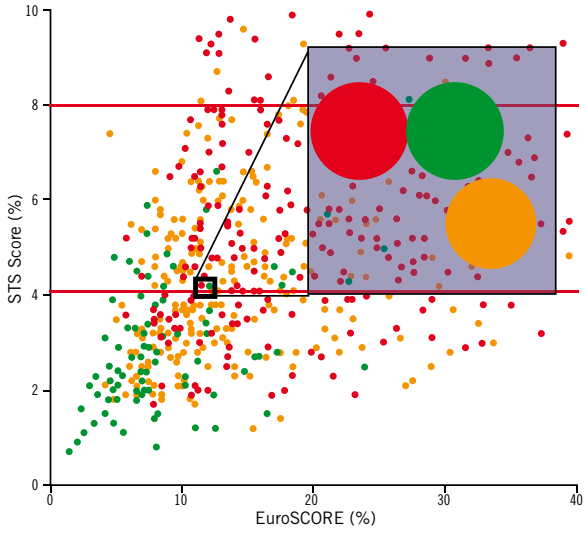

Figure 5 **The STS and EuroSCORE of each individual patient in the propensity matched database from the BERMUDA initiative**

The colour code refers to the risk classification according to the SURTAVI mode; green = low risk, orange = intermediate risk, red = high risk. The shaded are magnifies three patients with an STS score of 4% and a Logistic EuroSCORE of 10%. According to the SURTAVI model this combination could result in low, intermediate or high risk.

a patient's operative risk. An STS score of 4 for instance did not correlate with a logistic EuroSCORE nor with the proposed SURTAVI model. Apparently, the established risk models do not uniformly determine a patient's operative risk.

RISK FACTOR SELECTION PROCESS

The risk algorithm should be applicable to potential TAVI candidates. Therefore, particular variables that would preclude TAVI are excluded (e.g., infectious endocarditis, concomitant valve surgery, emergent procedure, multivessel or left main stem coronary artery disease with a SYNTAX score >33). Selected risk factors should be relatively prevalent, easy to capture and have a reasonable impact on operative mortality.

We reviewed the risk models evaluated in the last 15 years and ranked the contained variables according to their corresponding odds ratio in the respective risk models (Table 1, Figure 6).[14, 16, 17, 19, 22-31] Apart from age, cardiac reoperation, depressed LV function; chronic obstructive pulmonary disease (COPD), renal insufficiency, cerebrovascular disease, peripheral arterial disease, pulmonary hypertension and diabetes emerged. Particular variables not listed in previous models appear relevant in a higher risk population eligible for TAVI, and would therefore merit consideration. Previous mediastinal radiation, liver failure, chest deformity, porcelain aorta and frailty were evaluated.[32-37]It is especially frailty

Table 1 Preoperative risk models

Database	Year	Variables (n)	Patients (n)	30-day mortality
Providence Health System	2005	12	4,914	5%
Northern New England	2004	11	5,793	6.2%
Ambler	2005	14	32,839	6.4%
Department of Veterans Affairs	2004	14	7,450	6.1%
NIS	2000	16	46,397	6.4%
New York State*	2007	11	10,702	4.4%
New York State*	2007	12	8,823	8.9%
NWQIP	2007	10	4,450	4.6%
Baden	2006	20	2,198	3.8%
EuroSCORE	1999	17	13,302	4.7%
Halifax	2010	10	3,826	4.9%
STS NCD†	2009	23	67,292	3.2%
STS NCD†	2009	23	66,074	5.6%

*† These models have been developed for different patient populations, including patients undergoing coronary artery bypass grafting and aortic valve replacement.

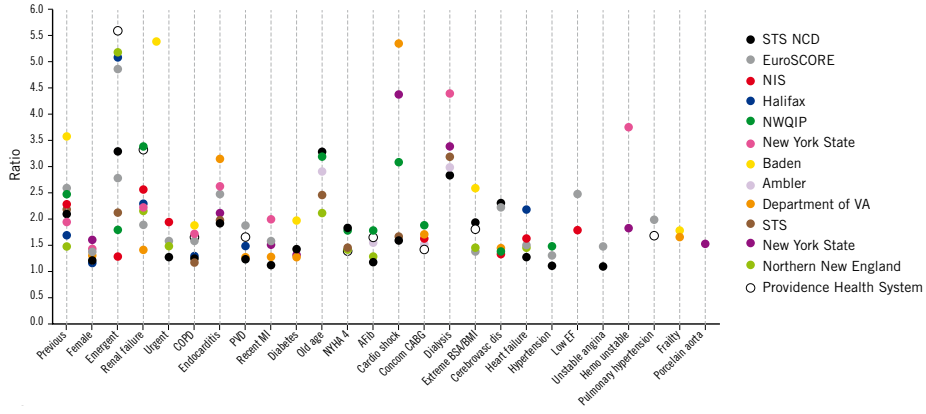

Figure 6 **Odds ratio of variables in different surgical risk models**

that has emerged as a significant and prevalent risk factor for operative mortality. Depending on the definition used, its prevalence in an AS population would vary from 4 to 50%.[36-38]

Eventually, ten risk factors were selected. Each variable was defined according to contemporary literature and those used by professional societies/organisations:

1. SIGNIFICANT CONCURRENT CORONARY ARTERY DISEASE (CAD) REQUIRING REVASCULARISATION

Multivessel CAD and/or left main stem disease with a calculated SYNTAX score >33 make catheter bound therapies less favourable, and would be considered a relative contraindication for TAVI. Previous CABG or PCI is not considered to have considerable impact on short-term outcome.

2. FRAILTY

In the absence of a generally accepted consensus definition, frailty is defined as suggested by Lee and co-workers by the presence of any one of the following:[36] 1. Katz score (independence in "activities of daily living"); 2. Ambulation (walking aid/assist?); 3. Diagnosis of (pre)dementia.

3. LEFT VENTRICULAR DYSFUNCTION

Defined as an EF <35%, with respect to the pivotal position of this particular threshold in the heart failure population.[39]

4. NEUROLOGICAL DYSFUNCTION

Neurologic disease severely affecting ambulation or day-to-day functioning excluding TIA and carotid artery disease, adapted from the Logistic EuroSCORE.[19]

5. PULMONARY DISEASE

COPD Gold Stage II: moderate COPD with worsening airflow limitation (FEV1/FVC <70%; 50% ≥FEV1 <80% predicted), with shortness of breath typically developing on exertion.[40]

6. PERIPHERAL VASCULAR DISEASE

Adapted from the STS risk model: claudication, either with exertion or at rest; amputation for arterial vascular insufficiency; vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities; documented aortic aneurysm with or without repair; positive noninvasive test (e.g., ankle brachial index ≤0.9, ultrasound, magnetic resonance or computed tomography imaging of >50% diameter stenosis in any peripheral artery, i.e., renal, subclavian, femoral, iliac); noninvasive carotid test with >60% diameter occlusion or prior carotid surgery or symptomatic carotid stenosis >50%.[16, 41-43]

7. RENAL DISEASE

At least moderate chronic kidney disease with GFR <60 mL/min according to the National Kidney Foundation kidney disease outcome quality initiative advisory board.[44]

8. REDO CARDIAC SURGERY

9. PULMONARY HYPERTENSION

>60 mmHg at most recent measurement.

10. DIABETES MELLITUS

On oral or insulin therapy.

An expert panel of interventional cardiologists and cardiac surgeons assessed and confirmed the selected variables and introduced the feature of the "open box" in order to capture those risk variables that would appear less prevalent, but nevertheless would merit consideration for the risk stratification of the individual AS patient. Typical entities in the "open box' will be (among others) porcelain aorta, complex chest deformity, previous extensive mediastinal radiation and advanced liver failure (Child-Pugh class C).

APPLICATION OF THE SURTAVI MODEL IN PRACTICE

As proof of concept, we applied the SURTAVI risk algorithm to all AS patients undergoing SAVR or TAVI over a 5-year period in the Thoraxcenter, Rotterdam, The Netherlands. Data collection was complete for the TAVI cohort, whereas frailty was not reliably monitored in the SAVR cohort. Figure 7 illustrates the subdivision of patients into three risk groups

according to the SURTAVI algorithm. Over 60% of cases would be deemed low risk, whereas 26% would be adjudicated at intermediate risk. This implies that the anticipated SURTAVI trial entails grossly one fourth of contemporary AS practice. The incomplete data on frailty and the "open box" items (porcelain aorta, liver failure, mediastinal radiation…) suggest that patients could shift to a higher risk cohort based on the presence of additional

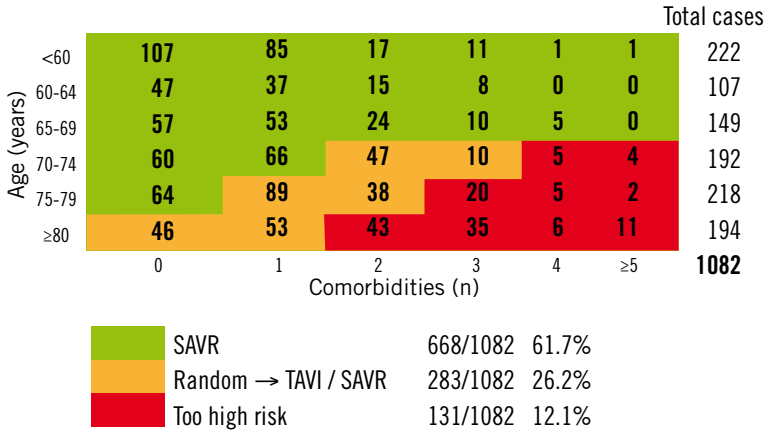

Figure 7 **Patients with aortic stenosis treated with TAVI or SAVR in Rotterdam, categorized into 3 risk groups according to the SURTAVI model**

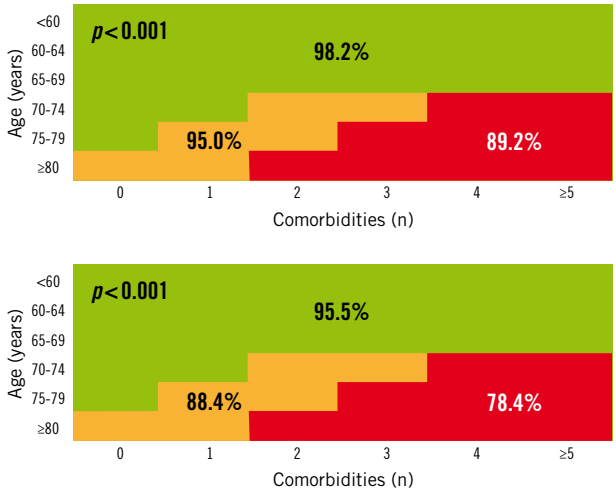

Figure 8 **Short-term 30-day (A) and 1-year (B) outcomes of patients with aortic stenosis treated with TAVI or SAVR in Rotterdam, stratified according to the SURTAVI risk model**

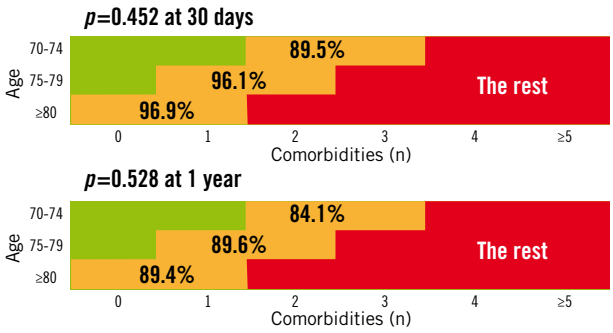

Figure 9 **Evaluation of internal consistency for 30-day and 1-year outcomes in intermediate-risk patients with aortic stenosis treated with TAVI or SAVR in Rotterdam**

risk variables not captured in the predefined "list of 10 comorbidities" or frailty. With these limitations in mind, the 30-day mortality was 98.2, 95.0 and 89.2% ($p < 0.001$) and the 1-year mortality was 95.5, 88.4 and 78.4% ($p < 0.001$) in the low, intermediate and high-risk groups respectively (Figure 8). As for the intermediate risk group in particular, we could not detect any difference in outcome between the three age cohorts underscoring the SURTAVI concept of risk stratification (Figure 9).

FDA PERSPECTIVE

Initially started as an investigator driven trial, SURTAVI evolved into a so-called industry sponsored (i.e., Medtronic Inc.) trial seeking Investigational Device Exemption (IDE) approval by the Federal Drug Administration (FDA). Since TAVI heralds the use of a "significant risk device", FDA approval is essential to qualify for future regulatory purposes and product labelling in the USA. Therefore, a complete pre-IDE application was submitted to the FDA for critical review.

According to the FDA, the STS Risk Calculator should be used for mortality prediction with outliers allowed by qualitative surgical assessment for patients with risk factors not captured by the STS score. A calculated risk between 4 and 8% would define intermediate risk. The FDA argued against the introduction of arbitrary age-range groups. Furthermore, the FDA suggested many of the comorbidities could be interpreted as representing minimal risk. Finally, the FDA also stated that less prevalent risk factors to be captured in the "open box" (like porcelain aorta, immunosuppressive disorders, mediastinal radiation…) would place a patient immediately in the high-risk category. Although the protocol has been revised according to the FDA suggestions, we still believe the above-stipulated SURTAVI

risk paradigm is valid, and indeed may prove to be an accurate and yet user-friendlier tool, in identifying the "intermediate risk" patient.

CONCLUSIONS

The forthcoming SURTAVI trial introduces a new concept of risk stratifying patients with severe AS undergoing surgical or catheter based therapy. Risk stratification is based on the combination of age and a fixed number of predefined risk variables. Retrospective application of this algorithm to a contemporary academic practice dealing with clinically significant severe AS patients allocates about one fourth of patients as being at intermediate operative risk, which will constitute the target patient population for the SURTAVI trial. Further testing is required for validation of this new paradigm in risk stratification.

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Barcelona

Chapter 6

A systematic review of risk prediction in adult cardiac surgery: considerations for future model development

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ABSTRACT

Objective

Risk prediction in adult patients undergoing cardiac surgery remains inaccurate and should be further improved. Therefore we aimed to identify risk factors that are predictive of mortality, stroke, renal failure, and/or length of stay after adult cardiac surgery in contemporary practice.

Methods

We searched the Medline database for English-language original contributions from January 2000 through December 2011 to identify preoperative independent risk factors of one of the following outcomes after adult cardiac surgery: death, stroke, renal failure, and/or length of stay. Two investigators independently screened the studies. Inclusion criteria were: (i) the study described an adult cardiac patient population; (ii) the study was an original contribution; (iii) multivariable analyses were performed to identify independent predictors; (iv) ≥1 of the predefined outcomes was analyzed; (v) at least one variable was an independent predictor, or a variable was included in a risk model that was developed.

Results

The search yielded 5,768 studies. After the initial title screening a second screening of the full texts of 1,234 studies was performed. Ultimately, 844 studies were included in the systematic review. In these studies, we identified a large number of independent predictors of mortality, stroke, renal failure, and length of stay, which could be categorized in variables related to: disease pathology, planned surgical procedure, patient demographics, patient history, patient co-morbidities, patient status, blood values, urine values, medication use, and gene mutations. Many of these variables are frequently not considered as predictive of outcomes.

Conclusions

Risk estimates of mortality, stroke, renal failure, and length of stay may be improved by inclusion of additional (non-traditional) innovative risk factors. Current and future databases should consider collecting these variables.

INTRODUCTION

Predicting procedural mortality in adult cardiac surgery is critical for decision-making purposes particularly when there are different treatments options available, as well as for benchmarking and outcome evaluation both at institutional and surgeon level. Several prediction models have been developed with the main goal of estimating the risk of operative mortality for patients undergoing coronary artery bypass grafting (CABG), aortic valve replacement (AVR), or cardiac surgery in general.[1-4] Despite their usefulness, it remains challenging to develop a risk model that performs accurately across the spectrum of low-, intermediate-, and high-risk patients evaluated for cardiac surgery. Although the recently developed EuroSCORE II may be associated with improvements when compared to the original additive and logistic EuroSCOREs,[5] risk prediction remains a challenge in European patients.[6-8] The Society of Thoracic Surgeons (STS) score has shown to outperform the EuroSCORE,[9-11] but still a number of studies has demonstrated poor model performance in certain patient subgroups.[12-14] Especially in high-risk patients, risk models have been shown to be poorly calibrated and overpredict mortality.

The reasons for suboptimal model performance are multifactorial. While conventional cardiovascular risk factors (e.g. renal failure, diabetes) are considered for inclusion in a model, less obvious factors may be valuable as well. Many risk models are developed through standard statistical approaches not taking into account risk factor interactions or procedure-specific weightings.[15] A mismatch is frequently present between the model development patient cohort and the patient cohort that it is used for in practice; some patient subgroups are continuously underrepresented. Considering these arguments, it is important to i) clarify the purpose of a model, ii) develop a model that is useful, and iii) define the limits of that usefulness. Any model should be based on the available literature and clinical intuition to define the appropriate dataset for model development.

The EACTS is establishing a quality improvement programme for adult cardiac surgery with an international database as an important component, aiming to bring forward an EACTS risk model. We performed a systematic review of the literature to identify which variables may need to be collected to be able to develop a better risk prediction model.

METHODS

Search strategy

We systematically searched the Medline database for English-language original contributions from January 2000 through December 2011 to identify preoperative independent risk factors of one of the following outcomes after adult cardiac surgery: death, stroke, renal failure, and/or length of stay. Our search entry consisted of *outcome* keywords: 'mortality'

OR 'death' OR 'stroke' OR 'cerebrovascular event' OR 'renal failure' OR 'length of stay' OR 'LOS'; *subject* keywords: 'cardiac surgery' OR 'heart surgery' OR 'heart valve surgery' OR 'valve replacement' OR 'AVR' OR 'MVR' OR 'valve repair' OR 'MVP' OR 'coronary artery bypass grafting' OR 'CABG'; and *analysis* keywords: 'risk model' OR 'risk score' OR 'risk factor' OR 'independent' OR 'multivariate' OR 'multivariable' OR 'c-index' OR 'c-statistic' OR 'area under the curve' OR 'AUC'.

Study inclusion

Two investigators (S.J.H. and R.L.J.O) independently screened the studies identified by the search. During the first round of screening all titles were judged for their relevance. Studies evaluating non-cardiac surgery, percutaneous or transcatheter therapies, or diagnostic modalities were excluded. Many risk models have been developed for coronary artery bypass surgery and/or valvular surgery, therefore to be homogeneous but also comprehensive, we excluded studies that focused on pediatrics, congenital cases, aortic arch or root surgery, or heart transplants. Studies that were inconclusive with respect to the performed procedures and reported outcomes of a non-defined group, for example "patients that underwent cardiac surgery", were included.

After identifying potentially relevant studies, the full-length articles were screened using the following criteria: (i) the study indeed described an adult cardiac patient population; (ii) the study was an original contribution; (iii) multivariable analyses were performed to identify independent predictors; (iv) the outcome of mortality, stroke, renal failure, and/or length of stay was assessed; and (v) at least one variable was an independent predictor, or a variable was included in a risk model that was developed.

Data extraction

For each endpoint, independent predictors were extracted from the included studies.

The terminology of predictors differed significantly among studies. For example, "aortic calcification" was also reported as "extend of atherosclerotic ascending aorta disease", "thoracic aorta total plaque-burden", or "severe atheromatous aortic disease". Risk factors were measured and reported according to different indexes; for example, renal function was indicated with serum creatinine, creatinine clearance, or estimated glomerular filtration rate. Such variations were merged into a single variable to avoid repetition.

RESULTS

The search yielded 5,768 results (Figure 1). After excluding non-relevant studies from an initial title screening a second screening of the full texts of 1,234 studies was performed. Another 351 studies were found to be irrelevant because the patient population did not meet the criteria, the endpoint used was not death, stroke, renal failure, or length of stay, or no independent predictors were identified. The full texts of 78 studies could not be retrieved so the abstracts were screened for their relevance. Ultimately, 844 studies were included in the systematic review.

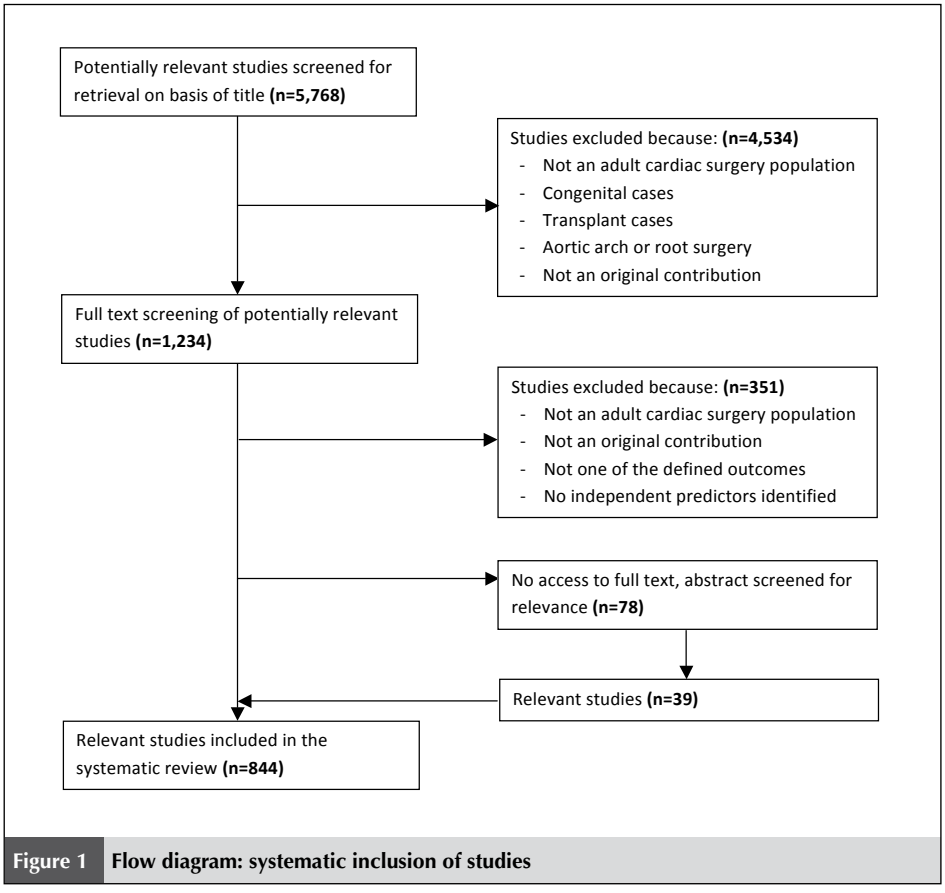

Figure 1 **Flow diagram: systematic inclusion of studies**

The diagnosed disease pathology and planned surgical procedure are essential elements in a risk model and always need to be documented (Table 1). The independent predictors of death, stroke, renal failure, and length of stay are listed in Tables 2-5. The predictors were categorized as patient demographics, patient history, patient co-morbidities, patient status, blood values, urine values, medication use, and gene mutations.

Table 1 Patient's disease pathology and planned surgical procedure

Disease pathology	Planned surgical procedure
Number of coronary vessel disease	Coronary artery bypass grafting
Significant left main stenosis	Aortic valve replacement
Coronary artery disease complexity (e.g. SYNTAX score)	Aortic valve repair
Aortic valve stenosis	Aortic root surgery
Aortic valve regurgitation	Mitral valve replacement
Mitral valve stenosis	Mitral valve repair
Mitral valve regurgitation	Tricuspid valve replacement
Tricuspid valve regurgitation	Tricuspid valve repair
Persistent atrial fibrillation	Aortic surgery
Ascending aorta aneurysm	MAZE
Aortic arch aneurysm	

DISCUSSION

In this systematic review we screened 5,768 studies and included 844 studies in which we identified relevant independent predictors of death, stroke, renal failure, and length of stay after adult cardiac surgical procedures. This study was the first to identify systematically all predictors of adverse events after coronary artery bypass grafting and/or valvular surgery in adults. Many risk factors with a significant impact are frequently not considered when evaluating patients for major invasive procedures. Decision-making may be improved by taking into account these neglected yet predictive risk factors. Beside demographics (e.g. age, gender), disease complexity (e.g. coronary and/or valve lesions), and co-morbidities (e.g. renal failure), other factors such as medication intake and the patient's psychiatric, mental, and social-economic status have also been shown to have a predictive power.[16-17]

Over the last decade(s) there has been a growing interest in risk prediction models both for monitoring innovations and benchmarking outcomes as well as for clinical use to multidisciplinary shared-decision making. The latter is especially true in an era of expanding multi-modality therapy for coronary artery and aortic valve disease when risk prediction plays an important role to determine which patients would benefit most from surgery or interventional therapy.[18]

The inaccuracy of risk models may in part be due to the selection of variables.[18] As

Table 2 Independent predictors of death

Demographics	Age; Gender; Race; Weight; Height; Body surface area; Geographic region (city, rural); Social economic status; Employment status (unemployed); Type of personality; Family history; Primary payer; Current smoker; Alcohol abuse; Depression; Anxiety; Psychosis
History	Pack-years smoking; Previous hospitalization for heart failure; Timing and number of previous PCI(s); Timing of congestive heart failure; Timing and location of previous MI*; Timing of dialysis; Timing of previous TIA/CVA; Timing or previous angina; History of hematological disorder/coagulopathy; Previous surgery for thrombosis; History of thyroid disease; Immune deficiency; Connective tissue disease; Pathological weight-loss; Pacemaker implantation; Number and type of reoperations
Co-morbidities	Diabetes; Metabolic syndrome; Cerebrovascular disease; Neurological disorder; Carotid artery disease; Peripheral vascular disease; (Severity of) Atherosclerotic aortic disease; Atrial fibrillation; Type of arrhythmia; Hypertension; Pulmonary function/disease (e.g. COPD); Pulmonary hypertension; Renal function/failure; Liver function/disease; Malignancy; Peptic ulcer disease
Status	Frailty; Energy level; Problems with self-care; Non-ambulatory state; Mental component score (SF-36); Physical component score (SF-36); Health status (EQ-5D); CCS classification; NYHA classification; LVEF; LV end-systolic diameter/volume; LV hypertrophy; LV end-diastolic pressure/diameter; Restrictive LV filling; LV posterior wall thickness; LV mass index; Lack of contractile reserve; Left atrial diameter; Small annulus; RV end-diastolic pressure; Cardiothoracic ratio; Heart rate; Conduction defect; Corrected QT interval; Amount of ST-segment depression; Preoperative ICU stay; On intubation/ventilation; Sepsis; Active endocarditis; Vegetation size (endocarditis); Prosthetic valve endocarditis; Staphylococcus endocarditis infection; Pulmonary edema; Ventilator-associated pneumonia; Multi-organ failure; Ventricular assist device; Resuscitation; Posterior septal rupture; Unstable/shock; Intra-aortic balloon pump; Urgency of surgery; ASA score; Pulse pressure
Blood values	Hemoglobin; Hematrocrit; Homocysteine; Creatinine; HbA1c; Glucose; CRP; BNP; NT-proBNP; IL-6; Endotoxin core antibody; Sodium; Magnesium; Protein; Albumin; Bilirubin; ASAT; uric acid level; CK-MB; High-sensitive Troponin T; Troponin T; Troponin I; Lactate dehydrogenase; INR group; PTT; Antithrobin 3; HPF4 antibodies; Thrombocytes; Lymfocytes; Neutrophils; Total cholesterol; Non-HDL cholesterol; Cholesterol esters; Triglycerides
Urine values	Proteinuria
Medication	Aspirin; Warfarin or coumadin; Other anticoagulant; Thrombolysis; Nitroglycerine; Statin; Beta-blocker; Catecholamine; Digoxin; Digitalis; Antidepressant (SSRI); Inotropic support; Immunosuppressive therapy
Gene mutations	C677T mutation in MTHFR gene; VEGF +405 GG; rs10116277 (2 allele) -- Chromosome 9p21; rs1042579 recessive

*Inferior/anterior myocardial infarction. ACE = angiotensin-converting enzyme; ASA = American Society of Anaesthesiologists; BNP = brain natriuretic peptide; CCS = Canadian Cardiovascular Society; CK-MB = creatine kinase myocardial band; COPD = chronic obstructive pulmonary disease; CRP = c-reactive protein; CVA = cerebrovascular accident; HDL = high density lipoprotein; HPF4 = heparin-platelet factor 4; INR = international normalized ratio; MI = myocardial infarction; NT-proBNP = N-terminal-pro-brain natriuretic peptide; NYHA = New York Heart Association; PTT = partial thromboplastin time; SSRI = selective serotonin reuptake inhibitor; TIA = transient ischemic attack

shown by previous studies, risk models are inconsistent in including variables and are missing several different yet important risk factors,[19-20] although until now it has been unclear which factors need to be considered. Furthermore, different definitions are used for some of the risk factors, resulting in a different weighting of that factor between models. Collection

Table 3 Independent predictors of stroke.

Demographics	***Status***
Age	Left ventricular ejection fraction
Gender	Active infection
Race	Active endocarditis
Body surface area	Intra-aortic balloon pump
Current smoker	Unstable/Shock
History	Urgency of surgery
Timing of smoking	Pulse pressure
Timing of previous TIA/CVA	***Blood***
Timing of previous MI	Hemoglobin
Previous deep vein thrombosis	Creatinine
Number of reoperations	INR group
Dialysis	***Medications***
Co-morbidities	Aspirin
Diabetes	Statin
Cerebrovascular disease	ACE inhibitor
Neurologic status (e.g. deficit, dementia)	Beta-blocker
Carotid artery disease	Inotropic support
Peripheral vascular disease	***Gene mutations***
(Severity of) Atherosclerotic aortic disease	Interleukine 6 (-174G/C)
Atrial fibrillation	CRP 3'UTR1846C/T
Hypertension	
Hypercholesterolemia/lipidemia	
Renal function/failure	
Pulmonary hypertension	
Left ventricular hypertrophy	

ACE=angiotensin-converting enzyme; CVA=cerebrovascular accident; INR=international normalized ratio; MI=myocardial infarction; TIA=transient ischemic attack

of the variables identified in this study may help to improve future risk models, and standardize risk factor definitions best suitable for inclusion.

A number of studies has identified genetic variations or mutations that carry an increased risk of adverse events after cardiac surgery. Indeed, collection of these variables in a large database could potentially provide insights into the understanding of the patient's risk, but it might be too optimistic to apply genetic profiling to a large international database. Costs of sequencing technologies are decreasing, but genetic profiling is still not widely used. It will be interesting to see whether genetic phenotyping might be more suitable to identify patients at higher risk of adverse events,[21] although little evidence is available at this time to use this technique for risk stratification in cardiac surgery. Some of the laboratory values or echocardiographic measures that have shown to be independent predictors may be too costly to collect. Quality of life assessments are time-consuming activities that will need to

Table 4	Independent predictors of renal failure
Demographics	Age; Gender; Race; Weight; Height; Body surface area
History	Timing of previous MI; Timing of recent cardiac catheterization; Timing of previous PCI; Dialysis; Congestive heart failure; Number of reoperations
Co-morbidities	Diabetes; Metabolic syndrome; Cerebrovascular disease; Peripheral vascular disease; Atrial fibrillation; Hypertension; Renal function/failure; Pulmonary disease (e.g. COPD); Pulmonary hypertension; Charlson comorbidity index
Status	CCS classification; NYHA classification; Left ventricular ejection fraction; Sepsis; Active endocarditis; Intra-aortic balloon pump; Unstable/shock; Urgency of surgery; ASA physical status
Blood values	Hemoglobin; Hematocrit; Creatinine; Platelet count; HbA1c; Hyperuricemia; urea nitrogen; Bicardbonate; Sodium; Albumin; Bilirubin
Urine values	Albumin to creatinine ration; Proteinuria
Medication	Statin; Calcium channel blocker; ACE inhibitor; Renin-angiotensin system inhibitor; Diuretic; Immunosuppressive therapy
Gene mutations	Catechol-O-methyltransferase LL

ACE = angiotensin-converting enzyme; ASA = American Society of Anaesthesiologists; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention

Table 5	Independent predictors of length of stay
Demographics	Age; Gender; Race; Weight; Height; Body surface area; Geographic region (e.g. rural); Social status; Post-traumatic stress disorder; Depression
History	Previous TIA/CVA; Previous embolism; Timing or previous MI; Timing of previous PCI; (Duration of preceding) Hypertension; Previous arrhythmia treatment; Dialysis; Previous endocarditis; Congestive heart failure; Number of reoperations
Co-morbidities	Diabetes; Cerebrovascular disease; Peripheral vascular disease; Atherosclerotic aortic disease; Atrial fibrillation; Arrhythmia; Hypertension; Pulmonary function/disease (e.g. COPD); Pulmonary hypertension; Renal function/failure; Liver function/failure; Malignancy; Dyslipidemia/hypercholesterolemia; Hyperglycemia
Status	SF-36 quality of life; CCS classification; NYHA classification; Left ventricular ejection fraction; Diastolic dysfunction; Right ventricular end-systolic diameter; Cardiothoracic ratio; Frailty; Immunosuppressive therapy; Rheumatic fever; Active infection; Active endocarditis; Large endocarditis vegetation (15 mm); Unstable/shock; Intra-aortic balloon pump; Urgency of surgery
Blood values	Hemoglobin; NT-proBNP; BNP; Creatinine
Medication	Beta-blocker; Nonaspirin platelet inhibitor; Inotropic support
Gene mutations	Il-8-251AA; Catechol-O-methyltrasferase LL

BNP = brain natriuretic peptide; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; MI = myocardial infarction; NT-proBNP = N-terminal-pro-brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack

be performed by educated research nurses. Therefore, a model will always be lacking some variables that could potentially increase its performance.

The balance between the number of variables and model performance should be carefully considered when developing a risk model. Although many variables may be predictive (Tables 2-5), they cannot all be included because this will decrease the user-friendliness of

the model.[22] Furthermore, a great number of variables will likely result in missing data that will have a negative impact on the accuracy of a newly developed risk model. On the other hand, ignoring some of these variables may produce a model with modest performance at best. It is recommended to exclude only variables with little impact on the predictive value of the model. Factors must be relatively present in the population, and enough adverse events must occur in a frequent manner to be able to have enough power for each risk factor to weight it in a multivariate model. Factors that are only present in a very small minority (<1%) of patients may not be relevant to collect, although their relative weight may be high. Ideally, the impact of the identified risk factors would be used to select which factors are more important to collect than others. However, to obtain an accurate estimate of the impact on the model, a broad range of risk factors need to be collected -- including (non-)conventional factors -- in a large database. Only then can unnecessary risk factors be excluded. Collection of these factors will furthermore identify specific factors with international variation in prevalence or dynamic effect weights, which might result in different or a changing impact of factors on short- and/or long-term risk.[23]

It is unrealistic to collect for each patient the hundreds of variables that were identified in this study. It might be appropriate to start data collection with a small selection of centers as a feasibility project. This helps to determine the relative impact of certain variables and whether it is necessary and possible to collect these on a larger scale. Nevertheless, even in a feasibility design there are variables that may need to be prioritized over others. This study provides a framework for future model development, from which certain variables can be chosen depending on the prevalence of a risk factor, its relative impact, the patient population, the type of model (e.g. short-or long-term), the endpoints for which the model is developed, and the cost and resources available.

Risk models that have been developed on a cohort of patients undergoing a specific procedures may have limited value when applied to other population groups, as the impact of any one variable can have a very different weighting when applied to a cohort of patients undergoing another procedure. This may also be one of the reasons why risk models fail to predict accurately outcomes of low- to high-risk patient cohorts. This is clearly evident when examining the predictive power of the original EuroSCORE. It was developed on relatively low-risk patients undergoing CABG [24] but subsequently has been widely used with limited value for high-risk AVR, probably because such patients were hardly represented in the EuroSCORE database.

The EuroSCORE II was developed with 22381 patients of which 46.7% and 46.3% underwent isolated CABG and valve procedures, respectively.[5] However, recent evidence suggests that this more balanced inclusion of procedures was at the expense of decreased model performance in isolated CABG procedures.[8] Although generic risk models are useful in describing the risk profile of large patient populations included in randomised clinical trials or registries, procedure-specific models for CABG, AVR, and mitral valve surgery are

advocated to increase risk prediction for individual patients. Clearly some of the risk factors we identified will more likely be included in a CABG risk model while others are more specific for an AVR model, such as the SYNTAX score or prosthetic valve endocarditis, respectively. The predictive power of some factors remains unclear when evaluating a cohort of patients undergoing a specific procedure, which is why there is a need to collect these factors in a generic database. This will furthermore provide the opportunity to examine whether useful generic models with procedure-related interaction terms can be constructed or whether only procedure-specific models are required for accurate risk prediction.

One major limitation of the widely used European risk scores remains that they have been developed to predict operative mortality although this is not the only outcome of interest to either patients, health care systems or policy makers. Many variables predictive of death will also be significant for other outcomes including renal failure, stroke, and length of stay. However, the associated odds ratios might be different for specific outcomes. For example, in the STS model for isolated valve surgery the OR of active infectious endocarditis for mortality is 1.95 (95% CI 1.68-2.27) but 2.79 (95% CI 2.51-3.09) for prolonged length of stay.[4] One of the goals of the forthcoming EACTS risk model will be to develop a model able to predict accurately multiple outcomes using outcome-specific ORs, similar to the STS risk model.

Although risk models can be improved, random events will always occur and a prediction model can therefore never be perfect. Thus, clinical guidelines recommend that clinical decision-making related to interventional and surgical interventions should be performed by a multidisciplinary Heart Team that consists of at least an interventional cardiologist and cardiovascular surgeon to interpret and weight risk models and additional information to come up with the most appropriate treatment recommendation for the individual patient.[25]

Limitations

The focus of this study was adult patients undergoing coronary artery bypass grafting and/or valve surgery, because the available surgical risk models have predominantly been developed for these populations. Although there may indeed be significant overlap, the identified independent risk factors may not be applicable to other surgeries such as on the aortic root or aorta, congenital cases, or heart transplantations.

CONCLUSIONS

This systematic review identified a significant number of independent predictors of adverse outcomes after adult coronary and valvular procedures, many of which are frequently not considered. These variables will be collected in a dedicated European database, and used for the development of the forthcoming EACTS risk model. However, the clinical value of these risk factors needs to be weight against the cost and effort of collecting them.

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Washington

Chapter 7

The SYNTAX Score and its clinical implications

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ABSTRACT

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are both treatment options for coronary revascularisation in selected patients with stable coronary artery disease and ischemia. In 2006 the anatomical SYNTAX Score was introduced to quantify the complexity of coronary artery disease. The SYNTAX Score was found to be a good predictor of major adverse cardiac or cerebrovascular events after PCI but not CABG. Currently available studies have shown that the SYNTAX Score is a useful tool to determine the optimal revascularisation strategy in patients with left main and/or three-vessel disease. Both European and US revascularisation guidelines recommend treatment selection based on the SYNTAX Score. Both guidelines do however state that decision-making between CABG and PCI should be performed by a dedicated coronary Heart Team that includes a non-interventional/clinical cardiologist, interventional cardiologist, and cardiovascular surgeon (Class I indication).

INTRODUCTION

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are both treatment options for coronary revascularization in selected patients with stable coronary artery disease and ischemia. Current European and US revascularization guidelines indicate that the treatment selection depends on patient preferences, co-morbidity, and complexity of coronary artery disease.[1, 2] Less complex single- or double-vessel coronary artery disease is preferably treated with PCI, where the level of acceptance is higher for PCI compared to CABG, whereas complex three-vessel disease is best treated with CABG, where the level of acceptance is higher for CABG compared to CABG.[1, 2]

Not only the number of diseased coronary vessels is a marker for the extensiveness of coronary artery disease. The location of the lesions and their impact on blood flow,[w1] the degree of vessel stenosis, lesion classifications, and the diameter and calcification of the vessel are also important factors that affects the technical feasibility by PCI, and prognosis. Considering these factors, there are different degrees of multi-vessel disease and the preferred revascularization strategy may be different for specific lesion complexities. To assess this hypothesis the angiographic SYNTAX Score was introduced.[3]

Figure 1 **Components of the complexity of coronary artery disease that are used to calculate a patient's SYNTAX Score**

THE SYNTAX SCORE

The SYNTAX Score was developed through expert consultation, and integrated previous angiographic scores that assessed lesion complexity: the AHA classification modified for the ARTS study,[w2, w3] the Leaman score,[w4] the ACC/AHA lesions classification system,[w5]the total occlusion classification system,[w6] and the Duke and ICPS classification systems for bifurcation lesions.[w7] Subsequently the Medina classification of bifurcation lesions was introduced.[w8]

The SYNTAX Score was designed to quantify the complexity of left main or three-vessel disease. Using the open accessible web-based score calculator (www.syntaxscore.com) one is able to calculate each patient's SYNTAX Score by answering a series of questions. The SYNTAX Score corresponds to the lesion complexity measured by the coronary tree characteristics and the lesion locations and specifics (Figure 1). One of the most crucial features of the SYNTAX Score is that it is a lesion-based score, which integrates all lesions to determine the degree of myocardium that is at risk and the technical success rate of treating the each lesion. Three general questions are asked, and for every lesion, 8 questions need to be answered to determine the lesion's individual score, which accumulates to form the overall SYNTAX Score of the patient.

Case examples

Figure 2 illustrates the SYNTAX Scores of two patients. The first patient has three lesions in three arteries: two >50% lesions in the mid portions of the right coronary artery (RCA) and left circumflex artery (LCX), and a left main (LM) bifurcation lesion. The second patient also has three-vessel disease, but the complexity of disease is greater. Patient 2 has a trifurcation involving the LM artery (segment 5), the proximal left anterior descending (LAD) artery (segment 6), the proximal LCX (segment 11), and the intermediate/anterolateral artery (lesions 12). In addition, the angiogram shows a totally occluded first diagonal with a severe angulated (>70˚) bifurcation, a >50% stenosis in the intermediate/anterolateral artery, and diffusely diseased and narrowed vessels in the distal LCX.

Comparing these two patients, it is clear that one can easily distinguish less complex and complex disease; this is translated in SYNTAX Scores of 18 and 42 in these patients, respectively. When evaluating these patients for coronary revascularisation through either PCI or CABG, the technical feasibility of percutaneous revascularisation may be questioned in the second patient, while the targets in patient #1 can be easily stented. Therefore, the SYNTAX Score may be helpful to discriminate which patients can safely undergo revascularisation by PCI or should preferably undergo CABG.

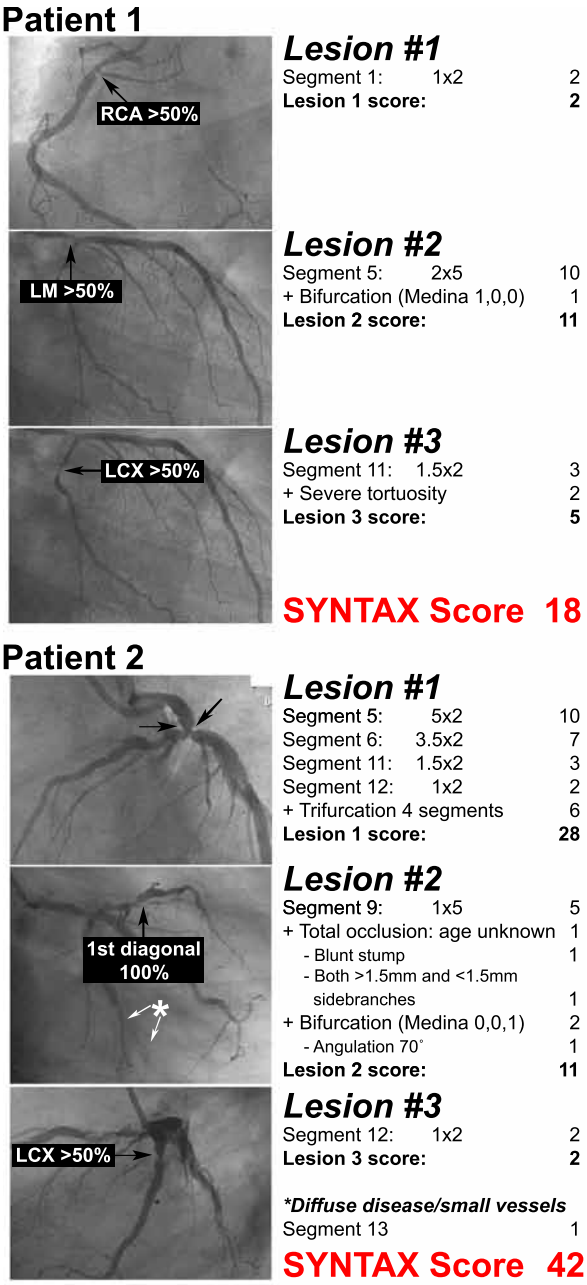

Figure 2 Case examples of two patients with three-vessel disease

THE SYNTAX SCORE AS A PREDICTION TOOL

Initial validation of the SYNTAX Score was accomplished by retrospective application to 1,292 lesions in 306 patients who had undergone PCI for three-vessel disease in the Arterial Revascularisation Therapies Study part II (ARTS-II).[4] Thirty-day results showed a stepwise increase in major adverse cardiac or cerebrovascular events (MACCE) for patients with an increasing SYNTAX Score from low (≤18) to intermediate (19-26) to high (≥26): 3% vs. 5% vs. 12%, p=0.03. This was mainly driven by peri-procedural myocardial infarction (p=0.04) and target vessel revascularisation (p=0.02). After a median follow-up of 370 days, patients with SYNTAX Scores ≥26 had significantly higher MACCE rates. Multivariate analyses showed that the raw SYNTAX Score was an independent predictor of MACCE (HR=1.07, 95% CI 1.03-1.11). A number of studies have since evaluated the predictive power of the SYNTAX score in patients undergoing PCI. The SYNTAX Score has repeatedly been identified as a strong independent predictor of death and MACCE during long-term follow-up.[w9, w10, w11, w12]

The data regarding the predictive ability of the SYNTAX Score in patients undergoing CABG has been conflicting. Although some reports have shown that the SYNTAX Score is related to adverse events during follow-up after CABG,[w13, w14, w15] the majority of studies have shown that the SYNTAX Score is less valuable as a predictor in patients undergoing CABG (Table 1).[w16, w17, w18] Therefore, the general agreement is that the SYNTAX Score is of less significance in patients undergoing CABG, particularly since the randomised SYNTAX trial did not associate any prognostic value of the SYNTAX Score at 5 years.[5] The rationale is that for a coronary bypass it does not matter how complex the proximal lesions in the vessel are. These are always bypassed without any additional procedural complexity or surgical risk, provided there are suitable distal graftable targets. The SYNTAX Score may be regarded as a marker of coronary anatomical disease complexity, and therefore is an indirect marker of plaque burden. Greater plaque burden, as evident by higher SYNTAX Scores, may be one of the reasons higher SYNTAX Score patients confer more benefit from CABG, secondary to the graft 'protecting' the vessel, whereas a stent would treat the individual lesion. Nevertheless, the SYNTAX Score will likely be related to outcomes in some degree; it is perceptible that a patient with a SYNTAX Score of 80 will have an increased risk of adverse events as compared to a patient with a SYNTAX Score of 20,[6] since the SYNTAX Score may be regarded as a marker for systemic atherosclerosis.[7]

Table 1 Summary of studies assessing the predictive ability of the SYNTAX Score in cohorts of patients that underwent coronary artery bypass grafting

Author, year	No. of patients	SYNTAX Score cut-offs	Follow-up (years)	Primary endpoint	Event rate: Low vs. intermediate vs. high	HR (95% CI)	C-statistic
Lemesle, 2009	320	<24.5 and >34	1	Death, MI, and stroke	9.4% vs. 7.5% vs. 10.4% (p=0.77)	…	…
Birim, 2009	148	≤19 and >25	1	MACCE	0% vs. 6% vs. 31% (p<0.001)	Multivariate: 1.2 (1.1-1.2)	0.90
Holzhey, 2010	154	≤18 and >26	5	MACCE	0% vs 6% vs 31% (P<0.001)	Multivariate: p=0.29	…
Kim, 2010	761	≤23 and >36	3	Death, MI, and stroke MACCE	8.9% vs. 8.2% vs 12.1% (p=0.29) 11.6% vs. 11.5% vs. 14.4% (p=0.59)	… …	Raw score: 0.53, Tertiles: 0.54 Raw score: 0.51, Tertiles: 0.52
Mohr, 2011	1541	≤22 and ≥33	2	MACCE	15.6% vs. 14.3% vs. 15.4% (p=NS)	Univariate: p=0.79	…
Capodanno, 2011	549	≤22 and ≥33	2	Cardiac mortality	2.3% vs. 5.3% vs. 5.8% (p=0.59)	…	Tertiles: 0.56
Carnero-Alcázar, 2011	716	≤33 and >37	4	Death MACCE	8% vs. 18% vs. 27% (p=0.032) 21% vs. 46% vs. 33% (p=0.009)	Multivariate: 1.05)1.01-1.09) Multivariate: 1.03 (1.00-1.07)	…
Melina, 2012	191	≤22 and ≥33	5	Death	19% vs. 23% vs. 47% (p=0.001)	…	Raw score: 0.70

CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac or cerebrovascular event; MI =myocardial infarction

COMPARATIVE EFFECTIVENESS: PCI VERSUS CABG

The most compelling data about the difference in outcome between CABG and PCI according to the SYNTAX Score comes from the SYNTAX trial itself.[8, 9] The SYNYAX Scores were assessed by all participating centres in the SYNTAX Trial (18 countries, 85 centres), as a tool to force the surgeon and interventional cardiologist to examine the coronary angiogram in detail, and agree that equivalent anatomical revascularization could be achieved. The SYNTAX Score performed by the study sites was corroborated by an independent core laboratory, blinded to the treatment assignment and all clinical events. Since the distribution of SYNTAX Score was normal (Gaussian) in the SYNTAX Trial, patients were stratified by the complexity of coronary disease (tertiles), to allow meaningful comparisons with enough statistical power in each group. The division into tertiles of the randomised cohort of 1,800 patients produced the following cohorts: patients with low lesion complexity had SYNTAX Scores ≤22, intermediate lesion complexity was defined as a SYNTAX Score 23-32, and high lesion complexity as a SYNTAX Score ≥33.

At one-year follow-up, there was a significant treatment-by-SYNTAX Score interaction (p=0.01) in the hypothesis-generating subgroup analysis according to lesion complexity. Although the general trial conclusion was that PCI with drug-eluting stents was not non-inferior to CABG, no differences between CABG and PCI in MACCE in patients with a SYNTAX Score ≤22 were reported (respectively 13.6% versus 14.7%, p=0.71). There was clear superiority of CABG over PCI in patients with SYNTAX Scores ≥33 (respectively 10.9% versus 23.4%, p<0.001). With follow-up extending to 3 and 5 years,[9] the Kaplan-Meier curve of MACCE after PCI or CABG in patients with low SYNTAX Scores (≤22) remained superimposed (Figure 3A). In patients with intermediate SYNTAX Scores 23-32 there was no significant difference at one year (CABG: 12.0% versus PCI: 16.7%, p=0.10), but the diverging curves during follow-up suggest that CABG may be of greater benefit in these patients (Figure 3B). For patients with SYNTAX Scores ≥33, the difference between CABG and PCI further increased during follow-up, demonstrating the superiority of CABG compared to PCI in this subgroup (Figure 3C). Detailed separate analyses of patients with left main and three-vessel disease demonstrated similar findings, except for patients with an intermediate SYNTAX Scores of 23-32, where outcomes between CABG and PCI were comparable. Here the difference between CABG and PCI seems negligible in patients with LM disease (Figure 3H), while in those with three-vessel disease the rate of MACCE after CABG is significantly lower than after PCI (Figure 3E).

Two recent large randomized trials have since compared CABG with PCI: the PRECOMBAT and FREEDOM trials.[10,11] The PRECOMBAT trial was performed in the setting of left main coronary disease and enrolled 300 patients in each treatment arm; 180 patients with SYNTAX Scores ≤19, 198 patients with SYNTAX Scores >19-≤29, and 180 patients with SYNTAX Scores >29.[10] After two years of follow-up, there was no interaction between

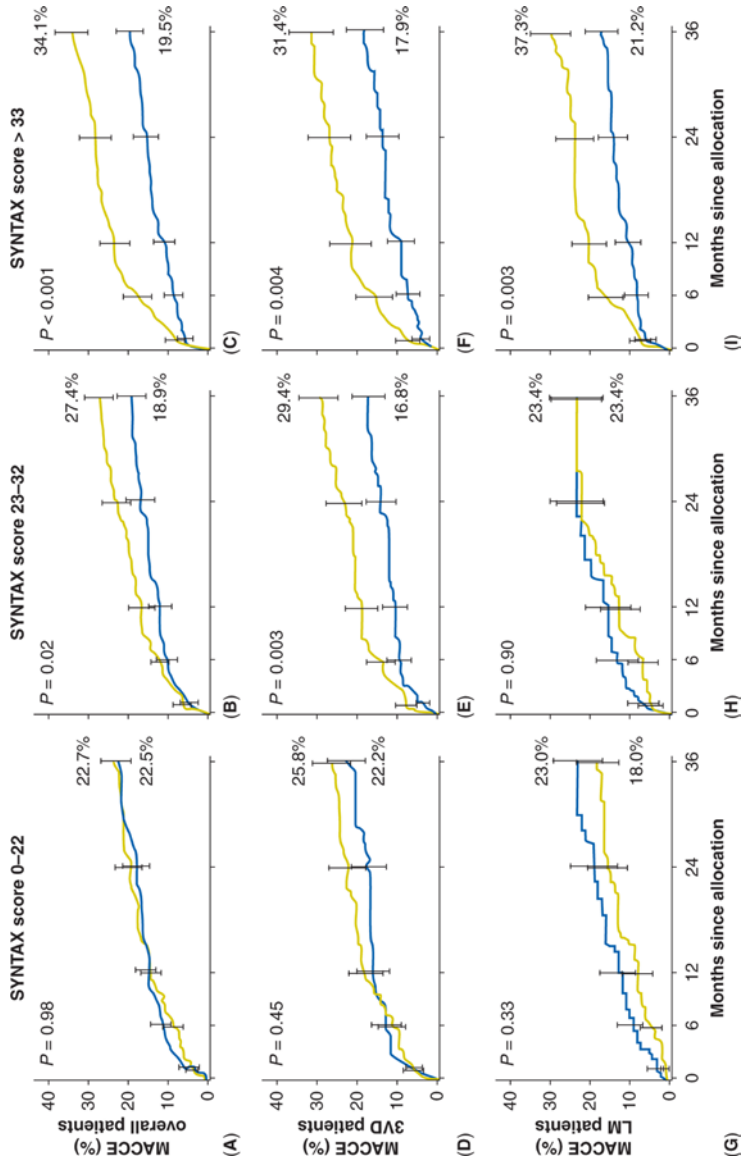

Figure 3 **Long-term follow-up of the SYNTAX trial comparing CABG with PCI with paclitaxel-eluting (Taxus) stents**

In patients with low lesion complexity (SYNTAX Score ≤22) there was no difference in the rate of MACCE. In patients with SYNTAX Scores 23-32 there was a significant benefit of CABG over PCI, and this was even more profound in patients with high lesion complexity of SYNTAX Scores ≥32. Copied with permission from the SYNTAX Investigators.[7] CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular events; PC I= percutaneous coronary intervention

treatment and SYNTAX Score for the primary composite endpoint of MACCE (p=0.80). From low to intermediate to high SYNTAX Scores, the hazard ratio non significantly changed from 1.38 (95% CI 0.40-4.21) to 2.32 (95% CI 0.82-6.57) to 1.60 (95% CI 0.73-3.54). Remarkably, a subgroup analysis according to left main + additional vessel disease --a proxy for SYNTAX Score-- showed a stepwise increase from isolated left main to left main +1, +2, and +3 vessel disease. The hazard ratio in favour of CABG increased from 0.39 to 0.70 to 1.04 to 3.05. Thus, although the SYNTAX Score subgroup analysis found no interaction, the trial was underpowered to detect a difference, possibly secondary to an unexpectedly low event rate, and recruitment of patients with less complex coronary artery disease (mean SYNTAX score 25 versus 30 for left main patients in the SYNTAX trial) and a low clinical risk profile (mean additive EuroSCORE 2.7 versus 3.8 for left main patients in the SYNTAX trial). The non-inferiority margin of the study was wide making the results of the study none clinically directive.[12]

The FREEDOM trial was performed in 1900 diabetic patients with multivessel disease, of which 669, 844, and 374 patients had SYNTAX Scores ≤22, 23-32, and ≥33, respectively.[11] There was no interaction between SYNTAX Score and treatment (p=0.58). In both treatment arms the 5-year event rate of the primary composite endpoint for death, myocardial infarction, or stroke increased with higher lesion complexity (PCI: 23 versus 27 versus 31%; CABG: 17 versus 18 versus 23%). This result is inconsistent with the 5-year follow-up in diabetic patients enrolled in the SYNTAX trial.[13] Although the interaction was not significant in that study either, there was a stepwise increase in death, MI, or stroke in patients that underwent PCI (19.4% versus 22.2% versus 31.0%) but not in those treated with CABG (20.1% versus 21.5% versus 16.0%). The lack of a treatment-by-SYNTAX Score interaction in the FREEDOM trial may be the result of low power. Only 678/1900 patients reached 5-year follow-up (197 deaths and 481 remained at risk). Furthermore, it may have been better to use their own Gaussian distribution instead of the SYNTAX Score tertiles to include more patients in the high SYNTAX Score group and allow an even comparison with more statistical power.

Apart from randomized trials, several registries performed comparative effectiveness analyses. Two studies (n=556, n=932) were able to confirm the findings of the left main subgroup analysis from the SYNTAX trial,[w19, w20] by showing similar event rates of death, myocardial infarction, or stroke between CABG and PCI in patients with SYNTAX Scores ≤32. The effect that SYNTAX Score tertiles have on outcome differences between CABG and PCI have also been denied in an analysis from the MAIN-COMPARE registry that included 1,580 patients with left main disease.[w21] However, the authors correctly stated that unavoidable selection biases may be present in studies retrospectively assessing the SYNTAX Score, in particular when comparing outcomes between PCI and CABG without being blinded for treatment and outcome. These results should therefore be interpreted as hypothesis generating, subject to outcomes from ongoing randomised trials.

THE SYNTAX SCORE IN PRACTICE

Based on the data showing the usefulness of the SYNTAX Score in PCI patients, the most recent European guidelines recommended that the SYNTAX Score be calculated for risk stratification in candidates for PCI (level of evidence IIa B).[1] Since the SYNTAX Score lacks a prognostic value in patients undergoing CABG, the guidelines consider the SYNTAX Score not to be effective/useful in candidates for CABG (level of evidence III B). This recommendation is however somewhat monochrome, since the SYNTAX Score is useful for selecting PCI patients, a fact that allows the SYNTAX Score to be useful for decision making between CABG and PCI. The SYNTAX Score is helpful to identify which patients would benefit most from either revascularization strategy and thus in clinical practice it is useful to calculate in CABG patients as well. In this regard, the American guidelines do take this into consideration and recommend calculation of the SYNTAX Score in patients considered for both CABG and PCI equally with a level of evidence IIa B.[2]

The guidelines are consistent in their optimal treatment recommendations for three-vessel disease as determined by the SYNTAX Score. It is reasonable to perform PCI in patients with less complex three-vessel disease (SYNTAX Score ≤22), while CABG is clearly preferable in patients with more complex three-vessel disease (SYNTAX Score >22).[1, 2] In patients with left main disease the guidelines are more progressive. In Europe the indication to perform PCI in left main disease is a SYNTAX Score ≤32 [1] while the American guidelines use a SYNTAX Score ≤22 as the cutoff.[3] However, a SYNTAX Score cutoff of ≤32 can be used if there is a low or intermediate risk of procedural PCI complications.

The current treatment recommendations have been interpreted by many as a broadening indication to perform PCI. The introduction of the SYNTAX Score has mainly reduced the uncertainty in selecting which patients should undergo either CABG or PCI,[w22] although the patient distribution to CABG and PCI has remained relatively stable. Data from the SYNTAX run-in phase showed that 74% and 26% of patients with de novo three-vessel or left main disease underwent CABG and PCI, respectively (Figure 4A).[14] If the current revascularization guidelines are adhered to in clinical practice, the 'new' distribution of patients recommended to undergo CABG and PCI might be considered to be approximately 75% and 25%, respectively (Figure 4B). There remains an area of investigation regarding patients with left main disease and a SYNTAX Score of 23-32 (approximately 6% of population). The ongoing EXCEL trial will provide the necessary insights into the safety and efficacy of PCI in this cohort.[15] With a stronger recommendation to perform PCI in patients with left main disease and intermediate coronary complexity (SYNTAX Score 23-32), 40% of the total left main patient cohort can be referred to PCI. Using the SYNTAX trial and registries (Figure 4), the estimated CABG/PCI distribution of patients with left main or three-vessel disease will then be 69%/31%, respectively.

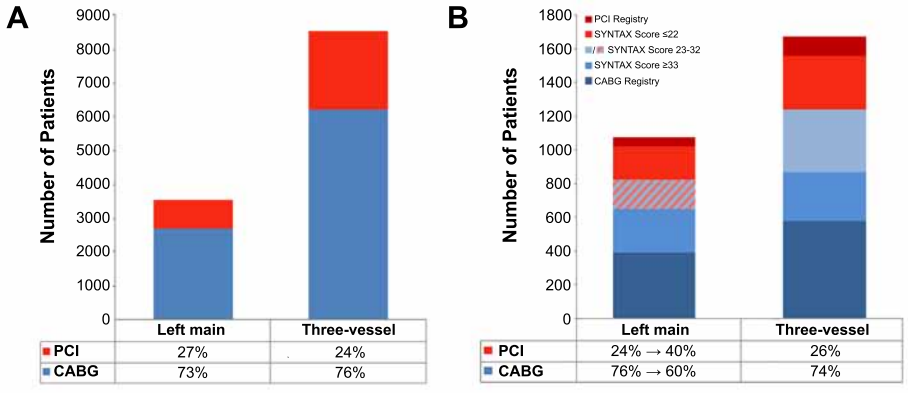

Figure 4 **The distribution of patients undergoing CABG or PCI before (A) and after (B) the SYNTAX trial and the introduction of the SYNTAX Score**

Current American and European guidelines recommend the use of the SYNTAX Score in the decision-making process to determine the optimal revascularisation strategy. Applying these recommendations, approximately 75% and 25% of patients with left main or three-vessel disease are referred to CABG and PCI, respectively. However, this distribution will likely change in the near future due to new data from randomized controlled trials. Adapted with permission from the SYNTAX Investigators.[7, 14]

LIMITATIONS OF THE SYNTAX SCORE

SYNTAX Score assessments have shown variability among investigators (inter-observer agreement) and even within different assessments of the same investigator (intra-observer agreement).[16-17] This variability may be problematic because the optimal treatment recommendation could depend on the SYNTAX Score. Introduction of observer bias may therefore result in inappropriate treatment decisions, especially when the SYNTAX Score value is close to accredited cutoff values 23 or 32. Genereux and colleagues showed that appropriate physician training substantially reduced this issue.[16] Non invasive assessment of the SYNTAX Score with computed tomography and non invasive functional assessment of lesions are being developed,[w23-w25] will simplify the calculation of the SYNTAX Score in the near future.

To prevent inappropriate treatment recommendations, the SYNTAX Score value should not be a blind indication for treatment. Although from the SYNTAX trial it is clear that patients with severe complex three-vessel disease (SYNTAX Score ≥33) have superior outcomes with CABG, even patients with a SYNTAX Score ≥33 may still undergo PCI if there are co-morbidities that exclude the patient from undergoing CABG. In the SYNTAX PCI nested registry, 43% (82/189 patients) had a score ≥33.[6] The SYNTAX Score should therefore merely be one of the factors that is weighted by a multidisciplinary Heart Team consisting

of a non-interventional/clinical cardiologist, interventional cardiologist, and cardiovascular surgeon.[18]

The SYNTAX Score is limited by the assessment of coronary disease complexity while there are other clinical patient factors that are prognostically important and should be weighted by the Heart Team; for example age, pulmonary disease, and renal function. In an attempt to combine these factors, a number of new prediction models have been established.[19-20] Initial alidation of such models has been encouraging and further studies are forthcoming.[w24]

GLOBAL USE OF THE SYNTAX SCORE

Evidently the inclusion of the SYNTAX Score in practice guidelines and the growing evidence supporting the anatomical SYNTAX Score have led to an increase in its use. As of 31 December 2012, the SYNTAX Score website (www.syntaxscore.com) has been visited 277,039 times, and the online SYNTAX Score calculator has been used 197,201 times. A peak in site visits was seen after the main publication of the SYNTAX trial in 2009.[6] Nevertheless, the monthly visits have been continuously increasing (Figure 5 and Table 2) despite missing returning visitors who have downloaded the application (n>90,000 downloads). The number of pages per visit and the average visit duration are continuously declining (Table 2), likely because returning visitors have become familiarized with the website.

The SYNTAX Score is currently being used as inclusion criteria in randomized trials evaluating optimal treatment strategies for coronary artery disease, such as the EXCEL trial.[w26] Moreover, new clinical trials evaluating transcatheter aortic valve implantation in patients at intermediate surgical risk are using the SYNTAX as an exclusion criteria: PARTNER 2 (NCT01314313) and SURTAVI (NCT01586910). Therefore, it is expected that not only coronary Heart Teams but also valvular Heart Teams will integrate the SYNTAX Score in their decision-making.

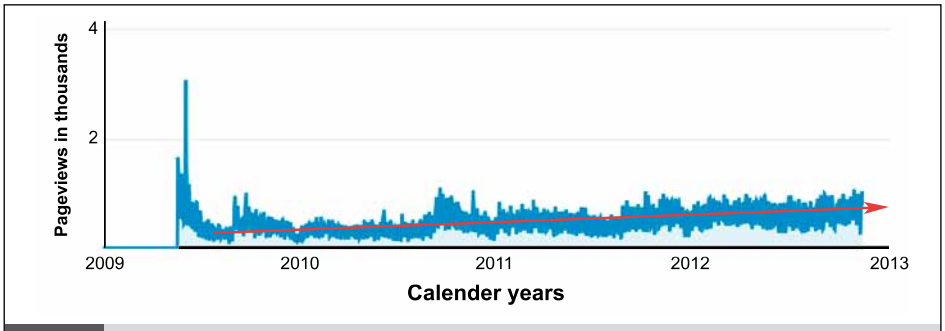

Figure 5 **The number of page-views that www.syntaxscore.com has received since its introduction**

Table 2 Statistics of the SYNTAX Score website (www.syntaxscore.com)

	Time period							
	17 May 2009 – Jun 2009	Jul 2009 – Dec 2009	Jan 2010 – Jun 2010	Jul 2010 – Dec 2010	Jan 2011 – Jun 2011	Jul 2011 – Dec 2011	Jan 2012 – Jun 2012	Jul 2012 – Dec 2012
Visits	11,130	25,860	23,056	33,248	36,977	41,628	51,161	53,979
Pageviews	36,906	71,152	61,024	89,865	92,481	100,019	120,250	122,506
Pages per visit	3.32	2.75	2.65	2.70	2.50	2.40	2.35	2.27
Average visit duration (min:s)	04:30	03:40	03:22	03:49	03:15	02:58	02:51	02:42

CONCLUSIONS

The anatomical SYNTAX Score has emerged as a valuable tool to grade the complexity of patients with left main or three-vessel coronary artery disease. Although there is inter-and intraobserver variability in calculating the SYNTAX Score, this appears to be no longer a clinically relevant issue after appropriate training. The SYNTAX Score is now advocated in clinical guidelines and its use has been increasingly used around the world in everyday clinical practice. Integrating the SYNTAX Score in multidisciplinary coronary and valvular Heart Team decision-making appears inevitable, as current trials and clinical guidelines continue to expand the use of the anatomical SYNTAX Score.

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Rotterdam

Chapter 8

A crucial factor in shared decision-making: the team approach

Head SJ, Bogers AJ, Serruys PW, Takkenberg JJ, Kappetein AP

Lancet 2011;377:1836

TO THE EDITOR:

As discussed in your Editorial on shared decision making (March 5, p 784),[1] treatment decisions are unfortunately often dominated by physician-related factors.[2] The current efforts to include patients in a shared decision-making process concerning treatment are encouraged. Even in a shared setup, however, patients rely on the pros and cons conveyed by the treating physician. Certain details of alternative treatments can intentionally or unintentionally be omitted, resulting in a failure to allow the patient to make a well-informed decision.

To move away completely from this physician-centric model, physicians should group themselves around the patient as a multidisciplinary team which can better disclose both the pros and cons of available therapies, thereby making the individual patient's choice objective and optimal. As an example, the SYNTAX study[3] pioneered the multidisciplinary "heart team approach" in a randomised trial to establish a discussion between different specialties leading to sufficiently deliberated patient advice. This approach has since gained popularity in an attempt to eliminate "competition" between percutaneous and surgical treatment. Several randomised trials now include patients only after a team discussion, and in the recently published guidelines on myocardial revascularisation, the heart team has been introduced as a class I recommendation for decision making.[4]

We propose that a guidelines-driven team approach that formally includes patients' preferences be implemented throughout all specialties to achieve optimal evidence-based and well-informed decisions in medicine.

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Paris

Chapter 9

The rationale for Heart Team decision-making in patients with stable, complex coronary artery disease

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Eur Heart J 2013;34:2510-2518

ABSTRACT

Stable complex coronary artery disease can be treated with coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or medical therapy. To select the most optimal treatment strategy for individual patients with stable complex coronary artery disease, multidisciplinary decision-making has gained more emphasis over the recent years. However, the so called "Heart Team" concept has not been widely implemented. Yet, decision-making has shown to remain suboptimal; there is large variability in PCI-to-CABG ratios, which may predominantly be the consequence of physician-related factors that have raised concerns regarding overuse, underuse, and inappropriate selection of revascularization. In this review we summarize these and additional data to support the statement that a multidisciplinary Heart Team consisting of at least a clinical/non-invasive cardiologist, interventional cardiologist, and cardiovascular surgeon, can together better analyze and interpret the available diagnostic evidence, put into context the clinical condition of the patient as well as consider individual preference and local expertise, and through shared decision-making with the patient can arrive at a most optimal joint treatment strategy recommendation for patients with stable complex coronary artery disease.

INTRODUCTION

There is precedence in the field of medicine that the level of care can be improved and made more consistent with the use of multidisciplinary teams to recommend the most optimal treatment. An example of this is the introduction of the tumor board in the 1960s, which has shown to significantly improve the quality of care.[1-3] A pre-treatment multidisciplinary discussion was associated with improved survival as well as reduced hospital-variations in survival rates [1] and has been identified as an independent predictor of treatment recommendations' conformity to clinical practice guidelines.[3]

The area of cardiovascular diseases has seen the development of Heart Teams early on for treatment of heart failure, pediatric and adult cases of congenital heart disease, and more recently for aortic and mitral valve interventions. In the context of coronary revascularization, multidisciplinary Heart Teams have been introduced through randomized trials. While decision-making for patients with acute indications or less complex coronary disease may be straightforward, for patients with stable complex (e.g. left main and/or multivessel) coronary artery disease (CAD), a Heart Team consisting of a clinical/non-invasive cardiologist, interventional cardiologist, and cardiac surgeon is considered optimal to best assess the advantages and disadvantages of the various treatment strategies. The Heart Team has recently become a class 1C recommendation in European and American guidelines on coronary revascularization.[4-5] However, while in oncology 63% of centers in the western countries have embraced multidisciplinary teams[6], this approach has not yet been widely implemented for cardiovascular indications for a myriad of reasons including the novelty of the concept, lack of experience, lack of proven benefit, logistical issues, as well as turf protection.[7-8] Yet, there is clearly a need for improved decision-making. A recent study suggests that noncompliance to guidelines can result in inappropriate or underuse of revascularization.[9] In patients with an indication for coronary artery bypass grafting (CABG), only 53% received such treatment, 34% underwent percutaneous coronary intervention (PCI), 12% received medical management, and 1% did not receive any treatment.

The purpose of the current manuscript is to explorethe rationale behind Heart Team evaluation and to advocate for wider, regular use of Heart Teams in an orderly fashion, thereby enhancing the value of care for patients with stable complex CAD.

REVASCULARIZATION: WHAT THE HEART TEAM COULD IMPROVE

Since CABG was demonstrated in the 1980s to be superior to medical therapy in patients with three-vessel or left main (LM) disease, many patients have been revascularized by this approach. The introduction of PCI with balloon angioplasty and subsequently stents resulted in a consideration of both therapies as treatment options. The different treatment strategies

should ideally be considered complementary. However, evidence suggests that the current decision-making process and treatment selection is questionable, thereby potentially resulting in suboptimal care and increased health care expenditures.

Variability

Due to technical and therapeutic advancements and reduced invasiveness, PCI has been utilized increasingly since its introduction over 3 decades ago. Evidence from Europe, the United States, and Canada suggests that the PCI-to-CABG ratio has shifted significantly towards more PCI procedures.[10-12]This is in some degree caused by expanding indications for PCI. However, the Organization of Economic Cooperation and Development (OECD) reported a mean PCI-to-CABG ratio of 3.29 in 2007 in those countries affiliated with the organization, ranging from a low of 0.67 in Mexico to a high of 8.63 in Spain (Figure 1).[13] Even within the same health care system, a large difference in PCI-to-CABG ratios has been reported across different regions (Figure 2).[13] This wide variability in the type of revascularization utilization might be driven by economic and reimbursement considerations[14], but other factors may also be contributory. Consistency and generality of recommendations might be best approached by Heart Team based care.

Differences in baseline patient characteristics might explain part of the variance in the PCI-to-CABG ratio. However, physician-related factors dominate treatment decisions. Surgeons and cardiologists significantly differ in the information they provide the patient regarding the

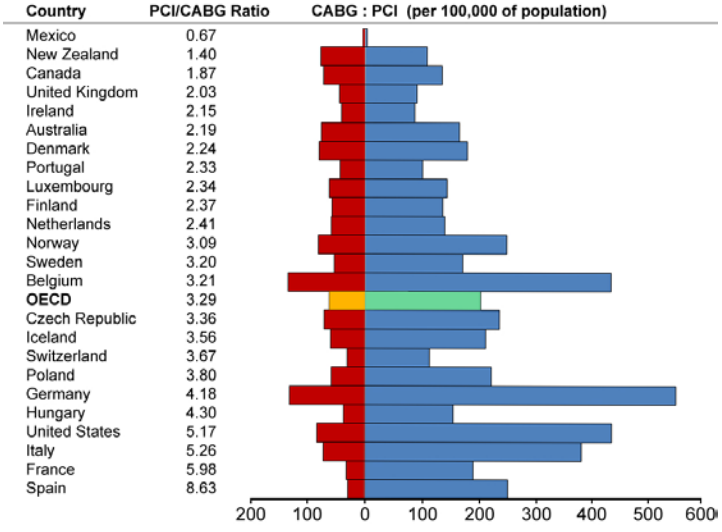

Figure 1 **Revascularization procedures performed in countries throughout the Western world**

Data from the Organisation for Economic Cooperation and Development (OECD) shows a great variety in the number of revascularization procedures per 100,000 inhabitant.[13] CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

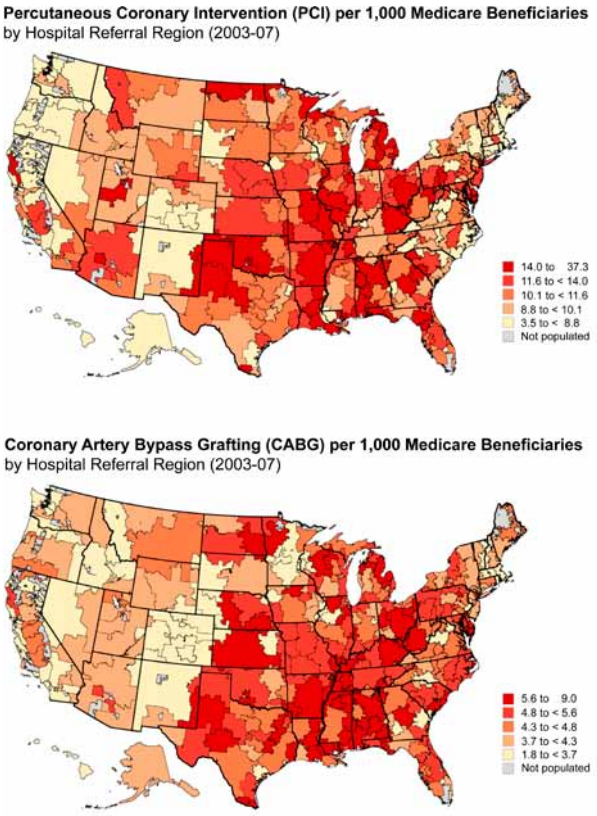

Figure 2 **Rates of PCI and CABG in hospital referral regions within the United States**

The mean rate of CABG was 5.2 per 1000 Medicare enrollees and 11.3 for PCI. Rates are adjusted for age, sex, and race. Copied from the Dartmouth Atlas of Health Care.[84] Abbreviations as previous

Table 1	**Overt and subconscious factors that influence whether comprehensive and well-balanced information of revascularization strategies is provided by physicians**
‘Building an empire’ leading to (inter)national recognition	
Conflict of interest with industry	
Knowledge of patient’s preferences	
No appreciation of personal therapeutic limits	
Not being up-to-date regarding PCI and/or CABG (technology, outcomes, indications, etc)	
Opportunity to include a patient in an enrolling randomized trial	
Personal conflict between interventional cardiologist and/or surgeon	
Physician-patient bonding	
Preservation of patient-referral pathways	
The physician’s center is a center of excellence in PCI or CABG	
‘Turf protection’ (protection of patient access and salary)	

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

choice between PCI and CABG, thereby creating a bias towards a specific treatment.[15] Studies have shown that in 68% of patients who underwent PCI and 59% who underwent CABG, the alternative revascularization strategy was not discussed with the patient.[16] Several overt and subconscious physician-related factors may influence these treatment recommendations (Table 1). To overcome these issues, the Heart Team may increase agreement among surgeons and cardiologists regarding the choice of the preferred treatment.[17]

Decision-making

Typically, and according to the guidelines, revascularization is indicated if there is significant angiographic diameter stenosis (≥50-70%) with documented ischaemia or fractional flow reserve <0.80.[4]

Factors that should be taken into account prior to decision-making are patient co-morbidities, the patient's history, coronary lesion complexity, and operative risk, but also the anticipated goals of therapy and the life-expectancy or expected quality of life improvement. Several risk models have been developed to estimate the operative risk and long-term outcome,[18-22] which can provide guidance for the Heart Team regarding safe and efficient treatment recommendations. However, these risk models should inform, not replace, clinical judgment and local operator expertise in estimating the overall benefit-risk balance of treatment interventions.

The STS score [18] and logistic EuroSCORE [19] are the most commonly used models to assess the patients' operative mortality risk.Both models include patient characteristics, co-morbidities, previous events, and operative factors to calculate a risk of mortality. The EuroSCORE has a satisfactory inter-observer variance (κ=0.71), but still the calculation is subject to many errors, ranging from simple encoding errors to re-calculation errors (e.g. creatinine plasmatic level to creatinine clearance).[23] It can be expected that errors are more likely to occur in complex models with more variables, such as the STS score or the new EuroSCORE II.[24] As a joint group the Heart Team enables an extra check with regard to the accuracy of the scores but cannot overcome the modest prognostic utility of scores. Simpler risk models with a limited number of variables, such as the ACEF score that includes only three factors,[25] may also provide satisfactory risk stratification and are likely to have fewer errors.[26]

The SYNTAX score, established in 2005, was developed to grade complexity of CAD.[27] Validated in the SYNTAX trial, the score was found to be a good predictor of adverse events in the PCI population, however, not in CABG patients.[28] Although it is vital to acknowledge the hypothesis-generating nature of the SYNTAX trial subgroup data, the score is a promising tool to stratify which patients can be revascularized with PCI or CABG and numerous publications support the prognostic capacity of the score in various patient populations.[29-33] Therefore, the SYNTAX score is increasingly used to guide treatment decisions and the new revascularization guidelines recommend the use of the SYNTAX score for treatment

Table 2 Observer variability in assessment of the SYNTAX score

Author, year	Patients	No. of patients	Score evaluation	Intra-observer variability (κ)*	Inter-observer variability (κ)*
Serruys, 2009[38]	LM and/or 3VD	100	2 corelab technicians	0.59 for raw scores	0.45 for raw scores
				0.61 for score tertiles	0.52 for score tertiles
Garg, 2010[35]	LM and/or 3VD	100	3 interventional cardiologists	0.54 for raw scores	-
Shiomi, 2011[39]	LM	101	2 interventional cardiologists	0.69 for score tertiles	0.58 for score tertiles
Tanboga, 2011[37]	-	76	2 interventional cardiologists	0.69 for score tertiles	0.56 for score tertiles
Généreux, 2011[36]	MVD	30	3 interventional cardiologists - before training	-	0.33 for score tertiles
		50	3 interventional cardiologists - after training	0.88, 0.64, 0.66 for score tertiles	0.76 for score tertiles

*The kappa (κ) values represent the strength of agreement and agreement is considered to be fair between 0.21-0.40, moderate between 0.41-0.60, substantial between 0.61-0.80, and almost perfect between 0.81-1.00.[86]
3VD = three-vessel disease; LM = left main; MVD = multivessel disease

selection.[4-5] Despite the encouraging use of established SYNTAX Score threshold values (≤22 and ≥33), the SYNTAX Score needs to be weighted in the context of the overall evaluation by the Heart Team which might overrule these threshold-based decisions.[34] A limitation of the SYNTAX Score is its notable intra-observer and inter-observer variability, which can cause inappropriate revascularization strategies (Table 2).[35-39]

The inconsistency in the SYNTAX score is in part due to interpretations of coronary angiogram. The inaccuracy of grading vessel stenosis on angiograms has been addressed in a number of different studies in which a high inter-observer and intra-observer variability of angiogram analysis was demonstrated.[40-41] However, the correlation between angiogram interpretations and the "normal" phantom study reference values increased when taking the mean of three (r=0.88) and five (r=0.89) physicians instead of the value of individual physicians (r=0.79).[41] Another study showed that by replacing individual readings by panel readings, the appropriateness of the indication for CABG and PCI changed from necessary or appropriate to uncertain or inappropriate in 33% and 10% of the cases, respectively.[40] Within the Heart Team the members can interpret the angiograms together and reduce errors, so that the SYNTAX score correctly represents the patients' lesions,[36] leading to more appropriate revascularization. Nevertheless, Heart Team treatment decisions in which the angiographic complexity is weighted with clinical co-morbidity, operator skills, local expertise, and patient preference are more likely to yield improved outcomes than those based on evaluation of angiographic complexity alone.

Interactive web-based programs can be used to provide information on different treatment strategies with corresponding risks and benefits, which could be helpful for both patients and physicians. For patients it is mandatory that the program is user-friendly and easily interpretable so that it helps establish patient treatment preferences, and improve patient satisfaction.[42]For physicians, such programs can be used for comprehensive risk assessment and simulation of outcomes based on different treatment strategies. New insights into how the individual patient can potentially be treated with novel techniques could furthermore be provided. An example that is frequently used in oncology is the www.adjuvantonline.com

Table 3 Inappropriateness of revascularization procedures

Author, year	Country	Inclusion	Procedures for stable angina	Rate of inappropriateness	Rate of uncertian appropriateness
PCI					
Hilborne, 1993[52]	USA	1990	519	1%	42%
Bengtson, 1994[46]	Sweden	1990	56	5%	9%
Meijler, 1997[55]	Netherlands	1992	891	33.4%	36.4%
Bernstein, 1999[47]	Sweden	1994-1995	447	36.7%	37.8%
Hemingway, 1999[50]	UK	1995	~328	43%	48%
Fitch, 2000[49]	-	-	204	15%	44%
Aguilar, 2001[43]	Spain	1997	467	15%	23%
Yim, 2004[44]	Korea	1997	228	8.8%	67.1%
Chan, 2011[48]	USA	2009-2010	144,737	11.6%	38.0%
Hannan, 2012[58]	USA	2009-2010	24,545	14.3%	49.6%
CABG					
Winslow, 1988[57]	USA	1979-1980, 1982	213	13%	-
Gray, 1990[45]	UK and USA	1987-1988	319	16%	
Bengtson, 1994[46]	Sweden	1990	307	1%	8%
McGlynn, 1994[54]	Canada and USA	1989-1990	~980	~15%	
Meijler, 1997[55]	Netherlands	1992	1054	4.5%	13.4%
Bernstein, 1999[47]	Sweden	1994-1995	1038	8.5%	13.2%
Hemingway, 1999[50]	UK	1995	~323	43%	38%
Fitch, 2000[49]	-	-	204	19%	40%
O'Connor, 2008[56]	USA	2004-2005	806	2.1%	0%
Hannan, 2012[58]	USA	2009-2010	8,168	1.1%	8.6%

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

website. To the best of our knowledge, no program exists for cardiology and its development should be promoted.

Inappropriate revascularization

Even though the imbalance in recommendations for therapy has been identified as early as the 1980s, recent study showed that inappropriateness rates remain high (Table 3).[43-58] Of 24,545 PCI procedures performed for non-acute indications of stable CAD, 14.3% were performed inappropriately and in another 49.6% there was not sufficientinformation and either approach could be considered ('uncertain').[58] Evaluation of CABG procedures showed an inappropriateness rate of 1.1% and 8.6% were judged uncertain. However, it should be noted that a "zero tolerance" for inappropriate procedures is not expected, due to patient preferences and factors not captured in the criteria.[48, 59] In addition, the recently updated appropriateness criteria have been criticized for several limitations[59], including the composition of the panel, the role of pre-procedural diagnostic testing, and the fact that it does not account for all possible scenarios of clinical care.

Substantial inter-hospital variation of treatment recommendation may explain why the rates of inappropriateness vary significantly between studies.[48, 57] Cardiologists and surgeons frequently favor PCI or CABG, respectively.[17, 60-61] Appropriateness ratings can therefore depend on specific individual choices that have been shown to vary across geographic regions, which in turn could be a surrogate for cultural differences.[62] However, it could also be evidence of particular excellence in PCI or CABG in certain centers. Thus, evaluation of an accurate rate of inappropriate revascularization will require adjustment for all these factors.

Underuse of revascularization

An important limitation of the appropriateness criteria is that it can only be applied to patients that underwent revascularization. Preferably, it should be applied to all patients after a diagnostic angiogram or stress test, so that these criteria can also be used to identify patients in whom revascularization is underused (Table 4).[51, 63-66] Based on existing studies, in 18-34% of patients in whom PCI was rated necessary or appropriate, no revascularization took place. For CABG patients this number is approximately 25%. The incidence can vary for several patient groups; men are more likely to undergo revascularization than women, and whites more than blacks.[63] The study by Leape and colleagues also found a large in-hospital variance in performance of necessary revascularization, ranging from 21 to 87% ($p<0.001$).[66] The clinical relevance of these findings was demonstrated by significantly higher rates of angina at 1-year (odds ratio = 1.97 [1.29-3.00]) in patients that received medical therapy while PCI would have been appropriate.[51] In a CABG patient group this effect was even more pronounced, with an odds ratio of 3.03 [2.08-4.42] for angina. Furthermore, CABG patients appeared to have significantly lower rates of death or

MI compared to patients that should have had revascularization (HR=0.25 [0.17-0.35]). In contrast, there was no evidence of a difference in death or MI rates between PCI and patients that received medical therapy (HR=1.30 [0.80-2.08]).[51] A recent study by Hannan and colleagues contradicted this finding.[67] They showed that patients who should have had PCI were more likely to experience death (14.5 vs. 10.2%, HR=1.46 [1.08-1.97]) or the composite of death or MI (21.2 vs. 16.5%, HR=1.49 [1.16-1.93]) at 4 years when compared to those patients that did undergo PCI. Furthermore, Filardo and colleagues showed that underuse of any revascularization was associated with significantly increased mortality during follow-up (multivariate HR=3.23 [2.00-5.26]).[64]

Table 4 Underuse of revascularization procedures

Author, year	Country	Inclusion	Number of patients	Revascularization not given (%)	Outcome
PCI necessary/appropriate					
Kravitz, 1995[65]	USA	1990-1991	107	34% no PCI	3.7 versus 5.6%
				25% no revascularization	-
Leape, 1999[66]	USA	1995	57	18% no revascularization	-
Hemingway, 2001[51]	UK	1996-1997	908	34% no revascularization	Death or nonfatal MI: HR=1.30 [0.80-2.08]
CABG necessary/appropriate					
Kravitz, 1995[65]	USA	1990-1991	424	41% no CABG	16.7 versus 9.7%
				25% no revascularization	-
Leape, 1999[66]	USA	1995	442	25% no revascularization	-
Hemingway, 2001[51]	UK	1996-1997	1353	26% no revascularization	Death or nonfatal MI: HR=0.25 [0.17-0.35]
Revascularization necessary/appropriate					
Kravitz, 1995[65]	USA	1990-1991	671	25%	23.3% (none) versus 9.3% (CABG) or 8.9% (PCI)
Leape, 1999[66]	USA	1992	631	26%	-
Filardo, 2001[64]	Italy	1995	1213	29%	Survival: HR=0.31 [0.19-0.51]
Epstein, 2003[63]	USA	1991-1992	1526* and 2049†	23.9%* and 24.6%†	-

*According to RAND method. †According to ACC/AHA method. HR=hazard ratio; MI=myocardial infarction; other abbreviations as previous.

HISTORY OF THE CORONARY HEART TEAM

Initiated in early randomized trials comparing CABG with medical therapy for stable CAD,[68-69] a Heart Team was used to select patients eligible for randomization. Partly due to the introduction of PCI, interventional cardiologists and cardiac surgeons were increasingly targeting the same patient population. Randomized trials comparing CABG and PCI followed,[70-71] in which specialties worked in close proximity to ensure accurate patient selection and assume clinical equipoise between treatments. This provided new insights into decision-making as performed by a Heart Team. The EAST [72] and BARI [73]trials included nested registries along with the randomized cohorts, to demonstrate if physician or patient treatment preferences yielded different results than patients in whom equipoise was assumed. Remarkably, three-year survival of the EAST registry patients was slightly better than randomized patients (96.4% versus 93.4%, p=0.044), which suggests that the selection of treatment after discussion with a cardiologist, cardiac surgeon, and the patient provides better outcomes in comparison to randomization. Similar results were confirmed by the BARI trial, showing improved survival of registry patients over randomized patients at seven-year follow-up. The SYNTAX trial also included nested registries but differed from previous trials such as EAST and BARI registries in that inclusion was not due to patient preferences,

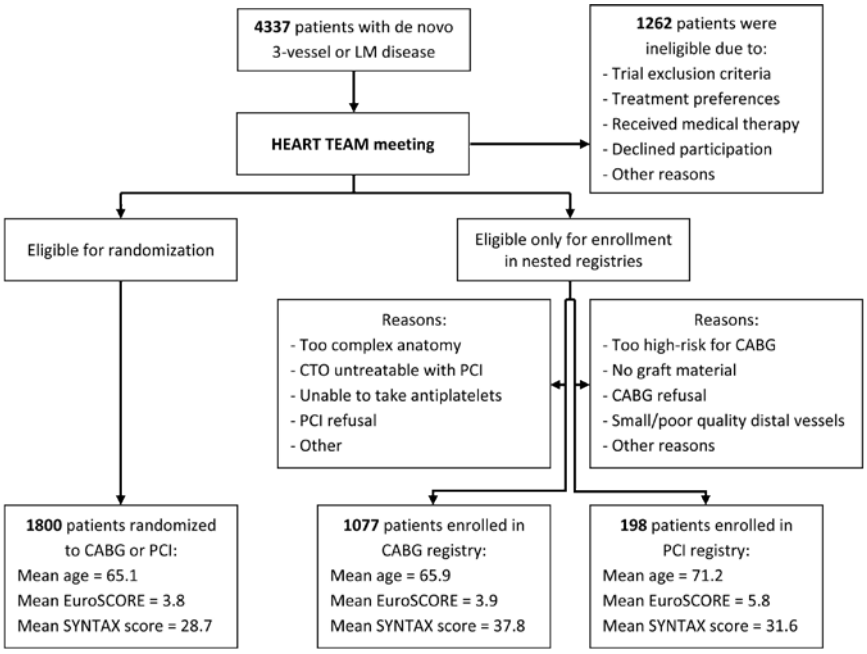

Figure 3 **SYNTAX trial recruitment**

CTO = chronic total occlusion; LM = left main; other abbreviations as previous.

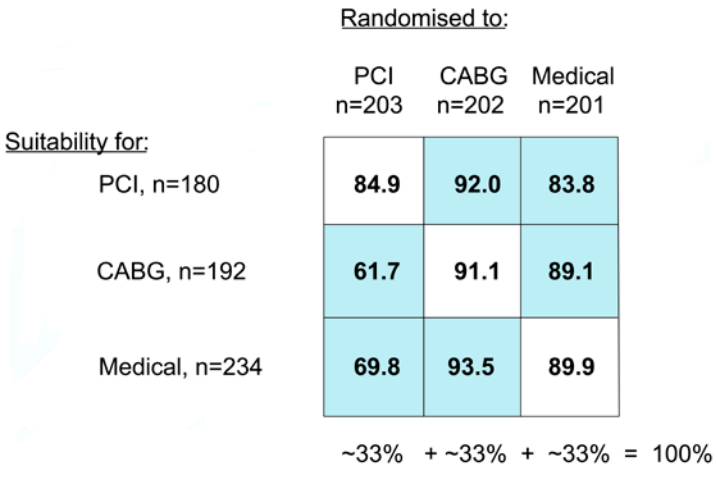

Figure 4 **Probability of survival according to the treatment selection per randomization or clinical judgment**

Before randomization in the MASS II trial took place, two experienced cardiologists had to state their preference of therapy. This table shows the survival of patients as they were treated by the randomized therapy, set out against the survival that would have been the case if the preferred treatment had been given. Copied with permission from Pereira and colleagues.[74] Abbreviations as previous.

but specifically focused on inclusion of patients with assumed superiority of either PCI or CABG.[28] The SYNTAX Heart Team demonstrated the contemporary PCI/CABG distribution of patients with left main and/or three-vessel disease (Figure 3); in 58.5% of patients both PCI and CABG was suitable, while 6.4% and 35.0% could only undergo PCI and CABG, respectively, due to co-morbid and lesion specific factors according to the Heart Team.[34]

Further evidence supporting Heart Team decision-making originated from the MASS-II trial in which patients were randomized to PCI, CABG, or medical therapy.[74] Before randomization, experienced clinical/non-interventional cardiologists recorded their personal choice of treatment. Survival comparison between the chosen and randomized treatment showed excellent outcomes and good clinical judgment with respect to CABG and medical therapy (Figure 4). However, survival was significantly worse in patients randomized to PCI in whom CABG or medical therapy would have been preferred. This speaks to the value of additional expertise that could have improved patient selection.

At present time, both European (2010) and American (2011) guidelines on coronary revascularization were a joint effort of cardiology and surgical associations.[4-5] This concept recapitulates the Heart Team, where specialists work together to optimize treatment recommendations based on an exchange of knowledge and experience with specific therapies.

HEART TEAM ORGANIZATION AND INVOLVEMENT

Organization and logistics

It has been shown that in cancer teams up to 15% of treatment recommendations are not implemented.[75]This is most often the case when co-morbid conditions are not discussed at the meeting, if patient preferences are unknown, or if further diagnostics became available after the meeting. As emphasized by the 'uncertain' classification in the appropriateness criteria, treatment decisions are frequently not substantiated because there is insufficient diagnostic data or inadequate documentation for an evidence-based decision. Therefore, it is crucial that all necessary patient information is available during the Heart Team meeting. The appointment of a non-clinical coordinator would be particularly helpful for gathering patient information or making sure this is accessible electronically, ensuring the necessary attendance and documentation of specialties that are present, and recording treatment recommendations.

Leadership is of the utmost importance for a team to be efficient as objectives need to be made clear, it can stimulate participation, encourage commitment to excellence, and drive innovation.[76] Active participation of all team members is a prerequisite, and the discussion should take place in a non-autocratic setting. To achieve a positive dynamic it is essential to have mutual respect where all input is acknowledged with transparent positive and negative feedback.

The frequency and length of Heart Team meetings depends strongly on the case-load and complexity of patients. Ideally, the Heart Team should convene on a regular basis so that the length of the meetings can be kept to a minimum and each case can be discussed in 5-10 minutes. A lower number of meetings results in a higher number of cases to be discussed and physicians can become less motivated to actively attend lengthy meetings. For centers that do not have an on-site surgical department, Heart Team meetings can be organized through teleconference with the potential for integrated WebEx screen-sharing. For complex cases, surgical consultation may be obtained through weekly meetings. Tumor boards often convene through teleconference to discuss patients to obtain multiple experts' opinions about treatment strategies and discuss whether referral to centers of excellence is warranted.

Logistics are of course the major barrier to convening the Heart Team. In some institutions, at least initially, ad hoc meetings between interventional cardiologist and cardiac surgeon may be the best approach to initiate collaboration. What works well in one institution may not be the optimal approach in another. Successful realization of regular multidisciplinary team evaluation is based on participation of all the necessary physicians.

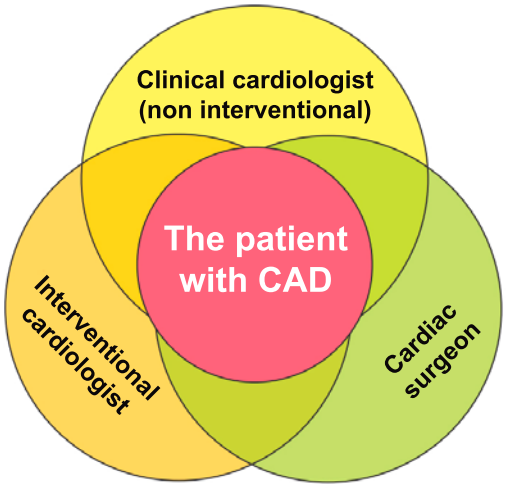

Figure 5 **The basis for a Heart Team is involvement of necessary specialties and the patient to facilitate shared decision-making**

Copied with permission from Wijns and colleagues.[85] CAD = coronary artery disease

Involvement

Clinical/non-invasive cardiologists, interventional cardiologists, and cardiac surgeons should always be present to evaluate whether optimal medical therapy, PCI, or CABG is the preferred treatment. However, other physicians with specific expertise can be added if necessary. An anesthesiologist can assess surgical risk in potential CABG patients by providing input about the ability of the patient to safely undergo general anesthesia. Residents and/or schooled research nurses should have gathered the necessary data to interpret, and share the prepared score assessments on a plenary screen so that definition, typing, or re-calculation errors can be avoided through feedback by the rest of the team.

The concept of shared decision-making with physicians and patients has received more emphasis, and patients should be integrated in the process of decision-making (Figure 5). Involvement of patients' families and friends in the Heart Team can increase patient satisfaction.[77] A prospective cohort study of 3,045 CABG patients treated at 16 hospitals showed that a "supportive group culture" in hospitals was significantly correlated with higher patient physical and mental health scores as determined by SF-36 questionnaires 6 months post-CABG.[78]

Decision-making should be based on three key points: i) knowledge transfer, in which it is equally important that the physician provides information to the patient and the patient to the physician, ii) discussion, and iii) reaching an agreement on which revascularization

strategy will be performed in which patient preferences should be prioritized. It is crucial that during the exchange of information at least a team of one clinical/non-invasive cardiologist, an interventional cardiologist, and a cardiac surgeon is present to ensure that sufficient information on pros and cons of all therapies is provided to the patient.

ADDITIONAL ADVANTAGES

Physicians can be held accountable for inappropriate decision-making and can ultimately face medico-legal consequences. In general, team physicians "share the burden" and this approach might potentially minimize medical malpractice exposure, because there is a shared responsibility of recommending the most optimal therapy to the patient. Nevertheless, all members of the team can be held accountable for decisions within their expertise.[79]

In a group discussion it is gratifying and self-assuring to be acknowledged for an opinion that is shared with peers, and multidisciplinary approaches have been linked to improved wellbeing of physicians.[80]

Another benefit of the Heart Team approach is creating a more robust clinical research program with enhanced quality of care monitoring. Studies suggest that the use of multidisciplinary teams can increase trial recruitment.[81] Information regarding existing and new therapies is more complete, and patients can interpret the advantages and disadvantages of these treatments to decide whether they are willing to be enrolled in a randomized trial.

VALIDATION OF THE HEART TEAM

Although we have summarized the rationale in support of a Heart Team approach, it is difficult to upgrade the class 1C recommendation in the current guidelines.[4-5] Because of the lack of randomized data, it is crucial to perform observational studies to produce data on the pros and cons of the Heart Team. Currently only a single study has been reported, which showed that decisions made by the Heart Team are reproducible.[82] Several hypothetical designs are listed in Table 5. Although there are limitations to such designs, these studies will provide the necessary insights into adoption of the Heart Team and determine whether joint decision-making and treatment recommendations can increase uniformity of care, adherence to practice guidelines, and decrease the number of patients receiving inappropriate care.

Table 5	Possible study designs to validate and evaluate the Heart Team concept
Exploring the reproducibility of the Heart Team by presenting treatment decision of specific cases to different Heart Teams. For example, this can be done for teams in different regions or teams with different inclusion/consistencies of physicians	
Assessing the change in treatment recommendation by comparing an initial individual physicians' evaluation to a re-evaluation by the Heart Team	
Cluster randomized trial in which centers evaluate patients either in a Heart Team or according to the original referral patterns by the surgeon or cardiologist	
Before-and-after study to compare treatment decisions and outcomes before and after implementation of a Heart Team	
Comparison of treatment decisions and outcomes of different centers with and without Heart Team evaluation	

LIMITATIONS OF THE HEART TEAM

The Heart Team approach can cause delays in decision-making and treatment, inefficiency in care and increased expense by foregoing "ad hoc" decisions. Heart Team meetings furthermore require an investment in time of surgeons, cardiologists and ancillary personal, thereby increasing direct costs. One might therefore suggest that the Heart Team should only convene specifically for those cases in which there is a legitimate question regarding which revascularization strategy should be recommended, and whether treatment decisions can be made without a formal Heart Team meeting. Surgeons and (interventional) cardiologists can specify in a local protocol which patients can be left out from a Heart Team meeting, for example, patients with single vessel disease or a SYNTAX score ≤22; according to the 2010 ESC/EACTS revascularization guidelines, patients with low lesion complexity (e.g., single or double-vessel disease) may undergo ad-hoc stenting to avoid two separate catheterizations.[4] It is recommended to schedule an informal 'time-out' to allow surgical consultation in the catheterization laboratory; this concept could therefore accelerate the decision-making process in relatively simple cases and in patients with acute coronary syndromes. However, ischaemia, fractional-flow reserve, or SYNTAX score should be recorded to allow the opportunity for active decision-making as well as the reasons for preclusion of a formal Heart Team discussion so that treatment decisions can retrospectively be acknowledged.

Still, the increased short-term costs associated with multidisciplinary meetings may be of concern. However, in the Netherlands for example, health care providers reimburse the Heart Team as it is likely to reduce inappropriate revascularization and improve outcomes on the long-term, which will compensate for these investments. In some fragmented health care systems, some payers might be concerned with increased short-term cost without acknowledging benefit from reduced long-term costs, and the different parties should attempt to come to an agreement so that the Heart Team approach is beneficial for all those involved.

In the early phase of PCI introduction, surgeons had the ability to influence hospital decisions postponing large-scale PCI use; in several institutions with highly influential cardiac

surgeons the adoption rate of PCI was lower than in other institutions where they were less influential.[83] There have been concerns that multidisciplinary decision-making can be based on autocratic individuals that consider themselves highest on the hierarchical tree.[80] This could result in revascularization strategies that are chosen by the highest rank without a real team discussion. Adherence to current clinical guidelines can then become questionable. Nevertheless, oncology studies have shown that the use of multidisciplinary teams resulted in treatment that is more congruent with evidence-based recommendations and guidelines.[3, 77] Although it has been implied that improved concordance with revascularization guidelines can be achieved by multidisciplinary input[9], this requires further investigation.

There is evidence suggesting that the longer a team has worked together, the more pleasant, interactive and successful it becomes. The initial experiences of a Heart Team might therefore not always be positive, but it is crucial to maintain the initiative as it could eventually lead to better treatment recommendations and personal well-being.

CONCLUSIONS

Underutilization, overutilization, and inappropriate use of coronary revascularization are common, and rates differ significantly between geographic regions and hospitals. Clinical and anatomical risk scores that are used for decision-making have high inter- and intra-observer variability and this can therefore lead to inaccurate recommended revascularization strategies. A balanced multidisciplinary Heart Team, consisting of at least a clinical/non-invasive cardiologist, interventional cardiologist, and cardiac surgeon, has the potential to i) better interpret the available diagnostics, ii) implement guideline directed therapy, iii) consider local expertise, and iv) through shared-decision making take into account patient preferences, to provide a more objective and uniform decision-making process. Even though definitive data from trials demonstrating a direct patient benefit to the Heart Team approach is lacking, indirect evidence from both cardiac disease and oncology fields strongly recommends the implementation of the Heart Team.

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Part 2

Surgical or transcatheter therapy for aortic stenosis


Dallas

Chapter 10

The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27186 patients with 133141 patient-years

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ABSTRACT

Aims

Numerous studies have linked prosthesis–patient mismatch (PPM) after aortic valve replacement (AVR) to adverse outcomes. Its correlation with long-term survival has been described but with contradicting results. This systematic review and meta-analysis of observational studies aims to determine the hazard of PPM after AVR.

Methods and results

The Medline and EMBase databases were searched for English-language original publications. Two researchers independently screened studies and extracted data. Pooled estimates were obtained by random effects model. Subgroup analyses were performed to detect sources of heterogeneity. The search yielded 348 potentially relevant studies; 34 were included comprising 27 186 patients and 133 141 patient-years. Defined by the universally accredited indexed effective orifice area <0.85 cm^2/m^2, 44.2% of patients were categorized as having PPM. In 34.2 and 9.8% of patients moderate (0.65–0.85 cm^2/m^2) and severe (<0.65 cm^2/m^2) PPM was present, respectively. Prosthesis–patient mismatch was associated with a statistically significant increase in all-cause mortality (HR = 1.34, 95% CI: 1.18–1.51), but only a trend to an increase in cardiac-related mortality (HR = 1.51, 95% CI: 0.88–2.60) was recognized. Analysis by severity of PPM demonstrated that both moderate and severe PPM increased all-cause mortality (HR = 1.19, 95% CI: 1.07–1.33 and HR = 1.84, 95% CI: 1.38–2.45) and cardiac-related mortality (HR = 1.32, 95% CI: 1.02–1.71 and HR = 6.46, 95% CI: 2.79–14.97). Further analyses showed a consistent effect over separate time intervals during follow-up.

Conclusions

Prosthesis–patient mismatch is associated with an increase in all-cause and cardiac-related mortality over long-term follow-up. We recommend that current efforts to prevent PPM should receive more emphasis and a widespread acceptance to improve long-term survival after AVR.

INTRODUCTION

The problem of prosthesis–patient mismatch (PPM) after valvular surgery has been a topic of discussion ever since it was first described in 1978.[1] Prosthesis–patient mismatch occurs when the effective orifice area (EOA) of the prosthesis is physiologically too small in relation to the patient's body size, thus resulting in abnormally high post-operative gradients. Hence, the parameter that has been used to characterize PPM is the indexed EOA (iEOA), i.e. the EOA of the prosthesis divided by the patient's body surface area.[2–4]

Results from clinical studies demonstrated the negative effect of PPM following aortic valve replacement (AVR) on left ventricular (LV) mass regression, recovery of LV systolic function, New York Heart Association functional class, quality of life, and bioprosthetic valve durability.[5,6] Furthermore, aortic PPM has been associated with increased incidence of operative mortality and late cardiac events.[7–11]

Although, patients with PPM have been shown to have worse haemodynamic and functional outcomes following AVR, survival analyses have not yet uniformly demonstrated that PPM is a predictor of increased mortality.[12,13] In an attempt to further explore the association of PPM and long-term survival after AVR in adults, a systematic review and meta-analysis was performed of both retro- and prospective cohort studies that stratify survival by the presence of PPM.

METHODS

The reporting of this systematic review and meta-analysis is according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[14]

Search strategy

In January 2011 the Medline and EMBase databases were systematically searched to identify published full-length English studies reporting the long-term survival of patients after AVR, stratified by the presence of PPM. No year of publication exclusion was implied. Studies were identified by a search using the following key words in all fields: 'mismatch OR PPM' AND 'AVR OR aortic valve replacement'. To ensure that no potentially valid studies were missed, the reference lists from reviews and included studies were checked.

Study inclusion

The title and abstract of studies identified by the search were independently screened by two investigators (S.J.H. and M.M.M) using the following criteria: (i) the publication was an original full-article contribution in a peer-reviewed journal; (ii) patients were adults; (iii) patients had undergone AVR with a bioprosthetic or mechanical valve; (iv) PPM was

assessed; and (v) long-term survival a minimum of 5 years of follow-up was available and stratified for PPM. Studies reporting only a specific patient group (e.g. patients with renal failure) were excluded. For studies that met these criteria, or in case of uncertainty, the full-texts were further evaluated.

Finally, the study site(s), inclusion period, patient demographics (e.g. age), and diagnosis of potential studies were compared to ensure minimal patient overlap in different publications. If extensive overlap existed, only the publication with the largest or diagnostically most complete cohort (e.g. all patients instead of only patients with aortic stenosis) was included.

Data extraction

From each study, we collected the design, number of patients, patient baseline characteristics, type of implanted valve, presence of PPM according to the corresponding iEOA cut-off threshold, follow-up, and patient-years of follow-up. If the number of patient-years was not mentioned, it was calculated by multiplying the number of patients with the mean follow-up. If data were unclear or unavailable, the authors were contacted by e-mail.

Studies that reported results of a PPM (iEOA <0.85, <0.80, or <0.75 cm^2/m^2) vs. no PPM group were included in the 'any PPM' analysis. Studies that reported results for moderate PPM (iEOA 0.65/0.60–0.90/0.85 cm^2/m^2) or severe PPM (iEOA <0.65 or <0.60 cm^2/m^2) separately were included in 'moderate PPM' and 'severe PPM' pooled analyses.

All-cause mortality and cardiac-related mortality were evaluated. Mortality was extracted as an HR. For studies that did not report an HR with corresponding variance, this was extracted per 6-month period from the Kaplan–Meier survival curve by two independent investigators (S.J.H. and R.L.J.O). Survival was obtained up to a representative number of patients at risk.[15,16] The method described by Williamson et al.[17] was used to estimate a logarithmic HR with corresponding variance when the number of patients at risk was given at each time frame. If these data were not provided, the method by Parmar et al. was used.[18] For each study, we used a spreadsheet programmed to estimate the overall HR with 95% confidence intervals (CI) using an inverse variance-weighted average.[19,20]

Statistical analysis

Statistical analyses were performed using Review Manager version 5.0 for Windows (The Cochrane Collaboration, 2008). A random-effects model was used to obtain pooled estimates. Weighting of studies was based on the standard error (SE) of the logarithmic HR, in which studies with a large SE are weighted less than studies with a small SE. Heterogeneity was examined with the I^2 statistic; whether this was statistically significant in subgroup analyses was explored with the Q test. Sources of heterogeneity were explored by subgroup analyses of study characteristics (study design, study location, year of publication, mean follow-up), patient characteristics (age, type of valve implanted), and the method used to

define PPM. Sensitivity analyses were performed for the year of patient inclusion to study the effect of characteristics that may have changed over time.

A separate analysis was performed with obtained HRs and corresponding SEs per 1-year period, calculated with the extraction spreadsheet. An overall pooled HR estimate per separate time period was obtained with a random effects model. Subsequently, the pooled year estimates were again combined to assess whether the HRs were different between intervals.

Funnel plots were produced for visualization of possible publication bias.[21]

RESULTS

The database search yielded 348 potentially relevant studies (Figure 1). After the title and abstract were screened, 176 studies were excluded because they did not focus on AVR with bioprosthesis or mechanical valve and the association of PPM with survival. Another 73 studies were excluded because they were not original full-length contributions.

Ninety-nine full-text original articles were reviewed in more detail. Studies were further excluded for various reasons (Figure 1), and a remainder of 34 studies were included in the

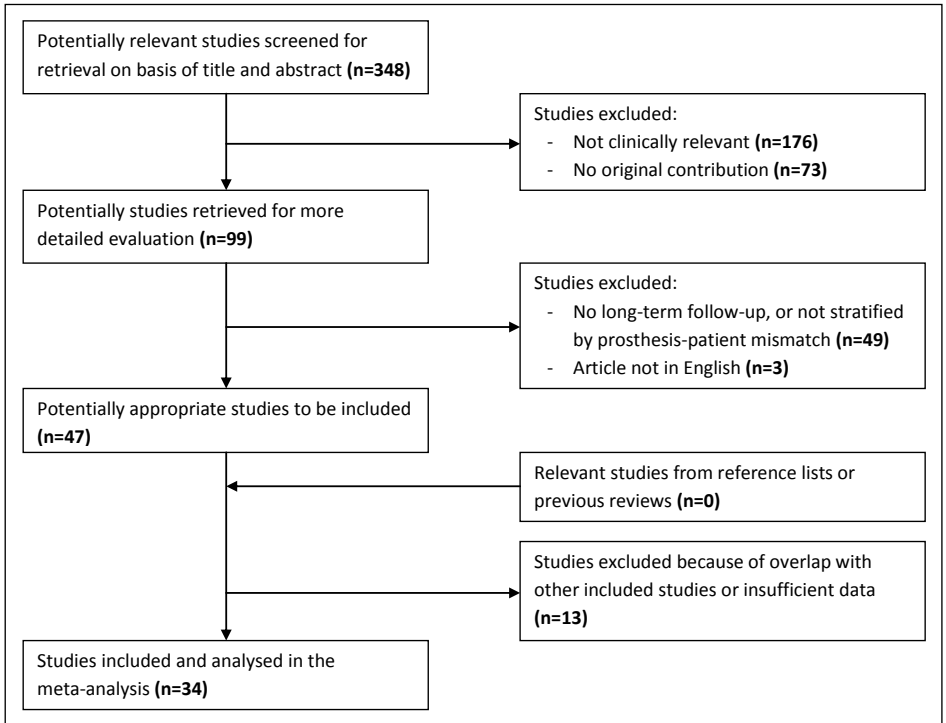

Figure 1 **Flow diagram: systematic inclusion of studies for meta-analysis**

Table 1 **Study characteristics**

First author	Year of publication	Study location	Inclusion	Study design	No. of patients	Male gender (%)	Mean age (Years)	Type of valve	iEOA cut-off (cm2/m2)	PPM (%)	Mean follow-up (years)	Mortality analysis
Sakamoto	2010	Japan	1996-2008	retrospective	342	61.7	69.7	bioprosthetic	<0.85	28	3.2	overall
Jamieson	2010	Canada	1982-2003	retrospective	3343	65.7	68.1	mix	≤0.85	54	6.2	overall
Flameng	2010	Belgium	1991-2003	retrospective	564	51	73.6	bioprosthetic	<0.85	51	6.1*	overall
Bleiziffer	2010	Germany	2000-2007	retrospective	645	56.4	72.3	bioprosthetic	<0.85	40	2.7	cardiac
Urso	2009	Spain	2000-2007	retrospective	163	49.7	78.0	mix	≤0.85	43	3.1	overall
Mrowczynksi	2009	Germany	1995-2004	retrospective	309	63.6	71.6	mix	<0.85	66	2.8*	overall
Moon	2009	USA	1992-2007	retrospective	1399	58.5	71.1	bioprosthetic	<0.85	62	3.8	overall
Mohty	2009	Canada	1992-2005	retrospective	2576	61	68.5	mix	≤0.85	32	4.8	both
Mannacio	2009	Italy	1997-2002	retrospective	157	67.4	66.7	mix	≤0.75	61	7.0	overall
Vicchio	2008	Italy	1988-2006	retrospective	345	33.0	74.5	mechanical	<0.85	60	4.2	overall
Tsutsumi	2008	Japan	1990-2009	retrospective	124	50.8	59.3	mechanical	<0.85	20	9.1	cardiac
Ryomoto	2008	Japan	1990-2007	retrospective	101	45.5	72.4	mix	≤0.85	34	3.1	overall
Mascherbauer	2008	Austria	1998-2005	prospective	361	47.4	69.5	mix	≤0.80	54	4.2	overall
Kohsaka	2008	USA	1993-1998	prospective	469	66.7	56.1	mechanical	≤0.85	43	7.9*	overall
Kato	2008	Japan	1986-2006	retrospective	84	50	68.5	mix	≤0.85	25	4.5	both
Florath	2008	Germany	1996-2005	retrospective	533	54.2	71.1	mix	≤0.85	80	4.7	overall
Tao	2007	Japan	2000-2005	retrospective	150	45.3	68.7	mechanical	≤0.85	23	2.5	both
Nozohoor	2007	Sweden	1996-2006	retrospective	1797	…	…	mix	≤0.85	53	4.3	overall
Monin	2007	France	1994-2005	prospective	139	74.1	72	mix	≤0.85	57	3.7*	overall
Kato	2007	Japan	1990-2005	retrospective	146	56.8	68.2	mix	≤0.85	45	4.5	both
Garcia Fuster	2007	Spain	1994-2005	retrospective	339	55.8	66.5	mix	≤0.85	38	6.9	cardiac
Walther	2006	Germany	1996-2004	prospective	4131	62.8	58.9	mix	<0.85	29	5.2	overall
Tasca	2006	Italy	1997-2003	prospective	315	49.8	70.8	mix	≤0.80	47	3.7	overall

Table 1 *Continued*

First author	Year of publication	Study location	Inclusion	Study design	No. of patients	Male gender (%)	Mean age (Years)	Type of valve	iEOA cut-off (cm2/m2)	PPM (%)	Mean follow-up (years)	Mortality analysis
Moon	2006	USA	1992-2004	retrospective	1400	57.2	66.8	mix	<0.75	38	3.8	overall
Mohty	2006	USA	1985-2000	retrospective	388	31.4	62.3	mechanical	≤0.85	43	5.3	overall
Howell	2006	UK	1997-2005	prospective	1418	61.6	65.5	mix	<0.85	56	3*	overall
Flameng	2006	Belgium	1985-2003	retrospective	506	50	73.3	bioprosthetic	<0.85	20	6.1	overall
Penta de Peppo	2005	Italy	1991-2002	prospective	83	71.1	46.5	mechanical	<0.85	28	6.7	cardiac
Ruel	2004	Canada	1976-2001	prospective	1226	58.6	63.8	mix	≤0.85	77	4.3	cardiac
Milano	2002	Italy	1981-1995	retrospective	229	20.1	63.7	mechanical	≤0.90	73	10	both
Hanayama	2002	Canada	1990-2000	prospective	768	66.0	64.7	mix	<0.60	10	3.5	overall
Frapier	2000	France	1986-1990	retrospective	90	62.2	72.6	bioprosthetic	≤0.85	71	7.3*	both
Rao	2000	Canada	1976-1996	prospective	2154	60.1	66.1	bioprosthetic	≤0.75	11	6.2	both
Pibarot	1998	Canada	1986-1995	prospective	392	71.7	68.4	bioprosthetic	≤0.85	45	...	overall

*median follow-up. iEOA = indexed effective orifice area; PPM = prosthesis-patient mismatch

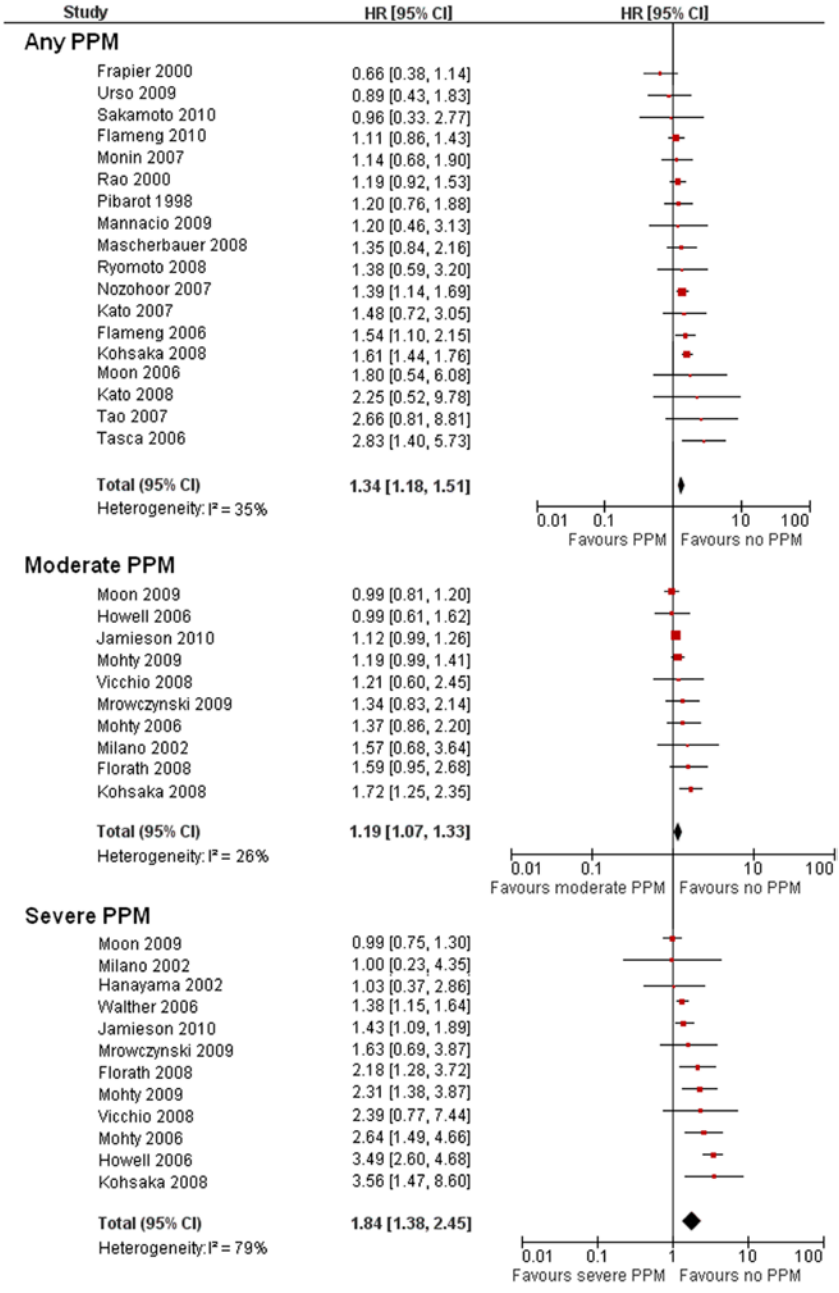

Figure 2 **Pooled estimate for all-cause mortality**

Ratios demonstrate the additional hazard with prosthesis-patient mismatch in relation to a no prosthesis-patient mismatch reference group. Studies that stratified results according to the severity of prosthesis-patient mismatch are analysed individually. HR = hazard ratio; CI = confidence interval; PPM = prosthesis-patient mismatch

present systematic review (Table 1).[4,5,8,10,11,22–50] They comprised a total of 27 186 patients and 133 141 patient-years. In 27 studies with 21 802 patients, the iEOA threshold of 0.85 cm^2/m^2 was used, and 44.2% of patients were diagnosed with PPM. Seven studies found that 34.2% of patients had moderate PPM (>0.65 to >0.85 cm^2/m^2), and 9.8% had severe PPM (<0.65 cm^2/m^2).

Long-term outcomes

Prosthesis–patient mismatch was associated with decreased long-term survival (HR = 1.34, 95% CI: 1.18–1.51) when compared with patients without PPM (Figure 2). In studies that stratified outcomes by the severity of PPM, both moderate (HR = 1.19, 95% CI: 1.07–1.33) and severe (HR = 1.84, 95% CI: 1.38–2.45) PPM showed a statistically significant increase in all-cause mortality.

Prosthesis–patient mismatch was associated with a 1.51-fold (95% CI: 0.88–2.60) non-significant increase in cardiac-related mortality (Figure 3). Differentiation by moderate and severe PPM demonstrated HRs of 1.32 (95% CI: 1.02–1.71) and 6.46 (95% CI: 2.79–14.97), respectively.

There was a constant hazard over time for all-cause mortality (P = 0.93) (Figure 4). The cardiac-related analysis showed more variation in HRs over time.

Sensitivity analysis with studies that included patients operated after 1990 and after 1995 demonstrated that the effect was slightly higher with later inclusion, but this difference was not statistically significant (Table 2). No analyses were performed for the moderate and severe PPM group for cardiac-related mortality, due to the low number of studies included (n = 3).

Sources of heterogeneity

The subgroup analyses detected statistical heterogeneity between bioprosthetic and mechanical valves (Figure 5). There was also a statistically significant heterogeneity in the all-cause mortality analysis by determining the EOA, but this is likely due to the low number of studies that used echocardiographic measurement because this heterogeneity was not significant in other analyses. Again, no analyses were performed for the moderate and severe PPM group for cardiac-related mortality.

Publication bias

There was no evidence of publication bias in funnel plots of all-cause and cardiac-related mortality survival assessments.

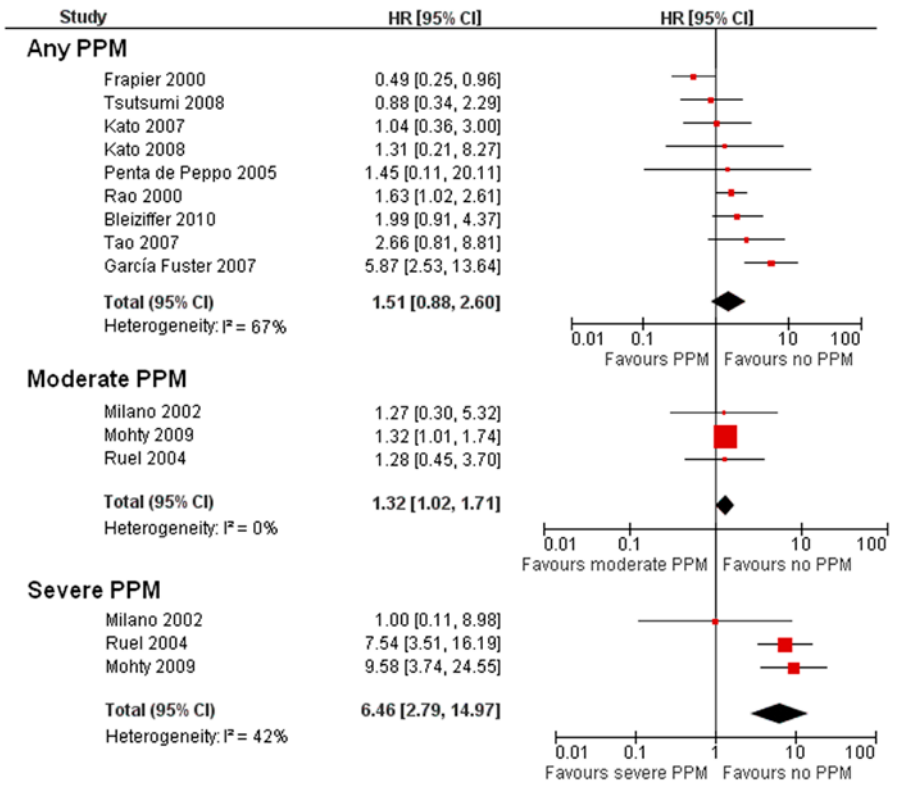

Figure 3 **Pooled estimate for cardiac-related mortality**

Ratios demonstrate the additional hazard with prosthesis-patient mismatch in relation to a no prosthesis-patient mismatch reference group. Studies that stratified results according to the severity of prosthesis-patient mismatch are analysed individually. HR = hazard ratio; CI = confidence interval; PPM = prosthesis-patient mismatch

DISCUSSION

Prosthesis–patient mismatch has been associated with reduced LV mass regression, impaired physical recovery, and higher incidence of adverse cardiac events after AVR; however, no consistent association between PPM and long-term survival has been established.[13] The current unprecedented meta-analysis shows a significant reduction in overall and cardiac-related long-term survival for patients with PPM after AVR. Moreover, this association increases with PPM severity and appears constant over time. These results have important clinical implications given that PPM is a potentially modifiable risk factor.

The marked statistical significant heterogeneity in the explorative subgroup analyses is mainly related to the type of prosthesis, whether this was a bioprosthetic or mechanical valve. The type of prosthesis could be a confounding factor, as mechanical valves are

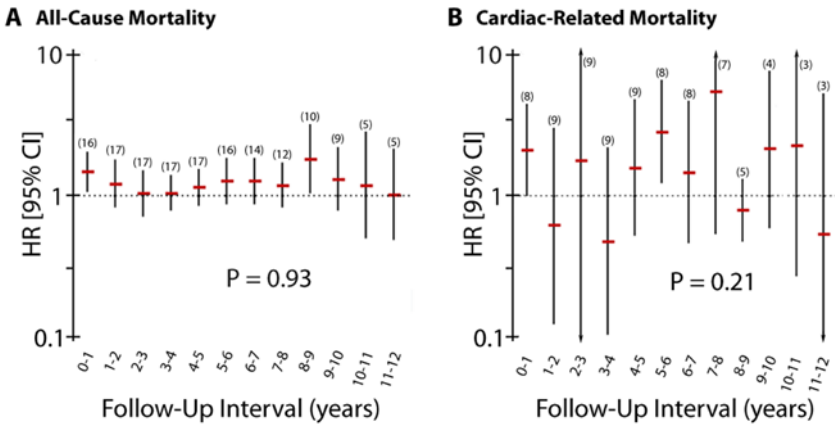

Figure 4 **Hazard of mortality in separate time intervals**

Pooled estimates of studies to detect variance in all-cause (A) and cardiac-related (B) hazard over separate intervals during follow-up. Within the first year of follow-up, studies were excluded if analyses were performed without hospital mortality. The number of studies with corresponding lengths of follow-up is indicated between brackets. HR = hazard ratio; CI = confidence interval

Table 2 **Sensitivity analysis with patient inclusion after 1990 and 1995**

	HR (95% CI)	P for heterogeneity
All-cause Mortality		
Any PPM		0.71
All studies (n=18)	1.34 (1.18-1.51)	
Patient inclusion >1990 (n=13)	1.43 (1.27-1.61)	
Patient inclusion >1995 (n=7)	1.42 (1.13-1.77)	
Moderate PPM		0.87
All studies (n=10)	1.19 (1.07-1.33)	
Patient inclusion >1990 (n=6)	1.24 (1.03-1.49)	
Patient inclusion >1995 (n=3)	1.27 (0.96-1.69)	
Severe PPM		0.94
All studies (n=12)	1.84 (1.38-2.45)	
Patient inclusion >1990 (n=8)	1.86 (1.26-2.73)	
Patient inclusion >1995 (n=4)	2.06 (1.33-2.39)	
Cardiac-related Mortality		
Any PPM		0.67
All studies (n=9)	1.51 (0.88-2.60)	
Patient inclusion >1990 (n=6)	1.97 (1.04-3.74)	
Patient inclusion >1995 (n=2)	2.18 (1.13-4.19)	
Moderate PPM	…*	
Severe PPM	…*	

*Not assessed due to low number of studies. PPM = prosthesis-patient mismatch

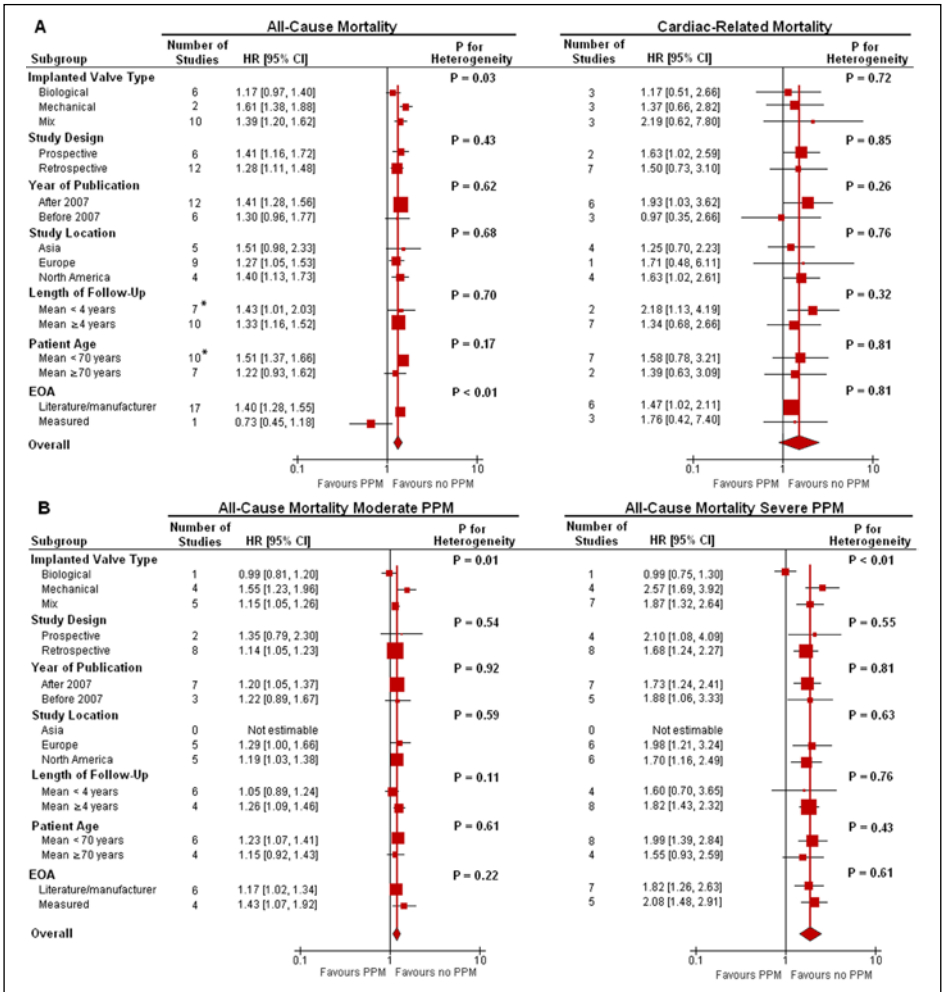

Figure 5 **Subgroup analyses to explore the source of heterogeneity**

All-cause and cardiac-related results were analyses according to baseline- and study-related factors (A). Moderate and severe analyses (B) were also performed for all-cause mortality, but not for cardiac-related mortality due to the low number of studies included (n = 3). HR = hazard ratio; CI = confidence interval; PPM = prosthesis-patient mismatch. *Analysis excluded one study because of missing data.

implanted more often in younger patients. These patients generally have a more active life style and higher metabolic rate, thereby increasing the flow and thus the gradient across the valve in case of PPM.[13] In this regard, some studies have suggested that the impact of PPM on post-operative survival is more pronounced in younger patients than in older ones.[31,45] In this study, individual patient data were unavailable and the results from subgroup analyses should be regarded as hypothesis-generating. Future PPM studies should report the incidence and outcomes of patients with a mechanical and bioprosthetic valve separately, so that evidence is more substantiated.

Several factors may explain the association between PPM and reduced survival after AVR. The persistent LV afterload imposed by PPM may impair the post-operative recovery of the coronary flow reserve [51] and hinder the regression of LV hypertrophy and dysfunction.[8,27,52] Other negative outcomes previously reported in association with aortic PPM may have contributed to increase post-operative mortality, including: abnormalities of the Von Willebrand factor and associated bleeding complications,[53,54] higher occurrence of exercise-induced arrhythmias,44 and higher incidence of late congestive heart failure.[8] Unger *et al.* also observed that, in patients with severe aortic stenosis and concomitant mild mitral regurgitation, PPM is associated with more important residual regurgitation after operation. [55] A recent study showed that PPM is an important risk factor for early structural valve deterioration of aortic bioprostheses.[5] Finally, PPM may also be a surrogate marker for other co-morbidities (e.g. small calcified aortic root).

Prevention of prosthesis–patient mismatch

The observed increased mortality hazard should encourage surgeons to prevent PPM. As opposed to most other risk factors for post-operative mortality, PPM may be avoided or its severity may be reduced by the application of a preventive strategy at the time of operation.[6,56,57] The first step in this strategy is to calculate the minimal prosthetic valve EOA required to avoid PPM by multiplying patient's body surface area by 0.85.[6] The second step is to select a prosthetic valve model and size that fits into the patient's aortic annulus/root and that meets the minimum EOA calculated in the first step. It is important to emphasize that the currently available prosthetic valve models are not equivalent in terms of sizing and haemodynamic performance.[6,58] For example, the implantation of a 21-mm valve can produce an EOA ranging between 1.2 ± 0.1 and 2.0 ± 0.7 cm^2, depending on the type of prosthesis.[13,58] Given the significant improvements in prostheses design, contemporary prevention of PPM can largely be accomplished by the implantation of prosthetic valve models providing better haemodynamic performance. In cases where severe PPM cannot be avoided with the use of currently available prosthetic valves, aortic root enlargement may be contemplated if the risk–benefit ratio is considered acceptable. Root enlargement is a surgical technique to accommodate a valve with a larger EOA and thereby avoiding PPM. This procedure has shown to be effective in reducing rates of PPM, although none of these studies have shown that annulus enlargement results in improved long-term survival.[59,60]

Two recent studies have reported that valve haemodynamics are superior with transcatheter aortic valve implantation (TAVI) than with surgical AVR, especially in the subset of patients with small aortic root.[61,62] In these studies, PPM was less frequently present in TAVI patients (11 and 17.8%) than those who underwent AVR (27 and 30.5%, respectively).[61,63] Transcatheter aortic valve implantation may thus provide another potential alternative to avoid PPM in high-risk patients and yet provide a less invasive procedure. Although initial results with TAVI are promising, studies to date have only included a small number of

patients. These results should thus be interpreted with caution and further studies in larger series of patients are needed to corroborate the usefulness of this procedure for the prevention of PPM.

Prevention of PPM needs to be stressed especially in younger patients. These patients often receive a mechanical valve, and PPM may have a higher impact on survival. Other studies have also emphasized the importance of avoiding PPM in patients with depressed LV systolic function given that they are most vulnerable to the residual LV afterload associated with PPM.[7,64,65]

Haemodynamics and effective orifice area

There is a strong inverse relationship between pressure gradients and iEOA, which has led to a widely accepted iEOA cut-off for defining PPM at 0.85 cm^2/m^2 for moderate and 0.65 cm^2/m^2 for severe PPM. Significant valve gradients at rest or during exercise can be avoided with an iEOA >0.85 cm^2/m^2.[13] It has been shown that patients without PPM have stable haemodynamics, while an increase in gradient has been demonstrated in patients with an iEOA ≤0.85 cm^2/m^2, which is even worse in patients with severe PPM (≤0.65 cm^2/m^2).[4] Hence,

Table 3 Literature derived effective orifice areas of popular valves

	Valve size (mm)					
	19	**21**	**23**	**25**	**27**	**29**
Stented bioprostheses						
Mosaic	1.1 ± 0.2	1.2 ± 0.3	1.4 ± 0.3	1.7 ± 0.4	1.8 ± 0.4	2.0 ± 0.4
Hancock II	…	1.2 ± 0.1	1.3 ± 0.2	1.5 ± 0.3	1.6 ± 0.2	1.6 ± 0.2
CE Perimount	1.1 ± 0.3	1.3 ± 0.4	1.5 ± 0.4	1.8 ± 0.4	2.1 ± 0.4	2.2 ± 0.4
CR Magna*	1.3 ± 0.3	1.7 ± 0.3	2.1 ± 0.4	2.3 ± 0.5	…	…
Biocor (Epic)*	…	1.3 ± 0.3	1.6 ± 0.3	1.8 ± 0.4	…	…
Mitroflow*	1.1 ± 0.1	1.3 ± 0.1	1.5 ± 0.2	1.8 ± 0.2	…	…
Stentless bioprostheses						
Medtronic Freestyle	1.2 ± 0.2	1,4 ± 0.2	1.5 ± 0.3	2.0 ± 0.4	2.3 ± 0.5	…
SJM Toronto SPV	…	1.3 ± 0.3	1.5 ± 0.5	1.7 ± 0.8	2.1 ± 0.7	2.7 ± 1.0
Mechanical prostheses						
Medtronic Hall	1.2 ± 0.2	1.3 ± 0.2	…	…	…	…
Medtronic Advantage*	…	1.7 ± 0.2	2.2 ± 0.3	2.8 ± 0.6	3.3 ± 0.7	3.9 ± 0.7
SJM Standard	1.0 ± 0.2	1.4 ± 0.2	1.5 ± 0.5	2.1 ± 0.4	2.7 ± 0.6	3.2 ± 0.3
SJM Regent	1.6 ± 0.4	2.0 ± 0.7	2.2 ± 0.9	2.5 ± 0.9	3.6 ± .13	4.4 ± 0.6
On-X	1.5 ± 0.2	1.7 ± 0.4	2.0 ± 0.6	2.4 ± 0.8	3.2 ± 0.6	3.2 ± 0.6
CarboMedics	1.0 ± 0.4	1.5 ± 0.3	1.7 ± 0.3	2.0 ± 0.4	2.5 ± 0.4	2.6 ± 0.4

CE = Carpentier-Edwards, SJM = St Jude Medical

*Results are based on a limited number of patients.

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the difference in gradient that is observed at rest between patients with PPM vs. those with no PPM increases dramatically with exercise and is associated with an increase in the flow rate. It should, however, be emphasized that some patients may exhibit a relatively low gradient despite the presence of a small iEOA. This 'pseudo-normalization' of gradient is related to the presence of a low-flow state, similar to what occurs in patients with low-flow, low-gradient aortic stenosis. Patients with PPM and a low gradient are likely at higher risk for adverse events.

Over time valve companies have developed prosthetic valves with better haemodynamic performance and thus with larger EOAs. The older generation of prostheses tends to have smaller EOAs for a given prosthesis size (Table 3). This meta-analysis includes studies with a long-time period of patient inclusion. Many centres, however, are still using certain popular valves (e.g. St Jude Medical Standard mechanical valve, CarboMedics mechanical valve, Perimount bioprosthesis, etc). The use of a newer generation of valve prostheses may influence the prevalence of PPM, but, as shown in this analysis, the effect of PPM on mortality will not change.

Company-provided iEAO charts should be interpreted with caution. There are no standards for creating these charts and it has been shown that the most optimistic EOA values are often chosen to be reported.[56,66,67] A more reliable and manufacturer-independent source of reference EOA data has been published by Pibarot *et al*. and is displayed in Table 3.[58] This table can be used to predict the average post-operative EOA for each given model and size of prosthesis. This information is particularly useful to anticipate the risk of PPM at the time of operation. If, after calculating the predicted iEOA from Table 3 (with information of valve model and sizing) and patient's body surface area, the surgeon concludes that there is risk of PPM, and especially of severe PPM, an alternative prosthesis model and/or surgical technique could be used to avoid PPM or, at least, reduce its severity. A comparison of the different models of prostheses based on the label size in Table 3 may be misleading given that the dimensions of the sizers and the correspondence with the label prosthesis size may vary from one manufacturer to the other. The establishment of universal sizers and a sizing process that would be the same for all prosthetic valves of all manufacturers would certainly help to implement operative strategies for the prevention of PPM.

Study limitations

To reduce the limitations inherent to meta-analysis, we included multiple databases in the literature search, and used minimal exclusion criteria. As a result, a wide time horizon of patient inclusion is present, which some consider problematic due to changes in cardiac surgery and echocardiography. However, sensitivity analysis by years of patient inclusion could not demonstrate a difference in HRs when only studies with inclusion of patients operated after 1990 and 1995 were used.

First of all, many of the studies were retrospective by design and, therefore, follow-up was incomplete. The method by Williamson et al.[17] to estimate HRs from Kaplan–Meier is a widely accepted method recommended in the PRISMA guidelines,[19] but the corresponding HR is not as accurate as to when reported in the original paper. Nonetheless, a subgroup analysis by study design was unable to detect a difference in effect between retro-and prospective studies. The quality of studies was generally high because completion of follow-up was often >95%.

Secondly, only 8 of the 34 studies used EOAs determined by echocardiographic measurement. Although direct measurement is considered a more appropriate method, the other studies used previously reported reference values of the EOA to calculate the iEOA, due to a lack of post-operative echocardiographic data.[5,13] It is possible that some patients may thus have been mis-classified with the use of this 'projected' iEOA. However, the utilization of the iEOA measured by Doppler echocardiography early after operation also has limitations. Its accuracy may be altered by LV outflow or chronotropic conditions and by technical pitfalls or measurement errors. Furthermore, data are not available on patients who died in the operative or early post-operative periods. Nevertheless, the subgroup analysis demonstrated no difference in outcomes in studies using measured or reference values, and long-term survival is significantly impaired in both categories of studies (Figure 5).

Thirdly, despite significant efforts to instruct authors to report results according to guidelines,[68] outcome reporting in the included studies differed considerably. In some studies hospital or procedure-related mortality was in-or excluded. In several instances, the in-or exclusion was not even specified. Both authors and editors of journals should be encouraged to use uniform definitions and reporting of outcomes. Meta-analysis is an important method in clinical research. With standardized methods and reporting, a larger number of studies can be included in meta-analyses and evidence can be more accurately and less spuriously defined.[69]

CONCLUSIONS

Although the adverse effect of PPM on long-term survival has been denied in some studies, this meta-analysis of 34 studies with 27 186 patients demonstrates a significant increase in all-cause and cardiac-related mortality over long-term follow-up after AVR. Current efforts to prevent PPM should therefore receive more emphasis and widespread acceptance to improve long-term survival.

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Rotterdam

Chapter 11

Persistent annual permanent pacemaker implantation rate after surgical aortic valve replacement in patients with severe aortic stenosis

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ABSTRACT

Background

Degenerative aortic valve stenosis (AS) is associated with conduction abnormalities. Pacemaker implantation is encountered after surgical aortic valve replacement (SAVR). Not much is known about the pacemaker implantation rate during midterm follow-up after SAVR. Our objectives were to determine the incidence of permanent pacemaker implantation (PPI) in the midterm after SAVR in a tertiary care facility.

Methods

We reviewed procedural data of 734 consecutive patients (56% men; mean age, 68.9 ± 9.5 years) with degenerative severe AS who underwent SAVR between January 1, 2003, and December 31, 2008. Perioperative electrocardiograms were assessed for occurrence of conduction abnormalities, and we sought to determine the incidence and indication for PPI with a median follow-up of 3.76 years (interquartile range, 2.44 to 5.59 years). Univariate and multivariate logistic regression models were applied to identify predictors for early (≤ 30 days) and late (> 30 days) PPI.

Results

Isolated SAVR was performed in 56%, SAVR with coronary artery bypass grafting in 35%, and SAVR with any other valve therapy in 5.8%. Complete bundle branch block (BBB) was present in 7% and first-degree atrioventricular block in 11%. New BBBs were detected in 63 patients (8.6%). Fifteen patients (2.0%) required a PPI within 30 days after SAVR, and 28 (4.0%) underwent PPI more than 30 days after SAVR. The linearized rate of PPI after SAVR was 1.01% ± 0.37% per patient-year. Patients with BBB at baseline had a higher PPI incidence after SAVR than patients without BBB, both within 30 days (8% vs 1.5%, p = 0.001) and after 30 days (10% vs 2.9%, p = 0.006). PPI incidence after 30 days was also significantly higher in patients with a new BBB after SAVR (7.8% vs 2.9%, p = 0.038). By multivariate logistic regression analysis, BBB and the combination of AS and regurgitation predicted PPI within 30 days after SAVR (hazard ratio [HR], 470; 95% confidence interval [CI], 1.55 to 14.27; and HR, 1.33; 95% CI, 0.03 to 1.73, respectively). BBB (HR, 3.26; 95% CI, 1.41 to 7.54), previous cardiac operation (HR, 3.40; 95% CI, 1.16 to 9.94), and severe left ventricular dysfunction (HR, 9.82; 95% CI, 2.90 to 33.26) were predictors for PPI after 30 days post-SAVR.

Conclusions

Patients with severe AS who underwent SAVR have a persistent 1% annual risk for PPI. Postoperative presence of BBB predicted the need for PPI both within 30 days and after 30 days after SAVR.

INTRODUCTION

Surgical aortic valve replacement (SAVR) is the standard of care for patients with symptomatic severe aortic valve stenosis (AS). Since the pioneering work by Ross, Starr and Harken in the early 1960s, continued procedural refinements have turned SAVR into a reliable and life-prolonging procedure at a reasonable operative risk in most patients.[1-4] Despite the shift to an older and higher-risk patient population undergoing SAVR, overall mortality rates have dropped to approximately 3%, with a postoperative permanent stroke risk of less than 2%.[5, 6]

Degenerative AS is associated with electrical conduction abnormalities because calcification in and around the aortic valve can progress and extend to involve the electrical conduction system of the heart.[7] SAVR can impair the atrioventricular (AV) conduction bundles by operative trauma during valve excision and debridement of the aortic annulus and placement of the sutures.[8-18] The reported 30-day permanent pacemaker implantation (PPI) incidence after SAVR varies between 3.0% and 8.5%.[9-11, 13-16, 18] Little is known about pacemaker requirement during midterm follow-up (up to 5 years). Nevertheless, continuous degenerative changes at the level of the sino-AV conduction system may lead to clinically significant conduction disturbances mandating PPI or, in the worst-case scenario, evoke sudden cardiac death.

Better insight into pacemaker requirement during follow-up after SAVR is clinically relevant because it may underscore the importance of clinical and electrocardiographic follow-up and improve patient counseling. The aim of this study was to report the midterm (up to 5 years) incidence of postoperative conduction disturbances and PPI and to identify relevant predictive risk variables.

MATERIAL AND METHODS

From January 2003 to December 2008, 919 consecutive patients with severe AS, with or without concomitant aortic regurgitation (AR), underwent SAVR in the Thoraxcenter, Erasmus Medical Center, Rotterdam. The study excluded patients with congenital AS and active infectious endocarditis and those undergoing coronary artery bypass grafting (CABG) with concomitant moderate AS or periprocedural death. No aortic root replacement procedures were included. Fifteen patients were excluded because of a permanent pacemaker at baseline.

Similar SAVR techniques were applied throughout the study period in all patients, including a midline sternotomy, antegrade cardioplegia with cold St. Thomas solution, and implantation of mechanical or stented bioprostheses with interrupted sutures after prior aortic root decalcification.

Baseline patient characteristics undergoing valve operations in our department are prospectively collected in a dedicated database in accordance with Institutional Review Board approval. The Institutional Review Board formally approved the study and waived the need for additional patient consent. Two experienced cardiologists analyzed the standard resting 12-lead electrocardiograms at baseline and during the postoperative period.

For the purpose of the present study, specifically, heart rhythm and conduction abnormalities were collected. The presence of first-, second-, or third-degree AV block, complete left or right bundle branch block (BBB), and QRS duration exceeding 150 ms was documented and entered in a separate database. Data on PPI were gathered by reviewing the patient records, contacting the treating physicians (treating cardiologist and general practitioner), and finally, by sending questionnaires to the patients. Postoperative in-hospital PPI was based on persistent high-grade AV block or symptomatic bradycardia up to 14 days after the operation. The indication for PPI after the index hospital discharge was at the discretion of the treating cardiologist in accordance with the American College of Cardiology/American Heart Association guidelines.[19]

Data related to mortality rates and cause of death were obtained from the hospital records and the Dutch Civil Registry. Follow-up data on death and PPI up to October 2010 was 100% and 92% complete, respectively, with a mean follow-up duration of 3.76 years (interquartile range, 2.44 and 5.59 years).

Statistical analysis

Continuous variables are presented as mean ± standard deviation or as median (interquartile range [IQR]). Categorical variables are presented as absolute numbers and percentages and compared with the χ^2 test or Fisher exact test, when appropriate. Cumulative survival probability was calculated by means of Kaplan-Meier estimator curves. Hazard ratios (HR), with their 95% confidence intervals (CI), were generated using a Cox regression analysis. A hazard plot was used to evaluate the yearly pacemaker risk after SAVR.

Age, sex, previous cardiac operation, recent myocardial infarction, systolic left ventricular function, atrial fibrillation (AF) at baseline, any AF, concomitant CABG, and combined AS and AR were the variables selected to assess as potential predictors for (1) PPI within 30 days after SAVR, (2) PPI more than 30 days after SAVR, and (3) any PPI after SAVR. Baseline and new-onset BBB was also evaluated as a predictor for early and late PPI after SAVR. Variables with a value of p of less than 0.10 in the univariate analysis were entered in the multivariate logistic regression model. A two-sided $\alpha = 0.05$ was considered statistically significant. All analyses were performed with SPSS 17.0 software (SPSS Inc, Chicago, IL).

RESULTS

Baseline characteristics

A total of 734 patients (56% men) underwent SAVR for a primary diagnosis of symptomatic degenerative severe AS. Median follow-up was 3.76 years (IQR, 2.44 to 5.59 years). Baseline characteristics and procedural details are reported in Table 1. Patients were a mean age

Table 1 **Baseline and procedural characteristics**

	Patients (n=734)
Age (mean ±SD)	68.9 ± 9.5
Male	409 (56%)
Diabetes	131 (18%)
PVD	52 (7%)
COPD	89 (12%)
Renal Failure (Creat > 200µmol)	13 (2%)
Previous stroke	35 (5%)
Previous Cardiac Surgery	38 (5%)
Recent MI	17 (2%)
Atrial fibrillation	92 (13%)
LV Function	
Normal	546 (74%)
Moderate	69 (9%)
Mild	103 (14%)
Poor	15 (2%)
Unstale Angina	10 (1%)
Logistic EuroSCORE	6.7 ± 5.8
Bicuspid Aortic Valve	48 (7%)
Combined AS and AR	91 (13%)
Baseline ECG	
LBBB	22 (3%)
RBBB	28 (4%)
Long QRS (>150 msec)	22 (3%)
1st Degree AV-Block	79 (11%)
Procedures	
Isolated AVR	416 (57%)
AVR + CABG	257 (35%)
AVR + other Valve Repair/Replacement	43 (6%)
AVR + CABG + Valve Repair/Replacement	18 (2%)

AR = aortic regurgitation; AS = aortic stenosis; CABG = coronary artery bbypass grafting; COPD = chronic obstructive pulmonary disease; ECG = electrocardiography; EF = ejection fraction; QRS = ventricular complex on ECG; SD = standard deviation

of 68.9 ± 9.5 years. Isolated SAVR was performed in 56%, SAVR with CABG in 35%, and SAVR with any other valve therapy in 5.8%. AS with concomitant AR was present in 13% of patients. From an electrocardiographic perspective at baseline, permanent AF, complete BBB, and first-degree AV block were present in 12.5%, 7%, and 11%, respectively (patients who had undergone PPI at baseline were excluded from the analysis).

Postoperative outcome

The 30-day mortality was 1.9%. Survival was 95.2% at 1 year and 84.0% at 5 years (Figure 1). During follow-up, there were 113 deaths. Cause of death was unknown in 10% and cardiac in 38%. Total AV block was documented as cause of death in 2 patients with out-of-hospital cardiac arrest.

AF (transient or permanent) in the postoperative phase was noted in 42% of patients. New-onset AF requiring inter-vention (medication or electrical cardioversion) occurred in 66 patients (9%). BBB was documented in 92 patients (12.5%) after SAVR. New BBB was detected in 63 patients (8.6%), left BBB (LBBB) in 47 (6.4%) and right BBB (RBBB) in 16 (2.2%; Table 2). PPI was required in 15 patients (2.0%), who were a mean age of 71.5 ± 8.4 years, within 30 days after SAVR; the indication was equally divided in high-grade AV block and sick sinus syndrome (and unknown in 1 patient). Thereafter, another 28 patients (4.0%), who were a mean age of 67.0 ± 10.0 years, underwent a PPI at a median of 580 days after SAVR (IQR, 34 to 2,159 days [6 years]) for high-grade AV block in 75%.

The linearized rate of PPI after SAVR was 1.01% ± 0.37% per patient-year (Figure 2). Patients with a BBB at baseline had a higher PPI incidence after SAVR than patients without BBB before 30 days (8% vs 1.5%, p = 0.001) and also after 30 days (10% vs 2.9%, p =

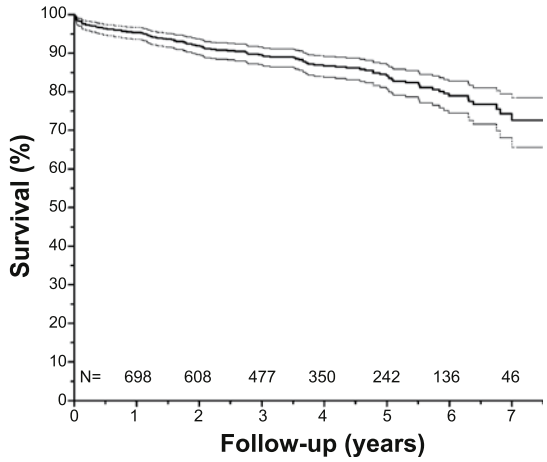

Figure 1 **Kaplan-Meier curve shows survival after surgical aortic valve replacement**

Table 2 **Univariate predictors for permanent pacemaker implantation after surgical aortic valve replacement**

	Univariate OR (95% CI)	P value
PPI ≤30 days		
Combined AS/AR	1.33 (1.03-1.72)	0.031
Any pre-or postop BBB	4.70 (1.55-14.27)	0.006
PPI >30 days		
Male gender	2.55 (1.08-5.99)	0.032
Previous cardiac surgery	3.18 (1.10-9.19)	0.032
Severe LV dysfunction	13.16 (4.56-38.00)	<0.001
Logistic EuroSCORE	1.07 (1.03-1.11)	<0.001
Any pre-or postop BBB	3.67 (1.67-8.09)	0.001
Any PPI		
Male gender	2.42 (1.22-4.80)	0.012
Severe LV dysfunction	8.91 (3.50-22.69)	<0.001
Logistic EuroSCORE	1.06 (1.02-1.09)	0.001
Any pre-or postop BBB	3.80 (2.02-7.15)	<0.001

AR = aortic regurgitation; AS = aortic stenosis; BBB = bundle branch block; CI = confidence interval; HR = hazard ratio; LV = left ventricle; PPI = permanent pacemaker implantation

0.006; Figure 3). Patients with newly acquired BBB after SAVR had a higher incidence of PPI after 30 days after SAVR (7.8% vs 2.9%, p = 0.038). Postoperative LBBB and RBBB correlated with any PPI after SAVR, only RBBB was associated with significantly more PPI within 30 days or after 30 days after SAVR separately (Figure 3).

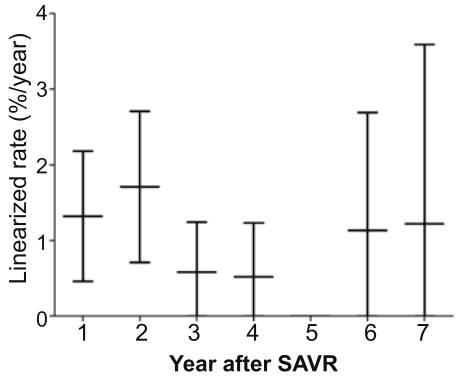

Figure 2 **Annual hazard is shown for permanent pacemaker implantation after surgical aortic valve replacement (with 95% confidence intervals)**

SAVR = surgical aortic valve replacement.

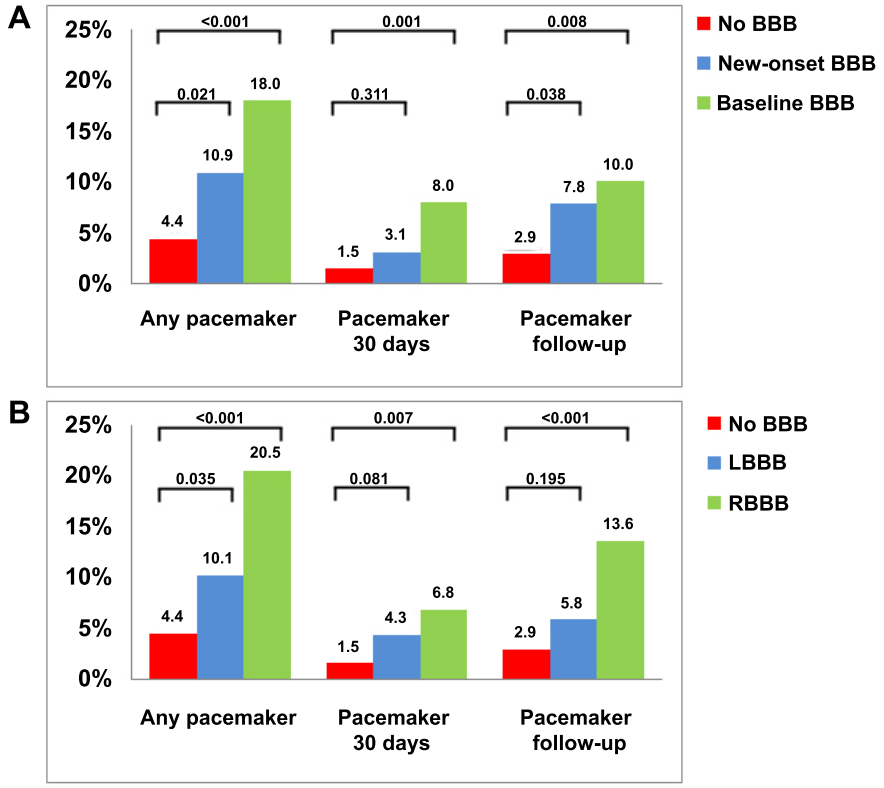

Figure 3 **Bundle branch block (BBB) and incidence of permanent pacemaker implantation**

(A) No BBB (red bars) versus baseline BBB (green bars) versus newly acquired BBB (blue bars). (B) No BBB (red bars) versus left BBB (green bars) versus right BBB (blue bars).

Predictors for PPI within and after 30 days

Univariate predictors of PPI are listed in Table 2. Multivariate logistic regression analysis showed that BBB and the combination of AS and AR predicted PPI within 30 days after SAVR (odds ratio, 4.70 [95% CI, 1.55 to 14.27] and 1.33 [95% CI, 1.03 to 1.73], respectively; Figure 4). BBB (HR, 3.26; 95% CI, 1.41 to 7.54), previous cardiac operation (HR, 3.40; 95% CI, 1.16 to 9.94), and severe left ventricular dysfunction (HR, 9.82; 95% CI, 2.90 to 33.26) were predictors for PPI after 30 days post-SAVR. BBB (HR, 3.69; 95% CI, 1.95 to 6.99), male sex (HR, 2.12; 95% CI, 1.05 to 4.27), and severe left ventricular dysfunction (HR, 5.31; 95% CI, 1.85 to 15.28) were predictors for any PPI after SAVR.

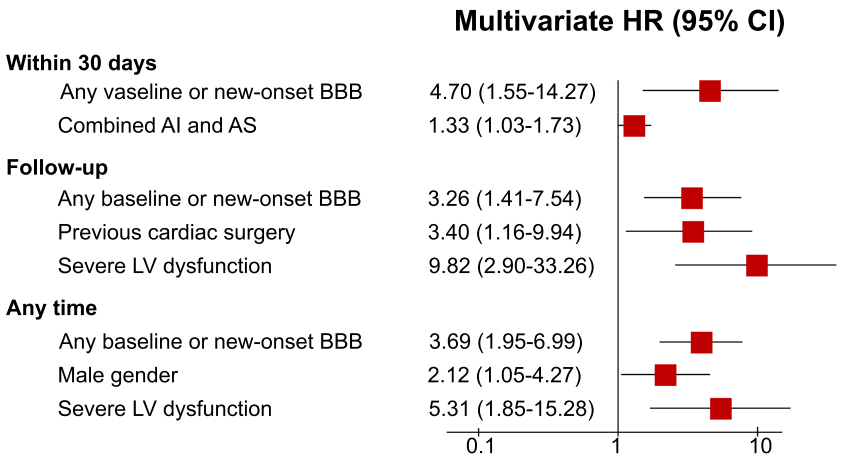

Figure 4 **Multivariate predictors of permanent pacemaker implantation after surgical aortic valve replacement**

AI = aortic insufficiency; AS = aortic stenosis; BBB = bundle branch block; CI = confidence interval; LV = left ventricle

DISCUSSION

In our series of patients with severe degenerative AS who underwent SAVR, the incidence of PPI was 2.0% within 30 days and 4.0% thereafter at a median follow-up of 3.76 years. This study demonstrates a persistent 1% annual risk for PPI after SAVR in the first years after SAVR. Baseline and newly acquired BBB after SAVR was the only consistent predictor for both early (≤ 30 days) and late (> 30 days) PPI after SAVR.

Cardiac operations are associated with a postoperative need for PPI in approximately 1.5% of patients; however, this rate appears higher after SAVR.[20]The 30-day PPI rate in our series compares favorably with rates that have previously been reported. Several groups have presented 30-day PPI rates after SAVR, yet considerable heterogeneity among these reports exists. Bagur and colleagues [10] found a 30-day PPI incidence of 3.2% in 780 patients undergoing isolated SAVR (concomitant CABG was excluded) for severe degenerative AS. In mixed cohorts consisting of AS and AR patients, the incidence of PPI varied between 3.2% and 8.5%.[9, 12, 14, 20, 21]. SAVR for severe AR is associated with a higher PPI frequency compared with SAVR for AS.[11]

In our study population with a median follow-up of 3.8 years, the post-SAVR PPI rate was 4.1% after 30 days, with a persistent 1% annual risk for PPI. Data on late PPI rates after SAVR are scarce. In a mixed cohort of 102 patients with severe AS or AR and at a median follow-up of 4.2 years, Keefe and colleagues [9] noted a PPI rate of 3.2% late after SAVR. In 342 patients with AS or AR and a median follow-up of 114 ± 192 days, Dawkins and

colleagues [14] reported a global PPI rate of 8.5%; of these, 90% of PPIs occurred during the index hospitalization, with the latest PPI at 57 days after SAVR.

The anatomy of the aortic valvular complex and its intimate relationship with the cardiac conduction system has been described previously.[22, 23] With advancing age, progressive conduction fiber degeneration, fibrosis, and calcification of the cardiac skeleton may cause compression and sometimes disruption of the conduction fibers.[24] A small study with histopathologic analysis of the conduction system from deceased patients with electrocardiographically confirmed LBBB disclosed total or subtotal destruction of the connection between the left main bundle and the bundle of His.[25] Studies demonstrating structural His bundle and bundle branch lesions in almost all patients with AS suggest accelerated conduction fiber degeneration. Spontaneous conduction disturbances seem related to the extent of calcium deposits in the aortic valve and adjacent structures.[9] Electro-physiologic assessment in AS patients has also shown AV conduction disturbances below the His bundle characterized by longer HV intervals.[7]

Mechanical and ischemic pathophysiologic mechanisms have been suggested for newly acquired conduction abnormalities, including complete AV block after SAVR. Decalcification and debridement of annular tissue before AVR may decrease the interface between the AV node/bundle of His and the aortic cusps.

A pathology study in 57 patients who died within 30 days after SAVR demonstrated that the sutures used to anchor the prosthesis were the most common cause of conduction system injury, followed by compression from residual calcific material or directly from the prosthesis on the conduction bundles.[26] Interestingly, a continuous suture technique to secure the aortic prosthesis was associated with a higher incidence of PPI compared with an interrupted suture technique.[27] Hypoxia and focal hemorrhage also may damage the conduction bundles.[26]

In our study, BBBs increased the incidence of both early and late PPI approximately fourfold. The prevalence of BBB at baseline was 7%. Newly acquired BBB after SAVR was found in 8.6%. In patients with baseline BBB, the incidence of both early and late PPI after SAVR was significantly higher compared with patients without BBB. Newly acquired BBB postoperatively only increased PPI requirement after 30 days post-SAVR. This finding suggests a newly acquired BBB after SAVR may expedite the process of conduction degeneration and identify additional patients at risk for future conduction abnormalities. Previous reports have consistently indicated BBB as an independent predictor of 30-day PPI after SAVR.[10, 12, 13] The coexistence of AR at baseline (present in 13% of the patients) also predicted PPI within 30 days after SAVR and corroborates the findings by others.[11, 14] AR causes left ventricular and aortic annular enlargement with consequently increased wall tension (by Laplace's Law) and thus excessive mechanical stretch on the nearby AV node and His bundle, which catalyzes fibrous endocardial thickening. Female sex, hypertension, prior myocardial infarction, severe mitral insufficiency, and smaller annulus size have been

suggested as predictors of PPI.[11, 12, 18, 28, 29] Unsurprisingly, concomitant complex cardiac operations (concomitant CABG, reoperation, multivalve operations, sub-AS resection) were previously found to be associated with early PPI.[12, 15, 18, 29]

The annual risk for PPI after SAVR in an AS patient cohort with a mean age of 68.9 ± 9.5 years was 1% per year and is higher than what can be expected in a general population. A retrospective cohort study based on the adult population of Olmsted County, Minnesota, covering the interval between 2000 and 2004, noted a PPI rate of 99.1/100,000 person-years.[30] Incidence rates for PPI per 100,000 person years-were 21.5 for age quartiles 18 to 69, 364.1 for 70 to 79, 901.6 for 80 to 84, and 1,026.8 for 85 to 110. The amplified and continuous process of conduction fiber degeneration, fibrosis, and calcification in patients with AS may hypothetically explain the steady annual rate of PPI after SAVR. This hypothesis is indirectly supported by data suggesting that new pacemaker dependency developed in 23% of patients who initially required a PPI after their cardiac operation vs 4% of patients who required a PPI without a prior cardiac operation.[31, 32] Another study indicated 17% of patients who developed a new BBB after SAVR had experienced complete AV block, syncope, or sudden death at a mean follow-up of 54 months.[8]

Our findings may create awareness among surgeons treating patients with AS about the continuous PPI rate in the years after AVR and also underscore the effect of conduction abnormalities. The need for regular office visits and rhythm follow-up assessment is evident and may lead to better midterm and longer-term outcome. Cardiac surgeons should inform their patients about these issues before proceeding with AVR. Better information may then stimulate patients to comply with these essential follow-up visits.

Limitations

This retrospective study is subjected to the well-known limitations related to all retrospective analyses. Information on perioperative rate-controlling therapies was not available. The timing of postoperative electrocardiogram analysis was not standardized, and transient conduction abnormalities may have been missed. The indication for PPI after hospital discharge was left to the treating physician's discretion, which introduces inherent bias. Specific perioperative variables, such as cardiopulmonary bypass time, were not systematically collected and therefore not evaluated. Cause of death was cardiac in 43 patients and unexplained in 11. Although speculative, these patients may have suffered from life-threatening conduction abnormalities, which would only reinforce our findings that patients who underwent SAVR for degenerative AS are at persistent risk for such conduction abnormalities after SAVR. Finally, the event rate was too small to make any firm statement regarding the relative effect of LBBB and RBBB separately.

CONCLUSIONS

Degenerative AS is associated with conduction abnormalities. SAVR has a 2.0% PPI rate within 30 days after the operation and a persistent 1% per-year risk for PPI thereafter. These findings suggest patients with a BBB after SAVR should be monitored closely for progressive conduction disturbances with fixed office visits, including electrocardiogram and Holter monitoring, to avoid major adverse events, including syncope, complete AV block, and sudden death.

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Washington

Chapter 12

Clinical outcomes after transcatheter aortic valve replacement using VARC definitions; a weighted meta-analysis of 3519 patients from 16 studies

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ABSTRACT

Background

Recently, the published Valve Academic Research Consortium (VARC) definitions have helped to add uniformity for reporting outcomes after Transcatheter Aortic Valve Replacement (TAVR).

Objectives

We sought to perform a weighted meta-analysis to determine rates of major outcomes after TAVR using VARC definitions and to evaluate their current use in the literature.

Methods

A comprehensive search of multiple electronic databases from January 1st 2011 through October 12th 2011 was conducted using predefined criteria. We included studies reporting at least one outcome using VARC definitions.

Results

A total of 16 studies including 3,519 patients met inclusion criteria and were included in the analysis. The pooled estimate rate of outcomes were determined according to VARC's definitions: device success: 92.1%, 95%CI [88.7,95.5]; all cause 30-day mortality: 7.8%, 95%CI [5.5,11.1]; myocardial infarction: 1.1%, 95% CI [0.2,2.0]; acute kidney injury stage II-III: 7.5%, 95%CI [5.1,11.4]; life threatening bleeding: 15.6%, 95% CI [11.7,20.7]; major vascular complication: 11.9%, 95% CI [8.6,16.4]; major stroke 3.2%, 95%CI [2.1,4.8]; and new permanent pace maker (PPM) implantation: 13.9%, 95% CI [10.6,18.9]. Medtronic Corevalve™ prosthesis use was associated with a significant higher rate of PPM implantation compared to the Edwards's prosthesis (28.9%, 95% CI [23.0,36.0] vs. 4.9%, 95% CI [3.9,6.2], p value < 0.0001). The 30-day safety composite endpoint rate was 32.7%, 95%CI [27.5,38.8] and the 1-year total mortality was 22.1%, 95% CI [17.9,26.9].

Conclusions

VARC definitions have already been used by the TAVR clinical research community, establishing a new standard for reporting clinical outcomes. Future revisions of the VARC definitions are needed based upon evolving TAVR clinical experiences.

INTRODUCTION

Since the first transcatheter aortic valve replacement (TAVR) case in 2002,[1] >35,000 transcatheter aortic valve procedures have been performed worldwide. This has resulted in a substantial number of published case series, registries, and, lately, randomized controlled trials.[2-13] Diversity in technique and study devices as well as disparity in the learning curve may potentially explain some of the discrepancies in outcomes that have been reported. However, the absence of standardized definitions may be the most significant factor to explain inconsistencies in the early literature. The recent publication of the Valve Academic Research Consortium (VARC) definitions has provided uniformity in outcome reporting after TAVR, which should ensure a more balanced interpretation of clinical results.[14] Currently, there is a growing body of literature applying these new VARC definitions. Therefore, we sought to perform a meta-analysis of all published studies reporting outcomes using VARC definitions after TAVR to evaluate current acceptance and use patterns and to determine whether future revisions are warranted.

METHODS

Studies and endpoint definitions

All studies reporting outcomes using at least 1 VARC definition from January 1, 2011, to October 12, 2011, were selected and included in the current analysis. Only outcomes properly reported conforming to VARC definitions (clear mention in the paper) were included in the pooled analysis. Intrahospital 30-day and 1-year outcomes are reported conforming to the VARC definitions previously described.[14]

Data source and study selection

Relevant studies were identified through PubMed, Cochrane, and EMBASE database searches, using the key words *trans-catheter aortic valve implantation*, *trans-catheter aortic valve replacement*, *percutaneous aortic valve implantation*, *percutaneous aortic valve replacement*, *transfemoral aortic valve implantation*, *transapical aortic valve implantation*, *transarterial aortic valve implantation*, *direct aortic valve implantation*,*aortic stenosis*, and *valve academic research consortium*. Two investigators (P.G., S.J.H.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Conflicts between reviewers were resolved by consensus.

Statistical analysis

Outcome rates were first presented as the minimum and maximum rates reported among selected articles. Cumulative rates for each VARC outcome were then obtained from a pooled analysis among selected studies. Given the high heterogeneity among reported

rates, summary rate estimates and 95% confidence intervals (CIs) were obtained using a random-effects model, as described by DerSimonian and Laird.[15] The random-effects model was chosen for its conservative summary estimate and incorporating both between and within study variance. To assess heterogeneity across trials, we used the Cochrane Q statistic (a p value ≤0.1 was considered significant). The I^2 statistic was also used to measure the consistency among studies with values of 25%, 50%, and 75% showing, respectively, low, moderate, and high heterogeneity.

Data collection, study selection, processing of the data, and reporting of the results were performed according to accepted principles related to systematic review and meta-analysis.[16-19] The Mann-Whitney test was used to compare proportions, with a significance level of $p < 0.05$. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

Of 482 potentially relevant articles initially screened, 16 unique studies with 3,519 patients met the inclusion criteria and were included in the final pooled analysis (Figure 1). [10, 20-34]

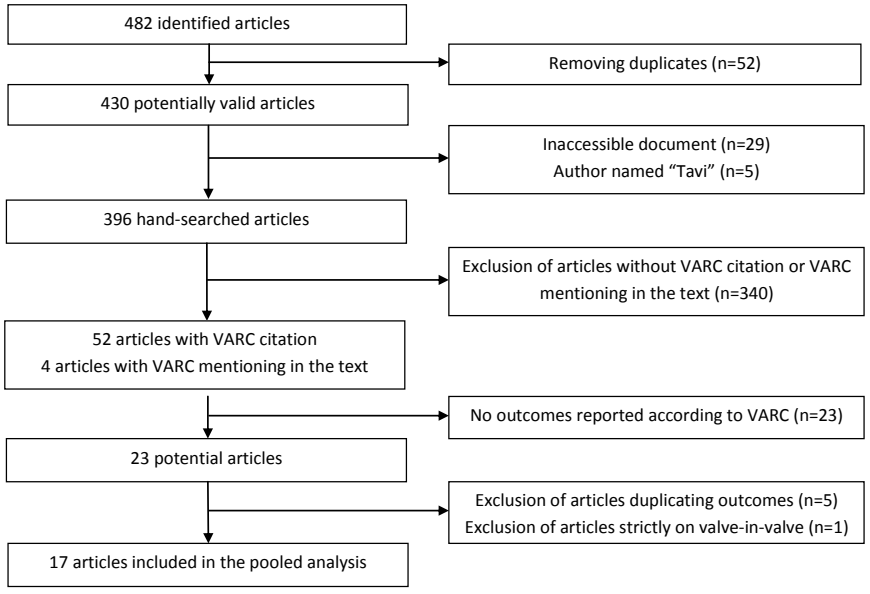

Figure 1 **Flow diagram of the study**

Among the 482 potentially relevant articles, 16 were included in the final pooled analysis. VARC = Valve Academic Research Consortium

Table 1 Selected publications reporting at least 1 VARC criteria in a TAVR population

Authors	n 3,519	Approach	Device	Mean STS	Mean Euro-Score	Mean age (years)	Female (%)	Mean gradient (mmHg)	AVA (cm^2)	NYHA III-IV (%)
D'Onofrio et al.	504	TA	Sapien	11%	26.3%	81.2 ± 6.5	306 (60.7%)	47.4 ± 15.4	0.53 ± 0.18	419 (83%)
Buchanan et al.	305	TF/TAx/TAo	Mix	8.6%	24.2%	79.4 ± 7.3	(48%)	…	inclusion <1.0	204 (67%)
Grube et al.	186	TF	Corevalve	…	23.4%	81.4 ± 6.4*	104 (56%)	47.1 ± 15.7*	0.7 ± 0.2*	146 (78%)
Gurvitch et al.	310	TF/TA	Sapien	9.4%	…	82.2 ± 8.1	…	…	…	273 (88%)
Hayashida et al.	127	TF	Mix	…	25.8%	83.3 ± 5.9	65 (51%)	…	inclusion ≤0.8	113 (89%)
Lange et al.	412	TF, TA, SC, TAo	Mix	5.6%	20.2%	80.3 ± 7.2	258 (63%)	47.9 ± 16.3	0.67 ± 0.20	400 (97%)
Mussardo et al.	120	TF	Sapien & XT	7.2%	24.9%	80.2 ± 8.1	60 (50%)	55.6 ± 17.4	inclusion <1.0	84 (70%)
Nuis et al.	165	TF/SC	Corevalve	4.6%	13.1%	81 ± 7	82 (55%)	46 ± 17	0.64 ± 0.20	118 (79%)
Stahli et al.	130	TF/TA	Mix	…	22.7%	83 (78.8-86)	66 (51%)	49 (38-57)	0.6 (0.5-0.7)	94 (72%)
Wenaweser et al.	256	TF/TA/SC	Mix	6.4%*	24.8%*	82.1 ± 6*	144 (56%)	44.4 ± 17*	0.7 ± 0.2	Mean 2.6 ± 0.8
Ussia et al.	143	TF/SC	Mix	7.9%	23.4%	81.0 ± 6	85 (59%)	56.6 ± 17.4	0.59 ± 0.19	92 (64%)
Bagur et al.	64	TF/TA	Sapien	7.5%	21%	80 ± 8	21 (33%)	43 ± 17	0.60 ± 0.15	64 (100%)
Dehédin et al.	125	TF/SC	Mix	13%	24%	83 (78-87)	57 (46%)	47 (39-61)	0.39 (0.31-0.46)	103 (82%)
Gotzmann et al.	145	TF/SC	Corevalve	…	21%	79.1 ± 6.4	…	47.8 ± 13.6	inclusion ≤1.0	117 (96%)
Leon et al.	179	TF	Sapien	11.2%	26.4%	83.1 ± 8.6	97 (54%)	44.5 ± 15.7	0.6 ± 0.2	165 (92%)
Smith et al.	348	TF/TA	Sapien	11.8%	29.3%	83.6 ± 6.8	147 (42%)	42.7 ± 14.6	0.7 ± 0.2	328 4%)

*Mean was reported from 2 groups. The mean reported here is calculated as ((mean x n1) + (mean x n2))/(n1 + n2). AVA = aortic valve area; MCV = Medtronic CoreValve; NYHA = New York Heart Association; SC = subclavian; STS = Society of Thoracic Surgeons; TA = transapical; TAo = transaortic; TAVR = transcatheter aortic valve replacement; TAx = transaxillary; TF = transfemoral; VARC = Valvular Academic Research Consortium

A total of 1,903 Edwards Lifesciences (Irvine, California) prosthesis (54.1%) and 1,186 Medtronic CoreValve (Minneapolis, Minnesota) prosthesis (33.7%) implantations were identified. The type of implanted device was not clearly reported by authors in 430 patients (12.2%). Basic study characteristics are shown in Table 1. The 30-day Society of Thoracic

Table 2 Proportion of Studies reporting outcomes using appropriately VARC definitions

Outcomes	n (%)
Device success	10/17 (58.8)
30-day mortality	16/17 (94.1)
30-day cardiovascular mortality	15/17 (88.2)
1-year mortality	7/17 (41.2)
1-Year cardiovascular mortality	4/17 (23.5)
Myocardial infarction ≤ 72h	14/17 (82.4)
Acute kidney injury	9/17 (52.9)
Bleeding	7/17 (41.2)
Transfusions	7/17 (41.2)
Vascular complications	16/17 (94.1)
Stroke 30-day	14/17 (82.4)
PPM	14/17 (82.4)
30-day composite endpoint safety	6/17 (35.3)
1-year composite endpoint efficacy	2/17 (11.8)
Failure to delivery or implantation of the valve in the correct position	10/17 (58.8)
Multiple valve implanted	9/17 (52.9)
Aortic valve area ≤ 1.2 cm2	2/17 (11.8)
Mean gradient ≥ 20 mm Hg	4/17 (23.5)
Aortic regurgitation ≥ moderate	11/17 (64.7)
Valve embolization	10/17 (58.8)
Valve in valve	8/17 (47.1)
Conversion to open surgery	10/17 (58.8)
Repeat procedure for valve dysfunction	8/17 (47.1)
Unplanned cardiopulmonary bypass use	3/17 (17.6)
Coronary obstruction	7/17 (41.2)
Left ventricular perforation	3/17 (17.6)
Tamponade	6/17 (35.3)
Annulus rupture	3/17 (17.6)
Aortic dissection	2/17 (11.8)
Aortic rupture	2/17 (11.8)
Endocarditis	3/17 (17.6)
Valve thrombosis	2/17 (5.9)
Left ventricular outflow tract rupture	1/17 (5.9)
Ventricular septal defect	1/17 (5.9)

Surgeons score and logistic EuroSCORE were 8.7% (95% CI: 7.0% to 10.3%) and 22.8% (95% CI: 20.3% to 25.3%), respectively. Table 2 shows the proportion of articles that appropriately used and reported outcomes according to VARC definitions.

Table 3 30-day and 1-year VARC outcomes after TAVR

Outcomes	Reported rate min - max (%)	Cumulative rate	I^2 (%)	P value for heterogeneity	Pooled estimate rate (%)	95% CI
Device success	80.0 - 100.0	1748/1899	93.2	<0.0001	92.1	88.7 , 95.5
30-day mortality	1.7 - 14.3	258/3465	74.1	<0.0001	7.8	5.5 , 11.1
30-day cardiovascular mortality	1.7 - 11.5	142/2645	72.5	<0.0001	5.6	3.7 , 8.3
1-year mortality	15.3 - 30.7	336/1530	78.3	0.0001	22.1	17.9 , 26.9
1-year cardiovascular mortality	14.3 - 19.6	113/800	85.2	0.0002	14.4	10.6 , 19.5
Myocardial infarction ≤ 72h	0.0 - 5.6	34/3018	88.9	<0.0001	1.1	0.2 , 2.0
Acute kidney injury						
I	3.2 - 24.6	149/1150	91.1	<0.0001	13.3	9.8 , 18.0
II	0.8 - 5.3	29/1150	64.9	0.02	2.7	1.5 , 5.3
III	1.0 - 10.2	98/1929	73.0	0.0005	5.3	3.5 , 8.2
II-III	3.0 - 15.0	93/1275	80.9	<0.0001	7.5	5.1 , 11.4
I I-II-III	6.5 - 34.1	232/1150	94.8	<0.0001	20.4	16.2 , 25.8
Bleeding						
Life-threatening	7.0 - 25.9	207/1350	86.1	<0.0001	15.6	11.7 , 20.7
Major	2.9 - 47.0	298/1363	96.6	<0.0001	22.3	17.8 , 28.3
Minor	3.0 - 16.0	95/987	81.9	0.0002	9.9	6.9 , 14.3
All	26.8 - 77.0	408/987	98.4	<0.0001	41.4	35.5 , 47.6
Transfusion ≥1 unit	6.3 - 80.0	386/906	85.3	<0.0001	42.6	19.8 , 62.4
Vascular Complications						
Major	5.0 - 23.3	282/2417	81.3	<0.0001	11.9	8.6 , 16.4
Minor	5.6 - 28.3	203/2142	88.8	<0.0001	9.7	6.7 , 14.0
All	9.5 - 51.6	511/2740	92.6	<0.0001	18.8	14.5 , 24.3
Stroke 30-day						
Major	0.8 - 9.0	84/2730	70.7	<0.0001	3.2	2.1 , 4.8
Minor	0.0 - 1.7	12/1450	54.6	0.03	1.0	0.5 , 1.9
TIA	0.0 - 12.0	18/1826	83.4	<0.0001	1.2	0.0 , 2.3
Major + minor	1.0 - 6.8	68/1,706	67.4	0.005	4.0	2.4 , 6.3
All	1.3 - 21.0	103/1892	72.8	0.0003	5.7	3.7 , 8.9
Permanent pacemaker	3.4 - 50.0	396/2914	95.9	<0.0001	13.9	10.6 , 18.9
Composite endpoint Safety 30-day	17.0 - 61.8	420/1286	96.6	<0.0001	32.7	27.5 , 38.8
Composite endpoint efficacy 1-year	70.2 - 72.2	209/294	0	0.58	71.1	65.6 , 76.0

CI = confidence interval

Table 4 Prosthesis-related complications according to VARC

Outcomes	Reported rate min - max (%)	Cumulative rate	I^2 (%)	P value for heterogeneity	Pooled estimate rate (%)	95% CI
Failure to delivery or implantation of the valve in the correct position	0.8 - 5.6	79/2,383	53.8	0.02	3.5	2.2 , 5.6
Multiple valves implanted	0.6 - 4.1	38/2,208	62.1	00.69	1.8	1.1 , 3.1
Aortic valve area ≤ 1.2 cm2	0.0 - 9.7	30/814	98.2	<0.0001	4.8	3.0 , 6.6
Mean gradient ≥ 20 mm Hg	0.0 - 2.9	11/1,064	85.2	0.0002	1.0	0.0 , 2.1
Aortic regurgitation ≥ moderate	0.0 - 30.0	167/2,601	95.3	<0.0001	7.4	4.6 , 10.2
Valve embolization	0.0 - 5.6	45/2,329	85.9	<0.0001	1.7	0.2 , 3.3
Valve in valve	0.0 - 9.0	43/2,014	80.9	<0.0001	2.3	1.3 , 4.5
Conversion to open surgery	0.0 - 5.6	23/2,189	84.1	<0.0001	1.3	0.0 , 2.6
Repeat procedure for valve dysfunction	0.0 - 4.1	31/1,920	51.7	0.04	1.8	1.0 , 3.7
Unplanned cardiopulmonary bypass use	0.0 - 1.9	15/1,081	78.0	0.01	1.3	0.3 , 2.2
Coronary obstruction	0.0 - 3.0	13/1,984	54.1	0.04	0.7	0.4 , 1.1
Left Ventricle perforation	0.2 - 0.8	3/702	0	0.43	0.4	0.1 , 1.5
Tamponade	0.6 - 4.6	29/1,097	74.4	0.0015	2.7	1.7 , 4.2
Annulus rupture	0.3 - 0.8	3/560	0	0.77	0.5	0.2 , 1.7
Aortic rupture	0.8 - 1.0	5/539	0	0.82	0.9	0.4 , 2.2
Aortic dissection	0.9 - 1.7	5/468	0	0.40	1.1	0.4 , 2.5
Endocarditis	0.3 - 1.1	5/832	0	0.39	0.6	0.2 , 1.4
Valve thrombosis	0.0 - 2.7	2/380	93.5	<0.0001	1.2	0.3 , 2.2
Left ventricular outflow tract rupture	0.6	1/165	-	-	0.6	0.1 , 4.3
Ventricular septal defect	0.6	1/165	-	-	0.6	0.1 , 4.3

CI = confidence interval

In-hospital and 30-day follow-up outcomes

Overall device success reported in the literature ranged from 80% to 100%, with a pooled estimate rate of 92.1% (95% CI: 88.7% to 95.5%) (Table 3). The most frequent modes of failure were moderate to severe aortic regurgitation (7.4%; 95% CI: 4.6% to 10.2%), aortic valve area (AVA) <1.2 cm^2 (4.8%; 95% CI: 3.0% to 6.6%), and failure of delivery or implantation of the valve in the correct position (3.5%; 95% CI: 2.2% to 5.6%) (Table 4).

All-cause 30-day mortality rates were reported between 1.7% and 14.3%, with a pooled estimate of 7.8% (95% CI: 5.5% to 11.1%). Cardiovascular death accounted for most of the 30-day mortality after TAVR, with a pooled estimate rate of 5.6% (95% CI: 3.7% to 8.3%) (Table 3 and Figure 2).

Myocardial infarction (MI) was repor-ted as a complication of TAVR in 0% to 5.6% of studies, with a pooled estimate rate 1.1% (95% CI: 0.2% to 2.0%). Acute kidney injury (AKI) at all stages was a frequent complication, with a pooled estimate rate of 20.4% (95% CI: 16.2% to 25.8%). However, most of the AKI was at stage I (13.3%; 95% CI: 9.8% to 18.0%),

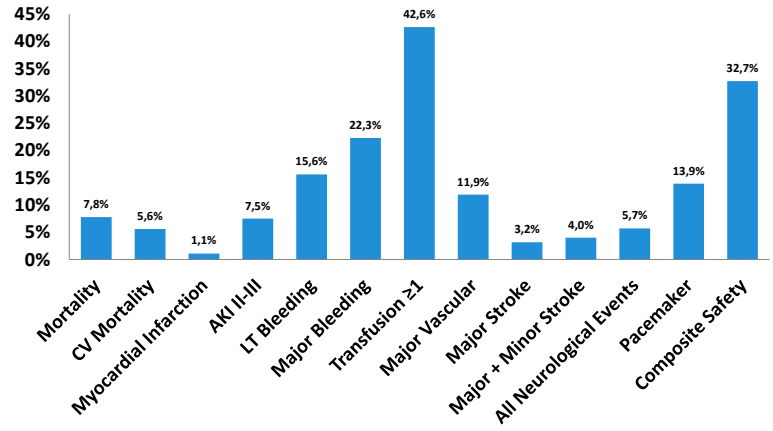

Figure 2 **Thirty-day event rates of major VARC-related outcomes**

AKI = acute kidney injury; CV = cardiovascular, LT = life-threatening; MI = myocardial infarction ≤72h after procedure; PPM = permanent pacemaker; VARC = Valve Academic Research Consortium

whereas the AKI at stages II/III (significant AKI according to VARC criteria) was less frequent (7.5%; 95% CI: 5.1% to 11.4%).

Life-threatening bleeding and major vascular complications occurred at a pooled estimate rate of 15.6% (95% CI: 11.7% to 20.7%) and 11.9% (95% CI: 8.6% to 16.4%). All neurologic events (all strokes and transient ischemic attacks) were reported from 1.3% to 21.0% and occurred at a pooled estimate rate of 5.7% (95% CI: 3.7% to 8.9%), and all strokes (major and minor) were reported from 1.0% to 6.8%, with a pooled estimate rate of 4.0% (95% CI: 2.4% to 6.3%). The reported rates for a new permanent pacemaker implantation after TAVR range from 3.4% to 50%, with a pooled estimate rate of 13.9% (95% CI: 10.6% to 18.9%). Medtronic CoreValve prosthesis use was associated with a significantly higher rate of new permanent pacemaker implantation compared with the Edwards prosthesis (28.9% [95% CI: 23.0% to 36.0%] vs. 4.9% [95% CI: 3.9% to 6.2%], $p < 0.0001$). Device-related outcomes and other complications are shown in Table 4.

Composite endpoint and 1-year follow-up outcomes

The 30-day safety composite endpoint was correctly reported in 6 studies (37.5%) (Table 2), with a pooled estimate rate of 32.7% (95% CI: 27.5% to 38.8%). The 1-year safety composite endpoint was reported in only 2 studies (12.5%), with a pooled estimate rate of 71.1% (95% CI: 65.6% to 76.0%). One-year all-cause mortality and cardiovascular mortality rates were reported in 7 studies (43.8%) and 4 studies (25.0%), respectively, with an associated pooled estimate rate of 22.1% (95% CI: 17.9% to 26.9%) and 14.4% (95% CI: 10.6% to 19.5%).

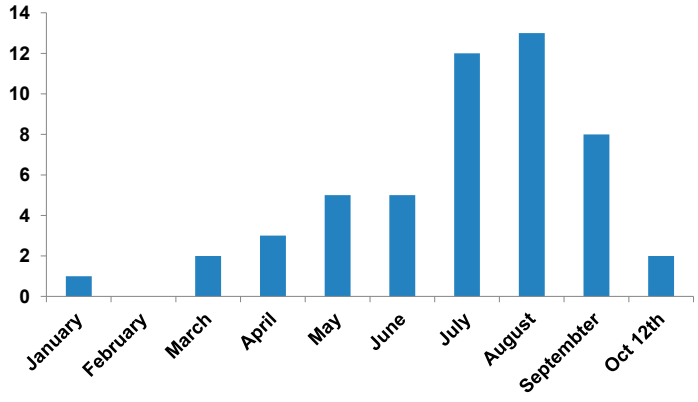

Figure 3 **VARC-related publications since original publication in January 2011**

Early after its publication in January 2011, VARC definitions were already in use and incorporated into clinical practice, showing acceptance by the TAVR community. TAVR = transcatheter aortic valve replacement; VARC = Valve Academic Research Consortium

DISCUSSION

The current report, which includes 3,519 patients from 16 unique studies, is the first pooled analysis reporting outcomes after TAVR according to the recently proposed VARC definitions. The main results of the current study are as follows: 1) VARC definitions have already been widely used by the TAVR community since their introduction earlier this year; 2) VARC definitions have established an important uniformity for outcomes after TAVR; 3) the pooled estimate outcomes after TAVR reported in this meta-analysis represent a new standard of quality for TAVR clinical research; 4) specific issues in the first version of the VARC definitions were identified; and 5) refinement and modifications of the current VARC definitions may be needed and are in progress.

Since January 2011,[14] VARC definitions have been rapidly incorporated into clinical and research practice (Figure 3). Although most of the VARC-related endpoints have been reported in high proportion among selected studies, the 30-day and 1-year composite endpoints and the 1-year mortality rates have been reported by only a few authors (Table 2). The relative complexity of the 2 hierarchical composite endpoints, the absence of all data fields required to compute the endpoints, and inadequate follow-up may explain the low reporting rates.

Not surprisingly, device-related outcomes, such as coronary obstruction, ventricular septal defect, annulus rupture, aortic rupture, aortic dissection, and left ventricle perforation, occurring less frequently after TAVR, were not systematically reported by authors (Table 4). However, considering that this technique is in its infancy, systematic reports of such compli-

cations (present or not) are strongly recommended to provide a complete understanding of the risks associated with TAVR procedures.

In-hospital, 30-day, and 1-year follow-up outcomes

The device success rate of the current pooled analysis appears to be lower than previously reported. This difference is mostly explained by the fact that VARC uses stricter definitions, with echocardiography-derived criteria not used before, such as AVA <1.2 cm^2 and residual moderate to severe prosthetic valve aortic regurgitation. Indeed, Gurvitch et al. [22] reported a relatively low success rate of 80% using VARC definitions and explained that the main reasons for"device failure"were a calculated AVA of <1.2 cm^2, a criterion that may not be reasonable for either a small annulus or low body weight patients. Despite this low success rate, clinical and symptomatic improvement in these patients was dramatic, with 97% of patients with procedural AVA <1.2 cm^2 improving to New York Heart Association functional class I or II. Ikeda et al. [35] also reported some concerns with the 1.2 cm^2 criterion for device success, especially in small body size populations, such as Asian patients, in whom an indexed valve area may be more appropriate. Until now, no evidence has been shown that patients with an AVA <1.2 cm^2 after TAVR have a worse outcome. Conversely, Ewe et al. [36] recently showed that patients with prosthesis–patient mismatch after TAVR, defined as an indexed effective orifice area ≤0.85 cm^2/m^2, had a slower and smaller reduction in mean transaortic gradient, limited left ventricular mass regression, and a higher proportion of patients not improving in New York Heart Association functional class compared with patients without mismatch. Moreover, no standardized method for echocardiographic measurement of the left ventricular outflow tract diameter after TAVR has been validated. Therefore, AVA may vary considerably, depending on where the left ventricular outflow tract measurement is performed after TAVR.[37] These issues will be addressed in future versions of VARC definitions.

The 30-day mortality rate in the current report is similar to the mortality rate reported in the early registries,[4, 5, 7, 8] reflecting the use of first-generation devices, early experience of operators, and a population of patients at high or prohibitive risk of surgery. Interestingly, the 30-day mortality rate pooled estimate of our report (7.8%; 95% CI: 5.5% to 11.1%) is similar to the 30-day predicted mortality rate by the Society of Thoracic Surgeons score (8.7%; 95% CI: 7.0% to 10.3%). Considering that the population of the current report represents a mix of several approaches (transapical, transfemoral [TF], subclavian) and different devices, this finding underlines the high-risk profile of the patients included in this meta-analysis.

The cardiovascular mortality rate, both at 30 days and 1 year, represents >65% of the total mortality in the present study. Although such results might be expected in a population of high-risk patients who underwent a major cardiac procedure, some authors have challenged the clinical relevance to systematically attribute unknown death to cardiovascular death and, consequently, its relationship to the device and underlying aortic pathology.[38] In fact, according to the current VARC definitions, unknown deaths should be considered

as cardiovascular in origin. Although VARC suggests the use of all-cause mortality as the primary endpoint of choice and cardiovascular mortality as a secondary endpoint, ascertainment and adjudication of cardiovascular death remain a challenge.

Periprocedural MI (≤72 h after TAVR) occurred at a rate of 1.1% (95% CI: 0.2% to 2.0%) after TAVR in the current analysis. Although coronary obstruction is a potential cause, other factors such as global ischemia due to hypotension, rapid pacing, microembolism induced by device delivery or implantation, myocardial tissue compression by the device expansion, and direct trauma of the apex during transapical access must also be considered. VARC proposed the use of a relatively conservative definition for MI, for which the recommended biomarker is the creatine kinase-myocardial band isoenzyme, and not troponin and clinical signs of infarction. This may explain the low rate of MI reported after TAVR. Conversely, Rodes-Cabau et al. [39] were the first to report the incidence and implication of troponin increase after TAVR, in which 97% of TF patients and 100% of the transapical patients showed some degree of troponin increase. After multivariate analysis, a greater magnitude of troponin T increase (15 times the upper normal range) was shown to be an independent predictor of mortality at a mean follow-up of 9 months as well as a factor correlated with lesser degrees of improvement in left ventricular ejection fraction. However, the inclusion of troponin as a criterion for MI after TAVR is still a matter of debate, and more data and validation are needed.

AKI was reported according to the VARC definition in 9 studies (56.3%). However, less than one-third of the authors appropriately reported AKI stage II or III, which is the proposed stage to be reported according to VARC definitions. Most of the AKIs were stage I, and the frequency of stage II/III was 7.5%. Noticeably, the rate of AKI stage I reported in the literature was as high as 24.6% in 1 study (Table 3). This may be explained by the low threshold chosen by the first VARC committee, in which any increase of >0.3 mg/dl is considered AKI stage I.

Life-threatening and major bleeding after TAVR occurred in 15.6% (95% CI: 11.7% to 20.7%) and 22.3% (95% CI: 17.8% to 28.3%), respectively (Table 3). These rates appear higher compared with previous reports. However, bleeding complications have been inconsistently reported and likely even underreported in the early literature.[5, 11, 40, 41] Among the 16 studies in our analysis, transfusion rates were reported by 7 authors (43.8%), with a pooled estimate rate of needing 1 or more transfusions after TAVR of 42.6% (95% CI: 19.8% to 62.4%). VARC strongly recommended reporting the rate of transfusions after TAVR. However, Gurvitch et al. [22] previously reported that a significant proportion of patients received blood transfusions without an obvious source of bleeding, in whom anemia was pre-existent or the cause of the hemoglobin decrease was unclear. Généreux et al. [42] also reported that among the 25% of patients who needed red blood cells after TAVR, 57% of the transfusions given were not directly related to the procedure (gastrointestinal bleeding, genitourinary bleeding, or no obvious source). Such findings may warrant a possible separate category

in future revised VARC criteria so that a clear distinction can be made between procedure-related blood loss and nonprocedural bleeding.

Major vascular complications occurred in 11.9% (95% CI: 8.6% to 16.4) of patients in the current study. Before VARC definitions, vascular complications were inconsistently reported, and when they were, it was mostly reported by site and according to the investigator definitions. Moreover, classification of severity was rarely done. Piazza et al. [5] reported their early data using the TF approach with the Medtronic CoreValve device with a low rate (1.9%) of vascular complications, whereas Eltchaninoff et al. [11] reported a much higher rate (7.5%) using the same device and the same access route. Similarly, early studies using the Edwards device via the TF route reported 30-day vascular complication rates ranging from 6.3% to 22.9%.[8, 11] The TA approach has been associated with a lower rate of vascular complications than the TF route.[8, 40, 43]

Moreover, further clarification of the current VARC criteria may be needed because the TF approach is moving toward a full-percutaneous procedure. Also, inclusion of "new" alternative access sites, such as the subclavian-axillary artery [41, 44, 45] and direct transaortic access,[46] should be considered in the elaboration of new definitions.

Stroke has emerged as one of the major foci of attention after TAVR. The major stroke rate reported in our study is 3.2% (95% CI: 2.1% to 4.8%). Interestingly, minor strokes and transient ischemic attacks were less frequently reported, underlying the difficulty to adequately identify such post-procedural events, especially in a population of elderly sick patients.

Before VARC definitions, the 30-day stroke rates had been variably reported, ranging from 1.5% (40) to 4.2% [11] for the Edwards device and 0% (11 and 47) to 10% [4] for the Medtronic device. These were mostly self- or site-reported results and nonadjudicated events. VARC emphasizes the necessity to confirm the diagnosis by neuroimaging technique (computed tomography and/or magnetic resonance imaging) and to classify the severity of stroke using conventional neurological assessment tools. VARC recommended the modified Rankin Scale score at 30 and 90 days for the stroke assessment. However, Ikeda et al. [35] suggested that the National Institutes of Health Stroke Scale should also be used, and the time point of the evaluations should also cover event onset (acute phase). Given the different level of invasiveness and pattern of recovery after surgical aortic valve replacement and TAVR, assessment and comparison of stroke rates between these 2 approaches has become challenging. Early recognition of events, use of an appropriate scoring system (National Institutes of Health Stroke Scale and the modified Rankin Scale), neuroimaging tools, and adjudication by a neurology specialist will provide a more accurate comparison of stroke frequency between different therapies.

The permanent pacemaker insertion rate in the current analysis is 13.9% (95% CI: 10.6% to 18.9%), resulting from the pooling of data including both devices (Medtronic CoreValve system and Edwards Lifesciences device). It is generally accepted that the self-expandable CoreValve, because of its higher and longer lasting radial force as well as the

deeper implantation site in the left ventricular outflow tract, has a higher rate of pacemaker requirement than the Edwards valve. Current evidence shows that 20% to 30% of patients after CoreValve implantation and 3% to 5% of patients after Edwards valve placement will require a new permanent pacemaker. An additional analysis was performed, pooling data from centers where TAVR were done with 1 type of device, showing similar results (Edwards valve, 4.9% [95% CI: 3.9% to 6.2%] vs. CoreValve, 28.9% [95% CI: 23.0% to 36.0%], $p < 0.0001$). However, differences between operator and institution relating to the threshold for permanent pacemaker insertion must also be considered.

Another important focus has been the higher incidence of paravalvular leak after TAVR compared with surgical aortic valve replacement. The pooled estimate for residual moderate or severe aortic regurgitation after TAVR was 7.4% (95% CI: 4.6% to 10.2%) in this report. Currently, however, there are no standardized methods to grade paravalvular regurgitation after TAVR. Whereas the current VARC definition suggests criteria such as jet density, jet width, and jet deceleration time for central aortic regurgitation, paravalvular leak assessment is based on the percentage of the circumferential extent of paraprosthetic aortic regurgitation, which has not been validated in a TAVR population. Uniformity and a standardized echocardiographic definition for paravalvular leak after TAVR is mandatory for the next version of VARC definitions.

As mentioned earlier, many authors have not reported composite endpoints. However, among those reporting the 30-day composite endpoint, disparity seems to exist, with rates ranging from 17.8% to 68%. Although differences in population risk profiles may explain a portion of this discrepancy, correct interpretation of the hierarchical order and use of proper echocardiographic findings are mandatory with this composite endpoint.

The 1-year safety endpoint rate was reported by 2 studies and occurred in ~70% of patients. The high rate of this endpoint is explained by the inclusion of recurrent heart failure requiring admission as a component of this outcome. Although important, this component can introduce"background noise,"reflecting more on the presence of suboptimal heart failure management, multiple comorbidities, or different severities of left ventricular depression, despite a perfectly functioning valve. In a recent comment, Ikeda et al. [35] also underlined the possible bias by each country's medical care setting, where thresholds for hospitalization would vary from country to country, according to local culture.

Study limitations

Several important limitations of the present analysis warrant discussion. This report represents a study-level pooled analysis of 16 TAVR articles. A patient-level analysis would have been preferable. We pooled data that were clearly reported in each article. Authors may not have reported outcomes simply because they did not occur, which may have led to some overestimation of events in our analysis. Reported outcomes from the 16 studies were mainly self- or site reported, with only 2 studies adequately reporting adjudicated events.[33, 34]

This is likely to have contributed significantly to the high heterogeneity that is observed in this report. Different devices and approaches were used in the selected studies, and no systematic comparison of the devices or approaches has been attempted thus far. Although unlikely, a publication bias is always possible. The aim of this meta-analysis was to evaluate the performance and the use of the VARC definitions among the most recent TAVR literature. A patient-level pooled analysis comparing the different devices and access approaches was beyond the scope of this paper.

CONCLUSIONS

VARC definitions have already been used successfully in the literature and are being rapidly adopted by the TAVR community. However, slight modifications are needed and may improve their application in the future. Although VARC definitions have brought uniformity and standardization in reporting outcomes after TAVR, appropriate recognition and ascertaining, reporting and adjudication of outcomes should be reinforced and will ensure that TAVR study results are a valid reflection of ″real-world″ clinical events.

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Paris

Chapter 13

Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature

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ABSTRACT

Paravalvular leak (PVL) is a frequent complication of transcatheter aortic valve replacement (TAVR) and is seen at a much higher rate after TAVR than after conventional surgical aortic valve replacement. Recent reports indicating that PVL may be correlated with increased late mortality have raised concerns. However, the heterogeneity of methods for assessing and quantifying PVL, and lack of consistency in the timing of such assessments, is a hindrance to understanding its true prevalence, severity, and effect. This literature review is an effort to consolidate current knowledge in this area to better understand the prevalence, progression, and impact of post-TAVR PVL and to help direct future efforts regarding the assessment, prevention, and treatment of this troublesome complication.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has become the treatment of choice for inoperable patients with severe aortic stenosis and is comparable to surgical aortic valve replacement (SAVR) for patients at high risk. [1, 2] However, paravalvular leak (PVL) is more frequently seen after TAVR than after SAVR, and its potential association with mortality has raised concerns.[3-6] Moreover, recent reports have suggested that PVL could negatively impact mid- and long-term prognosis following TAVR.[7, 8] Although concerning, the lack of standardized quantitative and qualitative methods to assess and categorize PVL and the heterogeneity in the timing of post-procedural assessment of PVL warrant caution in interpretation of these data. Therefore, we sought to perform a systematic review of the current literature to better define the rate, progression over time, predictors, and consequences of PVL after TAVR. Furthermore, recommendations for measuring PVL are provided to improve consistency throughout the literature.

RATE OF PARAVALVULAR LEAK

Multiple studies have reported the frequency and severity of PVL after TAVR.[9] There is, however, significant heterogeneity that is caused by differences in: 1) imaging modalities (transthoracic echocardiography, transesophageal echocardiography, angiography); 2) timing of assessment (immediately after implantation, before discharge, at 30 days); 3) transcatheter heart valve (THV) system; 4) grading scale; and 5) adjudication of events. When PVL was evaluated before hospital discharge and without central core laboratory analysis, its absence was reported in 6% to 59% of patients, whereas moderate or severe PVL was seen in 0% to 24% (Table 1).[1-5, 10-16]

Thus far, only the PARTNER (Placement of Aortic Transcatheter Valve) trial has used a central echocardiography core laboratory to evaluate PVL.[1, 2] PVL was graded in accordance with the American Society of Echocardiography recommendations for native valves [17] because there were no recommendations for prosthetic valve assessment at the start of the trial. In addition, because of the inevitable eccentric nature of the jet and the frequent "spray" of the jet contour in the outflow tract, the color Doppler in the available parasternal short-axis view(s) was weighted in a subjective fashion more heavily than other signals in providing an integrated assessment. The following definition was applied: no PVL (no regurgitant color flow), trace (pinpoint jet in atrioventricular [AV] short-axis view), mild (jet arc length <10% of the AV annulus short-axis view circumference), moderate (jet arc length 10% to 30% of the AV annulus short-axis view circumference), and severe (jet arc length >30% of the AV annulus short-axis view circumference). In the PARTNER trial, trace/mild PVL was found in 66% of patients and moderate/severe in 12%.[1, 2]

Table 1 Selected publications reporting aortic regurgitation after TAVR

Author, year	No. of patients	Approach	Prosthesis	Imaging modality	Severity gradation	Adjunctive techniques	AR post TAVR	Predictors of AR by multivariable Analysis
Detaint, 2009	74	TF 46 (62%) TA 28 (38%)	ES	Echocardiogram (TEE) Site reported (blinded echographist)	0=absent 1=trace-mild 2=mild-moderate 3=Moderate-severe 4=Severe	Post dilatation, 5/74; valve-in-valve, 2/74	*Early post TAVR (TEE)* 0 = 5 (7.0%) 1 = 53 (72.0%) 2 = 12 (16.0%) 3 = 4 (5.0%) 4 = 0 (0%)	[3]*2/4 AR* · Low cover index · Operators experience
Abdel-Wahab, 2011	690	TF 644 TA 26 SC 22 TAo 5	ES=110, 16% MCV= 580, 84%	Angiogram Site reported	0=absent 1=trace-mild 2=mild-moderate 3=Moderate-severe 4=Severe	-	*Early post TAVR (Angio)* 0 = 191 (27.7%) 1 = 380 (55.1%) 2 = 103 (14.9%) 3 = 14 (2.0%) 4 = 2 (0.3%)	[3]*2/4 AR* · AVA baseline · Annulus baseline · Cardiogenic shock · Renal failure · Male gender
Sherif, 2010	50	TF	MCV	Angiogram Echocardiogram Site reported	1=trivial-mild 2=moderate 3=moderate-severe 4=severe	-	*Early Post TAVR (Angio)* 0 = 3 (6.0%) 1 = 27 (54.0%) 2 = 13 (26.0%) 3 = 7 (14%) 4 = 0 (0%) *Early Post TAVR (TTE)* 0 = 9 (18.0%) 1 = 24 (48.0%) 2 = 13 (26.0%) 3 = 4 (8%) 4 = 0 (0%)	[3]*2/4 AR* · Increase angle of LVOT and ascending aorta · Depth of the device in relation to the non-coronary cups

Table 1 *Continued*

Author, year	No. of patients	Approach	Prosthesis	Imaging modality	Severity gradation	Adjunctive techniques	AR post TAVR	Predictors of AR by multivariable Analysis
John, 2010	100	TF=97 (97%) SC=3 (3%)	MCV	Angiogram Echocardiogram	0 1+ 2+ 3+ 4+	Post dilatation, 34/100; snare technique, 4/100; valve-in-valve, 3/100	*Early after TAVR (Angio)* 0 = 35 (35.4%) 1+ = 28 (28.3%) 2+ = 19 (19.2%) 3+ = 8 (0.8%) 4+ = 0 (0%) *Early after adjunctive technique (Angio)* 0 =38 (38.4%) 1+ = 49 (49.5%) 2+ = 11 (11.1%) 3+ = 1 (0.1%) 4+ = 0 (0%)	AgS and DLZ-CS showed a significant correlation with the grade of paravalvular leak post initial MCV deployement
Takagi, 2011	79	TF=62 (78.5%) SC=17 (21.5%)	MCV	Angiogram Echocardiogram Site reported	0=absent 1=mild 2= moderate 3-4=severe	Post dilatation, 21/79; valve-in-valve, 2/79; snare technique, 1/79	*Final result (Angio)* 0 = 21 (26.6%) 1 = 42 (53.2%) 2 = 13 (16.5%) 3 = 3 (3.8%) 4 = 0 (0%)	[3]*2/4 AR* · Larger annulus diameter · Low implantation · Peripheral vascular disease
Tamburino, 2011	663	TF	MCV	Echocardiogram Site reported, events reviewed by an independent CEC	-	Post dilatation, 68/663; valve-in-valve, 139/663; conversion to open surgery, 5/663	*Post TAVR* [3]2 PVL 139 (21.0%)	-

Table 1 *Continued*

Author, year	No. of patients	Approach	Prosthesis	Imaging modality	Severity gradation	Adjunctive techniques	AR post TAVR	Predictors of AR by multivariable Analysis
Gotzmann, 2011	145	TF/SC	MCV	Echocardiogram Angiogram (If poor TTE quality) Site reported	Mild Moderate Severe	-	*Early Post TAVR* Mild = 64 (44%) Moderate = 23 (16%) Severe = 2 (1%) *Early Post TAVR* *For 30-day survivor only* Mild = 55 (45%) Moderate = 1 6 (13%) Severe = 0 (0%)	-
Moat, 2011	870	TF=599 Other=271	ES=410, 47% MCV=459, 53%	Angiographic Site reported	-	Conversion to open surgery, 6/850	AR ^{3} 1 = 516 (61%) AR >2 = 115 (13.6%)	-

AgS = Agatston score; AR = aortic regurgitation; AVA = aortic valve area; CEC = clinical events committee; DLZ-CS = device-landing zone calcification score; ES = Edwards Sapien; LVOT = left ventricular outflow tract; MCV = Medtronic CoreValve; PVL = paravalvular leak; SC = subclavian; TA = transapical; TAo = transaortic; TAVR = transcatheter aortic valve replacement; TEE = transesophageal echocardiography; TF = transfemoral; TTE = transthoracic echocardiography

No prospective direct comparison of the rate of PVL after TAVR has been published between the 2 most frequently used THV systems (balloon-expandable THV, Edwards Lifesciences, Irvine, California; self-expandable CoreValve THV, Medtronic, Minneapolis, Minnesota). However, moderate to severe post-procedural PVL seems to be slightly higher with the CoreValve (9% to 21%) than the Edwards (6% to 13.9%) device.[1-6, 18-22] Recent 1-year data presented from the FRANCE 2 (French Aortic National CoreValve and Edwards 2) Registry seemed to confirm this finding—the use of self-expandable prosthesis was identified as one of the major determinants of significant PVL after TAVR. At patient discharge, self-expandable prosthesis was associated with a moderate to severe PVL rate of 19.8%, compared with 12.2% for balloon-expandable prosthesis (p value not available).[23]

PROGRESSION OVER TIME

One of the initial concerns about PVL was potential worsening during extended follow-up. Because a large percentage of patients are discharged with trace or mild PVL, worsening of PVL could have important consequences on the volume load imposed on the left ventricle (LV), ultimately resulting in significant heart failure. In addition, if many cases progress to clinically significant leakage, hemolysis requiring repeated transfusions or reoperation may further complicate the course of patients.

Despite the lack of "common language" among previous reports in assessment of PVL severity, several studies have reported comparable findings with respect to time trends of PVL severity. Webb et al. [24] reported the evolution of PVL over time in a cohort of 168 patients and found that PVL was generally mild and remained stable between 30-day and 1-year follow-ups, a result that has been confirmed by other studies (Table 2). A recent report by Ussia et al. [16] showed that rates of mild (53%) and moderate (15%) post-procedural PVL had been reduced to 47% and 10%, respectively, at a follow-up of 3 years. Some attrition of the "sickest" patients might have been due to patients with worsening PVL dying, but there were no cases of worsening from mild to moderate/severe regurgitation in individual patient progression of PVL.

Data from the PARTNER trial suggested, however, that PVL at 2 years had increased by ≥1 grade in 22.4% of patients, whereas it remained unchanged in 46.2% and improved by ≥1 grade in 31.5% of patients (Fig. 1).[8] So far, no studies have explored the mechanisms behind improvement or worsening of PVL in individual patients, and measurement methods may explain, at least in part, these changes.

Table 2 Progression of aortic and/or paravalvular regurgitation over time

Author, year	No. of patients	Significant post-procedural	Significant at 6 months	Significant at 1 year	Significant at 2 years	Significant at 3 years
Paravalvular leakage						
Webb, 2009,	168	*30 days* 2+ = 37% 3+ = 5%	…	"Stable"	…	…
Muñoz-Garcia, 2011	144	*72 hours* mild = 40% moderate = 23%	mild = 47% moderate = 19%	…	…	…
Ussia, 2012	181	*Post-procedure* mild = 53% moderate = 15%	…	mild = 48% moderate = 18%	mild = 50% moderate = 17%	mild = 47% moderate = 10%
Ye, 2010	71	*30 days* mild = 26% moderate = 5%	…	…	…	"Remained unchanged and clinically insignificant during follow-up"
Takagi, 2011	79	*30 days* 1+ = 51% 2+ = 20% 3+ = 3%	1+ = 49% 2+ = 27% 3+ = 0%	…	…	…
Ewe, 2011	107	*Post-procedure* 1+ = 58% 2+ = 16% 3+ = 5%	*≥6 months* 1+ = 51% 2+ = 31% 3+ = 0%		…	…
Godino, 2010	137	*Post-procedure* 1+ ≈ 60% 2+ ≈ 12% 3+ = 4% 4+ = 2%	1+ ≈ 65% 2+ ≈ 9% 3+ ≈ 5% 4+ = 0%	…	…	…

Table 2 *Continued*

Author, year	No. of patients	Significant post-procedural	Significant at 6 months	Significant at 1 year	Significant at 2 years	Significant at 3 years
Aortic regurgitation						
Bauer, 2010	88	2+ = 29% 3+ = 7%	…	2+ = 24% 3+ = 0%	2+ = 23% 3+ = 0%	…
Rajani, 2010,	46	*Within 5 days* mild = 33% moderate = 19% moderate-severe = 5%	…	mild = 31% moderate = 8% moderate-severe = 15%	…	…
Clavel, 2009,	50	*Discharge* trivial = 38% mild = 42% moderate = 8% severe = 0%		*6 to 12 months* trivial = 26% mild = 46% moderate = 6% severe = 0%	…	…
Lefevre, 2011	130	*Discharge* 2+ = 42% 3+ = 5%	…	2+ = 25% 3+ = 0%	…	…
Buellesfeld, 2011	126	*30 days* 1+ = 32% 2+ = 9% 3+ = 0%	1+ = 39% 2+ = 6% 3+ = 0%	1+ = 34% 2+ = 3% 3+ = 0%	1+ = 37% 2+ = 0% 3+ = 0%	…
Bleiziffer, 2012	227	*Discharge* mild = 31% mild-moderate = 13% moderate = 8% moderate-severe = 3%	mild = 45% mild-moderate = 11% moderate = 6% moderate-severe = 0% severe = 0%	mild = 40% mild-moderate = 16% moderate = 6% moderate-severe = 0.5% severe = 0.5%	mild = 41% mild-moderate = 15% moderate = 5% moderate-severe = 1% severe = 1%	…
Koos, 2011,	57	*After implant* 1+ = 77% 2+ = 9% 3+ = 5%	*Mean 83±80 days* 1+ = 82% 2+ = 5% 3+ = 0%	…	…	…

Table 2 *Continued*

Author, year	No. of patients	Significant post-procedural	Significant at 6 months	Significant at 1 year	Significant at 2 years	Significant at 3 years
D'Onofrio, 2011	504	*Discharge* 1+ = 30% 2+ = 9%	…	*Mean 9.2±6.5 months* "no changes in the degree of AR were found."	…	…
Gurvitch, 2010	70	*Post-procedure* trivial = 40% mild = 44% mod = 6%	…	…	…	trivial = 60% mild = 33% mod = 3%
Walther, 2011	168	…	*3-6 months* 1+ = 51% 2+ = 1% 3+ = 0%	1+ = 46% 2+ = 5% 3+ = 0%	…	…

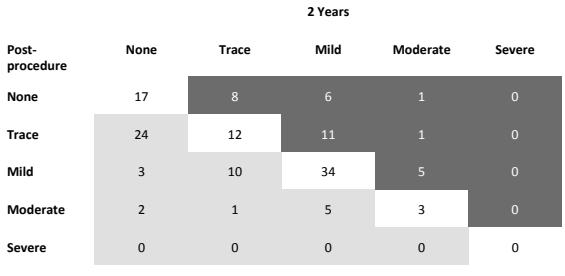

Figure 1 **Change in paravalvular leak severity over 2-year follow-up**

Adapted with permission from Kodali and colleagues.[8]

IMPACT ON CLINICAL OUTCOMES

After SAVR, moderate to severe residual aortic regurgitation (AR) occurs infrequently in approximately 4% of patients.[25] A recent study showed that AR after SAVR was an independent predictor of long-term mortality with a hazard ratio of 1.7 (95% CI: 1.2 to 2.3). The TAVR community has focused extensively on the effect of AR on survival because its prevalence is much higher after TAVR than after SAVR.[8] A number of studies have identified AR ≥2+ to be an independent predictor of short- and long-term mortality (Table 3).[3] Furthermore, patients with AR ≥2+ were 10 times more likely to be nonresponders to therapy at 6 months' follow-up; nonresponsiveness was defined as either death or New York Heart Association classification ≥2.

Few studies have devoted analyses specifically to PVL. This is not surprising because the low post-operative rate of PVL in surgical series makes statistical analysis not meaningful. However, even in TAVR after which post-procedural AR is largely paravalvular, there have been only a few large registries and randomized trials focused on PVL. Data on 663 patients from the Italian registry found that PVL grade ≥2+ was not associated with early 30-day mortality, but multivariate analysis did find a hazard ratio of 3.79 for patients with PVL ≥2+ for late mortality beyond 30 days.[6] More disturbingly, although it was generally believed that only moderate or severe regurgitation would impact long-term outcomes,[26] the recently published 2-year results from the PARTNER trial showed that even mild PVL was associated with significant mortality (Fig. 2).[8] Multivariable analyses did not identify AR or PVL as independent predictors of mortality in this trial, but, interestingly, there is a trend toward improved survival in patients undergoing TAVR compared with SAVR if PVL was negligible (70% vs. 65%).

Importantly, based on the current literature, the direct causal relationship between PVL and mortality (vs. PVL being a marker for other factors) still needs to be determined. Careful analyses of baseline patient characteristics, the repercussion of all degrees of PVL on LV geometry and remodeling, and the determination of the precise cause of death

Table 3 Outcomes associated with aortic and/or paravalvular regurgitation

Author, year	No. of patients	Variable	Outcome	Univariate analysis	Multivariate analysis
Abdel-Wahab, 2011	690	AR ≥2	In-hospital mortality	OR = 2.50 [1.37-4.55]	OR = 2.43 [1.22-4.85]
Gotzmann, 2011	122	AR ≥2	6-month mortality	…	OR = 4.26 [1.59-11.45]
			No clinical improvement	…	OR = 10.1 [3.20-31.94]
Takagi, 2011	41	AR ≥2	6-month mortality	12.2% vs. 25.0%, p=0.25	…
Hayashida, 2012	260	AR ≥2	median 217 days [IQR 54-401]	HR = 1.97 [1.19-3.28]	…
Leber, 2011	69	AR >2	1-year mortality	9% vs. 37.5%, p=0.07	…
Moat, 2011	870	AR ≥2	1-year mortality	HR = 1.49 [1.00-2.21]	HR = 1.66 [1.10-2.51]
Sinning, 2012	152	PVL ≥2	1-year mortality	HR = 4.0 [2.1-7.5]	HR = 4.9 [2.5-9.6]
Tamburino, 2011	663	PVL ≥2	Late mortality	…	HR = 3.79 [1.57-9.10]
Sinning, 2012	146	Moderate/ severe PVL	1-year survival	HR = 3.9 [2.0-7.5]	HR = 2.4 [1.0-5.4]
Unbehaun, 2012	358	None vs. trace vs. mild AR	2-year survival	66% vs. 72% vs. 67%, p=0.77	…
Kodali, 2012	158	Mild to severe AR	2-year survival	HR = 1.75 [1.17-2.61]	Not significant
		Mild to severe PVL	2-year survival	HR = 2.11 [1.43-3.10]	Not significant

AR = aortic regurgitation; HR = hazard ratio; IQR = interquartile range; OR = odds ratio; PVL = paravalvular leak

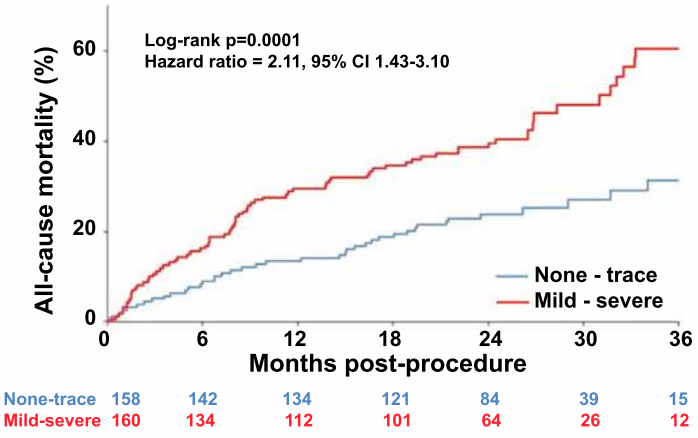

Figure 2 Impact of paravalvular leak on 2-year all-cause mortality

Reprinted with permission from Kodali and colleagues.[8] HR = hazard ratio

(cardiovascular vs. noncardiovascular) are needed to confirm the strength and the nature of this relationship. At this point, any previous observations linking PVL (especially mild) with mortality should be considered hypothesis generating.

PREDICTORS OF PARAVALVULAR LEAK

Significant PVL most commonly results from: 1) incomplete prosthesis apposition to the native annulus due to patterns or extent of calcification [11, 27-30] or annular eccentricity;[26] 2) undersizing of the device;[10, 31, 32] and/or 3) malpositioning of the valve.[33] These observations seem to be true for both balloon-expandable and self-expandable THVs.

Valve sizing has been shown to be one of the strongest predictors of PVL. A low cover index reflecting a lower degree of oversizing of the prosthesis based on transthoracic echocardiography annulus measurement predicts significant PVL.[10] More recently, studies have evaluated the use of multidetector computed tomography (MDCT) for THV sizing, and MDCT showed good predictability and reduced rates of significant PVL.[34-37] Furthermore, larger and eccentric annuli were identified as predictors of PVL in multiple studies and most likely reflect inadequate sizing of the THV.[3, 15, 26] A smaller aortic valve area was found to predict PVL in one study, but this was likely because the smaller area indicates a greater degree of calcification.[3] The extent of calcification and asymmetrical distribution, as well as the location of calcium on the aortic wall, valve commissure, or THV landing zone, as a predictor for PVL has been confirmed in several studies.[11, 26, 29, 37, 38]

In studies specifically evaluating the CoreValve (Medtronic), a lower depth of implantation and a greater angle between the aorta and LV outflow tract were found to predict PVL (14 and 15).

ASSESSMENT OF PARAVALVULAR REGURGITATION

Angiographic and hemodynamic assessment

Aortic root angiography is an established tool for qualitative and semiquantitative assessment of AR.[39] It is readily available during the TAVR procedure and can be quickly and safely executed to provide essential information and initiate adjunctive maneuvers if needed in case of significant (para) valvular AR. Typically, Sellers criteria are applied to grade AR:[40] 1) grade 1 or mild AR corresponds to a small amount of contrast entering the LV during diastole without filling the entire cavity and clearing with each cardiac cycle; 2) grade 2 or moderate AR corresponds to contrast filling of the entire LV in diastole but with less density compared with contrast opacification of the ascending aorta; 3) grade 3 or moderate to severe AR corresponds to contrast filling of the entire LV in diastole equal in density to the contrast

opacification of the ascending aorta; and 4) grade 4 or severe AR corresponds to contrast filling of the entire LV in diastole on the first beat with greater density compared with the contrast opacification of the ascending aorta. During the contrast injection, no material may cross the aortic valve leaflets (e.g., guidewires, catheters) because incomplete valve closure may artificially be generated, thus resulting in AR. Particularly with self-expanding systems, it is important to wait some time (empirically 10 min) after deployment of the bioprosthesis to allow the system to expand to its maximum. The downside of qualitative aortography AR assessment is that it relies on subjective interpretation of unidimensional images; therefore, interobserver and intraobserver variability can be an issue and additional contrast volume required. Moreover, it is difficult to determine the contribution of PVL and central AR.

Classic findings of acute AR (acute drop in the aortic diastolic pressure with or without elevated LV end-diastolic pressure [LVEDP]) may be seen after TAVR and may be suggestive of moderate to severe AR. However, these findings must be interpreted with caution because the concomitant use of sedatives, vasopressors, inotropes, and intravenous fluids all impact hemodynamics, and the presence of material through the aortic valve (e.g., wire) may interfere temporarily with the THV function. Recently, the AR index, the ratio of the end-diastolic gradient across the aortic valve bioprosthesis to systolic blood pressure ([ADP – LVEDP]/ASP; ADP-aortic diastolic pressure, ASP-aortic systolic pressure), was described.[41] An AR index <25 was associated with 1-year mortality. Although this association is interesting, more data and validation are needed to establish the role of this new index in the therapeutic decision process after TAVR.

Echocardiographic assessment

Although the native valve regurgitation quantitative grading scheme has been advocated for the evaluation of prosthetic valve regurgitation,[42] there are limited data to support the use of these parameters following TAVR. The majority of semiquantitative parameters for assessing AR apply to central regurgitant jets, which are more uniform, making semiquantitative grading schemes more reliable.

Unlike central jets, paravalvular regurgitant jets are commonly eccentric with crescentic, irregular orifices. Because these jets occur between the annulus and sewing ring, jet areas and lengths may not represent the same severity of regurgitation compared with central jets and these parameters cannot be used to reliably assess regurgitant severity. Although guidelines suggest using the circumferential extent of the regurgitant jet as a semiquantitative measure of severity,[42] this parameter has not been validated against any quantitative parameters of regurgitation. Even if we accept the limited validation of this scheme for surgical prostheses, the anatomy and physiology of THVs are different than that of surgical valves. In the balloon-expandable valve, paravalvular regurgitation should be assessed just below the skirt; for central jets, the regurgitation should be assessed at the coaptation point of the leaflets. In addition, there is no scheme that specifically addresses the unusual

regurgitation that accompanies the THV. The intact calcified cusps and annulus significantly influence the location and shape of paravalvular jets; typically, these jets appear smaller and more irregular at the level of the intact/calcified cusps and larger just apical to the THV stent.

Quantitative assessment of total AR, or advanced imaging techniques for assessing paravalvular regurgitant orifices, may be a more accurate way of assessing severity and thus a more accurate assessment of risk. Quantitative Doppler uses comparative flow measurements across a regurgitant valve and a nonregurgitant valve to calculate regurgitant volume or fraction.[17] The effective regurgitant orifice area is then calculated by dividing the regurgitant volume by the velocity time integral of the regurgitant jet continuous wave spectral profile. Alternatively, the LV stroke volume calculated by 2-dimensional (2D) biplane Simpson method of discs [43] can be used in place of total (regurgitant plus forward) stroke volume; however, systematic underestimation of ventricular volumes has been reported for this method. Although this quantitative assessment has been largely validated in the literature,[44-51] has shown reproducibility, and is endorsed by scientific authorities,[17, 52] it should be acknowledged that this assessment is based on 4 parameters, any one of which may be determined with significant inaccuracy.

Three-dimensional (3D) echocardiography can overcome the limitations of 2D and standard Doppler measurements for quantifying regurgitation.[43] Pitfalls of 2D LV imaging, including foreshortening, malrotation, and angulation, can be overcome by 3D imaging. However, limitations of 3D imaging (lower line density and low volume rates) may reduce the utility of this method for assessing total stroke volume. Color Doppler 3D volumes can be useful for the identification and localization of regurgitation jets, as well as planimetry of the vena contracta area.[53, 54] This imaging modality may be particularly useful for post-TAVR assessment of PVL.[55, 56]

Table 4 **VARC II recommendations for the evaluation of aortic and/or paravalvular regurgitation after TAVR**

	Mild	Moderate	Severe
Semi-quantitative Parameters			
Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)*	<10	10-29	≥30
quantitative Parameters‡			
Regurgitant volume (ml/beat)	<30	30-59	≥60
Regurgitant fraction (%)	<30	30-49	≥50
EROA (cm^2)	0.10	0.10-0.29	≥0.30

*Not well-validated and may overestimate severity compared to quantitative Doppler. ‡For LVOT >2.5 cm, significant stenosis criteria is <0.20. Adopted with permission from Kappetein and colleagues.[31]

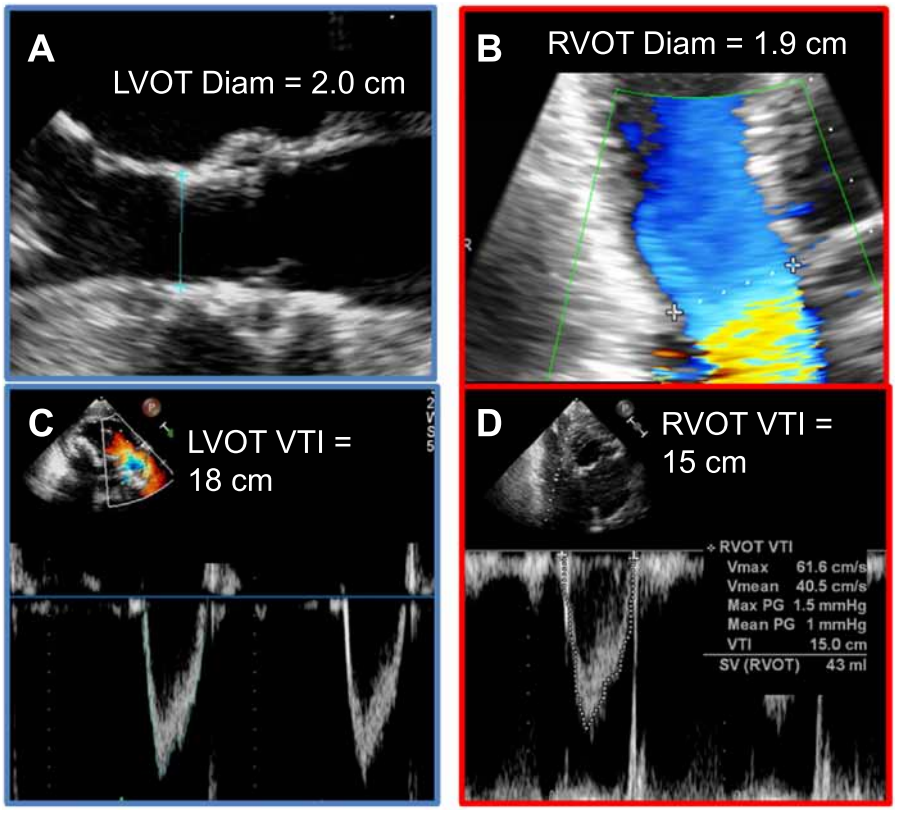

Figure 3 **Quantitative Doppler echocardiography can be used to calculate the regurgitant orifice and volume**

(A) Post-transcatheter heart valve (THV) left ventricular outflow (LVOT) diameter (just apical to the THV stent). ***(B)*** Right ventricular outflow tract (RVOT) diameter. ***(C)*** LVOT Doppler with sample volume located just apical to the THV stent aligned in the short-axis view of the LVOT pulse Doppler signal just below the THV stent. Stroke volume (SV) across the THV = LVOT area X LVOT velocity time intergral (VTI) = 56 ml. ***(D)*** RVOT VTI yields an SV across the RVOT of 43 ml. The regurgitation volume = LVOT SV – RVOT SV = 13 ml. AR = aortic regurgitation; PG = pressure gradient

With the increased use of multimodality imaging capable of 3D reconstruction of the aortic root,[36, 57-62] there has been intense interest in the shape of the annulus and appropriate sizing of the transcatheter heart valve to reduce PVL. The oval shape of the annulus has been well documented,[36, 60, 61, 63-65] and a single sagittal plane measurement is significantly smaller than the coronary plane measurement. Algorithms using 3D imaging tools have been suggested to improve annular sizing and reduce PVL.[34, 35]

Recently, the Valve Academic Research Consortium (VARC) published the VARC II definitions and suggested the use of TAVR-specific criteria for the assessment of AR and/or PVL after TAVR (Table 4).[66] Figure 2 and Figure 3 illustrate echocardiographic assessment of PVL after TAVR. Figure 4 illustrates a case using 3D echocardiography assessment of PVL.

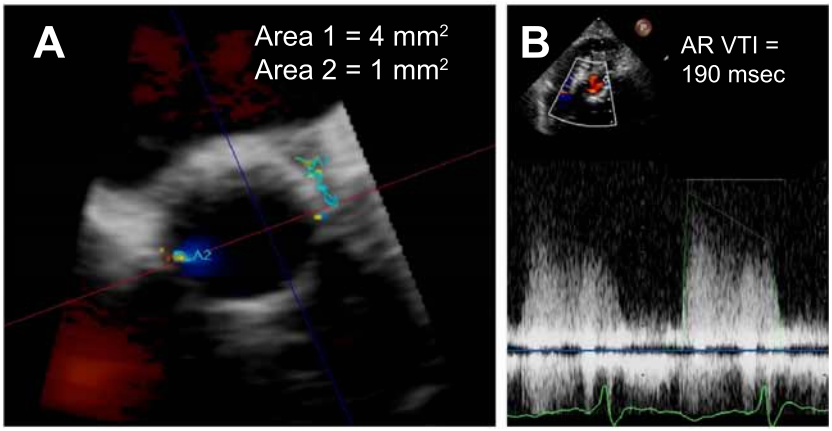

Figure 4 **Three-dimensional echocardiography can be used to quantitate the regurgitant orifice and volume**

(A) Multiplanar reconstruction of a 3-dimensional color Doppler volume set, aligned in the short-axis view of the LVOT just below the THV stent. The planimetered regurgitant orifices are 4 mm^2 and 1 mm^2, consistent with a total effective regurgitant orifice area (EROA) of 5 mm^2. ***(B)*** Aortic regurgitant continuous wave spectral Doppler with AR VTI of 190 ms. The regurgitant volume = EROA X AR VTI = 10 ml (same patient as in Figure 3). AR = aortic regurgitation; PG = pressure gradient

TREATMENT FOR SIGNIFICANT PARAVALVULAR LEAK

Improved positioning of the TAVR could require advanced imaging techniques for angiographic planning; having the best coplanar view will ensure accurate fluoroscopic localization of the valve before implantation. In addition, simultaneous "real-time" imaging, such as echocardiogram (both 2D and 3D), 3D angiographic reconstruction via rotational aortic root angiogram,[67] and the use of novel imaging systems,[68, 69] may assist in choosing intraprocedurally the optimal projection for THV positioning and deployment, leading potentially to less frequent PVL.

Intraprocedurally, several interventional alternatives to reduce regurgitation are available.[70] Severe calcification of the native valve might prevent the implanted valve from expanding completely against the annulus, leaving residual orifices through which PVL may occur. Post-implantation balloon dilation of the valve might be effective in reducing PVL and may be considered the initial option for patients with PVL.[71] A slightly oversized balloon is recommended to fully expand the valve. Studies have shown that post-dilation can be safely performed, with a reduction of the regurgitation in a majority of patients.[38] Calcification of the valve significantly influences the success of this intervention. However, in some patients, post-dilation has no effect in reducing AR;[15] in addition, post-dilation has been shown to be associated with a higher incidence of cerebrovascular events.[38] The effect of post-dilation on survival has yet to be determined.

Especially with the CoreValve, implantation of the valve that is too low is associated with PVL. Repositioning to a higher implantation depth could therefore reduce PVL. However, no retrievable valve is currently available on the market. Therefore, a snaring maneuver has been described, in which the valve is pulled up by attaching a snare to one of the frame loops.[72, 73] Although successful cases have been reported,[74] the valve may also move to the original (too low) position as soon as tension is released.[70] An extra word of caution is warranted when the snaring technique is considered in patients with extensively calcified valves because chunks of calcium may detach as a result of friction. Furthermore, there is a risk of damaging the ascending aorta during the snaring maneuver.

A valve-in-valve procedure may be necessary in some cases in which post-dilation or other techniques do not improve the degree of PVL. This is specifically indicated for patients in whom the valve was suboptimally positioned (i.e., too shallow or too deep). In the Italian registry, a valve-in-valve procedure was used in 3.6% of 663 patients.[75] Compared with patients who were implanted with a single valve, those who underwent valve-in-valve had similar safety and efficacy over a 1-year follow-up. Encouraging results have been reported from other series as well.[76]

As a final option for patients with continued severe PVL in whom interventional therapy does not suffice, conversion to conventional SAVR may be needed.[77] SAVR may be undesirable because these patients are generally at high or extreme risk, but the procedure may be unavoidable in some cases.

EMERGING TAVR TECHNOLOGIES

Currently, there is no proven or generally accepted treatment for PVL. However, there are emerging THV systems and technologies that are promising in minimizing PVL after TAVR (Fig. 5). These devices may reduce PVL by better supra-, infra-, or intra-annular sealing (cuff) or by allowing controlled deployment, repositioning, or removal of the THV. Preimplantation calcification debulking (surgically or not) also remains one of the most interesting areas of development to ensure adequate THV expansion and annulus sealing.

LIMITATIONS OF THE CURRENT LITERATURE

Many limitations of the current literature should be acknowledged. Although some studies have used echocardiography, others have used angiography to assess PVL immediately after THV implantation, making comparison between studies difficult. Most of the studies have used site self-reported PVL severity and lack independent adjudication of clinical events. Although the PARTNER trial had the advantage of a central echocardiography core

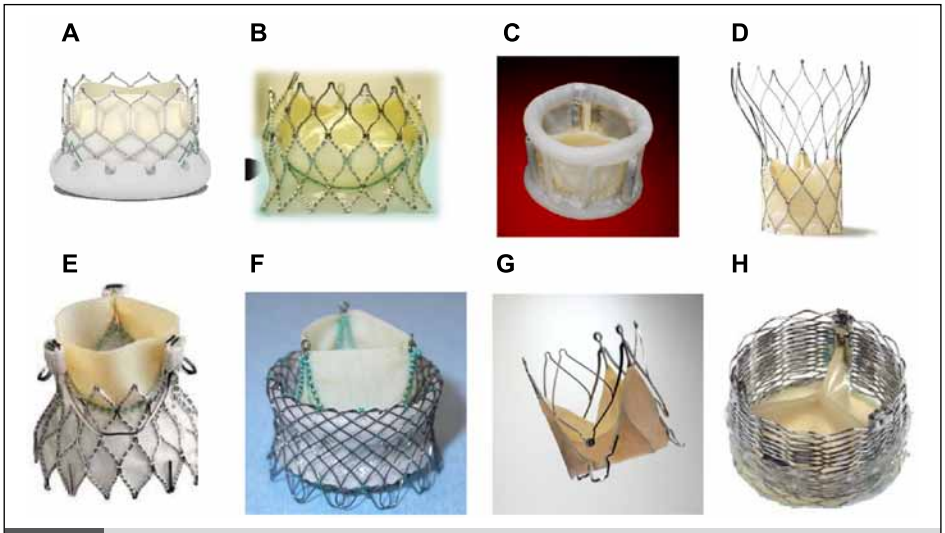

Figure 5 **Emerging TAVR devices involving improved technologies, potentially minimizing paravalvular leak after TAVR**

(A) SAPIEN 3 (Edwards Lifesciences, Irvine, California). ***(B)*** CENTERA (Edwards Lifesciences). ***(C)*** Direct Flow Medical (Direct Flow Medical, Santa Rosa, California). ***(D)*** Portico (St. Jude Medical, St. Paul, Minnesota). ***(E)*** Engager (Medtronic, Minneapolis, Minnesota). ***(F)*** Heart Leaflet Technologies (Heart Leaflet Technologies, Maple Grove, Minnesota). ***(G)*** JenaValve (JenaValve Technology, Munich, Germany). ***(H)*** Sadra Lotus Medical (Boston Scientific SciMed Inc., Maple Grove, Minnesota).

laboratory and adjudication of clinical events, we are still waiting for in-depth analysis of the outcomes associated with PVL. Baseline characteristics of patients with no/trace PVL may be different than those with mild to severe PVL and may explain the difference in mortality and the absence of PVL as a predictor for mortality in several reported multivariable analyses. Finally, better criteria to establish PVL severity are needed to ensure appropriate classification and uniformity among studies.

CONCLUSIONS

The association of PVL after TAVR with mortality has made it the new "in vogue" Achilles' heel of TAVR. Although post-procedural moderate to severe PVL can understandably be a predictor of a worse outcome, the association with mild PVL may be debatable. Given the limitations of the current literature, the nature and strength of the relationship between PVL and mortality are still to be determined. Future studies should standardize the evaluation of PVL and ensure an appropriate classification of its severity. Upcoming THV systems should be designed to minimize PVL, and emerging technology, such as noninvasive calcification debulking of the aortic valvular complex, brings promises of lower PVL rates after TAVR, potentially as low as those after SAVR.

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New York

Chapter 14

Transcatheter aortic valve implantation 10-year anniversary: review of current evidence and clinical implications

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ABSTRACT

Surgical aortic valve replacement (SAVR) is currently the standard of care to treat patients with severe symptomatic aortic stenosis (AS) and is generally accepted to alleviate symptoms and prolong survival. Based on the results of randomized trials, transcatheter aortic valve implantation (TAVI) is the new standard of care for patients with symptomatic AS who are deemed 'inoperable'. Debatably, TAVI is also an alternative to SAVR in selected patients who are at high risk but operable. As we approach 10 years of clinical experience with TAVI, with over 50 000 implantations in 40 countries, a review of the current literature and clinical outcomes with this rapidly evolving technology is appropriate.

INTRODUCTION

Symptomatic severe aortic stenosis (AS) has a poor prognosis when treated medically and inevitably leads to functional deterioration, heart failure, and death.[1] Surgical aortic valve replacement (SAVR) is currently the standard of care and is generally accepted to alleviate symptoms and prolong survival, but ~30% do not undergo SAVR.[2] However, since Dr Alain Cribier pioneered the first transcatheter aortic valve implantation (TAVI) procedure in 2002,[3] this relatively new technique has been used extensively in over 40 countries accumulating to >50 000 implantations.[4-19] With results from the randomized Placement of AoRTic TraNscathetER Valves (PARTNER) trial,[20] TAVI is now the standard of care for extremely high risk or 'inoperable' patients and is a valid alternative to surgery for selected high-risk but 'operable' patients with symptomatic AS.[21] Currently, two different TAVI devices are widely used: the balloon-expandable Edwards SAPIEN Transcatheter Heart Valve (Edwards Lifesciences, Irvine, CA, USA) and the self-expanding Medtronic CoreValve™ (Medtronic, Minneapolis, MN, USA) (Figure 1). Both devices received CE Mark approval for European commercial sale in 2007, and the Edwards SAPIEN valve received FDA pre-market approval in the USA in November 2011. As we approach 10 years of clinical experience with TAVI, a review of the current literature and clinical outcomes is appropriate.

INITIAL EXPERIENCE

First-in-man, initial reports, and feasibility studies

Cribier and co-workers [3] performed the first TAVI in an inoperable patient in 2002 using a transeptal antegrade approach and a balloon-expandable aortic valve prosthesis, demonstrating the feasibility of percutaneous valve implantation. The antegrade approach was further explored,[22] coinciding with the first-in-man retrograde experience of a self-expanding prosthesis (CoreValve™).[23] Larger series quickly followed, with early experiences of small initiatives using both the balloon-expandable Cribier valve (Edwards Lifesciences Inc.) and the self-expandable CoreValve™ system.[9, 19] The devices showed a procedural success rate of ~80%.

After these single-centre experiences, several larger multicentre feasibility studies were initiated first in Europe and later in the USA.[6, 24–26] These studies showed that transapical (TA) and transfemoral (TF) TAVI in high-risk patients was feasible and could be performed with a high procedural success rate and a 30-day mortality of ~10–15% (Table 1).

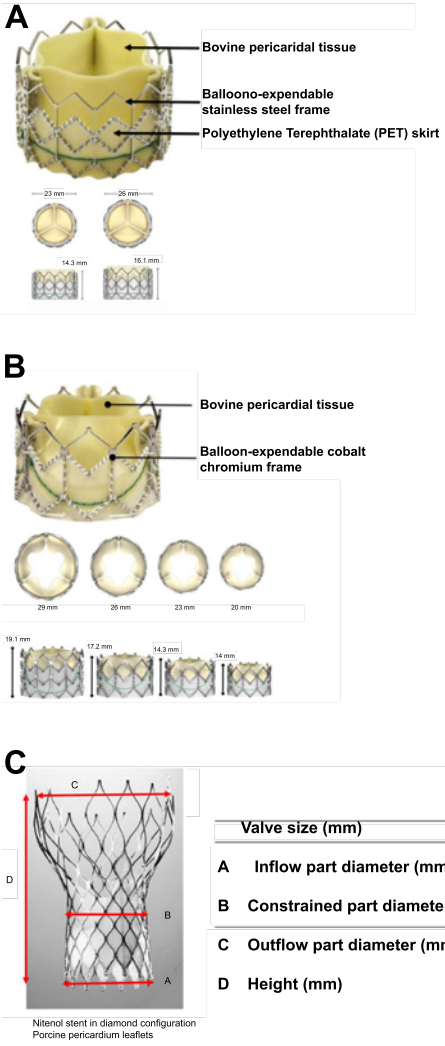

Figure 1 ***(A)*** **Edwards-SAPIEN transcatheter heart valve (Edwards Lifesciences)**
(B) **Edwards-SAPIEN XT transcatheter heart valve (Edwards Lifesciences)**
(C) **Medtronic CoreValve (Medtronic)**

REGISTRIES

Several large European and Canadian registries have been published, showing excellent short- and mid-term results after TAVI using both the TF and TA devices.[12,15] The largest registry reported to date is the SOURCE (SAPIEN Aortic Bioprosthesis European Outcome) registry.[17, 18] Overall, 1038 patients were enrolled at 32 European centres and were treated with either a TF (n = 463) or TA approach (n = 575). Patients treated by TA had more co-morbidities

Table 1 Multicenter feasibility studies

Study	Enrollment	Number of patients	Approach	Device	Procedural success	30-day mortality
I-REVIVE/RECAST	2003-2005	26	Transseptal	Edwards SAPIEN	85% (22/26)	16.7% (6/36)
		7	TF	Edwards SAPIEN	57% (4/7)	
Grube et al.	2005-2007	86	TF	CoreValve	74% (64/86)	11.6% (10/86)
TRAVERCE	2006-2008	168	TA	Edwards SAPIEN	95.8% (161/168)	14.9% (25/168)
REVIVAL	2006-2008	40	TA	Edwards SAPIEN	100% (40/40)	12.5% (7/40)
	2005-2006	55	TF	Edwards SAPIEN	87% (48/55)	7.3% (4/55)

TA = transapical; TF = transfemoral

at baseline than TF patients, resulting in a significantly higher EuroSCORE (European System for Cardiac Operative Risk Evaluation) (29.1 vs. 25.7%; $P < 0.001$). Procedural success was 95.2 and 92.7% and 30-day mortality was 6.3 and 10.3% in the TF and TA populations, respectively. The major limitations of this registry were that >70% of the enrolling centres had no prior experience with TAVI and all adverse events were site-reported without core lab analysis. In early 2011, 1-year results were published, demonstrating a 1-year survival of 76.1% overall, 72.1% for TA and 81.1% for TF patients. Among the surviving patients, 73.5% were New York Class Association (NYHA) class I or II.[17]

A number of large dedicated CoreValve registries have been reported; generally, these have been somewhat larger than Edwards registries.[14, 16] Promising 3-year results were recently reported by Ussia et al. [27] and although not yet published, the results of the ADVANCE CoreValve™ registry were presented recently.[28] ADVANCE represents a 100% monitored 'real-world' experience, with a core laboratory and an independent clinical events committee adjudicating events. The registry included 1015 patients from 44 experienced (>40 prior procedures) centres between March 2010 and July 2011. The mean logistic EuroSCORE was 19.2%. At 30 days and 6 months, the rate of all-cause mortality was 4.5 and 12.8%, respectively, with cardiac mortality of 3.4 and 8.4%, respectively. ADVANCE provides insights into contemporary TAVI data of experienced operators, and is a benchmark for comparing outcomes.

In 2011, results from four mixed CoreValve™ and Edwards European national registries have been reported, mostly using the TF and TA routes (Table 2).[4, 8, 29, 30] Overall, patients included in these registries were at high-risk according to surgical risk models; mean EuroSCORE 18–30%. These registries showed 1-year survival rates ranging between 71.9 and 81.6%. The UK registry reported the longest follow-up; survival was 73.7% at 2 years.[30] Several of these national initiatives performed access-route comparisons and reported that survival was generally higher in patients treated through the TF route.[4, 30] However, it should be noted that a transfemoral-first approach is often advocated, which may introduce selection bias and an unfair comparison between the two access routes.[31] Recently, the largest registry to date was reported by the FRANCE 2 (FRench Aortic National CoreValve

Table 2 Clinical outcomes after TAVI according to access site and device type

Authors	Type of study	Number of patients	STS	Logistic EuroScore	Follow-up	Procedural success rate	Mortality 30-day	Mortality 1-year	Major access complications 30-day	Stroke 30-day	Need for new PPM
Edwards SAPIEN: TF											
Lefevre et al.	Registry	61	11.3%	25.7%	12 months	95.4%	8.2%	21.3%	16.4%	3.3%	1.8%
Eltchaninoff et al.	Registry	95	17.4%	25.6%	1 month	98.3%*	8.4%	-	6.3%	4.2%	5.3%
Himbert et al.	Registry	51	15.0%	25.0%	12 months	90.0%	8.0%†	19.0%	12.0%	6.0%	6.0%
Rodes-Cabau et al.	Registry	162	9.0%	-	24 months	90.5%	9.5%	25.0%	13.1%	3.0%	3.6%
Thomas et al.	Registry	463	-	14.5%	1 month	95.2%	6.3%	18.9%	22.9%	2.4%	6.7%
Leon et al.	RCT	179	11.2%	26.4%	12 months	-	5.0%‖	30.7%‖	16.2%	6.7%¶	3.4%
Bosmans et al.	Registry	99	-	29.0%	12 months	97.0%	6.0%	18.0%	-	2.0%	4.0%
Smith et al.	RCT	244	11.7%	29.1%	12 months	-	3.3%‖	22.2%‖	14.0%	3.7%¶	3.7%
Edwards SAPIEN: TA											
Walther et al.	Feasibility study	168	-	27.0%	12 months	95.8%	15.0%	37.0%	1.2%	2.0%	2.3%
Svensson et al.	Feasibility study	40	13.4%	35.5%	6 months	87.5%	17.5%	-	-	5.0%	-
Lefevre et al.	Registry	69	11.3%	33.8%	12 months	96.4%	18.8%	50.7%	5.8%§	1.5%	3.8%
Eltchaninoff et al.	Registry	71	18.4%	26.8%	1 month	98.3%*	16.9%	-	5.6%**	2.8%	5.6%
Himbert et al.	Registry	24	18.0%	28.0%	12 months	100%	16.0%†	26.0%	8.0%	0%	4.0%
Rodes-Cabau et al.	Registry	177	10.5%	-	1 month	96.1%	11.3%	22.0%	13.0%**	1.7%	6.2%
Thomas et al.	Registry	575	-	16.3%	1 month	95.7%	10.3%	27.9%	4.7%	2.6%	7.3%
Bosmans et al.	Registry	88	-	33.0%	12 months	97.0%	14.0%	37.0%	-	8.0%	6.0%

Table 2 *Continued*

Authors	Type of study	Number of patients	STS	Logistic EuroScore	Follow-up	Procedural success rate	Mortality 30-day	Mortality 1-year	Major access complications 30-day	Stroke 30-day	Need for new PPM
Smith et al.	RCT	104	11.8%	29.8%	12 months	-	3.8%||	29.0%||	3.8%	6.8%	3.9%
D'Onofrio et al.	Registry	504	11.0%	26.3%	24 months	99.0%	8.3%	18.8%	-	3.0%	5.4%
Medtronic CoreValve™: TF											
Tamburino et al.	Registry	663	-	23.0%	12 months	98.0%	5.4%	15.0%	2.0%	2.5%ξξ	17.4%
Bosmans et al.	Registry	133	-	25.0%	12 months	98.0%	11.0%	22.0%	-	4.0%	22.0%
Grube et al.	Registry	86	-	21.6%	1 month	88.0%	12.0%	-	-	10.0%	-
Piazza et al.	Registry	646	-	23.1%	1 month	97.2%	8.0%	-	1.9%	1.9%	9.3%
Eltchaninoff et al.	Registry	66	21.3%	24.7%	1 month	98.3%*	15.1%	-	7.5%	4.5%	25.7%
Petronio et al.	Registry	460	-	19.4%	6 months	98.4%	6.1%	11.4%	2.0%	1.7%	16.1%
Buellesfeld et al.	Registry	126x	-	23.0%	24 months	72.6%	15.2%	28.1%	-	9.6%	26.2%
Medtronic CoreValve™: SC											
Eltchaninoff et al.	Registry	12	21.0%	24.6%	1 month	98.3%*	8.3%	-	8.3%	0%	25.0%
Bosmans et al.	Registry	8	-	25.0%	12 months	98.0%	11.0%	0%	-	4.0%	22.0%
Petronio et al.	Registry	54	-	25.3%	6 months	100%	0%	6.7%	0%	1.9%	18.5%
Zahn et al. ††	Registry	697	-	20.5%	1 month	98.4%	12.4%	-	19.5%	2.8%	39.3%‡‡

PPM = Permanent pacemaker; RCT = randomized controlled trial; SC = subclavian; STS = Society of Thoracic Surgeons; TA = transapical; TAVI = transcatheter aortic valve implantation; TF = transfemoral. * Global procedural success rate including Edwards SAPIEN TF, Edwards SAPIEN TA and Medtronic CoreValve TF and subclavian was 98.3%; † In-hospital mortality; || Intention-to-treat mortality rate; ¶ Major and minor stroke; § Vascular-related complications; ** Apex-related complications; †† Outcomes reported together: 566 (81.2%) Medtronic CoreValve™ TF, 22 (3.2%) Medtronic CoreValve™ SC, 106 (15.2%), Edwards SAPIEN TF; ‡‡ Medtronic CoreValve™ 42.5%, Edwards SAPIEN 22%; x 124 patients received a TF approach and 2 an SC approach; xx 1-year

and Edwards) investigators.[32] They included 3195 patients treated between January 2010 and December 2011 at 34 centres. The registry reflects contemporary real-life use of available TAVI devices in patients at high surgical risk; the Edwards SAPIEN and the Medtronic CoreValve devices were used in, respectively, 66.9 and 33.1%. The transfemoral approach was most popular (74.6%), followed by transapical (17.8%) and subclavian (5.8%), while 1.8% underwent some other approach. The procedural success rate was 96.9% and 1-year survival in patients was 76.0%.

RANDOMIZED TRIALS

Completed trials

While registry reports are of crucial value to assess 'real-world' use of TAVI, more rigorous assessments are available from the first multicentre, randomized clinical PARTNER trials (Placement of Aortic Transcatheter Valves; ClinicalTrials.gov Identifier: NCT00530894) (Figure 2).[20, 21]

As the first of two parallel trials was completed, the results of PARTNER IB showed that TF TAVI was superior to standard therapy in patients not deemed candidates for surgery.[20] The primary endpoint of all-cause mortality was markedly reduced by 46% ($P < 0.001$). Recently reported 2-year outcomes showed continued encouraging results (Figure 3A).[33] At 2 years, the primary endpoint of all-cause mortality was reduced from 67.6% in the standard treatment arm to 43.3% in the TAVI arm ($P < 0.001$).

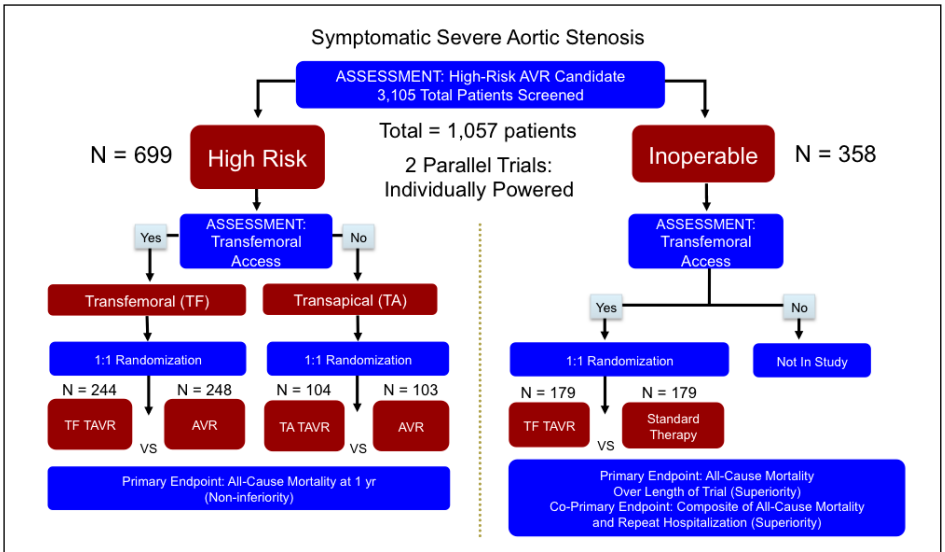

Figure 2 **PARTNER trial design**

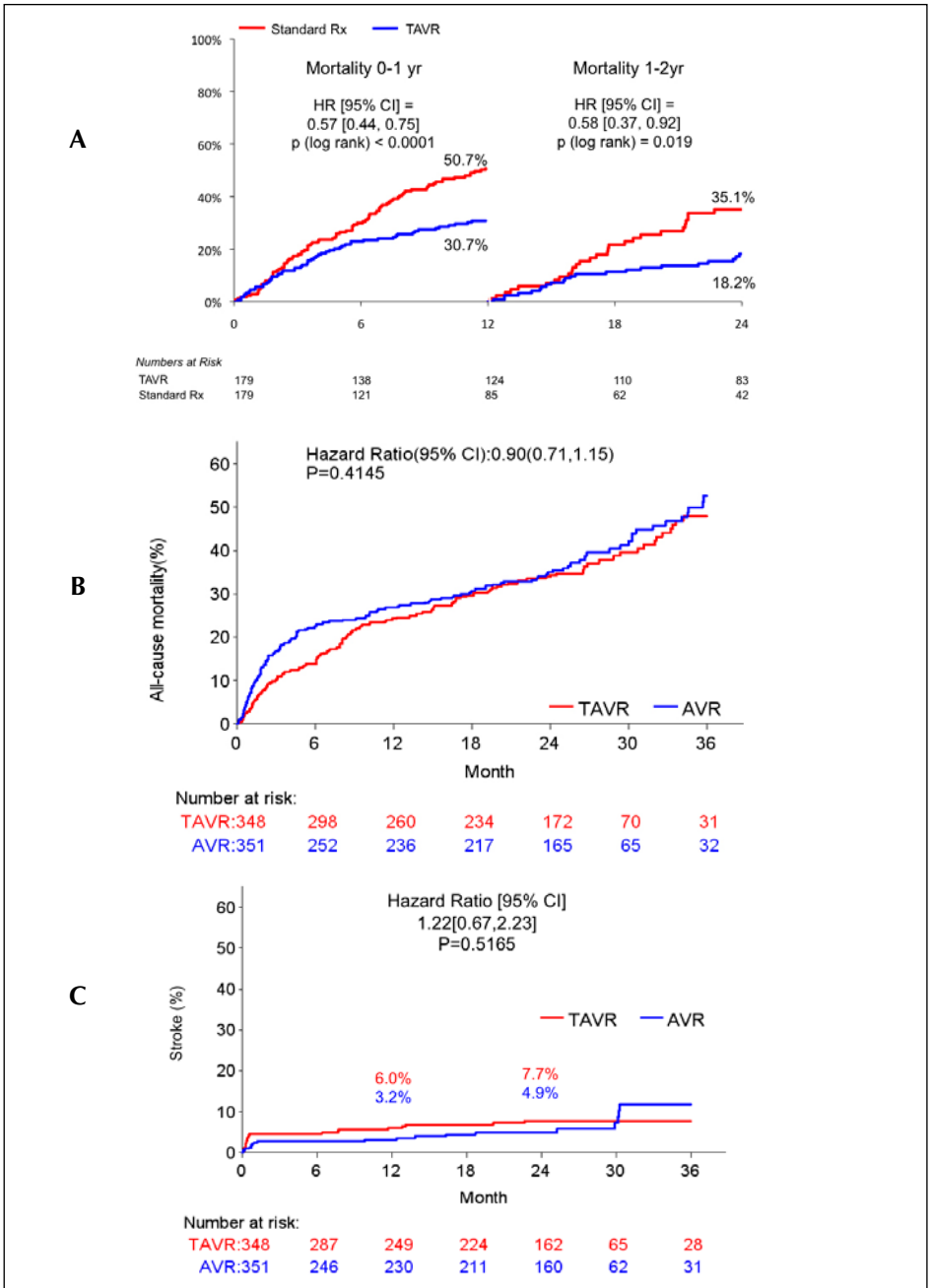

Figure 3 **Two-year outcomes of the PARTNER trial**

(A) Two-year with 1-year landmark analysis of all-cause mortality in the PARTNER 1B cohort. Reprinted with permission from Leon and colleagues[22] and Makkar and colleagues.[33] (B) Two-year all-cause mortality in the PARTNER 1A cohort. Adapted with permission from Kodali and colleagues.[34] (C) Two-year stroke in the PARTNER 1A cohort. Adapted with permission from Kodali and colleagues.[34]

The PARTNER cohort IA compared TAVI with SAVR and met its non-inferiority endpoint: the all-cause 1-year mortality in the TAVI group was non-inferior to the SAVR group (24.2 vs. 26.8%; $P = 0.44$; $P = 0.001$ for non-inferiority).[21]

Some concerns were raised with regard to neurologic events that were somewhat higher with TAVI than SAVR at 30 days (5.5 vs. 2.4%; $P = 0.04$) and 1 year (8.3 vs. 4.3%; $P = 0.04$). Although the recently published 2-year results showed that stroke rates were similar for TAVI and SAVR during 1 and 2 years with a hazard ratio of 1.22 (95% CI 0.67–2.23, $P = 0.52$), the issue of stroke warrants further investigation and should not be underestimated (Figure 3B and C).[34] The rate of the composite of all-cause death and stroke was encouragingly nearly identical after TAVI (37.1%) and SAVR (36.4%) at 2 years ($P = 0.85$).

Ongoing trials

In the USA, a randomized trial is currently ongoing to evaluate the safety and efficacy of the Medtronic CoreValve™ in the treatment of severe symptomatic AS in patients at high or extreme risk for SAVR (ClinicalTrials.gov Identifier: NCT01240902). The trial consists of two arms. Patients in a high-risk arm will be randomized between SAVR and TAVI; the primary endpoint consists of all-cause mortality at 1 year. An extreme risk arm will function as an observational arm in which a composite of all-cause mortality and major stroke is the primary endpoint.

As a sequel to the PARTNER I trial, a second randomized trial (PARTNER II) is currently ongoing. It was designed to investigate the performance and outcomes after TAVI with the next-generation Edwards SAPIEN XT valve, model 9300TFX, as well as the new low-profile 18-Fr NovaFlex™ delivery catheter in patients deemed non-operable (ClinicalTrials.gov Identifier:NCT01314313) (Figure 4A). Given the results of the control arm in PARTNER IB, it has been judged that a study comparing TAVI against a 'medical management' control group is no longer ethical.[35] Consequently, an 'old device' vs. 'new device' non-inferiority trial was designed. Enrolment began in January 2011 and it is anticipated that primary endpoint results will be published mid-2013.

In Denmark, a phase 2 randomized trial evaluating TAVI in patients ≥70 years of age started enrolment in December 2009 (ClinicalTrials.goc identifier: NCT01057173). The trial will randomize a total of 280 patients to TAVI ($n = 140$) and SAVR ($n = 140$). The primary endpoint is the composite of all-cause death, myocardial infarction, and stroke at 1 year and is scheduled to be completed late 2013.

In an attempt to expand the indication of TAVI to lower-risk patients, the PARTNER IIA trial will be randomizing patients between TAVI with the SAPIEN XT valve and SAVR in intermediate risk patients (ClinicalTrials.gov Identifier: NCT01314313) (Figure 4A). Similarly, the prospective randomized, international SURTAVI trial will randomize 1900 intermediate risk patients between TAVI with the Medtronic CoreValve™ and SAVR at ~80 centres throughout the USA, Canada, Europe, and Australia (ClinicalTrials.gov Identifier: NCT01586910) (Figure 4B).

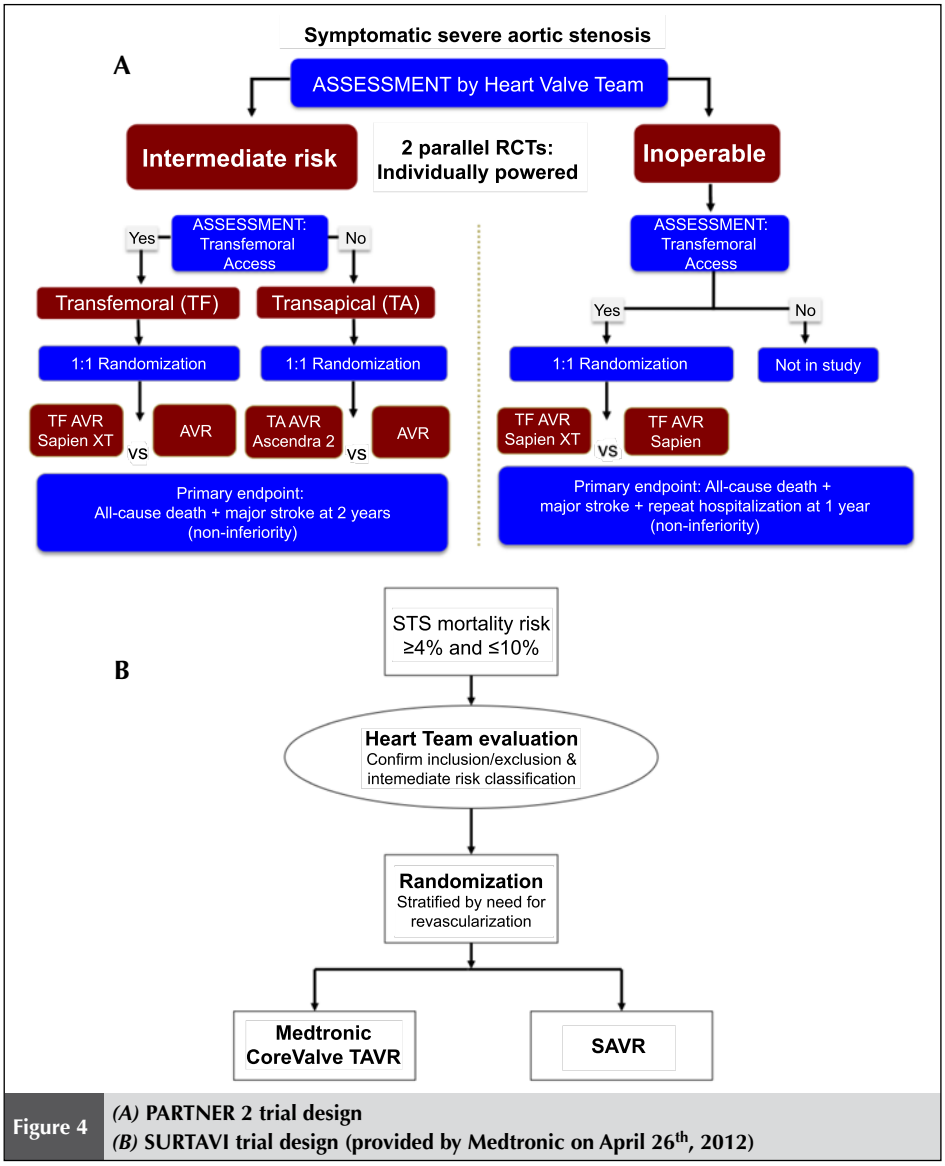

Figure 4 ***(A)*** **PARTNER 2 trial design**
(B) **SURTAVI trial design (provided by Medtronic on April 26th, 2012)**

COST-EFFECTIVENESS

Since TAVI has been shown to be superior to standard medical therapy and non-inferior to SAVR and is increasingly being used in current practice, the incremental costs and cost-effectiveness of this therapy warrant evaluation.

In the PARTNER IB trial, the mean cost for TF TAVI was $42 806 which accumulated to $78 542 for the initial hospitalization and $106 076 at 1 year.[36] Compared with medical therapy,

TAVI was ~$52 455 (95% CI, $40 635–$64 275) more expensive at 1 year, but quality of life was significantly better in patients who underwent TAVI. This resulted in an incremental cost-effectiveness ratio of $50 212 per life-year gained, and $61 889 per quality-adjusted life-year (QALY). The authors rightfully concluded that for patients not candidates for surgery in the USA, TAVI increases (quality-adjusted) life-years at reasonable costs similar to other cardiovascular technologies.

In the PARTNER IA trial, similar costs were found in TF patients as compared with the PARTNER IB trial; $71 955 for the index hospitalization and $94 206 at 1 year, which was comparable to patients who underwent SAVR ($74 452 and $96 417, respectively). However, there was only a minor gain in the number of life-years (0.065: 95% CI, 0.011–0.125) and QALYs (0.068: 95% CI, 0.017–0.123) in comparison with SAVR. Through bootstrap analysis it was concluded that TF TAVI cost was <$50 000 per QALY in 74.7% of times, clearly demonstrating cost-effectiveness in the USA. Patients who could not undergo TF due to anticipated vascular and/or bleeding complications were randomized between TA TAVI (n = 101) and SAVR (n = 91).

The index hospitalization was more expensive in the TA group, although not significantly so ($90 548 vs. $79 540, P = 0.08). At 1-year follow-up, costs accumulated to a mean of $107 779 for TA and $98 183 for SAVR, with a small detriment in life-years (–0.015: 95% CI, –0.103–0.080) and QALYs (–0.070: 95% CI, –0.151–0.012). Therefore, TA TAVI was found to be a less attractive alternative to SAVR, although this conclusion has been somewhat criticized because the analysis was not powered and operators were little experienced.[31]

ALTERNATIVE ACCESS SITES

Like the TA approach, a subclavian approach allows patients with unfavourable iliofemoral anatomy or extensive disease to be treated with TAVI. Petronio et al.[13] recently reported a series of 54 patients, showing a procedural success rate of 100%, a procedural mortality of 0, a 30-day mortality of 0%, and 6-month mortality of 9.4%. No specific vascular complications for subclavian access were reported. The subclavian approach is usually performed with the self-expanding CoreValve™ system and can be fully percutaneous.[37]

Recently, a transaortic approach with direct access to the ascending aorta though an anterior minithoracotomy has been advocated. Access is gained through a J-shaped partial upper sternotomy or using a small right thoracotomy through the intercostal space. Avoidance of LV apical injury or inadequate healing along with reduction in post-operative pain and its associated impairment of respiratory dynamics are potential advantages of this novel approach. Encouraging results have been published from small series using both devices.[38, 39] It may be suitable for patients with unfavourable iliofemoral and subclavian anatomy and

in whom a TA approach is considered too risky (chest deformity, severe respiratory disease or low ejection fraction). Also, TAVI via the carotid artery has been proposed. In such cases, it is crucial to evaluate the cerebral arteries, carotid and vertebral arteries, and circle of Willis, to assess the risk of ischaemic stroke.[40]

VALVE-IN-VALVE FOR FAILING BIOPROSTHESES

Since 2007, when the first TAVI was implanted in a failing surgical aortic bioprosthesis in order to avoid redo surgery, interest in this concept has grown and feasibility and safety have been established.[41, 42] Piazza and colleagues [43] published a series of 20 patients (mostly TA: 16/20) and reported successful implantation in 18 of 20 patients and in-hospital mortality in 3 patients. Indeed, transcatheter heart valves have also been implanted in failing mitral prostheses or even annuloplasty rings, and failing tricuspid prostheses, expanding the potential use of devices originally developed for the aortic position.[44, 45]

Knowledge of the basic construction, dimensions, and potential failure modes of the surgical bioprostheses is of paramount importance for this technique to succeed. Various complications such as coronary obstruction and device embolization may be implicated with certain surgical bioprostheses but not others.[46] Also, small surgical bioprostheses (e.g. 19 mm) may not respond well to valve-in-valve implantation because of device constraint within the rigid bioprosthesis and incomplete stent expansion, frequently leading to prosthesis–patient mismatch.[47, 48]

The presence of a functioning mitral prosthesis may further complicate device delivery, although a recent report has shown that optimal valve positioning through a TA approach should be technically achievable with modifications of the 'classic' procedure.[49]

EFFICACY AND LONG-TERM OUTCOMES

Symptom improvement

Improvement in cardiac symptoms and functional class has been reported at short- and medium-term after TAVI.[14, 18, 20, 21, 50] However, functional assessment of the population currently eligible for and treated with TAVI is difficult, mainly because of their multiple co-morbidities.[51]

Three-year follow-up data have been published and are consistent with lasting improvement in cardiac symptoms.[52] While 86% of patients were in NYHA class III or IV at baseline, 93% of surviving patients were in NYHA class I/II at 3-year follow-up. Similarly, the PARTNER trial showed that patients treated with TAVI compared with patients treated with standard medical therapy have better symptom control at 1 year.[20] Indeed, the 1-year rate of

NYHA class III or IV was 25.2% for the TAVI group compared with 58.0% for the standard medical therapy group ($P < 0.001$).

Valve durability and haemodynamic performance

TAVI has demonstrated excellent immediate and short-term durability of the prosthesis that is comparable to SAVR, sustaining to 3 years.[14, 15, 18, 20, 27, 34, 52] Actually, data suggest that transcatheter heart valves have greater valve areas and lower gradients than surgical bioprostheses (Figure 5),[34, 53] which could reduce the prevalence of prosthesis–patient mismatch.[54] For both the Edwards SAPIEN and Medtronic CoreValve™ there was no evidence of structural or non-structural valvular deterioration, stent fracture, deformation, or valve migration.

Predictors

As emphasized throughout the manuscript, many of the listed complications are predictors of short-term and/or long-term mortality. As current randomized trials are moving towards evaluating TAVI in a lower-risk patient population (SURTAVI, PARTNER 2) with a longer life expectancy, prediction of mid- and long-term outcomes (≥1 year) will become increasingly important. Some predictors should be similar to the surgical literature, but the mounting TAVI experience has shown that the incidence and ratio may vary significantly between the two therapies. For example, paravalvular leakage is more common after TAVI than after SAVR and has been identified as a potential significant predictor for long-term mortality.[34]

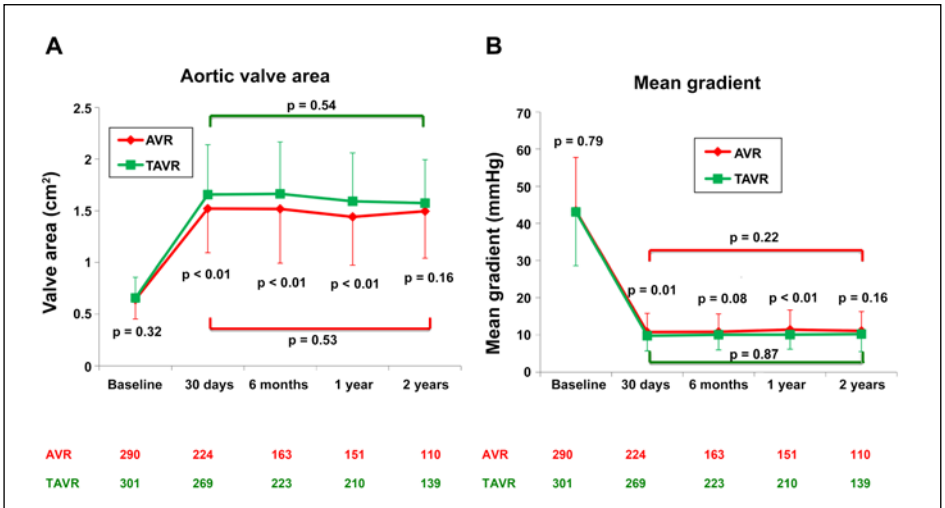

Figure 5 **Two-year time trends in haemodynamics after TAVI versus SAVR**

Adapted with permission from Kodali and colleagues.[34]

Table 3	Independent predictors of long-term mortality after TAVI
Advanced age	
Smoking	
Logistic EuroSCORE	
STS score	
Calcium score	
Baseline renal failure	
Baseline anaemia	
Pulmonary hypertension	
Chronic obstructive pulmonary disease	
Liver disease	
Prior stroke	
Post-procedural paravalvular leak ≥2+	
Myocardial injury	
Systematic inflammatory response syndrome	
Major vascular complication	
Acute kidney injury	
Early experience with TAVI	

STS = Society of Thoracic Surgeons; TAVI = transcatheter aortic valve implantation

Table 3 provides a summary of independent predictors of mortality that have been identified in previous studies. Due to the relative infancy of TAVI and the lack of large databases for SAVR,[55] it is likely that additional predictors will come to light over the years. Furthermore, accurate hazard ratios of predictors cannot be given at the current time, due to the severe heterogeneity between studies.

LESSONS LEARNED

Patient selection

One of the critical aspects of TAVI we have learned so far is that patient selection is crucial but cumbersome due to inaccuracy of current risk models to predict outcomes in high-risk patients.[56] Several variables that have shown to be predictive are not included, such as frailty, liver disease, and the presence of a porcelain aorta. Decision making should therefore not be based exclusively on clinical risk scores. Instead, it is accepted that the heart team can better judge patient eligibility for TAVI or SAVR. Such a team is dynamic and can include general cardiologists, interventional cardiologists, surgeons, imaging specialists, neurologists, anaesthesiologists, geriatricians, and other specialists.[57, 58]

Besides the decision to treat by means of TAVI or SAVR, one must consider multiple access approaches. Frequently, a 'transfemoral-first' attitude is advocated and comprehensive

screening of the peripheral arteries and aorta by angiography or preferably by multislice CT-scan (MSCT), is necessary to assess feasibility.[59] MSCT also allows for evaluation of left ventricular dimensions and function, and other potential diseases (e.g. coronary artery disease), which can further help to contemplate feasibility, safety, and efficacy.

Sizing

Accurate preoperative annular sizing is one of the main predictors of a successful TAVI procedure. Several modalities have been proposed for accurate sizing. At first, trans-thoracic and/or trans-oesophageal echocardiography were used to decide which size valve would best be implanted to achieve procedural success with limited or no residual para-valvular aortic regurgitation. More recently, the use of three-dimensional and even four-dimensional MSCT has been shown to be most effective in sizing for TAVI.[60,61] In contrast to trans-esophageal echocardiography, it is non-invasive and has a high reproducibility.[62] Recent studies have shown that the area-derived diameter and basal ring average diameter of the annulus are the most suitable measurements for valve-sizing. Nevertheless, oversizing of

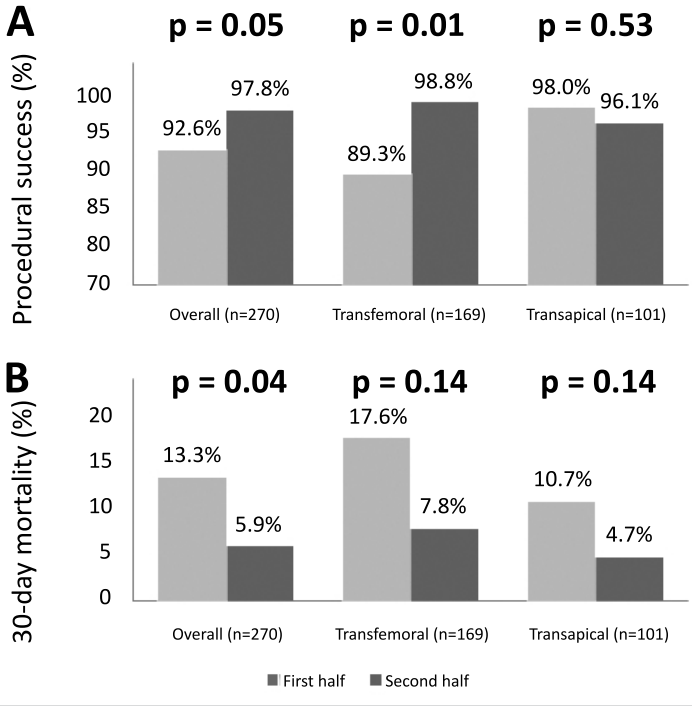

Figure 6 **Effect of learning curve on procedural success *(A)* and 30-day mortality *(B)* after TAVI**

Data from Gurvitch and colleagues.[63]

the transcatheter heart valve in relation to the annulus size remains necessary to obtain procedural success with limited aortic regurgitation.

Learning curve

Understanding the importance of patient selection, utilizing better anatomical screening to clarify both the aortic root and iliofemoral geometry, and the development of new devices have led to notable improvements in outcome over time. A report highlighting the importance of the learning curve in 270 patients showed that procedural experience was an independent predictor of 30-day survival.[63] Furthermore, the procedural success rate has significantly increased (Figure 6);[63, 64] the use of contrast volume use and radiation doses has decreased;[65] and procedural complications have declined.[66]

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Chapter 15

Transcatheter aortic valve implantation 10-year anniversary. Part II: clinical implications

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has been increasingly recognized as a curative treatment for severe aortic stenosis (AS). Despite important improvements in current device technology and implantation techniques, specific complications still remain and warrant consideration. Vascular complications and peri-procedural neurological events were the first concerns to emerge with this new technology. Recently, significant post procedural para-valvular leak has been shown to be more frequent after TAVI than after surgical aortic valve replacement (SAVR), and its potential association with worse long-term prognostic has raised concerns. In moving toward treatment of lower risk populations, structural integrity and long-term durability of heat valve prosthesis are becoming of central importance. Emerging technologies and newer generations of devices seem promising in dealing with these matters.

INTRODUCTION

First-generation devices for transcatheter aortic valve implantation (TAVI) were associated with specific complications. Although newer technologies, improved devices, and more appropriate patient selection and screening, paired with increased operators' experience have shown to reduce the occurrence of such complications, they still deserve special attention.

COMPLICATIONS

Stroke

Depending on the definition used, reported incidence of stroke in the current literature varies between 1.7 and 8.4%.[1-7] Neurological events may occur at different time-points during the procedure and may be related to several factors: manipulation of a wire and/or large-diameter catheter through the aortic arch, positioning of the device, performance of balloon aortic valvuloplasty, and inadequate blood flow to the brain during rapid pacing and device deployment.[8, 9] Moreover, the population currently undergoing TAVI consists of very elderly patients in whom the incidence of atrial fibrillation and atherosclerotic disease is high, increasing the risk of peri-procedural cerebrovascular events.[2, 10, 11] Although stroke clearly manifests in clinical symptoms, recent studies have shown 'silent' new cerebral ischaemia on diffusion-weighted magnetic resonance imaging in up to 70% of patients.[12-14] Although rarely associated with clinical events, the long-term consequences of these phenomena are unknown.

Initially it was anticipated that stroke associated with TAVI occurred during the procedure, but in-depth analysis of stroke demonstrated a continuous hazard extending beyond the early phase.[15] This hazard was thought to be higher after TAVI in comparison with surgical aortic valve replacement (SAVR). However, recent data showed that although the difference is significant in the first 30 days, the late hazard is similar between TAVI and SAVR.[16]

Predictors of early neurological events with TAVI included a prior neurological event, more severe atherosclerotic burden, and smaller valve area, although other variables predict the constant hazard phase over follow-up: more advanced functional disability, previous stroke, and transapical access.[15] The role of atrial fibrillation as a potential mechanism of stroke after TAVI has been emphasized in two recent reports, showing a four times increased risk of stroke.[17, 18] Further work is needed to determine the clinical significance of these findings. Several embolic protection devices are under investigation. Early reports are encouraging, and it is hoped that future use of these devices will lead to a decrease in silent and clinical neurological events after TAVI.[19]

Vascular complications

Vascular complications remain an important limitation of TAVI performed via TF access. The use of large-diameter catheters and the high-risk characteristics of the current treated population explain the high incidence. Small vessel diameter, severe atherosclerotic disease, bulky calcification, and tortuosity are the main determinants of vascular complications. The incidence of major vascular complications using the Edwards SAPIEN system (introducer sheath of 23 and 26 Fr, outer diameter of 8.38 and 9.14 mm) varies between 8.3 and 23% [2, 5, 7, 20, 21] and between 1.9 and 14% [3, 4, 21, 22] using the CoreValve™ system (18 Fr introducer sheath, outer diameter of 7 mm). However, the use of arbitrary definitions and difficulty in identifying and systematically reporting all vascular complications make interpretation of the current literature difficult.

Common vascular complications include arterial dissection, closure device failure, arterial closure device-induced stenosis, and haematoma at the puncture site. Artery avulsion ('artery on a stick'), vessel perforation leading to retroperitoneal haematoma, aortic dissection, annulus rupture, and left ventricular perforation represent more severe complications which are fatal if not rapidly recognized and treated. Although urgent surgical intervention may be necessary in the management of major vascular complications, innovative percutaneous techniques involving proximal balloon occlusion of the iliac arteries and/or endovascular stent deployment have been suggested as useful in preventing and treating some of these issues.[23-25]

An association between the occurrence of major vascular complications and survival has been demonstrated by several authors (Figure 1).[2, 5, 20, 21, 26] In the light of these data, it is crucial to reduce the rate of vascular complications. Improved experience and patient selection as well as exploring alternative access routes have shown to be effective.[27]

Bleeding complications

Bleeding rates have been reported without much consistency in the use of definitions. Using standardized endpoint definitions, life-threatening bleeding has been reported occurring in 15.6%, whereas any minor, major, or life-threatening bleeding occurred in >40% of patients.[28] At this rate, it is the most frequent complication post-TAVI, with 42.6% of patients requiring ≥1 unit of transfused blood. This, however, might be an overestimation of the true burden of TAVI; it has been reported that many patients receive blood transfusions although no obvious source of bleeding is present,[29] which may be the result of the high prevalence of baseline anaemia in this elderly cohort of patients.[30] In addition, no regulations exist on when to transfuse patients, and haemoglobin cut-off values as indication for transfusion may be very different between institutions.

Predictors of bleeding complications are similar to those for vascular complications, since both complications frequently occur in parallel. A recent study shows that patients who received ≥1 unit of blood had a significantly higher rate of in-hospital mortality (14.8

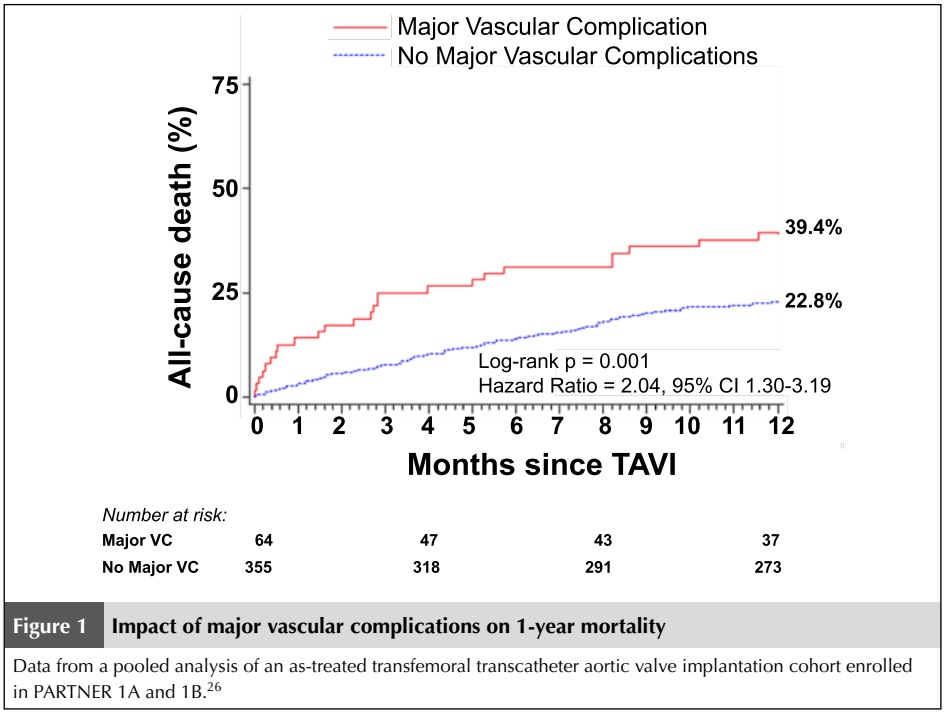

Figure 1 **Impact of major vascular complications on 1-year mortality**

Data from a pooled analysis of an as-treated transfemoral transcatheter aortic valve implantation cohort enrolled in PARTNER 1A and 1B.[26]

vs. 4.3%, *P*< 0.05) and a longer length of stay (17 ± 2 vs. 7 ± 1 days, *P*< 0.05). Those patients that received ≥3 units of blood had significantly lower 6-month survival, whereas those with 0–2 units had similar survival to patients without any transfusion.[31]

The use of newer generations of transcatheter heart valves and smaller delivery systems as well as increasing operator experience will likely reduce the rate of bleeding complications. The study by Gurvitch et al. [32] showed that, although not statistically significant, the rate of patients who received >4 units of packed red blood cells decreased from 11.1% in the first half of their experience to 5.9% in their last patients (*P*= 0.13).

Acute kidney injury

Several reports have focused on acute kidney injury (AKI), and significant injury [risk, injury, failure (RIFLE) ≥2] has been reported with an incidence of ~7–8%.[28] Many of these studies were consistent in identifying blood transfusions as a predictor of AKI, but other factors are associated as well: hypertension, chronic obstructive pulmonary disease, baseline renal function, previous myocardial infarction, and the logistic EuroSCORE.[33, 34]

Bagur et al. [34] reported on 213 patients who underwent TAVI. According to their definition (a decrease of >25% in eGFR at 48 h following the procedure, or the need of haemodialysis during index hospitalization), 11.7% (25 out of 213) of patients had AKI. Those patients

had significantly higher in-hospital mortality (28 vs. 7.4%, *P*= 0.005), and AKI was, even in multivariate analysis, a predictor of hospital mortality (OR= 4.14, 95% CI 1.42–12.13).

Long-term survival in patients with AKI has recently been reported by Nuis et al. [33] In their cohort of 118 patients, AKI as defined by the RIFLE criteria occurred in 18.6% (*n*= 22). At a median of 13 months of follow-up, AKI was the only independent predictor of late mortality (HR= 2.79, 95% CI 1.36–5.71).

Conduction disturbances

Multiple reports have been published on conduction disturbances post-TAVI.[35-37] It is generally accepted that the self-expandable CoreValve™ system, because of the higher and longer-lasting radial forces as well as the deeper implantation site in the left ventricle outflow tract, has a higher rate of pacemaker requirement than the Edwards SAPIEN system. A recent meta-analysis reported that ~28.9% (23–36%) of patients implanted with the CoreValve™ valve and 4.9% (4–6%) of patients implanted with the Edwards SAPIEN valve will require a new permanent pacemaker.[28] However, the rates reported in the literature have varied greatly. Variations in practice and threshold for pacemaker implantation among physicians may explain the discrepancy in new pacemaker insertion rates in current published series.

Persistent new left bundle branch block has been shown to be the most prevalent ECG finding post-TAVI, being present in up to 55 and 20% at 1 month after implantation of the CoreValve™ or Edwards SAPIEN valve, respectively.[37, 38] However, the long-term clinical significance of this finding is unknown.

Right bundle branch block, low implantation of the prosthesis, small annulus diameter compared with implanted valve size, complete atrio-ventricular (AV) block at the time of the procedure, and CoreValve™ device have been shown to be potential predictors of complete AV block post-TAVI.[39, 40] Given the variable timing of occurrence of high-degree AV block, continuous post-procedural ECG monitoring should be performed for at least 72 h in all patients at increased risk for this complication. Furthermore, recent data suggest that not only brady-arrhythmic events are important, but that the occurrence of new tachyarrhythmia, such as new-onset atrial fibrillation, also has a prognostic importance after TAVI.[17]

Paravalvular regurgitation

Significant transvalvular regurgitation is rare after TAVI. However, paravalvular regurgitation, due to incomplete annular sealing, is common. Some degree of paravalvular aortic regurgitation is reported in 80 to 96% of cases. In most cases, the degree of regurgitation is trivial or mild. Grade ≥2+ regurgitation is found in 7–24% of patients.[2, 41-44] Although no trial has directly compared the Edwards SAPIEN and CoreValve™ devices, the rates of regurgitation reported in the literature seem to be similar for the two devices.

Data from the PARTNER trial shows that significant paravalvular regurgitation ≥2+ is much more prevalent after TAVI than after SAVR (12 vs. 0.9%, *P*< 0.001).[6] During the

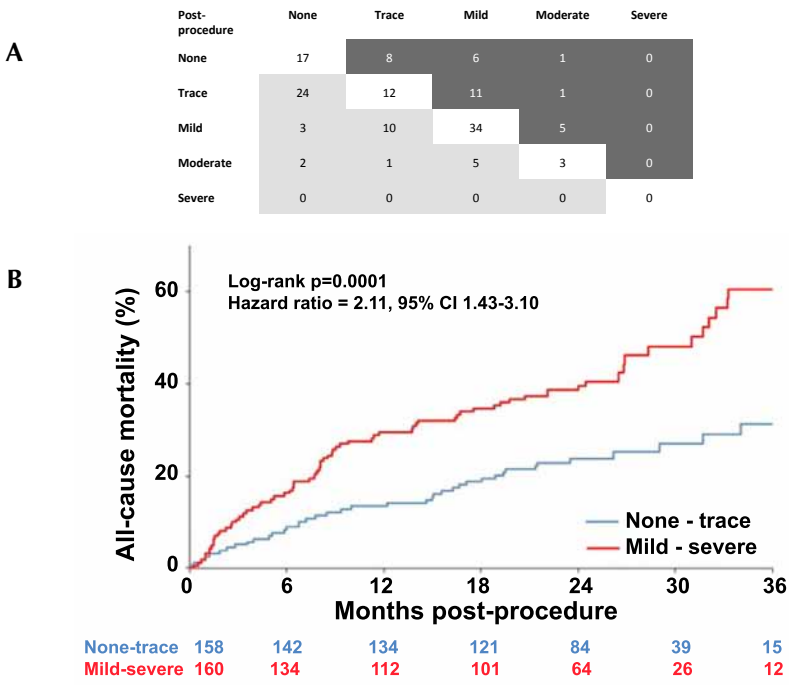

Figure 2 **Analysis of paravalvular leak in the PARTNER trial**

(A) Change in paravalvular leak severity over 2-year follow-up. (B) Impact of paravalvular leak on 2-year all-cause mortality. Adapted with permission from Kodali and colleagues.[16]

follow-up, regurgitation is more often reduced rather than worsening after TAVI (Figure 2A).[16, 43, 45] Nevertheless, its clinical importance has been emphasized in several reports where grade ≥2+ regurgitation has shown to be an independent predictor of short- and long-term mortality (Figure 2B).[16, 46-48]

Therefore, correction of significant regurgitation post-implantation is needed, especially when moving to younger and lower risk patients (e.g. PARTNER II and SURTAVI). Re-dilation or implantation of a second, overlapping transcatheter valve can often correct the problem. Also, low implantation of the CoreValve™ might be corrected by a snaring manoeuvre in which the valve is pulled to the correct position.[49]

Predictors of ≥1+ paravalvular leakage for the Edwards SAPIEN device have been found to be larger annulus size, height, male sex, age, and cover index ≤8% [cover index= 100 × (prosthesis diameter – TEE annulus size)/prosthesis diameter]. In a study, no aortic regurgitation (AR) of at least moderate degree was observed with a cover area >8%.[41] For the CoreValve™ system, greater angle of the left ventricular outflow tract is associated with an increased risk of significant regurgitation, whereas a depth of 10 mm of the device in relation to the non-coronary cusp is associated with a decreased likelihood of AR.[50]

Coronary obstruction and myocardial injury

Non-revascularized coronary artery disease is common in TAVI patients and, when severe, can increase procedural risk. In some patients, percutaneous revascularization may be desirable; however, clinical experience suggests that the majority of coronary disease in elderly patients can be managed conservatively.

Coronary obstruction of the left main or the ostium of the right coronary artery is a rare but potentially fatal event.[51] It might occur if a calcified native leaflet is displaced over a coronary ostium[52] or if the valve frame or the sealing cuff is positioned directly over a coronary origin. It could happen either at the time of balloon valvuloplasty or during the TAVI procedure. Factors that increase the risk of coronary obstruction include an unusually bulky native leaflet (adjacent to a coronary ostium), a low origin of the coronary ostium (often defined as <12 mm from the basal leaflet insertion as assessed by multidetector computed tomography), a shallow sinus of Valsalva (offering less room for the native leaflet), an oversized prosthesis, and high implantation. Anecdotal cases have been reported in which acute coronary obstructions were successfully managed by immediate percutaneous angioplasty or bypass surgery.[51, 53-55] Careful evaluation by echocardiography or multidetector computed tomography is crucial to avoid this complication.

Myocardial injury associated with an elevation in cardiac markers following TAVI procedures could be explained by some degree of myocardial tissue compression caused by the device itself, global ischaemia instigated by short episodes of severe hypotension, and, finally, myocardial damage produced by the apical puncture and passage of the large catheter through the ventricular apex when the TA route is employed. Interestingly, transient ST-elevations, mostly in the anterior and lateral leads, have been described post-TA-TAVI immediately after the procedure in ~20% of patients and are probably related to incision and suturing of the apex.[36] In fact, Rodés-Cabau et al. [56] showed that TAVI is associated with some degree of cardiac troponin T rise above the upper normal limit in 97% of TF patients and in 100% of TA patients. Interestingly, after multivariate analysis, a greater elevation of cardiac troponin T was an independent predictor of mortality at 9 months as well as a factor correlated with less improvement in left ventricular ejection fraction.

Other complications

Other acute complications, less frequent but potentially lethal, have been described after TAVI: aortic rupture,[57] aortic dissection,[58] peri-aortic haematoma,[59] ventricular or aortic embolization of the valve,[60] and tamponade.[61] Mitral valve apparatus damage resulting in severe acute mitral regurgitation has also been reported, especially with the TA approach.[62] The wire used to deliver the device could have been malpositioned, either under or through chordae, resulting in severe distortion or irreversible damage of the mitral valve apparatus. Not unexpectedly, endocarditis has been described anecdotally.[63, 64] Acute structural valve

failure, including prosthesis rupture or malfunctioning leaflet ('frozen leaflet'), is a rare but possible complication after TAVI.

CONCLUSIONS

Currently, SAVR remains the standard of care for most patients with symptomatic severe aortic stenosis. However, with the publication of several real-world registries and lately, the pivotal PARTNER randomized trials, transcatheter AVR has become the standard of care for patients for whom surgical risk is prohibitive and a reasonable alternative for selected operable patients in whom the risk of either mortality or morbidity is 'high'. Although initial reports confirmed the feasibility and safety of TAVI, observational registries and completed randomized trials have been limited by the use of older generation devices, enrolment of small numbers of patients, the initial learning curve of the TAVI operators, self-reported outcomes, and the use of non-standardized endpoints. Although bleeding and vascular complications are decreasing as TAVI technology improves and continues to miniaturize, stroke and residual paravalvular leak remain important challenges. Embolic protection devices, improved delivery systems, and restriction of the procedure to high-volume centres with a well-trained TAVI heart team offer potential solutions. Improvement of the current technology combined with adoption of standardized definitions [65] for important clinical endpoints will enable meaningful comparisons and future well-conducted randomized trials.

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Antwerp

Chapter 16

Transcatheter aortic valve implantation after PARTNER: what is up next?

Head SJ, Kappetein AP

EuroIntervention 2010;6:560-561

COMMENT:

Recently, the results of the Placement of Aortic Transcatheter Valves (PARTNER) trial were published in the New England Journal of Medicine.[1] A group of high-risk patients with severe aortic stenosis (AS) deemed non-surgical candidates were randomised to either transcatheter aortic valve implantation (TAVI) or standard medical therapy including balloon aortic valvuloplasty (BAV). The authors need to be congratulated on their excellent results. The one-year results showed a reduced rate of death to 30.7% in the TAVI group, compared to 50.7% in the standard therapy group. Safety assessment was however less in favour of the percutaneous technique, as 6.7% suffered a stroke or TIA 30 days within randomisation, compared to only 1.7% in the standard therapy patients (p=0.03). After one year, this difference was still significant (10.6% vs 4.5%, p=0.04).

Despite this increased incidence of thromboembolic events, the authors conclude that TAVI is the new golden standard for patients with severe AS who are too sick for surgery. However, in the spring of 2011, the trial will provide the long anticipated answers to whether randomisation to TAVI is superior to surgical aortic valve replacement (AVR) in patients categorised as surgical candidates.

Since its introduction in 2002,[2] TAVI has been used to treat high-risk or inoperable patients. In the PARTNER study as well, only high-risk patients were included having in the TAVI and standard therapy groups a mean Logistic EuroSCORE (LES) of 26.4% and 30.4%, respectively, and the Society of Thoracic Surgery (STS) predicted risk of mortality scores of 11.2% and 12.1%, respectively. Other published data have also shown these high surgical risks in TAVI treated patients.[3, 4] Bern and Rotterdam gathered data on 1,122 patients who underwent TAVI or AVR. In this cohort, the mean LES of patients treated with TAVI (n=114) or AVR (n=1,008) was 20.1%±13.4% and 9.1%±10.2%, respectively. Hence, the scores can

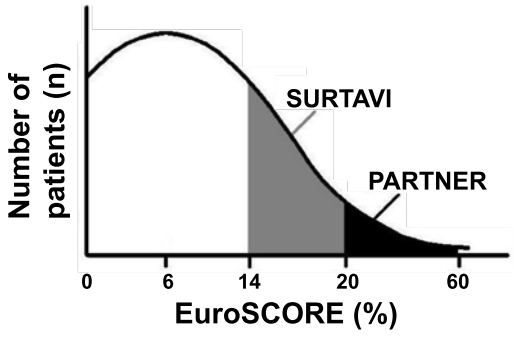

Figure 1 **Expected EuroSCORE distribution of patients with aortic stenosis who undergo treatment (aortic valve replacement or transcatheter aortic valve implantation)**

Table 1 Risk factors
Heart failure (Left ventricular dysfunction and NYHA class ≥3)
Poor metabolic state (diabetes, cachexia, albumin ↓, bilirubine ↑)
Peripheral vascular disease (PVD)
Renal disease/dialysis
Coronary artery disease (CAD)
Frailty
Neurological dysfunction
Porcelain aorta
Redo cardiac surgery
Pulmonary disease (COPD)
Pulmonary hypertension
Poor metabolic state (diabetes, cachexia, albumin ↓, bilirubine ↑)

be displayed in a distribution curve, with, in the far right, the group of patients treated with TAVI, similar to those in the PARTNER study (Figure 1).

The identification of this patient group is however, easier said than done. An intermediate risk group could include patients between 70-74 years of age with ≥2 but ≤4 comorbid factors; 75-79 year-olds with ≥1 but ≤3 factors; and ≥80 years of age with ≤2 factors. If we convert these risk factors (Table 1) to corresponding STS score and EuroSCORE, this immediately shows the limitations of these scoring systems. The STS score ranges from 0.9% to 14.1%, while the EuroSCORE predicts mortality ranging from 9.1%-54.5% (Figure 2). Not only does EuroSCORE calculate scores many times higher than the STS score, the discrepancy is not consistent. This is caused by the incomparable magnitude in which comorbidities influence the score.

One major shortcoming of both scores is the lack of entry fields. Both scores miss an entry for frailty and porcelain aorta. Other risk factors need to be entered in the STS score, but are not incorporated in the EuroSCORE, and vice versa. Therefore, a new score including

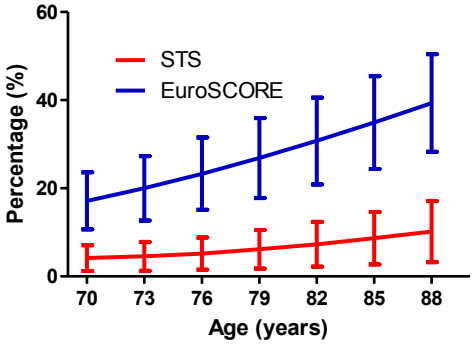

Figure 2 **STS score and EuroSCORE range in a patient with 2 comorbidities**

all factors should be developed to identify which patients will benefit from TAVI or surgical AVR. This score should not only include hospital mortality, but also long-term benefit in terms of survival and quality of life. Registries and future trials should not only evaluate techniques, but also provide data that eventually can lead to the development of a new scoring system.

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Rotterdam

Chapter 17

Cost of transcatheter versus surgical aortic valve replacement in intermediate risk patients

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ABSTRACT

Background

Transcatheter aortic valve replacement (TAVR) offers a new treatment option for patients with aortic stenosis, but costs may play a decisive role in decision making. Current studies are evaluating TAVR in an intermediate-risk population. We assessed the in-hospital and 1-year follow-up costs of patients undergoing TAVR and surgical aortic valve replacement (SAVR) at intermediate operative risk and identified important cost components.

Methods

We prospectively collected clinical data on 141 patients undergoing TAVR and 405 undergoing SAVR. Propensity score matching yielded 42 matched pairs at intermediate risk. Costs were assessed using a detailed resource-use approach and compared using bootstrap methods.

Results

In-hospital costs were higher in TAVR patients than in SAVR patients (€40802 vs €33354, respectively; $p = 0.010$). The total costs at 1 year were €46217 vs €35511, respectively ($p = 0.009$). The TAVR was less costly with regard to blood products, operating room use, and length-of-stay.

Conclusions

For intermediate-risk patients with severe aortic stenosis the costs at 1 year are higher for TAVR than for SAVR. The difference was mainly caused by the higher costs of the transcatheter valve and was not compensated by the lower costs for blood products and hospital stay in TAVR patients. Therefore, SAVR remains a clinically and economically attractive treatment option.

INTRODUCTION

Surgical aortic valve replacement (SAVR) is the standard treatment for patients with symptomatic aortic stenosis. However, transcatheter aortic valve replacement (TAVR) has rapidly emerged as a less invasive treatment option. A TAVR reduces mortality by 20% as compared with medical treatment in patients with severe aortic stenosis who are not eligible for surgery due to comorbidities and cardiovascular abnormalities.[1] Moreover, TAVR is equivalent to SAVR in terms of 1-year survival for patients at high risk.[2]

Therefore, considerations such as quality-of-life and costs are crucial in the decision-making process.[3] The only randomized controlled trial that reported quality-of-life in high-risk patients undergoing TAVR demonstrated a small increase in quality-adjusted life years at 1 year.[4] With equipoise in quality-of-life and survival, costs may play a pivotal role in the decision to perform TAVR or SAVR and therefore merit analysis.

Current studies evaluate TAVR in intermediate-risk populations, making the procedure more widely available. For these reasons our study assessed the in-hospital and 1-year follow-up costs of TAVR and SAVR in intermediate-risk patients with aortic stenosis using a detailed resource-use approach. A second objective was to identify important cost components.

PATIENTS AND METHODS

Study population

Between January 2006 and November 2010 we prospectively collected data on consecutive patients with aortic stenosis who underwent self-expanding transfemoral TAVR or SAVR at the Erasmus MC, Rotterdam, The Netherlands. All patients were discussed among cardiologists, interventional cardiologists, and cardiac surgeons during heart team meetings, considering risk scores and additional factors such as frailty, porcelain aorta, and patient's preferences.[5, 6] Patients underwent either TAVR (n = 141) or SAVR (n = 405). After propensity score matching 42 TAVR and 42 SAVR patients remained for the cost analysis (Table 1). One-year follow-up data was collected for all 84 propensity-matched patients. The study was approved by the Institutional Research Ethics Committee.

Resource use and costs

We retrospectively collected in-hospital diagnostic, procedural, and postprocedural resource use data from electronic patient records. All patients had at least 1 outpatient clinic visit prior to the procedure and several diagnostic and preprocedural tests; laboratory tests, chest X-rays, a dental consult, electrocardiography, cardiac ultrasound, coronary angiography, and lung function tests. We assumed that all patients had this standard clinical workup and that

Table 1 Baseline characteristics

Characteristic Parameter	Before propensity score matching			After propensity score matching		
	TAVR (n = 141)	SAVR (n = 405)	P Value	TAVR (n = 42)	SAVR (n = 42)	P Value
Age, mean ± SD (years)	81.3 ± 6.7	70.1 ± 9.0	<0.0001	78.8 ± 6.6	79.3 ± 5.5	0.66
Male sex	78 (55%)	240 (59%)	0.41	21 (50%)	22 (52%)	>0.99
Logistic EuroSCORE, mean ± SD	16.2 ± 10.9	6.2 ± 5.5	<0.0001	12.9 ± 6.8	12.5 ± 6.4	0.77
Diabetes mellitus	31 (22%)	97 (24%)	0.64	11 (26%)	8 (19%)	0.61
Coronary artery disease	56 (40%)	167 (41%)	0.75	20 (48%)	20 (48%)	>0.99
LVEF			<0.0001			0.68
>0.50	73 (52%)	371 (92%)		27 (64%)	30 (71%)	
0.30–0.50	55 (39%)	29 (7%)		14 (33%)	10 (24%)	
<0.30	13 (9%)	5 (1%)		1 (2%)	2 (5%)	
Cerebrovascular accident	34 (24%)	18 (4%)	<0.0001	2 (5%)	2 (5%)	>0.99
Peripheral vascular disease	12 (9%)	31 (8%)	0.75	3 (7%)	4 (10%)	>0.99
COPD	36 (26%)	54 (13%)	0.001	10 (24%)	8 (19%)	0.77
Pulmonary hypertension	17 (12%)	16 (4%)	0.001	2 (5%)	3 (7%)	>0.99
Serum creatinine, mean ± SD (μmol/L)	116.6 ± 94.3	99.7 ± 55.7	0.011	104.7 ± 92.2	102.8 ± 64.6	0.92
MI within 90 days before procedure	31 (22%)	12 (3%)	<0.0001	0	4 (10%)	0.13

COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

every TAVR patient underwent computed tomography. Associated costs were retrieved from the hospital's financial unit and subunits in the departments of cardiology, cardiothoracic surgery, and radiology.

The self-expanding third generation CoreValve (Medtronic, Minneapolis, MN; €17,590) was used for TAVR and SAVR was performed with the bioprosthetic Carpentier-Edwards PERIMOUNT Magna Valves (Edwards Lifesciences, Irvine, CA; €2,700). All TAVR valves were inserted through a transfemoral approach. Other materials included disposables, sutures, needles, anesthesia, sterilized gauzes, and disposables for the heart-lung machine. We retrieved these costs from the electronic ordering system and hospital pharmacy. Procedural and postprocedural blood products comprised packaged cells, fresh frozen plasma, and platelets and were priced according to The Dutch Manual for Cost-analysis in Health Care.[7]

Interventional rooms or operating room costs were calculated as costs per minute by using a micro-costing approach. A typical surgical team that carried out SAVR consisted of 1 cardiothoracic surgeon, 1 anesthesiologist, 1 anesthesia assistant, 1 resident, 2 nurses, and 2 technicians. Interventional teams were composed similarly, except that the team also comprised 2 interventional cardiologists, while no resident was involved. We assumed the

standby time of the cardiothoracic surgeon during TAVR to be 50% of the total procedure time as he was unavailable for other surgeries. Salaries were obtained from the Manual and where necessary from collective agreements.[7]

Postoperative diagnostic tests included electrocardiography, laboratory tests, chest X-ray, cardiac ultrasound, coronary angiography, computed tomographic imaging, and lung scintigraphy. Additional procedures included chest drain placement, tracheostomy, reinterventions for pacemaker implantation, postdilatation of the transcatheter aortic valve, paravalvular leakage, sternal wound infection, and bleeding. Associated costs were retrieved using a micro-costing approach with data from financial subunits.

Data on length-of-stay (LOS), 1-year follow-up visits, and readmissions to the cardiology and neurology departments were collected through our electronic databases or databases from readmitting hospitals; where necessary the general practitioner was contacted. While TAVR patients were monitored in the academic hospital, SAVR patients were discharged to a general hospital to recover from surgery. After that, patients were usually discharged home. For TAVR patients, physician visits and tests were scheduled at 1 and 4 months after the initial procedure. Patients who underwent SAVR were referred to a general hospital for further follow-up. Hospital stay (€2,241, €591, and €447 per night for intensive care, academic ward stay, and general hospital ward stay, respectively) and follow-up costs were retrieved from the Manual.[7] These general average costs were based on various micro-costing studies and include physician consultations, nursing, nutrition, materials, equipment, overhead, and housing.[7]

For the individual patient costs we combined the Manual with actual costs of tests, procedures and materials as described because in The Netherlands individually specified charge data are not available. No adjustment with a cost-to-charge ratio was needed as all costs were actual costs. Furthermore, administration and overhead, maintenance of the building, and equipment were taken into account. The health care perspective was applied and consumer price indices were used to convert all costs to the year 2011.[8] The total costs at 1 year comprise the total in-hospital and follow-up costs.

Propensity score matching and statistical analysis

Comparison of the patient characteristics in the unmatched cohort was done using an unpaired *t* test for continuous variables and using a χ^2 test or Fisher exact test for categoric variables. In the matched cohort, comparisons were performed using McNemar tests and paired sample *t* tests. Normality of the data was assessed using the Kolmogorov-Smirnov test and, if non-normality was proven, the Wilcoxon rank sum test was used. All tests were 2-sided with an α-level of 0.05.

The propensity score of a patient is defined as the probability to receive the experimental treatment conditional on pretreatment covariables.[9] After propensity score matching we expect TAVR and SAVR cohorts to have comparable baseline characteristics, providing a

fair comparison between groups.[10] The propensity score for receiving TAVR was estimated using a multivariable probit (probability unit) model at a *p*value less than 0.10, including gender, age, and other baseline characteristics such as logistic European system for cardiac operative risk evaluation (EuroSCORE), diabetes, coronary artery disease, left ventricular ejection fraction, creatinine level, pulmonary hypertension, peripheral vascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Subsequently, we performed Mahalanobis 1:1 matching, where a SAVR patient is matched to a randomly chosen TAVR patient using a caliper width of 0.05.[11] The SAVR patients who were matched to a TAVR patient were no longer considered as a possible match. The resulting 42 matched pairs were used for the cost analysis.

Missing values were LOS in the intensive care unit (missing in 1 of 84 patients), length of ward stay (missing in 3), procedure time (missing in 3), and number of visits (missing in 1). The missing values were imputed by assuming they were the mean value of the non-missing values for that variable.[12]

Consistent with intention-to-treat analysis, in-hospital and follow-up costs were calculated by taking all patients (n = 84) into account, including those who died. To account for the skewed distribution of costs, we used bootstrap resampling to construct standard errors and confidence intervals of the mean costs for TAVR, SAVR, and the difference between treatments.[13]

Outliers in total costs at 1 year were defined by a Cook distance larger than 4/n, where n is the number of data points. We performed sensitivity analysis excluding outliers and their matched partners.[14]We also performed sensitivity analysis in a restricted dataset of matched pairs who did not undergo revascularization to deal with the unbalanced number of coronary revascularizations in the treatment groups. Analyses were performed by using Excel 2007 (Microsoft, Redmond, WA), SPSS for Windows (version 17.0.2; SPSS, Chicago, IL), and STATA 11.1 (Stata Corp, College Station, TX).

RESULTS

Patients and clinical outcomes

Baseline characteristics of the unmatched and matched cohorts are given in Table 1. The logistic EuroSCORE was 12.9 in the TAVR and 12.5 in the SAVR group, which reflects the intermediate operative risk. During SAVR, 20 patients underwent a concomitant coronary artery bypass grafting (CABG), whereas a concomitant percutaneous coronary intervention (PCI) during TAVR or as a staged procedure within the same hospital stay was performed in 3 patients (Table 2).

There were no conversions from TAVR to SAVR. Procedure duration and total LOS was shorter after TAVR than after SAVR (11.3 vs 18.8 days, respectively; Table 2). This was true

Table 2 Initial hospital stay

Parameter	TAVR (n = 42)	SAVR (n = 42)	P Value
Procedure duration, mean ± SD (minutes)	229 ± 79	294 ± 76	<0.001
Concomitant PCI/CABG	3 (7%)	20 (48%)	<0.001
Length of postoperative stay, mean ± SD (days)	11.3 ± 8.1	18.8 ± 13.3	<0.001
ICU	1.1 ± 0.48	4.5 ± 8.2	<0.001
Ward stay[a]	10.3 ± 8.2	14.3 ± 7.3	0.008
Ward academic hospital	10.2 ± 8.0	7.1 ± 4.2	0.004
Ward general hospital	0.14 ± 0.93	7.2 ±6.6	<0.001
In-hospital complications[b]	22 (52%)	14 (33%)	0.08
Major stroke	4 (10%)	1 (2%)	0.38
Myocardial infarction	0	1 (2%)	>0.99
Major bleeding	4 (10%)	5 (12%)	>0.99
Major vascular	4 (10%)	0	0.13
Reintervention	2 (5%)	5 (12%)	0.45
Infection	7 (17%)	5 (12%)	0.77
Pacemaker	6 (14%)	1 (2%)	0.13
Pneumothorax	0	1 (2%)	>0.99
In-hospital mortality[b]	2 (5%)	3 (7%)	>0.99

[a]All patients were operated in the academic center. Patients who underwent TAVR were usually discharged home, whereas patients who underwent SAVR were usually discharged to a general hospital for recovery. [b]In-hospital mortality is defined as death <30 days after procedure or death during initial hospital stay. CABG = coronary artery bypass graft; ICU = intensive care unit; MI = myocardial infarction; PCI = percutaneous coronary intervention; PPI = permanent pacemaker implantation; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

for both intensive care unit stay and ward stay, taking into account the stay in our academic hospital and in the general hospital to which the patient was discharged for recovery. In our propensity matched cohort no patients were discharged to a skilled nursing facility. We found no statistically significant difference in complications, mortality at 1 year, follow-up duration, readmissions, and outpatient clinic visits (Table 2 and Table 3).

In-hospital costs (Table 4)

The in-hospital costs were higher with TAVR than SAVR (€40,802 vs €33,354, respectively). The largest difference was found in the procedure costs (€28,785 vs €13,096, respectively) and in-hospital stay (€8,481 vs €17,409, respectively). Procedural costs that were signify-cantly dif-ferent between the treatment groups were operating room use, materials, and blood products.

Table 3 Follow-up

	TAVR (n = 42)	SAVR (n = 42)	P Value
One-year follow-up death	7 (17%)	5 (12%)	0.73
Mean follow-up, mean ± SD (days)	332.1 ± 88	339.8 ± 88	0.51
Outpatient clinic visits, n of patients (%)	33 (79%)	35 (83%)	0.75
Number of outpatient clinic visits per patient, n ± SD	1.8 ± 1.8	2.0 ± 1.6	0.24
Hospital readmission during follow-up[a], n of patients	8 (19%)	10 (24%)	0.80
Hospital readmission[a], days ± SD	5.3 ± 19.0	2.4 ± 7.7	0.86

[a]Reasons for readmission included dyspnea, chest pain, endocarditis of the prosthesis, cardiac arrhythmias, additional dilatation of the valve, reoperation, transient ischemic attack, and heart failure. SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

Follow-up costs

The costs incurred during follow-up were nonsignificantly higher in the TAVR group than in the SAVR group (Δ costs = €3,258; Table 5). In addition, components of the follow-up costs were not significantly different. The total costs at 1 year were higher for TAVR than for SAVR (€46,217 vs €35,511, respectively; $p = 0.009$; Figure 1).

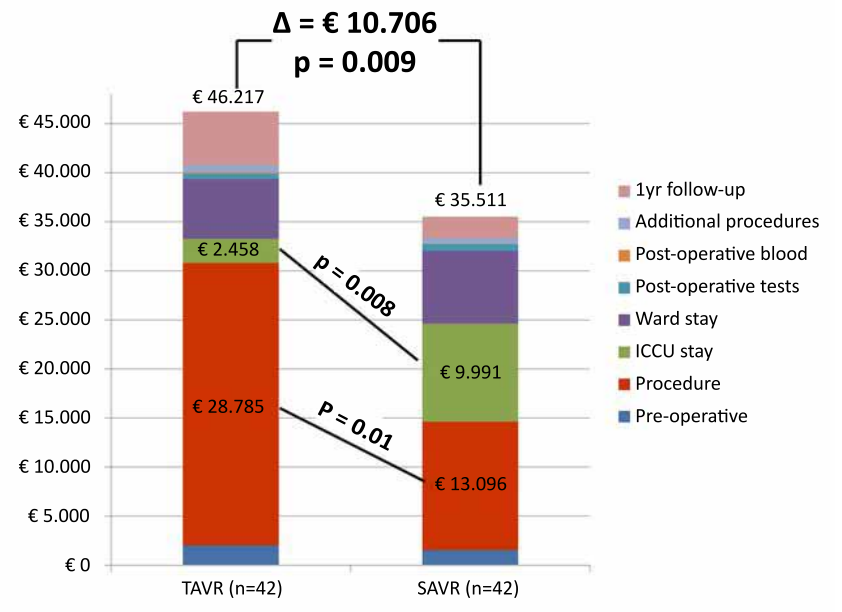

Figure 1 Total costs at 1 year; Euros for year 2011

Blocks containing numbers represent cost components which differ significantly between treatment groups. ICU = intensive care unit; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

Sensitivity analyses

We identified 3 outliers due to prolonged postprocedural or readmission hospital stay. In a sensitivity analysis of the remaining 39 pairs we found similar results as in the original analysis for in-hospital costs (€39,945 vs €29,251; $p < 0.001$), follow-up costs (€3,426 vs €2,286; $p = 0.37$), and total costs at 1 year (€43,370 vs €31,537; $p < 0.001$) for TAVR and SAVR, respectively.

In the sensitivity analysis of 22 matched pairs who did not undergo revascularization we found in-hospital costs of €40,154 (standard error of the mean [SE] = 1,504) for TAVR and €26,776 (SE = 1,087) for SAVR (Δ costs = €13,378; $p < 0.001$). The total costs at 1 year were, respectively, €48,102 (SE = 4,800) and €29,349 (SE = 1,608) ($p < 0.001$).

DISCUSSION

The results of our study suggest that TAVR is significantly more expensive than SAVR for intermediate-risk patients with aortic stenosis. This conclusion refers to both the in-hospital costs and the total costs at 1 year. The difference is mainly explained by the costs of materials, which was roughly 4 times higher in TAVR than SAVR. The fact that the patients in the TAVR group were less costly with regard to blood products and LOS did not outweigh the difference in costs of materials (Figure 1). Furthermore, close monitoring of TAVR patients may explain the trend toward higher follow-up costs.

The costs of the procedure were higher for TAVR than for SAVR (Table 4), while procedure times with TAVR were shorter (Table 2). This can be explained by the more expensive equipment in intervention rooms than in the operating room (€1.54 vs €4.91 per minute for TAVR and SAVR). However, room use is only a fraction of the overall procedural costs (Table 4).

We observed more revascularizations in patients undergoing SAVR because guidelines recommend concomitant CABG for patients with moderate to severe coronary artery disease;[15] no such recommendations exist for TAVR. In the sensitivity analysis of matched pairs who did not undergo revascularization we found that the difference in costs between TAVR and SAVR was larger than in the original analysis. A concomitant procedure such as CABG is likely to make SAVR more expensive as the procedure and hospital stay may take longer and the complication rate is higher.[16] However, PCI in addition to TAVR has shown to be of less influence on procedural and midterm outcomes.[17] From an economic perspective, an additional advantage for SAVR is to be expected if PCI and TAVR are performed as staged procedures.

The transcatheter valve is currently priced at €17,590, whereas the surgical aortic bioprosthesis costs only €2,700. With more valves being developed, market forces are likely to decrease the price of transcatheter valves, similar to the trend previously seen in coronary stents.[18] Using the mean difference in costs at 1 year and the price of the transcatheter

Table 4 In-hospital costs

	TAVR (n = 42)	SAVR (n = 42)	P Value
Preoperative costs	2,024 ± 0	1,538 ± 0	
Procedure costs	28,785 ± 1,014	13,096 ± 315	<0.001
Operating room use	1,124 ± 60	453 ± 18	<0.001
Personnel	2,303 ± 117	2,413 ± 90	0.41
Materials	22,055 ± 869	5,162 ± 0	<0.001
Blood products	176 ± 41	1,869 ± 233	<0.001
Overhead and housing	3,127 ± 48	3,181 ± 38	0.40
Total stay	8,545 ± 776	17,409 ± 3,116	<0.001
ICU stay	2,458 ± 168	9,991 ± 2,280	0.008
Ward stay[a]	6,087 ± 733	7,418 ± 544	0.087
Academic hospital	6,023 ± 715	4,208 ± 370	0.016
General hospital	64 ± 64	3,210 ± 446	<0.001
Postoperative tests	545 ± 50	674 ± 108	0.31
Postoperative blood products	136 ± 43	63 ± 27	0.17
Additional procedures	768 ± 273	573 ± 209	0.56
Total in-hospital costs	40,802 ± 1,399	33,354 ± 3,357	0.010

All costs are in Euros for the year 2011. [a]All procedures were performed in the academic center. TAVR patients were usually discharged home, whereas SAVR patients were usually discharged to a general hospital for recovery. The subdivision of ward stay reflects this difference. ICU = intensive care unit; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

valve, we calculated that the valve would have to be priced at €6,884 to be a cost neutral alternative for SAVR.

One other study reported the costs of TAVR, showing quite different estimates compared with our results.[19] The discordance with our study might be caused by different cost calculation methods, which were briefly described and partly based on a costing study of percutaneous pulmonary valves. In studies that used the in-hospital costs for SAVR, the

Table 5 One-year follow-up costs

	TAVR (n = 42)	SAVR (n = 42)	P Value
Visit costs	182 ± 28	135 ± 16	0.10
Visit diagnostic tests	582 ± 86	587 ± 69	0.97
Readmission hospital stay	3,336 ± 1,882	1,086 ± 528	0.25
Readmission procedures	1,168 ± 589	245 ± 172	0.13
Readmission diagnostic tests	146 ± 59	104 ± 41	0.58
Total 1-year follow-up	5,414 ± 2,224	2,157 ± 627	0.17

All costs are in Euros for the year 2011. SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

estimates were also quite different from our results.[16, 20] However, comparison is difficult as none of these studies primarily focused on costs and therefore the methodology for assessing costs varied and was not very detailed.

We have found no published report that compared costs in TAVR versus SAVR in intermediate-risk patients. In the high-risk patients of the PARTNER (Placement of Aortic Transcatheter Valve) trial the total costs at 1-year follow-up were higher than the costs in our study.[4] Moreover, there was no significant difference in costs between TAVR and SAVR. In comparison with our results, the nonprocedural costs were higher, whereas the LOS and other resource use were similar. Differences might therefore be attributed to higher costs of hospital stay in the United States.[21]

Using our results we can make some crude statements on the cost effectiveness of TAVR versus SAVR. The PARTNER trial showed a quality-of-life gain of 0.068 at 1 year for TAVR as compared with SAVR.[4] Combining our cost results with this quality-of-life gain yields an ICER (incremental cost-effectiveness ratio) of around €150,000 per quality-adjusted life year saved, which in general is considered higher than the threshold willingness-to-pay. Although ICERs should be calculated using life-time costs, 1-year follow-up costs in our study were similar for the 2 treatments and show that periprocedural costs will be the driver of cost effectiveness of TAVR. However, more elaborate analyses are needed to confirm these results.

Limitations

Cost data were not based on a randomized trial but were retrospectively collected from a relatively small single-center observational study. However, economic data from well-performed observational studies are equally valuable to policy makers as such data reflect the real-life economic consequences of new treatments.[22] Moreover, industry sponsored economic evaluations alongside trials are more likely to report favorable results,[23] increasing the value of independent economic observational studies.

To overcome the limitation that our study was not randomized, we used propensity score matching. This technique corrects for measured confounders but there may have been unmeasured confounding in our study. However, we used a very conservative caliper in the matching process while other studies have used wider margins.[24]Thestatistically similar clinical outcomes in the matched cohort allow for a valid cost comparison between the groups.

Because propensity score matching does not take into account procedural variables, it was possible that we found an imbalance in the concomitant revascularization rate. A regression model could adjust for this imbalance but makes assumptions on the distribution of the outcome variable and would require more revascularizations in the TAVR group. Due to the skewed nature of cost variables and the small sample size, the distribution free bootstrap method is preferred.[13]

Since 2005 our center has performed roughly 250 TAVRs, whereas there is a multitude of experience with SAVR. This may result in longer procedures, more personnel being present, and longer hospital stay. As experience with TAVR in intermediate-risk patients develops, and with the refinement of techniques and protocols, it is likely that costs, LOS, and complication rates will decrease.

The logistic EuroSCORE was used as a matching variable and indicator of operative risk. The score fails to include factors such as porcelain aorta, frailty, chest deformities, and malnutrition. Therefore we might have underestimated the operative risk of TAVR patients, leading to higher costs in this group. It is unlikely that this affected the main conclusion of our study as the cost of the transcatheter valve is the main cause of the difference in costs between the 2 groups.

In the current study the costs were specific for Dutch centers. However, our results may be translated to other countries using regression techniques.[25]These models can adjust for differences in the cost of medical treatments due to demography, epidemiologic factors, and differences in medical practice, resource use, and funding of health care.

CONCLUSIONS

For intermediate-risk patients with severe aortic stenosis the costs at 1 year are higher for TAVR than for SAVR. The difference was mainly caused by the higher costs of the transcatheter valve and was not compensated by the lower costs for blood products and hospital stay in TAVR patients. Therefore, SAVR remains a clinically and economically attractive treatment option.

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Part 3

Stenting versus bypass surgery

San Francisco

Chapter 18

Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries

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ABSTRACT

Objectives

The aim of this study was to evaluate the use of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in "real-world" patients unsuitable for the alternative treatment.

Background

No data are available on the risk profile and outcomes of patients that can only undergo PCI or CABG.

Methods

In the SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial, a multidisciplinary Heart Team reached a consensus on whether PCI and CABG could result in clinical equipoise; if so, the patient was randomized. If not, the patient was enrolled in a CABG-ineligible PCI registry or PCI-ineligible CABG registry. A proportion (60%) of patients in the CABG registry was randomly assigned to be followed up for 5 years. No statistical comparisons were performed between randomized and registry patients. Major adverse cardiac or cerebrovascular event (MACCE) rates are presented as observational only.

Results

A total of 3,075 patients were treated in the SYNTAX trial; 198 (6.4%) and 1,077 (35.0%) patients were included in PCI and CABG registries, respectively. The main reason for inclusion in the CABG registry was too complex coronary anatomy (70.9%), and the main reason for inclusion in the PCI registry was too high-risk for surgery (70.7%). Three-year MACCE was 38.0% after PCI and 16.4% after CABG. Stratification by SYNTAX score terciles demonstrated a step-wise increase of MACCE rates in both PCI and CABG registries.

Conclusions

The SYNTAX Heart Team concluded that PCI and CABG remained the only treatment options for 6.4% and 35.0% of patients, respectively. Inoperable patients with major comorbidities that underwent PCI had high MACCE rates. In patients not suitable for PCI, surgical results were excellent. (SYNTAX Study: NCT00114972)

INTRODUCTION

Since the 1980s, coronary artery bypass graft surgery (CABG) is the treatment of choice for patients with multivessel and/or left main (LM) coronary artery disease. Numerous trials have compared CABG with percutaneous coronary intervention (PCI) but have not been able to produce favorable outcomes after PCI due to an excess in repeat revascularization.[1]

The recent SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial showed that CABG remains superior to PCI, even with the usage of drug-eluting stents (DES).[2] It has been demonstrated that PCI is as effective as CABG in subgroups of patients with less complex coronary artery disease and LM lesions.[2-4] Other recent trials have confirmed more favorable outcomes with CABG.[5, 6]

Although CABG is still the gold standard, there are some patients who cannot undergo surgery. In addition, a proportion of patients are not eligible for PCI. The SYNTAX study was designed as an all-comers trial, but patients could be excluded if the Heart Team concluded that either PCI or CABG could not be performed.[2, 7] This decision was based on a team judgment and not on predefined criteria. Excluded patients were entered in a CABG registry to define the population at too high-risk for PCI and in a PCI registry to define the patients deemed unsuitable for surgery. Little is known of the characteristics and outcomes of these populations. Separate analysis is necessary to fully understand the strengths and limitations of PCI and CABG in the "real world".[8]

This study presents characteristics and 3-year outcomes of patients that were deemed nonrandomizable and therefore were included in the SYNTAX PCI and CABG nested registries.

METHODS

Study design

The SYNTAX trial design has been described previously.[2, 9] In brief, patients with 3-vessel or LM coronary artery disease were screened for enrollment in the randomized trial. During a multidisciplinary Heart Team discussion, including at least 1 surgeon and 1 interventional cardiologist, consensus was reached on whether both PCI and CABG would result in clinical equipoise.[7] If a patient was not eligible for randomization, the patient was enrolled in the nested registry for CABG-ineligible patients (PCI registry) or PCI-ineligible patients (CABG registry).

Patients in the PCI registry were treated according to local practices with regard to technique and device preference, either with or without DES.

To compare the risk profile and outcomes of patients in the registries with the randomized arms, a randomly selected proportion of patients from the CABG registry and all PCI registry

patients were scheduled to undergo clinical follow-up at 1, 6, 12, 36, and 60 months after treatment allocation.[9]

The study protocol was approved by the institutional review board of all 85 enrollment sites and is consistent with the International Conference on Harmonisation Guidance of Industry E6 Good Clinical Practice, the Declaration of Helsinki, and all local regulations. Written consent was obtained from all participating patients. SYNTAX is registered at ClinicalTrials.gov (NCT00114972).

Definitions

The primary outcome of this study was the composite of major adverse cardiac or cerebrovascular events (MACCE) at 3 years of follow-up. MACCE included all-cause death, stroke, myocardial infarction (MI), and any repeat revascularization. The composite safety endpoint consisting of all-cause death, stroke, and MI, was also analyzed as well as individual outcomes. Adverse events were adjudicated by an independent Clinical Events Committee.

Definitions have been reported elsewhere.[4] Briefly, stroke was defined as a focal neurological deficit of central origin lasting >72 h resulting in permanent brain damage or body impairment. Myocardial infarction was defined in relation to intervention status as follows: 1) after allocation but before treatment: Q-wave MI (new pathological Q waves in ≥2 leads lasting ≥0.04 s with creatine kinase-myocardial band [CK-MB] levels elevated above normal) and non–Q-wave MI [elevation of CK levels >2× the upper limit of normal [ULN] with positive CK-MB or elevation of CK levels to >2 × ULN without new Q waves if no baseline CK-MB was available); 2) <7 days after intervention: new Q waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5 × ULN; and 3) ≥7 days after intervention: new Q waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5 × ULN or plasma level of CK 5 × ULN (4).

Statistical analysis

Analyses were performed with SAS system software, version 8.0 or higher (SAS Institute, Cary, North Carolina). Outcomes are presented according to the as-treated-principle. The composite MACCE endpoint was analyzed as the time to the first event, whereas individual MACCE components are presented as proportions. Patient characteristics are presented as proportions (%, count/sample size) or mean ± SD.

We decided that no statistical comparisons between PCI and CABG should be performed, because entry into the registries depended on different variables specific for the corresponding registry. Thus, the patient characteristics and outcomes are only representative of patients ineligible to undergo PCI or CABG. Results are presented as observational only.

Subgroup analyses of separate SYNTAX score cohorts (low 0 to 22, intermediate 23 to 32, and high ≥33) were performed.[10] The assessment of coronary anatomic complexity by SYNTAX score was based on tercile cohorts established in the randomized trial.[2] Statistical

comparison was performed by overall and pairwise log-rank testing, with a 2-sided p value <0.05 considered statistically significant.

RESULTS

Inclusion

Between March 2005 and April 2007, a total of 4,337 patients were screened for eligibility of enrollment in the trial. After exclusion due to variable reasons (e.g., refusal of informed consent or concomitant valvular heart disease, among others), a total of 3,075 patients were treated within the SYNTAX trial. In the trial 1,800 patients were randomly assigned to undergo PCI (n = 903) and CABG (n = 897). Another 198 (6.4%) and 1,077 (35.0%) patients were included in the PCI and CABG registries, respectively (Figure 1). From the 1,077 in the CABG registry, 649 were randomly selected to be followed-up for 5 years.

Of the 198 patients in the PCI registry, 192 were treated with PCI, 4 patients were treated medically, 1 underwent CABG, and 1 patient withdrew consent. Of the 649 CABG registry patients randomly assigned to 5-year follow-up, 644 were treated with CABG, 3 did not receive treatment, and 2 were managed medically. Another 9 patients were lost to follow-up, and 3 patients withdrew consent. Three-year MACCE rates were evaluable in 100% and 97.2% of the PCI and CABG patients, respectively.

Patients included in the PCI registry were considered too high-risk for CABG (70.7%), had no graft material for anastomosis (9.1%), refused CABG (5.6%), had small or poor quality of distal vessels (1.5%), or were excluded from randomization because of other reasons (13.1%). Reasons for inclusion in the CABG registry included too complex coronary anatomy to undergo PCI (70.9%), chronic total occlusion untreatable with PCI (22.0%),

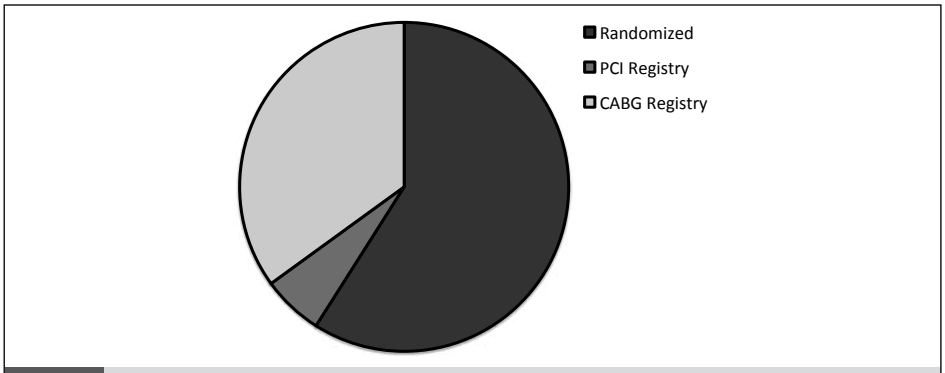

Figure 1 **SYNTAX patient distribution**

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SYNTAX = synergy between PCI with TAXUS and cardiac surgery

unable to take antiplatelet medication (0.9%), refusal to undergo PCI (0.5%), or other reasons (5.7%).

Patient characteristics

In general, compared with the patients that were randomized in the SYNTAX trial, the patients in the PCI registry were older (71.2 ± 10.4 years vs. 65.2 ± 9.7 years) and had a high-risk profile because of comorbidities and an eventful cardiovascular and noncardiovascular history; this was manifested in a higher Logistic EuroSCORE of 7.7 ± 9.0 (vs. 3.8 ± 4.5 in the randomized PCI group) and Parsonnet score of 14.4 ± 9.5 (vs. 8.5 ± 7.0 in the randomized PCI group) (Table 1). In addition, the lesion complexity by SYNTAX score was 31.6 ± 12.3 in the PCI registry, which was slightly higher than the 28.4 ± 11.5 in the randomized PCI group. A total occlusion was present in 36.5%, whereas this rate was only 24.2% in the trial.

Table 1 **Baseline patient demographics and lesion characteristics**

	PCI (N=192)	CABG	
		With follow-up (N=644)	All (N=1072)
Age, years	71.2 ± 10.4 (192)	65.7 ± 9.4 (644)	65.9 ± 9.4 (1072)
Male sex	70.3% (135/192)	80.7% (520/644)	81.1% (869/1072)
Characteristic			
Body-Mass Index (kg/m2)	28.0 ± 5.5 (191)	28.0 ± 4.6 (643)	28.0 ± 4.6 (1069)
Medically treated diabetes			
Any	35.4% (68/192)	29.7% (191/644)	30.3% (325/1072)
Requiring insulin	15.1% (29/192)	9.2% (59/644)	9.2% (99/1072)
Triglycerides ≥150 mg/dl (1.7 mmol/liter)	33.6% (37/110)	39.6% (114/288)	40.4% (182/451)
Blood pressure ≥130/85 mmHg	69.8% (134/192)	68.5% (441/644)	68.9% (735/1067)
Fasting Glucose ≥110 mg/dl	47.2% (67/142)	49.8% (210/422)	49.7% (338/680)
Increased waist circumference	40.8% (58/142)	46.4% (245/528)	48.1% (414/861)
Hyperlipidemia	67.5% (129/191)	76.4% (480/628)	77.1% (809/1049)
Current smoker	11.2% (21/188)	21.9% (140/639)	19.7% (209/1062)
Previous myocardial infarction	40.4% (76/188)	33.5% (211/629)	32.5% (341/1049)
Previous stroke	7.8% (15/192)	5.5% (35/639)	4.5% (48/1065)
Previous transient ischemic attack	7.9% (15/191)	5.6% (36/638)	6.0% (64/1062)
Previous cardiac surgery	1.6% (3/192)	0.0% (0/644)	0.0% (0/1072)
Congestive heart failure	9.7% (18/186)	5.5% (35/633)	5.1% (54/1057)
Peripheral vascular disease	16.1% (31/192)	13.8% (89/644)	12.5% (134/1072)
Carotid artery disease	10.4% (20/192)	12.3% (79/644)	10.2% (109/1072)
Creatinine >200 micromol/liter	5.7% (11/192)	2.0% (13/644)	2.1% (23/1072)
Chronic obstructive pulmonary disease	19.3% (37/192)	7.9% (51/644)	7.3% (78/1072)

Table 1 ***Continued***

	PCI (N=192)	CABG	
		With follow-up (N=644)	All (N=1072)
Angina			
Stable	46.4% (89/192)	62.9% (405/644)	63.3% (678/1071)
Unstable	38.0% (73/192)	21.6% (139/644)	22.5% (241/1071)
Ejection fraction <30%	5.7% (11/192)	4.5% (29/644)	3.9% (42/1072)
Logistic EuroSCORE	7.7 ± 9.0 (192)	4.0 ± 4.4 (644)	4.0 ± 4.8 (1072)
Additive EuroSCORE	5.8 ± 3.1 (192)	3.9 ± 2.7 (644)	3.9 ± 2.7 (1072)
Parsonnet score	14.4 ± 9.5 (192)	9.0 ± 7.1 (644)	9.1 ± 7.2 (1072)
Lesion complexity			
SYNTAX score	31.6 ± 12.3 (189)	37.8 ± 13.3 (632)	Not available
Diffuse disease or small vessels	18.5% (35/189)	13.6% (86/631)	Not available
Total occlusion	36.5% (69/189)	56.4% (356/631)	Not available
Bifurcation	74.6% (141/189)	80.8% (510/631)	Not available
Lesion characteristics			
Number of lesions	4.5 ± 1.8 (189)	4.6 ± 1.7 (632)	Not available
Left main, any	33.3% (63/189)	40.3% (254/631)	Not available
Left main only	2.6% (5/189)	1.6% (10/631)	Not available
Left main + 1 vessel	5.8% (11/189)	2.7% (17/631)	Not available
Left main + 2 vessel	11.6% (22/189)	8.4% (53/631)	Not available
Left main + 3 vessel	13.2% (25/189)	27.6% (174/631)	Not available
Three vessel disease only	66.7% (126/189)	59.7% (377/631)	Not available

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

Patients in the CABG registry had a Logistic EuroSCORE comparable to the CABG patients in the randomized trial (4.0 ± 4.4 vs. 3.9 ± 4.4 in the randomized trial) as well as a similar mean Parsonnet score (9.0 ± 7.1 vs. 8.4 ± 6.8 in the randomized CABG group) (Table 1). However, the lesions were more complex in the registry: the SYNTAX score was 37.8 ± 13.3 in the registry versus 29.1 ± 11.4 in the randomized trial. A total occlusion was present in 56.4% versus 22.2% in the randomized trial. More patients had LM and 3-vessel disease in the registry (27.6% vs. 13.0% in the trial).

Procedural characteristics

In the PCI registry, a mean of 2.5 ± 1.3 lesions were treated with 3.1 ± 1.8 stents and a mean total length of 58.5 ± 41.2 mm. This is much lower than in the randomized trial where 3.6 ± 1.6 lesions were treated with 4.6 ± 2.3 stents and a mean length of 86.1 ± 47.9 mm. In 76% of cases a DES stent (57% TAXUS) was used. Completeness or revascularization was only 36.5% in the registry compared with 56.7% in the trial.

A total of 3.0 ± 0.9 conduits were used per CABG patient (vs. 2.8 ± 0.7 in the randomized trial), of which 1.3 ± 0.7 were arterial and 1.7 ± 1.0 venous grafts. Complete arterial revascularization was performed in 11.2% compared with 18.9% in the randomized trial.

Table 2 Perioperative medication use

	PCI (N=192)	CABG (N=644)
Aspirin		
Baseline	83.3% (160/192)	74.7% (481/644)
Discharge	92.7% (178/192)	88.4% (569/644)
Thienopyridine		
Baseline	71.9% (138/192)	16.1% (104/644)
Discharge	92.7% (178/192)	16.9% (109/644)
Nonthienopyridine antiplatelet		
Baseline	9.9% (19/192)	8.7% (56/644)
Discharge	6.8% (13/192)	6.1% (39/644)
Warfarin derivative		
Baseline	4.7% (9/192)	3.9% (25/644)
Discharge	3.6% (7/192)	9.6% (62/644)
Statin		
Baseline	64.1% (123/192)	70.0% (451/644)
Discharge	71.9% (138/192)	68.3% (440/644)
Beta-blocker		
Baseline	67.7% (130/192)	77.3% (498/644)
Discharge	70.3% (135/192)	79.3% (511/644)
ACE inhibitor		
Baseline	43.8% (84/192)	47.2% (304/644)
Discharge	54.2% (104/192)	45.2% (291/644)
Calcium-channel blocker		
Baseline	30.2% (58/192)	27.8% (179/644)
Discharge	27.1% (52/192)	21.9% (141/644)
Angiotensin II-receptor antagonist		
Baseline	16.1% (31/192)	11.3% (73/644)
Discharge	12.5% (24/192)	5.3% (34/644)
Anti-arrythmic (Amiodarone)		
Baseline	1.6% (3/192)	2.5% (16/644)
Discharge	2.6% (5/192)	12.3% (79/644)
H2-recepter blocker		
Baseline	4.7% (9/192)	8.9% (57/644)
Discharge	8.9% (17/192)	19.9% (128/644)

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

In 96.7% at least 1 arterial graft was used; in the randomized trial this rate was 97.3%. Off-pump surgery was performed slightly more often in the registry (18.6% vs. 15.0% in the trial). Completeness of revascularization was 74.7% in the registry, compared with 63.2% in the trial.

Mean post-procedure hospital stay was 8.2 ± 5.5 days and 4.8 ± 12.0 days in the CABG and PCI registries, respectively. Perioperative medication use is displayed in Table 2.

PCI outcomes

Procedural 30-day MACCE occurred in 7.6% of the patients (Table 3). This was mainly driven by the 3.1% death rate and 3.6% MI rate. After 3 years of follow-up, the MACCE rate was 38.0% (Figure 2 and Table 3), with 18.3% death, 8.4% MI, 1.8% stroke, and 20.0% repeat revascularization (repeat PCI 17.8%, and repeat CABG 2.8%).

According to the SYNTAX score terciles, 44 patients had low lesion complexity (mean SYNTAX score 16.5 ± 5.1), 63 patients had intermediate complexity (mean SYNTAX score 27.7 ± 2.8), and 82 patients had high complexity (mean SYNTAX score 42.4 ± 9.2). Subgroup analyses revealed a MACCE rate of 29.5% in the cohort with a score ≤22 and increasing rates with intermediate (33.3%) and high (46.3%) scores (overall p = 0.09) (Figure 3A). Difference in MACCE was not statistically significant between the low- and intermediate-score groups (p = 0.64) and intermediate- and high-score groups (p = 0.11). There was a trend toward a difference between the low- and high-score groups (p = 0.06). Breaking down MACCE into separate endpoints (Figure 4A), there was a significant difference between the groups in terms of the composite safety endpoint of death, stroke, and MI (13.9% vs. 32.9% and 20.6% vs. 32.9%, p = 0.04), which was driven by increased rates of death in the high

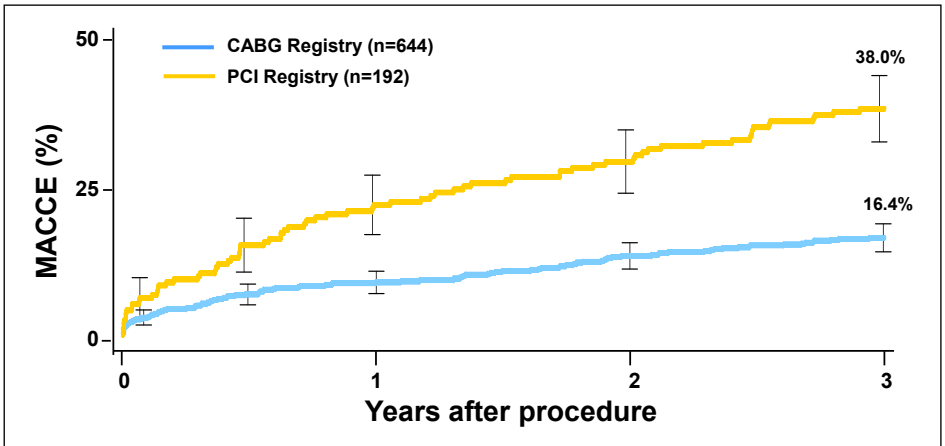

Figure 2 **Cumulative incidence of MACCE after PCI or CABG**

CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular event(s); PCI = percutaneous coronary intervention

Table 3 Outcomes of patients in the PCI and CABG registries

	PCI (N=192)				CABG (N=644)			
	30 Days	6 Months	1 Year	3 Years	30 Days	6 Months	1 Year	3 Years
Composite MACCE	7.3% (14)	14.1% (27)	20.4% (39)	38.0% (73)	3.4% (22)	6.7% (43)	8.8% (56)	16.4% (104)
Composite death/stroke/MI	6.3% (1)	8.4% (16)	10.5% (20)	24.6% (47)	3.3% (21)	5.8% (37)	6.6% (42)	12.6% (80)
Death	3.1% (6)	5.2% (10)	7.3% (14)	18.3% (35)	0.6% (4)	2.2% (14)	2.5% (16)	6.9% (44)
Cardiac death	2.6% (5)	3.7% (7)	4.7% (9)	7.0% (13)	0.5% (3)	1.4% (9)	1.4% (9)	2.5% (16)
Stroke	0.0% (0)	0.0% (0)	0.0% (0)	1.8% (3)	1.2% (8)	2.0% (13)	2.2% (14)	3.8% (24)
Myocardial infarction	3.6% (7)	3.7% (7)	4.2% (8)	8.4% (15)	1.6% (10)	2.2% (14)	2.5% (16)	3.7% (23)
Repeat revascularization, any	1.6% (3)	7.3% (14)	12.0% (23)	20.0% (36)	0.3% (2)	1.4% (9)	3.0% (19)	5.7% (35)
PCI	1.0% (2)	6.8% (13)	11.0% (21)	17.8% (32)	0.2% (1)	1.3% (8)	2.8% (18)	5.5% (34)
CABG	0.5% (1)	0.5% (1)	1.0% (2)	2.8% (5)	0.2% (1)	0.2% (1)	0.2% (1)	0.2% (1)

CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention

SYNTAX score group (24.4% vs. 9.3% in the low SYNTAX score group, p = 0.04). Other endpoints were comparable between groups (Figure 4A).

CABG outcomes

Procedural outcomes after CABG showed low rates of MACCE (3.4%), for the composite safety endpoint of death/stroke/MI (3.3%), and the individual components of MACCE: stroke (1.2%), MI (1.6%), and repeat revascularization (0.3%) (Table 2). After 3 years, the MACCE rate was 16.4% (Figure 2 and Table 3).

Patients were divided into low lesion complexity (n = 68, SYNTAX score 16.8 ± 4.1), intermediate complexity (n = 161, SYNTAX score 28.2 ± 2.7), and high complexity (n = 403, SYNTAX score 45.2 ± 10.1). Subgroup analysis demonstrates a stepwise increase in MACCE with higher SYNTAX score; 9.0% in the low-, 13.8% in the intermediate-, and 18.3% in the high-score cohorts (overall p = 0.10) (Figure 3B). Pairwise testing demonstrated no statistically significant differences (low vs. intermediate, p = 0.32; intermediate vs. high, p = 0.19; low vs. high, p = 0.07). Individual MACCE components were not statistically significant between groups, except for the endpoint of death where there was a difference between the intermediate and high score groups (p = 0.03) (Figure 4B).

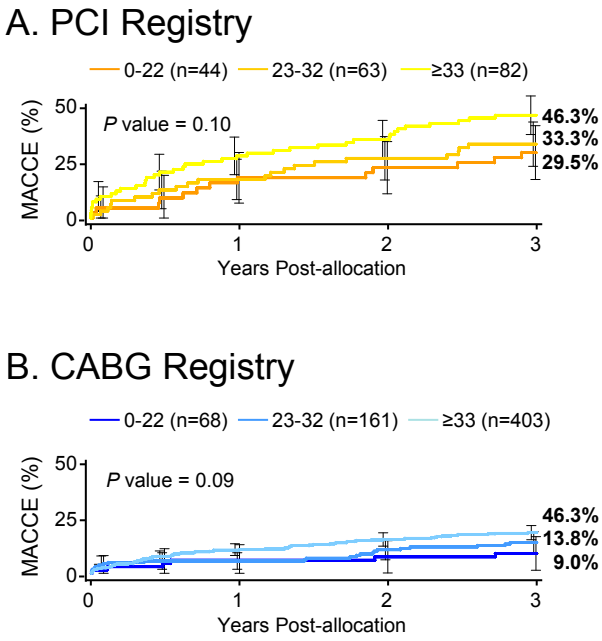

Figure 3 **MACCE after PCI or CABG stratified by SYNTAX Score**

Kaplan-Meier incidence of MACCE in the PCI registry ***(A)*** and CABG registry ***(B)***. CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular event(s); PCI = percutaneous coronary intervention

DISCUSSION

The SYNTAX nested registries presented in this study are important to complete the knowledge of the current use of PCI and CABG for 3-vessel or LM coronary artery disease in the real world. The SYNTAX randomized trial, among other trials, included only selective patients in whom both PCI and CABG could be performed with satisfactory results. Those patients not suitable for randomization are crucial to fully understand the indications, strengths, and limitations of PCI and CABG, with the corresponding outcomes. In this study we showed that the Heart Team decided that 35.0% of patients were not suitable for PCI and therefore underwent CABG. Patients were deemed inoperable and received PCI treatment in 6.4% of the cases.

Other studies

Patients in these registries were selected on the basis of clinical judgment of a multidisciplinary team of physicians.[7] Results from other studies cannot be compared with the SYNTAX registry results, because this study presents patients in whom only 1 treatment option was considered appropriate. Therefore these patients represent not the total PCI or

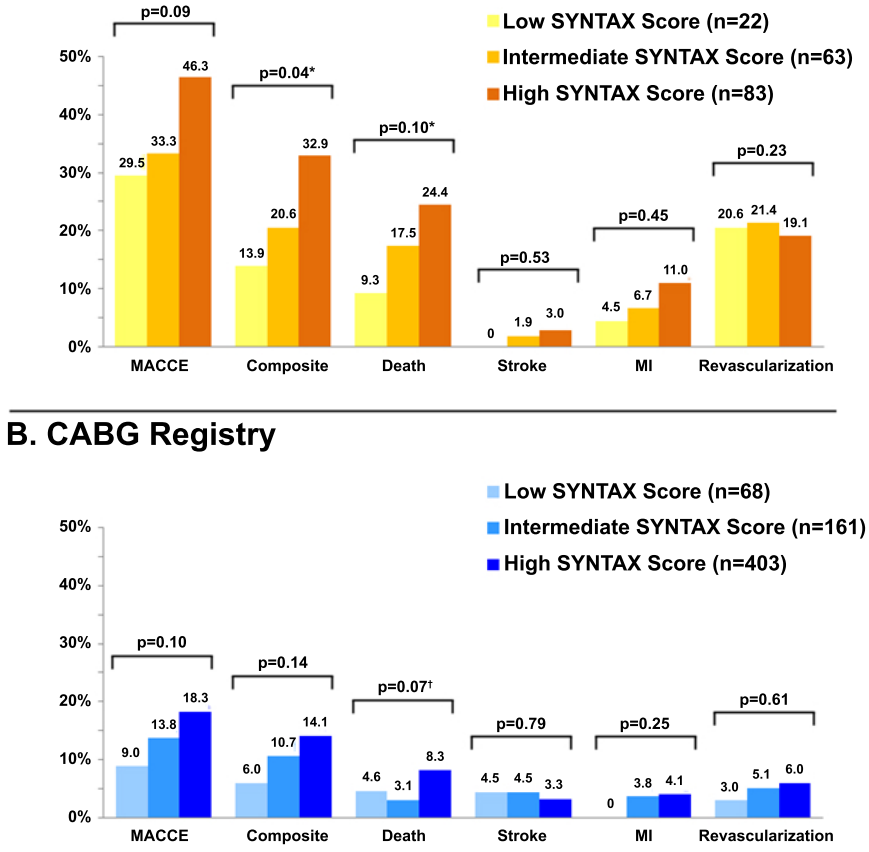

Figure 4 **Outcomes within the PCI and CABG registries stratified by SYNTAX Score**

Event rates in the PCI registry ***(A)*** and CABG registry ***(B)***. *p < 0.05 for low versus high SYNTAX Score group comparison. †p < 0.05 for intermediate versus high SYNTAX Score group comparison. CABG = coronary artery bypass grafting; Composite = composite of death/stroke/myocardial infarction; MACCE = major adverse cardiac or cerebrovascular event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention

CABG cohort but only a selected group with different baseline risk and lesion complexity. Many patients receiving either PCI or CABG in other studies would probably have been randomized in the SYNTAX trial.[2]

PCI registry

Patients in the SYNTAX PCI registry present a completely different patient population as the patients described in other registries or trials.[1, 2, 11-13] First, the mean age was 71.2 ± 10.4, and nearly 75% of patients were ≥65 years of age; thus patients were significantly older. Second, patients more often presented with an eventful cardiac and noncardiac history. The

mean Logistic EuroSCORE was higher in the registry (7.7 ± 9.0) than in the randomized arm (3.8 ± 4.5) as well as the Parsonnet score (14.4 ± 9.5 compared with 8.5 ± 7.0, respectively).

Indeed, the 3-year 38.0% MACCE rate in the PCI registry was much higher than the 28.0% in the randomized trial. However, this is not unexpected, due to the advanced age and severe comorbidities. Both the EuroSCORE and Parsonnet score have been associated with increased rates of adverse events during follow-up.[13-15] In addition, some of the patients were included in the PCI registry because they had cancer or other severe diseases. This could be one of the reasons that the death rate is very high.

The high-risk profile of these PCI patients was influential in choosing the treatment strategy. Fewer lesions were stented and the number of stents that were used was much lower. It might be the case that only the culprit lesion was stented, whereas other lesions remained untreated, resulting in a 63.5% rate of incomplete revascularization in the registry. Also, 24% of patients received a bare-metal stent; this might have had an influence on the results as well.[16]

CABG registry

Patients included in the CABG registry represent a population completely different from the patients in the PCI registry. Where in the PCI registry patients were high-risk but had similar lesion complexity, in the CABG registry it was the exact opposite. Patients had a similar mean EuroSCORE (4.0 ± 4.4 vs. 3.9 ± 4.4) and Parsonnet score (9.0 ± 7.1 vs. 8.4 ± 6.8) as the randomized patients. However, they were most often denied PCI because of too complex coronary anatomy, demonstrated in a higher SYNTAX score (37.8 ± 13.3 vs. 29.1 ± 11.4), more patients with a total occlusion (56.4% vs. 22.2%), and a slightly higher rate of bifurcation (80.8% vs. 73.3%).

The 3-year MACCE rate in the CABG registry (16.4%) is actually lower than in the randomized patients (20.2%), which was caused by lower rates of repeat revascularization.[4, 17] Interestingly, however, the actual difference in MACCE rates between the registry and trial do not increase over follow-up. At 1 year the difference was 3.2%, and at 3 years this was still only 3.8%. Therefore, it seems that the registry patients did significantly better especially during short-term follow-up. This was confirmed by a trend in lower rates of hospital and 30-day MACCE rates in the registry patients.[17] This lower incidence of MACCE cannot be described by a difference in risk profile, because patients had similar risk. A previous study showed that it was likely related to procedural characteristics.[17] In the registry, patients had a 74.7% rate of complete revascularization, whereas this was only 63.2% in the randomized trial. Furthermore, the number of grafts and distal anastomoses per patient was higher, which was identified to be independently associated with reduced rates of MACCE.[17]

SYNTAX score

Since 2009, a large number of studies have tested the accuracy of the SYNTAX score as a risk algorithm in predicting adverse outcomes. A recent review summarized these data and

concluded that, especially in LM patients treated with PCI, the score is a useful prognostic tool.[18] Although Birim et al. [19] reported a stepwise increase in MACCE rates with higher SYNTAX scores, in patients treated with CABG generally less discriminative power could be attributed to the SYNTAX score. Remarkably, this study shows that in both PCI and CABG patients a stepwise increase of MACCE rates can be seen with higher SYNTAX scores, although this was not statistically significant in the CABG registry.

There was, however, a significant difference in death between the intermediate- and high-score groups. A hypothesis behind this finding is that in the high SYNTAX score group more patients with extreme high scores were present. Although the predictive power of the SYNTAX score is limited in CABG patients, with extreme scores it is likely that ultimately the score will identify those patients at higher risk. The fact that death did not increase stepwise from low- to high-score groups demonstrates that the increased death in cohort with scores ≥33 might be caused by these extreme cases. Furthermore, these intragroup comparisons are post hoc subgroup analyses with relatively low statistical power, thus a change finding cannot be ruled out.

Study limitations

It is important to recognize that an emphasis should lay on long-term results after PCI and CABG. From this study, follow-up is only available up to 3 years. Ongoing prospective data collection will provide 5-year results.

The PCI registry contains a relatively small number of patients. Therefore some of the results should be interpreted with caution. Furthermore, explorative subgroup analyses by lesion subsets could not performed, due to the low patient number in separate groups.

CONCLUSIONS

In the SYNTAX trial the Heart Team concluded that, for 6.4% and 35.0% of patients, the only treatment option was PCI or CABG, respectively. Patients with complex coronary anatomy often underwent CABG, whereas inoperable high-risk patients were included in the PCI registry. Patients deemed inoperable for CABG had a high-risk profile, resulting in a suboptimal outcome after PCI. In patients who are not candidates for PCI, bypass surgery produces excellent results. To identify those patients at high risk for MACCE, the SYNTAX score discriminates well.

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Lisbon

Chapter 19

Incidence, predictors, and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data

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ABSTRACT

Objective

To assess whether incomplete revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) has an effect on long-term outcomes.

Methods

During a heart team discussion to evaluate whether patients were eligible for randomization in the SYNTAX trial, both the cardiologist and surgeon agreed on which vessels needed revascularization. This statement was compared with the actual revascularization after treatment. Incomplete revascularization was defined as when a preoperatively identified vessel with a lesion was not revascularized. Outcomes were major adverse cardiac or cerebrovascular events (MACCE), the composite safety endpoint of death/stroke/myocardial infarction (MI), and individual MACCE components death, MI and repeat revascularization at 3 years. Predictors of incomplete revascularization were explored.

Results

Incomplete revascularization was found in 43.3% (388/896) PCI and 36.8% (320/870) CABG patients. Patients with complete revascularization by PCI had lower rates of MACCE (66.5 versus 76.2%,$P < 0.001$), the composite safety endpoint (83.4 versus 87.9%, $P = 0.05$) and repeat revascularization (75.5 versus 83.9%, $P < 0.001$), but not death and MI. In the CABG group, no difference in outcomes was seen between incomplete and complete revascularization groups. Incomplete revascularization was identified as independent predictor of MACCE in PCI (HR = 1.55, 95% CI 1.15–2.08, $P = 0.004$) but not CABG patients. Independent predictors of incomplete revascularization by PCI were hyperlipidaemia (OR = 1.59, 95% CI 1.04–2.42, $P = 0.031$), a total occlusion (OR = 2.46, 95% CI 1.66–3.64, $P < 0.001$) and the number of vessels (OR = 1.58, 95% CI 1.41–1.77, $P < 0.001$). Independent predictors of incomplete revascularization by CABG were unstable angina (OR = 1.42, 95% CI 1.02–1.98, $P = 0.038$), diffuse disease or narrowed (< 2 mm) segment distal to the lesion (OR = 1.87, 95% CI 1.31–2.69, $P = 0.001$) and the number of vessels (OR = 1.70, 95% CI 1.53–1.89, $P < 0.001$).

Conclusions

Despite the hypothesis-generating nature of this data, this study demonstrates that incomplete revascularization is associated with adverse events during follow-up after PCI but not CABG.

INTRODUCTION

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are both options for the treatment of coronary disease. Whether PCI or CABG is preferred for a particular patient often depends on the number of diseased vessels, lesion complexity and co-morbidities. Complete revascularization cannot always be achieved due to procedural difficulties.[1, 2]

Previous studies have tried to address whether incomplete revascularization is associated with reduced survival and increased revascularization.[3-6] However, these have been methodologically restricted by a retrospective design and most often relied on post-procedural classification of completeness of revascularization by the treating physician. The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial[7] had a more accurate method to determine the completeness of revascularization. Preoperatively, both the interventional cardiologist and surgeon had to agree which vessels needed revascularization on a basis of any lesion with more than 50% diameter stenosis in coronary vessels ≥1.5 mm. Patients were categorized as incompletely revascularized when the number of diseased segments that were treated did not match the Heart Team decision. The objective of this study was to assess whether incomplete revascularization according to the SYNTAX definition had an effect on the 3-year outcome of the SYNTAX trial.

METHODS

Study design

The SYNTAX trial design and methods have been described previously.[7, 8] It was a prospective, multicentre randomized trial in which patients with *de novo* left main and/or three-vessel disease were randomly assigned to undergo PCI with the TAXUS drug-eluting stent or CABG.

The institutional review board of each of the 85 participating cites approved the protocol. The trial is registered on the National Institute of Health website with identifier NCT00114972.

Definitions

During the Heart Team meeting when patients were assessed for randomization,[9] both the interventional cardiologist and surgeon documented which vessels with a ≥1.5 mm diameter and a 50% stenosis needed revascularization. Incomplete revascularization was assessed by correlating this preoperative statement to the actual revascularization.

The composite endpoint of major adverse cardiac or cerebrovascular events (MACCE) included all-cause death, myocardial infarction (MI), cerebrovascular accident (CVA) or

repeat revascularization (subsequent PCI or CABG).[10] Cerebrovascular events, or stroke, were defined as focal neurological deficits of central origin lasting >72 h, resulting in permanent brain damage or body impairment. MI was defined in relation to intervention status as follows: (i) after allocation but before treatment: Q-wave [new pathological Q-waves in ≥2 leads lasting ≥0.04 s with creatine kinase-MB (CK-MB) levels elevated above normal] and non-Q-wave MI [elevation of CK levels >2× the upper limit of normal (ULN) with positive CK-MB or elevation of CK levels to >2× ULN without new Q-waves if no baseline CK-MB was available]; (ii) <7 days after intervention: new Q-waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN; and (iii) ≥7 days after intervention: new Q-waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN or plasma level of CK 5× ULN. The CK/CK-MB enzyme levels were obtained and measured by a core laboratory for all randomized patients. All events were adjudicated by a Clinical Event Committee.

Statistical analysis

Baseline data were presented as proportions or mean ± standard deviation. Continues variables were compared using Student's *t*-tests. Discrete variables were compared with the Chi-square test. Uni- and multivariate logistic regression analyses were performed to identify predictors of incomplete revascularization in PCI and CABG patients. Variables tested in the univariate analysis were: age, gender, any medically treated diabetes, diabetes requiring insulin, triglycerides ≥150 mg/dl (1.7 mmnol/l), fasting glucose ≥110 mg/dl, hyperlipidaemia, current smoker, previous MI, previous stroke, previous TIA, congestive heart failure, peripheral vascular disease, carotid artery disease, renal failure (creatinine >200 micromol/l), unstable angina, low left ventricular ejection fraction (<35%), logistic EuroSCORE, Parsonnet score, SYNTAX score tercile, total occlusion, bifurcation lesion, diffuse disease or narrowed (<2 mm) segment distal to the lesion and the number of lesions. If a variable had a trend towards an association with incomplete revascularization ($P < 0.20$), it was entered in the multivariate forward Wald model. Univariate cox-regression was used to determine the effect of incomplete revascularization on outcomes. Variables with a trend towards an association ($P < 0.20$) were included in a final forward Wald multivariate model.

For all analyses, a *P*-value <0.05 was considered to be statistically significant. Analyses were performed using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

In the SYNTAX trial, 1800 patients were randomized to PCI ($n = 903$) or CABG ($n = 897$). Revascularization was not performed or informed consent was withdrawn in 34 patients. A total of 1766 patients were analysed. In the PCI cohort, 43.3% (388/896) had incomplete

revascularization, compared with 36.8% (320/870) in the CABG cohort. Table 1 shows the baseline characteristics of complete and incomplete revascularized patients.

Incomplete revascularization was especially present in patients with three-vessel disease (Figure 1). Within SYNTAX score terciles, an increasing score is associated with an increased rate of incomplete revascularization (Figure 2).

In the PCI group, patients with incomplete revascularization had a higher prevalence of diabetes and hyperlipidaemia. Patients with complete and incomplete revascularization had a comparable logistic EuroSCORE (3.7 ± 5.0 versus 3.9 ± 3.8, respectively, in the complete and incomplete revascularization groups) and Parsonnet score (8.2 ± 6.8 versus 9.0 ± 7.1, respectively). The coronary disease complexity, however, was significantly worse in patient with incomplete revascularization. The SYNTAX score was 31.4 ± 11.8 compared with 26.2 ± 10.6 in the complete revascularization group. More often, a total occlusion (33.4 versus 16.9%, P < 0.001) or bifurcation (67.3 versus 58.9%, P = 0.010) lesion was present. Patients with incomplete revascularization had more frequently diffuse disease or narrowed (<2 mm) segments distal to the lesion (26.5 versus 19.1%, P = 0.008). A higher mean number of lesions were seen in incompletely revascularized patients (4.6 ± 1.5 versus 3.5 ± 1.6, P < 0.001).

In the CABG cohort, patients with incomplete revascularization had a higher logistic EuroSCORE (4.3 ± 4.9 compared with 3.6 ± 4.0 in the complete revascularization group, *P* = 0.014) (Table 1). Similar to the PCI cohort, CABG patients with incomplete revascularization had more complex coronary disease according to the SYNTAX score (31.3 ± 11.4 versus 27.9 ± 11.1), and higher incidences of diffuse disease or narrowed vessels (29.1 versus 16.4%, *P* < 0.001), a total occlusion (27.4 versus 19.3%, *P* = 0.006) and a bifurcation (69.3

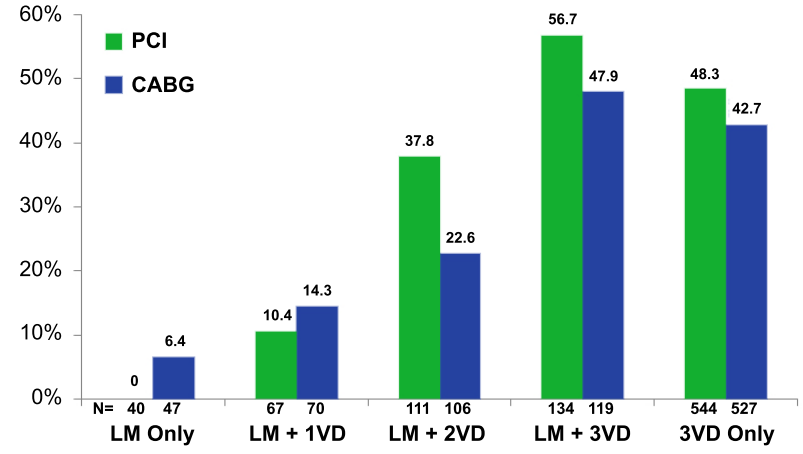

Figure 1 **Rates of incomplete revascularization within patient lesion subsets**

CABG = coronary artery bypass grafting; LM = left main; PCI = percutaneous coronary intervention; VD = vessel disease

Table 1 Baseline characteristics

Characteristics	PCI (n=896)			CABG (n=870)		
	Complete (n=508, 56.7%)	Incomplete (n=388, 43.3%)	P value	Complete (n=550, 63.2%)	Incomplete (n=320, 36.8%)	P value
Age, years	65.1 ±9.4	65.6 ± 10.0	0.392	64.7 ± 9.9	65.3 ± 9.8	0.339
Male sex	74.2% (377/508)*	79.6% (309/388)	0.057	79.4% (439/550)*	78.8% (252/320)	0.707
Comorbid risk factors						
Body-Mass Index (kg/m2)	28.2 ± 4.9	28.0 ± 4.7	0.408	28.0 ± 4.5	27.8 ± 4.3	0.540
Medically treated diabetes						
Any	22.2% (113/508)	30.2% (117/388)	0.007	22.7% (125/550)	25.3% (81/320)	0.387
Requiring insulin	7.5% (38/508)	13.1% (51/388)	0.005	8.9% (49/550)	12.2% (39/320)	0.122
Triglycerides ≥150 mg/dl (1.7 mmol/liter)	32.4% (158/488)*	32.1% (116/361)	0.940	38.5% (191/496)*	39.1% (111/284)	0.874
Blood pressure ≥130/85 mmHg	68.7% (349/508)	69.6% (270/388)	0.776	64.2% (353/550)	63.1% (202/320)	0.754
Fasting Glucose ≥110 mg/dl	41.8% (151/361)	49.8% (139/279)†	0.044	39.5% (149/377)	39.3% (95/242)†	0.947
Increased waist circumference	48.6% (221/455)	45.9% (158/344)	0.459	46.7% (221/473)	44.9% (129/287)	0.634
Hyperlipidemia	75.7% (383/506)	82.2% (315/383)	0.018	77.5% (424/547)	76.8% (242/315)	0.816
Cardiovascular history						
Current smoker	19.1% (97/508)	17.8% (69/388)	0.617	23.8% (130/547)	19.2% (61/318)	0.117
Previous myocardial infarction	32.1% (160/499)	32.0% (124/387)	0.994	31.0% (168/542)	37.1% (118/318)	0.066
Previous stroke	3.9% (20/507)	3.9% (15/385)	0.970	4.9% (27/546)	5.0% (16/319)	0.963
Previous transient ischemic attack	3.3% (17/508)	5.7% (22/386)	0.088	4.2% (23/544)	6.3% (20/318)	0.180
Previous cardiac surgery	0.2% (1/508)	0% (0/388)	0.382	0.2% (1/550)	0.3% (1/320)	0.698
Congestive heart failure	4.2% (21/505)	3.9% (15/386)	0.838	5.0% (27/539)	5.4% (17/314)	0.797
Peripheral vascular disease	7.9% (40/508)	10.8% (42/388)	0.129	8.7% (48/550)	13.4% (43/320)	0.029
Carotid artery disease	8.3% (42/508)	8.0% (31/388)	0.880	7.5% (41/550)	9.7% (31/320)	0.249
Creatinine >200 micromol/liter	1.2% (6/508)	1.0% (4/388)	0.832	1.3% (7/550)	1.9% (6/320)	0.480

Table 1 ***Continued***

Characteristics	PCI (n=896)			CABG (n=870)		
	Complete (n=508, 56.7%)	Incomplete (n=388, 43.3%)	P value	Complete (n=550, 63.2%)	Incomplete (n=320, 36.8%)	P value
Chronic obstructive pulmonary disease	7.5% (38/508)	8.5% (33/388)	0.574	10.0% (55/550)	7.8% (25/320)	0.282
Angina						
Stable	57.9% (294/508)	56.2% (218/388)	0.613	60.7% (334/550)	52.2% (167/320)	0.014
Unstable	27.6% (140/508)	30.4% (118/388)	0.350	26.0% (143/550)	32.5% (104/320)	0.040
Ejection fraction <35%	1.4% (7/508)	1.3% (5/388)	0.908	2.4% (13/550)	2.2% (7/320)	0.867
Logistic EuroSCORE	3.7 ± 5.0	3.9 ± 3.8	0.614	3.6 ± 4.0	4.3 ± 4.9	0.014
Parsonnet score	8.2 ± 6.8	9.0 ± 7.1	0.117	8.1 ± 6.7	8.9 ± 7.2	0.079
Lesion complexity						
SYNTAX score	26.2 ± 10.6*	31.4 ± 11.8	<0.001	27.9 ± 11.1*	31.3 ± 11.4	<0.001
Diffuse disease or small vessels	19.1% (97/508)	26.5% (103/388)	0.008	16.4% (90/550)	29.1% (93/320)	<0.001
Total occlusion	16.9% (85/504)	33.4% (129/386)	<0.001	19.3% (106/548)	27.4% (87/317)	0.006
Bifurcation	58.9% (299/508)	67.3% (261/388)	0.010	62.0% (341/550)	69.3% (221/319)	0.030
Number of lesions	3.5 ± 1.6	4.6 ± 1.5	<0.001	3.5 ± 1.5	4.8 ± 1.6	<0.001
Lesion		†	<0.001		†	<0.001
Left main, any	44.7% (227/508)	32.2% (125/388)		45.1% (248/550)	29.5% (94/319)	
Left main only	7.9% (40/508)	0% (0/320)		8.0% (44/550)	0.9% (3/320)	
Left main + 1 vessel	11.8% (60/508)	1.8% (7/388)		10.9% (60/550)	3.1% (10/320)	
Left main + 2 vessel	13.6% (69/508)	10.8% (42/388)		14.9% (82/550)	7.5% (24/320)	
Left main + 3 vessel	11.4% (58/508)	19.6% (76/388)		11.3% (62/550)	17.8% (578/320)	
Three vessel disease only	52.4% (266/508)	67.3% (261/388)		53.5% (294/550)	67.5% (216/320)	

* P<0.05 for comparison PCI complete revascularization versus CABG complete revascularization

†P<0.05 for comparison PCI incomplete revascularization versus CABG incomplete revascularization

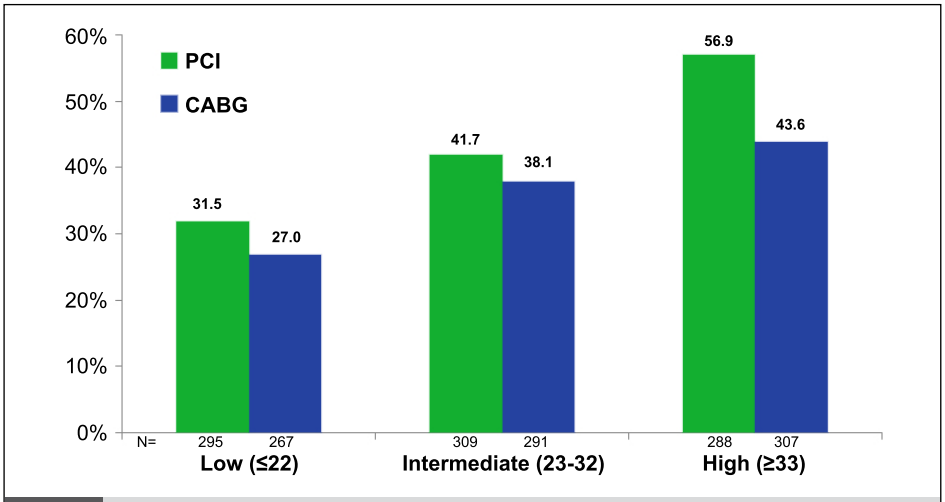

Figure 2 **Rates of incomplete revascularization within SYNTAX Score terciles**

CABG = coronary artery bypass grafting; ; PCI = percutaneous coronary intervention

versus 62.0%,*P* = 0.030). The number of lesions was significantly higher in the incomplete revascularization group (4.8 ± 1.6 versus 3.5 ± 1.5 in the complete revascularization group, *P* < 0.001).

In the PCI cohort, incomplete and complete revascularization groups had similar number of stents implanted (respectively, 4.6 ± 2.0 versus 4.7 ± 2.4, *P* = 0.55) and a comparable total stent length in mm (respectively, 83.6 ± 42.3 versus 88.0 ± 51.7, *P* = 0.18). CABG patients in the incomplete revascularization group had similar procedure time as those with complete revascularization (respectively, 3.4 ± 1.0 versus 3.5 ± 1.5, *P* = 0.13).

Predictors of incomplete revascularization

Predictors of incomplete revascularization are displayed in Table 2. For stent patients, hyperlipidaemia (OR = 1.59, 95% CI 1.04–2.42), a total occlusion (OR = 2.46, 95% CI 1.66–3.64) and the number of lesions (OR = 1.58, 95% CI 1.41–1.77) were independent predictors of incomplete revascularization in the multivariate model (Table 2).

In CABG patients, multivariate analysis identified only unstable angina (OR = 1.42, 95% CI 1.02–1.98), the diffuse disease or small vessels (OR = 1.87, 95% CI 1.31–2.69) and the number of lesions (OR = 1.70, 95% CI 1.53–1.89) as independent predictors.

Outcomes

Incomplete revascularization was associated with a higher MACCE rate at 3 years follow-up in patients who underwent PCI (33.5 versus 23.8% in patients with complete revascularization, *P* < 0.001) (Figure 3) but not in patients that underwent CABG (21.9 versus 18.9% in patients with complete revascularization, *P* = 0.29).

Table 2 **Univariate and multivariate predictors of incomplete revascularization within PCI and CABG cohorts**

	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
PCI				
Any medically treated diabetes	1.51 (1.12-2.04)	0.007		
Insulin requiring diabetes	1.87 (1.20-2.91)	0.006		
Fasting glucose ≥110 mg/dl	1.38 (1.01-1.89)	0.044		
Hyperlipidemia	1.49 (1.07-2.07)	0.019	1.59 (1.04-2.42)	0.031
SXS tercile	1.70 (1.43-2.01)	<0.001		
Diffuse disease or small vessels	1.53 (1.12-2.10)	0.008		
Total occlusion	2.45 (1.81-3.39)	<0.001	2.46 (1.66-3.64)	<0.001
Bifurcation	1.44 (1.09-1.89)	0.010		
Number of lesions	1.60 (1.46-1.77)	<0.001	1.58 (1.41-1.77)	<0.001
CABG				
Peripheral vascular disease	1.62 (1.05-2.51)	0.030		
Unstable angina	1.37 (1.01-1.85)	0.041	1.42 (1.02-1.98)	0.038
Logistic EuroSCORE	1.04 (1.01-1.07)	0.017		
SXS tercile	1.44 (1.21-1.71)	<0.001		
Diffuse disease or small vessels	2.10 (1.51-2.93)	<0.001	1.87 (1.31-2.69)	0.001
Total occlusion	1.58 (1.14-2.18)	0.006		
Bifurcation	1.38 (1.03-1.85)	0.031		
Number of lesions	1.71 (1.55-1.90)	<0.001	1.70 (1.53-1.89)	<0.001

CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention; OR = odds ratio; SXS = SYNTAX score

The composite safety endpoint (16.6 versus 12.1%, $P = 0.05$) was higher with incomplete revascularization in the PCI cohort, but within the CABG cohort there was no difference (12.5 versus 11.4%, respectively, in incomplete and complete revascularization groups, $P = 0.62$).

Mortality was not significantly different between incomplete and complete revascularization groups in patients that underwent PCI (respectively, 10.1 versus 7.4%, $P = 0.13$) or CABG (respectively, 7.1 versus 6.2%, $P = 0.60$). Rates of MI were also not significantly different in PCI (8.2 versus 6.2% in incomplete and complete revascularization, $P = 0.25$) and CABG (respectively, 4.5 versus 2.9%, $P = 0.26$). However, in the incomplete revascularization group, there was a significantly higher rate of repeat revascularization in PCI (24.5 versus 16.1%, $P < 0.001$), but not CABG (13.0 versus 9.4%, $P = 0.11$).

Predictors of MACCE

Univariate Cox regression analysis identified incomplete revascularization as one of the predictors of MACCE, among others (Table 3). In the PCI arm, significant multivariate predictors

for increased MACCE at 3 years were incomplete revascularization (HR = 1.55, 95% CI 1.15–2.08, *P* = 0.004), insulin requiring diabetes (HR = 1.94, 95% CI 1.33–2.84,*P* = 0.001), previous MI (HR = 1.42, 95% CI 1.04–1.92, *P* = 0.026) and carotid artery disease (HR = 1.96, 95% CI 1.24–3.11, *P* = 0.004). In the CABG cohort, only PVD (HR = 1.82, 95% CI

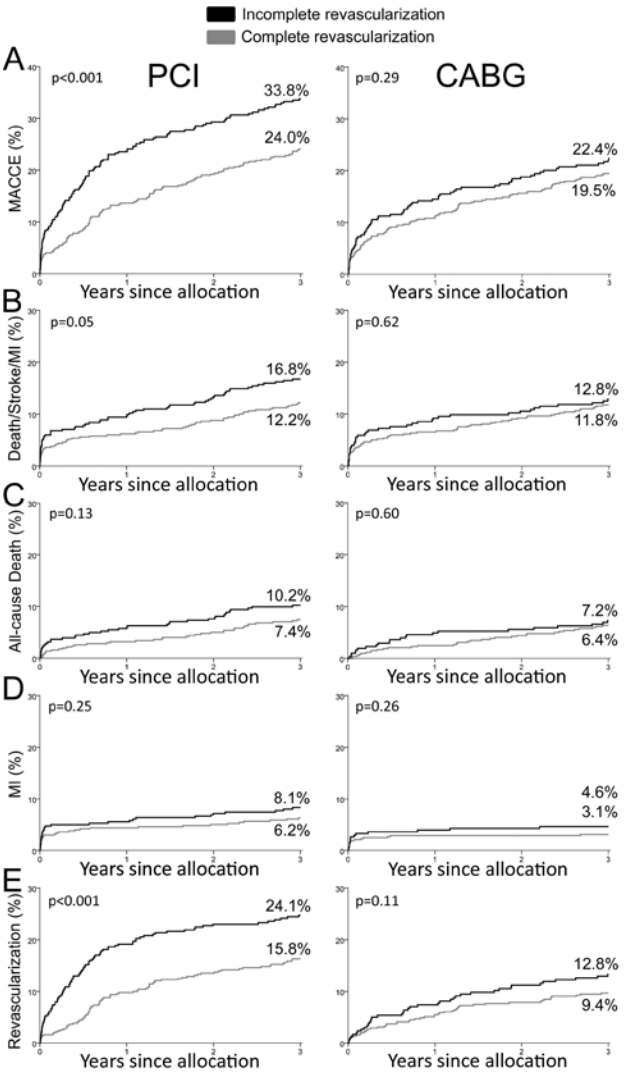

Figure 3 **Three-year outcomes of incomplete revascularization versus complete revascularization**

Kaplan-Meier estimates of total MACCE ***(A)***, the composite endpoint of death/stroke/myocardial infarction ***(B)***, all-cause mortality ***(C)***, myocardial infarction ***(D)***, and repeat revascularization ***(E)*** in PCI (left) and CABG (right) cohorts.

Table 3 Univariate and multivariate predictors of MACCE within PCI and CABG cohorts

	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
PCI				
Incomplete revascularization	1.54 (1.20-1.97)	0.001	1.55 (1.15-2.08)	0.004
Age	1.02 (1.01-1.03)	0.008		
Any medicaly treated diabetes	1.62 (1.25-2.11)	<0.001		
Insulin requiring diabetes	1.94 (1.38-2.74)	<0.001	1.94 (1.33-2.84)	0.001
Previous myocardial infarction	1.33 (1.03-1.72)	0.030	1.42 (1.04-1.92)	0.026
Peripheral vascular disease	1.68 (1.16-2.42)	0.006		
Carotid artery disease	1.58 (1.06-2.36)	0.024	1.96 (1.24-3.11)	0.004
Unstable angina	1.39 (1.07-1.81)	0.013		
Logistic EuroSCORE	1.02 (1.01-1.04)	0.002		
Parsonnet score	1.02 (1.00-1.04)	0.029		
Number of lesions	1.09 (1.01-1.17)	0.024		
SXS terciles	1.29 (1.11-1.51)	0.001		
CABG				
Age	1.02 (1.01-1.04)	0.010		
Congestive heart failure	1.85 (1.07-3.19)	0.028		
Peripheral vascular disease	2.02 (1.36-2.99)	<0.001	1.82 (1.21-2.74)	0.004
Low ejection fraction (<35%)	2.19 (1.03-4.67)	0.042		
Logistic EuroSCORE	1.05 (1.03-1.08)	<0.001		
Parsonnet score	1.04 (1.02-1.06)	<0.001	1.03 (1.01-1.05)	0.006

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention

1.21–2.74, $P = 0.004$) and the Parsonnet score (HR = 1.03, 95% CI 1.01–1.05, $P = 0.006$) remained associated with MACCE in the multivariate model.

DISCUSSION

This study shows that in the SYNTAX population of patients with left main and/or multi-vessel coronary disease, PCI with complete revascularization is associated with improved outcome compared with incomplete revascularization. In CABG patients, there was no additional risk of adverse events with incomplete revascularization.

The increased rate of MACCE in incomplete revascularized PCI patients is mainly attributed to a higher rate of repeat revascularization. The composite endpoint of death, MI and stroke was also higher with incomplete PCI, but for the individual components of MACCE no significant difference between complete and incomplete revascularization could be demonstrated.

The impact of incomplete revascularization on adverse events after CABG has been studied extensively since the early 1980s.[11-13] These studies uniformly concluded that survival and symptom relief after complete revascularization is favourable compared with incomplete revascularization. After the introduction of stents, many studies have also focused on the impact of completeness of revascularization in PCI patients. Several studies found that incomplete revascularization was associated with higher risk of long-term mortality or repeat revascularization.[14] There are, however, only a handful of studies that compared the influence of complete revascularization on MACCE in CABG and PCI patients simultaneously and there is only one report from a randomized study.[6, 15, 16] The evaluation of incomplete revascularization in non-randomized CABG and PCI cohorts is therefore limited because of differences in patient characteristics. Studies can also not be compared due to differences in definitions of complete revascularization.

Rates of complete revascularization vary significantly between studies. The ARTS trial showed an 82.1 and 70.5% rate of complete revascularization after CABG and PCI for multivessel disease.[17]These rates are much higher compared to this study, which rates were 63.2 and 56.7%, respectively. The rate of revascularization in the ARTS trial was probably higher due to less complex coronary lesions, but also due to the fact that the significant coronary lesions that needed treatment were not defined by the heart team prior to randomization. The surgical procedure was scored as complete revascularization if the diseased segments had been treated according to the surgical report. The ARTS trial showed a significant higher MACCE rate after PCI in the incomplete revascularization group compared with complete revascularized patients (30.6 versus 23.4% respectively, $P < 0.05$), which was driven by a higher rate of repeat CABG (10.0 versus 2.0%, $P < 0.05$).[6] Similar as in ARTS (12.2 versus 10.1%), however, we found no differences between incomplete and complete revascularization groups within CABG patients.[6, 16]

The 43% incompletely revascularized rate with PCI in SYNTAX is lower than 69% that was reported from 39 centres in a study with 11 294 PCI patients.[18] ARTS-II performed PCI with a drug-eluting stent and had a 49% incomplete revascularization rate, quite similar to other studies that reported rates above 50%.[15, 16]

In other studies, the rate of incomplete revascularization in CABG patients is ~10–19%, which is much lower than in the SYNTAX trial,[5, 6, 19, 20] although Kim *et al.*,[15] who also used the SYNTAX score to classify lesions, found a rate of 33% which is close to the 37% in SYNTAX. The reason for such a high incomplete revascularization rate in the SYNTAX CABG cohort is due to the used definition. Previous studies have often based incomplete revascularization on the surgeons report without a pre-operative statement which vessels contained a significant lesion that needed treatment. In the SYNTAX trial, the heart team was obliged to state before the randomization process took place which vessels needed revascularization. Linking this statement to the actual revascularization concludes whether revascularization was complete.

The number of lesions and total occlusion were predictive of incomplete revascularization in the multivariate model, while the SYNTAX score terciles were significant in the univariate analysis. Therefore, incomplete revascularization with PCI is more likely in patients with extensive coronary disease and technically more challenging lesions. In CABG patients, incomplete revascularization was higher in patients with diffusely diseased or narrowed (<2 mm) segments distal to the lesion.

Study limitations

We are aware that this subgroup analysis has limited power due to the methodological limitations of such analyses. The complete and incomplete revascularization subgroups were not predefined in the study protocol. We have performed and reported 10 subgroup analyses and this will produce one significant result by chance only. These results should be interpreted with caution and be considered hypothesis generating.

CONCLUSIONS

At 3 years, incomplete versus complete revascularization with PCI is associated with increased rates of MACCE and repeat revascularization. In patients treated with CABG, adverse events are similar in incomplete and complete revascularization groups.

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Dallas

Chapter 20

Analysis of stroke occurring in the SYNTAX trial comparing coronary artery bypass surgery and percutaneous coronary intervention in the treatment of complex coronary disease

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ABSTRACT

Objectives

To analyze stroke rates in the SYNTAX randomized and registry cohorts of patients being treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) for treatment of complex coronary artery disease.

Background

The SYNTAX trial (NCT00114972) compared PCI to CABG in patients with *de novo* three-vessel and/or left main coronary disease.

Methods

The SYNTAX randomized trial was conducted at 85 US and European sites (n=1,800). All strokes (up to 4 years) were independently adjudicated by a Clinical Events Committee that included a neurologist. An additional 644 and 192 patients were included in the CABG and PCI registries, respectively.

Results

In the randomized cohort, a total of 31 CABG and 19 PCI patients experienced 33 and 20 strokes post-randomization at 4-year follow-up, respectively (p=0.06). Three strokes occurred preprocedurally but following randomization in CABG-treated patients. After CABG, a large proportion of strokes occurred acutely (0-30 days: 9/33) while in the PCI arm most strokes occurred >30 days after the procedure (18/20). Stroke resulted in death in 3 patients in both the PCI and CABG group. Of the patients who developed stroke, 68% (21/31) in the CABG group had residual deficits at discharge; in the PCI group, 47% (9/19) had residual deficits. In a multivariate analysis, treatment with CABG was not significantly associated with increased stroke rates (OR=1.67, 95% CI 0.93-3.01, p=0.089). The incidence and outcomes of stroke were similar in the randomized trial and registries.

Conclusions

There is a higher risk of periprocedural stroke in patients undergoing CABG compared with PCI; however, the risk converges over the first 4 years of follow-up.

INTRODUCTION

In the past few decades, differences in the rates of adverse cardiac events including death and myocardial infarction after percutaneous coronary intervention (PCI) have converged with coronary artery bypass grafting (CABG), predominantly because PCI techniques and technology as well as adjuvant medical therapy have improved.[1-5] Though CABG is the established method of revascularization in patients with left main (LM) and three-vessel disease (3VD), PCI has become an increasingly utilized alternative in this group of high-risk patients.

Stroke, especially early postoperative stroke, is considered a serious risk for patients undergoing CABG but not as much for patients receiving PCI.[4-7] The causes of stroke following CABG are multifactorial and the impact of newer surgical revascularization techniques – no touch off-pump CABG – on the incidence of stroke is uncertain. With the improved outcomes for PCI using drug-eluting stents, the increase in the risk of stroke with CABG needs to be weighed against the increased likelihood of repeated revascularization.

Few randomized studies comparing CABG and PCI have focused on stroke, and especially stroke during follow-up has been an underrepresented analysis.[8] The objective of this *post hoc* analysis was to assess stroke in the large, complex patient population enrolled in both the SYNTAX randomized trial and nested registries, and to define the risk factors and outcomes of patients who experienced a stroke within the first 4 years of follow-up.

METHODS

Study design and treatment description

SYNTAX is a prospective, multinational, randomized clinical trial (RCT; N=1800, CABG N=897, PCI N=903) with parallel nested registries (CABG N=1077, N=644 followed for 5 years; PCI registry N=192) designed to assess clinical outcomes after PCI with TAXUS Express stents compared with CABG for the treatment of *de novo* LM and/or 3VD. By consensus of the Heart Team, consisting of at least one interventional cardiologist and cardiac surgeon, CABG-ineligible patients were enrolled in a PCI registry and PCI-ineligible patients were enrolled in a CABG registry.[9-10] Trial design and detailed methods of this study have been previously published.[5, 11] Analysis of the subset of patients in the randomized controlled trial with stroke was not prespecified. Additionally, as the primary endpoint of the overall SYNTAX study was not met,[5] the results of these subgroup analyses are intended to be observational and hypothesis-generating and should, therefore, be interpreted with caution.

The Institutional Review Board at each participating site approved the study and all subjects provided written informed consent before enrollment. The protocol and consent forms were consistent with the International Conference on Harmonisation Guidance for

Industry E6 Good Clinical Practice, the Declaration of Helsinki, and all local regulations, as appropriate. The study is registered as identifier NCT00114972 on the National Institute of Heath website (www.clinicaltrials.gov).

Definitions

A cerebrovascular event, or stroke, was characterized by a focal neurological deficit lasting >72 hours resulting in irreversible brain damage or permanent impairment. Confirmation of neurological injury by head CT scan or MRI was recommended. Strokes were also classified as ischemic or hemorrhagic. In the randomized controlled cohort of SYNTAX, all strokes and TIAs were confirmed by a local neurologist and adjudicated by an independent Clinical Events Committee (CEC) that included a neurologist. In the CABG and PCI registries, strokes were site-reported but not adjudicated by a CEC. Atrial fibrillation (AF) and/or atrial flutter was reported by the investigative sites as a serious adverse event and was not adjudicated by the CEC. Stroke was assumed to be directly correlated with AF whenever the timing of events was interlinked and/or when this association was confirmed in the patient chart narratives.

Statistical methods

Analysis was based on the intent-to-treat principle and was conducted using SAS System Software, Version 8.0 or higher (SAS Institute, Cary, North Carolina, USA). Data are summarized using descriptive statistics, presented as percent, count/sample size or mean ± standard deviation. The Student t-test was used to compare continuous variables; differences in discrete variables were assessed by means of the chi-square or Fisher exact test, as appropriate.

The cumulative incidence of stroke was analyzed using the Kaplan-Meier method. The rate of stroke was analyzed in pre-specified subgroups by lesion subsets (3VD and LM), gender, age (≤70 and >70), and the presence of diabetes. *Post hoc* analyses according to prior stroke/TIA, peripheral vascular disease, carotid artery disease, and SYNTAX score tertiles were furthermore performed (low ≤22, intermediate 23-32, high ≥33).[5] In-hospital outcome comparisons between treatments and stroke rates within these subgroups does not seem appropriate because of the low stroke rate at this 30-day time-point. Landmark analyses after one-year follow-up were performed.

Univariate analysis including a combination of preoperative and intraoperative variables; in the overall model: age per 10 years increase, gender, previous MI, prior TIA or stroke, medically treated diabetes, angina class, cigarette use, hypertension, hyperlipidemia, carotid artery disease, 3VD/LM, moderate or poor LVEF, renal failure (creatinine ≥200), peripheral vascular disease, overall SYNTAX score, number of vessels treated, treatment group. In addition for the PCI model the variable anti-platelet medication compliance was included, and off-pump surgery was specifically included in the CABG model. These variables were

believed to be clinically relevant to identify potential predictors of 4-year post-allocation stroke. Subsequently, multivariate predictors were identified using step-wise selection with a significance level of <0.10 for entry and exit in a logistic regression model in the overall, CABG, and PCI cohorts separately; medically treated diabetes and left main/three-vessel disease were forced into the model based on previous findings. Predictors are expressed as odds ratio (OR) ± 95% confidence interval.

RESULTS

Randomized arms

Incidence of stroke

The 30-day stroke rate was 1.0% (9/897) after CABG and 0.2% (2/903) after PCI (p=0.037). At 4 years of follow-up, 3.7% of CABG-randomized patients experienced stroke (n=31 patients, n=33 strokes) compared with 2.3% of PCI-randomized patients (n=19 patients, n=20 strokes; p=0.06) (Figure 1). The majority of strokes were ischemic (CABG 29/33 and PCI 13/20).

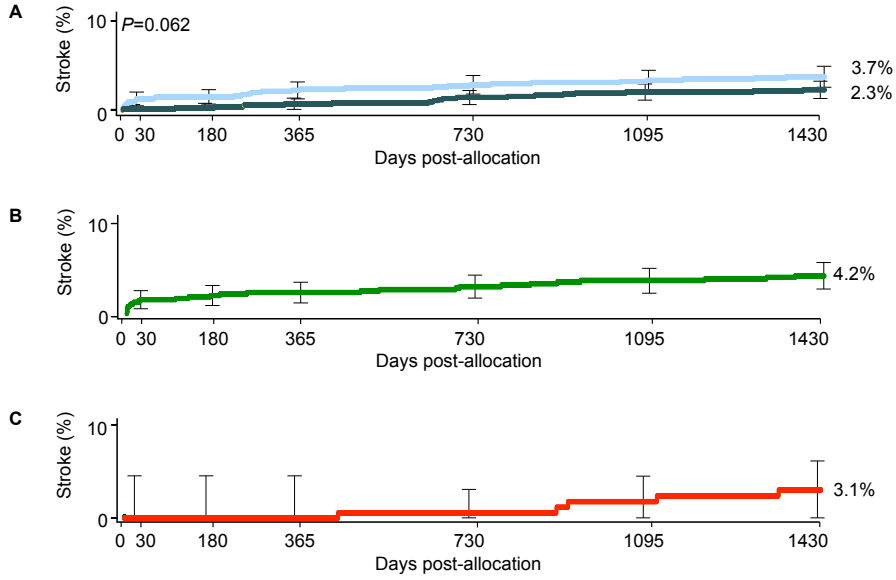

Figure 1 **Unadjusted cumulative stroke rate to 4 years post-allocation**

Kaplan-Meier estimates (± 1.5 x SE) for stroke in randomized patients treated with CABG (light line) or PCI (dark line) ***(A)***, CABG registry patients ***(B)*** or PCI registry patients ***(C)***. *P* value in ***(A)*** from log-rank test.

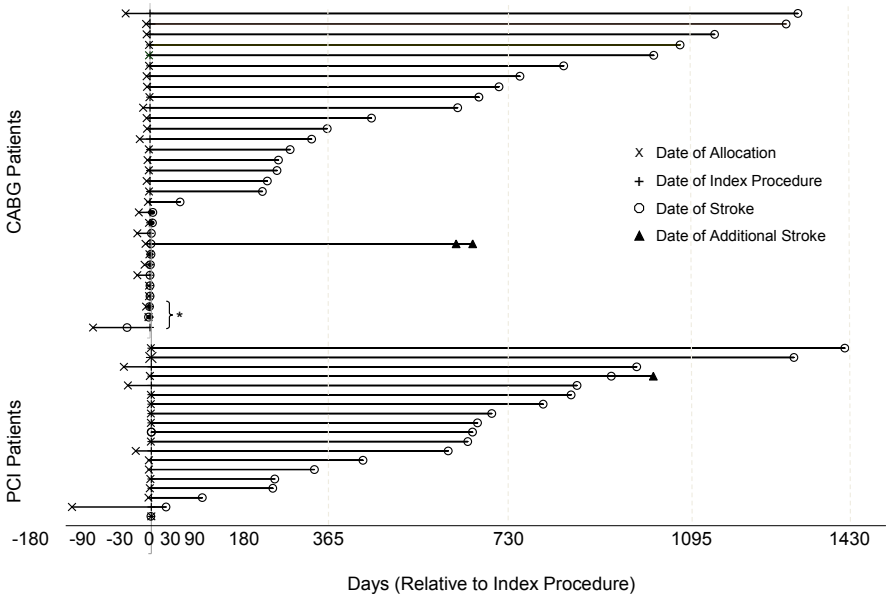

Figure 2 **Timing of stroke relative to treatment group allocation and index procedure in the randomized controlled trial**

The date of allocation (x), index procedure (+), first stroke (●) and second stroke (if applicable, ▲) in each patient are represented on a single line. The dotted grey lines indicate yearly follow-up intervals and the * indicates those strokes which occurred before the index procedure. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

Three patients in the CABG arm of the RCT suffered a stroke before the index procedure (Figure 2); 47 days before treatment in 1 patient and on the day of randomization (3 days before surgery) in a second patient.One patient had a stroke the day before the index procedure, 7 days after allocation; this patient ultimately received medical therapy and not CABG but was counted in the CABG group by intention-to-treat. No pre-procedural strokes occurred in the PCI arm. In those patients who experienced stroke, the length of time between randomization and index procedure was similar between treatment arms (CABG: 12.6 ± 22.4 days [median and IQR: 6, 2-11 days] vs. PCI 17.5 ± 38.8 days [median and IQR: 2, 1-6 days]).

Baseline and procedural characteristics

Baseline characteristics of the randomized cohort of SYNTAX are presented in Table 1. Patients who experienced stroke were older and had more severe cardiovascular disease as defined by increased incidences of prior cerebrovascular events, peripheral vascular disease, hypertension, and a higher mean logistic EuroSCORE.

The rate of off-pump bypass surgery was 15.0% (128/853) in the randomized CABG patient population, with a similar cumulative 4-year stroke rate of 3.6% in the off-pump group compared to 3.5% in patients that underwent on-pump surgery (p=0.98 by log rank).

Table 1 Baseline characteristics of RCT stroke patients

Parameter	All Patients (n=1800)	CABG		PCI	
		Stroke Patients (n=31)	Non-stroke Patients (n=866)	Stroke Patients (n=19)	Non-stroke Patients (n=884)
Age, yr	65.1±9.7 (1800)	67.7±9.2 (31)	64.9±9.8 (866)	71.5±8.0 (19)	65.1±9.7 (884)
Female gender	22.3% (402/1800)	29.0% (9/31)	20.8% (180/866)	26.3% (5/19)	23.5% (208/884)
Prior stroke	4.4% (78/1789)	0% (0/30)	5.0% (43/860)	10.5% (2/19)	3.8% (33/880)
Prior TIA	4.7% (84/1789)	10.0% (3/30)	4.9% (42/858)	10.5% (2/19)	4.2% (37/882)
Carotid artery disease	8.2% (148/1800)	16.1% (5/31)	8.1% (70/866)	0% (0/19)	8.3% (73/884)
Peripheral artery disease	9.8% (177/1800)	22.6% (7/31)	10.2% (88/866)	15.8% (3/19)	8.9% (79/884)
History of smoking	64.7% (1160/1793)	74.2% (23/31)	68.9% (592/859)	63.2% (12/19)	60.3% (533/884)
Current smoker	20.2% (363/1793)	29.0% (9/31)	21.8% (187/859)	15.8% (3/19)	18.6% (164/884)
Medically treated diabetes	25.1% (452/1800)	29.0% (9/31)	24.5% (212/866)	26.3% (5/19)	25.6% (226/884)
Hypertension	75.5% (1349/1787)	93.5% (29/31)	76.4% (657/860)	89.5% (17/19)	73.7% (646/877)
Logistic EuroSCORE	3.8±4.5 (1800)	4.6±3.3 (31)	3.9±4.4 (866)	6.1±5.9 (19)	3.7±4.5 (884)
Mean SYNTAX score	28.7±11.4 (1789)	29.1±11.2 (31)	29.1±11.4 (859)	31.8±10.4 (19)	28.3±11.5 (880)

Numbers are % (n), or as mean ± standard deviation (n). CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; TIA = transient ischemic attack

Atrial fibrillation/flutter during follow-up was reported in 3.4% (31/903) after PCI and in 7.9% (71/897) after CABG. The rate of stroke in patients with versus without arrhythmia was 9.7% (3/31) versus 1.8% (16/872) after PCI, and 5.6% (4/71) versus 3.3% (27/826) after CABG.

In general, patients in the PCI cohort received dual antiplatelet therapy at greater rates before, during and after the index procedure compared with CABG patients up to 3 years post randomization (4-year data not available).[12]

Outcomes after stroke

Of the RCT patients who had strokes, 3 in each treatment arm died as a result of the event (PCI vs. CABG, p=0.66) (Figure 3). The median length of stay in the hospital – whether this was the index hospitalization or readmission – in patients experiencing stroke was 8 days in the CABG arm (IQR 7-14 days) and 7 days (IQR 2-21 days) in the PCI arm. Overall, stroke patients were discharged equally to home or to a rehabilitation facility.

There were 7 patients (23%) in the CABG group and 7 patients (37%) in the PCI group that were alive with no long-term residual deficits after stroke (p=0.28) (Figure 3). The

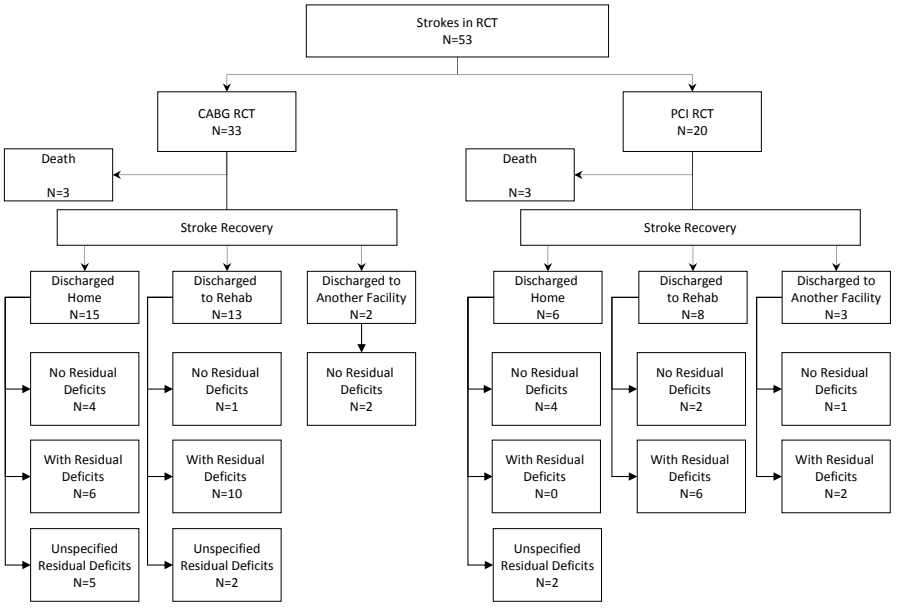

Figure 3 Outcomes after stroke

Nearly all patients who experienced a stroke were either discharged to home or to a rehabilitation centre. Almost half of CABG stroke patients and a third of PCI stroke patients had long-term residual deficits. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; RCT = randomized clinical trial; other abbreviations as previous.

remaining 21 (68%) and 9 (47%) alive CABG and PCI patients, respectively, had residual deficits including (but were not limited to): hypoesthesia/numbness, motor deficits, language deficits, visual deficits, muscle weakness, muscle spasms, paresis/paralysis, and dysphasia. The most common residual symptoms were language deficit and paresis/paralysis.

Subgroups

In the subgroup of RCT patients with LM disease, stroke was significantly increased in CABG-treated patients (CABG 4.3% [n=14] vs. PCI 1.5% [n=5], p=0.03); whereas, in patients with 3VD no significant difference was found (3.4% [n=17] vs. 2.8% [n=14], p=0.53). No significant differences in stroke were found between pre-specified subgroups of gender, age, or the presence of diabetes, nor in *post hoc* analyses according to prior stroke/TIA, or the presence of carotid artery disease (Figure 4).

Although no statistical comparisons were made because of the low number of events, it was noted that the stroke rate in the CABG and PCI arms of the RCT was differentially affected by complexity of coronary artery disease as measured by the SYNTAX score. In CABG-randomized patients, the stroke rate was similar in each SYNTAX score tertile (low SYNTAX score 4.0% [n=10], intermediate 3.6% [n=10], and high 3.7% [n=11]). A step-wise

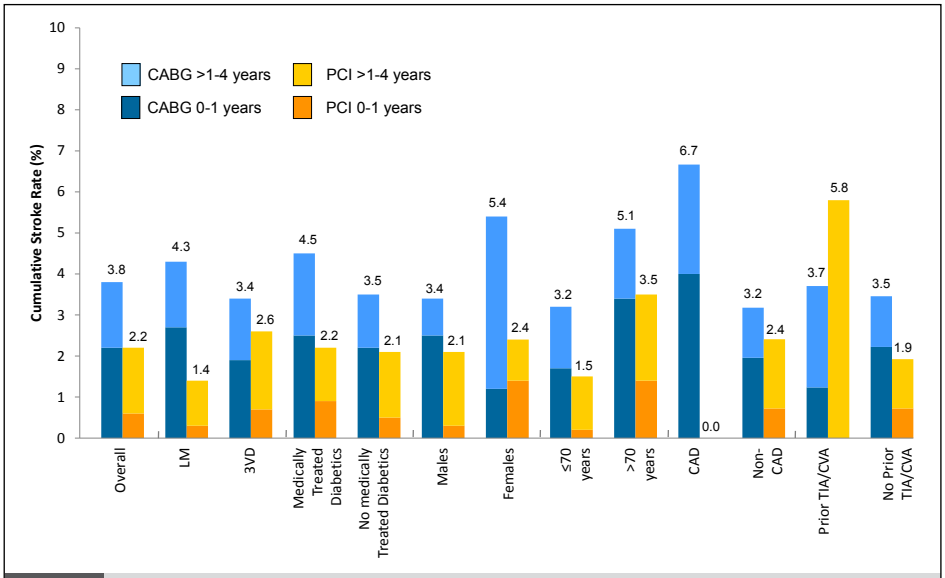

Figure 4 **Rate of stroke at 4 years in predefined and *post hoc* subgroups**

The percentage of patients experiencing a stroke within the first through fourth years of follow-up (CABG blue; PCI orange/yellow) in the overall patient population, patients with LM or 3VD (without LM disease), patients with or without medically-treated diabetes, males and females, patients younger or older than 70 years of age, patients with or without carotid artery disease, and patients with or without prior TIA/stroke. Numbers are from the Kaplan-Meier estimate (%) for the cumulative event rates (cumulative number of patients with events in the specified time window). 3VD = three-vessel disease; CABG = coronary artery bypass grafting; CAD = carotid artery disease; LM = left main; PCI = percutaneous coronary intervention; TIA = transient ischemic event

increase in the risk of stroke was found within SYNTAX score tertiles in PCI-treated patients (low 1.4% [n=4], intermediate 2.0% [n=6] and high 3.5% [n=9]).

Predictors of stroke

By multivariate analysis, the predictors with the greatest impact on likelihood of stroke within 4 years in all randomized patients were age per 10 years, hypertension, moderate or poor LVEF, and angina class CSS 3/4 (Table 2). Treatment with CABG was not significantly associated with increased stroke rates (OR=1.67, 95% CI 0.93-3.01, p=0.089).

In the PCI arm, several markers of the severity of cardiovascular disease (e.g. previous MI, peripheral vascular disease, moderate or poor LVEF, and angina class CSS 3/4) were found to be predictors of stroke within 4 years. In the CABG arm, patients had an increased risk of stroke if they were older and had previously experienced a TIA or stroke.

Nested registries

The CABG registry (N=644 followed for 5 years) predominantly included patients in whom PCI was not considered technically feasible by the Heart Team, and the PCI registry (n=192) included patients in whom it was felt that the outcome of CABG would be unfavorable.[10]

Table 2 Univariate and multivariate predictors of stroke

	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
Overall cohort (n=1800)				
Age per 10 years	1.65 (1.21-2.25)	0.001	1.56 (1.14-2.14)	0.006
Hypertension	4.02 (1.44-11.24)	0.008	3.47 (1.23-9.80)	0.019
Peripheral vascular disease	2.37 (1.16-4.84)	0.017	1.96 (0.94-4.10)	0.071
Moderate or poor LVEF	2.02 (1.10-3.71)	0.023	2.06 (1.08-3.95)	0.029
Angina class CSS 3/4	1.79 (0.99-3.22)	0.052	1.84 (1.01-3.35)	0.048
CABG treatment group	1.78 (1.00-3.18)	0.051	1.67 (0.93-3.01)	0.089
Medically treated diabetes*	…	…	0.91 (0.47-1.77)	0.790
Left main disease*	…	…	0.83 (0.46-1.53)	0.559
PCI cohort (n=903)				
Previous MI	0.29 (0.10-0.84)	0.023	0.18 (0.05-0.62)	0.007
Hypertension	4.67 (1.10-19.76)	0.036	4.10 (0.95-17.62)	0.058
Peripheral vascular disease	2.58 (1.08-6.18)	0.033	2.73 (1.09-6.83)	0.031
Moderate or poor LVEF	1.99 (0.92-4.32)	0.081	2.62 (1.12-6.14)	0.027
Angina class CCS 3/4	2.27 (1.09-4.73)	0.028	2.54 (1.18-5.46)	0.017
Medically treated diabetes*	…	…	0.88 (0.37-2.06)	0.762
Left main disease*	…	…	1.04 (0.49-2.23)	0.915
CABG cohort (n=897)				
Age per 10 years	2.41 (1.38-4.20)	0.002	2.57 (1.43-4.63)	0.002
Prior TIA or stroke	3.43 (1.11-10.66)	0.033	3.58 (1.13-11.38)	0.031
Medically treated diabetes*	…	…	1.03 (0.36-2.94)	0.956
Left main disease*	…	…	0.49 (0.17-1.40)	0.186

*Forced into the model. CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack

As a result, patients in the CABG registry are comparable to the randomized trial except on SYNTAX score (37.8±13.3 versus 29.1±11.4 in the trial). In contrast, patients in the PCI registry had similar lesion complexity but higher Logistic EuroSCORE (7.7±9.0 versus 3.8±4.5 in the trial).

The rate of stroke in the CABG registry was 4.2% (n=26 patients, n=29 strokes) at 4 years of follow-up; there were 3 patients that had 2 strokes. The rate was 3.1% (n=5 patients, n=5 strokes) in the PCI registry (Figure 1B and 1C). Baseline characteristics of the PCI and CABG registries are presented in Table 3. Similar as to the randomized cohorts, patients who experienced stroke more often had prior cerebrovascular events, peripheral vascular disease, or hypertension.

Off-pump CABG was performed in 120 patients, of which 6 patients had a stroke. Twenty patients suffered a stroke after on-pump CABG. The cumulative rate of stroke was 5.3% and 4.0% in patients that underwent off-pump and on-pump surgery, respectively (p=0.57 by log rank).

Table 3 Baseline characteristics of registry stroke patients

Parameter	CABG Registry			PCI Registry		
	Overall (n=644)	Stroke Patients (n=26)	Non-stroke patients (n=618)	Overall (n=192)	Stroke Patients (n=5)	Non-stroke Patients (n=187)
Age, yr	65.7±9.4 (644)	67.0±9.7 (26)	65.6±9.3 (618)	71.2±10.4 (192)	74.4±7.2 (5)	71.1±10.5 (187)
Female gender	19% (124/644)	35% (9/26)	18.6% (115/618)	30% (57/192)	40% (2/5)	29.4% (55/187)
Prior stroke	6% (35/639)	12% (3/25)	5.2% (32/614)	8% (15/192)	40% (2/5)	7.0% (13/187)
Prior TIA	6% (36/638)	19% (5/26)	5.1% (31/612)	8% (15/191)	20% (1/5)	7.5% (14/186)
Carotid artery disease	12% (79/644)	19% (5/26)	12.0% (74/618)	10% (20/192)	0% (0/5)	10.7% (20/187)
Peripheral artery disease	14% (89/644)	19% (5/26)	13.6% (84/618)	16% (31/192)	60% (3/5)	15.0% (28/187)
History of smoking	64% (411/639)	65% (17/26)	64.3% (394/613)	57% (108/188)	40% (2/5)	57.9% (106/183)
Current smoker	22% (140/639)	19% (5/26)	22.0% (135/613)	11% (21/188)	0% (0/5)	11.5% (21/183)
Medically treated diabetes	26% (170/644)	35% (9/26)	26.1% (161/618)	30% (58/192)	80% (4/5)	28.9% (54/187)
Hypertension	74% (465/633)	88% (23/26)	72.8% (442/607)	76% (145/191)	80% (4/5)	75.8% (141/186)
Logistic EuroSCORE	4.0±4.4 (644)	5.2±5.2 (26)	4.0±4.4 (618)	7.7±9.0 (192)	10.3±12.4 (5)	7.7±8.9 (187)
SYNTAX score	37.8±13.3 (632)	35.8±12.8 (25)	37.9±13.3 (607)	31.6±12.3 (189)	36.0±11.2 (5)	31.5±12.4 (184)

Numbers are % (n), or as mean ± standard deviation (n). CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; TIA = transient ischemic attack

In the CABG registry, 3 patients suffered strokes that led to death. There were 26 discharges of which 14 were to home, 8 were to a rehabilitation centre, and 4 to another facility. Seven (27%) CABG registry patients recovered from the stroke without residual deficits. The median hospital stay post-stroke was 11 days (range 6-21 days). In the PCI registry, one patient died as the result of a stroke. Three patients were discharged with residual deficits; one was discharged home and 2 to another facility. One patient recovered from the stroke without residual deficits. The median hospital stay after the stroke in PCI registry patients was 12 days (range 7-14 days).

DISCUSSION

The overall incidence of stroke was low at 4 years in the SYNTAX trial and was not significantly different between PCI and CABG. In the short-term after treatment, patients that

underwent CABG were more likely to experience a stroke compared with PCI-treated patients. After this procedure-related risk, a similar stroke hazard was found in PCI and CABG patients during follow-up.

While large registries and randomized trials comparing PCI and CABG have mainly focused on survival, MI, and repeat revascularization, stroke is particularly underrepresented from such studies.[13-15] Especially assessments of stroke over long-term follow-up have been limited. Yet, in-depth analysis of stroke is crucial to determine the true risk/benefit ratio of PCI and CABG, weighting the risk of stroke versus the risk of repeat revascularization.[16] In our report the hazard of stroke during follow-up was low and there was a similar incidence of stroke after PCI and CABG, providing reassuring information especially for the surgical perspective. Nevertheless, the outcome of patients in this cohort was poor; stroke led to death in 6 patients (CABG n=3, PCI n=3) and a significant amount of surviving patients experience residual impairment after the stroke (CABG 68% and PCI 47%).

Procedure-related stroke remains a serious complication after isolated CABG occurring in as many as 1-4% of patients.[5, 8, 17, 18] Previous nonrandomized studies of CABG versus PCI in LM or multivessel disease (MVD) patient populations have found either an increase in stroke in CABG-treated patients [6, 7] or no difference in stroke rate.[19-21] However, data from randomized trials is limited and, like SYNTAX, not powered to detect a significant difference in stroke rate. A meta-analysis of 7 randomized trials comparing PCI (with balloon angioplasty of bare-metal stents) with CABG for multivessel disease showed that the 90-day stroke rate after randomization to PCI was significantly lower (0.5% vs. 1.1%, p=0.02).[8] Moreover, Daemen and colleagues reported in a meta-analysis of 5 randomized trials using bare metal stents that rates appear to be comparable at 5-year follow-up; 3.6% versus 3.1% for CABG and PCI, respectively.[22] After adjustment for several clinical characteristics, there was little evidence of a benefit for either treatment, with an adjusted hazard ratio of 1.16 (95% CI 0.73-1.83). Considering these data, the results presented here of the SYNTAX trial are comparable to other trials comparing PCI with CABG. However, the recent results from the FREEDOM trial showed a significant increase in stroke at 5-year follow-up after CABG as compared to PCI in 1,900 randomized diabetic patients.[23]

Attempts in improving outcomes after surgical coronary revascularization should be directed towards reducing the rate of stroke. Indeed, some studies have shown a stroke benefit with off-pump surgery due to avoidance of cardiopulmonary bypass and indirect by reducing the rate of AF.[24] In SYNTAX, 15% of randomized and 18.6% of registry CABG patients underwent off-pump surgery. No differences in rates of stroke in the trial (3.1% vs. 3.7% with on-pump) nor in the registry (5.0% vs. 3.8% with on-pump) were found, suggesting no benefit of off-pump CABG in reducing the rate of stroke. However, no data was available on manipulation of the ascending aorta or the use of epiaortic scanning so whether off-pump surgery would truly be beneficial cannot be evaluated. Furthermore, the numbers treated with the off-pump technique were small and no firm conclusions should

be based on these data. It should not be expected that off-pump surgery is useful in all patients undergoing isolated CABG, but it could be more beneficial to consider it merely for subgroups of patients with, for example, severe aortic calcification.[25, 26] Further efforts should be directed in screening the aorta and the use of 'no touch' off-pump CABG if severe calcification is found.

New-onset atrial fibrillation occurs in up to 40% of patients shortly after cardiac surgery and has clearly been associated with an increase in the incidence of stroke.[27] Very limited data is available on AF during follow-up after revascularization. One study reported AF during follow-up in 11.4% of patients after CABG, but did not find show that this was related to stroke.[28] In the SYNTAX trial, we found a low rate of atrial fibrillation/flutter during follow-up (PCI: 3.4% and CABG: 7.9%). The low incidence of AF and the smaller fraction of AF patients who experienced stroke make it difficult to draw any meaningful conclusions regarding the relationship between AF and stroke, especially when considering that the arrhythmia event was not adjudicated by the CEC. In this regard, the correlation between AF and stroke was only base on chart narratives, while the rate of stroke was clearly higher in patients with late arrhythmia. Unfortunately, AF could not be added to the univariate and multivariate analyses because it was considered an adverse event by itself, occurring late during follow-up.

Despite technical improvements, the cause of stroke after revascularization is multifactorial and depends on many more factors, which are also relevant for patients treated with PCI. The presence of multivessel disease has been shown to independently predict stroke after both PCI and CABG.[29, 30] In SYNTAX, the incidence of stroke in the PCI arm, but not the CABG arm, increased with SYNTAX score tertile, suggesting that stroke occurs more frequently in complex disease. Looking more specifically to LM or 3VD subgroups, LM disease has been shown to be a correlate of carotid artery disease, which may increase stroke in LM CABG patients.[30-32] Additionally, aortic manipulation may be more prevalent in the LM compared with the 3VD subgroup, suggesting that the likelihood of stroke is higher in the LM subgroup. Nevertheless, LM/3VD was not significantly associated with stroke in the overall, PCI, or CABG multivariate model.

There is significant variation in the incidence of stroke among different subgroups of patients. Diabetes, female gender, prior TIA or stroke, and advanced age may influence the risk of stroke potentially because of widespread cerebrovascular disease, impaired cerebral blood flow and/or increased susceptibility to atheroembolism or thromboembolism.[29, 30, 33-37] Examining these subgroups in the SYNTAX patient population, there is a non-significant difference in the timing of stroke events in these subgroups that could impact potential preventative or treatment strategies. The timing of strokes in the PCI arm of these subgroups occurs throughout follow-up, whereas in CABG treated patients the majority of strokes occur in the first year. In the multivariate analysis we found that advanced age emerged as a significant independent predictor of stroke in the overall patient population as well as in the

CABG-treated cohort. Furthermore, several factors (e.g., hypertension, moderate or poor left ventricular ejection fraction) that have been shown to predict stroke [38] indeed emerged as independent predictors in our analysis. Patients in the randomized trial and nested registries that suffered a stroke more often had prior cerebrovascular events. Clearly this factor is related to an increased risk of stroke after revascularization, although we were only able to confirm this through multivariate analyses in the CABG cohort. Furthermore, female gender and diabetes did not emerge as significant predictors of stroke, but these results may be the consequence of the low number of events.

The length of time between randomization and treatment was similar in those CABG and PCI patients who suffered a stroke suggesting the numeric increase in preprocedural stroke in the CABG arm was not related to a delay in surgical therapy. Nevertheless, patients randomized to CABG would have been less likely to receive antiplatelet therapy while awaiting their index revascularization. This may have influenced the preprocedure stroke rate as dual antiplatelet therapy has been shown to reduce the risk of a major vascular event compared with aspirin alone (though it is less effective than oral anticoagulant therapy).[39, 40] There were three preprocedure strokes in the CABG arm; one stroke may have been the result of preoperatively discontinuing antiplatelet medications, since the stroke occurred on the day before the procedure when the platelet count would have been relatively high. The other 2 strokes were unlikely to be related to discontinued medications due to the timing of the stroke.

As dual antiplatelet therapy is not the accepted standard of care for post-CABG patients, the overall increase in stroke could have been influenced by the reduced use of aspirin or other antiplatelet agents in the CABG arm. However, the cause of stroke in PCI and CABG cohorts could be different, and even if medication use was comparable this may therefore only have a limited affect on stroke rates. Still, establishing clinical directives for aggressive medical therapy in CABG patients might result in a decrease in stroke risk and is worthy of further study.

Study limitations

Although this analysis provides contemporary insights into the incidence of stroke in a complex PCI and CABG-treated patient population, it is underpowered to detect a difference in stroke rate. Furthermore, more patients withdrew consent (or were lost to follow-up) in the CABG treatment arm, which may have affected our findings, although this is unlikely.[12]

Data on preoperative atrial fibrillation or new atrial fibrillation during index revascularization admission was not recorded in the SYNTAX trial and therefore such analyses could not be included. Follow-up data on atrial fibrillation or flutter were reported by investigator sites as adverse events and were not adjudicated by an independent Clinical Events Committee, and therefore the conclusions derived from these data are limited. Furthermore, patient level details concerning the level of aortic manipulation and the presence of asymptomatic

carotid stenosis and mild neuropsychological disturbance pre- and post-revascularization were not captured.

Finally, a rule of thumb regarding multivariate analyses is to include one covariate per approximately 10 events. We have limited the inclusion of covariates strictly to those deemed clinically relevant, but still have over-fitted the model to include more covariates. These data from the multivariate analyses should therefore be interpreted with caution. However, the limited number of stroke comparisons from randomized PCI versus CABG trials was an incentive to over-fit the model as this may provide novel hypothesis-generating data as to the multifactorial cause of stroke after myocardial revascularization.

CONCLUSIONS

The overall incidence of stroke was low at 4 years in the SYNTAX trial in both CABG and PCI-treated patients. Though more strokes occurred in the CABG arm versus the PCI arm early in the study, no significant differences were found at 4 years and the outcome of stroke after PCI and CABG was similar.

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Utrecht

Chapter 21

Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of coronary artery bypass grafting and percutaneous coronary intervention in the SYNTAX trial

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ABSTRACT

Objective

This prespecified subgroup analysis examined the effect of diabetes on left main coronary disease (LM) and/or three-vessel disease (3VD) in patients treated with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) in the SYNTAX trial.

Methods

Patients (N=1800) with LM and/or 3VD were randomized to receive either PCI with TAXUS Express paclitaxel-eluting stents or CABG. Five-year outcomes in subgroups with (N=452) or without (N=1348) diabetes were examined: major adverse cardiac or cerebrovascular events (MACCE), the composite safety endpoint of all-cause death/stroke/myocardial infarction (MI), and individual MACCE components death, stroke, MI, and repeat revascularization. Event rates were estimated with Kaplan-Meier analyses.

Results

In diabetic patients, 5-year rates were significantly higher for PCI versus CABG for MACCE (PCI: 46.5% versus CABG: 29.0%; $p<0.001$) and repeat revascularization (PCI: 35.3% versus CABG: 14.6%; $p<0.001$). There was no difference in the composite of all-cause death/stroke/MI (PCI: 23.9% versus CABG: 19.1%; $p=0.26$), or individual components all-cause death, stroke, or MI. In non-diabetic patients, rates with PCI were also higher for MACCE (PCI: 34.1% versus CABG: 26.3%; $p=0.002$) and repeat revascularization (PCI: 22.8% versus CABG: 13.4%; $p<0.001$), but not for the composite endpoint of all-cause death/stroke/MI (PCI: 19.8% versus CABG: 15.9%; $p=0.069$). There were no differences in all-cause death or stroke, but rates of MI (PCI: 9.9% versus CABG: 3.4%; $p<0.001$) were significantly increased in the PCI arm in non-diabetic patients.

Conclusions

In both diabetic and non-diabetic patients, PCI resulted in higher rates of MACCE and repeat revascularization at 5 years. Although PCI is a potential treatment option in patients with less complex lesions, CABG should be the revascularization option of choice for patients with more complex anatomic disease, especially with concurrent diabetes.

INTRODUCTION

The global prevalence of diabetes mellitus has continuously increased over the last decades, currently affecting more than 347 million people.[1, 2] Diabetes is a common co-morbidity in patients with coronary artery disease that are evaluated for revascularization, and is shown to be a predictor of adverse events during ollow-up after coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).[3, 5] However, long-term data from randomized trials are limited, particularly for the comparison between CABG and PCI with drug-eluting stents.

The Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial compared PCI with paclitaxel-eluting stents (PES) and CABG for patients with *de novo* three-vessel and/or left main disease.[6, 7] Prespecified subgroup analyses of diabetic versus non-diabetic patients have been reported at one- and three-year follow-up.[8, 9] This study examined the impact of diabetes on 5-year outcomes after PCI and CABG.

METHODS

Study design

The design and methods of the SYNTAX trial have been reported previously.[10] It was a prospective multinational randomized (1:1) trial in which 1800 patients with *de novo* three-vessel and/or left main coronary artery disease were randomly assigned to undergo PCI with TAXUS Express paclitaxel-eluting stents (Boston Scientific, Natick, MA, USA) or CABG. Based on the clinical judgment and consensus of a multidisciplinary Heart Team consisting of an cardiovascular surgeon and interventional cardiologist,[11] patients with anticipated clinical revascularization equipoise through PCI and CABG were randomized (CABG n=897, PCI n=903). Those with expected unfavourable outcomes for PCI or CABG were included in the CABG-ineligible PCI registry (n=198) or PCI-ineligible CABG registry (n=1077), respectively.[12] Five-year clinical follow-up was completed by a clinic visit or telephone call in 86.5% of CABG patients and 94.5% of PCI patients. Follow-up was complete (clinical follow-up or death) in 88.0% and 95.2%, respectively.

Randomization was stratified according to the status of diabetes and left main disease. The subgroup analysis according to diabetes status was prespecified in the trial protocol, although no formal statistical hypothesis was defined *a priori*.

The institutional review board of each of the 85 participating cites approved the protocol. All patients provided written informed consent before enrolment. The trial is registered on the National Institute of Health website with identifier NCT00114972.

Definitions

Medically treated diabetes was defined as treatment with oral hypoglycemic agents or insulin at the time of enrollment. The composite endpoint of major adverse cardiac or cerebrovascular events (MACCE) included all-cause death, cerebrovascular accident (CVA), myocardial infarction (MI), or repeat revascularization (subsequent PCI or CABG). Cerebrovascular events, or stroke, were defined as focal neurological deficits of central origin lasting >72 h, resulting in permanent brain damage or body impairment. Myocardial infarction was defined in relation to intervention status as follows: (i) after allocation but before treatment: Q-wave [new pathological Q-waves in ≥2 leads lasting ≥0.04 s with creatine kinase-MB (CK-MB) levels elevated above normal] and non-Q-wave MI [elevation of CK levels >2× the upper limit of normal (ULN) with positive CK-MB or elevation of CK levels to >2× ULN without new Q-waves if no baseline CK-MB was available]; (ii) <7 days after intervention: new Q-waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN; and (iii) ≥7 days after intervention: new Q-waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5× ULN or plasma level of CK 5× ULN. The CK/CK-MB enzyme levels were obtained and measured by a core laboratory for all randomized patients. An independent Clinical Event Committee adjudicated the events.

Statistical analysis

All analyses were according to the intention-to-treat principle, and performed using SAS software version 8.0 or higher (SAS Institute, Cary, NC, USA). Data are summarized using descriptive statistics, presented as proportions (%, count/sample size) or mean ± standard deviation. Continuous variables were compared using the Student *t* test; differences in discrete variables were assessed with the χ^2 test or Fisher's exact test, where appropriate. Time-to-event Kaplan-Meier estimates with log rank testing were used to compare PCI and CABG in diabetic and nondiabetic patients, and to compare diabetics versus nondiabetics in PCI and CABG groups. *P* values for interaction were generated by logistic regression χ^2 test. *Post hoc* subgroup analyses according to SYNTAX Score tertiles (low 0-22, intermediate 23-32, high ≥33) were performed using time-to-event Kaplan-Meier estimates.[13] Univariate analysis including a combination of preoperative and intraoperative variables was used to identify potential predictors of 5-year outcomes. Subsequently, multivariate predictors of MACCE, the composite safety endpoint of all-cause death/stroke/MI, and repeat revascularization after PCI and CABG were identified using step-wise selection with a significance level of <0.10 for entry and exit in a logistic regression model. A p value <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

In the SYNTAX trial 1800 patients were randomly assigned to PCI (n=903) and CABG (n=897), producing two well-matched treatment groups.[6] Compared to non-diabetic patients (n=1348), patients with diabetes (n=452) had a significantly higher risk profile, which was reflected in a higher EuroSCORE of 4.0 ± 2.7 versus 3.7 ± 2.6, respectively (p=0.027) (Table 1). Diabetics also had more coronary lesions (4.6 ± 1.8 versus 4.3 ± 1.8, p=0.003) and a trend towards more diffuse disease or small vessels (13% versus 10%, p=0.061), although the mean SYNTAX Score was comparable to non-diabetics (29.0 ± 11.2 versus 28.6 ± 11.5, p=0.52).

Diabetes status subgroups

Table 2 lists the clinical outcomes according to diabetes status and treatment arm. The rate of MACCE was significantly different between CABG and PCI among both nondiabetic patients and diabetic patients (Figure 1). There were no differences in the composite safety endpoint of all-cause death/stroke/MI in nondiabetic or diabetic patients. Rates of all-cause death were similar among nondiabetic CABG and PCI patients (HR=1.12 [95% CI 0.81-1.55], p=0.48), and diabetic patients (HR=1.57 [95% CI 0.97-2.55], p=0.065). Cardiac death was significantly more frequent in patients treated with PCI than those who underwent CABG, in nondiabetics (HR=1.62 [95% CI 1.03-2.55]; p=0.035) and diabetics (HR=2.01 [95% CI 1.04-3.88]; p=0.034). Increased repeat revascularization after PCI as compared to CABG was present in nondiabetic (HR=1.82 [95% CI 1.39-2.38]; p<0.001) and diabetic (HR=2.75 [95% CI 1.78-4.24]; p<0.001) patients. There was a significantly higher rate of myocardial infarction after PCI than after CABG in nondiabetic patients (HR=2.90 [95% CI 1.79-4.70]; p<0.001), but this was not significant in diabetic patients (HR=1.62 [95% CI 0.77-3.41]; p=0.20). There were no differences in stroke or graft occlusion/stent thrombosis between groups.

Although patients with diabetes who underwent CABG had numerically higher rates of clinical adverse events than nondiabetic CABG patients, there were no statistically significant differences at 5-year follow-up. However, diabetic patients who underwent PCI had significantly higher rates of MACCE (p<0.001), death (p=0.003), and repeat revascularization (p<0.001) than nondiabetic patients. There were no significant interactions between diabetes status and treatment.

Diabetes control subgroups

Subgroup analyses according to diabetes treatment (oral hypoglycemic agents or insulin) (Table 3) showed that the MACCE rate was significantly increased after PCI in the group on oral hypoglycemic agents (PCI: 40.4% versus CABG: 26.4%; p=0.022) and insulin (PCI:

Table 1 Baseline characteristics

	Nondiabetic (n=1348)	Diabetic (n=452)	p Value
Age, years	65.0 ± 9.9 (1348)	65.4 ± 9.2	0.049
Male gender	79.9 (1077/1348)	71.0 (321/452)	<0.001
Comorbid risk factors			
Body mass index, kg/m2	27.5 ± 4.4	29.5 ± 5.2	<0.001
Metabolic syndrome	37% (398/1064)	70% (258/369)	<0.001
Waist >40 inch male, >35 inch female	42% (502/1194)	61% (238/393)	<0.001
Triglycerides ≥150 mg/dL	33% (409/1230)	42% (170/408)	0.002
HDL <40 mg/dL male, <50 mg/dL female	45% (544/1199)	61% (238/389)	<0.001
Blood pressure ≥130/85 mm Hg	65% (80/1348)	70% (316/452)	0.071
Fasting glucose ≥110 mg/dL	28% (260/934)	82% (286/348)	<0.001
Hemoglobin A1c ≥7.0%	3% (31/1179)	57% (215/378)	<0.001
Hyperlipidemia	77% (1029/1341)	82% (362/444)	0.035
Medically treated diabetes	0% (0/1348)	100% (452/452)	<0.001
Insulin-requiring diabetes	0% (0/1348)	40% (182/452)	<0.001
Cardiovascular history			
Current smoker	22% (292/1343)	16% (71/450)	0.006
Prior myocardial infarction	33% (442/1333)	32% (143/447)	0.65
Congestive heart failure	4% (50/1334)	7% (33/444)	0.001
Carotid artery disease	7% (99/1348)	11% (49/452)	0.019
Prior cerebrovascular accident	4% (51/1341)	6% (27/448)	0.046
Prior transient ischemic attack	4% (58/1341)	6% (26/448)	0.20
Peripheral vascular disease	8% (111/1348)	15% (66/452)	<0.001
Creatinine >200 μmol/L	1% (13/1348)	3% (13/452)	0.003
Unstable angina	28% (378/1348)	30% (134/452)	0.51
LVEF <30%	2% (21/1348)	3% (13/452)	0.075
Parsonnet score	7.5 ± 6.8	11.3 ± 6.4	<0.001
Additive EuroSCORE	3.7 ± 2.6	4.0 ± 2.7	0.027
Lesion complexity			
Diffuse disease or small vessels	10% (136/1338)	13% (60/449)	0.061
SYNTAX score	28.6 ± 11.5	29.0 ± 11.2	0.52
Lesion Characteristics			
Number of lesions	4.3 ± 1.8	4.6 ± 1.8	0.003
Left main, any	36% (480/1338)	29% (130/449)	0.007
Left main only	4% (52/1338)	2% (10/449)	0.096
Left main + 1 vessel	6% (75/1338)	4% (18/449)	0.19
Left main + 2 vessel	12% (160/1338)	11% (50/449)	0.64
Left main + 3 vessel	14% (193/1338)	12% (52/449)	0.13
Three-vessel disease only	64% (858/1338)	71% (319/449)	0.007

HDL = high-density lipoprotein; LVEF = left ventricular ejection fraction

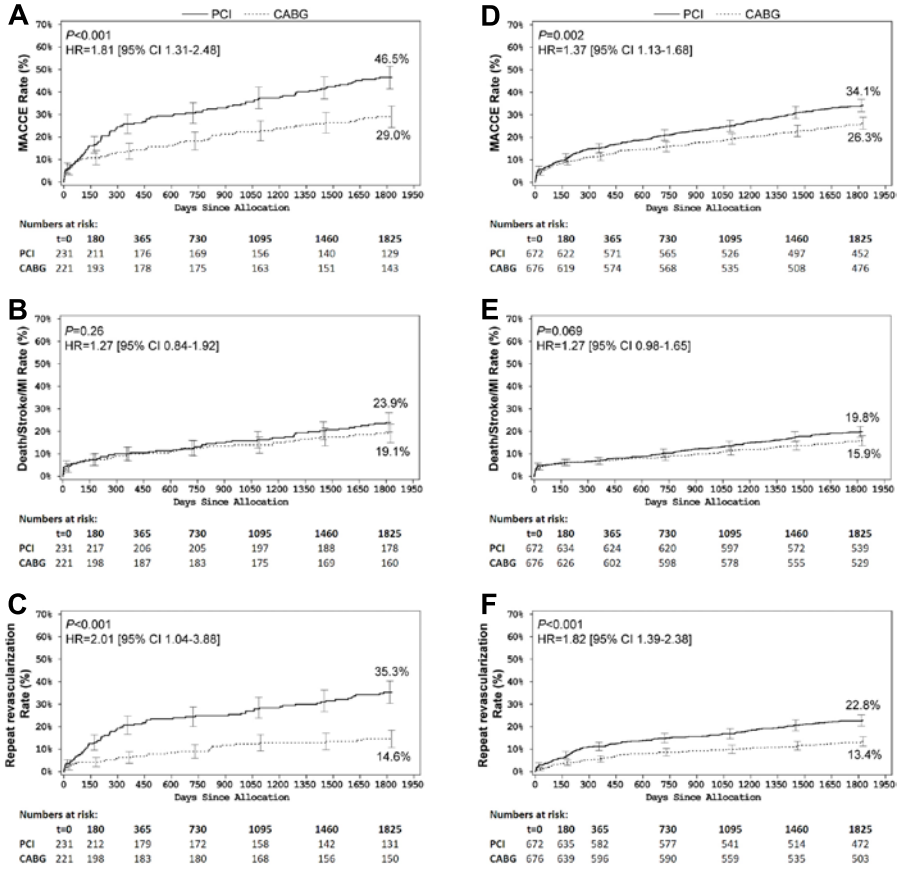

Figure 1 **Five-year outcomes of percutaneous coronary intervention versus coronary artery bypass grafting in diabetic patients and nondiabetic patients**

Kaplan-Meier estimates of major adverse cardiac or cerebrovascular events (MACCE) (***A and D***), the composite endpoint of all-cause death/stroke/myocardial infarction (***B and E***), repeat revascularization (***C and F***) in diabetic patients (***A-C***) and nondiabetic patients (***D-F***). CABG = coronary artery bypass grafting (solid lines); PCI = percutaneous coronary intervention (dotted lines)

56.2% versus CABG: 32.6%; *p*=0.002). Rates of repeat revascularization were also higher in both the insulin dependent and oral hypoglycemic groups (PCI: 29.9% versus CABG: 12.0%; *p*<0.001 and PCI: 44.3% versus CABG: 18.1%; *p*=0.001, respectively). However, the composite safety endpoint of all-cause death/stroke/MI was comparable between PCI and CABG in the group on oral hypoglycemic agents (PCI: 18.8% versus CABG: 17.7%; *p*=0.92), although there was a significantly higher rate of cardiac death (PCI: 18.8% versus CABG: 7.1%; p=0.023) in patients that underwent PCI. There were no differences in stroke or myocardial infarction in either the groups of patients on oral hypoglycemic agents or insulin.

Table 2 Five-year clinical outcomes according to diabetes status

	Nondiabetic (n=1348)			Diabetic (n=452)			Nondiabetic versus Diabetic		
Clinical Outcome	**CABG (n=676)**	**PCI (n=672)**	***p* Value**	**CABG (n=221)**	**PCI (n=231)**	***p* Value**	***p* Value (CABG)**	***p* Value (PCI)**	**Interaction *p* Value[a]**
MACCE	26.3% (167)	34.1% (226)	0.002	29.0% (59)	46.5% (105)	<0.001	0.37	<0.001	0.17
All-cause death/Stroke/ myocardial infarction	15.9% (101)	19.8% (131)	0.069	19.1% (39)	23.9% (54)	0.26	0.25	0.18	0.76
All-cause death	10.9% (68)	12.0% (79)	0.48	12.9% (26)	19.5% (44)	0.065	0.34	0.003	0.43
Cardiac death	4.9% (30)	7.7% (50)	0.035	6.5% (13)	12.7% (28)	0.034	0.31	0.018	
Stroke	3.5% (22)	2.2% (14)	0.15	4.7% (9)	3.0% (6)	0.34	0.49	0.55	0.97
Myocardial infarction	3.4% (22)	9.9% (64)	<0.001	5.4% (11)	9.0% (19)	0.20	0.22	0.66	0.18
Repeat revascularization	13.4% (82)	22.8% (145)	<0.001	14.6% (28)	35.3% (75)	<0.001	0.60	<0.001	0.081
PCI	12.9% (78)	19.3% (123)	0.001	12.9% (24)	28.5% (60)	<0.001	0.95	0.004	
CABG	1.1% (7)	5.8% (36)	<0.001	1.9% (4)	8.7% (18)	0.004	0.35	0.12	
Graft occlusion/ stent thrombosis	3.9% (24)	5.6% (36)	0.14	4.3% (8)	5.3% (11)	0.61	0.84	0.84	0.73

[a]Binary logistic regression interaction term for diabetes status by treatment arm. CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular events; PCI = percutaneous coronary intervention

The rate of graft occlusion or stent thrombosis was not significantly different in the oral hypoglycemic agents group (PCI: 3.2% versus CABG: 5.7%; p=0.35) or the patients that were on insulin (PCI: 8.6% versus CABG: 2.5%; p=0.081). However, the interaction term was statistically significant (p=0.046), suggesting a different impact of diabetes treatment effect on outcomes after PCI and CABG. None of the interaction terms for the other outcomes were significant.

SYNTAX Score subgroups

Subgroup analyses according to the complexity of coronary artery disease demonstrated that there was a consistent increase in adverse events after PCI with increasing SYNTAX Scores, while this was not the case for CABG patients (Figure 2). Event rates of MACCE and the composite safety endpoint therefore showed a stepwise increase in the difference between PCI and CABG with increasing SYNTAX Scores, irrespective of the diabetes status. Among nondiabetic patients the rates of repeat revascularization showed a similar trend

Table 3 Five-year clinical outcomes according to diabetes treatment

	Oral Hypoglycemic Agents (n=270)			Insulin (n=452)			Oral versus Insulin Treatment		
Clinical Outcome	**CABG (n=128)**	**PCI (n=142)**	***p* Value**	**CABG (n=93)**	**PCI (n=89)**	***p* Value**	***p* Value (CABG)**	***p* Value (PCI)**	**Interaction *p* Value[a]**
MACCE[b]	26.4% (31)	40.4% (56)	0.022	32.6% (28)	56.2% (49)	0.002	0.37	0.023	0.34
All-cause death/Stroke/myocardial infarction	17.7% (21)	18.8% (26)	0.92	21.0% (18)	32.1% (28)	0.091	0.65	0.018	0.25
All-cause death	12.0% (14)	16.6% (23)	0.32	14.0% (12)	24.1% (21)	0.082	0.70	0.15	0.53
Cardiac death	6.0% (7)	8.9% (12)	0.42	7.1% (6)	18.8% (16)	0.023	0.79	0.030	
Stroke	5.2% (6)	1.6% (2)	0.094	4.0% (3)	5.2% (4)	0.65	0.56	0.13	0.17
Myocardial infarction	5.1% (6)	7.5% (10)	0.49	5.7% (5)	11.6% (9)	0.23	0.83	0.34	0.76
Repeat revascularization	12.0% (13)	29.9% (40)	<0.001	18.1% (15)	44.3% (35)	0.001	0.19	0.063	>0.99
PCI	12.9% (78)	24.8% (33)	0.004	15.0% (12)	34.6% (27)	0.005	0.41	0.21	
CABG	1.1% (7)	7.0% (9)	0.020	3.3% (3)	11.6% (9)	0.064	0.19	0.23	
Graft occlusion/stent thrombosis	5.7% (6)	3.2% (4)	0.35	2.5% (2)	8.6% (7)	0.081	0.30	0.072	0.046

Data are Kaplan-Meier time-to-event estimates expressed as % (n); log rank *p* value. [a]Binary logistic regression interaction term for diabetes status by treatment arm. [b]MACCE consists of all-cause death, stroke, myocardial infarction, or repeat revascularization (CABG or PCI) in any vessel. CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular events; PCI = percutaneous coronary intervention

as for MACCE and the composite safety endpoint. However, in diabetic patients even in the low SYNTAX Score tertile was there a significantly higher event rate after PCI than after CABG (PCI: 39.4% versus CABG: 17.2%; p=0.006).

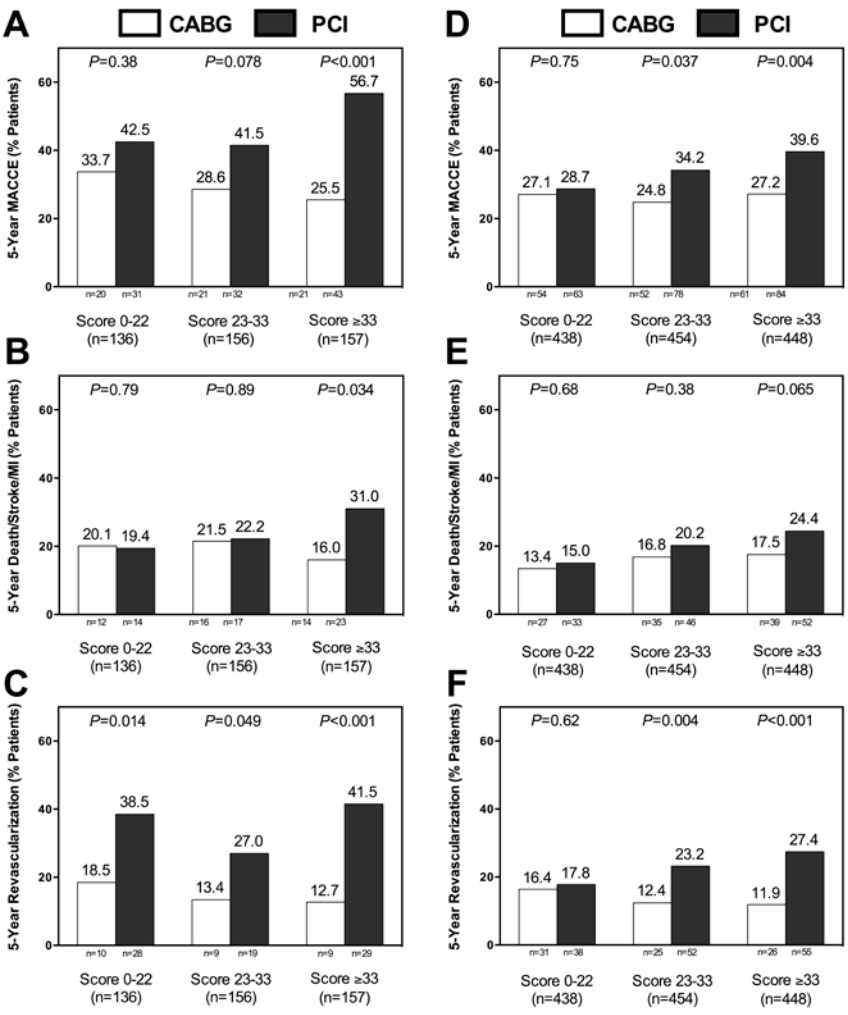

Figure 2 **Five-year outcomes for diabetic patients and nondiabetic patients according to anatomic lesion complexity, as measured by the SYNTAX Score**

Binary event rates of major adverse cardiac or cerebrovascular events (MACCE) *(**A and D**)*, the composite endpoint of all-cause death/stroke/myocardial infarction*(**B and E**)*, repeat revascularization *(**C and F**)* in diabetic patients *(**A-C**)* and nondiabetic patients *(**D-F**)*. Rates are separated according to SYNTAX Score tertiles, indicating low (0-22), intermediate (23-32), and high (≥33) anatomic lesion complexity. CABG = coronary artery bypass grafting (open bars); PCI = percutaneous coronary intervention (solid bars)

Multivariate analysis

The final multivariate model did not identify medically treated diabetes as an independent predictor in the CABG cohort. However, for patients that underwent PCI, medically treated diabetes was an independent predictor of MACCE (OR=1.71 [95% CI 1.22-2.39]; p=0.002) and repeat revascularization (OR=1.73 [95% CI 1.27-2.36]; p<0.001), but not for the composite safety endpoint of all-cause death/stroke/MI.

DISCUSSION

This study examined the impact of diabetes on clinical outcomes after PCI and CABG in the SYNTAX trial. The rates of MACCE were significantly higher after PCI as compared with CABG in both the diabetic and nondiabetic patient subgroups, and this difference is mainly driven by an increase in repeat revascularization. However, the difference between PCI and CABG is larger for patients with diabetes than for those without. In contrast to the previous one- and three-year follow-up reports, patients that underwent PCI also had significantly higher rates of cardiac death at five years.

Randomized comparisons between PCI and CABG for the treatment of coronary artery disease in diabetic patients have mainly been limited by subgroup analyses of large trials. These trials found no significant difference in long-term survival between the two treatment strategies for diabetic patients, but were underpowered and limited by being *post hoc* exploratory subgroup analyses. The only analysis that found a significant benefit of CABG over PCI from the BARI trial included 353 patients and reported 10-year survival rates of 57.9% and 45.5% (p=0.025), respectively.[14] These data of 10 randomized trials (of which only four used bare-metal stents) were summarized in a meta-analysis of 7794 patients, demonstrating that CABG is superior over PCI in diabetic patients.[3] A pooled analysis of trials exclusively using stents showed no difference in outcomes between PCI and CABG, irrespective of diabetes status.[15] The debate between PCI and CABG remained ongoing but the introduction of drug-eluting stents was promising since it showed a reduction in the rate of restenosis in diabetic patients.[16, 17] This drove new analyses of CABG versus PCI with drug-eluting stents. Although results were indeed better with drug-eluting stents, PCI failed to reach non-inferiority to CABG in the first randomized trial dedicated to patients with diabetes (CARDia).[18] Recently the results from the randomized FREEDOM trial (n=1900) even showed that CABG was superior to drug-eluting stents for the composite primary endpoint of death, stroke, and MI (p=0.005).[19]

This substudy of the SYNTAX trial was also from a hypothesis-generating subgroup analysis and, although predefined, should be interpreted with caution. Nevertheless, the results are similar to that from the CARDia and FREEDOM trials.[18, 19] There was a significant difference between PCI and CABG in clinical outcomes, which was more pronounced in

diabetic than nondiabetic patients. This suggests that diabetes may be more relevant in PCI patients than in CABG patients. Clinical outcomes in CABG patients were similar for diabetic and nondiabetic patients, while outcomes after PCI were significantly worse for diabetic patients as compared with nondiabetic patients. A reason for this might be that a patent distal graft functions as protection for future more proximal lesions caused by progressing diffuse disease. After PCI, progression of diffuse disease in diabetic patients forms new lesions that may cause ischemia and/or symptoms. This may also explain why diabetes was not an independent predictor of MACCE after CABG in the SYNTAX trial.[20, 21]

Analyses according to diabetes control show that especially insulin-dependent diabetic patients are at higher risk of adverse events during follow-up. Diabetic patients on insulin that underwent PCI had significantly higher rates of MACCE, the composite safety endpoint of all-cause death/stroke/MI, and cardiac death than patients on oral hypoglycemic agents who underwent PCI. Apart from MACCE and repeat revascularization, there were no significant differences between PCI and CABG for patients on oral hypoglycemic agents. In contrast, compared with insulin-dependent patients that underwent CABG, those who underwent PCI had significantly more cardiac deaths (p=0.023). Therefore, the Heart Team may particularly advocate for CABG to treat insulin-dependent patients, while it should be carefully assessed whether PCI should be preferred over medical therapy for insulin-dependent patients unsuitable for CABG. The SYNTAX trial did not include a medical therapy treatment arm, but it will be interested to see what new developments in improved antiplatelet therapy (e.g. prasugrel, ticagrelor) will contribute to the debate regarding PCI versus medical therapy for diabetics with complex coronary disease.

The complexity of coronary artery disease is crucial when considering different revascularization options. In contrast to the results from the FREEDOM trial where there was no treatment-by-SYNTAX Score interaction,[19]previous studies found that the SYNTAX Score was a predictor of adverse events after PCI but not after CABG. In the current study, differences in outcomes increased incrementally with lesion complexity, even more so in diabetics than nondiabetics. However, recent evidence suggests that a Logistic Clinical SYNTAX Score -- consisting of the SYNTAX Score, age, creatinine clearance, and left ventricular ejection fraction -- is a better predictor of 1-year all-cause death than the SYNTAX Score itself.[22] The addition of diabetes added little improvement of model performance of the Logistic Clinical SYNTAX Score. Nevertheless, in our study the presence of diabetes seems to reinforce the superiority of CABG over PCI and current SYNTAX Score thresholds may need to be adjusted accordingly for patients with diabetes.

According to the SYNTAX study CABG should remain the gold standard for patients complex coronary artery disease, especially those with diabetes. However, new stents may have the potential of reducing rates of adverse events after PCI. In the SYNTAX trial paclitaxel-eluting stents were exclusively used, a stent that is less frequently used in current practice due to superiority of other sirolimus- and everolimus-eluting stents. It is still unclear

which stent should be preferred for patients with diabetes, since improved outcomes with sirolimus- or everolimus-eluting stents over paclitaxel-eluting stents for diabetics has been debated.[23, 24] In the FREEDOM trial both paclitaxel- and sirolimus-eluting stents were used, but the absolute difference in the primary endpoint between stenting and CABG did not differ: Δ6.5% and Δ6.7%, respectively.[19]

Study limitations

Subgroup analyses have been criticized by methodologists and should be interpreted with caution. The diabetes subgroup was predefined and stratified randomization was performed to ensure equal distribution of diabetic patients over the PCI and CABG treatment arms. Nevertheless, the current analyses were not adequately powered and the results should be viewed as *hypothesis-generating* only.

The SYNTAX trial enrolled patients with complex left main and/or three-vessel disease and the results should therefore not be extrapolated to the overall cohort of patients with symptomatic coronary artery disease evaluated for coronary revascularization.

CONCLUSIONS

In both diabetic and non-diabetic patients, PCI resulted in higher rates of MACCE, cardiac death, and repeat revascularization at 5 years. Although PCI is a potential treatment option in patients with less complex lesions, CABG should be the revascularization option of choice for patients with more complex anatomic disease, especially with concurrent diabetes.

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Chapter 22

Drug-eluting stent implantation for coronary artery disease: current stents and a comparison with bypass surgery

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ABSTRACT

Percutaneous coronary intervention (PCI) with bare-metal stents (BMS) has been performed increasingly ever since its introduction in the late 1970s. BMS have been replaced by drug-eluting stents (DES), and many interventional cardiologists consider this as a breakthrough therapy that might compete with coronary artery bypass grafting (CABG) as the standard treatment for coronary artery disease. Several DES are currently used and elute different agents. This review described what these agents are and provides an overview regarding the outcomes and associated adverse events. More importantly, this review compares outcomes of PCI with DES to CABG for patients with left anterior descending coronary artery involvement, left main involvement, or multivessel disease.

INTRODUCTION

Coronary artery disease (CAD) effects a large population, approximately 5000 per million US adults undergo revascularization treatment, accumulating to over 1 million procedures annually.[1] Coronary artery bypass surgery (CABG) has been the golden standard for revascularization of CAD since the early 1980s. However, the introduction of percutaneous coronary interventions (PCI) has decreased the annual rate of CABG to only ~20% of all coronary revascularizations in 2008, and it continues to decline.[1] Of all revascularization procedures with PCI approximately 68% are performed with drug-eluting stents (DES), around 28% are performed with bare-metal stents (BMS), and still around 3.5% of patients receive balloon angioplasty. In patients with complex multivessel disease and/or left main involvement CABG is the golden standard as it offers the best long-term outcome. However, owing to its invasiveness, CABG is not always offered to the patient. The heart team, a team of interventional cardiologists and surgeons,[2] should decide whether PCI or CABG is the preferred treatment according to the coronary characteristics and co-morbidities of the patient. The multidisciplinary approach unfortunately only exists in a minority of centers. This may result in unnecessary revascularization procedures, mainly PCI. A recent study showed that 11.6% of PCIs for nonacute indications were performed inappropriate as it was unlikely to improve patient's health status or survival. Another 38.0% were classified as 'uncertain' appropriateness since the correctness of indication could not be based on the available patient information and/or diagnostics.[3]

Despite the fact that the introduction of DES has converged outcomes after PCI and CABG, it is crucial to remain reticent towards the capacity of DES in reducing adverse events in coronary patients, especially since CABG shows excellent results.[4] In this review we discuss the current DES with their eluting agents and the negative events associated with DES. More importantly, we review the available literature of studies comparing DES to CABG and discuss which treatment is preferred in specific left anterior descending (LAD), MVD, or LM patient cohorts.

DES VERSUS BMS - FIRST GENERATION STENTS

Sirolimus-eluting stent (SES)

Sirolimus, originally developed as antifungal agent, is an immunosuppressant and has been linked with a reduction of neointimal proliferation by inhibition of cytokine-mediated and growth-factor-mediated proliferation of lymphocytes and smooth muscle cells.[5] The first DES ever implanted was the sirolimus coated Cypher stent (Cordis, Warren, New Jersey, USA) in 1999, after which studies succeeded rapidly.

A randomized comparison between SES and BMS was published in 2002.[6] Results were very promising, with lower late luminal loss and restenosis at 6 months, and significantly less major cardiac events. Many following studies confirmed these results, and SESs were the first DES to be approved for treatment of CAD. Meta-analyses of SES versus BMS have shown similar rates of death and MI, but have seen a tremendous improvement regarding repeat revascularization.[7-9] The largest analysis by Stettler et al. reported a hazard ratio as low as 0.30 (0.24–0.37) in reducing subsequent interventions.[8]

Paclitaxel-eluting stent (PES)

Simultaneously with the SES, the TAXUS Express PES (Boston Scientific, Natick, Massachusetts, USA) was developed. This is a stent coated with paclitaxel, an anticancer agent, which reduces smooth cell proliferation and migration.[10] The initial study compared PES to BMS and showed favorable results for PES, similar to what SES had shown.[10] No restenosis at 6 months, and lower rates of late lumen loss. Randomized trials that followed all confirmed these findings.[11] Meta-analyses of individual patient data showed again similar rates of death and MI after PES implantation compared to BMS and a reduction of repeat revascularization (HR = 0.42, 95% CI 0.33–0.53).[8, 9]

The TAXUS Liberté PES was introduced soon after Food and Drug Administration (FDA) approval of the EXPRESS stent. The new stent was designed to improve deliverability, conformability, and homogeneous drug distribution.[12]It showed to be non-inferior to the old Express stent in revascularization rates after 9 months, with similar rates of death and MI.

The SES and PES competed to be the golden standard replacing bare-metal stenting, and several trials have thus compared both stents in a randomized fashion.[11] A meta-analysis showed that SES performed slightly better, with events of MI (HR = 0.83, 95% CI 0.71–1.00) and target lesion revascularization (TLR) (HR = 0.70, 95% CI 0.56–0.84) significantly lower than after PES. Other outcomes of overall death, cardiac death, and stent thrombosis were comparable.[8] It is debated whether SES should be preferred over PES in diabetic patients, since sirolimus may be less effective in the inhibition of smooth muscle cell migration than paclitaxel. A recent meta-analysis, however, showed that also in diabetic patients SES was associated with lower rates of TLR and restenosis.

DES VERSUS BMS - SECOND GENERATION STENTS

Zotarolimus-eluting stents (ZES)

Zotarolimus is an immunosuppressant drug that has been shown to induce complete and uniform neointimal coverage of the stent, with better strut coverage then other DES and lower rates of late-acquired incomplete stent apposition.[13] Naked uncovered struts are associated with increased risk of thrombotic events.[14] In addition, stent polymer coatings of

first generation DES have been linked with allergic reactions and inflammation, which also contribute to stent thrombosis.[15] Second generation polymers better mimic the endothelial lining, preventing thrombosis.[16] Thus, the Endeavor ZES (Medtronic, Minneapolis, Minnesota, USA) would, on paper, have a lower adverse event rate.

The first randomized trial showed similar safety and improved efficacy of the ZES over BMS,[17] and was important for gaining FDA approval in early 2008. Compared to first generation stents, however, ZES could not prove to be better. In a study that compared ZES to SES, the new stent did reduce rates of MI, but also had significantly higher late lumen loss, rates of in-stent restenosis, and TLR. Increased rates of TLR were later confirmed by other studies,[18, 19] which furthermore questioned the safety profile of the ZES as it showed increased rates of death and MI.[19] Compared to the PES, the ZES also showed significantly higher late lumen loss and rates of TLR, while at longer follow-up (3 years), MI was lower in the ZES group.[20] These results were contradicting of an earlier publication, which reported similar rates of death and MI, but higher rates or TLR with PES at 12 months.[18]

Everolimus-eluting stents (EES)

Everolimus was originally developed as an immunosuppressant for organ transplant rejection and is a derivative of sirolimus. Two EES are currently available, the Xience V EES (Abbott Vascular, Santa Clara, California, USA) and the Promus (Boston Scientific, Natick, Massachusetts, USA).

The initial study with EES compared the stent to BMS in only 56 patients total, but already showed improvement in late lumen loss, in-stent restenosis, and TLR rates [21]. Comparisons of the EES with PES followed, and not only demonstrated improvements in late lumen loss, in-stent restenosis, in-stent thrombosis, and TLR, but also in death, MI, and MACE rates.[11, 22-25] In a large propensity matched analysis of EES versus SES with results up to 3 years, EES showed reduced rates of MI (3.3% versus 5.0%, $p = 0.017$), target vessel revascularization (7.0% versus 9.6%, $p = 0.039$), and definite stent thrombosis (0.5% versus 1.6%, $p = 0.01$).[26]

Two recent trials compared EES to ZES and found no differences in death, MI, or repeat revascularization between the two stents.[16, 27] Thus the results of EES are very promising, but are limited because no trials have yet compared outcomes of EES to SES. The EXCELLENT study is expected to report such results sometime in 2012.[28]

COMPLICATIONS OF DES

Despite the obvious advantages of DES over balloon angioplasty and BMS therapies, there are still some complications associated with DES. The possibility of stent fracture raises concerns, as the true incidence is uncertain. It has, however, been found in 29% of cases

in a recent pathologic study.[29]Another complication which incidence is largely unknown is coronary aneurysms. An angiographic follow-up study found aneurysms in 1.3% of the patients treated with DES,[30] but others consider this an underreporting.[31] Both these phenomenons are associated with restenosis, ST elevation, and embolization.[11]

Stent implantation warrants long-term antiplatelet therapy. However, which agent should be used, whether dual or triple antiplatelet therapy is superior, and the length of therapy is debated, since studies report controversial findings. Nevertheless, patients needing CABG after PCI for an acute coronary syndrome are at high risk of increased blood-loss and reoperation for bleeding.[32] Novel agents might be able to reduce these negative aspects, but data remain limited.[33, 34]

DES VERSUS CABG

Several meta-analyses and large registries have shown favorable outcomes after CABG compared to PCI.[35-37] However, the Heart Team has agreed that certain patient groups can be treated with a DES as standard therapy.[38, 39] Especially patients with single-vessel or two-vessel disease benefit from DES by replacing the need to undergo intensive surgery and rehabilitation. Contraindications for DES are a previously stented vessel which cannot receive anymore new stents, or whenever previous stenting has lead more than once to in-stent thrombosis. There are more contraindications, but many of these are physician dependent and vary between hospitals. The preference for CABG over PCI is most often lesion specific, which is discussed below.

Proximal LAD

The current guidelines on myocardial revascularization indicate that CABG should be preferred over PCI in patients with proximal LAD lesions.[38] This advice is supported by historical data from studies that compared PCI with BMS to CABG. A meta-analysis which included 8 studies that compared PCI with BMS to CABG demonstrated that CABG is associated with significantly lower rates of recurrent angina (OR = 2.62, 95% CI 1.32–5.21), repeat revascularization (OR = 4.55, 95% CI 2.47–8.37), and major adverse cardiac or cerebrovascular events (MACCE) (OR = 2.86, 95% CI 1.62–5.08).[40] A later meta-analysis reported similar findings.[41]

Since the rates of recurrent angina and repeat revascularization have been significantly reduced with DES compared to BMS, several studies again attempted to show similar results between PCI and CABG in patients with LAD lesions (Table 1).[42-47] A recent analysis of 5 year ARTS I and II data showed that SES and CABG had similar rates of death, stroke, and MI, but DES still had significantly increased rates of repeat revascularization (HR = 0.37, 95% CI 0.21–0.65, $p < 0.001$). The authors rightfully concluded comparable safety of DES and

Table 1 Key studies comparing PCI with DES to CABG in patients with proximal LAD involvement

Author, Year	Year of procedure	Study design	Follow-up	No. of patients (DES:CABG)	All-cause death, % (DES vs CABG)	Recurrent angina, % (DES vs CABG)	MI, % (DES vs CABG)	Revascularization, % (DES vs CABG)	MACE, % (DES vs CABG)	MACCE, % (DES vs CABG)
Toutouzas, 2008	2001-2006	SVD, Diabetes	mean 20 mths	39:38	2.6 vs 0	5.1 vs 7.9	0 vs 2.6	5.1 vs 0	7.7 vs 2.6	NA
Thiele, 2009	2003-2007	SVD	1 yr	65:65	1.5 vs 3.0	19 vs 26	1.5 vs 7.7	6.2 vs 0†	7.7 vs 7.7	NA
Hong, 2005	2003	undefined	6 mths	119:70	1.7 vs 4.3	2.6 vs 4.4	5.1 vs 5.8	3.4 vs 1.5†	NA	NA
Ben-Gal, 2006	2002-2003	SVD or MVD	2 yrs	83:83*	2 vs 7	35 vs 8.4	NA	16.8 vs 3.6	20.5 vs 7.2	NA
Yan, 2009	2003-2005	MVD	2 yrs	600:709	2.2 vs 5.2	NA	NA	10.2 vs 2.0	NA	13.3 vs 9.6
Garg, 2011	1997-2003	MVD	5 yrs	289:206	3.5 vs 6.3	NA	4.5 vs 6.8	18.3 vs 6.8	NA	24.9 vs 18.0
Hannan, 2008	2003-2004	2VD or 3VD	18 mths	2600:1486 1178:3833	5.5 vs 5.4 7.2 vs 6.7	NA	NA	NA	NA	NA

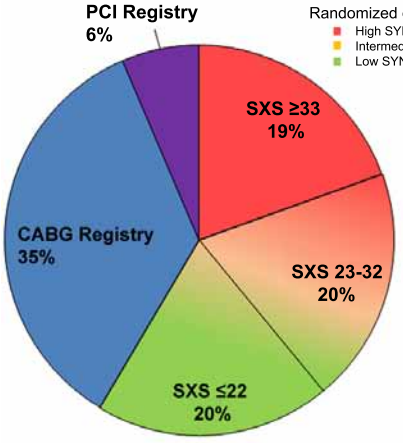
*Propensity matched analysis. †Target vessel revascularization. CABG = coronary artery bypass grafting; DES = drug-eluting stent; NA = not available; MACE = major adverse cardiac event; MACCE = major adverse cardiac or cerebrovascular event; MI = myocardial infarction; MVD = multivessel disease; SVD = single-vessel disease

CABG, but stated that CABG has superior efficacy.[42] Therefore, CABG should indeed remain the standard therapy for patients with proximal LAD involvement.

Multi-vessel disease

PCI versus CABG in MVD has been a topic of discussion for decades. Outcomes after PCI improved after the introduction of BMS compared to balloon dilatation, but CABG remained the standard of care. This was supported by numerous randomized trials in the mid 1990s, but also by later trials performed after improvement of antiplatelet therapy and peri-procedural care. A meta-analysis of trials that compared BMS to CABG showed that PCI had similar rates of death, and death or MI, but repeat revascularization was significantly higher.[36] A more comprehensive meta-analysis that furthermore included trials comparing PCI to off-pump or minimally invasive CABG did also show increased rates of angina and repeat revascularization with PCI.[48] Next to outcomes within delineated patient groups in randomized trials, 'real-world' studies found similar results and furthermore concluded superior outcomes with CABG for MVD.[49]

With the introduction of DES, interventional cardiologist became more optimistic in expecting results of PCI and CABG to converge even more, and many patients were treated with PCI even though randomized trials had not yet proven similar results.[50] The randomized 'all comers' SYNTAX trial [39] confirmed that CABG remains the standard of care for treatment of MVD.[51, 52] Rates of MACCE were significantly higher in the PCI cohort (28.0%



		PCI	CABG	P value
All patients	Low SYNTAX score (0-22)	22.7%	22.5%	0.98
	Intermediate SYNTAX score (23-32)	27.4%	18.9%	0.02
	High SYNTAX score (≥33)	34.1%	19.5%	<0.001

		PCI	CABG	P value
3VD	Low SYNTAX score (0-22)	25.8%	22.2%	0.45
	Intermediate SYNTAX score (23-32)	29.4%	16.8%	0.003
	High SYNTAX score (≥33)	31.4%	17.9%	0.004

		PCI	CABG	P value
Left main	Low SYNTAX score (0-22)	23.0%	18.0%	0.33
	Intermediate SYNTAX score (23-32)	23.4%	23.4%	0.90
	High SYNTAX score (≥33)	37.3%	21.2%	0.003

Figure 1 Distribution and outcomes of patients enrolled in the SYNTAX Trial

The Heart Team concluded that 6% and 35% of patients were best treated with respectively PCI and CABG. Within the randomized cohort of 1,800 patients, patients were divided into three terciles based on their SYNTAX Score: low SYNTAX Score (green), intermediate SYNTAX Score (orange), and high SYNTAX Score (red). Outcomes within subgroups showed that PCI could be an alternative to CABG in patients with a low coronary lesion complexity, while CABG is preferred for patients with complex lesions.

versus 20.2%), driven by an increase in repeat revascularization (19.7% versus 10.7% after CABG). With the SYNTAX study the SYNTAX score was introduced which characterizes the complexity of the coronary disease. A hypothesis-generating subgroup analyses showed similar results with PCI compared to CABG in patients with low SYNTAX scores (<23, with less complex lesions),[53] thus showing promising results that patients with lower lesion complexity can undergo PCI with satisfactory results, which might broaden the indication of PCI to those patients with less complex 3VD (Figure 1).

Patients that suffer from diabetes have historically been a subgroup of patients that show better results after CABG than after PCI.[36] The introduction of DES and improved antiplatelet therapy has provided better outcomes after PCI than before, but the SYNTAX trial continued to demonstrate significantly better outcomes with CABG.[54, 55]These results are in line with the CARDia randomized comparison of PCI versus CABG in diabetics.[56] This should therefore remain the current standard of therapy in diabetic patients, independent of the coronary complexity.

Nevertheless, despite these conclusions, decisions should be made within a heart team. A large registry demonstrated that specialists should be praised for their clinical judgment. From similar unadjusted rates of death and MI in PCI and CABG cohorts it seems that the current decision-making process to determine PCI or CABG treatment seems appropriate for certain indications.[35, 57]

Left main disease

Even more so than for MVD, a debate is ongoing about the optimal treatment for patients with LM disease.[4] Despite efforts to demonstrate non-inferiority of PCI with DES to CABG, the current guidelines on myocardial revascularization still recommend CABG as the most appropriate revascularization strategy.[38] Recent meta-analyses report satisfactory outcomes with stenting, but uniformly agree that CABG provides significantly better rates of less repeat revascularization.[58, 59]

The SYNTAX trial reported a pre-defined hypothesis-generating subgroup analysis in left main patients.[39, 60] In 705 randomized LM patients, rates of repeat revascularization were significantly lower after CABG, but higher rates of stroke complicated surgery. Especially in patients with a SYNTAX score <33 PCI showed comparable results. This was recently confirmed in a 'real-world' registry.[61]The number of patients in the left main group in SYNTAX was however too small to draw firm conclusions and the ongoing EXCEL study will address the issue in an adequately powered trial.[62]

The recently published PRECOMBAT trial reported data of exclusively LM patients. It concluded that PCI with DES is non-inferior to CABG with results up to 2 years. The primary end-point of death, MI, stroke, or ischemia-driven TVR was 12.2% and 8.1% respectively in the PCI and CABG cohorts.[63] Nevertheless, the trial was subject to extensive methodological flaws, with (1) an event rate much lower than projected, (2) a large number of cross-overs

from CABG to PCI, and (3) a very generous non-inferiority margin. The authors therefore rightfully stated that these results should not be clinically directive.

Thus, data remain limited, and it should be stressed again that both SYNTAX and PRECOMBAT data have low statistical power. Results from the ongoing EXCEL trial should be awaited before any definitive conclusions can be drawn.

CONCLUSIONS

PCI with stenting has shown major improvements gained over the past decades, resulting in significant converged outcomes after PCI and CABG. Patients with low complexity coronary lesions show good results after PCI with DES. However, both currently available observational and trial data suggest that CABG should, for the time being, remain the preferred treatment for patients with LAD or LM involvement and complex MVD.

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Bali

Chapter 23

Coronary artery bypass grafting: optimizing outcomes and future directions

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ABSTRACT

Since first introduced in the mid-1960s, coronary artery bypass grafting (CABG) has become the standard of care for patients with coronary artery disease. Surprisingly, the fundamental surgical technique itself did not change much over time. Nevertheless, outcomes after CABG have dramatically improved over the first 50 years. Randomised trials comparing percutaneous coronary intervention (PCI) to CABG have shown converging outcomes for select patient populations, providing more evidence for wider use of PCI. It is increasingly important to focus on the optimization of the short- and long-term outcomes of CABG and to reduce the level of invasiveness of this procedure. This review provides an overview on how new techniques and widespread consideration of evolving strategies have the potential to optimize outcomes after CABG. Such developments include off-pump CABG, clampless/anaortic CABG, minimally invasive CABG with or without extending to hybrid procedures, arterial revascularisation, endoscopic vein harvesting, intraprocedural epiaortic scanning, graft flow assessment and improved secondary prevention measures. In addition, this review represents a framework for future studies by summarizing the areas that need more rigorous clinical (randomised) evaluation.

INTRODUCTION

Coronary artery bypass grafting (CABG) was first introduced in the mid-1960s and evolved rapidly as the standard of care for patients with extensive coronary artery disease.[1] However, the introduction of percutaneous coronary intervention (PCI) led to a reconsideration of therapeutic strategies.[2] Improvements in stent design, adjuvant medical therapy and technical skills quickly turned PCI into a very attractive alternative treatment option for patients with acute coronary syndromes and less complex coronary disease.[3-7] The broader use of PCI is reflected by declining CABG rates over the last decades,[8] even though recent long-term results from the SYNTAX,[9] ASCERT [10] and FREEDOM [11] trials showed significantly better survival rates after CABG than after PCI. Despite converging outcomes between the two treatments in select patient populations, coronary surgery currently remains the standard of care for most elective patients, including those with diabetes and/or complex left main or three-vessel disease.[9, 12]

Although short-term outcomes have dramatically improved over the first 50 years, surprisingly, technical aspects of the CABG procedure did not change significantly. Particularly in an era of increasing and sometimes overuse of PCI, several aspects of CABG should be improved to further optimize short- and long-term outcomes, while at the same time improving the appeal of CABG which is regarded as an overly invasive attractive treatment option by some. A number of advancements have been proposed, but adoption rates for these techniques are low.

This review provides a summary of how CABG outcomes can be optimized by adoption of new developments. These developments include off-pump, clampless/anaortic, and minimally invasive CABG with or without extending to hybrid procedures, arterial revascularisation, endoscopic vein harvesting, intraprocedural epiaortic scanning and graft flow assessment and improved secondary prevention measures. Furthermore, this review represents a framework for future studies by summarizing the areas that need more rigorous clinical evaluation.

OPERATIVE TECHNIQUES

Off-pump CABG

In 2001, approximately 25% of CABG procedures were performed off-pump.[13] In the Western world, the contemporary rate of off-pump CABG procedures is about 20%, while in Asia the majority of procedures are performed off-pump.[14]Theoretically off-pump CABG could reduce morbidity --particularly stroke-- and even mortality by avoiding cardiopulmonary bypass that is associated with formation of microemboli, an increased blood-brain barrier permeability and aortic manipulation during cross-clamping and cannulation.[15]

Numerous risk-adjusted studies have found that the off-pump technique appears favourable in terms of both hard and surrogate endpoints.[16, 17] A meta-analysis of propensity score adjusted studies that included more than 120,000 patients demonstrated the superiority of the off-pump technique with respect to 11 selected short-term outcomes, particularly for mortality as the most important one (OR=0.69; 95% CI 0.60-0.75; p<0.0001) and for stroke (OR=0.42; 95% CI 0.33-0.54; p<0.0001).[18]In addition, the most recent meta-analysis of 59 randomised trials on a total of 8,961 patients comparing on-pump with off-pump CABG demonstrated a 30% [95% CI 1-51%] relative risk reduction for stroke.[13] However, some studies have shown increased rates of mortality and repeat revascularisation during follow-up;[19, 20] probably caused by reduced graft patency after off-pump vs. on-pump CABG.[21, 22] Although single-centre prospective angiographic studies have shown similar excellent graft patency rates with off-pump and on-pump CABG [23], the one-year results from the ROOBY trial showed a 27% higher risk of graft occlusion in the off-pump group (95% CI 9-48%); graft patency was 87.8% in the on-pump and 82.6% in the off-pump patients (p<0.001).[24] These results were criticized for the lack of sufficient experience that contributing surgeons had with off-pump procedures..[25] However, several other trials involving highly experienced surgeons and a meta-analysis pointed in a similar direction as the findings from the ROOBY trial.[25-27] Off-pump CABG has also been associated with increased rates of incomplete revascularisation, and could result in reduced long-term survival.[28]

The CORONARY trial showed no benefit of off-pump CABG over on-pump CABG at 30 days or 1 year in 4,752 randomised patients.[29, 30] Although there appears to be a significant benefit of off-pump over on-pump CABG in patients at high operative risk [31] and in patients with atherosclerotic aortas,[32] the hypothesis that off-pump CABG is beneficial for 'all-comers' may be too optimistic.[33] Despite the encouragement to a general use of off-pump techniques, it has been recommended specifically for high-risk patients.[34] However, even this recommendation was recently challenged by the results of the GOPCABE trial, which did include elderly higher-risk patients (n=2,539) but was still unable to confirm superiority of the off-pump over the on-pump approach in this subset of patients.[35] Patient selection is critical, since the majority of patients can safely and efficiently undergo on-pump CABG without the risk of increased 30-day repeat revascularisation rates associated with off-pump procedures in the latest trials. [29, 30, 35]It may therefore be cumbersome for trainees to gain experience in a procedure with a steep learning curve that is infrequently performed only in selected patients.

It is worth noting that although evidence for a survival benefit of off-pump CABG is inconsistent across the peer-reviewed literature, a preponderance of evidence suggests that off-pump CABG is associated with significant reductions in transfusion requirements, prolonged ventilation, ICU and hospital length of stay, new renal failure, stroke/neurocognitive decline and other clinical endpoints.[36]

Clampless / Anaortic off-pump CABG

If off-pump CABG is performed, the degree of aortic manipulation should be reduced to a minimum. The benefit of off-pump CABG may be limited unless partial clamping of the aorta is avoided. Aortic clamping produces a significantly higher number of solid microemboli on transcranial Doppler than clampless surgery and can therefore lead to procedural stroke.[37] It is to note that in most trials, including the major randomised trials, off-pump CABG was not performed using an anaortic technique, the major driver for reducing stroke.

The number of studies that compared clampless CABG to 'regular' CABG with clamping is limited (Table 1). In the absence of a large randomised comparison, Börgermann and colleagues used propensity matching to compare mortality and stroke rates between patients who underwent clampless off-pump or conventional CABG.[38] In the propensity-matched cohort of 395 pairs, clampless off-pump CABG reduced rates of death (OR=0.25, 95% CI 0.05-1.18; p=0.080) and stroke (OR=0.36, 95% CI 0.13-0.99; p=0.048). More specifically, one of the largest studies to date found significantly lower stroke rates after off-pump than on-pump CABG, if an all-arterial "no touch" technique was applied or when the proximal vein graft anastomoses were performed clampless using the HeartString device (Guidant, Indianapolis, USA).[39] This evidence is complemented by a meta-analysis including 11,398 patients that showed that the absence of aortic manipulation was associated with a significant reduction of neurologic complications (OR=0.46, 95% CI 0.29-0.72; p=0.0008).[40]

Minimally invasive CABG / Hybrid revascularization

One of the drawbacks of CABG remains its invasiveness, even without the use of cardiopulmonary bypass. Quality of life scores at 30 days and patient treatment satisfaction surveys throughout the first 6 months are significantly higher after PCI than after CABG.[41] Moreover, CABG is sometimes referred to as a procedure where "the chest is cracked open", which from a patient's perspective presents a frightening prospect of postoperative pain and extended rehabilitation. As a result, patients often prefer PCI to CABG because of "temporal discounting", i.e. disproportionally emphasize short-term results even though CABG has been shown to be superior to PCI with respect to long-term survival and angina relief.[10, 41-44] Less invasive surgical techniques may present an attractive alternative; minimally invasive direct coronary artery bypass (MIDCAB) does not require sternotomy and is therefore more acceptable to patients than conventional CABG.[45] The left minithoracotomy incision is smaller, the risk of scarring is less, and risks of deep sternal wound infection and problems with sternum healing are omitted. Although MIDCAB may be associated with slightly increased pain postoperatively due to spreading of the ribs, the length of stay is markedly reduced and there is an early postoperative quality of life benefit over conventional CABG.[46-48] MIDCAB was shown to be as safe and efficient as off-pump CABG, while reducing the recovery time.[49] Holzhey and colleagues recently reported long-term results from their single-centre experience on 1,768 patients.[50] Five and 10 year survival was 88.3% and 76.6%, respectively.

Table 1 Studies comparing clampless or 'aortic no touch' off-pump CABG with conventional off-pump or on-pump surgery

Author, year	Inclusion	Design	No. of patients	Use of devices	Unadjusted 30-day outcomes			Comment
					Mortality	Stroke	Perioperative MI	
Clampless								
Lev-Ran, 2004	2000-2002	Retrospective	103 vs 57 with clamp	No	2.9 vs 7%	0 vs 5.3%	3 vs 5%	Side clamping an independent predictor of stroke or mortality: OR = 6.28, 95% CI 1.39-28.4; p = 0.017
Kempfert, 2008	2003-2005	RCT	51 vs 48 with clamp	Connector: PAS-Port	0 vs 2.1%	…	…	
Manabe, 2009	2004-2007	Retrospective	109 vs 185 no touch vs 241 with clamp	HeartString (n=81) Enclose II (n=28)	1.8 vs 1.1 vs 1.2%	2.8 vs 0.5 vs 0.8%	…	
El Zayat, 2012	2009	RCT	29 vs 28 with clamp	HeartString	0 vs 0%	0 vs 6.9%	…	
Emmert, 2012	1999-2009	Prospective	507 vs 524 with clamp	HeartString	1.8 vs 2.5%	0.4 vs 2.9%	1.5 vs 3.1%	Clampless off-pump CABG was a significant predictor of reduced stroke in a propensity-score adjusted analysis: OR = 0.04, 95% CI 0.003-0.48
Börgermann, 2012	2009-2010	Prospective	395 vs 887 with clamp	Connector: PAS-Port (n=310)	3.3 vs 7.6%	…	…	In a propensity matched cohort of 395 pairs, clampless off-pump CABG was a predictor of less death (OR = 0.25, 95% CI 0.05-1.18; p = 0.080) and stroke (OR = 0.36, 95% CI 0.13-0.99; p = 0.048)
Aortic No Touch								
Patel, 2002	1997-2001	Prospective	597 vs 520 off-pump with manipulation vs 1210 on-pump	No	1.5 vs 1.0 vs 2.5%	0.5 vs 0.4 vs 1.6%	…	Aortic manipulation was not a significant predictor of neurologic outcome in off-pump patients
Calafiore, 2002	1998-2000	Retrospective	1533 vs 3290 any manipulation (on- or off-pump)	No		0.2 vs 1.4%		In multivariable stepwise logistic regression, any aortic manipulation was associated with an OR of 8.4 (95% CI 2.4-28.9; p = 0.0008) for stroke

Table 1 *Continued*

Author, year	Inclusion	Design	No. of patients	Use of devices	Unadjusted 30-day outcomes			Comment
					Mortality	Stroke	Perioperative MI	
Kim, 2002	1998-2001	Prospective	222 vs 123 'regular' off-pump vs 76 on-pump	No	0.9 vs 2.4 vs 2.6%	0 vs 0.8 vs 3.9%	1.4 vs 5.7 vs 6.6%	
Leacche, 2003	1996-2001	Retrospective	84 vs 556 'regular' off-pump	No	1.6 vs 1.7%	0 vs 1%	1.3 vs 1.8%	
Kapetanakis, 2004	1998-2002	Retrospective	476 vs 2527 moderate vs 4269 extensive aortic manipulation off-pump	No	1.5 vs 1.9 vs 2.1%	0.8 vs 1.6 vs 2.2%	1.1 vs 0.7 vs 0.5%	No touch surgery was independently associated with reduced stroke when compared with extensive (OR = 1.7, 95% CI 1.11-2.48; p < 0.01) and even moderate aortic manipulation (OR = 1.8, 95% CI 1.15-2.74; p < 0.01). Propensity-matched analysis failed to show similar findings.
Lev-Ran, 2005	2000-2003	Retrospective	471 vs 229 off-pump with side-clamp	No	2.1 vs 2.6%	0.2 vs 2.2%	1.4 vs 1.5%	The use of side-clamping was an independent predictor of stroke: OR = 28.5, 95% CI 2.27-333.3; p = 0.009)
Bolotin, 2007	2000-2001	Prospective	110 vs 216 on-pump CABG	No	2.7 vs 1.9%	0 vs 2.3%	0.9 vs 1.4%	
Vallely, 2008	2002-2006	Prospective	1201 vs 557 off-pump with aortic manipulation	No	1.4 vs 1.3%	0.3 vs 1.1%	0.6 vs 0.4%	No touch surgery was an independent predictor of reduced rates of neurologic events: OR = 0.23, 95% CI 0.06-0.92; p = 0.037
Misfeld, 2010	2002-2007	Retrospective	1346 vs 600 'regular' off-pump vs 1753 on-pump	No	1.0 vs 1.0 vs 2.3%	0.1 vs 0.5 vs 0.9%	0.5 vs 0.5 vs 0.6%	Compared to no touch off-pump CABG, on-pump CABG (OR = 12.3, 95% CI 2.9-52.2; p = 0.0006) and 'regular' off-pump CABG (OR = 7.0, 95% CI 1.4-35.0; p = 0.018) were independent predictors of neurologic complications
Emmert, 2011	2004-2009	Prospective	1365 vs 567 off-pump with clamp	HeartString	1.8 vs 1.6%	0.7 vs 2.3%	0.9 vs 1.9%	No touch clampless off-pump CABG was a significant predictor of reduced stroke in a propensity-score adjusted analysis: OR = 0.39, 95% CI 0.16-0.90; p = 0.04

CABG = coronary artery bypass grafting; MI = myocardial infarction; OR = odds ratio

The rates of freedom from major adverse cardiac or cerebrovascular events and angina were 85.3% and 70.9%, respectively.

Exposure during MIDCAB is largely limited to the left anterior descending (LAD) artery and eventually diagonal branches, and therefore almost exclusively performed in patients with isolated LAD stenosis or occlusion. An open left internal mammary artery (IMA) graft to the LAD is without doubt the single most important conduit that offers a prognostic benefit based on its proven long-term patency and improved survival. Patients with multivessel disease - especially at younger age - also derive a survival benefit from total arterial grafting with bilateral IMA grafts.[51] The added benefit of a second arterial graft in older patients is less well documented;[52] however, the rate of early vein graft failure, especially to distal targets and severely diseased small vessels, is high and ranges from 10 to 26% between 12 and 18 months after surgery.[53, 54] In some patients, a hybrid procedure can combine the benefits of a MIDCAB --providing a left IMA (LIMA) graft to the LAD-- and stenting of the circumflex and/or the right coronary artery. This type of management may yield results similar to those of a full CABG procedure,[55] but randomised trials are still lacking (Table 2). The hospitalization costs of hybrid revascularisation are similar to the costs of off-pump CABG, but the time to return to work is shorter and patient satisfaction higher.[56] Halkos and colleagues showed that survival after hybrid revascularisation at 5-year follow-up was comparable with off-pump CABG in patients with left main disease (88.6% versus 83.4%, respectively; p=0.55) and in patients with multivessel disease (86.8% versus 84.3%, respectively; p=0.61) (Figure 1).[57, 58]

Complete revascularisation in patients with multivessel disease by minimally invasive CABG can also be achieved via a totally endoscopic coronary artery bypass (TECAB) procedure,[59] by combining an endoscopic with an open approach,[60] or by a hybrid endoscopic and percutaneous procedure.[61] Such procedures are only performed in selected patients at specialized centres and require extensive operating times. Earlier series reported unsatisfactory patency results, but with the evolution of better endoscopic stabilizers the results from

Table 2 Reasoning supporting hybrid revascularisation

Patients with double vessel disease and chronic total occlusion of the LAD
Patients with multivessel disease and an indication for CABG requiring complete revascularisation in whom a full sternotomy is contraindicated or not desired
Patients with multivessel disease with a dominant LAD or complex proximal LAD lesion morphology and poor surgical targets in the distal CX or RCA territory amenable for PCI
Patients with multivessel disease with an indication for PCI (SYNTAX score <22) or CABG in clinical trials comparing hybrid revascularisation with PCI or CABG (SYNTAX score >23)
Patients with multivessel disease undergoing emergent PCI of a culprit lesion of a CX or RCA lesion (in the setting of STEMI, Non-STEMI or ACS) with a staged surgical revascularisation of the LAD

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; Cx = Circumflex; LAD = left anterior descending artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-elevation myocardial infarction; Non-STEMI = Non-ST-elevation myocardial infarction

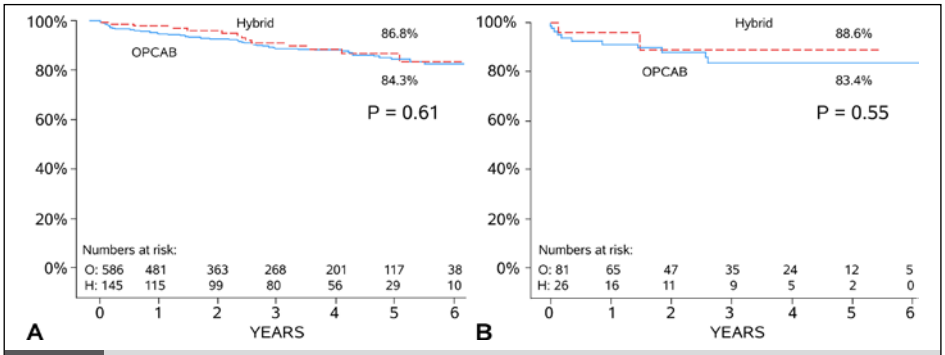

Figure 1 **Long-term survival of hybrid revascularisation in comparison with off-pump coronary artery bypass grafting**

A comparison between treatment strategies shows no differences in 5-year survival in patients with multivessel disease ***(A)***, nor in patients with left main disease ***(B)***. Adapted with permission from Halkos and colleagues.[57, 58]

these highly experienced centres are similar to conventional CABG with a reported mortality rate of 1-2% [59-62] and a five-year survival in the range of 85-95%.[61-63]

Adoption of minimally invasive CABG procedures has been slow. For MIDCAB, this may be explained in part by the low incidence of isolated proximal LAD stenosis [64] and also by the high technical demands of this procedure. Hybrid revascularisation for multivessel disease, theoretically, has a much larger target population. However, a systematic search of the literature shows that the accumulated evidence is based on small non-randomised studies comprising just over 1,000 patients in total (Table 3).

Between October 2003 and April 2010, only 174 patients underwent hybrid revascularisation in the United States.[57, 58] Apart from technical issues, the low adoption rate is partly due to logistic reasons; the staging of two procedures in a (hybrid) operating room and/or catheterisation laboratory, and the administration or discontinuation of antiplatelet therapy. A survey performed in 2002 indicated that 80% of US surgeons perform <5 MIDCAB procedures annually.[65] When asked about hybrid procedures, only 10% of surgeons were in favour. In contrast, 50% of 180 cardiologists were in favour of hybrid revascularisation. Yet, only two cardiologists (1.1%) had referred patients for MIDCAB (with or without PCI). Stronger evidence to support a recommendation for hybrid revascularisation is expected from a number of currently on-going registries, the largest of which is the Hybrid Revascularisation Observational Study (NCT01121263) that includes patients throughout the US and is sponsored by the National Heart, Lung, and Blood Institute (NHLBI).

Table 3 Systematic review of studies evaluating hybrid revascularisation

Author, year	Inclusion	Design	No. of patients	Type of lesions	Strategy	30-day outcomes			Long-term outcomes		
						Conversion	Death	Revasc.	Mean follow-up	Mortality	Revasc.
Lloyd, 1999	1996-1998	Prospective	18	Multivessel	Simultaneous, n=4 PCI following MIDCAB, n=14	0	0	5.6%	at 18 months	0	5.6%
Zenati, 1999	1996-1998	Retrospective	31	Multivessel	Staged	0	0	3.2%	11 months	0	9.6%
Wittwer, 2000	1996-1999	…	35	Multivessel	PCI following MIDCAB	0	0	0	11 ± 8 months	0	6.5% (of 31 pts)
de Canniere, 2001	1997-1997	Retrospective	20	2-vessel	MIDCAB following PCI, n=9 PCI following MIDCAB, n=11	0	0	0	at 2 years	0	15%
Cisowski, 2002	1999-2001	Retrospective	50	2-vessel	PCI following MIDCAB	0	0	0	…	0	12.7%
Riess, 2002	1997-2001	Retrospective	57	Multivessel	PCI following MIDCAB	0	0	0	101 ± 38 weeks	1.8%	…
Stahl, 2002	…	Retrospective	54	Multivessel	PCI following MIDCAB, n=35 MIDCAB following PCI, n=19	0	0	0	12 months	0	…
Davidavicius, 2005	2001-2003	Prospective	20	Multivessel	MIDCAB following PCI, n=14 PCI following MIDCAB, n=6	0	0	0	19 ± 10 months	0	0
Katz, 2006	…	Prospective	27	2-vessel	Simultaneous, n=4 PCI following MIDCAB, n=12 MIDCAB following PCI, n=11	0	0	0	at 3 months	0	18.5%
Us, 2006	2002-2004	Prospective	17	Multivessel	MIDCAB following PCI	0	0	0	21 ± 7 months	0	17.6%
Gilard, 2007	2000-…	Prospective	70	Multivessel	MIDCAB following PCI	0	1.4%	2.9%	33 months	1.4%	0
Holzhey, 2008	1996-2007	Retrospective	117	Multivessel	Simultaneous, n=5 PCI following MIDCAB, n=59 MIDCAB following PCI, n=53	0	1.9%	1.9%	208 patient-years	92.5% at 1 year 84.8% at 5 years	…

Table 3 *Continued*

Author, year	Inclusion	Design	No. of patients	Type of lesions	Strategy	30-day outcomes			Long-term outcomes		
						Conversion	Death	Revasc.	Mean follow-up	Mortality	Revasc.
Kiaii, 2008	2004-2007	Prospective	58	2-vessel	Simultaneous	1.7%	0	0	20.2 months	0	…
Kon, 2008	2005-2006	Prospective	15	Multivessel	Simultaneous	0	0	0	at 1 year	0	6.7%
Gao, 2009	2007-2008	Prospective	10	Multivessel	PCI following MIDCAB	0	0	0	5 months	0	0
Vassiliades, 2009	2003-2007	Prospective	91	Multivessel	Staged	2.0%	0	0	…	94% at 3 years	5.5% at 1 year
Zhao, 2009	2005-2007	Retrospective	112	Multivessel	Simultaneous CABG and PCI	N/A	2.6%	0	…	…	…
Delhaye, 2010	2006-2008	Prospective	18	Multivessel	PCI following MIDCAB	0	0	0	at 1 year	0	5.6% (TVR)
Halkos, 2011	2003-2010	Retrospective	27	LM	PCI following MIDCAB	0	0	0	median 3.2 years	88.6% at 5 years	7.4%
Halkos, 2011	2003-2010	Retrospective	147	Multivessel	Simultaneous n<10 Staged for the remaining	0	0.7%	0	median 3.2 years	86.8% at 5 years	12.2% 8.8% (TVR)
Hu, 2011	2007-2009	Retrospective	104	Multivessel	Simultaneous	1.0%	0	0	18 months	0	1.9%
Rab, 2012	2003-…	Retrospective	22	LM	PCI following MIDCAB	0	0	0	39 ± 23	4.5%	0

The PubMed database was searched from its inception through June 2012, which yielded the included studies. CABG = coronary artery bypass grafting; MIDCAB = minimally invasive coronary artery bypass; N/A = not applicable; LM = left main; PCI = percutaneous coronary intervention; TVR = target vessel revascularisation

Arterial grafting

The use of one IMA graft, most often the left IMA anastomosed to the LAD combined with venous conduits represents the standard therapy for patients undergoing CABG.[66, 67] However, venous bypass grafts tend to fail: a recent study by Kim and colleagues found that 11.8% of saphenous vein grafts failed within 7 days,[68] which is similar to the failure rate reported by FitzGibbon in 1978.[69] Therefore, bilateral IMA (BIMA) grafting should be strongly considered in patients with multivessel coronary disease, because BIMA grafting is associated with reduced mortality during the first year post-surgery and during long-term follow-up.[70] A meta-analysis of 7 pooled studies with 11,269 single and 4,693 bilateral IMA grafts demonstrated that BIMA was associated with a reduced risk for death: HR=0.81 [95% CI 0.70-0.94].[51]

In the Arterial Revascularization Trial (ART), the only randomised trial to date comparing BIMA and single IMA (SIMA), 3,102 patients were randomised in 28 centres in 7 countries.[71] Mortality rates at 30 days were 1.2% in both groups, and 2.3% versus 2.5% at one-year for SIMA and BIMA groups, respectively. There were also no differences in the incidence of stroke, MI and repeat revascularization. While the use of a second IMA graft added 23 minutes to the operative procedure which in itself took 3-4 hours, the trial clearly demonstrated that BIMA grafting was as safe as SIMA grafting, even though the risk of a need for later sternal reconstruction was increased: relative risk 3.24 [95% CI 1.54-6.83]. An extended follow-up (for up to 10 years) is expected for this study and will hopefully determine whether survival with BIMA grafts is indeed superior. The trial, however, also highlighted the difficulties with BIMA grafting; 16.4% of patients randomised to BIMA did not receive the allocated treatment compared with 3.3% patients not receiving SIMA grafting.[72]

The proportion of procedures that are performed with IMA grafts is increasing, but a large inter-hospital variance remains. The use of at least one IMA can be as low as 45-65% in some centres, failing to provide optimal care to patients.[73] It is disconcerting that in the United States the use of BIMA grafts was only 4.0% among 541,368 patients.[73] The respective figures are 12% in Europe and 30% in Japan.[74] Among 1,541 procedures performed in the SYNTAX trial and registry, 97.1% included a single arterial conduit while 22.7% received a second IMA graft. Due to the technically more challenging and time-consuming nature of BIMA grafting, the fear of higher morbidity (i.e. sternal wound complications) and mortality, and the absence of clear randomised data showing a survival benefit, some surgeons may be reluctant to use BIMA grafts. Nevertheless, in order to improve CABG outcomes, the use of both IMA grafts should be considered more frequently.

When unilateral IMA grafting is performed, the saphenous vein is the most frequently chosen conduit for additional graft(s). Because of high failure rates of venous grafts, the radial artery has been investigated as an alternative. The long-term results from the RSVP trial (n=142) suggested favourable radial artery graft patency rates.[75] More recent 5-year

results from the larger randomised RAPS trial (n=510) showed that, compared with the saphenous vein grafts, the radial artery had lower rates of functional graft occlusion (12.0% versus 19.7%, respectively; p=0.03) and complete occlusion (8.9% versus 18.6%, respectively; p=0.002), although the string sign was observed more frequently in radial artery grafts (3.4% versus 0%, p=0.01).[76] Several large observational studies have confirmed excellent graft patency and have even reported superior long-term survival rates,[77, 78] also after applying propensity matching.[79-81] However, widespread utilisation of the radial artery has been hampered by concerns regarding vessel spasm, graft atherosclerosis and unfavourable results from a number of studies. The largest trial (n=733) to date found no differences in graft patency at 1-year follow-up;[82] similar results have been reported from a number of observational studies.[80, 83] At least one study has shown radial artery graft patency to be significantly worse than right IMA graft patency.[84] To ensure good graft patency, the radial artery should be used preferably in high-grade lesions.[85] Data from the STS database suggest that only 9% of CABG procedures are performed with the radial artery.[86]

A higher rate of disease progression to total occlusion in native coronaries has been reported after CABG than after PCI.[87] Patent arterial grafts, by virtue of their nitric oxide secreting properties, may protect against future atherosclerotic lesions. Therefore, arterial grafting can be viewed as a preventive measure that goes beyond pure treatment.[88, 89]

Endoscopic vein harvesting

Traditional open saphenous vein graft harvesting requires a large incision, resulting in a large scar and a risk of postoperative wound complications. Endoscopic vein harvesting was introduced in the mid-1990s as an alternative.[90]This method has the advantages of reduced scarring, less pain, decreased postoperative complications, and shorter length of stay.[91]

Several randomised studies and meta-analyses have shown that endoscopic harvesting significantly reduces rates of wound infection, wound dehiscence, and overall complications.[92] However, subgroup analyses from the PREVENT IV and ROOBY randomised trials suggested that endoscopic vein harvesting resulted in reduced graft patency during follow-up.[93, 94] In PREVENT IV, there even were significantly higher rates of death. Although this is of potential concern, long-term follow-up analyses from large observational studies have not been able to confirm that clinical outcomes are worse in patients that underwent endoscopic vein harvesting.[95, 96] A recent study that included 235,394 patients with 3-year follow-up showed no increased risk of mortality (adjusted HR=1.00 [95% CI 0.97-1.04]; p<0.99) or the composite of mortality, myocardial infarction, and repeat revascularisation (adjusted HR=1.00 [95% CI 0.98-1.05]; p=0.34).[96]

Current data indicate a paradigm shift towards endoscopic harvesting as opposed to open vein graft harvesting. Between 2003 and 2008, 52% of grafts were harvested endoscopically at 989 sites in the United Stated; in 2008, the rate was already 70%.[96] Trainees in the United States now almost exclusively learn how to perform endoscopic harvesting.[91] It is important

to start using this technique at an early stage, especially because inexperienced surgeons are known to cause significantly more vein injury.[97] The International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) Consensus statement has given a Class IB recommendation for endoscopic vein harvesting.[98] Still, endoscopic harvesting is performed in only a minority of cases in Europe. A recent single-centre study showed that only 12.4% of veins were harvested endoscopically between 2008 and 2010.[99] Unfortunately, large-scale real-world data from European centres are scarce.

INTRAOPERATIVE ASSESSMENTS

Epiaortic scanning

Atherosclerosis of the ascending aorta is present in >50% of patients undergoing CABG.[100] Aortic atherosclerosis was found to be a significant predictor of postoperative neurologic events and renal failure, both caused by atheroembolism.[101, 102] Palpation of the aorta is frequently employed prior to cannulation and/or aortic manipulation, but the sensitivity of this technique is very limited.[103] Therefore, imaging is advocated to detect atherosclerosis if an anaortic technique cannot be applied. Depending on the findings, the operative technique can be modified as needed.[104]Both transesophageal echocardiography and epiaortic ultrasonography were introduced as methods for detecting severe atherosclerosis. While transesophageal echocardiography severely underestimates the degree of atherosclerosis, epiaortic scanning is an easy, safe and efficient procedure and is preferred.[105]

Epiaortic scanning is not routinely used probably because of the cost of the machine (>€100,000) and the fact that there have been no direct randomised comparisons between CABG with and without epiaortic scanning that demonstrate a benefit. Such a study would be problematic because of the large sample size required. However, although one small study indicated no reduction in transcranial Doppler-detected cerebral emboli,[106] several studies have suggested that early postoperative stroke is significantly reduced when the operative technique is modified in accordance with results of epiaortic scanning.[107-110] Wareing and colleagues reported that in 14% of elderly patients undergoing cardiac procedures (CABG in 89%), the site of aortic cannulation and/or clamping, the sites for attaching vein grafts, and/or the sites for instillation of cardioplegic solution were altered.[111] The precise rates of such modifications provided in the literature vary, between 4% and 31%.[100] A recent study by Daniel and colleagues showed that epiaortic scanning was increasingly performed from 2002 to 2009 (45% and 90%, respectively) and coincided with less frequent aortic clamping (98% and 73%, respectively).[112]

Graft flow measurement

Data from the PREVENT IV trial showed a suboptimal rate of saphenous vein graft failure after on- and off-pump CABG at one year;[113] a meta-analysis reported a failure rate of approximately 5% and 25% at 3 and 12 months, respectively.[114] Several mechanisms of graft failure have been described. Early graft failure can occur as a result of anastomotic problems, limited outflow, graft kinking upon chest closure and thrombosis, while thrombosis and processes of intimal hyperplasia and atherosclerosis are causes of late failure. Intraoperative graft assessment has been introduced to evaluate grafts and identify anastomotic problems and limited outflow. Disturbingly, Balacumaraswami and colleagues demonstrated that intraoperative graft assessment identified 9% of grafts with inadequate flow in 25% of CABG patients, which led to revision in 3% of grafts and 8% of patients.[115] Multiple techniques for intraoperative graft assessment have been proposed: coronary angiography, transit time flow measurement (TTFM), high-frequency epicardial echocardiography, thermal coronary angiography, and intraoperative fluorescence imaging (IFI).[116] Although angiography is thought to be the best and most reliable method for assessing flow,[117] the infrastructure required for coronary angiography is rarely available in standard operating rooms. Wider implementation of hybrid operating rooms could potentially facilitate the use of coronary angiography. Currently, intraoperative graft assessment is most frequently performed by TTFM or IFI.

Both TTFM and IFI have strengths and weaknesses and have been criticized for their inability to identify grafts with minor abnormalities that present a risk for failure. Furthermore, inconsistent and variable measurements may lead to unnecessary graft revisions.[115] Two parameters, graft function and anatomy, are required for complete assessment of bypass grafts. TTFM assesses function and can very accurately detect truly poor and truly good grafts (true positives, true negatives), but there is an issue with respect to detecting poor grafts with a low pulsatility index (PI) (false negatives). False positives (good graft, high PI) rarely occur. IFI evaluates anatomy but is associated with more inter-observer error than standard angiography. Comparisons between TTFM and IFI suggest that IFI is more sensitive.[114, 115, 118] TTFM combined with epicardial ultrasonic scanning is a recently introduced approach that may provide both a functional as well as anatomic assessment.

Despite issues, the clinical value of TTFM has been demonstrated in studies that found that TTFM predicted graft failure at 3, 6 and/or 12 months post-CABG.[119-121] Inadequate graft flow as defined by PI >5 on TTFM was found to be an independent predictor of major adverse cardiac events, operative death in particular.[122] No studies have yet explored the impact of IFI measurements on clinical outcomes during follow-up. In general, randomized comparisons between CABG with and without graft flow measurement remain absent. Such studies would be required to evaluate the true benefit their routine intraoperative use would have on early and late rates of reintervention, myocardial infarction, and death. One issue that remains, however, is that long-term graft failure would still occur as caused by other mechanisms that those controlled by intraoperative graft assessment. This could be one of

the reasons why surgeons doubt its clinical impact and consequently why routine use has been limited.

SECONDARY PREVENTION

Apart from technical and procedural considerations, further optimization of long-term outcomes after CABG can be achieved through a strict medical regimen. Progression of atherosclerosis in the native coronary arteries continues after CABG and is associated with deterioration of left ventricular function. However, this can be prevented by administration of antiplatelet agents,[123] β-blockers,[124] angiotensin-converting enzyme inhibitors (ACE-I),[125] statins[126, 127] and fatty acids,[128] all of which have been identified as independent predictors of survival after CABG. The PREVENT IV trial found that secondary prevention medications were associated with significantly reduced rates of death or myocardial infarction after CABG.[129] Moreover, data suggests that graft patency may be better in patients taking statins,[130] fatty acids,[131] aspirin [66] and possibly dual antiplatelet therapy.[132] Administration

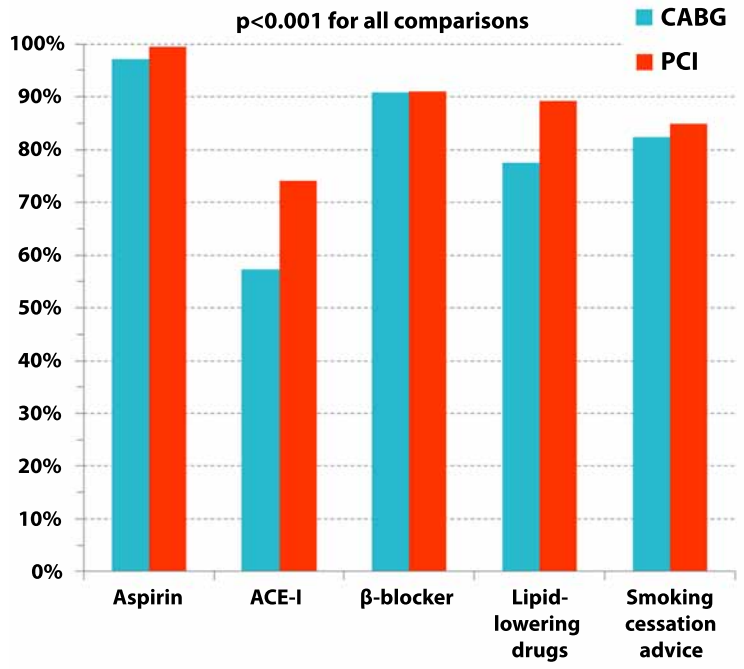

Figure 2 **Difference in secondary prevention measures after percutaneous coronary intervention and coronary artery bypass grafting**

Data from Hiratzka and colleagues.[158] ACE-I = Angiotensin-converting-enzyme inhibitor CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

Table 4 Trends in the use of secondary preventive medication and the difference between coronary artery bypass grafting and percutaneous coronary intervention

		EUROASPIRE I 1995-1996 N=9 countries	EUROASPIRE II 1999-2000 N=15 countries	EUROASPIRE III 2006-2007 N=22 countries
Antiplatelets	CABG	87,9%	86,8%	92,9%
	PCI	89,4%	90,0%	94,9%
	Δ	-1,5%	-3,2%	-2,0%
Beta-Blockers	CABG	56,5%	68,0%	90,7%
	PCI	61,7%	73,6%	84,4%
	Δ	-5,2%	-5,6%	+6,3%
Blood-pressure-lowering drugs	CABG	86,2%	90,1%	98,7%
	PCI	87,4%	91,3%	95,9%
	Δ	-1,2%	-1,2%	+2,8%
Lipid-lowering drugs	CABG	36,7%	67,6%	90,5%
	PCI	42,2%	69,9%	89,4%
	Δ	-5,5%	-2,3%	+1,1%

Data from Kotseva and colleagues.[134] CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

of secondary prevention medications has increased remarkably [133, 134] and differences between PCI and CABG have shown to converge (Table 4).Nevertheless, some data have shown that differences between PCI and CABG still remain and again stressed the need for further progress (Figure 2).[135-137]

Furthermore, the effect of lifestyle interventions on outcomes may be underestimated. A plethora of data exists on the impact of lifestyle intervention on outcomes after CABG. Van Domburg and colleagues, for example, reported that patients who quit smoking had significantly improved 30-year survival as compared with persistent smokers after CABG (HR=0.60 [95% CI 0.48-0.72]).[138] Education and counselling on eliminating risk factors, healthy food choices, stress relief, and exercise provide substantial benefit for patients.[139] A meta-analysis that combined 63 randomised clinical trials with follow-up data on 21,295 patients found that implementation of secondary prevention programs significantly reduced all-cause mortality (risk ratio (RR)=0.85 [95% CI 0.77-0.94]) and myocardial infarction (RR=0.83 [95% CI 0.74-0.94]).[140] Notably, specific patient subgroups may benefit most from rigorous behavioural modifications: young (age <60 years) or old (age ≥75 years) patients, patients with a sedentary lifestyle and/or a smoking habit, patients with a low Mediterranean diet score and those who live alone.[141] However, data from 3 EUROASPIRE surveys showed that there was a clear need for more effective lifestyle management among patients with previous coronary revascularisation.[142] The authors rightfully stated that treatment of coronary artery disease "*without addressing the underlying causes of the disease is futile; we need to invest in prevention*".

Initiatives should be undertaken to increase the rate of prescribing appropriate discharge medications and to emphasize the need for long-term medication compliance and lifestyle changes. In particular home-based programs may be efficient and more acceptable to patients -- with the additional benefit of lower costs.[143]Such quality improvement programs can be easily instated and could potentially improve patient care significantly.

DECISION-MAKING

Despite the potential for further optimization of CABG outcomes, PCI will remain an excellent alternative in specific patients. Evidence suggests that there is overuse, underuse and inappropriate selection of revascularisation strategies.[144] Inappropriateuse and underuse may partly explain the preferences expressed by patients,[145] who prefer less invasive techniques with minimized pain over the long-term prospect of improved survival. In that respect, MIDCAB or hybrid procedures may present an alternative, but often patients are not

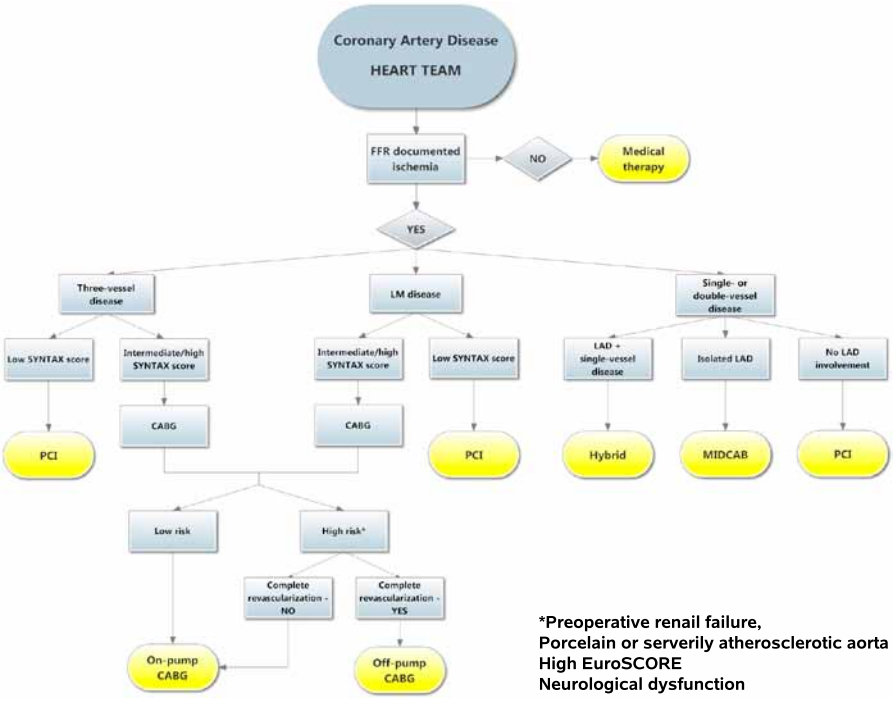

Figure 3 **Proposal for a decision-tree for revascularisation**

Some of these recommendations have not yet been validated and still require randomised evaluation. CABG, coronary artery bypass grafting; LAD, left anterior descending; LM, left main; MIDCAB, minimally invasive coronary artery bypass; PCI, percutaneous coronary intervention

Table 5 Pros and cons of different surgical revascularisation techniques

	Conventional CABG	Off-pump CABG	MIDCAB	TECAB	Hybrid revascularisation
Lesions	Multivessel disease (+)	Multivessel disease (+)	Isolated LAD stenosis (+/-)	Multivessel disease (+)	Multivessel disease (+)
Technical difficulty	None (+)	Moderate (+/-)	Moderate (+/-)	Difficult (-)	Moderate (+/-)
Incision	Sternotomy (-)	Sternotomy (-)	J-incision (+/-)	Endoscopic (+)	J-incision (+/-)
Cardiopulmonary bypass	Yes (-)	No (+)	No (+)	No (+)	No (+)
Procedure time	Short (+)	Prolonged (+/-)	Long (-)	Long (-)	Long (-)
Blood products	Many (-)	Less (+/-)	Few (+)	Few (+)	Few (+)
Completeness of revascularisation	Complete (+)	Complete (+) or incomplete (+/-)	Complete (+) or incomplete (+/-)	Complete (+) or incomplete (+/-)	Complete (+)
Postoperative length of stay	Long (-)	Prolonged (+/-)	Short (+)	Short (+)	Short (+)
Postoperative pain	Yes (-)	Yes (-)	Yes (-)	Less (+/-)	Yes (-)
Recovery time	Long (-)	Long (-)	Short (+)	Short (+)	Short (+)
Rate of stroke	High (-)	Less (+/-)	Less (+/-)	Less (+/-)	Less (+/-)
Rate of repeat revascularisation	Good (+)	Moderate (+/-)	Good (+)	Moderate (+/-)	Moderate (+/-)

The various features are scored as following: in favour of the technique (+), reasonable in favour (+/-), detrimental for the technique (-). CABG = coronary artery bypass grafting; LAD = left anterior descending; MIDCAB = minimally invasive coronary artery bypass

even informed about the survival advantage with CABG.[146]Naturally, if two treatments are considered to produce similar results, patients will opt for the least invasive.

Reflecting on the current revascularisation guidelines, recent trial results, and weighting risk-benefit ratios of (new) developments, Figure 3 provides a proposal for a decision-tree for revascularisation. The myriad of treatment options emphasize the need for targeted patient selection, and the mix of surgical and interventional therapies provides rationale for multidisciplinary Heart Team decision-making to discuss al potential treatment options and obtain informed consent. Clinical cardiologists, interventional cardiologists, and cardiovascular surgeons should convene on a regular basis to recommend the most appropriate treatment strategy for individual patients.[144, 147] The importance of a Heart Team was once more stressed in the SYNTAX trial [148] and was subsequently included in the European and American guidelines.[3, 149] Practice may be different across centres and countries, and a local protocol should be established to define patient populations that are candidates for certain therapies. The various pros and cons of surgical revascularisation strategies should then be considered by the Heart Team(Table 5).

FUTURE STUDIES

Rigorous evaluation of potential advancements remains crucial before they are introduced on a wide scale. Even an extensive body of evidence supporting some interventions is not necessarily sufficient to provide evidence-based recommendations. This is exemplified by the more than 60 randomised trials comparing off-pump with on-pump surgery:[13, 30, 35] a benefit of off-pump CABG has been suggested in many studies that included different patient populations. Nevertheless, the two latest and largest randomized trials that included low- and high-risk patients found no difference between the two treatment options.[30, 35]

In contrast, data on some new therapeutic strategies remain scarce, but the existing data may demonstrate excellent safety and efficacy. Such results often represent outcomes from highly selected patients treated by experienced surgeons in high-volume centres. This introduces a bias; the generalizability of such results is limited and caution is advised. An example of this is the evaluation of TECAB procedures.

PCI versus CABG studies

Continuous evaluation of PCI versus CABG calls for a specific focus on new developments in both interventions. For PCI patients, new stents will become available and the use of fractional flow reserve to assess the need and completeness of revascularisation

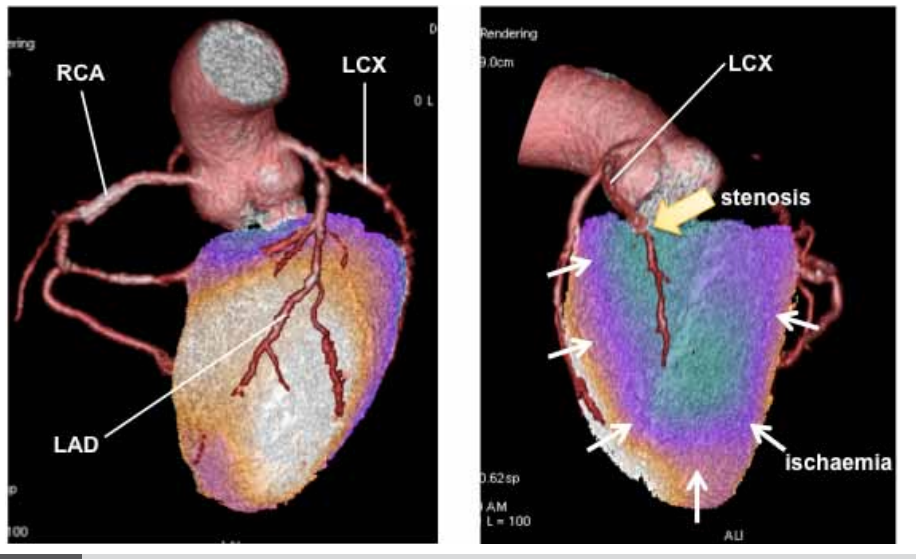

Figure 4 **Functional and anatomical imaging using PET computed tomography**

Case: 70-year old male with three-vessel coronary artery disease for which he underwent stenting of the RCA in 2012, had atypical symptoms. Scan is positive for inferolateral wall ischaemia (purple). LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery

is emphasized.[150, 151] Equivalent data on FFR-guided CABG are scarce.[152] Future studies should explore the use and differences of FFR-guided revascularisation between PCI and CABG.[153] The impact of the degree of ischemia and viability on the outcomes of both CABG and PCI in patients with stable angina is still under debate. Whether image guided revascularization that is based on a combination of functional and anatomical imaging -- for example PET computed tomography (Figure 4) -- can improve the outcomes as compared to the traditional occulostenotic approach warrants further trials.

Traditionally, trials are limited to their internal validity, i.e. the results are only applicable to the included patient cohort; large 'real-world' registries are required to demonstrate whether trial results are also applicable to the general population.[10] Alternatively, an 'all-comers' trial design with none to limited patient exclusion criteria increases external validation, and presents a more balanced trade-off between internal and external validation.[154] Furthermore, reporting the experience of centres and operators will also contribute to the internal and external validity of trial results: superior outcomes in experienced centres as opposed to inexperienced centres unveils limited external validity and should restrict one from over-extrapolating trial results to real-world clinical settings.

In the SYNTAX trial a new angiographic score was validated --the SYNTAX score-- for grading the complexity of coronary artery disease.[155] This score appears to be a very promising tool for deciding if PCI or CABG would be preferable. Use of the score is therefore recommended for decision-making. Recently the SYNTAX II score was introduced and showed an improvement in guiding decision-making.[156] Yet, further validation of these hypothesis-generating data are needed and future studies should provide a larger body of evidence about the SYNTAX (II) score.

Pharmacologic management of patients after PCI and CABG differs significantly and has an impact on long-term results. It would be interesting to see the results of PCI and CABG if the pharmacological management and treatment adherence after PCI and CABG would be identical.

DISCUSSION

Broadening indications for and increasing use of PCI calls for more focus on the optimization of short- and long-term outcomes after CABG. Expanding the use of lesser invasive techniques may persuade patients to accept surgery as the preferable treatment option. Particularly studies comparing PCI with CABG require the most optimal surgical revascularisation strategy to show superiority over PCI. Arterial revascularisation with minimized aortic manipulation and intraoperative graft flow measurement is a relatively easy way to improve outcomes.

Adoption rates of new techniques have been low, despite all advances. This may be due to: (i) the familiarity that surgeons have with existing techniques, a reluctance to change and the willingness to go through the learning curve typical for a new technique, (ii) the more demanding nature of some technical advances, (iii) complications related to the use of a new technique and/or device, (iv) time-consuming steps that may have to be carried out during the procedure, and (v) logistic reasons with regard to the need for additional equipment, planning and sterility. Particularly when the presumed benefits with new techniques are not yet clearly proven, these factors play a major role in maintaining existing protocols. However, the benefit of advancements will often become evident when overcoming the learning curve. On the other hand, some techniques will always be time-consuming and reserved for highly specialized centres.

Guidelines

One explanation for the underuse of new techniques and secondary prevention measures may be the lack of data supporting their benefit. This calls for large registries and randomised trials to provide additional rigorous evaluation of, in particular, MIDCAB, hybrid revascularisation, epiaortic scanning and graft flow measurement. Another reason for lack of widespread implementation and geographic variations may be the differing recommendations of the American and European guidelines concerning their use (Table 6). This is illustrated by recommendations for epiaortic scanning and graft flow assessment. The current European ESC/EACTS revascularisation guidelines include a class 1C recommendation for intra-operative graft flow assessment [3] and the American guidelines state that "*epiaortic ultrasound is reasonable to evaluate…*", which translates to a class IIa B recommendation.[149] However, the American guidelines do not include a recommendation for graft flow assessment, while the European guidelines lack a recommendation for epiaortic scanning.

Patient, cost, and market considerations

Adoption of minimally invasive techniques that result in lower postoperative complications and reduced length of stay will significantly improve patient satisfaction, and raise patients' willingness to undergo CABG as opposed to PCI. On the background of the issue of rising health care expenditures, these improvements may also help reduce overall costs.

Continued optimization of short- and long-term outcomes of CABG will reduce costs for health insurance providers who may therefore favour adoption of new techniques associated with shorter initial in-hospital stays, reduced complication rates and fewer repeat revascularisations. In addition, pay for performance is increasingly instated.[157]This system provides additional incentives to innovate and improve outcomes.

Containing costs to both health insurance providers and societies may in some health care systems require a reduction of the number of centres performing CABG. Innovation and integrating technological advances into everyday clinical practice may be rewarded

Table 6 American and European guideline recommendations

	Guidelines	
	American	**European**
Off-pump CABG	"In patients with preoperative renal dysfunction (creatinine clearance <60 mL/min), off-pump CABG may be reasonable to reduce the risk of acute kidney injury" **IIb B** "It is reasonable to consider off-pump CABG to reduce perioperative bleeding and allogeneic blood transfusion" **IIa A**	"Off-pump CABG may be considered, rather than on-pump CABG for patients with mild to moderate chronic kidney disease" **IIb B**
MIDCAB	No recommendation	No recommendation
Hybrid revascularisation	"Hybrid coronary revascularisation is reasonable in patients with 1 or more of the following: limitations to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI); lack of suitable graft conduits; unfavourable LAD artery for PCI (i.e., excessive vessel tortuosity or chronic total occlusion)" **IIa B** "Hybrid coronary revascularisation may be reasonable as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk-benefit ratio of the procedures" **IIb C**	"Hybrid procedure, defined as consecutive or combined surgical and interventional revascularisation may be considered in specific patient subsets at experienced centres" **IIb B**
Clampless / 'no touch'	Patients with extensive disease of the ascending aorta pose a special challenge for on-pump CABG; for these patients, cannulation or cross-clamping of the aorta may create an unacceptably high risk of stroke. In such individuals, offpump CABG in conjunction with avoidance of manipulation of the ascending aorta (including placement of proximal anastomoses) may be beneficial. **(No formal recommendation, no level of evidence)**	No recommendation
Endoscopic vein harvesting	No recommendation	Endoscopic vein-graft harvesting cannot be recommended at present as it has been associated with vein-graft failure and adverse clinical outcomes. **(No formal recommendation, no level of evidence)**
Epiaortic scanning	"Routine epiaortic ultrasound scanning is reasonable to evaluate the presence, location, and severity of plaque in the ascending aorta to reduce the incidence of atheroembolic complications" **IIa B**	No recommendation

Table 6 ***Continued***

	Guidelines	
	American	**European**
Graft flow assessment	No recommendation	"Graft evaluation is recommended before leaving the operating theatre" **IC**
Arterial revascularisation/ Complete revascularisation	"If possible, the LIMA should be used to bypass the LAD artery when bypass of the LAD artery is indicated" **IB** "When anatomically and clinically suitable, use of a second IMA to graft the left circumflex or right coronary artery (when critically stenosed and perusing LV myocardium) is reasonable to improve the likelihood of survival and to decrease reintervention" **IIa B** "Complete arterial revascularisation may be reasonable in patients ≤60 years of age with few or no comorbidities" **IIb C**	"Arterial grafting to the LAD system is indicated" **IA** "Complete revascularisation with arterial grafting to non-LAD coronary systems is indicated in patients with reasonable life expectancy" **IA**
Secondary prevention	"All smokers should receive in-hospital educational counselling and be offered smoking cessation therapy during CABG hospitalisation" **IA** "[Aspirin] should be initiated within 6 hours postoperatively and then continued indefinitely to reduce the occurrence of SVG closure and adverse cardiovascular events" **IA** "All patients undergoing CABG should receive statin therapy, unless contraindicated" **IA** "β-blockers should be prescribed to all CABG patients without contraindications at the time of hospital discharge" **IC** "ACE inhibitors and ARBs should be initiated postoperatively and continued indefinitely in CABG patients who were not receiving them preoperatively, who are stable, and who have an LVEF ≤40%, hypertension, diabetes mellitus, or CKD, unless contraindicated" **IA**	In general, an 'ABCDE' approach is proposed: 'A' for antiplatelet therapy (Table 36), anticoagulation, ACE inhibition, or angiotensin receptor blockade; 'B' for b-blockade and blood pressure control; 'C' for cholesterol treatment and cigarette smoking cessation; 'D' for diabetes management and diet; and 'E' for exercise." Several recommendations are provided with regard to lifestyle and risk factor management (e.g., counselling on physical activity and exercise training, **IA**; diet and weight control management, **IB**; smoking cessation, **IB**). "Secondary prevention demands lifelong antiplatelet therapy with 75-325 mg acetylsalicylic acid daily" "ACE inhibitors should be started and continued indefinitely in all patients with LVEF ≤40% and for those with hypertension, diabetes, or CKD, unless contraindicated" **IA** "It is indicated to start and continue β-blocker therapy in all patients after MI or ACS or left ventricular dysfunction, unless contraindicated" **IA** "High-dose lipid lowering drugs are indicated in all patients regardless of lipid levels, unless contraindicated" **IA** "Fibrates and omega-3 fatty acids (1 g/day) should be considered in combination with statins and in patients intolerant of statins" **IIb B**

The level of evidence is shown in bold. ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; LAD = left anterior descending; LVEF = left ventricular ejection fraction; (L)IMA = (left) internal mammary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention

by certification as a centre of excellence, by continued issuance of a practice licence and by more patient referrals. Implementation of the Heart Team decision-making process may furthermore strengthen the position of a centre. This approach highlights the centre's collaborative environment between specialties, which is appreciated by patients.[144] There may also be major cost implications by eradicating suboptimal treatment: health care costs will be contained as rates of adverse events requiring rehospitalisation and additional procedures are reduced.

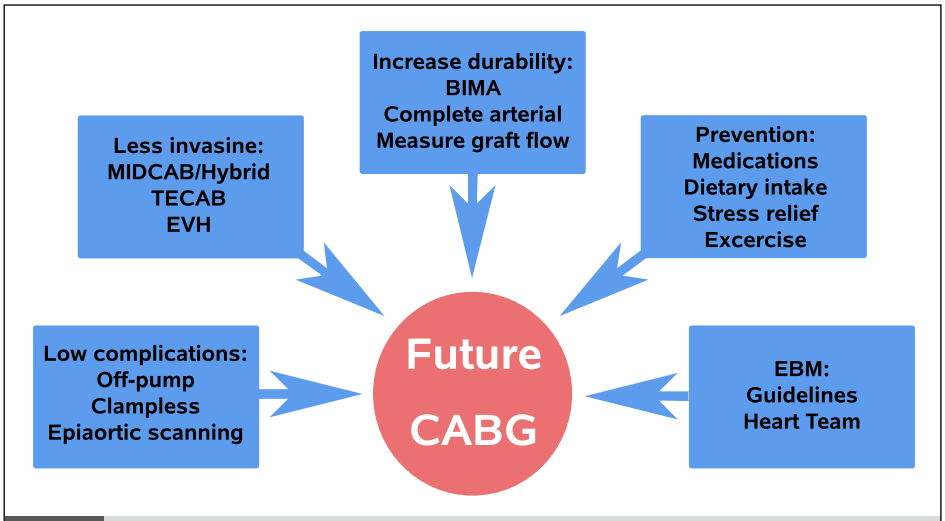

Figure 5 **Summary of developments to optimize short- and long-term results after coronary artery bypass grafting**

BIMA = bilateral internal mammary artery; CABG = coronary artery bypass grafting; EBM = evidence-based medicine; EVH = endoscopic vein harvesting; MIDCAB = minimally invasive coronary artery bypass; TECAB = totally endoscopic coronary artery bypass

CONCLUSIONS

Outcomes after surgical revascularisation have the potential to improve beyond the level achieved during recent decades (Figure 5). However, to facilitate these improvements, surgeons need to be willing to adopt new techniques that increase procedural safety, patient satisfaction, and long-term survival. To achieve these goals, guidelines should be conclusive about recommending certain techniques and provide guidance for their use. Future trials will need to provide sufficient evidence for such recommendations by focussing on specific areas where optimal therapy has yet to be substantiated.

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Part 4

Interpretation of cardiovascular clinical research


Borneo

Chapter 24

Non-inferiority study design: lessons to be learned from cardiovascular trials

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ABSTRACT

The non-inferiority trial design has gained popularity within the last decades to compare a new treatment to the standard active control. In contrast to superiority trials, this design is complex and is based on assumptions that cannot be validated directly. Many readers and even investigators, therefore, have difficulty grasping the full methodological nature of non-inferiority trials. Non-inferiority margins are often arbitrarily chosen such that a favourable margin can bias a trial towards declaring non-inferiority. Pitfalls of non-inferiority trials are not fully appreciated, and without having identified these shortcomings, objective conclusions from non-inferiority trials cannot be made. This methodological review elaborates on what is a non-inferiority trial, why such a trial is performed, what the hazards are, and how conclusions from non-inferiority trials are derived, by providing examples of recent cardiovascular trials.

INTRODUCTION

Unlike superiority trials that are designed to show that one treatment is better than another, a non-inferiority trial is designed to show that a new treatment is 'not unacceptably worse' than the current standard therapy. Since the introduction of non-inferiority trials in the mid-1990s it has been debated whether such trials should be performed.[1, 2] The design of a non-inferiority trial is complicated and is founded on assumptions that are difficult to verify.[3–6] Readers often fail to fully understand the concept, statistical approaches, and conclusions; even some trialists may have difficulties with grasping the sense of a non-inferiority study. Non-inferiority studies often have 'substantial methodological flaws' with the risk of incorrectly claiming non-inferiority.[3] This could potentially expose patients to the possibility of receiving a treatment that is inferior to the 'gold standard'. In addition, the reporting of analyses and conclusions has been shown to be misleading in a review of 116 non-inferiority trials.[3, 7]

In the last few years, several cardiovascular trials have been published that compared surgical to catheter-based therapies for the treatment of heart diseases, with a great impact on clinical practice.[8–10] More trials are currently underway and it is crucial that these and future trials are adequately designed, well performed, rigorously analysed, and prudently interpreted.[11]

In this review, we discuss the aspects of non-inferiority trials; when to perform such a study, how to design a non-inferiority trial, and how to derive conclusions from such a trial. To elaborate on these topics, examples of recent cardiovascular trials are provided.

SUPERIORITY, EQUIVALENCE, NON-INFERIORITY

A superiority trial is designed to show that a new treatment is better than an active control or placebo. The null hypothesis states that no difference between treatments exists. The trial is determined to reject this hypothesis and show a statistically significant difference in favour of the new treatment. In equivalence trials, which are rarely performed, the difference between two treatments is pre-defined as Δ, and the goal of the trial is to demonstrate that treatment with either therapy is equally good and the confidence intervals (CIs) do not exceed a difference of −Δ and +Δ.

A non-inferiority trial is different as it is designed not to show that treatments are equal, or 'not different', but that the new treatment is not unacceptably worse than, or 'non-inferior' to, an active control. Statistically, such a study differs from an equivalence trial because the Δ is only one-sided towards −Δ. Non-inferiority is claimed if the lower bound of the CI of the treatment effect difference does not exceed −Δ, thus meaning that the risk of it being inferior is within acceptable boundaries (Figure 1).

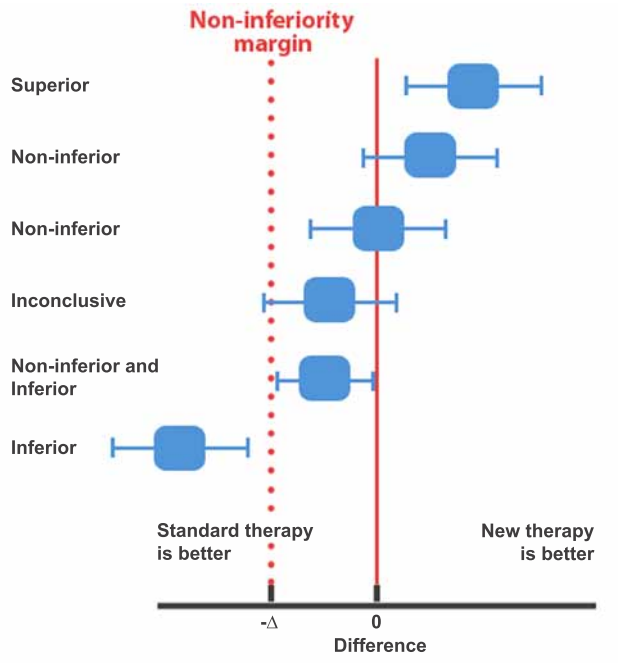

Figure 1 **Possible conclusions from non-inferiority trials**

WHY A NON-INFERIORITY TRIAL?

Non-inferiority trials have become more popular in the last decades, especially in cancer and cardiovascular studies. A common misunderstanding is that this is caused by safety and efficacy regulations, which would suggest that a new therapy first needs to show non-inferiority before it can be tested in a superiority trial. However, non-inferiority trials were originally designed for studies in which it is unethical to include a placebo arm. For cancer and cardiovascular conditions where a 'gold standard' therapy already exists, it would be unethical to perform a placebo-controlled trial with a newly introduced treatment. For example, elderly patients with symptomatic severe aortic stenosis are generally treated by means of surgical aortic valve replacement (SAVR). Whenever patients are considered to be at too high a risk for surgery, they are managed medically. Transcatheter aortic valve replacement (TAVR) is a new less invasive therapy suited for these extreme high-risk patients, with initially good results from the PARTNER trial.[12, 13] However, in lower risk patients TAVR has to compete with the gold standard SAVR, which shows excellent long-term results in these patients. A TAVR vs. medical management trial would therefore be unethical in lower risk patients due to the superiority of SAVR over medical management in patients who are good

candidates for surgery. Patients randomized to medical management would then not receive established effective therapy.

Even if a new treatment is shown to be non-inferior to the 'gold standard' therapy with regard to an efficacy endpoint, it would still need to demonstrate an ancillary benefit, i.e. lower procedural risks (safety), favourable costs, or improved convenience for it to be considered the preferred treatment. In the previous example, if TAVR shows non-inferior efficacy (and safety), its preference over SAVR might be potentially justified due to the lower invasiveness (avoidance of sternotomy and cardiopulmonary bypass) and reduced length of stay. An example where a non-inferiority trial would be adequate in a pharmacologic trial is the comparison between warfarin and new anticoagulant drugs. Warfarin has been the standard anticoagulant therapy for over 60 years but has some disadvantages including the requirement for routine monitoring of the international normalized ratio (INR). Several new drugs that are more convenient with regard to drug administration have been shown to demonstrate non-inferiority compared with warfarin.[14, 15]

Not only are there clinical indications to perform a non-inferiority trial, but also the costs of a randomized trial are very high, and the stakes for companies are crucial. In a non-inferiority trial investigators can choose unreasonably wide margins and high active control event rates that yield lower sample sizes, and thus improve the trial efficiency, i.e. achieve a positive trial result at a minimized cost. For example, the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) V trial used an unreasonably generous non-inferiority margin of a 2% absolute risk difference (ARD) and an expected warfarin event rate of 3.1% per year [equivalent to a relative risk margin of (3.1 + 2)/3.1 = 1.65]; with 90% power this produced a sample size of 3156 patients.[16] Using the more accurate expected warfarin event rate of 1.9% per year derived from pooled historical data, the study would have needed 4875 patients for a similar 90% power and a relative risk margin of 1.65 (equivalent to an ARD margin of 1.23%). The sample size would even be 8190 patients if the observed warfarin event rate of 1.2% per year had been used for the sample size calculation.[11] Thus only 39% (3156/8190) of the actually needed sample was included, thereby drastically reducing costs. Although the cost of a trial is merely one of the factors influencing trial design, it should not be the main contributor.

METHODOLOGY OF NON-INFERIORIY TRIALS

One major issue with a non-inferiority trial is that, unlike a superiority trial, it is biased towards non-inferiority if the trial is poorly designed and sloppily conducted.[17] Part of the basis of a randomized trial is the expected event rate with the corresponding sample size calculation. A non-inferiority trial has the same principle, but an additional non-inferiority margin is included. This margin quantifies when the new therapy is considered

to be non-inferior to the standard therapy. Several factors need to be considered during the trial design before a reasonable margin can be adopted. If these factors are not taken into account, it could lead to a phenomenon called 'biocreep' or 'technology creep'; an inferior therapy is granted non-inferiority and becomes the control group in future trials, ultimately leading to an active therapy being no better than a placebo.[4]

Choise of margin: absolute vs. relative risk difference

A non-inferiority margin can be chosen as an ARD or risk ratio (RR). It is recommended to use a relative difference to account for changes in event rates; fixed RRs provide more conservative margins in trials in which the event rate is unpredictable or the observed rate is lower than expected.[11]

In the previously used example of the SPORTIF V trial, non-inferiority was met using an ARD of 2%, even with the observed event rate of 1.2% instead of the expected 3.1%/year. This lower event rate caused inflation of the RR from 1.65 to 2.67 (Table 1). Had the investigators fixed the RR at 1.65 (and correspondingly used a more conservative ARD margin of 0.78% [(1.65 × 1.2) – 1.2], non-inferiority would not have been met. However, it is evident that conservative margins result in larger sample sizes.

Margins based on ARD can potentially introduce a bias towards non-inferiority, since it can result in an underpowered trial due to lower than expected event rates.[9,11] For example, in the recent PRECOMBAT trial that compared percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) for left main disease, the expected event rate in the CABG arm was 13%, and the pre-specified margin was an ARD of 7%.[9] In an analysis with a one-sided alpha of 0.025, the upper bound of the difference was 6.3%. Because this was below the predefined margin of 7%, the investigators declared non-inferiority. Had they fixed the margin as an RR [(13 + 7)/13 = 1.54], the upper bound of the RR would be 2.12 (1.30, 95% CI: 0.81–2.12), thereby not allowing a claim of non-inferiority. In trials that use an ARD, a judgement of non-inferiority would be more convincing if analyses on the basis of absolute and relative difference were concordant.[3, 11]

Table 1 **Inflation of the relative risk in the SPORTIF V trial**

	Expected	Pooled historical	Observed
Standard Rx event rate	3.1%/year	1.9%/year	1.2%/year
New Rx event rate acceptable	5.1%/year	3.9%/year	3.2%/year
RR	1.65	2.05	2.67

RR = Relative risk difference

Active control event rate

It is crucial that the active control event rate be chosen properly, since an overestimation can result in an underpowered trial. Frequently the event rate is unsubstantiated. For example, the PRECOMBAT trial used a 1-year event rate of 13% based on a previously published meta-analysis, while the actual observed event rate was only 6.7%.[9, 18] The investigators could, however, have foreseen differences in the event rate. The meta-analysis was not representative of the current clinical practice as it included four trials that enrolled patients between 1995 and 2000 treated with bare-metal stents, while PRECOMBAT enrolled patients between 2004 and 2009 that were treated with drug-eluting stents. Furthermore, their own clinical practice demonstrated low rates similar to PRECOMBAT, but these data were not taken into account when performing the sample size calculation.[19] An interim analysis during the trial would have demonstrated lower than expected event rates and a sample size adjustment would have been appropriate given the contemporary data.[19] Although the trial extended the primary endpoint to 2 years, this still did not result in an adequate number of events.[20]

In some instances, there are no previous trials to reliably estimate the expected active control event rate. In such cases, investigators have no other option but to extrapolate from their own experiences or use pooled feasibility data for a propensity-matched analysis. An advantage of this technique is that it can provide a ratio of the new treatment vs. the active control. This is, however, often cumbersome due to diverse 'all-comer' patients treated with the control and the highly selected patients treated with the new intervention.

Nature of events

One must be aware of the fact that the margin should be based on the number and nature of the events that are included in a composite endpoint. The use of composite endpoints that are driven by 'softer' events poses a dilemma in the estimation of the margin. On the one hand, one is willing to accept a greater degree of inferiority (given the ancillary benefits), thereby resulting in a wider margin. On the other hand, 'softer' events occur more frequently and inflate the event rate, which would require more stringent margins. Whether composite endpoints should include both safety and efficacy outcomes remains debatable. For example, in the SYNTAX trial the composite of death, stroke, myocardial infarction, and repeat revascularization was used as the primary endpoint. Some argue that repeat revascularization should not have been included in the endpoint, since this was a 'softer' efficacy event. The primary endpoint of non-inferiority was not met in the analysis that included revascularization, while PCI would have been non-inferior to CABG in the composite analysis without repeat revascularization. However, this composite of death, myocardial infarction, and stroke was not a predefined endpoint. Had it been chosen as the primary endpoint of the trial, sample size adjustments due to a lower event rate would have been required, resulting in a prohibitively large sample size.[21]

The recently published EVEREST II trial randomized patients to percutaneous mitral valve repair or mitral valve surgery.[8] For the primary endpoint, the investigators chose a combination of clinical (death and surgery for mitral valve dysfunction) and echocardiographic endpoints (grade ≥3 + mitral regurgitation), which is unusual for a device vs. surgery trial. Ideally, the regurgitation endpoint should not have been included in the primary endpoint, but this 'softer' and more frequent endpoint drove the event rate. A composite endpoint of death or need for surgery (hard, but less frequent, endpoints) would have required a prohibitively large sample size. In contrast, the PARTNER trial had a clinical primary endpoint, while valve function was considered a secondary endpoint.[12]

Clinical relevance

A crucial step in determining a margin is to contemplate what difference between therapies is clinically acceptable. An overly conservative margin might result in a high risk of not being able to claim non-inferiority when it actually is non-inferior. Conversely, overly liberal margins could result in a high risk of claiming non-inferiority when it actually is not non-inferior. A reasonable margin would be best derived from a combination of factors: the expected event rate, the duration of follow-up, and the number and nature of the events. However, arbitrary clinical judgment and the sponsor budget are of a great influence, resulting in a somewhat subjective non-inferiority margin.

A formal approach for choosing the margin is based upon a combination of statistical reasoning and clinical judgment.[4, 5, 11] The first step is to reliably estimate the efficacy of the active control compared with placebo, often derived from a meta-analysis of historical placebo-controlled superiority trials. The lower 95% CI of this effect is the largest acceptable non-inferiority margin, M1, to provide assurance that the new treatment is at least better than placebo.[4, 5, 22] The second step in selecting the margin is choosing a reasonable fraction of the control effect (M1) that needs to be preserved, typically set at 50% of M1. This new non-inferiority margin is called M2, and is typically based upon clinical judgment. An example of a trial using this method is the RE-LY trial (Table 2).[14] The investigators used a meta-analysis of trials of vitamin K antagonist compared with control therapy in patients with atrial fibrillation. The hazard ratio of 1.46 was used as the margin in RE-LY, which was defined by using half the upper bound of the 95% CI derived from the estimated effect of control therapy over warfarin.

Follow-up

The duration of follow-up for the primary endpoint is important as well. The shorter the follow-up, the more conservative a margin should be. While after 1 year a certain difference in events might be acceptable, the same difference at 30 days could raise serious concerns regarding the safety of the treatment. This becomes more important whenever a trial is designed with an ARD (Δ) as the non-inferiority margin, as opposed to a trial with a hazard

Table 2 Examples of recent non-inferiority trials

Trial, year	Device vs surgery trials				Pharmacologic trials				
	SYNTAX, 2009	**PRECOMBAT, 2011**	**PARTNER 1A, 2011**	**EVEREST II, 2011**	**PROTECT AF, 2009**	**RE-LY, 2009**	**RE-LY, 2009**	**ROCKET AF, 2011**	**ARISTOTLE, 2011**
New Rx	TAXUS DES	DES	TAVR	Mitraclip	Watchman LAA closure	Dabigatran 150mg	Dabigatran 110mg	Rivaroxaban	Apixaban
Standard Rx	CABG	CABG	SAVR	MV surgery	Warfarin	Warfarin		Warfarin	Warfarin
Primary endpoint	MACCE	MACCE	All-cause mortality	Freedom from death, MV surgery or >2+	Stroke, cardiovascular death, and systemic embolism	Stroke or systemic embolism		Stroke or systemic embolism	Stroke or systemic embolism
Standard Rx event rate (expected)	13.2%	13%	32%	90%	6.15% per 100 patient-years	Not specified		2.3% per 100 patient-years	Not specified
Standard Rx event rate (observed)	12.4%	6.7%	26.8%	88%	4.9% per 100 patient-years	1.7% per 100 patient-years		2.2% per 100 patient-years	1.6% per 100 patient-years
Trial power	96%	80%	85%	80%	80%	84%		95%	90%
Alpha	One-sided, 0.05	One-sided, 0.05	One-sided, 0.05	One-sided, 0.05	One-sided, 0.025	One-sided, 0.025		One-sided, 0.025	One-sided, 0.025
Sample-size	1800	600	699	279	707	15000		14000	18000
Follow-up duration	1 year	1 year	1 year	1 year	mean of 1.5 years	median 2.0 years		median 1.9 years	median of 1.8 years
Standard Rx effect	Not quantified	Not quantified	Not quantified	90% (84% - 96%)	0.36 (0.25 - 0.53) for stroke and embolism Not quantified for additional death endpoint	0.36 (0.25 - 0.53)		0.36 (0.25 - 0.53)	0.36 (0.25 - 0.53)

Table 2 *Continued*

Trial, year	Device vs surgery trials				Pharmacologic trials				
	SYNTAX, 2009	**PRECOMBAT, 2011**	**PARTNER 1A, 2011**	**EVEREST II, 2011**	**PROTECT AF, 2009**	**RE-LY, 2009**	**RE-LY, 2009**	**ROCKET AF, 2011**	**ARISTOTLE, 2011**
Non-inferiority margin	ARD = 6.6% RR = 1.51	ARD = 7% RR = 1.54	ARD = 7.5% RR = 1.23	ARD = 31% (PP)	Rate ratio = 2.0	Relative Risk = 1.46		Relative Risk = 1.46	Relative Risk = 1.44
% preservation of standard Rx effect	…	…	…	65% of point estimate	…	50% of lower bound of 95% CI of placebo vs standard		50% of lower bound of 95% CI of placebo vs standard	50% of lower bound of 95% CI of placebo vs standard
New Rx vs standard Rx	ARD = 5.5% (2.8 - 8.3%) RR = 1.44 (1.15 - 1.81)	ARD = 2.0% (-1.6 - 5.6%) RR = 1.30 (0.81 - 2. 08)	ARD = -2.6% (-9.3 - 4.1%) HR = 0.93 (0.71 - 1.22)	ARD = 15.4% (4.8 - 26.1%) RR = 2.3 (1.2 - 4.4)	Rate Ratio = 0.62 (0.35 - 1.25)	Relative Risk = 0.65 (0.52 - 0.81)	Relative Risk = 0.90 (0.74 - 1.10)	Hazard Ratio = 0.79 (0.66 - 0.96)	Hazard Ratio = 0.79 (0.66 - 0.95)
Non-inferiority met	No	Yes (ARD margin) No (RR margin)	Yes (ARD margin) Yes (RR margin)	Yes (ARD margin)	Yes (RR margin)	Yes (RR margin)		Yes (RR margin)	Yes (RR margin)
Ancillary advantage	Less invasive, less stroke	Less invasive, lower stroke	Less invasive	Less invasive, lower bleeding	No lifelong anticoagulation	Lower bleeding, no monitoring		Lower bleeding, no monitoring	Lower bleeding, no monitoring

*Estimations based on the rates provided in the papers. DES = drug-eluting stent; CABG = coronary artery bypass grafting; TAVR = transcatheter aortic valve replacement; MV = mitral valve; LAA = left atrial appendage; MACCE = major adverse cardiac or cerebrovascular events; ARD = absolute risk difference; RR = relative risk; PP = per-protocol; ITT = intention-to-treat

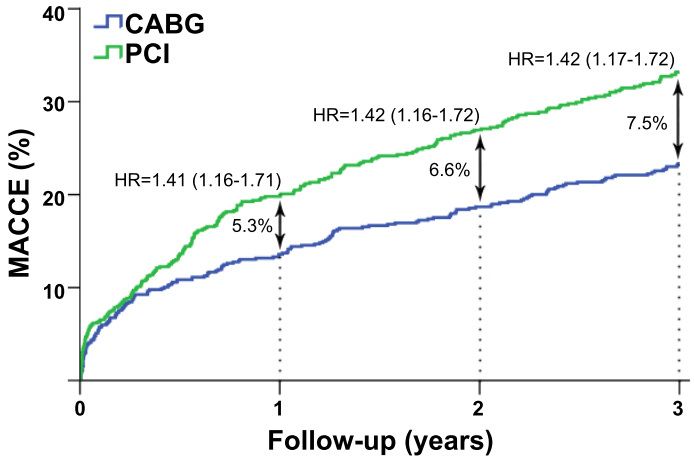

Figure 2 **The influence of the length of follow-up on the non-inferiority margin**

Data from the SYNTAX trial demonstrate that the duration of follow-up is of different influence on an absolute risk difference or risk ratio. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

ratio.[23] As shown in Figure 2, data from the SYNTAX trial show that the hazard ratio remains constant over time, while the absolute difference may increase.

Statistical power

The minimal acceptable standard for statistical power in superiority trials generally is 80% with a two-sided alpha of 0.05. Both superiority and non-inferiority trials should ideally be designed with a ≥90% statistical power. In non-inferiority trials this is more crucial, since lower power biases the results towards non-inferiority. In addition, although practice varies, a one-sided alpha of 2.5% is considered to be more robust for non-inferiority assessment; the CI is wider and therefore more likely to cross the non-inferiority margin.

Assumptions

An adequately powered superiority trial allows one to conclude that a new treatment is superior to placebo. Conclusions from non-inferiority trials, however, are based on assumptions that cannot be verified directly.[11] In contrast to superiority trials, a major issue in non-inferiority trials is that although a new treatment can be non-inferior to the active control, it does not necessarily imply that the active control is more effective, and to what extent, than a placebo. This is referred to as the 'constancy' and 'assay sensitivity' principle. The effect of the active control in relation to the placebo could be different from historical data.[4, 5, 24, 25] For example, in a trial comparing PCI with CABG, if the non-inferiority margin exceeds the treatment difference between CABG and medical treatment, non-inferiority of PCI does not mean it would be superior to medical treatment. To overcome these problems, one can

include a third (placebo) arm in a trial, so that a check of the superiority of the active control over the placebo ('assay sensitivity') is available. In case of the example, the PCI vs. CABG trial should include a medical treatment arm, to show that CABG is indeed superior to the placebo. If a third arm is not included, investigators can perform a separate analysis in which the new treatment is compared with historical placebo data, but this relies on the assumption that the observed outcomes are constant over trials ('constancy'). This is frequently not the case as treatment effects can be heterogeneous due to differences in patient populations, outcome definitions, treatment allocation, or other study factors.

REPORTING OF NON-INFERIORITY TRIALS

Analysis

Conclusions from non-inferiority trials are highly sensitive to the method of analysis. The intention-to-treat analysis, typically preferred as the more robust analytical framework in a superiority trial, can be biased towards non-inferiority. For example, if a large number of patients 'cross-over'—patients randomized to treatment A receive treatment B or vice versa—groups will be 'blended' and it is likely that outcomes will be similar in an intention-to-treat analysis. In a superiority trial this strengthens the final effect of a difference, because the analysis makes the results of two arms more similar and thus harder to detect a significant difference. Loss to follow-up will also increase the similarity between groups, because of the assumption that none of these patients met the primary endpoint. Other protocol deviations such as non-adherence to the assigned therapy can bias the results towards non-inferiority.[26] Therefore, a non-inferiority trial should always report both the intention-to-treat and per-protocol (or as-treated) analyses, since either analysis has strengths and limitations. However, the intention-to-treat analysis should be the primary analysis as it preserves the advantages of randomization, while the per-protocol analysis can be used as the supporting sensitivity analysis for non-inferiority assessment.

Patients who cross over or drop out need close examination. If a specific reason for a cross-over or drop-out is found in one treatment group, this shows that the two treatments are not similar by concept, thereby providing evidence of lack of non-inferiority.[26]

Trial conclusions

Non-inferiority can be concluded when the CI does not exceed $-\Delta$ (the non-inferiority margin). It is, however, often misinterpreted as equivalence. Non-inferiority means that the new treatment is not significantly worse (inferior) than the active control, while equivalence means that the new treatment is not significantly worse (inferior) or better (superior) (Figure 1). If non-inferior, the new treatment can be preferred because of an associated ancillary benefit in terms of invasiveness, cost, or convenience.

If the non-inferiority endpoint is not met, the interpretation becomes more difficult. Frequently one concludes that the new treatment is inferior to the active control. It could also mean, however, that the trial result is 'inconclusive'. To conclude which is the case, it depends on the side of the CI being considered (Figure 1). An inconclusive result is the case when the mean difference is larger than $-\Delta$ and the lower bound of the CI exceeds $-\Delta$. Inferiority is concluded if the mean difference is smaller than $-\Delta$ and the upper bound of the CI does not exceed the $-\Delta$. From a statistical point of view, a trial can show both non-inferiority and inferiority at the same time (Figure 1). This can potentially occur in two ways: (i) if the trial is too large, so that an extremely narrow CI can exclude both 0 and a reasonably conservative margin, or (ii) when the choice of the margin is too generous, providing the opportunity for the CI to fit in between $-\Delta$ and 0. Although rare, it is often the result of a poor trial design and should be avoided. From a clinical standpoint, a treatment can be inferior and non-inferior when non-inferiority is met but the margin might have been chosen too generously. The EVEREST II trial is an example of this, where the MitraClip was non-inferior to surgery but this conclusion was difficult to accept due to unduly wide ARD margins of 31 and 25% for the per-protocol and 'comparison of strategy' analyses, respectively.[8] Even the claim of superior safety of the device was driven by blood transfusions that were more frequent with surgery. Excluding these transfusions, the rate of major adverse events in the MitraClip group was not significantly lower (5 vs. 10% after surgery, $P = 0.23$). Thus, one can reasonably argue that MitraClip is less effective than surgery while not demonstrating a clinically relevant safety advantage. In the EVEREST trial the investigators chose a 65% preservation of the active control (surgery) effect over the placebo. This treatment effect being 90%, the investigators were willing to accept an unreasonably large decline in efficacy. In contrast, the ARISTOTLE trial comparing apixaban with warfarin for atrial fibrillation was designed to maintain at least 50% of the 62% relative reduction in warfarin over the placebo.[27] In general, large standard treatment effects require greater preservation (and correspondingly narrow margins) for non-inferiority assessment.

Even in a non-inferiority trial, a new treatment can show superiority over the active control, a sort of 'bonus' in the trial. This is the case if the lower bound CI exceeds 0 in which there is only a 5% chance (alpha) that the active control is better (Figure 1). Sequential testing for superiority is only justified after non-inferiority has been successfully demonstrated. Although somewhat obvious, *post hoc* non-inferiority testing in a negative superiority trial is not appropriate, as the margins are not pre-specified and the trial not adequately powered for non-inferiority.

Table 1 provides an overview of recent non-inferiority trials. It demonstrates the differences in trial design, conduct, and analysis based on the expected event rate, power, sample size, non-inferiority margin, and preservation of the effect of standard therapy.

CONCLUSIONS

The design and interpretation of non-inferiority trials is more complex than for superiority trials. Therefore, many readers and investigators have difficulties understanding the full concept of these trials. When starting a non-inferiority trial, investigators need to make several assumptions and should be aware of not choosing inaccurate or unreasonably generous active control event rates or non-inferiority margins. For readers, to objectively interpret non-inferiority trial results, one must be conscious of several pitfalls of the methodology. Assay sensitivity and trial inconsistency impede conclusions from non-inferiority trials.

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Cape Town

Chapter 25

Nonrandomized data on drug-eluting stents comparing with bypass surgery: caution with interpretation

Head SJ, Bogers AJ, Kappetein AP

J Am Coll Cardiol 2011;57:2457-2458

TO THE EDITOR:

In a recent issue of the *Journal*, Park et al. presented long-term follow-up results from the Asan-Multivessel Registry in which patients are followed after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) or coronary artery bypass grafting (CABG) for the treatment of multivessel coronary artery disease.[1] After 5 years, similar rates of death or the composite endpoint of death, myocardial infarction, or stroke were found in the DES and CABG groups. This is the first paper to compare these groups after such long follow-up, but it should be highlighted that this is a nonrandomized study. To date, only the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trial compared patients randomized to DES or CABG and after 1 year already showed that DES failed to reach noninferiority to CABG.[2] A possible explanation for the contradicting results of Park et al. [1] is that apart from baseline characteristics (age, sex, body mass index) and comorbid conditions (hypertension, hyperlipidemia, diabetes requiring insulin, heart failure, prior myo-cardial infarction), the severity of multivessel disease is less worse than in the SYNTAX trial (Table 1), with an overall SYNTAX coronary score that is much lower in the DES group (SYNTAX trial 28.4% vs. 17.4% in the present study). The SYNTAX trial also included more than twice as many patients with a left main lesion; these patients have been identified as having the worst prognosis.[3] Furthermore, CABG has always shown a better prognosis in patients with

Table 1 **Baseline characteristics comparison**

	SYNTAX (N=1,800)		Asan registry (N=3,042)	
	DES	CABG	DES	CABG
Age (years)*	65.2	65.0	62.0	61.8
Male (%)*	76.4	78.9	69.4	73.2
Mean body mass index (kg/cm^2)*	28.1	27.9	25.1	24.8
Current smoker (%)†	18.5	22.0	29.5	33.6
Hypertension (%)*	68.9	64.0	57.1	47.9
Hyperlipidemia (%)*	78.7	77.2	24.1	31.7
Medically treated diabetes				
Any (%)†	25.6	24.6	31.6	26.9
Requiring insulin(%)*	9.9	10.4	5.6	5.1
Ejection fraction <30% (%)	1.3	2.5	0.9	3.3
Congestive heart failure (%)*	4.0	5.3	1.4	4.5
Prior myocardial infarction (%)*	31.9	33.8	10.1	19.7
Left main lesion (%)*	39.5	38.8	11.5	24.9
Total occlusion (%)	24.2	22.2	7.1	43.9
SYNTAX score (%)*	28.4	29.1	17.4	29.9

* Higher risk profile patients in SYNTAX. †Higher risk profile patients in Asan-Multivessel Registry. DES = drug-eluting stent; CABG = coronary artery bypass grafting

more extensive coronary artery disease. Outcomes in the study by Parks et al.,[1] therefore, represent results from a patient cohort in whom it is unlikely that an advantage of surgery could be demonstrated.

To conclude, the recently published results show interesting data on patients treated with DES in perspective to CABG in a real-world design, but this should not lead to treatment preferences for patients with multivessel coronary artery disease. SYNTAX remains the only randomized trial addressing this issue, and although we anticipate the stronger long-term results from this trial, conclusions from the Asan-Multivessel Registry can only be drawn with caution.

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Rotterdam

Chapter 26

Invited commentary to "Long-term survival of patients with ischemic cardiomyopathy treated by coronary artery bypass grafting versus medical therapy"

Head SJ, Mokhles MM, Kappetein AP

Ann Thorac Surg 2012;93:530

COMMENT:

Randomized trials provide crucial information about "competing" treatment options, but the implementation of the results are often limited because of highly selective patient groups. Observational data is needed to examine treatment differences within the "real world." However, differences in patient characteristics between groups frequently prevent one from drawing robust conclusions. Propensity analysis is a method that includes patients who have been evaluated according to clinical judgment instead of randomization, and it provides the option of examining the true effect of competing treatments.

The study presented by Velazquez and colleagues [1] is important because it attempts to mimic the randomized STICH (Surgical Treatment for Ischemic Heart Failure) trial.[2] Inclusion and exclusion criteria of the trial were applied and the propensity score was used to determine whether patients, based on their baseline characteristics, were more likely to be treated medically or with coronary artery bypass grafting (CABG). To represent a similar population as in the STICH trial, they excluded patients with a high propensity score for CABG according to the hypothesis that these patients would not be eligible for randomization in the trial. This might be considered controversial because patients are now excluded based on their score and not on clinical profile; thus whether patients would really be ineligible is unclear. Furthermore, baseline characteristics were not really comparable; 1:1 or 2:1 propensity matching to CABG instead of the current propensity score analysis would perhaps have been a better option in obtaining comparable cohorts.[3]

Nevertheless it is remarkable that the current method using a "real world" cohort with different baseline characteristics shows outcomes similar to those of the STICH trial. The authors rightfully concluded that "carefully collected prospective observational data can complement the results of randomized trials," with obvious benefits of observational studies over randomized trials (eg, costs, patient inclusion, data management, study approval). However there are also limitations to the current article. The STICH trial showed comparable outcomes between patients treated with CABG and medically treated patients according to the intention-to-treat analysis. Only in the as-treated analysis was CABG associated with better survival when compared with medical management. The article concerning the STICH trial did not specify why patients crossed over to CABG; were there specific clinical characteristics that altered the treatment to CABG? The current study, being an observational study, also reports results from an as-treated analysis, but it remains unclear as to which characteristics patients were selected to undergo CABG. Therefore identification of patients who benefit from CABG is still lacking. Without clear identification, the heart team consisting of cardiologists, surgeons, and heart failure specialists can best weigh the different pros and cons of medical and surgical treatment.[4]

To conclude, this study provides a useful perspective of the STICH trial in daily clinical practice. Currently it remains challenging to select patients in ischemic heart failure for CABG. Future studies, however, should compare medical management and CABG in specific patient cohorts of single- or multivessel disease, low- or high-risk patients, coronary lesion complexity,[5] or other characteristic stratification.

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Rotterdam

Chapter 27

Long-term survival of young patients with coronary artery disease is best realized through surgical revascularization with mammary arteries

Head SJ, Osnabrugge RL, Kappetein AP

J Am Coll Cardiol 2013;61:2312-2313

TO THE EDITOR:

In a recent issue of the *Journal*, Flather et al. [1] reported a subgroup analysis of individual patient data from 10 randomized trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for multivessel coronary disease. Their analysis showed that there was a significant treatment-by-age interaction for 10-year mortality ($p<0.001$). Strikingly enough, in the youngest age group of patients ≤56.2 years old there was no difference in mortality (hazard ratio for PCI = 1.23; 95% CI 0.95-1.59), while the hazard ratio shifted towards a significant benefit of CABG over PCI in older patients ≥65.2 years old (hazard ratio = 0.79; 95% CI 0.67-0.94).

Although the data from these trials are compelling, they were not performed according to the 'all-comers' design and it is therefore likely that there was a severe selection bias in the inclusion of patients. Young patients were probably those with low lesion complexity and it is known that in these patients CABG does not offer a survival benefit.[2] In contrast, even though the results of this study suggest superiority of CABG over PCI in elderly patients, this is counterintuitive and these results may not be generalizable to the majority of patients requiring coronary revascularization. Those patients with a higher risk profile were excluded from randomization because of procedural risks associated with CABG.[3] The advantage of PCI in the elderly patients could therefore not be identified in this pooled analysis.

Furthermore, long-term survival of young patients with more complex coronary artery disease is best realized through surgical revascularization with a left internal mammary artery to the left anterior descending artery. This will optimize long-term survival due to excellent graft patency,[4] which is critical especially in young patients with a relatively long life expectancy. Young patients that undergo PCI will have a high risk of multiple repeat revascularizations and are susceptive to the associated procedural risks.

The ancillary benefit of PCI to be preferred over CABG is its lesser invasiveness and shorter initial hospitalization.[5] However, the short-term deterrence of CABG in younger, fitter patients is less due to lower complication rates and shorter length-of-stay and time needed to resume normal activities of daily living. The benefit of PCI over CABG in younger patients may therefore be small, while long-term efficacy is clearly superior in the majority of young patients. The treatment of choice in young patients should therefore preferable be CABG.

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Rotterdam

Chapter 28

Off-pump or on-pump coronary-artery bypass grafting

Head SJ, Kappetein AP

N Engl J Med 2012;367:577-578

TO THE EDITOR:

In the article by Lamy et al. (April 19 issue)[1] regarding the CABG Off or On Pump Revascularization Study (CORONARY), coronary-artery bypass grafting with a beating-heart technique (off-pump CABG) showed no benefit over cardiopulmonary bypass (on-pump CABG) in reducing adverse events among 4752 patients at 30 days. The trial was designed to show that off-pump CABG could reduce the expected on-pump event rate of 8.86% by a relative 28%. This hypothesis might have been appropriate for high-risk subgroups,[2,3] but we believe it is unrealistic and too optimistic in a population that includes low-risk patients. (In the study, 82.3% of patients had a grade of 5 or less on the European System for Cardiac Operative Risk Evaluation [EuroSCORE] at baseline). Since data from recent trials have already suggested that the benefit of off-pump CABG is limited,[4] Lamy et al. could have used an adaptive study design and modified their sample size accordingly.[5] With a less liberal estimate of a relative risk reduction of about 15%, a prohibitively large sample size of 15,000 to 20,000 patients would have been required. As a result, it is unlikely that the 5-year CORONARY results will be able to show a benefit for off-pump CABG.

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San Francisco

Chapter 29

What is the evidence allowing us to state that transcatheter aortic valve replacement via the femoral artery is a more attractive option compared to transapical valve replacement?

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EuroIntervention 2011;7:903-904

INTRODUCTION

Recently, transcatheter aortic valve replacement (TAVR) has been shown to result in similar 12-month survival as surgical aortic valve replacement (SAVR) for high-risk patients with severe aortic stenosis.[1] For patients deemed inoperable TAVR showed a 20% survival benefit at one year compared to medical treatment.[2]

THE PARTNER TRIAL

During the focused late-breaking clinical trial session at TCT in San Francisco new data on TAVR were presented. Good news came from the PARTNER B trial which tested TAVR with the SAPIEN device (Edwards Lifesciences, Irvine, CA, USA) in inoperable patients against best medical care. Data showed that survival curves are continuing to diverge. By two years, 67.6% of patients in the medical group had died, compared with 43.3% in the TAVR group, a difference of 24.3%. The number needed to treat to save one life therefore dropped to four patients, which was five patients at one year.

The potential cost-effectiveness of TAVR versus SAVR in the PARTNER trial was examined and the results were presented by Matthew Reynolds. Health-state utilities were estimated using the EuroQOL (EQ-5D) at baseline, one, six and 12 months. Medical resource utilisation data were collected on all study patients, and hospital billing data were collected for both index and follow-up hospitalisations for any cause. The costs of the SAPIEN valve were projected at $30.000. The objectives of the study were to combine cost data with survival and quality of life (QoL) data in order to estimate the 12-month cost-effectiveness of TAVR compared with AVR. The secondary objective was to explore potential differences in costs and cost-effectiveness of TAVR vs. SAVR for the transfemoral and transapical populations.

The PARTNER A cohort randomised patients with severe, symptomatic aortic stenosis and high surgical risk to either TAVR (N=348) or SAVR (N=351), and followed them for a minimum of 12 months. The PARTNER A study was designed to test the SAPIEN valve against surgery in high-risk patients. Patients randomised to TAVR had a *transfemoral-first approach*; only when the patient was unsuitable for transfemoral valve delivery did they undergo a transapical procedure. This type of study design is biased towards finding more favourable results with transfemoral TAVR.

Quality of life data of the PARTNER A trial was presented by David Cohen. He showed that there was a quality of life benefit of transfemoral TAVR compared to surgery at one month, but similar benefits at later time points. For the small group of transapical patients (n=104) the quality of life measurements tended to be slightly better with surgical AVR at six months only. From a clinical standpoint this is difficult to explain.

Transfemoral TAVR provided small but significant advantages in 12-month quality adjusted life expectancy. TAVR was associated with higher procedural costs, but slightly lower index hospitalisation and costs at one year. The study also indicated that for the transapical approach there was no difference in quality of life compared to SAVR at one year and the costs were somewhat higher compared to surgery (about $10,000/patient) due to the same length of hospital stay as with surgery. Transcatheter aortic valve replacement therefore seems an economically attractive intervention especially for the transfemoral approach.

STACCATO

In the STACCATO trial patients were randomised to transapical TAVR or surgical AVR. The design of the trial can be criticised. The only inclusion criterion was that patients had to be older than 70 years of age. As a result, the enrolled patients had a mean STS score of only 3.1 and 3.4 in the TAVR and SAVR groups, respectively. So far TAVR has only been investigated in high-risk or inoperable patients, while this trial looked at patients at low risk for SAVR.

The primary endpoint of the trial was a composite of all-cause death, stroke, and renal failure requiring haemodialysis. The sample-size calculation of the trial was based on data that did not correspond to current outcomes. A surgical event rate of 13.5% was anticipated, which, based on data from the STS database, is far too high. The STS score of 3.1-3.4% corresponds to similar mortality rates, and is the same as reported by O'Brien et al.[3] This mortality risk coincides with only a 1.5% stroke rate (total event rate would be ±5%). Although the addition of renal failure requiring haemodialysis would increase the event rates somewhat, this will never be 13.5%.

In the TAVR arm, only a 3% event rate was expected, which is much lower than in most European registries or the PARTNER trial. Two Danish centres participated after more than 40 TAVR procedures had been performed. Whether these were transfemoral or transapical cases was not presented.

The trial was first stopped after inclusion of 11 of the 200 planned patients due to three adverse events in the TAVR group. The inclusion and exclusion criteria were modified and after enrolling 70 patients the study was stopped again due to an excess of events in the transapical patients. The events that occurred, however, are more related to TAVR in general than to the transapical route. Primary endpoints included one patient who died on the waiting list, two major strokes (day 16 and 27), one left coronary blockage and one patient that needed dialysis. Other events were TIA (n=1), left main occlusion during balloon valvuloplasty (n=1), aortic rupture (n=1), severe paravalvular leakage (n=2), valve embolisation (n=1), abnormally positioned heart (n=1) and bleeding complication (n=1). It is clear that only the bleeding event might possibly be attributed to the transapical route.

Multislice computed tomography (MSCT) was not used in the pre-operative assessment for valve sizing, and this could have led to valve under-sizing and the high rate of paravalvular leakage.[4] MSCT could also have been used to assess the annulus to left main distance and potentially avoid coronary ostia blockage.

The conclusion that "transapical aortic valve replacement is inferior to surgical valve repair" seems not to be justified. Transapical AVR has the advantage of being an antegrade approach as opposed to all the other techniques; the transaortic, subclavian artery and transfemoral being retrograde. This may have potential advantages like reduction of periprocedural strokes due to a minimum of manipulations in the aortic arch.

It is important to note that the STACCATO trial was designed three years ago and the PARTNER trial enrolled patients up until two years ago – techniques have changed since then. In the PARTNER trial, the first generation of the SAPIEN device was used, while in Europe new generation devices and improved techniques are currently employed. Thus the results from these studies cannot be translated to other devices or newer generations of these devices, and new studies with these devices are necessary in order to define the role of transapical valve replacement. Sizing of the valve has improved by the use of MSCT, incisions for transapical replacement have become smaller and the spreading of the ribs reduced, leading to less postoperative pain. The centres in the PARTNER trial did not have any previous experience with TAVR and still achieved remarkably good results. These will improve even further with experience. Procedural times for transapical TAVR were 224 min in the PARTNER US trial much longer than the 132 min in the PARTNER EU trial. The transapical group in the PARTNER trial was rather small; only 104 patients were enrolled at a large number of sites with, therefore, little experience for a technically more demanding procedure than transfemoral replacement. The transfemoral and transapical groups were not powered to look at the quality of life or cost-effectiveness endpoints separately, and it is very likely that in an inexperienced centre the costs will be higher.

The costs of the procedure depend very much on the cost of the device and it is to be expected that in the coming years, with more competition, the costs of the device will come down and transapical TAVR will mimic the cost of surgical AVR.

CONCLUSIONS

From the data presented at TCT it is clear that TAVR will play an important role in the future. To which extent the valve will be replaced transfemorally or transapically cannot be concluded from the data, but will need additional research.

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Amsterdam

Chapter 30

Subgroup analyses in a continuum of trial reports comparing percutaneous coronary intervention to bypass surgery

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Submitted

ABSTRACT

Objectives

The objective of this study was to describe and evaluate the use of subgroup analyses in a continuum of publications that arise from randomized trials comparing percutaneous coronary intervention (PCI) to coronary artery bypass grafting (CABG) for coronary artery disease.

Methods

PubMed was systematically searched through January 1, 2012. Primary endpoint papers were extracted. Subsequently follow-up and separate publications that focus on specific subgroups of patients were identified by a combined search of author and trial names. Two researchers collected data on subgroup pre-specification, analyzed outcomes, emphasis of results, and whether authors advised caution with interpreting subgroup result.

Results

From 17 trials we included 17 primary, 19 follow-up, and 28 subgroup papers. Thirteen (76%) trials reported subgroup analyses. In 5 primary, 13 follow-up, and 28 subgroup papers the number of reported subgroup analyses was 70, at least 372, and 952, respectively. Subgroups were pre-specified in only 7 (54%) trials, and 9 (69%) trials also performed post hoc exploratory analyses on subgroups that were not pre-specified. Analyses were performed on secondary endpoints 71%. Subgroup differences were claimed in all primary papers, 33% of follow-up papers, and 68% of subgroup papers. Appropriate interaction tests were reported in only 43%. Subgroup results were emphasized in the conclusion or abstract in 40%, 68% and 100% of primary, follow-up, and subgroup papers, respectively. In 78% of papers the authors failed to advise appropriate caution with subgroup analysis interpretation. From primary papers to follow-up papers to subgroup papers, the quality of reporting is increasingly flawed.

Conclusions

An excessive number of subgroup analyses (n >1,394) have been reported in PCI versus CABG trials. The method of reporting subgroup analyses is suboptimal and frequently methodologically invalid due to an inadequate statistical basis for validity, which has led to unsubstantiated treatment recommendations.

INTRODUCTION

Reports of randomized trials according to the rules from the CONSORT statement are considered to be the highest standard of original research.[1-3] Data originating from randomized trials are often used to determine whether a treatment effect varies across patient subgroups. It is important to identify potential treatment heterogeneity; after all, personalized medicine emphasizes treatment differences between individuals. An example is the impact of diabetes on outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), where it was suggested that long-term survival after CABG is superior over PCI particularly in diabetics.[4-6]

However, methodologists have warned against the validity of such subgroup results.[7-13] Although the statistical methodology of subgroup analyses requires additional consideration, literature reviews of subgroup analyses in primary endpoint papers of randomized trials found low credibility of subgroup results due to methodological issues.[7, 11, 13, 14]

In addition to the primary report, authors often publish separately secondary results for longer follow-up or focusing on specific subgroups of patients (e.g. diabetics). These follow-up or subgroup papers are frequently of a lower standard than primary reports, and subgroup claims derived from these papers are even more methodologically flawed. However, no studies have systematically examined the frequency and methodological accuracy of subgroup analyses across subsequent papers. Our aim was therefore to i) describe and critically evaluate the use of subgroup analyses in the primary report, and follow-up or subgroup papers, ii) assess the difference in quality among a continuum of publications, and iii) point out the corresponding hazardsof over-emphasizing subgroup conclusions in a clinical-trial context of randomized studies comparing PCI with CABG. Furthermore, the CONSORT statement provides little guidance on how subgroup analyses should be reported and lacks any specific guidance in drafting follow-up or subgroup papers.[1-3] We therefore provide recommendations to improve analysis and interpretation of subgroup data in order to prevent many, if not all, spurious observations and minimize treatment errors.[7, 15, 16]

METHODS

Search strategy and study inclusion

The PubMed database was searched from its inception through January 1st 2011 to identify published English-language parallel-group randomized trials comparing PCI with CABG for complex coronary artery disease. We searched the title and abstract using the following keywords: ("randomized" OR "randomised" OR "randomly") AND ("bypass" OR "CABG") AND ("angioplasty" OR "PCI" OR "PTCA"). Trials focusing exclusively on off-pump or minimally invasive CABG were excluded. Reference lists from meta-analyses, systematic

reviews, and other relevant publications were audited to ensure no potentially valid trials were missed.

We identified papers that reported the primary (clinical) endpoint of the trial (later referred to as "mainpaper"). By combining author and trial names, the PubMed database was searched through January 1st 2012 to identify subsequent publications that reported follow-up analyses ("follow-up paper") or results on specific subgroups of patients ("subgroup paper"). The timing of the search is different than for primary papers because we allowed sufficient time (≥1 year) to publish subsequent papers. Follow-up papers were defined as manuscripts that focused specifically on long-term follow-up of at least the primary endpoint. Subgroup papers were defined as manuscripts that focused on a subpopulation of the original cohort or focused exclusively on the effect of a single baseline variable (e.g. diabetes) on outcomes, or determined to find a difference in primary or secondary endpoints between subgroups with(in) PCI and CABG. We excluded subgroup papers that performed analyses with combined randomized and registry patients.

Identification of papers and data extraction were independently performed by multiple researchers (S.J.H., E.L.S.), and checked (A.P.K.). In case of disagreement consensus was reached by discussion.

Criteria of subgroup analyses and strength of a subgroup claim

Pre-specification. Pre-specification is recommended to avoid excessive post-hoc exploratory analyses (e.g. data mining), to limit the risk of false-positive findings.

Endpoints. In the context of randomized trials, primary endpoints are frequently composite endpoints. Subgroup analyses have limited power to detect differences in the primary endpoint because of a smaller patient cohort. However, power may be even lower for individual secondary or tertiary endpoints because event rates are lower.

Interaction test. To detect a difference in outcomes between subgroups, a subgroup-by-treatment interaction should be performed.[17, 18] Such a test is necessary to assess whether a treatment effect is different across subgroups.

Emphasis. Interaction tests have low statistical power and thus subgroup analyses should always be interpreted with caution despite significant interaction. Emphasis of subgroup analyses in the conclusion section or abstract can distract readers from the overall conclusion of the trial.

Advised caution. Caution with interpretation of subgroup results should be specified explicitly, and it needs to be clarified that results are hypothesis-generating. Policy or guideline recommendations of clinical practice based on results of subgroup analyses should therefore be avoided.

Assessment of analyses

The total of subgroup analyses was calculated as the product of the number of factors (e.g. diabetes) and the number of outcomes (e.g. death) the subgroup was tested for, except for trials with varying baseline factors for different outcomes.[7] We extracted information from the included papers using a standardized extraction spreadsheet. Information on whether subgroups were pre-specified in the trial protocol was collected per trial. Furthermore, we assessed: i) whether subgroup analyses were reported for primary or secondary endpoints, ii) if an interaction test was reported for none, part, or all analyses, iii) whether subgroup analyses were emphasized in the manuscript conclusion or abstract, iv) if caution was advised with interpretation of subgroup results, and v) whether analyses were reported as hypothesis-generating.

Analysis

Results were reported as proportions, mean ± standard deviation, or median. All results were reported as observational and no statistical comparisons were performed.

RESULTS

Seventeen randomized trials comparing PCI to CABG were identified. We included 17 main (19-34), 19 follow-up (eReferences 1), and 28 subgroup papers (eReferences 2) in the final analyses.

There were 13 trials (76%) that reported subgroup analyses in the main paper (n=5), and/or in follow-up papers (n=8), and /or in specific subgroup papers (n=9) (Table 1). Pre-specification of subgroups was present in 4 (31%) trials, 3 trials also performed exploratory post-hoc analyses in addition to these pre-specified groups, and 6 (46%) trials only had post-hoc defined subgroups.

Table 1 **Reported subgroup analyses in PCI versus CABG randomized trials**

Reporting of subgroup analyses	Number of Trials (n=17)	Trials
In the main paper	5 (29%)	CABRI, BARI, ERACI-II, SYNTAX, CARDia
In subsequent follow-up papers	9 (53%)	RITA, EAST, BARI, ERACI-II, ARTS, GABI, SoS, MASS-II, SYNTAX
In subgroup papers	9 (53%)	MASS, CABRI, BARI, AWESOME, ERACI-II, ARTS, SoS, MASS-II, SYNTAX
No subgroup analyses reported	4 (24%)	ERACI, Lausanne, FMS, SIMA

Main papers

A total of 70 subgroup analyses were reported in main papers (Table 2). Four of the 5 trials that reported subgroup analyses performed the analyses on the primary endpoint, of which 2 also reported analyses on secondary endpoints. One trial, ERACI-II, reported subgroup analysis only for secondary endpoints. In total, 53 (76%) subgroup analyses were performed for the primary endpoint and 17 for a secondary endpoint.

An interaction test was reported in only 3 of the 5 trials, with one trial (SYNTAX) reporting an interaction term for some of the analyses. All trials claimed that there was a subgroup difference, while this was not always confirmed by a significant interaction term. Three trials reported subgroup results with a major emphasis on the result by reporting them in the manuscript conclusion or in the abstract. Only the SYNTAX trial labeled results as hypothesis-generating, although the BARI and CARDia trials did advise some caution with interpretation of the subgroup results.

Follow-up papers

Of 19 follow-up papers, 6 papers did not report any subgroup analyses. Thirteen papers from 9 trials reported a total of at least 372 subgroup analyses (Table 3). Of 3 papers, the exact number of subgroup analyses could not be extracted from the text. Five trials reported pre-specified subgroups, but in addition the BARI, ARTS, and SYNTAX trials reported a large number of subgroups that were not pre-specified. In all but one paper, analyses of secondary outcomes were reported. Of all subgroup analyses, 52% were performed on secondary endpoints.

An interaction test was frequently not reported, but this did not withhold authors from claiming subgroup differences. In only 2 (17%) papers the authors advised caution with interpretation of subgroup analyses. Only the 3-year follow-up paper of the SYNTAX trial reported subgroup analyses as hypothesis-generating.[35]

Subgroup papers

Nine trials reported 28 subgroup papers (CABRI (n=2), MASS (n=1), BARI (n=5), ERACI II (n=1), ARTS (n=7), AWESOME (n=4), SoS (n=3), MASS II (n=1), and SYNTAX (n=4); eReferences 2). These papers reported a total of 952 subgroup analyses; a mean of 34 ± 5.8 (median = 26) analyses per paper (Table 4). Both the CABRI and AWESOME study reported the least number (n=3) of subgroup analyses in a single paper, the SYNTAX trial the most (n=136).

In 93% of the papers at least one subgroup analysis was performed for the primary endpoint and only in two papers (7%) the authors reported results exclusively of the primary endpoint (Table 4); of the 952 analyses in total, 82% were performed on secondary endpoints (versus 18% on the primary endpoint). An interaction test was reported in 9 papers (32%). A difference in treatment effects among subgroups was claimed in 19 (68%) of the papers.

Table 2 Subgroup analyses reported in main papers

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
CABRI, 1995	Gender	Yes	2	Primary endpoint	Yes	Yes. However, interaction was not significant.	"[PTCA patients] were also more likely to have clinically significant angina; this association was present in both sexes but was significant only in females."	Yes, the gender subgroup difference is emphasized in the manuscript discussion and in the abstract.	No
BARI, 1996	**Among all patients and diabetics** Angina grade Left ventricular function Number of vessel disease Type C lesion Diabetes	Partly; subgroups were pre-specified, except for diabetes.	24	Primary endpoint	No	Yes, for diabetics.	"Among diabetic patients who were being treated with insulin or oral hypoglycemic agents at base line, a subgroup not specified by the protocol, five-year survival was 80.6 percent for the CABG group as compared with 65.5 percent for the PTCA group (P=0.003)." "For treated diabetics, five-year survival was significantly better after CABG than after PTCA."	Yes, the results from the diabetic subgroup received major emphasized in the abstract and were mentioned in the conclusion of the abstract.	No, but caution is advised by stating that "this finding should be confirmed in other populations".

Table 2 *Continued*

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
ERACI-II, 2001	Angina grade	No	3	Secondary endpoint	No	Yes	"There was a trend for a higher 30-day mortality rate in patients with unstable angina randomized to surgery."	No, results were not mentioned in the discussion or conclusion, nor in the abstract.	No
SYNTAX, 2009	Type of vessel disease SYNTAX score	Partly; the LM/3VD subgroups were pre-specified, but the SYNTAX score subgroups were not.	21	Primary (n=17) and secondary (n=4) endpoints	Partly; yes for SYNTAX score subgroups. No interaction reported for the type of vessel disease.	Yes, for SYNTAX score terciles with significant interaction (p=0.01).	"This finding suggests that a percutaneous approach should be avoided in patients with high SYNTAX scores."	No, the result within SYNTAX score subgroups was shortly mentioned in the discussion, but no subgroup results were reported in the abstract.	Yes
CARDia, 2010	Number of vessel disease BMS or DES use Diabetes on insulin Gender Age	Yes	20	Primary (n=10) and secondary (n=10) endpoints	Yes	Yes, for DES use. However, interaction was not significant.	"Because the CARDia trial was underpowered, we cannot make any clear statements about the subgroups, even though these are presented; however, there seems to be a trend suggesting that DES provide a better outcome than BMS."	Yes, the subgroup of DES patients is reported in the abstract.	No, but caution is advised because the trial was underpowered.

3VD = three-vessel disease; BMS = bare-metal stent; CABG = coronary artery bypass grafting; DES = drug-eluting stent; LM = left main; PTCA = percutaneous transluminal coronary angioplasty

Table 3 Subgroup analyses reported in follow-up papers

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed in subgroup analyses	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
RITA, 1998	Number of vessel disease Diabetes Angina grade	No	33	Primary (n=3) and secondary (n=30) endpoints	Partly; yes for the diabetics. No interaction reported for the baseline angina subgroups. Number of vessel disease inter-action was reported for some outcomes.	No	"The results of RITA-1 were similar in patients with single-vessel and multi-vessel disease, although there was a trend for patients with single-vessel disease treated by PTCA to have a higher rate of myocardial infarction than those treated by CABG." "In our study, outcome was non-significantly worse for diabetic patients assigned CABG than for those assigned PTCA."	Yes, the diabetes subgroup and number of vessel disease subgroups are emphasized in the discussion of the manuscript. However, there is no mentioning of subgroups in the conclusion of the manuscript or the abstract.	No

Table 3 *Continued*

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed in subgroup analyses	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
EAST, 2000	Number of vessel disease Proximal LAD lesion Diabetes	No	At least 12	Secondary endpoints	No	Yes, for diabetes.	"Although no difference in the diabetic population was seen at three years, the eight-year follow-up was in the direction of the better late survival in the surgery group as seen in BARI." "In addition, the clinical impression that patients with more diffuse disease and those with proximal left anterior descending disease (almost all of whom received internal mammary artery grafts in the surgical group) may have better outcomes with surgery was not established by this study. There was a trend toward better survival with surgery for the patients with proximal left anterior descending coronary artery lesions (p = 0.16)."	Yes, the diabetes and proximal LAD lesion subgroups were emphasized in the discussion of the manuscript and mentioned in the abstract. The diabetes subgroup result was stated in the conclusions of the manuscript and abstract.	No, but the authors generally commented: "The study was not powered to detect a difference in survival."

Table 3 *Continued*

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed in subgroup analyses	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
BARI, 1997, 2000, and 2007	**Among all patients, and diabetes subgroups** Congestive heart failure Angina grade Left ventricular function Number of vessel disease Type C lesion Proximal LAD lesion Diabetes Age Gender Peripheral vascular disease Smoking Normal electro-cardiography	Partly; some subgroups were pre-specified, except for the diabetes, age, gender, peripheral vascular disease, smoking, and electrocardio-graphy subgroups. The subgroups within the diabetes and non-diabetes subgroups were not pre-specified.	179	Primary (n=128) and secondary (n=51) endpoints	Partly; in the initial follow-up paper published in 1997 inter-actions were reported for all subgroup analyses. In sub-sequent follow-up papers in 2000 and 2007, inter-action terms were reported for some but not all analyses.	Yes, for diabetes. The interaction term was significant for cardiac death or any MI.	"To make informed clinical decisions for all diabetic, patients requiring revascularization, more information is required. Based on the BARI results, diabetic patients with multivessel disease and unstable or severe symptoms should receive CABG rather than balloon PTCA." "In patients with type 2 diabetes, CABG conferred a consistent, clinically relevant, absolute survival benefit over balloon angioplasty that diminished somewhat over extended follow-up because patients in both groups had higher event rates."	Yes, the diabetes subgroups are emphasized in the discussion and conclusion of the manuscript, as well as in the abstract and the conclusion of the abstract.	No

Table 3 *Continued*

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed in subgroup analyses	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
ARTS, 2003, 2004, and 2005	Diabetes Number of vessel disease Proximal LAD lesion Renal status Gender Age Hyper-cholesterolemia	Partly; the diabetes and number of vessel disease subgroups were pre-specified. Other subgroups were *post hoc*.	At least 56 (it is un-clear from the text how many analyses were per-formed).	Primary (n=13) and secondary (n=43) endpoints	No	Yes, for diabetes.	"In view of the relatively greater difference in outcome in patients with diabetes, surgery clearly seems to be the preferable form of treatment for these patients." "There were also no significant differences in event-free survival within the respective treatment groups based on renal function, gender, age, or hypercholesterolemia at the time of randomization."	Yes, the diabetes subgroup is mentioned in the conclusion of the abstract.	No, but the authors stated: "the study was not powered to show mortality differences be-tween diabetic and nondiabetic patients."
ERACI-II, 2005	Diabetes	No	2	Secondary endpoints	No	No	None	No, the subgroup results are not mentioned in the discus-sion or conclusion of the ma-nuscript, nor in the abstract.	No

Table 3 *Continued*

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed in subgroup analyses	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
GABI, 2005	Gender Previous MI Age Diabetes Number of vessel disease Left ventricular function	No	At least 12 (the actual data is not reported).	Secondary endpoints	No	No, but universal applicability was claimed.	"Hazard ratios for mortality following PTCA or CABG were not different with regards to [subgroups]."	No, none of the subgroup analyses are reported in the conclusion or abstract, however, they were mentioned in the discussion.	Yes, "the subset analyses should be viewed with caution".
SoS, 2008	Diabetes Angina grade Number of vessel disease	Yes	14	Primary (n=12) and secondary (n=2) endpoints	Yes	No	"The statistical test for interaction gave little evidence that the treatment effect on mortality differed between diabetic and non-diabetic patients (P=0.15)."	Yes, the subgroup results were extensively discussed in the discussion and reported in the conclusion of the manuscript. Furthermore, subgroup results were reported in the abstract.	No

Table 3 *Continued*

Trial, year	Subgroup	Were subgroups reported as pre-specified?	No. of reported subgroup analyses	Endpoints analyzed in subgroup analyses	Interaction analyses reported	Subgroup difference claimed	Comment about subgroup finding	Emphasis on subgroup results	Results reported as hypothesis-generating
MASS II, 2010	Gender Age Previous MI Hypertension Diabetes Smoking	Yes	12	Primary endpoint	No	No, but universal applicability was claimed.	"The effect of treatment on 10-year event-free survival was not changed by clinical characteristics of PCI versus CABG."	No attention is directed to any of the PCI versus CABG subgroup analyses.	No
SYNTAX, 2011	3VD/LM disease Diabetes SYNTAX Score	Yes	52	Primary (n=12) and secondary (n=40) endpoints	Partly, not for all endpoints	Yes, for 3VD and LM disease	"Major adverse cardiac and cerebrovascular event rates were no significantly different between arms in the LM subgroup but were higher with PCI in the 3VD subgroup." "In patients with less complex disease (low SYNTAX scores for 3VD or low/intermediate terciles for LM patients), PCI is an acceptable revascularization."	"Additionally, analyses of the LM and 3VD subgroups, although sufficiently powered, can only be considered hypothesis-generating as SYNTAX did not meet its primary endpoint. The analyses of LM or 3VD patients by SYNTAX score were not pre-specified and should be considered exploratory and hypothesis-generating only."	Yes

3VD=three-vessel disease; LAD=left anterior descending; LM=left main; MI=myocardial infarction; PCI=percutaneous coronary intervention; other abbreviations as previous.

Table 4 Reported subgroup analyses in subgroup papers

	Number of papers (n=28)
Number of subgroup analyses reported	
1-10	7 (25%)
11-20	5 (18%)
21-30	4 (14%)
≥31	12 (43%)
Outcomes analyzed in subgroup analyses was	
Primary endpoint	2 (8%)
Secondary endpoint	2 (8%)
Both primary and secondary endpoints	24 (86%)
Reported test for interaction	
Yes	9 (32%)
No	19 (68%)
Subgroup difference claimed in abstract or conclusion	
Yes	19 (68%)
No	9 (32%)
Indicate caution with interpretation of subgroup results	
Yes	12 (43%)
No	16 (57%)
Reported results as hypothesis-generating	
Yes	7 (25%)
No	21 (75%)

Since subgroups were the main topic of the publication, an emphasis on these results was always present. However, in only 12 of 26 papers (43%) the authors advised caution with the interpretation of the results. In even fewer papers (n=7, 25%) the results were specifically reported as hypothesis-generating.

Cumulative results

At least 1,394 subgroup analyses in 17 trials comparing PCI with CABG were reported. In papers that reported subgroup analyses, subgroup differences were claimed in all primary papers, in 33% of follow-up papers, and 68% of subgroup papers. However, appropriate interaction tests were performed in only 43% of papers and not even for all analyses. Still, subgroup results were emphasized in the conclusion or abstract in 40%, 68%, and 100% of primary, follow-up, and subgroup papers, respectively. In 78% of the papers, the authors failed to advise appropriate caution with subgroup analysis interpretation by reporting them as hypothesis-generating.

Table 5 Summary of studies systematically assessing the quality of subgroup analyses

Author, year	Specialty area	Design	Study inclusion	Main findings	Conclusion
This study	PCI versus CABG for coronary disease	Systematic electronic database search	17 main, 18 follow-up, and 26 subgroup papers of RCTs	29%, 47%, and 53% of trials reported subgroup analyses in main, follow-up, and subgroup papers; 76% of trials reported subgroup analyses. Analyses most frequently on secondary endpoints. Lack of interaction testing. Lack of indicating that results should be hypothesis-generating.	In 17 RCTs comparing PCI versus CABG, more than 1,394 subgroup analyses were reported. Quality of analysis and reporting of subgroup analysis in main papers of trials is poor, but the quality decreases even more in subsequent follow-up and subgroup papers.
Sun, 2011	None in particular	Systematic electronic database search	469 main papers of RCTs	Subgroup analyses in 42% of trials. Several factors influence the reporting of subgroup analyses: sample size, journal impact factor, type of trial (surgical), and industry funding. Industry funding is also associated with lower methodological quality.	Industry funding influences reporting and the quality of subgroup analyses. These results should be viewed with caution.
Wang, 2007	None in particular	Hand-search *NEJM*	97 main papers of RCTs	Subgroup analyses in 61% of trials. Unclear whether subgroup analyses are predefined or *post hoc*. Lack of interaction testing.	Reporting of subgroup analyses is neither uniform nor complete. Encourage to report subgroup analyses more clear and complete.
Hernández, 2006	Cardiovascular clinical trials	Hand-search 4 major impact journals	63 main papers of RCTs	Subgroup analyses in 62% of trials. No trial was powered to detect subgroup effects. Low rate of prespecification of subgroups. Lack of interaction testing. Significant inappropriate emphasis on subgroup results.	Several shortcomings in reporting subgroup analyses. Reporting of subgroup analyses needs to be improved substantially.
Bhandari, 2006	Orthopaedic surgical RCTs	Hand-search 4 journals	72 main papers of RCTs	Subgroup analyses in 38% of trials. Inappropriate emphasis on subgroup analyses occurred frequently. Analyses most often *post hoc* (91%).	

Table 5 ***Continued***

Author, year	Specialty area	Design	Study inclusion	Main findings	Conclusion
Hernández, 2005	Traumatic brain injury	Systematic electronic database search	18 main papers of RCTs	Subgroup analyses in 61% of trials. Significant inappropriate emphasis on subgroup results. Subgroup analyses were insufficiently described and clearly different as planned in the protocol.	Methodological shortcomings in subgroup analyses reporting. Improvement of appropriate performance and reporting is needed.
Assmann, 2000	None in particular	Hand-search 4 major impact journals	50 main papers of RCTs	Subgroup analyses in 70% of trials. Interaction testing was used in <50%. Difficult to determine whether analyses were predefined or *post hoc*. Low statistical power.	A predefined statistical plan is needed. Caution is advised when drawing conclusions from subgroup findings.

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; RCT = randomized clinical trial; NEJM = New England Journal of Medicine

DISCUSSION

In the results of clinical trials comparing PCI to CABG, more than 1,394 subgroup analyses were reported in the main, follow-up, and subgroup papers. We have identified many shortcomings in these subgroup analyses, with a step-wise increase in the number of subgroup analyses and the methodological issues from main papers to follow-up papers to subgroup papers. Although previous systematic reviews have identified significant methodological flaws of subgroup analyses in main papers of randomized clinical trials (Table 5), we found that to assessinterpretations and conclusions that arise from trials one must consider not only the main article, but also the follow-up papers and the separate publications that focus on specific subgroups of patients. This is of concern because many subsequent papers are published and used to guide treatment recommendations, while the conclusions are frequently not substantiated and are not sufficiently robust to change treatment policy in certain types of patients.

Follow-up and subgroup papers are often encouraged by study sponsors and investigators to produce multiple publications. However, subgroup analyses should only be performed when a proper rationale is given and groups have been pre-specified in the study protocol. Post hoc analyses in "interesting" groups are, nevertheless, frequently conducted. These analyses are of lower credibility and raise concerns because of confounding [36] and because there are no limitations to how many analyses are performed. These large number of analyses (k) cause inflated error rates [18] and should be corrected either through adjusted P-values (adjusted P = unadjusted P-[1-unadjusted P]^k) or adjusted α (Bonferroni: adjusted α = 0.05/k,

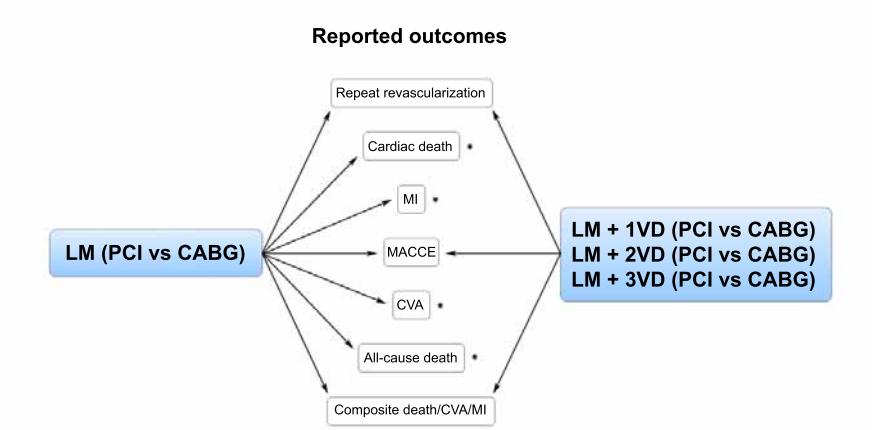

Figure 1 Reported outcomes

Different outcomes reported from the SYNTAX trial for subgroups of patients with left main disease and left main disease with additional vessel involvement. Outcomes indicated by the asterisk are likely to have been performed, but are not reported. LM = left main; PCI = percutaneous coronary intervention; CABG = coronary artery bypass surgery; MI = myocardial infarction; MACCE = major adverse cardiac and cerebrovascular events; CVA = cerebrovascular event; VD = vessel disease

or Sidák: adjusted $\alpha = 1-(1-\alpha)^{1/k}$).[11, 37] In this study, we found 70 subgroup analyses in the main, at least 372 in follow-up, and 952 in subgroup papers, while only 5 trials planned subgroup analyses. These analyses were not corrected for multiplicity.

The total number of analyses we found may even be an underestimate. It is likely that a larger number of subgroups were tested for a greater number of endpoints. Figure 1 provides an example from the SYNTAX trial where multiple subgroup analyses were reported for the left main cohort, while fewer analyses were reported for other subgroups.[33] It is possible many subgroup analyses were performed but may not have been reported, suggesting a possible publication bias; non-significant results are less likely to be reported.[15, 38, 39] Therefore, even pre-specified subgroups may not always be reported. For example, the CABRI trial stated in the methods section that mortality and angina would be analyzed by gender, but analyses were only performed for the angina endpoint.[24]

An interaction test is mandatory to analyze a difference in treatment effect between subgroups of patients. Frequently this statistical approach is violated and subgroup differences are claimed by a comparison of p-values within subgroups.[40] For example, from a subgroup analysis of the SoS trial the authors concluded in the abstract that PCI and CABG resulted in similar 1-year health status in older patients ($P>0.05$), while younger patients had more health status benefits from CABG as compared with PCI ($P<0.05$).[41] However, the interaction test was not significant ($P>0.05$) and thus a true difference of treatment effects cannot be claimed.

Some subgroup papers are designed such that they exclude the possibility of performing an interaction test. These reports warrant extra caution, since the conclusions are inherently methodologically incorrect. For example, the main analysis of the AWESOME trial showed similar survival for PCI and CABG while the authors concluded that PCI should be preferred over surgery in the subgroup of post-CABG patients.[29, 42] This paper, however, focused exclusively on post-CABG patients and not the de novo coronary artery disease cases. Whether the results in post-CABG patients were really different from de novo cases could therefore not be assessed with an interaction term.

Even with an interaction test there is a high chance of false-positive findings.[17] For example, an illustrative subgroup analysis from the ISIS-2 study demonstrated an adverse effect of aspirin on mortality (9% increase) for patients with Gemini or Libra as astrological birth signs, while patients with other signs had a 28% reduction.[43]

It is also important to assess whether an interaction is quantitative in which the treatment effect is in similar direction but varies in magnitude, or qualitative, in which the direction of the effect is different (Figure 2A).[44, 45] Quantitative interactions are more credible and very likely to be present, while qualitative interactions are seldom replicated and should not be emphasized.[12, 44] In addition, when continuous variables are divided into (arbitrary)

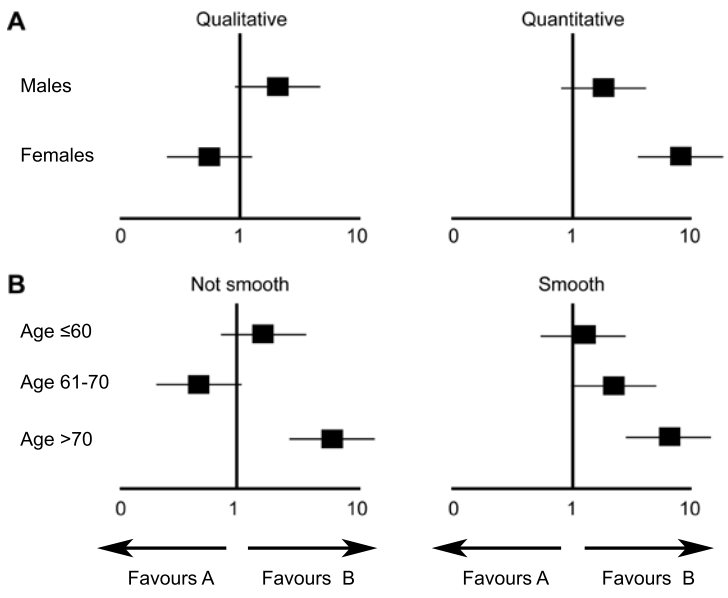

Figure 2 **Features of interactions between treatment effects**

The type of interaction ***(A)*** and smoothness ***(B)*** give necessary insights into the credibility of interactions. Quantitative and smooth interactions are more likely to be genuine.

subgroups, the 'smoothness' of treatment differences may be an indication of whether the interaction is genuine, where smooth interactions are more likely to reflect a true difference in treatment effect (Figure 2B).

Still, when subgroup interactions appear genuine, they must not be overemphasized. Authors should highlight the limited applicability of subgroup results by emphasizing that subgroup results warrant caution in that they are hypothesis-generating only, and that no clinically directive recommendations should be derived from subgroup results. In reality, however, these statements are frequently ignored and the community may still overemphasize subgroup results. For example, the result of the SYNTAX trial left main subgroup analysis were clearly reported as hypothesis-generating,[46, 47] yet some physicians may already consider left main stenting as a good alternative to CABG,[48] resulting in wider adoption of PCI for this indication. In addition, the current revascularization guidelines have based many of their recommendations on these and other (e.g. SYNTAX score) subgroup analyses from the SYNTAX trial.[49, 50] Only until the results from the ongoing EXCEL trial are available can a substantiated conclusion be derived.[51]

In a negative trial, as were several of the PCI versus CABG trials, there is an additional incentive to perform subgroup analyses to find specific subgroups of patients in whom certain treatment does appear beneficial. However, if the overall trial result is negative, subgroup differences are even less substantiated because of data mining in search of a subgroup in which PCI is indeed equivalent to CABG. Hierarchical testing --where subgroup analyses are performed only if the overall trial result is positive-- could be a solution to protect against fishing for false-positive results.

As shown by the example of the SYNTAX trial, subgroup analyses can be meaningfulto identify treatment heterogeneity among patient subgroups and thereby generate hypotheses for new trials. However, it is necessary to perform adequately powered trials to validate these hypotheses. Additional underpowered subgroup analyses from other trials are no solution. For example, the BARI trial reported better survival in diabetic patients randomly assigned to CABG as opposed to PCI patients.[26] After BARI, several post hoc subgroup analyses of diabetic patients were reported from randomized trials. None of these 9 analyses showed a difference in survival,[52, 53] likely due to the low statistical power. Even though there might be concordance of subgroup findings in different trials, this does not validate the assumption that the result is accurate. In this case, the recently published FREEDOM trial indeed showed a significantly significant benefit of CABG over PCI in diabetics, thereby validating the hypothesis first generated from the post hoc observations in BARI.[6]

Pooling individual patient data could provide more power for subgroup analyses and could demonstrate the true treatment effect difference amongst subgroups. Establishing large research collaborations for subgroup analyses may be difficult and costly and therefore are unlikely to be done in many areas. Subgroup papers of individual randomized trials may then be particularly helpful, as it will allow systematic reviews and meta-analyses. However,

Table 6 Recommendations for reporting subgroup analyses

In General:
Avoid subgroup analyses on outcomes that are not primary endpoints.
Subgroup analyses should be performed on pre-specified patient subgroups only.
Restrict subgroup analyses ideally to those that represent approximately 35-40% of the original study size.
To prevent spurious findings, exploration of subgroups should be limited to analyses with an a priori power of at least about 45-50%.
Do not overemphasize subgroup analyses by reporting specific findings in the abstract or conclusion.
A systematic review and meta-analyses can be used to put subgroup results in perspective and deal with inconsistency among subgroup analyses from different trials.
In the Methods section:
Report whether subgroups were pre-specified and powered.
In the Results section:
Perform a test for interaction and report heterogeneity of subgroup analyses.
Correct for multiple subgroup testing.
Report both significant and non-significant subgroup results.
In the Discussion section:
Indicate the total number of subgroup analyses in the present and previous papers from the trial.
Indicate the potential effect of multiple subgroup analyses on type I errors (false positives) across the present and previous papers from the trial.
Address multiplicity to inform readers of the power of subgroup results.
Use the general term hypothesis-generating to advise caution with interpretation of subgroup results.
Address if the subgroup effect is in the direction that was expected, and whether the treatment effect is clinically plausible.
Discuss whether other trials have performed similar subgroup analyses and compare findings.

in this study we found evidence of methodological deficiencies in subgroup papers which may complicate accurate meta-analyses. Therefore, to prevent spurious subgroup findings, some experts have suggested to limit exploration of subgroups to those analyses with an a priori power of at least 40-50% which corresponds to subgroup sizes of 30-40% of the original study size.[54] With low power the risk of claiming equivalent outcomes between treatments is inflated, when actually one treatment may be superior. Because the CONSORT statement provides little guidance on how subgroup analyses should be reported and lacks any specific guidance in drafting follow-up or subgroup papers,[1-3] several recommendations for reporting subgroup analyses are provided (Table 6).

CONCLUSIONS

The method of reporting subgroup analyses from PCI versus CABG trials is suboptimal and methodologically invalid in most studies due to an inadequate statistical basis for validity, which can lead to false or exaggerated subgroup claims. From primary papers to follow-up papers to subgroup papers, the quality of reporting is increasingly flawed. We recommend that subgroup analyses be performed only when pre-specified in the original study, when an

appropriate interaction test has been performed and if adequately powered to support the analysis. Although our study focused on a specific area of interest, the problem of erroneous and misleading subgroup analyses is likely common to other scenarios as well. The next version of the CONSORT statement should provide additional guidance in reporting subgroup papers of randomized controlled trials. Adherence to these principles will help avoid erroneous conclusions and unsubstantiated treatment recommendations based on invalid evidence.

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Part 5

Improving clinical research in the future

Miami

Chapter 31

Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valvular Academic Research Consortium-2 concensens document

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ABSTRACT

Objectives

The aim of the current Valve Academic Research Consortium (VARC)-2 initiative was to revisit the selection and definitions of transcatheter aortic valve implantation (TAVI) clinical endpoints to make them more suitable to the present and future needs of clinical trials. In addition, this document is intended to expand the understanding of patient risk stratification and case selection.

Background

A recent study confirmed that VARC definitions have already been incorporated into clinical and research practice and represent a new standard for consistency in reporting clinical outcomes of patients with symptomatic severe aortic stenosis (AS) undergoing TAVI. However, as the clinical experience with this technology has matured and expanded, certain definitions have become unsuitable or ambiguous.

Methods and Results

Two in-person meetings (held in September 2011 in Washington, DC, USA, and in February 2012 in Rotterdam, the Netherlands) involving VARC study group members, independent experts (including surgeons, interventional and non-interventional cardiologists, imaging specialists, neurologists, geriatric specialists, and clinical trialists), the US Food and Drug Administration (FDA), and industry representatives, provided much of the substantive discussion from which this VARC-2 consensus manuscript was derived. This document provides an overview of risk assessment and patient stratification that need to be considered for accurate patient inclusion in studies. Working groups were assigned to define the following clinical endpoints: mortality, stroke, myocardial infarction, bleeding complications, acute kidney injury, vascular complications, conduction disturbances and arrhythmias, and a miscellaneous category including relevant complications not previously categorized. Furthermore, comprehensive echocardiography recommendations are provided for the evaluation of prosthetic valve (dys)function. Definitions for the quality of life assessments are also reported. These endpoints formed the basis for several recommended composite endpoints.

Conclusions

This VARC-2 document has provided further standardization of endpoint definitions for studies evaluating the use of TAVI, which will lead to improved comparability and interpretability of the study results, supplying an increasingly growing body of evidence with respect to TAVI and/or surgical aortic valve replacement. This initiative and document can furthermore be used as a model during current endeavors of applying definitions to other transcatheter valve therapies (for example, mitral valve repair).

INTRODUCTION

The first Valve Academic Research Consortium (VARC) consensus manuscript was published in January 2011 with the goal of achieving consensus for (i) *selecting appropriate clinical endpoints* reflecting device, procedure and patient-related effectiveness and safety, and (ii) *standardizing definitions for single and composite clinical endpoints,* for transcatheter aortic valve implantation (TAVI) clinical trials.[1, 2] A recent pooled analysis, which included 3,519 patients from 16 unique studies, confirms that VARC definitions have already been incorporated into clinical and research practice and represent a new standard for consistency in reporting clinical outcomes of patients with symptomatic severe aortic stenosis (AS) undergoing TAVI.[3] However, as the clinical experience with this technology has matured and expanded, certain definitions have become unsuitable or ambiguous.[3-7] The aim of the current VARC was therefore to revisit the selection and definitions of TAVI-related clinical endpoints to make them more suitable to the present and future needs of clinical trials. In addition, this document is intended to expand the understanding of patient risk stratification and case selection.

Similar to the VARC-1 process, two in-person meetings (held in September 2011 in Washington, DC, USA, and in February 2012 in Rotterdam, the Netherlands) involving VARC study group members, independent experts (including surgeons, interventional and non- interventional cardiologists, imaging specialists, neurologists, geriatric specialists, and clinical trialists), the US Food and Drug Administration (FDA), and industry representatives, provided much of the substantive discussion from which this VARC-2 consensus manuscript was derived.

RISK SCORES AND COMORBIDITIES

Risk stratification of patients is crucial to identifying appropriate candidates for specific cardiac procedures. The EuroSCORE and Society of Thoracic Surgeons (STS) score are the most widely used risk scores to predict operative mortality in cardiac surgery. These models were developed and validated in a standard surgical risk population. The predictive power of both models is therefore suboptimal in high-risk patients with valvular disease, although the STS score has shown to outperform the Logistic EuroSCORE.[8] These models are even more limited in application to patients who are considered at prohibitive risk for cardiac surgery, a cohort that could particularly benefit from TAVI. Current models could be improved by the addition of specific clinical and anatomical variables that affect mortality.[9] As an example, the presence of a porcelain aorta and frailty are important factors not included in either risk model but are routinely considered during patient evaluation (Figure 1, Table 1).

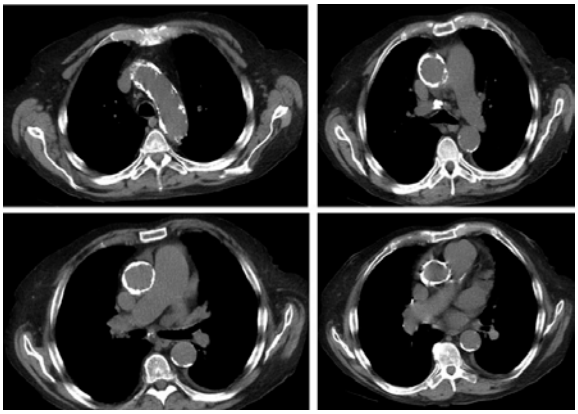

Figure 1 **Porcelain aorta or severely atherosclerotic aorta**

Table 1 **Risk factors not captured by traditional risk scores**

Co-morbidities	Definition/Criteria	Diagnostic modalities
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible	Non-contrast axial CT at levels: Sinotubular junction Tubular ascending aorta between sinotubular junction and innominate Innominate artery Entire transverse arch
Frailty	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence Criteria: 5 meter walking time* Grip strength* BMI <20 kg/m^2 and/or weight loss 5 kg/yr Serum albumin <3.5 g/dL Cognitive impairment or dementia	Medical history Physical examination Physical performance measures Cognitive assessments Laboratory tests
Severe liver disease/ cirrhosis	Any of the following: Child-Pugh class C MELD score ≥10 Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt, Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction	Medical history Physical examination Laboratory tests Child-Pugh classification MELD score Liver biopsy

Table 1 *Continued*

Co-morbidities	Definition/Criteria	Diagnostic modalities
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) Complications from prior surgery Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) History of multiple recurrent pleural effusions causing internal adhesions	Medical history Physical examination Chest X-Ray CT scan
IMA or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum	A patent IMA graft that is adherent to the sternum such that injuring it during re-operation is likely. A patient may be considered extreme risk if any of the following are present: The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3 mm of the posterior table.	Axial CT scan images illustrating graft crossing the midline so the distance from sternum to graft can be measured. Angiogram from the lateral and PA projections and/or a CPR or VR (Volume rendering) 3-D reconstructed CT scan image showing relationships between graft and sternum
Severe pulmonary hypertension Severe right ventricular dysfunction	Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure Criteria as defined by the guidelines (e.g. TAPSE <15mm, RV end-systolic area >20cm^2, etc)†	Echocardiography, right-and left heart-catheterization documenting PA and systemic pressures Documentation of secondary causes of pulmonary hypertension

*Variable with respect to age and gender without validated scientific thresholds. †Rudski et al.[72] CT = computed tomography; MELD = Model for End-Stage Liver Disease; INR = international normalized ratio; IMA = internal mammary artery; PA = pulmonary artery

Perhaps the most important patient characteristic not included in current risk models is frailty.[10] Frailty is frequently assessed subjectively based upon an informal 'eyeball test'. However, physical performance assessments such as gait speed and grip strength are more objective performance measures that may capture an individual's overall functional status.[11] These continuous measures are reproducible and can be re-assessed at various time points. In addition, they require no language translation. Assessments of cognition, weight (loss), activity level, and independence in the activities of daily living provide additional information on the overall health state of the individual.[11] These limitations are more often found in patients with a high comorbidity burden and may co-exist with certain laboratory findings

Figure 2 **Hostile chest**

(e.g. low serum albumin, elevated inflammatory markers, anemia) that further reflect the health state and physiological reserve of the frail patient.

Baseline evaluation of the presence of cognitive dysfunction (mild cognitive impairment or dementia) has also emerged as an essential part of the initial risk stratification, especially in older populations, where the risk, benefit, and cost-effectiveness of invasive procedures must be weighed judiciously. Pre-procedural cognitive assessment may also help avoid attributing post-procedural mental status changes to stroke categories. Among the several clinically established rating scales [e.g. Mini-Mental State Examination, modified Telephone Interview of Cognitive Status (TICS-M), Clinical Dementia Rating Scale],[12] there is no particular standard for TAVI. Nevertheless, some systematic cognitive assessment by neuropsychological experts should be a part of the initial heart team evaluation.Table 1 provides an overview of these and other risk factors (Figure 1, Figure 2 and Figure 3) *and* VARC-2 recommendations on how each should be assessed. In clinical trials, it will be important to capture variables that predict extreme operative risk and to standardize the evaluation criteria and process. This will help to determine which subsets of patients are likely to benefit from TAVI treatment.

Patient stratification: the Heart Team approach

Valve Academic Research Consortium-2 recommends the use of a heart team for patient evaluation. The heart team should consist of at least (interventional) cardiologists, cardiovascular surgeons, and imaging specialists, but its composition is dynamic and can also include anesthesiologists, geriatricians, neurologists, etc. This multi-disciplinary team should convene as a group on a regular basis to review and interpret clinical data to arrive at a consensus on the optimal treatment strategy for each patient. The heart team approach

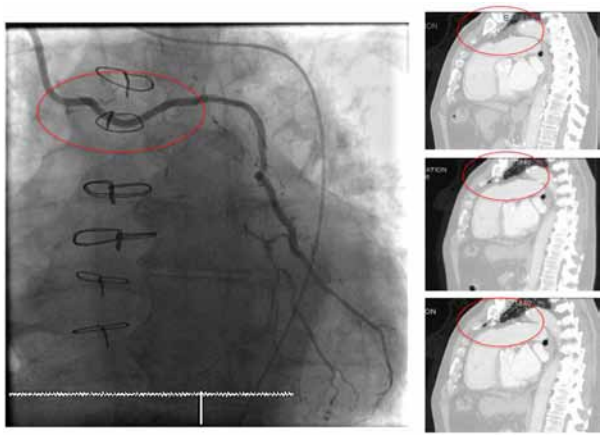

Figure 3 **Patient IMA graft crossing midline and/or adherent to the posterior table of the sternum**

also allows for the adjustment of the decision-making process according to local experience and circumstances.

The heart team should agree on an estimated 30-day mortality risk for each patient based upon integrating a careful clinical assessment and utilizing appropriate risk prediction scoring systems, preferably the STS score. Surgical mortality risk strata are difficult to precisely assign, but an estimated 30-day mortality of <4% is considered low risk, 4–10% is intermediate risk, >10% is high risk, and >15% is very high risk. A patient is considered at extreme risk if at least two cardiovascular surgeons from a tertiary centre of excellence deny surgery because of prohibitive operative risks, estimated to be a combined >50% risk of irreversible morbidity or mortality.[13] In addition to the specific risk factors that can prohibit patients from undergoing TAVI or surgical aortic valve replacement (SAVR) (Table 1), the operative risk assessment is also important to identify patients who are likely not to benefit from either TAVI or SAVR (the so-called 'futility' category of high-risk patients). An expected improvement in the quality of life (QOL) may further be necessary to identify treatment responders vs. non- responders. Individualized life expectancy assumptions should be incorporated by the heart team in the clinical decision-making process as a central factor in weighing the risk-benefit ratio. Prognostic indices of life expectancy may play a central role in moving beyond arbitrary age-based cut-offs.[14]

The most important role of the heart team is to provide customized management decisions for common and unusual clinical scenarios in terms of patient selection, procedural performance, and complication management. An example is the frequent situation of severe AS and concomitant coronary artery disease (CAD). The complexity of CAD and appropriate revascularization strategies in the setting of AS should be determined by consensus from interventional cardiologists and cardiovascular surgeons.[15, 16] In new TAVI clinical trials, angiographic risk scores (e.g. SYNTAX score) may be utilized to help determine the

complexity of CAD, as a basis for the inclusion in the trial. Thresholds for coronary revascularization and the choice for a staged or concomitant PCI with TAVI should be guided by the complexity of the CAD and other factors as determined by the heart team.[17, 18] In general, the plan to deal with other co-existing conditions [such as atrial fibrillation (AF), other valvular lesions, and other congenital lesions] should be pre-specified and all complications encountered in the treatment of associated conditions (including treatment after the TAVI procedure) should be captured. Such thorough pre-procedural assessment is also valuable in discriminating new post-procedural complications from simple exacerbations of pre-existing conditions.

CLINICAL ENDPOINTS

Mortality

In addition to the original VARC definitions, VARC-2 recommends the collection of *immediate procedural mortality* to capture intra-procedural events that result in immediate or consequent death <72 h post-procedure. Taking into account the surgical literature, *procedural mortality* consists of all-cause mortality within 30 days or during index procedure hospitalization—if the postoperative length of stay is longer than 30 days.

The cause of death should be captured, based on a careful review of narrative summaries and source material. All-cause, cardiovascular, and non-cardiovascular mortality should be reported after 30 days during the follow-up (Table 2). In determining the cause of death, the adjudication committee should consider the clinical context at the time of the index procedure and during the time interval leading up to death. All efforts (including the use of

Table 2 Mortality

All-cause mortality
Cardiovascular mortality Any of the following criteria: Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure) Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events Sudden or unwitnessed death Death of unknown cause
Non-cardiovascular mortality Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

national death registries) should be made to identify, precisely characterize, and appropriately classify any death.

Myocardial infarction

Myocardial injury as determined by a significant rise in cardiac biomarkers occurs frequently following TAVI, and a significant magnitude of myocardial injury has been associated with worse outcomes.[19] Valve Academic Research Consortium-2 recommends the systematic collection of biomarkers of myocardial injury prior to the procedure, within 12–24 h after the procedure, at 24 h thereafter, at 72 h or at discharge, and, if still elevated, daily until values show a decline. Similar to the previous VARC recommendations, the definition of peri-procedural (<72 h following TAVI) MI will be based on a combination of clinical criteria and cardiac biomarkers. However, the threshold values have been adjusted (Table 3). Acute ischemic events occurring after 72 h should be considered spontaneous myocardial infarctions and defined in accordance with the universal MI guidelines.[20]

Table 3 Myocardial infarction

Peri-procedural MI (≤72 h after the index procedure)
New ischaemic symptoms (e.g. chest pain or shortness of breath), or new ischaemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, haemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND
Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB.* If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.
Spontaneous MI (>72 h after the index procedure)
Any one of the following criteria:
Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischaemia with at least one of the following:
Symptoms of ischaemia
ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)]
New pathological Q waves in at least two contiguous leads
Imaging evidence of new loss of viable myocardium or new wall motion abnormality
Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Pathological findings of an acute myocardial infarction.

*Previously in the original VARC it was 10x and 5x for troponin and CK-MB, respectively.

Stroke

With increasing attention to stroke as an important peri-procedural complication of TAVI,[21] the FDA has emphasized the need for an accurate assessment of stroke and has participated actively in recommending specific details of the VARC-2 definitions. In an attempt to further align with the fundamental definitions now endorsed by the FDA,[22] consensus was reached at VARC-2 to further refine the definition of stroke and recommend the use of these definitions in future TAVI clinical trials (Table 4). The definitions endorsed by the FDA are intended to apply to a wide range of clinical trials and to enable those trials to assess the clinically relevant consequences of vascular brain injury for determining the safety or effectiveness of an intervention.

Table 4 Stroke and TIA

Diagnostic criteria
Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
Stroke – Duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
TIA – Duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist*
Confirmation of the diagnosis by at least one of the following:
Neurologist or neurosurgical specialist
Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
Stroke classification
Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue
Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic
Stroke definitions†
Disabling stroke – a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline
Non-disabling stroke – a mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline

*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or Brain MRI). †Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.[23-25] mRS = modified Rankin Scale

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Stroke may be classified as ischemic or hemorrhagic with appropriate subdefinitions. Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. A stroke may be classified as 'undetermined' if there is insufficient information to allow the categorization as ischemic or hemorrhagic.

An entity closely related to an ischemic stroke that should be assessed is a transient ischemic attack (TIA). Transient ischemic attack is defined as a transient episode of focal neurological dysfunction caused by the brain, spinal cord, or retinal ischemia, without acute infarction. The difference between TIA and ischemic stroke is the presence of tissue damage on neuro-imaging studies or new sensory-motor deficit persisting >24 h. By definition, a TIA does not produce a lasting disability.

Valve Academic Research Consortium-2 recognizes that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke. Valve Academic Research Consortium-2 recommends the use of the modified Rankin Scale (mRS) to assess this clinical disability.[23-25] The assessment of the mRS should occur at all scheduled visits in a trial and at 90 days after the onset of any stroke. This approach will maximize the detection of new or recurrent strokes, assist in the ongoing evaluation of events previously determined as TIAs, and provide an accepted and reliable indicator of the long-term impact of a given stroke.

Previously, VARC recommended categorizing strokes as 'major' and'minor' based upon mRS scores. To enhance the accuracy in the description of a given stroke and to provide accurate categorization of strokes within a given trial, VARC-2 now recommends the use of the terms 'disabling' and 'non-disabling'. A disabling stroke is one that results (at 90 days after stroke onset) in an mRS score of >2 and an increase in >1 mRS category from an individual's pre-stroke baseline. A non-disabling stroke is one that results (at 90 days after stroke onset) in an mRS score of <2 or that does not result in an increase in >1 mRS category from an individual's pre-stroke baseline. In addition to this categorization of disabling and non-disabling strokes, the endpoint of all strokes should be reported.

Although brain imaging (typically, MRI for acute and chronic ischemia and hemorrhage, and CT for acute and chronic hemorrhage and chronic ischemia) is often used to supplement the clinical diagnosis of stroke,[26] a diagnosis of stroke may be made on clinical grounds alone. Valve Academic Research Consortium-2 recognizes that stroke symptoms are protean and not well suited to a pre-specified itemized listing. Accordingly, VARC-2 recommends that a vascular neurologist experienced in clinical trials involving stroke be included in all phases of trial planning, execution, and monitoring, including involvement in the Clinical Events Committee and the Data and Safety Monitoring Board.

New insights into the timing of events show delayed or late occurrence of strokes, beyond the early post-implantation phase.[27] This may suggest that the cause of stroke is additionally related to other factors or patient susceptibilities and should necessitate active investigation of devices and adjunctive pharmacotherapy to reduce the frequency and severity of strokes after TAVI, including precise documentation of the use and dosage of antithrombotic and antiplatelet medication. Patient baseline characteristics (e.g. carotid stenosis) and postoperative complications (e.g. AF) need to be carefully documented to be able to identify the contributing causes of stroke.

Invasive stroke management (catheter-based intracranial intervention) is gaining an increasingly important role and may impact morbidity and mortality. Valve Academic Research Consortium-2 therefore recommends the ascertainment of any acute stroke management strategy (e.g. aspiration, thrombolysis, or conservative management).

Bleeding complications

Valve Academic Research Consortium-2 acknowledges the fact that the Bleeding Academic Research Consortium (BARC) recently convened and established standardized bleeding define-tions for patients receiving antithrombotic therapy and undergoing coronary revascularization (PCI or CABG).[28, 29] However, because the current definitions have been well adopted and shown to be accurate in predicting adverse events,[30] VARC-2 has chosen to maintain the original VARC definitions with BARC classifications (Table 5), recognizing that

Table 5 Bleeding

Life-threatening or disabling bleeding
Fatal bleeding *(BARC type 5)* OR
Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR
Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR
Overt source of bleeding with drop in haemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* *(BARC type 3b)*
Major bleeding *(BARC type 3a)*
Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND
Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding *(BARC type 2 or 3a, depending on the severity)*
Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life-threatening, disabling, or major

*Given one *unit* of packed RBC typically will raise haemoglobin concentration by 1 g/dL, an estimated decrease in haemoglobin will be calculated. BARC = Bleeding Academic Research Consortium [29]; RBC = red blood cell

future validation of BARC criteria in this population may warrant revision of the current recommendations.

With respect to blood transfusions, it is critical to acknowledge that a bleeding complication has to be the result of *overt bleeding* and cannot be adjudicated based on blood transfusions alone.

Acute kidney injury

The original VARC definitions recom-mended the use of a modified version of the RIFLE classification. However, we now recommend using the AKIN system (Table 6), which is a

Table 6 **Acute kindey injury (AKIN classification*).**

Stage 1
Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR
Urine output <0.5 ml/kg per hour for >6 but <12 hours
Stage 2
Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) OR
Urine output <0.5 ml/kg per hour for >12 but <24 hours
Stage 3†
Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR
Urine output <0.3 ml/kg per hour for ≥24 hours OR
Anuria for ≥12 hours

The increase in creatinine must occur within 48 hours. *Mehta et al.[31] †Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.

modified version of RIFLE that has been adopted by many in the nephrology community, including the KDIGO initiative.[21, 31] As a result, acute kidney injury (AKI) can also be diagnosed according to urine output measures (Table 6).

In comparison with the original VARC, the timing for the diagnosis of AKI is extended from 72 h to 7 days. Patients who experience AKI should have follow-up renal function assessments after 7 days until stabilization.

Vascular complications

Table 7 lists VARC-2 definitions for major and minor vascular complications. Further clarifications of these definitions to supplement the original VARC document are as follows. Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g. 'pre- closure') [33, 34] should be considered as part of the TAVI procedure and not as a complication, unless untoward clinical consequences are documented (e.g. bleeding complications, limb ischemia, distal embolization, or neurological impairment). Unplanned endovascular stenting or surgical repair for any vascular complications during the index

Table 7 Vascular access site and access-related complications

Major vascular complications
Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment OR
Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment OR
Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
Surgery for access site-related nerve injury OR
Permanent access site-related nerve injury OR
Minor vascular complications
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment OR
Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) OR
Percutaneous closure device failure
Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

*Refers to VARC bleeding definitions

procedure without other clinical sequelae should be considered a minor vascular complication, except if associated with qualifying consequences (Table 7). Complications related to alternative access sites, including the left-ventricular apex, subclavian artery, or aorta should be systematically recorded. To ensure accurate capture of these elements, VARC-2 strongly recommends that detailed information regarding the access site and pre-planned vascular closure technique be recorded as well as the use of any additional unplanned access or closure techniques (surgical repair, endovascular stenting, or endovascular balloon therapy). Since many vascular complications will also result in a bleeding complication, events that meet VARC-2 definitions for both categories should be reported in both categories. Finally, VARC-2 recommends that all vascular complications be recorded as either access (e.g. iliac rupture) or non-access site-related (e.g. ascending aorta dissection or rupture unless aortic access is used and the event originates from the cannulation site).

Conduction disturbances and arrhythmias

Valve Academic Research Consortium-2 proposes the systematic collection of data on the frequency of implant-related new and/or worsened conduction disturbances and the

Table 8 Conduction sisturbances and arrhythmias

Up to 72 h, continuous rhythm monitoring is recommended in order to maximize detection of arrhythmias
Data elements to be collected should include:
Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and presence of permanent pacemaker*
Implant-related new or worsened cardiac conduction disturbance (new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant
Persistent or transient high degree AV block. High grade AV block is persistent if it is present *every* time the underlying rhythm is checked
New permanent pacemaker implantation, with precision of the indication and number of days post-implant of placement of new permanent pacemaker
New-onset atrial fibrillation (or flutter)†
Any new arrhythmia resulting in hemodynamic instability or requiring therapy‡

‡ Therapy includes electrical/medical cardioversion or initiation of a new medication (oral anticoagulation, rhythm or rate controlling therapy). * Type of permanent pacemaker should be recorded (e.g. defibrillator, single versus dual chamber, biventricular) † New-onset atrial fibrillation (or flutter)* is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip.

incidence and indication for permanent pacemaker implantation (Table 8). In addition, the frequency of specific arrhythmias following TAVI should be recorded as they may result in prolonged hospitalization and impaired clinical outcomes. New-onset AF (or flutter) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of AF and lasts sufficiently long to be recorded on a 12-lead ECG, or for at least 30 s on a rhythm strip.[35] The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion,

initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be thoroughly documented in the case report form.

Other TAVI-related complications

The original VARC document recommended the collection of a number of TAVI-related complications, but did not provide specific endpoint definitions for several endpoints. Valve Academic Research Consortium-2 recommends reporting any other complications related to the TAVI procedure, even those occurring less frequently, and provides formal VARC-2 definitions (Table 9).[36-38]

Additional considerations

For studies or trials where the occurrence, prevention, or treatment of cerebral infarction is a fundamental feature (e.g. embolic protection devices) additional appropriate imaging in all or a subset of patients may be necessary to allow determination of effectiveness.

Table 9 Other TAVI-related complications

Conversion to open surgery Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications
Unplanned use of cardiopulmonary bypass (CPB) Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure
Coronary obstruction Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure
Ventricular septal perforation Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure
Mitral valve apparatus damage or dysfunction Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the THV) of the mitral valve during or after the TAVI procedure
Cardiac tamponade Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure
Endocarditis Any one of the following: Fulfillment of the Duke endocarditis criteria* Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy
Valve thrombosis Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis
Valve malpositioning **Valve migration** After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, with or without consequences **Valve embolization** The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus **Ectopic valve deployment** Permanent deployment of the valve prosthesis in a location other than the aortic root
TAV-in-TAV deployment An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the index procedure

* Durack et al.[73] TAVI = transcatheter aortic valve implantation; THV = transcatheter heart valve

VALVULAR FUNCTION

Valve Academic Research Consortium-2 maintains the original recommendations to use echocardiography as the primary imaging modality for the assessment of prosthetic valve function.[39] This should include the valve position, morphology, function, and evaluation of the left ventricle (LV) and right ventricle (RV) size and function. The suggested time points for routine follow-up transthoracic echocardiography (TTE) following valve implantation are: immediately (before discharge) following the implantation for transarterial approaches or within 30 days for transapical or transaortic approaches, 6 months following implantation, 1

Table 10 Prosthetic valve dysfunction

	Prosthetic aortic valve stenosis*		
	Normal	**Mild Stenosis**	**Moderate/Severe Stenosis**
Quantitative parameters (flow-dependent)†			
Peak velocity	<3 m/s	3-4 m/s	>4 m/s
Mean gradient	<20 mmHg	20-40 mmHg	>40 mmHg
Quantitative parameters (flow-independent)			
Doppler velocity index‡	>0.35	0.35-0.25	<0.25
Effective orifice area¶	>1.1 cm^2	1.1-0.8 cm^2	<0.8 cm^2
Effective orifice area§	>0.9 cm^2	0.9-0.6 cm^2	<0.6 cm^2
	Prosthesis-patient mismatch (PPM)		
	Insignificant	**Moderate**	**Severe**
Indexed effective orifice area**	>0.85 cm^2/m^2	0.85-0.65 cm^2/m^2	<0.65 cm^2/m^2
Indexed effective orifice area††	>0.70 cm^2/m^2	0.90-0.60 cm^2/m^2	<0.60 cm^2/m^2
	Prosthetic aortic valve regurgitation		
	Mild	**Moderate**	**Severe**
Semi-quantitative parameters			
Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)¶ ¶	<10%	10-29%	≥30%
Quantitative Parameters‡			
Regurgitant volume (ml/beat)	<30 ml	30-59 ml	≥60 ml
Regurgitant fraction (%)	<30%	30-49%	≥50%
EROA (cm^2)	0.10 cm^2	0.10-0.29 cm^2	≥0.30 cm^2

*In conditions of normal or near normal stroke volume (50–70 mL). †These parameters are more affected by flow, including concomitant aortic regurgitation. ‡For LVOT >2.5 cm, significant stenosis criteria is <0.20. ¶ Use in setting of BSA ≥1.6 cm^2 (note: dependent on the size of the valve and the size of the native annulus). §Use in setting of BSA <1.6 cm^2. **Use in setting of BMI <30 kg/cm^2. ††Use in setting of BMI ≥30 kg/cm^2. ¶ ¶ Not well-validated and may overestimate severity compared to quantitative Doppler.

year following implantation, and yearly thereafter. At these endpoints, prosthetic aortic valve stenosis and regurgitation should be reported.

Transcatheter valve stenosis

The assessment of prosthetic valve stenosis should be an integrative process utilizing multiple parameters of valve function. Table 10 outlines the primary parameters used for assessing prosthetic valve function based on published guidelines.[40] Divergence from the guidelines is based on a number of studies,[41, 42] as well as methods used in large randomized control trials of TAVI.[43, 44] In addition, VARC-2 does not recommend using acceleration time, which is dependent on ventricular function and heart rate.[42] The limitation of flow-dependent parameters such as peak jet velocity or mean transprosthetic gradient is obvious, however, even flow-independent parameters such as the effective orifice area (EOA) and the Doppler velocity index (DVI) have limitations: (i) the absolute EOA does not account for the cardiac output requirements in relation to the patient's body size; thus lower criteria should be used to define prosthetic valve stenosis in patients with BSA <1.6 m^2 (Table 10), (ii) the indexed EOA may overestimate the valve-related hemodynamic burden in obesity; hence, lower criteria may be more appropriate in patients with a body mass index >30 kg/m^2, (iii) DVI severity criteria are dependent on the left ventricular outflow tract (LVOT) size; thus a lower threshold may be more appropriate in patients with LVOT diameters of >25 mm. The EOA should generally be calculated with the use of the LVOT diameter and the velocity measured just underneath the apical margin of the valve stent.[45, 46] In cases where the landing zone of the stent is low in the LVOT, the diameter and velocity may both be measured in the proximal portion of the stent. Unlike the surgically implanted valve, the transcatheter prosthetic valve EOA is defined not only by the size of the valve but also by the patient's aortic valve/annular anatomy and procedural variables. Thus, well-established normal transcatheter valve gradients and EOAs based on pre-implant aortic annular dimensions do not currently exist. Clinicians should be aware of this variability when assessing a patient for transcatheter valve function and VARC-2 strongly recommends that the patient's own initial post-implant study be used as a reference for serial comparisons.

The assessment of transcatheter valve dysfunction includes the immediate post-TAVI hemodynamics and the follow-up evaluation. The immediate post-TAVI evaluation documents initial valve appearance (position and circularity of the stent, and leaflet morphology and motion) and a comprehensive hemodynamic evaluation. Valve Academic Research Consortium-2 advocates using the integrative approach outlined in the algorithm shown in Figure 4 as part of a comprehensive hemodynamic evaluation by initially using one flow dependent (e.g. mean gradient) and one flow independent criterion (e.g. EOA) for the initial hemodynamic evaluation. If there is discordance between these measurements, then the DVI should be calculated. An abnormal DVI indicates possible prosthetic valve dysfunction. A normal DVI indicates intrinsically normal prosthetic valve function, and the indexed EOA

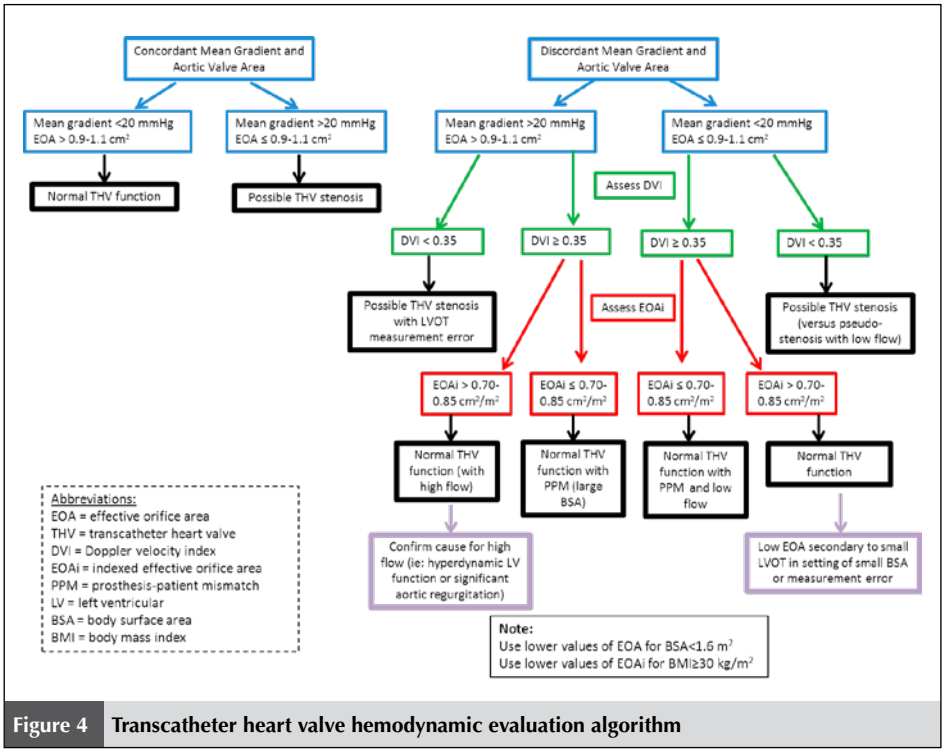

Figure 4 **Transcatheter heart valve hemodynamic evaluation algorithm**

can then be used to determine the reason for the initial measurement discordance. When the indexed EOA is low in the setting of a normal DVI, the patient probably has a prosthesis-patient mismatch (PPM), an indicator of the intrinsic relationship of the implanted valve to the cardiac output requirements of the patient.[47] Prosthesis-patient mismatch occurs in the setting of a morphologically normal valve and is considered to be hemodynamically insignificant if the indexed EOA is >0.85 cm^2/m^2, moderate if between 0.65 and 0.85 cm^2/m^2, and severe if <0.65 cm^2/m^2. However, for obese patients (body mass index >30 kg/m^2) lower criteria may be more appropriate (Table 10).

Transcatheter valve regurgitation

There is growing evidence suggesting a significant association of post-procedural paravalvular aortic regurgitation (AR) with short- and long- term mortality.[48, 49] As the duration of implanted transcatheter heart valves increases, valve durability and dysfunction become more crucial issues. Evaluating the presence and severity of regurgitation should include an assessment of both central and paravalvular components, with a combined measurement of 'total' aortic regurgitation (AR) reflecting the total volume load imposed on the LV (Table 10). The quantitative and semi-quantitative hemodynamic assessment of AR severity should be performed with Doppler echocardiography according to the guidelines.[39, 50, 51] Color

Doppler evaluation should be performed just below the valve stent for paravalvular jets, and at the coaptation point of the leaflets for central regurgitation. Although all imaging windows should be used, the parasternal short-axis view is critical in assessing the number and severity of paravalvular jets. Whenever possible, the quantification of the prosthetic regurgitant volume, effective regurgitant orifice area, and regurgitant fraction (Table 10) should be performed.[40, 51, 52] The regurgitant volume may be calculated as the difference between the stroke volume across any non-regurgitant orifice (RVOT or mitral valve) and the stroke volume across the LVOT.

It is important to realize that at this time the body of evidence supporting the numerical criteria used in Table 10 as well as Figure 4 may be limited. These criteria should be used as guidelines for clinical decision-making and require further validation as our experience continues to expand.

Follow-up assessments

The follow-up assessment should also begin with valve imaging and documentation of changes in morphology. When determining whether a patient has developed hemodynamically significant structural valve failure, the patient's own baseline echocardiographic parameters should be used as a reference. An increase in the mean gradient >10 mm Hg, a decrease in the EOA >0.3–0.4 cm^2, or a reduction in the DVI >0.1–0.13 probably indicates a change in valve function and should trigger a comprehensive hemodynamic evaluation. Whenever valve dysfunction is suspected, the careful evaluation of valve morphology should confirm a structurally abnormal valve. In addition, measurement error must be excluded; the use of a consistent LVOT diameter for more accurate follow-up study comparisons is recommended. Finally, changes in ventricular morphology would be expected in the setting of long-standing significant valvular dysfunction and this parameter may support the clinical assessment of severity.

Although the rate of moderate or severe regurgitation may appear to be less at the follow-up, this may be the result of attrition of the sickest patients. To assess such time trends, it is recommended to report an individual patient's progression of regurgitation, in a table that provides changes between short-term and long-term regurgitation, including mortality.[48]

QUALITY OF LIFE

Quality of life evaluation in aortic stenosis

New York Heart Association (NYHA) classification is limited by the discrete nature of the scale, which provides only modest resolution to detect clinically relevant changes. Moreover, since the NYHA class is assessed by an external body rather than the patient, it does

not reflect the patient's perspective. Thus, the NYHA class is more properly considered a measure of the functional status than the QOL.

The Minnesota Living with Heart Failure Questionnaire (MLHF) [53] and the Kansas City Cardiomyopathy Questionnaire (KCCQ) [54, 55] have a number of desirable properties for the evaluation of health-related QOL (HRQOL) in the setting of AS. Both instruments produce outcomes on a continuous scale, which improves responsiveness and sensitivity. Although only the MLHF has been specifically validated in patients with aortic valve disease,[56] preliminary experience with the KCCQ in patients undergoing TAVI has also demonstrated a high degree of responsiveness and internal consistency.[57]

Recommended endpoints and timing of assessment

Valve Academic Research Consortium-2 recommends that a comprehensive assessment of HRQOL for patients undergoing TAVI incorporate both a heart failure-specific measure (such as the KCCQ or MLHF) as well as one or more generic measures [such as the Medical Outcomes Study Short-Form 36 (SF-36), the Short-Form 12 (SF-12), or the EuroQOL (EQ-5D)].[58-60] The disease-specific measures offer improved sensitivity/responsiveness as well as clinical interpretability, whereas the inclusion of a generic health status measure is useful because it captures some additional domains. Furthermore, generic measures can enhance the comparability across different diseases and populations and can be used to compare patients with population-level benchmarks.

For the comparison of TAVI vs. SAVR (or for the comparison of alternative access sites for TAVI), we recommend that early QOL assessment be performed at 2 weeks, 1 month, and 3 months using a combination of generic instruments and pain scales (e.g. visual analogue scale) to assess the early recovery process. The evaluation of the QOL at an intermediate time point (e.g. 6 months) could also be considered in order to confirm that QOL recovery is complete by this stage. At later time points (1–5 years), the use of heart failure-specific instruments to identify the consequences of long-term valve performance may be more useful. Finally, the assessment of cognitive function at later time points (1–5 years) may be valuable for the comparison of surgical vs. catheter-based techniques, although these endpoints generally require highly specialized and demanding neuropsychiatric testing.[61] In contrast, for the comparison of alternative TAVI systems (as may be expected in the near future), HRQOL assessment should focus mainly on heart failure-specific endpoints at intermediate and later time points (1–5 years), wherein between-device differences in the hemodynamic performance or structural valve deterioration may emerge. The inclusion of disease-specific QOL measures in these studies can also provide insight into the consequences of valve-related complications such as the need for pacemaker insertion.

Additional considerations

It is essential to ensure complete ascertainment of HRQOL at each time point, as missing data cannot be retrieved retrospectively and statistical adjustment techniques (e.g. multiple imputation) that assume that data are 'missing at random' may not be adequate. Differential mortality between two treatments may complicate the interpretation of QOL results since the QOL may appear to 'improve' over time even with an ineffective therapy simply because of attrition of the sickest patients. The use of categorical endpoints that characterize outcomes as favorable (e.g. survival AND improvement of QOL endpoints) [44, 57] or endpoints that integrate survival and the QOL (e.g. quality-adjusted life expectancy) may provide more interpretable results. In such cases, reporting the outcomes in both ways (i.e. among the entire study cohort and separately among only the surviving patients) will provide the most complete description of the results.

COMPOSITE ENDPOINTS

Rationale and caveats

Comparisons of the success, safety, and effectiveness with achievable study cohort sample sizes may at times require the use of composite endpoints. However, it is important that composites contain components that have roughly similar impacts on the patient. A family of single endpoints tending in the same direction may, as a family of hypotheses, be statistically significant when individual endpoints are not.

Each post-procedural event has a different temporal risk profile (hazard function) modulated by different risk factors. Therefore, traditionally, the evaluation of the safety and efficacy of procedures has focused on in-hospital events (complications and morbidity), events within 30 days of the procedure, and 'late' events.

Specific composite endpoints

The assessment of TAVI, SAVR, and their alternatives or new devices should include device, procedure, and patient-oriented endpoints. These endpoints have been devised to be applicable to both TAVI and SAVR. Previous clinical trials have used the all-cause mortality at 1 year as the primary clinical endpoint. Owing to the emergence of stroke as an important clinical event, future trials should also require the composite of all-cause mortality and disabling stroke as a primary or secondary endpoint.

The first VARC document proposed three composite endpoints: device success, early safety, and clinical efficacy. Valve Academic Research Consortium-2 goes beyond the early and intermediate experience of TAVI, drawing upon prior surgical AVR guidelines to include time-related safety endpoints.[62] Therefore, VARC-2 recommends a new composite endpoint,

time-related valve safety, which combines valve dysfunction, endocarditis, and thrombotic complications of the prosthesis (Table 11).

Table 11 Composite endpoints

Device success
Absence of procedural mortality AND
Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch* and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation*)
Early safety (at 30 days)
All-cause mortality
All stroke (disabling and non-disabling)
Life-threatening bleeding
Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)
Coronary artery obstruction requiring intervention
Major vascular complication
Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)
Clinical efficacy (after 30 days)
All-cause mortality
All stroke (disabling and non-disabling)
Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure†
NYHA class III or IV
Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm2‡ and/or DVI<0. 35m/s, AND/OR moderate or severe prosthetic valve regurgitation*)
Time-related valve safety
Structural valve deterioration:
Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm2‡ and/or DVI<0.35m/s, AND/OR moderate or severe prosthetic valve regurgitation*)
Requiring repeat procedure (TAVI or SAVR)
Prosthetic valve endocarditis
Prosthetic valve thrombosis
Thromboembolic events (e.g. stroke)
VARC bleeding, unless clearly unrelated to valve therapy (e.g. trauma)

*Refers to VARC definitions. †As basis for calculation of *"days alive outside the hospital"* endpoint. Supplementary appendix of Leon et al.[74] Includes heart failure, angina or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion or documented volume overload AND administration of IV diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (IABP or ventilation for pulmonary edema) or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to CAD or ACS; documented loss of consciousness not related to seizure or tachyarrhythmia. ‡Depending on body surface area. BAV = balloon aortic valvuloplasty; TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement

DISCUSSION

Although the original VARC standardized endpoint definitions were fundamentally useful and have been widely adopted, growing experience with TAVI studies has identified some definitions as ambiguous, of limited clinical utility, or in need of updating or extension.[5, 6, 63, 64] This need provided the rationale for a VARC-2 document with such improvements and additions. As was the case with the original VARC process, it should be emphasized that this consensus manuscript is not intended to be a guidelines document, but rather a practical tool to facilitate and inform clinical research in TAVI.

Current clinical trials are focusing more on intermediate risk patients, and more studies are comparing TAVI with surgical AVR. Therefore, it becomes increasingly important to identify those patients who benefit from either treatment. Specific risk categories have been defined to allow universal clinical study designs and outcome comparisons.

Changes and additions that have been applied to improve the interpretation of clinical endpoint definitions and provide further insights on TAVI-related outcomes are as follows: (i) risk stratification should be done by a dedicated 'heart team' and include other factors (e.g. frailty, porcelain aorta) beyond the traditional risk scores, and should take into account co-existing conditions; (ii) *immediate procedural mortality* has been added to capture intra-procedural events that result in immediate or consequent death; (iii) stroke ascertainment requires the use of precise definitions, standardized assessments, close collaboration with neurology experts including the consideration of acute stroke management, and has been re-categorized as*non-disabling* or *disabling;* (iv) detailed documentation of the etiology of strokes and concomitant therapies is needed to provide insights into the multi-factorial nature of acute, early, and late strokes; (v) closure device failure is now a separate category within vascular complications, and if unplanned percutaneous or surgical intervention does not lead to adverse outcomes, these are not considered as a major vascular complication*per se;* (vi) the time for AKI diagnosis has been extended from 72 h to 7 days; (vii) AKI is diagnosed according to AKIN guidelines, which include classification by the urine output to detect a wider range of etiologies; (viii) peri-procedural myocardial infarction is defined by troponin or CK-MB elevation and the troponin threshold has changed from 10× ULN to 15× ULN based on recent data;[19] (ix) assessment of conduction disturbances and arrhythmias has been reinforced;[65-68] (x) new definitions for several TAVI-related complications and valve malpositioning are reported; (xi) echocardiography parameters of prosthetic valve stenosis and regurgitation have been updated and now include the assessment of the prosthesis-patient mismatch; (xii) for the QOL assessment, VARC-2 recommends the use of both heart failure-specific and generic measures during the follow-up between 30 days and 5 years to fully assess the impact of the procedure and the durability of clinical benefit. These definitions can be used in studies comparing TAVI to surgical AVR, as well as in future trials comparing first generation to next generation TAVI devices.

The composite endpoint of device success has specifically been criticized for being too strict with regard to valve performance; for example, an AVA >1.2 cm^2 seems unachievable in patients with smaller body habitus.[5] The current VARC-2 definition therefore corrects for the body surface area so that valve performance is now assessed through the indexed EOA. It is notable that valve-in-valve procedures for failing bioprostheses will frequently have a low device success, even with this modified definition.[69] Considering that stroke has emerged as an important concern, the composite of all-cause mortality and disabling stroke should be considered as a primary or secondary endpoint in future trials. Two ongoing large randomized trials [PARTNER II (NCT01314313) and SURTAVI (NCT01586910)] are already incorporating these composite endpoints.

With longer follow-up duration, it becomes more critical to include time-related valve safety composite endpoints. This will eventually provide linearized rates of complications with transcatheter valves, known as 'objective performance criteria', as has been used to evaluate surgical valves.[70]

CONCLUSIONS

With this VARC-2 document, we have provided further standardization of endpoint definitions and hope that the adoption of these criteria will continue to increase, ultimately leading to improved comparability and interpretability of the study results.[32]

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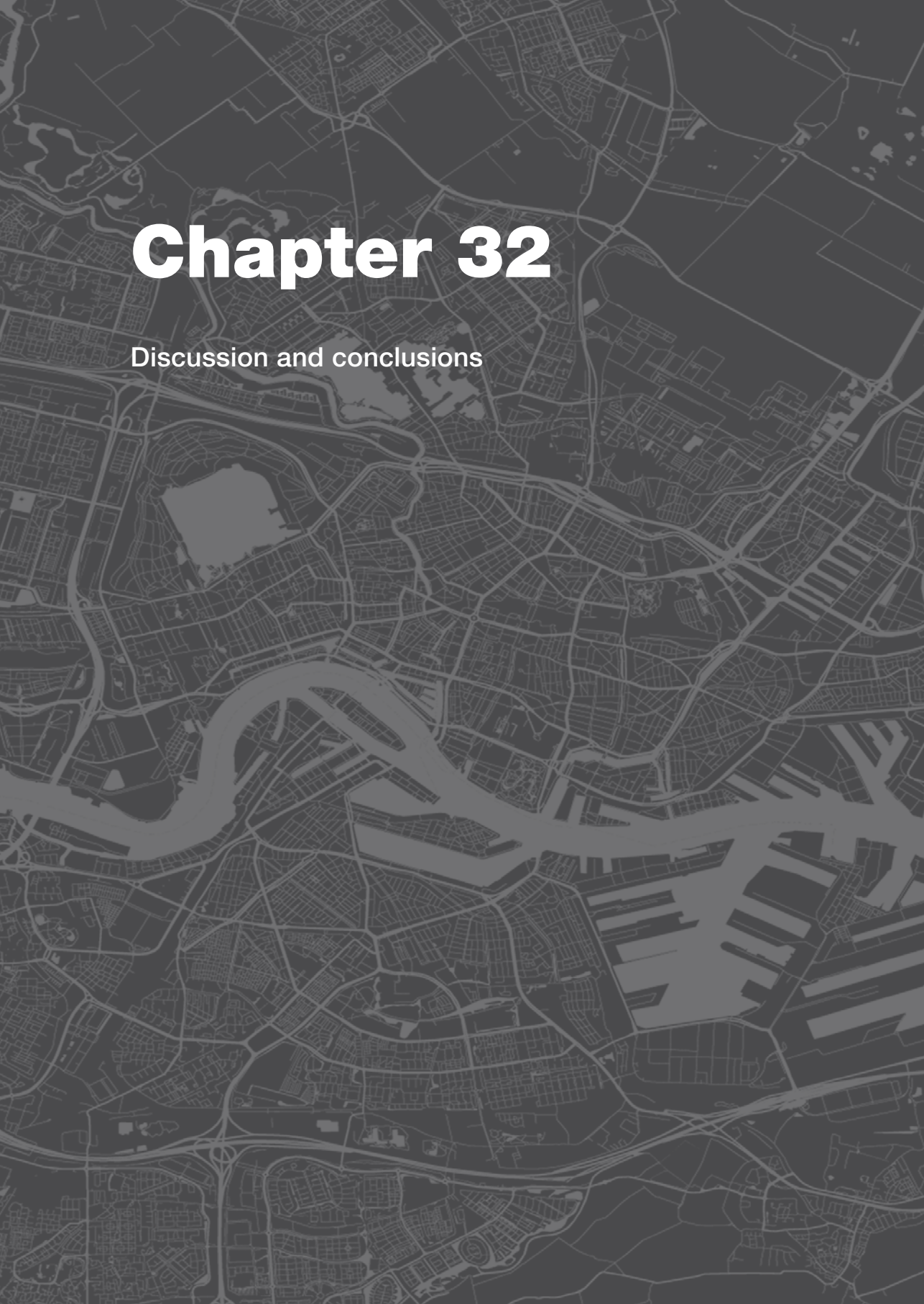
Part 6

General discussion and conclusions

Summary

Epilogue


Rotterdam



Chapter 32

Discussion and conclusions

PATIENT SELECTION AND DECISION-MAKING

Risk stratification in cardiac surgery has significant limitations. Current research is devoted to increase the predictability of risk models and its usefulness in decision-making. The new EuroSCORE II failed to be superior over the earlier additive and logistic EuroSCORE models in an analysis that included high-risk patients (Chapter 3). This may be the result of the lack of relevant risk factors in current risk models. For this reason, the European Association for Cardiothoracic Surgery has initiated a quality improvement programme with the objective to produce a new risk model.[1] The first step of this process was to perform a systematic review of the literature to identify all independent predictors of mortality, stroke, renal failure, and length of stay after adult cardiac surgery (chapter 6). We found a great number of variables that are usually not taken into consideration; these factors could be used as a framework for future risk model development.

One of the risk factors that showed to be a predictor of adverse events was the SYNTAX Score.[2] The SYNTAX Score is an angiographic anatomical risk model specifically designed to quantify the complexity of coronary artery disease. Several studies have proven its predictive power in patients undergoing percutaneous intervention, but it fails to be a predictor in patients undergoing bypass surgery (Chapter 7). It showed to be useful in decision-making, differentiating between percutaneous coronary intervention and coronary artery bypass grafting (Chapter 18).

We reviewed the literature on coronary revascularization and found that a great number of patients receive inappropriate revascularization, or are treated medically when there is an indication for revascularization (Chapter 9). These factors were associated with increased mortality during follow-up, and higher rates of myocardial infarction and recurrent angina. Therefore, to improve decision-making, the most recent American and European revascularization guidelines recommend multidisciplinary Heart Team decision-making with a class IC recommendation.[3, 4] The rationale behind the Heart Team is that a team consisting of at least a clinical/non-invasive cardiologist, interventional cardiologist, and cardiovascular surgeon, can better analyze and interpret the available diagnostic evidence, put into context the clinical condition of the patient as well as consider individual preference and local expertise, and through shared decision-making with the patient can arrive at a most optimal joint treatment strategy recommendation for patients with stable complex coronary artery disease (Chapters 8-9).

SURGICAL OR TRANSCATHETER TREATMENT FOR AORTIC STENOSIS

Surgical aortic valve replacement has been the standard of care for patients with symptomatic severe aortic stenosis. Since the introduction of transcatheter aortic valve implantation

(TAVI) in 2002,[5] the Heart Team evaluates patients with aortic stenosis. Transcatheter heart valve therapy has been a rapidly evolving technology. When compared to Europe, adoption of TAVI in the United States has been slower. The need for more rigorous data from randomized studies has led to the PARTNER trials.[6, 7] Transcatheter aortic valve implantation was not only superior over medical therapy in patients deemed at prohibitive operative risk, it was also non-inferior to surgical valve replacement in patients at high operative risk for surgery.

Nevertheless, despite its established role, continuous evaluation remains critical (Chapters 12-15). There are several complications that occur with high regularity. In a meta-analysis we performed with data from 16 unique studies that included a total of 3,519 patients, the pooled rate of major stroke was 3.2%, acute kidney injury stage II/III was 7.8%, major vascular complications was 11.9%, and life-threatening bleeding occurred in 15.6% of patients (Chapter 12). The relatively high rate of stroke led to a debate, but other complications such as paravalvular leakage and permanent pacemaker implantations still cause some skepticism around transcatheter therapy. Especially since these complications hardly occur after aortic valve replacement (Chapter 11). However, apart from being less invasive, an advantage of transcatheter heart valves is the improved hemodynamics as compared to surgical valves. Prosthesis-patient mismatch occurs less frequently after transcatheter aortic valve implantation than after aortic valve replacement, which may pose a benefit in long-term survival (Chapter 10).

Where surgical heart valves have shown to last about 12-15 years, no such durability data is yet available with respect to transcatheter valves. Caution should thus be advised to implant these devices in younger patients, although current trials are already performing comparative effectiveness studies between transcatheter therapy and surgical aortic valve replacement in (younger) patients at intermediate operative risk (Chapters 14 and 16). An additional factor that could weigh in when evaluating transcatheter and surgical therapy in intermediate risk patients is the cost (Chapter 17). A propensity-matched analysis of 42 pairs showed that in-hospital costs were significantly higher for patients that underwent transcatheter therapy as opposed to those who underwent surgical therapy (€40,802 versus €33,354, respectively; $p = 0.010$). At one year this difference was even more pronounced; €46,217 vs €35,511, respectively ($p = 0.009$). In an era of increasing health care expenditures and an economical crisis, cost-effectiveness considerations become increasingly important. Transfemoral aortic valve implantation only showed a quality-adjusted life-year gain of 0.068 in patients at high operative risk.[8] In intermediate-risk patients the results of surgical aortic valve replacement will improve as compared with high-risk patients; the benefit of the lower deterrence of transcatheter therapy will be less. It will be interesting to see whether the (even more minimal) expected quality-adjusted life-year gain can weigh up against the higher costs.

STENTING VERSUS BYPASS SURGERY

The SYNTAX trial is the first randomized study to compare percutaneous coronary intervention with drug-eluting stents with coronary artery bypass grafting. The main result of the trial was that percutaneous intervention did not show to be non-inferior to bypass surgery at one year.[9] A secondary analysis of the SYNTAX trial was in patients with and without diabetes (Chapter 21). Although previous analyses had shown a significant benefit of bypass surgery over percutaneous intervention in patients with diabetes but not in those without,[10] the results of the SYNTAX trial are a contradiction to that. Bypass surgery was better in both patient subgroups, however, diabetes did reinforce the difference between the two treatment strategies.

Novel in the design of the SYNTAX trial was the inclusion of nested registry where patients were included if either percutaneous or surgical treatment was preferred by the Heart Team (Chapter 18). According to the Heart Team, in 58.5% of the patients there was expected clinical equipoise between percutaneous and surgical treatment, while in 6.4% percutaneous treatment was preferred and in 35.0% surgical treatment. This distribution was largely influenced by the preoperative risk of patients, which in the majority of patients in percutaneous registry was deemed to be too high for surgical treatment. Patients in whom surgical treatment was preferred most often had too complex disease for percutaneous treatment. This complexity can probably be correlated to the expected incompleteness of revascularization (Chapter 19),[11] where the risk of inappropriate incomplete revascularization [12] would be too high in patients with complex lesions (a high SYNTAX Score). Incomplete revascularization in patients that are treated with percutaneous intervention is a significant predictor of adverse events and should therefore be avoided. These results present the contemporary distribution of patients with coronary artery disease as assessed by the Heart Team and can be used as a benchmark to compare percutaneous-to-surgical treatment ratios across centers and countries.

One of the emphasized results of the SYNTAX trial was the higher cumulative incidence of stroke at one year follow-up in patients who underwent bypass surgery (2.2% versus 0.6%; p=0.003). With 4-year follow-up, we performed an in-depth analysis of stroke (Chapter 20). Interestingly, the short-term difference deluded during follow-up and there was no longer a difference between percutaneous and surgical treatment (3.7% versus 2.3%; p=0.07). Stroke resulted in death in 3 patients in both the treatment groups. Of the patients who developed stroke, 68% (21/31) in the bypass group had residual deficits at discharge; in the percutaneous group, 47% (9/19) had residual deficits. This is similar to the recent results of the FREEDOM trial.[13]

However, the SYNTAX trial was performed with a first generation paclitaxel-eluting stent, while newer stents have shown significant benefits over these stents (Chapter 22). The SYNTAX trial has thus been criticized by being outdated, and it has been suggested

that percutaneous coronary intervention would have been non-inferior to bypass surgery if everolimus-eluting stents would have been used.[14] Nonetheless, bypass surgery in the SYNTAX trial might not have been at its best either. The rate of bilateral internal mammary artery grafting was only 27.6% and off-pump surgery was performed in 15.0% of cases.[15] Percutaneous coronary intervention can only show to be non-inferior to coronary artery bypass grafting in a new trial and it will be up to the surgeons to continue improvements in outcomes of bypass surgery as well.

There are several considerations for surgeons that can improve short- and long-term outcomes and/or provide a less invasive surgical option, such as the use of both mammary arteries, minimally invasive bypass surgery, 'aortic no touch' surgery, endoscopic vein harvesting, but also secondary prevention measures (Chapter 23). Further adoption of these techniques and actions could ensure that bypass surgery regains some ground as an attractive therapy for patients with coronary artery disease, although thorough evaluation of some of these relatively new promising strategies should still take place.

INTERPRETATION OF CARDIOVASCULAR CLINICAL RESEARCH

Randomized trials have strict in- and exclusion criteria, while observational studies evaluate therapies in real-world practice. Where randomized trials show treatment feasibility, effectiveness, and/or safety in a niche, observational studies include patients without any restrictions. Nevertheless, the results of randomized trials are frequently extrapolated out of its original validation (Chapter 25), resulting in 'experimental' treatment of patient populations in whom treatment evaluation has not (yet) taken place. Observational studies should therefore complement randomized trial data to assess comparative effectiveness in both a trial and real-world setting (Chapter 26). Hypothesis-generating observational data can furthermore be used to strengthen the results of randomized trials. For example, data suggested that off-pump coronary artery bypass grafting disproportionally benefitted high-risk patients. However, a randomized trial of on- versus off-pump surgery did not take these data into consideration. The design overestimated the effect of off-pump surgery within a population that included a majority of low-risk patients in whom on-pump surgery provides excellent results (Chapter 28).

Research in medicine often seeks a single therapy to treat all patients with a certain condition. However, personalized medicine has emerged over the recent years as an approach to provide the best care on an individual patient level. To evolve into such a health care setting, one needs to evaluate different therapies in different subgroups of patients with specific characteristics or disease subtypes. Frequently data from randomized trials is used for these subgroup analyses, although there are considerable limitations to subgroup analyses. They are often underpowered and have limited ability in showing genuine interactions

between patient baseline characteristics and treatment effects. In addition, they are often not performed correctly and have misleading conclusions. Nevertheless, these limitations are often not appreciated, leading to unsubstantiated treatment recommendations that could result in suboptimal patient outcomes (Chapter 30). For example, a subgroup analysis of the randomized PARTNER trial showed that transfemoral aortic valve implantation was cost-effective when compared to surgical therapy, while this was not the case for transapical aortic valve implantation. These results have discredited transapical therapy even though this analysis included only 104 patients and was not powered (Chapter 29).

Another pitfall of randomized trials is the interpretation of a non-inferiority trial (Chapter 24). As compared to superiority trials, non-inferiority trials are more complex and need additional methodological consideration. These trials are designed to show that a new therapy is not significantly worse than the standard therapy. However, one should always ask themselves *"What do I consider to be not significantly worse?"* Several aspects should be taken into account: the length of follow-up, the type of events, and the margin that quantifies the acceptable maximum loss of effectiveness. Even though a group of investigators has designed a trial, this does not necessarily corresponds with someone else's appreciation of effectiveness, and the non-inferiority trial design should therefore always be subject to one's own perception.

FUTURE RESEARCH AND PROSPECTS

It will need to be shown that Heart Team decision-making can influence the trade-off between surgical and catheter-based interventions, translating into more appropriate treatment recommendations and eventually improved clinical outcomes. There is some resistance to coronary Heart Teams and so there is a clear need to evaluate its potential. However, the true effect on clinical outcomes can be difficult to proof due to the complexity of a potential study design.

Transcatheter aortic valve intervention is here to stay as a treatment option for patients at prohibitive or high risk for surgery. How it will serve as an alternative in patients at intermediate risk is being investigated in current randomized trials. Furthermore, the coming years it will become apparent whether the Valve Academic Research Consortium definitions can further increase uniformity among studies of aortic valve interventions (Chapter 31).

Although the SYNTAX trial failed to show non-inferiority of percutaneous coronary intervention with drug-eluting stents when compared with coronary artery bypass surgery, the more recent generations of drug-eluting stents might show improved comparability to bypass surgery. Especially the EXCEL trial will answer part of these questions in the setting of left main disease; and also whether the global use of the SYNTAX Score can further be enhanced through expanding indications of the score in revascularization guidelines.

CONCLUSIONS

This thesis evaluated developments in surgical and catheter-based therapy to treat aortic valve disease and coronary artery disease. Rigorous assessment of randomized trials and observational studies are needed to ensure that treatment recommendations are based on appropriate results that are properly weighted, based on their design and methodology. Hopefully this will results in even more strict guidelines with regard to study designs, as well as appreciation of study limitations when interpreting evidence to produce clinical guidelines.

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Rotterdam

Chapter 33

Summary

PATIENT SELECTION AND DECISION-MAKING

Patient selection and decision-making remain essential to ensure good results of therapies. Risk models can be helpful in this regard. In **chapter 3** the most recent version of the EuroSCORE, the EuroSCORE II, is applied to a cohort of high-risk patients that underwent cardiac surgery to assess its predictive ability. EuroSCORE II fails to be superior to the original additive and logistic EuroSCOREs, and several potential causes are discussed in **chapter 4**.

On the one hand, risk models can be user-friendly by incorporating a limited number of variables, while on the other hand clinically important variables may then be excluded, resulting in only limited usefulness. **Chapter 5** provides an example of a pragmatic risk model that can be used to decide whether a patient can better be referred to surgical aortic valve replacement or transcatheter aortic valve implantation. In **chapter 6** the results of a systematic review show that a great number of variables are frequently not considered during decision-making and patient selection.

For coronary artery disease, one of the recently emerged risk factors is the SYNTAX Score. The SYNTAX Score has proven its ability to predict adverse events after percutaneous coronary intervention but not coronary artery bypass grafting. Therefore, the score can be used to differentiate between surgical and interventional treatment feasibility, and provides a reliable estimate with regard to patient prognosis. **Chapter 7** provides an overview of the SYNTAX Score in the literature.

Treatment decisions can be noticeable influenced by physician-related factors. The concept of shared decision-making involving patients and physicians has therefore received emphasis over the recent years. Moreover, there is precedence in the field of medicine that a multidisciplinary approach to decision-making can furthermore optimize treatment recommendations and consequently outcomes. This is discussed in **chapters 8 and 9**.

SURGICAL OR TRANSCATHETER TREATMENT FOR AORTIC STENOSIS?

Surgical aortic valve replacement is the standard treatment for patients with aortic stenosis. The choice of valve type translates to postoperative valve function, and too small prostheses can cause prosthesis-patient mismatch and mimic aortic stenosis. While the evidence on the impact of mismatch on long-term survival has been contradictory, **chapter 10** presents a meta-analysis that shows a significantly reduction in survival of patients with prosthesis-patient mismatch.

One of the complications of aortic valve replacement is the need for a pacemaker early after surgery. **Chapter 11** describes the risk of permanent pacemaker implantation during follow-up.

Contemporary detailed data on surgical aortic valve replacement has become even more crucial since the introduction of transcatheter aortic valve implantation. As shown in **chapter 12**, the risk of postoperative complications after transcatheter therapy is considerable. This needs to be thoroughly evaluated and compared with surgical treatment. In this regard, especially the presence of paravalvular leakage after transcatheter therapy may pose an additional risk during follow-up, a factor that is not apparent after aortic valve replacement (**chapter 13**).

Chapter 14 summarizes the extensive literature showing the feasibility and evaluation of transcatheter aortic valve implantation. It concludes that outcomes have significantly improved over the last decade and that transcatheter therapy is an alternative to surgical aortic valve implantation for patients at prohibitive or high risk for surgery.

To improve outcomes even further, efforts should be directed to reduce the rate of complications. Knowledge of complication rates and predictors are necessary to focus on specific aspects of treatment. This is discussed in **chapter 15**.

The positive results of randomized trials and the widespread enthusiasm around transcatheter aortic valve implantation have led to current randomized trials focusing on lower risk patients (**chapter 16**). However, as indications for transcatheter aortic valve implantation may be expanding, cost considerations become a more important decisive factor during decision-making. Particularly in an era of increasing health care expenditures and reduced funds due to the economical crisis. This is investigated in **chapter 17**.

STENTING VERSUS BYPASS SURGERY

The introduction of drug-eluting stents has provided an incentive to compare stenting with bypass surgery. The SYNTAX trial was the first large-scale trial to do so for treatment of complex coronary artery disease. Moreover, it reinforced the coronary Heart Team for evaluation of patients. In **chapter 18** the results of Heart Team decision-making are reported, demonstrating which factors are most decisive in the balance between percutaneous coronary intervention and bypass surgery. Further analyses of the SYNTAX trial are provided, focusing on the impact of incomplete revascularization in **chapter 19**, the incidence and outcomes of stroke in **chapter 20**, and diabetic patients in **chapter 21**.

The SYNTAX trial was performed with a first-generation drug-eluting stent, but several new stents have since been developed. In **chapter 22** an overview of these new stents is provided. However, not only standards for percutaneous coronary intervention have evolved over the last decades. A number of surgical techniques have been introduced to reduce the invasiveness and complication rate of coronary artery bypass surgery. These and other considerations to improve bypass surgery are discussed in **chapter 23**.

INTERPRETATION OF CARDIOVASCULAR CLINICAL RESEARCH

It is crucial to have insights into the methodology and study design of randomized clinical trials to be able to correctly interpret the conclusions. Non-inferiority trials are increasingly performed, but these designs are more complex; many readers and even investigators, therefore, have difficulty grasping the full nature of non-inferiority trials. **Chapter 24** is a statistical review of recent cardiovascular non-inferiority trials and discusses the aspects that need to be taken in consideration when interpreting such trials.

Generalizability and selection bias are issues frequently associated with both randomized trials and observational registries. **Chapters 25-28** provide a number of 'letters to the editor' in which these issues are discussed in the context of recent studies on revascularization for coronary artery disease. Such commentaries are needed to point to study limitations and provide awareness of unsubstantiated conclusions.

Chapter 29 asks the question whether treatment recommendations for transcatheter aortic valve implantation are based on reliable data. Is transfemoral aortic valve implantation truly better than transapical implantation? Or are we inappropriately looking at underpowered analyses?

Chapter 30 focuses even more specifically on the power of analyses. It addresses subgroup analyses of trials comparing percutaneous to surgical treatment for complex coronary artery disease. Specific attention is directed to these analyses because they are often methodologically flawed. This needs to be emphasized to improve analysis and ensure correct interpretation of subgroup data.

IMPROVING CLINICAL RESEARCH IN THE FUTURE

The comparability of studies can be improved by uniform trial design and endpoint definitions. The Academic Research Consortium is a group of clinical experts (including surgeons, interventional and non-interventional cardiologists, imaging specialists, neurologists, geriatricians, and clinical trialists), regulatory bodies, and industry representatives. It provides standardized endpoint definitions as a framework for future trials. In the early years of transcatheter aortic valve implantation, no harmonized definitions were available. As a result, fair comparisons between studies were challenging. **Chapter 31** is the latest version (VARC-2) of endpoint definitions for transcatheter aortic valve implantation.


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Chapter 34

Samenvatting

PATIËNT SELECTIE EN BESLUITVORMING

Strikte selectie van patiënten en adequate besluitvorming zijn essentieel voor goede resultaten van behandelingen. Risico modellen kunnen hierbij helpen. In **hoofdstuk 3** wordt de meest recente versie van de EuroSCORE, de EuroSCORE II, toegepast op een groep van hoog risico patiënten om de bruikbaarheid van de score te evalueren. De nieuwe EuroSCORE II blijkt niet beter dan de eerdere additieve en logistische EuroSCORE, en een aantal oorzaken hiervoor worden besproken in **hoofdstuk 4**.

Enerzijds moeten risico modellen gebruiksvriendelijk zijn door slechts een aantal variabelen te includeren, terwijl anderzijds in een te simpel model belangrijke variabelen geëxcludeerd worden. Hierdoor kan een model minder goed een uitkomst voorspellen. **Hoofdstuk 5** geeft het voorbeeld van een pragmatisch model dat gebruikt kan worden voor de selectie van patiënten voor transcatheter of chirurgische aortaklep therapie. In **hoofdstuk 6** worden de resultaten van een uitgebreide systematische review gepresenteerd. Hieruit komt voort dat meerdere variabelen niet beschouwd worden tijdens patiënt selectie en het besluitvormingsproces.

Eén van de recent geïntroduceerde risico modellen voor invasieve behandeling van coronairlijden is de SYNTAX Score. Het risicomodel blijkt goed te kunnen stratificeren in laag, middel, en hoog risico bij patiënten die een percutane interventie ondergaan maar niet bij patiënten die chirurgie ondergaan. De score kan daarom goed gebruikt worden om te differentiëren tussen patiënten die percutaan of chirurgisch behandeld zouden moeten worden. **Hoofdstuk 7** geeft een overzicht van het gebruik van de SYNTAX Score.

Besluitvorming kan beïnvloed worden door arts-gerelateerde factoren. Het concept van gezamenlijke besluitvorming met patiënten en artsen heeft daarom meer nadruk gekregen gedurende de laatste jaren. In het bijzonder is er bewustwording dat een multidisciplinaire besluitvorming een beter resultaat kan opleveren. Dit zou aanbevelingen over de optimale behandeling voor patiënten verder kunnen optimaliseren en zo dus ook de uitkomsten van percutane en chirurgische therapie. Dit is de focus van **hoofdstukken 8 en 9**.

CHIRURGISCHE OF TRANSCATHETER THERAPIE VOOR AORTAKLEP STENOSE?

Chirurgische aortaklep vervanging is de standaard therapie voor patiënten met aortaklep stenose. Welk type klep wordt gekozen resulteert in een bepaalde hemodynamische functie; een te kleine klep kan een mismatch veroorzaken tussen de grote van de klep en de grote van de patiënt. Dit kan resulteren in een te hoge klepgradiënt en een (nieuwe) aortaklep stenose betekenen. Het bewijs over de invloed van mismatch op lange-termijn overleving is

tegenstrijdig; **hoofdstuk 10** is een meta-analyse van de huidige literatuur en concludeert dat er inderdaad een significante reductie in overleving is van patiënten met mismatch.

Eén van de complicaties van aortaklep vervangingen is de beschadiging van het geleidingsweefsel van het hart en de noodzaak van een pacemaker implantatie direct na chirurgie. In **hoofdstuk 11** wordt het lange-termijn risico van een permanente pacemaker implantatie besproken.

Het resultaat van chirurgische aortaklep vervangingen wordt over de laatste jaren nog meer benadrukt omdat tegenwoordig transcatheter aortaklep implantatie een alternatieve behandeling vormt voor patiënten met een aortaklep stenose. Zoals bediscussieerd in **hoofdstuk 12** is het risico op complicaties na transcatheter aortaklep implantatie belangrijk. Deze zullen moeten worden vergeleken met complicaties na chirurgische aortaklep vervanging. Met name de aanwezigheid van paravalvulaire lekkage na transcatheter therapie kan tot een verhoogde sterfte leiden terwijl deze complicatie nauwelijks wordt gezien na chirurgische behandeling (**hoofdstuk 13**).

Hoofdstuk 14 beschrijft de literatuur met betrekking tot de uitvoerbaarheid en evaluatie van transcatheter aortaklep implantatie. Er wordt geconcludeerd dat de uitkomsten geweldig verbeterd zijn gedurende de laatste jaren en dat transcatheter aortaklep implantatie een alternatieve therapie is voor patiënten met een (te) hoog operatie risico.

Om de uitkomsten nog verder te verbeteren is het noodzakelijk om de incidentie van complicaties te verlagen. Kennis over de voorspellende factoren van complicaties is dan ook belangrijk om een specifieke invloed op deze factoren uit te kunnen oefenen. Dit is de focus van **hoofdstuk 15**.

De positieve resultaten van gerandomiseerde onderzoeken en het enthousiasme rondom transcatheter aortaklep implantatie hebben ervoor gezorgd dat huidige onderzoeken zich richten op patiënten met een lager risico (**hoofdstuk 16**). Omdat de indicaties voor transcatheter therapie zouden kunnen uitbreiden, is het noodzakelijk om in tijden van toenemende uitgaven voor gezondheidszorg en economische crisis ook naar de kostenimplicaties te kijken. In **hoofdstuk 17** worden deze aspecten onderzocht.

DOTTEREN IN VERGELIJKING TOT BYPASS CHIRURGIE

De introductie van drug-eluting stents heeft gezorgd voor nieuwe initiatieven om wederom een vergelijking tussen dotteren en coronaire bypass chirurgie uit te voeren. De SYNTAX trial was de eerste grootschalige studie die onderzocht heeft of drug-eluting stents even goed waren als chirurgie. Bovendien heeft de studie de bespreking in het coronaire Heart Team aangewakkerd om patiënten te evalueren. In **hoofdstuk 18** worden de resultaten van deze Heart Team besluitvorming besproken en wordt aangetoond welke factoren doorslaggevend

waren voor behandeling met percutane interventie met drug-eluting stents of coronair chirurgie. Nadere analyses van de SYNTAX trial worden besproken: de invloed van onvolledige revascularisatie (**hoofdstuk 19**), de incidentie en uitkomsten van cerebrovasculaire accidenten (**hoofdstuk 20**), en de resultaten bij patiënten met diabetes mellitus (**hoofdstuk 21**).

De SYNTAX trial werd uitgevoerd met de eerste generatie drug-eluting stents, maar nieuwe stents zijn sindsdien op de markt gekomen. In **hoofdstuk 22** worden deze stents besproken. Niet alleen de uitkomsten van percutane interventie zijn verbeterd over de jaren maar er zijn ook een aantal chirurgische technieken geïntroduceerd om complicaties en de invasiviteit van bypass chirurgie te verminderen. Deze worden bediscussieerd in **hoofdstuk 23**.

INTERPRETATIE VAN KLINISCH ONDERZOEK OP HET GEBIED VAN HART-EN VAATZIEKTEN

Kennis over methodologie en de studieopzet van gerandomiseerde onderzoeken is noodzakelijk om conclusies op juiste wijze te kunnen interpreteren. 'Non-inferiority' studies worden steeds vaker uitgevoerd, maar de opzet en interpretatie is lastiger. **Hoofdstuk 24** geeft inzicht in recent uitgevoerde non-inferiority studies op het gebied van cardiovasculaire afwijkingen en geeft aan op welke punten gelet moet worden tijdens het beoordelen van zo een studie.

Generaliseerbaarheid en selectie bias zijn tekortkomingen van gerandomiseerde en observationele onderzoeken. **Hoofdstukken 25-28** zijn commentaren die wijzen op beperkingen van studies ter bewustwording van niet voldoende onderbouwde conclusies. **Hoofdstuk 29** beschouwt de aanbevelingen omtrent de behandeling met transcatheter aortakleppen, met name of deze gebaseerd zijn op voldoende gegevens. Is er genoeg informatie om te stellen dat een klep implantatie via de lies beter is dan via de apex van het hart?

Hoofdstuk 30 gaat nog specifieker in op de kracht van analyses. Dit is een systematische uiteenzetting van onderzoeken die percutane interventie en coronair chirurgie hebben vergeleken voor de behandeling van complex coronairlijden. Deze analyses zijn vaak methodologisch niet juist. Het is nodig om de interpretatie van subgroep resultaten te verbeteren om zo onjuiste bevindingen en aanbevelingen te minimaliseren.

VERBETERINGEN VOOR TOEKOMSTIG KLINISCH ONDERZOEK

De vergelijkbaarheid van onderzoeken kan verbeterd worden door uniformiteit in studieopzet en definities. De 'Academic Research Consortium' is een groep klinische experts

(chirurgen, interventie en klinische cardiologen, beeldvorming specialisten, neurologen, geriaters, en onderzoekdeskundigen), regelgevende instanties, en industrie vertegenwoordigers. Deze groep organiseert vergaderingen om zo standaarden voor eindpunten in klinisch onderzoek te bewerkstelligen. In de vroege jaren van transcatheter aortaklep interventies waren er geen geharmoniseerde definities. Hierdoor was het moeilijk om studies met elkaar te vergelijken. **Hoofdstuk 31** presenteert de laatste versie van gestandaardiseerde eindpunten voor het evalueren van transcatheter aortaklep interventies.


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Chapter 35

PhD portfolio

PHD PORTFOLIO

Erasmus MC Department: Cardiothoracic Surgery
PhD period: 2010-2013
Promotors: Prof.dr A.P. Kappetein
Prof.dr A.J.J.C. Bogers

Conferences (15.0)	Year	ECTS
Dallas-Leipzig International Valve (Dallas)	2010	0,9
EuroPCR (Paris)	2011	0,9
European Association of CardioThoracic Surgery (Lisbon)	2011	1,2
Transcatheter Cardiovascular Therapeutics (San Francisco)	2011	1,5
Society of Thoracic Surgeons (Fort Lauderdale)	2012	0,6
European Association of CardioThoracic Surgery Symposium (London)	2012	0,3
Asian Society for Cardiovascular and Thoracic Surgery (Bali)	2012	0,9
EuroPCR (Paris)	2012	1,2
Transcatheter Cardiovascular Therapeutics (Miami)	2012	1,2
European Association of CardioThoracic Surgery (Barcelona)	2012	1,2
Dallas-Leipzig International Valve (Dallas)	2012	0,9
Association of Thoracic and Cardiovascular Surgeons of Asia (Borneo)	2012	0,9
EuroPCR (Paris)	2013	0,9
European Association of CardioThoracic Surgery (Vienna)	2013	1,2
Dutch Association for Cardiothoracic Surgery (Utrecht)	2010-2013	1,2
Presentations (12.0)		
Dallas-Leipzig International Valve (Dallas)	2010	0,6
European Association of CardioThoracic Surgery (Lisbon)	2011	0,6
Transcatheter Cardiovascular Therapeutics (San Francisco)	2011	0,6
European Association of CardioThoracic Surgery Symposium (London)	2012	0,6
Asian Society for Cardiovascular and Thoracic Surgery (Bali)	2012	0,6
Transcatheter Cardiovascular Therapeutics (Miami)	2012	1,2
European Association of CardioThoracic Surgery (Barcelona)	2012	2,4
Dutch Association for Cardiothoracic Surgery (Utrecht)	2012	0,6
Dallas-Leipzig International Valve (Dallas)	2012	0,6
Association of Thoracic and Cardiovascular Surgeons of Asia (Borneo)	2012	2,4
Symposium (Calgary)	2012	0,6
European Association of CardioThoracic Surgery (Vienna)	2013	1,2

Teaching (7.2)		
Supervising students	2011-2013	3,0
Clinical Research Associate training (Düsseldorf)	2012	0,6
Minor students lecture: how to perform a systematic review?	2012	0,6
Supervising clinical researchers	2012-2013	3,0
Courses and seminars (5.4)		
COEUR PhD day	2011	0,4
COEUR Heart Valve Implantation	2012	0,4
Academic Research Consortium meetings	2011-2012	1,6
Local scientific meetings department of cardiothoracic surgery	2010-2013	3,0
Local scientific meetings department of cardiothoracic surgery	2010-2013	3,0


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Chapter 36

List of publications

PAPERS

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2. **Head SJ**, Börgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggart DP, Puskas JD, Gummert JF, Kappetein AP. Coronary artery bypass grafting -- part 2: optimizing outcomes and future directions. *Eur Heart J*; in press.
3. Farooq V, **Head SJ**, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX Score. *Heart* 2013; in press.
4. **Head SJ**, Kaul S, Tijssen JG, Stoop EM, Holmes DR Jr, Mack MJ, Serruys PW, Brown DL, Bogers AJ, Kappetein AP. Subgroup analyses in trial reports comparing percutaneous coronary intervention with coronary artery bypass surgery. *JAMA* 2013; in press.
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11. Piazza N, Kalesan B, van Mieghem NM, **Head SJ**, Wenaweser P, Carrel T, Bleiziffer S, de Jaegere P, Gahl B, Anderson R, Kappetein AP, Lange R, Serruys PW, Windecker S, Jüni P. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement based on propensity matched scoring among intermediate surgical risk patients. *JACC Cardiovasc Interv* 2013;6:443-451.
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13. Van Leeuwen WJ, **Head SJ**, de Groot-de Laat LE, Geleijnse ML, Bogers AJ, van Herwerden LA, Kappetein AP. Single centre experience with mitral valve repair in asymptomatic patients with severe mitral valve regurgitation. *Interact CardioVasc Thoracic Surg* 2013;16:731-737.
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16. Mack MJ, **Head SJ**, Holmes DR Jr, Ståhle E, Feldman TE, Colombo A, Morice MC, Unger F, Erglis A, Stoler R, Dawkins KD, Serruys PW, Mohr FW, Kappetein AP. Analysis of stroke occurring in the SYNTAX trial comparing coronary artery bypass surgery and percutaneous coronary intervention in the treatment of complex coronary artery disease. *JACC Cardiovasc Interv* 2013;6:344-354.
17. Kappetein AP, **Head SJ**, Morice MC, Banning AP, Serruys PW, Mohr WF, Dawkins KD, Mack MJ, SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 2013;43:1106-1013.
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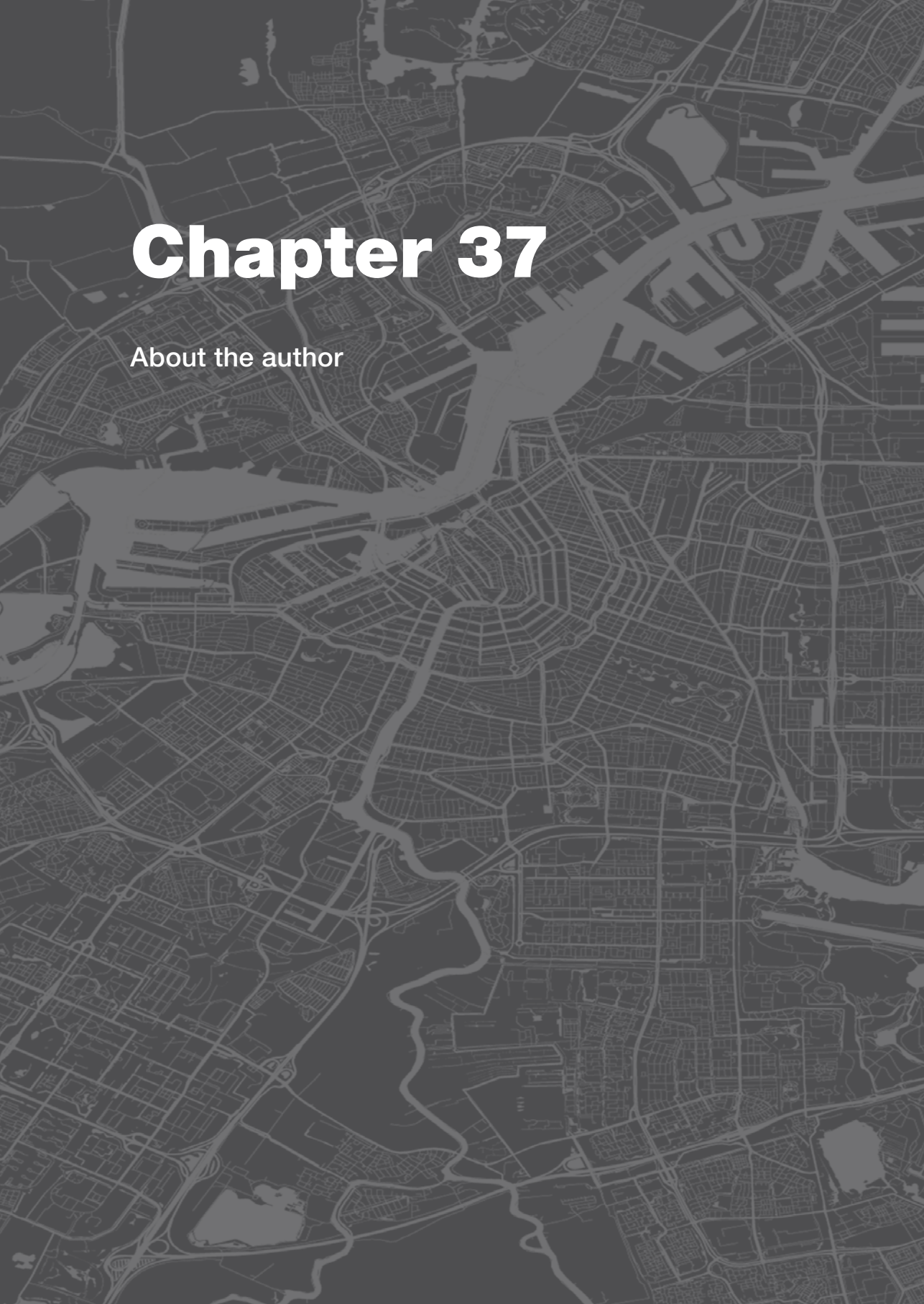

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About the author

Stuart Head was born October 11, 1986 in Badhoevedorp, The Netherlands. After moving to Maastricht at the age of 8, he graduated there from Sint Maartens College in 2005. He started medical school at the Erasmus University Rotterdam in 2006. Finishing his doctoral degree in 2010 while involved with a number of research projects both in Rotterdam and Dallas, USA, where he spent 5 months, the appeal of further academic evolvement led him to start his PhD project at the Department of Cardiothoracic Surgery of the Erasmus University Medical Center. He has started his clinical internships mid-2013 and will subsequently persue a residency in cardiothoracic surgery.


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