Coronary revascularization in ischemic heart disease: Lessons from observational studies and randomized clinical trials

Nestor Mercado

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Coronaire revascularisatie bij patiënten met een ischemische hartziekte: Wat hebben wij geleerd van observationele studies en gerandomiseerde klinische onderzoeken?

THESIS

To obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
Rector Magnificus

Prof.dr.ir. J.H. van Bemmel

and according to the decision of the Doctorate Board
The public defense shall be held on June 11, 2003 at 11:45 hrs

by

Nestor Felipe Mercado Ramirez

Born in Cali, Colombia

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To my parents Nestor and Nancy and my sister Anaisabel for their
unreserved love and support throughout all these years

Part 2: Predictors of adverse angiographic and clinical outcome

Part 3: Special subgroups on coronary revascularization

Outline of the thesis

At the end of the past century, cardiovascular diseases accounted for nearly half of deaths in the developed world and 25 percent in the developing world. Among cardiovascular disease deaths, approximately 43 percent are due to coronary artery disease, and by 2020 coronary artery disease will eventually become the world's number one cause of death and disability[1].

Currently, coronary revascularization is recommended to alleviate symptoms caused by myocardial ischemia, improve the likelihood of long-term survival and reduce the risk of future non-fatal cardiac events[2]. Approximately 60 percent of patients with symptomatic coronary artery disease have multivessel disease that could be treated by either percutaneous coronary intervention or coronary artery bypass graft surgery[3]. Therefore, given the magnitude of the problem, a better understanding of the invasive management and clinical outcome of patients with coronary artery disease is of critical public health importance.

The initial description of the saphenous vein graft technique for the surgical treatment of coronary artery disease by Favaloro[4] paved the way for a number of studies that compared coronary artery bypass graft surgery versus medical treatment in the 1970s. The results of these studies were consistent and found survival advantage only in patients with multiple risk factors or left main disease. Percutaneous coronary intervention was introduced into clinical practice by Gruentzig in 1977[5] and compared to medical treatment in various clinical settings. As the procedure gained acceptance and safety, its use was also extended to many different groups of patients with coronary artery disease. Finally, in the late 1980s and early 1990s, randomized trials comparing percutaneous coronary intervention with coronary artery bypass graft surgery were planned and executed. The results from these studies found a similar prognosis and symptomatic relief for the two initial revascularization strategies. Documented differences between the two procedures include a lower rate of repeat revascularization in patients initially treated with coronary artery bypass graft surgery.

The use of coronary stents, initially introduced by Puel and Sigwart[6,7] in the late 1980s, rapidly gained acceptance among the interventional community. Coronary stenting was associated with superior and predictable angiographic results. Coronary stents also improved the safety of the procedure and significantly reduced the incidence of angiographic restenosis. This background made it necessary to re-evaluate the relative benefits of surgery and percutaneous coronary intervention in the stent era and second-generation trials that compared percutaneous coronary intervention with multiple stenting versus coronary artery bypass graft surgery in patients with multivessel disease were designed and carried out[8-11].

This thesis presents an overview of clinical trials and observational studies on coronary revascularization and evaluates the results obtained with revascularization in different subsets of patients treated with percutaneous coronary intervention or coronary artery bypass graft surgery. The lessons learned from these studies are presented in three parts.

Part 1: Clinical trials and observational studies on coronary revascularization

Chapter 1 of this thesis critically investigates the clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting (Coronary plaque sealing, i.e. dilatation of angiographically nonsignificant lesions) compared to moderate and severe stenoses.

In **Chapter 2,** we provide an updated quantitative analysis of the clinical outcomes of patients with multivessel coronary artery disease (CAD) enrolled in four contemporary trials of PCI with multiple stenting versus Coronary Artery Bypass Surgery (CABG): The Arterial Revascularization Therapies Study (ARTS)[9], Stent or Surgery (SoS)[10], Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Multivessel Disease (ERACI-2)[8] and Medicine, Angioplasty or Surgery Study for Multivessel Coronary Artery Disease (MASS-2)[11].

Chapter 3 of this thesis provides an extensive clinically relevant description of the major observational studies and randomized clinical trials of coronary stenting versus bypass surgery carried out over the past two decades.

In **Chapter 4,** we describe the 6-month clinical outcome of patients with multivessel CAD and complete angiographic data enrolled in PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Supression Using Integrilin Therapy) stratified according to the treatment strategy applied early during hospitalization (Medical treatment – PCI (Balloon) – PCI (Stent) – CABG).

Part 2: Predictors of adverse angiographic and clinical outcome

In **Chapter 5**, we sought to assess whether coronary stents have modified the predictive value of demographic, clinical and quantitative coronary angiographic predictors of coronary restenosis identified during the balloon era.

In **Chapter 6**, we evaluate the treatment of in-stent restenosis with six different modalities (Stent-in-stent, rotational atherectomy, balloon angioplasty, laser angioplasty, directional atherectomy and vascular brachytherapy) and its clinical outcome. We also pool all the available data from the radiation (Beta and gamma) studies for the treatment of in-stent restenosis. Finally, we describe preliminary data on drug eluting stents for the treatment of in-stent restenosis.

Restenosis and consequent adverse cardiac events are increased in diabetic patients undergoing percutaneous coronary intervention (PCI). Use of intracoronary stents may ameliorate such risks. In **Chapter 7**, we investigate the clinical and angiographic factors influencing the likelihood of restenosis following stent deployment in this high-risk patient subgroup.

Part 3: Special subgroups on coronary revascularization

Obesity is considered one of the major modifiable risk factors for coronary heart disease. However, the impact of BMI on the outcomes after coronary artery revascularization remains controversial. In **Chapter 8**, we describe the impact of body mass index on the long-term outcomes in patients with multivessel coronary artery disease randomized to either stenting or coronary artery bypass surgery (CABG).

Chronic renal insufficiency (CRI) is associated with adverse outcomes after CABG and PCI. In **Chapter 9**, using data from the Arterial Revascularization Therapies Study (ARTS), we evaluate the effect of CRI on outcomes after coronary revascularization and we compare the outcomes of patients with CRI who were randomly assigned to CABG or PCI.

In **Chapter 10,** we assess the effect of fluvastatin on the outcome of patients with or without renal dysfunction in the Lescol Intervention Prevention Study (LIPS). Additionally, we evaluate the effect of fluvastatin on renal function and the relation between changes in renal function on the incidence of adverse cardiovascular events.

Finally, **Chapter 11** evaluates the impact of the extent of angiographic coronary artery disease (single- or multivessel) and of fluvastatin treatment on the incidence of late cardiac atherosclerotic complications in the Lescol Intervention Prevention Study (LIPS).

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Part 1: Clinical trials and observational studies on coronary revascularization

Chapter 1

Clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting: Implications for mechanical plaque sealing

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Eur Heart J 2003; 24: 541-551

Clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting

Implications for mechanical plaque sealing

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Aims To investigate the clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting (coronary plaque sealing, i.e. dilatation of angiographically non-significant lesions) compared to moderate and severe stenoses.

Methods and results Patients with chronic stable angina and a single de novo lesion in a native coronary vessel scheduled to undergo percutaneous coronary intervention (PCI) were selected from 14 different studies. Off-line analysis of angiographic outcomes was assessed in all patients using identical and standardised methods of data acquisition, analysis and definitions. Clinical endpoints were adjudicated by independent clinical events committees. All quantitative coronary angiographic (QCA) analyses were performed in the same core laboratory. Stenosis severity prior to PCI was categorised into three groups: <50% diameter stenosis (DS), 50–99%DS and >99%DS pre. A total of 3812 patients were included in this study; 1484 patients (39%) were successfully treated with balloon angioplasty (BA) only and stented angioplasty was performed in 2328 patients (61%).

One-year mortality and rate of non-fatal myocardial infarction (MI) (Kaplan–Meier) did not differ between BA and stented angioplasty for any of the stenosis severity categories. Following BA, the combined event rate (death and non-fatal MI) was 4.8, 4.6 and 0% in the <50, 50–99 and >99%DS categories, respectively. Following stented angioplasty, the combined event rate was 3.1, 4.4 and 4.8% in the same categories. The need for repeat revascularisation corrected for stenosis severity in the Cox proportional-hazards regression model was reduced by 20% after stented angioplasty (hazard ratio (HR) 0.80, 95%CI 0.69–0.93).

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Conclusion The concept of plaque sealing is appealing from the theoretical point of view. However, with current technology, plaque sealing cannot prevent death and future non-fatal MIs in the long-term because 1-year event rates after PCI of non-significant stenoses remain unacceptably elevated when compared with the estimated 1-year probability of a non-fatal MI in lesions with a <50%DS. Moreover, major adverse cardiac events at 1-year after PCI are not directly related to the degree of pre-procedural stenosis severity.

Introduction

Revascularisation by percutaneous coronary intervention (PCI) is performed to relieve symptoms in patients with coronary artery disease and angiographically significant coronary stenosis. However, coronary stenoses vary in severity and even mild stenoses harbour an unpredictable risk of acute occlusion that may cause myocardial infarction (MI) and sudden death. Balloon angioplasty typically induces plaque splitting which engenders a tissular reaction covering the plaque. The smooth muscle-rich neointima later transforms into a collagen-rich layer, which results in plaque sealing. Thus, once the acute effect of vessel trauma with its inherent risk of abrupt occlusion has passed, the subsequent risk of acute occlusion of a sealed plaque should be markedly reduced thanks to the repaired fibrous cap, which has overgrown the inflicted wound.[1,2]

Therefore, plaque sealing by balloon angioplasty has been advocated to prevent acute coronary events in patients with angiographically non-significant coronary lesions.[3]

Endorsing this concept and recommending PCI for angiographically non-significant lesions would mean a potentially large increase in procedures that needs sound justification. So far, the plaque-sealing concept has not been tested in prospective randomised clinical trials. A few observational case series from single centre experiences[4,5] have cautioned against the use of BA in non-significant lesions. We therefore aimed to investigate the clinical and angiographic outcome of coronary plaque sealing, i.e. dilatation of angiographically non-significant lesions compared to moderate and severe stenoses, selected from a large cohort of registries and clinical trials of patients undergoing PCI.

Methods

Patient selection

Patients with chronic stable angina and a single de novo lesion in a native coronary vessel scheduled to undergo PCI were selected from 14 different studies: two placebo-active randomised trials aimed at coronary restenosis prevention after balloon angioplasty (BA) alone or with additional stenting (FLARE[6] and TRAPIST[7]), nine stent registries (BENESTENT-2 Pilot,[8] WEST-1,[9] WEST-2,[10] Wellstent Native,[11] ROSE,[12] DUET,[13] EASI,[14] SOPHOS[15] and MAGIC 5-L[16]), two randomised trials comparing coronary stenting against BA alone (BENESTENT-1[17] and BENESTENT-2[18]) and the intravascular ultrasound (IVUS) substudy of a randomised clinical trial that evaluated the safety and efficacy of long-term treatment with an oral GP IIb/IIIa inhibitor in patients undergoing PCI (EXCITE[19]). A general description of these studies and the individual contribution of each clinical trial and registry, in terms of the number of single-lesion patients with chronic stable angina selected for this analysis is depicted in Table 1.

These studies are considered representative of the current practice of PCI but antedated the use of intracoronary brachytherapy and drug-eluting stents. Off-line analysis of angiographic outcomes was assessed in all patients using identical and standardised methods of data acquisition, analysis and definitions of the variables in the same core laboratory (Cardialysis, Rotterdam, The Netherlands) using the Cardiovascular Angiography Analysis System II (CAAS II) (Pie Medical, Maastricht, The Netherlands).

Patients were included if they had three adequate angiograms, one immediately before the intervention, one immediately after and one at 6-month follow-up. Patients with an unsuccessful procedure or patients with treated saphenous vein grafts were excluded.

Clinical endpoint definition

Clinical endpoints were uniformly defined across the different trials and registries as follows. Death was defined to include all deaths, regardless of cause. However, for the purposes of this study, only cardiac deaths were considered in the analysis of clinical events and any death was considered cardiac origin unless unequivocally proven otherwise. Non-fatal MI was diagnosed if there were new

Table 1 General overview of randomised clinical trials and device registries

Acronym-year	Study	Type of study	Treatment for single-lesion patients		Objective
			BA	Coronary stenting	
BENESTENT-1—1994	BElgian NEtherlands STENT	Randomised PTCA vs Stent	258	262	Evaluation of long-term angiographic and clinical outcomes of coronary stenting compared to standard PTCA
BENESTENT-2 Pilot—1996	BElgian NEtherlands STENT-2 Pilot	Stent registry	1	202	Determine the safety of elective implantation of a heparin-coated Palmaz–Schatz stent in patients with a single de novo lesion in a native coronary artery
WEST-1—1997	West European Stent Trial	Stent registry	2	85	Safety and efficacy of ACS Multi-Link coronary stenting in patients with chronic stable angina due to a single lesion in a native coronary artery
WEST-2—1998	West European Stent Trial 2	Stent registry	0	165	Assess the use of aspirin alone following successful implantation of an ACS Multilink-Stent under IVUS and QCA guidance in patients with chronic stable or unstable angina
BENESTENT-2—1998	BElgian NEtherlands STENT-2	Randomised PTCA vs Stent	379	276	Compare event-free survival in patients after heparin-coated stent implantation plus antiplatelet therapy with standard balloon angioplasty
FLARE—1999	Fluvastatin Angiographic REstenosis	Randomised active treatment vs placebo	713	0	Evaluate the ability of Fluvastatin to reduce restenosis after successful PTCA
Wellstent Native—1999	Wellstent native study	Stent registry	0	55	Assess the safety and efficacy of the self-expanding Wallstent in patients with stable or unstable angina
ROSE—2000	Registry for Optimal beStent Evaluation	Stent registry	0	66	Assess the procedural safety of beStent Brava implantation, 6-month angiographic and 12-month clinical outcomes of this population
DUET—2000	Evaluation of the ACS-Multi-Link DUET coronary stent system	Stent registry	0	113	Assess the safety and efficacy of the ACS Multi-Link DUET coronary stainless steel balloon-expandable stent
SOPHOS—2000	Study Of Phosphorylcholine coating On Stents	Stent registry	0	241	Assess the safety and efficacy of the BiodivYsio stent
EXCITE—2000	Evaluation of oral Xemilofiban in Controlling Thrombotic Events	Randomised active treatment vs placebo	131	430	To evaluate whether long-term Administration of a glycoprotein IIb/IIIa receptor antagonist would provide sustained protection from death, MI, and the need for urgent revascularisation
EASI—2001	European Antiplatelet Stent Investigators	Stent registry	0	113	Assess event-free survival after implantation of the Cordis coil cross-flex stent
MAGIC-5L—2001	MAGIC—5L Study	Stent registry	0	136	Assess the safety and efficacy of 5 different lengths of the self-expanding Magic Wallstent
TRAPIST—2001	Trapidil on restenosis after stenting	Randomised active treatment vs placebo	0	184	Assess the safety and efficacy of Trapidil (PDGF and Thromboxane A2 synthetase inhibitor) in restenosis prevention after coronary stenting

pathologic Q waves (>0.04 s) with a depth of more than one quarter of the corresponding R-wave amplitude in two or more contiguous leads considered by the investigator as not present at study inclusion[20] or if there was an increase in serum creatine kinase (CK) to more than twice the normal value, together with a pathological increase in muscle brain creatine kinase (CK-MB) iso-enzyme. If CK-MB data were not available, CK values were accepted as sufficient evidence of MI. These enzymes were measured per protocol at screening, 6 h before and 12 h after intervention. Repeat revascularisations (by CABG or repeat PCI) were defined as those involving a previously treated vessel between the initial procedure (considered complete when the guiding catheter was removed from the arterial sheath) and 1-year.

The primary clinical endpoint of this study was cardiac death and the combined rate of death and non-fatal MI. Secondary combined endpoint included the rate of repeat revascularisation.

QCA analysis and angiographic endpoints

The standard definitions used in this study for QCA variables: vessel size, pre-procedural minimal luminal diameter (MLD pre), post-procedural minimal luminal diameter (MLD post), minimal luminal diameter at 6-month follow-up (MLD f-up), diameter stenosis greater than 50% at 6-month follow-up (DS >50% at 6-month), acute gain, late loss and loss index have been described elsewhere.[21,22] The pre-procedural reference diameter (RD pre) was the diameter obtained by an interpolated method and the lesion length was defined by the curvature analysis.[21]

Data analysis

Data was divided into quintiles according to the degree of severity of pre-procedural diameter stenosis (DS pre) as assessed by QCA and based on the definitions used in the CASS registry study.[23] Separate baseline, QCA and clinical endpoint analyses were performed in patients treated with balloon angioplasty only (BA group) and patients in whom coronary stents were implanted (stent group). Because the event rates for BA and stent groups were similar for patients in the middle three quintiles (50–69, 70–89 and 90–99%DS), we combined the middle three quintiles into a single group (50–99%DS). Therefore, stenosis severity was categorised into three groups as follows: <50, 50–99 and >99%DS pre.

The statistical analysis was performed using the SAS 8.0 software package (SAS Institute, Cary, NC).

Quantitative values were given as median (25th, 75th percentiles) or mean±standard deviation. To test for differences in categorical variables the Fisher's exact test was applied and to test for differences in continuous baseline variables across the studies, the Kruskal–Wallis test was used.

Event rate curves were constructed by means of Kaplan–Meier methods, and event rate differences between the three groups of stenosis severity were compared with the use of the log-rank test.[24] The Cox proportional-hazards regression model was used to examine the effect of coronary stenting on the primary and secondary clinical endpoints of this study, corrected for stenosis severity (<50, 50–99 and >99%DS pre). Statistical significance was inferred at $P<0.05$.

Results

A total of 3812 patients with chronic stable angina and a single coronary lesion in a native vessel were included in this study; 1484 patients (39%) were successfully treated with BA only and stented angioplasty was performed in 2328 patients (61%). Comparisons between the three groups of stenosis severity (<50, 50–99 and >99%DS pre) were summarised for baseline characteristics, angiographic and clinical outcomes for BA and Stent groups in Tables 2–4 and Figs. 1–3.

Baseline clinical characteristics

BA group
The three groups of patients with varying degrees of stenosis severity were similar with regard to age, gender, height, weight, history of hypertension, diabetes mellitus, peripheral vascular disease, previous bypass surgery (CABG), smoking status and treated vessel.

Baseline comparisons between the three groups that were statistically different included: history of prior MI, previous PCI and multiple vessel disease (MVD). History of prior MI was more frequent in the <50%DS category, whereas MVD occurred more often in the intermediate and highest categories of stenosis severity. A significant decreasing trend in the percentage of patients with a previous angioplasty was observed in 12.4, 7.5 and 2.4% in the <50, 50–99 and >99%DS categories, respectively (Table 1).

Stent group
The three different groups of patients with varying degrees of stenosis severity were similar with regard to age, gender, height, weight, history of

Table 2 Baseline characteristics

	Balloon angioplasty population				Stent population			
	<50% DS pre (n=124)	50–99% DS pre (n=1266)	>99% DS pre (n=94)	P-value	<50% DS pre (n=96))	50–99% DS pre (n=2128)	>99% DS pre (n=104)	P-value
Age,	60 (52, 68)	60 (52, 67)	59 (51,65)	0.356	60 (52, 69)	60 (52, 66)	59 (52, 67)	0.689
Men, %	78	81	85	0.458	78	80	79	0.884
Height, cm	170 (164, 175)	170 (165, 176)	170 (165, 180)	0.355	170 (164, 177)	171 (165, 176)	172 (166, 178)	0.373
Weight, kg	76 (69, 84)	78 (70, 85)	80 (74, 89)	0.096	77 (70, 85)	78 (70, 86)	80 (74, 90)	0.073
History								
Hypertension, %	37	36	34	0.914	37	37	34	0.888
Diabetes mellitus, %	6.6	7	9.7	0.593	14	12	11	0.760
MI, %	40	27	34	0.009	30	29	49	0.004
PVD, %	7.4	5.6	4.8	0.659	3.2	6.5	3	0.364
Angioplasty, %	12.4	7.5	2.4	0.029	11	10	9	0.955
Bypass surgery, %	2.4	3.4	0	0.258	3.2	2.8	0	0.408
Smoking status, %								
Current	26	28	27	0.835	30	28	23	0.486
Prior history	49	48	46	0.874	41	48	53	0.214
MVD, %	2.5	8	3.6	0.035	26	23	14	0.160
Vessel treated, %								
RCA	26	27	28	0.936	21	36	42	0.056
LAD	52	47	36	0.086	63	46	33	0.002
LCx	21	26	35	0.061	15	17	24	0.414

Data presented are median (25th, 75th percentiles) or percentages.
MI=prior history myocardial infarction; PVD=peripheral vascular disease; MVD=multiple vessel disease; DS pre=pre-procedural diameter stenosis.

Table 3 Pre-procedural, post-procedural and 6-month follow-up QCA analysis of treated lesions

	Balloon angioplasty population				Stent population			
	<50% DS pre (n=124)	50–99% DS pre (n=1266)	>99% DS pre (n=94)	P-value	<50% DS pre (n=96)	50–99% DS pre (n=2128)	>99% DS pre (n=104)	P-value
Vessel size, mm	2.61 (2.3, 2.85)	2.78 (2.47, 3.14)	2.47 (2.23, 2.79)	<0.0001	2.75 (2.52, 3.14)	2.91 (2.64, 3.25)	2.96 (2.7, 3.37)	0.006
Lesion length, mm	6.89 (5.59, 8.03)	7.48 (6.01, 9.48)	7.86 (6.33, 9.79)	0.009	6.74 (5.55, 8.81)	8.15 (6.48, 10.3)	17.4 (12, 25.8)	<0.0001
MLD pre, mm	1.4 (1.24, 1.62)	1.01 (0.85, 1.18)	0 (0, 0)	<0.0001	1.53 (1.36, 1.68)	1.01 (0.86, 1.18)	0 (0, 0)	<0.0001
MLD post, mm	1.86 (1.61, 2.16)	1.93 (1.68, 2.22)	1.7 (1.47, 1.89)	<0.0001	2.62 (2.3, 2.93)	2.64 (2.39, 2.91)	2.46 (2.2, 2.7)	0.0002
MLD f-up, mm	1.7 (1.35, 2)	1.62 (1.25, 1.98)	1.24 (0.73, 1.73)	<0.0001	1.89 (1.52, 2.37)	1.88 (1.44, 2.27)	1.6 (1, 1.98)	<0.0001
DS >50% at 6-month f-up, %	24	30	44	0.008	19	21	32	0.005
Acute gain	0.45 (0.29, 0.6)	0.9 (0.67, 1.14)	1.7 (1.47, 1.89)	<0.0001	1.1 (0.88, 1.28)	1.6 (1.35, 1.86)	2.46 (2.2, 2.69)	<0.0001
Late loss	0.19 (-0.09, 0.5)	0.25 (-0.02, 0.6)	0.41 (0.04, 1.03)	0.002	0.69 (0.42, 1.1)	0.74 (0.42, 1.1)	0.9 (0.54, 1.34)	0.024
Loss index	0.44 (-0.1 5, 1.07)	0.28 (-0.02, 0.67)	0.25 (0.02, 0.58)	0.171	0.59 (0.42, 1.01)	0.46 (0.26, 0.72)	0.37 (0.21, 0.5)	<0.0001

Data presented are median (25th, 75th percentiles) or mean±standard deviation.
MLD pre=pre-procedural minimal luminal diameter; MLD post=post-procedural minimal luminal diameter; MLD f-up=minimal luminal diameter at 6-month follow-up; acute gain=MLD post-MLD pre; late loss=MLD post-MLD f-up; loss index=acute gain/late loss± DS pre=pre-procedural diameter stenosis.

Table 4 Frequency of clinical end-points in descending order of severity

	Balloon angioplasty population			Stent population		
	<50%DS pre (n=124)	50–99%DS pre (n=1266)	>99%DS pre (n=94)	<50%DS pre (n=96)	50–99%DS pre (n=2128)	>99%DS pre (n=104)
Cardiac death	3 (2.4)	12 (0.9)	0 (0)	0 (0)	19 (0.9)	1 (1)
Non-fatal MI	3 (2.4)	48 (3.8)	0 (0)	3 (3.1)	79 (3.7)	4 (3.8)
Repeat revascularisation (CABG or Re-PCI)	23 (18.5)	268 (20.7)	28 (29.7)	18 (18.7)	308 (14.5)	20 (19.2)
Cardiac death or non-fatal MI	6 (4.8)	59 (4.6)	0 (0)	3 (3.1)	95 (4.4)	5 (4.8)
Cardiac death, non-fatal MI or repeat revascularisation	26 (21)	301 (24)	28 (29.7)	18 (18.7)	365 (17)	23 (22)
Any event	29 (23)	328 (26)	28 (29.7)	21 (22)	406 (19)	25 (24)

MI, acute myocardial infarction; repeat revascularisation includes coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI). Log–Rank test comparing the three categories of stenosis severity at 1-year was: cardiac death (BA, 3.41; $P=0.18$; stent, 0.78; $P=0.67$); non-fatal MI (BA, 4.65; $P=0.9$; stent, 0.01, $P=0.99$) and cardiac death or non-fatal MI (BA, 4.97; $P=0.83$; stent, 0.197; $P=0.90$). DS pre=pre-procedural diameter stenosis.

Balloon Angioplasty population

Fig. 1 One-year event rate curves for patients treated with balloon angioplasty and varying degrees of stenosis severity measured by QCA. Left: event rate curves for repeat revascularisation (CABG or Re-PCI). Right: event rate curves for death, non-fatal MI or repeat revascularisation (CABG/Re-PCI). <50%DS pre=<50% pre-procedural diameter stenosis; 50–99%DS pre=50–99% pre-procedural diameter stenosis, >99%DS pre=>99% pre-procedural diameter stenosis. QCA=quantitative coronary angiography; MI=myocardial infarction; PCI= percutaneous coronary intervention; CABG=coronary artery bypass graft surgery.

hypertension, diabetes mellitus, peripheral vascular disease, previous PCI, CABG, smoking status and treated vessel. Baseline comparisons between the three groups that were statistically different included: previous MI and a treated lesion located in the LAD. A previous MI was more frequent in the >99%DS category whereas mild lesions where most often treated while located in the LAD (Table 2).

Baseline, post-procedural and 6-month follow-up QCA

Several angiographic variables were highly correlated with the degree of stenosis severity (Table 3). Lumen and vessel dimensions were smaller as the stenosis severity progressed. The acute gain increases with increasing stenosis severity as does
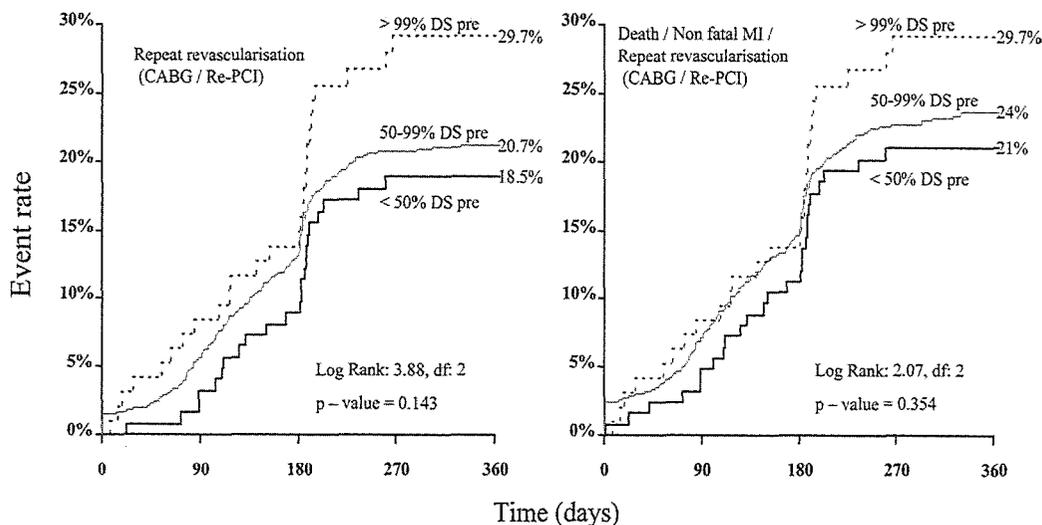
Stent population
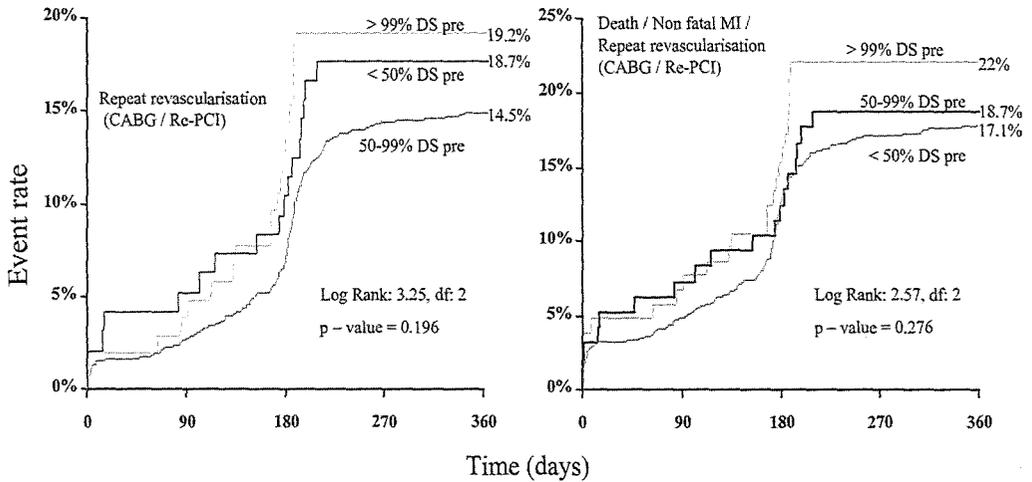
Fig. 2 One-year event rate curves for patients treated with coronary stenting and varying degrees of stenosis severity measured by QCA. Left: event rate curves for repeat revascularisation (CABG or Re-PCI). Right: event rate curves for death, non-fatal MI or repeat revascularisation (CABG/Re-PCI). <50%DS pre=<50% pre-procedural diameter stenosis, 50–99%DS pre=50–99% pre-procedural diameter stenosis, 99%DS pre=>99% pre-procedural diameter stenosis. QCA=quantitative coronary angiography; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft surgery.

the late loss, but the loss index diminished with increased stenosis severity. A significant and direct relationship between stenosis severity, lesion length and DS>50% at 6-month follow-up was observed across the three categories (<50, 50–99 and >99%DS) for both BA and stented patients.

Clinical endpoints at 1 year

BA group
The incidence of cardiac death and non-fatal MI was not different between the <50, 50–99 and >99%DS groups (Table 4). Repeat revascularisation (CABG or Re-PCI) occurred in 18.5% of patients in the <50%DS group, 20.7% patients in the 50–99%DS group and 29.7% patients in the >99%DS group (Table 4).

Stent population
The incidence of cardiac death and non-fatal MI did not differ with stenosis severity (Table 4). Repeat revascularisation (CABG or Re-PCI) occurred in 18.7% of patients in the <50%DS group, 14.5% patients in the 50–99%DS group and 19.2% patients in the >99%DS group (Table 4).

Event-rate analysis for BA and stent populations
The log–rank test did not reveal a statistically significant difference in the event-rates over time among the subgroups of increasing stenosis severity

(Table 4, Figs. 1 and 2). The primary event rate (cardiac death, death or MI) following BA or stenting of angiographically non-significant stenoses was equivalent to the event rate observed after BA or stenting of angiographically significant stenoses. Irrespective of stenosis severity, death or non-fatal MI at 1 year occurred in nearly 5% of both BA and stent cases. A significant difference (Fig. 3) in favour of coronary stenting (corrected for stenosis severity) was observed with respect to the need for repeat revascularisation (HR 0.80; 95% CI 0.69–0.93) and the combined clinical end-point of cardiac death, non-fatal infarction or repeat revascularisation (HR 0.83; 95% CI 0.72–0.96).

Discussion

Our findings indicate that event rate at 1 year is substantial (over 20%) when angiographically non-significant stenoses (<50%DS) are treated by BA or stenting. In fact, the event rate after PCI was not related to stenosis severity. Originally, the concept of plaque sealing was intended to be applied with BA, which is no longer realistic since current practice involves stent implantation in over 70% of PCI procedures.[25] Therefore, the concept was extended to the use of stents, hoping this would improve the outcome. Even after implantation of

Cardiac Death

Non fatal myocardial infarction

Repeat revascularisation
(CABG or repeat PCI)

Cardiac Death or non fatal
myocardial infarction

Cardiac Death, non fatal
Myocardial infarction or repeat
revascularisation

| 0 | 0.5 | 1 | 1.5 | 2 | 2.5 |

Stent   **Ballon Angioplasty**
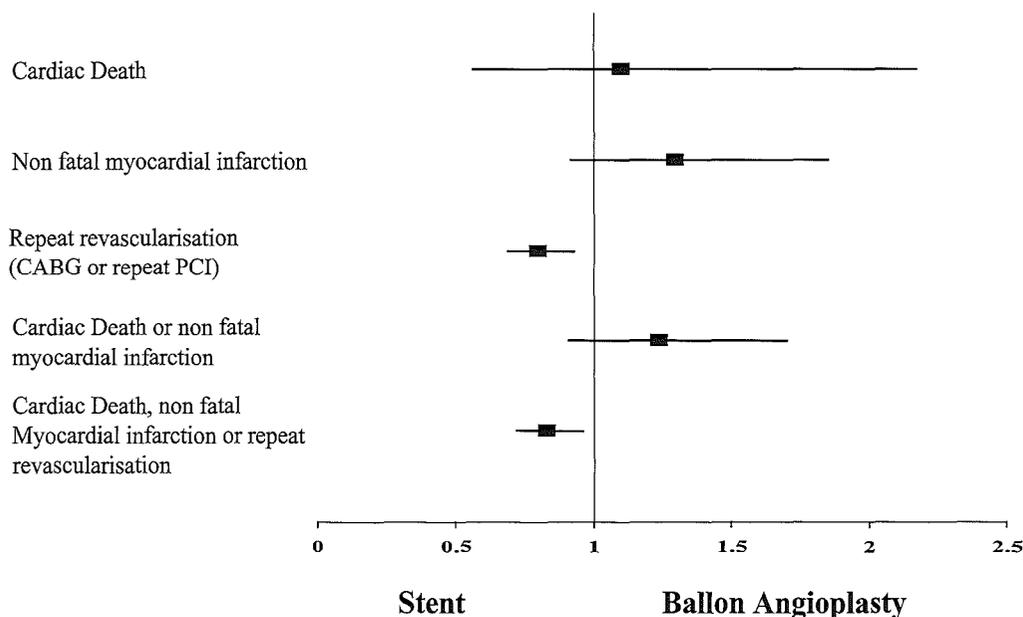
Fig. 3   HR for clinical endpoints. HR are shown with 95% CI. HR with upper confidence limits that are less than 1 represent a benefit with the use of coronary stents. Point estimates and CI have been corrected for pre-procedural stenosis severity (<50, 50–99 and >99%DS pre).

currently available stainless steel stents, the event rate remained as high as 22% at 1 year. The present data argue against the performance of PCI on angiographically non-significant stenoses because high short-term event rates outweigh any hypothetical long-term benefit that might be derived from this type of intervention.

Similar conclusions could be drawn from previously published studies. Based on the Coronary Artery Surgery Study (CASS) registry data,[23] the estimated 1-year probability of an anterior MI in LAD lesions with a <50%DS is 0.6% and 2.2% in lesions between 50 and 70%DS. In the present study, the observed non-fatal MI rate after PCI of non-significant stenoses was four- to fivefold greater than the estimated spontaneous risk in the first and two-fold in the latter group.

The first report of BA in mild lesions was published 19 years ago by Ischinger et al.[4] Patients with chronic stable angina pectoris poorly controlled by previous medical treatment in whom <60%DS were dilated (n=64) were compared with a random sample of patients in whom >60%DS were dilated. After a mean follow-up of 7 months, these investigators cautioned against the application of BA in patients with mildly diseased vessels due to the high incidence of periprocedural MI (6.2% vs 0% in >60%DS, P<0.05) and restenosis (29%).

A decade later, data from Hamon et al.[5] provided additional evidence for this point of view. Angiographic outcome from 26 patients in whom dilated lesions were <50%DS (n=29) was disappointing compared to lesions >50%DS (n=32). When mild stenoses were treated by BA, the DS at follow-up (40%) was the same as the DS prior to BA (42%). No net angiographic benefit was obtained because some non-significant lesions became significant at 6 months.

In the DEFER trial,[26] patients with chest pain and an angiographic stenosis but without objective documentation of ischaemia by non-invasive testing, were randomised to deferral or performance of PCI based on the results of the fractional flow reserve (FFR) of the target lesion prior to intervention. Two-year event rates for death, non-fatal MI, and repeat revascularisation were 1.1, 3.3 and 7.8% in the perform group, which was not different from 2.2, 0 and 5.6% in the defer groups. This proved that there is no clinical benefit of PCI for non-significant stenoses at 2 years. It remains possible that a benefit will develop later and that deferred intervention needs to be performed subsequently, thereby reducing the percentage of patients spared the procedure.

The incidence of hard endpoints (cardiac death and MI) is comparable between our series and

the performance group of the DEFER trial. The increased rate of repeat revascularisation in our series is due to the fact that protocol-driven angiography was applied in all patients at 6 months.[27] This is obvious from Figs. 1 and 2 in which most revascularisation events occurred at 6 months. It has been well documented that when repeat angiography is guided by clinical symptoms rather than per protocol, the rates of repeat revascularisation decrease.[18]

Limitations

It should be stressed that the present results were gathered from multiple, high-performance, international sites and that the data collection was performed under rigorous control (common definitions, use of individual case record forms, independent data monitoring and source verification). The observed event rates may still represent a biased underestimation of the results obtainable in the 'real world'.

In this retrospective analysis, event rates were limited to a 1-year follow-up period. We also lack data from a control group, patients with <50% DS medically treated and followed over time. Furthermore, all these studies were conducted before the introduction of glycoprotein IIb-IIIa inhibitors, which could have decreased event rates in the study groups.

We realize that any potential benefit of plaque sealing will only become evident in the long-term. However, the trade-off between high short-term event rates and long-term benefit appears to be unfavourable. This balance may be reverted with improved procedural and short-term results. The introduction of glycoprotein IIb-IIIa inhibitors has significantly decreased the incidence of non-fatal periprocedural MI.[28] Likewise, restenosis could be virtually eliminated in the near future with the use of drug-eluting stents, as suggested by recently published data.[29] The evaluation of plaque vulnerability by IVUS imaging[30] or temperature measurements[31] may help to identify which patients are at increased risk and may benefit the most from mechanical plaque sealing.[32] When this new therapeutic armamentarium is at hand, the concept of plaque sealing will need to be revisited and may become clinically viable. Until such evidence eventually becomes available, one should refrain from dilating non-significant stenoses.

Conclusion

The concept of plaque sealing is appealing from the theoretical point of view. However, with the currently available technology, its clinical goals (prevention of death and MI in the long-term) cannot be reached because 1-year event rates after PCI of non-significant stenoses still are unacceptably high.

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Chapter 2

Coronary artery bypass surgery versus stenting for the treatment of multivessel disease: A meta-analysis with individual patient data from the ARTS, SoS, ERACI II and MASS II trials

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Coronary artery bypass surgery versus stenting for the treatment of multivessel disease: A meta-analysis with individual patient data from the ARTS, SoS, ERACI II and MASS II trials

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ABSTRACT:

Background: The combined evidence comparing percutaneous coronary intervention (PCI) with coronary artery bypass graft (CABG) surgery suggest a similar prognosis for these two initial revascularisation strategies. Documented differences between the two procedures include a lower rate of angina and repeat revascularisation in patients initially treated with CABG. Our aim was to provide an updated quantitative analysis of the clinical outcomes of patients with multivessel coronary artery disease (CAD) included in contemporary trials of PCI with multiple stenting versus CABG.

Methods: We composed an individual patient database on 3051 patients of four trials (ARTS, SoS, ERACI-2 and MASS-2) that compared PCI with multiple stenting (n=1518) versus CABG (n=1533). The primary clinical endpoint of this study was the combined rate of death, non-fatal MI or stroke at one year. Secondary combined endpoints included death and the rate of repeat revascularisation at one year. All analyses were based on the intention to treat principle.

Results: After one year of follow-up, 132 (8.7%) of those randomised to stenting versus 140 (9.1%) of those randomised to CABG reached the primary clinical endpoint (Adjusted Hazard Ratio=0.95 [95%CI 0.74-1.23], p=0.71). Mortality was similar in both groups (PCI 3% [n=46], CABG 2.8% [n=43]; Adjusted HR=1.02 [95%CI 0.64-1.60], p=0.93). Repeat revascularisation procedures occurred more frequently in the PCI as compared to the CABG group (PCI 18% [n=272], CABG 4.4% [n=68]; Adjusted HR=4.42 [95%CI 3.33-5.87], p<0.0001).

Conclusions: After one year of the initial procedure, PCI with multiple stenting and CABG provided a similar degree of protection against death, non-fatal MI or stroke for patients with multivessel CAD. Repeat revascularisation procedures remain higher in PCI with stenting as compared to CABG.

INTRODUCTION

At the end of the past century, cardiovascular disease (CVD) accounted for nearly half of deaths in the developed world and 25 percent in the developing world. Among CVD deaths, approximately 43% are due to coronary artery disease (CAD), and by 2020 CAD will eventually become the world's number one cause of death and disability[1]. Approximately 60 percent of patients with CAD have multivessel disease that could be treated by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery[2]. Therefore, given the magnitude of the problem, a better understanding of the invasive management and clinical outcome of patients with CAD is of critical public health importance.

The last two decades witnessed major advances in coronary revascularisation techniques for CAD and several randomised clinical trials compared percutaneous transluminal coronary angioplasty (PTCA) against CABG surgery for the treatment of CAD[3-10]. Additionally, three systematic overviews of these trials, one[11] with information gathered in a standard proforma from every principal investigator and two with data extracted from the published literature with intermediate[12] and long term follow-up outcomes[13], have also been reported. However, these studies were designed in the late 80s, conducted and reported in the early 90s and since then, major technological advances have been achieved in both PCI and CABG surgery. The results from trials that antedated the stent era are not reflective of the current practice of coronary revascularisation since coronary stents are implanted in approximately 80% of all percutaneous coronary interventions nowadays[14].

A systematic overview with individual patient data from contemporary clinical trials comparing PCI with multiple stenting against CABG surgery will provide the clinician caring for patients with multivessel CAD with precise treatment effect estimates and more robust and reliable data regarding the advantages and drawbacks of each treatment

strategy. The timing of this analysis is also advantageous, as it provides baseline data for comparisons with the results of drug-eluting stents in similar patients.

METHODS

There are substantial differences between meta-analyses of the literature and meta-analyses of individual patient data[15,16]. The most important reason for these differences is that meta-analyses of individual patient data are based on a time to event analysis, whereas meta-analyses of the literature are based on endpoint analysis at a specific point in time[17]. Results obtained from meta-analyses of individual patient data offer least biased and more reliable treatment effect estimates due to the flexibility and extent of analyses that can be done in subgroups and whenever possible, should be preferred over meta-analyses of the literature.

Selection of patients and data management

We intended to include all major contemporary randomised clinical trials that compared PCI with stenting versus CABG in patients with multiple vessel CAD. To identify eligible trials we did a MEDLINE search using the keywords "coronary stenting", "coronary artery bypass surgery" and "multivessel disease". Furthermore, we examined the reference lists of identified articles, as well as the scientific sessions abstracts in *Circulation, Journal of the American College of Cardiology* and *European Heart Journal*. Five trials were identified: ARTS (Arterial Revascularisation Therapies Study)[18], SoS (Stent or Surgery)[19], ERACI-2 (Argentine Randomised Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Multivessel Disease)[20], MASS-2 (Medicine, Angioplasty or Surgery Study for Multivessel Coronary Artery Disease)[21] and AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial[22]. There were substantial differences in trial design. ARTS and SoS were multinational studies, ERACI-2 was multicentre and MASS-2 was single centre. The

patient population of these trials also differed in terms of comorbidity, coronary anatomy and periprocedural risk. In ARTS, high-risk patients were excluded and approximately two thirds of the patients enrolled had two-vessel disease. SoS had fewer restrictions on case selection, few rules on how the procedure was to be performed, and little specifications regarding adjunctive therapy. In ERACI-2, the study population was composed predominantly by patients with unstable angina and patients with left main stenosis judged to be good candidates for stenting were included (approximately 5%). Finally, MASS-2 trial included a slightly higher number of diabetics and patients with 3-vessel disease than the other 3 trials. We excluded the medical treatment arm from MASS-2 and specifically, did not include the AWESOME trial[22], a major study that compared long-term survival among patients assigned to either CABG or PCI with medically refractory myocardial ischaemia and high risk of adverse outcomes. Approximately 80% of the patients enrolled in this study had multiple vessel disease. Patients with prior heart surgery, ongoing or very recent MI and left ventricular ejection fraction <35% were included in AWESOME and this type of patients is clearly different from the patient population of the four other trials included in this meta-analysis in which all previously mentioned variables were considered as exclusion criteria.

Each principal investigator was contacted and individual patient data was requested regarding baseline demographics, clinical characteristics, use of cardiac medications at screening, status of coronary anatomy at baseline angiography, ejection fraction, allocated treatment strategy (coronary stenting or CABG), date of randomisation, dates of scheduled and actual end of treatment, total number of successfully dilated lesions per patient, total number of stents implanted in each patient, total number of anastomoses and conduits per patient, completeness of revascularisation, use of platelet glycoprotein IIb/IIIa inhibitors as adjuncts to PCI, outcome events of interest limited to one year follow-up included death, myocardial infarction (MI), stroke, repeat revascularisation

(PCI or CABG); and anginal status at one-year. Data was transferred in electronic format to the coordinating centre, Clinical Epidemiology Unit, Thoraxcenter, Rotterdam, the Netherlands. Rigorous checks for data completeness, consistency and agreement with the main published reports were performed and finally an electronic database was composed consisting of individual patient data of all four trials. Table 1 shows the design characteristics of the four trials included in this meta-analysis.

Definitions of variables and clinical end points

We found substantial heterogeneity in clinical endpoint definitions in ARTS, SoS, ERACI-2 and MASS-2. However, when pooling the data and with the knowledge that heterogeneity in endpoint definitions across trials will not lead to biased results[23], we did not attempt to retrospectively reclassify clinical endpoints and we retained the original trial-specific definition for each clinical endpoint.

The primary clinical endpoint of this study was the combined rate of death, non-fatal MI or stroke at one year. Secondary combined endpoints included death and the rate of repeat revascularisation (PCI or CABG). Major adverse cardiac and cerebrovascular (MACCE) events were death, non-fatal myocardial infarction, cerebrovascular events or repeat revascularisation by PCI or CABG.

Statistical analysis

The statistical analysis was performed using the SAS 8.0 software package (SAS Institute, Cary, North Carolina). Quantitative values were given as median (25th, 75th percentiles) or mean ± standard deviation. To test for differences in categorical variables the Fisher's exact test was applied and to test for differences in continuous baseline variables, the Kruskal-Wallis test was used. Event rate curves were constructed by means of Kaplan-Meier methods, and event rate differences between the two groups were compared with the use of the log-rank test[24]. The Cox proportional-hazards regression model was applied to determine the pooled HR for the effect of CABG or coronary

stenting on the primary and secondary clinical endpoints of this meta-analysis. Results are presented as hazard ratios (HR) and 95% confidence intervals (CI). Statistical significance was inferred at p < 0.05. To check for statistical evidence of heterogeneity, we fitted different unadjusted and adjusted (Adjusted for trial outcome differences and important patient baseline characteristics: Age, gender, previous myocardial infarction, diabetes mellitus, peripheral vascular disease, hypertension, enrolment diagnosis, ejection fraction, smoking status, aspirin use, ß-blocker use, calcium channel blocker use, long acting nitrates use and statin use) models introducing interactions terms (trial*allocated treatment [CABG or coronary stenting]) into the Cox model and compared the full model (Interaction term for treatment) with the reduced model (No interaction term for treatment) with the χ^2 test. Furthermore, subgroup analyses of treatment effects (CABG versus coronary stenting) were also evaluated with Cox regression modelling (including a subgroup*allocated treatment [CABG or coronary stenting] interaction arm), with adjustment for trial.

RESULTS

Between June 1995 and June 2000, 3051 patients at 113 participating centres were randomly allocated to undergo multiple stent implantation (1518 patients) or CABG (1533 patients). Patient baseline profile, medications and periprocedural characteristics according to the revascularisation strategy applied are presented in table 2. The average interval between randomisation and treatment was 15 ± 22 days (range, 0 to 243) for patients in the stenting group and 20 ± 29 days (range, 0 to 362) for patients in the CABG group. A total of 98 percent of the patients in the stenting group (1487 patients) and 96 percent of those in the CABG group (1467 patients) received the assigned treatment.

Among the patients in the PCI group, a mean (±SD) 2.4±1.1 lesions with stenosis of more than 50 percent of the luminal diameter were successfully revascularised, and 2.3±1.1

lesions had stents implanted (79%). The median number of stents implanted per patient was 2 (2, 3), and five or more stents were implanted in 3% (66) patients. 6.7% (102) of patients received platelet glycoprotein IIb/IIIa inhibitors at the index procedure. Among the patients in the CABG group, a mean of 2.7±0.8 anastomoses were performed with the use of a mean of 2.5±0.7 conduits. In 90% of the patients in the surgery group, at least one arterial conduit was used. Complete revascularisation was achieved in 82% of the patients in the CABG group as compared to 54% of the patients in the PCI group (p<0.0001).

30-day clinical outcomes

The 30-day composite endpoint of death, myocardial infarction or stroke occurred in 122 patients. 48 (3.1%) of those randomised to stenting versus 74 (4.8%) of those randomised to CABG reached this composite clinical endpoint (Adjusted HR=0.61 [95%CI 0.42-0.89], p=0.01). As shown in table 3, there were no significant differences in mortality (Adjusted HR=0.89 [95%CI 0.42-1.87], p=0.77), stroke (Adjusted HR=0.32 [95%CI 0.10-1.03], p=0.05) or myocardial infarction (Adjusted HR=0.69 [95%CI 0.44-1.08], p=0.11) between the two initial revascularisation strategies at 30 days. However, repeat revascularisation procedures were performed more frequently in those initially treated with PCI with multiple stenting (Adjusted HR=7.79 [95%CI 3.32-18.29], p<0.0001).

One-year clinical outcomes

As shown in Figure 1, the cumulative event rates for the primary clinical endpoint of death, non-fatal MI or stroke after one year of follow-up were 8.7% (132) for those randomised to stenting (n=1518) versus 9.1% (140) for those randomised to CABG (n=1533). The log-rank test did not reveal a statistically significant difference between the event rates over time (p=0.63). Further investigation with Cox proportional hazard regression analysis did not demonstrate any difference between the two revascularisation strategies and the primary endpoint of this study (Unadjusted HR=0.94 [95%CI 0.74-

1.19], p=0.61; Adjusted HR=0.95 [95%CI 0.74-1.23], p=0.71). Mortality (Figure 2) was also similar in both groups (PCI 3% [n=46], CABG 2.8% [n=43]; Adjusted HR=1.01 [95%CI 0.64-1.60], p=0.93). However, repeat revascularisation procedures occurred more frequently in the PCI with multiple stenting as compared to the CABG group (PCI 18% [n=272], CABG 4.4% [n=68]; Adjusted HR=4.42 [95%CI 3.33-5.87], p<0.0001); and finally the combined rate of MACCE events (Figure 3) also occurred more often in the PCI compared with the CABG group (PCI 24% [n=363], CABG 13% [n=201]; Adjusted HR=1.94 [95%CI 1.61-2.34], p<0.0001). As shown in table 4, anginal status at one year assessed with the Canadian Cardiovascular Society (CCS) functional class demonstrated a significant difference in terms of freedom from angina (CCS 0) in the CABG group compared with the PCI group (CABG 82% [n=1230], PCI 77% [n=1145], p=0.001).

Heterogeneity

In unadjusted and adjusted analysis, we found global quantitative evidence of heterogeneity between the four trials for the primary clinical endpoint of this study (χ^2; p < 0.001); we also found heterogeneity when ERACI-2 (χ^2; p < 0.01), MASS-2 (χ^2; p < 0.01) and SoS (χ^2; p < 0.001) were removed from the model but there was no heterogeneity when ERACI-2 and MASS-2 where both excluded (χ^2; Unadjusted p > 0.2, adjusted p > 0.1). However, the heterogeneity was limited to the first 30 days (χ^2; p < 0.001) and no longer present from 30-days to one year (χ^2; p > 0.2). Moreover, the adjusted hazard ratio at one-year of ARTS and SoS was similar to the pooled hazard ratio of ARTS, SoS, ERACI-2 and MASS-2 for the primary (HR=0.97 [95%CI 0.71-1.32], p=0.85 vs. HR=0.95 [95%CI 0.74-1.23], p=0.71) and secondary endpoints of this study like mortality (HR=1.30 [95%CI 0.66-2.57], p=0.44 vs. HR=1.02 [95%CI 0.64-1.60], p=0.94) and repeat revascularisation procedures (HR=5.46 [95%CI 3.82-7.80], p<0.0001 vs. HR=4.42 [95%CI 3.33-5.87], p<0.0001).

Subgroup analyses

The two revascularisation strategies did not differ with regard to rates of death, non-fatal MI or stroke across various prognostically important subpopulations, including those grouped by age, gender, status with regard to diabetes mellitus, smoking and number of diseased vessels (Figure 4). We also carried out a specific sub-analysis on mortality in diabetic patients. Mortality occurred at one-year in 15 (5.6%) of 266 diabetics in the PCI group versus 10 (3.5%) of 283 diabetics in the CABG group (HR=1.61 [95%CI 0.72-3.61], p=0.245).

DISCUSSION

To our knowledge, this is the first by patient systematic overview of PCI with multiple stenting versus CABG in patients with multivessel disease undergoing coronary revascularisation. The 30-day event rates indicate that both PCI with stenting and CABG are procedures still associated with relatively high event rates and that short-term mortality (1.2% and 1% for PCI with stenting and CABG, respectively), even with the advent of newer surgical and interventional techniques, remain similar to those in-hospital mortality rates reported in the BARI[10] trial (1.1% and 1.3% for PCI and CABG, respectively). Our findings are also in accordance with previous reports that compared PCI with CABG[10-12], indicating that the two revascularisation strategies are associated with similar rates of death, non-fatal MI or stroke at a follow-up of one year. However, the widespread use of coronary stenting had significantly decreased the need for emergency CABG to approximately 1% among patients treated with PCI. The observed gap between CABG and PCI in terms of MACCE at one-year, has narrowed from 32% reported in the pre-stent era[9] to 11% in the present report, representing the stent era. This gap will continue to narrow with the newly introduced drug-eluting stents that have been shown to remarkably reduce restenosis and repeat revascularisation rates[25]. Preliminary

data from the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry[26] have shown a 91.2% 6-month MACCE-free survival in 307 consecutive patients with multivessel disease treated with sirolimus-eluting stents compared to 81.4% in 427 patients treated with bare metal stents (p<0.01). In this scenario, the adoption of measures aiming to modify the natural course of the atherosclerotic disease itself (i.e. non restenosis-related complications) becomes the main focus of attention after percutaneous or surgical treatment of multivessel disease. In this regard, statins could decrease perioperative mortality[27] and reduce the risk of coronary atherosclerotic events in patients undergoing PCI[28].

The fact that we found statistical evidence of heterogeneity present after adjustment for important patient characteristics is not surprising. In ARTS and SoS, PCI and CABG had similar event rates for the primary endpoint. In ERACI-2, PCI was better and finally in MASS-2, CABG was better. ERACI-2 was the first randomised trial to report a significant survival advantage with PCI versus CABG in any subset. These results could be attributed to the fact that 28% of ERACI-2 patients had angina at rest with ST-segment changes in the 48 hours prior to revascularisation and 27% of patients randomised to CABG had also peripheral vascular disease, an additional risk factor for adverse outcomes with CABG[29]. Taken together, these demographic data suggest that the surgical mortality in ERAC-2 was not unreasonably high for this type of population. The survival advantage with CABG versus PCI found in MASS-2 for the primary endpoint could be explained by the occurrence of each individual endpoint. At one year, complications in the PCI group included death in 4.5%, myocardial infarction in 8.3% and stroke in 1% as compared to death in 4%, myocardial infarction in 2% and stroke in 3% in the CABG group.

The BARI trial demonstrated a higher mortality rate at five[30] (34.5% versus 19.4%, p=0.003) and seven[31] years (44.3% versus 23.6%, p=0.001) among diabetic patients with

multivessel disease treated with PCI compared with CABG. In this meta-analysis, CABG did not provide any survival advantage over PCI at one-year among the 549 diabetics studied. One-year mortality in the diabetic patients assigned to PCI was higher as compared to those assigned to CABG (5.6% versus 3.5%, p=NS). However, this difference was not statistically significant. Similar mortality rates among diabetics have been reported in the ARTS trial at one[32] (6.3% versus 3.1%, p=NS) and three[33] years (7.1% versus 4.2%, p=NS). We cannot exclude that with a longer follow-up, the survival advantage will achieve statistical significance. The hypothesis that late lesion progression in nontreated coronary segments is an important cause of mortality in diabetic patients with multivessel disease[34] may explain the difference in results observed with shorter-term (<3 years) versus longer-term (>5 years) follow-up. Moreover, the periprocedural use of platelet glycoprotein IIb/IIIa inhibitors in the PCI group may have played a role in decreasing the mortality associated with PCI[35] in our patient population. Ongoing studies (FREEDOM[36], ARTS-2 and BARI-2D[37]) will provide further insights on the optimal management of multivessel disease in diabetic patients.

The main limitation of this meta-analysis is the relatively short follow-up period limited to one year. Long term (5 year) follow-up of this cohort of patients is planned. Another potential limitation is inherent to the fact that a highly selected population was included into these studies, limiting the generalizability of the results to more complex subsets of patients.

CONCLUSIONS

After one year of the initial procedure, PCI with multiple stenting and CABG provided a similar degree of protection against death, non-fatal MI or stroke for patients with multivessel CAD. Repeat revascularisation procedures remain higher in PCI with stenting as compared to CABG.

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FIGURE 1

One-year cumulative risk of death, non-fatal myocardial infarction or cerebrovascular events of patients with multivessel disease randomised to percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery in ARTS, SoS, ERACI-2 and MASS-2 trials

*Adjusted for age, gender, previous myocardial infarction, diabetes mellitus, peripheral vascular disease, hypertension, enrolment diagnosis, ejection fraction, smoking status, aspirin use, ß-blocker use, calcium channel blocker use and long acting nitrates use

FIGURE 2

One-year cumulative risk of death

FIGURE 3

One-year cumulative risk of death, non-fatal myocardial infarction, cerebrovascular events or repeat revascularisation

FIGURE 4

Hazard ratio of one-year death, non-fatal myocardial infarction or cerebrovascular events in subgroups of patients according to important baseline characteristics. The areas of the black squares are proportional to the amount of statistical information

TABLE 1. DESIGN CHARACTERISTICS OF TRIALS ON PCI WITH STENTING VERSUS CABG

	ARTS	SoS	ERACI-2	MASS-2
Enrolment period	March 1997 to June1998	November 1996 to December 1999	October 1996 to October 1998	June 1995 to June 2000
Number of screened patients	NA	NA	2759	18692
Number of eligible patients	NA	NA	1076	2076
Number of randomized patients	1205	988	450	611 (408§)
Major inclusion criteria	Stable, unstable angina or silent ischemia	Stable or unstable angina	Stable, unstable angina or asymptomatic patients with myocardium at risk (> 2 areas with perfusion defects)	Stable angina or asymptomatic patients with objective evidence of myocardial ischemia
	Angiographically proven multivessel disease with one or more significant stenoses in at least 2 major epicardial coronary arteries	Angiographically proven multivessel disease with one or more significant stenoses in at least 2 major epicardial coronary arteries	Angiographically proven multivessel disease with one or more significant stenoses in at least 2 major epicardial coronary arteries	Angiographically proven multivessel disease with one or more significant stenoses in at least 2 major epicardial coronary arteries
	Equivalent degree of revascularization was Mandatory#	Equivalent degree of revascularization was not mandatory#	Complete functional Revascularization#	Equivalent degree of revascularization was mandatory#
Major exclusion criteria	Previous CABG or PCI	Previous CABG or PCI	Previous CABG or PCI (In the last year)	Previous CABG or PCI
	Need for concomitant major cardiovascular surgery¶	Need for concomitant major cardiovascular surgery¶	Concomitant severe valvular heart disease	Concomitant valvular heart disease
	Left main stenosis			Left main stenosis
	Transmural MI within the Previous week	AMI in the 48 h before the revascularization procedure	AMI in the 48 h before the revascularization procedure	AMI or unstable angina requiring emergency revascularization
Primary endpoint	12-month MACCE*-free survival	Rate of repeat Revascularisation	MACE‡ rate within 30 days and need for emergency or elective repeat revascularisation procedures at 30 days	Composite endpoint of cardiac death, nonfatal myocardial infarction, and refractory angina requiring revascularisation
Mean LV ejection Fraction	60%	57%	53%	68%

NA = Not available

*MACCE = Major adverse cardiac or cerebrovascular events, defined as death; stroke, transient ischaemic attacks, and reversible ischaemic neurologic deficits; documented nonfatal myocardial infarction; and repeated revascularisation by percutaneous coronary intervention or surgery

‡MACE = Major adverse cardiac events defined as death, Q-wave MI or stroke

§Patients randomized to percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery

#All these trials included patients in which coronary revascularization was indicated and appropriate by either strategy (PCI with multiple stenting or CABG by consensus agreement between the interventionalist and cardiac surgeon

¶Defined as valve surgery, resection of aortic or left ventricular aneurysm, carotid endarterectomy or abdominal aortic aneurysm surgery

TABLE 2. BASELINE PROFILE, MEDICATIONS AND PERIPROCEDURAL CHARACTERISTICS OF THE PATIENTS INCLUDED IN THE INTENTION TO TREAT ANALYSIS*

	STENTING	BYPASS SURGERY
	(n=1518)	(n=1533)
Male gender (% of patients)	76.5	76.6
Age (yr)	61 (53, 68)	61 (54, 68)
Previous myocardial infarction	43	41
Diabetes Mellitus	17.5	18.4
Hypertension	50.4	50.6
Hypercholesterolaemia	53.8	52.7
Family History of CAD	40	39
Peripheral vascular disease	7	8.2
Current smoker (% of patients)	20	26
Cardiac medications (%)		
Aspirin	93.5	90
B-blockers	73.3	75.3
Calcium channel blockers	37.3	40.2
Nitrates	68	70.3
Statins	49	47
Enrollment diagnosis		
Stable angina (% of patients) ‡	66.5	69
Unstable angina (% of patients) §	28.5	27
Silent ischaemia (% of patients)	5	4
Ejection fraction (%)	59±11	59±11
No of segments with stenosis > 50% of luminal diameter	2.74±0.98	2.79±0.95
Number of diseased vessels (% of patients)		
2	59	54
3	41	46
Vessel territory with stenosis (% of patients)		
Right coronary artery	74	76
Left anterior descending artery	90.5	91.2
Left circumflex artery	62.7	67.4
Left main coronary artery	1	0.6
Length of hospital stay (days)	2 (1, 4)	8 (6, 10)

*Data presented as the median value (25th, 75th percentiles) or as the mean value ± SD.
‡Stable angina was defined according to the system of the Canadian Cardiovascular Society. §Unstable angina was defined according to the Braunwald classification

TABLE 3. 30-DAY CLINICAL END POINTS

	STENTING	BYPASS SURGERY	UNADJUSTED HAZARD RATIO (95% CI)	ADJUSTED HAZARD RATIO (95% CI)
OUTCOME EVENTS AT 30 DAYS	**(N=1518)**	**(N=1533)**		
Death, myocardial infarction or Stroke	48 (3.1%)	74 (4.8%)	0.64 (0.45-0.93)	0.61 (0.42-0.89)
Death	18 (1.2%)	16 (1%)	1.13 (0.57-2.21)	0.89 (0.42-1.87)
Cerebrovascular accident	5 (0.3%)	11 (0.7%)	0.46 (0.16-1.32)	0.32 (0.10-1.03)
Myocardial infarction	34 (2.2%)	51 (3.3%)	0.67 (0.43-1.03)	0.69 (0.44-1.08)
Repeated revascularization	51 (3.3%)	8 (0.5%)	6.56 (3.11-13.83)	7.79 (3.32-18.29)
CABG	26 (1.7%)	5 (0.3%)	5.31 (2.04-13.83)	8.81 (2.64-29.41)
PCI	28 (1.8%)	3 (0.2%)	9.52 (2.89-31.33)	7.91 (2.38-26.28)
Event-free survival	1434 (94.5%)	1452 (94.7%)	-	-
Any event	84 (5.5%)	81 (5.3%)	1.05 (0.77-1.42)	1.01 (0.73-1.39)

*Adjusted for age, gender, previous myocardial infarction, diabetes mellitus, peripheral vascular disease, hypertension, enrolment diagnosis, ejection fraction, smoking status, aspirin use, ß-blocker use, calcium channel blocker use, long acting nitrates use and statin use

TABLE 4. CLINICAL ENDPOINTS AND FUNCTIONAL STATUS AT ONE YEAR

	STENTING	BYPASS SURGERY	UNADJUSTED HAZARD RATIO (95% CI)	ADJUSTED HAZARD RATIO (95% CI)
OUTCOME EVENTS AT ONE-YEAR	**(N=1518)**	**(N=1533)**		
Death, myocardial infarction or Stroke	132 (8.7%)	140 (9.1%)	0.94 (0.74-1.19)	0.95 (0.74-1.23)
Death	46 (3%)	43 (2.8%)	1.07 (0.70-1.62)	1.02 (0.64-1.60)
Cerebrovascular accident	17 (1.1%)	23 (1.5%)	0.75 (0.40-1.40)	0.74 (0.37-1.51)
Myocardial infarction	88 (5.8%)	85 (5.5%)	1.04 (0.77-1.41)	1.07 (0.78-1.47)
Repeated revascularization	272 (18%)	68 (4.4%)	4.36 (3.34-5.69)	4.42 (3.33-5.87)
CABG	94 (6.2%)	21 (1.4%)	4.64 (2.89-7.44)	4.57 (2.77-7.57)
PCI	196 (13%)	48 (3%)	4.36 (3.18-5.98)	4.42 (3.16-6.18)
Event-free survival	1155 (76%)	1332 (87%)	-	-
Any event	363 (24%)	201 (13%)	1.90 (1.60-2.26)	1.94 (1.61-2.34)
Canadian Cardiovascular Society functional class at one year			**p - value**	
0	1145 (77%)	1230 (82%)	0.001	
I	199 (13%)	107 (7%)	<0.0001	
II	114 (8%)	146 (9.6%)	0.048	
III	24 (1.6%)	20 (1.3%)	0.515	
IV	4 (0.4%)	2 (0.1%)	0.404	

*Adjusted for age, gender, previous myocardial infarction, diabetes mellitus, peripheral vascular disease, hypertension, enrolment diagnosis, ejection fraction, smoking status, aspirin use, ß-blocker use, calcium channel blocker use, long acting nitrates use and statin use
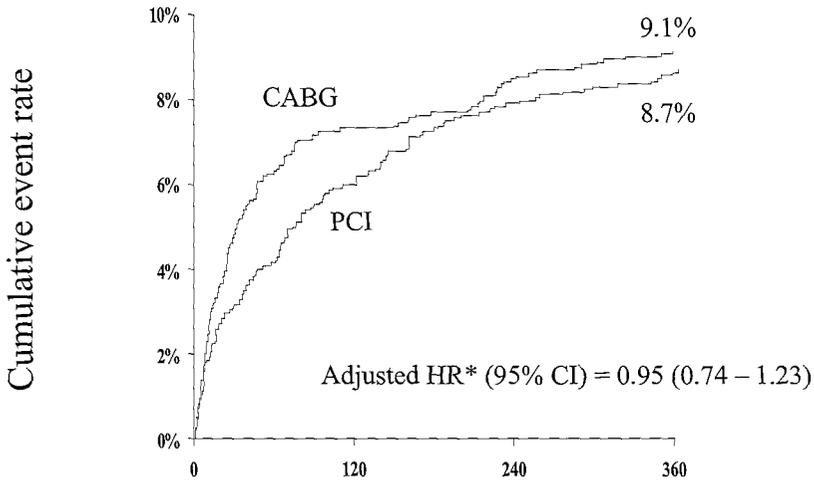
Numbers at risk

PCI	1518	1427	1398	1387
CABG	1533	1422	1404	1393

FIGURE 1
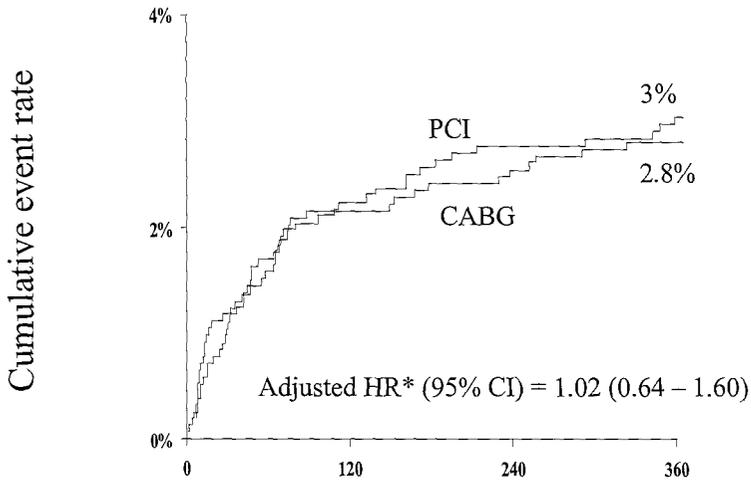
Numbers at risk

PCI	1518	1484	1476	1472
CABG	1533	1501	1495	1490

FIGURE 2
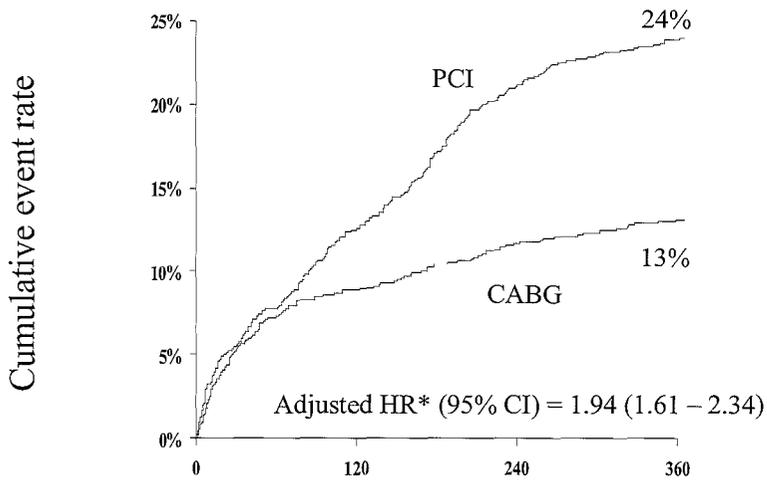
Numbers at risk

PCI	1518	1327	1198	1156
CABG	1533	1397	1354	1332

FIGURE 3
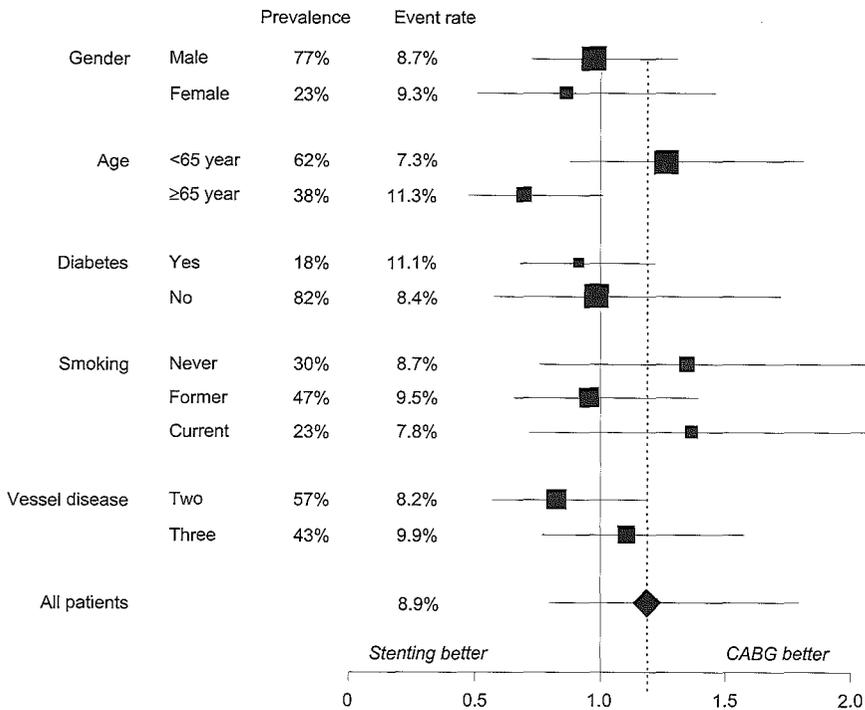
FIGURE 4

Chapter 3

**Multivessel stenting: Observational data and randomized
controlled trials of coronary stenting versus bypass surgery**

Lemos PA, **Mercado N**, Morrison DA, Sigwart U, Serruys PW

V. Lesion-specific stenting: Technique and results

Editors: Jean Marco and Marie-Claude Morice

Textbook of Coronary Stenting

Editors: Gregg W. Stone and Martin B. Leon

In press

Multivessel Stenting: Observational Data and Randomized Controlled Trials of Coronary Stenting versus Bypass Surgery

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Section V. Lesion-specific stenting: Technique and results.

Section editors: Jean Marco, Marie-Claude Morice and William W. O'Neill.

Textbook of Coronary Stenting

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Introduction

The extent of the atherosclerotic disease has been shown to be one of the most important factors affecting the outcomes of patients with coronary heart disease [1-5]. In medically treated patients, the presence of angiographic multifocal disease, together with reduced ventricular function, reliably predicts late-term mortality [4]. Shortly after the introduction of coronary artery bypass graft surgery (CABG), several randomized trials demonstrated the benefit of surgical treatment on the mortality of patients with multivessel coronary heart disease. A metanalysis has been performed with individual patient data from seven randomized studies comparing CABG with medical treatment in stable patients treated between 1972 and 1984 [6]. Although at 10 years of follow-up 41% of the patients initially assigned to medical treatment had undergone CABG, the initial strategy of surgical treatment was associated with a 42% risk reduction of mortality for patients with 3-vessel disease. This body of evidence convincingly establishes the role of invasive treatment as an important therapeutic measure for patients with multivessel disease.

Percutaneous coronary intervention (PCI) was first introduced in the clinical scenario in the late 1970's. As initially applied, angioplasty was addressed to treat highly selected coronary lesions in patients with single-vessel disease. However since then, interventional methods and technology have evolved with improved success in more complex clinical and anatomic settings, including multivessel coronary disease.

Annually, it is estimated that over 1,0000,000 percutaneous coronary interventions and 500,000 surgical revascularizations are performed worldwide, and patients with multivessel disease account for the majority of cases treated. Commonly, both modalities, either PCI or CABG, are technically feasible for an individual patient with multivessel disease and selection of the most appropriate revascularization method may constitute a challenging clinical problem. Several randomized studies have addressed this question in the late 80's and early 90's, enrolling over 4000 patients in total [7-15]. The results are consistent among these trials (Table 1). Overall, post-procedure myocardial

infarction was higher for CABG-treated patients, while no difference was observed between both treatments in late occurrence of myocardial infarction. Short- and long-term survival was similar between both strategies in all trials, except in the BARI trial, in which surgically treated patients showed a better survival at 7.8 years (80.9% for PCI vs. 84.4% for CABG; p=0.04). However, this difference was largely explained by a greater mortality among diabetics treated with PCI (survival 55.7% in PCI vs. 76.4% in CABG; p = 0.001). Among non-diabetics, survival was identical between both treatments (survival 86.8% in PCI vs. 86.4% in CABG; p = 0.72) [15]. Nevertheless, the most striking difference between percutaneous and surgical treatment for multivessel disease in these first studies was the evident higher need for repeat revascularization among those treated with angioplasty [7-10,12,13,15] (Table 1). In-hospital (commonly due to early vessel occlusion) and late repeat revascularization (directly associated with restenosis) were both significantly higher after treatment with percutaneous techniques. Emergent early re-intervention occurred in 8.4% of patients treated with angioplasty in the BARI trial [15], and as much as 65.3% of PCI-treated patients have had a new revascularization procedure after 8 years in the EAST trial [10].

Both surgical and percutaneous treatments, and especially PCI techniques, have been substantially improved in the last years. It is of note that several of these implementations were not available at the time of the early comparative studies. In particular, coronary stent implantation was performed in only a minority of patients enrolled in these "pre-stent era" trials [7,8,10,12,13,15] (Table 1). As compared to balloon angioplasty, the main technique applied in the first randomized trials of PCI vs. CABG, stents have been proven to reduce the incidence of acute complications and the need of further revascularization in a broad range of clinical and anatomical settings. Due to the significant change in safety and clinical efficacy consequent of coronary stent utilization, the findings of the first randomized CABG vs. balloon angioplasty trials for multivessel disease cannot be extrapolated to the current clinical scenario, in which a widespread use of stenting accounts for more than 80%

of all PCI. In this regard, the impact of multivessel coronary stenting has been evaluated in the several observational and randomized trials in the last years.

Multivessel Stenting – Observational Studies

Several non-randomized studies evaluating the impact of coronary stenting on patients with multivessel disease have been recently published [16-23] (Tables 2 and 3). In most studies, the included patient population had preserved left ventricular function, approximately 20% were diabetics, and 3-vessel disease was present in only a minority of patients. Overall, procedural success rates and in-hospital complications after multivessel stenting were notably favorable. At long-term follow-up (1 to 3 years), multivessel stenting was associated with a low mortality rate (0% to 5.1%) and 10% to 30% of cases required additional revascularization procedures during the observation period. Consistently among these studies, at least 70% of patients remained free of any events.

In one study, patients treated with multivessel stenting were reported to have similar early and late outcomes as compared to patients with single vessel-disease treated with stenting [17]. At 1 year, there was no difference in death (0.7% vs. 1.4% respectively; p=0.6), Q-wave myocardial infarction (0% vs. 1.5% respectively; p=0.6), or target lesion revacularization (15% vs. 16% respectively; p=0.5), with a similar proportion of patients remaining free of events at the end of follow-up (78% for both groups).

In a large observational study comparing stenting with surgery, similar mortality rates at 2.5 years were observed between both strategies in patients with double-vessel disease (93% vs 92% respectively for those with proximal left anterior descending artery disease; p=NS) or triple-vessel disease (80% vs 85% respectively for those with proximal left anterior descending artery disease; p=NS)[16].

For single-lesion treatment, coronary stenting has virtually eliminated the occurrence of acute vessel occlusion shortly after the procedure, a complication seen in up to 16% of complex lesions after balloon angioplasty [24]. Accordingly, in-hospital urgent re-revascularization has been reported in a negligible number of patients, commonly less than 1% of cases. In addition to the benefit in the

early outcomes, stent implantation has been demonstrated to reduce restenosis and the need of repeat revascularization in single-lesion dilatation [25-27]. The process of restenosis formation is a local phenomenon triggered by the vascular trauma imposed by coronary dilatation and stent deployment. However, several systemic, or patient-related factors may significantly modulate the ultimate vascular response after angioplasty. Indeed, in patients treated with multistent implantation, a clear intra-patient predisposition has been demonstrated to affect the occurrence of restenosis, since the occurrence of restenosis in one lesion appeared to significantly increase the likelihood of restenosis in another lesion in the same patient [28]. The restenosis rate was observed to increase with the number of lesions treated, from 24.4% for single-lesion stenting (per patient analysis) to 63.1% for those with 3 or more lesions treated (p<0.001) [28]. However, even considering an eventual increased risk of restenosis, multivessel stenting represents an evident improvement in the long-term efficacy of multi-lesion percutaneous interventions, as compared to the historical series with non-stent techniques (i.e. balloon dilatation).

Srinivas et al. have compared the outcomes of multivessel patients treated in the "pre-stent era" with those treated more recently [19] (Tables 2 and 3). From 915 patients randomized to percutaneous treatment in BARI trial, a total of 904 had attempted angioplasty and were analyzed as a "pre-stent era" group. These patients were enrolled from 1988 and 1991 and actual stent utilization was performed in only 1% of cases. For comparison, a group of 857 patients treated from 1997 to 1999 and included in the National Heart, Lung and Blood Institute Dynamic Registry was selected based on the same BARI eligibility criteria (i.e. angiographically documented multivessel disease amenable to percutaneous treatment in the absence of left main disease, recent acute myocardial infarction, or previous revascularization). Stents were utilized in 76% of cases and glycoprotein IIbIIIa inhibitors were used in 24% (not available at the time of BARI trial). Several baseline and procedural differences were observed between both populations, however, after multivariable adjustment, treatment in the "stent era" was associated with better short- and long-term outcomes.

More recently treated patients had an 82% reduction in the risk of in-hospital surgery ($p<0.001$) and a 55% reduction in the risk of either in-hospital death, myocardial infarction, or surgery ($p<0.001$). Moreover, at 1-year patients treated in the "stent era" had significantly less re-interventions (risk reduction 59%; $p<0.001$) and a strong trend towards less death or myocardial infarction (risk reduction 26%; $p<0.07$).

Multivessel Stenting – Randomized Trials

To date, 5 randomized trials have been completed comparing percutaneous coronary intervention with stent implantation and surgical revascularization for patients with multivessel disease [Rodriguez, 2001 #589;Serruys, 2001 #27;, 2002 #649;Hueb, 2001 #671]. The individual results of these studies and the findings of a metanalysis with the pooled patient population are presented below.

ARTS – The Arterial Revascularization Therapies Study [29]

The ARTS randomized 1205 elective patients with multivessel disease (without left main disease) to treatment with PCI or CABG. The study design and main results are summarized in Tables 4 to 7. High-risk patients were excluded and approximately two thirds of the patients enrolled in the trial had two-vessel disease. In both groups, a mean of 2.8 lesions per patient were identified in the pre-procedure angiogram. In the stent group, 2.6 lesions were treated per patient (89% with stents). In the surgery group, 2.6 distal anastomoses were performed per patient. However, complete anatomical revascularization was achieved in only 71% vs. 84% after PCI or CABG respectively (p<0.01) [30].

In the stent group, 40% of all events occurring at 30 days were due to stent thrombosis (2.8% of patients and 1.1% of stented lesions). At 1 year, patients treated with PCI had significantly more adverse cardiac and cerebrovascular events than patients treated with CABG (26.2% vs. 12.2% respectively; p<0.01). However, this difference in outcomes was exclusively due to a higher rate of repeat revascularization in the stent group. The incidence of death, MI, or cerebrovascular accident was similar between patients treated percutaneously or surgically (9.3% vs. 8.8% respectively; p=NS). Overall, 21.0 % of the patients in the PCI group received an additional revascularization, as compared with 3.8 % of those in the CABG group. An elevated periprocedural CKMB level was the

only multivariable predictor of adverse events in the surgical group (creatine kinase values > 5 times the normal limit were found in 12.6 % of the surgical patients and in 6.2 % percent of stenting patients [p<0.001]). The presence of diabetes was the only predictor of events among patients treated with PCI.

SoS trial – The Stent Or Surgery trial [, 2002 #649]

The SoS trial randomized 988 patients with symptomatic multivessel disease to treatment with PCI or CABG. The study design and main results are summarized in Tables 4 to 7. There were few restrictions on case selection, few rules on how the procedure was to be performed, and little specifications regarding adjunctive therapy. Patients were considered for enrollment if the revascularization was judged to be clinically indicated and appropriate by either invasive strategy. At least one lesion had to be suitable for stent implantation. Included patients had predominantly 2-vessel disease and preserved left ventricular function. Diabetes was present in approximately 15%.

In the patients actually treated with PCI as randomized, 94% of all attempted lesions were successfully dilated (2.7 lesions and 2.0 mean epicardial vessels successfully treated per patient). At least 1 stent was implanted in 78% of lesions (median 2.0 stents per patient). Glycoprotein IIb/IIIa inhibitors were utilized in 8% of patients. In patients treated with CABG as allocated, the mean number of grafts was 2.8 per patient. Internal mammary grafts were utilized in 93%

The incidence of death or myocardial infarction was similar between both groups. However, mortality at 1 year was lower in CABG than PCI patients (0.8% vs. 2.5%; p = 0.05), and the difference at two years was even greater (2% vs. 5%; p = 0.01). This was in large part due to a difference in non-cardiac mortality; there were 8 cancer deaths among the PCI patients versus one among the CABG patients, a difference most likely explained by chance. Clearly, the remarkably low mortality in the CABG group further contributed to the significant difference in mortality between the two groups. Among patients allocated to PCI, 21% had one or more repeat

interventions (PCI or CABG) after 2 years of follow-up, compared with 6% in the CABG group (p<0.01). Most of the additional revascularization procedures occurred in the first year.

MASS 2 trial – The Medicine, Angioplasty or Surgery Study for Multivessel Coronary Artery Disease-2 [31]

In the MASS 2 trial, 611 patients were randomized to either medical therapy (n = 203), PCI (n = 205), or CABG (n = 203). The primary endpoint was the combined frequency of cardiac death, myocardial infarction or unstable angina at one year. The trial included a slightly higher number of diabetics and patients with 3-vessel disease than the other 3 studies. At 1 year, the mortality rate was similar in all three arms: 4.5% with CABG, 4.0% with PCI and 2.0% with medical therapy. However, the frequency of myocardial infarction was 2% among CABG patients, 2% among medically treated patients, and 8% among PCI patients (p = 0.015). The frequency of stroke was 3%, 1% and 2% in the CABG, PCI and medical arms, respectively. Patients treated with PCI presented a significantly higher incidence of repeat revascularization or crossover at 1 year than those included in the other 2 arms (0% for the CABG group vs. 8% for the medical group vs. 14% for PCI; p<0.01 for all).

ERACI 2 trial – The Argentine Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease-2 [32]

The ERACI 2 trial randomized 450 patients with symptomatic multivessel disease to treatment with stenting or CABG. The study design and main results are summarized in Tables 4 to 7. Patients with left main stenosis judged to be good candidates for stenting were included (approximately 5%). The study population was composed predominantly of patients with unstable angina

(Braunwald class IIb, IIIb, and C in 91.1%). Diabetes mellitus was present in 17% of patients and glycoprotein IIbIIIa inhibitors were administered to 28% of the PCI group. The Gianturco-Roubin II stent was the primary stent used (mean stent utilized per patient = 1.4) and approximately 90% of patients received a LIMA graft. At 30 days, the combined frequency of death, Q-wave myocardial infarction, need for repeat revascularization procedures, and stroke (primary endpoint of the study) was significantly lower in patients treated with PCI than in those treated with CABG (3.6% vs. 12.3% respectively; $p < 0.01$). Similarly, mortality alone was lower for PCI than for CABG at 30 days (0.9% vs. 5.7% respectively; $p = 0.01$). Although patients with unstable angina were observed to have a higher surgical risk, CABG was identified as the only multivariable predictor of 30-day adverse events (odds ratio 3.91; 95% confidence interval: 1.71– 8.89; $p<0.01$). Even though no further difference was observed in the incidence of death between both groups after 30 days, at 18 months the total mortality rate was still lower for the percutaneous group (3.1% vs. 7.5% respectively; $p = 0.02$). In contrast, the need of repeat revascularization during the follow-up was significantly worse in the PCI group (16.8% vs. 4.8% respectively; $p<0.01$). Moreover, after 18 months, patients allocated to CABG were more frequently free of angina than those treated with PCI (92% vs. 84.5%, respectively, $p = 0.01$).

A separate analysis of the ERACI 2 was performed only with patients presenting significant stenosis in the proximal left anterior descending (LAD) artery (113 patients treated with PCI and 117 with CABG) [33]. Although no major differences were observed between both treatment groups, when compared to the overall population of ERACI 2, patients included in this substudy had significantly less 3-vessel disease (36% vs. 62%; $p=0.008$) and peripheral vascular disease (15% vs. 27%; $p=0.04$). Patients with proximal LAD lesions had a strong trend towards more in-hospital death or myocardial infarction when treated surgically (7.6% vs. 1.8%; $p=0.089$). However, at 2 years the incidence of death or myocardial infarction was similar between the CABG and stenting groups (89% vs. 92% respectively; $p=0.9$).

Stenting versus coronary surgery for multivessel disease – a pooled analysis of ERACI-2, SoS, ARTS, and MASS-2 randomized trials

A metanalysis has been performed with the individual data of all patients treated with PCI or CABG enrolled in the four randomized trials described above (ERACI 2, ARTS, SoS, and MASS 2 trials). The main results of this metanalysis are presented in Table 8 and Figure 1. In total, more than 3000 patients have been randomized, with 1518 being treated with stenting and 1533 with surgery. Baseline characteristics were well balanced between both groups. Overall, relatively non-complex patients have been included, generally with preserved left ventricular function (mean ejection fraction 59%) and a diabetes rate of 18%. As a rule, patients were treated electively with only approximately 30% with unstable angina. Stenting was associated with a significantly shorter in-hospital stay as compared to CABG (5±29 vs. 10±26 days; p<0.0001). Both treatments were associated with virtually similar in-hospital outcomes (Table 8). Notably, coronary stent implantation improved considerably the safety of percutaneous treatment for patients with multivessel disease. The incidence of periprocedural repeat revascularization was approximately 3% in the pooled analysis of patients treated with multivessel stenting in the 4 randomized trials, while rates were as high as 13% in the BARI trial [15] had been previously observed in the first series with balloon angioplasty. In the ARTS trial, 40% of all events occurring in the first month after stenting were due to stent thrombosis, a complication that could be potentially reduced with utilization of heparin-coated stents or a more liberal use of glycoprotein IIbIIIa inhibitors [29].

At 1 year, multivessel stenting and CABG were associated with similar rates of death as well as of death, myocardial infarction or cerebrovascular accident (Table 8 and Figure 1). As depicted in Figure 1, the corresponding event curves were observed to almost overlap between both treatment modalities during the entire observation period. Interestingly, as historically compared to the early balloon versus CABG trials, the 1-year death rate remained grossly constant across both the "pre-stent" and the "stent" eras for both treatments (range from 3-4%) (Figure 2A) [34].

However, the incidence of major events after 1 year was significantly higher for patients treated with multivessel stenting (23.9% vs. 13.1%; p<0.01), which was almost entirely explained by the increased rate of re-intervention in this group (18% vs. 4%; p<0.01). This effect was mainly due to late restenosis. As observed in Figure 1, the curves of survival free of MACE begin to separate at about 2-3 months, coincident with the well-known time frame of restenosis occurrence [35].

Although the need of repeat revascularization was still higher after stenting than after CABG, the utilization of coronary stents had clearly improved the late outcomes of patients with multivessel disease treated percutaneously. In a metanalysis performed with the data from randomized trials on balloon versus CABG, the incidence of repeat revascularization at 1 year was 34% and 3% respectively [34]. This figures contrast with the numbers observed in the pooled analysis of the ERACI 2, ARTS, SoS, and MASS 2 trials, where the need for additional revascularization was 18% after multivessel stenting (versus 4% after CABG). The absolute difference of repeat revascularization between surgery and PCI has decreased from 31% to 14% after stents were utilized, while no major modification was seen in the incidence of re-intervention after CABG (Figure 2).

The AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial [36]

The impact of percutaneous and surgical revascularization for patients at a higher risk for short- or long-term complications has been largely unexplored in randomized trials. The AWESOME trial was designed with the main purpose of evaluating the advantages and disadvantages associated with PCI or CABG for cases with a higher risk of procedural and post-procedural mortality (Table 9) [36]. Patients were selected over a period of 5 years (from 1995 and 2000) and randomly allocated to either invasive treatment. Patients with medically refractory myocardial ischemia and coronary anatomy judged to be amenable to both invasive modalities were considered for randomization if

presenting one or more of the 5 high-risk factors for CABG (age>70 years; LVEF<0.35%; myocardial infarction <7 days; prior CABG; IABP required to stabilize).

In total, 22662 patients were screened and 2431 (11%) met the first 3 clinical criteria for high-risk refractory angina. From these, 781 were deemed to be acceptable for both treatment modalities and 454 (58%) were actually randomized to be treated with either CABG or PCI. The included study population had a relatively high age, a high prevalence of diabetes, recent MI, and prior CABG. Multivessel disease was present in more than 80% of patients. Overall, 57% of patients received a LIMA graft. However, the utilization of arterial grafts varied along the study (LIMA grafts were used in 57% of cases in 1995 and 78% in 1999/2000). Similarly, coronary stent implantation varied along the study, from 26% in 1995 to 88% in 1999/2000 (overall 54% of cases received at least one stent).

Both surgical and percutaneous treatments were associated with similar mortality rates during the index hospitalization, at 30 days, 6 months, and 1 year (Table 9). Indeed, the incidence of death or an episode of unstable angina was similar between both treatment groups at 3 years (CABG: 35% vs. PCI: 41%; p=NS). Patients treated with PCI had a higher incidence of repeat intervention during the follow-up (3-year death, UA or re-intervention for CABG or PCI: 39% vs. 52% respectively; p<0.001 by log-rank test).

The AWESOME investigators conducted a parallel registry to evaluate the outcomes of patients not included in the main randomized study [37]. During the screening phase, a total of 1650 patients were identified with high-risk refractory angina (the first 3 criteria above) but were not randomized based on the coronary angiogram findings according to the physicians' consensus. These patients were treated with CABG (n=692), PCI (n=651) or medical therapy only (n=307) and constituted the "physician-directed registry". Furthermore, among the 781 patients evaluated as candidates for both treatments, 327 patients declined randomization and were further followed-up as a "patient-choice registry". The mortality rates at 3 years between CABG and PCI in the randomized population and

in the "physician-directed" and the "patient-choice" registries were: 21% vs. 20%, 24% vs. 24%, and 20% vs. 11% respectively (p=NS for all). Therefore, percutaneous treatment of high-risk patients with multivessel disease (~80%) utilizing coronary stents in most of the cases was observed to be an alternative to surgical treatment.

Patients with previous cardiac surgery were analyzed separately in an AWESOME substudy [38]. In the randomized cohort, the physician-directed registry, and the patient-choice registry there were 142, 719, and 327 patients with previous CABG respectively. The vast majority of patients in all groups presented with 3-vessel disease. At 3-year follow-up, the re-CABG and PCI survival rates were 73% and 76% for the randomized patients (p=NS), 71% and 77% for the physician-directed registry (p= NS) and 65% and 86% in the patient-choice respectively (p<0.01). The authors concluded that, instead of re-CABG, PCI could constitute a preferable choice for many patients with previous CABG.

"Low-Risk" and "High-Risk" Patients with Multivessel Disease

Patients with multivessel disease comprise a heterogeneous population with a wide range of risk profiles. Several factors have been identified as important predictors of perioperative mortality in patients treated with CABG, such as prior heart surgery, older age, poor left ventricular function, hemodynamic compromise, recent myocardial infarction, peripheral vascular disease, renal dysfunction, or chronic obstructive pulmonary disease [36,39]. Notably, patients with these characteristics have been systematically excluded from the randomized MASS-2, ARTS, and SoS trials [Hueb, 2001 #671;, 2002 #649;Serruys, 2001 #27]. The comparison between PCI with stent and CABG in *low-risk* patients with multivessel disease derived from these trials can be summarized as follows:

- Short and long-term mortality and myocardial infarction rates are comparable,

- The need for repeat revascularization favors CABG but stents have narrowed the gap, and drug-eluting stents may narrow it further,

- Hospital length of stay and length of recovery both favor PCI,

- The relief of symptoms are comparable, but some studies favor CABG.

According to these concepts, the choice between CABG and PCI for an individual patient with multivessel disease but at a lower risk of complications usually involves a 'balancing act' of multiple benefits and risks. In this context, although stents have reduced early and late repeat procedures, the need for repeat procedures is the single most important factor tipping the balance towards CABG. Clearly, measures to reduce late restenosis will shift the balance in favor of PCI.

Patients at high risk for operative mortality have been mainly characterized by clinical factors (e.g. urgency of surgery, age, and prior CABG), while variables related to coronary anatomy had less predictive power [39-41]. The AWESOME trial has specifically addressed the impact of percutaneous or surgical treatments in patients with *high-risk clinical* characteristics [36]. Furthermore, *high-risk* patients composed most of the study population included in the ERACI-2 trial, which randomized to PCI or CABG patients with medically refractory angina, including post-myocardial infarction unstable angina and patients with peripheral vascular disease [32]. In AWESOME, short- and long-term mortality rates were similar between both treatments [36]. In ERACI-2, patients treated with PCI had a significantly lower incidence of death than those treated with surgery [32]. These findings are in line with the documented benefit of primary angioplasty in patients with acute myocardial infarction, a clinically *high-risk* group [42]. Importantly, although randomized studies comparing CABG with PCI have focused on the occurrence of major cardiac and cerebrovascular events, greater concerns have been raised about post-CABG morbidity related to diffuse encephalopathy, prolonged post-operative obtundation, mediastinitis, acute and even permanent respiratory disability and acute and long-term renal failure [40]. As a rule, these complications are significantly increased in patients with a higher baseline risk profile [40]. Together these findings suggest that "clinical high-

risk" usually favors PCI, with the need to consider both the technical feasibility and risk provided by the coronary anatomy, but much less influenced by the threat of restenosis.

Special Considerations

Diabetic Patients

Diabetes has been recognized as one of the most important risk factors for adverse outcomes after percutaneous interventions [43-46]. In the randomized EAST and RITA-1 trials, although not reaching statistical significance, diabetics tended to present a higher late mortality rate [10,12]. In the BARI trial, which had the largest multivessel diabetic population, balloon angioplasty was observed to be associated with an increased risk of death at 5 years (20.6% vs. 5.8%; p=0.0003), a difference that was more evident among those using insulin and that was largely restricted to surgical patients receiving internal mammary artery grafts [47]. The worse outcomes after angioplasty had been justified by the increased tendency to atheroscletotic disease progression in patients with diabetes, who would then be "more protected" after the more generalized surgical treatment than after the more localized percutaneous treatment[48]. Interestingly, the analysis of the BARI-registry patients showed different results [49]. Clinically eligible patients in the BARI trial who did not consent to randomization were followed-up as a parallel registry, with patients being treated in a non-randomized fashion with PCI, CABG, or non-invasively. Differently from the randomized patients, the presence of diabetes was not observed to significantly increase the risk of 5-year mortality among those treated with angioplasty in the registry. Patients treated with CABG or PCI in the registry differed in their baseline profile, which ultimately reflect the individual characteristics influencing the physicians' and/or patients' final therapeutic choice. Diabetics treated with PCI in the BARI registry had less severe coronary disease than those treated with surgery, which most likely had favorably influenced the outcomes of patients treated percutaneously.

In the ARTS trial, a subanalysis with diabetics treated with multivessel stenting showed no difference in the incidence of death or MI at 1 year, as compared to CABG [50]. Patients with diabetes showed a trend towards more cerebrovascular events when treated with surgery than with PCI (6.3% vs. 1.8% respectively; p=0.096). In the ARTS trial, patients with diabetes treated with multivessel stenting showed a significantly higher incidence of re-intervention at 1 year than after CABG (22.3% vs. 3.1% respectively; p<0.01). Furthermore, the rate of repeat revascularization after stenting was higher in diabetics than in non-diabetics (22.3% vs. 15.6%; p=0.04), reflecting the increase risk for restenosis in patients with diabetes [45,46]. Although both treatments did not differ in terms of mortality at 1 year in the ARTS, a more prolonged observation time is required to further evaluate the impact of multiple stent implantation on diabetics. In the EAST and BARI trials, a more evident separation in the survival curves of diabetics treated with either CABG or PCI occurred mainly after the first year of follow-up [10,49]. However, in the AWESOME study, no differences in survival were observed among "high-risk" diabetics treated with CABG or PCI over a 3-year follow-up period. Patients with diabetes included in the randomized trial or in the parallel registry (physician-directed treatment or patient-choice treatment) had similar 3-year survival rates for CABG and PCI (72% vs. 81%; 73% vs. 71%; 85% vs. 89%, respectively; p=NS for all) [51].

It is worth noting that the worse outcomes of diabetics treated with PCI in the randomized BARI trial [47] is supported by a similar tendency observed in the EAST and RITA-1 trials [10,12], but is not supported by their own (BARI) registry [49], ARTS [50], AWESOME (randomized or registry) [36,37,51], or ERACI 2 trials [32]. Furthermore, the increased occurrence of adverse events after PCI in patients with diabetes was reported as post hoc subset analyses (which should be hypothesis generating, not policy formulating) of studies conducted in the pre-stent and pre-glycoprotein IIb/IIIa era. Currently, several reports have documented that glycoprotein IIb/IIIa inhibitors may be particularly helpful in diabetics [52,53].

Completeness of Revascularization

The completeness of revascularization has been defined as anatomical, where all significant lesions are successfully treated, or functional, where the treatment is ultimately directed to stenotic vessels supplying a viable myocardial territory. Overall, incomplete revascularization is believed to negatively influence the outcomes of patients treated with surgical revascularization [54,55], however its impact on PCI-treated patients is far less clear [56-58]. The randomized studies on stenting versus CABG for multivessel disease have differed in their requirements for complete revascularization. As summarized in Table 4, in the ARTS and MASS 2 trials, PCI and CABG should provide an "equivalent" degree of revascularization, while a more liberal strategy was applied in the SoS trial. Conversely, complete functional revascularization was considered for all cases in the ERACI 2 trial.

In the ERACI 2 trial, anatomical complete revascularization was more frequently achieved in the surgical group (85% vs. 50% in the PCI group; p=0.002). However, both groups had a similar degree of functional complete revascularization, with an equivalent frequency of normal or nonreversible perfusion areas at 30 days (85% in CABG vs. 84% in PCI; p=NS) [32]. In the ARTS trial, complete anatomical revascularization was achieved in 84% of surgical patients and in 71% of stented patients (p<0.01) [30]. Among patients treated with PCI, incomplete revascularization was associated with a significantly worse 1-year event rate than those with complete revascularization (incidence of death, myocardial infarction, cerebrovascular accident and re-intervention: 30.6% vs. 23.4 respectively; p<0.05), a difference that was mainly explained by a higher incidence of additional bypass procedures in the first group (10.0% vs. 2.0%; p<0.05). Conversely, the degree of completeness showed virtually no impact on the outcomes of CABG patients after 1 year (event-free survival 87.8% vs. 89.9% for complete vs. incomplete revascularization; p=NS).

Procedural Aspects

Although a high likelihood of acute success is expected with the currently available techniques [17,29,32,37,59-61], multivessel stenting tends to be a more complex procedure than single-vessel dilatation. Increased contrast utilization and prolonged intra-arterial manipulation may lead to peri-procedural complications in these patients. The volume of contrast utilized during the angioplasty significantly increases the risk of post-procedure renal failure, which is a strong predictor of both early and late death after percutaneous interventions [62]. The utilization of iso-osmolar, nonionic contrast agents and of acetylcysteine have been shown to significantly reduce the incidence post-procedure renal impairment in patients with mild to moderate decrease in baseline kidney function [63,64]. Such protective measures may be valuable for selected patients with planned multivessel dilatation. Furthermore, direct stenting without balloon predilatation has been demonstrated to decrease iodine contrast utilization as well as fluoroscopy time, material utilization, and procedural costs [65-68]. Although not yet tested in procedures with multiple stent implantation, it seems reasonable to priorize a strategy of direct stent deployment for suitable lesions in patients with multivessel disease.

Percutaneous dilatation of multiple lesions may be performed in one or more sessions. A strategy of elective staging with an interval of 4 to 8 weeks between procedures has been shown to be safe at 30 days and associated with a trend towards less complications at 1 year (event rate 26% vs. 36% for staged vs. non-staged; p=0.08) [69]. Although not evaluated in a randomized trial, the choice for elective staging seems to be attractive for selected patients treated with multivessel stenting.

Costs

The costs associated with health care have been increasingly reported as a matter of concern [70,71]. In this regard, although coronary stenting may be less effective than surgery in reducing the need for re-intervention, its utilization had been demonstrated to significantly reduce by US$ 3,000.00 the

total direct medical costs at 1 year in the ARTS trial (Table 10) [29]. Moreover, stenting was associated with reduced costs, as compared to CABG, both in diabetics and in non-diabetics (Table 10) [50]. Surgery was initially more expensive than stenting in diabetics and non-diabetics. This difference in costs was partially lost during the follow-up in the non-diabetics, due to the need of additional re-interventions in the PCI group. However, in the diabetic group the costs during follow-up were similar between the CABG and the stent group. Although diabetics treated with PCI had a higher repeat revascularization rate than the surgical group, these extra costs were almost completely offset by an increased re-hospitalization rate in surgically treated patients. In total, 42% of diabetics treated with CABG were readmitted during the first year primarily due to comorbid factors (e.g. sternal infection, cerebrovascular events, and renal insufficiency). In ERACI 2, no differences in costs were observed between both strategies at 1 year. On average, after a mean follow-up of 18 months, the overall cost per patient was US$ 12,320 for stenting and US$ 11,160 for CABG (p=NS).

Future Directions

Recently, coronary stents coated with paclitaxel or sirolimus have been demonstrated in large randomized trials to almost abolish the need for further revascularization [72-76]. Persistent inhibition of neo-intimal proliferation has been demonstrated by intravascular ultrasound after 2 years of sirolimus-eluting stent implantation [77]. However, these studies included relatively simple cases treated with single-lesion dilatation and therefore the impact of the new drug-eluting stents on the treatment of patients with multivessel disease is currently unknown. The ongoing Arterial Revascularization Therapies Study 2 (ARTS-2) will evaluate the outcomes of patients with 2- or 3-vessel disease treated with sirolimus-eluting stent implantation [78]. This study was designed to compare patients treated with the sirolimus stent with a historical group composed by the CABG arm of the ARTS-1 trial. Final results (1-year follow-up) are expected by 2004. Additionally, a

major randomized trial is planned to evaluate the outcomes of diabetics with multivessel disease treated with sirolimus-eluting stent in comparison with CABG (FREEDOM trial). The sirolimus-eluting stent has been used as the device of choice for every percutaneous intervention in our institution (PLN, NM, and PWS) since April 2002, as part of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry [79]. Patients were treated without clinical or anatomical restrictions and the incidence of major adverse cardiac events (MACE; death, non-fatal myocardial infarction or repeat revascularization) has been evaluated and compared to a control group composed by patients treated with conventional techniques in the period immediately prior. After 6 months of enrollment, a total of 307 consecutive patients with MVD had been treated with sirolimus-eluting stents and compared to 427 controls treated with bare metal stents (Figure 3). In a preliminary analysis, baseline characteristics were similar between both groups, with 38 % of patients presenting 3-vessel disease. In an interim analysis (to date, only 70% had completed 6-month follow-up after the sirolimus stent implantation), sirolimus-eluting stent implantation was associated with a significantly better survival free of major events than those treated with conventional techniques (MACE-free survival at 6 months: 91.2% vs. 81.4%, respectively; p<0.01) (Figure 4). Albeit promising, further analyses are still needed to better evaluate the effect of this device on multivessel disease patients.

In this new "low-restenosis" context, the implementation of disease-modifying measures targeting the reduction of 'coronary atherosclerotic events' (i.e. non restenosis-related complications) has emerged as the major therapeutic goal, especially for the multivessel population, known to be at an increased risk for future complications. In a subanalysis of the Lescol Intervention Prevention Study (LIPS), long-term statin treatment after coronary intervention in multivessel patients was shown to effectively reduce the incidence of cardiac death, myocardial infarction, or repeat revascularization not due to restenosis [80]. In fact, statin had equalized the outcomes of multivessel patients with those

of single-vessel disease, virtually eliminating the negative impact of the disease extension on the late prognosis (Figure 4).

Table 1 – Randomized trials comparing PCI versus CABG in patients with multivessel disease in the "Pre-Stent Era"

		ERACI [7]		GABI [8]		EAST [9,10]		RITA [11,12]		CABRI [13]		BARI [14,15]	
Number		127		359		392		1011		1054		1829	
% randomized		9		4		8		6		5		7	
2-vessel		55		82		60		43		58		59	
3-vessel		45		18		40		12 *		40		41	
LVEF (%)		61		56		62				63		57	
stent utilization (%)		0		0		0		0					
IMA (%)		77		37		90		74		81		82	
PCI success †		92		92		88		87		91		88	
		CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI
In-hospital	Death (%)	4.7	1.5	2.5	1.1	1	1	1.2	0.7	1.3	1.3	1.3	1.1
	Q- MI (%)	6.0	6.0	8.1	2.3 ‡	3	10.3 §	2.4	3.5	-	-	4.6	2.1‖
	re-inter (%)	1.5	1.5	1.9	11.4 §	-	10.1	-	4.5	-	3.5	0.1	12.8 §
Cumm. Late events	Death (%)	4.7	9.5	6.5	2.6	17.3	20.7	8.6	7.9	2.7	3.9	15.6	19.1 ¶
	Q- MI (%)	7.8	7.8	9.4	4.5 **	-	-	7.2	8.7	3.5	4.9	9.1	7.4
	re-interv (%)	6.3	37 §	6	44 §	26.5	65.3 §	14.3	49.8§	2.1	35.6 §	13.1	59.7 §
Follow-up period		3 years		1 year		8 years		6.5 years		1 year		7.8 years	

CABG=coronary artery bypass graft surgery, IMA=internal mammary artery; LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention; Q-MI=Q-wave myocardial infarction
* Single-vessel disease in 45%
† Successful dilatation of at least one lesion
‡ p=0.02 CABG vs PCI
§ p<0.001 CABG vs PCI
‖ p<0.01
¶ p<0.05
** Death/MI = 13.6 vs 6.0; p=0.02 (CABG vs PCI)

Table 2 – Observational Studies in PCI for multivessel disease in the "Stent Era" – Baseline and in-hospital outcomes

Study	Design	size	DM (%)	Ejection fraction (%)	3-vessel disease (%)	success (%)	IMA (%)	Death (%)	MI (%)	re-intervention (%)
Kornowski 1999 [17]	– SV stenting *	1941	23	48	-	97	-	0.6	0.7	1.6
	– MV stenting	398	24	48	-	96	-	0.5	0.9	0.5
Hernández-Antolin 1999 [18]	– MV stenting	136	21	66		95	-	0.7	4.4	0
Srinivas 2002 [19]	– MV disease treated with PCI in "pre-stent era" (BARI trial; stent 1%)	904	19 †	‡	39 †	86.2 †	-	1.1	2.1	10.2 †
	– MV disease treated with PCI in "stent era" (NHLBI registry; stent 76%)	857	23 †	‡	29 †	93.4 †	-	0.9	0.8	1.9 †
Mathew 1999 [20]	– MV stenting	175	18	63	31	100	-	1.7	0	1.1
Kim 2000 [21]	– MV stenting	100	30	59	51	-	-	1.0	3.0	2.0
	– MV CABG	100	22	57	61	-	76	2.0	3.0	0
Moussa 1997 [22]	– MV stenting	100	10	57	26	100	-	1.0	2.0	4.0
Laham 1997 [23]	– MV stenting	103	44	-	-	99	-	1.0	1.9	0
Villareal 2002 [16]	– MV stenting	2793	23	§	13 ‖	NA	NA	0.8 ¶	NA	NA
	– MV CABG	2826	34	§	64 ‖	-	-	3.6 ¶	NA	NA

SV = single vessel; MV = multivessel; pts = patients; MI = myocardial infarction; TLR = target lesion revascularization; IMA=internal mamary artery graft; DM=diabetes mellitus; NHLBI=National Heart, Lung and Blood Institute; BARI=Bypass Angioplasty Revascularization Investigation trial
* 20% of the patients had multivessel disease
† p< 0.05
‡ EF<50% in 19% BARI vs. 24% registry (p=0.01)
§ EF<50% in 27% stent vs. 38% surgery (p<0.001)
‖ Single-vessel disease was present in 7.1% of surgical cases and 46.7% of stent cases (p<0.01)
¶ Adjusted odds ratio 8.43 (95% confidence interval: 4.2 – 16.9)

Table 3 – Observational Studies in PCI for multivessel disease in the "Stent Era" – Long-term outcomes

Study	Design	size	Follow-up	Death (%)	MI (%)	TVR (%)	EFS (%)
Kornowski 1999 [17]	– SV stenting	1941	1 year	1.4	1.2	16.0	77.0
	– MV stenting	398		0.7	0 *	15.0	78.0
Hernández-Antolin 1999 [18]	– MV stenting	136	18±13 mo.	5.1	0.7	9.5	75.0
Srinivas 2002 [19]	– MV disease treated with PCI in "pre-stent era" (BARI trial; stent 1%)	904	1 year	4.1	†	40.7 *	-
	– MV disease treated with PCI in "stent era" (NHLBI registry; stent 76%)	857		4.9	†	19.4 *	-
Mathew 1999 [20]	– MV stenting	175	1 year	-	-	18.3	79.8
Kim 2000 [21]	– MV stenting	100	21±10 mo.	0	1.0	19.0 *	70.0 ‡
	– MV CABG	100		1.0	2.0	2.0	86.0
Moussa 1997 [22]	– MV stenting	100	21±10 mo.	2.0	2.0	30.0	87.0 §
Laham 1997 [23]	– MV stenting	103	13±8 mo.	3.9	3.9	16.5	80.0
Villareal 2002 [16]	– MV stenting	2793	2.5 years	20 ‖			
	– MV CABG	2826		15 ‖			

EFS=event-free survival; MI = myocardial infarction; MV = multivessel; pts = patients; SV = single vessel; TLR = target vessel revascularization;
* p<0.05
† Death/MI in 11.0% BARI vs 7.9% registry (p=0.036)
‡ p<0.01
§ Survival free of MI or CABG
‖ Mortality rates for patients with 3-vessel disease and proximal left anterior descending stenosis. Adjusted odds ratio for suvival (CABG:stent):
0.93 (95% confidence interval: 0.53 – 1.6); p=0.8

Table 4 – Randomized Trials ERACI-2, ARTS, SoS, MASS-2: coronary stenting versus surgical revascularization for patients with multivessel disease – Study Design

Study	Inclusion criteria	Exclusion criteria	Revascularization strategy	Total occlusion	LM stenosis	Screened (%)	Eligible (%)	Randomized
ERACI 2 [32]	- Large ischemic myocardial area, high grade stable angina (CCS III–IV) or unstable angina - Stenosis ≥ 70% in one major vessel and at least one other vessel with stenosis ≥ 50% - At least one treated vessel with diameter ≥ 3.0mm - All treated lesions should be amenable to PCI or CABG	- 1-vessel disease - previous CABG - PCI in the last year - previous stenting - AMI < 24 hours - EF ≤ 35% - valvular disease	- Complete functional revascularization	Yes *	Yes	2759	1076	450
ARTS [29]	- silent ischemia, stable angina pectoris, or unstable angina - ≥ 2 lesions potentially amenable to stent implantation and located in different vessels and territories.	- LM stenosis - Previous CABG or PCI - AMI < 1 week - EF < 30% - valvular disease - Previous CVA	- PCI and CABG should provide an equivalent degree revascularization	Yes †	No	–	–	1205
SoS [, 2002 #649]	- Symptomatic multivessel coronary artery disease - consensus view of the surgeon and interventionist was that revascularisation was appropriate by either strategy. - At least one lesion as suitable for stent implantation.	- Previous thoracotomy or coronary revascularization. - valvular disease	- Equivalent revascularization not mandatory	–	–	–	– ‡	988
- MASS 2 [31]	- Symptomatic multivessel coronary artery disease - consensus view of the surgeon and interventionist was that revascularisation was appropriate by either strategy. - At least one lesion suitable for stent implantation.	- Previous thoracotomy or coronary revascularization. - valvular disease - unstable angina	- PCI and CABG should provide an equivalent degree revascularization	NA	No	18692	2076	408 ‖

AMI=acute myocardial infarction; CABG=coronary artery bypass graft surgery; CCS=Canadian Canadian Cardiovascular Society class; TO=total occlusion; CVA=cerebro-vascular accident; IABP=intra=aortic balloon pump; LCx=left circumflex artery; LM=left main coronary; PCI=percutaneous coronary intervention.

* No more than 2 lesions with TO
† Duration < 1 month
‡ estimation based on patients undergoing multivessel revascularisation in each institution.
§ Patients were also randomized to a third group without invasive treatment (n=203)
‖ An additional group of 203 patients was randomized for medical treatment (in total 611 patients were enrolled in the MASS-2 trial)

Table 5 – Randomized Trials ERACI-2, ARTS, SoS, MASS-2: coronary stenting versus surgical revascularization for patients with multivessel disease – Baseline clinical and angiographic characteristics

Study		Male (%)	Age (years)	DM (%)	Previous MI (%)	Previous CABG (%)	PVD (%)	EF (%)	2-vessel (%)	3-vessel (%)	LM (%)	LAD (%)
ERACI 2 [32]	PCI	77	63	17	29	0	19	53	40	55	5	91
	CABG	81	61	17	28	0	27	68	38	58	4	93
ARTS [29]	PCI	77	61	19	44	0	6	61	68	30	0	90
	CABG	76	61	16	42	0	5	60	67	33	0	90
SoS [, 2002 #649]	PCI	80	61	14	44	0	31	57	62	38	1	92
	CABG	78	62	15	47	0	35	57	52	47	1	92
MASS 2 [31]	PCI	67	60	23	51	0	0	68	42	58	0	93
	CABG	72	60	29	41	0	0	68	41	59	0	93

CABG=coronary artery bypass graft surgery; DM=diabetes mellitus; EF=ejection fraction; MI=myocardial infarction; PCI=percutaneous coronary intervention; peripheral vascular disease; SD= standard deviation; LM=left main stenosis > 50%; LAD stenosis>50%

Table 6 – Randomized Trials ERACI-2, ARTS, SoS, MASS-2: coronary stenting versus surgical revascularization for patients with multivessel disease – Procedural findings

Study		Number of lesions successfully treated (%)	Lesions with stent (%)	IIbIIIa inhibitor (%)	IMA (%)	Grafts per pt	off-pump CABG (%)	Complete anatomical revascularization (%)	time from randomization to treatment (days)	hospitalization time (days)
ERACI 2 [32]	PCI	1.9*	NA †	28	-	-	-	50 §	4.2	5 §
	CABG	-	-	-	89	2.2	0.9	85 §	13.2	9 §
ARTS [29,30]	PCI	2.6	89	0	-	-	-	71 §	11	2 ¶
	CABG	-	-	-	93 ‖	2.5	NA	84 §	27	6 ¶
SoS [, 2002 #649]	PCI	2.7	78	8	-	-	-	NA	14	3
	CABG	-	-	-	93	2.8	3	NA	23	10
MASS 2 [31]	PCI	2.1	72	0	-	-	-	41	34	3
	CABG	-	-	-	93	3.3	0	74	49	14

CABG=coronary artery bypass surgery; IMA=internal mammary artery graft; PCI=percutaneous coronary intervention; pt=patient
* 2 lesions treated successfully in 81% of patients
† 1.4 stents / patient
‡ Success rate for all planned lesions
§ p<0.01
‖ patients with at least one arterial graft
¶ Non-coronary care unit,non-intensive care unit hospitalization days (p<0.01 for PCI vs CABG)
# Use of stents increased during the study from 26% in 1995 to 88% in 1999/2000
** Use of glycoprotein IIbIIIa inhibitors increased during the study from 1% in 1995 to 52% in 1999/2000
†† IMA increased during the study from 57% in 1995 to 78% in 1999/2000

Table 7 – Randomized Trials ERACI-2, ARTS, SoS, MASS-2: coronary stenting versus surgical revascularization for patients with multivessel disease – Long-term outcomes

Study		FUP time (years)	Death (%)	MI (%)	any re-PCI or CABG (%)	MACE (%)	Free of angina (%)
ERACI 2 [32]	PCI	1.5	3.1 *	2.3 *	16.8 *	20	85 *
	CABG		7.5 *	6.3 *	4.8 *	18.6	92 *
ARTS [29]	PCI	1.0	2.5	6.2	21.0 *	26.2 †	79 *
	CABG		2.8	4.8	3.8 *	12.2 †	90 *
SoS [, 2002 #649]	PCI	2.0	5 *	5 ‡	21 *	22.5 *	66 *
	CABG		2 *	8 ‡	6 *	12.4 *	79 *
MASS 2 [31]	PCI	1.0	4.3	7.8	12.1 *	24.8 *	78 *
	CABG		4.5	1.9	0.5 *	6.4 *	86 *

CABG=coronary artery bypass surgery; EFS=event-free survival; FUP=follow-up; MACE=major adverse cardiac events (death, myocardial infarction, or repeat-revascularization); MI=myocardial infarction; PCI=percutaneous coronary intervention
* p<0.05
† Includes cerebro-vascular accident (p<0.05 PCI vs CABG)
‡ The incidence of MI or death was similar between both groups (p=0.8)
§ Death, unstable angina, or repeat revascularization

Table 8 – Coronary stenting versus surgical revascularization: pooled population from the ERACI 2, ARTS, SoS, and MASS 2 randomized trials

	Stent (n=1518)	CABG (n=1533)
Clinical and angiographic characteristics		
Male (%)	77	77
Age (yr)	61	61
Diabetes mellitus (%)	18	18
Previous myocardial infarction (%)	43	41
Peripheral vascular disease (%)	7	8.2
Ejection fraction (%)	59±11	59±11
Unstable angina (%)	29	27
2-vessel disease (%)	59	54
3-vessel disease (%)	41	46
Left anterior descending artery (%)	91	91
Left main coronary artery (%)	1	1
Procedural characteristics		
IIb / IIIa inhibitor (%)	6.7	-
Number of Stents implanted per patient (%)	2.3±1.14	-
Number of conduits (%)	-	
Complete revascularization (%)		
Length of hospital stay (days [interquartile range])	2 (1, 4)	8 (6, 10)
30-day outcome		
Death (%)	1.2	1.0
Non-fatal myocardial infarction (%)	2.2	3.3
Repeat revascularization (PCI or CABG) (%)	3.3	0.5
MACE (%)	5.5	5.3
1-year outcome		
Death (%)	3.0	2.8
Non-fatal myocardial infarction (%)	5.8	5.5
Repeat revascularization (PCI or CABG) (%) *	17.9	4.4
MACE (%) *	23.9	13.1
EFS (%)*	76	87
Free of angina (%) *	77	82

CABG=coronary artery bypass surgery; EFS=event-free survival; MACE=major adverse cardiac events (death, myocardial infarction, or repeat-revascularization); PCI=percutaneous coronary intervention
* $p<0.05$

Table 9 - The AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial. Study design and main findings [36].

		CABG (n=232)	PCI (n=232)
Rationale and objective	– High-risk patients have been excluded from randomized trials comparing PCI vs CABG – Objective: to evaluate the survival of patients with a high risk profile for CABG and refractory myocardial randomly allocated to treatment with CABG or PCI		
Inclusion criteria	1) Medically refractory myocardial ischemia AND 2) At least one risk factor for 1-month surgical mortality * 3) Coronary anatomy judged to be acceptable for both surgical or percutaneous		
Population size	484 patients (58% of all illegible)		
Follow-up time	3 years		
Baseline characteristics			
Age > 70 years (%)		53	50
Diabetes (%)		34	29
Previous MI (%)		71	70
Prior CABG (%)		32	30
LVEF<0.35 (%)		23	18
intraaortic balloon pump (%)		2	2
MI < 7 days (%)		32	35
2-vessel disease (%)		33	40
3-vessel disease (%)		40	40
LAD disease (%)		88	87
Procedural characteristics			
number of anastomosis (%)		2.9	-
LIMA graft (%) †		70	-
Stent (%)‡		-	54
IIbIIIa inhibitor (%) §		-	11
Clinical outcome			
In-hospital death (%)		4	1
30-day death (%)		5	3
6-month death (%)		10	6
3-year death (%)		21	20
3-year death or UA (%)		35	41
3-year death, UA or re-intervention (%) ‖		39	52

CABG=coronary artery bypass graft surgery; LAD=left anterior descending artery; LIMA=left internal mammary artery; LVEF=left ventricular ejection fraction; MI=myocardial infarction; PCI=percutaneous coronary intervention; UA=unstable angina

* Risk factors for post-CABG mortality: prior heart surgery, age >70 years, LVEF<0.35, intraaortic balloon pump before surgery, and MI < 7 days before CABG
† LIMA utilization varied along the enrollement period, from 57% in 1995 to 78% in 1999/2000
‡ Stent utilization varied along the enrollment period, from 26% in 1995 to 88% in 1999/2000
§ Use of IIbIIIa inhibitors varied along the enrollment period, from 1% in 1995 to 52% in 1999/2000
‖ p<0.001 (by log-rank test)

Table 10 – Total direct medical costs at 1 year for percutaneous and surgical revascularization of multivessel disease in the ARTS trial [29,50].

	Total Population			Diabetics			Non-diabetics		
	Stenting (n=600)	CABG (n=605)	p-value	Stenting (n=112)	CABG (n=196)	p-value	Stenting (n=488)	CABG (n=509)	p-value
Total direct medical costs at 1 year (US$)	10,665	13,638	<0.001	12,855	16,585	<0.001	10,164	16,585	<0.001
Event free-survival at one-year, %*	73.8	87.8	<0.001	63.4	84.4	<0.001	76.2	84.4	<0.001

*includes death, cerebrovascualr accident, myocardial infarction, and repeted revascularization

Evidence Based Medicine: The Arterial Revascularization Therapies Study [29]

Acronym: ARTS

Principal Investigator: Patrick W. Serruys

Number of patients and sites: 1205 patients at 67 sites

Trial design: Patients with multivessel disease randomly treated with coronary stenting or bypass surgery

Primary endpoint: freedom from major adverse cardiac and cerebrovascular events at one year.

Major findings:

1. No significant difference between stenting and surgery in terms of death, stroke, or myocardial infarction at one year

2. Stenting was associated with a significantly higher rate of repeat revascularization than surgery (21.0% vs. 3.8% respectively; relative risk: 5.52 [95 percent confidence interval: 3.59 to 8.49]).

3. The event-free survival at one year was 73.8% among the stent patients and 87.8% among surgical patients (P<0.001 by the log-rank test).

4. Initial costs were $4,212 less for stenting but the difference was reduced during follow-up due to the need for re-interventions in this group. At one year, the net difference was estimated to be $2,973 per patient in favor of stenting

Evidence Based Medicine: The Stent or Surgery trial [, 2002 #649]

Acronym: SoS

Principal Investigator: Ulrich Sigwart

Number of patients and sites: 988 patients at 53 sites

Trial design: Patients with multivessel disease randomly treated with coronary stenting or bypass surgery

Primary endpoint: Incidence of repeat revascularization

Major findings:

1. Additional revascularization procedures were needed in 21% of patients in the stenting group and in 6% of patients in the surgical group (hazard ratio 3.85; 95% CI: 2.56–5.79, p<0.0001)

2. Death or Q-wave myocardial infarction rates were were similar in both groups (stent: 9% vs. surgery: 10%; hazard ratio 0.95 [95% CI: 0.63–1.42, p=0.80]).

3. Death rate was lower in the surgical group than in the stent group (surgery: 2% vs. stent: 5%; hazard ratio 2.91 [95% CI: 1.29–6.53, p=0.01]).

Evidence Based Medicine: The Medicine, Angioplasty or Surgery Study for Multivessel Coronary Artery Disease-2 [31]

Acronym: MASS-2

Principal Investigator: Whady A. Hueb

Number of patients and sites: 611 patients at 1 site

Trial design: Patients with multivessel disease randomly treated with medical therapy, coronary stenting or bypass surgery.

Primary endpoint: Combined frequency of cardiac death, myocardial infarction or unstable angina at one year

Major findings:

1. Similar mortality rate in all three arms at 1 year: 4.5% with surgery, 4.0% with stent and 2.0% with medical therapy .

2. Higher frequency of myocardial infarction in the stent arm at 1 year: 2% with surgery, 8% with stent and 2.0% with medical therapy (p = 0.015).

3. Higher frequency of repeat revascularization or crossover in the stent arm at 1 year: 0% with surgery, 14% with stent and 8% with medical therapy (p < 0.01).

Evidence Based Medicine: The Argentine Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease-2 trial [32]

Acronym: ERACI 2 trial

Principal Investigator: Alfredo Rodriguez

Number of patients and sites: 450 patients at 7 sites

Trial design: Patients with multivessel disease randomly treated with coronary stenting or bypass surgery.

Primary endpoint: Major adverse events (death, Q-wave myocardial infarction, stroke, or repeat revascularization) at 30 days.

Major findings:

1. Lower incidence of major adverse events in the stent arm at 30 days (3.6% vs. 12.3%, p=0.002)

2. Lower incidence of death in the stent arm at 30 days (0.9% vs. 5.7%, p<0.013) and at 18.5 ± 6.4 months (3.1% vs. 7.5%, p<0.017)

3. Lower incidence of myocardial infarction in the stent arm at 30 days (0.9% vs. 5.7%, p<0.013) and at 18.5 ± 6.4 months (2.3% vs. 6.4%, p<0.017)

4. Higher incidence of repeat revascularization in the stent arm during follow-up (16.8% vs. 4.8%, p<0.002).

Evidence Based Medicine: Angina With Extremely Serious Operative Mortality Evaluation trial [36]

Acronym: AWESOME

Principal Investigator: Douglass A. Morrison

Number of patients and sites: 454 patients at 16 sites

Trial design: High-risk patients with refractory myocardial ischemia randomly treated with coronary stenting or bypass surgery. Included patients had at least one of the following characteristics: including prior cardiac surgery, age > 70 years, left ventricular ejection fraction < 0.35%, recent myocardial infarction (<7 days), or intraaortic balloon pump required.

Major findings:

1. 30-day survival rate for surgery and angioplasty: 95% and 97%, respectively (p=NS)

2. 6-month survival rate for surgery and angioplasty: 90% and 94%, respectively (p=NS)

3. 36-month survival rate for surgery and angioplasty: 79% and 80%, respectively (p=NS)

4. 36-month rates of death, unstable angina or re-intervention for surgery or angioplasty: 39% vs. 52%, respectively (p<0.001)

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Randomized trials of Stenting vs. CABG in multivessel disease
Overview

•Five randomized trials are currently available comparing
percutaneous coronary intervention and coronary artery bypass
surgery for patients with multivessel disease in the "stent
era":ARTS, SoS, MASS-2, ERACI-2, and AWESOME
(multivessel disease in ~80%)

•Relatively non-complex patients were included in ARTS, SoS,
and MASS-2.

•Patients with a higher risk profile were enrolled in the ERACI-
2, and AWESOME trials

Randomized trials of Stenting vs. CABG in multivessel disease
Short-term outcomes

•Stenting was consistently associated with a significantly shorter in-hospital
stay

•Overall, both stenting and surgery were associated with similar in-hospital
outcomes

•Periprocedural repeat revascularization occurred in approximately 3% after
stenting (pooled analysis with patients from ARTS, SoS, MASS-2, ERACI-
2), which compares favorably with the findings of studies conducted in the
balloon angioplasty era (13% periprocedural reintervention in the BARI trial)

•In the ARTS trial, 40% of all events occurring in the first month after
stenting was due to stent thrombosis

•In AWESOME, high-risk patients presented a 30-day mortality after CAGB
or PCI of 5% vs. 3% respectively (p=NS)

Randomized trials of Stenting vs. CABG in multivessel disease
Long-term outcomes

•At 1 year, multivessel stenting and CABG were associated with similar rates of death as well as of death, myocardial infarction or cerebrovascular accident.

•The incidence of major events after 1 year was significantly higher for patients treated with multivessel stenting (23.9% vs. 13.1%; p<0.01), which was almost entirely explained by the increased rate of re-intervention in this group (18% vs. 4%; p<0.01) (pooled analysis of ARTS, SoS, MASS-2, ERACI-2)

•Although stenting still presented a higher rate of repeat revascularization than CABG, coronary stents clearly improved the late outcomes seen after balloon angioplasty (the incidence of repeat revascularization at 1 year was usually over 30%).

Randomized trials of Stenting vs. CABG in multivessel disease
Diabetes

- In the pre-stent era, diabetes was associated with identified with higher mortality rates in the randomized EAST and RITA-1 trials (although not reaching statistical significance) and in the BARI trial (death rate at 5 years for angioplasty vs,. surgery: 20.6% vs. 5.8%, repectively; p=0.0003)

- This difference in the BARI was more evident among those using insulin and was largely restricted to surgical patients receiving internal mammary artery grafts.

- However, in the BARI-registry (eligible patients in the BARI trial who did not consent to randomization), diabetes have not increased the risk of 5-year mortality among those treated with angioplasty.

- In the ARTS trial, diabetics had similar rates of death or MI at 1 year in the stent and CABG arms. Patients with diabetes showed a trend towards more cerebrovascular events when treated with surgery than with PCI (6.3% vs. 1.8% respectively; p=0.096).

- In the ARTS trial, patients with diabetes treated with multivessel stenting showed a significantly higher incidence of re-intervention at 1 year than after CABG (22.3% vs. 3.1% respectively; p<0.01). The rate of repeat revascularization after stenting was higher in diabetics than in non-diabetics (22.3% vs. 15.6%; p=0.04)

- In the AWESOME study, no differences in 3-year survival rates were observed in "high-risk" diabetics treated with CABG or PCI in the randomized trial or in the parallel registry (physician-directed or patient-choice treatments) (72% vs. 81%; 73% vs. 71%; 85% vs. 89%, respectively; p=NS for all) .

Randomized trials of Stenting vs. CABG in multivessel disease
Completeness of Revascularization

- In the ERACI 2 trial, anatomical complete revascularization was more frequent in the surgical group (85% vs. 50% in the PCI group; p=0.002). Both groups had a similar degree of functional complete revascularization, with an equivalent frequency of normal or nonreversible perfusion areas at 30 days (85% in CABG vs. 84% in PCI; p=NS).

- In the ARTS trial, complete anatomical revascularization was achieved in 84% of surgical patients and in 71% of stented patients (p<0.01). In the PCI group, incomplete revascularization was associated with worse 1-year (incidence of MACE: 30.6% vs. 23.4%; p<0.05), mainly due to a higher incidence of additional bypass procedures (10.0% vs. 2.0%; p<0.05). Conversely, the degree of completeness showed virtually no impact on the outcomes of CABG patients after 1 year (event-free survival 87.8% vs. 89.9% for complete vs. incomplete revascularization; p=NS).

Randomized trials of Stenting vs. CABG in multivessel disease
Costs

- As compared to surgery, stenting significantly reduce by US$ 3,000.00 the total direct medical costs at 1 year in the ARTS trial.
- In ERACI 2, no differences in costs were observed between both strategies at 1 year (overall cost per patient: US$ 12,320 for stenting and US$ 11,160 for CABG [p=NS] after a mean follow-up of 18 months).

Actuarial Survival

Coronary Stenting 97.2%

CABG 97%

Hazard Ratio = 1.07
(95% CI 0.70-1.62)
p - value = 0.71

Days

Survival free of MI or CVA

Hazard Ratio = 0.94
(95% CI 0.74-1.19)
p – value = 0.62

Coronary Stenting 91.3%

CABG 90.9%

Days

Survival free of MACE

CABG 87%

Hazard Ratio = 1.90
(95% CI 1.60-2.26)
p - value < 0.0001

Coronary Stenting 76%

Days
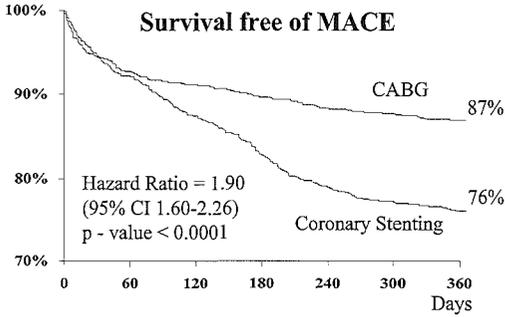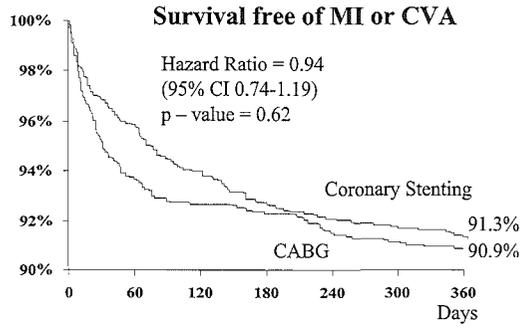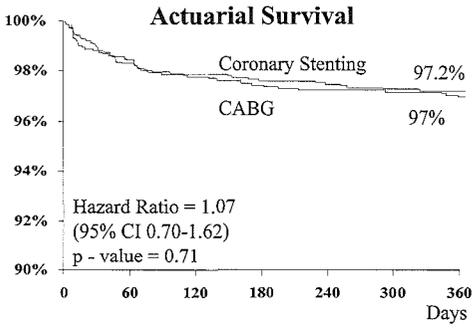
Figure 1 – Coronary stenting versus surgical revascularization: pooled population from the ERACI 2, ARTS, SoS, and MASS 2 randomized trials. Survival and survival free of events curves.

Figure 2 – Death and repeat revascularization rates at 1 year in multivessel disease. Percutaneous and surgical treatment in the "pre-stent era"and "stent era".

Death rate at 1 year (%)

3.7% 3.9% 2.8% 3.0%

CABG "pre-stent era" | PCI "pre-stent era" | CABG "stent era" | PCI "stent era"

Repeat revascularization at 1 year (%)

31%

34%

14%

18%

3% 4%

CABG "pre-stent era" | PCI "pre-stent era" | CABG "stent era" | PCI "stent era"

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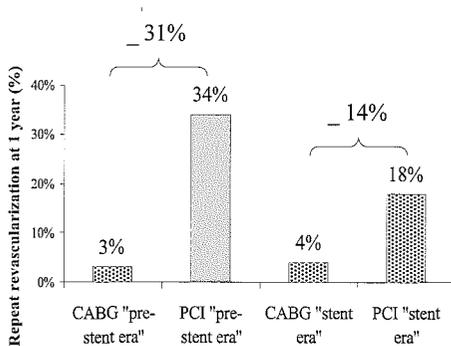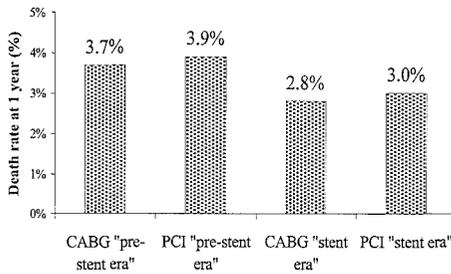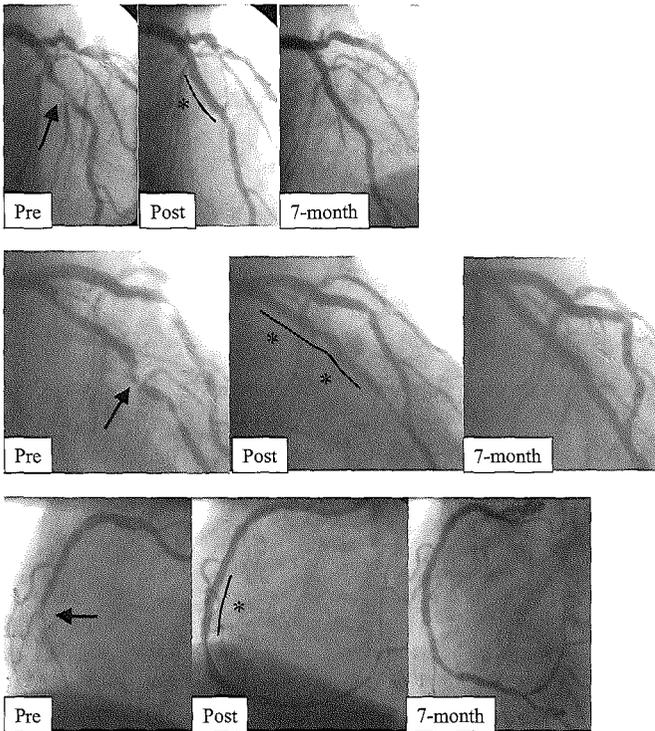
Figure 3 -

74 year-old male, smoker, with previous myocardial infarction, admitted with stable angina (CCS 3). The pre-procedure coronary angiogram showed a severe stenosis in the mid left anterior descending artery (upper panel), which was treated with implantation of a 3 x 18-mm sirolimus-eluting stent (*). The first obtuse marginal branch (middle panel) presented a severe stenosis treated with the implantation of two overlapping 3 x 18-mm sirolimus-eluting stents (*). A chronic total occlusion in the mid portion of the right coronary artery (lower pannel) was treated with implantation of a 3 x 18-mm sirolimus-eluting stent (*). The procedure was uneventful. After 7 months, the patient remained asymptomatic and no evidence of restenosis was observed at elective 7-month control angiogram.

Figure 4 – MACE-free survival curves for patients with multivessel disease treated with sirolimus-eluting stent implantation or conventional percutaneous techniques in te RESEARCH registry
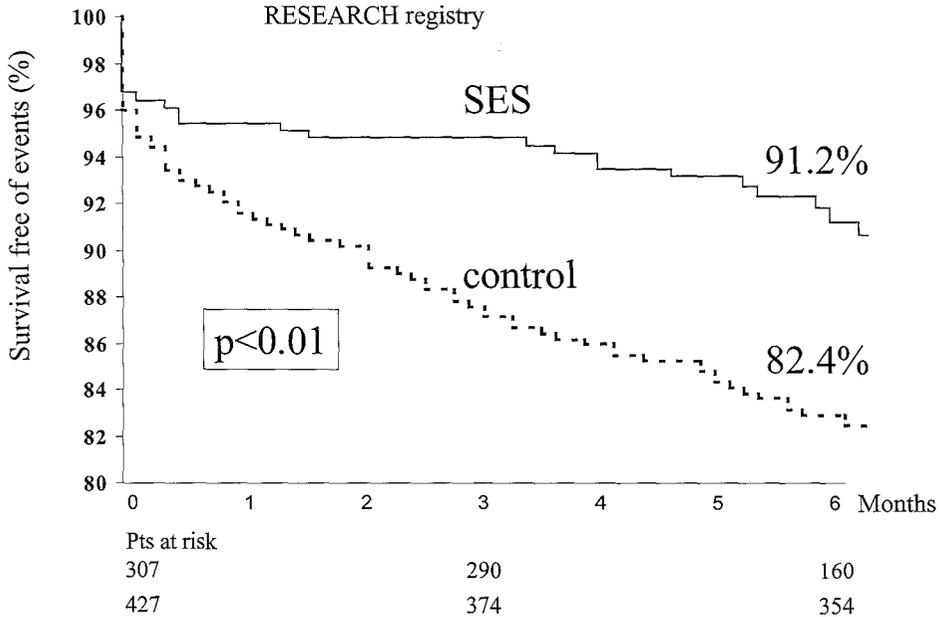
Figure 5 – Impact of long-term fluvastatin treatment on the occurrence of cardiac atherosclerotic events in the LIPS trial
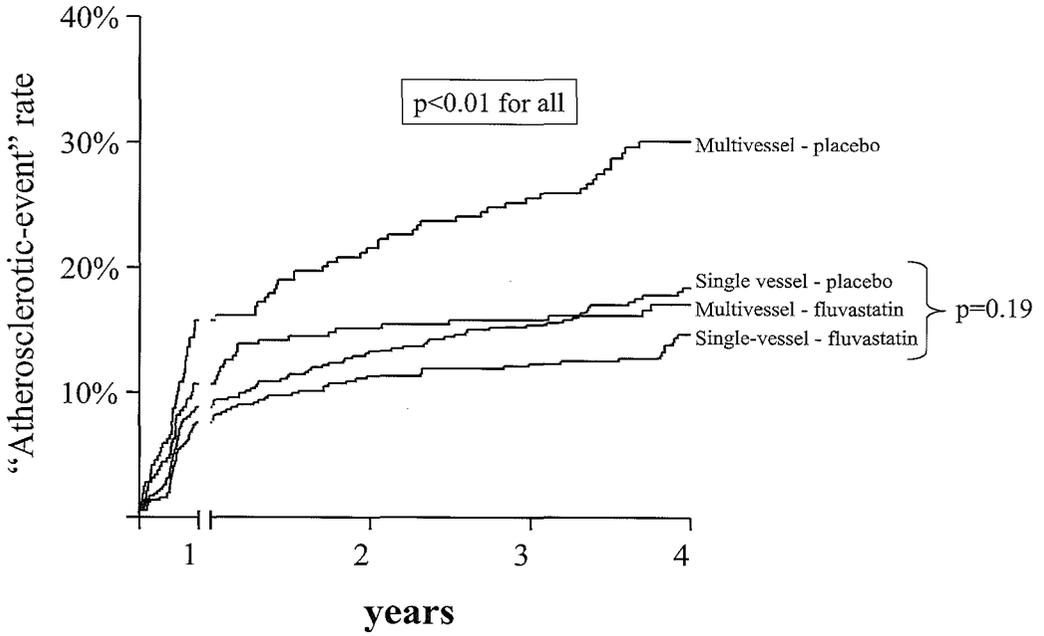
Chapter 4

Characteristics, treatment and outcome of patients with non ST-elevation acute coronary syndromes and multivessel coronary artery disease: Observations from PURSUIT

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Cardiology 2002; 98: 195-201

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)

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Key Words

Multivessel disease · Medical treatment · Percutaneous coronary interventions · Coronary artery bypass grafting

Abstract

Background: The 6-month clinical outcome of patients with multivessel disease enrolled in PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) is described. Patients with complete angiography data were included; multivessel disease was stratified according to the treatment strategy applied early during hospitalization, i.e. medical treatment, percutaneous coronary intervention (PCI) (balloon), PCI (stent), or coronary artery bypass grafting (CABG). *Methods:* Patients were divided into three groups according to the treatment strategy applied during the first 30 days of enrolment. Patients who did not undergo a percutaneous or surgical coronary intervention were classified as medically treated. Patients who underwent a PCI (prior to a possible CABG) were sepa-rated from those who underwent a CABG (prior to a possible PCI). The PCI group was further subdivided: patients receiving ≥1 coronary stents were separated from those in whom no stents were used. *Results:* The mortality rate at 30 days was 6.7, 3.9, 2.4 and 4.8% for the medical treatment, PCI (balloon), PCI (stent) and CABG groups, respectively (p value = 0.002). Differences as observed at 30 days were still present at 6-month follow-up with 11.1, 5.8, 5.5 and 6.5% mortality event rates for the aforementioned groups (p value = 0.002). The 30-day myocardial infarction (MI) rate according to the opinion of the Clinical Events Committee was lower among medically than non-medically treated patients, with the highest event rate observed in the CABG group (27.7%). Approximately half of the MIs in the PCI and CABG subgroups occurred within 48 h after the procedure. *Conclusions:* The observed differences in clinical outcomes are explained by an imbalance in baseline characteristics and comorbid conditions between the analyzed groups of patients.

Introduction

Several clinical trials have been performed to evaluate whether patients with coronary artery disease benefit most from medical treatment only, percutaneous coronary intervention (PCI), or coronary bypass surgery (CABG) [1, 2]. Other studies have specifically compared percutaneous transluminal coronary balloon angioplasty (PTCA) against CABG [3–9] and finally contemporary trials of coronary stenting and optimal adjunctive pharmacological therapy versus CABG have recently been reported [10–12]. However, most of these studies have predominantly included patients with chronic stable angina and few data are available on the characteristics and clinical outcome of patients with multivessel disease presenting with an acute coronary syndrome.

The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial was a large-scale randomized clinical trial on the effects of eptifibatide versus placebo in patients with acute coronary syndromes without persistent ST elevation [13]. As the enrolment criteria were broad, PURSUIT encompasses a wide variety of patients, hospital settings and treatment policies, and therefore accurately reflects standard clinical practice.

The aim of this study was to describe the characteristics and short-term clinical outcome of patients with multivessel coronary artery disease in the PURSUIT population according to the treatment strategy applied early during hospitalization.

Materials and Methods

Patient Population

The design and methods of the PURSUIT trial have been previously published [13]. In summary, patients were eligible if they presented within 24 h of an episode of ischemic chest pain (>10 min), and had either transient ST elevation (>0.5 mm), transient or persistent ST depression (>0.5 mm), T wave inversion (>0.1 mm), or elevation of the creatine kinase MB fraction (CK-MB) above the upper limit of normal (ULN). Patients with persistent (>30 min) ST elevation were excluded. Eligible patients were randomly assigned to treatment with eptifibatide or placebo. All other treatment decisions, including the use and timing of PCI or CABG were left at the discretion of the treating physician.

Coronary angiography was performed within 30 days of enrolment in 5,937 (63%) of the 9,461 patients who participated in PURSUIT (fig. 1). Among patients with complete angiographic data, 3,067 (58%) had a significant stenosis (>50% diameter stenosis by visual inspection) in ≥2 major native coronary arteries or in the left main stem. These patients were classified as having multivessel coronary artery disease and are the subjects of interest for the current analysis.

Classification According to Applied Treatment Strategy

Patients were divided into three groups according to the applied treatment strategy during the first 30 days of enrolment. Patients
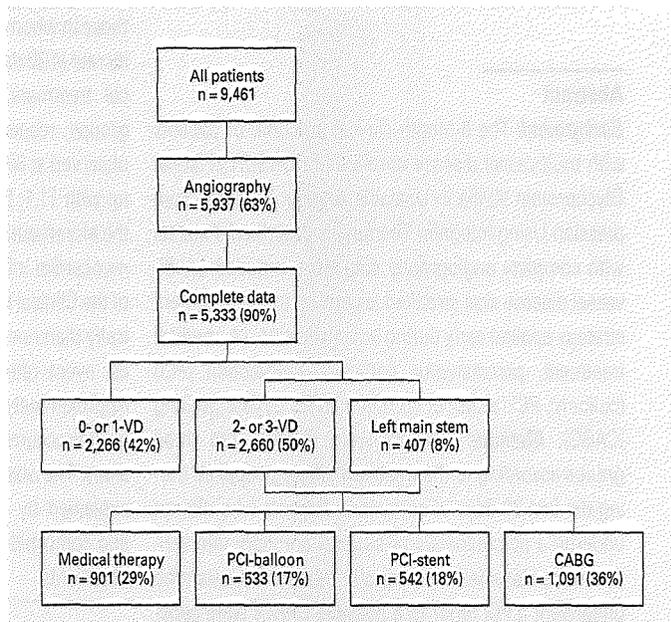
Fig. 1. PURSUIT patient population flow chart stratified according to the number of diseased vessels and treatment strategy applied to patients with multivessel coronary disease. VD = vessel disease.

who did not undergo a percutaneous or surgical coronary intervention were classified as medically treated. Patients who underwent a PCI (prior to a possible CABG) were separated from those who underwent a CABG (prior to a possible PCI). The PCI group was further subdivided: patients receiving ≥ 1 coronary stents were separated from those in whom no stents were used (fig. 1).

Definition of Myocardial Infarction

The primary endpoint of PURSUIT was a composite of death or nonfatal myocardial infarction (MI) at 30 days. A computerized algorithm was used to review the clinical events. If a possible event was identified, further documentation was collected and the case reviewed in detail and adjudicated by a central Clinical Events Committee (CEC). MI was diagnosed on the basis of new ST segment elevations, new Q waves, or new or repeated CK-MB elevations above the ULN. Following percutaneous or surgical intervention, the elevation of CK-MB level was required to be at least 3–5 times the ULN.

Data Analysis

The statistical analysis was performed using the SAS 8.0 software package (SAS Institute, Cary, N.C., USA). Continuous variables are presented as mean values ± standard deviation and dichotomous variables as percentages. One-way analyses of variance (ANOVA) and χ^2 tests were applied to evaluate differences in baseline characteristics, death, MI rates and rates of repeated coronary interventions (both at the 30-day and 6-month follow-up) between the different subgroups classified according to the applied treatment strategy. In case of a statistically significant difference in clinical events or repeated coronary interventions, which was specified at the conventional $p < 0.05$ level, repeated tests were performed to further evaluate the inter-subgroup differences. The Bonferroni method [14] was used to avoid spurious significant results after multiple testing, and the level of significance was lowered to $p < 0.0167$ and $p < 0.0083$ in case of 3 (balloon – stent – surgery) and 6 possible comparisons (medical treatment – balloon – stent – surgery), respectively.

Table 1. Clinical baseline characteristics

	Medical (n = 901)	PCI (n = 1,075) balloon (n = 533)	stent (n = 542)	CABG (n = 1,091)
Demographics				
Mean age ± SD, years	65 ± 10	63 ± 11	62 ± 11	64 ± 10***
Male gender, %	70	74	73	73
Caucasian, %	86	89	91	90*
Medical history and risk factors				
Hypertension, %	62	60	61	57
Diabetes mellitus, %	30	26	23	27
Current smoker, %	28	29	29	26
Hypercholesterolemia, %	50	46	53	47
Prior PCI, %	17	23	23	14***
Prior CABG, %	36	24	29	9***
Prior MI, %	47	40	36	34***
Heart failure, %	14	8	10	6***
Prior CVA, %	7	4	5	3**
Peripheral vessel disease, %	13	8	9	9**
Cardiac medication prior to admission				
Aspirin, %	73	74	76	74
Beta-blocker, %	48	50	49	49
Calcium antagonist, %	39	34	36	36
Nitrates, %	73	75	77	74
ACE inhibitors, %	30	23	24	21***
Clinical presentation				
CK-MB > 1 ULN, %	52	52	44	48*
ST depression > 0.5 mm, %	52	47	52	58***
ST elevation > 0.5 mm, %	12	17	15	13*
T wave inversion > 0.5 mm, %	48	51	50	45

ACE = Angiotensin converting enzyme; CVA = cerebrovascular accident; other abbreviations, as defined in the text. Statistical tests (integral comparison of 4 groups): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Results

Patient Characteristics

During the first 30 days of randomization, a PCI was performed in 1,075 of 3,067 (35%) patients, with stent placement in 542 cases (50% of the PCI procedures), whereas 1,091 of 3,067 (36%) patients underwent CABG. The remaining 901 (29%) patients were medically treated (fig. 1). A significant difference was evident between the treatment subgroups with respect to age; medically treated and CABG patients were older than those undergoing PCI (table 1). There were also differences regarding history of prior cardiovascular events and interventions. Almost one quarter of the PCI patients had a previous PCI versus 17 and 14% in the medical and surgical subgroups, respectively. A prior CABG was performed in 36% of medically treated patients, and this figure was only 9% in the CABG subgroup. A history of MI, heart failure, cerebrovascular accident, as well as peripheral vessel disease was more frequently observed in the medically versus non-medically treated patients. No important differences were observed in the use of cardiac medications except for the use of ACE inhibitors, which was more frequent in medically treated patients.

Angiographic Findings

Patients who underwent CABG had more severe coronary artery disease (52% had 3-vessel and 21% left main disease), immediately followed by medically treated patients with a similar percentage of 3-vessel disease (51%) but less often, left main disease (11%) (table 2). A total occlusion in any of the major native coronary arteries was more often present in medically than in non-medically treated patients. Medically and surgically treated patients not only had more severe, but also more diffuse coronary artery disease than PCI patients, as in 34% (CABG) to 40% (medically treated) of the patients, the culprit artery could not be identified; this percentage was only 8–10% in PCI patients. Left ventricular ejection fraction was lowest among medically treated patients. There were no apparent differences in coronary angiography results between PCI patients receiving stents and those that did not receive stents.

Clinical Outcome

The 30-day mortality rate was significantly higher among medically treated patients (6.7%) than among those undergoing PCI either with (2.4%) or without stent placement (3.9%) (fig. 2). The observed difference in mortality rate (p value = 0.067) between medically treated and

Table 2. Coronary angiography results

	Medical	PCI		CABG
		balloon	stent	
Vessel disease, %				
2	38**	62**	61**	28***
3	51	32	30	52
LM	11	6	9	21
Significant stenosis (DS >50%) in				
RCA, %	84	79	81	85**
LAD, %	88	77	82	91***
LCX, %	84	77	72	79***
LM, %	12	6	10	22***
Total occlusion (DS = 100%) in				
RCA, %	48	33	33	33***
LAD, %	35	24	26	20***
LCX, %	32	21	21	17***
Culprit artery, %				
RCA	14	27	25	16***
LAD	21	25	29	29***
LCX	14	31	21	9
LM	2	1	1	9***
Graft	9	8	14	3***
None/unknown	40	8	10	34***
Mean LVEF ± SD	50±16	55±14	54±14	53±14***

DS = Diameter of stenosis; LAD = left artery, descending; LCX = left circumflex; LM = left main; LVEF = left ventricular ejection fraction; RCA = right coronary artery; other abbreviations, as defined in the text. Statistical tests (integral comparison of 4 groups): ** p < 0.01; *** p < 0.001.

CABG patients (4.8% mortality) did not reach the required level of significance, which was prespecified as p < 0.0083.

The 30-day MI rate according to the opinion of the CEC was lower among medically than non-medically treated patients, with the highest event rate observed in the CABG group (27.7%); approximately half of the MIs in the PCI and CABG subgroups occurred within 48 h after the procedure. Differences in event rates as observed at 30 days were still present at the 6-month follow-up. Mortality was highest in the medically treated subgroup (11.1%). Mortality rates were similar in the non-medical treatment subgroups (ranging from 5.5 to 6.5%). MI rates as judged by the CEC were lowest in the medically treated patients (20.8%) and highest in patients undergoing CABG (29.6%).
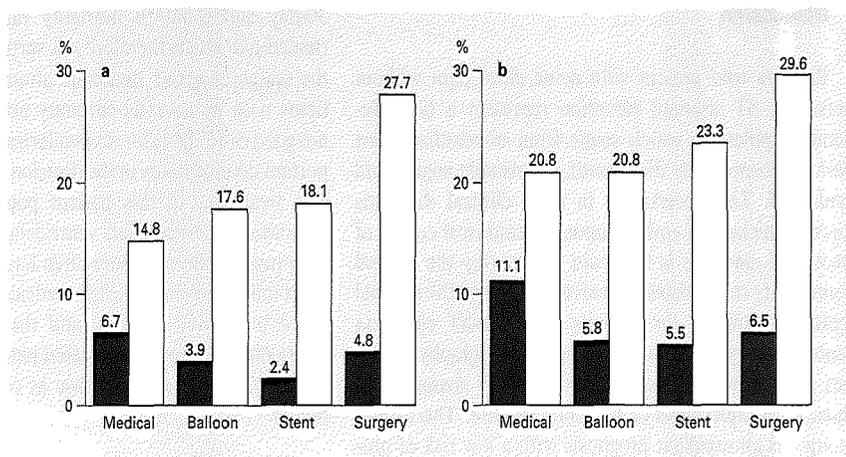
Fig. 2. 30-day (**a**) and 6-month (**b**) clinical outcome according to the treatment strategy applied. Black bars indicate mortality and white bars indicate MI adjudicated by the CEC. p Values for the overall comparison between any of the treatment strategies applied (medical treatment, balloon, stent or surgery) and each clinical endpoint are as follows: **a** death: p = 0.002, MI: p = 0.001 both at 30 days and 6 months.
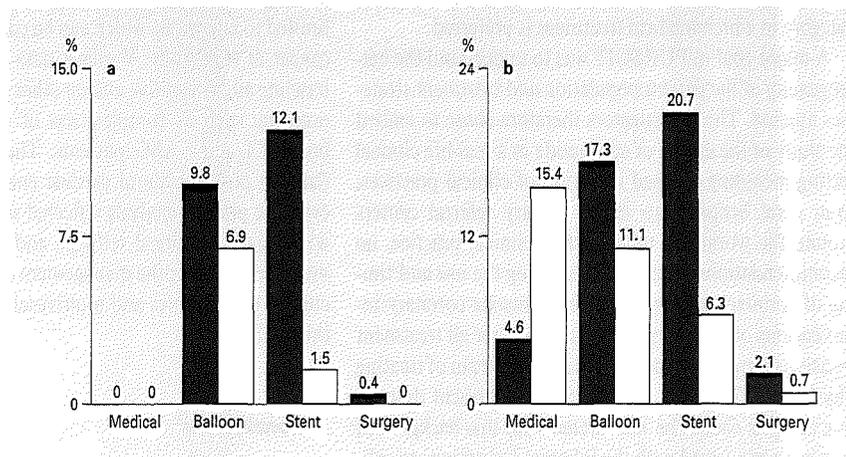
Fig. 3. 30-day (**a**) and 6-month (**b**) repeat revascularization procedures according to the treatment strategy applied. Black bars indicate PCI and white bars indicate CABG. p Values for the overall comparison between any of the re-interventions and each group based on the treatment strategy applied initially (medical treatment, balloon, stent or surgery) are as follows: PCI, CABG: p < 0.001 both at 30 days and 6 months.

Repeat Revascularization Procedures

The rate of repeat revascularization at the 30-day and 6-month follow-up were significantly lower after CABG than after PCI (fig. 3). Patients undergoing stent implantation during the initial PCI had lower CABG rates at each of these 2 points in time when compared to non-stented patients. No apparent differences were observed in the rates of repeat interventions between stented and nonstented patients. A substantial number of medically treated patients still underwent a PCI (4.6%) or CABG (15.4%) procedure between 1 and 6 months after admission.

Discussion

Patients who present with acute chest pain without persistent ST segment elevation represent a heterogeneous population, which spans from noncardiac chest pain (retrospectively diagnosed), to unstable angina and acute MI. The uncertainty in early clinical diagnosis forces clinicians to embark upon an empirical course of treatment, and this is the main reason why the clinical community still debates intensively regarding the optimal treatment strategy for patients with non-ST elevation acute coronary syndromes. Coronary angiography identifies patients with nonsignificant coronary stenoses and those with multivessel or left main disease. The former group has an excellent prognosis with a low risk of progression to MI or death, whereas the latter group, which is at an increased risk of progression to any of the aforementioned events, may derive a survival benefit from revascularization (either PCI or CABG) [15, 16]. Patients who are not suitable candidates for standard revascularization or those who are at high risk of major perioperative complications due to comorbid conditions represent a distinct category in which medical treatment is preferred.

A major goal in PURSUIT was to understand the heterogeneity of the patient population and treatment strategies applied. The investigators therefore chose to embed the study of the effects of epifibatide in a real-life clinical setting including a broad spectrum of clinical practices, from rural hospitals to major tertiary referral centers around the world. To reflect actual clinical practice, no recommendations were made regarding the use and timing of coronary angiography, percutaneous coronary interventions or coronary bypass surgery, but all treatment decisions were left at the discretion of the team of treating physicians. Therefore, the results of the present descriptive analysis should be interpreted with this background in mind and viewed with the inherent limitations to subgroup analysis of randomized clinical trials [17].

Although not prospectively randomized to each of the treatment strategies compared, it is important to note that the medical therapy, early PCI and CABG ratio in these subgroups of 3,067 patients with an acute coronary syndrome and multivessel coronary artery disease was almost 1:1:1.

Indeed, important differences were observed in clinical characteristics and coronary anatomy between the distinct subgroups. Patients who did not undergo a coronary intervention within 30 days after enrolment, generally were in a less favorable clinical condition than patients undergoing early invasive treatment. The relatively high 30-day and 6-month mortality rate among medically treated patients is therefore not surprising and argues for the search of better treatment strategies in unstable patients with multivessel coronary artery disease that are not good candidates for revascularization procedures. Important determinants in the decision to refrain from invasive treatment in this patient population seem to be comorbid conditions, left ventricular dysfunction (medically treated patients more often had a history of CABG, heart failure, and a worse left ventricular function as compared to CABG patients) and the extent of coronary artery disease (medically treated patients more often had 3-vessel and left main disease as compared to PCI patients).

Limitations

This was a retrospective assessment of clinical, angiographic characteristics and clinical events in patients enrolled in a multicenter clinical trial and stratified according to the treatment strategy applied with a follow-up limited to 6 months, which can be considered as the main caveat of this study. We lack data on anginal status at baseline and 6 months; and on other predictors of adverse outcome such as completeness of revascularization; in both PCI and CABG patients. There were insufficient data on postprocedural cardiac enzymes as well. However, the present analysis reflected standard practice in a wide range of clinical settings, and contemporary treatment strategies for the management of patients with acute coronary syndromes and multivesel disease were used in this trial.

Conclusions

The observed major differences in clinical outcome are explained by an imbalance in baseline and angiographic characteristics between the groups of patients analyzed according to the treatment strategy applied.

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Part 2: Predictors of adverse angiographic and clinical outcome

Chapter 5

Clinical and quantitative coronary angiographic predictors of coronary restenosis: A comparative analysis from the balloon to stent era

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Clinical and Quantitative Coronary Angiographic Predictors of Coronary Restenosis

A Comparative Analysis From the Balloon-to-Stent Era

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OBJECTIVES   We sought to assess whether coronary stents have modified the predictive value of demographic, clinical and quantitative coronary angiographic (QCA) predictors of coronary restenosis.

BACKGROUND   A systematic analysis in a large cohort of registries and randomized trials of the percutaneous transluminal coronary angioplasty (PTCA) and stent era has never been performed.

METHODS   A total of 9,120 treated lesions in 8,156 patients included in nine randomized trials and 10 registries, with baseline, post-procedural and six-month follow-up QCA analyses, were included in this study. Predictors of restenosis were identified with univariate and multivariate logistic regression analyses. Interaction terms were introduced in the regression equation to evaluate whether the predictors of restenosis were common to both eras or specific for either one of the revascularization techniques.

RESULTS   The restenosis rate was 35% after PTCA and 19% after angioplasty with additional stenting. In the univariate analysis, favorable predictors were previous coronary artery bypass graft surgery (CABG), stent use, stent length and a large pre-procedural minimal lumen diameter (pre-MLD); unfavorable predictors were weight, body mass index, diabetes mellitus, multi-vessel disease, lesion length and a high residual post-procedural diameter stenosis (post-DS). Predictors specific for the PTCA population were a large post-procedural MLD (post-MLD) as favorable and a severe pre-procedural DS (pre-DS) as unfavorable. Favorable predictors specific for the stent population were a large post-MLD and a large pre-procedural reference diameter (pre-RD). In the multivariate analysis, the best model included the following favorable predictors: stent use, a large post-MLD, previous CABG and the interaction term between stent use and a large post-MLD; unfavorable predictors were lesion length and diabetes mellitus.

CONCLUSIONS   There are no major differences in demographic and clinical predictors of coronary restenosis between PTCA and stent populations. In the modern (stent) era, a severe pre-DS is no longer an unfavorable predictor of restenosis. Still important, but more so in the stent population, is a large post-MLD (optimal result). Finally, a larger pre-RD became a favorable predictor with the advent of stenting. (J Am Coll Cardiol 2001;38:645–52) © 2001 by the American College of Cardiology

Coronary restenosis after a percutaneous intervention is a complex multifactorial phenomenon. With the advent of coronary stenting, constrictive vascular remodeling (a major component of the process of restenosis) has been prevented, and restenosis has decreased to a great extent. Nonetheless, restenosis remains an important clinical problem that continues to exert a major negative impact on patients' long-term outcome after percutaneous coronary interventions. Several demographic, clinical, quantitative coronary angiographic (QCA) and intravascular ultrasound (IVUS)

variables have been described previously as predictors of restenosis in either percutaneous transluminal coronary angioplasty (PTCA) or stent populations (1–8).

From the mechanistic point of view, there is a clear difference between restenosis after PTCA alone and PTCA plus stenting. As assessed by IVUS studies, the prevailing mechanism in restenosis after PTCA alone is arterial remodeling, with late vessel contraction responsible for >60% of late lumen loss (9), whereas accelerated intimal hyperplasia predominantly causes in-stent restenosis (10).

Previous reports, which are hampered by their small sample sizes, have analyzed a limited number of potential predictors of restenosis in either the stent or PTCA population analyzed separately. The aim of this study was to assess to what extent the introduction of coronary stents has modified the predictive value of previously identified demographic, clinical and QCA predictors of coronary restenosis in the balloon era. We combined two patient populations: patients treated with PTCA only (PTCA population) and

Abbreviations and Acronyms

CABG	=	coronary artery bypass graft surgery
CI	=	confidence interval
DS	=	diameter stenosis
IVUS	=	intravascular ultrasound
LAD	=	left anterior descending coronary artery
MLD	=	minimal lumen diameter
PTCA	=	percutaneous transluminal coronary angioplasty
OR	=	odds ratio
QCA	=	quantitative coronary angiography
RD	=	reference diameter

patients who also had coronary stents implanted (stent population).

METHODS

Patients were selected from 19 different studies: six randomized trials comparing the use of active medications aimed at coronary restenosis prevention after PTCA alone or PTCA plus stenting with placebo (Coronary Artery Restenosis Prevention On Repeated Thromboxane A_2-antagonism [CARPORT] study [11], Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction with Restenosis [MERCATOR] [12], Prevention of Angioplasty Reocclusion with Ketanserin [PARK] [13], Multicenter American Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction with Restenosis [MARCATOR] [14], FLuvastatin Angiographic REstenosis [FLARE] [15] and TRAPidil In Stent [TRAPIST] [16]); 10 stent registries (BElgian NEtherlands STENT [BENESTENT-2] pilot study [17], stent Primary Angioplasty in Myocardial Infarction [PAMI] pilot study [18], West European Stent Trial [WEST-1] [19], WEST-2 [20], Wallstent native study [21], Registry for Optimal beStent Evaluation [ROSE] [22], DUET [23], European Antiplatelet Stent Investigation [EASI] [24], Study Of PHosphorycholine coating On Stents [SOPHOS] [25] and MAGIC 5-L [26]); and finally, three randomized trials comparing PTCA plus coronary stenting with PTCA alone (BENESTENT-1 [27], BENESTENT-2 [28] and stent PAMI [29]).

These 19 studies were chosen because they are highly representative of the randomized trials and registries of PTCA and coronary stenting that have been performed in the past decade, antedating the use of intracoronary brachytherapy. In eight studies, treatment of more than one lesion per patient was allowed (CARPORT, MERCATOR, PARK, MARCATOR, BENESTENT-2, FLARE, stent PAMI, MAGIC 5-L); the remaining studies included only patients with a single lesion. For patients with multilesion PTCA or multilesion coronary stenting, all lesions were analyzed, and each was considered independently.

Patients were included in this analysis if they had three adequate angiograms—one immediately before the inter-

vention, one immediately after and one at six-month follow-up. Patients with an unsuccessful procedure or with a lesion in a saphenous vein graft were excluded.

Off-line analysis of angiographic outcomes was done using identical and standardized methods of data acquisition and analysis and definitions of the variables in the same core laboratory (Cardialysis, Rotterdam, The Netherlands) using the Cardiovascular Angiography Analysis System II (CAAS II) (Pie Medical, Maastricht, The Netherlands) (30).

Definitions. Procedural success was defined as a post-procedural diameter stenosis (post-DS) <50% on visual inspection in the early trials (CARPORT, MERCATOR, PARK, MARCATOR and FLARE). Subsequently (BENESTENT-1, BENESTENT-2 pilot, EASI, BENESTENT-2, stent PAMI pilot, WEST-1, WEST-2, Wallstent native, stent PAMI, ROSE, DUET, TRAPIST and SOPHOS), procedural success was defined as <50% post-DS by on-line QCA and no occurrence of an in-hospital major adverse cardiac event (death, acute myocardial infarction, coronary artery bypass graft surgery [CABG] or repeat PTCA), and finally, in the latest trial (MAGIC 5-L), procedural success was reset to <20% post-DS by on-line QCA in the absence of an in-hospital major adverse cardiac event. Coronary restenosis was defined uniformly in all but one randomized trial according to the binary criteria with a cut-off point ≥50% DS at follow-up (31). In this randomized trial (CARPORT), a noncategorical approach was used, and restenosis was defined as a loss of ≥0.72 mm in the MLD from post-PTCA to six-month follow-up. For standardization purposes, we computed the binary restenosis rate of this trial based on the DS on the follow-up angiogram. The standard definitions for proximal and distal segments of the right coronary artery, left anterior descending coronary artery (LAD) and left circumflex coronary artery have been described elsewhere (32). The pre-procedural reference diameter (pre-RD) was obtained by the interpolation method, and the lesion length was defined by curvature analysis (33).

Statistical analysis. Statistical analysis was performed using the SAS version 8.0 software package (SAS Institute, Cary, North Carolina). To test for differences in baseline variables across the studies, the Kruskal-Wallis test (continuous data) and the chi-square test (categorical data) were applied. Univariate and multivariate logistic regression analyses were used to evaluate the relationships between demographic data, clinical characteristics, stent use, QCA variables and the six-month outcome of angiographic occurrence of restenosis, which was coded as a binary variable according to the partial method. The stent length was ≤15 mm (with a minimal length of 8 mm) in 68% of patients with stents. In the remaining patients, the stent length varied from 18 mm (DUET study) to 48 mm (MAGIC 5-L study). For restenosis assessment, these two different subsets of the stent population (≤15 and >15 mm) were compared with the PTCA population.

Table 1. Baseline Characteristics

	PTCA Population	Stent Population	Pooled Group	p Value*
No. of patients	5,230	2,926	8,156	
No. of treated lesions	6,110	3,010	9,120	
Age (years)	59 (51, 65)	60 (52, 67)	59 (51, 66)	<0.0001
Men (%)	80.5	78	79	0.003
Height (cm)	172 (165, 178)	171 (165, 177)	172 (165, 178)	0.025
Weight (kg)	78 (70, 86)	78 (70, 87)	78 (70, 87)	0.732
History				
Hypertension	33%	38%	35%	<0.0001
Diabetes mellitus	10%	12%	11%	<0.0001
MI	35%	29%	32%	<0.0001
PVD	5.3%	5.6%	5.4%	0.562
Angioplasty	6%	10%	8%	<0.0001
Bypass surgery	3.7%	2.7%	3.2%	0.010
Smoking status				
Current	25%	29%	27%	<0.0001
Previous	60%	40%	50%	<0.0001
MVD	29%	28%	28.5%	0.089
Clinical diagnosis				
CSA	84%	49%	66%	<0.0001
UA	8%	35%	21%	<0.0001
AMI	8%	16%	12%	<0.0001
Vessel treated				
Proximal RCA	27%	34%	30.5%	<0.0001
Distal RCA	6.4%	6%	6.2%	0.493
Proximal LAD	20%	24%	22%	0.0003
Distal LAD	25%	20%	22.5%	<0.0001
Proximal LCx	6.2%	6.4%	6.3%	0.776
Distal LCx	15.4%	9.3%	12.3%	<0.0001

*Differences between the PTCA and stent populations. Data are presented as the median value (25th, 75th percentiles) or as percentages.
AMI = acute myocardial infarction; CSA = chronic stable angina; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; MVD = multiple-vessel disease; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; RCA = right coronary artery; UA = unstable angina.

Interaction terms between demographic data, clinical characteristics, QCA variables and stent use were introduced to evaluate the influence of coronary stents on the predictors of coronary restenosis. To prevent associations by chance, $p < 0.001$ was considered significant for these interaction terms. All variables were entered into the multivariate model, irrespective of the results of the univariate analysis (excluding the interaction terms in which the specified level of significance was not reached). The final multivariate model was constructed by backward deletion of the least significant variables, while the Akaike criterion was applied—that is, the applied threshold of significance depended on the degrees of freedom *(df)* associated with the variable at hand; if $df = 1$, then $p = 0.157$ (34). The predictive accuracy of the final multivariate model was evaluated using the C-index (35) and the goodness of fit of the model was tested with the Hosmer-Lemeshow goodness-of-fit test (36).

RESULTS

A total of 9,120 treated lesions in 8,156 patients were considered for this study. Sixty-four percent of the patients were treated with PTCA only (PTCA population: n =

5,230; 6,110 lesions), and coronary stents were implanted in 36% of patients (stent population: n = 2,926; 3,010 lesions).

The restenosis rate at six-month QCA follow-up was 35% after PTCA, compared with 19% after stenting. The baseline characteristics of the PTCA and stent populations are described in Table 1.

As might be expected (in such a heterogeneous population), the demographic data and clinical characteristics were significantly different across registries and trials. The patients' median age increased from 57 years in the oldest trial (CARPORT) to 62 years in the latest trial (MAGIC 5-L). The percentage of diabetic patients varied from 5.8% (MERCATOR) to 17% (Wallstent native); no temporal trend was observed for this condition. The prevalence of previous CABG varied from 1% (BENESTENT-1 and stent PAMI pilot) to 5.6% (MARCATOR).

The pre- and post-procedural and six-month follow-up QCA variables are described in Table 2. It is important to note that the restenosis rate decreased from 38% in PARK (1993, PTCA) to 12.8% in WEST-2 (1998, PTCA plus stenting). This decrease in the restenosis rate was observed despite a parallel increase in the length of treated lesions, from a median of 5.8 mm in MERCATOR (1992, PTCA) up to 14.3 mm in MAGIC 5-L (1999, PTCA plus

Table 2. Pre-Procedural, Post-Procedural and Six-Month Follow-Up Quantitative Coronary Angiographic Analysis of Treated Lesions

	PTCA Population	Stent Population	Pooled Group	p Value
No. of patients	5,230	2,926	8,156	
No. of treated lesions	6,110	3,010	9,120	
Pre-RD (mm)	2.65 (2.3, 3.02)	2.93 (2.64, 3.27)	2.75 (2.4, 3.12)	<0.0001
Lesion length (mm)	6.45 (5.03, 8.28)	8.94 (6.86, 12.38)	7.06 (5.4, 9.4)	<0.0001
Stent length (mm)	—	15 (15, 18)	15 (15, 18)	—
Pre-MLD (mm)	1 (0.81, 1.21)	0.98 (0.77, 1.18)	0.99 (0.79, 1.2)	0.0003
Post-MLD (mm)	1.77 (1.52, 2.05)	2.65 (2.38, 2.93)	2.02 (1.65, 2.5)	<0.0001
Pre-DS (%)	63 ± 15.8	69 ± 15	65 ± 15.7	<0.0001
Post-DS (%)	34 ± 9.6	16.7 ± 7.6	28 ± 12	<0.0001
Restenosis rate at 6-month follow-up (%)	35	19	27	<0.0001

Data are presented as the median value (25th, 75th percentiwles) or as the mean value ± SD.
Pre- and post-DS = pre- and post-procedural diameter stenosis; pre- and post-MLD = pre- and post-procedural minimal lumen diameter; pre-RD = pre-procedural reference diameter; PTCA = percutaneous transluminal coronary angioplasty.

stenting). The post-procedural minimal lumen diameter (post-MLD) increased as well, with median values ranked between 1.67 mm in PARK (1993, PTCA) to 2.89 mm in EASI (1997, PTCA plus stenting).

By univariate analysis (Fig. 1), stent use clearly showed a highly protective effect against restenosis (odds ratio [OR] 0.48, 95% confidence interval [CI] 0.43 to 0.53) when compared with PTCA alone. Interestingly, the interaction term for stent use was not significant when applied to demographic and clinical variables. For post-MLD, pre-procedural DS (pre-DS) and pre-RD, the interaction term between stent use and the predictor was highly significant (p = 0.0009, p = 0.0002 and p < 0.0001, respectively), meaning they have different predictive values in the PTCA and stent populations.

Favorable predictors common to the PTCA and stent populations were previous CABG, stent use, stent length <15 mm, stent length ≥15 mm and a large pre-procedural MLD (pre-MLD); unfavorable predictors were weight, body mass index, diabetes mellitus, multi-vessel disease, lesion length and a high residual post-DS. Predictors specific for the PTCA population were a large post-MLD as favorable and a severe pre-DS as unfavorable. Favorable predictors specific for the stent population were a large post-MLD and a large pre-RD.

In the multivariate analysis, the model with the best predictive accuracy and that best fit the entire population (Table 3) was composed of the following favorable predictors: stent use (OR 0.83, 95% CI 0.72 to 0.97), a large post-MLD (OR 0.53, 95% CI 0.46 to 0.61), previous CABG (OR 0.69, 95% CI 0.53 to 0.9) and the interaction term between stent use and a large post-MLD (OR 0.34, 95% CI 0.31 to 0.39); unfavorable predictors were lesion length (OR 1.05, 95% CI 1.04 to 1.06) and diabetes mellitus (OR 1.33, 95% CI 1.16 to 1.54). The Hosmer-Lemeshow goodness-of-fit test indicated that the model fit well with the data (goodness-of-fit statistic 2.81, p = 0.94).

The C-index for predictive accuracy initially demonstrated a poor ability for demographic and clinical charac-

teristics to discriminate between patients who did and those who did not develop coronary restenosis (C-index = 0.51), which subsequently improved slightly when the post-procedural variables (mainly QCA) were added to the final multivariate model (C-index = 0.63).

DISCUSSION

In this study, several clinical and QCA predictors of coronary restenosis were identified in a large number of patients in two distinct populations. Significant demographic and clinical predictors of restenosis did not differ between patients treated with PTCA alone and those with stents. In contrast, three QCA variables were differentially associated with restenosis. A large post-MLD was a favorable predictor in both the PTCA and stent populations, but the protective effect was more marked in the stent population. A severe pre-DS was an unfavorable predictor in the PTCA population only, and a large pre-RD was a favorable predictor in the stent population.

Clinical predictors. DIABETES MELLITUS. Patients with diabetes mellitus have been repeatedly shown to have an increased risk of developing restenosis, as compared with nondiabetics (37,38). The mechanisms responsible for the increased proclivity for restenosis in the diabetic patient are not completely understood. In an IVUS analysis, it was concluded that the main reason for increased restenosis in diabetic patients was exaggerated intimal hyperplasia in both stented and nonstented lesions (38). However, data from Van Belle et al. (39) do not support this hypothesis, but rather favor vessel remodeling (i.e., vessel constriction) as the main mechanism.

Alterations in the expression of components of the fibrinolytic system within the lesions of diabetic patients may also be an important determinant of restenosis. Sobel et al. (40) demonstrated, in a detailed immunohistochemical analysis of coronary atherectomy samples, a disproportionate elevation of concentrations of the prothrombotic plasminogen activator inhibitor type 1, which may induce

Age (per decade)
Men
Height (per 10 cm)
Weight (per 10 kgr)
BMI (per 5 kgr/m2)
HTA
DM
MI
PVD
Previous PTCA
Previous CABG
Current Smoking
Previous Smoking
CSA
UA
AMI
Prox. RCA
Dist. RCA
Prox. LAD
Dist. LAD
Prox. LCX
Dist. LCX
MVD
Stent use
Stent length < 15 mm
Stent length > 15 mm
Lesion length (mm)
MLD pre (mm)
MLD post (mm)
DS post (%)
DS pre (%)
RD pre (%)

OR: 0   0.25   0.5   0.75   1   1.25   1.5   1.75
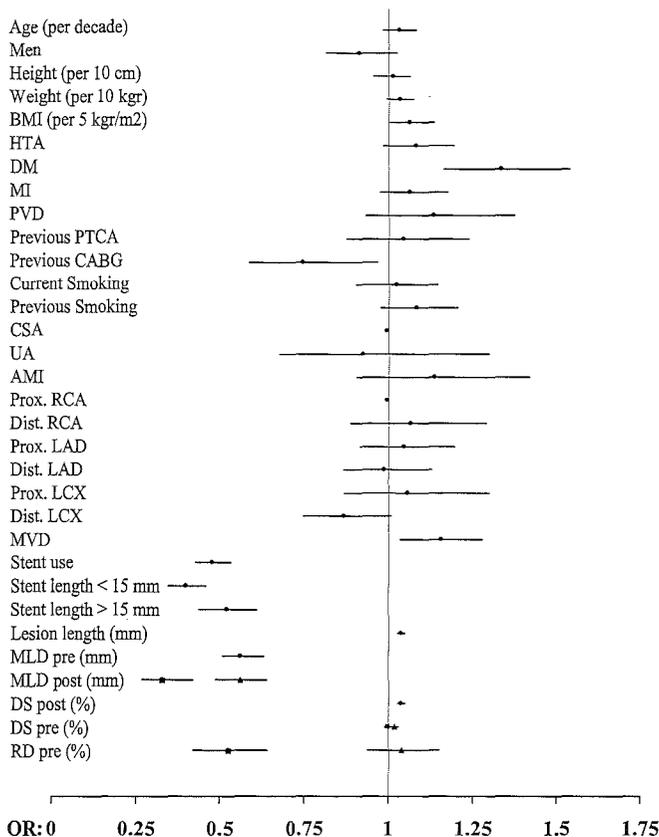
Figure 1. Univariate analysis of demographic, clinical and quantitative coronary angiography (QCA) predictors of coronary restenosis. When a common odds ratio (OR) is presented, the interaction term between stent use and each of the variables was not significant (p ≥ 0.001), and then this is the OR (and its corresponding 95% confidence interval [CI]) for the percutaneous transluminal coronary angioplasty (PTCA) and stent populations **(solid circles)**. The interaction term between stent use and each of the variables was significant (p < 0.001) if the PTCA **(solid triangles)** and stent **(solid squares)** populations each had two ORs (with 95% CIs) presented. AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass graft surgery; CSA = chronic stable angina; DM = diabetes mellitus; DS = diameter stenosis; HTA = hypertension; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; MLD = minimal lumen diameter; MVD = multi-vessel disease; PVD = peripheral vascular disease; RCA = right coronary artery; RD = reference diameter; UA = unstable angina.

restenosis by clot-associated mitogens. More recently, atherectomy specimens from restenotic lesions after PTCA showed a reduced intimal hypercellular tissue content in patients with diabetes (41). Collagen-rich sclerotic content

Table 3. Multivariate Analysis: Clinical and Quantitative Coronary Angiographic Predictors of Coronary Restenosis

Variable	OR	95% CI	p Value
Intercept coefficient = 0.12	—	—	—
Stent use	0.83	0.72–0.97	0.0193
Lesion length	1.05	1.04–1.06	<0.001
Post-MLD	0.53	0.46–0.61	<0.001
Previous CABG	0.69	0.53–0.9	0.006
Diabetes mellitus	1.33	1.16–1.54	<0.001
Stent use* post-MLD	0.34	0.31–0.39	0.002

*Interaction term between stent use and post-MLD. Hosmer and Lemeshow goodness-of-fit statistic = 2.81; p = 0.94; C-index = 0.63.
CABG = coronary artery bypass graft surgery; CI = confidence interval; post-MLD = post-procedural minimal lumen diameter; OR = odds ratio.

is increased, suggesting an accelerated fibrotic rather than a proliferative response in diabetics with restenosis after PTCA, putting into context again the fundamental importance of vessel remodeling in diabetics.

PREVIOUS CABG. In the present study, restenosis was less likely to occur in the subgroup of patients with previous CABG. Vein graft intervention was excluded from our analysis. We can only speculate about possible mechanisms leading to less restenosis in patients with previous CABG. Some baseline characteristics differed between patients with and those without previous CABG, such as a lower percentage of current smokers (14% vs. 26%) and a higher proportion of patients with chronic stable angina (85% vs. 75%). However, these variables did not independently predict restenosis by univariate analysis. The association is weak, and residual confounding factors may have played a role.

WEIGHT. Overweightness was positively associated with restenosis by univariate, but not by multivariate analysis. It may be argued that a potential relationship between obesity and restenosis is mediated through increased lipid levels. However, we found no association between total cholesterol, cholesterol subfractions and restenosis after successful PTCA by either a categorical or continuous approach (42).

CLINICAL DIAGNOSIS. We did not find the clinical diagnosis at the time of enrollment to be a predictor of restenosis in either the PTCA or stent populations. However, in patients treated with directional coronary atherectomy, clinical instability was associated with signs of plaque inflammation, which may promote restenosis (43).

Angiographic predictors. CORONARY STENTING. The protective effect of coronary stenting against restenosis was demonstrated unequivocally by two major randomized trials (27,44). Further improvements in the technique of stent deployment and new stent designs have also contributed to decreasing the restenosis rate (45).

PRE-RD. The pre-RD is a predictor of restenosis in the stent population, but not in the PTCA population. Because the implantation of stainless-steel stents invariably results in neointimal regrowth, >50% stenosis is more likely to occur in vessels of small diameter. Supporting this concept, Bauters et al. (3) showed that stenting in vessels with a small RD was not associated with a greater lumen loss.

POST-MLD. The post-MLD clearly influences restenosis development. The "bigger is better" paradigm proposed by Kuntz et al. (46) means that for every millimeter of increase in the post-MLD, there is an OR of 0.56 (95% CI 0.49 to 0.64) for restenosis in the PTCA population and an OR of 0.33 (95% CI 0.27 to 0.42) in the stent population. Our findings indicate that the additional gain in post-MLD for restenosis prevention is more relevant after stent deployment than after plain balloon angioplasty.

LESION LENGTH. Previous reports (5,47) have shown that lesion length was positively related with restenosis in PTCA alone and stented lesions. In these studies, lesion length was dichotomized with cut-off values ≥6.8 mm for patients treated with balloons and >15 mm for those treated with stents. In this study, we used a continuous approach for lesion length and for each millimeter of increase in length, we found an OR of 1.04 (95% CI 1.03 to 1.05) for lesions treated with both PTCA and stents.

STENT LENGTH. Our dichotomous approach for stent lengths ≤15 mm and stent lengths >15 mm, each compared to PTCA, indicated that the protective effect of stenting against coronary restenosis is reduced by ~12% when longer stents are used. Kobayashi et al. (48) similarly demonstrated, in an analysis of 1,090 lesions in 725 patients, that a progressively longer stented segment is associated with an increased risk of restenosis, with six-month restenosis rates of 24%, 35% and 47% for stented segment lengths ≤20, >20 to ≤35 and ≥35 mm, respectively. In a recent pooled analysis of four Multi-Link stent trials (49), stent length was found to be a significant predictor of restenosis both by univariate and multivariate analyses, and for each millimeter of increase in stent length, there was an or of 1.04 for restenosis development.

LOCATION OF TREATED LESION. The impact of the location of the treated lesion on restenosis has been described in previous PTCA (1) and stent (2) studies. Evidence is conflicting, but most often, it is claimed that LAD lesions are more prone to restenosis. In one study (1), an OR of 1.7 (95% CI 1.5 to 2.1) was found for proximal, as compared with nonproximal LAD lesions treated with PTCA alone in a sample of 2,500 patients. Another analysis of binary restenosis at follow-up in 1,399 lesions reported an OR of 1.31 for stented lesions in the LAD (2). In these two previous studies, a positive association was found, whereas others noted that the location of the stented lesion had no impact on restenosis after coronary stenting (3). After a detailed analysis, our results indicate that there is no evidence to support the idea that a given treatment location plays a role in the restenotic process.

Study limitations. Short- and long-term clinical and angiographic outcomes after PTCA and stenting certainly have improved over the past decade as a result of better stent deployment strategies and more effective antithrombotic regimens. Both balloon-expandable stents (Palmaz-Schatz [PS]-153: 8.7%; heparin-coated PS-153: 33%; MULTI-LINK: 9%; beStent: 4%; MULTI-LINK DUET: 5.2%; Crossflex: 9.2%; and BiodivYsio: 6.7%) and self-expanding stents (Magic Wallstent: 10.4%; Wallstent: 13.8%) were used, and we did not stratify for the potential influence of different stent types on restenosis.

New techniques, such as vascular brachytherapy (50) and drug-eluting stents (51), have become available recently. Patients treated with these modalities represent a distinctive population in which the results of our analyses should not be applied.

Conclusions. There are no major differences in demographic and clinical predictors of coronary restenosis between PTCA and stent populations. In the modern (stent) era, a severe pre-DS is no longer an unfavorable predictor of restenosis. Still important, but more so in the stent population, is a large post-MLD (optimal result). Finally, a larger pre-RD became a favorable predictor with the advent of stenting.

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Chapter 6

A meta-analytical approach for the treatment of in-stent restenosis

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Eur Heart J 2003; 24: 217-218

A meta-analytical approach for the treatment of in-stent restenosis

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As noted repeatedly, the treatment of in-stent restenosis remains one of the most vexing shortcomings in interventional cardiology. Coronary restenosis is often manifested by symptom recurrence, which is translated into an increased rate of repeat revascularization.

In this issue, Radke and colleagues[1] report the results of a well-conducted meta-analysis with data gathered from published reports of 28 different studies. These studies included a total of 3012 patients with in-stent restenosis treated with six different modalities (stent-in-stent, rotational atherectomy, balloon angioplasty, laser angioplasty, directional atherectomy and vascular brachytherapy) and their clinical outcome at a follow-up of 9±4 months. Any major adverse cardiac event (MACE) as defined by death, myocardial infarction, and target lesion revascularization (TLR) occurred in 30% of the patients, irrespective of the type of device used. In 90% of these cases, this MACE rate was driven by the need for TLR as a result of restenosis. In the meta-regression analysis, post-procedural diameter stenosis (DS post) was significantly correlated with the MACE rate. The lower the DS post, the lower the MACE rate.

After the adjustment of confounding factors (lesion length, pre-procedural diameter stenosis and diabetes), vascular brachytherapy was associated with a non-significant reduction of 16.9% in the probability of MACE, as compared to balloon angioplasty. The authors concluded that balloon angioplasty should be the preferred modality for the treatment of in-stent restenosis, particularly in focal lesions and that vascular brachytherapy should be considered in patients with diffuse in-stent restenosis.

Several other issues deserve further credit and are worth mentioning in the light of recently published data. First, the authors are to be commended for addressing the difficult issue of how to treat in-stent restenosis, an area where little randomized controlled clinical data is available. However, if one looks specifically at intracoronary radiation for in-stent restenosis, the authors included only four studies in this analysis.

These studies were two registries (Beta WRIST and Lausanne registry) and two randomized clinical trials (WRIST and GAMMA-1). In the mean time, several additional studies have emerged.[2–4] A pooled analysis from the β trials (Beta WRIST, START 30, START 40 and INHIBIT) showed a 33% relative reduction (RR) in MACE favouring brachytherapy. Similarly, a pooled analysis from the γ trials (SCRIPPS-2, WRIST, GAMMA-1, GAMMA-2, long WRIST, long WRIST high-dose and SVG WRIST) demonstrated a 36% RR and finally, when pooling the β and γ trials, altogether, a 35% RR was exhibited. These data clearly support vascular brachytherapy as the preferred treatment of in-stent restenosis.

Second, comparing individual treatment modalities (stent-in-stent, rotational atherectomy, laser angioplasty, directional atherectomy and vascular brachytherapy) to balloon angioplasty without taking into account the angiographic pattern of in-stent restenosis may be inappropriate. In this respect, the authors fall short in correlating the angiographic presentation (lesion length and

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geographic location of neointimal proliferation relative to the initially implanted stent) of in-stent restenosis (focal, diffuse intrastent, diffuse proliferative or total occlusion) with the subsequent need for TLR, which in turn, is the clinical event that mainly drives the MACE rate, as previously mentioned. The pre-intervention angiographic pattern of in-stent restenosis is a powerful predictor of future TLR; as the 1-year rate of TLR increases in parallel with increasing severity of angiographic in-stent restenosis, ranging from 19% for patients with focal in-stent restenosis to 83% for patients with total occlusions.[5]

Finally, registry data on sirolimus-eluting stents for the treatment of in-stent restenosis have also become recently available, and thus far 41 patients (16 in Rotterdam, The Netherlands and 25 in Sao Paulo, Brazil) were treated with a sirolimus-eluting stent for in-stent restenosis. The 1-year MACE rate in these patients was 9.8%. These results, although based on a small number of patients, are extremely encouraging and should pave the way for randomized clinical trials of drug-eluting stents for the treatment of in-stent restenosis, which perhaps will be its most important and ultimate challenge.

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Chapter 7

Clinical and angiographic predictors of restenosis following stent deployment in diabetic patients

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Submitted for publication

Clinical and angiographic predictors of restenosis following stent deployment in diabetic patients.

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Running title: Diabetic in-stent restenosis

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Abstract

Background: Restenosis and consequent adverse cardiac events are increased in diabetics undergoing percutaneous coronary intervention. Use of intracoronary stents may ameliorate such risks; however, factors influencing the likelihood of restenosis following stent deployment in this high-risk patient subgroup are unknown.

Methods and Results: We retrospectively analyzed all stented diabetic patients from the ADVANCE, BENESTENT I, BENESTENT II pilot, BENESTENT II, DUET, EASI, EXCITE, FINESS 2, MAGIC 5L, MUSIC, ROSE, SOPHOS, TRAPIST, WEST 1, WEST 2 and WELLSTENT native studies. Univariate and multivariate analyses, with 37 clinical and angiographic variables, compared those with and without restenosis, and predicted restenosis rates calculated using reference charts derived from angiographic data. Within the studies, 418/3090 stented patients with 6 month angiographic follow-up (14%) had diabetes. Restenosis ($\geq$50% diameter stenosis at follow-up) occurred in 550/2672 non-diabetic (20.6%) and 130/418 (31.1%) diabetic patients (p<0.001). Univariate predictors of restenosis in those with diabetes were vessel reference diameter (RD) (p<0.001), minimal luminal diameter (MLD) before stenting (p=0.01), MLD and % diameter stenosis after stenting (p<0.001, p=0.04), stented vessel length (p<0.001), and lower body mass index (BMI) (p=0.04). Using multivariate analysis, only RD (p=0.003), stented length (p=0.04) and lower BMI (p=0.04) were associated with restenosis. Reference charts demonstrated an incremental risk of restenosis dependent solely on vessel reference diameter

Conclusions: Restenosis following stent deployment is significantly increased in diabetic patients; vessel calibre, stented vessel length and lower BMI are predictors of in-stent restenosis in patients with diabetes.

Condensed abstract

We sought to identify clinical and angiographic factors associated with in-stent restenosis in patients with diabetes mellitus. Stented diabetic patients from the ADVANCE, BENESTENT I, BENESTENT II pilot, BENESTENT II, DUET, EASI, EXCITE, FINESS 2, MAGIC 5L, MUSIC, ROSE, SOPHOS, TRAPIST, WEST 1, WEST 2 and WELLSTENT native studies were analyzed. In the studies, 418/3090 patients were diabetic; restenosis occurred in 20.6% of non-diabetics and 31.1% of diabetics. By multivariate analysis, vessel diameter, stented length and lower body mass index were associated with in-stent restenosis in diabetics. Moreover, there was an incremental increase in restenosis risk as vessel diameter decreased.

Introduction

Patients suffering from diabetes mellitus have a substantially higher cardiovascular mortality than the general population, even after adjustment for confounding factors [1,2]. Coronary angiographic studies have demonstrated higher incidences of multivessel and left mainstem disease in diabetics [3,4], as well as more distal disease with a higher plaque burden, smaller vessel reference diameter and poorer collateral formation [5-9]. Such propensity for coronary disease may be related to an underlying atherosclerosis-prone state involving such factors as endothelial dysfunction, dyslipidaemia, hyperglycaemia, insulin resistance and the presence of advanced glycosylation end-products [10-16]. The increasing incidence of diabetes (reaching epidemic proportions) [17] has important implications for the management of coronary artery disease in this patient subset.

Diabetes has been shown to be a predictor of poor outcomes in all modes of coronary revascularization, and therefore the optimal treatment strategy for these patients remains unclear. Randomized trials of PCI versus coronary artery bypass graft surgery (CABG) for multivessel disease in diabetics (BARI, EAST, ARTS) have consistently demonstrated a benefit for CABG in terms of symptomatic relief of angina, freedom from subsequent cardiac events and absolute survival [18-21]. Factors influencing this observed benefit include the increased rates of occlusive-type restenosis [22] and of new lesion formation in diabetic patients [23] following PCI. Procedural success rates for single-vessel PCI have been demonstrated to be similar for diabetic and non-diabetic individuals [24-26] and currently-available data suggests that stent deployment decreases restenosis and cardiac event rates in diabetic patients [24,26,27].

However, there is little data regarding the differences between those diabetics who develop restenosis following stent deployment and those who do not; whether diabetics are at higher risk owing to longer lesions, smaller vessel calibre and

therefore higher restenosis rates or whether simply being diabetic adds a constant increment to restenosis risk to all patients, is unclear.

This study evaluates patients from 16 interventional trials, using multivariate analysis to determine clinical and angiographic factors that might be associated with diabetic in-stent restenosis.

Methods

Patient population

All patients from 16 percutaneous coronary interventional (PCI) studies including stent deployment were considered for analysis [28-43]. Of these studies, three were randomized trials of stent deployment versus balloon angioplasty (ADVANCE, BENESTENT I, BENESTENT II), ten were registries of newer stent designs (BENESTENT II pilot, DUET, EASI, FINESS 2, MAGIC 5L, ROSE, SOPHOS, WEST 1, WELLSTENT), two assessed the efficacy of intravascular ultrasound guided stent implantation (MUSIC, WEST 2) and two assessed the efficacy of novel oral treatments to prevent restenosis following PCI (EXCITE, TRAPIST) (abbreviations and acronyms – table 1).

Baseline characteristics of patients enrolled in these studies have been published. BMI was calculated by dividing an individual's weight in kilograms by the height in meters squared (kg/m2). According to the WHO classification, a BMI between 18.5 and 24.9 was considered normal, between 25 and 30 overweight, and a BMI greater than 30 was considered obese [44,45]. All clinical information was monitored and forwarded to the core laboratory (Cardialysis, Rotterdam) and entered into the study databases. Studies were approved by institutional ethics committees and written informed consent was obtained from all patients.

All patients who received intracoronary stents, underwent 6-month angiographic follow-up and had complete clinical and angiographic data were included in the final analysis. Angiographic restenosis, defined as $\geq$ 50% diameter stenosis at the treated site, was determined for diabetic and non-diabetic cohorts within each of the included studies. Univariate analyses were performed using 37 clinical and angiographic factors to establish whether any were predictive of restenosis in the overall diabetic cohort; significant findings were then entered into a multivariate analysis to remove confounding factors.

Reference charts to predict 6 month in-stent restenosis were constructed, using RD pre-procedure and stented length post-procedure as variables, as previously described [46]. Based on the data available, a statistical model was constructed to predict the probability of restenosis for given parameters. In general, probability of restenosis increases continuously for smaller RD and longer stented lengths. In order to visualize this, ranges designed to examine the data categorically rather than continuously were defined. As an estimate of the probability of restenosis in each category, the midpoint of the intervals was used, on the assumption that within each interval, the probability of restenosis is constant. A reference chart with a probability for restenosis in each interval/range was thereby generated, providing probabilities rather than actual/measured rates in the input dataset.

Angiographic analysis

All procedural and follow-up angiograms were sent to the core laboratory (Cardialysis, Rotterdam, The Netherlands) and analysed by the Cardiovascular Angiography Analysis System, which has previously been validated. For each patient, multiple matched angiographic views were obtained after intracoronary administration of nitrate. Patients with an unsuccessful procedure or without angiographic follow-up were excluded from the analysis. For patients who had undergone multi-lesion coronary angioplasty, the most severe restenotic lesion at follow-up was entered into the analysis. The MLD and RD obtained by an interpolated method were determined on an end-diastolic frame.

Statistical analysis

Statistical analysis was performed using the SAS software package (SAS Institute, Cary, North Carolina). Continuous variables were compared using Student's t test and the categoric variables by the Fisher's exact test. We performed a logistic regression on the dependent variable Y, where Y=1 for diabetic patients with

restenosis and Y=0 for patients without restenosis. As explanatory variables we considered 37 clinical and angiographic variables. We executed a univariate logistic regression defined by the formula $\text{Log} (P[Y=1] / (P[Y=0])) = A + B*X$, with X as the explanatory variable, A the intercept, and B the regression parameter. Multivariate logistic regression defined by the formula $\text{Log} (P[Y=1] / (P[Y=0])) = A + B(1)*X(1) + B(2)*X(2) + \ldots + B(n)*X(n)$ with $X(1),\ldots,X(n)$ as the explanatory variables, A the intercept and $B(1),\ldots,B(n)$ the regression parameters was then performed. With the stepwise procedure a group of explanatory variables was selected that as a group were multivariate significant. A p value of <0.05 was considered significant.

Results

In the 16 studies analyzed, 3090 patients received intracoronary stents and completed planned 6 month follow-up angiography. The proportion of diabetics and individual restenosis rates for the included trials are summarized in table 2. Of the overall population, 418 were diabetic, in whom a total of 467 lesions were treated with PCI. Restenosis, defined as ≥ 50% diameter stenosis at follow-up, was significantly increased in the diabetic population (550/2672 (20.6%) non-diabetic patients compared with 130/418 diabetics (31.1%); p<0.001) (table 2).

By univariate analysis, favorable predictors of in-stent restenosis in diabetics were RD (OR=0.40 [95% CI 0.25-0.63]; p=0.0001) and MLD (OR=0.46 [0.25-0.83]; p=0.01) before stenting, MLD (OR=0.37 [0.23-0.60]; p=0.0001) and RD (OR=0.45 [0.28-0.71]; p=0.0008) after stenting, and higher BMI (OR=0.94 [0.89-1.00]; p=0.04]. Unfavorable predictors of restenosis were percentage diameter stenosis after stenting (OR=1.03 [1.00-1.06]; p=0.04) and stented vessel length (OR=1.04 [1.02-1.06]; p=0.0008) (table 3). By stepwise multivariate logistic regression analysis, only RD before stenting (p=0.003; OR 0.38), stented length of vessel (p=0.04; OR 0.92) and lower BMI (p=0.04; OR=1.03) predicted restenosis in diabetics.

Cumulative frequency curves for MLD and % diameter stenosis at 6-month follow-up angiography were similar for diabetic and non-diabetic patients (Figure 1).

Reference charts to predict 6 month rates of in-stent restenosis were constructed using pre-procedure RD and stented length post-procedure as variables (Figure 2). Diabetic patients, as expected, had an increased frequency of restenosis for all vessel RD and stented lengths. When non-diabetic values were subtracted from diabetic predicted restenosis rates, a 'subtraction' graph was constructed, removing the baseline effect of non-diabetic restenosis in order to investigate the effect of diabetes alone. The striking finding was that vessel RD, rather than stented vessel

length appeared to govern the increased rate of restenosis, with rates being constant across the range of RD (Figure 3). There was a basic 6% increase in predicted restenosis rate for all diabetics, with further increments of an additional 3% for vessel RD between 2.65 and 3 mm and a further 4% for RD less than 2.65 mm. This gives overall additional restenosis rates over and above the risk for non-diabetic individuals of 6% for larger vessels, 9% for intermediate-sized vessels and 13% for small vessels.

Discussion

Large studies of patients undergoing percutaneous coronary intervention with planned 6 month angiographic follow-up have identified the clinical and angiographic predictors of restenosis [7]. These studies have also demonstrated that angiographic restenosis is more frequent than clinically driven repeat target lesion revascularisation [47,48]. Our analysis demonstrates that diabetic patients develop in-stent restenosis significantly more frequently than non-diabetics 6 months post-intervention. Our finding that 31.1% of diabetic patients develop restenosis at 6 months concurs broadly with the studies of Van Belle et al. [27], where restenosis in stented diabetics was 27% at 6 months, and that of Elezi et al. [26], where the restenosis rate was 37.5%. Furthermore, the occurrence of in-stent restenosis in diabetics signifies a worse prognosis in terms of both cardiac morbidity and overall mortality [22]. Clinical outcomes were not specifically investigated in this study; given increased restenosis in diabetics compared with non-diabetics and the known correlation of restenosis with coronary events, it would be expected that diabetics should fare less well than their non-diabetic counterparts following intracoronary stenting in terms of event-free suvival and mortality, as has been borne out in previous clinical studies [24,26].

In this series of patients enrolled in 16 PCI studies, univariate predictors of in-stent restenosis in diabetics were: indices of vessel calibre (RD pre- and post-PCI, MLD pre- and post-PCI), percentage diameter stenosis after stenting, stented vessel length and lower BMI. By multivariate analysis, only RD pre-procedure, stented vessel length and lower BMI were predictors of restenosis in diabetics. Both vessel calibre and stent length are determinants of restenosis in non-diabetic patients also, but hitherto, BMI has not been described as influencing restenosis. It is also interesting that lower BMI was associated with increased restenosis, although by WHO criteria, both groups were, on average, overweight but not obese, and the

absolute difference in BMI between the two groups was small (mean BMI without restenosis 28.9, mean with restenosis 27.9). It is interesting to speculate on the interpretation of such a result; whether the lower BMI in the restenosis group might reflect a smaller body habitus with consequent smaller coronary vessel calibre is unclear, as height was not recorded. Further studies might seek to elucidate the reason for this finding and explore the relationship between BMI, vessel calibre and restenosis risk.

Vessel calibre was a predictor of restenosis in this study; previous authors have described increased risk of restenosis for percutaneous intervention to small vessels [49], a risk that may not be offset by coronary stent placement in diabetics [50]. Our data suggest that vessel calibre is the principal determinant of in-stent restenosis in diabetic patients, with an escalating risk not affected by stented vessel length. This finding concurs with the findings of Kastrati et al. [51] and of Ormiston et al. [52], who described no effect of stented vessel length on risk of restenosis, including after deployment of long (25-35 mm) stents.

Not only does diabetes and its atherogenic vascular milieu influence the risk of restenosis following vascular injury such as stent deployment, but also this may be dictated by the antidiabetic drugs employed. Novel thiazolidinedione agents demonstrate greater inhibition of arterial smooth muscle cell proliferation than biguanides and sulphonylureas [53] and have been shown in preliminary trials to be effective in preventing restenosis [54]. As we do not have data on the split within our study population between diet-controlled, insulin or non-insulin-dependent diabetics and in the latter case on the type of oral antidiabetic therapy employed, it is difficult to comment on how these variables may have affected our findings.

Study limitations

Although there was some standardization of clinical and angiographic data collection, only data common to all 16 study databases were included in the analysis. Furthermore, in these studies, diabetes was recorded as a binary (yes/no) variable and therefore we cannot accurately define whether these results apply strictly to insulin-dependent or non-insulin-dependent diabetes mellitus, nor to the mode of treatment (diet/oral hypoglycaemic agents/insulin). In addition, exclusion criteria for PCI studies mean that this study population was carefully selected and probably at lower risk for restenosis than an unselected "everyday" PCI population. Finally, it should be noted that the different trials that make up this study population used different stent types, including both balloon-expandable and self-expanding designs. All stents used in these populations were bare metal stents, and it is possible that these results may not be applicable to current practice in view of the expanding implementation of the use of drug-eluting stents, a strategy that appears to be equally as effective in preventing major adverse cardiac events and restenosis in this high-risk patient subgroup [55].

Conclusions

Coronary in-stent restenosis following PCI occurs more frequently in diabetic individuals than non-diabetics. Predictors of in-stent restenosis at 6 months post-procedure by multivariate analysis are vessel calibre, stented vessel length and low BMI. The rate of restenosis calculated by constructed reference charts demonstrated that vessel RD was the principal determinant of restenosis, with rates of 6%, 9% and 13% over non-diabetic restenosis rates for large, medium and small-sized vessels respectively.

Acknowledgements

We would like to thank all investigators who participated in the 16 studies analysed. We also acknowledge the sponsoring companies for their support and the Cardialysis core laboratory technicians and database managers.

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ADVANCE	Additional stenting after balloon angioplasty for long lesions study
BENESTENT	Belgium & Netherlands stent study
DUET	Evaluation of the ACS-Multilink DUET coronary stent system
EASI	European Antiplatelet Stent Investigation
EXCITE	Evaluation of oral Xemilofiban in Controlling Thrombotic Events
FINESS 2	First International NIR Endovascular Stent Study
MAGIC 5L	Influence of Magic Wallstent length on restenosis
MUSIC	Multicenter Ultrasound Stenting in Coronaries study
ROSE	Registry for Optimal Stent Evaluation
SOPHOS	Study of Phosphorylcholine on Stents
TRAPIST	Trapidil for Prevention of In-Stent Restenosis
WEST 1,2	West European Stent Trial
WELLSTENT	Self-expanding Wallstent for longer native coronary lesions study

Table 1. Abbreviations and acronyms for trials included in this study.

	n with QCA followup			Restenosis rates (%)		
	Non-diabetic	Diabetic	(%)	Non-diabetic	Diabetic	p value
ADVANCE	76	13	14,6	26,3	46,2	0,19
BENESTENT I	221	16	6,8	21,3	25,0	0,75
BENESTENT II pilot	178	14	7,3	11,2	21,4	0,23
BENESTENT II	161	33	17,0	15,5	27,3	0,13
DUET	161	24	13,0	16,1	20,8	0,56
EASI	220	29	11,6	15,5	31,0	0,06
EXCITE	435	91	17,3	26,4	34,1	0,16
FINESS 2	109	29	21,0	18,3	24,1	0,60
MAGIC 5L	217	32	12,9	39,6	34,4	0,70
MUSIC	127	17	11,8	11,0	0,0	0,37
ROSE	92	16	14,8	18,5	37,5	0,10
SOPHOS	157	22	12,3	16,6	27,3	0,24
TRAPIST	231	35	13,2	24,2	48,6	0,004
WEST 1	87	8	8,4	11,5	12,5	1,00
WEST 2	129	21	14,0	9,3	33,3	0,007
WELLSTENT NATIVE	71	18	20,2	31,0	44,4	0,40
Total	**2672**	**418**	**13,5**			
Overall				**20,6**	**31,1**	**<0.001**

Table 2

	No restenosis	(%)	Restenosis	(%)	P	OR	95% CI	P
						Univariate analysis		
n=	288		130					
Demographics								
Age, mean (range), y	61.6 (40.0-82.9)		63.2 (38.4-81.1)		0,11			0,11
Male sex	221	76,7	93	71,5	0,27			0,26
Body Mass Index, mean (range)	28.9 (17.7-41.7)		27.9 (20.3-37.3)		0,03	0,94	0.89-1.00	0,04
Risk factors								
Hypertension	111	48,7	49	49,5	0.90			0,89
Hypercholesterolemia	125	54,8	53	53,5	0.90			0,83
Never smoked	81	28,1	35	26,9	0,91			0,80
Ex-smoker	138	47,9	70	53,8	0,29			0,26
Current smoker	69	24,0	25	19,2	0,31			0,28
Family history	71	34,8	33	36,3	0.90			0,81
Anginal status at screening								
Silent ischemia	8	3,5	3	3,1	1.00			0,84
Stable angina	128	56,4	57	58,8	0,71			0,69
Unstable angina	91	40,1	37	38,1	0.80			0.80
Vascular disease at screening								
Previous MI	80	35,1	39	39,4	0,46			0,46
Q waves on ECG	26	17,9	10	21,3	0,67			0,61
Previous CABG	8	3,5	5	5,1	0,54			0,51
Previous PCI	33	14,5	14	14,1	1.00			0,94
Peripheral vascular disease	16	7,6	12	12,1	0,21			0.20
Medications at screening								
Beta blocker	79	59,4	26	60,5	1.00			0.90
Nitrate	87	65,4	29	67,4	0,86			0,81
Calcium channel blocker	62	46,6	14	32,6	0,11			0,11
Aspirin	112	91,8	35	87,5	0,53			0,42
ACE inhibitor	25	21,6	14	32,6	0,21			0,15
Diuretic	14	12,1	4	9,3	0,78			0,63
Heparin	13	12,4	3	7,5	0,56			0,41
Warfarin/Coumadin	3	2,9	2	5,0	0,62			0,53
Coronary angiography								
Multivessel disease	69	30,3	29	29,3	0.90			0,86
Left mainstem lesion	0	0,0	2	1,6	1.00			0,99
LAD lesion	130	48,1	56	43,4	0,39			0,38
Circumflex lesion	79	29,3	32	24,8	0.40			0,35
Right coronary lesion	102	37,8	52	40,3	0,66			0,63
RD pre-PCI, mean (range), mm	2.9 (1.6-5.5)		2.7 (1.6-4.0)		<0.001	0.40	0.25-0.63	0,0001
% DS pre-PCI, mean (range)	64.7 (39.0-100.0)		65.6 (31.0-100.0)		0,48			0.44
MLD pre-PCI, mean (range), mm	1.0 (0.0-2.1)		0.9 (0.0-2.4)		0,02	0.46	0.25-0.83	0.01
Lesion/stented length, mean (range), mm	12.1 (2.2-47.6)		15.3 (2.8-53.6)		0,003	1.04	1.02-1.07	0.0008
RD post-PCI, mean (range), mm	3.2 (1.8-4.4).		3.0 (2.0-4.7)		<0.001	0.45	0.28-0.71	0.0008
% DS post-PCI, mean (range)	15.7 (2.0-42.0)		17.4 (0.5-52.0)		0.05	1.03	1.00-1.06	0.04
MLD post-PCI, mean (range), mm	2.7 (1.2-3.9)		2.5 (1.1-4.1)		<0.001	0.37	0.23-0.60	0,0001

Table 3
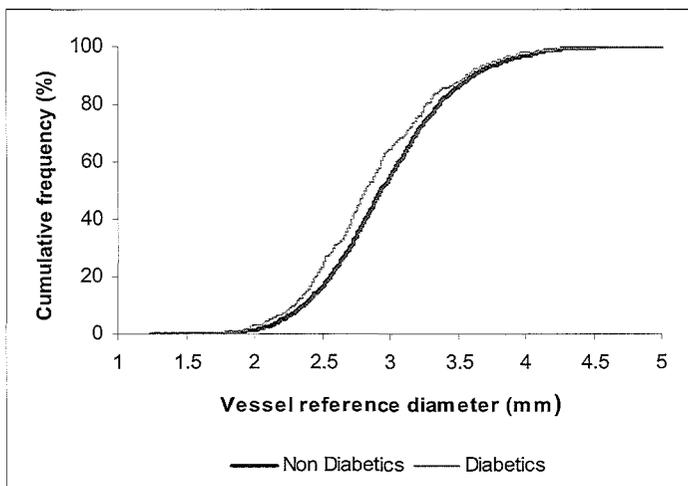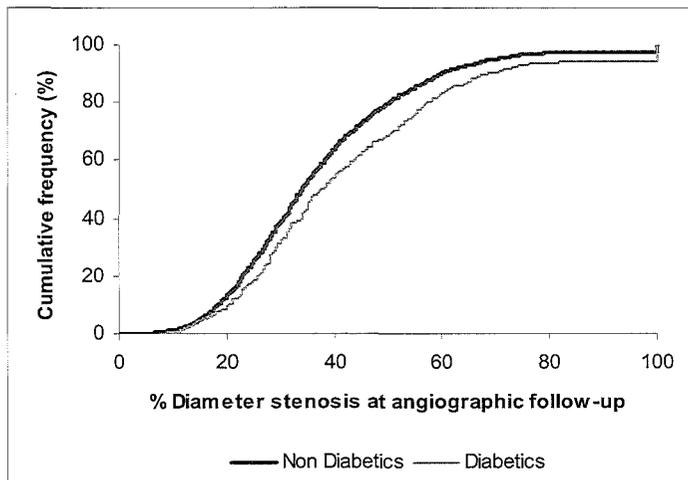
Figure 1. Cumulative frequency curves for % diameter stenosis (top panel) and vessel RD comparing diabetic and non-diabetic patients at 6-month angiographic follow-up.
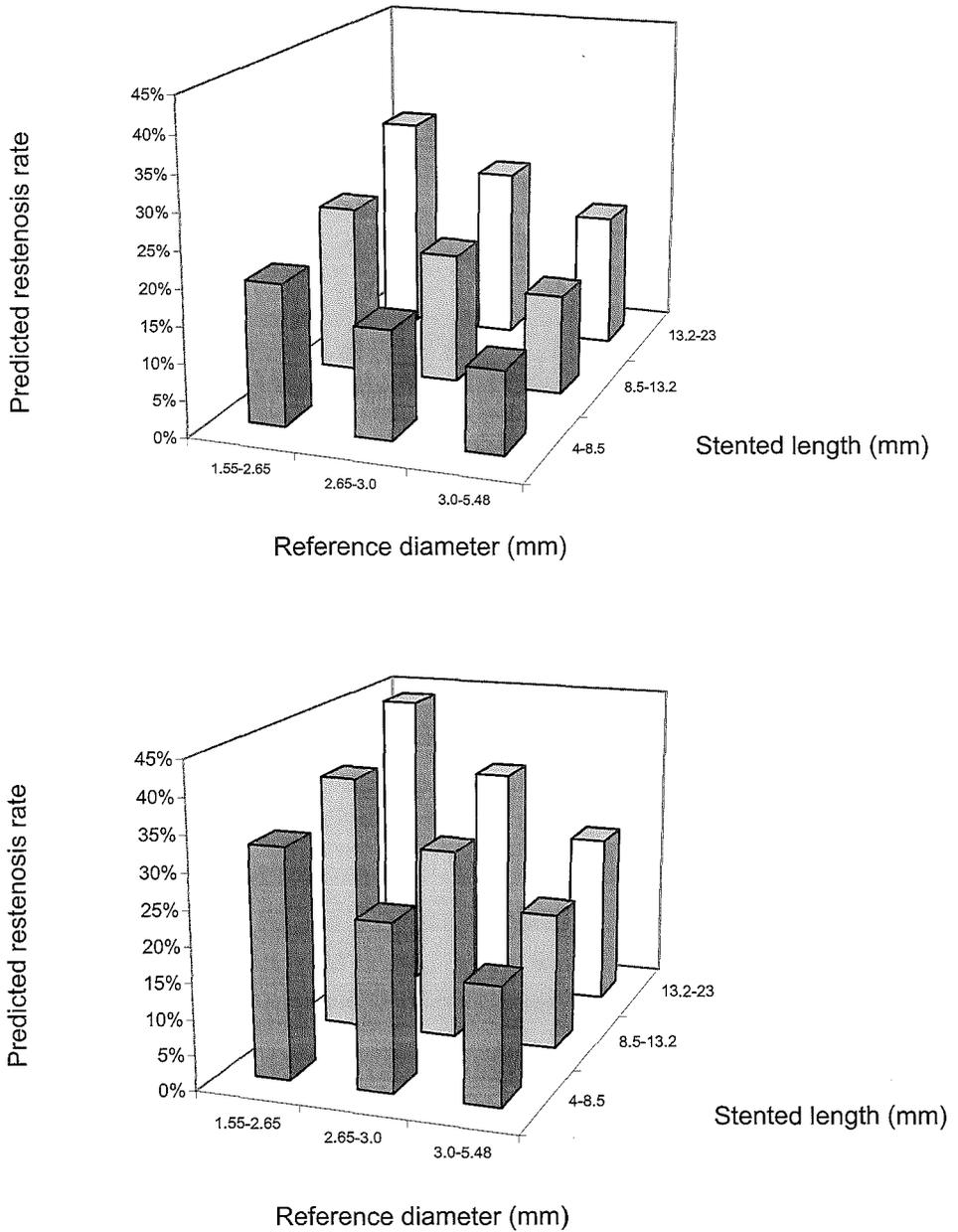
Figure 2. Reference charts constructed to predict 6 month in-stent restenosis rates for non-diabetic (top panel) and diabetic patients (bottom panel).
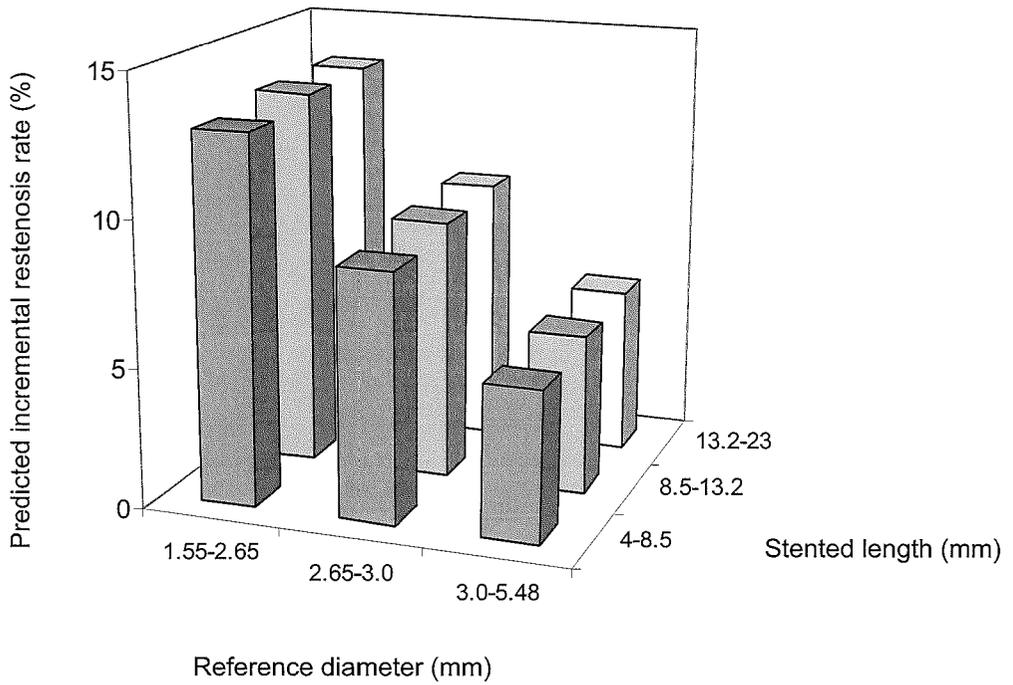
Figure 3. Subtraction graph derived from subtraction of non-diabetic predicted risk of restenosis from diabetic predicted risk, generating incremental risk for effect of diabetes alone on restenosis.

Part 3: Special subgroups on coronary revascularization

Chapter 8

The Impact of Body Mass Index on the Outcome of Patients With Multivessel Disease Randomised to Either Coronary Artery Bypass Surgery or Stenting in the ARTS Trial: The Obesity Paradox II?

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The Impact of Body Mass Index on the Outcome of Patients With Multivessel Disease Randomized to Either Coronary Artery Bypass Surgery or Stenting in the ARTS Trial: The Obesity Paradox II?

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STRUCTURED ABSTRACT

Objectives: The purpose of this study was to evaluate the impact of body mass index (BMI) on the long-term outcomes in patients with multivessel coronary artery disease randomized to either stenting or coronary artery bypass surgery (CABG).

Background: Obesity is considered one of the major modifiable risk factors for coronary heart disease. However, the impact of BMI on the outcomes after coronary artery revascularization remains controversial.

Methods: We studied 1,203 patients with multivessel coronary artery disease who underwent either stenting (n=599) or CABG (n=604) in the Arterial Revascularization Therapies Study (ARTS). Patients were divided into three groups according to BMI: normal BMI between 18.5 and 24.9, overweight with a BMI between 25 and 30 and obese with a BMI greater than 30.

Results: At three-years follow-up, the incidence of death or cerebrovascular events or myocardial infarction was similar for each one of the three BMI categories, regardless the revascularization technique employed. Repeat revascularization procedures were significantly higher among patients randomized to stenting, but similar among the different BMI groups. For patients randomized to CABG, there was a trend towards lower repeat revascularization procedures in obese patients (p=0.07). Among patients who underwent stenting, BMI had no impact on the three-year combined endpoint of major adverse cardiac or cerebrovascular events (MACCE) rates. Among patients who underwent CABG, MACCE rates were significantly lower for obese (11%) or overweight (15%) patients compared to normal BMI patients (23%)(p=0.012).

Conclusions: In a large cohort of patients with multivessel coronary artery disease who underwent either surgical or percutaneous revascularization, BMI had no impact on the three-year outcome of patients who underwent stenting. Conversely, among patients who underwent CABG, overweight and obese patients had a significantly better outcome than normal BMI patients regarding MACCE-free survival, mainly due to lower rates of repeat revascularization procedures. Therefore, obesity should not be a factor favoring stenting in multivessel disease.

CONDENSED ABSTRACT

We analyzed the impact of body mass index on the long-term outcomes of 1,203 patients who underwent either multivessel stenting or coronary artery bypass surgery in the Arterial Revascularization Therapies Study. Overall three-year survival or survival without cerebrovascular events or myocardial infarction was similar among the different body mass index groups, regardless of the type of revascularization procedure. There was no significant difference in terms of death, cerebrovascular events, myocardial infarction or repeat revascularization procedures in normal body mass index patients who underwent either stenting or surgical revascularization. However, for patients who underwent surgical revascularization, event-free survival was significantly better for obese or overweight patients compared to normal body mass index patients, mainly due to a lower rate of repeat revascularization procedures. Among patients who underwent stenting, body mass index had no impact on the three-year outcomes.

ABBREVIATIONS

ARTS = Arterial revascularization Therapies Study

BARI = Bypass Angioplasty Revascularization Investigation

BMI = Body mass index

CABG = Coronary artery bypass graft

CK-MB = Creatinine kinase myocardial band fraction

MACCE = Major adverse cardiac or cerebrovascular events

MI = Myocardial infarction

PCI = Percutaneous coronary intervention

INTRODUCTION

Excess body fat, overweight and obesity have become major public, medical and social concerns of our times. In the last two decades the prevalence of this metabolic disorder has increased significantly, and according to recent data, it affects more than 61% of the adult population (1,2). Obesity is associated with a variety of diseases, including hypertension, non-insulin dependent diabetes mellitus, cardiovascular and cerebrovascular disease, dyslipidemia, cancer and sleep disorders (3). Diets high in fat and calories and a sedentary lifestyle with reduced physical activity are more likely to be blamed for this increase in the prevalence of obesity (4,5). In view of epidemiological studies that have linked obesity and cardiovascular disease, the American Heart Association has included obesity as one of the major modifiable risk factors for coronary heart disease on par with cigarette smoking, physical inactivity and elevated blood cholesterol levels (6,7). Although long-term longitudinal studies have also shown that obesity is associated with excess cardiovascular morbidity and mortality (7,8), there is limited data on coronary artery revascularization and obesity. Recent studies have shown that in patients with known coronary artery disease who undergo percutaneous coronary artery revascularization, patients with body mass index (BMI) within the normal range are at the highest risk for in-hospital complications and cardiac death (9,10) as compared to patients with elevated BMI. Furthermore, overall one-year mortality rates and cardiac related-deaths were significantly higher in these patients, compared to overweight or obese patients (9,10). However, data from the randomized and observational registry of the Bypass Angioplasty Revascularization Investigation (BARI) (11) has shown that among patients who underwent coronary artery

bypass graft surgery (CABG), an increased BMI is associated with a worse long-term outcome after CABG, but not after percutaneous coronary intervention (PCI). Currently, no definite conclusion can be obtained regarding the impact of BMI on the outcome after PCI or following CABG.

The Arterial Revascularization Therapies Study (ARTS) was a multicenter, randomized trial that was designed to compare PCI with stenting versus CABG in patients with multivessel coronary artery disease. The purpose of the present analysis was to assess the impact of BMI on the three-year outcomes following multivessel stenting or CABG in patients who participated in the ARTS trial.

METHODS

Study Design

A total of 1,205 patients with multivessel coronary artery disease, who were considered to be equally treatable with both modalities, were randomized to either stenting (n=600) or CABG (n=605) between April 1997 and June 1998 at 67 participating centers worldwide as parts of the ARTS trial. Details of this study have been described previously (12,13). In brief, patients who had not had a previous revascularization procedure were included in the study. Inclusion criteria included stable or unstable angina, silent ischemia, and at least two new lesions that were located in different vessels and territories that were potentially amenable to stent implantation. Exclusion criteria included left main disease, reduced left ventricular function (<30%), overt heart failure, prior cerebrovascular accident, recent myocardial infarction (less than a week), severe hepatic and renal dysfunction or the need for major concomitant surgery. Conventional balloon angioplasty was permitted in

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vessels with a diameter 1.50 mm and 2.75 mm, as complementary to stenting, if at least two substantial lesions were targeted for stenting (each patient required to have more than one stent). Bypass surgery was performed according to standard techniques, preferably using the left internal mammary to graft the left anterior descending coronary artery.

Clinical Definitions

The National Heart, Lung, and Blood Institute and the World Health Organization have introduced a weight classification for BMI, which is calculated by dividing an individual's weight in kilograms by the height in meters squared (kg/m^2). According to their classification, a BMI between 18.5 and 24.9 was considered normal, between 25 and 30 overweight, and a BMI greater than 30 was considered obese (14,15). Clinical and angiographic data were analyzed and adjudicated by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands). Myocardial infarction was defined in the presence of documented new Q-waves and either a ratio of serum creatinine kinase MB (CK-MB) isoenzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value greater that 5 times normal values. Non Q-wave myocardial infarction after PCI was defined as a creatinine kinase MB enzyme elevation at least 5 times the upper normal value without new Q waves. Major adverse cardiac or cerebrovascular events (MACCE), defined as death; stroke, transient ischemic attacks and reversible ischemic neurological deficits; documented nonfatal myocardial infarction; and repeated revascularization either percutaneous or surgical was the primary endpoint of this study.

Statistical Analysis

Continuous variables are expressed as mean ± 1 standard deviation and categorical variables as percentages. Comparisons among the groups were performed by analysis of variance (ANOVA) for independent samples and the chi-square test for comparison of categorical values. Event-free survival was estimated by the Kaplan-Meier method, and differences were assessed by means of the log-rank test. Cox proportional hazards methodology was used to develop models for three-year mortality. Variables included in the multivariate model were: age, diabetes, hypertension, gender, hyperlipidemia and BMI. Statistical analysis was performed with SAS software, (SAS Institute, Cary, NC). A p value <0.05 was considered significant.

RESULTS

Clinical and Angiographic Characteristics of the Patients

Data on 1,203 consecutive patients who underwent PCI was available for complete analysis (two patients did not have complete data for the calculation of the BMI). Half of the patients were overweight and 72% were either overweight or obese with only 28% having normal BMI in both arms of the study. The baseline clinical characteristics of all patients are shown in Table 1. There was a higher incidence of unstable angina and current smoker status in normal BMI patients who underwent PCI compared to overweight or obese counterparts, whereas normal BMI patients who underwent CABG were usually older and had less hypertension than overweight or obese patients who underwent CABG. When we compared patients by BMI status, a higher percentage of overweight female

patients underwent CABG (23% vs. 16%, p=0.04) whereas a higher percentage of obese

patients with diabetes were randomized to the PCI arm of the study (30% vs. 18%,

p=0.027). Angiographic and periprocedural characteristics are shown in Table 2. There was

a higher incidence of three-vessel disease in obese patients assigned to either stenting or

CABG.

Clinical Outcomes

Three-year clinical outcomes for all groups are shown in Table 3. First, it should be

emphasized that there was no effect of obesity on mortality independent of the treatment

modality, suggesting that obese patients can safely undergo percutaneous or surgical

coronary artery revascularization as their normal BMI counterparts. Three-year Kaplan-

Meier survival curves are shown in Figure 1. There was no difference in mortality rates

between the two revascularization procedures according to BMI. Likewise, the incidence of

cerebrovascular accidents (CVA) and/or myocardial infarction was similar among the

different BMI groups, regardless of the revascularization technique (Figure 2 and Table 3).

Although repeat revascularization procedures were significantly higher for patients

randomized to stenting compared to those randomized to CABG, there was a trend towards

fewer revascularization procedures in obese patients randomized to CABG (p=0.07) (Table

3). BMI did not seem to influence on the method chosen for repeat revascularization (PCI

or CABG) among patients with different BMI who required repeat intervention during the

follow-up period. While a trend in the benefit of CABG over PCI with stents was shown in

MACCE-free survival (including repeat revascularization procedures) for normal BMI

patients (77% vs. 70%, p=0.159) (Figure 3), overweight and obese patients who underwent

CABG had a significantly better outcome compared to their counterpart who underwent

stenting (85% vs. 63%, p<0.0001 and 89% vs. 67%, p<0.0001, respectively) (Figure 3). BMI had no influence on the long-term outcomes of patients who underwent stenting, but three-year MACCE rates were significantly lower for obese (11%) or overweight (15%) patients who underwent CABG compared to normal BMI patients (23%)(p=0.012) (Figure 4). In unadjusted analysis, overweight and obese patients treated with CABG had a 47% risk reduction in MACCE at three years as compared to patients with normal BMI (Hazard ratio=0.56; 95%CI: 0.37-083). After multivariate adjustment for age, diabetes mellitus, hypertension, gender and hypercholesterolemia, the association of BMI with MACCE was weakened, but remained statistically significant (HR=0.58; 95%CI: 0.38-0.88).

DISCUSSION

In this study, we analyzed the impact of BMI on the three-year outcomes of a large cohort of patients with multivessel disease who were randomized to either percutaneous revascularization with stents or CABG as part of the ARTS Trial. We observed that normal BMI patients (BMI <24.9) had similar MACCE-free survival (including death, cerebrovascular events, myocardial infarction or repeat revascularization) regardless the type of revascularization procedure, whereas overweight and obese patients who had been randomized to CABG had a better MACCE-free survival, compared to patients who underwent stenting. Furthermore, among patients who had been randomized to CABG, normal BMI patients had a worse outcome compared to overweight or obese patients, whereas for patients randomized to stenting, BMI did not influence on the overall outcome.

In the present study, BMI was not a predictive factor for death, myocardial infarction or cerebrovascular events at three years after either PCI with stents or CABG.

The better long-term MACCE-free survival in high BMI patients randomized to CABG was mainly related to a lower rate of repeat revascularization procedures in these patients, which was not seen in patients randomized to stenting. This difference can't be ascribed to lower physical activity in obese patients that would reduce the clinical expression of coronary artery lesions, as it would not explain for the lack of difference in patients randomized to stenting. Nevertheless, it is important to take into account that despite the fact that obese patients who underwent stenting had a significantly higher rate of adverse risk factors (i.e., female gender, hypertension, three vessel disease and diabetes), their outcome was still similar regarding irreversible clinical events (death, myocardial infarction or stroke) and repeat revascularization procedures. The potential influence of new developments in anti-restenosis therapy (e.g., drug-eluting stents) in the outcomes of patients with multivessel disease is unknown and will need to be addressed in the future.

Previous Studies

These results are in discrepancy with a recent report that analyzed the impact of BMI in patients who underwent coronary artery revascularization with either balloon angioplasty or CABG in the Bypass Angioplasty Revascularization Investigation (BARI) (11). In this study, a higher BMI was associated with a worse long-term prognosis after CABG. In point of fact, a higher BMI was associated only with a better in-hospital outcome (regarding death, MI, stroke or coma) and exclusively among patients who underwent percutaneous balloon angioplasty. It is important to take into account that the BARI trial was initiated in 1988 and coronary artery revascularization has undergone major changes since then. Previous results from a recently published large retrospective analysis of a series of patients who underwent PCI at the Washington Hospital Center (9), the

Cleveland Clinic (10,16) and from the British Regional Heart Study (17) have shown that low or normal BMI patients who undergo PCI are at the highest risk for in-hospital and long-term worse outcome, including increased cardiac mortality.

The increasing prevalence of obesity in the developing world has augmented our awareness on the impact of BMI on the prognosis of different cardiovascular diseases. Contrary to initial expectations, patients with essential hypertension or heart failure and increased BMI have a better survival compared to patients of recommended weight (18,19). Furthermore, obesity was not only associated with increased survival, but also there was a lower risk of stroke compared to lean patients in the Systolic Hypertension in the Elderly Program (SHEP) study (19). The mechanism by which overweight and obese patients have a better outcome has not been complete understood. There are plenty of theories that try to explain the potentially protective effect of obesity, including altered cytokines, lower plasma renin and epinephrine levels and larger coronary arteries. Also, the lean population is often a combination of patients who have lost weight due to underlying debilitating diseases and smokers (who have a tendency to weight less and have higher mortality rates compared to non-smokers) (8,20,21). Conversely, other studies have shown that the apparent excess risk associated with leanness among middle aged-women was artifactual and disappeared after accounting for cigarette smoking and subclinical disease (22). Among women that never smoked, the leanest had the lowest mortality and among obese women, mortality was more than twice that amid lean women (22).

It is important to take into account that the consequence of excess body weight on mortality is delayed and may not be seen in a relatively short period of time. The effects of obesity increase with the duration of follow-up and the age of the subjects, with increased

mortality in the very lean patients during the first years of follow-up, and increased mortality in the obese patients in subsequent years (23-26).

Limitations

The ARTS trial was designed as a multinational, multicenter, randomized study that was not intended to assess the impact of BMI on the short- and long-term outcomes after multivessel coronary revascularization. Therefore, the conclusions may be slanted. There were significant differences in baseline clinical characteristics among the groups, which may have had an influence in the outcomes. In the evaluation of our results, we also need to address the possibility of bias. Because both, interventional cardiologists and surgeons had to agree before randomization on the eligibility of all candidates to undergo revascularization by either technique, selection bias is improbable. The number of patients in the obese arm was small, limiting the statistical power of the analysis.

Conclusions

The results of this study suggest the following: 1) more than 70% of all patients who underwent stenting or CABG for the treatment of multivessel coronary artery disease in the ARTS trial were either overweight or obese, with only 28% of all patients having a normal BMI. This is a clear reflection of the increasing prevalence of obesity in the western world and a cause of concern for the developing countries; 2) BMI had no impact on the long-term outcomes of patients who underwent PCI with stents. However, despite a significantly higher rate of adverse risk factors in obese patients, they had similar outcomes regarding all endpoints as their normal BMI counterparts; 3) overweight and obese patients who underwent CABG had a significantly better outcome than normal BMI patients who underwent CABG; 4) normal BMI patients had similar outcomes regardless of the type of

revascularization procedure, whereas overweight and obese patients did significantly better with surgical revascularization; 5) Three-year mortality rates were similar for each one of the three BMI categories, regardless of the revascularization technique employed, and; 6) the relatively short follow-up period (three years) does not allow for the assessment of long-term adverse effects of obesity in any one of the two arms. We are only beginning to understand the effects of obesity on the short- and long-term outcomes of patients with cardiovascular diseases. The discrepancy of results observed in recent studies, only underscore the need for further research in this field.

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FIGURE LEGENDS

Figure 1. Three-year Kaplan-Meier survival curves among patients assigned to coronary stenting (dashed line) vs. coronary bypass surgery (solid line) stratified according to body mass index (BMI): normal BMI (BMI <24.9), overweight (BMI=25-30) and obese (BMI >30).

Figure 2. Three-year Kaplan-Meier estimates of survival without cerebrovascular events or myocardial infarction among patients assigned to coronary stenting (dashed line) vs. coronary bypass surgery (solid line) stratified according to body mass index (BMI) in three categories: normal BMI (BMI <24.9), overweight (BMI=25-30) and obese (BMI >30).

Figure 3. Three-year Kaplan-Meier event-free survival curves for MACCE (including death, cerebrovascular events, myocardial infarction or repeat revascularization) of patients assigned to coronary stenting (dashed line) vs. coronary bypass surgery (solid line) stratified according to body mass index (BMI): normal BMI (BMI <24.9), overweight (BMI=25-30) and obese (BMI >30).

Figure 4. Three-year Kaplan-Meier event-free survival curves for MACCE (including death, cerebrovascular events, myocardial infarction or repeat revascularization) among patients assigned to coronary stenting or coronary bypass surgery stratified according to body mass index (BMI) at three categories: normal BMI (BMI <24.9), overweight (BMI=25-30) and obese (BMI >30).

Table 1. Baseline Clinical Characteristics.

	Coronary Stenting (n=599)				*Bypass Surgery* (n=604)			
	Normal n=168	*Overweight* n=307	*Obese* n=124	*p*	*Normal* n=169	*Overweight* n=299	*Obese* n=136	*p*
Age (years)	61±10	61±10	60±10	0.43	63±10	61±9	59±9	0.009
Female (%)	29.2	16.3	30.7	0.0004	22.5	23.0	28.0	0.47
Unstable angina (%)	42.2	37.8	30.0	0.09	38.4	34.7	33.2	0.58
Stable Ischemia (%)	52.3	56.6	62.9	0.20	56.2	59.8	63.2	0.46
Silent Ischemia (%)	5.5	5.6	7.1	0.75	5.4	5.5	3.6	0.73
Prior MI (%)	47.0	45.6	38.0	0.25	42.6	40.0	45.5	0.56
Hypertension (%)	37.5	45.0	53.2	0.03	37.3	44.4	55.1	0.007
Diabetes mellitus (%)	8.9	19.5	30.0	<0.0001	14.2	15.7	17.6	0.71
PVD (%)	6.5	4.9	5.6	0.75	7.1	5.3	2.2	0.15
Family history (%)	39.3	36.0	45.0	0.07	42.6	42.4	40.0	0.82
Hypercholesterolemia (%)	51.8	58.6	63.0	0.14	52.6	59.8	59.0	0.21
Current smoker (%)	37.0	24.4	24.2	0.007	26.6	24.0	28.6	0.65
Ejection fraction (%)	61±12	60±12	62±13	0.34	60±13	60±13	62±14	0.15
BMI	23±1.6	27±1.3	32±2.3	<0.0001	23±1.5	27±1.4	32±2.3	<0.0001

MI = myocardial infarction; CABG = coronary artery bypass graft surgery; PVD = peripheral vascular disease.

Table 2. Periprocedural Characteristics.

	Coronary Stenting (n=599)				Bypass Surgery (n=604)			
	Normal n=168	Overweight n=307	Obese n=124	p	Normal n=169	Overweight n=299	Obese n=136	p
One-vessel disease (%)	0.6	0.6	0	0.45	0	0.6	0	0.3
Two-vessel disease (%)	68.4	70.0	62.0	0.75	69.3	64.0	60.0	0.48
Three-vessel disease (%)	31.0	29.4	38.0	0.045	30.7	35.4	40.0	0.04
Vessel territory with stenosis								
Left anterior descending (%)	91.6	88.2	91.1	0.44	88.7	90.3	89.7	0.87
Left circumflex (%)	69.0	66.0	71.7	0.45	71.0	73.0	74.2	0.81
Right coronary (%)	69.6	74.2	75.0	0.48	71.0	71.5	76.4	0.50
Complete revascularization (%)	74.8	73.7	68.0	0.51	93.3	93.2	97.0	0.08
Number of stents	2.6±1.0	2.7±1.2	2.6±1.2	0.85	-	-	-	-
Number of grafts	-	-	-	-	2.4±0.6	2.5±0.7	2.5±0.6	0.48

Table 3. Clinical outcomes at three-year follow-up

	Coronary Stenting (n=599)				Bypass Surgery (n=604)			
	Normal n=168	*Overweight* n=307	*Obese* n=124	*p*	*Normal* n=169	*Overweight* n=299	*Obese* n=136	*p*
Death (%)	6 (3.6)	11 (3.6)	5 (4)	0.97	8 (4.7)	14 (4.7)	5 (3.7)	0.87
CVA (%)	6 (3.6)	13 (4.2)	1 (0.8)	0.19	7 (4)	9 (3)	4 (3)	0.77
MI (%)	12 (7)	20 (6.5)	12 (9.7)	0.52	13 (7.7)	12 (4)	7 (5)	0.23
Repeat revascularization (%)	36 (21.4)	91 (29.6)	33 (26.6)	0.15	16 (9.5)	19 (6.3)	4 (3)	0.07
CABG (%)	13 (7.7)	30 (9.7)	12 (9.7)	0.74	4 (2.4)	3 (1)	0 (0)	0.15
PCI (%)	26 (15.5)	70 (22.8)	24 (19.3)	0.16	14 (8.3)	18 (6.0)	4 (3)	0.15
Total MACCE	51 (30.4)	114 (37)	41 (33)	0.31	39 (23)	45 (15)	15 (11)	0.012

MACCE = Major adverse cardiac and cerebrovascular events; MI = myocardial infarction; CABG = coronary artery bypass graft surgery; CVA= cerebrovascular accident; PCI = percutaneous coronary intervention

Figure 1

Normal BMI · Overweight · Obese

Days since Randomization

Figure 2

Normal BMI · Overweight · Obese

Days since Randomization

Figure 3

Normal BMI   Overweight   Obese

Days since Randomization

Figure 4

Coronary Stenting   CABG Surgery

Days since Randomization
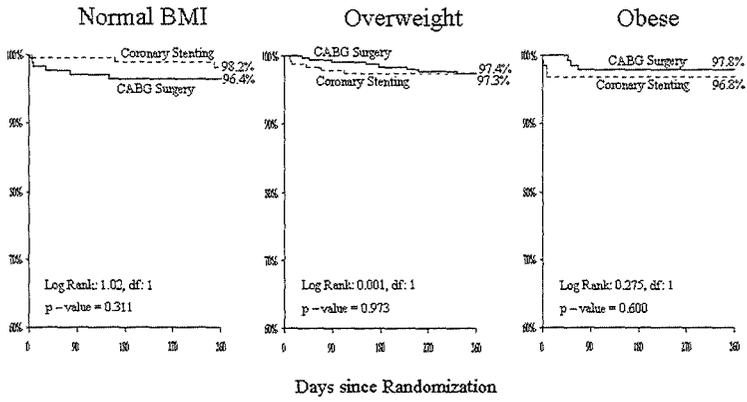
Chapter 9

The Impact of renal failure on clinical outcomes in patients with multivessel disease undergoing coronary revascularization: The Arterial Revascularization Therapies Study (ARTS)

Ix JH, **Mercado N**, Shlipak M, Boersma E, Lemos PA, Lindenboom W, O'Neill WW, Wijns W, Serruys PW

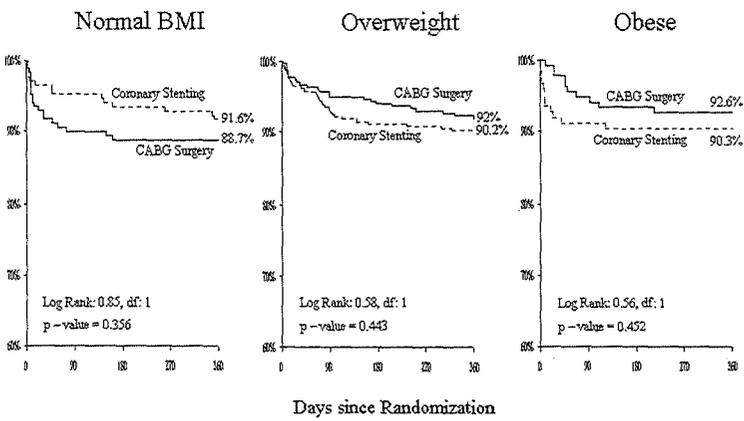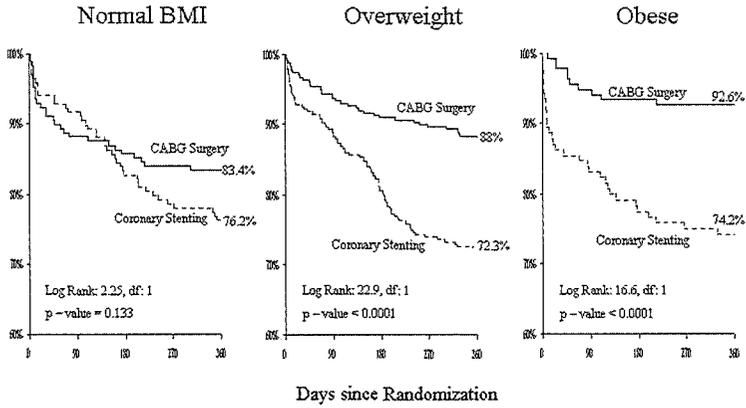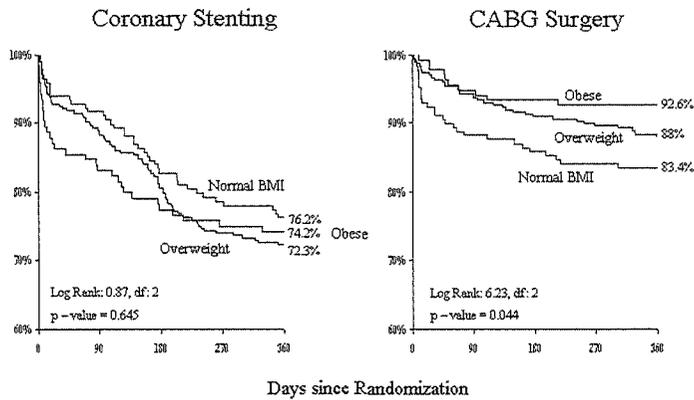# The Prognostic Impact of Renal Insufficiency on Long-term Clinical Outcomes in Patients with Multivessel Coronary Artery Disease Undergoing Coronary Revascularization: The Arterial Revascularization Therapies Study (ARTS)

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ABSTRACT

Background

Chronic renal insufficiency (CRI) is associated with adverse outcomes after coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI). In the Arterial Revascularization Therapies Study (ARTS) we evaluated the effect of CRI on outcomes after coronary revascularization and we compared the outcomes of patients with CRI who were randomly assigned to CABG or PCI.

Methods and Results

The ARTS study randomly assigned 1205 patients with multivessel coronary artery disease (CAD) to CABG or PCI. Of 1205 patients enrolled, 1176 (97%) had baseline creatinine data, among whom 290 (25%) had CRI, defined by creatinine clearance $\leq$ 60 ml/min estimated by the Cockroft-Gault equation. The primary clinical endpoint was the composite of death, myocardial infarction (MI), or stroke; and, a secondary outcome was repeat revascularization. The primary outcome occurred in 18% of patients with CRI and 10% of patients without CRI at 3-years of follow-up (adjusted HR=1.61; 95%CI: 1.10-2.35; P < 0.01). Within the CRI subgroup, no difference was observed in the primary endpoint after CABG vs. PCI (adjusted HR=0.93; 95%CI: 0.54-1.60; P = 0.97). However, CABG was associated with a reduced risk for repeat revascularization. (HR=0.28; 95%CI: 0.14-0.54; P < 0.01).

Conclusions

In patients with multivessel CAD, CRI is a risk factor for death, MI, or stroke after coronary revascularization. These outcomes occurred at equal rates among CRI patients treated with CABG or PCI, but CABG was associated with decreased repeat revascularizations.

CONDENSED ABSTRACT

The effect of chronic renal insufficiency (CRI) on clinical outcomes after coronary revascularization was evaluated among the 1176 subjects randomized to PCI or CABG in the ARTS trial. CRI was associated with increased risk of MI, stroke, or death within 3 years after revascularization (adjusted HR=1.6; 95% CI 1.1-2.3; $P < 0.01$). Amongst the 290 CRI subjects, no difference in the primary outcome was observed between those treated with CABG vs. PCI (adjusted HR=0.93; 95% CI 0.54-1.60; $P = 0.97$). However, CABG was associated with reduced risk for repeat revascularizations (HR 0.28; 95% CI 0.14-0.54; $P < 0.01$).

INTRODUCTION

Chronic renal insufficiency (CRI) is common in the general population, estimated to affect over one forth of persons aged 65 and older in the United States[1], and is an independent predictor of incident stroke, myocardial infarction (MI) and all cause mortality[2-7]. In addition, CRI is associated with increased mortality after coronary artery bypass grafting (CABG)[8-10], perhaps because such patients have longer post-operative mechanical ventilation time, higher post-operative bleeding rates and transfusion requirements, and increased length of hospital stay[8]. However, percutaneous coronary intervention (PCI) in these patients is also high-risk due to their increased incidence of acute renal failure, restenosis, and mortality[11-15]. Whether CABG or PCI offers a better clinical outcome and prognosis has not been prospectively studied.

The Arterial Revascularization Therapies Study (ARTS) was a multinational trial that randomly assigned patients with multivessel coronary artery disease (CAD) to either CABG or PCI with multivessel coronary stenting. In the present study, we evaluated the effect of CRI on outcomes after coronary revascularization, and we compared the outcomes of patients with CRI who were randomly assigned to CABG or PCI to assess if the alternative strategies were associated with different clinical outcomes.

METHODS

Patient selection

Study design and primary results of the ARTS have been described previously[16,17]. Briefly, the study was a randomized trial comparing CABG vs. PCI with multivessel coronary stenting in patients with ischemic symptoms. Patients who had not previously

undergone CABG or angioplasty were eligible for coronary revascularization if they had either stable angina pectoris, unstable angina pectoris or if they had silent ischemia with at least two lesions on angiography located in different vessels and territories and amenable to stenting. All patients were thought to be equal candidates for either CABG or PCI with stenting by the cardiac surgeon and interventional cardiologist at each participating center. Patients gave written consent and were randomly assigned to either procedure via a central telephone service with stratification by clinical site. Patients were excluded if they had a left ventricular ejection fraction < 30 percent, overt congestive heart failure, prior stroke, transmural MI in the previous week, intolerance of aspirin or ticlopidine, need for other concomitant major surgery, presence of severe hepatic disease, diseased saphenous veins, neutropenia, or thrombocytopenia. Patients were also excluded if they had a serum creatinine > 1.7mg/dL (150mmol/L). Creatinine clearance was estimated by the Cockcroft-Gault formula[18] [(140-age) * body weight (kg)/serum creatinine (mg/dL) * 72] (* 0.85 in women), and CRI was defined as $\leq$ 60 ml/min.

Clinical outcomes

The primary outcome was the event free survival without stroke, transient ischemic attack, nonfatal MI, or death. The secondary outcome was the need for repeat revascularization by percutaneous intervention or surgery. Within the first seven days after revascularization, the diagnosis of MI required documentation of a new abnormal Q wave (according to the Minnesota code)[19] plus a ratio of serum creatine kinase MB (CK-MB) isoenzyme to total cardiac enzyme > 0.1 or a CK-MB value five times the upper limit of normal. After the first week, either abnormal Q waves or enzymatic changes were sufficient to diagnose MI[20,21]. All MIs were confirmed by the electrocardiographic core laboratory and the clinical-events adjudications committee. Cerebrovascular events were

divided into three categories: stroke, transient ischemic attacks, and reversible ischemic neurologic deficits. Events were classified in ischemic or non-ischemic categories, and were confirmed by the clinical-events adjudications committee.

Follow-up was initiated at the time of randomization and clinical information was obtained by telephone contact with the patient or patient's family or via the referring physician at 1, 6, 12, 24 and 36 months. Questionnaires, which included information on the occurrence and date of a primary clinical endpoint, angina status according to the Braunwald[22] or Canadian Cardiovascular Society[23] classifications, working status and cardiac medications were completed at each time point.

Statistical analysis

Baseline characteristics of patients with and without CRI were compared with the chi-square test for discrete variables, and the Student's unpaired t-test for continuous variables. Fisher's exact test was used for categorical variables with nominal scales and the Wilcoxon rank-sum test for those with ordinal scales. Event-free survival distribution was estimated according to the Kaplan-Meier method, and the incidence of adverse events was tested with the log-rank test. To determine the association of CRI with clinical outcomes after revascularization, we used Cox proportional hazard models that were adjusted for baseline differences. Variables that were associated with the primary clinical outcome with a P-value <0.1 in the univariate analysis were selected as potential covariates. The final multivariate model was constructed after backward deletion of the least significant variables[24]. The analyses comparing randomized subjects with CRI were conducted as intention-to-treat analysis; however, because smoking status was

unbalanced in the two groups, we used a Cox proportional hazards model that adjusted for smoking status. We also tested for interaction with age, hypertension, diabetes mellitus, and ACE inhibitor use. All statistical analyses were performed using the SAS 8.0 software package (SAS Institute, Cary, North Carolina); a two-sided p-value ≤ 0.05 was considered statistically significant.

RESULTS

Baseline characteristics and treatment

From April 1997 to June 1998, a total of 1205 patients at 67 centers were randomly assigned to undergo PCI with multivessel stenting (600 patients) or CABG (605 patients). A total of 99% of the patients in the stenting group (593) and 96% of those in the surgery group (579) received the assigned treatment. The average interval between randomization and revascularization was 11 ± 16 days for PCI, and 27 ± 39 days for the CABG. Of the 1176 (97%) patients with baseline creatinine values, 290 (25%) had renal insufficiency. Compared with patients who had normal renal function, those with CRI were more likely to be female, older, hypertensive, and to have stable angina (Table 1). Those with CRI also had lower body mass index and were less likely to be current smokers. Medication use, and number of diseased vessels were similar between renal function groups.

Effect of renal insufficiency on clinical outcomes

In unadjusted analysis, renal insufficiency was associated with a nearly two-fold increased risk of the primary outcome (HR=1.9; 95% CI: 1.4-2.7; $P < 0.01$). After multivariate adjustment, the association of CRI with the primary outcome was weakened, but remained statistically significant (HR=1.6; 95% CI: 1.1-2.4; $P < 0.01$) (Figure 1 and Table 2). In addition, CRI was the strongest independent predictor of the primary

outcome based on the wald chi square statistic. For comparison, diabetes was less strongly associated with the primary outcome (HR=1.4; 95%CI 0.95-2.1; P = 0.34). We examined the individual outcomes of death, stroke, non-fatal MI and repeat revascularization and found CRI to be particularly associated with stroke (Table 2). The point estimate for death was also strong, although the P value did not reach statistical significance.

We tested for interactions with age, hypertension, diabetes mellitus, and ACE inhibitor use. Among these, only hypertension had a statistically significant interaction (HR=0.45; 95%CI 0.22-0.90; P = 0.02). Compared with patients with neither hypertension nor CRI, those with either hypertension alone (HR=1.7; 95%CI 1.1-2.7; P = 0.01) or CRI alone (HR=2.8; 95%CI 1.7-4.6; P < 0.01) were at increased risk of the primary outcome, but the combination of both risk factors (HR=1.3; 95%CI 0.8-2.1; P = 0.52) was not associated with additive risk.

Given the interaction with hypertension, subjects with CRI with and without hypertension were also analyzed separately. In multivariate analysis, CRI predicted a significant increased risk of the primary outcome in persons without hypertension (HR=2.2, 95% CI: 1.3-3.8, P < 0.01), but the association did not reach statistical significance among subjects with hypertension (HR=1.2, 95% CI 0.7-2.1, P = 0.43).

Comparison of clinical outcomes after CABG and PCI in subjects with CRI

Among the 290 subjects with CRI, 151 were assigned to PCI, and 139 to CABG. Baseline and angiographic characteristics of subjects within each treatment group were similar except that higher smoking rates were observed in the PCI group (Table 3).

The incidence of the primary outcome was similar in patients assigned to CABG and to PCI (Figure 2) and there was no difference in the frequency of the individual outcomes of stroke, MI or death between treatment groups (Table 4). However, CABG was associated with one-third the rate of repeat revascularization as compared with PCI at 3 years of follow-up (HR= 0.28; 95%CI 0.14-0.54; P < 0.01) (Figure 3).

DISCUSSION

In this analysis from the ARTS trial, we found subjects with CRI to have a 50% increased risk for the combined outcome of death, MI or stroke within three years after coronary revascularization. However, in analyses limited to subjects with CRI, we found no difference in the incidence of these major outcomes among patients treated with CABG or PCI. Subjects with CRI undergoing CABG did have substantially lower rates of repeat revacularization compared with those undergoing PCI at three-year follow-up.

This study represents the first randomized prospective study to evaluate differences in outcomes between CABG and PCI in subjects with CRI. Observational data have been conflicting about the implications of CRI on clinical outcomes following coronary revascularization. Szczech and colleagues found no difference in survival between

CABG and PCI in subjects with serum creatinine < 2.5mg/dL in a large community based observational study[25]. In another study evaluating 4500 subjects with CAD, Reddan and colleagues found a survival advantage with CABG compared with PCI, which appeared to increase as renal function declined[26]. These studies, however, may have been susceptible to confounding by indication. Other studies have found CRI to be associated with worse outcomes after either PCI or CABG, in isolation[20,21,27]. Our study differs from these prior studies because it was nested within a randomized trial, and as all subjects randomized to PCI were treated with stents, it represents cardiovascular practices that more closely resemble those now in standard clinical practice.

The strong association of CRI with adverse outcomes in our study is particularly striking because subjects with severe renal disease were excluded from our study population. The average estimated creatinine clearance amongst those with CRI in our study was 50 ml/min. The strength of the association of this degree of CRI with adverse events highlights the significance of even mild renal impairment as a prognostic indicator. CRI was in fact a stronger predictor of the primary outcome than any other risk factor, including diabetes mellitus.

The results of our study indicate that coronary revascularization, regardless of procedure type, is a high-risk procedure in subjects with CRI. To our knowledge, there is no study comparing aggressive medical management to coronary revascularization in subjects with multivessel CAD and CRI. In subjects with normal renal function, the presence of symptomatic multivessel CAD is considered a high-risk condition for adverse cardiac events and is an indication for coronary revascularization. Because CRI is a strong risk

factor for cardiovascular events either with[20,25-27] or without[6,7] coronary revascularization, we believe that patients with high-risk coronary anatomy and concomitant CRI should benefit from revascularization despite their increased risk from these procedures. These patients should therefore not be denied these potentially useful procedures based on our findings.

The equivalent rates of death, stroke, or non-fatal MI between treatment groups amongst subjects with CRI should reassure clinicians that multivessel stenting is an acceptable and less invasive alternative to CABG, but at the expense of increased repeat revascularization procedures within three years. However, the recent introduction of drug-eluting stents have strikingly decreased the incidence of coronary restenosis and the need for repeat revascularization[28,29]. Whether future stent technology will decrease the rates of repeat revascularization in CRI patients to rates equivalent to those after CABG is an exciting possibility that will need to be assessed in future studies.

It is not clear why subjects with CRI are at increased risk for adverse cardiovascular outcomes. The excess risk with CRI is explained in part by a higher prevalence of well-established cardiovascular risk factors such as hypertension and diabetes. However, CRI remains a powerful predictor for cardiovascular events even after controlling for these standard risk factors[5-7,15,27]. Multiple novel cardiac risk factors are now being evaluated as possible mediators of this effect. A pro-inflammatory state present in renal disease is a potential mechanism. Elevated levels of C-reactive protein, interleukin-6, and fibrinogen are associated with increased cardiovascular risk in healthy populations[30-32] and are known to be markedly elevated in subjects with CRI of similar magnitude to that in our

study[33]. Alternatively, alterations in lipid metabolism[5,34,35], or increased levels of homocysteine[36] which in turn enhances oxidation of low-density lipoproteines[37] may contribute to the increased cardiovascular risk. The relative contribution of these novel risk factors to the increased risk merits further investigation.

The primary limitation of this study was its sample size. Although the relative risk for CABG compared with PCI for the primary outcome was unity, the confidence intervals cannot exclude a moderate advantage with either therapy. Secondly, we relied on estimated creatinine clearance, which is an imprecise measure of renal function. However, the gold standard for measurement of glomerular filtration is cumbersome and expensive[38]. Subjects were excluded if their serum creatinine was > 1.7mg/dL (150mmol/L), and our results may therefore not be generalizable to patients with more severe decrements in renal function. Lastly, although this was a randomized sample, CRI was not a pre-specified subgroup for stratified randomization. Because CRI is clearly a risk factor for adverse cardiovascular outcomes, larger numbers of patients with CRI should be included in future cardiovascular clinical trials. Such studies could identify interventions to improve the health status and survival of persons with CRI.

In conclusion, the present study demonstrates that subjects with mild to moderate renal insufficiency have similar rates of death, stroke and non-fatal MI at 3-years follow-up after revascularization with CABG or PCI, but that PCI is associated with a three-fold increased risk for repeat revascularization. We found that even mild renal insufficiency is an important risk factor for patients undergoing coronary revacularization. Clinicians should be aware of the excess risk associated with even mild CRI and should factor it into their decision to pursue coronary revascularization.

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Table 1. Characteristics of the 1176 patients assigned to CABG or PCI, by presence of renal insufficiency*

	Normal Renal Function (n = 886)	Renal Insufficiency (n = 290)	p – Value
Male gender (% of patients)	83	57	< 0.01
Age (yr)	58±9	68±6	< 0.01
Creatinine (mg/dl)	1.0±0.3	1.3±0.3	< 0.01
Creatinine Clearance (ml/min)	134±180	50±8	< 0.01
Body Mass Index	28±4	26±3	< 0.01
Previous MI (%)	44	39	0.19
Diabetes Mellitus (%)	17	18	0.79
Hypertension (%)	43	50	0.03
Hypercholesterolemia (%)	58	55	0.34
Peripheral vascular disease (%)	5	6	0.30
Current smoker (%)	31	13	< 0.01
Cardiac medications			
ACE inhibitors (%)	24	29	0.08

Aspirin (%)	89	86	0.17
B-blockers (%)	69	71	0.71
Enrollment diagnosis			
Stable angina (%) ‡	56	64	0.01
Unstable angina (%) §	39	31	0.02
Silent ischemia (%)	6	5	0.46
Ejection fraction (%)	61±12	60±13	0.44
Number of diseased vessels (%)			
2	66	65	0.70
3	33	34	0.79

*Data presented as percent or as the mean value ± SD. ‡Stable angina was defined according to the system of the Canadian Cardiovascular Society. §Unstable angina was defined according to the Braunwald classification

Table 2. Association of renal insufficiency with 3-year clinical outcomes following coronary revascularization

	Normal Renal Function (n = 886)	Renal Insufficiency (n = 290)	Unadjusted Hazard Ratio (95% CI);	P - Values	Adjusted Hazard Ratio (95% CI)*	P - Values
	n (%)	n (%)				
Composite of death, stroke or MI	86 (10)	52 (18)	1.9 (1.35–2.70)	< 0.01	1.6 (1.10-2.35)	< 0.01
Death	26 (3)	19 (7)	2.2 (1.25-4.09)	< 0.01	1.6 (0.84-3.29)	0.09
Stroke	19 (2)	18 (6)	2.9 (1.56-5.67)	< 0.01	2.3 (1.15-4.70)	< 0.01
MI	52 (6)	20 (7)	1.2 (0.71-2.0)	0.50	1.0 (0.58-1.83)	0.96
Total repeated revascularization #	143 (16)	49 (17)	1.1 (0.78-1.50)	0.64	1.1 (0.75-1.50)	0.68
CABG	42 (5)	18 (6)	1.3 (0.76-2.30)	0.32	1.3 (0.70-2.35)	0.57
PCI	111 (13)	39 (13)	1.1 (0.77-1.60)	0.57	1.1 (0.74-1.62)	0.53

*Adjusted for diabetes mellitus, hypertension, ejection fraction, ACE inhibitor use, aspirin use, peripheral vascular disease, hemoglobin, silent ischemia, COPD, and hyperlipidemia.

Table 3. Characteristics of subjects with renal insufficiency randomly assigned to PCI or CABG*

	PCI (n = 151)	CABG (n = 139)	P – Value
Male gender (% of patients)	57	56	0.91
Age (yr)	68±6	69±7	0.51
Creatinine (mg/dl)	1.3±0.3	1.3±0.3	0.90
Creatinine Clearance (ml/min)	50±8	49±8	0.54
Body Mass Index	26±3	26±3	0.98
Previous MI (%)	39	40	0.90
Diabetes Mellitus (%)	20	16	0.44
Hypertension (%)	47	54	0.24
Hypercholesterolemia (%)	54	57	0.64
Peripheral vascular disease (%)	5.3	8	0.48
Current smoker (%)	17	9	0.04
Cardiac medications			
ACE inhibitors (%)	30	29	0.80

Aspirin (%)	88	85	0.49
B-blockers (%)	67	75	0.16
Enrollment diagnosis			
Stable angina (%) ‡	65	64	0.90
Unstable angina (%) §	31	31	0.97
Silent ischemia (%)	4	5	0.78
Ejection fraction (%)	60±13	59±13	0.94
Number of diseased vessels (%)			
2	69	61	0.16
3	30	38	0.17

*Data presented as percent or as the mean value ± SD. ‡Stable angina was defined according to the system of the Canadian Cardiovascular Society. §Unstable angina was defined according to the Braunwald classification

Table 4. Clinical outcomes amongst subjects with renal insufficiency randomly assigned to CABG or PCI at 3 year follow-up*

	PCI (n = 151)	CABG (n = 139)	Hazard Ratio* (95% CI)	P - Value
Composite of death, stroke, or MI	28 (19)	24 (17)	0.93 (0.54-1.61)	0.80
Death	10 (7)	9 (7)	0.98 (0.40-2.42)	0.97
Stroke	12 (8)	6 (4)	0.54 (0.20-1.45)	0.22
MI	9 (6)	11 (8)	1.34 (0.55-3.23)	0.42
Total repeated revascularization #	38 (25)	11 (8)	0.28 (0.14-0.54)	< 0.01
CABG	15 (10)	3 (2)	0.21 (0.06-0.73)	0.01
PCI	30 (20)	9 (7)	0.30 (0.14-0.63)	< 0.01

*Hazard ratios adjusted for smoking status.

FIGURE LEGENDS

FIGURE 1

Three-year Kaplan-Meier event-free survival curves for death, stroke or myocardial infarction stratified according to renal function

*Adjusted for diabetes mellitus, hypertension, ejection fraction, ACE inhibitor use, aspirin use, peripheral vascular disease, hemoglobin, silent ischemia, COPD, and hyperlipidemia
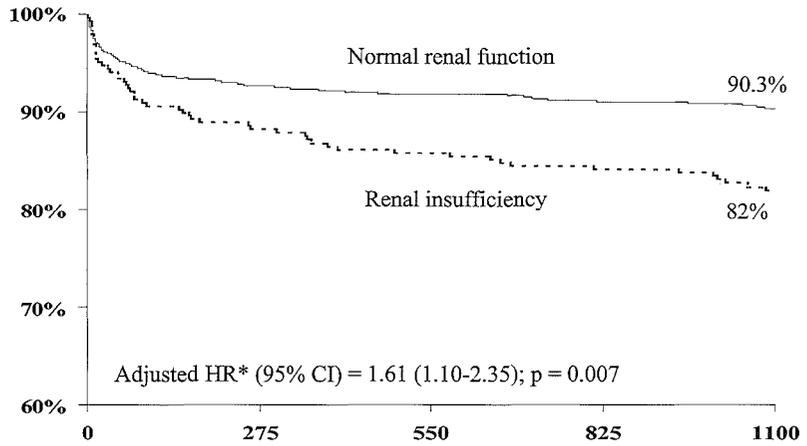
FIGURE 2

Three-year Kaplan-Meier event-free survival curves for death, stroke, or myocardial infarction of patients with renal insufficiency randomized to PCI (Solid line) or CABG surgery (Dotted line)

FIGURE 3

Three-year Kaplan-Meier event-free survival curves for repeat revascularization in patients with renal insufficiency randomized to PCI (Solid line) or CABG surgery (Dotted line)
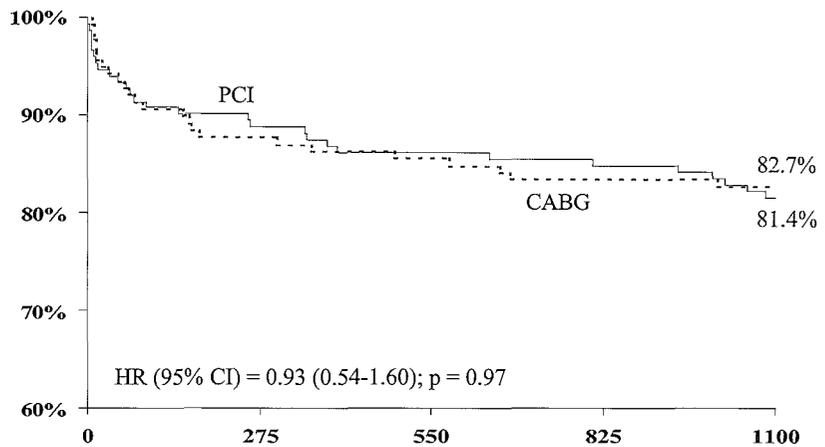
ARTS patient population

Normal renal function

90.3%

90%

Renal insufficiency

82%

80%

70%

Adjusted HR* (95% CI) = 1.61 (1.10-2.35); p = 0.007

60%

| | 0 | 275 | 550 | 825 | 1100 |

Numbers at risk   Days since Randomization

Normal renal function	886	821	814	806	800
Renal insufficiency	290	256	249	244	238

FIGURE 1

Renal insufficiency

100%

PCI

90%

82.7%

CABG

80%

81.4%

70%

HR (95% CI) = 0.93 (0.54-1.60); p = 0.97

60%

| | 0 | 275 | 550 | 825 | 1100 |

Numbers at risk   Days since Randomization

PCI	151	134	130	128	123
CABG	139	122	119	116	115

FIGURE 2

221

Renal insufficiency

HR (95% CI) = 0.28 (0.14-0.54); p = 0.0002

Days since Randomization

Numbers at risk

PCI	151	122	117	114	113
CABG	139	133	130	129	128

FIGURE 3

Chapter 10

Long-Term Fluvastatin Reduces the Hazardous Effect of Renal Impairment on the 4-year Atherosclerotic Outcomes – A LIPS Substudy

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Submitted for publication

Long-Term Fluvastatin Abolishes the Hazardous Effect of Renal Impairment on the 4-year Atherosclerotic Outcomes – A LIPS Substudy

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Abstract

Background: Mild renal impairment is an important risk factor for late cardiovascular complications. The present study assessed the effect of fluvastatin on the outcome of patients with or without renal dysfunction in the Lescol Intervention Prevention Study. Additionally, the effect of fluvastatin on renal function and the relation between changes in renal function on the incidence of adverse events were evaluated.

Methods: Complete data for creatinine clearance calculation were available for 1558 patients (93% of the total population), who were randomised to fluvastatin (normal renal function, n=631; impaired renal function, n=150), or placebo (normal, n=617; impaired, n=160) following successful completion of a first PCI. Follow-up time was 3–4 years. The primary endpoint was survival time free of coronary atherosclerotic events (cardiac death, non-fatal myocardial infarction, and coronary reinterventions not related to restenosis).

Findings: Renal impairment significantly increased the incidence of coronary atherosclerotic events in placebo-treated patients (RR 1.42 [95% CI: 1.00 - 2.01]; p=0.048). Among those treated with fluvastatin, however, no differences were observed between patients wit and without renal impairment (RR 0.97 [95% CI: 0.61 - 1.56]; p=0.912). No further deterioration in creatinine clearance was observed during follow-up, regardless of baseline renal function or allocated treatment. The occurrence of adverse events was not related to changes in renal function during follow-up.

Interpretation: Fluvastatin treatment strikingly reduced the risk of coronary atherosclerotic events after percutaneous intervention in patients with mild renal impairment. The benefit of fluvastatin was unrelated to any effect on renal function.

Introduction

Mild-to-moderate renal impairment has been identified as an important risk factor for future adverse events in patients with diagnosed cardiovascular disease,[1-8] an effect observed even after surgical or percutaneous treatment[4-6] mainly due to an increased rate of death and myocardial infarction, without a major impact on restenotic complications, among those treated with angioplasty.[4,5] Although renal impairment is commonly associated with a higher frequency of conventional risk factors[1,4-8] and increased levels of inflammatory, procoagulant, and atherogenic markers,[9-16] the mechanisms involved with the augmented risk in this population remain unclear.[10]

Blood pressure reduction and long-term treatment with ramipril have both been described to improve the outcomes of patients with mild renal impairment.[7,17] However, patients with renal impairment treated with therapeutic schemes were still at a higher risk than patients with normal renal function, indicating that the hazardous effect of renal dysfunction was only partially reduced by these treatments.[7,17] Recently, treatment with HMG-CoA reductase inhibitors (statins) has been observed to be safe and to decrease the incidence of adverse events in patients with previous myocardial infarction regardless of the baseline renal function.[18] In addition to lowering lipid levels, statins may give beneficial effects through their so-called pleiotropic effects, which may or may not be related to changes in lipid metabolism.[19] Previously, statin treatment has been shown to significantly decrease proteinuria[20] and renal function deterioration in hypertensive patients.[21]

In the Lescol Intervention Prevention Study (LIPS), treatment with long-term fluvastatin has been recently shown to decrease the incidence of cardiac events in patients treated with percutaneous coronary intervention (PCI).[22] The aim of the present study was to analyse the results of LIPS in order to investigate: 1) the impact of mild renal impairment on the occurrence of long-term adverse events, 2) whether treatment with fluvastatin reduces the expected hazardous effect of mild renal impairment, 3) the effect of fluvastatin on the renal function during the follow-up period, and 4) and the relation between the changes in renal function over time and the occurrence of adverse events.

Methods

Study Design and Patient Population

The study design and primary results of LIPS are described elsewhere.[22] Briefly, following a first successful PCI (residual stenosis <50%, absence of post-procedure in-hospital myocardial necrosis, repeat revascularisation, or death) patients were randomised to receive treatment with either fluvastatin (Lescol, Novartis Pharma AG, Basel, Switzerland) 40 mg bid or placebo for 3 to 4 years.

At enrolment, patients had to fulfil at least one of the following lipid profile criteria: 1) total cholesterol (TC) between 3.5–7.0 mmol/l (135–270 mg/dl) with fasting triglycerides (TG) <4.5 mmol/l (400 mg/dl); 2) TC <5.5 mmol/l (212 mg/dl) for patients whose lipids levels were measured between 24 hours and 4 weeks after an episode of myocardial infarction; or 3) TC <6.0 mmol/l (232 mg/dl) for patients with diabetes mellitus. Exclusion criteria included a baseline serum creatinine value >160 µmol/l (1.8 mg/dl). The study protocol was approved by local ethics committees and all patients gave informed written consent.

Lipoproteins and Renal Function Evaluation

Each patient was clinically evaluated at least eight times after randomisation. Blood lipid levels were measured at all visits and serum creatinine was measured at baseline, at 52, 104 and 156 weeks. All biochemical analyses were performed at a central laboratory (Analytico Medinet, Breda, The Netherlands). The creatinine clearance was calculated according to the formula proposed by Cockcroft and Gault: creatinine clearance (ml/min)=(140 - age) x weight (kg) ÷ 72 x serum creatinine (mg/dl) (x 0.85 for women).[23]

Clinical Endpoints

Outcomes were evaluated as a composite of atherosclerosis-related adverse cardiac events defined as the incidence of cardiac death (all deaths except those unequivocally related to a non-cardiac cause), non-fatal myocardial infarction (new pathological Q-waves or a total plasma creatine kinase [CPK] level greater than twice the normal upper limit with presence of CPK isoenzyme MB), and all re-interventions (either surgical or percutaneous) not caused by coronary restenosis occurring after the index procedure. Atherosclerosis-related adverse cardiac events were a pre-defined endpoint of LIPS[22], based on the fact that the benefit of fluvastatin after PCI have been previously demonstrated to be unrelated to any effect of the drug on restenosis[24]. Additionally, the incidence of target lesion revascularisation was analysed in both renal function groups.

Statistical Analysis

All analyses were carried out on an intention-to-treat basis. Continuous variables were expressed as mean ± standard deviation (SD) and were compared using Student's two sample t-test. Fisher's exact test was used for categorical variables, and Wilcoxon scores were used for categorical variables with an ordinal scale. Discrete variables were expressed as counts and percentages, and were compared in terms of relative risks with 95% CI. All statistical tests were 2-tailed. Event-free survival distribution was estimated according to the Kaplan-Meier method, and the overall incidence of adverse events was tested using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

The Cox proportional hazards models were used to assess risk reduction of adverse events. Patients were divided into two groups according to the baseline creatinine clearance. An abnormal creatinine clearance was defined as a value in the lowest quintile (55.9 ml/min). Such restrictive definition was applied in considering the LIPS study protocol, which excluded patients with frankly decreased renal function. The treatment/renal impairment interaction was calculated in a multivariate approach with allocated treatment, renal impairment and an interaction factor specifying the simultaneous absence or presence of both previous factors in the model. When considering the baseline creatinine clearance as a continuous variable, estimated risk ratios were calculated from the observed data with the mean clearance of the entire study population chosen as a reference point for the placebo group (risk ratio = 1). To ensure a

better fit to gaussian distributions, creatinine clearance measurements were converted by logarithmic transformation.

All baseline clinical, angiographic and procedural characteristics available in the study's database were tested to evaluate their relation with the incidence of clinical adverse events. Variables presenting a univariate $p<0.1$ were tested as candidates in a multivariate analysis and a final model was constructed by stepwise selection of the most significant variables (the following variables were selected from the univariate analyses: allocated treatment, creatinine clearance, stable/unstable angina, smoking, high density lipoprotein cholesterol levels [HDL-C], gender, hypertension, diabetes, previous stroke, previous myocardial infarction, cholesterol lowering diet, height, body-mass index, diastolic blood pressure, systolic blood pressure, multi-vessel disease, pathological Q-wave in lead aVL, number of stents implanted, and number of sites with TIMI grade 3 flow).

Lipid profiles, and the clearance-time profile, were analysed by analysis of covariance models incorporating the baseline values as covariate, adding the factors treatment, visit number and renal function subgroup with all possible interaction terms. In order to evaluate the relation between the occurrence of clinical events and the behavior of renal function over time, separate analyses were performed evaluating the clearance-time profile for patients with or without adverse events during follow-up.

Results

Patient Population

Between April 1996 and October 1998, a total of 1677 patients were enrolled in LIPS. Complete data for creatinine clearance calculation were available for 1558 patients (92.9%) and were included in the present study. Table 1 shows the baseline characteristics of the 1248 patients with normal renal function (creatinine clearance above the first quintile [$\geq$ 55.9 ml/min]) and of the 310 patients with impaired renal function (creatinine clearance in the lowest quintile [< 55.9 ml/min]). Overall, patients with renal impairment were more likely to be older, female, to have lower weights and heights and more severe coronary artery disease and co-morbidities.

Four groups were considered for analysis: 1) Normal renal function treated with placebo (n=617); 2) Normal renal function treated with fluvastatin (n=631); 3) Impaired renal function treated with placebo (n=160); 4) Impaired renal function treated with fluvastatin (n=150). Baseline characteristics did not differ between fluvastatin and placebo groups (pooled across renal function categories) except that fluvastatin-treated patients were of greater height (169.8±8.4 cm vs. 168.9±8.4 cm; p=0.02) and weight (77.2±11.4 kg vs. 75.6±11.4 kg; p<0.01), and showed a higher prevalence of diabetes (14.3% vs. 10.0%; p<0.01).

Cardiovascular Events

Over a mean follow-up period of 3.8±0.1 years, the presence of mild renal impairment significantly increased the incidence of coronary atherosclerotic events in patients allocated to the placebo group (29.4% vs. 20.3% in patients with normal renal function; RR 1.42 [95% CI: 1.00 – 2.01]; p=0.048) (Table 2 and 3). Fluvastatin treatment, however, virtually abolished the negative influence of renal impairment on the incidence of adverse events, with no difference being observed between the outcomes of patients with and without renal dysfunction (15.3% vs. 15.7% respectively; RR 0.97 [95% CI: 0.61 – 1.56]; p=0.912) (Table 2 and 3; Figure 1).

Fluvastatin significantly reduced the incidence of coronary atherosclerotic events both in patients with normal renal function (15.7% vs. 20.3% in patients allocated to placebo; RR 0.73 [95% CI:0.56 – 0.95]; p=0.020) and in patients with renal impairment (15.3% vs. 29.4% in patients allocated to placebo; RR 0.50 [95% CI: 0.30 – 0.84]; p=0.008) (Table 2 and 3; Figure 2). No significant difference was observed between the benefit of fluvastatin for patients with renal dysfunction as compared to the benefit for those with normal renal function (Treatment/Disease interaction: p=0.203). No differences were observed in the incidence of repeat revascularisation caused by restenosis in patients with and without restenosis (4.4% vs. 5.2% respectively; p=0.65).

Lipoprotein Levels and Renal Function Outcome

Baseline lipoprotein levels were similar in both renal function groups, with the exception of HDL-C levels (Table 1). By 6 weeks, fluvastatin significantly reduced LDL-C levels compared with placebo in patients with renal impairment (median change with fluvastatin, –24% [95% CI: -28 – -20%] vs. +13% [95% CI: +9 – +17%]; p<0.001), and with normal renal function (–28% [95% CI: -30 – -25%] vs. +11% [95% CI: +9 – +13%]; p<0.001). The reduction was similar between patients with and without renal impairment and was maintained throughout the study. At the end of the study no significant differences in TG levels were observed between treatment groups. HDL-C levels increased by a median of 12% regardless of the allocated treatment or baseline renal function.

Renal function remained stable throughout follow-up and the predicted clearance-time profile was not influenced by fluvastatin treatment regardless of baseline creatinine clearance (Figure 3). No significant changes were observed in the renal function either in patients with or without adverse events during the observation period (Figure 3).

Predictors of Increased Cardiovascular Risk

Figure 4 shows the estimated risk ratios according to baseline creatinine clearance calculated by the Cox Proportional Hazards Model from the observed data (the mean clearance of the entire study population

was chosen as a reference point for the placebo group [risk ratio = 1]). A progressive increase in the risk of long-term complications is predicted with lower values of creatinine clearance. However, fluvastatin treatment caused a downward shift and flattening of the entire risk ratio curve. Interestingly, a risk ratio of 1 was associated with a baseline creatinine clearance of approximately 70 ml/min in the placebo group, but only 25 ml/min in fluvastatin-treated patients.

Multivariate Cox proportional hazards analysis identified creatinine clearance as an independent predictor of atherosclerosis-related adverse cardiac (Table 4). Other variables significantly associated with the incidence of adverse events included fluvastatin treatment, diabetes mellitus, multivessel disease, and the number of stents implanted during the procedure (Table 4).

Discussion

The major finding of the present study is that the presence of mild renal impairment significantly increases the incidence of coronary adverse atherosclerotic events after a first successful PCI, and that this effect is virtually abolished by long-term treatment with fluvastatin. The benefit of fluvastatin in patients with renal impairment could not be explained by a differential action on lipid levels or on renal function during follow-up. Moreover, no association was observed between the incidence of adverse events and changes in renal function during the follow-up period.

Together with measures to alleviate symptoms and myocardial ischemia, secondary prevention of further adverse events constitutes the core action in the chronic management of patients with diagnosed coronary disease. Although the need for repeat intervention has been recognized as the major limitation of angioplasty, the newly introduced drug-eluting stents has been shown to remarkably reduce restenosis rates.[25] In this scenario, the adoption of measures aiming to modify the natural course of the atherosclerotic disease itself (i.e. non restenosis-related complications) becomes the main focus of attention after percutaneous treatment. In the present study, fluvastatin was shown to significantly reduce the incidence of adverse events after angioplasty both in patients with and without renal dysfunction.

Secondary prevention strategies comprehend a conjoint of measures directed to reduce the impact of known risk factors on the outcomes of patients with already diagnosed coronary disease. The ideal treatment of a particular risk factor should decrease the risk of treated patients to the level of subjects not having the condition. Mild renal impairment has been identified as an important predictor of adverse events in patients with previous cardiovascular disease.[1-8] Although diuretic-based blood pressure control as well as long-term ramipril have previously been reported to improve the clinical outcomes, the hazardous effect of mild renal impairment was only partially decreased by these treatments.[7,17] Pravastatin has recently been demonstrated to reduce the incidence of events in patients with renal dysfunction. However, differently from the vast majority of reports, in that study the presence of renal impairment have not influenced the late clinical outcomes.[18] Moreover, the extent to which the statin reduced the risk was not evaluated in relation to patients with normal renal function.[18] In the current study, mild renal impairment was detected to significant and independently impair the long-term clinical outcomes after coronary intervention. Notably, fluvastatin treatment was shown to equalize the outcomes of patients of mild renal impairment and patients with normal renal function, virtually abolishing the hazardous effect of the renal dysfunction.

In contrast to previous studies,[21] no effect of fluvastatin treatment on renal function was observed during the 4-year follow-up period. These results suggest that the benefit of fluvastatin was not mediated by a direct effect to stabilize or improve creatinine clearance. Moreover, the occurrence of adverse events was not related to changes in renal function. In addition, the effect of fluvastatin in patients with renal dysfunction could not be explained by a more pronounced lipid reduction in this group. These results suggest that the benefit of statins on patients with renal impairment may be associated to mechanisms not related to a direct effect on the kidney physiology and independent of their lipid-lowering effects. Although not assessed in this study, statins have been extensively reported to positively influence a variety of pathophysiological atherogenic mechanisms known to be altered in patients with renal impairment.[9-16,19]

Study Limitations

It should be noted that the findings of the present study may not be extrapolated to all patients with coronary heart disease, as only patients who underwent successful elective percutaneous interventions were included. Therefore, medically- and surgically-treated patients, and those undergoing unsuccessful procedures, were not represented in the study population. Furthermore, the impact of fluvastatin on patients with severe renal impairment was also not assessed in the present study, while more detailed investigations of the nature of the renal impairment (e.g. diagnosis of underlying renal pathology or assessment of microalbuminuria or proteinuria) and measurements of biochemical pro-atherogenic markers were not available. These limitations do not alter the overall conclusion that fluvastatin treatment has a clinically relevant impact in patients with mild renal impairment.

Conclusions

Patients with mild renal impairment show an increased risk of long-term complications following coronary intervention. Long-term treatment with fluvastatin, however, provides a safe and effective means of obviating this risk acting through mechanisms not related to an improvement in kidney function. Effective diagnosis of mild renal dysfunction therefore represents an important step in the risk assessment evaluation of patients with coronary heart disease, and treatment with fluvastatin should be included as an important intervention to minimize the occurrence of long-term adverse events in this population.

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Table 1. Baseline patient characteristics according to renal function

	Normal renal function (n=1248)	Mild renal impairment (n=310)	p-value
Age, y±SD	58±9	69±7	<0.01
Female sex, n (%)	146 (11.7)	102 (32.9)	<0.01
Height, cm±SD	170±8	165±8	<0.01
Weight, kg±SD	79±11	68±10	<0.01
Risk factors and cardiovascular antecedents			
Previous MI, n (%)	540 (43.3)	144 (46.5)	0.34
Diabetes, n (%)	152 (12.2)	38 (12.3)	1.00
Hypertension, n (%)	435 (34.9)	159 (51.3)	<0.01
Previous stroke, n (%)	28 (2.2)	14 (4.5)	<0.03
Peripheral vascular disease, n (%)	62 (5.0)	33 (10.6)	<0.01
Current smoker, n (%)	363 (29.1)	53 (17.1)	<0.01
Cholesterol lowering diet, n (%)	217 (17.4)	76 (24.5)	0.01
Family history of CAD, n (%)	372 (30.0)	76 (24.7)	0.07
Ejection fraction, %±SD	62.3±11.8	61.4±12.7	0.24
Single-vessel disease, n (%)	818 (65.5)	175 (56.5)	0.01
Multivessel disease, n (%)	430 (34.5)	135 (43.6)	0.01
Clinical presentation			
stable angina, n (%) *	618 (50.2)	164 (53.2)	0.37
unstable angina, n (%)	618 (50.2)	164 (53.2)	0.37
Treated vessel †			
RCA, n (%)	484 (29.8)	128 (29.5)	0.91
LAD, n (%)	766 (47.2)	207 (47.7)	0.87
LCx, n (%)	371 (22.9)	98 (22.63)	0.95
Lesions treated per patient, les/pt±SD	1.30±0.6	1.40±0.7	0.03
Lesion type			
A, n (%)	325 (20.1)	70 (16.2)	0.07
B1, n (%)	566 (35.0)	153 (35.5)	0.91
B2, n (%)	540 (33.4)	150 (34.8)	0.65
C, n (%)	185 (11.4)	58 (13.5)	0.28
Lesions treated with stent, n (%)	910 (56.1)	245 (56.5)	0.91

Lipids, mmol/l±SD [mg/dl±SD]

Total cholesterol	5.17±0.81 [200±31]	5.18±0.88 [200±33]	0.87
LDL-C	3.43±0.76 [133±29]	3.38±0.82 [131±31]	0.40
HDL-C	0.96±0.30 [37±12]	1.02±0.29 [39±12]	<0.01
Triglycerides	1.75±0.77 [154±68]	1.71±0.69 [150±69]	0.51
Serum creatinine, mmol/l±SD [mg/dl±SD]	99±16 [1.11±1.7]	121±27 [1.33±2.8]	<0.01
Creatinine clearance, ml/min±SD	80±18	47±7	<0.01

CAD=coronary atherosclerotic disease; RCA=right coronary artery; LAD=left anterior descending; LCx=left circumflex artery; SD=standard deviation

* Includes patients with silent ischemia

† Categories are not mutually exclusive

Table 2. Incidence of adverse coronary atherosclerotic events at follow-up according to renal function at baseline and allocated treatment.

	Normal renal function			Renal impairment		
	Placebo (n=617)	Fluvastatin (n=631)	p-value*	Placebo (n=160)	Fluvastatin (n=150)	p-value*
Adverse Coronary Atherosclerotic Events†, n(%)	125 (20.3)	99 (15.7)	0.039	47 (29.4)	23 (15.3)	0.004
Cardiac death, n(%)	14 (2.3)	7 (1.1)	0.13	3 (1,9)	3 (2.0)	1.0
Non-cardiac death, n(%)	0	0	--	0	0	--
All-cause death, n(%)	14 (2.3)	7 (1.1)	0.13	3 (1,9)	3 (2.0)	1.0
Cardiac death/myocardial infarction, n(%)	37 (6.0)	28 (4.4)	0.25	13 (8.1)	7 (4.7)	0.25
All-cause death/myocardial infarction, n(%)	37 (6.0)	28 (4.4)	0.25	13 (8.1)	7 (4.7)	0.25

* Placebo vs. fluvastatin by Fisher's exact test

† cardiac death, non-fatal myocardial infarction, and re-interventions not related to restenosis

Table 3. Risk of adverse coronary atherosclerotic events* at follow-up according to renal function at baseline and allocated treatment (derived from Cox proportional hazards analysis accounting for the treatment/disease interaction†).

Effect	Risk reduction
Effect of renal impairment on patients with placebo	RR 1.42 (95% CI: 1.00–2.01); p=0.048
Effect of renal impairment on patients treated with fluvastatin	RR 0.97 (95% CI: 0.61–1.56); p=0.912
Fluvastatin effect on patients normal renal function	RR 0.73 (95% CI:0.56–0.95); p=0.020
Fluvastatin effect on patients with renal impairment	RR 0.50 (95% CI: 0.30–0.84); p=0.008
Treatment/Disease interaction †	RR 0.83 (95% CI: 0.62–1.11); p=0.203

* cardiac death, non-fatal myocardial infarction, and re-interventions not related to restenosis

† The treatment/disease interaction reflects the effect of fluvastatin treatment in the renal impairment subgroup relative to the treatment effect in the non-renal impairment subgroup

Table 4. Multivariate predictors of adverse coronary atherosclerotic events at follow-up.

|	Hazard Ratio (95% CI)	p-value
Fluvastatin treatment	0.66 (0.52–0.83)	0.0005
Diabetes Mellitus	1.57 (1.14–2.16)	0.0063
Multivessel disease	1.33 (1.04–1.69)	0.0236
Number of stents implanted	1.25 (1.04–1.51)	0.0186
Creatinine clearance*	0.63 (0.42–0.95)	0.0271

*logarithmic transformation

Patients treated with placebo

p=0.009 (log-rank)
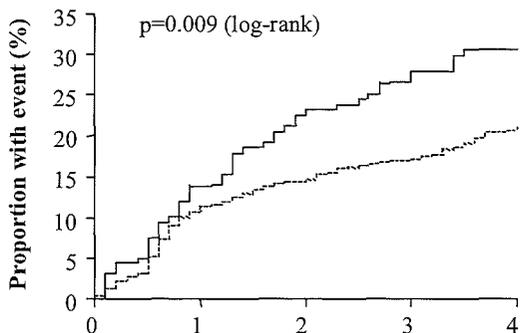
Patients at risk

	0	1	2	3	4
Renal impaiment	160	133	117	107	42
Normal renal function	617	546	519	498	192

Patients treated with fluvastatin

p=0.92 (log-rank)

—— Renal impairment
‾‾‾‾‾ Normal renal function
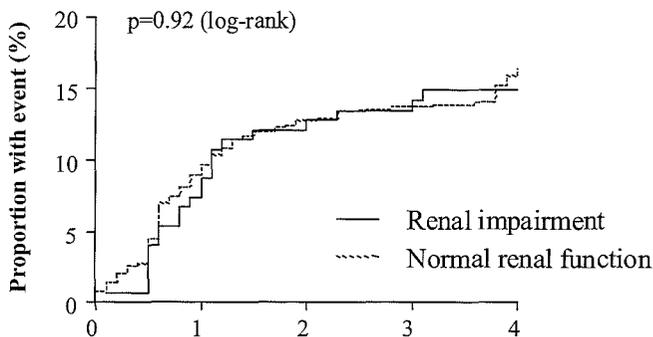
Patients at risk

Time (Years)	0	1	2	3	4
Renal impairment	150	137	126	122	40
Normal renal function	631	568	537	523	217

Figure 1. Cumulative risk of atherosclerosis-related adverse cardiac (cardiac death, non-fatal myocardial infarction and all reinterventions not caused by coronary restenosis) in patients treated with placebo (upper) or with fluvastatin (lower) according to the baseline renal function.

Patients with renal impairment

p=0.003 (log-rank)

Patients at risk					
Placebo	160	133	117	107	42
Fluvastatin	150	137	126	122	40

Patients normal renal function

p=0.04 (log-rank)

Placebo
Fluvastatin

Patients at risk		Time (Years)			
Placebo	617	546	519	498	192
Fluvastatin	631	568	537	523	217
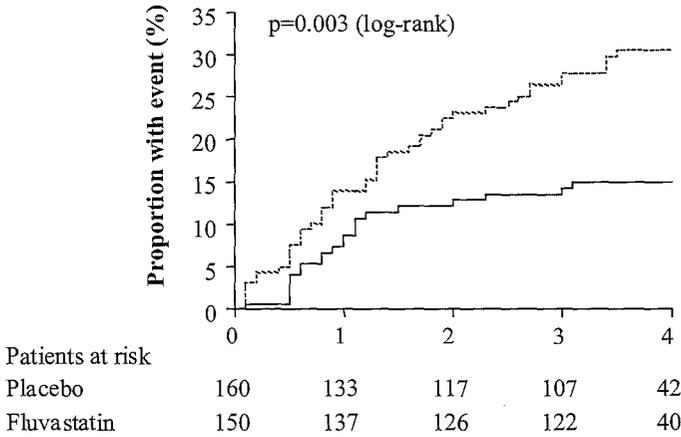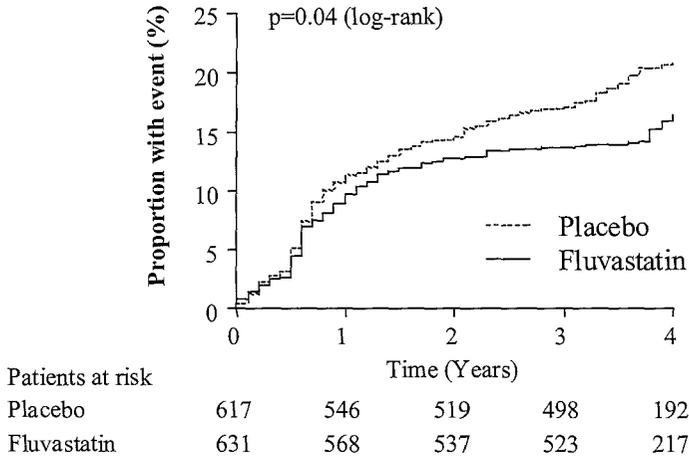
Figure 2. Cumulative risk of atherosclerosis-related adverse cardiac (cardiac death, non-fatal myocardial infarction and all reinterventions not caused by coronary restenosis) in patients with renal impairment (upper) or normal renal function (lower) treated with placebo or with fluvastatin.
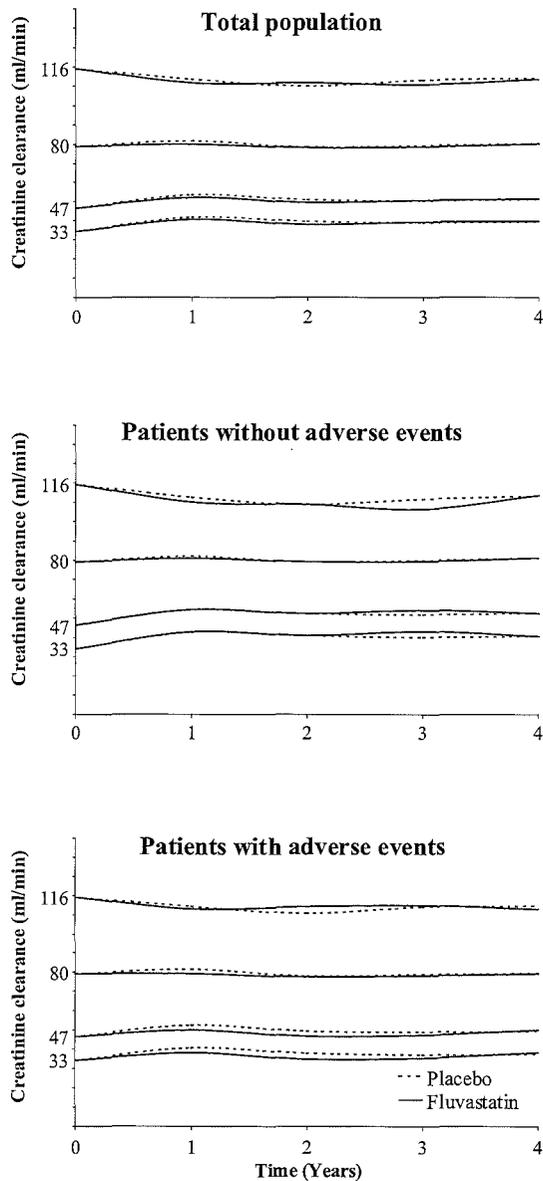
Figure 3. Predicted changes in creatinine clearance (ml/min) throughout follow-up in patients randomised to receive placebo or fluvastatin. Four baseline clearance levels are depicted in the figure: 47 ml/min (actual mean clearance of patients with renal impairment), 80 ml/min (actual mean clearance of patients with normal renal function), 33 ml/min (mean clearance of patients with renal impairment –2 S.D.) and 116 ml/min (mean clearance of patients with normal renal function +2 S.D.). Changes in renal function are shown for the total population (upper), for patients without events (med), and for patients with at least one adverse event during follow-up (lower).
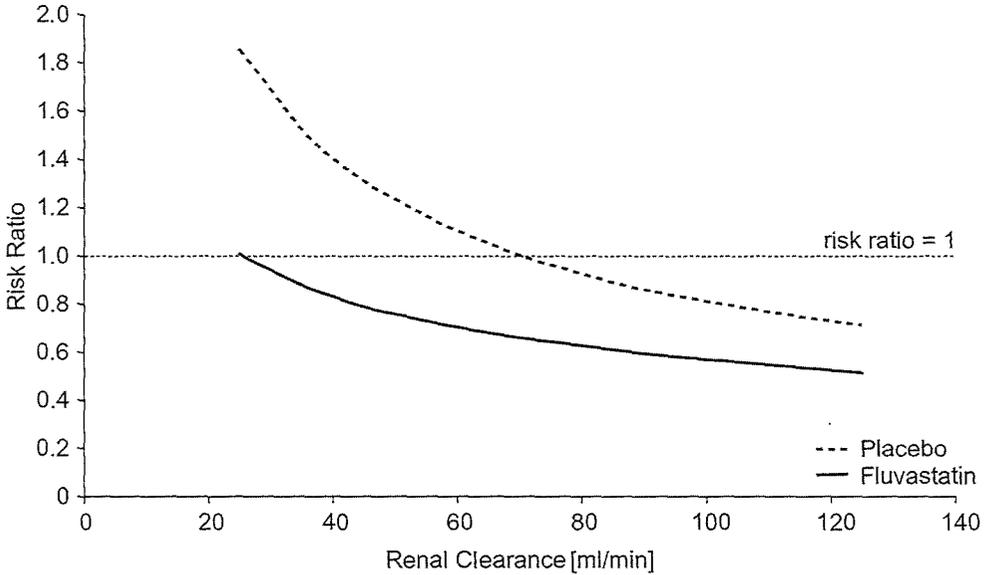
Figure 4. Estimated risk ratios as a function of creatinine clearance (ml/min) in patients randomised to receive treatment with either fluvastatin or placebo. The hazard ratio curves were estimated according to the Cox Proportional Hazards Model (risk ratios calculated with the mean creatinine clearance of the entire study population chosen as a reference point for the placebo group [risk ratio = 1]).

Chapter 11

Long-Term Fluvastatin after Coronary Intervention Reduces the Risk of Patients with Multivessel Disease to the Level of those with Single-vessel Disease - A LIPS Substudy

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Submitted for publication

Long-Term Fluvastatin after Coronary Intervention Reduces the Risk of Patients with Multivessel Disease to the Level of those with Single-vessel Disease - A LIPS Substudy

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Abstract

Aims: To evaluate the impact of the extent of coronary disease (single- or multivessel) and of fluvastatin treatment on the incidence of long-term cardiac atherosclerotic complications in the Lescol Intervention Prevention Study.

Methods and Results: 1063 patients with single-vessel disease and 614 patients with multivessel disease were randomized to receive fluvastatin (40 mg bid) or placebo for at least 3 years following a first successful percutaneous coronary intervention. The incidence of cardiac atherosclerotic events (cardiac death, non-fatal myocardial infarction, and coronary re-interventions not related to restenosis) was evaluated. Patients with multivessel disease tended to be older and presented a higher prevalence of associated risk factors and cardiovascular antecedents. In patients allocated to placebo, the presence of multivessel coronary disease was associated with a significantly higher rate of cardiac atherosclerotic events compared with single-vessel disease (RR 1.67 [95% CI: 1.24 – 2.25]; p<0.001). However, patients with multivessel or single-vessel disease treated with fluvastatin presented similar long-term outcomes (RR 1.28 [95% CI: 0.90 – 1.81]; p=0.168).

Conclusions: Long-term fluvastatin after percutaneous intervention reduced the risk of patients with multivessel disease to the level of those with single-vessel disease.

Key words: HMG-CoA reductase inhibitors, coronary disease, cholesterol, angioplasty

INTRODUCTION

The extent of atherosclerotic disease has been identified as one of the most important predictors of long-term cardiac events in patients with coronary heart disease [1-5]. In previous studies, the presence of multifocal disease on coronary angiography, together with low ventricular function, has been shown to be a reliable predictor of long-term mortality in patients who have not undergone early invasive treatment [1-5]. Currently, patients with multivessel coronary disease account for a significant proportion of patients undergoing invasive procedures [6]. Although a high likelihood of procedural success can be expected [7-13], neither percutaneous nor surgical approaches have been shown to decrease the long-term risk of multivessel disease to the level of risk associated with less severe disease stages (i.e. single-vessel disease) [2,3]. Despite reducing ischemia-related symptoms, myocardial revascularization techniques do not delay the underlying pathophysiological processes involved in atherosclerotic disease progression.

Long-term administration of HMG-CoA reductase inhibitors (statins) is established as an effective means of reducing the incidence of cardiovascular complications, especially in patients with higher individual baseline risk [14-18]. In the recent randomized Lescol Intervention Prevention Study (LIPS), long-term fluvastatin significantly reduced the incidence adverse events in patients with coronary atherosclerotic disease treated with percutaneous intervention [18]. The present study constitutes a prespecified, post-hoc analysis of the LIPS trial and aimed to evaluate the impact of the extent of coronary disease and of fluvastatin treatment on the incidence of late cardiac atherosclerotic complications.

METHODS

Study Design and Patient Population

The study design and primary results of LIPS have been described elsewhere [18,19]. Briefly, LIPS was a prospective, multinational, placebo-controlled, double-blind trial in which patients were randomized to receive either fluvastatin (Lescol, Novartis Pharma AG, Basel, Switzerland) 40 mg twice per day or placebo. Study medication was administered for at least 3 years, but no longer than 4 years, and dietary and lifestyle counseling was given to all patients.

Patients who had undergone a first successful PCI (angiographic residual stenosis < 50% and absence of post-procedure in-hospital myocardial necrosis, repeat target lesion revascularization, or death) were considered eligible for the study. At enrollment, patients had not received lipid-lowering therapy in the preceding 6 weeks and fulfilled one of the following baseline lipid profile criteria: 1) total cholesterol between 135 mg/dl (3.5 mmol/l) and 270 mg/dl (7.0 mmol/l) with fasting triglycerides < 400 mg/dl (4.5 mmol/l), 2) total cholesterol < 212 mg/dl (5.5 mmol/l) for patients whose lipids levels were measured between 24 hours and 4 weeks after an episode of myocardial infarction, or 3) total cholesterol < 232 mg/dl (6.0 mmol/l) for patients with diabetes mellitus. Local investigators were blinded to the results of the biochemical analysis, unless total cholesterol levels were > 278 mg/dl (7.2 mmol/l). If total cholesterol values remained above this level for more than 3 months, open-label statin treatment or other interventions could be administered. All blood analyses were performed at a central laboratory (Analytico Medinet, Breda, The Netherlands).

Patients were divided into two groups (single-vessel or multivessel) based on the extent of coronary disease, which was evaluated in the baseline pre-procedure angiogram [5]. Single-vessel disease was diagnosed if significant luminal stenosis (> 50% diameter stenosis by visual analysis) was restricted to one vessel territory. Patients were included in the multivessel group if obstructive lesions were identified in two or three vessel territories. The actual number of treated lesions as well as the choice of the

interventional strategy was left to the discretion of the operator. The study protocol is in accordance with the Declaration of Helsinki and was approved by local ethics committees. All patients gave informed written consent.

Follow-up and Clinical Endpoints

In this substudy, outcomes were evaluated as the incidence of atherosclerosis-related adverse cardiac events, defined as: 1) cardiac death, 2) non-fatal myocardial infarction (new pathological Q-waves or a total CPK level greater than twice the normal upper limit with presence of CPK-isoenzyme MB), or 3) all new revascularizations (either surgical or percutaneous) not caused by the occurrence of coronary restenosis. Atherosclerosis-related adverse cardiac events were a pre-defined endpoint of LIPS [18,19], and was specified due to the fact that the benefits of fluvastatin after PCI have been previously shown to be unrelated to any effect of the drug on restenosis [20].

Statistical Analysis

All analyses were carried out on an intention-to-treat basis. Continuous variables were expressed as mean ± SD and were compared using Student's unpaired *t*-test. Fisher's exact test was used for categorical variables, and Wilcoxon scores were used for categorical variables with an ordinal scale. Discrete variables were expressed as counts and percentages and were compared in terms of relative risks (for multivessel disease compared with single-vessel disease) with 95% CI. All statistical tests were 2-tailed. Event-free survival distribution was estimated according to the Kaplan-Meier method, and the overall incidence of cardiac events was tested using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. The Cox proportional hazards model and the Cochran-Mantel-Haenszel test were used to assess risk reduction and to compare the incidences of the primary and secondary clinical endpoints, respectively.

The treatment/multivessel disease interaction was calculated in a multivariate approach with treatment, extent of multivessel disease, and an interaction factor specifying the simultaneous absence or presence of

both previous factors in the model. This enabled calculation of the effect of fluvastatin in patients without multivessel disease (i.e. single-vessel) separately from the effect in patients with multivessel disease. This approach also allowed calculation of the effect of disease extent in patients treated with placebo or fluvastatin. Lipid profiles were analyzed in an analysis of covariance model incorporating the baseline (at visit 1) as covariate, and adding as factors, treatment, visit number (visits > 1) and subgroup with all possible interaction terms.

RESULTS

Patient Population and Baseline Characteristics

Between April 1996 and October 1998, a total of 1677 patients were enrolled in LIPS. Of these, 1063 patients (63.4%) had single-vessel disease (541 randomized to placebo and 522 to fluvastatin treatment) and 614 patients (36.6%) had multivessel disease (292 randomized to placebo and 322 to fluvastatin treatment).

Patient characteristics, subdivided according to the coronary disease pattern and allocated treatment, are shown in Table 1. Several differences were observed between patients with single- and multivessel disease (pooled over treatment groups). Patients with multivessel disease were more likely to be older, and to have suffered previous myocardial infarction, peripheral vascular disease and stroke. Patients with multivessel disease were also less likely to be current smokers, and showed ejection fractions that were slightly, but significantly, reduced. Treated vessels differed between single- and multivessel patients. The right coronary artery and the left circumflex were treated more frequently in patients with multivessel disease, while the left anterior descending artery was more frequently treated in patients with single-vessel disease. The number of lesions treated in the index procedure was higher in the multivessel group; two or more lesions were dilated in 42.5% of multivessel patients and in 14.2% of single-vessel patients (p<0.001). Baseline characteristics did not differ between the fluvastatin and placebo groups (pooled over the single-vessel and multivessel groups) with the exception of weight, which was higher in fluvastatin-treated patients. A higher prevalence of diabetes was observed in multivessel patients treated with fluvastatin than those treated with placebo.

Long-term Atherosclerosis-Related Adverse Cardiac Events

Fluvastatin treatment significantly reduced the risk of coronary atherosclerotic events by 43% compared with placebo in patients with multivessel disease (17.7% vs 29.5%, respectively; RR 0.57 [95% CI: 0.41 -

0.81]; p=0.002) (Table 2). The benefit of fluvastatin treatment in single-vessel patients (14.9% vs 18.7% in single-vessel with placebo; RR 0.75 [95% CI: 0.56 - 0.01]; p=0.057) was not significantly different from the benefit observed in patients with multivessel disease (treatment/disease interaction: p=0.25) (Table 2).

In patients receiving placebo, the presence of multivessel disease significantly increased the risk of cardiac events compared with patients with single-vessel disease (RR 1.67 [95% CI: 1.24 – 2.25]; p<0.001) (Table 2 and Figure 1). After treatment with fluvastatin, however, no significant difference in outcomes between patients with multivessel or single-vessel disease was observed (RR 1.28 [95% CI: 0.90 – 1.81]; p=0.168) (Table 2). As shown in Figure 1, multivessel and single-vessel disease patients treated with fluvastatin showed similar curves for survival free of cardiac events after 4 years of follow-up (p=0.19 by log-rank test).

A multivariate Cox proportional hazards analysis was performed to determine whether the severity of coronary disease could independently predict the incidence of long-term coronary atherosclerotic events. Additionally, separate analyses were performed in order to identify the predictors in patients randomized to placebo or fluvastatin (Figure 2). The final multivariate model for the entire patient population included the following variables: fluvastatin treatment, diabetes, multivessel disease, number of stents implanted, and calculated creatinine clearance (logarithmic transformation) [21]. Similarly, when the analysis was restricted only to patients in the placebo group, the presence of multivessel disease independently predicted the occurrence of long-term coronary atherosclerotic events. In patients treated with fluvastatin, however, multivessel disease did not influence the risk of future cardiac events (Figure 2).

Lipoprotein Levels

There were no differences in baseline blood lipid levels between individual groups (Table 1). By 6 weeks, fluvastatin significantly reduced LDL cholesterol levels compared with placebo in patients with both single-vessel disease (median change with fluvastatin, -28.2% [95% CI: -30.3% – -25.8%] vs +10.2%

[95% CI: +8.1% – +13.5%]; p<0.001), and with multivessel disease (median change with fluvastatin, -25% [95% CI: -28.3% – -22.7%] vs +12.5% [95% CI: +9.1% – +16.7%]; p<0.001). The reduction in LDL cholesterol levels produced by fluvastatin was maintained throughout the study and was of similar magnitude in patients with single- and multivessel disease (Figure 3).

HDL cholesterol levels increased by a median of 11.1%, regardless of treatment or coronary disease pattern. By 6 weeks, fluvastatin produced a significant decrease in triglycerides compared with placebo in patients with single-vessel disease (median change with fluvastatin -14.3% [95% CI: -17.9% – -11.1%] vs 0% [95% CI: -3.7% – +5.6%]; p<0.001). A similar reduction was observed in patients with multivessel disease (median change with fluvastatin -17.2% [95% CI: -23.5% – -10%] vs 0% [95% CI: -4.3% – +4.8%]; p<0.001). By the end of the study, however, triglyceride levels were similar regardless of allocated treatment or coronary disease pattern.

DISCUSSION

The results of the present study show that long-term fluvastatin effectively eliminated the negative effect of multivessel disease on the incidence of future coronary atherosclerotic events after percutaneous intervention. Although the presence of multivessel disease significantly and independently increased the rates of adverse events among patients treated with placebo, patients with multivessel disease receiving fluvastatin presented similar outcomes during the 4-year follow-up period as compared with patients with single-vessel disease.

Fluvastatin Effect on Atherosclerotic Disease Progression

The extent of atherosclerotic disease, both coronary and at extra-cardiac sites, has been recognized as a powerful predictor of cardiovascular events, especially during long-term follow-up [1-5,22-24]. Indeed, the presence of multivessel disease and other well-known clinical risk factors, such as diabetes and hypercholesterolemia, were demonstrated to be the only predictors of 20-year survival in patients with coronary heart disease [2], with no influence of the type of initial revascularization strategy employed, whether surgical or percutaneous [2]. These findings demonstrate the critical importance of the underlying chronic disease progression, which is not affected by current invasive treatments. In the present study, patients with multivessel disease treated with fluvastatin showed a flattened curve for survival free of events beyond 1 year, in clear contrast to the placebo group, which showed a persistent occurrence of events throughout the follow-up period. Indeed, fluvastatin virtually equalized the long-term outcomes of multivessel and single-vessel patients. These favorable clinical effects may be due to an effective, sustained action of fluvastatin on atherosclerotic disease stabilization. Importantly, these findings were observed in a study population with average baseline lipid levels. Nevertheless, fluvastatin treatment was associated with a significant reduction in blood cholesterol that was maintained during the entire study period, with no significant differences between patients with single- or multivessel disease.

Repeat Revascularization

The need for subsequent repeat revascularization has been recognized as the main limitation of percutaneous procedures in the treatment of multivessel disease, and this complication has been only partially overcome by the use of coronary stent implantation [10-13,25]. However, drug-eluting stents have been proven to strikingly decrease the incidence of restenosis [26,27]. Although it has not yet been tested in patients with multivessel disease, this new therapy is expected to decrease the rate of target lesion revascularization after PCI to levels observed in surgical patients. Therefore, in this 'restenosis-free' context, the implementation of disease-modifying measures to reduce cardiac events related to the atherosclerotic disease process itself (i.e. non restenosis-related complications) becomes the major focus of medical attention after percutaneous interventions. In light of the marked clinical benefit observed in our study, long-term fluvastatin treatment can clearly be considered to be an important measure in the post-procedure management following PCI. Both patients with single- or multivessel disease were shown to benefit from fluvastatin treatment, which essentially equalized the long-term clinical outcome of the two patient groups. To the best of our knowledge, this is the first report to evaluate the relative impact of the angiographic extent of coronary disease on the long-term incidence of atherosclerotic complications in patients treated with statins.

Study Limitations

The findings of this study cannot be extrapolated to all patients undergoing PCI because only patients who had undergone a successful procedure were considered for enrollment. The present investigation also suffers from the inherent limitations of subgroup analysis, namely a lack of statistical power due to limited sample sizes. In addition, coronary angiograms were analyzed locally, rather than at a central angiographic laboratory. The fact that the extent of coronary artery disease was evaluated by angiography may lead to an underestimate of the actual atherosclerotic burden [28]; nevertheless, angiography alone has been extensively demonstrated to be one of the most powerful predictors of long-term outcomes in patients with coronary artery disease. Indeed, in the present study, angiographic characterization was able to distinguish

effectively between patients at two different risk levels (single- or multivessel disease) among those treated with placebo.

Conclusions

Fluvastatin represents an effective therapeutic measure to reduce the occurrence of late cardiac atherosclerotic adverse events after percutaneous coronary interventions. During a 4-year follow-up period, fluvastatin reduced the risk of patients with multivessel disease to the level of those with single-vessel disease.

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Table 1 – Baseline patient characteristics according to coronary disease pattern and treatment

	Single-vessel disease		Multivessel disease		p value*
	Placebo (n=541)	Fluvastatin (n=522)	Placebo (n=292)	Fluvastatin (n=322)	
Age, y ± SD	58.9 ± 10.1	59.4 ± 10.4	61.9 ± 9.0	61.0 ± 9.7	<0.01
Male sex, n (%)	454 (83.9)	431 (82.6)	241 (82.5)	280 (87.0)	0.39
Height, cm ± SD	169 ± 8	170 ± 9	168 ± 9	170 ± 8	0.13
Weight, kg ± SD †	75.5 ± 11.5	77.1 ± 11.6	75.9 ± 11.2	77.3 ± 11.1	0.55
Risk factors and cardiovascular antecedents					
Previous MI, n (%)	219 (40.5)	203 (38.9)	154 (52.7)	168 (52.2)	<0.01
Diabetes, n (%) ‡	52 (9.6)	64 (12.3)	30 (10.3)	56 (17.4)	0.06
Hypertension, n (%)	192 (35.5)	202 (38.7)	125 (42.8)	128 (39.8)	0.09
Previous stroke, n (%)	12 (2.2)	8 (1.5)	15 (5.1)	9 (2.8)	0.01
Peripheral vascular disease, n (%)	31 (5.7)	20 (3.8)	26 (8.9)	30 (9.3)	<0.01
Current smoker, n (%)	160 (29.6)	140 (26.8)	75 (25.7)	71 (22.0)	0.05
Family history of CAD, n (%)	157 (29.2)	151 (29.2)	94 (32.3)	88 (27.5)	0.79
Ejection fraction, % ± SD	62.1 ± 11.2	63.0 ± 11.6	61.2 ± 13.2	61.0 ± 12.4	0.03
Clinical presentation					
stable angina, n (%) §	267 (49.8)	248 (47.9)	149 (51.9)	170 (53.5)	0.13
unstable angina, n (%)	269 (50.2)	269 (52.0)	138 (48.1)	148 (46.5)	0.13
Number of segments with significant stenosis	1.2 ± 0.5	1.2 ± 0.5	2.8 ± 1.0	2.8 ± 1.0	<0.01
Treated vessel					
RCA, n (%)	165 (26.0)	169 (28.0)	145 (32.3)	177 (32.9)	<0.01
LAD, n (%)	346 (56.2)	310 (51.4)	179 (39.9)	214 (39.8)	<0.01
LCx, n (%)	113 (17.8)	123 (20.4)	124 (27.6)	147 (27.3)	<0.01
2 or more lesions treated, n (%)	79 (14.6)	72 (13.8)	115 (39.4)	146 (45.3)	<0.01
Lesions treated per patient (± SD)	1.2 ± 0.4	1.2 ± 0.4	1.5 ± 0.8	1.7 ± 0.9	<0.01
Lesions treated with stent, n (%)	359 (56.6)	350 (58.0)	239 (53.2)	289 (53.7)	0.07

Lipids, mg/dl ± SD [mmol/l ± SD]

Total cholesterol	199.5±32.9 [5.16±0.85]	199.9±32.9 [5.17±0.85]	200.7±31.3 [5.19±0.81]	199.5±30.5 [5.16±0.79]	0.90
LDL cholesterol	131.5±30.5 [3.40±0.79]	133.8±30.5 [3.46±0.79]	131.9±28.6 [3.41±0.74]	132.3±29.4 [3.42±0.76]	0.43
HDL cholesterol	37.5±12.0 [0.97±0.31]	36.7±10.8 [0.95±0.28]	37.9±11.2 [0.98±0.29]	37.9±13.1 [0.98±0.34]	0.57
Triglycerides	154.0±67.3 [1.74±0.76]	151.3±56.6 [1.71±0.64]	157.5±70.0 [1.78±0.79]	151.3±6.4 [1.71±0.75]	0.20

SD = standard deviation; CAD = coronary atherosclerotic disease; RCA = right coronary artery; LAD = left anterior descending; LCx = left circumflex artery

* Related to the comparison between the single-vessel and multivessel groups, regardless of treatment allocation.

† p = 0.006 for difference between placebo vs fluvastatin treatments pooled over single- and multivessel groups.

‡ p = 0.01 for the difference between placebo vs fluvastatin in the multivessel group

§ Includes patients with silent ischemia

Table 2. Incidence and relative risks of adverse atherosclerotic events at follow-up according to coronary disease extent at baseline and allocated treatment.
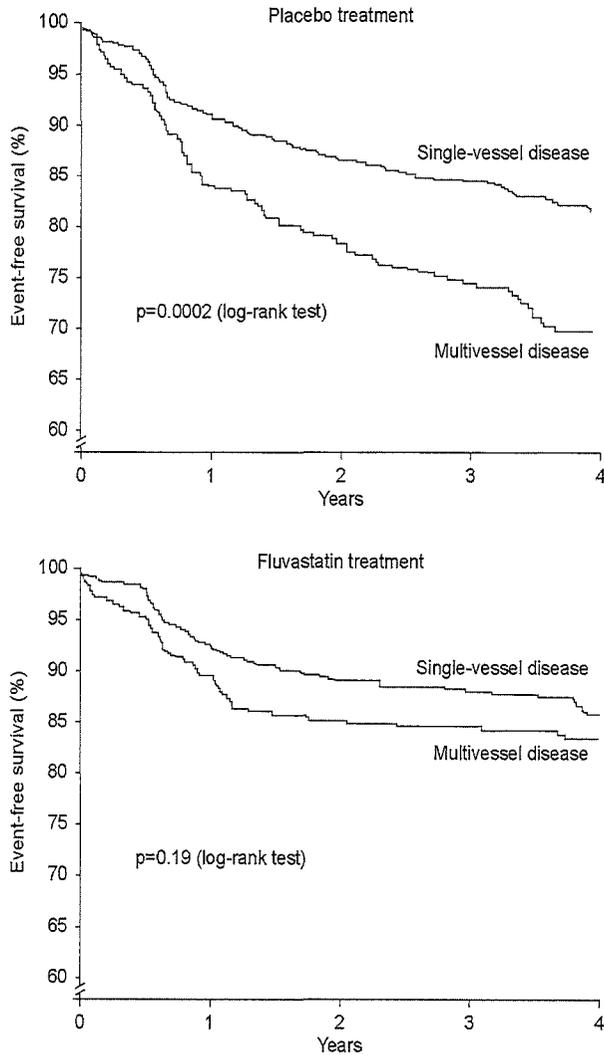
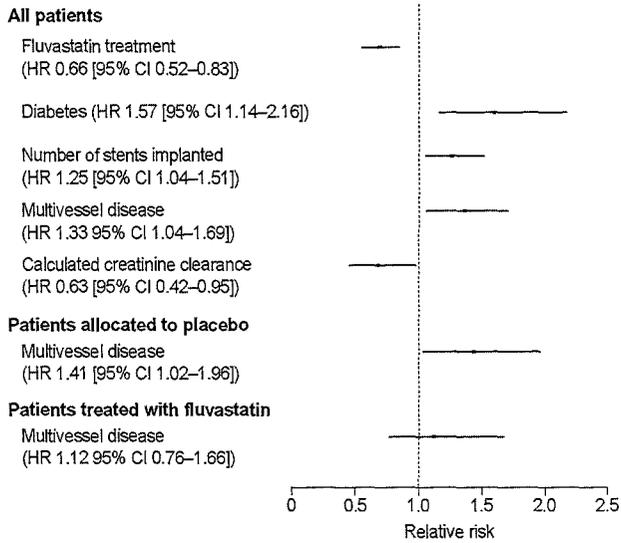| *Relative Risks of atherosclerosis-related adverse cardiac events**	
Fluvastatin effect on patients with multivessel disease	RR 0.57 (95% CI: 0.41 - 0.81); p=0.002
Fluvastatin effect on patients with single-vessel disease	RR 0.75 (95% CI: 0.56 - 1.01); p=0.057
Effect of CAD extension (single- vs multivessel disease) on patients with fluvastatin	RR 1.28 (95% CI: 0.90 - 1.81); p=0.168
Effect of CAD extension (single- vs multivessel disease) on patients with placebo	RR 1.67 (95% CI: 1.24 – 2.25); p<0.001
Treatment/Disease interaction †	RR 0.88 (95% CI: 0.70 - 1.10); p=0.252

CAD=coronary artery disease

* cardiac death, non-fatal myocardial infarction, and re-interventions not related to restenosis. Relative risks derived from the Cox proportional hazards analysis.

† The treatment/disease interaction reflects the effect of fluvastatin treatment in the multivessel group relative to the treatment effect in the single-vessel group
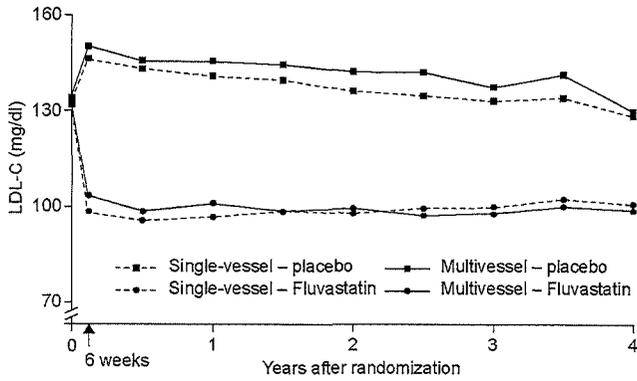
Figures

Figure 1. Cumulative curves for survival free atherosclerosis-related adverse cardiac events in patients with either single- or multivessel disease randomized to receive treatment with placebo (upper graph) or fluvastatin (lower graph). Event-free survival distribution was estimated as described in the text, and p values were obtained from the log-rank test.

Figure 2. Relative risks and 95% confidence intervals of independent predictors for atherosclerosis-related adverse cardiac events in all patients (upper). Also the relative risks and 95% confidence intervals for the presence of multivessel disease is shown for patients randomized to placebo (mid) or fluvastatin (lower). Relative risks were calculated according to a multivariate Cox proportional hazards analysis, as described in the text. NS, not significant. A logarithmic transformation was used for the calculated creatinine clearances.

Figure 3. Mean change in LDL cholesterol levels (mg/dl) throughout follow-up in patients with either single- or multivessel disease randomized to receive treatment with either fluvastatin, 40 mg twice daily or placebo.

Summary and Conclusions

Coronary revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery is used for the treatment of obstructive coronary atherosclerosis in symptomatic patients. In this thesis, we evaluated the results obtained after coronary revascularization in different subsets of patients.

Part 1: Clinical trials and observational studies on coronary revascularization

The concept of plaque sealing by balloon angioplasty for mild lesions at strategically important sites (proximal locations in large vessels) has been proposed to prevent acute coronary events in patients with angiographically non-significant coronary lesions[1]. The hypothetical clinical benefit of reducing the risk of subsequent thrombotic occlusions thanks to the neoendothelium overgrowing the inflicted wound has not yet been prospectively validated. In **chapter 1,** we investigated the clinical and angiographic outcome of patients with chronic stable angina and a single de novo lesion, categorized in 3 groups based on the angiographic degree of stenosis severity prior to percutaneous coronary intervention (<50%, 50%-99% and >99% pre-procedural diameter stenosis). The one-year mortality and rate of non-fatal myocardial infarction did not differ between balloon and stented angioplasty for any of the stenosis severity categories. These results argue against the performance of PCI on angiographically non-significant stenoses because the relatively high one-year event rates outweigh any hypothetical long-term benefit that might be derived from this type of intervention.

In **Chapter 2,** we examined the clinical outcome of patients with multivessel disease undergoing coronary revascularization with either percutaneous coronary intervention with multiple stenting or bypass surgery. After one year of follow-up, 8.7% of 1518 patients randomized to coronary stenting versus 9.1% of 1533 patients randomized to bypass surgery reached the primary clinical endpoint of death, nonfatal myocardial infarction or stroke (Hazard Ratio=0.95; 95%CI 0.74-1.23). Mortality was also similar in both groups (3.0% vs. 2.8%, HR=1.02; 95%CI 0.64-1.60). In contrast, repeat revascularization procedures occurred more frequently in the coronary stenting as compared to the bypass surgery group (18% vs. 4.4%, HR=4.4; 95%CI 3.3-5.9). In summary, coronary stenting could provide a similar on-year clinical outcome for patients with multivessel coronary artery disease as bypass surgery, albeit at the cost of more repeat revascularization procedures.

In **Chapter 3** of this thesis, we described the evolutionary changes that have taken place in the field of coronary revascularization over the past decades. In the early days, both balloon angioplasty and bypass surgery were applied to patients who were significantly symptomatic, had documented myocardial ischemia and had predominantly single-vessel disease with discrete stenosis. By the late 1980s, a number of studies comparing balloon angioplasty to bypass surgery in patients with multivessel coronary artery disease were underway. The lessons learned from these trials are delineated in this chapter and complemented with the lessons from the second-generation trials that compared coronary stenting versus bypass surgery in patients with multivessel disease. In general, these studies found a similar prognosis and symptomatic relief for the two initial revascularization strategies (Balloon angioplasty or bypass surgery). Documented differences between the two procedures included a lower rate of repeat revascularization in patients initially treated with bypass surgery. However, the widespread use of coronary stenting had significantly decreased the need for

emergency bypass surgery to approximately 1% among patients treated with percutaneous coronary intervention. The observed gap between bypass surgery and percutaneous coronary intervention in terms of major adverse cardiac and cerebral events at one-year, has narrowed from 32% reported in the pre-stent era[2] to 11% in the stent era. This gap could continue to narrow with the newly introduced drug-eluting stents that have been shown to remarkably reduce restenosis and repeat revascularization rates[3]. Preliminary data from the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry[4] have shown a 91.2% 6-month major adverse cardiac and cerebral events free survival in 307 consecutive patients with multivessel disease treated with sirolimus-eluting stents compared to 81.4% in 427 patients treated with bare metal stents (p<0.01). In this scenario, the adoption of measures aiming to modify the natural course of the atherosclerotic disease itself (i.e. non restenosis-related complications) becomes the main focus of attention after percutaneous or surgical treatment of multivessel disease. In this regard, statins could decrease perioperative mortality[5] and reduce the risk of coronary atherosclerotic events in patients undergoing percutaneous coronary intervention[6].

Results of randomized trials on the survival benefits of early revascularization after acute coronary syndromes have yielded inconsistent in regard to whether an early invasive strategy is associated with better clinical outcomes compared to a conservative non-invasive strategy. In **Chapter 4,** we describe the 6-month clinical outcome of patients with multivessel CAD presenting with an acute coronary syndrome and complete angiographic data enrolled in PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Supression Using Integrilin Therapy) stratified according to the treatment strategy applied early during hospitalization (Medical treatment – PCI (Balloon) – PCI (Stent) – CABG). The mortality rate at 30 days was 6.7%, 3.9%, 2.4% and 4.8% for medical treatment, PCI (Balloon), PCI (Stent) and CABG groups, respectively (p=0.002). Differences as observed at 30 days were still present at 6-month follow-up with 11.1%, 5.8%, 5.5% and 6.5% mortality rates for the aforementioned groups (p=0.002). The 30-day MI rate was lower among medically than non-medically treated patients, with the highest event rate observed in the CABG group (27.7%). Approximately half of the MIs in the PCI and CABG subgroups occurred within 48 hours after the procedure. Differences in event rates as observed at 30 days were still present at 6-month follow-up. The differences in clinical outcomes in this study are in accordance to those from the FRISC-II[7] trials, in which an early invasive strategy was associated with a survival benefit. On the other hand, in TACTICS-TIMI 18[8] and TIMI-IIIB[9] studies, mortality was similar irrespective of whether revascularization was undertaken or not. The benefits of an invasive strategy may have been diluted in these studies by events occurring in patients allocated to an invasive strategy without or awaiting revascularization or by a crossover from the non-invasive to the invasive group, as in 36% in TACTICS-TIMI 18 and 37% in TIMI-IIIB.

Part 2: Predictors of adverse angiographic and clinical outcome

In **Chapter 5,** we carried out a comprehensive comparative analysis from the balloon to the stent era on demographic, clinical and quantitative coronary angiographic predictors of coronary restenosis in a total of 9,120 treated lesions in 8,156 patients.
The restenosis rate was 35% after balloon angioplasty and 19% after angioplasty with additional stenting.
There were no major differences in demographic and clinical predictors of coronary restenosis between balloon angioplasty and stent populations. In the modern (stent) era, a severe pre-

procedural diameter stenosis is no longer an unfavorable predictor of restenosis. Still important, but more so in the stent population, is a large post-procedural minimal luminal diameter (optimal result). Finally, a larger pre-procedural reference diameter became a favorable predictor with the advent of stenting. Patients treated with drug-eluting stent represent a distinctive population in which the results of our analyses may not be applicable.

In **Chapter 6,** we evaluated the clinical outcome of patients with in-stent restenosis treated with 6 different interventional devices (Stent-in-stent, rotational atherectomy, balloon angioplasty, laser angioplasty, directional atherectomy and vascular brachytherapy). In more detail, we specifically pooled all the data available from radiation therapy for the treatment of in-stent restenosis. A pooled analysis from the β trials (Beta WRIST, START 30, START 40 and INHIBIT) showed a 33% relative reduction (RR) in MACE favoring brachytherapy. Similarly, a pooled analysis from the γ trials (SCRIPPS-2, WRIST, GAMMA-1, GAMMA-2, long WRIST, long WRIST high-dose and SVG WRIST) demonstrated a 36% RR and finally, when pooling the β and γ trials, altogether, a 35% RR was exhibited. Finally, we described the encouraging results (9.8% major adverse cardiac event rate at one-year) obtained in the first 41 patients treated with sirolimus-eluting stents for in-stent restenosis.

Currently-available data suggests that stent deployment decreases restenosis and cardiac event rates in diabetic patients. However, there is little data regarding the differences between those diabetics who develop restenosis following stent deployment and those who do not; whether diabetics are at higher risk owing to longer lesions, smaller vessel calibre and therefore higher restenosis rates or whether simply being diabetic adds a constant increment to restenosis risk to all patients, is unclear. In **chapter 7,** we analyzed the clinical and angiographic variables associated with restenosis in diabetic patients from a large cohort of studies. Restenosis occurred in 20.6% of non-diabetic and 31.1% of diabetic patients. Multivariate predictors associated with restenosis included only vessel reference diameter, stented length and a lower body mass index. Moreover, we developed reference charts that demonstrated that the incremental risk of restenosis was dependent solely on vessel reference diameter.

Part 3: Special subgroups on coronary revascularization

The impact of body mass index on the outcomes after coronary artery revascularization remains controversial. In **Chapter 8**, we describe the influence of body mass index on the long-term outcomes in patients with multivessel coronary artery disease randomized to either multiple coronary stenting or coronary artery bypass graft surgery. Patients were divided in three groups: normal body mass index between 18.5 and 24.9, overweight with a body mass index between 25 and 30 and obese with a body mass index greater than 30. At three-years follow-up, the incidence of death or cerebrovascular events or myocardial infarction was similar for each one of the three body mass index categories, regardless the revascularization technique employed. Repeat revascularization procedures were significantly higher among patients randomized to stenting, but similar among the different body mass index groups. For patients randomized to bypass surgery, there was a non-significant trend towards lower repeat revascularization procedures in obese patients. Among patients who underwent multiple stenting, body mass index had no impact on the three-year combined endpoint of major adverse cardiac or cerebrovascular event rates. However, among patients who underwent bypass surgery, major adverse cardiac or cerebrovascular event rates were significantly lower for obese (11%) or overweight (15%) patients compared to patients with a normal body mass index (23%)(p=0.012).

Chronic renal insufficiency is associated with adverse outcomes after bypass surgery and percutaneous coronary intervention. In **Chapter 9**, we evaluated the effect of chronic renal insufficiency on outcomes after coronary revascularization and we compared the outcomes of patients with chronic renal insufficiency who were randomly assigned to bypass surgery or percutaneous coronary intervention. Of 1205 patients enrolled in the Arterial Revascularization Therapies Study (ARTS), 1176 (97%) had baseline creatinine data, among whom 290 (25%) had chronic renal insufficiency, defined by creatinine clearance   60 ml/min estimated by the Cockroft-Gault equation. The primary clinical endpoint was the composite of death, non-fatal myocardial infarction, or stroke; and, a secondary outcome was repeat revascularization. The primary outcome occurred in 18% of patients with chronic renal insufficiency and 10% of patients without chronic renal insufficiency at 3-years of follow-up (HR=1.61; 95%CI 1.10-2.35). Within the chronic renal insufficiency subgroup, no difference was observed in the primary endpoint after bypass surgery vs. percutaneous coronary intervention (HR=0.93; 95%CI 0.54-1.60). However, bypass surgery was associated with a reduced risk for repeat revascularization. (HR=0.28; 95%CI 0.14-0.54). In patients with multivessel coronary artery disease, chronic renal insufficiency is a risk factor for death, non-fatal myocardial infarction, or stroke after coronary revascularization. These outcomes occurred at equal rates among chronic renal insufficiency patients treated with bypass surgery or percutaneous coronary intervention, but bypass surgery was associated with decreased repeat revascularizations.

In **Chapter 10,** we assessed the effect of fluvastatin on the outcome of patients with or without renal dysfunction in the Lescol Intervention Prevention Study (LIPS). We also evaluated the effect of fluvastatin treatment on renal function and the relation between changes in renal function over time on the incidence of adverse cardiovascular events. Complete data for creatinine clearance calculation were available in 93% of the total population, who were randomised to fluvastatin (normal renal function, n=631; impaired renal function, n=150), or placebo (normal, n=617; impaired, n=160) following successful completion of a first percutaneous coronary intervention. Follow-up time was 3–4 years. The primary endpoint was survival time free of coronary atherosclerotic events (cardiac death, non-fatal myocardial infarction, and coronary reinterventions not related to restenosis). Renal impairment significantly increased the incidence of coronary atherosclerotic events in placebo-treated patients (Relative Risk=1.42; 95% CI 1.00-2.01). Among those treated with fluvastatin, however, no differences were observed between patients with and without renal impairment (RR=0.97; 95% CI 0.61-1.56). No further deterioration in creatinine clearance was observed during follow-up, regardless of baseline renal function or allocated treatment. The occurrence of adverse events was not related to changes in renal function during follow-up. Fluvastatin treatment reduced the risk of coronary atherosclerotic events after percutaneous intervention in patients with mild renal impairment and this benefit was unrelated to any effect on renal function.

Finally, in **Chapter 11** we assessed the incidence of cardiac atherosclerotic events (cardiac death, non-fatal myocardial infarction, and coronary re-interventions not related to restenosis) in patients with single-vessel and multivessel disease randomized fluvastatin (40 mg bid) or placebo for at least 3 years following a first successful percutaneous coronary intervention in the Lescol Intervention Prevention Study (LIPS). In patients allocated to placebo, the presence of multivessel disease was associated with a significantly higher rate of cardiac atherosclerotic events compared with single-vessel disease (Relative Risk=1.67; 95% CI 1.24–2.25).

However, patients with multivessel or single-vessel disease treated with fluvastatin presented similar long-term outcomes (RR=1.28; 95% CI 0.90–1.81). The long-term treatment with fluvastatin after percutaneous intervention reduced the risk of patients with multivessel disease to the level of those with single-vessel disease.

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Curriculum Vitae

I. Personal Data

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II. Education

Date	Degree	Institution
June 22, 1991	High School	Berchmans School Cali, Colombia
June 4, 1998	Medical Doctor	Pontificia Universidad Javeriana, Bogota, Colombia
August 25, 2000	Master of Science in Clinical Epidemiology	the Netherlands Institute for Health Sciences Erasmus University Medical Center Rotterdam, the Netherlands
August 31, 2001	Doctor of Science in Clinical Epidemiology	the Netherlands Institute for Health Sciences Erasmus University Medical Center Rotterdam, the Netherlands
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June 11, 2003	Doctoral thesis Coronary revascularization in ischemic heart disease: Lessons from observational studies and randomized clinical trials	Erasmus University Medical Center Rotterdam, the Netherlands

III. Appointments

Year	Position	Institution
2000-2003	Junior Clinical Epidemiologist	Clinical Epidemiology Unit, Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands

Publications in peer-reviewed journals:

1. **Mercado N**, Boersma E, Wijns W, Gersh BJ, Morillo CA, de Valk V, van Es G-A, Grobbee DE, Serruys PW. Clinical and Quantitative Coronary Angiographic predictors of coronary restenosis: A comparative analysis from the Balloon to Stent era. J Am Coll Cardiol 2001; 38: 645-52

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1. **Mercado N,** Morillo CA. Capitulo 6: Fibrilacion Auricular. En: Velasco VM, Rosas F. Arritmias Cardiacas: Temas Selectos. Sociedad Colombiana de Cardiología. Biblioteca de Cardiologia. 2001. (Atrial Fibrillation. In: Velasco VM, Rosas F. Cardiac Arrhythmias: Selected Topics. 2001)

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1. **Mercado N,** Castillo VR, Hernández G. Ruptura del septum interventricular post-infarto: Presentación de 2 casos y revisión de la literatura (Post-infarction ventricular septal defect: Presentation of 2 cases and review of the literature). Cardiol. día 1998; 2: 96 – 104

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I spent some time thinking about how to put together all the pieces of this journey. The inspiration actually came from my past experiences as a medical student, intern and novice clinical researcher; and it is fair to believe what people often say *that lessons learned along the way are what make a journey worthwhile*. I feel that I have been very fortunate. I have worked in a great institution with extraordinarily talented colleagues and I have had the opportunity to meet some of the finest cardiovascular specialists from all over the world.

I would like to thank my first teacher in Cardiology Dr. Jorge Pineros Bernal, who trained with Demetrio Sodi-Pallares and Enrique Cabrera during the golden era of the National Institute of Cardiology "Ignacio Chavez". Thank you for teachings in electrocardiography and for giving me your original copy of the beautiful book: The Hemiblocks by Mauricio Rosenbaum. Dr. Carlos A. Morillo deserves a special word of acknowledgement. He is an astute cardiac electrophysiologist who taught me for the first time the indelible meaning of the word mentor and encouraged me to pursue my research career abroad. I deeply treasure our friendship and I am grateful with you for coming to Rotterdam to my thesis defense.

It is without any doubt that my deepest appreciation goes to my promoter Prof. Maarten L. Simoons, my co-promoter Dr. Eric Boersma and the outstanding Dr. William Wijns.
Dear Prof. Simoons, thank you very much for being my promoter. You are such a strong role model for new generations of cardiology trainees as a brilliant clinician, successful clinical researcher and physician entrepreneur. I was always challenged by your vast knowledge, creative thinking and sharpness. Thank you for repeatedly pushing me with my thesis. I whish you continued success in the years to come as chief of cardiology of the Thoraxcenter.
Dear Dr. Boersma, dear Eric, thank you for giving me the opportunity of joining your group and for introduce me to the joy of clinical research. Eric showed me for the first time, the power of clinical research on patient care. I thank you also for your patience and for sharing your tips and tricks on how to turn a simple idea into a first rate manuscript. I think you are not only one of the best cardiovascular epidemiologists but also a great person. Dear Dr. Wijns, dear William, thank you very much for reinforcing my notion of mentorship. I have learned a great deal of interventional cardiology from you but more importantly, I have learned how to "make things happen". I sincerely believe that you deserve all you have got. My appreciation is also extended to William's lovely family (Gratia and the girls) who warmly welcomed me at their house in Brussels and made me feel like at home on many occasions. I would also like to thank my second promoter Prof. Patrick W. Serruys, one of the world leading forces in interventional cardiology. Thank you Prof. for allowing me to get involved in some of your clinical studies. It has been a real honor for me to work with you.
I want to express my gratitude to the other members of my thesis committee: Prof. Jos R. Roelandt, Prof. Ad Bogers and Prof. Bernard J. Gersh. Beste Prof. Roelandt, you are a very knowledgeable physician and historian. I still have vivid memories on our talk about medicine in the Renaissance. Dear Dr. Gersh, I really look up to everything that you stand for; you epitomize the model of lifelong learning. Thank you for your influence in my career and for your constructive critics on all of our papers.

Thank you also to my colleagues from the Clinical Epidemiology Unit: Ron van Domburg (Thank you for translating many, many forms for me), Mattie Lenzen (Good luck with the ancillary studies that will come from the revascularization survey), Miklos Kertai (Hopefully you will get that clinical position you are so eagerly looking for and be able to settle in

Holland with your wife and son), Wilma Scholte op Reimer (Congratulations with you first-born daughter), Susan Smith-Pedersen (Congratulations on your new appointment as an Assistant Professor), Esther de Swart, Anneke de Torbal (Good luck with your thesis), Marjo Trion (The best of luck with your residency), Chris Jansen, Colinda Koppelaar, Paul Cummins and Arno Ruiter (I fully realize your efforts in gathering high quality data from the patients for so many studies).

Thank you also to Robby Niewlaat (University Hospital Maastricht) and Tanja Megens (Academic Medical Center Amsterdam). I wish you a lot of success in the upcoming European surveys on atrial fibrillation and congenital heart disease

I am indebted to Cecile Sweers, Jolanda van Wijk, Maria Kamps, Willeke Korpershoek, Sarah Fransen, Tineke van der Kolk, Yvonne Kalkman and Anneke Kooijman for the superb secretarial support over the past three years. I thank also Arita Orgers and Ad van Druinen for taking care of the daily administration.

I owe a great deal to Dr. William W. O'Neill, Dr. Sandor Soichet and Dr. Leslie Rocher, who created the opportunity and made possible my move to William Beaumont Hospital. Dear Dr. O'Neill, I am already looking forward to join the world-renowned house-staff of Beaumont. Thank you very much for believing in me and for your unreserved support.

I thank Gerrit-Anne van Es, Yvonne van Lint, Clemens Disco, Wietze Lindeboom, Peter-Paul Kint, Marie-Angele Morel and Eline Montauban van Swijndregt from Cardialysis, for all the help that I received from them for some of the studies presented in this thesis.

Thank you also to Nico Bruining, Max Patijn and Sebastiaan de Winter for technical assistance and for solving many computer problems.

Many thanks to Annet Louw and dr. Jan Willem de Jong for keeping me appraised of the deadlines for this thesis. I appreciate your pivotal role at the office of medical education.

I would like to thank Don Poldermans, Jaap Deckers and Gene McFadden for their teachings in clinical medicine over the past years.

The cardiology fellows deserve also special attention: Pedro A. Lemos (Dear Pedro, dear friend, congratulations on all the good things you have got during your fellowship at the Thoraxcenter. I whish you all the best with your own thesis, I am pretty sure that it is going to be great. Please do not forget to send a copy. Hopefully this is just the beginning of a long-standing friendship), Mussafer Degertekin (I whish you a lot of success with your new appointment in Turkey. Thank you for all the great intellectual and "non-intelectual" discussions), Francesco Saia (Thank you for showing me around in Verona), Arend Schinkel, Kengo Tanabe (Thank you for such a wonderful dinner at the Japanese restaurant), Timo Lenderik (Good luck with you own thesis) and Johannes "The plaque vulnerability" Schaar (Good luck with your research).

The members of the expert committee of the Euro Heart Survey on Coronary Revascularization also played an important part in the design, conduct and analysis of the Survey. I would like to thank them: Prof Michel E. Bertrand, Dr. Willibald Maier, Prof

Bernhard Meier, Dr. Cesar Moris, Prof. Federico Piscione, Prof. Elisabeth Stahle, Dr. Jeroen Vos and Prof. Petr Widimsky.

I want to thank my friends Danny Giraldo, Edgar Celis, Vicky Garcia, Sandra Silva, Cathy Mendez, Julio Munoz, Fernando Rivadeneira, Carolina Pardo, Alejandro Arias, Esther de Vries and Ryan Franca, who have promised me to come for my defense. Dear Danny, thank you for being such a good and inconditional friend, I promise to rent you a tuxedo at another time!. Dear Edgar, thank you for coming. I have to congratulate you for your appointment at the Brigham's and Women Hospital, which of course is absolutely well deserved. Keep the good work my friend!

Many thanks also to Erna Blok, Dick Leeflang and Roman Zantman.

Finally, I would like to thank my parents Nestor and Nancy and my sister Anaisabel for their unreserved love and support throughout all these years.