General discussion

The current thesis aimed to determine procedural and clinical outcomes after contemporaneous revascularisation treatment strategies for patients with coronary artery disease, and sought to distinguish treatment benefits and risk-predictors in patients that underwent percutaneous (PCI) versus surgical myocardial revascularisation (CABG) at short-(≤1 year), mid-(1-3 year) and long-term follow-up (≥ 10 year).

Since the introduction of surgical and percutaneous coronary interventions over four decades ago, the field of coronary artery revascularisation has progressed significantly.[1-4] Continuous developments in surgical and percutaneous techniques together with optimization of guideline directed medical treatment ensured the possibility of treating more complex patients with CAD. Numerous randomized and observational studies have reported outcomes after PCI versus CABG and herewith contributed to the continuous developments and improvements of both revascularisation strategies.[5-8] The great majority of these studies, however, only reported outcomes at short to mid-term follow-up (e.g. 30 days - 5 years). Since the overall life-expectancy of patients with coronary artery disease is steadily increasing worldwide, the presence of various cardiovascular comorbidities in these patients will affect perioperative, short-, mid- and long-term outcomes. Understanding how, and to which extent, these patients characteristics will influence clinical outcomes will offer a major advantage in determining the optimal myocardial revascularisation strategy in an individual patient with coronary artery disease requiring revascularisation PCI versus CABG.

Short-term outcomes

Risk-stratification tools showed to be useful instruments to accurately assess perioperative risks and clinical outcomes in patients undergoing CABG or PCI. To date, various risk models have been published and are used during multi-disciplinary heart team meetings to determine the optimal revascularisation strategy in patients with CAD.[9-11] Now that PCI has become a suitable treatment, as an alternative to CABG, for selected patients with coronary artery disease, accurate risk assessment is crucial to accurately determine the preferred treatment in these specific patients.[12-19]

In **chapter 2** the predictive performance of Society of Thoracic Surgeons (STS)[10] risk models for perioperative mortality, stroke and renal failure in patients undergoing CABG (n=923) for LMCAD from the randomized EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was analysed.[20] Furthermore, the efficacy of these risk models in PCI-treated subjects from the EXCEL trial (n=935) was examined.

In brief, the EXCEL trial was an international, multicenter randomized trial that compared PCI with everolimus-eluting stents with CABG in patients with LMCAD and a low to intermediate SYNTAX score (≤32). The study was designed to determine whether PCI was non-inferior to CABG regarding the primary composite endpoint of major adverse cardiac and cerebrovascular events (MACCE) defined by all-cause death, stroke or MI at 3 years. The study showed that at 3-years MACCE occurred in 15.4% of the PCI cohort and in 14.7% of the CABG cohort (hazard ratio (HR) 1.00, 95% confidence interval (CI) [0.79-1.26], *P*=0.98 for superiority and *P*=0.02 for inferiority).

The STS risk scores showed good discrimination for 30-day predicted risk of mortality (PROM) and stroke in CABG patients, with average calibration. For patients treated by PCI, the STS risk scores had no discrimination for mortality, comparable to "flipping a coin", yet average discrimination for stroke with good calibration. The predictive performance of STS renal failure risk scores was excellent in the CABG cohort, yet poor in those treated with PCI. Overall, an updated risk score model is warranted in order to accurately assess perioperative clinical outcomes and to determine which treatment strategy appears optimal for a specific patients with LMCAD, bearing in mind that between-treatment differences might emerge beyond the perioperative (30 days) timeframe.

In daily clinical practice, patients with stable coronary artery disease should be discussed in a multidisciplinary heart team.[21] During this discussion several risk prediction models can be used to better inform the heart team about the perioperative risk. Besides the STS risk models, there are multiple other risk prediction models that could be used, such as the SYNTAX score (predicts the risk of major adverse cardiovascular and cerebral events at 12 months follow-up)[5], the SYNTAX score II (predicts the risk of 4-year mortality)[22], and the EuroSCORE II (predicts in-hospital mortality)[9]. Each of these risk scores have their own advantages, shortcomings, and degrees of accuracy (calibration and discrimination). In addition to a physician's clinical judgement, these risk scores help optimize clinical outcomes and strive for optimal "personalised medicine", instead of "one-size-fits-all".

Mid-term outcomes

The overall treatment goals of myocardial revascularisation by CABG or PCI in patients with coronary artery disease is i) providing relief of angina and ii) reducing the risk of "premature" mortality together with other major adverse cardiac and cerebrovascular events. In order to determine the most appropriate revascularisation strategy in an individual patient, a structured heart team discussion weighs the benefits and shortcomings of both treatment strategy against perioperative risk

and benefit, and takes into account a patients personal preference and the existence of comorbidities (diabetes mellitus, renal insufficiency, pulmonary disease and left ventricular function). Besides, perioperative risk assessment, the expected mid- and long-term outcomes are of utmost importance to determine the best treatment strategy.[21,23]

Myocardial revascularisation guidelines recommend CABG in patients with complex multivessel CAD and severely impaired LVEF (≤35%).[17,18] Nonetheless, what the preferred treatment strategy is in patients with LMCAD and impaired LVEF (<50%) remains unclear. To date, randomized data on the impact of LVEF on clinical outcomes in patients with coronary artery disease is restricted to CABG versus medical therapy since contemporaneous randomized trials exclude patients with severely reduced LVEF (≤35%). Therefore, the impact of left ventricular ejection fraction (LVEF) on clinical outcomes at 3-years in patients with LMCAD from the EXCEL trial was evaluated in **chapter 3**.[24] Patients with preserved (≥50%) and impaired LVEF (<50%) undergoing CABG or PCI were analysed in this study. Although no treatment interaction of CABG or PCI according to baseline LVEF was found, patients with impaired LVEF showed to possess a significantly higher risk of 3-year all-cause mortality compared to patients with preserved LVEF. To date, randomized data that directly compares the impact of CABG and PCI in patients with impaired LVEF, especially patients with LMCAD, is lacking. Although our current study was not a randomized controlled trial (RCT), it provides valuable insights on treatment outcomes in patients with LMCAD and impaired LVEF that require revascularisation.

The Surgical Treatment for Ischemic Heart Failure (STICH) evaluated whether CABG with intensive medical therapy versus medical therapy alone would decrease mortality in patients with severely impaired LVEF (≤35%).[25] The intention-to-treat analysis showed no difference in mortality at a median follow-up of 56 months (HR with CABG, 0.86; 95% CI [0.72-1.04], P=0.12). In the per-treatment analysis, however, a significant survival benefit of CABG with optimal medical treatment versus medical treatment alone was found (HR 0.70, 95% CI [0.58-0.84], P<0.001). No comparisons between PCI or CABG were made in the STICH trial. The systematic review by Wolff *et al.* compared revascularisation with medical therapy. They reported an overall survival benefit of CABG over PCI in 8782 patients with LVEF ≤40% (HR 0.82; 95% [0.75-0.90]).[26] However, results are restricted by important limitations, such as a great spread in follow-up (range 12-180 months) and a heterogeneous patient population (I^2=47%).

In **chapter 4** the safety and effectiveness of performing CABG using a single internal thoracic artery (SITA) with additional venous grafts versus bilateral internal thoracic artery (BITA) was determined in patients with LMCAD and low to intermediate SYNTAX scores (≤32) from the randomized EXCEL trial.[8,27] Clinical outcomes such as all-cause death, stroke, MI and sternal wound dehiscence were assessed at 30-days and 3-year follow-up. Whether CABG should be performed by complete arterial revascularisation using BITA grafts, remains a matter of debate[28-31] Besides, some surgeons may discourage BITA-use in patients with LMCAD, especially in those where a pin-point (bi/tri-furcation) lesion is present, since the entire myocardium will be supplied of oxygen rich blood by a "new main stem"'; being a composite LITA-RITA-Y graft (e.g. LIMA-RIMA-Y graft). Our study in **chapter 4** showed low rates of sternal wound dehiscence at 30-days in both the SITA as the BITA cohort, without any statistical difference. Furthermore, at 3-years, no differences existed in the multivariable adjusted primary composite endpoint of all-cause death, stroke or MI, or the individual endpoints of ischemia-driven revascularisation and major bleeding complications. Although the rate of unplanned hospitalization was higher in SITA compared to BITA, this difference was not seen after multivariable adjustment.

Previous studies have shown that patients receiving BITA, especially those that have diabetes and/or chronic obstructive pulmonary disease (COPD), have an increased risk of developing sternal wound complications at short-term follow-up (e.g. 30-days).[32-34] Although, by meticulously selecting suitable patients, this risk can be reduced, possibly even more when ITA grafts are being harvested skeletonized.[27]

Potential clinical benefits at long-term, especially regarding survival, might only appear after long-term follow-up (≥ 10 years). This is most likely due to superior arterial graft patency compared with venous graft patency.[35-37] Various observational studies showed a significant long-term survival benefit of BITA over SITA[38-41], yet randomized data were not able to confirm this finding.[27,42] The results of the Arterial revascularisation Trial (ART), investigating differences between SITA and BITA revascularisation were therefore highly awaited.[43] Nonetheless, results at 10-year follow-up appeared disappointing for those that advocate the use of BITA during CABG procedures; as no mortality difference was found between BITA (20.3%) and SITA (21.2%, HR 0.96, 95% CI [0.82-1.12]) in the intention-to-treat analysis. The shortcomings that most likely influenced the outcomes in the ART trial were i) a high cross-over rate in the BITA (13.9%) cohort and ii) the use of a radial artery in the SITA cohort (21.8%). The as-treated analysis, comparing multiple (2 or more) arterial grafts with a single arterial graft, however, did show a survival benefit in patients

receiving multiple arterial grafts (18.6%) versus a single arterial graft (23.1%) (HR 0.81, 95% CI [0.68-0.95]).

To conclude, although arterial grafts most likely outperform venous grafts from a physiological standpoint [44], mainly circumstantial evidence is currently available that supports the use of BITA, or multi-arterial grafts, in selected patients with coronary artery disease requiring CABG. The Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts (ROMA) trial aims to determine the impact of using 2 or more arterial grafts on long-term survival and results are expected in 2025.[45] Until then, complete arterial revascularisation with the use of BITA could be seen more of "an ART than a science", as Prof. Mario Gaudino quoted.[46,47]

Over the recent decade, myocardial revascularisation for patients with LMCAD progressed significantly. Where CABG historically was the golden standard for revascularisation in patients with a left main stenosis, PCI appeared to be a suitable alternative in selected patients.[14-16] The basis for these advancements came from various randomized and observational studies. The publication of these individual studies, however, was followed up by the publication of an abundant number of meta-analyses evaluating PCI versus CABG in LMCAD. **Chapter 5**, reports a critical appraisal by systematically reviewing all published meta-analyses that focused on PCI versus CABG in LMCAD revascularisation over the past decade.[48] The search resulted in 51 meta-analyses that all published data the same topic. Of those, interestingly, 33 meta-analyses were published after the EXCEL and NOBLE publications. This resulted in overlapping and redundant outcomes, which could be attributed to study differences, such as (i) randomized versus observational studies, or a combination of both, (ii) differences in methodology, (iii) differences in sample sizes, and (iv) the timing of publication of specific meta-analyses (2009 versus 2018). Hence, caution is advised when interpreting results from these meta-analyses. Encouraging physicians and scientists to collaborate in conducting, reviewing and publishing scientific content possibly minimizes redundant, overlapping and inefficient work. By performing an individual patient-data meta-analysis, by combining patient-level outcomes from multiple randomized trials, statistical power increases and possible treatment differences between revascularisation procedures can be determined with more statistical certainty.[49]

Long-term outcomes

In the SYNTAX trial, patients that were randomized to undergo CABG or PCI with paclitaxel-eluting stents (DES) experienced a non-significant survival difference in favour of CABG at 1-year follow-up (CABG 3.5% vs PCI 4.4%, *P*=0.37).[5] This numerical

survival difference continued to increase until trail completion at 5-year follow-up. However, no statistical difference between CABG and PCI was found (CABG 11.4% vs PCI 13.9%, *P*=0.10).[50] Furthermore, the post-hoc landmark analysis from the EXCEL trial reported differences in risk of death after PCI and CABG depending on the duration of follow-up.[8] Longer-term follow-up data was warranted to adequately identify risk predictors and differences in clinical outcomes, which can subsequently aid the multidisciplinary-decision making process, in order to determine the optimal evidence-based revascularisation strategy for individual patients with coronary artery disease.

The SYNTAX Extended Survival study was presented in **Chapter 6**, which reported the long-term survival outcomes of patients with *de novo* three-vessel and left main coronary artery disease randomized to PCI with paclitaxel-eluting stents or CABG in the SYNTAX trial.[51] At 10-year, 94% of vital status information was complete for the overall cohort of 1800 included patients in the SYNTAX trial (n=1800). In the overall cohort, no significant difference existed between PCI versus CABG (28% versus 24%, p=0.066). However, CABG provided a significant survival benefit (30% risk reduction of all-cause death) in those patients with 3VD and those with high SYNTAX Scores (≥33), yet not in patients with LMCAD. Furthermore, among patients with medically treated diabetes or without diabetes no survival differences were noticed. The SYNTAXES study was the first study to report 10-year outcomes of patients with *de novo* 3VD and LMCAD randomized to PCI with DES or CABG. It provides important insight in long-term survival outcomes after CABG and PCI with DES, and will aid in determining the optimal revascularisation strategy in patients with coronary artery disease.

To date, long-term outcome of contemporaneous randomized trials comparing PCI with CABG with DES is scarce and limited to the publication of only 2 other studies. First, the LE MANS trial randomized 105 patients with unprotected LMCAD with low to intermediate complexity of coexisting coronary artery disease to CABG or PCI with bare metal stents and DES.[52] At 10-year follow-up no difference in mortality between PCI (21.6%) and CABG (30.2%) was found (*P*=0.41). These results of the LE MANS trials are like the results found in the SYNTAX Extended Survival study, being that PCI provides a numerically, yet not statistically significant, survival benefit over CABG in patients with LMCAD. Nonetheless, due to the low sample size the LE MANS study lacks statistical power and findings should be interpreted with caution. Moreover, BMS were used in 65% of patients and therefore survival outcomes of those specific patients might not be relevant to contemporary revascularisation practice.

Second, the FREEDOM trial randomized 1900 patients with diabetes mellitus and multivessel coronary artery disease (MVD) to PCI with sirolimus-eluting stents or CABG. Both treatments were performed under optimal guideline-directed medical therapy.[53] Recently, long-term follow-up data up to 8-years of 943 patients (49.6% of the original cohort) was published. In this limited cohort, all-cause mortality occurred in 23.7% of patients that underwent PCI (99 deaths) and in 18.7% of patients that underwent CABG (72 deaths) (HR 1.32, 95% CI[0.97;1.78], *P*=0.076). The SYNTAX Extended Survival study included 452 patients with diabetes mellitus that were medically treated (oral medication and/or insulin therapy). All-cause death occurred in 38.7% of patients that underwent PCI and in 36.5% of patients that underwent CABG (*P*=0.50). The relatively modest sample size could have resulted in less statistical power, besides the substantial difference in duration of follow-up between the FREEDOM trial (median 7.5 years) and the SYNTAXES study (median 11.2 years).

Besides analysing the outcomes in the randomised cohorts from the SYNTAX trial, we also investigated 10-year survival outcomes of patients enrolled in the SYNTAX trial that were entered into nested registries. The registry patients were ineligible for randomization i) due to significant comorbidities which increased the surgical perioperative risk of morbidity and mortality, and/or ii) due to extensive and complex coronary artery disease unsuitable for PCI. Such registries overcome the major limitation of randomized trials that only include a highly selected patient cohort because patients entered in such registries are a more accurate representation of patients that are discussed in daily multidisciplinary hear teams. **Chapter 7** provided insights in the risk profiles and 10-year all-cause death rates of patients that were found ineligible by a multidisciplinary heart team to be randomized to undergo PCI or CABG. When clinical equipoise with either PCI or CABG could not be reached due to coronary anatomy, comorbidities, perioperative risk, or a combination of all afore mentioned factors patients were entered into nested registries; CABG-ineligible PCI registry (198 patients) or PCI-ineligible CABG registry (1077 patients).[5,54] Of those, all 198 PCI-registry patients were selected to be followed-up for 5- and 10-years. In the CABG registry, 649 randomly selected patients were followed-up for 5- and 10 years. Patients that were entered in the CABG-registry showed excellent 10-year survival (all-cause death rate of 25.9%); comparable to outcomes in the randomized CABG cohort of the SYNTAX trial. Patients that were enrolled in the PCI-registry showed relatively poor 10-year survival with an all-cause death rate of approximately 51.6%, almost twice as high as in the randomized SYNTAX PCI cohort (28%). This study provided unique long-term survival insights in patients representing “real-word” patients with coronary artery disease included in the SYNTAX trial.

Randomized controlled trials have been considered as the gold standard to report the overall treatment effect of comparing two treatment strategies and provide a relative risk (odds ratio or hazard ratio) for the overall cohort of patients. However, not each individual patient might experience these mean relative risks derived from the calculation of the entire cohort [55,56]. Therefore, one could assume that only providing such an average risk is not meaningful for an individual patient that requires myocardial revascularisation.

The present thesis set out to establish treatment-benefits and risk-predictors for individual patients with coronary artery disease that require myocardial revascularisation. In **chapter 8** we assessed the impact of bypass surgery using multiple arterial grafts (MAG) versus a single arterial graft (SAG) on vital status at very-long term follow-up in patients enrolled in the SYNTAX trial. To date, it remains fiercely debated which graft configuration used during coronary bypass surgery provides optimal results at long-term follow-up. Studies have shown that venous graft patency, compared to arterial graft patency, is significantly worse at long-term follow-up (venous patency: 61% vs. arterial patency: 85%).[44] Various observational studies reported long-term advantages of multiple arterial grafting, compared to the use of a single arterial graft. Therefore, the long-term results of the Arterial Revascularization Trial (ART) were highly anticipated.[33,43,57] The unadjusted intention-to-treat analysis, at 10-year follow-up, appeared however disappointing for those "BITA-believers". No difference in survival was found between single versus bilateral internal thoracic grafts (21.2% vs 20.3% all-cause death, respectively). Nonetheless, the as-treated analysis showed a significant survival benefit with multiple arterial grafting compared with the use of a single arterial graft (18.6% vs 23.1% all-cause death; HR 0.81, 95% CI [0.68-0.95]).

In our prespecified post-hoc analysis (**chapter 8**), MAG resulted in a significantly lower incidence of all-cause death at 12.6 years follow-up. The survival benefit of using MAG over SAG remained significant after adjusting for differences in preselected clinically and statistically relevant patient characteristics, such as age, sex, body mass index, diabetes mellitus and vascular disease. These markedly 12.6-year survival benefits derived from using MAG revascularisation over SAG, in the SYNTAX trial encourages a more extensive use of multiple arterial grafting in contemporaneous coronary bypass surgery. Although our results are "hypothesis-generating" due to the non-randomized nature of the study, it provides very reassuring and important long-term insights in the benefits of multiple arterial grafting. We recommend that a patient's baseline and angiographic characteristics should always be adequately assessed during multidisciplinary heart team meetings when deciding

on the optimal strategy of surgical revascularisation striving for ideal short-and-long-term outcomes.

The ongoing ROMA trial randomizes coronary artery disease patients to either CABG with MAG versus SAG. The trial aims to answer two hypotheses; (i) MAG is associated with a reduction in the composite outcome of all-cause death, any stroke, post-discharge myocardial infarction and/or repeat revascularisation and (ii) MAG is associated with improved survival.[45] The ROMA trial is expected to be completed around 2030, therefore the first long-term randomized data on MAG versus SAG will not be available soon. Until then, high quality observational data, such as the insights provided by the SYNTAXES study, should inform cardiothoracic surgeons on the optimal graft configuration during CABG.

Besides the potential benefits of multiple arterial grafting during bypass surgery, completeness of revascularisation plays an important role in optimizing procedural and patient outcomes. The impact of complete versus incomplete revascularisation has been assessed by multiple studies.[58-63] A recent meta-analysis of 83,695 patients reported a significant survival benefit at 4.7 years follow-up with complete versus incomplete revascularisation (relative risk 0.76, 95% CI [0.63-0.90]).[64] Long-term outcomes after complete versus incomplete are scarcely available. Only the MASS II trial evaluated outcomes beyond 5 years, however the impact of these findings are limited due to the use of bare metal stents during PCI and the limited number of patients included in the study (PCI 205 patients, CABG 203 patients, medical therapy 203 patients). Besides evaluating the impact of (in)complete revascularisation the residual SYNTAX score (rSS) was introduced as a more accurate risk-predictor specifically for those patients that underwent PCI.[63] The rSS quantifies the remaining burden of coronary atherosclerosis after incomplete revascularisation and is divided in four subgroups; rSS of 0, rSS >0-4, rSS >4-8 and rSS 8, where a high rSS was associated with increased risks of all-cause death, stroke, myocardial infarction and repeat revascularisation. In **Chapter 9** the effect of incomplete revascularisation on 10-year survival in patients randomized to PCI versus CABG in the SYNTAX trial was evaluated. Incomplete revascularisation was more common after PCI compared with CABG. Especially those patients with three-vessel coronary artery disease were at increased risk of receiving incomplete revascularisation irrespective of the revascularisation strategy. The risk of 10-year all-cause death was similar in patients that underwent PCI with complete revascularisation compared to those that underwent CABG with complete revascularisation. On the contrary, PCI with incomplete revascularisation was associated with a significantly increased risk of all-cause death at 10-year follow-up. A rSS >8 was furthermore associated with a 3.5-fold increased risk

of 10-year all-cause death, while a rSS across 0 to 8 showed a similar risk of all-cause death. Each heart team discussion should consider the potential risk of incomplete revascularisation with either percutaneous or surgical myocardial revascularisation- Interventional cardiologists should furthermore aim to reduce the residual SYNTAX score as far as possible below the cut-off value of 8, otherwise patients will be at increased risk of MACCE during the first 5 years and at increased risk of all-cause death at 10-year. The rSS remains a purely angiographic and anatomical index which does not evaluate the hemodynamic relevance of any remaining coronary artery stenoses. It is furthermore challenging to use as a prediction-tool prior to the intervention, especially since incomplete revascularisation is influenced by multiple factors such as diffuse, small vessel coronary artery disease, heavy calcifications, extreme tortuosity, and/or chronic total occlusions. Future methods of assessing functional flow reserve, by CT FFR for example, could provide a non-invasive insight on the impact of residual coronary stenosis after both PCI as CABG.

In **Chapter 10** the predictive performance of the SYNTAX score II on 10-year all-cause death was estimated in 1800 patients with *de novo* three-vessel and left main disease followed-up by the SYNTAXES study. Although randomized trails provide the highest level of evidence and are often used to establish recommendation in clinical guidelines for most patients with coronary artery disease, it provides information for a large cohort of patients. It is however crucial to be able to recommend the best treatment-strategy for an individual patient requiring myocardial revascularisation. As mentioned before, risk stratification models are useful to steer a multidisciplinary heart team treatment recommendation by balancing be perioperative, as well as long-term risks and benefit of each treatment. Where the original SYNTAX score predicts the risk of 12-month MACCE, the SYNTAX score II was designed to predict the risk of 4-year all-cause death for an individual patient. The SYNTAX score II risk model is an instrument that combines clinically important and prognostic patient characteristics (age, renal function, left ventricular ejection fraction, left main coronary artery disease gender, chronic obstructive pulmonary disease and peripheral vascular disease) with the anatomical SYNTAX score.[22] Now, the SYNTAX Score II 2020 (SSII-2020) has been introduced, showing good calibration and discrimination to adequately assess the risk of 10-year all-cause death, using 7 clinical predictors (age, diabetes, renal function, LVEF, COPD, PVD and current smoking) in combination with type of coronary artery disease (3VD or LMCAD) and the anatomical SYNTAX score. Due to the absence of other available randomized long-term follow-up data (≥10 years), the updated SSII-2020 could not yet be externally validated. This furthermore stresses the necessity of extending follow-up of contemporaneous randomized trials, such as the EXCEL and NOBLE trials, up to 10-year follow-up

and beyond. Eventually, when more long-term data becomes available, one could pool individual patient data from various randomized trials a therewith estimate a potential treatment-benefit, of either PCI or CABG, with more statistical certainty.

Left main coronary artery revascularisation

Recently, three of the major randomized clinical trials comparing outcomes after PCI with drug-eluting stents versus CABG have published data on longer-term follow-up in patients with left main coronary artery disease, being the SYNTAX trial (10-year data), the EXCEL trial and the NOBLE trial (both reported 5-year data).[51,65,66]

In 2016, the EXCEL trial reported its 3-year outcomes, suggesting that PCI with 2nd generation everolimus-eluting stents was non-inferior to CABG in unprotected left main revascularisation regarding the primary endpoint of MACCE (major adverse cardiac or cerebrovascular events), a composite of death, stroke or myocardial infarction.[8] At 3-year follow-up, no difference in all-cause death between PCI and CABG was present. In September 2019, the EXCEL trial presented their 5-year outcomes at the Transcatheter Cardiovascular Therapeutics meeting (TCT), and simultaneously published these outcomes in the *New England Journal of Medicine*.[65] At 5-year follow-up, PCI showed to be non-inferior to CABG regarding the composite primary endpoint (difference of 2.8 percentage points; 95% CI[−0.9-6.5]; P=0.13). Death from any cause was more common after PCI compared with CABG (13.0% vs. 9.9%; 95% CI [0.2-6.1]).

The publication of the 5-year EXCEL trial outcomes substantially shook up the cardiovascular society, leading to fierce (inter)national discussions at scientific meetings, television program (BBC) and social media platforms related to the definition of myocardial infarction used in the trial (a biochemical periprocedural Myocardial Infarction definition[18] versus the Universal Definition of Myocardial Infarction[67,68]) and the increased rate of all-cause death after PCI compared with CABG at 5-year follow-up, amongst many other arguments. Eventually the European Association of CardioThoracic Surgery (EACTS) withdrew its support from the 2018 Guideline on Myocardial Revascularisation that stated that PCI is an appropriate alternative to CABG in selected patients with left main coronary artery disease, while the European Society of Cardiology (ESC) continued to support the Myocardial Revascularisation guideline.[17] The raw EXCEL 5-year data is currently being analyzed by an independent research group and results are, of course, highly anticipated.

In December 2019, the NOBLE trial published its 5-year results in *The Lancet* showing PCI with 2nd generation stents resulted in inferior clinical outcomes compared with CABG in patients with unprotected left main coronary artery disease.[66] Also NOBLE

reported on the primary endpoint of MACCE, a composite of all-cause death, non-procedural myocardial infarction, repeat revascularisation and stroke. At a median of 4.9 years of follow-up, 28% of patients that underwent PCI experienced MACCE versus 19% of patients that underwent CABG (HR 1.58, 95% CI [1.24-2.01]). There was no difference in all-cause death between PCI and CABG (NOBLE: 9% vs 9%, HR 1·08 [95% CI 0.74–1.59] compared to EXCEL: 13% vs 10% OR 1.38 [95%CI 1.-030–1.85]). Of note, the individual endpoints of MACCE used in the NOBLE trial differ substantially from the MACCE primary composite endpoints used in the EXCEL trial, making it impossible to compare these MACCE outcomes directly head-to-head. Nonetheless, the undisputed endpoint of all-cause death in the NOBLE trial did not differ between PCI and CABG.

In October 2019, the SYNTAX Extended Survival study published data on vital status up to 10-year of follow-up in patients with *de novo* three-vessel and/or left main coronary artery disease randomized to PCI with 1st generation drug-eluting stents versus CABG.[51] At 10-year follow-up, no difference in all-cause death existed in patients with left main coronary artery disease that underwent PCI or CABG (27% vs 28%, respectively).

To date, there appears not to be one correct and all-inclusive answer that eludes which revascularisation strategy, PCI versus CABG, provides optimal results in patients with left main disease due to the variety of clinical endpoints and definitions used in each individual randomized trial. It is therefore strongly recommended that the entire body of available evidence published by trails such as SYNTAX, PRECOMOBAT, NOBLE and EXCEL is adequately appraised and used to base evidence-based treatment recommendations on, accounting for all MACCE associated benefits and shortcomings of each treatment.[5,7,8,51,65,66,69,70] Multidisciplinary heart teams remain of utmost importance to ensure a well-informed, unbiased and collaborative treatment recommendation in each individual patients with coronary artery disease requiring myocardial revascularisation An undisputed collaboration between interventional cardiologists, clinical cardiologists and cardiothoracic surgeons forms the solid foundation of such successful heart team meetings.

Technological advencements in coronary artery bypass surgery

In the 2018 EACTS/ESC Guidelines on myocardial revascularisation intraoperative graft flow assessment and epiaortic ultrasound scanning were classified with a Class IIa recommendation.[17] Nonetheless, the adoption-rate of intraoperative quality assessment during CABG varies substantially between institutions and surgeons. Moreover, contemporaneous published data is mostly restricted to non-randomized

single-centre studies that report heterogeneous outcomes which furthermore complicate drawing uniform conclusions.

In **chapter 11** the results of a comprehensive systematic search and meta-analysis on the impact of using transit-time flow measurements (TTFM) during CABG to improve surgical and clinical outcomes were reported.[71] Of the 66 included studies, 35 reported on abnormal grafts or graft revisions in 8943 patients (n=15673 grafts). Of those patients, 4.3% (95% CI 3.3-5.7%) required a graft revision based on abnormal TTFM findings. This corresponded with a graft revision rate of 2.0% of grafts (95% CI 1.5-2.5%). Of the grafts classified as abnormal, the pooled rate of graft revisions was 25.1% (95% CI 15.5-37.9%). Although this was a relatively modest amount, and the diagnostic accuracy of TTFM alone was limited, TTFM has the potential to be of great importance during CABG procedures. Especially, when used in combination with high frequency ultrasound (HFUS) the diagnostic accuracy increased substantially.[72] Besides informing a well-experienced surgeon on intraoperative graft patency, TTFM could also be used to train cardiothoracic residents by providing real-time flow-data that aids surgical and tactical knowledge and optimizes surgical skills. An important limitation of the present study was that the included studies were of moderate overall quality and showed great heterogeneity regarding inclusion- and exclusion criteria, variations in endpoints and methods of reporting clinical outcomes (as indicated by high I^2 statistics).[73] This made drawing uniform conclusions challenging and underlined the need for well-structured multicenter studies.

The multicenter international REQUEST study evaluated the impact of performing intraoperative TTFM in combination with HFUS in 1016 patients that underwent CABG.[74] The REQUEST study aimed to prospectively document any changes to the initially proposed surgical strategy based on TTFM and/or HFUS findings. These surgical changes were classified as changes related to the aorta, in-situ conduits, coronary targets, completed grafts and anastomoses. Outcomes of the REQUEST study were reported in **chapter 12**. In 25.2% of patients (256/1016) a surgical change was made after TTFM and/or HFUS assessment. In 7.8% a graft revision was performed. This corresponded with any surgical revision rate in 3.4% of anastomosis (100/2959). Together with low rates of in-hospital adverse events (all-cause death in 0.6, stroke or TIA in 1.0% and myocardial infarction of 0.3%), the REQUEST study showed that intraoperative quality assessment is feasible and safe. Moreover, TTFM with HFUS may improve the quality, safety and efficacy of CABG procedures. Although the REQUEST study was the first large-scale, multicenter prospective study that assessed the impact of using TTFM and HFUS for intraoperative quality assessment based

on a structured protocol, randomized data is warranted to contribute to guideline directed CABG.

CONCLUSION AND FUTURE PROSPECTS

The present thesis set out to determine procedural and clinical outcomes in patient with coronary artery disease that underwent PCI or CABG and aimed to define treatment-specific benefits and risk-predictors for patients who require myocardial revascularisation The short- and midterm outcomes (0-5 years) of patients with left main coronary artery disease randomized to PCI with 2nd generation drug-eluting stents or CABG in the randomized EXCEL trial, together with evaluating (very) long-term (≥10 year) survival outcomes in patients with *de novo* three-vessel and/or left main coronary artery disease who underwent PCI with 1st generation drug-eluting stents versus CABG in the SYNTAX trial, were analysed. Finally, the impact of using technological advancements during bypass surgery, such as transit-time flow measurement and high frequency ultrasound, in order to improve graft patency and patient outcomes were evaluated.

Determining the most appropriate treatment strategy for an individual patient with coronary artery disease requiring myocardial revascularisation should be put forward by a multidisciplinary heart team that adequately appraises myocardial revascularisation guidelines. The heart team should take into account i) a patients revascularisation risk profile, such as the left ventricular ejection fraction, the presence or absence of diabetes and any additional comorbidities, ii) the anatomical coronary complexity, defined by the SYNTAX score, iii) combined with a patient's own treatment-preference. Procedural risks and benefits should be appropriately weighed by using various risk prediction models, such as the STS risk score, the SYNTAX score, and the SYNTAX score II 2020, to predict the risk of morbidity and mortality associated with each revascularisation strategy. In addition, an unbiased and evidence-based treatment recommendation should be formed by taking into account all PCI-and CABG-specific characteristics that influence the risk of myocardial infarction, repeat revascularisation stroke and all-cause death during short- mid and (very) long-term follow-up. This heart-team treatment recommendation should be incorporated with the preferences of an individual patient, striving to come to an individualized evidence-based shared decision regarding the optimal revascularisation strategy.

Future studies should continue to focus on optimizing treatment outcomes after PCI and CABG by aiming to analyse the most important clinical outcomes (such as all-cause death, myocardial infarction, stroke and repeat revascularisation) and treatment goals (such as quality of life, event free survival, cost-effectiveness) that will benefit both the cardiovascular patients as well as their treating physicians. Studies will most likely enrol more complex patients since the overall life-expectancy of patients with coronary artery disease will increase, which will be accompanied by a more complex cardiovascular risk profile. Continuation of the progress that has been made over the past four decades in the field of myocardial revascularisation could be achieved by i) focussing on less invasive techniques to quantify the burden and hemodynamical consequences of coronary artery disease by for example CT FFR, ii) further diminishing post-operative adverse events by careful patient-selection, iii) improving stent design to prolong patency and iv) extent the use of multiple arterial grafting during bypass surgery in selected patients. Future studies should extent follow-up beyond the perioperative period and focus on treatment effects beyond 3 and 5 years, as was done by the SYNTAX Extended Survival study. Pooling individual patient data, of each PCI versus CABG randomized trial, may overcome any differences in definitions used by individual studies and substantially increases statistical power to accurately assess potential treatment risks-and benefits for patients with coronary artery disease who are randomized to undergo PCI or CABG.

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