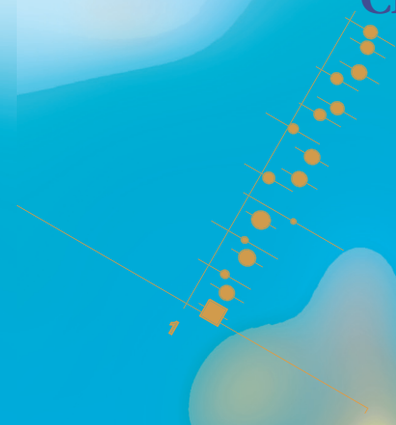
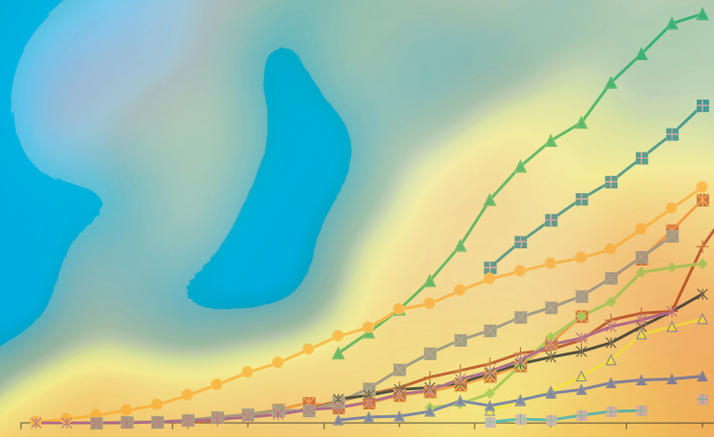
Evaluating the Application and Applicability of Treatment Gwwuidelines

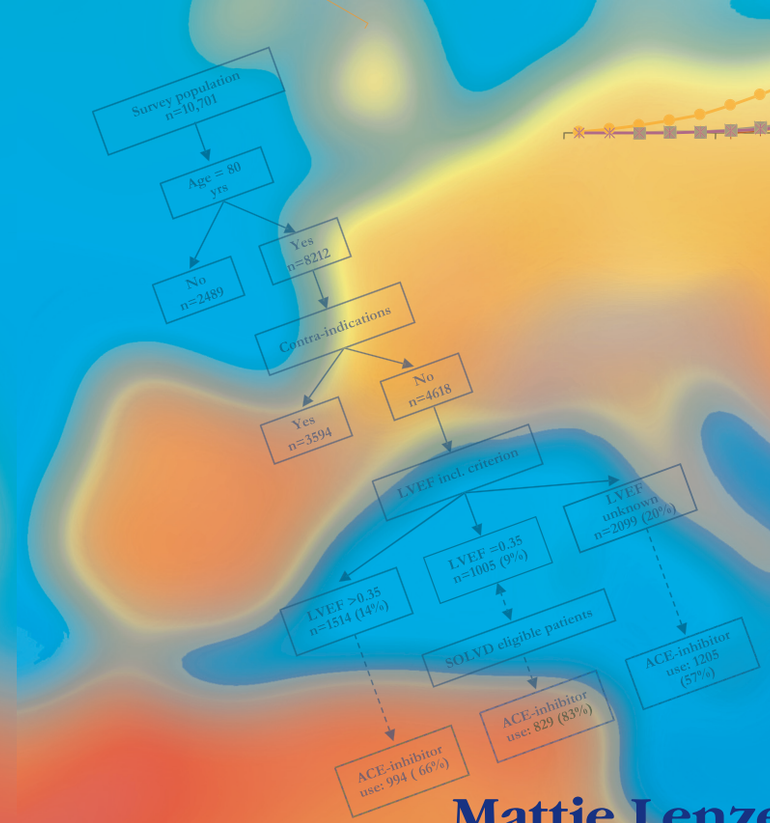
Mattie Lenzen

Evaluating the Application and Applicability of Treatment Guidelines in Daily Clinical Practice

Closing the loop with the Euro Heart Survey







Mattie Lenzen

Evaluating the Application and Applicability of Treatment Guidelines in Daily Clinical Practice

Closing the loop with the Euro Heart Survey programme

Mattie Lenzen

ISBN 90-8559-250-X

Print: Optima Grafische Communicatie, Rotterdam

Evaluating the Application and Applicability of Treatment Guidelines in Daily Clinical Practice

Closing the loop with the Euro Heart Survey programme

Evaluatie van de toepasbaarheid en toepassing van richtlijnen in de klinische praktijk. De cirkel sluiten met behulp van het Euro Heart Survey programma

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 6 december 2006 om 13:45 uur

door

Mathias Joseph Lenzen
geboren te Kerkrade

Promotiecommissie

Promotor:

Prof.dr. M.L. Simoons

Overige leden:

Prof.dr. W.J. van der Giessen

Prof.dr. J. Bakker

Prof.dr. D.J. van Veldhuisen

Copromotor:

Dr. W.J.M. Scholte op Reimer

Nederlandse Hartstichting
www.hartstichting.nl
Redt levens

The study described in this thesis was supported by a grant of the Netherlands Heart Foundation (NHS-2000T101)

Evaluating the application and applicability of treatment guidelines in daily clinical practice

Closing the loop with the Euro Heart Survey programme

Chapter 1

Introduction

INTRODUCTION AND OVERVIEW OF THIS THESIS

Cardiovascular disease is a major health burden and associated with a high morbidity and mortality in middle-aged and older adults in most developed European countries.[1,2] At the same time, significant progress has been made in prevention, detection, diagnosis and treatment of cardiovascular diseases. In this rapidly evolving field, the European Society of Cardiology (ESC) continuously develops and improves guidelines in order to assist cardiologists in every-day clinical decision making. These guidelines summarise and combine pathophysiological insight, the evolution of clinical experience as judged by panels of experts, and scientific evidence, which is mainly provided by randomized controlled clinical trials (RCTs).[3,4] Although cardiologists and other health care professionals are encouraged to apply these guidelines in their practice, numerous factors will influence the physician in treating individual patients, including lack of awareness of specific guidelines, lack of agreement with the guidelines, the lack of facilities, or waiting lists. Furthermore, it is appreciated that the management of individual patients often is more complex than simply following the guidelines.

To implement guidelines, the ESC, and national societies develop guideline-based educational programmes. Furthermore, physicians are informed about clinical practice, based on disparities that were observed in the treatment and outcome of patients among different countries and geographic regions in Europe.[5,6] In addition, the ESC initiated the *Euro Heart Survey* (EHS) programme in order to evaluate the application of recommended procedures management of cardiovascular disease in Europe. The Netherlands Heart Foundation (NHF) recognized the importance of the EHS programme, and supported this initiative through the NHF-Health Care programme (2000T101). Collecting information on patient management as seen in daily clinical practice is essential in identifying barriers in the application of evidence-based medicine, and improving the quality of care. All together, three activities (i.e. guidelines, education, and surveys) became part of an overall programme to improve the quality of care. In this overall programme, the development of guidelines is followed by specific education, and evaluated by means of surveys (Figure 1). The results of the EHS programme, therefore, can be used for further development of the guidelines and educational programmes.

In the Netherlands, a combined EHS and NHF-Health Care programme was conducted. In addition to the initial EHS programme, the support of the NHF resulted in the extension of the survey programme in the Netherlands with two extra topics, the incorporation of care aspects, prolonged follow up, and a larger number of participating hospitals in the Netherlands. The outline of the survey programme, which consists of a series of consecutive cardiovascular surveys, was developed to (i) evaluate to which extend clinical

practice corresponds with existing guidelines, (ii) evaluate the applicability of guideline-based medicine in every day clinical practice, and (iii) to evaluate the outcome of different disease management strategies.

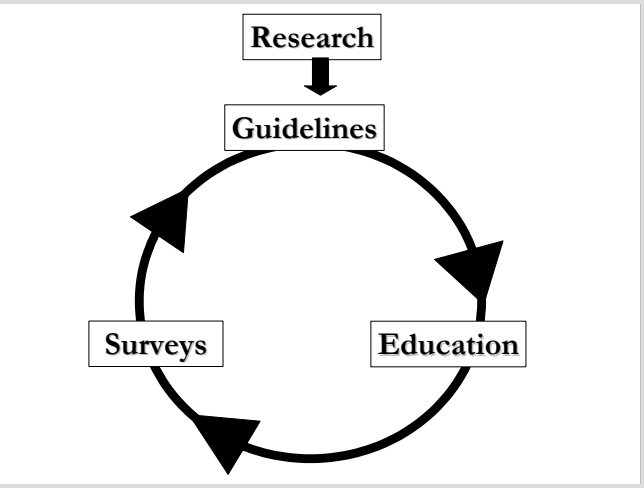


Figure 1. Closing the loop in which evidence-based guidelines are followed by educational programmes, and evaluated by means of surveys. Verification of guidelines implementation can result in further improvement of guidelines, education, and clinical practice.

Between 1999 and 2005 survey participation evolved from 47 hospitals in 15 countries to 182 hospitals in 35 ESC member countries. Participating hospitals were asked to enrol at least 25 consecutive patients. The Netherlands actively participated in the survey programme, as 21 hospitals in the Netherlands were involved (range 2 to 14 hospitals per survey) and 101 to 972 patients were enrolled per survey (approximately 12-13% of the total number of included patients in the survey programme).

Per survey, a scientific expert committee developed a protocol and Case Report Form (CRF) based on European and other guidelines. In the Netherlands, for each of the surveys a scientific expert committee was convened in order to assess applicability and feasibility of the protocol and Case Report Forms (CRF) in the Netherlands. Data collection was done by Data Collecting Officers (e.g. trained research nurses) on electronic CRF and sent to a central database. In addition to collecting data at baseline, follow up was systematically performed at 1-year. In the Netherlands, the follow up period was extended to 2- or 4-years for part of the surveys.

Since the start of the survey programme in 1999, 13 surveys have been conducted, and over 67.000 patients enrolled this programme. These surveys addressed secondary prevention (EuroAspire-II, n=5556), Heart Failure-I (n=10.701), Valvular Heart Disease (n=5001), Acute Coronary Syndromes-I (n=10.484), Coronary Revascularisation (n=5619), Stable Angina Pectoris (n=3779), Diabetes (n=4961), Adult Congenital Heart Disease (n=4110), Atrial Fibrillation (n=5333), Acute Coronary Syndromes-II (n=6554), Heart Failure-II (n=3647). The two extra topics that were added to the EHS programme in the Netherlands only were: Stroke (n=972) and Peripheral Arterial Disease (n=711).

I had the privilege to participate in the survey programme, conduct analyses and prepare a number of key papers on several of the above mentioned surveys: Heart Failure-I, Coronary Revascularisation, and Diabetes and the heart.

This thesis is closely related to the first two aims of the EHS programme: to evaluate to which extend every day clinical practice corresponds with evidence-based guidelines, and to identify patient groups which are under- or not represented in clinical trials which may effect the generalisability of evidence-based treatment.

In **part 1** (chapters 2-4) of this thesis, we investigated the management of patients as observed in daily clinical practice. In addition, we also evaluated to what extend patients in clinical practice were comparable to those who participated in RCTs. In chapters 2 and 3 the focus is on patients with coronary artery disease, whereas chapter 4 focuses on patients with heart failure.

In **part 2** (chapters 5-7) we evaluated the management of patients who were under-represented in clinical trials, and consequently in evidence-based guidelines. In this context, the management of patients with heart failure and a preserved left ventricular function, women with heart failure, and patients with established coronary artery disease who were ineligible for revascularization are discussed.

In **part 3** (chapters 8-9), the impact of health status and glucometabolic status on 1-year mortality is evaluated. The value of self-perceived health status in predicting mortality is discussed in chapter 8, while chapter 9 focuses on the impact of diabetes on adverse outcomes.

Finally, a general discussion is presented, including conclusions and recommendations for future research and clinical practice.

REFERENCES

1. Sans S, Kesteloot H, Kromhout D. The burden of cardiovascular diseases mortality in Europe. Task Force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. *Eur Heart J*. 1997;18:1231-48.
2. Scholte op Reimer WJM, Gitt AK, Boersma E, Simoons ML (eds.). Cardiovascular Diseases in Europe. Euro Heart Survey and National Registries of Cardiovascular Diseases and Patient Management. *Sophia Antilopis: European Society of Cardiology*. 2004.
3. Schwartz PJ, Breithardt G, Howard AJ, Julian DG, Rehnqvist Ahlberg N. Task Force Report: The legal implications of medical guidelines--a Task Force of the European Society of Cardiology. *Eur Heart J*. 1999;20:1152-7.
4. Bassand JP, Ryden L. Guidelines: making the headlines or confined to the sidelines? *Eur Heart J*. 1999;20:1149-51.
5. Boersma H, Doornbos G, Bloemberg BPM, Wood DA, Kromhout D, Simoons ML. Cardiovascular diseases in Europe. European registries of cardiovascular diseases and patient management. *Sophia Antilopis: European Society of Cardiology*. 1999.
6. Boersma E, Manini M, Wood DA, Bassand J-A, Simoons ML (eds.). Cardiovascular diseases in Europe. Euro Heart Survey and national registries of cardiovascular diseases and patient management. *Sophia Antipolis: European Society of Cardiology*. 2002.

Management of patients in daily clinical practice

Chapter 2

Management and outcome of patients with established coronary artery disease

Management and outcome of patients with established Coronary Artery Disease.

The Euro Heart Survey on Coronary Revascularisation

M.J. Lenzen, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
E. Boersma, Rotterdam, the Netherlands
M. E. Bertrand, Lille, France
W. Maier, Zurich, Switzerland
C. Moris, Asturias, Spain
F. Piscione, Naples, Italy
U. Sechtem, Stuttgart, Germany
E. Stahle, Uppsala, Sweden
P. Widimsky, Prague, Czech Republic
P.P.T. de Jaegere, Rotterdam, the Netherlands
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
N.F. Mercado, Rotterdam, the Netherlands
W. Wijns, Aalst, Belgium

European Heart Journal (2005) **26**: 1169-79

ABSTRACT

Aims: The purpose of the Euro Heart Survey Programme of the European Society of Cardiology is to evaluate to which extent clinical practice endorses existing guidelines as well as to identify differences in population profiles, patient management and outcome across Europe. The current Survey focuses on the invasive diagnosis and treatment of patients with established coronary artery disease.

Method: Between November 2001 and March 2002, 7769 consecutive patients undergoing invasive evaluation at 130 hospitals (31 countries) were screened for the presence of one or more coronary stenosis > 50% in diameter. Patient demographics and co-morbidity, clinical presentation, invasive parameters, treatment options and procedural technique were prospectively entered in an electronic database (550 variables + 29 per diseased coronary segment). Major Adverse Cardiac Events were evaluated at 30 days and 1 year.

Results: Out of 5619 patients with angiographically proven coronary stenosis (72% of screened population), 53% presented with stable angina while STEMI was the indication for coronary angiography in 16% and NSTEMI/UA in 30%. Medical therapy only was continued in 21% while mechanical revascularisation was performed in the remainder (PCI in 58% and CABG in 21%). Patients referred for PCI were younger, more active, had a lower risk profile and less co-morbid conditions. CABG was performed mostly in patients with left main (21%), double (25%) or triple (67%) vessel disease with 4.1 diseased segments, on average. Single vessel PCI was performed in 82% of patients with either one (45%), double (33%) or triple (21%) vessel disease. Stents were used in 75% of attempted lesions, with a large variation between sites. Direct PCI for STEMI was performed in 410 cases, representing 7% of the entire workload in the participating catheterisation laboratories. Time delay was within 90 minutes in 76% of direct PCI cases. In keeping with the recommendations of Practice Guidelines, the survey identified under-use of adjunctive medication (IIb/IIIa receptor blockers, statins and ACE inhibitors). Mortality rates at 30 days and 1 year were low in all subgroups. MACE primarily consisted of repeat PCI (12%).

Conclusion: The current Euro Heart Survey on Coronary Revascularisation was performed in the era of bare metal stenting and provides a global European picture of the invasive approach to patients with CAD. These data will serve as a benchmark for the future evaluation of the impact of drug-eluting stents on the practice of interventional cardiology and bypass surgery.

INTRODUCTION

The management of patients with coronary artery disease (CAD) is complex. Better understanding of the pathophysiology of the disease and the introduction of novel diagnostic techniques in conjunction with novel or more powerful pharmacologic and revascularisation therapies mandates continuous reassessment and evaluation of medical practice.[1-6]

Practice Guidelines for diagnostic procedures and patient management are established to help cardiologists in every day clinical decision making. The scientific foundation for these guidelines is provided by randomised clinical trials, although non-randomised trials, retrospective studies or consensus opinion of experts are also used. [7-9]

The European Society of Cardiology (ESC) is dedicated to improve health by reducing the impact of cardiovascular disease, by various means. The Euro Heart Survey programme is meant to evaluate to which extent clinical practice endorses existing guidelines as well as to identify differences in population profiles, patient management and outcome across Europe.[10]

The current survey focuses on patients with at least one >50% diameter stenosis, visualised during coronary angiography, who are potential candidates for coronary revascularisation.

METHODS

The Euro Heart Survey on Coronary Revascularisation was conducted in 130 voluntary participating hospitals from 31 ESC member countries with the objective to evaluate clinical practice, adherence to guidelines, differences in the management and outcome of patients and to assess to what extent the patients of daily practice are represented in randomised clinical trials. Participating hospitals represent both academic (40%) and non-academic (60%) institutions with (83%) and without (17%) cardiac surgery and/or interventional cardiology facilities. These centers were asked to enrol blocks of 40 consecutive patients. The present survey was designed to screen all consecutive patients undergoing invasive diagnostic or therapeutic catheterisation, of which all patients with >50% diameter stenoses in at least one major epicardial vessel were asked to participate. In each hospital, data (550 patient variables and 29 variables per treated coronary segment) were collected by data collecting officers on computers, using the Macro™ software (InferMed, UK) and sent by Internet connection to a central database located at the European Heart House. The used software implemented internal edit checks for missing or contradictory entries or for values out of the normal range. The data management staff of the European Heart House performed additional edit checks. Canadian Class Society functional class (CCS) and Risk stratification were evaluated

prospectively in patients with stable angina.[11,12] The EuroSCORE and TIMI risk score were calculated from the available variables.[13,14]

The survey on coronary revascularisation was conducted between November 2001 and March 2002. One year follow-up was made by personal or telephone contact and available in 4770 patients (83%). Fourteen hospitals (11%) were not able to provide follow-up information. Median (quartiles) follow-up period was 12 month (11-13 month). Statistical analyses were carried out with SPSS statistical software (version 12.0 for Windows), using mostly descriptive statistics between subsets of patients defined by treatment preference. Results are presented as mean and median with corresponding values (standard deviation and inter quartiles, respectively), and percentages. Given the large sample size, P-value of ≤ 0.001 was considered statistically significant.

RESULTS

A total of 7769 patients undergoing coronary angiography were screened of whom 5767 fulfilled the inclusion criteria. Patients with either insufficient or invalid data (n=148) were excluded from further analysis. Therefore, the total population of the present report numbers 5619. The baseline characteristics are summarised in Table 1. Stable angina was the most frequent indication to perform angiography (53%), followed by non-ST segment elevation myocardial infarction or unstable angina (NSTEMI/UA) (30%) and ST elevation myocardial infarction (STEMI) (16%). In 2002 of the screened patients (24%), no CAD or stenosis < 50% was found. Absence of significant CAD differed between patients with acute coronary syndrome (16%) and stable ischemic heart disease (35%) but was most prevalent when CAD was not the primary reason for performing angiography (48%).

Mechanical revascularisation (PCI: 58%, CABG: 21%) was often performed or planned while a substantial number of patients were continued on medical treatment (21%). PCI was predominantly performed in patients admitted with acute coronary syndromes (ACS) with or without ST-segment elevation or unstable angina (53%) while CABG and medical treatment were applied mostly in patients with stable angina (64% and 61%, respectively). Patients who underwent PCI were in general younger, more active and with fewer co-morbid conditions. Patients who received medical therapy had a higher prevalence of previous bypass surgery and myocardial infarction (Table 1).

Of all diseased segments at coronary angiography (15,856), 51% was considered suitable for PCI and 69% for CABG, while 24% of the lesions (1597 patients) were judged as only suitable for CABG, not for PCI. Most of these lesions, unsuitable for PCI were totally occluded (70%) or located in the left main (20%). PCI was predominantly performed in patients with single vessel disease and preserved ventricular function (Table 2). Nonetheless,

Table 1. Clinical characteristics of total cohort and patients in different treatment groups

(proportions are given per column)	Total (n=5619)	PCI (n=3254)	CABG (n=1188)	Medical (n=1177)	
Age (mean, SD)	63.2 ± 10.8	62.4 ±11.2	64.5 ±10.0	64.3 ±10.6	*
Male gender, n (%)	4268 (76)	2448 (75)	933 (79)	887 (75)	
Smoking, n (%):					
Current	1411 (25)	912 (28)	262 (22)	237 (20)	
Past	1924 (34)	1045 (32)	434 (37)	445 (38)	*
Never	2084 (37)	1170 (36)	452 (38)	462 (39)	
Diabetes mellitus, n (%):					
type 1	208 (4)	121 (4)	38 (3)	49 (4)	
type 2	1130 (20)	603 (19)	261 (22)	266 (23)	
Hypercholesterolemia, n (%)	3591 (65)	2130 (67)	737 (64)	724 (64)	
Hypertension, n (%)	3315 (60)	1851 (57)	714 (61)	750 (64)	*
Sedentary lifestyle, n (%)	1601(40)	869 (37)	357 (43)	375 (45)	*
Congestive heart failure, n (%)	1026 (18)	457 (14)	279 (24)	290 (25)	*
Chronic lung disease, n (%)	492 (9)	273 (8)	106 (9)	113 (10)	
Chronic renal failure, n (%)	226 (4)	137 (4)	33 (3)	56 (5)	
Peripheral vascular disease, n (%)	657 (12)	330 (10)	169 (14)	158 (14)	*
Cerebro-vascular disease, n (%)	427 (8)	205 (6)	116 (10)	106 (9)	*
Comorbidity per patient# (mean, SD)	0.5 ±0.8	0.4 ±0.7	0.6 ±0.8	0.6 ±0.8	*
Risk factors per patient≠ (mean, SD)	2.1 ±1.0	2.1 ±0.9	2.1 ±1.0	2.1 ±1.0	
Prior CABG, n (%)	601 (11)	307 (10)	41 (4)	253 (22)	*
Prior PCI, n (%)	1140 (20)	738 (23)	130 (11)	272 (23)	*
Prior myocardial infarction, n (%)	2258 (39)	1168 (36)	448 (38)	542 (47)	*
Diagnosis at admission, n (%):					
Stable angina	2936 (53)	1503 (47)	743 (64)	690 (61)	
Non-ST elevation ACS/ UA	1672 (30)	1014 (31)	331 (28)	327 (29)	*
ST elevation MI	906 (16)	710 (22)	88 (8)	108 (10)	
Hospitalisation in days (median, IQR)†	5 (3-11)	4 (3-8)	12 (7-22)	4 (2-10)	*

≠ risk factors included, smoking (ever), diabetes, hypercholesterolemia and hypertension
comorbidity included, congestive heart failure, chronic lung disease, renal failure, peripheral vascular disease and cerebro-vascular disease
† Data known in 5291 cases (3142 PCI, 1102 CABG, 1047 Medical)
* $p \leq 0.001$

two and three vessel disease was present in 33% and 21%, respectively, suggesting incomplete revascularisation by anatomy. Single vessel PCI was performed in 82% of all cases and the attempted lesions were of type A in 15%, B in 50% and C in 12%. Bypass surgery was mainly performed in patients with three vessel disease (67%), left main stem stenosis (21%) or extensive disease as reflected by the mean number of diseased segments (4.1). The LAD was

diseased in 90% of all patients undergoing CABG and extracorporeal circulation was used in 81% of all operations.

Table 2. Angiographic results based on chosen treatment option

(proportions are given per column)		Total (5619)	PCI (n=3254)	CABG (n=1188)	Medical (n=1177)	
Severity of coronary artery disease, n (%)#:						
	Single-vessel disease	2010 (36)	1469 (45)	87 (7)	454 (39)	
	Two-vessel disease	1701 (30)	1086 (33)	298 (25)	317 (27)	*
	Three-vessel disease	1882 (34)	687 (21)	797 (67)	398 (34)	
	Left main lesions	476 (9)	126 (4)	251 (21)	99 (8)	*
	Mean no. diseased segments, SD	2.8 ±1.9	2.3 ±1.7	4.1 ±1.9	2.9 ±2.1	*
Diseased	% valued as suitable for PCI	51	69	37	32	*
segments:	% valued as suitable for CABG	69	63	91	52	*
Left ventricular function known, n (%):		4854 (86)	2732 (84)	1096 (92)	1026 (87)	
Ejection fraction >50%		2904 (60)	1726 (63)	633 (58)	545 (53)	
Ejection fraction 40 – 50%		1281 (26)	710 (26)	295 (27)	276 (27)	*
Ejection fraction <40		669 (14)	296 (11)	168 (15)	205 (20)	
Intervention within 30 days after CAG, n (%)		3339	2744 (84)	595 (50)	-	
Total no. attempted / diseased segments‡		5426	3564/ 6477 (55)	1862 / 2483 (75)	- / 3404 (0)	
Attempted segments per patient, mean ‡		-	1.30	3.13	-	
Successfully dilated/bypassed segments (%)‡		-	95	96	-	
Procedural technique:	Stenting (%)‡	-	2050 (75)	-	-	
	≥1Arterial Graft (%)‡	-	-	531 (89)	-	

due to missing data (>1%) not counting up to total number of patients

‡ Based on number (%) of patients who underwent the intervention within 30 days after angiography

* $p \leq 0.001$

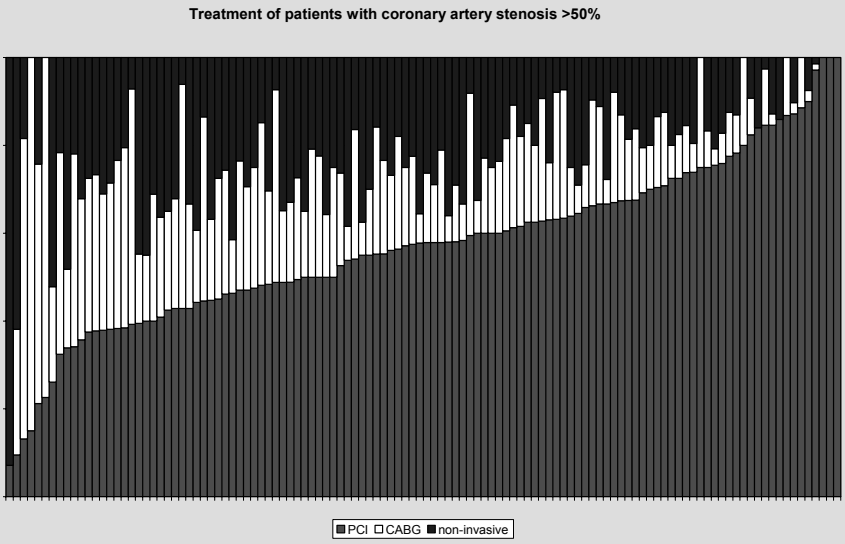
Patients who received medical therapy only, had a higher prevalence of advanced disease in comparison to PCI patients (61 vs 54% multivessel disease, 2.9 vs 2.3 diseased segments). Angiographic profile was worst in those who underwent CABG (92% multivessel disease, 4.1 diseased segments). Noteworthy, patients treated medically had the highest prevalence of poor ventricular function. Although the reason for choosing medical treatment was largely related to the clinical presentation and the severity and extent of CAD, we also observed large differences in treatment options between participating hospitals (Figure 1). Apart from contra-indications for mechanical revascularisation (i.e. vessels not suitable: 34%,

high risk procedure: 17%), 13% of the medically treated patients had refused mechanical revascularisation.

Figure 1.

The percentage of invasive (PCI and CABG) and medically treated patients in hospitals participating in the EHS-CR.

Hospitals are ordered on the basis of patients referred for PCI.

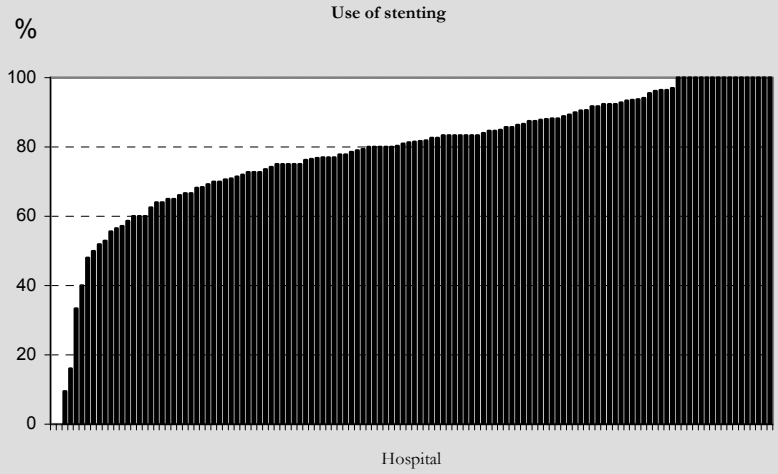


In conjunction with the differences in baseline characteristics, the total and average number of attempted segments differed between PCI and CABG treated patients (Table 2). The large majority of patients undergoing PCI (84%) were treated within 30 days, whereas 50% of CABG patients were treated within this period. The majority of patients undergoing PCI (59%), underwent the procedure within 24 hours after diagnostic angiography. There was a striking high use of stents (applied in 72% of all attempted segments and 75% of PCI patients) while at least one arterial graft was implanted in 89% of the surgical procedures.

Figure 2.

The variation in use of stents per hospital in patients who underwent PCI within 30 days after diagnostic angiography.

It should be noted that the ordering of hospitals differs between the three figures



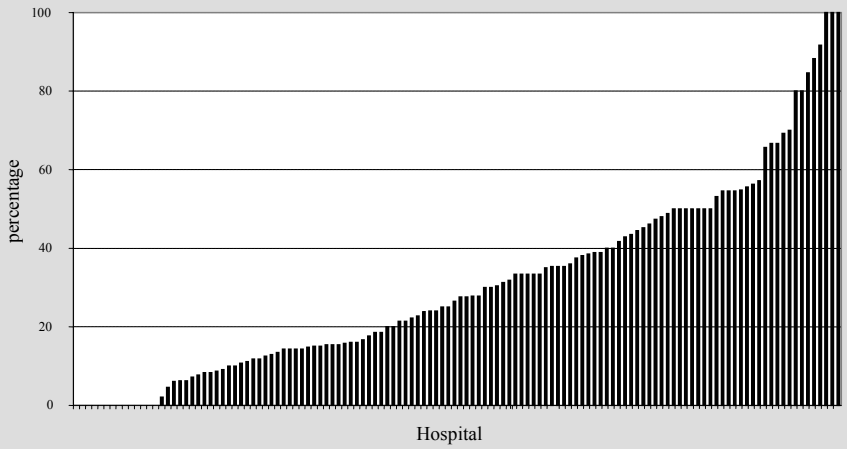
The variation in the use of stents in participating hospitals was huge as illustrated in figure 2. The assessment of procedure-related myocardial injury from serial sampling of necrosis markers was only performed in 61% of PCI and 31% of CABG cases. In accordance with Guidelines, consensus statements and data from clinical trials, PCI patients at increased risk (diabetes, ACS) should receive peri-procedural GP IIb/IIIa receptor blockers. GP IIb/IIIa receptor blockers were used only in 27% of all PCI procedures.

Almost half (46%) of all STEMI patients undergoing primary PCI (n=393), were treated with GP IIb/IIIa receptor blockers. In NSTEMI/UA patients undergoing PCI within 30 days after angiography, 32% received GP IIb/IIIa receptor blockers, mostly because of high risk features (60%). Among PCI patients with stable angina, 14% received GP IIb/IIIa receptor blockers and 23% were on thienopyridine treatment prior to the intervention. No difference in GP IIb/IIIa blocker use was observed between patients with or without diabetes mellitus. Furthermore, we observed large differences in the use of GP IIb/IIIa receptor blockers between the participating hospitals (Figure 3).

Figure 3.

The variation in the use of GP IIb/IIIa receptor blockers per hospital in patients who underwent PCI within 30 days after diagnostic angiography.

It should be noted that the ordering of hospitals differs between the three figures



In most patients with stable angina Canadian Class Society functional class (CCS) was known (96%). Almost two-third of these patients were in CCS class 1 or 2 (Table 3). Patients in CCS 3 or 4 were more likely to be classified as high-risk patients as compared to patients in CCS 1 or 2 (23% versus 13%). Comparison of this risk stratification with the EuroSCORE, revealed a mean score of 3.3 in low-risk, 3.7 in intermediate, and 4.4 in high-risk patients. When calculating the EuroSCORE per treatment-group in patients with stable angina and NSTEMI/UA, we observed a lower risk in PCI patients, as compared to CABG and medically treated patients (Table 4). In NSTEMI/UA patients, the TIMI score was similar amongst the three treatment options (mean score 3.1 ±1.1). Despite proven CAD, a normal ECG was present in 23% of all NSTEMI/UA cases.

Table 3. Risk assessment and outcome in patients with stable angina

		Total	1 yr mortality	1 yr mortality / non-fatal MI	1 yr mortality / non-fatal MI / rehosp for cardiac reason
		2936 (53)			
Canadian Class	CCS 1 or 2	1795 (63)			
Estimated risk	Unknown	203 (11)	5 (3)	9 (4)	51 (25)
	Low (<1% annual mortality)	536 (30)	14 (3)	22 (4)	108 (20)
	Intermediate (1-3% annual mortality)	818 (46)	16 (2)	27 (3)	156 (19)
	High (>3% annual mortality)	238 (13)	10 (4)	13 (6)	59 (25)
	CCS 3 or 4	1037 (37)			
Estimated risk	Unknown	144 (14)	7 (5)	10 (7)	35 (24)
	Low (<1% annual mortality)	158 (15)	8 (5)	10 (6)	42 (27)
	Intermediate (1-3% annual mortality)	496 (48)	18 (4)	26 (5)	120 (24)
	High (>3% annual mortality)	239 (23)	18 (8)	20 (8)	69 (29)

High-risk features or recurrent/persistent angina in NSTEMI/UA patients, and recurrent ischemia or complications in STEMI patients were the most frequent indications for angiography (62% and 42%, respectively). Cardiogenic shock was registered in 8% of STEMI patients. The rate of reperfusion therapy including fibrinolytic treatment and primary PCI in this selected group of STEMI patients who reached the catheterisation laboratory was 64% of which 68% underwent primary PCI. The median time from admission to the intervention was 45 minutes (interquartiles: 15-90 minutes) and the procedure started within 90 minutes after admission in 76 %, indicating that the majority of patients was treated within the advocated timeframe of 90 minutes. It should be noted, however, that no information on in-hospital time delay was available in 28% of patients. Delayed angiography was performed on a systematic basis in 44% of the 513 STEMI patients who did not undergo primary PCI.

Of the 5619 participating patients, 1.9% (104 patients) died within 30 days. The overall 1 year mortality was 4.7% (263 patients). The mortality differed between diagnosis and treatment groups (Table 4). One-year mortality was lowest in patients with stable angina who underwent PCI (1.9%), and highest in STEMI patients not undergoing mechanical revascularisation (8.4%). However, significantly reduced one-year mortality between the three treatment groups was observed only in patients with stable angina, reflecting the large proportion of low-risk patients undergoing PCI.

After one year, 13% of the PCI patients required repeat revascularisation (10% at least one repeat PCI, 3% were operated), whereas only 1% of patients initially treated with CABG

needed repeat revascularisation. A small proportion of patients, who were initially treated medically, eventually underwent mechanical revascularisation (4%). Re-hospitalisation for cardiac reasons was more frequent in PCI and medical patients (28% and 25%, respectively), as compared to those undergoing CABG (15%).

Table 4. Risk assessment and outcome in three different diagnosis groups, based on treatment option

	Total	PCI	CABG	Medical	
Stable angina, n	2936	1503	743	690	
Hospitalisation in days (median, IQR)	3 (2-9)	3 (2-5)	10 (5-18)	3 (2-6)	*
EuroSCORE (mean, SD)	3.8 ±2.7	3.3 ±2.4	4.4 ±3.0	4.2 ±2.6	*
30 day mortality, n (%):	25 (1)	5 (0)	17 (2)	3 (0)	*
Total mortality at 1 year	101 (3)	28 (2)	41 (6)	32 (5)	*
Non-fatal MI‡	41 (2)	24 (2)	8 (1)	9 (2)	
Rehospitalisation for cardiac reason‡	559 (24)	354 (29)	80 (14)	125 (23)	*
(Repeat) revascularisation‡	183 (7)	150 (12)	6 (1)	27 (5)	*
NSTEMI/UA, n	1672	1014	331	327	
Hospitalisation in days (median, IQR)	7 (3-12)	5 (3-10)	16 (9-25)	7 (3-12)	*
EuroSCORE (mean, SD)	5.8 ±2.8	5.4 ±2.6	6.1 ±3.2	6.5 ±2.8	*
30 day mortality, n (%):	35 (2)	19 (2)	8 (2)	8 (2)	
Total mortality at 1 year	82 (5)	41 (4)	17 (5)	24 (7)	
Non-fatal MI ₸	43 (3)	30 (4)	11 (4)	2 (1)	
Rehospitalisation for cardiac reason ₸	376 (29)	249 (31)	48 (19)	78 (31)	*
(Repeat) revascularization ₸	133 (10)	119 (14)	5 (2)	9 (3)	*
STEMI, n (%)	906	710	88	108	
Hospitalisation in days (median, IQR)	7 (4-12)	7 (4-11)	13 (9-27)	9 (4-18)	*
30 day mortality, n (%):	42 (5)	30 (4)	7 (8)	5 (5)	
Total mortality at 1 year	67 (7)	51 (7)	7 (8)	9 (8)	
Non-fatal MI†	18 (3)	13 (3)	2 (3)	3 (4)	
Rehospitalisation for cardiac reason†	148 (23)	122 (24)	7 (11)	19 (24)	
(Repeat) revascularisation†	63 (9)	58 (11)	0	5 (6)	

‡ Data known in 2472 patients (84%) of patients with stable angina (1279 PCI, 608 CABG, 585 Medical).
₸ Data known in 1403 patients (84%) of patients with NonSTEMI/UA (862 PCI, 267 CABG, 274 Medical).
† Data known in 704 patients (78%) of patients with STEMI (550 PCI, 66 CABG, 88 Medical).
* $p \leq 0.001$

At discharge, most patients (>90%) were prescribed at least one anti-thrombotic drug (either aspirin, thienopyridine or anticoagulants), irrespective of treatment allocation (Table 5).

When coronary stenting was performed, 94% were discharged on clopidogrel or ticlopidine. Other prophylactic drug classes, like beta-blockers, ACE-inhibitors and statins were used less frequently. Except for beta-blockers, comparison between the three treatment groups revealed significant differences in prescription profile. At one year follow-up, pharmacological treatment remained unchanged and below the target. Only the use of statins increased from discharge (54%) to one year in patients undergoing CABG (69%), but remained below the target.

Table 5. Pharmacological treatment at discharge

	Total (5619)	PCI (n=3254)	CABG (n=1188)	Medical (n=1177)	
Aspirin, n (%)	4857 (86)	2972 (91)	922 (78)	963 (82)	*
Any anti-thrombotic drug, n (%)†	5356 (95)	3179 (98)	1087 (92)	1090 (93)	*
Bèta-blocker, n (%)	4133 (74)	2442 (75)	833 (70)	858 (73)	
ACE-inhibitor, n (%)	3190 (57)	1845 (57)	590 (50)	755 (64)	*
Statin, n (%)	3740 (67)	2301 (71)	643 (54)	796 (68)	*

† any anti-thrombotic drug includes anti-platelet drugs and coumadin
* $p \leq 0.001$

DISCUSSION

Acute presentations of CAD represented the primary indication for diagnostic angiography in 46% of all cases while in patients with stable angina, the selection of patients to undergo diagnostic angiography was based on symptomatic status and/or risk evaluation. In line with previous reports, we observed a global normalcy rate of 24%.[10,15] This proportion was higher when the primary diagnosis leading to the angiography was stable angina rather than acute CAD. An indication for mechanical revascularization followed the diagnostic angiogram in 57% of all cases screened and in 79% of those with at least one significant stenosis, indicating appropriate use of this invasive and expensive diagnostic procedure. This survey of current practice in Europe shows a clear preference for PCI over CABG (ratio 3:1), possibly suggesting under-use of the more invasive bypass operation.[16]

In accordance with Guidelines, patients selected for CABG were sicker and had more extensive CAD; however, a sizable proportion of patients with multivessel or left main disease, impaired left ventricular function or diabetes did not undergo bypass surgery.

Patient and/or physician preference as well as the shorter time delay between angiography and PCI (versus between angiography and CABG) may have contributed to this choice. In patients with multivessel disease, recent meta-analyses show no difference in the

rate of major irreversible adverse events between PCI and CABG.[17,18] However, after one year follow-up, repeat PCI was performed in 10 % and 3% eventually required CABG, indicative of the lower durability of the result after PCI. Coronary stenting using bare metal devices was applied in 72% of all segments and PCI was limited to a single vessel in 82% of cases. Use of stents varied widely from 0% in 2 hospitals to 100% in 17 hospitals, a wide range that probably relates to differences in local reimbursement policies. It should be remembered that all data from the current survey have been acquired prior to the clinical availability of drug-eluting stents. Increased availability of these more durable devices will likely increase the confidence of interventional cardiologists in treating more complex patient and/or lesion subsets by means of PCI.[19]

Another proportion of patients who were at high-risk did not undergo revascularisation. This probably results from the limitations of currently available mechanical revascularization procedures in treating diffuse disease, or from the poor general condition of some patients unable to undergo an invasive treatment, or from estimated unacceptably high procedural risks.

Despite their proven beneficial effects in high-risk patients (e.g. diabetes) and/or procedures,[20,21] overall a sizable proportion of patients fulfilling these criteria did not receive GP IIb/IIIa receptor blockers. In addition, major variations across European hospitals in the use of GP IIb/IIIa receptor blockers were observed. Most surprising was the low use of these drugs in diabetic patients undergoing PCI for stable angina (15%). Also of concern was the failure to measure post-procedural necrosis markers in 39% of all PCI procedures. Increased levels of cardiac enzymes are indeed an independent predictor of cardiac mortality and subsequent myocardial infarction.[22,23] Similarly, in patients undergoing CABG, necrosis markers were measured in only one-third, most likely reflecting the disputable value of these markers following surgery.[24]

As to the treatment of STEMI, this survey concurs with previous studies in showing that reperfusion treatment remains underused,[25] even in this selected subgroup of patients referred for angiography. By design, we cannot analyze the factors that contribute to this sobering observation. In accordance with the Guidelines, primary PCI is the preferred treatment for STEMI, provided this procedure can be performed by an experienced team within 90 minutes after first medical contact.[9] It was encouraging to observe that the majority of patients undergoing primary PCI were treated within the advocated timeframe of 90 minutes. However, due to missing admission or procedure times, the in-hospital delay was unknown in a sizeable proportion of patients. The current prospective survey clearly shows that in clinical practice, reporting of all relevant time intervals was not optimal. This failure stresses the importance of a thorough registration as well as the need for implementing in

each institution appropriate procedures and pathways that will permit to select the optimal treatment for an individual patient.[26,27]

The overall mortality figures were low (1.9% at 30 days and 4.7% at 1 year) in all patient groups and treatment modalities, even after risk-adjustment using for instance the EuroSCORE. As expected, one year mortality rate was larger in STEMI (7%) and in NSTEMI/UA (5%) compared to stable angina patients (3%).

Patients with established CAD enrolled in this survey should benefit from secondary prevention measures.[28] Changing the patient risk behaviour (unhealthy diet, smoking, sedentary lifestyle) and prescribing drugs with proven prophylactic effects are essential aspects of current treatment, even after mechanical revascularisation.[29-33] Furthermore, effective secondary prevention in clinical practice, using evidence-based treatment, has been proven effective in reducing the composite of death, myocardial infarction and stroke.[34,35] Although the majority of patients used anti-thrombotics and beta-blockers, as recommended, ACE-inhibitors were underused in all subgroups and statins were particularly underused after CABG. Overall, prescription of these prophylactic drugs was increased as compared to EuroAspire II,[36] indicating that time is required before Guidelines are progressively endorsed. In any case, the moment that patients are admitted in the hospital to undergo an invasive procedure should be taken as an opportunity to further optimise their pharmacological treatment.

The limitations of this study are those inherent to observational surveys involving voluntarily participating hospitals. Although we have attempted to include a wide spectrum of hospitals in different countries, almost certainly the results are biased towards better than average practices. The sample size only represents a small fraction of all patients admitted in catheterisation laboratories throughout Europe during the study period. Nevertheless, because patient inclusion was consecutive at the participating sites, we trust that the Survey depicts the ongoing clinical practice. Data on the one year follow-up were not obtainable in 14 hospitals (from 10 countries) due to management problems unrelated to individual patient characteristics. Presumably this did not introduce significant selection bias. Data quality was checked through queries for missing or contradictory entries. However, no site visits or source data verification were performed. However, since many participating sites are part of other Euro Heart Surveys, their performance is regularly evaluated.

To summarize, the current Euro Heart Survey on Coronary Revascularisation provides a global European picture of the invasive approach to patients with CAD, as they present with either stable angina, STEMI or NSTEMI/UA. While the recommendations of Guidelines are mostly endorsed, the main area for improvement pertains to the under-use of adjunctive pharmacology (GP IIb/IIIa inhibitors, statins and ACE inhibitors). These data on the

indications for revascularisation, the choice between PCI or CABG and their outcome in the era of bare metal stenting will serve as a benchmark for the future evaluation of the impact of drug-eluting stents on the practice of coronary revascularisation.

REFERENCES

1. Braunwald E. Cardiovascular Medicine at the Turn of the Millennium: Triumphs, Concerns, and Opportunities. *N Engl J Med* 1997;337:1360-1369.
2. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *The Lancet* 1994;344:1383-1389.
3. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *The Lancet* 1995;345:669-682.
4. Yusuf S LJ, Jha P, Lonn E. Primary and secondary prevention of myocardial infarction and strokes: an update of randomly allocated, controlled trials. *J Hypertens Suppl* 1993;11:S61-73.
5. Cleland JGF. For Debate: Preventing atherosclerotic events with aspirin. *BMJ* 2002;324:103-105.
6. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJRM, Schonberger JPAM, Buller N, Bonser R, van den Brand MJB, van Herwerden LA, Morel M-AM, van Hout BA, The Arterial Revascularization Therapies Study Group. Comparison of Coronary-Artery Bypass Surgery and Stenting for the Treatment of Multivessel Disease. *N Engl J Med* 2001;344:1117-1124.
7. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 1997;18:394-413.
8. Bertrand ME SM, Fox KA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W; Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002;23:1809-40.
9. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KAA, Julian D, Lengyel M, Neumann FJ, Ruzyllo W, Thygesen C, Underwood S R, Vahanian A, Verheugt FWA, Wijns W. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2003;24:28-66.
10. Boersma H DG, Bloemberg BPM, Wood DA, Kromhout D, Simoons ML. Cardiovascular diseases in Europe. European registries of cardiovascular diseases and patient management. *Sophia Antipolis: European Society of Cardiology*. 1999.
11. Campeau L. Letter: Grading of angina pectoris. *Circulation* 1976;54:522-523.
12. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 1999;33:2092-2197.
13. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16:9-13.
14. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST

elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-842.

15. Maier W, Enderlin MF, Bonzel T, Danchin N, Heyndrickx G, Muhlberger V, Neuhaus KL, Piscione F, Reifart N, Antoni J, Ogurol Y, Wischnewsky MB, Meier B. Audit and quality control in angioplasty in Europe: procedural results of the AQUA Study 1997: assessment of 250 randomly selected coronary interventions performed in 25 centres of five European countries. *Eur Heart J* 1999;20:1261-1270.
16. Hemingway H, Crook AM, Feder G, Banerjee S, Dawson JR, Magee P, Philpott S, Sanders J, Wood A, Timmis AD. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med* 2001;344:645-654.
17. Pocock SJ, Henderson RA, Rickards AF, Hampton JR, King SB 3rd, Hamm CW, Puel J, Hueb W, Goy JJ, Rodriguez A. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;346:1184-1189.
18. Mercado N, Wijns W, Serruys PW, Sigwart U, Flather MD, Stables RH, O'Neill WW, Rodriguez A, Lemos PA, Hueb WA, Gersh BJ, Booth J, Boersma E. One-Year Outcomes of Coronary Artery Bypass Graft Surgery versus Percutaneous Coronary intervention with Multiple Stenting for Multisystem Disease: A Meta-Analysis of Individual Patient Data from Randomized Clinical Trials. J Thorac Cardiovasc Surg (accepted for publication, 2004).
19. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 2004;109:190-195.
20. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189-198.
21. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, Hamm CW, Moliterno DJ, Califf RM, White HD, Kleiman NS, Theroux P, Topol EJ. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation* 2001;104:2767-2771.
22. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr; American College of Cardiology; American Heart Association Task Force on Practice Guidelines. Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 2001;37:2215-2239.

23. Kong TQ, Davidson CJ, Meyers SN, Tauke JT, Parker MA, Bonow RO. Prognostic implication of creatine kinase elevation following elective coronary artery interventions. *JAMA* 1997:277:461-466.
24. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA; American College of Cardiology; American Heart Association. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 2004;110:e340-437.
25. Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, Fioretti PM, Simoons ML, Battler A. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J* 2002;23:1190-1201.
26. Mehta RH, Montoye CK, Faul J, Nagle DJ, Kure J, Raj E, Fattal P, Sharrif S, Amlani M, Changezi HU, Skorcz S, Bailey N, Bourque T, LaTarte M, McLean D, Savoy S, Werner P, Baker PL, DeFranco A, Eagle KA; American College of Cardiology Guidelines Applied in Practice Steering Committee. Enhancing quality of care for acute myocardial infarction: shifting the focus of improvement from key indicators to process of care and tool use: the American College of Cardiology Acute Myocardial Infarction Guidelines Applied in Practice Project in Michigan: Flint and Saginaw Expansion. *J Am Coll Cardiol* 2004;43:2166-2173.
27. Mukherjee D, Eagle KM. Improving quality of care in the real world: Efficacy versus effectiveness? *Am Heart J* 2003;146:946-947.
28. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D; Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003;24:1601-1610.
29. Arnold JM, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, Lonn E, Pogue J, Bosch J; HOPE Investigators. Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation* 2003;107:1284-1290.
30. Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B, Meier B; Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215-3222.
31. Fox KM; EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-788.

32. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;108:1682-1687.
33. Budaj A, Brieger D, Steg PG, Goodman SG, Dabbous OH, Fox KA, Avezum A, Cannon CP, Mazurek T, Flather MD, Van De Werf F; GRACE Investigators. Global patterns of use of antithrombotic and antiplatelet therapies in patients with acute coronary syndromes: insights from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2003;146:999-1006.
34. Chan AW, Bhatt DL, Chew DP, Quinn MJ, Moliterno DJ, Topol EJ, Ellis SG. Early and sustained survival benefit associated with statin therapy at the time of percutaneous coronary intervention. *Circulation* 2002;105:691-696.
35. Mukherjee D, Lingam P, Chetcuti S, Grossman PM, Moscucci M, Luciano AE, Eagle KA. Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: insights from the University of Michigan Peripheral Vascular Disease Quality Improvement Initiative (PVD-QI2). *Circulation* 2002;106:1909-1912.
36. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001;22:554-572.

Management of patients in daily clinical practice

Chapter 3

Patients enrolled in coronary intervention trials are not representative of patients in clinical practice

Patients enrolled in coronary intervention trials are not representative of patients in clinical practice.

Results from the Euro Heart Survey on Coronary Revascularization.

M Hordijk, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
M.J. Lenzen, Rotterdam, the Netherlands
W. Wijns, Aalst, Belgium
P.P.T. de Jaegere, Rotterdam, the Netherlands
M.L. Simoons, Rotterdam, the Netherlands
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
M.E. Bertrand, Lille, France
N.F. Mercado, Rotterdam, the Netherlands
E. Boersma, Rotterdam, the Netherlands

European Heart Journal (2006) **27**: 671-678

ABSTRACT

Aims: Revascularization in patients with coronary artery disease changed over the last two decades, favouring the number of patients treated by means of percutaneous coronary interventions (PCI) as compared to coronary artery bypass grafting (CABG). Many randomised controlled trials (RCTs) have been performed to compare these two competing revascularization techniques. Due to the strict enrolment criteria of RCTs in which highly selected patients are recruited, the applicability of the results may be limited in clinical practice. The current study evaluates to what extent patients in clinical practice were similar to those who participated in RCTs comparing PCI with CABG.

Methods and Results: Clinical characteristics and 1-year outcome of 4,713 patients enrolled in the Euro Heart Survey on Coronary Revascularization were compared with 8,647 patients who participated in 14 major RCTs, comparing PCI with CABG. In addition, we analysed which proportion of survey patients would have disqualified for trial participation (n=3033, 64%), aiming at identifying differences between trial-eligible and trial-ineligible survey patients. In general, important differences were observed between trial participants and survey patients. Patients in clinical practice were older, more often had comorbid conditions, single vessel disease, and left main stem stenosis as compared to trial participants. Almost identical differences were observed between trial-eligible and trial-ineligible survey patients. In clinical practice, PCI was the treatment of choice, even in patients who were trial-ineligible (46% PCI, 26% CABG, and 28% medical). PCI remained the preferred treatment option in patients with multivessel disease (57% in trial-eligible and 40% in trial-ineligible patients, respectively, $p<.001$); yet, the risk profile of patients treated by PCI was better than for patients treated either by CABG or medical therapy. In the RCTs, there was no mortality difference between PCI and CABG. In clinical practice, however, we observed one-year unadjusted survival benefit for PCI vs. CABG (2.9 vs. 5.4%, $p<0.001$). Survival benefit was only observed in trial-ineligible patients (3.3 vs. 6.2%, $p<0.001$).

Conclusion: Many patients in clinical practice were not represented in RCTs. Moreover, only 36% of these patients were considered eligible for participating in a trial comparing PCI with CABG. We demonstrated that RCTs included younger patients with a better cardiovascular risk profile as compared to patients in every day clinical practice. This study highlights the disparity between patients in clinical practice and patients in whom the studies that provide the evidence for treatment guidelines are performed.

INTRODUCTION

Cardiovascular diseases are the major cause of mortality in the western world, and it is expected that this will remain so during the foreseeable future.[1-3] Treatment of patients with coronary artery disease (CAD) includes risk factor management, drug therapy and revascularization techniques. The last decades, changes in revascularization techniques were observed, favouring the number of patients treated by means of percutaneous coronary interventions (PCI) as compared to the more invasive coronary artery bypass grafting (CABG). As these competitive techniques are both feasible in many patients, randomized controlled clinical trials (RCTs) have been performed in order to compare the two procedures. Based on these RCTs, the results of registries and consensus of experts, international societies developed guidelines in order to support physicians in clinical decision making.[4-7] In these guidelines, RCTs are valued as the highest level of evidence in the ranking order. It should be noted however, that RCTs have strict enrolment criteria. Consequently, patients who participate in trials may represent a selected group of patients that is poorly representative of the majority of patients treated in routine clinical practice.[8] This may complicate the applicability of the results of clinical trials in everyday practice and limit the generalisability of recommendations.[9]

In the current study, we aimed to evaluate to what extent patients in clinical practice were similar to those who participated in randomized clinical trials comparing CABG with PCI. Patient outcome was compared as well between the selected treatment options.

METHODS

We performed a comparison between participants in RCTs and patients enrolled in the Euro Heart Survey on Coronary Revascularization (EHS-CR). Details of the survey were published previously.[10] Briefly, between September 2001 and March 2002, a total of 5.619 patients from 130 hospitals throughout 31 countries belonging to the ESC were included in this survey. All consecutive patients entering the catheterization laboratory were screened, and patients with >50% diameter stenosis in at least one major epicardial vessel were asked to participate. Data were collected on medical history, demography, clinical, hemodynamic and angiographic status, and sent by Internet connection to a central database located at the European Heart House. A follow up was performed at 1-year (median 11-13 months). Follow up information, including vital status, was available in 83%, as 14 hospitals (11%) were not able to provide follow up information. The survey was approved by the relevant national authorities.

Selection of Trials

We intended to identify all major randomised phase III clinical trials of CABG versus PCI which were published in the English language during 1980-2005, using the Medical Subject Heading terms "angioplasty, transluminal, percutaneous coronary", "coronary artery bypass", "randomized controlled trial", and "comparative study", as was used in a recent meta-analysis by Hoffman et al.[11] We identified 15 major trials comparing initial strategies of PCI and CABG. Since the AWESOME trial[12] included patients that would have been excluded in the other trials (i.e. patients with severe heart failure or very recent myocardial infarction), this trial was excluded from the analysis. Table 1 shows the characteristics of 14 trials with a total of 8647 patients that were selected for this analysis. In 10 of these trials, only patients with multivessel coronary disease were included while in one trial patients with single or multivessel disease could be enrolled.[8,13-22] In the remaining three trials, only patients with single vessel disease were included.[23-25] Medical therapy alone was added to the two invasive treatment options in one trial.[22,24] The tabulated patient characteristics, as presented in the main publication article of the separate clinical trials were compiled in an electronic database and the data were pooled. In case of a discrepancy between the text of the manuscript and a table, we used the values as shown in the tables.

Selection of Patients

Patients enrolled in the EHS-CR were considered eligible for the comparison between trial participants and clinical practice unless the primary diagnosis was ST-elevation myocardial infarction (n=4713), as these patients were excluded from all trials comparing CABG with PCI. In addition, we analysed which proportion of survey patients would have been disqualified for participation in a coronary intervention trial, aiming at separating trial-eligible from trial-ineligible patients in our clinical practice population. Since all patients in this survey had at least one >50% diameter stenosis in a major epicardial vessel, we considered patients as trial-eligible if no major exclusion criteria were observed. As Table 2 clearly reveals, we only selected the most important exclusion criteria. If we would use the enrolment criteria of the individual trials that we were able to identify in our database, approximately 11-25% of the survey patients would be eligible for participation in the individual trials. However, by using only major exclusion criteria, we aimed at comparing an average of patients as seen in clinical practice with RCT participants, decreasing the risk of identifying a highly selective group of survey patients. It should be noted, however, this selection is, by necessity, crude. We also would like to state that defining patients from clinical practice as trial-eligible or trial-ineligible was done in retrospect.

Table 1. Characteristics of the major coronary intervention trials comparing CABG with PCI^.

Study	No. of patients	Publication year	Vessel disease	Trial exclusion criteria	Outcome (CABG vs. PCI, respectively)				
					Follow-up	Mortality	Non-fatal MI	Repeat revasc.	P (death/MI)
ERACI [13]	127	1993	multi	left main disease, EF* ≤ 35%, valvular disease	1 yr	0 - 3%	2 - 3%	3 - 32%	.17
RITA [14]	1011	1993	multi / single	prior PCI, prior CABG, left main disease, valvular disease	2.5 yr	4 - 3%	5 - 7%	7 - 31%	.50
Lausanne [23]	134	1994	single	prior PCI, prior CABG, EF ≤ 50%	2.5 yr	2 - 0%	3 - 12%	3 - 25%	ns§
EAST [15]	392	1994	multi	prior PCI or CABG, left main disease, EF ≤ 25%, PCI or CABG unsafe	3 yr	6 - 7%	20 - 15%	13 - 54%	.81
GABI [16]	359	1994	multi	prior PCI, prior CABG, age ≥ 75 years, left main disease	1 yr	6 - 3%	7 - 4%	3 - 39%	<.05†
CABRI [8]	1054	1995	multi	prior PCI or CABG, age ≥ 76 years, left main disease, EF ≤ 35%, valvular disease	1 yr	3 - 4%	--	13 - 66%	.30‡
MASS [24]	214	1995	single	prior PCI, prior CABG, left main disease, left ventricular dysfunction, valvular disease	3 yr	1 - 1%	1 - 3%	0 - 29%	ns§
BARI [17]	1829	1996	multi	prior PCI or CABG, age ≥ 80 years, left main disease, valvular disease, unsuitable for CABG or PCI	5.4 yr	11 - 14%	20 - 21%	8 - 54%	.84
Toulouse [18]	152	1997	multi	prior PCI, prior CABG, left main disease, valvular disease, contraindication to CABG or PCI	5 yr	11 - 13%	1 - 5%	9 - 29%	.69‡
SIMA [25]	121	2000	single	prior PCI, prior CABG, EF ≤ 45%	2.4 yr	3 - 2%	7 - 7%	0 - 24%	.90
ERACI II [19]	450	2001	multi	prior stenting, PCI in last year, prior CABG, older age, EF ≤ 35%	1.5 yr	8 - 3%	6 - 2%	5 - 17%	<.05†
ARTS [20]	1205	2001	multi	prior PCI, prior CABG, concomitant valve surgery	1 yr	3 - 3%	4 - 5%	4 - 17%	.71
SoS [21]	988	2002	multi	prior thoracotomy, prior coronary revascularisation, valvular disease, EF ≤30%	2 yr	2 - 5%	8 - 5%	6 - 21%	.80
MASS II[22]	611	2004	multi	prior PCI, prior CABG, valvular disease, left main, contraindication to CABG or PCI, EF <40%	1 yr	4 -5%	2 – 8%	1 - 13%	<.05†

^ CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention
* EF = ejection fraction
Ŧ All cardiac events includes: coronary angiography, revascularisation, angina
§ Actual p value not given, but difference stated as non-significant
† Actual p value not given, but difference stated as significant
‡ Only mortality

Statistical analyses

Differences in baseline characteristics between survey patients and pooled intervention trials were analysed by chi-square tests, using EpiInfo (version 5.0). To analyse continuous variables we used the highest standard deviation presented in the selected coronary intervention trials. Comparison between trial-eligible and trial-ineligible survey patients was analysed by chi-square tests, Fisher's exact tests or t-tests as appropriate, using SPSS for Windows (version 12.0). Data are presented as percentage and 95% confidence interval (95%, C.I.), unless indicated otherwise. A p-value of <.001 was considered significant (two-sided).

As we acknowledged the fact that patients, who were treated medically, differ considerable from those who were intended to undergo revascularization we repeated all analyses excluding medically treated patients. As the results of these analyses were highly consistent, we report our original choice on the basis of all three treatment groups (i.e. PCI, CABG, and medical).

RESULTS

In total 8647 patients enrolled the identified RCTs that compared CABG with PCI. The duration of follow-up varied between 1 and 5.4 years. As table 1 visualizes, the competitive procedures differed hardly in survival rates and non-fatal myocardial infarction. The need for repeat revascularization, however, differed largely between the two revascularization techniques, favouring CABG.

Table 2. Major exclusion criteria, used in RCTs[8,13-25] applied to patients included in this study.

		RCTs	EHS-CR
	Exclusion criteria	Number of trials	Number of patients (%)
A	Age ≥ 80 years	2	195 (4)
B	Prior PCI	13	1054 (22)
C	Prior CABG	13	566 (12)
D	Ejection fraction ≤ 35%	5	294 (6)
E	Left main disease	8	427 (9)
F	Valvular heart disease	8	319 (7)
G	CABG or PCI not suitable	14	1757 (37)
Three of the above	(B,C,G)	14	2585 (55)
Five of the above	(B,C,D,E,G)	14	2841 (60)
Any of the above	(A – G)	14	3033 (64)

Based on the selection of major exclusion criteria, we estimated that almost two-third (n=3033, 64%) of the 4713 EHS-CR patients would have disqualified for trial participation (Table 2). Most frequently observed obstacles for trial participation were prior

revascularization and non suitability of the diseased vessels for CABG and/or PCI. The remaining 36% (n=1680) was considered trial-eligible.

Table 3. Characteristics of patients enrolled in randomised trials as compared to EHS-CR patients*.

Characteristics	Pooled trials	Number of trials	EHS-CR	P^1	EHS-CR mvd‡	P^2
Patients (n)	8647	[14]	4713		3081	
Mean age, yr (sd)	60 ±12	[12]	63 ±11	< .01	64 ±10	<.01
Male gender (%, 95%CI)	77 (76-78)	[14]	76 (75-77)	.29	77 (76-79)	.40
History (%, 95%CI)						
Hyperlipidemia	56 (54-57)	[8]	67 (66-69)	<.001	68 (67-71)	<.001
Hypertension	47 (46-48)	[12]	62 (60-63)	<.001	63 (62-66)	<.001
Diabetes	20 (19-20)	[13]	24 (22-26)	<.001	27 (25-28)	<.001
Peripheral vascular disease	8 (7-9)	[5]	13 (12-14)	<.001	14 (13-16)	<.001
Renal failure	n.a.	[14]	4 (4-5)	--	6 (5-7)	--
Prior myocardial infarction	44 (43-45)	[13]	41 (39-42)	<.001	44 (42-46)	.91
Congestive heart failure	n.a.	[14]	17 (16-19)	--	20 (19-21)	--
Cerebro-vascular disease	4 (4-5)	[4]	8 (7-9)	<.001	9 (8-10)	<.001
Presentation(%, 95%CI)						
Unstable angina	42 (41-43)	[8]	35 (34-37)	<.001	35 (33-37)	<.001
Stable angina	n.a.	[15]	62 (61-64)	--	63 (61-65)	--
CCS 3-4 (%)	42 (41-43)	[7]	35 (34-37)	<.001	39 (37-41)	.006
Chronic medication (%, 95%CI)						
Antiplatelet agents	83 (81-84)	[4]	85 (84-86)	.02	86 (84-87)	.006
ACE-i/ Angiotensin-II blockers	23 (20-26)	[2]	50 (49-51)	<.001	52 (50-53)	<.001
Bèta-blocker	68 (66-69)	[6]	69 (67-70)	.35	70 (68-71)	.12
Calcium-antagonist	65 (63-66)	[6]	28 (26-29)	<.001	28 (27-30)	<.001
Nitrates	61 (59-63)	[6]	56 (54-57)	<.001	59 (57-61)	.30
Statins	n.a.		52 (51-54)	--	52 (50-54)	--
Coronary angiogram (%, 95%CI)						
Diseased left anterior descending	73 (72-75)	[11]	74 (72-75)	.73	86 (84-87)	<.001
Diseased right coronary artery	68 (66-69)	[4]	62 (60-63)	<.001	78 (78-81)	<.001
Diseased left circumflex	69 (67-71)	[4]	59 (57-60)	<.001	79 (77-80)	<.001
Diseased left main stem	2 (1-3)	[2]	9 (8-10)	<.001	14 (13-15)	<.001
Number of diseased vessels				<.001		--
1	11 (10-12)	[14]	35 (33-36)		0	
2	53 (52-55)	[14]	31 (29-32)		47 (45-49)	
3	35 (34-36)	[14]	34 (33-36)		53 (51-54)	
Treatment (preference/option) (%)				--		--
PCI	49		54		46 (44-47)	
CABG	48		23		33 (31-35)	
Medical only	3		23		21 (20-23)	

* Patients, admitted with ST-elevation infarction were excluded
‡ MVD= multi vessel disease
P^1 pooled trials versus EHS-CR population
P^2 pooled trials versus EHS-CR population with MVD

There were important differences in clinical and angiographical characteristics between participants of the identified RCTs and patients as seen in clinical practice (Table 3). In general, patients in clinical practice were older and more often had comorbid conditions as compared to trial participants. Interestingly, unstable angina was more frequent in trial populations as well as in trial-eligible patients. As most RCTs included only patients with

multivessel disease, we identified survey patients with multivessel disease and compared this major subgroup (65%) with those who participated in RCTs. On top of the observed differences between survey patients and trial participants, patients enrolled in the EHS-CR with multivessel disease were more likely to have three-vessel disease as compared to trial participants.

Table 4. Comparison between trial-eligible and trial-ineligible EHS-CR patients.

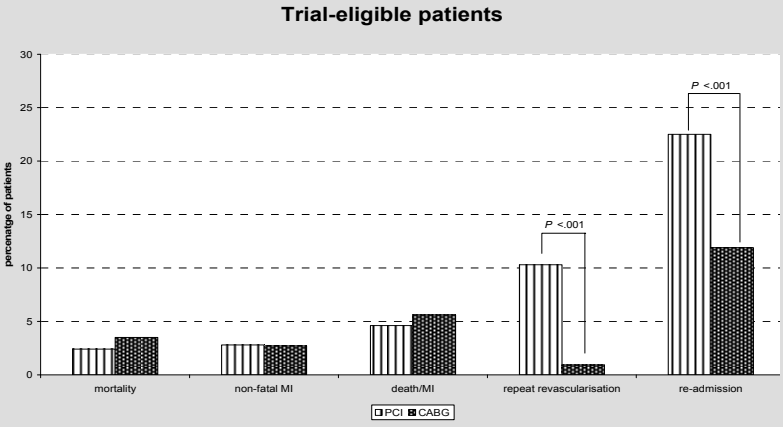
Patient characteristics	**Trial-eligible EHS-CR patients**	**Trial-ineligible EHS-CR patients**	***P***
Patients (n)	1680	3033	
Mean age, yr (±sd)	62 ±10	64 ±11	<.001
Male gender (%, 95%CI)	74 (72-76)	77 (75-78)	.052
History (%, 95%CI)			
Hyperlipidemia	66 (64-69)	68 (67-70)	.23
Hypertension	59 (57-61)	63 (61-65)	.006
Diabetes	21 (19-23)	26 (25-28)	<.001
Peripheral vascular disease	10 (8-11)	14 (13-15)	<.001
Renal failure	3 (2-4)	5 (4-6)	<.001
Prior myocardial infarction	32 (30-35)	46 (43-47)	<.001
Congestive heart failure	12 (11-14)	20 (19-22)	<.001
Cerebrovascular disease	7 (6-9)	8 (7-9)	.31
Presentation (%, 95%CI)			
Unstable angina	41 (39-44)	32 (30-34)	<.001
Stable angina	57 (55-59)	65 (64-67)	<.001
CCS class 3-4 (%)	35 (31-37)	36 (34-38)	.21
Chronic medication (%, 95%CI)			
Antiplatelet agents	85 (83-86)	85 (84-86)	.76
ACE-inhibitors/ Angiotensin-II blockers	45 (42-47)	53 (51-55)	<.001
Bèta-blocker	68 (66-71)	69 (67-70)	.69
Calcium-antagonist	25 (23-27)	29 (28-31)	.003
Nitrates	54 (52-56)	56 (55-58)	.11
Statines	46 (44-49)	55 (44-49)	<.001
Coronary angiogram (%, 95%CI)			
Diseased left anterior descending	73 (71-76)	74 (72-75)	.78
Diseased right coronary artery	58 (56-61)	64 (62-65)	<.001
Diseased left circumflex	54 (52-57)	61 (59-63)	<.001
Diseased left main stem	0	14 (13-15)	<.001
Number of diseased vessels			<.001
1	40 (37-42)	32 (30-33)	
2	34 (31-36)	29 (27-31)	
3	26 (24-28)	39 (37-41)	
RISK SCORE (mean, ±sd)			
EuroSCORE*	3.6 ±2.3	5.0 ±3.0	<.001
Treatment (preference/option) (%)			<.001
PCI	69	46	
CABG	19	26	
Medical only	13	28	

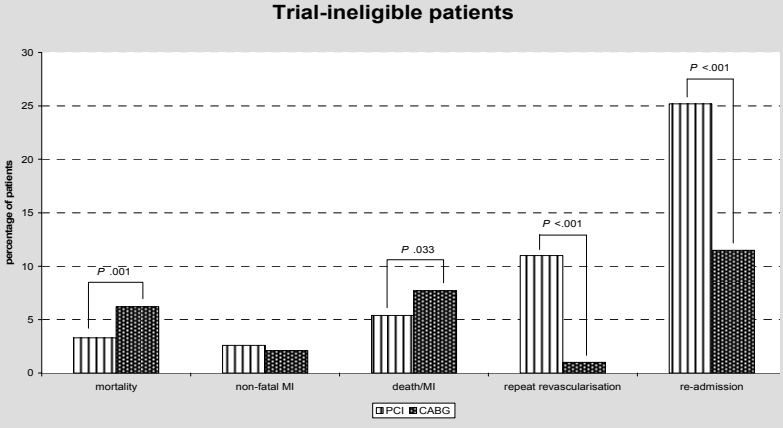
*) EuroSCORE was calculated from the available variables [31]

PCI was clearly the preferred treatment in clinical practice, whereas CABG and medical treatment was evenly distributed in RCTs, the choice of treatment being dictated by randomisation. In contrast to the observed differences, it is important to note that the under-representation of women as seen in RCTs was also observed in clinical practice.

Within the study population, a comparison between trial-eligible and trial-ineligible patients was made, and revealed that patients who would be excluded from trial participation had a worse clinical profile as compared to trial-eligible patients (Table 4). Trial-ineligible patients were older, more likely to have a comorbid condition, and had a higher proportion of diseased coronary arteries including left main stenosis. By means of the EuroSCORE, trial-ineligible patients would have a higher estimated peri-procedural risk. These trial-ineligible patients were treated more often surgically or medically as compared to trial-eligible patients, though PCI remained the treatment of choice. When excluding patients with single vessel disease from the analyses, PCI remained the preferred treatment option in 57% of trial-eligible, and 40% of trial-ineligible patients (p<.001). CABG did not differ between patients with multivessel disease in the two subgroups (31 vs. 34%, respectively). The majority of patients with left main disease (n=427) was treated by means of CABG (n=239), whereas 96 patients were treated percutaneously and 92 did not undergo revascularization. Of the 96 patients undergoing PCI, the left main was not protected by means of a prior CABG in 45 patients (47%).

Figure 1. Outcome at 1 year





Identical to the outcomes in RCTs, the most important difference between PCI and CABG was observed in the lower need for repeat revascularizations in CABG patients (Figure 1). In contrast to the trials, the overall

unadjusted one-year survival differed between PCI and CABG (2.9 versus 5.4%, p <0.001). As figure 1 clearly reveals, this survival benefit in PCI patients was only observed in those who would be excluded from trial participation (3.3 versus 6.2%, p <0.001). In trial-eligible patients neither treatment had a clear advantage over the other for preventing death.

DISCUSSION

This study revealed that participants of RCTs are not representative of patients treated in daily clinical practice. Moreover, only a minority of patients in clinical practice (36%) were potentially eligible for participation in one of the RCTs. These trial-eligible patients had a different clinical profile as compared to RCT participants.

The importance of this finding is related to the fact that RCTs are valued as highest in the hierarchy of evidence that is used in the guidelines and for the formulation of recommendations. That patients enrolled in these trials may not be representative for the general clinical practice[26], obviously depends on the in- and exclusion criteria. As the result of this and other factors such as physician preference, 58-96% of the screened patients and 84-98% of the eligible patients are eventually not enrolled.[8,13,15-17,23,27] As a result, many RCTs are known to have a limited generalisability.[9,28]

These observations highlight the difficulties experts have in writing guidelines, as well as for clinicians who have to choose the most appropriate treatment for individual patients. In addition to this, observational studies can be useful adjuncts to RCTs, as they are more likely to reflect clinical practice, and consequently can provide information on subpopulations that were disregarded in trials, as well as on the effectiveness of evidence-based treatments in routine practice.

Regarding the observed differences between RCT participants and patients enrolled in the EHS-CR, we would like to address the under-representation of women (25%) in both groups (i.e. pooled RCTs and the EHS-CR). This observation erroneously suggests that men are more likely to have CAD. In fact, approximately 50% of all patients with CAD are known to be women, though women are approximately 10 years older.[29] Apparently, and in line with previous findings, women are less likely to undergo invasive investigations and consequently revascularization.[30,31]

As most trials included only patients with multivessel disease, it was no surprise to observe that patients with two-vessel disease dominated in the RCTs. In clinical practice, the number of diseased coronary vessels was more evenly distributed. Although this suggests a more extensive coronary artery disease in RCT participants, it should be noted that left main disease was seen more often in clinical practice. Regarding demographics, risk factors and co-morbid conditions, patients in clinical practice were somewhat older and had a worse clinical

profile as compared to the trial patients. In addition to this, a high proportion of patients had a history of heart failure. Though no numbers were given regarding heart failure patients in the selected trials, it is unlikely that they approximate to the observed proportion as seen in the EHS-CR. This study therefore provides a valuable perspective on the disparity between patients in clinical practice and patients in whom the studies that provide the evidence for treatment guidelines are performed. It should be noted, however, that the AWESOME trial, which was excluded from the selection of trials, has specifically addressed the impact of PCI or CABG in patients with high-risk clinical characteristics and thus trying to overcome the gap between clinical practice and RCTs. In AWESOME, as in the other selected RCTs, mortality rates were similar between the two treatment groups.[12]

In clinical practice, treatment preference was unmistakable in favour of PCI (54%), whereas surgically and medically treated patients were comparable. Though PCI seemed to be the treatment of choice, we observed a shift toward fewer percutaneous interventions in those who did not qualify for trial participation. In contrast to RCTs, the choice of treatment in clinical practice is not dictated by randomization, but influenced by the weight clinicians and patients gave to a variety of factors. In this respect, the major advantages of PCI as compared to CABG (e.g. relative ease of use, no need for general anaesthesia, thoracotomy, and extracorporeal circulation) seemed superior to the disadvantages (e.g. higher risk of early restenosis, and lower ability to achieve complete revascularization).

Not surprisingly, as observed in the selected trials [8,12-21,32], the need for repeat revascularisation in clinical practice was considerably higher in the PCI group as compared to CABG. However, with respect to irreversible adverse events such as death, myocardial infarction and cerebro-vascular events, this study only partly supports the conclusion of most RCTs, that PCI and CABG patients have similar outcome. Indeed, trial-ineligible patients undergoing CABG had a worse survival as compared to trial-ineligible patients undergoing PCI. This difference is only partly explained by the fact that patients with unprotected left main stenosis were treated by CABG rather than by PCI [10] in line with the guidelines, advocating CABG in high-risk patients [5,7]. Previous real life studies likewise showed that patients selected for CABG have more extensive disease, more comorbidities, higher procedural risk, and therefore unadjusted event rates tend to be worse with CABG than with PCI. However, propensity analysis showed that under those circumstances, CABG actually improves outcome.[33,34] The implications are that trial results are indeed confirmed in real life, but only in trial-eligible patients. Clearly, this does not appear to be the case in trial-ineligible patients.

Limitations.

The limitations of this study are those inherent to observational surveys involving voluntarily participating hospitals. Although we have attempted to include a wide spectrum of hospitals in different countries, almost certainly the results are biased towards better than average practices. The sample size only represents a small fraction of all patients admitted in catheterisation laboratories throughout Europe during the study period. Patient inclusion was consecutive in all participating sites, therefore reflecting the ongoing clinical practice. Although we have attempted to include a wide spectrum of hospitals in different countries, almost certainly the results are biased towards better than average practices. Consequently, even though the results of this survey reflect the real world better than RCTs it should be noted that this may still be too far away from daily practice. Regarding the selection of trial-ineligible patients, we focussed on the major exclusion criteria of the pooled trials. Obviously, in retrospect, we could not trace the complete decision making process leading to trial-(in)eligibility of patients enrolled in this Survey.

Conclusions.

The present study revealed that only a minority of patients, enrolled in the Euro Heart Survey on Revascularization would have qualified for participation in a RCT comparing PCI and CABG. Furthermore, we demonstrated that trial participants had a better clinical profile as compared to patients in every day clinical practice. Nevertheless, the less invasive approach with percutaneous intervention was the preferred treatment over surgical and medical treatment.

REFERENCES

1. Boersma E MM, Wood DA, Bassand J-A, Simoons ML (eds.). Cardiovascular diseases in Europe. Euro Heart Survey and national registries of cardiovascular diseases and patient management. Sophia Antipolis: European Society of Cardiology. 2002.
2. Bobak M, Marmot M. East-West mortality divide and its potential explanations: proposed research agenda. *Bmj*. 1996;312:421-5.
3. Sans S, Kesteloot H, Kromhout D. The burden of cardiovascular diseases mortality in Europe. Task Force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. *Eur Heart J*. 1997;18:1231-48.
4. Julian D, Bertrand M, Hjalmarsson A, Fox K, Simoons M, Ceremuzynski L, Maseri A, Meinertz T, Meyer J, Pyorala K, Rehnqvist N, Tavazzi L, Treasure T. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J*. 1997;Mar; 18(3):394-413.
5. Smith SC, Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO. ACC/AHA Guidelines for Percutaneous Coronary Intervention (Revision of the 1993 PTCA Guidelines)--Executive Summary : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty) Endorsed by the Society for Cardiac Angiography and Interventions. *Circulation*. 2001;103:3019-3041.
6. ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery. *Circulation*. 2004;110:e340-437.
7. Authors/Task Force Members, Silber S, Chairperso, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug J-E, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for Percutaneous Coronary Interventions: The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J*. 2005:ehi138.
8. CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). *The Lancet*. 1995;346:1179-1184.
9. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. *Cardiovasc Drugs Ther*. 2002;16:75-7.
10. Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, Sechtem U, Stahle E, Widimsky P, de Jaegere P, Scholte op Reimer WJM, Mercado N, Wijns W. Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization. *Eur Heart J*. 2005;26:1169-1179.
11. Hoffman SN, TenBrook J, John A., Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes*1. *Journal of the American College of Cardiology*. 2003;41:1293-1304.
12. Morrison DA, Sethi G, Sacks J, Henderson W, Grover F, Sedlis S, Esposito R, Ramanathan K, Weiman D, Saucedo J, Antakli T, Paramesh V, Pett S, Vernon S, Birjiniuk V, Welt F, Krucoff M, Wolfe W, Lucke JC, Mediratta S, Booth D, Barbiere C, Lewis D. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the

Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol.* 2001;38:143-9.

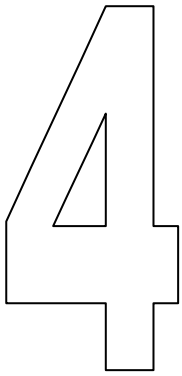
13. Rodriguez A, Boullon F, Perez-Balino N, Paviotti C, Liprandi MI, Palacios IF. Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease (ERACI): in-hospital results and 1-year follow-up. ERACI Group. *J Am Coll Cardiol.* 1993;22:1060-7.
14. Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. *Lancet.* 1993;341:573-80.
15. King SB, 3rd, Lembo NJ, Weintraub WS, Kosinski AS, Barnhart HX, Kutner MH, Alazraki NP, Guyton RA, Zhao XQ. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med.* 1994;331:1044-50.
16. Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Engl J Med.* 1994;331:1037-43.
17. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med.* 1996;335:217-25.
18. Carrie D, Elbaz M, Puel J, Fourcade J, Karouny E, Fournial G, Galinier M. Five-year outcome after coronary angioplasty versus bypass surgery in multivessel coronary artery disease: results from the French Monocentric Study. *Circulation.* 1997;96:II-1-6.
19. Rodriguez A, Bernardi V, Navia J, Baldi J, Grinfeld L, Martinez J, Vogel D, Grinfeld R, Delacasa A, Garrido M, Oliveri R, Mele E, Palacios I, O'Neill W. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. *J Am Coll Cardiol.* 2001;37:51-8.
20. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117-24.
21. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet.* 2002;360:965-70.
22. Hueb W, Soares PR, Gersh BJ, Cesar LAM, Luz PL, Puig LB, Martinez EM, Oliveira SA, Ramires JAF. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: One-year results. *Journal of the American College of Cardiology.* 2004;43:1743-1751.
23. Goy JJ, Eeckhout E, Burnand B, Vogt P, Stauffer JC, Hurni M, Stumpe F, Ruchat P, Sadeghi H, Kappenberger L. Coronary angioplasty versus left internal mammary artery grafting for isolated proximal left anterior descending artery stenosis. *Lancet.* 1994;343:1449-53.
24. Hueb WA, Bellotti G, de Oliveira SA, Arie S, de Albuquerque CP, Jatene AD, Pileggi F. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized

trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol.* 1995;26:1600-5.

25. Goy JJ, Kaufmann U, Goy-Eggenberger D, Garachemani A, Hurni M, Carrel T, Gaspardone A, Burnand B, Meier B, Versaci F, Tomai F, Bertel O, Pieper M, de Benedictis M, Eeckhout E. A prospective randomized trial comparing stenting to internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA trial. Stenting vs Internal Mammary Artery. *Mayo Clin Proc.* 2000;75:1116-23.
26. Lewsey JD, Leyland AH, Murray GD, Boddy FA. Using routine data to complement and enhance the results of randomised controlled trials. *Health Technol Assess.* 2000;4:1-55.
27. Mercado N, Wijns W, Serruys PW, Sigwart U, Flather MD, Stables RH, O'Neill WW, Rodriguez A, Lemos PA, Hueb WA, Gersh BJ, Booth J, Boersma E. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. *J Thorac Cardiovasc Surg.* 2005;130:512-9.
28. Lloyd-Williams F, Mair F, Shiels C, Hanratty B, Goldstein P, Beaton S, Capewell S, Lye M, Mcdonald R, Roberts C, Connelly D. Why are patients in clinical trials of heart failure not like those we see in everyday practice? *Journal of Clinical Epidemiology.* 2003;56:1157-1162.
29. Duvall W. Cardiovascular disease in women. *Mt Sinai J Med.* 2003;70:293-305.
30. Miller TD, Roger VL, Hodge DO, Hopfenspirger MR, Bailey KR, Gibbons RJ. Gender differences and temporal trends in clinical characteristics, stress test results and use of invasive procedures in patients undergoing evaluation for coronary artery disease. *J Am Coll Cardiol.* 2001;38:690-7.
31. Weisz D, Gusmano MK, Rodwin VG. Gender and the treatment of heart disease in older persons in the United States, France, and England: a comparative, population-based view of a clinical phenomenon. *Gender Medicine.* 2004;1:29-40.
32. Vacek JL, Rosamond TL, Stites HW, Rowe SK, Robuck W, Dittmeier G, Beauchamp GD. Comparison of percutaneous transluminal coronary angioplasty versus coronary artery bypass grafting for multivessel coronary artery disease. *Am J Cardiol.* 1992;69:592-7.
33. Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. *Circulation.* 2004;109:2290-5.
34. Hannan EL, Racz MJ, Walford G, Jones RH, Ryan TJ, Bennett E, Culliford AT, Isom OW, Gold JP, Rose EA. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med.* 2005;352:2174-83.
35. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16:9-13.

Management of patients in daily clinical practice

Chapter



Under-utilization of evidence-based drug treatment in patients with heart failure is only partly explained by dissimilarity to patients enrolled in landmark trials

Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials.

A report from the Euro Heart Survey – Heart Failure

M.J. Lenzen, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
E. Boersma, Rotterdam, the Netherlands
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
A.H.M.M. Balk, Rotterdam, the Netherlands
M. Komajda, Paris, France
K. Swedberg, Göteborg, Sweden
F. Follath, Zurich, Switzerland
M. Jimenez-Navarro, Málaga, Spain
M.L. Simoons, Rotterdam, the Netherlands
J.G.F. Cleland, Kingston upon Hull, UK

European Heart Journal (2005) **26**: 2706-13

ABSTRACT

Background: Surveys on heart failure management suggest under-utilization of life-saving evidence-based treatment. Evidence-based medicine and clinical guidelines are based on the results of Randomized Controlled Trials. Therefore, we investigated how patients who fulfilled the enrolment criteria of randomized trials were treated in "real-life".

Methods: We selected three large placebo-controlled trials of patients with chronic heart failure in which ACE-inhibitors, β-blockers, and spironolactone proved to be safe and effective. The trials' major enrolment criteria were identified and applied to patients enrolled in the Euro Heart Survey on Heart Failure to identify the proportion of patients eligible for treatment and also treated appropriately.

Results: Of the 10,701 patients who were enrolled in the Euro Heart Survey on Heart Failure, only a small percentage (13%) would have qualified for participation in at least one of the selected trials. Patients who fulfilled enrolment criteria of the identified trials were more likely to be treated with ACE-inhibitors (83% of SOLVD-eligible patients), β-blockers (54% of MERIT-HF-eligible patients), and aldosterone antagonists (43% of RALES-eligible patients) than trial-ineligible patients. Almost half of SOLVD-eligible patients who were treated with ACE-inhibitors received the target dose as recommended in the guidelines, but less than 10% of MERIT-HF eligible patients who were treated with β-blockers received the target dose.

Conclusions: ACE-inhibitors are widely utilized but given in lower doses than proven effective in clinical trials. β-blockers are underused and given in lower doses to patients who fulfil the enrolment criteria of relevant landmark trials.

INTRODUCTION

Chronic heart failure is a major health problem with a high morbidity and mortality.[1,2] Over the last two decades, major advances have occurred in the treatment of heart failure patients. Randomized clinical trials (RCTs) showed that ACE-inhibitors,[3-5] β-blockers,[6-8] and aldosterone antagonists[9,10] could reduce morbidity and mortality in patients with heart failure. Guidelines have been established to support physicians in clinical decision making in this rapidly evolving field.[11-14] In these guidelines, RCTs are accorded the highest level of evidence. However, although physicians are increasingly encouraged to apply these guidelines in their practice, it is repeatedly observed that a considerable proportion of heart failure patients do not receive evidence-based treatment.[15-20]

Several factors may explain the reported under-utilization of evidence-based treatment such as lack of knowledge, lack of expertise in the use of such drugs, lack of time, and economic restraints. Another issue that is often brought forward is the limited generalisability (external validity) of RCTs and it is emphasized that these trials usually enrol highly selected patients.[21-27] In reality, clinicians may be right to withhold treatment in patients who do not fulfil the inclusion and exclusion criteria used to select patients for RCTs. Information is scarce on whether evidence-based treatment is offered more often to patients who match the profile of patients who were enrolled in RCTs as compared to those who were not.

Therefore, we investigated what proportion of patients with suspected or known heart failure who enrolled the Euro Heart Survey on Heart Failure,[19] were eligible for participation in the largest placebo controlled trials of ACE-inhibitors, β-blockers, and aldosterone antagonists that demonstrated the effectiveness and safety of these agents. We then analyzed what proportion of patients met or did not meet these criteria, and were treated according to the guidelines.

METHODS

Euro Heart Survey on Heart Failure

Between March 2000 and May 2001, 46,788 patients from 115 hospitals in 24 ESC member countries were screened for enrolment in the Euro Heart Survey on Heart Failure.[19,20,28] Briefly, all consecutive discharges and deaths from general medical, cardiology or cardiac surgery wards were screened over a 6-week period. Patients who fulfilled one or more of the following four criteria were enrolled: 1) a clinical diagnosis of heart failure during the admission; 2) a diagnosis of heart failure recorded at any time in the last three years; 3) administration of a loop diuretic for any reason other than renal failure in the 24h before death or discharge; and/or 4) pharmacological treatment for heart failure or ventricular

dysfunction in the 24h before death or discharge. Information on patient characteristics, diagnosis, and treatment on 10,701 enrolled patients was collected.[19,20]

Trial selection

To compare patients in the RCTs with those enrolled in the Euro Heart Survey, we selected the largest placebo-controlled trials in which ACE-inhibitors, β-blockers, and aldosterone antagonists had been shown to reduce mortality in patients with chronic heart failure. These were SOLVD (ACE-inhibitor), MERIT-HF (β-blocker), and RALES (aldosterone antagonist).[4,6,9] In addition, we compiled the tabulated patient characteristics, as presented in the main results papers of these trials ("pooled RCTs"). Data were pooled if the certain characteristics were available in at least two trials, either by reports of the actual counts or by percentages.

The major enrolment criteria for these trials were extracted from the main articles and summarized in Table 1. The most important inclusion criterion in these trials was the left ventricular ejection fraction (LVEF). Important exclusion criteria were renal failure, respiratory disease (including asthma and chronic obstructive respiratory disease during the index admission), obstructive valvular heart disease, acute coronary syndrome during the index admission, and limited life-expectancy by other diseases. We furthermore identified, pacemakers, ventricular assist devices, planned heart transplantation, congenital heart disease, laboratory values (i.e. creatinine and potassium), and administered cardiovascular drugs (i.e. calcium antagonists and amiodarone), as exclusion criteria in some of these trials.

Table 1. Major in- and exclusion criteria of selected trials

	SOLVD 1991	MERIT-HF 1999	RALES 1999
Drug comparison	enalapril	metoprolol	spironolactone
Number of participants	2569	3991	1663
Major enrolment criteria			
Age	≤ 80	40-80	-
NYHA	-	II-IV	III-IV
LVEF	≤ 0.35	≤ 0.40	≤ 0.35
Renal failure (creatinine level)	exclude (>2.0 mg/dl)	-	exclude (>2.5 mg/dl)
Severe pulmonary disease	exclude	exclude	-
Severe valve disease	exclude	-	exclude
(recent) ACS	exclude	exclude	exclude
Limited life -expectancy	exclude	exclude	exclude
ACE-inhibitor therapy	exclude	mandatory	mandatory
β-blocker therapy	-	exclude	-
Calcium antagonists	-	exclude	-
Diuretics		mandatory	mandatory*
Amiodarone	-	exclude	-

NYHA= New York Heart Association; LVEF= left ventricular ejection fraction; ACS= acute coronary syndrome.
* potassium-sparing diuretics excluded

Identifying trial-eligible survey patients

Based on the above mentioned criteria, survey patients with identifiable contra-indications (i.e. age, co-morbidity, etc) or a higher LVEF than allowed in the RCTs were classified as trial-ineligible patients. Trial-eligible patients were those, who had no contra-indications and fulfilled the LVEF criterion, while the remaining patients were classified as "other survey patients". In these patients no quantitative measurement of the LVEF was available, while no contra-indications were observed. It should be noted, however, that defining patients from clinical practice as trial-eligible or trial-ineligible is, by necessity, crude.

Within the subgroups of SOLVD, MERIT-HF and RALES-eligible patients, we analysed the administered dose of ACE-inhibitors and β-blockers on the day of discharge or the day prior to death as compared to the target dose. We defined the target dose as the minimum recommended maintenance dose or higher approved for the treatment of heart failure in Europe.[13] For ACE-inhibitors this is 75mg for captopril, 20mg for enalapril, 5mg for ramipril, 5mg for lisinopril, and 4mg for perindopril. For β-blockers these dosages were 150mg for metoprolol, 50mg for atenolol, 50mg for carvedilol, and 10mg for bisoprolol.

Statistical analysis

Descriptive statistics included percentages for dichotomous variables, and medians with corresponding 25th and 75th percentiles for continues variables. Differences between trial-eligible and trial-ineligible patients were analyzed by Chi-square, and Mann-Whitney or Kruskal-Wallis test as appropriate. For all tests a p value of 0.05 or less (two-sided) was consistent statistically significant. All analyses were performed with SPSS (version 12.0).

We acknowledge the fact that patients', who died during the initial hospitalisation, could have a worse clinical profile, and as a result influence the results. Therefore, we repeated the analyses excluding patients who did not survive to hospital discharge. Since the results of the analyses with and without patients who died during the initial hospitalisation were highly consistent, we report our original choice, based on the total survey population.

RESULTS

As shown in figure 1, only small proportions of patients enrolled in the Euro Heart Survey on Heart Failure would have qualified for participating in the SOLVD (9%), MERIT-HF (5%), and RALES (7%) trials. Exclusion criteria like age and identified contra-indications were the most important reasons for not classifying patients as trial-eligible. In addition to this, we were unable to classify a considerable proportion of patients as trial-eligible due to the absence of a LVEF measurement. Similarly, patients were only considered MERIT-HF eligible if they

were treated with a diuretic and ACE-inhibitor (or angiotensin-II-antagonist), and RALES-eligible when treated with an ACE-inhibitor and loop diuretic.

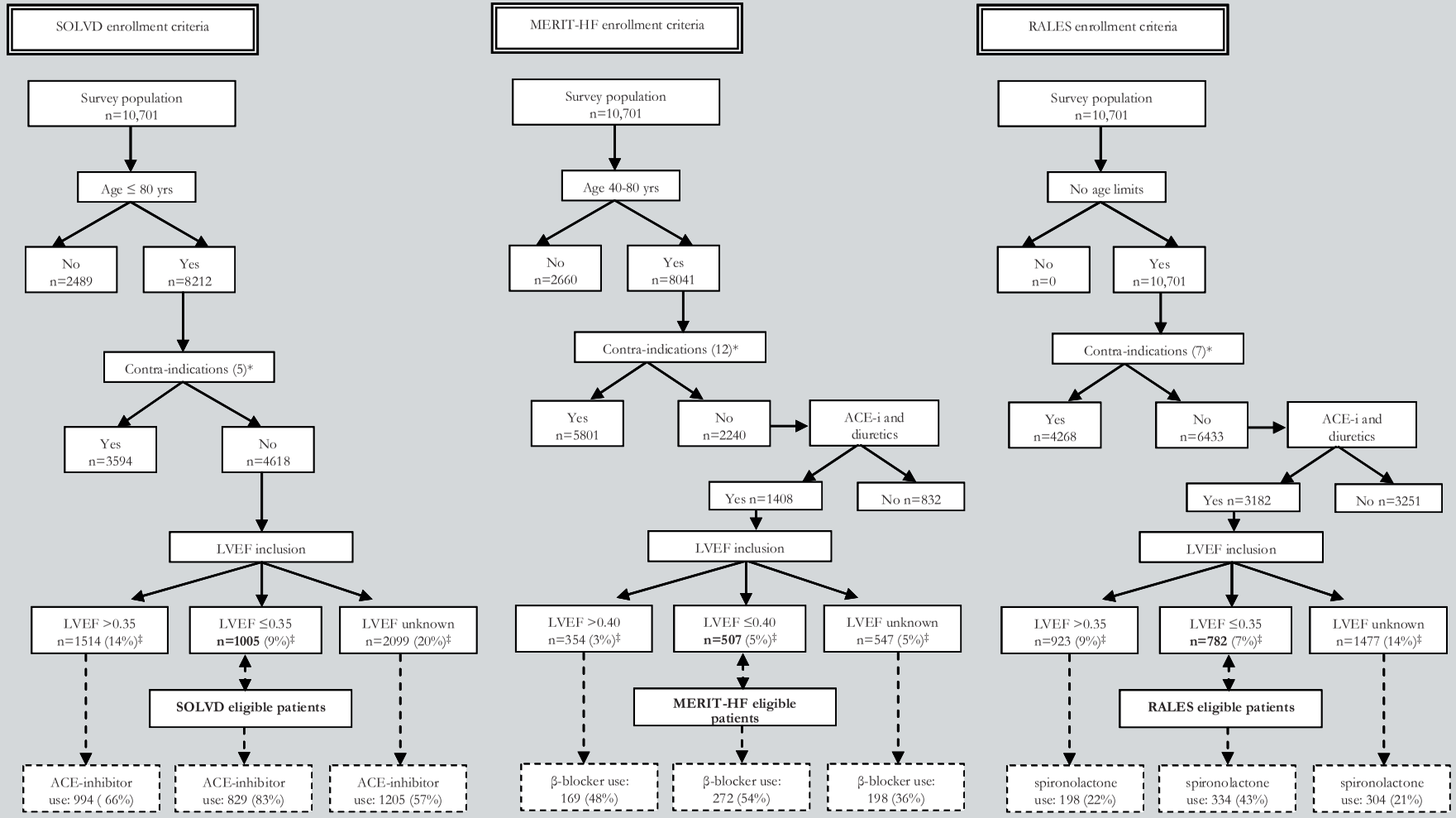
Overall, 1346 patients (13%) would have qualified for participating in at least one of the selected trials (Table 2). Within this pooled trial-eligible population, 256 patients would have qualified for all three trials, while 692 patients would have qualified for at least 2 trials.

These trial-eligible patients show considerable differences as compared to those who did not qualify for trial participation. Consistent with the results of clinical trials, the majority of trial-eligible patients were men (75%). It should be noted however, that almost half (47%) of the survey participants were women, whereas they represented only 27% of those with a LVEF $\leq$ 0.40. Ischemic heart disease was observed less frequently in patients without exclusion criteria but unknown LVEF (other survey patients) as compared to trial-eligible and trial-ineligible patients. Limited life-expectancy was defined as any known malignancy, and observed in 16% of the trial-ineligible patients.

Most patients who fulfilled trial-criteria were treated with ACE-inhibitors (83% to 100%) (Table 3). Almost two-third of all trial-eligible patients were treated with at least half of the target dose, and 40% to 50% received the minimum regulatory recommended dose.[13] As the recommended maintenance doses of ACE-inhibitors in the guidelines are given as dose ranges, we also repeated the analysis using the maximum regulatory recommended doses. This corresponded to 50% of SOLVD, and 57% of MERIT-HF and RALES eligible patients who were treated with at least half of this higher target dose. With regard to β-blockers, 54% of MERIT-eligible patients received a β-blocker, of whom in 20% at least half of the target dose was given, while only 6% received the target dose. Aldosterone antagonists were given to a large minority (43%) of heart failure patients, fulfilling the enrolment criteria of the RALES-trial. Of all survey patients, 3658 (34% of all patients or 54% of those who underwent imaging) had evidence of a left ventricular systolic dysfunction (LVSD), defined as a LVEF $\leq$ 0.40 or a report of moderate or severe LVSD on echocardiography. Of these patients, 78% was treated with an ACE-inhibitor, 46% with a β-blocker, and 29% with an aldosterone antagonist. In the absence of renal failure and asthma (n=2762, 26%), slightly more patients were given ACE-inhibitors (80%) and β-blocker (48%), while treatment with aldosterone antagonists remained 29%.

The incidence of all-cause mortality during the 12-week follow-up period of hospital survivors was lower in patients who received at least 50% of the target dose of ACE-inhibitors or β-blockers in respectively SOLVD (4.0% vs. 8.7%) and MERIT-HF (2.9% vs. 8.8%) eligible patients (Table 4). This beneficial effect of treating patients with 50% or more of the target dose was also observed in patients who did not fulfil the study criteria of the selected trials.

Figure 1. Flowdiagram, illustrating the proportion of trial-eligible patients.



*) number of contra-indications, used in the analysis
‡) percentage is based on total survey population

Table 2. Baseline characteristics of patients enrolled in the Euro Heart Survey on Heart Failure

	Total	Trial-eligible (pooled)	Trial-ineligible (pooled)	Other survey patients†	*P*-value
N	10701	1346*	6595	2760	
Age (median [25th–75th])	73 [64-80]	67 [57-74]	74 [64-82]	74 [66-79]	<0.001
Gender (women) (%)	5020 (47)	342 (25)	3207 (49)	1471 (53)	<0.001
Co-morbidity: (%)					
Hypertension	5679 (53)	636 (47)	3534 (54)	1509 (55)	<0.001
Diabetes Mellitus	2907 (27)	355 (26)	1723 (26)	829 (30)	<0.001
Ischemic heart disease	6419 (60)	841 (63)	4246 (64)	1332 (48)	<0.001
Acute coronary syndrome*	2883 (27)	166 (12)	2505 (38)	212 (8)	<0.001
Valvular heart disease*	768 (7)	41 (3)	677 (10)	50 (2)	<0.001
Renal insufficiency±*	1163 (11)	82 (6)	974 (15)	107 (4)	<0.001
Pulmonary disease	2876 (27)	245 (18)	1701 (26)	930 (34)	<0.001
Severe pulmonary disease*	1743 (16)	188 (14)	971 (15)	584 (21)	<0.001
Prior / current Stroke	939 (9)	83 (6)	541 (8)	315 (11)	<0.001
Chronic atrial fibrillation	2482 (23)	284 (21)	1520 (23)	678 (25)	0.04
Cancer*	1058 (10)	0 (0)	1058 (16)	0	--
LVEF known (%)	5311 (50)	1346 (100)	3965 (60)	0	--
LVEF (median [25th–75th])Ŧ	41 [30-55]	29 [22-33]	48 [40-60]	-	<0.001
Pharmacological treatment (%):					
ACE-inhibitors	6610 (62)	1158 (86)	3595 (55)	1857 (67)	<0.001
β-blockers	3744 (37)	650 (48)	2584 (39)	710 (26)	<0.001
Cardiac glycosides	3825 (36)	622 (46)	2147 (33)	1056 (38)	<0.001
Diuretics	9297 (87)	1241 (92)	5521 (84)	2535 (92)	<0.001
Aldosterone antagonists	2197 (21)	522 (39)	1135 (17)	540 (20)	<0.001

*) major exclusion criteria of the selected trials, as shown in table 1
†) patients without major exclusion criteria, but without known LVEF
±) creatinine ≥ 177 umol/L or ≥ 2.0mg/dl
Ŧ) only in patients with known LVEF

DISCUSSION

The present study clearly revealed that the patients enrolled in RCTs are highly selected. Only a small proportion of patients enrolled in the Euro Heart Survey on Heart Failure would have fulfilled the entry criteria of at least one of the selected landmark trials. In this subgroup of trial-eligible patients, barely one half were prescribed a β-blocker and the doses of ACE-inhibitors and β-blockers used were lower than those proven to be effective in large controlled clinical trials. Therefore, lack of similarity between patients with heart failure in clinical practice compared to those in clinical trials does not adequately explain under-utilization of therapy.

It is in keeping with earlier reports, that a minority of heart failure patients in clinical practice would have qualified for participation in landmark RCTs. [21-27] It should be noted, however, that the absence of a quantitative measurement of the left ventricular function and the failure to prescribe ACE-inhibitors excluded many patients from being considered trial-

eligible. As only few patients fulfilled all clinical trial criteria, we also tried to identify the maximum potential numbers of patients who should receive an ACE-inhibitor and β-blocker (i.e. those with evidence of LVEF, without contra-indications like renal failure or asthma). Treatment of these patients compared to trial-eligible patients revealed only minor differences with respect to ACE-inhibitors and β-blockers. Aldosterone antagonists, however, were given more frequently in trial-eligible patients.

Table 3. Patient characteristics and pharmacological treatment of trial-eligible patients enrolled in the EHS-Heart Failure

	SOLVD eligible	MERIT-HF eligible	RALES eligible	Pooled RCTs*	trials
N	1005	507	782	8223	1,2,3
Age (median [25th–75th])	65 [55-72]	67 [57-73]	68 [58-75]	63	1,2,3
Female gender (%)	224 (22)	141 (28)	179 (23)	1848 (22)	1,2,3
Non-excluding co-morbidity: (%)					
Hypertension	447 (45)	254 (50)	382 (49)	2835 (43)	2,3
Diabetes mellitus	262 (26)	140 (28)	207 (27)	1647 (25)	2,3
Chronic atrial fibrillation	212 (21)	104 (21)	166 (21)	689 (14)	2,3
Prior myocardial infarction	463 (46)	229 (45)	409 (52)	3611 (55)	2,3
Prior coronary intervention	216 (22)	106 (21)	139 (18)	--	--
Pharmacological treatment: (%)					
ACE inhibitors treated	829 (83)	472 (93)	782 (100)	6714 (91)	1,3
≥ 50% of target dose	605 (60)	337 (67)	564 (72)	--	--
≥ target dose	408 (41)	231 (46)	375 (48)	--	--
β-blockers treated	489 (49)	272 (54)	357 (46)	371 (9)	1,2
≥ 50% of target dose	172 (17)	102 (20)	129 (17)	--	--
≥ target dose	54 (5)	29 (6)	44 (6)	--	--
Cardiac glycosides treated	484 (48)	260 (51)	373 (48)	5479 (67)	1,2,3
Diuretics treated	900 (90)	507 (100)	782 (100)	7463 (91)	1,2,3
Aldosterone antagonists treated	418 (42)	213 (42)	334 (43)	--	--

*) Data based on results as presented in the main articles of the three RCTs (1=SOLVD, 2=MERIT-HF, 3=RALES)
Note: for ACE-inhibitors the daily target doses were defined as 75mg for captopril, 20mg for enalapril, 5mg for ramipril, 5mg for lisinopril and 4mg for perindopril. For β-blockers these doses were 150mg for metoprolol, 50mg for atenolol, 50mg for carvedilol, and 10mg for bisoprolol.[13]

This analysis shows that the under-representation of women in heart failure trials[23,24] is partly explained by the use of a low LVEF as an inclusion criterion and the higher prevalence of preserved LVEF amongst women. In order to increase the proportion of women in heart failure trials it would be necessary to introduce bias in favour of recruiting women or relax the LVEF entry criterion. This analysis also reveals that the exclusion of patients with preserved left ventricular function (PLVF) and those with renal dysfunction is an important reason for the average of patients in trials being about a decade younger than the epidemiological

population.[21-23] Indeed in CHARM-preserved,[29] which recruited only patients with PLVF, the proportion of women was substantially higher and the patients somewhat older than in other RCTs of heart failure.

Table 4. 12 week mortality of hospital survivors in relation to target doses

Subpopulation	Treatment	Target dose	N	Follow-up mortality	*P*-value
SOLVD eligible	ACE-inhibitors	≥ 50%	600	24 (4.0)	0.002
		< 50%	379	33 (8.7)	
MERIT HF eligible	β-blockers	≥ 50%	102	3 (2.9)	0.04
		< 50%	399	35 (8.8)	
Trial-ineligible (pooled)	ACE-inhibitors	≥ 50%	2367	102 (4.3)	<0.001
		< 50%	3671	317 (8.6)	
	β-blockers	≥ 50%	1224	47 (3.8)	<0.001
		< 50%	4814	372 (7.7)	

The limited generalisability of the results of RCTs is widely recognised. Trials with more varied enrolment criteria are required to provide information on the complete scope of a disease and its treatment in order to extend generalisability. This has happened with ACE-inhibitors over the last 15 years. Trials in post-infarction patients with LVSD and in patients with vascular disease without heart failure suggest that the benefits of ACE-inhibitors may be generalisible, although no trials have shown morbidity or mortality benefit in patients with PLVF as yet. ACE-inhibitors have a well-recognized side-effect profile and are well tolerated.[30] Similarly, trials of β-blocker have shown benefit in patients with heart failure and LVSD, and in patients who have had a myocardial infarction. The SENIORS[31] and a smaller study of propranolol[32] suggest that β-blockers are effective even in elderly patients, regardless of the left ventricular ejection fraction. A recent analysis of patients in this survey revealed that patients treated with ACE-inhibitors or beta-blockers, irrespective of the LVEF, had a better survival than those who did not.[33]

Treatment with aldosterone antagonists is based on only two clinical trials, RALES and EPHESUS,[9,10] and more RCTs are desirable in order to increase generalisability. Achieving the equipoise between the ethics of withholding a treatment that has shown striking reductions in mortality versus the desire to demonstrate generalisability may be difficult but important to demonstrate safety and efficacy in wider clinical practice.[34,35]

Although adherence to guidelines is encouraged by national and international societies, not all patients will or should be treated as advocated in the guidelines. Guidelines only

provide the general principle of how a patient should be treated; they do not address every individual patient's clinical problem. Management of individual patients is more complex than simply following the guidelines, as contra-indications, individual reactions to the medication side-effects, co-morbidity, and subsequent multiple co-medications as well as the treatment goals for the individual patient can effect management decisions.[27,36] However, this survey suggests that there is a shortfall in effective therapy, even when patients in clinical practice fulfil the criteria of landmark clinical trials of heart failure treatment.

These observations raise the question why a sizable proportion of patients were not treated according to evidence-based guidelines. Identified barriers in following clinical guidelines, like lack of awareness, lack of agreement with the guidelines, difficult to use (not concise enough), no motivation to change current practice, as well as economic pressure to limit the costs, etc. might partly explain the limited adherence to guidelines in clinical practice.[29,30,37] These barriers imply that more effort is needed in order to improve guideline adherence. It is acknowledged that initiation and up-titration of these drugs require careful repeated assessment in order to monitor individual responses. Especially in the case of β-blockers, treatment can provoke initial worsening. Concerns that initiation of a β-blocker too early during hospitalization could destabilize the patient[38] should also be taken into account when trying to explain why physicians were unable to initiate evidence-based therapy. Regarding up-titration of ACE-inhibitors and β-blockers, it should be noted that this requires an effective heart failure follow-up program, as it is to be expected that the majority of patients are not hospitalised during this phase. Conversely, some have advocated that fixed target doses may not be optimal for individual patients.[18] In addition to this, doctors may be satisfied with a symptomatic improvement already with smaller doses of drugs and not push for higher targets to avoid adverse events. Thus, smaller than recommended doses can and should not generally be regarded as suboptimal therapy. In our survey, however, the underlying reason for choosing dosage cannot be reliable analysed. The clinical trial evidence indicating that target doses of ACE inhibitors and beta-blockers are more effective than lower doses is sparse. Randomised controlled trials do suggest that higher doses of ACE inhibitors may be more effective.[39-41] There is less evidence that the dose of beta-blocker is important.[42,43] However, a beneficial effect in patients who were treated with at least 50% of the doses used in RCTs, as compared to patients who received less, was observed in this survey. It should be noted, however, that most of the evidence for benefit is based on titration to target doses recommended by landmark trials.

Limitations

As most hospitals volunteered, it is possible that the observed pharmacological treatment was even better than in every day clinical practice because they were energetic in implementing existing evidence. In selecting trial-eligible patients, we focussed on the most important entry criteria for the trials but did not include every detail. Finally, it is possible that some of the under-utilization of β-blockers reflects the fact that the patients had recently been hospitalized. At the time of the survey it was generally recommended to stabilize patients first, before initiating β-blockers.

Conclusions.

Only a minority of patients with heart failure would be eligible for participation in the majority of randomised controlled trials of heart failure. This reflects the general exclusion of patients with PLVF and to a lesser extent, renal dysfunction. Amongst patients who fulfilled the key enrolment criteria of selected landmark trials, ACE-inhibitors, β-blockers and aldosterone antagonists were under-utilized. This survey, however, gave no clues for the reason of under-utilization.

REFERENCES

1. Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? *J Am Coll Cardiol.* 2000;36:2284-6.
2. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol.* 1993;22:6A-13A.
3. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med.* 1987;316:1429-35.
4. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med.* 1991;325:293-302.
5. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med.* 1992;327:669-77.
6. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001-7.
7. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9-13.
8. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344:1651-8.
9. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J, The Randomized Aldactone Evaluation Study Investigators. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *N Engl J Med.* 1999;341:709-717.
10. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309-21.
11. Guidelines for the diagnosis of heart failure. The Task Force on Heart Failure of the European Society of Cardiology. *Eur Heart J.* 1995;16:741-51.
12. The treatment of heart failure. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. *Eur Heart J.* 1997;18:736-53.
13. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J.* 2001;22:1527-60.
14. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J.* 2005;26:1115-40.
15. Cohen-Solal A, Desnos M, Delahaye F, Emeriau JP, Hanania G. A national survey of heart failure in French hospitals. *European Heart Journal.* 2000;21:763-769.

16. Cowie MR, Wood DA, Coats AJS, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart*. 2000;83:505-510.
17. MacIntyre K, Capewell S, Stewart S, Chalmers JWT, Boyd J, Finlayson A, Redpath A, Pell JP, McMurray JJV. Evidence of Improving Prognosis in Heart Failure : Trends in Case Fatality in 66 547 Patients Hospitalized Between 1986 and 1995. *Circulation*. 2000;102:1126-1131.
18. Mehta PA, McDonagh S, Poole-Wilson PA, Grocott-Mason R, Dubrey SW. Heart failure in a district general hospital: are target doses of beta-blockers realistic? *QJM*. 2004;97:133-139.
19. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. *European Heart Journal*. 2003;24:442-463.
20. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, Dietz R, Gavazzi A, Van Gilst WH. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 2: treatment. *European Heart Journal*. 2003;24:464-474.
21. Cowie MR. Best practice: evidence from the clinical trials. *Heart*. 2002;88:2ii-4.
22. Lloyd-Williams F, Mair F, Shiels C, Hanratty B, Goldstein P, Beaton S, Capewell S, Lye M, Mcdonald R, Roberts C, Connelly D. Why are patients in clinical trials of heart failure not like those we see in everyday practice? *Journal of Clinical Epidemiology*. 2003;56:1157-1162.
23. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. *Cardiovasc Drugs Ther*. 2002;16:75-7.
24. Konstam MA. Progress in heart failure Management? Lessons from the real world. *Circulation*. 2000;102:1076-8.
25. Knottnerus JA, Dinant GJ. Medicine based evidence, a prerequisite for evidence based medicine. *Bmj*. 1997;315:1109-10.
26. Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF, Ordin DL, Krumholz HM. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *American Heart Journal*. 2003;146:250-257.
27. Hickling SRINJA. The barriers to effective management of heart failure in general practice. *British Journal of General Practice*. 2001;51:615-618.
28. Cleland JGF, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, Gavazzi A, Hobbs R, Korewicki J, Madeira HC. The Euro Heart Failure Survey of The EUROHEART Survey Programme: A survey on the quality of care among patients with heart failure in Europe. *European Journal of Heart Failure*. 2000;2:123-132.
29. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *The Lancet*. 2003;362:777-781.
30. Squire IB. Angiotensin Converting Enzyme Inhibition in Heart Failure: Clinical Trials and Clinical Practice. *Cardiovascular Drugs and Therapy*. 2002;16:67-74.
31. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova

L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA, on behalf of the SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26:215-225.

32. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus ACE inhibitors. *Am J Cardiol*. 1997;80:207-9.
33. Lenzen MJ, Scholte op Reimer WJM, Boersma E, Vantrimpont PJMJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. *European Heart Journal*. 2004;25:1214-1220.
34. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543-51.
35. Svensson M, Gustafsson F, Galatius S, Hildebrandt PR, Atar D. Hyperkalaemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study. *Bmj*. 2003;327:1141-2.
36. Cleland JGF, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F, Freemantle N, Gavazzi A, van Gilst WH, Hobbs FDR. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *The Lancet*. 2002;360:1631-1639.
37. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *Jama*. 1999;282:1458-65.
38. Pfeffer MA, Stevenson LW. {beta}-Adrenergic Blockers and Survival in Heart Failure. *N Engl J Med*. 1996;334:1396-1397.
39. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100:2312-8.
40. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. The NETWORK Investigators. *Eur Heart J*. 1998;19:481-9.
41. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. *Circulation*. 1999;100:2312-2318.
42. Wikstrand J, Hjalmarson Ak, Waagstein F, Fagerberg Bj, Goldstein S, Kjekshus J, Wedel H. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: Analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *Journal of the American College of Cardiology*. 2002;40:491-498.
43. Simon T, Mary-Krause M, Funck-Brentano C, Lechat P, Jaillon P, on behalf of CIBIS II investigators. Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study (CIBIS II). *Eur Heart J*. 2003;24:552-559.

Management of specific sub-groups of patients

Chapter 5

Differences between patients with a Preserved and Depressed Left Ventricular Function

Differences between patients with a Preserved and a Depressed Left Ventricular Function.

A report from the EuroHeart Failure Survey

M.J. Lenzen, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
E. Boersma, Rotterdam, the Netherlands
P.J.M.J. Vantrimpont, Rotterdam, the Netherlands
F. Follath, Zürich, Switzerland
K. Swedberg, Göteborg, Sweden
J. Cleland, Kingston upon Hull, UK
M. Komajda, Paris, France.

European Heart Journal (2004) **25**, 1214-20

ABSTRACT

Aims: Due to a lack of clinical trials, scientific evidence regarding the management of patients with chronic heart failure and preserved left ventricular function (PLVF) is scarce. The EuroHeart Failure Survey provided information on the characteristics, treatment and outcomes of patients with PLVF as compared to patients with a LVSD.

Methods and results: We performed a secondary analysis using data from the EuroHeart Failure Survey, including only patients with a measurement of LV function (n=6806). We selected two groups, patients with LVSD (54%) and patients with a PLVF (46%). Patients with a PLVF were on average 4 years older and more often women (55% vs. 29%, respectively, $p < 0.001$) as compared to LVSD patients, and more likely to have hypertension (59% vs. 50%, $p < 0.001$) and atrial fibrillation (25% vs. 23%, $p=0.01$). PLVF patients received less cardiovascular medication as compared to PLVF patients, with the exception of calcium antagonists. Multivariate analysis revealed that LVSD was an independent predictor for mortality, while no differences in treatment effect on mortality between the two groups was observed. A sensitivity analysis, using different thresholds to separate patients with and without LVSD revealed comparable findings.

Conclusions: In the Euro Heart Failure Survey, a high percentage of heart failure patients had PLVF. Although major clinical differences were seen between the groups, morbidity and mortality was high in both groups.

INTRODUCTION

Chronic heart failure is a major health problem and is associated with high morbidity and mortality.[1,2] Advances in therapy over the last two decades have proved highly effective in reducing morbidity and mortality rates. As a result, nowadays several effective treatment strategies are available, including β-blockers and ACE-inhibitors, which have contributed to improved outcome in the real world.[3,4] However, most clinical investigations in chronic heart failure focussed on patients with left ventricular systolic dysfunction (LVSD). Consequently, scientific evidence regarding the management of patients with preserved left ventricular function (PLVF) is scarce.

To support physicians in everyday clinical decision-making, the European Society of Cardiology (ESC) published guidelines for the investigation and treatment of heart failure patients.[5,6] Since guidelines are intended to be evidence-based treatment recommendations for patients with PLVF remain mainly speculative.[5] Still, it should be realised that these patients constitute a sizeable group: it is estimated that 30% to 50% of all heart failure patients do not have LVSD.[7] The EuroHeart Failure Survey was designed to evaluate to what extent treatment guidelines are implemented in clinical practice. A total of 10.701 suspected or confirmed heart failure patients were enrolled, of whom 3148 had PLVF. The survey provided a wealth of information on patient characteristics, diagnosis and treatment.[8,9] We aimed to describe to what extent the presence or absence of LVSD influenced patient profile, management and outcome.

METHODS

The EuroHeart Failure Survey was the second in a series of surveys that were conducted under the umbrella of the Euro Heart Survey Program, aiming to investigate the implementation of treatment guidelines in clinical practice. The design details of the Heart Failure Survey, which was undertaken during March 2000 and May 2001, were published previously.[9,10] In short, all consecutive discharges and deaths on the departments of cardiology, cardiovascular surgery, general internal medicine and geriatrics were screened over a 6-week period. The design of EuroHeart Failure survey included 115 hospitals from 24 ESC member countries on a voluntary basis, including general hospitals and university centers.

Patients who fulfilled at least one of the following criteria were enrolled:

(1) a clinical diagnosis of heart failure during the admission;
(2) a diagnosis of heart failure recorded at any time in the last three years;
(3) administration of a loop diuretic for any reason other than renal failure during 24h of death or discharge;

(4) pharmacological treatment for heart failure or ventricular dysfunction within 24h of death or discharge.

In all 10.701 enrolled patients, data were collected on co-morbid conditions including hypertension, diabetes, chronic atrial fibrillation and renal insufficiency. A clinical follow-up was performed, and vital status (death or alive) was determined at 12 weeks after discharge. We also collected data on re-admission(s). Surviving patients were then invited for an interview. During this visit, the NYHA classification was determined, and the quality-of-life was measured with among other things a single question "how would you rate your quality-of-life", using a 7 point rating scale (0=poor, 7=excellent).

This analysis included patients who had undergone a quantitative or qualitative assessment of the left ventricular function (n=6806, 64% of the entire cohort). Of these patients, in 80% (n=5451) left ventricular ejection fraction (LVEF) was reported. Patients with a LVEF ≥40%, as well as patients with a normal or mildly depressed systolic left ventricular function, as assessed by echocardiography were classified as PLVF. Patients with a LVEF <40%, patients with a moderate or severe left ventricular systolic dysfunction, and those with left ventricular dilatation, as assessed by echocardiography were classified as LVSD.

Statistical analysis

Continuous variables are described as mean values and corresponding standard deviations, or as median values and corresponding 25^{th} and 75^{th} percentiles. Dichotomous variables are reported as absolute numbers and percentages. To evaluate differences characteristics, in treatment and outcome between patients with and without LVSD, chi-square tests, student's *t*-tests or Mann-Whitney tests were applied as appropriate.

Multivariable logistic regression analysis was applied to study the relation between LVF and all-cause mortality during the 12-week follow-up period. LVSD, age, gender, hypertension, diabetes, ischemic heart disease, renal insufficiency, prior stroke, chronic atrial fibrillation and pharmacological treatment were forced into the regression model. We report odds ratio's (OR) and corresponding 95% confidence intervals (CI). To examine the differential effect of pharmacological treatment in patients with and without LVSD, interaction terms were included in the regression model. All calculations were carried out with SPSS 10.1 software package. For all tests a *P* value of 0.05 or less (2-sided) was considered statistically significant.

We acknowledge the fact that the discussion on how to define preserved left ventricular function in patients with heart failure is still ongoing, and that choice may be challenged. [11-14] Therefore, we repeated all analyses using different thresholds. We first analysed quantitative LVEF <40% versus LVEF ≥40% (excluding patients with only

qualitative assessment of the LV function), and secondly LVEF <40% versus LVEF >50% (leaving out patients with a LVEF ≥40% and ≤50%). Since the results of these analyses were highly consistent, we only report on our original choice.

RESULTS

Patient characteristics

The mean age (SD) of the 6806 patients was 69 (±13) years and 41% were female. A substantial proportion of patients had ischemic heart disease (64%), a history of hypertension (54%), documented diabetes (27%) or chronic atrial fibrillation (24%). The median duration of the index hospitalisation was 10 days (interquartile range: 6–16).

Patients not in the analysis (n=3895) were older and included more females. Fewer patients were known with an ischemic heart disease, while a history of stroke was more common in these patients. Furthermore, out of the analyses, most patients (68%) where admitted to a general internal medicine ward, as compared to the patients who were in the analysis (Table 1).

Table 1. Differences in characteristics of patients with preserved and depressed left ventricular function

	Patients with known left ventricular function			Patients not in the analysis
	PLVF (n=3148)	LVSD (n=3658)	*P**	(n=3895)
Age (mean, SD)	71 ±12	67 ±13	< 0.001	76 ±11.6
Women (%)	1739 (55)	1065 (29)	< 0.001	2216 (57)
Men >70 years (%)	666 (21)	961 (26)	< 0.001	1039 (27)
Women > 70 years (%)	1099 (35)	607 (17)	< 0.001	1748 (45)
Co-morbidity:				
Hypertension (%)	1845 (59)	1829 (50)	< 0.001	2005 (52)
Diabetes Mellitus (%)	816 (26)	1016 (28)	0.09	1075 (28)
Ischemic heart disease (%)	1851 (59)	2508 (69)	< 0.001	2060 (53)
Previous revascularisation (%)	377 (12)	674 (18)	< 0.001	291 (8)
Renal insufficiency (%)	155 (5)	220 (6)	0.05	296 (8)
Prior Stroke (%)	492 (16)	501 (14)	0.02	814 (21)
Chronic atrial fibrillation (%)	795 (25)	827 (23)	0.01	860 (22)
LVEF (mean, SD)	56 ±9.8	33 ±10.9	<0.001	n.a.
Speciality at admission (%):			<0.001	
General internal medicine	1299 (42)	1164 (32)		2659 (68)
Cardiology / cardiovascular surgery	1615 (51)	2288 (63)		769 (20)
Other	231 (7)	197 (5)		458 (12)
Hopitalisation in days (median,IQR)	10 (6 -16)	10 (6-15)	0.26	9 (5-14)
Contribution of HF to index admission (%)	1189 (38)	1904 (52)	< 0.001	1141 (29)

LVEF= left ventricular ejection fraction

* the p-value refers to the statistical difference between PLVF and LVSD

The comparison between patients with and without LVSD revealed that almost half of all patients (n=3148, 46%) had PLVF. Patients with PLVF were on average 4 years older and more often women (55% versus 29%, p<0.001) than patients with LVSD (Table 1). Patients with PLVF were also more likely to have a history of hypertension (59% vs. 50%, p<0.001) and chronic atrial fibrillation (25% vs. 23%, p=0.01), whereas ischemic heart disease (59% vs. 69%, p<0.001) was more prevalent in those with LVSD. Patients with PLVF were more likely to be hospitalised in general internal medicine than those with LVSD (42% vs. 32%, p <0.001) and contribution of heart failure to index admission was less prominent (38 % vs. 52% < 0.001).

Pharmacological treatment

Table 2 gives an overview of the pharmacological treatment during hospitalisation in patients with or without LVSD. The vast majority of patients received diuretics (87% versus 85%, p=0.01), most often loop diuretics. The use of loop diuretics was the sole enrolment criterion in 5% of all patients (2% and 10% in patients with and without LVSD, respectively). Patients with LVSD were more likely to receive ACE inhibitors or Angiotensin II receptor blockers (ARBs) (82% versus 62% in PLVF, p< 0.001), as well as β-blockers (46% and 39%, p<0.001) or cardiac glycosides (41% vs 31%, p < 0.001). Calcium channel blockers were the only class of agents that was prescribed significantly more often in patients with PLVF than in patients with LVSD (28% versus 16%, p< 0.001).

Table 2. Differences in pharmacological treatment between patients preserved and depressed left ventricular function

	PLVF (n=3148)	LVSD (n=3658)	*P*
ACE inhibitors (%)	1839 (58)	2848 (78)	< 0.001
Angiotensin II receptor blockers (%)	140 (4)	218 (6)	0.005
-ACE or ARB (%)	1956 (62)	3009 (82)	< 0.001
β-Blockers (%)	1231 (39)	1679 (46)	< 0.001
Calcium channel blockers (%)	867 (28)	583 (16)	< 0.001
Cardiac glycosides (%)	986 (31)	1512 (41)	< 0.001
Diuretics (%)	2679 (85)	3188 (87)	0.01
-Loop diuretic (%)*	2431 (91)	2952 (93)	0.01
-Thiazide diuretic (%)*	343 (13)	381 (12)	0.32
i.v. inotropic agents (%)	204 (7)	380 (10)	< 0.001
Nitrates (%)	1451 (46)	1811 (50)	0.005
Spironolactone (%)	527 (17)	1070 (29)	< 0.001
Statins (%)	668 (21)	937 (26)	< 0.001

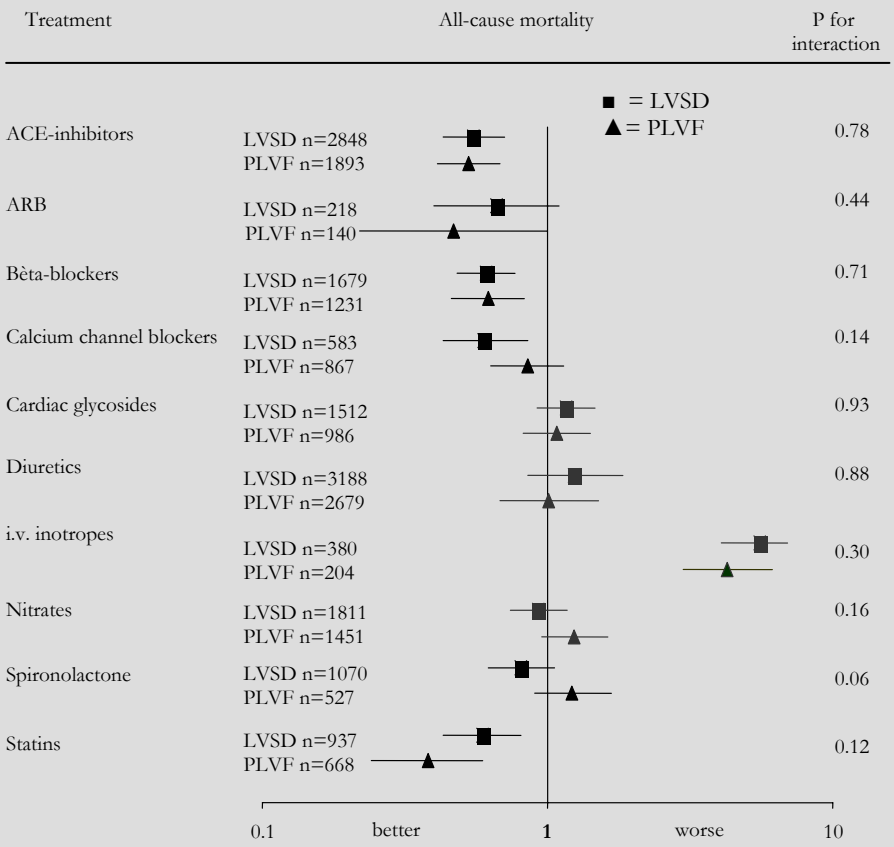
* the proportions may add up more than 100% as patients received both diuretics

Pharmacological treatment (multivariable analysis)

Patients receiving ACE-inhibitors had lower 12-week death rates than those not receiving ACE-inhibitors (OR 0.55, 95% CI 0.43-0.71; Figure 1). Similar results were observed in relation to treatment with β-blockers (OR 0.61, 95% CI 0.48-0.77) and statins (OR 0.59, 95%

CI 0.43-0.81). In contrast, treatment with IV inotropic agents was associated with worse outcome (OR 5.53, 95% CI 4.07-6.95). Patients receiving cardiac glycosides, diuretics and nitrates had similar 12-week mortality as those not receiving these agents. Noteworthy, there was no statistical evidence of a heterogeneous effect of any agent between patients with and without LVSD (P for interaction, all >0.05).

Figure 1. All cause mortality with respect to pharmacological treatment



Adjusted for age, gender, hypertension, diabetes, ischemic heart disease, renal failure, prior stroke, chronic atrial fibrillation and pharmacological treatment.

LVSD = left ventricular systolic dysfunction

PLVF = preserved left ventricular function

Outcome

The incidence of all-cause mortality during 12-week follow-up although high in both groups was higher in patients with LVSD than those without (12% versus 10%, OR 1.35, 95% CI 1.13-1.62). No significant differences were observed in the need for re-admission (22% versus 21%), time to first re-admission or number of days that patients were hospitalised during the follow-up period (Table 3). NYHA classification at follow-up did not differ between patients with and without LVSD (25% and 24% had NYHA III/IV, respectively). More patients with

LVSD (29%) viewed their quality of life as "quite poor" to "very poor" as compared to 23% in the preserved group (p=0.04).

Table 3. Differences in outcome between patients with preserved and depressed left ventricular function

	PLVF (n=3148)	LVSD (n=3658)	*P*
Total mortality (%)‡	307 (10)	425 (12)	0.01
Re-admission < 12 weeks (%)	676 (22)	759 (21)	0.47
-time to 1ste re-admission in days (median, IQR)	29 (10-54)	28 (10-53)	0.66
-hospitalisation time in days during follow-up (median,IQR)	11 (6-22)	11 (5-22)	0.30
12-week follow-up interview† (n,%)	1124 (36)	1304 (36)	
NYHA classification:			0.64
Class I/II (%)	844 (76)	965 (75)	
Class III/IV (%)	270 (24)	327 (25)	
Quality-of-life:			0.04
Very good-quite good (%)	516 (46)	545 (42)	
Average (%)	340 (30)	380 (29)	
Quite poor- very poor (%)	257 (23)	369 (29)	

‡ Patients who died during index hospitalization or within the 12 week follow-up period
† Only patients who attended the 12-week follow-up interview
NYHA= New York Heart Association classification

Outcome (multivariate analysis)

After adjustment for age, gender, co-morbidity and pharmacological treatment, patients with LVSD had higher mortality than patients with PLVF (OR 1.4, 95% CI 1.1-1.6, p=0.001). No differential effect of the presence or absence of left ventricular systolic function on all-cause mortality was observed in subgroups of patients according to clinical characteristics, except for diabetes (p=0.03) (Figure 2).

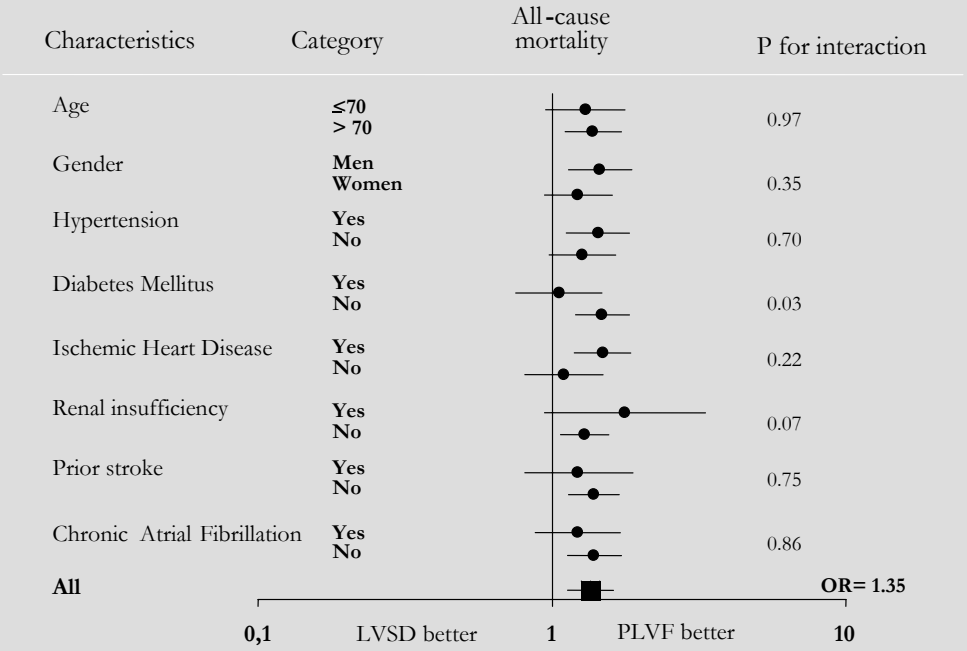
DISCUSSION

Almost half of heart failure patients enrolled in the EuroHeart Failure Survey with left ventricular function determination had preserved left ventricular function. This group of patients had different patient characteristics to that of patients with LVSD, including advanced age, a higher proportion of women, history of hypertension and chronic atrial fibrillation. We furthermore observed higher mortality in patients with LVSD, but mortality was high in both groups.

Our findings are in agreement with prior reports suggesting that patients with LVSD are at increased risk for mortality.[15-21] However, there is growing recognition that heart failure caused primarily by abnormalities in relaxation / diastole represents a substantial proportion of all heart failure patients and is also associated with a high morbidity and mortality. We

showed that 12-week mortality was high in both groups, whereas every fifth patient, regardless of LV function, was re-admitted within 12 weeks. In the recently published CHARM-Preserved trial, 24% of patients in the placebo arm experienced a composite endpoint of cardiovascular death or hospital admission for heart failure, while 18.5% of these patients were hospitalised for heart failure over 36.6 months of follow-up.[22] The cardiovascular mortality among these patients were 58% lower than in CHARM patients with low LVEF <40%.[23,24]

Figure 2. Relation between left ventricular systolic function and mortality in subgroup of patients according to patient characteristics.



Adjusted for age, gender, hypertension, diabetes, ischemic heart disease, renal failure, prior stroke, chronic atrial fibrillation and pharmacological treatment.

LVSD = left ventricular systolic dysfunction / PLVF = preserved left ventricular function

The definition of heart failure with preserved systolic function or diastolic heart failure remains a matter of controversy[12,25] and a difficult exercise in clinical practice. This probably explains why clinical trials have been lacking and guidelines on the management of this subset of patients remain mainly speculative.[6] So far, only a subset of patients enrolled in the DIG trial with EF >45% and the CHARM preserved arm have extensively studied the effect of Digoxin and Candesartan, respectively in PLVF patients. Digoxin reduced heart failure hospitalisations and the Angiotensin II receptor blockers (ARB) reduced cardiovascular hospitalisations in these trials.[22,26] Our analysis on the large EuroHeart Failure Survey

population provides additional information on the specific clinical profile of patients with PLVF and the way these patients are treated in Europe.

We included only patients with a known LV function, thus excluding 3895 patients (36%) of whom we had no information in this context. However, according to the guidelines, echocardiography is encouraged in all heart failure patients.[5,6] The high percentage of patients who could not be included in this secondary analysis reflects the lack of this diagnostic procedure in patients with proven or suspected heart failure.

As discussed in the main article of the EuroHeart Failure Survey[8], adherence to the guidelines regarding ACE-inhibitors was observed in a majority of patients with a documented ventricular dysfunction, whereas treatment with β-blockers was clearly under-prescribed. As mentioned earlier, treatment guidelines lack evidence based recommendations for patients with a preserved left ventricular function. It is therefore not possible to compare the treatment of these patients with the guidelines. Moreover, since more patients with PLVF were hospitalised in general internal medicine as compared to those with LVSD, this clearly could affect management. Although there is currently no evidence available from randomised controlled trials on treatment of patients with a preserved LVF with ACE-inhibitors or β-blockers, a considerable percentage of these patients were treated with the above mentioned drugs (58% and 39%, respectively). For ACE-inhibitors, the rate of prescription among this hospitalised preserved LVF group compares favourably to the rate reported in CHARM Preserved (58% versus 18.6%) whereas the use of β-blockers (39% versus 55.5%) was lower than in the clinical trial.[22] In CHARM preserved there was a statistically marginal effect of the ARB candesartan on the outcome of cardiovascular mortality or heart failure hospitalisations. However, the total number of these hospitalisations, both for patients and episodes, was significantly reduced in this trial. The use of cardiac glycosides was significantly lower in the PLVF group although the rate of atrial fibrillation was slightly greater in the LVSD group. The relatively high rate of prescription of calcium channel blockers in the preserved group, one of the few drugs that are (according to the guidelines) indicated in this subgroup of patients, probably reflects the greater proportion of patients with a history of hypertension.

This study is the first to compare the effects of pharmacological treatment in patients with or without LVSD. We would like to stress however, that one should be very cautious in interpreting these observational data. Use of ACE-inhibitors or β-blockers was associated with improved survival, reflecting either the effects of treatment or patient selection. Therapy with diuretics, cardiac glycosides and nitrates seemed to have no influence on mortality, whereas those treated with intravenous inotropic agent had a worse prognosis indicating the poor clinical condition of patients who need intravenous support with these drugs. Interestingly,

this analysis revealed no interaction between the apparent effects of treatment on mortality and the presence or absence of LVSD.

Our study also observed the sub-optimal use of diagnostic procedures to evaluate LVF in daily practice, as 3895 patients were left out of this analysis due to the absence of this evaluation. Knowing the cardiac function is of great importance, as the guidelines primarily focus on heart failure patients with LVSD.[6] Given the limited number of randomised trials conducted in PLVF patients, the treatment of these patients is referred to as highly speculative. Several ongoing trials address specifically the interest of beta-blockers (SENIOR), ACE-Inhibitors (PEP-CHF) or ARBs (I-Preserve) in the setting of patients with preserved systolic function. Taken this into account one could argue that a large majority of the 10,701 patients in the EuroHeart Failure Survey was not treated evidence-based. This was mainly due to the missing evidence of cardiac dysfunction and the absence of evidence-based treatment aiming at PLVF patients. In order to provide optimal treatment to all heart failure patients, we should be more aware of the under-utilisation in evaluating the LVF. Furthermore, we would like to stress that the observed absence of a heterogeneous effect between patients with or without LVSD does not mean that patients with PLVF will derive the same benefit from pharmacological treatment as those with LVSD. This observation deserves confirmation in randomised trials. Thus the evaluation of LVF remains an area for improvement.

This study has certain limitations that should be taken into account when interpreting the results. It should be noted that surveys like the EuroHeart Failure Survey are prone to information and selection bias. Since a limited number of centers were recruited across the 24 countries, interpretation of the results must be cautious due to a potential center effect. However, our findings with respect to the proportion of patients with PLVF and use of various treatments were in agreement with the IMPROVEMENT survey, which was performed by primary care physicians in the same European countries.[27]

Furthermore, we acknowledge the fact that only 64% of our overall population had undergone an assessment of the left ventricular function and cannot exclude selection bias, as the excluded patients slightly differed from those who were in the analysis. Nevertheless, our findings regarding patients with heart failure are in line with other observational studies.[15-17,21] By design, the EuroHeart Failure survey included clusters of University hospitals and general hospitals. We cannot therefore extend our observation to the overall heart failure population as this selection of centers might impact on patients' profile and treatment modalities. The selection of patients studied here was based on the record of the value of ejection fraction whatever the method used. We also used an arbitrary threshold of 40% to separate depressed and preserved or mildly reduced systolic function. However, a sensitivity analysis showed comparable results whatever the threshold for ejection fraction used. Finally, the impact of the

various cardiovascular medications was made in the context of an observational study, not of a randomised trial.

In conclusion, this study showed that a high percentage of hospitalised heart failure patients had PLVF. Although major statistical differences exist regarding clinical characteristics and treatment, morbidity and mortality was high in both groups. A considerable number of patients in the preserved group were treated with drugs (ACE-inhibitors and β-blockers) that have a documented impact on survival in patients with a depressed LV systolic ventricular function. Although there was still under-utilisation of these drugs according to the guidelines in the depressed group, far more patients in this group received ACE-inhibitors or β-blockers compared to patients with a preserved ventricular function. Finally, only a limited number of patients were treated by ARBs in both groups. A comparison of the effect of pharmacological treatment, in the context of an observational study did not reveal an interaction of the treatment effect on mortality between LVSD and PLVF.

REFERENCES

1. Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? *J Am Coll Cardiol*. 2000;36:2284-6.
2. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol*. 1993;22:6A-13A.
3. Cleland JG, Swedberg K, Poole-Wilson PA. Successes and failures of current treatment of heart failure. *Lancet*. 1998;352 Suppl 1:SI19-28.
4. Schaufelberger M SK, Köster M, Rosén M, Rosengren A. Decreasing One-year Mortality and Hospitalisation Rates for Heart Failure in Sweden. Data from the Swedish Hospital Discharge Registry 1988 to 2000. *Eur Heart J*. Accepted Eur Heart J 2003.
5. The treatment of heart failure. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. *Eur Heart J*. 1997;18:736-53.
6. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001;22:1527-60.
7. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? *J Am Coll Cardiol*. 2002;39:138-41.
8. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, Dietz R, Gavazzi A, Van Gilst WH. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 2: treatment. *European Heart Journal*. 2003;24:464-474.
9. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. *European Heart Journal*. 2003;24:442-463.
10. Cleland JGF, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, Gavazzi A, Hobbs R, Korewicki J, Madeira HC. The Euro Heart Failure Survey of The EUROHEART Survey Programme: A survey on the quality of care among patients with heart failure in Europe. *European Journal of Heart Failure*. 2000;2:123-132.
11. Guidelines for the diagnosis of heart failure. The Task Force on Heart Failure of the European Society of Cardiology. *Eur Heart J*. 1995;16:741-51.
12. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *European Heart Journal*. 1998;19:990-1003.
13. Zile MR. Heart failure with preserved ejection fraction: is this diastolic heart failure? *Journal of the American College of Cardiology*. 2003;41:1519-1522.
14. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J, Yusuf S. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *The Lancet*. 2003;362:759-766.
15. Cowie MR, Wood DA, Coats AJS, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart*. 2000;83:505-510.
16. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, Grobbee DE. The prognosis of heart failure in the general population. The Rotterdam Study. *European Heart Journal*. 2001;22:1318-1327.

17. Cohen-Solal A, Desnos M, Delahaye F, Emeriau JP, Hanania G. A national survey of heart failure in French hospitals. *European Heart Journal*. 2000;21:763-769.
18. Senni M, Redfield MM. Heart failure with preserved systolic function : A different natural history? *Journal of the American College of Cardiology*. 2001;38:1277-1282.
19. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol*. 2003;41:1510-8.
20. Masoudi FA, Havranek EP, Smith G, Fish RH, Steiner JF, Ordin DL, Krumholz HM. Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol*. 2003;41:217-23.
21. Gustafsson F, Torp-Pedersen C, Brendorp B, Seibaek M, Burchardt H, Kober L. Long-term survival in patients hospitalized with congestive heart failure: relation to preserved and reduced left ventricular systolic function. *Eur Heart J*. 2003;24:863-870.
22. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *The Lancet*. 2003;362:777-781.
23. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *The Lancet*. 2003;362:772-776.
24. McMurray J, Ostergren J, Pfeffer M, Swedberg K, Granger C, Yusuf S, Held P, Michelson E, Olofsson B. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure--Assessment of Reduction in Mortality and morbidity (CHARM) programme. *European Journal of Heart Failure*. 2003;5:261-270.
25. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation*. 2002;105:1387-93.
26. The Digitalis Investigation Group. The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. *N Engl J Med*. 1997;336:525-533.
27. Cleland JGF, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F, Freemantle N, Gavazzi A, van Gilst WH, Hobbs FDR. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *The Lancet*. 2002;360:1631-1639.

Management of specific sub-groups of patients

Chapter 6

Management of patients with heart failure in clinical practice: differences between men and women

Management of patients with heart failure in clinical practice: differences between men and women

Lessons from the Euro Heart Survey on Heart Failure

M.J. Lenzen, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
A. Rosengren, Göteborg, Sweden
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
F. Follath, Zürich, Switzerland
E. Boersma, Rotterdam, the Netherlands
M.L. Simoons, Rotterdam, the Netherlands
J.G.F. Cleland, Kingston upon Hull, UK
M. Komajda, Paris, France

Submitted

ABSTRACT

Objectives: This study evaluated gender differences in clinical characteristics, treatment and outcome among patients with heart failure, and to which extent these differences are due to age and differences in ventricular function.

Background: Although gender differences are observed among heart failure patients, few studies have been adequately powered to investigate these differences.
Methods: The Euro Heart Survey on Heart Failure screened discharge summaries of 10,653 patients (47% women) with heart failure over a 6-week period in 115 hospitals from 24 countries belonging to the European Society of Cardiology (ESC).

Results: Men were younger (68.5 vs. 74.5 years, p<.001), and more often had evidence of coronary artery disease (66% vs. 55%, age-adjusted odds ratio (OR) 0.61; 95%CI 0.57-0.67). Women were more likely to have hypertension, diabetes, or valvular heart disease. Fewer women had an investigation of left ventricular function (58% vs. 72%, age-adjusted OR 0.66; 95%CI 0.61-0.72), and among those investigated, fewer had moderate or severe left ventricular systolic dysfunction (41% vs. 67%, age-adjusted OR 0.36; 95%CI 0.33-0.40). Drugs with a documented impact on survival, i.e. ACE-inhibitors and beta-blockers were given less often to women, even after adjusting for age and left ventricular function (OR 0.77; 95%CI 0.68-0.86) OR 0.87; 95%CI 0.78-0.98, respectively). Age-adjusted 12-week mortality was similar for men and women (OR 0.98; 95%CI 0.88-1.11).

Conclusions: Fewer women had an assessment of left ventricular function, but, when investigated, had better ventricular function. Women were less often treated with evidence-based drugs, even after taking age and ventricular function into account. Clinicians need to be aware of deficiencies in the treatment of women with heart failure and measures should be taken to rectify them.

INTRODUCTION

Chronic heart failure is a major cause of morbidity and mortality, and the reason for at least 20% of all hospital admissions in patients older than 65 years.[1,2] Major advances over the last two decades in the diagnosis and treatment of heart failure have proven highly effective in reducing morbidity and mortality among both men and women. However, survival is still poor among both men and women, and the absolute number of women dying of heart failure each year still increases.[3] Men and women with heart failure have different clinical characteristics, in that women are older, and have more hypertension but less evidence of coronary heart disease and better ventricular function, compared to men with heart failure.[3] Few studies have been adequately powered to investigate how much of these known differences between men and women are due to gender alone, and how much is due to known other differences such as the discrepancies in age, ventricular function, or cause of heart failure. The large number of both men and women, enrolled in the Euro Heart Survey on Heart Failure (EHS-HF), the extensive data collection of patient characteristics, investigations and treatment provide a unique opportunity to analyze gender differences in patients with confirmed or suspected heart failure.

METHODS

We performed a comparison of men and women who were enrolled in the EHS-HF. The design details of this observational study, which was undertaken between March 2000 and May 2001, were published previously.[4,5] Briefly, all consecutive discharges and deaths in the departments of cardiology, cardiovascular surgery, general internal medicine, non-vascular surgery and geriatrics were screened over a 6-week period. Patients who fulfilled at least one of the following criteria were enrolled:

(1) a clinical diagnosis of heart failure during the admission;
(2) a diagnosis of heart failure recorded at any time in the last three years;
(3) administration of a loop diuretic for any reason other than renal failure within 24h of death or discharge;
(4) pharmacological treatment for heart failure or ventricular dysfunction within 24h of death or discharge.

From a total of 46,788 deaths and discharges from 115 hospitals in 24 ESC member countries, 10,701 patients with suspected or confirmed heart failure were enrolled in the EHS-HF. After exclusion of 48 patients with missing data for age and gender, the total study population consisted of 10,653 patients.

Information on clinical characteristics, diagnosis, co-morbid conditions, investigations, treatment, was obtained from medical records. Median (quartiles) follow up was 12 (11-14)

weeks. CAD was defined as a history of coronary revascularization procedure or myocardial infarction or angina pectoris. Patients were considered to have left ventricular systolic dysfunction (LVSD) if they had a left ventricular ejection fraction of < 45%, or moderate or severe impairment of left ventricular (LV) systolic function on echocardiography. Patients with an ejection fraction of ≥ 45%, as well as patients with a normal or only mildly depressed LV systolic function were classified as having preserved LV function.

Statistical analysis

Continuous variables are described as mean values with their corresponding standard deviation (SD), and dichotomous variables are described as counts and percentages. To evaluate the differences in clinical characteristics between men and women, chi-square tests and Student's *t*-tests were applied as appropriate. In addition, univariate and multivariate analyses were performed to study the association in clinical variables and outcome between men and women. In the multivariate analyses we adjusted for age and a number of clinical variables with a *p*-value of < 0.10 in the univariate analyses. These variables included history of hypertension, diabetes, stroke or TIA, respiratory disease, coronary artery disease, cardiomyopathy, and atrial fibrillation. Adjustment for LVSD was done in a subgroup of patients, in whom the left ventricular function was known (n=6986). We report odds ratios (OR) and corresponding 95% confidence intervals (CI). For all tests, a *p*-value of <0.05 (two-sided) was considered statistically significant. All calculations were performed using the SPSS 12.0.1 software package.

RESULTS

In table 1, the baseline characteristics of the 10,662 patients (47% women) with suspected or confirmed heart failure are summarized. Women were significantly older than men (74.5 versus 68.5 years, p <0.001) with more patients aged >80 years (36% versus 19%, p <0.001). A history of hypertension and diabetes was more prevalent among women, whereas men more often were smokers and heavy alcohol drinkers. Fifty-five per cent of the women but 66% of the men had known CAD (p<0.001), and corresponding figures for coronary revascularization were 18% and 36% (p<0.001), respectively. Older patients (≥ 70 years) had more co-morbid conditions such as stroke (20% versus 12%, p <0.001), renal dysfunction (19% versus 14%, p <0.001), or atrial fibrillation (47% versus 35%, p <0.001).

Table 2 shows that women less often were admitted to a cardiology ward compared to men (35% versus 51%, p <0.001). Left ventricular function was measured less often in women (58% versus 72%, p<0.001), and when measured, fewer women had left ventricular systolic dysfunction (41% versus 67%, p<0.001). In a subgroup of patients who had an

Table 1. Baseline characteristics by sex and age

		Total (N)	All patients (n=10.653)			Patients < 70 years (n=4196)			Patients ≥ 70 years (n=6457)		
			Men (%)	Women (%)	*P*	Men (%)	Women (%)	*P*	Men (%)	Women (%)	*P*
N		10,653	5637	5016		2776	1420		2861	3596	
Age (mean, SD)		71.3 ±12.7	68.5 ±12.7	74.5 ±11.9	<.001	58.3 ±9.0	59.7 ±9.0	<.001	78.3 ±6.4	80.4 ±6.7	<.001
	< 60	1827	23	11		47	37		--	--	
Age group	60 – 69	2369	26	18		53	63	<.001	--	--	
	70 – 79	3611	32	36	<.001	--	--		63	50	
	> 80	2846	19	36		--	--		37	50	<.001
Current smoker		1288	17	6	<.001	24	11	<.001	11	4	<.001
Heavy alcohol drinker, ever		684	11	2	<.001	15	4	<.001	6	1	<.001
History of hypertension		5653	48	58	<.001	48	56	<.001	48	59	<.001
Diabetes		2894	26	29	<.001	25	29	<.05	26	29	<.05
Stroke or TIA		1803	16	18	<.05	11	13	ns	21	20	ns
History of renal dysfunction		1823	19	15	<.001	14	13	ns	24	16	<.001
Respiratory disease		3368	33	30	<.05	27	29	ns	38	31	<.001
Cumulative evidence for CAD*		6451	66	55	<.001	65	53	<.001	66	56	<.001
Myocardial infarction, ever		4121	71	55	<.001	73	54	<.001	45	31	<.001
History of angina, ever		4533	69	72	<.05	71	77	<.05	45	39	<.001
Revascularization (PCI or CABG), ever		1933	36	18	<.001	45	30	<.001	18	8	<.001
Dilated cardiomyopathy		255	3	1	<.001	5	3	<.05	2	1	<.001
Atrial fibrillation, ever		4485	41	44	<.05	34	35	ns	47	47	ns
Chronic AF		2469	22	24	<.05	17	18	ns	27	26	ns

* CAD (coronary artery disease): myocardial infarction, angina, or revascularization
ns=not significant

Table 2. Clinical characteristics by sex and age

	Total (N)	All patients (n=10.653)			Patients < 70 years (n=4196)			Patients ≥ 70 years (n=6457)		
		Men (%)	Women (%)	*P*	Men (%)	Women (%)	*P*	Men (%)	Women (%)	*P*
N	10,653	5637	5016		2776	1420		2861	3596	
Ward of admission:										
Cardiology (incl. cardiovascular surgery)	4653	51	35		65	53		38	28	
General internal medicine	5097	41	55	<.001	30	42	<.001	52	60	<.001
Non-vascular surgery or geriatrics	903	7	10		4	5		10	12	
Assessment of left ventricular (LV) function	6986	72	58	<.001	82	73	<.001	64	52	<.001
LVSD*	3920	67	41	<.001	72	44	<.001	62	39	<.001
LVEF measured, ever	6228	66	51	<.001	76	65	<.001	55	45	<.001
Ejection fraction < 45%	3048	59	34	<.001	63	38	<.001	53	32	<.001
Echocardiography performed:	6832	70	58	<.001	78	70	<.001	63	53	<.001
Normal / Mild LV systolic function	3030	39	65		35	60		44	67	
Moderate / Severe LV systolic dysfunction	3078	61	35	<.001	65	40	<.001	56	33	<.001
LV dilatation	1702	33	13	<.001	39	17	<.001	26	12	<.001
Moderate/severe diastolic dysfunction	816	14	9	<.001	15	9	<.001	12	10	<.05
Mitral stenosis	206	2	5	<.001	2	6	<.001	1	5	<.001
Aortic stenosis	497	6	10	<.001	4	6	<.05	8	11	<.001
Mitral regurgitation	1918	27	30	<.05	28	26	ns	26	32	<.001
Aortic regurgitation	498	7	8	<.05	6	6	ns	8	9	ns

* LVSD= ejection fraction <45% or moderate to severe LV systolic dysfunction
ns=not significant

echocardiogram, valvular heart disease was seen more often in women (41% versus 34%, p <0.001). The most frequently observed valvular heart disease was mitral regurgitation (30% and 27% for men and women, respectively (p=0.02)). In addition to these gender differences, it is also important to note that younger patients were more likely to be admitted to cardiology wards (61% versus 32%, p <0.001), and more often had an assessment of the LV function (79% versus 57%, p <0.001).

After adjusting for age, most of the observed gender differences remained statistically significant (Table 3), however, gender differences with respect to stroke or TIA, atrial fibrillation and aortic regurgitation did not persist after adjustment for age. Irrespective of left ventricular function, women were more likely to have hypertension but less often a history of an ischemic heart disease (Table 4).

Table 3. Unadjusted and adjusted ORs for the association in clinical characteristics between men and women (total population, n=10,653)

	Gender differences (reference group is men)	
	Unadjusted OR* (95% CI)	OR* adjusted for age (95%CI)
Current smoker	0.32 (0.28-0.36)	**0.40 (0.35-0.46)**
Heavy alcohol drinker, ever	0.14 (0.11-0.18)	**0.17 (0.14-0.22)**
History of hypertension	1.50 (1.39-1.62)	**1.46 (1.35-1.58)**
Diabetes	1.17 (1.07-1.27)	**1.15 (1.05-1.26)**
Stroke or TIA	1.15 (1.04-1.27)	0.98 (0.88-1.09)
History of renal dysfunction	0.77 (0.69-0.85)	**0.66 (0.60-0.74)**
Respiratory disease	0.90 (0.83-0.98)	**0.83 (0.76-0.90)**
Cumulative evidence for CAD†	0.64 (0.59-0.70)	**0.61 (0.57-0.67)**
Dilated cardiomyopathy	0.40 (0.30-0.53)	**0.57 (0.43-0.76)**
Atrial fibrillation, ever	1.13 (1.05-1.22)	0.99 (0.92-1.08)
Ward of admission:		
Cardiology	0.51 (0.48-0.56)	**0.66 (0.61-0.72)**
General internal medicine	1.75 (1.62-1.89)	**1.43 (1.32-1.55)**
Other ward	1.35 (1.17-1.54)	1.07 (0.93-1.23)
Assessment of LV function:	0.52 (0.48-0.57)	**0.66 (0.61-0.72)**
LVSD‡	0.34 (0.31-0.37)	**0.36 (0.33-0.40)**
Echocardiography performed:	0.58 (0.53-0.62)	**0.71 (0.65-0.77)**
Mitral stenosis	3.46 (2.55-4.69)	**3.90 (2.86-5.33)**
Aortic stenosis	1.74 (1.45-2.09)	**1.48 (1.23-1.80)**
Mitral regurgitation	1.13 (1.02-1.26)	**1.13 (1.01-1.26)**
Aortic regurgitation	1.28 (1.06-1.53)	1.19 (0.98-1.43)

* Women compared to men
† CAD (coronary artery disease): myocardial infarction, angina, or revascularization
‡ LVSD= EF<45% or moderate to severe LV systolic dysfunction

Men and women differed with respect to pharmacological treatment (Table 5). Fewer women were treated with drugs with a documented impact on survival (ACE-inhibitors (OR 0.66; 95%CI 0.61-0.71), beta-blockers (OR 0.73; 95%CI 0.67-0.79), and spironolactone (OR 0.70; 95%CI 0.64-0.77), whereas they were more often treated with diuretics (OR 1.30; 95%CI 1.16-1.46) and cardiac glycosides (OR 1.11; 95%CI 1.03-1.20). In addition, women were also

Table 4. Age, hypertension and CAD by gender and LVF among patients with known LV function (n=6986)

	Men (n=4082)	Women (n=2904)	OR* adjusted for age (95%CI)
Left ventricular systolic dysfunction (n)	2738	1182	
Mean age, SD	65.8 ±12.5	71.1 ±12.5	
History of hypertension (%)	1292 (47)	678 (57)	**1.39 (1.21-1.60)**
Myocardial infarction, ever (%)	1529 (56)	574 (49)	**0.67 (0.59-0.78)**
History of angina (%)	1307 (48)	543 (46)	**0.86 (0.75-0.99)**
Revascularization (PCI, CABG) (%)	768 (28)	197 (17)	**0.54 (0.45-0.64)**
Cumulative evidence for CAD† (%)	1939 (71)	784 (66)	**0.69 (0.59-0.80)**
Preserved left ventricular function (n)	1344	1722	
Mean age, SD	68.3 ±12.5	72.7 ±11.7	
History of hypertension (%)	710 (53)	1075 (62)	**1.41 (1.22-1.63)**
Myocardial infarction, ever (%)	497 (37)	394 (23)	**0.49 (0.41-0.57)**
History of angina (%)	650 (48)	686 (40)	**0.69 (0.60-0.80)**
Revascularization (PCI, CABG) (%)	334 (25)	196 (11)	**0.41 (0.34-0.50)**
Cumulative evidence for CAD† (%)	861 (64)	913 (53)	**0.60 (0.52-0.70)**

* Women compared to men
† CAD (coronary artery disease): myocardial infarction, angina, or revascularization
PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting

less likely to be treated with anti-thrombotic drugs (OR 0.67; 95%CI 0.61-0.73). After adjusting for age and clinical characteristics including CAD, the observed gender differences, remained significant for ACE-inhibitors, beta-blockers and spironolactone. Diuretics and cardiac glycosides, however, lost their statistical significance. We repeated the analyses in a subgroup of patients who had an assessment of LV function (n=6991). After adjustment for age and clinical variables in addition to left ventricular systolic dysfunction, ACE-inhibitors and beta-blockers were still less likely to be used in women, whereas diuretics and cardiac glycosides were more often prescribed to women than to men. Patients admitted to cardiology wards (including cardiovascular surgery), were treated more often with ACE-inhibitors (73%), beta-blockers (53%), and spironolactone (26%) compared to patients admitted to general internal medicine wards (65%, 29%, and 20% respectively), or patients admitted on non-vascular surgery or geriatric wards (57%, 27%, and 20% respectively). The observed gender differences in treating patients with ACE-inhibitors, beta-blockers and spironolactone remained significant, irrespective of admission to cardiology or general internal medicine. In patients who were admitted to non-vascular surgery or geriatric wards, however, no gender differences in treatment with ACE-inhibitors, beta-blockers and spironolactone was found.

No substantial gender differences could be demonstrated with respect to 12-week mortality and readmission within 12 weeks (Table 6). Although the percentage of women who died during the observation period was slightly higher (14.1% versus 11.9%), gender was not an independent predictor of mortality (OR 1.15; 95%CI 0.97-1.35).

Table 5. Pharmacological treatment by gender, including unadjusted and adjusted ORs for the association in treatment (total population, n=10,653)

			Gender differences		
Total population (n=10,653)	Men (n=5637)	Women (n=5016)	Unadjusted OR* (95% CI)	OR* adjusted for age (95%CI)	Adjusted OR*, excluding LVSD (95%CI) †
ACE-inhibitors	67%	57%	**0.66 (0.61-0.71)**	**0.73 (0.67-0.79)**	**0.68 (0.63-0.74)**
Beta-blockers	40%	33%	**0.73 (0.67-0.79)**	**0.87 (0.80-0.95)**	**0.90 (0.83-0.99)**
Spironolactone	23%	18%	**0.70 (0.64-0.77)**	**0.79 (0.72-0.87)**	**0.80 (0.72-0.88)**
Diuretics	85%	88%	**1.30 (1.16-1.46)**	1.13 (1.00-1.27)	1.09 (0.96-1.23)
Cardiac glycosides	35%	37%	**1.11 (1.03-1.20)**	1.08 (1.00-1.17)	1.08 (0.99-1.18)
Anti-thrombotic agents	81%	74%	**0.67 (0.61-0.73)**	**0.68 (0.62-0.75)**	**0.73 (0.66-0.81)**
			Gender differences		
Patients with known LV function (n=6986)	Men (n=4082)	Women (n=2904)	Unadjusted OR* (95% CI)	OR* adjusted for age (95%CI)	Adjusted OR*, including LVSD (95%CI) †
ACE-inhibitors	73%	63%	**0.63 (0.57-0.70)**	**0.68 (0.61-0.75)**	**0.77 (0.68-0.86)**
Beta-blockers	46%	37%	**0.70 (0.63-0.77)**	**0.80 (0.73-0.89)**	**0.87 (0.78-0.98)**
Spironolactone	26%	21%	**0.76 (0.68-0.85)**	**0.83 (0.74-0.93)**	0.93 (0.82-1.05)
Diuretics	85%	89%	**1.45 (1.25-1.67)**	**1.26 (1.09-1.46)**	**1.31 (1.12-1.53)**
Cardiac glycosides	35%	39%	**1.16 (1.05-1.28)**	**1.15 (1.04-1.28)**	**1.27 (1.13-1.42)**
Anti-thrombotic agents	86%	80%	**0.66 (0.59-0.75)**	**0.65 (0.57-0.74)**	**0.76 (0.66-0.87)**

* Women compared to men

† Adjusted for age, hypertension, diabetes, stroke or TIA, renal failure, respiratory disease, coronary artery disease, cardiomyopathy, and atrial fibrillation

Table 6. Unadjusted and adjusted ORs for outcome (mortality and re-admission) among women, compared to men.

	Men / Women (%)	Gender differences			
		Unadjusted OR (95% CI)	OR adjusted for age (95%CI)	Adjusted OR, excluding LVSD (95%CI) †	Adjusted OR, including LVSD (95%CI) †‡
12 week mortality	11.9 / 14.1	**1.23 (1.10-1.38)**	0.98 (0.88-1.11)	1.10 (0.97-1.24)	1.15 (0.97-1.35)
Re-admissions during follow up period	19.9 / 18.7	0.93 (0.84-1.02)	0.93 (0.84-1.02)	0.96 (0.87-1.06)	0.98 (0.86-1.11)

* Women compared to men
† Adjusted for age, hypertension, diabetes, stroke or TIA, renal failure, respiratory disease, coronary artery disease, cardiomyopathy, and atrial fibrillation
‡ Patients with assessment of LV function only, n=6986

DISCUSSION

This study confirms earlier reports that women with heart failure have a different clinical profile as compared to men, and more often have a preserved left ventricular function.[3,6] These differences remained significant after adjusting for age. In addition, women were admitted less often to cardiology wards, or had an assessment of left ventricular function, and were also less often treated with evidence-based drugs. The observed differences were still evident after adjusting for age, and other clinical variables. Despite the fact that women had better left ventricular systolic function and less often had CAD, outcomes with respect to in-hospital and total 12-week mortality were similar in men and women.

Consistent with previous reports, women were older, more often had hypertension, diabetes, cerebrovascular disease, and valvular heart disease, but had a lower prevalence of CAD and LVSD.[3,6-9] Because women were less likely to undergo assessment of the left ventricular function a substantial proportion could not be identified as having depressed or preserved left ventricular function. Although this gender difference with respect to lack of information on ventricular function confirms results from other studies,[10,11] the fact that women were less likely than men to undergo qualitative or quantitative assessment of left ventricular function causes concern, because this information is critical to confirm heart failure, to provide optimal treatment and to estimate prognosis.[12] Although our study did not identify reasons for the observed diagnostic deficiency, we were able to exclude age as an important confounder.

As discussed in previous reports, recommended drugs in patients who were enrolled in the EHS-HF, were underused.[13,14] The current study adds another dimension to this observation, namely that men and women were treated differently. Univariate analyses revealed that women were less likely to be treated with drugs that have a proven effect on reducing mortality (ACE-I, beta-blockers, and spironolactone), but were treated more often

with cardiac glycosides and diuretics. Although the observed differences decreased after adjusting for age and a number of clinical characteristics, treatment with drugs with a proven effect on reducing mortality were still less often prescribed to women compared to men. This indicates that older age and a different clinical profile in women does not altogether explain the observed gender differences in pharmacological treatment between men and women. Even in a selected group of patients, those with known LV function, women were less likely to be treated with ACE-I and beta-blockers and more often treated with diuretics and cardiac glycosides. It is in this context important to note that guidelines do not discriminate between men and women, and treatment with evidence-based drugs is advocated in all patients with heart failure and left ventricular dysfunction.[12] However, women are known to have more side effects when treated with ACE-I[15,16], and the use of cardiac glycosides may even be associated with an increased mortality among women, but not men, with LVSD.[17]

In our study, no differences were observed in the adjusted analyses regarding in-hospital and 12-week mortality despite the fact that women were less likely to be diagnosed with CAD or LVSD, both markers of increased risk. The lack of a sex difference in mortality is consistent with a large Italian registry[18], but contrasts with others.[19-21] However, our data are limited by short-term (12 weeks) follow-up and lack of certainty about the preceding duration of heart failure. Studies suggest that LVEF and CAD are stronger predictors of prognosis in women, as for every 1% increase of LVEF the decrease in mortality was 4% in women versus 1% in men, and women with CAD and heart failure have a 2.5-fold increase in the risk of mortality as compared to a 1.5-fold increase in men.[7] Potentially, fewer investigations in women might have led to prognostically important information being missed.

The limitations of this study are those inherent to observational studies involving voluntarily participating hospitals for a clinical syndrome that does not have a clear, simple objective definition. Although we attempted to include a wide spectrum of hospitals in many European countries, the results will almost certainly be biased towards better than average practices. However, a high proportion of relevant patients at each centre were included (approximately 16 patients each week per centre) suggesting that the population was relatively unselected and likely to be representative of clinical practice. One of the strengths of the survey was that it included a large number of unselected and consecutively enrolled patients from multiple hospitals across Europe with both suspected and confirmed diagnosis of heart failure. We were able to perform multivariate analyses in which we could adjust for age and a number of relevant clinical characteristics.

In conclusion, in this large population of patients with confirmed or suspected heart failure, who were enrolled in the Euro Heart Survey on Heart Failure, we confirmed that, compared to men, women are older and more likely to have preserved left ventricular

function, hypertension, diabetes, and valvular heart disease, but less likely to have a diagnosis of CAD. Women were also less likely to be admitted to cardiology wards, or have an assessment of left ventricular function and, in addition, were treated to a lesser extent with guideline recommended drugs compared to men. After adjusting for age and important clinical characteristics, the observed differences decreased, but remained statistically significant for ACE-I, beta-blockers and spironolactone. Despite better left ventricular function and less CAD, women and men had similar age-adjusted 12-week mortality. There is no evidence-based justification for treating women with heart failure less intensively than men. Clinicians need to be aware of these deficiencies in the treatment of women with heart failure and measures should be taken to rectify them.

REFERENCES

1. Jessup M, Brozena S. Heart Failure. *N Engl J Med.* 2003;348:2007-2018.
2. Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? *J Am Coll Cardiol.* 2000;36:2284-6.
3. Bello N, Mosca L. Epidemiology of coronary heart disease in women. *Prog Cardiovasc Dis.* 2004;46:287-95.
4. Cleland JGF, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, Gavazzi A, Hobbs R, Korewicki J, Madeira HC. The Euro Heart Failure Survey of The EUROHEART Survey Programme: A survey on the quality of care among patients with heart failure in Europe. *European Journal of Heart Failure.* 2000;2:123-132.
5. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. *European Heart Journal.* 2003;24:442-463.
6. Stromberg A, Martensson J. Gender differences in patients with heart failure. *Eur J Cardiovasc Nurs.* 2003;2:7-18.
7. Ghali JK, Krause-Steinrauf HJ, Adams KF, Khan SS, Rosenberg YD, Yancy CW, Young JB, Goldman S, Peberdy MA, Lindenfeld J. Gender differences in advanced heart failure: insights from the BEST study. *J Am Coll Cardiol.* 2003;42:2128-34.
8. Jessup M, Pina IL. Is it important to examine gender differences in the epidemiology and outcome of severe heart failure? *J Thorac Cardiovasc Surg.* 2004;127:1247-52.
9. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet.* 1997;350:829-33.
10. Mejhert M, Holmgren J, Wandell P, Persson H, Edner M. Diagnostic tests, treatment and follow-up in heart failure patients--is there a gender bias in the coherence to guidelines? *Eur J Heart Fail.* 1999;1:407-10.
11. Burns RB, McCarthy EP, Moskowitz MA, Ash A, Kane RL, Finch M. Outcomes for older men and women with congestive heart failure. *J Am Geriatr Soc.* 1997;45:276-80.
12. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J.* 2005;26:1115-40.
13. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, Dietz R, Gavazzi A, Van Gilst WH. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 2: treatment. *European Heart Journal.* 2003;24:464-474.
14. Lenzen MJ, Boersma E, Scholte Op Reimer WJ, Balk AH, Komajda M, Swedberg K, Follath F, Jimenez-Navarro M, Simoons ML, Cleland JG. Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials: a report from the Euro Heart Survey on Heart Failure. *Eur Heart J.* 2005;26:2706-13.
15. Shah MR, Granger CB, Bart BA, McMurray JJ, Petrie MC, Michelson EL, Tudor GE, Swedberg K, Stevenson LW, Califf RM, Pfeffer MA. Sex-related differences in the use

and adverse effects of angiotensin-converting enzyme inhibitors in heart failure: the study of patients intolerant of converting enzyme inhibitors registry. *Am J Med.* 2000;109:489-92.

16. Kostis JB, Shelton B, Gosselin G, Goulet C, Hood WB, Jr., Kohn RM, Kubo SH, Schron E, Weiss MB, Willis PW, 3rd, Young JB, Probstfield J. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). SOLVD Investigators. *Am Heart J.* 1996;131:350-5.
17. Rathore SS, Wang Y, Krumholz HM. Sex-Based Differences in the Effect of Digoxin for the Treatment of Heart Failure. *N Engl J Med.* 2002;347:1403-1411.
18. Opasich C, Tavazzi L, Lucci D, Gorini M, Albanese MC, Cacciatore G, Maggioni AP. Comparison of one-year outcome in women versus men with chronic congestive heart failure. *Am J Cardiol.* 2000;86:353-7.
19. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation.* 1993;88:107-15.
20. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol.* 1992;20:301-6.
21. Bourassa MG, Gurne O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S. Natural history and patterns of current practice in heart failure. The Studies of Left Ventricular Dysfunction (SOLVD) Investigators. *J Am Coll Cardiol.* 1993;22:14A-19A.

Management of specific sub-groups of patients

Chapter 7

Pharmacological treatment and perceived health status during 1-year follow-up in patients diagnosed with coronary artery disease, but ineligible for revascularization

Pharmacological treatment and perceived health status during 1-year follow up in patients diagnosed with coronary artery disease, but ineligible for revascularization.

Results from the Euro Heart Survey on Coronary Revascularization

M.J. Lenzen, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
T.M. Norekvål, Bergen, Norway
S. De Geest, Basel, Switzerland
B. Fridlund, Växjö, Sweden
J. Heikkilä, Jyväskylä, Finland
T. Jaarsma, Groningen, the Netherlands
J. Mårtensson, Jönköping, Sweden
P. Moons, Leuven, Belgium
K. Smith, Dundee, Scotland, UK
S. Stewart, Adelaide, Australia
A. Strömberg, Linköping, Sweden
D.R. Thompson, Hong Kong SAR China
W. Wijns, Aalst, Belgium

European Journal of Cardiovascular Nursing (2006) **5**: 115-21

ABSTRACT

Background: It has been recognized that a clinically significant portion of patients with coronary artery disease (CAD) continue to experience anginal and other related symptoms that are refractory to the combination of medical therapy and revascularization. The Euro Heart Survey on Coronary Revascularization (EHS-CR) provided an opportunity to assess pharmacological treatment and outcome in patients with proven CAD who were ineligible for revascularization.

Methods: We performed a secondary analysis of EHS-CR data. After excluding patients with ST-elevation myocardial infarction and those in whom revascularization was not indicated, 4409 patients remained in the analyses. We selected two groups: (1) patients in whom revascularization was the preferred treatment option (n=3777, 86%), and (2) patients who were considered ineligible for revascularization (n=632, 14%).

Results: Patient ineligible for revascularization had a worse risk profile, more often had a total occlusion (59% vs 37%, $p<0.001$), were treated more often with ACE-inhibitors (65% vs. 55%, $p<0.001$) but less likely with aspirin (83% vs. 88%, $p<0.001$). Overall, they had higher case-fatality at 1-year (7.0% vs. 3.7%, $p<0.001$). Regarding self-perceived health status, measured via the EuroQol 5D (EQ-5D) questionnaire, these same patients reported more problems on all dimensions of the EQ-5D. Furthermore, in the revascularization group we observed an increase between discharge and 1-year follow up (utility score from 0.85 to 1.00) whereas patients ineligible for revascularization did not improve over time (utility score remained 0.80)

Conclusion: In this large cohort of European patients with CAD, those considered ineligible for revascularization had more co-morbidities and risk factors, and scored worse on self-perceived health status as compared to revascularized patients in the revascularization group. With the exception of ACE-inhibitors and aspirin, there were no major differences regarding drug treatment between the two groups. Given these clinically significant observations, there appears to be a role for nurse-led, multidisciplinary, rehabilitation teams that target clinically vulnerable patients whose symptoms remain refractory to standard medical care.

INTRODUCTION

Angina pectoris, the most common manifestation of underlying coronary artery disease (CAD) is a condition that reportedly affects approximately 1.5-2% of the population in developed countries at one time.[1] Angina pectoris remains a significant cause of disability and reduced quality of life.[2] Treatment of patients with CAD includes risk factor management, drug therapy and revascularization techniques. In addition to drug therapy, mechanical revascularizations by means of coronary-artery bypass grafting (CABG) or, more increasingly[3] percutaneous coronary interventions (PCI) can be offered to relieve symptoms and improve quality of life and prognosis.[4-6] However, in recent years it has been recognized that there is a group of patients in whom revascularization is no option.[7] If these patients have reversible myocardial ischemia which cannot be controlled by a combination of medical therapy and revascularization, they are considered to have chronic refractory angina (CRA).[7] Yet, information on the overall proportion and prevalence of patients with proven CAD who are ineligible for revascularization is scarce. It is also observed that treatment guidelines do not focus on this clinically significant group of patients.[8] Accordingly, the management of these patients remains reserved to the preference of the treating clinician, without being directed by evidence-based guidelines.

As it is to be expected that health-related quality of life and perceived health status are inflicted by this chronic condition, it is suggested that patients with angina pectoris who are ineligible for revascularization may benefit from dedicated nurse-led multidisciplinary management programs.[9] In a range of other cardiac conditions, these nurse-led management programs have been demonstrated to cost-effectively improve health outcomes.[10]

The Euro Heart Survey on Coronary Revascularization (EHS-CR) was designed to evaluate invasive diagnosis, treatment, and 1-year outcome in patients with established CAD as seen in clinical practice.[11] As this survey also included a sizeable proportion of patients who were ineligible for revascularization, we were able to compare these patients with those who were eligible for revascularization.

STUDY AIMS

Based on compelling anecdotal and corroborating scientific evidence that a clinically significant portion of patients with CAD experience sub-optimal health outcomes and available data from the EHS-CR we examined the following important parameters in a large cohort of surveyed European patients with CAD who were either considered eligible or ineligible for coronary revascularization:

1) Pharmacological treatment
2) Perceived health status at discharge
3) One year case-fatality

It was anticipated that these data would provide supportive evidence for the application of nurse-led, multidisciplinary rehabilitation teams to improve health outcomes in clinically vulnerable patients with limited treatment options.[9]

METHODS

Design and setting

Data for this study were derived from the database of the EHS-CR. A more detailed description of this prospective, observational study were published previously.[11] In short, all consecutive patients undergoing invasive diagnostic or therapeutic procedures in the catheterisation laboratory were screened between November 2001 and March 2002. In total 130 hospitals from 31 member countries of the European Society of Cardiology (ESC) participated, and enrolled a total of 5619 patients. All consenting patients who had at least one >50% diameter stenosis in a major epicardial vessel were enrolled. Detailed information on medical history, demography, clinical and angiographic status, and treatment was collected and sent to a central database.

Study population

From the 5619 patients enrolled in the EHS-CR, patients were included in the analysis if they were admitted with a diagnosis of stable or unstable angina (the latter including non-ST elevation acute coronary syndromes), and information on the treatment option (revascularization or medical treatment) was available. Patients were excluded if they were admitted with ST-elevation myocardial infarction (n=906; 16% of the total cohort), when revascularization was not indicated (n=230; 4.1%), and if the reason for treating a patient medically was not specified (n=74; 1.3%). The remaining 4409 patients (79% of total) who were included in the analysis were then divided in two groups:

1. Those, who were eligible for revascularization (n=3777; 86%), and
2. Those, who were ineligible for revascularization (n=632; 14%).

Patients were identified as eligible for revascularization (group 1) if the treating physician indicated that revascularization was the preferred treatment option, and considered ineligible for revascularization (group 2) if they fulfilled the following criteria:

i. The general condition or vessels of the patient were not suitable for PCI or CABG (n=430; 68% of group 2),
ii. Presence of extra cardiac contra-indications for PCI or CABG (n=64; 10%), or
iii. The treating clinician estimated that the procedural risk was too high (n=138; 22%).

Measures

In addition to collecting clinical variables (e.g. demographics, risk factors, diagnosis at admission, etc), all patients were asked to fill in a generic health status questionnaire prior to hospital discharge, and at 1-year follow up. The used questionnaire, the EQ-5D[12], comprises five dimensions, namely: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each of these dimensions has three levels of severity, corresponding to "No problem", "Moderate problems", and "Severe problems". Patients were asked which statements best described their health status on the day the questionnaire was filled in. By combining one level from each of the five dimensions, a unique EQ-5D health state can be identified for individual patients. In addition, a weighted index (utility score) can be computed for each of the states based on the values of the general public elicited in the United Kingdom.[12]

These utility-scores range from –0.594 to +1, with scores < 0 being regarded as worse than death and 1 representing full health, from the perspective of the general population. The second part of the EQ-5D consists of a visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state), which is used for rating the overall health.

Statistical analysis

Statistical analyses were carried out with SPSS statistical software (version 12.01 for Windows), using mostly descriptive statistics between subsets of patients defined by treatment option. Results are presented as mean and median with corresponding values (standard deviation and inter quartiles, respectively), and percentages. To evaluate differences between the two groups, Chi-square tests, Student's *t*-test, and Kruskal-Wallis tests were applied as appropriate. Changes over time were analysed, using Wilcoxon Signed Rank test and McNemar test as appropriate. We also performed multivariate analyses to study the association in outcome and heart failure between the two groups. In the multivariate analyses we adjusted for left ventricular ejection fraction (LVEF) < 40% and a history of heart failure. We report odds ratios (OR) and corresponding 95% confidence intervals (CI). A p-value of < 0.05 was considered statistically significant (two-sided).

RESULTS

Table 1 summarises the baseline characteristics of the 4409 patients who were included in the current study, comparing patients on the basis of eligibility for revascularization. The overall proportion of patients considered ineligible for revascularization was 14% of the study population (and 11% of the total EHS-CR cohort). As compared to the revascularization

group, patients considered ineligible for revascularization often had a worse risk profile (including age, diabetes, and cardio-vascular history), but were less often current smokers (17% versus 24%, p <0.001). Nearly half of these patients (47%) had undergone a revascularization procedure prior to the current admission, versus 27% in the revascularization group (p <0.001).

Table 1. Differences in clinical characteristics between patients with and without option for revascularization

	Eligible for revascularisation	Ineligible for revascularisation	*P*
N	3777	632	
Age (mean, SD)	63.1 ±10.7	64.5 ±10.4	.003
Male gender, n (%)	2874 (76)	471 (75)	.41
Smoking, n (%):			
Current	877 (24)	102 (17)	<.001
Past	1360 (37)	267 (43)	
Diabetes mellitus, n (%):			
type 1	140 (4)	33 (5)	.001
type 2	745 (20)	163 (26)	
Hypercholesterolemia, n (%)	2516 (68)	412 (66)	.35
Hypertension, n (%)	2286 (61)	413 (66)	.002
Sedentary lifestyle, n (%)	1067 (39)	219 (48)	<.001
Congestive heart failure, n (%)	624 (17)	148 (24)	<.001
Chronic renal failure, n (%)	143 (4)	39 (6)	.005
Peripheral vascular disease, n (%)	450 (12)	105 (17)	.001
Cerebro-vascular disease, n (%)	274 (7)	71 (11)	<.001
Prior revascularisation, n (%)	1004 (27)	290 (46)	<.001
Prior CABG, n (%)	336 (9)	176 (28)	<.001
Prior PCI, n (%)	795 (21)	176 (28)	<.001
Prior myocardial infarction, n (%)	1462 (39)	313 (50)	<.001
Diagnosis at admission, n (%):‡			
Stable angina	2319 (61)	415 (66)	.002
Non-ST elevation ACS/ UA	1403 (37)	187 (30)	
Hospitalisation in days (median, IQR)	5 (3-11)	3 (2-8)	<.001

‡ Primary diagnosis missing in 91 patients

The angiographic results (Table 2) revealed that patients without option for revascularization more often had a total occlusion of a coronary artery (59% vs. 37%, p <0.001) and more often had a depressed left ventricular ejection fraction (23% vs. 10%, p <0.001).

Information on pharmacological treatment prior to admission and at discharge is presented in Table 3. At discharge a considerable number of patients were on prophylactic drugs, irrespective of eligibility status for revascularization. Between these two patient groups, those ineligible for revascularization were more often treated with ACE-inhibitors (65% vs. 55%, p < 0.001) but less likely with aspirin (83% vs. 88%, p <0.001). When broken down to patients with a LVEF < 40%, those who were ineligible for revascularization (23%) were treated more often with ACE-inhibitors as compared to patients with a depressed LVEF who were eligible for revascularization (84% versus 74%, p =0.03).

Table 2. Angiographic results

	Eligible for revascularisation	Ineligible for revascularisation	*P*
N	3777	632	
Severity of coronary artery disease, n (%):			
Single-vessel disease	1241 (33)	237 (38)	
Two-vessel disease	1199 (32)	159 (25)	.003
Three-vessel disease	1325 (35)	232 (37)	
Left main lesions	350 (9)	60 (10)	.86
Total occlusion, n (%)‡	1395 (37)	375 (59)	<.001
Left ventricular function known, n (%):	3301 (87)	546 (86)	.48
Ejection fraction >50%	2147 (65)	296 (54)	
Ejection fraction 40 – 50%	821 (25)	125 (23)	<.001
Ejection fraction <40	333 (10)	125 (23)	

‡ Total occlusion in at least one segment

In-hospital case-fatality rates were 1.4% for patients in both groups (Table 4). At 1-year the case-fatality was significantly higher in those ineligible for revascularization as compared to the revascularization group (7.0% vs. 3.7%, p <0.001). As a considerable number of patients were known to have heart failure, we adjusted for this potential confounder. The clear difference in case-fatality observed in the crude analysis (OR 1.92; 95% CI 1.36 – 2.73) disappeared almost after adjusting for LVEF < 40% (OR 1.47; 95% CI 1.00 – 2.15) and completely after adjusting for LVEF < 40% and a history of heart failure (OR 0.89; 95% CI 0.43 – 1.83). Despite initial ineligibility, a total of 24 patients (4%) underwent a revascularization procedure within one year.

Prior to discharge, patients ineligible for revascularization reported more problems (moderate or severe) on all dimensions of the EQ-5D health status questionnaire than the revascularization group (Table 5); the latter being less likely to report "no problems" on all five dimensions (33% vs. 43%, p <0.001). In addition, the EQ-5D utility score was lower in patients who were ineligible for revascularization (0.76 vs. 0.85, p <0.001).

Table 3. Pharmacological treatment at admission and discharge (in-hospital death excluded)

	Eligible for revascularisation	Ineligible for revascularisation	*P*
Treatment prior to admission, n (%)			
Aspirin	3180 (85)	520 (84)	.21
Bèta-blocker	2620 (70)	394 (63)	<.001
ACE-inhibitor	1820 (49)	354 (57)	<.001
Calcium channel blockers	1021 (27)	181 (29)	.75
Statin	1925 (52)	322 (52)	.40
Treatment at discharge, n (%)			
Aspirin	3283 (88)	514 (83)	<.001
Bèta-blocker	2756 (74)	453 (73)	.51
ACE-inhibitor	2030 (55)	404 (65)	<.001
Calcium channel blockers	1020 (27)	202 (32)	.009
Statin	2518 (68)	421 (68)	.99

Table 6 reveals the difference in perceived health status between discharge and 1-year follow up. In the revascularization group we observed an increase over time in the median utility score (0.85 to 1.00, p <0.001). Alternatively, the utility score did not improve in patients who were ineligible for revascularization (0.80 at discharge, and 0.80 at 1-year follow up, p =0.72). It should be noted, however, that information on self-perceived health status was available in 82% of patients prior to discharge, while only 63% of all patients completed the health-status questionnaire prior to discharge and at 1-year follow up.

Table 4. Outcome at discharge and 1-year follow up

(proportions are given per column)	Eligible for revascularisation	Ineligible for revascularisation	*P*
N	3777	632	
In-hospital mortality, n (%)	51 (1.4)	9 (1.4)	.88
Total mortality at 1-year, n (%)	141 (3.7)	44 (7.0)	<.001
Rehospitalization for cardiac reason, n (%)	776 (25)	130 (27)	.26
(repeat) Revascularisation, n (%)	286 (8)	24 (4)	.001

DISCUSSION

This study clearly revealed that a clinically significant proportion of patients, with at least one > 50% diameter stenosis in a major coronary artery, visualized during an invasive coronary procedure, were ineligible for revascularization. These patients had a worse clinical risk profile, were more likely to have a total occlusion of at least one coronary artery, and had worse outcomes at 1-year in respect to perceived health status and case-fatality, when compared to patients who were eligible for revascularization. With the exception of more ACE-inhibitors and less aspirin, no major differences with regards to the treatment with prophylactic drugs were observed between the two groups.

In addition to pharmacological therapy, revascularization can be offered to reduce symptoms and improve prognosis in subsets of patients with CAD. It should be noted, however, that there is a subgroup of patients with refractory angina in whom revascularization is not a viable option. It is this clinically important subgroup of patients that we identified among patients who enrolled via the EHS-CR. Although many of these patients are most likely to be diagnosed as chronic refractory angina (CRA), it is important to stress that identifying survey patients who were ineligible for revascularization as having CRA is, by definition, a crude assumption. However, all patients included in the analyses were admitted with a diagnosis of angina, had evidence of coronary insufficiency, had undergone an invasive coronary procedure in order to evaluate therapeutic option[8], and were considered ineligible for revascularization. In addition, it is important to note that we were only able to identify patients as having CRA who underwent an invasive diagnostic procedure and had a >50% diameter stenosis of at least one coronary artery.

Table 5. Perceived health status prior to discharge (n=3613)

	Eligible for revascularisation	Ineligible for revascularisation	*P*
EQ-5D parameter, n (%)	3109 (82)	504 (80)	
Mobility			<.001
No problems with walking around	2162 (69)	281 (56)	
Some problems with walking around	917 (30)	216 (43)	
Confined to bed	30 (1)	7 (1)	
Self-care			.004
No problems with self-care	2676 (86)	406 (81)	
Some problems with washing or dressing	408 (13)	91 (18)	
Unable to wash or dress	25 (1)	7 (1)	
Usual activities			<.001
No problems performing usual activities	1959 (63)	258 (51)	
Some performing usual activities	1037 (33)	222 (44)	
Unable to perform usual activities	113 (4)	24 (5)	
Pain / discomfort			<.001
Neither pain nor discomfort	1939 (62)	253 (50)	
Moderate pain or discomfort	1118 (36)	243 (48)	
Severe pain or discomfort	52 (2)	8 (2)	
Anxiety / depression			<.001
Neither anxious nor depressed	2153 (69)	295 (59)	
Moderate anxious nor depressed	862 (28)	191 (38)	
Severe anxious nor depressed	94 (3)	18 (4)	
No problems on all 5 dimensions	1343 (43)	167 (33)	<.001
EQ-VAS (median, inter quartile range)	70 (60-80)	65 (50-80)	<.001
EQ-utility score (median, inter quartile range)	0.85 (0.69-1.00)	0.76 (0.62-1.00)	<.001

The clinical judgement of being ineligible for revascularization at the time of the survey does not, of course, necessarily imply that these patients were not eligible for active treatment thereafter. Surprisingly, although optimizing medical treatment is advocated in the management of these patients[7], those, ineligible for revascularization did not receive, with the exception of ACE-inhibitors, more evidence based drugs as compared to patients who were eligible for revascularization; despite the latter requiring greater level of intervention in this regard. It is on this basis that this study showed that there remains substantial room for improvement in treatment patterns, as 30% of patients did not receive beta-blockers or statins, and more than half was not treated with calcium channel blockers.

In addition to optimizing medical treatment, there have been alternative therapeutic options developed in this clinical context. These include transcutaneous electric nerve stimulation, spinal cord stimulation, left stellate ganglion blockade, thoracic epidural anaesthesia, endoscopic thoracic sympathicotomy, transmyocardial laser revascularisation, and, more latterly, angiogenesis.[7,13] Within our study population, however, no information on these novel treatment options was available. We could not, therefore, estimate the proportion of CRA patients who could be considered for these therapeutic options. However, the clinical applicability and therapeutic impact of this novel arsenal of therapeutic options needs further

research and none of these options would have formed part of the gold-standard management of angina pectoris at the time of the survey.[7]

Table 6. Health status prior to discharge and at 1-year follow up*

	EQ-5D prior to discharge	EQ-5D at 1-year follow up	*P*
Eligible for revascularisation (n=2383)	n (%)	n (%)	
Mobility**	676 (28)	576 (24)	<.001
Self-care**	294 (12)	181 (8)	<.001
Usual activities**	828 (34)	537 (23)	<.001
Pain / discomfort**	857 (36)	716 (30)	<.001
Anxiety / depression**	695 (29)	646 (27)	.07
EQ-5D utility score (median, IQR)	0.85 (0.69-1.00)	1.00 (0.73-1.00)	<.001
Ineligible for revascularisation (n=373)	n (%)	n (%)	
Mobility**	154 (41)	140 (38)	.21
Self-care**	70 (19)	46 (12)	.007
Usual activities**	175 (47)	131 (35)	<.001
Pain / discomfort**	179 (48)	183 (49)	.79
Anxiety / depression**	153 (41)	143 (38)	.40
EQ-5D utility score (median, IQR)	0.80 (0.62-1.00)	0.80 (0.66-1.00)	.72

*) only patients included who completed the EQ-5D prior to admission and at 1-year follow up
**) patients indicating problems (moderate or severe) on the EQ-5D dimension

The unfavourable condition of patients considered ineligible for revascularization was partly expressed by the higher case-fatality at 1-year. This is to be expected as these patients had a worse clinical profile and fewer treatment options as compared to the revascularization group. However, the observed difference in case-fatality can be explained by a higher prevalence of heart failure in patients who were considered ineligible for revascularization. In addition, we also observed that a considerably more patients reported problems on the five dimensions of the EQ-5D questionnaire. This is in accordance with earlier reports, indicating disability and diminished quality of life, as these patients experience recurrent pain, lack of energy, poor sleep decreased physical capacity and increased prevalence of anxiety and depression.[14,15] In addition, we also observed that the self-perceived health status of these patients did not improve over time (even with higher attrition of "sicker" patients) compared to patients in the revascularization group who showed a significant improvement between discharge and 1-year follow up.

Patients not treated with revascularization might consider themselves as being at the "end of the line".[9,16] This type of misconception and maladaptive beliefs of angina increase anxiety and reduce functional status. [17] Even though their prognosis was poorer than patients receiving treatment with revascularization, a 93% 1-year survival is considerably higher than in patients with moderate to severe heart failure.[18,19]

Providing a cardiac rehabilitation programme to patients with CRA has proven to increase the health-related quality of life.[7,16] Most important areas of intervention in these rehabilitation programmes are: optimizing pharmacological therapy, physical training, life style, treatment adherence, psychosocial adaptation, and ongoing education. Given the broad range of these interventions, a multidisciplinary approach is recommended. In this context, we would like to stress the value of including nurses in these multi-disciplinary programmes as nurses are known to have expertise in these areas. Nurse-led multi-disciplinary management programs have not only been proven cost-effectively, but also improved the delivery and outcome of provided care in various patient populations.[10] In a recent study by Moore et al[16], in all patients who received education as part of a rehabilitation programme, they observed an improvement in health-related quality of life. In addition, experienced and dedicated nurses are well placed health-care workers that cannot only provide patient-tailored education, but also refer patients to other health care providers (e.g. dieticians and psychologists) if needed. For example, instruct patients how they can use nitroglycerine as prophylactic drug before doing physical activities, the importance of warming-up and cooling down before and after exercise, to inform patients about CAD and that their prognosis is not so poor, and to emphasize the importance of compliance.

In addition to the specific limitations outlined previously, the major limitations are commonly inherent to observational studies involving voluntarily participating hospitals in Europe, which may lead to a biased patient cohort. The results of this study therefore only reflect the treatment of a small percentage of all patients who were admitted with CAD throughout Europe. However, because patients were included consecutively at the participating hospitals, we assumed that the patients enrolled in the EHS-CR were representative for ongoing clinical practice in Europe. It should be noted, however, that we cannot exclude that the available expertise in local hospitals was decisive in considering patients as being ineligible for revascularization. In contrast, these patients have to cope with a palliative instead of a curative treatment, and consequently will have completed the EQ-5D with this knowledge. It should be re-emphasised that not all patients, enrolled in this study completed the EQ-5D questionnaire, and even less patients completed both the questionnaire prior to discharge and the questionnaire at 1-year follow up. Despite these limitations of this study, the major strength of this study is the large number of patients included from multiple hospitals across Europe.

In conclusion, patients with CAD who were considered ineligible for revascularization, representing 14% of those participating in the study, typically had more co-morbidities and risk factors as compared to patients who were eligible for revascularization. This difference was also reflected in the self-perceived health status. With the exception of ACE-inhibitors

and aspirin, we observed no major differences regarding drug treatment between the two groups. Optimizing management in this clinically significant patient group, via the application of nurse-led multidisciplinary rehabilitation programmes[9], using the same principles applied in parallel programs in cardiac disease[10] has clear potential to improve both perceived health and actual (e.g. mortality) health outcomes. Further research is obviously needed to reveal whether initiatives to implement nurse-led multidisciplinary teams will fulfil the potential to substantially improve outcomes in patients with CRA.

REFERENCES

1. Carroll K, Majeed A, Firth C, Gray J. Prevalence and management of coronary heart disease in primary care: population-based cross-sectional study using a disease register. *J Public Health Med.* 2003;25:29-35.
2. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJ. The current cost of angina pectoris to the National Health Service in the UK. *Heart.* 2003;89:848-53.
3. Maier W, Windecker S, Boersma E, Meier B. Evolution of percutaneous transluminal coronary angioplasty in Europe from 1992-1996. *Eur Heart J.* 2001;22:1733-40.
4. Mercado N, Wijns W, Serruys PW, Sigwart U, Flather MD, Stables RH, O'Neill WW, Rodriguez A, Lemos PA, Hueb WA, Gersh BJ, Booth J, Boersma E. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. *J Thorac Cardiovasc Surg.* 2005;130:512-9.
5. ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery. *Circulation.* 2004;110:e340-437.
6. Eagle KA GR, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA. ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery. *Circulation.* 2004;110:e340-437.
7. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, Follath F, Hellemans I, Herlitz J, Luscher T, Pasic M, Thelle D. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. *Eur Heart J.* 2002;23:355-70.
8. Julian D, Bertrand M, Hjalmarsson A, Fox K, Simoons M, Ceremuzynski L, Maseri A, Meinertz T, Meyer J, Pyorala K, Rehnqvist N, Tavazzi L, Treasure T. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J.* 1997;Mar; 18(3):394-413.
9. Stewart S. Refractory to medical treatment but not to nursing care: can we do more for patients with chronic angina pectoris? *Eur J Cardiovasc Nurs.* 2003;2:169-70.
10. Thompson DR, Stewart S. Nurse-directed services: how can they be made more effective? *Eur J Cardiovasc Nurs.* 2002;1:7-10.
11. Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, Sechtem U, Stahle E, Widimsky P, de Jaegere P, Scholte op Reimer WJM, Mercado N, Wijns W. Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization. *Eur Heart J.* 2005;26:1169-1179.
12. Dolan P. Modeling valuations for EuroQol health states. *Med Care.* 1997;35:1095-108.
13. Kim MC, Kini A, Sharma SK. Refractory angina pectoris: mechanism and therapeutic options. *J Am Coll Cardiol.* 2002;39:923-34.
14. Lewin RJ. Improving quality of life in patients with angina. *Heart.* 1999;82:654-5.
15. Lewin RJ, Furze G, Robinson J, Griffith K, Wiseman S, Pye M, Boyle R. A randomised controlled trial of a self-management plan for patients with newly diagnosed angina. *Br J Gen Pract.* 2002;52:194-6, 199-201.
16. Moore RK, Groves D, Bateson S, Barlow P, Hammond C, Leach AA, Chester MR. Health related quality of life of patients with refractory angina before and one year after enrolment onto a refractory angina program. *Eur J Pain.* 2005;9:305-10.

17. Furze G, Lewin RJ, Murberg T, Bull P, Thompson DR. Does it matter what patients think? The relationship between changes in patients' beliefs about angina and their psychological and functional status. *J Psychosom Res*. 2005;59:323-9.
18. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail*. 2001;3:315-22.
19. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:1115-40.

Outcome of patients

Chapter 8

The additional value of patient-reported health status in predicting 1-year mortality after invasive coronary procedures

The additional value of patient-reported health status in predicting 1-year mortality after invasive coronary procedures.

A report from the Euro Heart Survey on Coronary Revascularization

M.J. Lenzen, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
S.S. Pedersen, Tilburg University, the Netherlands
E. Boersma, Rotterdam, the Netherlands
W. Maier, Zurich, Switzerland
P. Widimsky, Prague, Czech Republic
M.L. Simoons, Rotterdam, the Netherlands
N.F. Mercado, Rotterdam, the Netherlands
W. Wijns, Aalst, Belgium

Accepted for publication in HEART (2006)

ABSTRACT

Objective: Self-perceived health status may be helpful in identifying patients at high-risk for adverse outcomes. The Euro Heart Survey on Coronary Revascularization (EHS-CR) provided an opportunity to explore whether impaired health-status was a predictor of 1-year mortality in patients with CAD undergoing angiographic procedures.

Methods: We used data from the EHS-CR that included 5619 patients from 31 member countries of the ESC. Inclusion criteria for the current study were completion of a self-report measure of health-status (EQ-5D) at discharge and information on 1-year follow-up, resulting in a study population of 3786 patients.

Results: The 1-year mortality was 3.2% (n=120). Survivors reported fewer problems on the five dimensions of the EQ-5D as compared to non-survivors. We adjusted for a broad range of potential confounders, which reached a *p*-value of <0.10 in the unadjusted analyses. In the adjusted analyses, problems with self-care (OR, 3.45; 95%CI 2.14-5.59) and a low rating (≤ 60) on health status (OR, 2.41; 95%CI 1.47-3.94) were the most powerful independent predictors of mortality, amongst 22 clinical variables included in the analysis. Furthermore, patients who reported no problems on all 5 dimensions had significantly lower 1-year mortality rates (OR, 0.47; 95%CI 0.28-0.81).

Conclusions This analysis demonstrates that impaired health-status is associated with a 2-3 fold increased risk of all-cause mortality in patients with CAD, independent of other conventional risk factors. These results highlight the importance of including patients' subjective experience of their own health-status in the evaluation strategy in order to optimize risk stratification and management in clinical practice.

INTRODUCTION

Treatment options for patients with coronary artery disease (CAD) have expanded considerably over the last two decades. In addition to pharmacological therapy, mechanical revascularization by coronary-artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) can be offered to relieve ischemic symptoms and improve prognosis in some subsets.[1-6] In addition, behavioural interventions, which include prevention and treatment of lifestyle risk factors and psychological risk factors (e.g. anger or anxiety), are known to be beneficial for patients with cardiovascular diseases.[7] Choosing the most appropriate treatment for the individual patient, however, remains controversial in many instances.[8]

As the observed differences in outcome between competitive treatment options (e.g. CABG and PCI) diminish, [9-11] researchers and clinicians have become increasingly interested in measuring patients' health status. In addition to using health related quality of life (HRQL) or health status as an endpoint in clinical trials, health status may prove useful in the clinical decision-making process as to which treatment to favour.[12,13] It is also important to note that health status is an important patient-centered outcome, and subsets of patients are known to prefer health status over prolonged survival.[14] In addition, measuring health status may identify patients at high-risk for adverse outcomes.[12,15-18] Identification of these patients is important as they may benefit from more invasive management and more intensive follow-up.[17] Yet, health status measures are rarely used in clinical practice.[19]

The aim of this study was to explore whether impaired health status was a predictor of 1-year all-cause mortality in a cohort of patients with established CAD enrolled in the Euro Heart Survey on Coronary Revascularization (EHS-CR).

METHODS

Patients

Data for this study were derived from the database of the EHS-CR. Details of this prospective, observational study were published previously.[20] In short, all consecutive patients undergoing invasive diagnostic or therapeutic procedures in the catheterization laboratory were screened between November 2001 and March 2002 in 130 hospitals from 31 member countries of the European Society of Cardiology (ESC). Consenting patients with a >50% diameter stenosis in at least one coronary artery were included and detailed information was retrieved from their medical records. The EuroSCORE was calculated from the available variables.[21] From the 5619 patients enrolled in the EHS-CR, 4515 (80%) patients had complete data on all five questions (dimensions) of the EQ-5D questionnaire at baseline. The study protocol included a one-year follow-up which was available in 3786 patients (84%).

Health status

In addition to collecting clinical variables, all patients were asked to fill in the self-report EQ-5D questionnaire[22] at the time of hospital discharge. The EQ-5D is a standardized generic instrument for assessing health status, with valid translations available for 29 of the 31 participating countries in the current study. This validated questionnaire comprises five dimensions, namely mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each of these dimensions has three levels of severity, corresponding to "No problems", "Moderate problems", and "Severe problems". Patients were asked which statement best described their health status on the day the questionnaire was filled in. Theoretically, 243 different health states can be generated by this classification. The ratings can be analyzed on individual-level using health-state utility scores. These scores range from –0.594 to +1, with scores < 0 being regarded as worse than death and 1 representing full health, from the perspective of the general population.[22] The second part of the EQ-5D consists of a visual analogue scale (VAS) ranging from 0 (best imaginable health state) to 100 (worst imaginable health state), which is used for rating the overall health.

Statistical analysis

Continuous variables are reported as mean or median scores with corresponding values (standard deviation and inter-quartiles ranges, respectively). Dichotomous variables are presented as numbers and percentages. To evaluate differences between the different groups, chi-square tests, student's *t*-test, ANOVA or Mann-Whitney tests were applied as appropriate. Univariate and multivariate logistic regression analyses were performed to evaluate the relation between the five dimensions of the EQ-5D at baseline and all-cause mortality at 1-year. To examine the relationship between the dimensions of the EQ-5D, we dichotomized the three levels of severity: "No problems" was coded 0, while "Moderate problems" and "Severe problems" were coded 1. The VAS was dichotomized by using the lowest 25th percentile indicating impaired health. These dichotomized variables were than entered separately in the adjusted analyses. Crude and adjusted odds ratios (OR) with their corresponding 95% confidence intervals (CI) are reported. We adjusted for a broad range of potential confounders, which reached a *p*-value of < 0.10 in the unadjusted analyses. These variables included age, risk factors, co-morbidity, admission diagnosis, and treatment. Goodness-of-fit was determined by the Hosmer-Lemeshow test, and discriminatory power was evaluated by using *c*-statistics. For all tests a *p* value of < 0.05 (two-sided) was considered statistically significant. Statistical analyses were performed using SPSS 12.0.1 for Windows.

RESULTS

Table 1 summarizes the baseline characteristics of the 3786 patients who were included in the current study, comparing survivors at 1-year follow-up with non-survivors. The all-cause mortality at 1-year was 3.2% (120 deaths). Cardiac death was observed in 69% of those with a known cause of death (n=97). Survivors were younger (62.8 versus 69.0, $p < 0.001$), had a better risk profile (including age, diabetes, cardio-vascular history and EuroSCORE), and were more often offered revascularization (80% versus 63%, $p < 0.001$) as compared to non-survivors. No significant differences were observed between the admission diagnosis of survivors and non-survivors.

Table 1. Baseline characteristics.

	Vital status at 1-year follow-up			
	Alive (n=3666)	Dead (n=120)	*Univariate predictor for mortality (OR, 95%CI)*	*P*
Male sex (%)	2785 (76)	93 (78)	1.09 (0.70-1.68)	.71
Age (mean, SD)	62.8 ±10.6	69.0 ±9.9	1.06 (1.04-1.08)	<.001
Risk factors (%):				
Smoking ever	2166 (61)	75 (63)	1.05 (0.72-1.53)	.79
Diabetes mellitus	850 (23)	43 (36)	1.85 (1.26-2.70)	.002
Hypertension	2254 (62)	75 (63)	1.04 (0.71-1.51)	.85
Hyperlipidemia	2417 (67)	78 (66)	0.98 (0.66-1.44)	.90
Cardio-vascular history (%):				
Peripheral vascular disease	412 (11)	32 (27)	2.87 (1.89-4.35)	<.001
Cerebral vascular disease	283 (8)	12 (10)	1.33 (0.72-2.44)	.36
Prior myocardial infarction	1440 (39)	72 (60)	2.31 (1.59-3.35)	<.001
Congestive heart failure	673 (18)	50 (42)	3.17 (2.19-4.61)	<.001
Prior percutaneous coronary intervention	764 (21)	19 (16)	0.71 (0.43-1.17)	.18
Prior coronary artery bypass grafting	368 (10)	24 (20)	2.24 (1.41-3.55)	<.001
Diagnosis at admission (%):				
Stable angina	1978 (55)	60 (52)	0.85 (0.59-1.23)	.39
NSTE-ACS	1105 (31)	40 (35)	1.16 (0.79-1.71)	.45
STEMI	537 (15)	16 (14)	0.90 (0.53-1.53)	.90
Angiographic results (%):				
Multi vessel disease	2308 (63)	89 (74)	1.68 (1.11-2.54)	.01
Left main lesions	284 (8)	15 (13)	1.70 (0.98-2.96)	.06
Ejection fraction <40%	296 (12)	34 (37)	4.25 (2.74-6.60)	<.001
EuroSCORE (mean, SD)	4.2 ±2.8	6.8 ±3.4	1.28 (1.21-1.35)	<.001
Treatment option (%)				
Percutaneous coronary intervention	2201 (60)	54 (45)	0.55 (0.38-0.79)	.001
Coronary artery bypass grafting	745 (20)	22 (18)	0.88 (0.55-1.41)	.59
Medical treatment only	720 (20)	44 (37)	2.37 (1.62-3.46)	<.001
Medical treatment at discharge (%):				
Anti-platelet agents/ oral anticoagulants	3464 (95)	105 (88)	0.41 (0.23-0.71)	.002
B-blockers	2796 (76)	86 (72)	0.79 (0.53-1.18)	.25
Statins	2498 (68)	71 (59)	0.68 (0.47-0.98)	.04
ACE-inhibitors	2027 (55)	76 (63)	1.40 (0.96-2.04)	.08

NSTE-ACS = non ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction

By univariate analysis, conventional variables negatively associated with death were: age, diabetes, peripheral vascular disease, previous myocardial infarction, history of heart

failure, previous CABG, multivessel disease, ejection fraction < 40%, EuroSCORE and medical treatment only. PCI, use of antiplatelet agents and use of statins were associated with improved outcome. Stable angina was the most frequent indication to perform angiography (54%), followed by non-ST myocardial infarction or unstable angina (30%) and ST elevation myocardial infarction (15%). On all five EQ-5D dimensions, survivors reported significantly fewer problems and had a better overall health (i.e. VAS) than non-survivors. The univariate analysis revealed that problems on these dimensions were negatively associated with death (Table 2). Identical results were observed in a subgroup of patients with cardiac mortality, instead of all-cause mortality.

Table 2. EQ-5D questionnaire and distribution, prior to hospital discharge

	Vital status at 1-year follow up		Univariate predictor for mortality	*P*
	Alive (n=3666)	Dead (n=120)	(OR, 95% CI)	
Mobility			3.00 (2.08-4.33)*	<.001
I have no problems in walking about	2579 (70)	53 (44)		
I have some problems in walking about	1064 (29)	61 (51)		
I am confined to bed	23 (1)	6 (5)		
Self-care			4.64 (3.18-6.67)*	<.001
I have no problems with self-care	3191 (87)	71 (59)		
I have some problems washing or dressing myself	453 (12)	46 (38)		
I am unable to wash or dress myself	22 (1)	3 (3)		
Usual activities (e.g., work, housework, family activities)			3.65 (1.93-3.85)*	<.001
I have no problems with performing my usual activities	2311 (63)	47 (39)		
I have some problems with performing my usual activities	1227 (33)	62 (52)		
I am unable to perform my usual activities	128 (4)	11 (9)		
Pain/discomfort			2.12 (1.47-3.05)*	<.001
I have no pain or discomfort	2295 (63)	53 (44)		
I have moderate pain or discomfort	1320 (36)	59 (49)		
I have extreme pain or discomfort	51 (1)	8 (7)		
Anxiety/depression			2.47 (1.71-3.55)*	<.001
I am not anxious or depressed	2505 (68)	56 (47)		
I am moderately anxious or depressed	1061 (29)	54 (45)		
I am extremely anxious or depressed	100 (3)	10 (8)		
EQ-VAS:			3.45 (2.29-5.19)**	<.001
Mean, SD	69 ±19	57 ±23		
Median, inter-quartile range	70 (60-80)	58 (45-80)		
EQ-utility score:			2.70 (1.87-3.90)**	<.001
Mean, SD	0.81 ±0.23	0.63 ±0.34		
Median, inter-quartile range	0.85 (0.69-1.0)	0.71 (0.52-0.85)		

*) patients indicating problems on the EQ-5D dimension
**) dichotomized (using the lowest 25th percentile indicating impaired health status)

On all five EQ-5D dimensions, survivors reported significantly fewer problems and had a better overall health (i.e. VAS) than non-survivors. The univariate analysis revealed that problems on these dimensions were negatively associated with death (Table 2). Identical

Table 3. Adjusted association between the dimensions of the EQ-5D and all-cause mortality*

	Mobility***		Self-care***		Usual activities***		Pain/ discomfort***		Anxiety/ depression***	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Clinical variables**:										
Age	1.03 (1.00-1.06)	.09	1.03 (1.00-1.06)	.08	1.03 (1.00-1.06)	.07	1.03 (1.00-1.06)	.05	1.03 (1.00-1.07)	.05
History of HF	1.63 (0.99-2.67)	.06	1.52 (0.92-2.51)	.10	1.62 (0.98-2.66)	.06	1.65 (1.00-2.71)	.05	1.67 (1.01-2.75)	.04
EF <40%	1.87 (1.10-3.20)	.02	1.82 (1.06-3.13)	.03	1.88 (1.10-3.21)	.02	1.83 (1.07-3.13)	.03	1.88 (1.10-3.22)	.02
Prior MI	1.96 (1.22-3.14)	.006	1.90 (1.18-3.05)	.008	1.93 (1.20-3.10)	.007	1.96 (1.22-3.16)	.005	1.95 (1.21-3.14)	.006
PVD	1.98 (1.10-3.56)	.02	2.19 (1.21-3.99)	.01	2.01 (1.11-3.62)	.02	1.91 (1.06-3.45)	.03	2.02 (1.12-3.64)	.02
Medical treatment	2.07 (1.05-4.07)	.04	2.26 (1.15-4.47)	.02	2.12 (1.08-4.16)	.03	2.13 (1.09-4.18)	.03	2.06 (1.05-4.05)	.04
EQ-5D dimensions***	2.20 (1.39-3.50)	<.001	3.45 (2.14-5.59)	<.001	2.13 (1.34-3.38)	<.001	2.12 (1.33-3.37)	.001	2.31 (1.48-3.59)	<.001

*) adjusted for age, diabetes, peripheral vascular disease, previous myocardial infarction, history of heart failure, previous CABG, multivessel disease, left main, ejection fraction < 40%, EuroSCORE, PCI, medical treatment, anti-platelet agents, statins, and ACE-inhibitors, which reach a p-value of 0.10 in the unadjusted analyses (Table 1).

**) Only clinical variables that remained statistically significant in the adjusted analyses are described in this table.

***) The five dimensions were entered separately in the adjusted analyses.

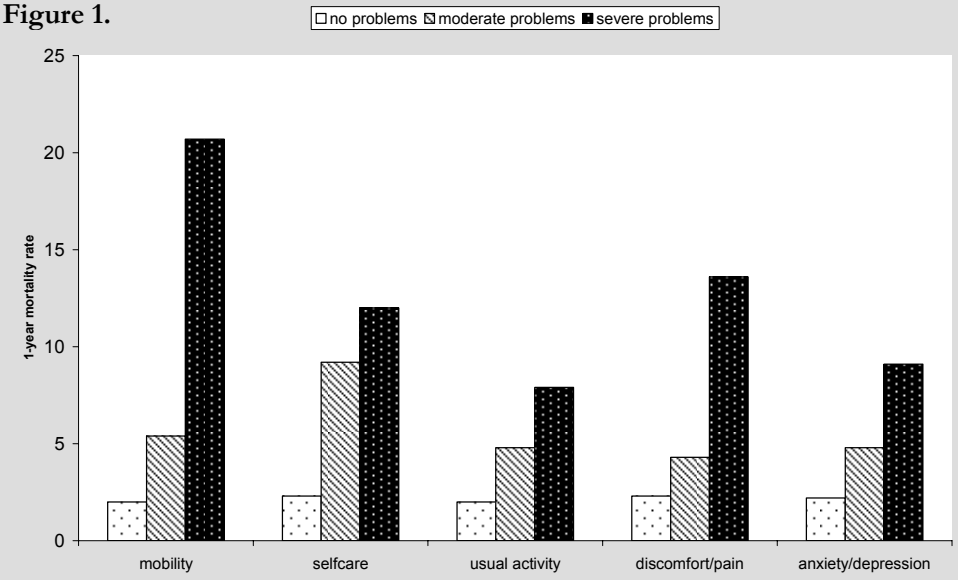
HF=heart failure, EF=left ventricular ejection fraction, MI=myocardial infarction, PVD=peripheral vascular disease

results were observed in a subgroup of patients with cardiac mortality, instead of all-cause mortality.

Table 3 shows the adjusted association between the EQ-5D and 1-year mortality. Patients who reported problems on perceived health status, and patients who had a relatively low score (≤ 60) on the EQ-VAS had a higher mortality rate as compared to patients who reported no problems. Problems with self-care (OR, 3.45; 95%CI 2.14-5.59) and a health rating ≤ 60 (OR, 2.41; 95%CI 1.47-3.94) were the most powerful predictors of mortality. Furthermore, patients who reported no problems on all 5 dimensions had significantly lower 1-year mortality rates (OR, 0.47; 95%CI 0.28-0.81), whereas patients who reported problems on all dimensions were in the highest risk group (OR, 3.85; 95%CI 2.30-6.44). The EQ-5D improved the model *c*-statistics (from 0.78 up to 0.81). Calibration was good for the adjusted analyses as Hosmer-Lemeshow tests showed no significant difference between the observed and predicted probabilities.

Figure 1 clearly reveals per dimension that patients who reported no problems had a low mortality rate (< 3%), whereas patients who had moderate or severe problems had considerably higher mortality rates (range: 4–21%).

Figure 1.



$P \leq 0.001$ for five dimensions between the three levels of severity.

Since 33% of all patients enrolled in the EHS-CR were excluded from this analysis, we compared the baseline characteristics of these patients with the study population. With the exception of a higher in-hospital mortality in those who were excluded (5.1% versus 0.3%), no major differences were observed.

DISCUSSION

This study demonstrated that impaired health status, as measured by the EQ-5D prior to discharge, is associated with a 2-3 fold increased risk of all-cause mortality in patients with established CAD. After adjustment for other prognostic variables, including age, risk factors, comorbidity and admission diagnosis, impaired health status remained an independent predictor of 1-year mortality.

Several studies have reported on the predictive value of HRQL and health status questionnaires in relation to adverse clinical outcomes in patients with cardiovascular diseases.[15,16,18,23] To our knowledge, this study is the first to use the EQ-5D, a brief generic self-perceived health status questionnaire to predict short-term mortality (i.e. after 1 year), independently of established bio-medical risk factors in CAD patients with a relatively low overall risk. We identified reduced self-care as the most powerful predictor of mortality. Of note, this dimension is strongly related to patients' abilities to care for themselves and adequately manage their condition. As a consequence, targeting and improving self-care behaviour in intervention programmes could not only lead to improved HRQL but also may enhance survival in this subset of patients.[24,25] In addition, a major advantage of the EQ-5D is that it is a brief and valid measure of health status that can easily be used in clinical practice.

Our findings support the recommendations of Krumholz et al [17] to include health status measurements in clinical practice as an "additional" tool to identify patients who are at high risk for adverse outcomes. These patients may consequently benefit from a more aggressive treatment, including invasive, pharmacological and/ or behavioural interventions or a combination hereof. An earlier report on the EHS-CR showed that there is room for improvement in the medical treatment of these patients, especially with respect to adjunctive pharmacology (GP IIb/IIIa inhibitors, statins and ACE-inhibitors).[20] Another important issue for advocating the use of health status assessment in clinical practice relates to the issue of discrepancy between patient-rated and physician-rated health-status.[26] As clinicians frequently underestimate patients' health status as reported by their patients[27], it is paramount that patients' evaluation of "how they feel" is taken into account. In addition, health status is an important patient-centered outcome, with patients emphasizing health status over prolonged survival. [14] Hence, entering health status into the equation when discussing treatment options with patients may also be considered an ethical obligation.

Although this study clearly revealed that the EQ-5D provides prognostic information, little is known about the "how and why" impaired health status predicts mortality, independently of biomedical risk factors. It should be noted, however, that health status involves a much broader range of the impact of disease as experienced by the patient (i.e. symptoms, functional limitation, and discrepancy between actual and desired function) compared to the focus of

clinicians (i.e. symptoms, signs, and diagnosis).[19] Further research is warranted into the mechanisms that may be responsible for the relation between health status and mortality, as this could guide treatment with- or the development of effective interventions. Emphasis should also be placed on the identification of the determinants of impaired health status, which has been advocated as a means to close the gap between research and clinical practice.[17] Both depression and the distressed (Type D) personality have been shown to predict impaired health status adjusting for measures of disease severity and other risk factors.[28,29] The question is whether these psychosocial risk factors are more important determinants of individual differences in clinical outcome than health status.

This study is the first to use the EQ-5D as a predictor of mortality. Although other generic and disease-specific health status questionnaires have been found to predict mortality, one of the major advantages of the EQ-5D is its brevity. It comprises only 6 questions, while most of the other questionnaires ask a multiplicity of questions (range 19 – 36) and are more taxing to patients.[12,15,16,23] In addition, it is important to note that in patients with CAD a simple questionnaire like the EQ-5D is able to discriminate between patients who have a higher mortality risk and those who do not. In contrast, we acknowledge that a lack of familiarity with the concept of health status, the perception of many clinicians that health status is a soft endpoint in evaluating a treatment[19], and the high workload of physicians in clinical practice may be identified as barriers for implementing self-perceived health status in every day clinical practice. It should be noted, however, that it takes less than 5 minutes to complete the questionnaire, and other health-care professionals than physicians can become involved in the assessment.

The current study has several potential limitations. First, patients who did not complete the EQ-5D questionnaire or who had missing follow-up data had to be excluded from analyses. However, a comparison between responders and non-responders did not reveal major differences. Second, it can not be excluded that ill health conditions, other than cardiovascular diseases, could have had an impact on the results, as only "classical" risk factors and co-morbidities were included in the database. Third, health status was only assessed once, and at that time not all patients had undergone a revascularization procedure. Fourth, we used a generic rather than a disease-specific instrument to evaluate health status; it is well known that generic measures may be less sensitive than disease-specific to tap dimensions pertinent to clinical populations. Future research is needed to address issues like the predictive value of a single measurement as compared to serial measurements, the effect of changes in health-status over time on outcomes, and comparing the results of the EQ-5D with disease-specific instruments. Despite these limitations, strengths of this study were the relative large number of patients included from multiple hospitals across Europe. We were also able to adjust for a number of

classical demographic and cardiovascular risk factors, showing that impaired health status is an independent predictor for mortality. Lastly, the enrolled patients are representative of "real life" practice, across a wide spectrum of European hospitals.

In conclusion, this study demonstrated the strong incremental value of the EQ-5D for the prediction of mortality in patients admitted with CAD, independently of other demographical, clinical and angiographic risk factors. Our results highlight the importance of including patients' subjective experience of their own health status in order to optimize risk stratification in clinical practice.

REFERENCES

1. Julian D, Bertrand M, Hjalmarsson A, Fox K, Simoons M, Ceremuzynski L, Maseri A, Meinertz T, Meyer J, Pyorala K, Rehnqvist N, Tavazzi L, Treasure T. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J*. 1997;Mar; 18(3):394-413.
2. Bertrand ME SM, Fox KA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W; Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2002;Dec;23(23):1809-40.
3. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KAA, Julian D, Lengyel M, Neumann F-J. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2003;24:28-66.
4. Smith SC, Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO. ACC/AHA Guidelines for Percutaneous Coronary Intervention--Executive Summary : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Endorsed by the Society for Cardiac Angiography and Interventions. *Circulation*. 2001;103:3019-3041.
5. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB, Jr, Fihn SD, Fraker TD, Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV, Alpert JS, Antman EM, Hiratzka LF, Fuster V, Faxon DP, Gregoratos G, Jacobs AK, Smith SC, Jr, Committee Members, Task Force Members. ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina--Summary Article. *Circulation*. 2003;107:149-158.
6. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM, Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA, Antman EM, Smith SC, Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2004;110:1168-1176.
7. Pickering T, Clemow L, Davidson K, Gerin W. Behavioral cardiology --has its time finally arrived? *Mt Sinai J Med*. 2003;70(2):101-12.
8. Mercado N, Wijns W, Serruys PW, Sigwart U, Flather MD, Stables RH, O'Neill WW, Rodriguez A, Lemos PA, Hueb WA, Gersh BJ, Booth J, Boersma E. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. *J Thorac Cardiovasc Surg*. 2005;130:512-9.
9. Pocock SJ, Henderson RA, Rickards AF, Hampton JR, King SB, Hamm CW, Puel J, Hueb W, Goy J-J, Rodriguez A. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *The Lancet*. 1995;346:1184-1189.
10. Hoffman SN, TenBrook J, John A., Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *J Am Coll Cardiol*. 2003;41:1293-1304.

11. Feit F, Brooks MM, Sopko G, Keller NM, Rosen A, Krone R, Berger PB, Shemin R, Attubato MJ, Williams DO, Frye R, Detre KM. Long-Term Clinical Outcome in the Bypass Angioplasty Revascularization Investigation Registry : Comparison With the Randomized Trial. *Circulation*. 2000;101:2795-2802.
12. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health Status Predicts Long-Term Outcome in Outpatients With Coronary Disease. *Circulation*. 2002;106:43-49.
13. Borkon AM, Muehlebach GF, House J, Marso SP, Spertus JA. A comparison of the recovery of health status after percutaneous coronary intervention and coronary artery bypass. *The Annals of Thoracic Surgery*. 2002;74:1526-1530.
14. Stanek EJ, Oates MB, McGhan WF, Denofrio D, Loh E. Preferences for treatment outcomes in patients with heart failure: symptoms versus survival. *J Card Fail*. 2000;6:225-32.
15. Soto GE, Jones P, Weintraub WS, Krumholz HM, Spertus JA. Prognostic value of health status in patients with heart failure after acute myocardial infarction. *Circulation*. 2004;110:546-51.
16. Rumsfeld JS, MaWhinney S, McCarthy M, Jr., Shroyer AL, VillaNueva CB, O'Brien M, Moritz TE, Henderson WG, Grover FL, Sethi GK, Hammermeister KE. Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. Participants of the Department of Veterans Affairs Cooperative Study Group on Processes, Structures, and Outcomes of Care in Cardiac Surgery. *Jama*. 1999;281:1298-303.
17. Krumholz HM, Peterson ED, Ayanian JZ, Chin MH, DeBusk RF, Goldman L, Kiefe CI, Powe NR, Rumsfeld JS, Spertus JA, Weintraub WS. Report of the National Heart, Lung, and Blood Institute working group on outcomes research in cardiovascular disease. *Circulation*. 2005;111:3158-66.
18. Heidenreich PA, Spertus JA, Jones PG, Weintraub WS, Rumsfeld JS, Rathore SS, Peterson ED, Masoudi FA, Krumholz HM, Havranek EP, Conard MW, Williams RE. Health status identifies heart failure outpatients at risk for hospitalization or death. *J Am Coll Cardiol*. 2006;47:752-6.
19. Rumsfeld JS. Health status and clinical practice: when will they meet? *Circulation*. 2002;106:5-7.
20. Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, Sechtem U, Stahle E, Widimsky P, de Jaegere P, Scholte op Reimer WJM, Mercado N, Wijns W. Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization. *Eur Heart J*. 2005;26:1169-1179.
21. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation. *Eur J Cardiothorac Surg*. 1999;16:9-13.
22. Dolan PD. Modeling Valuations for EuroQol Health States. [Article]. *Medical Care November*. 1997;35:1095-1108.
23. Rodriguez-Artalejo F, Guallar-Castillon P, Pascual CR, Otero CM, Montes AO, Garcia AN, Conthe P, Chiva MO, Banegas JR, Herrera MC. Health-related quality of life as a predictor of hospital readmission and death among patients with heart failure. *Arch Intern Med*. 2005;165:1274-9.
24. Grady KL, Dracup K, Kennedy G, Moser DK, Piano M, Stevenson LW, Young JB. Team management of patients with heart failure: A statement for healthcare professionals

from The Cardiovascular Nursing Council of the American Heart Association. *Circulation*. 2000;102:2443-56.

25. Jaarsma T, Stromberg A, Martensson J, Dracup K. Development and testing of the European Heart Failure Self-Care Behaviour Scale. *Eur J Heart Fail*. 2003;5:363-70.
26. Calkins DR RL, Cleary PD, Davies AR, Jette AM, Fink A, Kosecoff J, Young RT, Brook RH, Delbanco TL. Failure of physicians to recognize functional disability in ambulatory patients. *Ann Intern Med*. 1991;Mar 15;114(6):451-4.
27. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ*. 1998;316:736-41.
28. Rumsfeld JS, Ho PM. Depression and cardiovascular disease: a call for recognition. *Circulation*. 2005;111:250-3.
29. Schiffer AA, Pedersen SS, Widdershoven JW, Hendriks EH, Winter JB, Denollet J. The distressed (type D) personality is independently associated with impaired health status and increased depressive symptoms in chronic heart failure. *Eur J Cardiovasc Prev Rehabil*. 2005;12:341-6.

Outcome of patients

Chapter 9

Diabetes known and newly diagnosed but not impaired glucose regulation has a negative influence on 1-year outcome in patients with coronary artery disease

Diabetes known or newly detected but not impaired glucose regulation has a negative influence on 1-year outcome in patients with coronary artery disease.

A report from the Euro Heart Survey on diabetes and the heart

M.J. Lenzen, Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
L. Ryden, Stockholm, Sweden
J. Öhrvik, Stockholm, Sweden
M. Bartnik, Stockholm, Sweden
K. Malmberg, Stockholm, Sweden
W.J.M. Scholte op Reimer, Rotterdam, the Netherlands
M.L. Simoons, Rotterdam, the Netherlands

Provisionally accepted: European Heart Journal (2006)

ABSTRACT

Background: Although diabetes is known to be a major contributor to cardiovascular diseases, as well as an independent predictor for adverse outcomes in patients with coronary artery disease (CAD), information on the prognosis of patients with CAD and newly diagnosed diabetes or impaired glucose regulation is scarce. The objective of this study was to explore 1-year outcome in relation to different glucometabolic states of patients participating in the Euro Heart Survey on diabetes and the heart.

Methods and results: In 4676 out of 4961 patients, information on the relation between 1-year outcome and glucometabolic state, which was based on OGTT or fasting glucose plasma, was available. A normal glucose metabolism was identified in 947 patients, impaired glucose regulation (impaired fasting glucose or impaired glucose tolerance)) in 1116 patients, and diabetes in 1877 patients of whom 1425 were previously diagnosed and 452 newly diagnosed. 736 patients could not be classified, as no OGTT or fasting plasma glucose was performed. Previously recognized and newly detected diabetes was associated with an increased risk of 1-year mortality as compared to patients with normal glucose regulation (HR 2.4, 95%CI 1.5-3.8 and HR 2.0, 95%CI 1.1-3.6, respectively). Impaired glucose regulation, however, could not be identified as an independent predictor for 1-year mortality (HR 1.1, 95%CI 0.6-1.9).

Conclusions: This study confirmed that patients with CAD and known diabetes are at high risk for mortality and cardiovascular events and demonstrated that patients with newly diagnosed diabetes are at intermediate risk for adverse outcomes. Impaired glucose regulation, however, could not be identified as an independent predictor for adverse outcomes during the 1-year follow up period.

INTRODUCTION

Diabetes is a major contributor to cardiovascular diseases, including coronary heart, cerebrovascular, and peripheral artery disease, as well as an independent predictor for adverse outcomes in patients with coronary artery disease (CAD).[1-5] In addition, modestly elevated levels of blood glucose below the level defined as diabetes have been identified as an independent cardiovascular risk factor[6] and the GAMI study (Glucose tolerance in patients with Acute Myocardial Infarction) revealed that abnormal glucose tolerance is an important risk factor for future cardiovascular events after myocardial infarction.[7] This is of major concern, as Norhammer et al.[8] demonstrated that abnormal glucose regulation is present in most patients with CAD, a finding confirmed by the Euro Heart Survey on diabetes and the heart.[9] Yet, information on the prognosis of patients with CAD and newly diagnosed diabetes or impaired glucose regulation, as compared to patients with known diabetes and those who have normal glucose regulation is lacking.

The Euro Heart Survey on diabetes and the heart was designed to assess the prevalence of diabetes and impaired glucose regulation in patients with CAD in clinical practice.[9] This survey also included a 1-year follow-up providing a unique opportunity to explore 1-year outcome in relation to the different glucometabolic states of these patients.

METHODS

Euro Heart Survey on diabetes and the heart

Between February 2003 and January 2004, 4961 patients from 110 hospitals in 25 member countries of the European Society of Cardiology were recruited to the Euro Heart Survey on diabetes and the heart after informed consent. The details of this survey have been described elsewhere.[9] Briefly, all consecutive patients, admitted or visiting the cardiology outpatient clinic, were screened for a diagnosis of CAD. Clinical characteristics, treatment and results of tests (e.g. fasting glucose or OGTT) were collected in an electronic database. Patients were followed-up with respect to survival, cardiovascular procedures and events, and treatment for at least 1-year.

Glucometabolic state

Investigators were asked to provide measurements of fasting plasma glucose and Oral Glucose Tolerance Test (OGTT) in all patients without previously diagnosed diabetes. When an OGTT was available fasting plasma glucose obtained at that particular occasion was used for patient characterisation. Overall, fasting plasma glucose was measured in 2515 patients, an OGTT in 1819 patients, while in 736 patients without known diagnoses of diabetes no fasting plasma glucose or OGTT was measured. The results of the OGTT, or fasting plasma glucose

only when no OGTT was performed, was used to categorize patients as having "normal glucose regulation", "impaired glucose regulation" (IGR), or "newly diagnosed diabetes" in accordance with the World Health Organization (WHO) 1999 definitions.[10] Patients with a recorded history of diabetes were classified as "known diabetes" and those without FPG or OGTT as "not classified" (Table 1). IGR included impaired fasting glucose and impaired glucose tolerance.

Table 1. Classification of glucometabolic state

	Glucose concentration, mmol/l (mg/dl)	
Glucometabolic state	OGTT	FGP
Normal glucose regulation		
Fasting	< 6.1 (110)	< 6.1 (110)
2hr post-load	< 7.8 (140)	--
Impaired glucose regulation (IGR)		
Fasting	6.1 – 7.0 (126)	6.1 – 7.0 (126)
	or	
2hr post-load	7.8 – 11.0 (140-199)	--
Newly diagnosed diabetes		
Fasting	≥ 7.0 (120)	≥ 7.0 (120)
	or	
2hr post-load	> 11.0 (199)	--
Known diabetes	Previously diagnosed†	Previously diagnosed†
Patients "not classified"	Unknown	Unknown

* FGP was used to classify patients only if no OGTT was available
† no additional measurements

Statistical analysis

Descriptive statistics included counts and percentages for categorical variables, and mean values with corresponding standard deviations for continuous variables. Differences between patients with and without follow-up information were analyzed by chi-square and Student's *t*-test. Kaplan-Meier curves were computed for all cause mortality and the composite endpoint of major cardiovascular events, including all cause mortality, myocardial infarction, and stroke. The Log rank test was used for comparing the differences in survival and cardiovascular events. Multivariable Cox proportional hazard modelling was used to analyse the association between glucometabolic state at survey entry and 1-year outcome. We adjusted for variables which reached a *p*-value of < 0.15 in the unadjusted analyses. These variables were age, gender, history of myocardial infarction, heart failure, peripheral vascular disease, stroke, hyperlipidemia, diagnosis at admission, and treatment with anti-thrombotic agents, lipid lowering drugs, and beta-blockers at discharge. Results are reported as Hazard Ratios (HR) with associated 95% confidence intervals (CI). The assumption of proportional hazards was assessed and satisfied by visual inspection of the log-log survival curves for the categorical

variables and by using the Schoenfeld residuals. For the continuous variable (age), we constructed age-groups and used a graphical approach to verify the linearity assumption. All analyses were carried out with SPSS statistical software version 12.01. A *P*-value (two-sided) of <0.05 was considered statistically significant.

As we used a combination of OGTT measurements and, when not available, fasting plasma glucose only, we acknowledge that our glucometabolic classification of patients may be challenged. Therefore, we repeated the analyses using only patients who were classified according to OGTT and patients who were classified by fasting glucose only. In addition, the reference group as used in the multivariable Cox proportional hazard modelling was based on patients with normal glucose regulation measured by either fasting plasma glucose only or OGTT. As we acknowledge that patients with normal fasting glucose in whom no OGTT measurement was performed may have impaired glucose tolerance, we repeated the analysis using only patients with OGTT measurement and normal glucose regulation as reference group (n=668). Since the results of the additional analyses were highly consistent, we only report on our original choice.

RESULTS

A total of 4961 enrolled the Euro Heart Survey on diabetes and the heart, of which follow-up information was missing in 285 patients (6%). Therefore, the total study population of the present study included 4676 patients. When comparing the clinical characteristics between patients who were lost to follow-up and those who were included in our analyses, no major differences were observed (mean age 65 versus 67 years, diabetes 30% versus 33%). Only the proportion of males differed between these two groups (70% versus 78%, respectively).

The median follow-up duration was 374 days (interquartile range: 366-397 days). Three-quarter of all patients with a known glucometabolic state (n=3940) appeared to have diabetes or an abnormal glucose regulation (Table 2), as diabetes was previously diagnosed in 1425 patients, newly diagnosed in 452 patients, and an IGR was observed in 1116 patients. Only 947 of all patients who could be classified according to their glucometabolic state had a normal glucose metabolism. We were unable to classify 736 patients since no information on OGTT or FPG was available.

Differences in baseline characteristics between patients with different glucometabolic states are presented in Table 2. Patients with abnormal glucose regulation were older as compared to those with normal glucose regulation. Patients with previously diagnosed diabetes more often had a history of cardiovascular events and included more women as compared to the other patient groups (36% vs. 26-28%). The lowest prevalence of a

cardiovascular history was observed in patients with newly diagnosed diabetes (53% vs. 62-78%). Conversely, these newly diagnosed diabetics were more likely to be admitted with an acute coronary syndrome (58% vs. 24-40%). At the time of discharge or after consultation on the outpatients, most patients were prescribed on anti-thrombotic drugs, lipid lowering drugs (of which in 97% a statin), beta-blockers and ACE inhibitor or angiotensin receptor blockers (Table 2).

Table 2. Baseline characteristics in relation to glucometabolic state

	All	Normal	IGR†	DM new	DM known	Not classified
	n=4676	n=947	n=1116	n=452	n=1425	n=736
Age (mean, ±SD)	65 ±11	63 ±12	64 ±12	66 ±11	67 ±10	66 ±12
Males (%)	1398 (30)	704 (74)	807 (72)	332 (74)	907 (64)	528 (72)
Cardiovascular history (%)	*3154 (68)*	*590 (62)*	*687 (62)*	*238 (53)*	*1068 (75)*	*571 (78)*
Myocardial infarction	2059 (44)	396 (42)	471 (42)	162 (36)	672 (47)	358 (49)
Revascularization (PCI/CABG)	1699 (36)	319 (34)	363 (33)	115 (25)	510 (36)	392 (53)
Congestive heart failure	1052(23)	165 (17)	208 (19)	71 (16)	468 (33)	140 (19)
Peripheral artery disease	715 (15)	123 (13)	140 (13)	42 (9)	335 (24)	75 (10)
Stroke	264 (6)	36 (4)	60 (5)	23 (5)	116 (8)	29 (4)
Risk factors (%)						
Hypertension	3080 (66)	562 (59)	725 (65)	274 (61)	1111 (78)	408 (55)
Hyperlipidemia	3617 (77)	747 (79)	887 (80)	323 (72)	1095 (77)	565 (77)
Smoking (current)	989 (21)	244 (26)	259 (23)	116 (26)	216 (15)	154 (21)
Family history of CAD	528 (43)	447 (47)	476 (43)	150 (33)	598 (42)	321 (44)
Family history of diabetes	1188 (25)	154 (16)	212 (19)	97 (22)	622(44)	103 (14)
Obesity (BMI ≥ 30)	1205 (26)	189 (20)	290 (26)	123 (27)	488 (34)	115 (16)
Diagnosis (%)						
Acute coronary syndrome	1693 (36)	323 (34)	442 (40)	264 (58)	491 (35)	173 (24)
Stable coronary artery disease	2040 (44)	469 (50)	474 (43)	143 (32)	539 (38)	415 (56)
Heart failure	885 (19)	150 (16)	184 (17)	41 (9)	373 (26)	137 (19)
Other	58 (1)	5 (1)	16 (1)	4 (1)	22 (2)	11 (2)
*Medication at discharge (%)**						
ASA/anti-thrombotic drug	4509 (96)	920 (97)	1079 (97)	437 (97)	1366 (96)	707 (96)
Lipid lowering drugs	3740 (80)	758 (80)	921 (83)	359 (79)	1133 (80)	569 (77)
Beta-blockers	3589 (77)	749 (79)	911 (82)	361 (80)	1040 (73)	528 (72)
ACE-inhibitors/ARBs	3303 (71)	623 (66)	817 (73)	321 (71)	1161 (82)	381 (52)

† IGR= impaired glucose regulation
* at discharge or after the index outpatient visit
PCI= percutaneous coronary intervention, CABG= coronary artery bypass grafting, ARB= angiotensin receptor

Outcome

The worst outcome was observed in patients with known diabetes, as the mortality and incidence of myocardial infarction, and stroke were twice as high as in the other patients (Table 3). Patients with newly diagnosed diabetes clearly presented as an intermediate group with respect to outcome, as the 1-year mortality in these patients (5.5%) was in-between patients with known diabetes (7.7%) and patients with normal glucose regulation (2.2%), IGR

(2.7%) and those who could not be classified (3.7%).The highest incidence of the composite of mortality, myocardial infarction or stroke was also observed in patients with known diabetes (14.5%), followed by newly diagnosed diabetes (8.4%) and subsequently by the other subgroups (5.6-6.8%).

The Kaplan-Meier curves presenting time to mortality and the composite of mortality, myocardial infarction, or stroke over a 1-year period continuously diverged for patients with diabetes and those in the other glucometabolic states (Figure 1). Additionally, the curves also diverged for patients with known and newly diagnosed diabetes. Survival curves of patients with normal glucose regulation, IGR, or those who could not be classified were identical. Overall, log rank statistics showed significant differences in survival and survival free of myocardial infarction or stroke among the patient groups ($p < 0.001$).

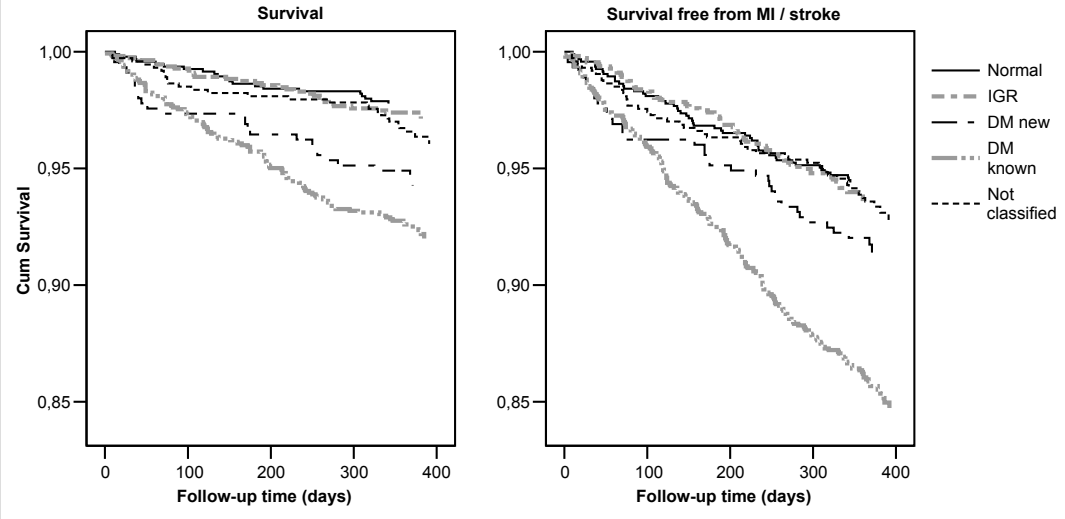
Table 3. Cumulative cardiovascular events during 1-year follow up in relation to glucometabolic state

	All (n=4676)	Normal (n=947)	IGR (n=1116)	DM new (n=452)	DM known (n=1425)	Not classified (n=736)	P for trend†
Death (%)	212 (4.5)	21 (2.2)	30 (2.7)	25 (5.5)	109 (7.7)	27 (3.7)	<.001
Myocardial infarction (%)	153 (3.3)	24 (2.5)	28 (2.5)	14 (3.1)	76 (5.3)	11 (1.5)	<.001
Stroke (%)	97 (2.1)	9 (1.0)	19 (1.7)	6 (1.3)	50 (3.5)	13 (1.8)	<.001
Death, MI, or stroke (%)	419 (9.0)	53 (5.6)	71 (6.4)	38 (8.4)	207 (14.5)	50 (6.8)	<.001
Revascularization (%)*	673 (14.4)	131 (13.8)	188 (16.8)	75 (16.6)	191 (13.4)	88 (12.0)	.38

IGR= impaired glucose regulation
† patients who could not be classified (n=736) were excluded from the analysis
* Percutaneous coronary intervention or coronary artery bypass surgery

After adjustment for a broad range of clinical and demographic characteristics (namely, age, gender, history of myocardial infarction, heart failure, peripheral vascular disease, stroke, hyperlipidemia, diagnosis at admission, and treatment with anti-thrombotic agents, lipid lowering drugs, and beta-blockers), both known diabetes and newly diagnosed diabetes remained associated with an increased risk of 1-year mortality (HR 2.4, 95%CI 1.5-3.8 and HR 2.0, 95%CI 1.1-3.6, respectively). Patients with known diabetes also had an increased higher risk of myocardial infarction and stroke (Table 4). Patients with IGR, however, were not at higher risk of adverse outcomes as compared to patients with normal glucose regulation.

Figure 1. 1-year follow-up outcome in relation to glucometabolic state.



Log rank test <.001 Log rank test <.001

In the methods section we acknowledged that our glucometabolic classification of patients may be challenged, and therefore performed analyses on the classification of patients according OGTT measurements or fasting glucose only. This additional analysis enabled us to look into more detail in patients with IGR. In 713 out of these 1116 patients an OGTT was performed, of whom 587 patients were known to have impaired glucose tolerance. Although we observed a higher prevalence of mortality, myocardial infarction and stroke in patients with impaired glucose tolerance (6%) as compared to those with impaired fasting glucose only (4%), neither of these glucometabolic states could be identified as an independent predictor for adverse outcomes (adjusted HR 1.7, 95%CI 0.7-4.5).

Table 4. Relative risk of adverse outcomes at 1-year according to glucometabolic state†

	Normal	IGR†	DM new	DM known	Likelihood ratio	P value
	(n=947)	(n=1116)	(n=452)	(n=1425)	test (df=3)	
	Adjusted HR (95%CI)					
Death	1.0	1.06 (0.61-1.85)	2.02 (1.12-3.63)	2.40 (1.50-3.84)	27.4	<.001
Myocardial infarction	1.0	0.88 (0.51-1.51)	1.03 (0.53-2.00)	1.64 (1.03-2.62)	10.4	.02
Stroke	1.0	1.71 (0.77-3.78)	1.48 (0.52-4.21)	2.79 (1.36-5.69)	11.4	.01
Death, MI, or stroke	1.0	1.02 (0.71-1.46)	1.30 (0.85-1.98)	1.95 (1.44-2.65)	33.5	<.001

IGR= impaired glucose regulation MI= myocardial infarction
† patients who could not be classified (n=736) were excluded from the analysis
* adjusted for age, gender, history of myocardial infarction, heart failure, peripheral vascular disease, stroke, hyperlipidemia, diagnosis at admission, and treatment with anti-thrombotic drugs, lipid lowering drugs, and beta-blockers.
** the Likelihood ratio statistics with and without glucometabolic state

DISCUSSION

The main finding of the present study is that the presence of diabetes, known or previously unrecognized, is an independent predictor of adverse outcomes in patients with CAD. Impaired glucose regulation (IGR; i.e. impaired fasting glucose or impaired glucose tolerance), however, could not be identified as an independent predictor for adverse outcomes.

As shown previously[9], abnormal glucose metabolism (i.e. diabetes or IGR) was frequently observed in patients with CAD who enrolled the Euro Heart Survey on diabetes and the heart. In only one-quarter of patients we observed a normal glucose regulation, whereas almost half of the patients had diabetes. Moreover, we confirmed that previously known diabetes was associated with an increased risk for adverse outcomes[1-5], and found that newly diagnosed diabetes also had a negative influence on prognosis.

Patients with newly diagnosed diabetes clearly were more likely to be admitted with an acute coronary syndrome, whereas a cardiovascular history was seen less often as compared to the other glucometabolic states. This finding may be indicative for the fact that these patients are more vulnerable for a cardiovascular disease and acute coronary syndrome was the first manifestation of this disease.

In accordance with the WHO[10] guidelines, the study protocol requested fasting plasma glucose and OGTT in all patients without previously diagnosed diabetes. A measurement of fasting glucose was performed in three-quarter of all these patients, while OGTT was performed in just over one half. Moreover, in 36% of the patients with IGR no OGTT was measured in order to exclude the diagnosis of diabetes, which is acknowledged as an important risk factor in patients with a cardiovascular disease. In the remaining 64%, the OGTT revealed that the majority of these patients had an impaired glucose tolerance. In contrast to the DECODE study[11,12], we could not identify impaired glucose tolerance as a better predictor of mortality than impaired fasting glucose alone. It should be noted, however, that due to the relatively small numbers of patients with IGR, diagnosed by means of an OGTT, the failure to confirm a worse outcome for patients with impaired glucose tolerance may be due to a Type II error. Additionally, the follow-up period in our study was restricted to 1-year, as compared to the median follow-up of almost 9 years in DECODE.[12]

Besides confirming that patients with previously known diabetes had an increased risk of death, myocardial infarction or stroke, we clearly identified patients with previously unrecognized diabetes as being at increased risk of major adverse events during the 1-year follow-up period. In contrast to the results of the GAMI-follow up trial[7], no differences were observed in event rates between patients with normal glucose regulation and IGR. It should be noted, however, that all participants of the GAMI trial were admitted with an acute myocardial infarction and followed for almost 3 years, whereas the present study included a

heterogeneous group of patients with CAD, admitted on cardiology wards or visiting the cardiology outpatient clinics and followed them for only about 1-year. This period may be a too short to observe an increased risk for adverse events in patients with CAD and IGR.

Although IGR could not be identified as an independent predictor for adverse outcomes, it has been shown that IGR markedly increases the risk of developing diabetes.[13,14] It is even estimated that the annual incidence of evolving diabetes is between 6-12% in patients with impaired glucose tolerance.[15,16] As diabetes is strongly associated with adverse outcomes, interventions aiming at delaying or preventing the onset of diabetes may prove beneficial for patients with IGR. Several studies have shown that lifestyle and pharmacological interventions are effective in delaying or preventing diabetes in patients with impaired glucose tolerance.[16-18]

Lifestyle changes aiming at preventing diabetes may also prove effective in modifying other risk factors like obesity, hypertension and dyslipidemia.[19] Future research, however, is needed to study the effect of these interventions on adverse outcomes in patients with CAD and IGR. In addition to promoting lifestyle changes, a more aggressive pharmacological treatment of patients with diabetes is advocated, as a number of modifiable factors are known to contribute to the unfavourable prognosis of these patients.[20,21] These factors include hyperglycaemia-induced endothelial cell dysfunction, increased pro-coagulation, impaired fibrinolysis, and dysfunctional arterial remodelling. Therefore, and in addition to good glycemic control, beta-blockers, anti-thrombotic drugs, statins and ACE-inhibitors should be considered in the pharmacological management of patients with established CAD and diabetes mellitus.[20,22-24] Although many patients were treated with these advised drugs, there is still room for improvement.

Diabetes and IGR are also known to be associated with an increased risk of stroke.[25] Although we observed a higher incidence of stroke in patients with known diabetes, no association between newly detected diabetes and stroke was found in our database. It should be noted, however, that the lack of significant association with stroke may be due to a lack of power. Similarly, we found no significant association between IGR and stroke.

In conclusion, in this large population of patients with CAD we confirmed that patients with known diabetes are at high risk for mortality and cardiovascular events and demonstrated that patients with newly diagnosed diabetes are at intermediate risk for adverse outcomes. Impaired glucose metabolism, however, did not significantly increase 1-year mortality or cardiovascular events. It should be noted, however, that the follow up period was only 1 year.

REFERENCES

1. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339:229-34.
2. Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. *J Am Coll Cardiol.* 2003;41:1071-7.
3. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation.* 2000;102:1014-9.
4. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenstrom A. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J.* 2005;26:650-61.
5. Norhammar A, Malmberg K, Diderholm E, Lagerqvist B, Lindahl B, Ryden L, Wallentin L. Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. *Journal of the American College of Cardiology.* 2004;43:585-591.
6. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care.* 1999;22:233-40.
7. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J.* 2004;25:1990-1997.
8. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet.* 2002;359:2140-4.
9. Bartnik M, Ryden L, Ferrari R, Malmberg K, Pyorala K, Simoons M, Standl E, Soler-Soler J, Ohrvik J. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J.* 2004;25:1880-90.
10. Report of the WHO Consultation, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. World Health Organisation, Department of Non-communicable Disease Surveillance, Geneva 1999.
11. The DECODE study group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet.* 1999;354:617-21.
12. The DECODE study group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med.* 2001;161:397-405.

13. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. *Jama*. 2001;285:2109-13.
14. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med*. 2002;19:708-23.
15. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care*. 1990;13:610-30.
16. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072-7.
17. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343-50.
18. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
19. Simmons R, Harding A-H, Jakes R, Welch A, Wareham N, Griffin S. How much might achievement of diabetes prevention behaviour goals reduce the incidence of diabetes if implemented at the population level? *Diabetologia*. 2006:1-7.
20. Chiquette E, Chilton R. Cardiovascular disease: much more aggressive in patients with type 2 diabetes. *Curr Atheroscler Rep*. 2002;4:134-42.
21. Mudaliar S. Intense management of diabetes mellitus: role of glucose control and antiplatelet agents. *J Clin Pharmacol*. 2004;44:414-22.
22. Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation*. 1999;99:2626-32.
23. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care*. 2004;27:15S-35.
24. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2003;24:1601-10.
25. Tanne D, Koren-Morag N, Goldbourt U. Fasting plasma glucose and risk of incident ischemic stroke or transient ischemic attacks: a prospective cohort study. *Stroke*. 2004;35:2351-5.

General discussion and conclusions

GENERAL DISCUSSION AND CONCLUSIONS

INTRODUCTION

Cardiovascular diseases are the main cause of mortality and loss of healthy life years in the western world and it is expected that this will remain so in the foreseeable future.[1-3] Over the last decades, major advances have occurred in diagnostic techniques and powerful pharmacological and interventional therapies were introduced.[4-7] In order to assist clinicians in every day clinical decision-making, evidence-based guidelines are prepared and published for appropriate use of diagnostic procedures and selection between patient management options. In these guidelines, randomized controlled trials (RCTs) are accorded the highest level of evidence. However, since RCTs have strict enrolment criteria, patients who participate in these trials often are a selected group that is only partly representative of patients seen in routine clinical practice. This limits the applicability of the results of RCTs in clinical practice.[8-12] Furthermore, the application of evidence-based guidelines in clinical practice may be hindered by physician related barriers (e.g. lack of agreement with the guidelines or lack of awareness) or economic constrains.[13,14]

The Euro Heart Survey (EHS) programme, initiated by the European Society of Cardiology (ESC), and adopted by the Netherlands Heart Foundation (NHF-Health Care programme, 2000T101), provides a cross-sectional overview of the management of patients with cardiovascular diseases in routine clinical practice. This thesis addresses the results of three surveys of the EHS/ NHF-Health Care programme: Heart Failure, Coronary Revascularization, and Diabetes and the Heart. The main research questions in this thesis are closely related to the aims of the EHS programme, namely to evaluate to which extend every day clinical practice corresponds with evidence-based guidelines, to evaluate the generalisability of evidence-based guidelines, and to identify patients that are under-represented in clinical guidelines.

GUIDELINE-BASED MANAGEMENT

Treatment of patients according to evidence-based guidelines is recommended by national and international societies, and have increasingly become a familiar part of clinical practice.[15] Most guidelines offer concise evidence-based instructions on diagnostic and therapeutic strategies, and contain systematically developed statements to assist physicians in clinical decision making. Guidelines, therefore, can be regarded as an important tool for improving the quality of care.[16]

This thesis revealed that the recommendations of evidence-based guidelines were endorsed to a great extend. For example, the majority of patients with heart failure were

treated with the advised ACE-inhibitors and the selection procedure of patients with coronary artery disease (CAD) for revascularization was in accordance with the guidelines, as patients selected for surgery were sicker and had more extensive CAD. However, we also identified areas for improvement. Such as, the under-use of beta-blockers in patients with heart failure, and the observation that the doses of ACE-inhibitors and beta-blockers as given to these patients were lower than proven effective in RCTs. Withholding evidence-based drugs or treating patients with lower doses than proven beneficial may result in the loss of event-free life years as was visualized in the higher mortality rates in patients who were not treated according the guidelines and did not receive at least 50% of the recommended treatment dose. Additionally, we observed under-use of GP IIb/IIIa receptor blockers in high-risk patients undergoing PCI, as well as under-use of statins and ACE-inhibitors in patients with proven CAD. The documentation of investigations also revealed the under-use of diagnostic tools, like echocardiography in patients with suspected or proven heart failure, particularly in women, and measurements of post-procedural necrosis markers in PCI patients. The observed discordance between evidence-based guidelines and clinical practice highlights the importance of performing observational studies like the EHS, in order to identify specific areas for improvement. Emphasizing these areas for improvement in scientific meetings, medical journals and educational programmes may increase the higher awareness of clinicians of the need for treating all patients according the guidelines, which ideally leads to a higher standard of evidence-based care.[17]

The application of evidence-based guidelines in clinical practice may be hindered by economic constrains, lack of motivation to change current practice, lack of agreement with the guidelines, lack of awareness, or because the guidelines are not concise enough (difficult to use).[13,14] Additionally, when evidence is contradictory, controversial or lacking, consensus procedures are used to formulate recommendations. These consensus procedures are prone to different interpretations, and consequently may result in inconsistencies between comparable guidelines.[18] Guidelines also can become outdated, as the development of novel techniques or new drugs often do not follow the same timetable as scientific working groups who are involved in preparing and updating the guidelines. For example, the most recent ACC/AHA guidelines for PCI (2001) suggests that thrombolysis-facilitated primary PCI may offer additional clinical benefit for patients, while the recently updated ESC guidelines for PCI (2005) conclude that there is no evidence for recommending thrombolysis-facilitated primary PCI.[19,20] Moreover, given the huge amount of published guidelines (over 100 in cardiology alone in the last 10 years)[21], the available information may become unmanageable for clinicians. Another important barrier in following guidelines can be identified in the limited

generalisability of evidence-based guidelines, as most trials providing the evidence usually enrol highly selected patients.[8-12]

GENERALISABILITY

This thesis clearly showed that the generalisability of RCTs is of concern indeed, as many patients in clinical practice did not match the characteristics of patients who participated in landmark trials. The EHS data indicated that less than 10% within a target population could be considered as trial-eligible. Patients in clinical practice were older, more often had co-morbid conditions, and were more likely to be treated with multi-pharmacy than clinical trial participants. As a result, the external validity of individual trials, enrolling highly selective patients, is questionable. However, when broader enrolment criteria are used, or a series of successive trials using different enrolment criteria it is to be expected that the external validity increases. For example, over the last 15-20 years, numerous ACE-inhibitor trials were performed, including most important subgroups of patients, resulting in a treatment benefit of ACE-inhibitors that is nowadays widely recognized as first-line treatment in all patients with left ventricular systolic dysfunction, unless patients are known to have contra-indications or side-effect. In contrast, treating heart failure patients with an aldosterone antagonist as is recommended in patients with advanced heart failure (NYHA III-IV), on top of ACE-inhibitors and diuretics, was based on only one RCT[22], and recently confirmed by a second trial.[23] It should be noted that it is not a prerequisite of evidence-based guidelines to perform multiple RCTs, however, the results of a single RCTs only can be translated to a group of patients with comparable clinical characteristics.

While advocating guideline-based management, it is important to note that guidelines cannot be applied to all individual patients.[21] Treating patients is more complex than simply following the guidelines, because co-morbidities, individual reactions to administered medication, observed side-effects, interaction with co-medications, as well as different treatment goals for individual patients can effect management decisions. At the other hand, if patients do fulfil the enrolment criteria of landmark trials that are included in the guidelines, it is to be expected that the majority of these patients can and should be treated in accordance with these guidelines. Although large groups of patients were treated according to the guidelines, this thesis also demonstrated under-utilization of evidence-based drugs (e.g. ACE-inhibitors) in patients who fulfilled enrolment criteria of RCTs. Under-utilization of evidence-based drugs in patients with heart failure was even more prominent in women than in men, indicating a gender difference in treating patients. Guidelines, however, do not discriminate between men and women, although women are often under-represented in RCTs.

UNDER-REPRESENTED SUBGROUPS

This thesis revealed information on subgroups of patients who were under-represented in RCTs, such as women with heart failure, heart failure patients with preserved left ventricular function, and patients with proven CAD who were considered ineligible for revascularization. Recognizing patient groups that are under-exposed in the guidelines is important, as this can (re-)direct the work of investigators and encourage funding to support studies that limit the identified flaws in the available guidelines.[15] Although the results of observational databases are prone to selection bias, they may be helpful in providing a broader understanding of the effectiveness of a treatment in populations that are underrepresented in clinical trials. Clearly, these observations deserve confirmation in randomised trials.

A major consequence of being underexposed in RCTs is the lacking evidence of treatments that have proven to be beneficial for subgroups of patients. For example, treatment recommendations are scarce and highly speculative in heart failure patients with preserved ventricular function.[24,25] Although most of cardiovascular drugs have only proven beneficial in heart failure patients with a depressed ventricular function, we observed similar treatment effects, irrespective of depressed or preserved ventricular function. Before recommending these drugs in patients with preserved ventricular function, RCTs are needed to confirm the observed findings. This clearly indicates that more trials are needed in patients with preserved systolic ventricular function to provide sufficient evidence to provide evidence-based guidance in treating these heart failure patients.

In addition to the observation that evidence-based guidelines are lacking in patients with preserved ventricular function, we observed that the majority of these patients are women. Women respond differently to a specific treatment than men as was illustrated by the gender-specific differences in the treatment effect of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes[26] and aspirin in primary prevention.[26,27] Additionally, the Digitalis Investigation Group trial showed that treatment with digoxine was associated with an increased risk of all-cause mortality among women, but not men.[28] These observations indicate that we always should be aware of possible gender differences in the treatment effect of cardiovascular drugs and the additional value of meta-analyses in providing a more reliable estimate of the treatment effect of subgroups that can be identified as being under-represented.

We identified a large proportion of patients with angina pectoris who were considered ineligible for revascularization. These patients reported a worse health status, failed to show an improvement over time, and had higher 1-year mortality rates as compared to patients in whom revascularization was the preferred treatment option. Although it is to be expected that these patients have worse outcomes, mortality rates are not excessively high in this subgroup

of patients who may consider themselves at the "end of the line".[29] In addition to optimizing pharmacological treatment, it is important to address issues like treatment adherence, physical training, life style, psychosocial adaptation, patients-tailored education (for example, how to use nitroglycerine as prophylactic drug before doing physical activities), etc. in order to refute the misconception and maladaptive beliefs of having no treatment options.[29-31] As cardiac rehabilitation programmes address most of the above mentioned topics and have proven to increase the health-related quality of life in these patients who are left with limited curative treatment options, we would like to encourage clinical practice to implement cardiac rehabilitation programmes for patients who are left with limited curative treatment options. However, further research is needed to reveal whether these rehabilitation programmes can fulfil the potential to substantially improve outcomes in these patients.

MORTALITY AND HEALTH STATUS

Major improvements in the management of patients with cardiovascular diseases have been realised in the last decades. The effectiveness of these beneficial treatment strategies is demonstrated by reduced mortality rates in RCTs. Regarding mortality and clinical practice we also observed an improved survival in patients who were treated according to the guidelines. For example, patients with depressed ventricular function, who were treated with ≥ 50% of the advised dose of ACE-inhibitors, had a lower mortality as compared to patients who received a lower dose or no ACE-inhibitor.

In contrast to confirming earlier observations that the presence of known or newly diagnosed diabetes was an independent predictor for adverse outcomes in patients with CAD, impaired glucose metabolism could not be identified as an independent predictor for 1-year mortality or cardiovascular events. It should be noted, however, that we followed these patients for not more than about 1-year, a period that may be too short to observe an increased risk for adverse events in patients with CAD and impaired glucose metabolism. Although impaired glucose metabolism could not be identified as an independent risk factor, interventions aiming at delaying or preventing the onset of diabetes in patients with impaired glucose metabolism may prove beneficial as the presence of diabetes clearly is associated with adverse outcomes.

In addition to analysing in-hospital and short-term mortality (3 month and/or 12 month), a health-related quality-of-life questionnaire was included in a number of surveys of the EHS programme. Measuring patients' health status is becoming an important outcome variable in clinical trials, as the observed differences in mortality between competitive treatment options diminishes.[32-34] This thesis confirmed the additional value of patient-reported health status in patients with CAD. Impaired health status at baseline was associated

with an increased risk of mortality, independent of conventional risk factors. In addition, others have identified self-perceived health status as an important patient-centered outcome and subsets of patients are known to prefer health status over prolonged survival.[35] These issues highlight the additional value of including patients' subjective experience of their own health status, by means of a short questionnaire, in order to optimize risk stratification and patient management in clinical practice.

LIMITATIONS

Several limitations should be taken into account when interpreting our results. It should be noted that the currently applied methodology in the EHS programme is prone to information and selection bias. For instance, hospitals participated voluntarily and participating hospitals did not resemble an equal geographical distribution. Additionally, the type of hospitals also did not fully represented clinical practice, as high proportions (30-40%) of university hospitals participated in the survey programme. As it was to be expected that university hospitals were more likely to participate, hospitals have been organised into clusters. A cluster is therefore composed of academic and non-academic hospitals, with and without cardiac catheterization laboratories and cardiac surgery facilities. Nevertheless, because patient inclusion was consecutive and a wide spectrum of hospitals in different countries participated, almost certainly the results are biased towards better than average practices. Another important limitation was the absence of o-site monitoring and source document verification. However, data-quality was checked electronically through queries for missing data.

Although we observed that many patients in clinical practice were treated in accordance with guidelines, areas for improvement were identified, including the incompleteness of the guidelines. Within the current survey programme, however, only limited data were available on the decision making process and reasons for not performing or not prescribing evidence-based treatment was underexposed. Adding this information to future survey programmes would reveal even more important information.

We acknowledge that data quality of a survey programme can hardly compete with the data quality of RCTs, but this was never intended. The EHS programme was developed to collect data on patient management as observed in clinical practice, and not to identify small differences between an experimental and control group as is done in RCTs. Another important difference between these two research designs is related in the different financial structures. Most RCTs are industry sponsored and physicians frequently receive payment for enrolling patients onto clinical trials (costs between €5000 and €10,000 per patient), whereas physicians involved in the EHS programme did not receive any payment for their effort and overall costs were less than €500 per patient.[36]

FINAL COMMENTS AND FUTURE DIRECTIONS

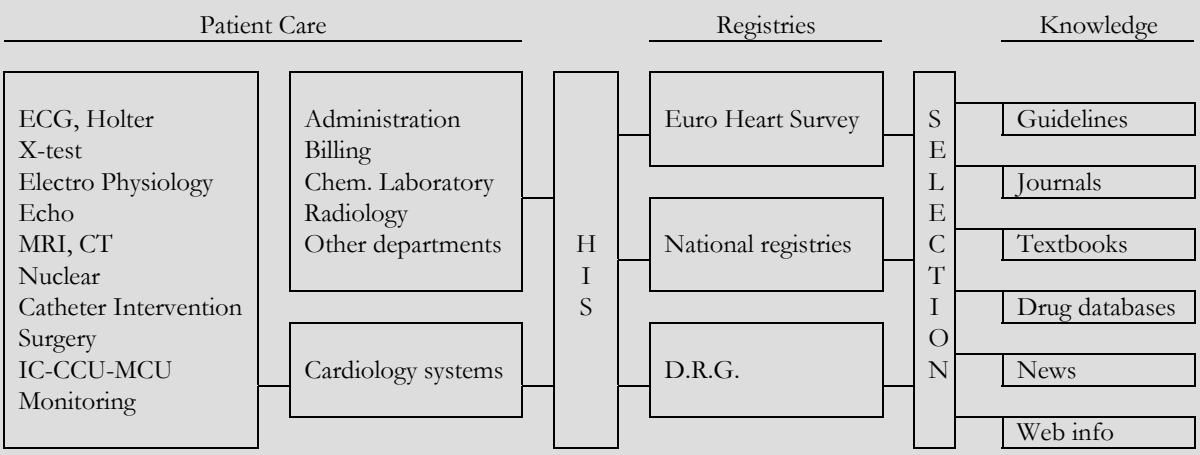
Observing every day clinical practice, as was done in the EHS programme, has proven to be feasible and valuable. The EHS programme provided a cross-sectional overview of current practice in Europe and can serve as benchmark for future evaluation when surveys are repeated. The value of doing repeated surveys was proven by EuroAspire-II revealing the increased use of ACE-inhibitors, beta-blockers, and lipid-lowering drugs in comparable patients over time.[37] Furthermore, participating hospitals taught us that they would welcome a system of benchmarking. Since the end of 2005 the EHS programme indeed supports a benchmark system in which participating hospitals get feedback on a regular basis and can compare these results with the mean of the other participating hospitals. It would be interesting to study the effect on guideline-based patient management and patient outcome when hospitals can compare themselves with peers (nationally and internationally).

Unfortunately, data as gathered in observational studies or registries throughout Europe do not always use identical items and definitions. For this reason the ESC recognized the importance of using data standards, throughout all ESC member countries. This resulted in the development and launch of the Cardiology Audit and Registration Data Standards (CARDS) in 2005. Since the launch of CARDS, these standardized data collection is implemented in the EHS programme, a number of national registries, and hospital registration systems.

Although guidelines are developed to assist clinicians in every day clinical decision-making, it should be noted that the development of guidelines can hardly compete with the speed of the development of pharmacological or interventional therapies. This discrepancy may lead to outdated guidelines, and consequently lack of enthusiasm to use treat patients accordingly. As discussed previously, the huge amount of existing guidelines may even become unmanageable for clinicians. We therefore advocate constructing a valid system of continuous updating guidelines and the implementing of such a system.

When international and national societies, governments, and information technology specialists co-operate in providing up-to-date evidence-based guidelines to clinicians in every day clinical practice, a major hurdle is taken in building a Cardiology Information System (CIS).[38] A CIS integrates all relevant sources of information (e.g. patient care, observational data, and the knowledge base), as is visualized in figure 1. This more than 30 years old dream of the ESC[38], however, is not realized yet. In this respect, we also would like to discuss the use of systematic verification of patient management by using a checklist. The positive effect of using a disease specific checklist in patients admitted with an acute myocardial infarction has been proven in the Guidelines Applied in Practice (GAP) project.[39] When initiatives like the

Figure 1. The different sources of information needed for an integrated CIS[38]



HIS= hospital information system; DRG= diagnosis related groups

GAP project could be integrated in the CIS and implemented in clinical practice, another step is taken in improving the application and applicability of evidence-based guidelines. This, however, warrants further research on how to build a user-friendly information system that not only registers patient-related information, but also provides the treating physician with the latest knowledge on evidence-based treatment for the individual patient.

REFERENCES

1. Boersma E MM, Wood DA, Bassand J-A, Simoons ML (eds.). Cardiovascular diseases in Europe. Euro Heart Survey and national registries of cardiovascular diseases and patient management. *Sophia Antipolis: European Society of Cardiology. 2002.*
2. Bobak M, Marmot M. East-West mortality divide and its potential explanations: proposed research agenda. *BMJ.* 1996;312:421-5.
3. Julian D, Bertrand M, Hjalmarsson A, Fox K, Simoons M, Ceremuzynski L, Maseri A, Meinertz T, Meyer J, Pyorala K, Rehnqvist N, Tavazzi L, Treasure T. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J.* 1997;Mar; 18(3):394-413.
4. Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; Data from the Swedish Hospital Discharge Registry 1988 to 2000. *Eur Heart J.* 2004;25:300-7.
5. Braunwald E. Cardiovascular Medicine at the Turn of the Millennium: Triumphs, Concerns, and Opportunities. *N Engl J Med.* 1997;337:1360-9.
6. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117-24.
7. Cleland JG, Swedberg K, Poole-Wilson PA. Successes and failures of current treatment of heart failure. *Lancet.* 1998;352 Suppl 1:SI19-28.
8. Cowie MR. Best practice: evidence from the clinical trials. *Heart.* 2002;88:2ii-4.
9. Lloyd-Williams F, Mair F, Shiels C, Hanratty B, Goldstein P, Beaton S, Capewell S, Lye M, Mcdonald R, Roberts C, Connelly D. Why are patients in clinical trials of heart failure not like those we see in everyday practice? *Journal of Clinical Epidemiology.* 2003;56:1157-62.
10. Sharpe N. Clinical trials and the real world: selection bias and generalisability of trial results. *Cardiovasc Drugs Ther.* 2002;16:75-7.
11. Knottnerus JA, Dinant GJ. Medicine based evidence, a prerequisite for evidence based medicine. *BMJ.* 1997;315:1109-10.
12. Hickling S. The barriers to effective management of heart failure in general practice. *British Journal of General Practice.* 2001;51:615-18.
13. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA.* 1999;282:1458-65.
14. Squire IB. Angiotensin Converting Enzyme Inhibition in Heart Failure: Clinical Trials and Clinical Practice. *Cardiovascular Drugs and Therapy.* 2002;16:67-74.
15. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: Potential benefits, limitations, and harms of clinical guidelines. *BMJ.* 1999;318:527-30.
16. Ryden L, Simoons ML. The european society of cardiology into the next decade. *Eur Heart J.* 2000;21:1193-201.
17. Swedberg K. What can we learn from Europe? *Heart.* 2005;91:ii21-23.
18. Burgers JS, Grol R, Klazinga NS, Makela M, Zaat J. Towards evidence-based clinical practice: an international survey of 18 clinical guideline programs. *Int J Qual Health Care.* 2003;15:31-45.

19. Smith SC, Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO. ACC/AHA Guidelines for Percutaneous Coronary Intervention (Revision of the 1993 PTCA Guidelines)--Executive Summary : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Endorsed by the Society for Cardiac Angiography and Interventions. *Circulation*. 2001;103:3019-41.
20. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug J-E, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for Percutaneous Coronary Interventions: The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J*. 2005;26:804-47.
21. Bassand JP, Ryden L. Guidelines: making the headlines or confined to the sidelines? *Eur Heart J*. 1999;20:1149-51.
22. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J, The Randomized Aldactone Evaluation Study Investigators. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *N Engl J Med*. 1999;341:709-17.
23. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309-21.
24. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001;22:1527-60.
25. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:1115-40.
26. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet*. 2002;359:189-98.
27. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293-304.
28. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med*. 2002;347:1403-11.
29. Moore RK, Groves D, Bateson S, Barlow P, Hammond C, Leach AA, Chester MR. Health related quality of life of patients with refractory angina before and one year after enrolment onto a refractory angina program. *Eur J Pain*. 2005;9:305-10.
30. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, Follath F, Hellemans I, Herlitz J, Luscher T, Pasic M, Thelle D. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. *Eur Heart J*. 2002;23:355-70.

31. Furze G, Lewin RJ, Murberg T, Bull P, Thompson DR. Does it matter what patients think? The relationship between changes in patients' beliefs about angina and their psychological and functional status. *J Psychosom Res*. 2005;59:323-9.
32. Pocock SJ, Henderson RA, Rickards AF, Hampton JR, King SB, Hamm CW, Puel J, Hueb W, Goy J-J, Rodriguez A. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *The Lancet*. 1995;346:1184-9.
33. Hoffman SN, TenBrook J, John A., Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *J Am Coll Cardiol*. 2003;41:1293-304.
34. Feit F, Brooks MM, Sopko G, Keller NM, Rosen A, Krone R, Berger PB, Shemin R, Attubato MJ, Williams DO, Frye R, Detre KM. Long-Term Clinical Outcome in the Bypass Angioplasty Revascularization Investigation Registry : Comparison With the Randomized Trial. *Circulation*. 2000;101:2795-802.
35. Stanek EJ, Oates MB, McGhan WF, Denofrio D, Loh E. Preferences for treatment outcomes in patients with heart failure: symptoms versus survival. *J Card Fail*. 2000;6:225-32.
36. Bassand JP, Martin J, Ryden L, Simoons M. The need for resources for clinical research: the European Society of Cardiology calls for European, international collaboration. *Lancet*. 2002;360:1866-9.
37. The EUROASPIRE group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. *Lancet*. 2001;357:995-1001.
38. Simoons ML, van der Putten N, Wood D, Boersma E, Bassand JP. The Cardiology Information System: the need for data standards for integration of systems for patient care, registries and guidelines for clinical practice. *Eur Heart J*. 2002;23:1148-52.
39. Eagle KA, Montoye CK, Riba AL, DeFranco AC, Parrish R, Skorcz S, Baker PL, Faul J, Jani SM, Chen B, Roychoudhury C, Elma MA, Mitchell KR, Mehta RH. Guideline-based standardized care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. *J Am Coll Cardiol*. 2005;46:1242-8.

Summary

The main research questions in this thesis correspond to those of the Netherlands Heart Foundation (NHF)-Health Care programme and were closely related to the aims of the Euro Heart Survey (EHS) programme, namely to evaluate to which extend every day clinical practice corresponds with evidence-based guidelines and to evaluate the generalisability of evidence-based treatment.

The EHS is initiated by the European Society of Cardiology (ESC) and recognized by the Netherlands Heart Foundation, resulting in a combined EHS and Netherlands Heart Foundation - Health Care programme. Since the start of the EHS programme in 1999, up to the end of 2006, over 80,000 patients have been included. These surveys provided systematic information on various groups of patients with cardiovascular diseases. In this thesis we present the results of three surveys, namely Heart Failure, Coronary Revascularization, and Diabetes and the Heart.

Our observations in the EHS on Coronary Revascularization showed a clear preference of percutaneous coronary intervention (PCI) over coronary bypass surgery (CABG) and pharmacological treatment after coronary angiography in clinical practice (**chapter 2**). In line with the guidelines, patients selected for CABG had more extensive coronary artery disease, and more often co-morbid conditions as compared to patients undergoing PCI. However, a sizeable proportion of patients with multivessel disease or left main, heart failure or diabetes did not undergo CABG but underwent PCI or were treated medically. We identified the under-use of adjunctive pharmacology, including GP IIb/IIIa inhibitors at time of intervention, statins and ACE-inhibitors as secondary prevention, as main areas for improvement in patient care. Yet, we confirmed that the recommendations of guidelines were applied in the majority of patients with proven coronary artery disease who underwent an invasive coronary procedure.

The comparison of patients with coronary artery disease from clinical practice (EHS on Coronary Revascularization) with patients who participated in 14 major randomised controlled trials (RCTs) comparing PCI with CABG revealed that almost two-third of patients as seen in clinical practice would have been disqualified for trial participation (**chapter 3**). Important differences were observed between trial participants and survey patients. Patients in clinical practice were older, more likely to have co-morbidity and left main stenosis, but less often multi-vessel disease as compared to trial participants. Although we observed important differences in clinical characteristics, the outcomes with respect to repeat revascularization and mortality of patients who underwent PCI or CABG in clinical practice were identical to those of the RCTs comparing PCI with CABG.

In addition to the observed differences between clinical practice and RCT participants in patients with coronary artery disease, we confirmed similar differences in patients with heart

failure (**chapter 4**). In this study we selected three landmark trials in which ACE-inhibitors, beta-blockers, and spironolactone proved to be save and effective. After identifying the major enrolment criteria, we identified patients who fulfilled the criteria of the SOLVD (ACE-i), MERIT-HF (beta-blocker), and RALES (spironolactone) trials. Only a small percentage (5-9%) of the patients enrolled in the EHS on Heart Failure would have qualified for one of these three trials. These trial-eligible patients were more likely to be treated with ACE-inhibitors, beta-blockers, and spironolactone than patients who did not fulfil the enrolment criteria. While the majority of trial-eligible patients who were treated with ACE-inhibitors received at least half of the target dose, only 20% of the patients treated with beta-blockers received at least half of the target dose.

It is important to note that guidelines do not provide recommendations for all subgroups of patients with heart failure. In particular, the guidelines for the treatment of patients with heart failure primarily focus on those with left ventricular systolic dysfunction (LVSD). Yet, almost half of all heart failure patients showed to have a preserved left ventricular function (PLVF). Treatment of these patients remains mainly speculative, as scientific evidence regarding treatment of heart failure patients with PLVF is scarce. In **chapter 5**, we evaluated patient characteristics and management of this major subgroup of heart failure patients. As compared to patients with LVSD, those with PLVF were older and more often women. Cardiovascular medication was given less often to patients with PLVF, with the exception of calcium antagonists. When comparing the treatment effect of cardiovascular drugs on mortality in patients with LVSD and PLVF, we could not identify significant differences. It should be noted, however, that this observation does not mean that patients with PLVF will derive the same benefit from pharmacological treatment as those with LVSD. This deserves confirmation in randomised trials. Although mortality was higher in patients with LVSD, it is important to note that mortality was high in both groups.

We expressed our concerns about the under-representation of women with heart failure in RCTs. In **chapter 6** we analyzed gender differences in patients with confirmed or suspected heart failure. The results of this study confirmed that women with heart failure have a different clinical profile as compared to men, which remained statistically significant after adjusting for age. Furthermore, we observed that women were less often admitted on cardiology wards, were less likely to undergo an assessment of the left ventricular function, and were treated less frequently with drugs as advised in the guidelines. These differences also remained significant after adjusting for age. Despite the fact that women had a better clinical profile, outcomes with respect to mortality were similar in men and women.

In **chapter 7** we evaluated the differences in clinical characteristics, management, and outcome of another group of patients identified as under-represented in the guidelines, namely

those with proven coronary artery disease who were considered ineligible for revascularization. Out of 4409 patients with angina pectoris, who enrolled the EHS on Coronary Revascularization, we identified 632 patients who were ineligible for revascularization. As compared to patients who were eligible for revascularization, we observed a worse clinical risk profile and more total occlusions in patients who were ineligible for revascularization. These patients had higher mortality rates at 1 year (7% vs. 3.7%), reported more problems on the EQ-5D health status questionnaire, and no showed no improvement in health status between discharge and 1-year follow-up. In contrast, a significant improvement was observed in the health status of patients who underwent revascularization between discharge and 1-year follow-up. Given these observations, we discussed the additional value of nurse-led multi-disciplinary rehabilitation programmes in improving perceived and actual health outcomes.

We also discussed the additional value of the EQ-5D in predicting 1-year mortality in patients with coronary artery disease undergoing an angiographic procedure (**chapter 8**). Impaired health status at baseline was associated with a 2-3 fold risk of all-cause mortality in patients with coronary artery disease, and after adjusting for other prognostic factors remained an independent risk factor for 1-year mortality. These findings support initiatives to include health status measurements when evaluating patients, in addition to other traditional risk factors as a tool to identify patients who are at high risk for adverse outcomes. In **chapter 9**, we discussed the glucometabolic status in relation to the 1-year mortality in patients with coronary artery disease. In addition to confirming that case-fatality is highest in patients who were known to have diabetes, we clearly identified patients with previously unrecognized diabetes as being an intermediate group for developing major adverse events. Impaired glucose metabolism, however, we could not identify as an independent predictor for 1-year mortality or cardiovascular events in patients with coronary artery disease.

Finally (**chapter 10**), we concluded that observational studies like the EHS have proven to be feasible and valuable. In addition to clarifying whether patients were treated according the guidelines, this thesis revealed subgroups of patients that were under-represented in clinical trials and consequently are left without evidence-based guidelines. These observations indicate areas for further research. To further improve quality of care, the co-operation of national societies, information specialists and governments in providing up-to-date evidence-based guidelines to clinicians in every day clinical practice is crucial. The "Cardiology Information System" as well as the "Guidelines Applied in Practice project" may prove valuable in improving the application and applicability of evidence-based guidelines.

Samenvatting

De laatste decennia is er grote vooruitgang geboekt bij de behandeling van patiënten met een cardiovasculaire aandoening. Om clinici van dienst te zijn bij het nemen van beslissingen over de beste behandeling voor hun patiënten, worden door onder andere de European Society of Cardiology (ESC) richtlijnen ontwikkeld en verbeterd. In dit proefschrift staat het evalueren van bestaande richtlijnen en de mate waarin de resultaten van grote klinische studies generaliseerbaar zijn naar de dagelijkse praktijk centraal. Deze evaluatie is één van de belangrijkste doelstellingen van het Euro Heart Survey (EHS) programma.

Het EHS programma is een door de ESC geïnitieerd observationeel onderzoeksprogramma, waarvan het belang door de Nederlandse Hartstichting wordt onderschreven. Dit resulteerde in 2001 tot de lancering van het gezamenlijke EHS/ Nederlandse Hartstichting-Zorgprogramma in Nederland. In dit survey programma wordt op een systematische wijze een veelheid aan gegevens in kaart gebracht over diagnostiek, behandeling en uitkomsten van patiënten met verschillende cardiovasculaire ziektebeelden. Sinds de start van het EHS programma in 1999 zijn meer dan 80.000 patiënten (eind 2006) uit meer dan 30 bij de ESC aangesloten landen geïncludeerd. In dit proefschrift worden de resultaten gepresenteerd van drie verschillende surveys, namelijk de EHS-Heart Failure, EHS-Coronary Revasculaization en de EHS-Diabetes and the Heart.

De EHS-Coronary Revascularization laat zien dat er in de klinische praktijk een duidelijke voorkeur bestaat voor percutane coronaire interventies (PCI) boven coronaire bypass operaties (CABG) en medicamenteuze behandeling bij patiënten met een coronaire hartziekte (**hoofdstuk 2**). In overeenstemming met de richtlijnen, hadden bypass patiënten een uitgebreidere vorm van coronairsclerose en meer comorbiditeit in vergelijking met PCI patiënten. Wel dient te worden opgemerkt dat een aanzienlijk aantal patiënten met meervatslijden, een hoofdstamleasie, hartfalen of diabetes niet werden geopereerd maar een PCI ondergingen of medicamenteus werden behandeld. Een aantal behandelingsstrategieën werden geïdentificeerd die voor verbetering vatbaar zijn, waaronder het toedienen van GP IIb/IIIa antagonisten tijdens de PCI en het voorschrijven van statines en ACE-inhibitors als onderdeel van secundaire preventie. Ondanks deze punten die voor verbetering vatbaar zijn, kan geconcludeerd worden dat de overgrote meerderheid van patiënten met een coronaire hartziekte volgens richtlijnen werden behandeld.

Een vergelijking tussen patiënten met een coronaire hartziekte uit de dagelijkse praktijk en patiënten uit 14 gerandomiseerde studies (PCI versus CABG) maakt duidelijk hoe geselecteerd deze laatste groep patiënten is (**hoofdstuk 3**). Immers tweederde van de patiënten uit de dagelijkse praktijk komt niet in aanmerking voor deelname aan deze studies. Voornamelijk leeftijd, het voorkomen van co-morbiditeit, aantal zieke coronair arteriën en het hebben van een hoofdstamleasie verschilde tussen studiepatiënten en patiënten uit de

dagelijkse praktijk. Ondanks deze belangrijke verschillen, laten de uitkomsten (noodzaak voor een herhalingsinterventie en mortaliteit) geen grote verschillen zien tussen studiepatiënten en patiënten uit de dagelijkse praktijk.

Dat verschillen tussen patiënten uit de dagelijkse praktijk en patiënten die deelnemen aan gerandomiseerde studies zich niet alleen beperken tot patiënten met een coronaire hartziekte, wordt duidelijk in **hoofdstuk 4**. In dit hoofdstuk zijn drie belangrijke gerandomiseerde studies (RCT's) bij patiënten met hartfalen geselecteerd die het gunstige effect van een ACE-inhibitor, betablokker, en spironolactone op mortaliteit hebben aangetoond, te weten de SOLVD, de MERIT-HF en RALES. Vervolgens zijn survey patiënten geïdentificeerd die voldeden aan de belangrijkste in- en exclusie criteria van deze studies. Uiteindelijk bleek minder dan 10% (5-9%) van de survey patiënten in aanmerking te komen voor deelname aan één van deze RCT's. Deze zogenaamde "trial-eligible" patiënten werden vaker behandeld met een ACE-inhibitor, beta-blokker en spironolactone dan patiënten die niet voldeden aan de studie criteria. De meeste trial-eligible patiënten die behandeld werden met een ACE-inhibitor werden met minimaal de helft van de aanbevolen dosering behandeld. Van de trial-eligible patiënten die met een beta-blocker behandeld werd kreeg slechts een minderheid (20%) minimaal de helft van de aanbevolen dosering.

Dat richtlijnen niet van toepassing blijken te zijn op alle patiënten is ook een belangrijk gegeven dat we in ogenschouw dienen te nemen. De richtlijnen bij patiënten met hartfalen richten zich vooral op patiënten met een linker ventrikel systolische disfunctie (LVSD). In de dagelijkse praktijk blijkt echter dat bijna de helft van alle hartfalen patiënten geen LVSD heeft, maar dat er sprake is van een behouden systolische ventrikel functie (PLVF). Helaas is er voor deze groep patiënten amper sprake van een wetenschappelijk onderbouwde behandeling. In **hoofdstuk 5** gaan we hier verder op in. Patiënten met een LVSD zijn jonger en vaker man in vergelijking met patiënten met een behouden ventrikel functie. Cardiovasculaire medicatie werd minder vaak voorgeschreven aan patiënten met PLVF, met uitzondering van calcium antagonisten. Overigens konden we bij de meeste cardiovasculaire medicijnen geen verschil in effect op mortaliteit aantonen tussen patiënten met een LVSD en PLVF. Wel is het belangrijk om hierbij te melden dat op basis van deze observationele studie niet geconcludeerd mag worden dat hartfalen patiënten met een behouden systolische ventrikel functie op eenzelfde wijze profiteren van deze cardiovasculaire medicatie. Hiervoor is het van groot belang dat de resultaten in een gerandomiseerd onderzoek worden bevestigd. Tot slot dient hier te worden opgemerkt dat hartfalen patiënten een slechte prognose hebben, ongeacht het hebben van een gestoorde of behouden systolische ventrikel functie.

In **hoofdstuk 6** wordt ingegaan op de ondervertegenwoordiging van vrouwen bij gerandomiseerde studies met hartfalen patiënten. Een belangrijke bevinding in dit hoofdstuk

betreft de constatering dat vrouwen minder vaak op cardiologische afdelingen werden opgenomen, minder vaak een diagnostisch onderzoek naar de ventrikelfunctie werd verricht en minder vaak volgens richtlijnen werden behandeld. Al deze verschillen bleven bestaan na een correctie voor verschillen in leeftijd. Het feit dat vrouwen een beter klinisch profiel hadden dan mannen, werd niet vertaald naar een betere uitkomst. Vrouwen hadden geen lagere mortaliteit dan mannen.

Een andere ondervertegenwoordigde groep betreft patiënten met een coronaire hartziekte die niet (meer) in aanmerking komen voor een coronaire revascularisatie (**hoofdstuk 7**). Veertien procent van de patiënten met angina pectoris die werden geïncludeerd in de EHS-Coronary Revascularization konden worden geïdentificeerd als inoperabel. In vergelijking met patiënten die een PCI of CABG ondergingen, hadden inoperabele patiënten een ongunstiger risicoprofiel (waaronder meer co-morbiditeit) en vaker een totale occlusie van minimaal één coronair arterie. Inoperabele patiënten hadden een hoger risico op overlijden (na 1 jaar 7% vs. 3.7%), rapporteerden meer problemen op de EQ-5D vragenlijst (kwaliteit van leven/ gezondheidsstatus) en lieten hierbij geen verbetering zien tussen ontslag en 1 jaar follow-up. Op basis van deze bevindingen wordt in dit hoofdstuk nader ingegaan op de aanvullende waarde die het opzetten van een multidisciplinair revalidatie programma kan hebben, waarin gespecialiseerde verpleegkundigen een centrale rol vervullen.

Het gebruik van vragenlijsten die de kwaliteit van leven/ gezondheidsstatus meten, zoals de EQ-5D, wordt ook in **hoofdstuk 8** besproken. Patiënten die een invasieve coronaire procedure hebben ondergaan in verband met een coronaire hartziekte blijken een 2-3 maal grotere kans op overlijden te hebben wanneer ze tijdens opname op deze vragenlijst invullen dat er sprake is van een gezondheidsprobleem. Zelfrapportage van gezondheidsproblemen blijkt dan ook een onafhankelijke voorspeller te zijn voor mortaliteit. Op grond van deze resultaten wordt nader ingegaan op de mogelijkheden en het belang van het meten van de gezondheidstoestand in de dagelijkse praktijk om patiënten vroegtijdig te identificeren die een hoger risico lopen op overlijden.

De laatste survey waaraan in dit proefschrift aandacht wordt geschonken betreft de EHS-Diabetes and the Heart (**hoofdstuk 9**). Het merendeel van de patiënten met een coronaire hartziekte die in deze survey werden geïncludeerd blijkt een gestoorde glucose huishouding te hebben. De hoogste mortaliteit werd geobserveerd bij patiënten die al langer bekend zijn met diabetes, gevolgd door patiënten bij wie de diagnose diabetes tijdens de initiële opname werd gesteld. Licht verhoogde glucosespiegels, waarbij de criteria van diabetes niet werden gehaald, bleek niet te resulteren in een slechtere prognose. Wel moet hier worden opgemerkt dat de duur van de follow-up periode slechts één jaar was, wat mogelijk tekort is

om een verschil aan te tonen tussen patiënten met een normale en een licht gestoorde glucose huishouding.

In het laatste hoofdstuk (**hoofdstuk 10**) van dit proefschrift, wordt nader ingegaan op de bevindingen van de afzonderlijke hoofdstukken. Op basis van de onderzoeksresultaten, zoals besproken in deze hoofdstukken, wordt geconcludeerd dat observationele studies zoals het EHS programma niet alleen haalbaar zijn, maar ook een waardevolle aanvulling zijn op RCT's. Behalve het evalueren van bestaande richtlijnen in de dagelijkse praktijk, wordt ook aandacht geschonken aan de ondervertegenwoordiging in RCT's van belangrijke subgroepen. Een belangrijk gevolg hiervan is het ontbreken van wetenschappelijk gefundeerde richtlijnen voor deze patiënten. Het wijzen op deze lacunes kan een stimulans zijn voor het initiëren van aanvullend onderzoek met als belangrijkste doel het genereren van kennis om óók deze patiënten een op wetenschappelijk onderzoek gebaseerde behandeling te kunnen aanbieden. Verder wordt in dit hoofdstuk ingegaan op het belang van een goede samenwerking tussen beroepsverenigingen, informatie specialisten en overheden om clinici van actuele en betrouwbare informatie te voorzien waarmee ze de aan hun zorg toevertrouwde patiënten zo optimaal mogelijk kunnen behandelen. Zowel het "Cardiology Information System" als het "Guidelines Applied in Practice project" zijn voorbeelden van projecten die de toepasbaarheid en toepassing van richtlijnen in de dagelijkse praktijk kunnen helpen verbeteren.

Dankwoord

De totstandkoming van een proefschrift is het resultaat van de inspanning van velen. Graag wil ik iedereen die hieraan heeft bijgedragen bedanken. In dit dankwoord wil ik graag een aantal van deze mensen persoonlijk bedanken.

Allereerst wil ik mijn promotor prof.dr. M.L. Simoons bedanken. Beste Maarten, ik ervaar het als een voorrecht om bij jou te mogen promoveren. Hartelijk dank voor dit vertrouwen. Je hebt me niet alleen de kans gegeven om als verpleegkundige aan een promotietraject te beginnen, je hebt met veel betrokkenheid mijn vorderingen gevolgd. Ik waardeerde je kritisch commentaar en ideeën voor het doen van (aanvullende) analyses en onderwerpen voor artikelen.

Dr. W.J.M. Scholte op Reimer verdient ook een bijzondere plek in dit dankwoord. Beste Wilma, ik weet nog als de dag van gisteren dat jij me probeerde over te halen om een nieuwe uitdaging aan te gaan. Niet alleen door het klinische werk te verruilen voor onderzoek, maar ook door aan de slag te gaan als promovendus op een groot observationeel onderzoek. Jij wist me te overtuigen dat dit niet te hoog gegrepen was (ook al bleven er twijfels bij mij). Het feit dat ik hier nu aan kan memoreren, geeft aan dat je dit goed hebt aangevoeld. Jouw bijdrage beperkte zich overigens niet alleen tot het stimuleren om deze overstap te maken. Tijdens onze vele voortganggesprekken waren je enthousiasme, constructieve kritiek en kennis van statistische analyses en interpretatie hiervan belangrijke factoren die hebben bijgedragen tot dit eindresultaat. Bedankt voor het vertrouwen, de vele goede adviezen, en bovenal de plezierige samenwerking.

Toch wil ik niet alleen Wilma bedanken voor het verbreden van mijn horizon. Ik ben veel dank verschuldigd aan Atie Immink. Atie, het was niet alleen een voorrecht om 18 jaar met jou op de IC Cardiologie te mogen werken. Jij stond aan de wieg van mijn verdere ontwikkeling. Een ontwikkeling die uiteindelijk resulteerde in dit proefschrift. Woorden schieten dan ook te kort om je hiervoor te bedanken.

Ook dr. E. Boersma wil ik vanaf deze plek bedanken. Beste Eric, groot is mijn dank als ik terug denk aan de hulp die ik kreeg bij het uitvoeren en interpreteren van statistische analyses. Vooral de complexere analyses had ik niet zonder jouw hulp kunnen uitvoeren. Ook heb ik het commentaar dat je leverde op concept artikelen altijd weten te waarderen. Zonder uitzondering hadden deze tot doel om de kwaliteit van het artikel te verbeteren. Ik ben je ook zeer dankbaar voor het vertrouwen dat je me hebt gegeven om tot dit mooie resultaat te komen.

De overige leden van de promotiecommissie, Prof.dr. W.J. van der Giessen, Prof.dr. J. Bakker, Prof.dr. D.J. van Veldhuisen, Prof.dr. H.J.G.M. Crijns, en dr. W. Wijns wil ik bedanken voor hun bereidheid dit proefschrift te beoordelen.

Maar, zoals eerder al gezegd, de inspanning van velen kenmerkt de totstandkoming van een proefschrift. Toen ik mijn vertrouwde werkplek op de IC Cardiologie na 18 jaar verruilde voor een functie op de KLEP groep moest ik niet alleen wennen aan het zitten achter een bureau. De nauwe en plezierige samenwerking binnen een multidisciplinair team zoals op een IC en het directe patiëntencontact, maakten plaats voor een veel individuelere manier van werken achter een computer. Het gemis aan het hechte teamverband op de IC werd al snel gecompenseerd door de goede werksfeer binnen de KLEP groep. Voornamelijk mijn toenmalige kamergenote en directe collega Esther de Swart, maar ook Anneke de Torbal, Cindy Westerhout en Miklos Kertai –de buren– hebben hier in belangrijke mate toe bijgedragen. Naast een goede werksfeer, dank ik jullie ook voor de vele waardevolle adviezen en praktische oplossingen die jullie gaven wanneer ik hieraan behoefte had. Naast deze collega's die inmiddels allen elders werkzaam zijn gaat mijn dank ook uit naar de blijvers. In het bijzonder wil ik Chris Jansen bedanken. Chris, het was meer dan plezierig om met jou samen te werken. Ook bleek je een waardevolle gesprekspartner om even "ruggespraak" te houden en mijn gedachten beter te ordenen. Maar niet alleen Chris, ook aan Colinda Koppelaar, Saskia Versluis en Maria Kamps ben ik veel dank verschuldigd. Niet alleen met betrekking tot de adequate dataverzameling, ook voor de plezierige samenwerking.

Niet onvermeld wil ik het enthousiasme van dr. Ron van Domburg en Sanne Hoeks laten, waarmee vragen als "hoe zouden jullie dit aanpakken" snel en adequaat werden beantwoord. Daarnaast heb ik met veel bewondering gezien hoe Sanne zich ontwikkelde als statisticus. Inmiddels kan ik niet meer tippen aan de statistische kennis die jij hebt opgedaan in de korte tijd dat we collega's zijn. Ook de overige leden van de KLEP groep, Arno Ruiter, Cecile Sweers, en Maarten Vermeulen dank ik voor de steun die ik van ze mocht ontvangen. Ook Annet Louw wil ik vanaf deze plaats bedanken. Annet jij was onmisbaar bij het doorlopen van het promotieprotocol. Maar ook de beide paranimfen, Eric van Velzen en Wim Verveer, verdienen hier een woord van dank voor de steun die ze mij gaven bij het voorbereiding van deze dag.

Naast de eerder genoemde collega's die betrokken waren bij het Euro Heart Survey programma/ NHS-Zorgprogramma, wil ik ook de collega's bedanken die in de andere clusters en ziekenhuizen werkzaam waren. Marjan Bijering, Herman Broers, Adrie van den Dool, Christel Ephraim, Heidi Fransen, Ingrid Middelveld, Karin Nijenbrinks, Nitolanda van Rijn, Henriette Tebbe, en Metske van der Wal, dank voor jullie inspanningen. Graag wil ik ook mijn collega-promovendus, Robby Nieuwlaat bedanken voor de plezierige samenwerking en het "delen" van de problemen die horen bij de (deel)coördinatie van een onderzoeksprogramma, het analyseren en schrijven van artikelen als onderdeel van een promotietraject. Speciale dank ook voor dr. W. Wijns. Beste William, tijdens de keren dat ik bij je was in Brussel om te

schrijven aan ons artikel heb ik me niet alleen zeer welkom gevoeld, ik heb deze momenten ook als zeer leerzaam ervaren. Hartelijk dank hiervoor.

Lieve Susan, Anouk en Karst, zonder jullie steun, stimulans en vertrouwen had ik dit project nooit tot een goed einde kunnen brengen. Aan jullie is dan ook dit proefschrift opgedragen.

Curriculum vitae

Mattie Lenzen was born on July 26, 1958 in Kerkrade, the Netherlands. In 1975 he finished High School in Vlissingen and started in 1976 his nursing studies at the University Hospital Dijkzig (former Erasmus University Medical Center), which he completed in 1979. After fulfilling his military service he started in 1981 his training in Intensive Care Nursing in the Thoraxcenter (Erasmus University Medical Center) and worked since his graduations in 1982 at the Intensive Care of Cardiology Unit in the Thoraxcenter. In 1989 he became assistant head-nurse. Since the early 90th he became interested in clinical research, and combined his work on the Intensive Care of Cardiology in 1996 with the position of trial co-ordinator. In 1998 he started the Master of Science in Nursing programme at the Hogeschool van Utrecht/ University of Wales and graduated in 2001. Subsequently he started working as a research fellow at the Department of Clinical Epidemiology of the Thoraxcenter. In 2005, he completed the Master of Science in Epidemiology programme as part of the Netherlands Institute for Health Sciences (NIHES) curriculum of the Erasmus University. The research described in this thesis was performed between 2001 and 2006 under the supervision of dr. Eric Boersma and dr. Wilma Scholte op Reimer.

List of publications

Original reports (peer reviewed articles)

Breeman A, Mercado N, Lenzen MJ, van den Brand MMJ, Harrington RA, Califf RM, Topol EJ, Simoons ML, Boersma E. Characteristics, treatment and outcome of patients with non-ST-elevation acute coronary syndromes and multivessel coronary artery disease: observations from PURSUIT (platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrelin therapy). Cardiology 2002;98: 195-201

Lenzen MJ, Gamel C, Immink A. Anxiety and well-being in first-time coronary angioplasty patients and repeaters. Eur J of Cardiovascular Nurs. 2002; 1: 195-201

Lenzen MJ, Ottervanger JP, Scholte op Reimer WJM, Lucas CMHB, Simoons ML, Boersma E. Hartfalen in de dagelijkse praktijk: patiëntenkenmerken, diagnostiek en behandeling. De Euro Heart Survey on Heart failure. Ned Tijdschr Geneeskunde 2004;148: 943-947

Lenzen MJ, Scholte op Reimer WJM, Boersma E, Vantrimpont PJMJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a Preserved and a Depressed Left Ventricular Function: a report from the Euro Heart Survey on Heart Failure. Eur Heart J 2004; 25:1214-1220

Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, Sechtem U, Stahle E, Widimsky P, de Jaegere P, Scholte op Reimer WJM, Mercado N, Wijns W. Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization. Eur Heart J. 2005;26: 1169-1179

MJ Lenzen, E Boersma, WJM Scholte op Reimer, AHMM Balk, M Komajda, K Swedberg, F Follath, M Jimenez-Navarro, ML Simoons, JGF Cleland. Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials. A report from the Euro HeartFailure Survey. Eur Heart J 2005;26: 2706-2713

M Hordijk-Trion, MJ Lenzen, W Wijns, P de Jaegere, ML Simoons, WJM Scholte op Reimer, ME Bertrand, N Mercado, E Boersma. Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: results from the Euro Heart Survey on Coronary Revascularization. Eur Heart J. 2006; 27: 671-678

MJ Lenzen, WJM Scholte op Reimer, T Norekvål, S De Geest, B Fridlund, J Haikkilä, T Jaarsma, J Mårtensson, P Moons, K Smith, S Stewart, A Strömberg, DR Thompson, W Wijns. Pharmacological treatment and perceived health status during 1-year follow up in patients diagnosed with coronary artery disease, but ineligible for revascularization. Results from the Euro Heart Survey on Coronary Revascularization. Eur J of Cardiovascular Nurs. 2006; 5: 115-21

R Nieuwlaat, MJ Lenzen, HJ Crijns, M Prins, WJM Scholte op Reimer, A Battler, D Hasdai, N Danchin, A Gitt, ML Simoons, E Boersma. Which factors are associated with the application

of reperfusion therapy in ST-elevation acute coronary syndromes? Lessons from the Euro Heart Survey on Acute Coronary Syndromes. Cardiology 2006;106:137–146

A Breeman, M Hordijk, MJ Lenzen, S Hoeks, JP Ottervanger, ME Bertrand, U Sechtem, R Zaliunas, V Legrand, MJ de Boer, N Mercado, W Wijns, E Boersma. Treatment decisions in stable coronary artery disease. Insights from the Euro Heart Survey on Coronary Revascularization. J Thorac Cardiovasc Surg (in press)

A Breeman, ME Bertrand, S Hoeks, MJ Lenzen, P Widimsky, JP Ottervanger, N Mercado, W Wijns, E Boersma. Diabetes does not influence treatment decisions regarding revascularization in patients with stable coronary disease. Insights from the Euro Heart Survey on Coronary Revascularization. Diabetes Care 2006;29(9):2003-11

M Lainščak, JGF Cleland, MJ Lenzen, I Keber, F Follath, M Komajda, K Swedberg. Non-pharmacological measures and drug compliance in heart failure patients: data from the EuroHeart Failure Survey. Eur J of Heart Fail (in press)

MJ Lenzen, WJM Scholte op Reimer, SS Pedersen, E Boersma, W Maier, P Widimsky, ML Simoons, NF Mercado, W Wijns. The additional value of patient-reported health status in predicting 1-year mortality after invasive coronary procedures: a report from the Euro Heart Survey on Coronary Revascularization. Heart (in press)

M Lainščak, JGF Cleland, MJ Lenzen, F Follath, M Komajda, K Swedberg. International variations in the treatment and co-morbidity of left ventricular systolic dysfunction: Data from the EuroHeart Failure Survey. Eur J Heart Fail (in press)

MJ Lenzen, A Rosengren, WJM Scholte op Reimer, F Follath, E Boersma, ML Simoons, JGF Cleland, M Komajda. Management of patients with heart failure in clinical practice: differences between men and women. Lessons from the Euro Heart Survey on Heart Failure. Submitted

M Lainščak, JGF Cleland, MJ Lenzen, S Nabb, I Keber, F Follath, M Komajda, K Swedberg. Patient recall of lifestyle advice in patients recently hospitalized with heart failure: a EuroHeart Failure Survey analysis. Submitted

MJ Lenzen, L Ryden, J Öhrvik, M Bartnik, K Malmberg, WJM Scholte op Reimer, ML Simoons. Diabetes known or newly diagnosed but not impaired glucose regulation has a negative influence on 1-year outcome in patients with coronary artery disease. A report from the Euro Heart Survey on diabetes and the heart. Submitted

WJM Scholte op Reimer, P Moons, S de Geest, B Fridlund, J Heikkila, T Jaarsma, MJ Lenzen, J Martensson, TM Norekval, K Smith, S Stewart, A Stromberg, D Thompson. Cardiovascular risk estimation by professionally active cardiovascular nurses: Results from the Basel 2005 Nurses Cohort. Eur J of Cardiovascular Nurs. (in press)

Accepted abstracts on scientific meetings (first author)

MJ Lenzen, JP Ottervanger, MJ Gardien, R van Domburg, ML Simoons. In-Hospital and Long-term Outcome After Angioplasty Following Circulatory Arrest. NVVC Congress, 25 – 26 April 2002 (Den Haag).

MJ Lenzen, C Gamel, A Immink. Anxiety and Well-being in First-time Coronary Angioplasty Patients and Repeaters. XXIV Congress of the European Society of Cardiology, August 31 – September 3, 2002 (Berlin)

MJ Lenzen, WJM Scholte op Reimer, E Boersma, T Jaarsma, M Komajda, J Cleland. Treatment of Heart Failure in daily practice (results of the EuroHeart Failure Survey): can nurses play a role in improving patients treatment. 3rd Annual Spring Meeting Cardiovascular Nursing, 11-12 April 12, 2003 (Stockholm)

MJ Lenzen, E De Teresa Galvan, WJM Scholte op Reimer, E Boersma, F Follath, M Komajda, K Swedberg, J Cleland. Comparing baseline characteristics of patients from routine clinical practice and those who enrolled in clinical trials. Information from the Euro-Heart Failure Study. XXV Congress of the European Society of Cardiology, 30 August-3 September, 2003 (Vienna)

MJ Lenzen, M Komajda, WJM Scholte op Reimer, E Boersma, F Follath, K Swedberg, J Cleland. Patient characteristics, treatment, prognosis and adherence to guidelines in patients with LV systolic dysfunction as compared to preserved LV function: a report from the Euro-Heart Failure Survey. XXV Congress of the European Society of Cardiology, 30 August-3 September, 2003 (Vienna)

MJ Lenzen, WJM Scholte op Reimer, E de Swart, R Nieuwlaat, W Wijns, E Boersma. Quality of Life in patients with established Coronary Heart Disease: results from the Euro Heart Survey on Coronary Revascularisation (EHS-CR). 4th Annual Spring Meeting Cardiovascular Nursing, 2-3 April, 2004 (Amsterdam)

MJ Lenzen, WJM Scholte op Reimer, E Boersma, J Vos, W Wijns. Quality of Life as outcome measure in patients with established Coronary Heart Disease: results from the Euro Heart Survey on Coronary Revascularisation (EHS-CR). XXVI Congress of the European Society of Cardiology, 28 August-1 September, 2004 (Munich)

MJ Lenzen, WJM Scholte op Reimer, E Boersma, K Swedberg, J Cleland, F Follath, M Komajda. Similar mortality in patients with heart failure and preserved or depressed myocardial function: results from the EuroHeart Failure Survey. XXVI Congress of the European Society of Cardiology, 28 August-1 September, 2004 (Munich)

MJ Lenzen, WJM Scholte op Reimer, E Boersma, J Vos, W Wijns. Kwaliteit van leven bij patiënten met een Coronaire hartziekte: resultaten van de Euro Heart Survey on Coronary Revascularisation / NHS-Zorgprogramma. Implementatiecongres over hart- en vaatziekten, 15 oktober 2004 (Den Haag)

MJ Lenzen, WJM Scholte op Reimer, E Boersma, T Jaarsma, J Cleland. Hoe worden patiënten met hartfalen in de klinische praktijk behandeld, en kunnen verpleegkundigen een rol spelen bij het optimaliseren hiervan? Implementatiecongres over hart- en vaatziekten, 15 oktober 2004 (Den Haag)

MJ Lenzen, M Komajda, WJM Scholte op Reimer, F Follath, K Swedberg, J Cleland, E Boersma. Klinische kenmerken, behandeling en prognose van patiënten met een behouden en gestoorde systolische linker ventrikel functie. Implementatiecongres over hart- en vaatziekten, 15 oktober 2004 (Den Haag)

MJ Lenzen, WJM Scholte op Reimer, M Simoons, E Boersma. Gender bias in research: randomized controlled trials and clinical practice as observed in the Euro Heart Survey programme. NHS-Wetenschapsdag, 11 October 2005 (Amsterdam)

MJ Lenzen, E Boersma, WJM Scholte op Reimer, A Balk, M Komajda, K Swedberg, F Follath, M. Jimenez-Navarro, ML Simoons, J Cleland. Under-utilization of evidenc-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials. A report from the Euro-Heart. NHS-Wetenschapsdag, 11 October 2005 (Amsterdam)

MJ Lenzen, WJM Scholte op Reimer, TM Norekvål, S De Geest, B Fridlund, J Haikkilä, T Jaarsma, J Mårtensson, P Moons, K Smith, S Stewart, A Strömberg, DR Thompson, W Wijns. Treatment and health status in patients with proven coronary artery disease, but ineligible for revascularization. A report from the Euro Heart Survey on Coronary Revascularization. 6th Annual Spring Meeting Cardiovascular Nursing; May 5-6, 2006 (Bergen)

MJ Lenzen, A. Rosengren, WJM Scholte op Reimer, F Follath, E. Boersma, ML Simoons, J Cleland, M Komajda. Gender differences in clinical practice: Lessons from the Euro Heart Survey on Heart Failure. World Congress of Cardiology, 2-6 September, 2006 (Barcelona)

MJ Lenzen, WJM Scholte op Reimer, TM Norekval, S Stewart, K Smith on behalf of UNITE. A 1-year follow up in patients diagnosed with coronary artery disease, but ineligible for revascularization. Results from the Euro Heart Survey on Coronary Revascularization. World Congress of Cardiology, 2-6 September, 2006 (Barcelona)

Stellingen behorende bij het proefschrift:

"Evaluating the Application and Applicability of Treatment Guidelines in Daily Clinical Practice. Closing the loop with the Euro Heart Survey programme"

1. De mogelijkheid tot medicamenteuze beïnvloeding van cardiovasculaire ziektebeelden wordt niet ten volle benut
2. Protocollair ziek zijn is geen garantie voor een protocollaire behandeling
3. Een gelijke behandeling van mannen en vrouwen met een cardiovasculaire ziekte is geen vanzelfsprekendheid
4. Kwaliteit van leven is een factor om rekening mee te houden
5. Observationele studies zijn een waardevolle aanvulling op gerandomiseerde klinische trials

6. Om selectiebias te reduceren worden patiënten geselecteerd
7. Gespecialiseerde verpleegkundigen zijn uitstekend toegerust om de coördinatie van zorg rondom een patiënt te verbeteren.
8. De behoefte van mensen aan zekerheid en de vrijheid om keuzes te maken vraagt om conflicten
9. Richtlijnen worden ontwikkeld om clinici te assisteren bij het maken van keuzes, nu nog een goede richtlijn om de juiste richtlijn te kunnen kiezen
10. Journalisten zijn vooral geïnteresseerd in de kwaliteit van zorg als deze tekort schiet

11. Het gunstige effect van een parachute op overleving bij het springen uit een vliegtuig is nooit aangetoond met behulp van gerandomiseerde studies