Long-term survival and predictors of mortality in Coronary Heart Disease

Lange termijn overleving en voorspellers van mortaliteit bij hartpatiënten

Voor Ellen,
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Chapter 1

INTRODUCTION AND REVIEW OF LONG-TERM OUTCOME IN CORONARY HEART DISEASE

INTRODUCTION

Coronary heart disease (CHD) is by far the most important cause of death, and a main cause of disability in the Netherlands. Accordingly, coronary heart disease has a great impact on society. In 1995 cardiac death occurred in about 40,000 persons (28% of all mortality) and ischemic heart disease was the reason for 170,000 hospital admissions.[1] Since the 1980s an immediate benefit is achieved in patients with acute manifestations of CHD, with pharmacologic therapy such as thrombolytic therapy in patients with evolving myocardial infarction and coronary interventions such as coronary aorto bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty procedure (PTCA). Together with improved secondary prevention through diet, reduced smoking and medical regimens such as antiplatelets, beta-blockers, ace-inhibitors and statins the life expectancy has been improved. This resulted in an increase of patients with chronic manifestations of CHD including heart failure and a population of survivors with a high risk of recurrent coronary events. This make the investigation of the long-term outcome after a cardiac event more important than ever.

We investigated subgroups of patients who underwent myocardial infarction (MI), an episode of unstable angina pectoris (UAP), CABG or PTCA. This chapter will give an overview of previous studies which reported the long-term outcome of the different groups of patients including: survivors of a myocardial infarction (1.1.1), patients with evolving myocardial infarction who were treated with thrombolytic therapy or conventional therapy (1.1.2), patients hospitalized for unstable angina (1.2), patients who underwent CABG surgery (1.3) and patients who underwent a PTCA procedure either without (1.4.1) or with stent implantation (1.4.2). The most important baseline characteristics of each of these subgroups and their effects on medium- and long-term outcome are presented.

1.1 MYOCARDIAL INFARCTION

1.1.1 SURVIVORS OF A MYOCARDIAL INFARCTION

The post MI studies vary with respect to definitions and inclusion criteria. Table 1 and Figure 1 presents the studies which reported the long-term outcome. In most studies more than three-quarter of the patients were male and mean age varied from 30 to 69 years in older studies[3-7] and from 50 to 61 in the more recent studies.[8-17] The presence of a prior MI varied from only 0% to 32%.

Mortality figures at one-year varied from 6% to 13% in hospital survivors of a myocardial infarction. After one-year the yearly mortality rate was constant (~3% to 5% per year) and reinfarction rate as well as the rate of any major adverse cardiac event (death, MI, CABG or PTCA) were low. Short- and medium follow-up studies reported a high intervention rate in the first year. Fioretti[11] reported a 75% event-free survival at one-year. In a meta analysis, Moss[13] reported 1-, 3- and 5-year freedom from mortality or reinfarction varying from 94%-95%, 82-86% and 69-77% , respectively in survivors of a MI.

A number of clinical, electrocardiographic and angiographic factors were related to survival. An increased mortality risk was found in elderly patients in most studies[4,7,8,12,17] in patients with prior MI[3,4,7,8,12,17] and in patients with heart failure.[3,4,6,12,17] In studies with angiographic data available more accurate risk assessment was possible using measurements of impaired left ventricular function and extend or severity of coronary lesions.

In Chapters 2-4 we describe a large series of postMI patients who were followed for 3-years (range 6 months-6 years). We especially investigated whether a low-risk subgroup could be identified which similar survival as the general population of the same age and gender (Chapter 2). In Chapter 3 we describe the increased risk of subsequent death after a second infarct and in Chapter 4 we investigate the predictive value of the discharge ECG.

1.1.2 REPERFUSION THERAPY IN EVOLVING MYOCARDIAL INFARCTION

The introduction of thrombolytic therapy has improved the immediate outcome of patients with evolving MI. Hospital survival is improved and this effect is maintained during reported follow-up up to 5 years. However, final assessment of the value of such therapy requires understanding of the long term effects, at least through the first decade.

Table 2 describes the studies which reported long-term outcome for at least one year and in Figure 2 long-term cumulative survival rates are shown. Mean age was around 58 years (56-61) and most trials included more than 80% males. Prior infarction varied from 8% to 23% with an exception of the Zwolle study[28] which reported a 32% prior MI rate in the PTCA subgroup. Mortality of the patients treated with thrombolytic agents varied from 6% to 17% in the first year following thrombolytic therapy and from 9% to 16% and 11% to 30% at 3- and 5-year, respectively. The GUSTO trial[26] reported a follow-up of 38,000 patients with a mortality rate of 9% to 10% at one-year. The benefit of thrombolytic therapy

compared to conventional treatment was significant in most trials and averaged 3% (0-8%) at one-year and was sustained thereafter. The reinfarction rate was higher after thrombolytic therapy. Event-free survival (without MI, CABG, PTCA) after thrombolytic therapy varied from 58% to 81% at one-year,[20,21,24,25,27] 60% at 3-years and 54% at 5-years.[21]

In about half of the thrombolytic trials risk assessment of medium- and long-term outcome of mortality was performed, mostly using Cox proportional hazard models. Among the clinical factors, advanced age,[18,20,21,28,29], prior MI[18,21,24,28,29] and anterior infarction[18,23] were found indicators of increased risk of mortality. However, if angiographic data were available, the clinical risk factors were replaced by the extend of coronary disease and impaired left ventricular function.[23,24,29] The benefit of thrombolytic therapy was also apparent using multivariate analysis when the status of the patient at discharge was included in the model.

In addition to these data we report the 10 to 14 year follow-up of the ICIN streptokinase trial in which 533 patients were randomized into two treatment modalities: thrombolytic therapy with streptokinase or conventional treatment (Chapter 5).

1.2 UNSTABLE ANGINA

The general term "unstable angina" is used for patients who present with a variety of symptoms, related to transient episodes of myocardial ischemia, and caused by obstruction of coronary flow by different pathophysiological mechanisms, including intracoronary atheromatous plaque rupture, platelet aggregation, thrombus formation and increased vasomotor tone. Other terms that have been used for this condition include "pre-infarction angina", "crescendo angina", "accelerated angina", "acute coronary insufficiency" and "intermediate coronary syndrome". While those terms were often defined only loosely, a clarification schema was developed in the 1980s (Braunwald).[2] The onset of unstable angina portends a significant risk for the occurrence of major cardiac events including death and MI. Description of the previous studies of long-term outcome are presented in Table 3 and in Figure 3.

Mortality after unstable angina was high in the 1950s and 1960s. Gazes[30] reported 1-, 3, 5 and 7-years mortality rates of 18%, 31%, 39% and 45% respectively. Thereafter improvement of treatment resulted in a lower death rate, Probably due to the large difference in the definitions of unstable angina (such as

diagnosis made at admission or discharge) survival rates varied from 2% to 10%[32,38,39,40] at one-year, 7% to 21% at 3-years[32,35,38,39,40] and 10% to 18%[35,38-40] at 5-years. Murphy[37] reported a high 21% mortality at three years in 86 patients.

Infarct-free survival rates varied from 83% to 93%[32,34,40,41] at one-year, 83% to 85%[32,34,40] at 3-years and 57% to 82%[38,40] at 5-years. Bentivoglio[40] reported unstable angina patients who all underwent a PTCA procedure 1-,3- and 5-year event-free survival rates (without MI, CABG or repeat PTCA) of respectively 66%, 55% and 44%.

Reports on risk assessment in unstable angina are rare. Only Bentivoglio,[40] de Feyter[33] and van Miltenburg[42] reported on risk factors of mortality. In addition to age, also the Braunwald classification turned out to be of prognostic value especially in the first 6 months.[41,42] Furthermore Bentivoglio[40] found that the angiographic factors impaired left ventricular function and extend of vessel disease were related to a higher risk of mortality.

Also long-term follow-up studies after unstable angina patients are rare. We report 7-year follow-up of 282 consecutive patients[42], who were admitted with unstable angina, to establish the prognosis of various subgroups of patients. These results are described in Chapter 6.

1.3 Coronary Artery Bypass Graft Surgery (CABG)

Aorto-coronary bypass grafting surgery (CABG) is an accepted treatment modality for patients with angina pectoris. The primary goal of such an operation was and still is relief of anginal symptoms and to obtain a better quality of life. It is evident now that a majority of patients are free of anginal symptoms after CABG, while another substantial group has a decrease in symptoms. Previous studies who have been reported long-term outcome of mortality are described in Table 4. Mortality is shown in Figure 4.

Most reported long-term follow-up studies date from patients operated during the 1970s. Mean age varied from 50-55 years, while two studies reported on a mean age of 62[48] and 64 years[50]. The majority of the patients were (again) male. Prior MI was frequent and varied from 48% to 61%. Most patients were smoking (23% to 84%). Multivessel disease varied between 82% to 99%. Survival after bypass surgery is excellent. One- and five-year mortality varied between 3-10% and 10% to 15%, respectively. After 7-8 years the yearly mortality rates increased with mortality

Table 1. Long-term outcome in survivors of myocardial infarction

Author	Intake 19xx	N	Male %	Age yr	Oldmi %	Antmi %	Killip A=2/3/4 B=3/4	Mortality 1	3	5	Riskfactors
Davis (3)	73-76	940	81	54	19	45	-	-	14	-	oldmi, hf, antmi,
Henning(4)	69-73	1256	75	60	30	26	19	-	-	41	age, oldmi, hf, hr, af, sgot
Sanz (5)	75-79	259	100	51	9	41	14	-	7	-	ef, vd, hf
MPRG (6)	79-80	866	78	59	24	36	38(A)	9	-	-	ef, killip
Martin (7)	70-71	666	75	30-69	25	-	16	12	26	33	age, sex, oldmi, dm, hypo
Madsen (8)	79-82	818	68	62	27	-	11	11	-	-	oldmi, age
Mukharji (9)	80-82	533	75	56	22	-		12	-	-	---
Norris (10)	77-82	325	100	50	0	29	-	-	13	-	ef
Fioretti (11)	81-83	405	80	57	30	37	32(A)	12	-	-	---
Pardaens (12)	73-79	1669	73	62	15	47	12(B)	13	23	32	age, killip, oldmi, dig, diu
Moss (13)		6392	80	58	8	27		6	15	26	heartsize, enzymes, ef
Rouleau (14)	90-92	2862	74	60	28	21	8(B)	7	-	3	prevap, tromb
Meeter (15)	81-83	706	78	58	32	38	19	10	17	20	---
Ottevanger (16)	78-80	304	85	55	23	41	-	17	-	-	---
This thesis	86-91	3404	80	61	9	24	6(B)	7	12	19	age,killip,oldmi,vtvf

Legend for this and subsequent tables. af=atrial fibrillation; antmi=anterior infarction; ap=angina pectoris; chf=congestive heart failure; dig=digitalis; diu=diuretics; dm=diabetes mellitus; ef=ejection fraction;fup=follow-up; hf=heart failure; hypert=hypertension; hypo=hypotension; hr=heart rate; Hx=history of; irv=infarct related vessel; killip=killip class; misize=infarct size; mvd=multivessel disease; negt=negative T; oldmi=prior infarction; prevap=history of angina; sap=stable angina; svg=saphenous vein graft; ps=palmaz schatz; tromb=thrombolytic therapy; uap=unstable angina; univ=univariate analysis only; vd=vessel disease; vtvf=ventricular tachycardia or fibrillation; xecg=exercise test.

Table 2. Long-term outcome after thrombolytic therapy in evolving myocardial infarction

Author	Intake 19xx years	Treatment	N	Male %	Age yr	Old mi	Ant mi %	Killip %	Mortality 1-yr	5-yr	10-yr	Design	Riskfactors
Schröder (17) ISAM	82-85	sk	859	81	58	12	43		13	14	-	sk vs ctrl	---
		Ctrl	882	82	58	12	47						
GISSI-1 (18)	82-85	sk	5851	80	57	16	36	6(B)	17	30	45	sk vs ctrl	age,oldmi,antmi, univ
		Ctrl	5846	80	56	15	37	6(B)					
ISIS-2 (19)		sk	8592	76	57	17						sk vs ctrl	
		ctrl	8595	76	57	17							
Califf (20) TAMI	82-85	all	386	79	56		40		6	-	-	tPA+interv	age, ef, mvd only survivors!
Cerqueira (21)	81-83	sk	325	85	57	13	40	-	11	16	-	sk vs ctrl	antmi, age, oldmi, hypotension
		Ctrl	293	85	57	13	41						
Terrin (22) TIMI													
Volpi (23) GISSI-2	88-89	all	10219	82	61	14	33	9(A)				sk vs ptca	xecg, ef, oldmi, hypert
Lenderink (24,25) ESCG	86-87	tpa	721	85	58	8	40	4(B)	9	11	-	sk vs CTRL	ef, misize, mvd, timi3
		ptca	367	89	56	7	40	3(B)	6	11	-	tpa+ptca vs tpa	
Califf (26) GUSTO	90-93	all	9080	76	61	15	37	1(B)	10	-	-	sk-sq/iv vs rtpa vs sk+rtpa	-
Every (27) MITI	88-94	throm	1050	76	60	13	37	4(B)	9	13	-	thromb vs ptca	hr, killip, Hxcabg, age, oldmi,antmi
		ptca	2095	77	60	15	34	3(B)					
Zijlstra (28)	91-94	sk	149	81	61	21	68	8(B)	8	12	-	sk vs ptca	age, irv, mvd, oldmi antmi, treatment, univ
		Ptca	152	84	59	32	79	9(B)					
This thesis (29)	81-85	sk	269	81	56	21	39	5(B)	9	11	31	sk vs ctrl	age, xecg, ef, mvd
		Ctrl	264	84	56	23	35	4(B)					

For the abbreviations see Table 1.

Table 3. Long-term outcome after unstable angina

Author	Intake	Nr of pts	Male %	Age yrs	Oldmi %	DM %	Smo-king %	Mortality 1-yr	3-yr	7-yr	Riskfactors + Description
Gazes (30)	<'61	140	81	56	56	9	--	18	31	45	accelerated ap 10yr fup
Mulcahy (31)	75-77	101	-	-	-	-	-	10	-	-	perstistent pain after uap at discharge therapy:bedrest, no antianginal therapy
Cairns (32)	79-83	139	73	57	43	18	32	6	12	-	antiplatelets vs placebo
De Feyter (33)	83-85	200	82	56	41	--	--	2	-	-	STelevation, negt,stenosis>65%, all ptca
Wilcox (34)	86-87	196	67	56	42	11	73				uap at discharge
Parisi (35)	76-82	100	56	42	17	17	--	-	12	-	uap at discharge, medication vs cabg all 3vd
Balsano (36)	86-87	338	73	60	50	8	26				ticlopidine vs conventional
Murphy (37)	86	141	75	58	54	--	50	-	21	-	uap at discharge
Romeo (38)	84-85	76	72	56	40	8	38	3	10	-	--
Sharma (39)	76-82	468	100	56	43	17	52	5	10	22	only mortality
Bentivoglio (40)	85-86	857	71	58	39	15	32	2	7	-	braunwald, chf, ef, mvd, dm, age
Kleinman (41)	90-92	??	50	64	41	26	24	10	-	-	timi-III (incl nonq mi)
This thesis (42)	88-89	417	64	62	46	12	34	6	12	24	age, hypert, braunwald class

For abbreviations see Table 1.

Table 4. Long-term outcome after Coronary Artery Bypass Graft surgery

Author	Intake	Nr of pts[r]	Male %	Age yrs	OldMI %	DM %	Smoking %	EF %	VD 1/2/3/lm	Mortality 1-yr	10-yr	20-yr	Risk factors & Description
Varnauskas (43) Eur CSS group	70-75	394	100	50						5	24	-	oldmi, age, xecg, 3vd hypert, lad
Johnson (44) Milwaukee	72-86	6181			?					3	25	-	univ age, ef, Hx cabg
Califf (45) Duke, Durham	69-84	2663	82	55	49	14	72	56	13-27-45-15	10	28	-	mvd, recent surgery
Lawrie (46) Houston 20yrs	68-75	1698	87	54	61	15	60	good: 70%	18-38-32-12	7	34	71	age, mvd, Hx stroke, chf
Ulicny (47) Cincinnati;	70-72	100	84	51	--	--	--		12-36-52-0	5	32	59	age, mvd (only univ) recabg: 34%
Rahimtoola (48)	74-91 ??	8906	78	62	39	14	43		14-19-54-13	5	28	62	ef, mvd, sap
Yusuf (49) Metaanalysis	72-84 trials	1324	97	51	60	10	84		10-32-51-7	3	26	-	---
Kaul (50) Birmingham, Alabama	80-93	1300	74	64	--	18	23	<30%: 12	1-8-78-13	4	24	-	---
Van Brussel (51) Nieuwegein,	76-77	428	90	53	48	2	41	66	14-32-43-12	4	20	-	age, ef, prevap, dm
VA (52)													
CASS (53)													
This thesis (54)	71-80	1041	89	54				<55%: 42%	19-31-42-8	3	23	60	mvd, ef, age

For the abbreviations see Table 1

Table 5. Long-term outcome after Percutaneous Transluminal Coronary Angioplasty

Author	Intake	Nr of pts	Male %	Age yrs	OldMI %	DM %	Smo-king	Prior interv	EF %	VD 1/2/3/lm	Mortality 1-yr	5-yr	10-yr	Risk factors
Talley (55)	81	427	77	54	11	--	--	--	<50: 5%	mvd=14%	0	2	-	univ:uap,mvd,ef
King (56)	77-80	169	85	50	--	--	--	--	--	mvd=42%	3	6	10	univ:mvd
Darros (57)	78-90	322	86	61	55	22	--	100	<35: 12%		3	22	-	svg,ef
Kelsey (58)	85-86	2136	74	58	35	13	29	12	<50: 19%	49-31-19-2	3	11	-	sex,age,chf,dm mvd
Wilson (59)	85-90	161	66	65	41	23	--		<50: 20%	2vd:55 3vd:45	4	10	-	ef; all mvd
Keelan (60)	81-93	3014	69	64	58	17	23	16	<40:8%	30-37-30-3	4	15	30	all UAP
De Feyter (61)	83-85	200	82	56	41	--	--							STelevation negt, sten>65%
Bentivolgio (62)	85-86	857	71	58	39	15	32	--	--		2	10	-	--
Ernst (63)	80-85	1352	--	--	19	--	--	9	<50:55%	mvd=30%	1	-	-	--
Rupprecht (64)	83-86	608	81	52	30	--	--	1	--	mvd=22%	1	-	-	--
This thesis	80-85	856	80	56	41	--		9	<50: 17%	63-24-12-1	2	10	22	age,mvd,ef,oldmi

For the abbreviations see Table 1.

Table 6. Long-term outcome after stent implantation

Author	Intake	Nr of pts	Male %	Age yrs	OldMI %	DM %	Smo-king	Prior interv	EF %	MVD	CCS 3 or 4	Mortality 1-yr	3-yr	7-yr	Description
Fenton (65)	90-91	198	84	66	60	24	67	--	43	<50:18%	88	9	-	-	all svg
Schoemig (66)	89-93	339	76	61	40	19	33	--	--	57	--	4	5	-	all ps, no svg
Versaci (67)	92-95	60	92	56	28	13	63	--	52			1	-	-	all ps
Savage (68)	87-90	300	79	58	--	16	13	--	--	--	67	2	-	-	all ps
Laham (69)	88-91	175	81	59	41	17	45	--	--	54		5	12	-	all prior cabg all ps
Kimura (70)	90-92	143	78	63	55	23	--	8	--	45	49	4	8	-	all ps
Macaya (71) Benestent	91-94	516	80	57	20	7	24	2	--	0	54	1	-	-	stent vs ptca
Klugherz (72)	88-90	65	75	59	43	28	60	29	--	--	57	4	12	-	all ps
Carozza (73)	88-91	250	82	60	60	17	50	30	--	52	--	1	-	-	all ps
This thesis Rotterdam	86-96	1000	73	59	39	10	26	41	13	46	73	5	9	14	

PS=Palmaz Schatz stents; SVG=Savenous vein graft stenting
For the other abbreviations see Table 1

weighted mean of the mortality rates

myocardial infarction

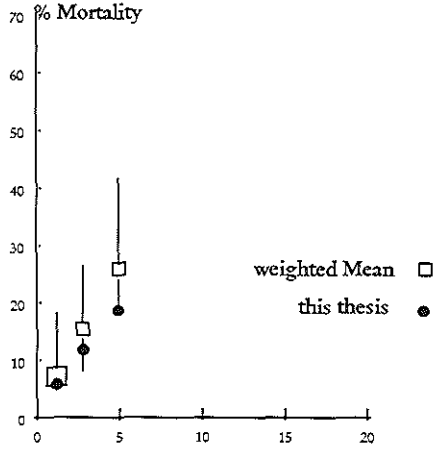

Figure 1

thrombolysis

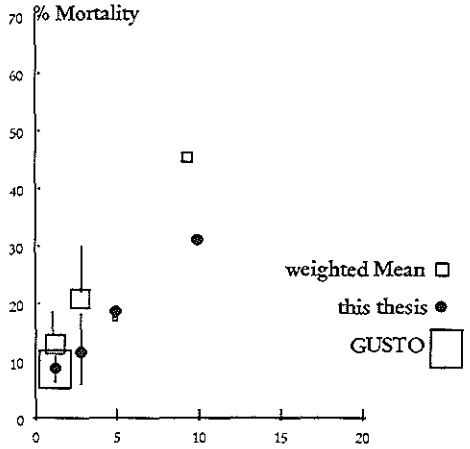

Figure 2

unstable angina

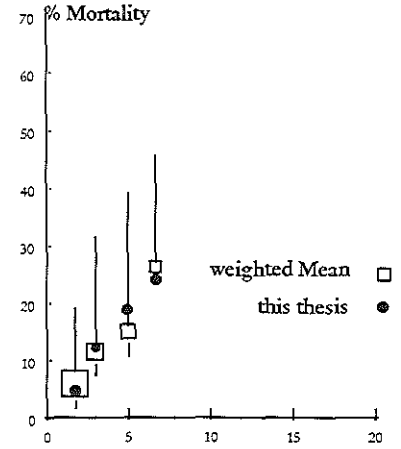

Figure 3

Figures 1-6 corresponds with Tables 1-6. The weighted mean of the mortality rates are presented The area of the squares represens the number of patients. The vertical lines indicate the minimum and maximum mortality rates

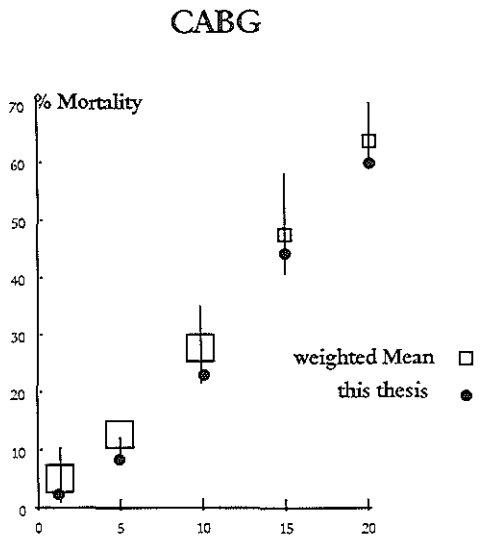

Figure 4

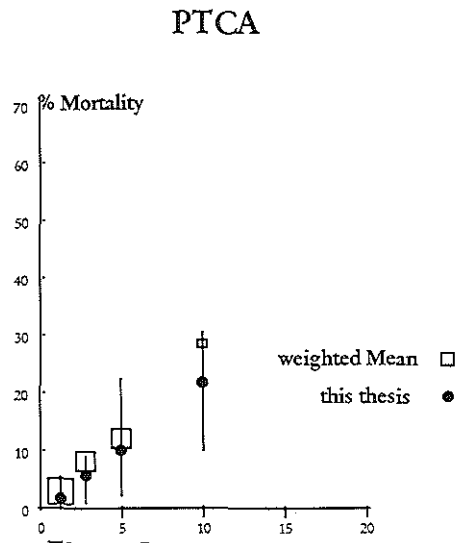

Figure 5

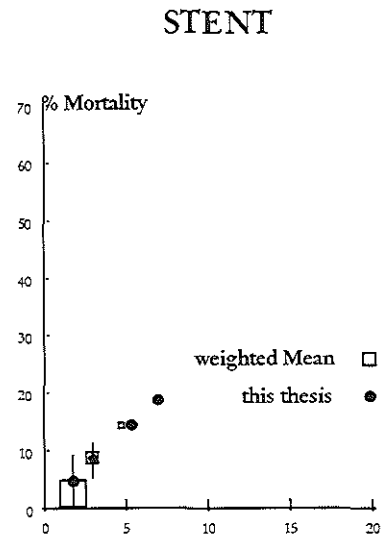

Figure 6

rates of 20% to 28%, 47% to 58% and 59% to 71% at 10, 15 and 20 years respectively. The variation in event-free survival (without MI, CABG or PTCA) was large, with rates varying from 62% to 91% at five years, 41% to 85% at 10 years and 20% to 60% at 15 years.[46,48,50,51]

Similar to all previous subgroups of patients with CHD advanced age was related to higher mortality[43,44,46,47,51,52] as was impaired left ventricular function and multivessel disease.[43,44,46,47,51,52] Califf[45] and Johnson[44] reported that a previous CABG was a risk factor of long-term outcome of mortality and the Nieuwegein group[51] found diabetes as a risk factor of increased mortality.

In order to evaluate the very long-term outcome (20-24 years) of mortality and recurrent interventions following CABG surgery and to identify pre-operative risk factors, we report in Chapter 7 a group of 1041 patients who were operated upon between 1971 and 1980.

1.4 CORONARY ANGIOPLASTY

1.4.1 PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)

Since the introduction of percutaneous angioplasty into clinical practice by Andreas Grüntzig in 1977, the efficacy of this technique in the treatment of coronary artery disease, both native and vein graft vessels, has clearly become established, with continuing growth such that the number of angioplasty procedures performed per year equals that or exceeds the number of coronary artery bypass operations. The immediate and medium-term outcomes are well described (Figure 5 and Table 5). Knowledge of the long-term outcome of coronary angioplasty continues to accumulate over time.

Patients who underwent a PTCA procedure were somewhat older than patients who underwent a CABG (54-64 years). More females were included in the PTCA studies as compared to CABG (14% to 34% Vs 0% to 22%), whereas prior MI was frequently (11% to 58%). Most patients had single vessel disease (49% to 86%). Only Keelan[60] included more (70%) patients with multivessel disease. Long-term outcome of survival after PTCA is excellent with 0% to 4% mortality at one-year and 1% to 10% at three years. At 5-years mortality varied between 6% to 22%, with one study reporting a very low 2% cardiac mortality at that time.[55] Ten-year survival rates varied between 10% to 30%.[56,60,62] Event-free survival rates (without MI,

CABG or repeat PTCA) were at 5- and at 10-years between 42% to 79% and 34% to 48%, respectively.

Risk factors of mortality were similar to those mentioned earlier in this preview: elderly age, impaired ejection fraction and extend of coronary disease.[58,62] In addition, Dorros[57] reported an increased risk of mortality after dilatation of a bypass graft and Kelsey[58] mentioned diabetes as an risk factor.

The data presented in this thesis are from the first 856 patients treated by coronary angioplasty in the years 1980 to 1985 and describe the 10-year survival and clinical events (Chapter 8).

1.4.2 CORONARY STENT IMPLANTATION

The heralded outcome of two simultaneously completed randomized trials BENESTENT and STRESS in 1994 showing superior angiographic and/or clinical outcome in selected patients, in comparison with balloon angioplasty, has led to widespread use of coronary stenting for diverse indications. Previous studies which reported long-term outcome (1-3 years) are described in Table 6 and mortality rates are shown in Figure 6.

Similar to the PTCA studies, mean age was 58 years (56-66). Percentage males varied between 73% to 92% and prior MI was frequent (20% to 60%). All reported studies used the Palmaz-Schatz stent. There was a large variation in the number of smokers (13% to 67%). Prior intervention occurred between 29% to 43%. Only Kimura[70] and the Benestent study[71] reported lower rates. Considering the early dramatic experiences with a high percentage of acute of subacute thrombosis (up to 20%) the long-term outcome after stenting is good. One-year survival varied between 95% to 99% which was somewhat lower in one study (91%).[65] Three- and five-year survival rates varied between 88% to 95% and 84% to 87%, respectively. One-year event-free survival rates (without MI, CABG, repeat PTCA) varied from 63% to 90% and 3- and 5-year rates were between 55-85% and 50% respectively.

One of the uncertainties of coronary stenting however, remains its long-term outcome. Therefore, we investigated the long-term occurrence of major cardiac events using the data of an observational study encompassing the first 1000 patients with a first stent implantation at the Thoraxcenter, who were followed for at least one-year (Chapter 9).

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CHAPTER 2

IDENTIFICATION OF A LOW RISK POPULATION AFTER MYOCARDIAL INFARCTION

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(submitted)

ABSTRACT

Aims
To identify a subgroup of patients after myocardial infarction, at low risk in whom treatment by a general practitioner without further investigation might be adequate.

Methods and results
A large series (n=3404) of patients after myocardial infarction (ASPECT trial) was followed for 3 years (6 month - 6 years). Mortality after 3-years was 11% (359 patients). In a multivariable Cox regression analysis advanced age, Killip class III or IV, prior myocardial infarction, late ventricular tachycardia or fibrillation, heart rate ≥70 bpm, diabetes, history of angina and absence of thrombolytic treatment were retained as independent predictors. We could identify a subgroup of 1304 patients (38%) without any or with only one of these risk factors with very low mortality (3-year: 2.8%; 5-year: 5.9%). This mortality rate was similar to the expected mortality rate of the reference general population.

Conclusions
The prognostic risk factors were similar to those established in previous studies. It appeared to be possible to select a subgroup of patients with an excellent survival prognosis who may not require further intensive treatment and follow-up.

INTRODUCTION

Risk assessment in survivors of post-myocardial infarction patients has been the subject of many investigations in recent years.[1-18] These studies emphasized predominantly identification of high-risk patients.[3,6,7,8,14] One year mortality in these studies varied from 7% to 13% after hospital discharge and 5 year mortality from 11% to 41%. Specific data on low-risk post myocardial infarction patients is scarce.[10,11] Yet, low-risk patients constitute between one third and one half of the population after myocardial infarction, particularly after reperfusion therapy and may require less intensive and less expensive diagnostic evaluation and less therapeutic intervention than high-risk patients.

The aim of this study was to provide a comprehensive analysis of relations between baseline clinical factors and 3-year mortality in a large series (n=3404) of patients after myocardial infarction, who were enrolled in the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial.[20] We analyzed specifically whether parameters, which may identify high risk subgroups[1-18] can also be used to identify a sizeable group of patients at low risk in whom treatment by a general practitioner without extensive further investigation might be adequate.

METHODS

Patients

Patients were enrolled in the ASPECT trial from September 1986 until December 1991. ASPECT was a multicenter, randomized, double-blind, placebo controlled trial, with two treatment arms: "active" anticoagulant therapy and matching placebo. The diagnosis of myocardial infarction was based upon (1) chest pain typical for myocardial infarction, (2) typical serum enzyme pattern and (3) evolving ST-T segment and/or Q waves. Exclusion criteria included indications for anticoagulant treatment (e.g. left ventricular thrombus, aneurysm or extensive left ventricular dysfunction and chronic atrial fibrillation), anticoagulant therapy within six months prior to the index infarction, increased bleeding tendency, anticipated coronary revascularization procedure and malignant disease with poor prognosis. Trial medication was started four days following hospital discharge (median). Aspirin, if prescribed, was discontinued at randomization. All patients were followed for 37 (6-

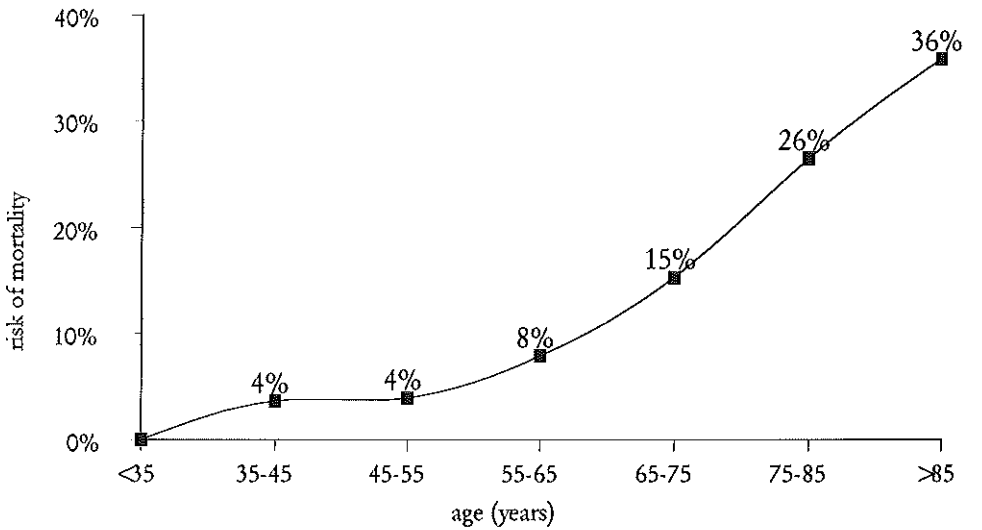

Figure 1. Age and risk of mortality after 3-year follow-up

67) months. Design, patient selection, data acquisition, data management and follow-up of ASPECT have been reported previously.[20,21]

Data acquisition

Before randomization, a set of demographic and historical variables was collected in each patient. In addition, information on the clinical course in hospital and subsequent major clinical events was collected from the hospital discharge letters, at the visits to the Thrombosis Centre and from the treating physician. Standard 12-lead electrocardiograms, recorded just prior to hospital discharge, were analyzed according to the Minnesota Codes.[22] The electrocardiograms of nine patients were missing. Infarct site was classified as anterior when pathological Q waves >0.03 msec were present in leads V2, V3 or V4.

Risk assessment and statistical analysis

Risk assessment was based on all-cause mortality, 79 % of which was cardiac, including fatal myocardial infarction.[20] Continuous variables were dichotomized as described by other investigators.[17-19] The following variables were considered: age, sex, diabetes mellitus, prior myocardial infarction, prior revascularization, current cigarette smoking, the presence of angina more than one month before index infarction, location of the infarct, treatment with thrombolytic agents, left heart

failure defined as Killip class III or IV on admission and ventricular tachycardia or ventricular fibrillation more than 24 hours after admission. From the 12-lead electrocardiogram the following items were selected: Q-waves (Minnesota code 1), ST-depression (codes 4-1 to 4-3), atrial fibrillation (code 8-3) and an elevated heart rate (≥70 bpm). T-wave abnormality correlates highly with ST abnormalities and was excluded from the analysis. These factors have all been identified as predictors of subsequent mortality in one or several previous investigations.[1-18]

The association of each selected variable with all-cause mortality was assessed by calculation of the univariate hazard ratio and its 95% confidence interval, and by multivariable Cox regression analysis.[23] Analyses were carried out with the statistical package BMDP,[24] and were adjusted for anticoagulant trial medication. Based on this multivariable analysis, the study population was split into in three categories with low, intermediate and high risk.

RESULTS

The baseline characteristics of the 3404 patients are shown in Table 1. Eighty percent were male, mean age was 61 (24,89) years. Few patients (9%) had a previous myocardial infarction and only 6% were in Killip class III or IV. During hospitalization thrombolytic therapy was administered in 25% of the patients. At hospital discharge half of the patients (51%) used beta-adrenergic-blocking agents, 37% used nitrates and 9 % were taking ace-inhibitors. Only few (3%) received antiarrhythmics, one-sixth (17%) calcium antagonists and more than one-fifth (22%) diuretics. Anticoagulant medication was taken by 50% of the patients according to the double-blind study protocol.

After 3 years there were 170 deaths (10%) in the actively treated group and 189 (11%) in the placebo treated group, a non-significant relative difference of 10%.[20] The cumulative 1-month, 6-month and 1-year mortality rates were 0.9%, 2.8% and 4.1% respectively. Nonfatal reinfarction occurred in 9% (300 patients) at three years and mortality or reinfarction occurred in 18%. Percutaneous transluminal coronary angioplasty (PTCA) was performed in 4.8 % of the patients at 3-year follow-up, while 7.9 % underwent coronary artery bypass graft surgery (CABG). Revascularization procedures were performed predominantly among patients with early documented ischemia. Among patients with myocardial ischemia during a predischarge exercise test, 17% underwent CABG and 7 % PTCA.

In Table 1, crude 3-year mortality rates are presented for different baseline characteristics. As in other studies, mortality increased with age. The relation between mortality and age was relative flat until 60 years, while the risk of death increased rapidly after that age (Figure 1). Several indices of impaired left ventricular function were associated with increased mortality such as a history of previous infarction, Killip class III or IV in hospital, heart rate over ≥70 bpm and atrial fibrillation. Thrombolytic treatment was a strong predictor of survival. In the multivariable analysis advanced age, Killip III or IV, previous myocardial infarction, ventricular tachycardia or fibrillation, heart rate, history of angina and absence of thrombolytic treatment were retained as independent predictors of subsequent mortality (Table 1).

Risk stratification

The relative risks of all independent risk factors were of similar strength (1.4-2.7). Summation of the independent risk factors of individual patients (no=0,yes=1) results in a simplified risk score for each patient. The study population was then divided in 3 risk groups. The low-risk group (n=1304) included those patients without any or with only one risk factor (Table 2). The intermediate group (n=1272) contained patients with two risk factors and the high-risk group (n=828) patients with three or more risk factors. Corresponding survival rates for each category of risk are presented in Figure 2. Mortality was very low indeed in the low-risk group (3-year: 2.8%, 5-year: 5.9%) compared to the moderate- and high-risk groups (3-year: 10.0% respectively 17.7%; 5-year: 13.9% respectively 29.6%). In fact, mortality in the low risk group was similar to the expected mortality in the normal population,[25] matched for age and gender which is 2.9% at three years and 6.1% at 5 years, while mortality exceeded the corresponding reference mortality in the higher risk groups. The reinfarction rate was the same (11% at 3 years) in all risk groups as were the rates of revascularization.

Apart from the selected risk indicators, other characteristics differed between the low and high-risk groups: less diabetes, more smoking and more males in the low risk group. This group also used less ace-inhibitors, nitrates, calcium-antagonists, digitalis and diuretics but more beta-blockers.

DISCUSSION

This study confirms that identification of a subgroup of patients after myocardial

Table 1. Mortality, hazard ratio's and confidence intervals for different variables, by univariate and multivariable analysis in 3404 post-myocardial infarction patients

		N	Mortality (%)	Univariate HR	95%CI	Multivariable HR	95%CI
Age							
<70 years		2671	193 (7%)				
≥70 years	*	733	166 (23%)	3.38	2.74-4.16	2.75	2.25-3.44
Killip III or IV							
no		3213	310 (10%)				
yes	*	189	49 (26%)	2.97	2.20-4.02	2.05	1.50-2.80
Previous MI							
no		3097	300 (10%)				
yes	*	307	59 (19%)	1.99	1.50-2.63	1.71	1.29-2.26
Late VT/VF (>24 hour)							
no		3330	340 (10%)				
yes	*	74	19 (26%)	2.35	1.48-3.74	1.79	1.11-2.88
Heart rate at discharge							
<70 bpm		1454	95 (7%)				
≥ 70 bpm	*	1950	264 (14%)	2.18	1.71-2.77	1.79	1.40-2.27
Previous angina							
no		2950	289 (10%)				
yes	*	454	70 (15%)	1.64	1.29-2.10	1.35	1.05-1.73
No thrombolytic therapy							
no		847	45 (5%)				
yes	*	2557	314 (12%)	1.42	1.49-2.78	1.45	1.06-1.99
Atrial fibrillation							
no		3340	341 (10%)				
yes		41	11 (27%)	2.83	1.55-5.16		
Diabetes mellitus							
no		3145	315 (10%)				
yes		259	44 (17%)	1.71	1.24-2.34		
ST depression							
no		2554	230 (9%)				
yes		850	129 (15%)	1.65	1.33-2.04		
Current smoking							
no		1622	203 (11%)				
yes		1782	156 (9%)	0.67	0.54-0.83		
Gender							
male		2717	267 (10%)				
female		687	92 (13%)	1.44	1.09-1.75		

In the analysis, the presence of Q waves (2489 patients), anterior location of the infarct (818 patients) or previous revascularization (47 patients) were not significantly associated with subsequent mortality by either univariable or multivariable analysis.

* Variables were independent predictors and used in the formula of Table 2

infarction with very low mortality risk is feasible and similar to a healthy population, matched for age and gender.

As in other studies[3,6,7,11,14,15,16,17] age was the most important risk factor. The risk of death was low until approximately 65 years and increased rapidly at older ages (Figure 1). Parameters reflecting impaired left ventricular function and the extent of coronary disease like prior MI, left heart failure (Killip class III or IV) and late VT/VF, high heart rate and prior angina were again shown to be independent predictors of mortality. In the present analysis the absence of such findings as well as thrombolytic therapy was associated with a lower mortality risk.[26] Diabetes and female gender were associated with increased mortality, while smokers had a lower mortality as in other studies.[3,12,18,28,29] The lower risk for subsequent mortality in smokers has been observed in previous studies.[29] This is explained to a large extent by the younger age of smokers compared to nonsmokers (57 vs 64 years in the present study). Furthermore, it should be appreciated that we recorded the history of smoking prior to the index infarct. It is likely that part of the smokers quit after the infarct thereby reducing their risk for subsequent coronary events. After adjustment for age and factors representing residual left ventricular function, smoking, gender and diabetes did not contribute to risk assessment in the multivariable model. A subgroup of 1304 patients could be identified with a 3-year mortality rate similar to a matched reference population in The Netherlands.[25] This subgroup represents 38% of the study population.

As in other studies it appeared not possible to identify risk factors for reinfarction.[3,9,13,14] In fact, reinfarction rates were similar among the low, medium and high risk groups, averaging 11% at 3 years (Table 2). In the recently published DANAMI study,[27] reinfarction rates were 10.5% in patients with postinfarction ischemia and only 5.6% in similar patients who underwent a revascularization procedure. This suggests that identification and treatment (by revascularization) of patients with postinfarction ischemia does reduce the risk of reinfarction. In the present study patients were excluded in whom revascularization were recently performed, or scheduled; usually after detection of postinfarction angina or ischemia during a stress test. This also emphasis why revascularization rates after enrollment in this study were low, averaging 14% at 3-years.

Identification and management of low risk patients

In the present study patients were enrolled after hospital discharge and after consent by the responsible cardiologist. No systematic investigations were required by the protocol. However, exercise tests, echocardiography, radionuclide

Table 2. Characteristics of patients with low-, intermediate and high-risk

	total number of risk factors							
	0 or 1 low-risk		2 inter-mediate		>2 high risk		total	
Nr of patients	1304		1272		828		3404	
1-year mortality	1.3		4.1		8.4		4	
3-year mortality %	2.8		7.7		17.7		9	
5-year mortality %	5.9		13.9		29.6		15	
Reinfarction %	8		9		14		11	
Angioplasty %	7		4		3		5	
CABG %	7		10		10		9	
Independent risk factors %								
Mean age (range)	57	(24,87)	60	(26,89)	69	(30,89)	61	(24,89)
Age ≥70 years	2		15		63		33	
Killip III/IV	0		3		17		6	
Previous MI	1		8		25		9	
VTVF	0		1		3		2	
Heart rate ≥70 bpm	23		73		87		57	
Previous angina	2		14		40		16	
No thrombolytic therapy	50		88		96		75	
Other baseline factors %								
Atrial fibrillation	1		1		3		1	
Diabetes	6		7		11		8	
ST segment depression	15		15		14		15	
Anterior infarction	21		24		28		24	
Smoking	65		51		33		52	
Male gender	85		80		72		80	
Qwave	73		73		73		73	
Prior revascularization	1		1		2		1	
XECG performed	65		55		38		55	
Medication at discharge %								
Nitrates	34		35		45		37	
Ca-antagonists	15		17		22		17	
Beta-blockers	61		48		40		51	
Ace-inhibitors	8		7		13		9	
Digitalis	3		5		12		6	
Diuretics	13		20		40		22	
Antiarrhythmics	2		3		6		3	

Used were the independent risk factors: age≥70, Killip III/IV, priorMI, lateVT/VF, heart rate≥70bpm, prior angina and no thrombolytic therapy

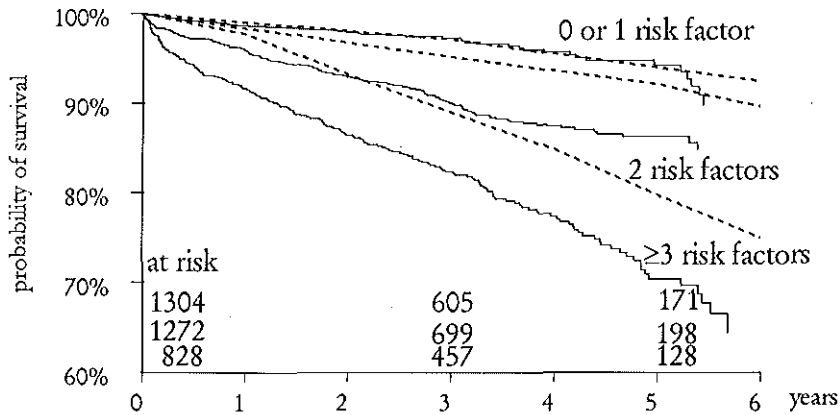

Figure 2. Cumulative survival rates according to the following risk groups: patients with 0 or 1 risk factor, patients with 2 risk factors and patients with 3 or more risk factors. The dotted lines represents the cumulative survival in the general Dutch population (matched for age and gender).

ventriculography and angiography were performed at discretion of the treating physician and will have influenced the decision to enroll patients in ASPECT. In particular patients scheduled for revascularization procedures were excluded. Such revascularization is indicated predominantly in patients with postinfarction ischemia.[27] Thus, the results of the present analysis apply particularly to patients without heart failure and without postinfarction ischemia, who would usually not undergo cardiac catheterization. In these patients simple clinical parameters allow further and meaningful risk stratification as shown by this analysis.

In particular, it appeared possible to identify a group of patients with survival prognosis similar to the general population. In these patients follow-up and management by a cardiology specialist is not required and not appropriate. The general practitioner can follow these patients, and should focus on secondary prevention with a prudent diet, no smoking, and aspirin. Treatment with beta-blockers and cholesterol Co-A reduction inhibitors (statins) has been shown to reduce recurrent coronary events in patients with known coronary artery disease.[30] However, it may be questioned whether such therapy will be cost-effective in this very low risk subgroup after myocardial infarction. Additional therapy will be required as well as reassessment by a cardiologist, as soon as new symptoms become apparent, particularly when angina pectoris develops. The patient should be instructed accordingly.

CONCLUSIONS

This analysis of the large database of ASPECT patients, with careful modeling of 3-year mortality has allowed identification of a subgroup of patients with an excellent survival prognosis who do not require further intensive treatment.

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CHAPTER 3

THE CARDIAC INFARCTION INJURY SCORE (CIIS) AS A PREDICTOR FOR LONG-TERM MORTALITY IN SURVIVORS OF A MYOCARDIAL INFARCTION

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ABSTRACT

Aims

The Cardiac Infarction Injury Score (CIIS) is an electrocardiographic (ECG) classification system that was developed as a diagnostic tool to assess the extent of cardiac injury in acute myocardial infarction. We investigated the prognostic value of the CIIS in post-myocardial infarction patients.

Methods and Results

The prognostic values of the CIIS for total and cardiac mortality was assessed in a large series (n=3395) of patients who were enrolled in the ASPECT trial. Standard 12-lead ECGs recorded prior to hospital discharge were coded according to the Minnesota Code and the CIIS. Mean CIIS was 26 (range -8 to 59). After adjustment for other baseline characteristics, the CIIS was directly related to the risk of total mortality and cardiac mortality. At one-year follow-up the relative risks of CIIS≥40, CIIS 30-40 and CIIS 20-30 were significantly higher than in those with a CIIS<20. The relative risks were respectively 2.3 (1.2-4.4), 2.2 (1.3-3.9) and 1.6 (0.9-2.9). At three-year follow-up the relative risks were respectively 2.1 (1.4-3.2), 1.7 (1.2-2.4) and 1.5 (1.0-2.1). The relative risks for total mortality were similar. When patients with major ECG abnormalities as defined by the Minnesota code were excluded, the associations were still significant in the CIIS classes 30-40 and ≥40.

Conclusion

The CIIS ECG scoring system is an important predictor for long-term cardiac mortality in post myocardial infarction patients. It can easily be automated and is efficient for classifying cardiac injury in epidemiological studies.

INTRODUCTION

Post-myocardial infarction risk assessment may be based upon non-invasive as well as invasive tests, which address various aspects of myocardial damage or residual cardiac function.[1,2] The Cardiac Infarction Injury score (CIIS) is an electrocardiographic measurement which was constructed as a diagnostic tool to assess the extent of cardiac injury in myocardial infarction and to discriminate between presence or absence of a recent myocardial infarction.[3] Selected electrocardiographic characteristics are weighted and combined into a single score. Subjects with a high CIIS score are likely to have had a (larger) myocardial infarction. As this score is weighted upon different elements of the ECG (including Q waves and T waves), it might be more reliable in larger groups of patients than single ECG markers.

A limited number of studies assessed the prognostic value of the CIIS in healthy populations[4,5] and hypertensive patients.[6,7] The present study addressed the prognostic value of the CIIS in post-myocardial infarction patients. The aim was to determine the independent contribution of the CIIS to the risk of total mortality, cardiac mortality and reinfarction in a large series of patients (n=3395), who were enrolled in the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial.[8]

METHODS

Patients

Patients were enrolled in ASPECT from September 1986 until December 1991. ASPECT was a multicenter, randomized, double-blind trial, with two treatment arms: "active" anticoagulant therapy and matching placebo.[8] The diagnosis of myocardial infarction was based upon (1) chest pain (2) typical serum enzyme pattern and (3) evolving ST-T segment and/or Q waves. Exclusion criteria included established indications for anticoagulant treatment (e.g. left ventricular thrombus, aneurysm, extensive left ventricular dysfunction and chronic atrial fibrillation), anticoagulant therapy within six months prior to the index infarction, increased bleeding tendency, anticipated coronary revascularization procedure and malignant disease with poor prognosis. All patients were followed for 37 (6-67) months. Design, patient selection, data acquisition, data management and follow-up of ASPECT have been reported previously.

Table 1: Baseline characteristics (%) in categories of the Cardiac Infarction Injury Score.

Score Model	CIIS <20 (I)	20-30 (II)	30-40 (III)	≥40 (IV)	total
N	958 (28%)	1002 (29%)	1053 (31%)	382 (11%)	3395
mean CIIS	11.6	25.0	34.2	44.0	26.2
%					
Age (yr)	61.0	60.3	60.7	62.7	60.9
Male gender	78	81	79	82	80
Current smoking	53	52	52	54	53
Diabetes	7	7	9	8	8
Revascularization	1	2	1	1	1
Angina	18	13	14	18	16
Previous infarction	7	9	10	14	9 *
Anterior MI	12	27	24	48	24 *
Killip III/IV	3	6	6	11	6 *
VT/VF > 24 hr	1	2	3	4	2 *
Thrombolytic therapy	17	26	29	32	25 *
12-lead ECG %					
Heart rate ≥70 bpm	49	60	60	65	57 *
ST segment depression	24	25	26	29	25
Q-wave	33	81	94	97	73 *
Ventricular cond.defect	4	6	5	5	5
AV conduction defect	5	5	5	5	8
LV hypertrophy	2	2	1	1	1
Atrial fibrillation	1	2	1	2	1
Premature atrial complex	2	3	3	4	3
Premature ventricular complex	8	6	6	9	7
Negative or flat T wave	69	82	91	95	83
Medication at discharge %					
Beta-blocker	57	52	47	46	51 *
Nitrates	39	37	34	43	37
Calcium antagonists	23	16	15	12	17 *
Ace-inhibitors	7	9	9	14	9 *
Digitalis	5	6	6	10	6 *
Diuretics	16	23	23	33	22 *
Anti-arrhythmics	3	2	5	5	3 *
Anticoagulants	48	48	52	50	50 *

* Test of significance for linear trend over the CIIS categories ($P<0.05$)

Data acquisition

Before randomization, a set of demographic and historical variables was collected in each patient: age, sex, prior myocardial infarction, current smoking habits, diabetes,

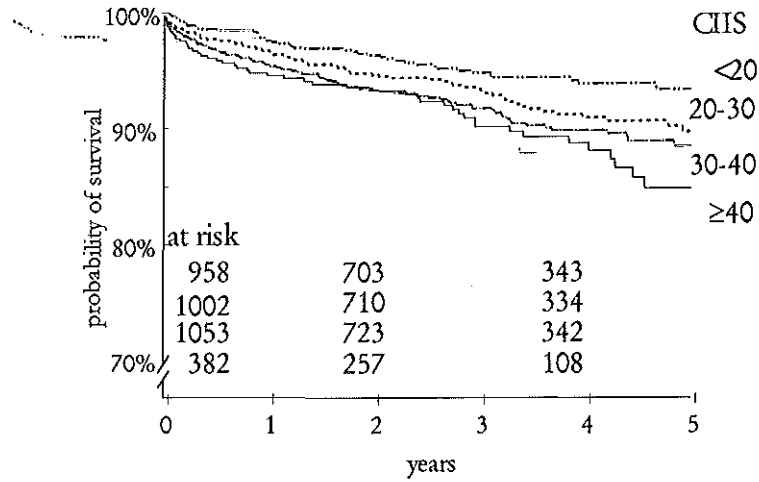

Figure 1. Cumulative survival rates of cardiac mortality according to the four CIIS categories <20, 20 to 30, 30 to 40 and ≥40.

prior revascularization, history of angina, location of the infarction, thrombolytic therapy and heart failure defined as Killip class III or IV on admission. In addition, information on the clinical course in hospital and subsequent major clinical events was collected from the hospital discharge letters, at the visits to the Thrombosis Centre and from the treating physician. Standard 12-lead electrocardiograms, recorded prior to hospital discharge were coded according to the Minnesota Code (MC)[9] and the CIIS. Twelve ECG features were used to compute the CIIS: five T-wave amplitude measurements; four Q-wave duration measurements or Q/R-amplitude ratios; and three R- or S-amplitude measurements (see Appendix). In 3395 out of 3404 patients in ASPECT a 12-lead electrocardiogram was coded. Coding of 9 electrocardiograms was not possible.

Major events during follow-up were cardiac death (sudden death, fatal myocardial reinfarction, congestive heart failure), non-cardiac death and myocardial reinfarction (nonfatal or fatal).

Data analysis

The CIIS was originally developed to detect myocardial infarction[3] and was categorized as <10 (no infarction), 10-20 (possible infarction), 20 or more (probable infarction). In this study population all patients had sustained a myocardial infarction. Therefore, we classified the patients also in (higher) cohorts of 10 in the

Table 2: Hazard ratios of total and cardiac mortality in categories of Minnesota codes.

Minnesota Code	number of patients(%)	total mortality HR	95% CI	3-year cardiac mortality HR	95% CI
any 1 Q-wave	2486 (74%)				
Age adjusted		1.15	0.91-1.46	1.18	0.88-1.57
Multivariable*		1.10	0.83-1.40	1.06	0.77-1.44
3-3 LV Hypertrophy	46 (1%)				
Age adjusted		0.53	0.17-1.66	0.51	0.13-2.04
Multivariable*		0.45	0.14-1.41	0.41	0.10-1.66
Any 4 ST depression	845 (29%)				
Age adjusted		1.29	1.04-1.61	1.37	1.06-1.78
Multivariable*		1.20	0.96-1.50	1.26	0.97-1.64
Any 5 Negative or flat T	2777 (83%)				
Age adjusted		0.72	0.56-0.92	0.63	0.47-0.84
Multivariable*		0.69	0.54-0.89	0.61	0.45-0.81
Any 6 A-V cond. Defect	183 (6%)				
Age adjusted		1.15	0.78-1.68	1.13	0.72-1.79
Multivariable*		1.10	0.75-1.61	1.07	0.67-1.69
Any 7 Bundle branch block	177 (5%)				
Age adjusted		2.56	1.91-3.47	2.94	2.10-4.12
Multivariable*		2.51	1.86-3.39	2.81	2.00-3.97
8.1 PACs	104 (3%)				
Age adjusted		2.11	1.41-3.15	2.74	1.78-4.21
Multivariable*		2.19	1.46-3.28	2.78	1.80-4.30
8-1,2,3 PVCs	226 (7%)				
Age adjusted		1.17	0.78-1.76	1.12	0.68-1.83
Multivariable*		1.18	0.79-1.78	1.14	0.70-1.88
8.3.1 AF	41 (1%)				
Age adjusted		1.68	0.92-3.08	1.52	0.71-3.23
Multivariable*		1.78	0.96-3.28	1.59	0.74-3.41
Any 8 Arrythmias	111 (3%)				
Age adjusted		1.56	1.18-2.06	1.66	1.21-2.30
Multivariable*		1.60	1.21-2.11	1.71	1.23-2.36

*Adjusted for age, previous MI, diabetes, history of angina, smoking, anterior infarction, killip III or IV, VTVF and thrombolytic therapy. HR=hazard ratio; CI=confidence interval.
PAC=premature atrial complex; PVC=premature ventricular complex; AF=atrial fibrillation

following four categories of the CIIS: (I) less than 20, (II) 20-30, (III) 30-40 and (IV) ≥40. This resulted in three groups of approximately equal size and one group (IV) which was 1/3 in size of the other groups. Overall between-group differences of baseline characteristics were tested using the Tukey-Cramer method, which adjust for multiple comparisons. Endpoints are presented as total mortality, cardiac

mortality and a combined endpoint of mortality and reinfarction. Probability of these endpoints is presented as Kaplan-Meier curves.[10] Differences between curves were analyzed with log-rank tests.[11] The association of the CIIS with cardiac mortality, total mortality and mortality or nonfatal reinfarction was analyzed using Cox proportional hazards models[12] and presented as hazard ratios. Since the prevalence of electrocardiographic abnormalities increases with age, all univariable analyses included age to adjust for possible confounding. To investigate whether the prognostic value of the CIIS was modified by duration of follow-up, we calculated hazard ratios at 6-months, at 1-year and at 3-year follow-up. In the multivariable models hazard ratios were adjusted for baseline characteristics as described in the data acquisition section, and for possible confounding and interaction factors. Proportional hazard assumptions were verified by inspection of log-log-survival curves.

The predictive value of each component of the CIIS was evaluated by including all 12 items separately in a multivariable model. To evaluate whether the predictive value of the CIIS was independent of the binary ECG abnormalities as used in the Minnesota code, we excluded the following ECG abnormalities one at a time: ST segment depression (Minnesota 4), negative or flat T wave (Minnesota 5), AV conduction defect (Minnesota 6), left ventricular hypertrophy (Minnesota 3-3), premature atrial complex (Minnesota 8-1.1), premature ventricular complex

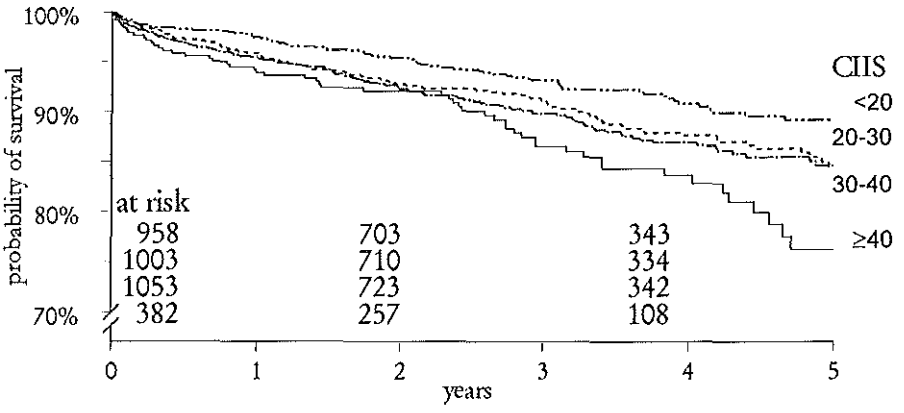

Figure 2. Cumulative survival rates of overall mortality in the four CIIS categories <20, 20 to 30, 30 to 40 and ≥40.

Table 3: Hazard ratios and 95% confidence intervals of total and cardiac mortality in categories of the Cardiac Injury Infarction Score.

Minnesota Code	total mortality HR	95% CI	cardiac mortality HR	95% CI
6-months follow-up				
CIIS<20	1.00		1.00	
CIIS 20-30				
Age adjusted	1.66	0.91-3.04	1.70	0.86-3.38
Multivariable*	1.62	0.88-2.98	1.61	0.80-3.22
CIIS 30-40				
Age adjusted	1.82	1.02-3.28	2.24	1.17-4.28
Multivariable*	1.74	0.96-3.14	2.06	1.07-3.97
CIIS ≥ 40				
Age adjusted	2.32	1.19-4.56	2.87	1.38-5.97
Multivariable*	2.01	0.99-4.06	2.22	1.03-4.78
1-year follow-up				
CIIS<20	1.00		1.00	
CIIS 20-30				
Age adjusted	1.74	1.05-2.88	1.69	0.94-3.03
Multivariable*	1.71	1.03-2.85	1.62	0.90-2.93
CIIS 30-40				
Age adjusted	1.90	1.16-3.09	2.36	1.37-4.08
Multivariable*	1.84	1.12-3.02	2.24	1.29-3.90
CIIS ≥ 40				
Age adjusted	2.24	1.26-3.96	2.73	1.46-5.13
Multivariable*	2.03	1.12-3.68	2.26	1.17-4.37
3-year follow-up				
CIIS<20	1.00		1.00	
CIIS 20-30				
Age adjusted	1.49	1.11-2.00	1.48	1.03-2.13
Multivariable*	1.49	1.10-2.02	1.46	1.01-2.11
CIIS 30-40				
Age adjusted	1.56	1.16-2.09	1.69	1.19-2.40
Multivariable*	1.52	1.13-2.05	1.63	1.14-2.33
CIIS ≥ 40				
Age adjusted	1.88	1.32-2.67	2.12	1.40-3.20
Multivariable*	1.68	1.16-2.42	1.84	1.20-2.83

*Adjusted for age, previous MI, diabetes, history of angina, smoking, anterior infarction, Killip III or IV, VTVF and thrombolytic therapy. HR=hazard ratio; CI=confidence interval.

(Minnesota 8.1-2,3), atrial fibrillation (Minnesota 8-3.1) or any arrhythmia's (Minnesota any 8 code). Finally we excluded all patients with any mentioned ECG abnormality.

RESULTS

Of the 3395 patients 80% were male and the mean age was 61 years (range 24 to 89). Mortality in this patient cohort was relative low. After 3-years follow-up there were 359 deaths (11%), of which 79% were cardiac. The cumulative 6-months and 1-year mortality rates were 2.8% and 4.1% respectively. Reinfarction occurred in 356 patients (11%) at three years and mortality or reinfarction occurred in 618 patients (18%). The mean CIIS was 26 (range -8 to 59). CIIS scores between 20-30 were observed in 29%, CIIS between 30-40 in 31%, and the highest scores (40 or more) in 11% of the patients. The sensitivity of CIIS <20 to confirm the index infarction was 72%.

Table 1 shows the distribution of baseline characteristics and mortality in the four CIIS categories. Patients with a CIIS of 40 or more were older compared to the other three groups. Previous infarction, anterior location of the infarct, heart failure and late VT/VF were found more frequently with increasing CIIS, while such patients received more frequent thrombolytic therapy. At discharge of the index infarction, the use of beta-blocking agents was lower with increasing CIIS. Digitalis and diuretics increased with higher CIIS. Of the ECG abnormalities based upon the Minnesota codes, heart rate ≥70 bpm, Q wave, and negative or flat T wave were more frequent in the highest CIIS category, while other ECG characteristics were equally divided over the CIIS categories.

Mortality rates in CIIS categories II-IV were significantly higher than the CIIS category I (Figures 1 and 2). Patients with a CIIS<20 had a lower risk of death or reinfarction than the other three CIIS categories (Figure 3). Age adjusted and multivariable adjusted hazard ratios of total and cardiac mortality for several binary ECG criteria on basis of the Minnesota codes are presented in Table 2. In multivariable analysis only ventricular conduction defects (right and left bundle branch block), premature atrial complex and arrhythmia's were predictive of mortality. In Table 3, hazard ratios for total mortality and cardiac mortality in categories of the CIIS at 6-months, 1-year and 3-year are presented. At any moment of follow-up, the hazard ratios demonstrate an increased relative risk for categories II-IV compared to category I. The CIIS categories 30-40 and ≥40 were independent

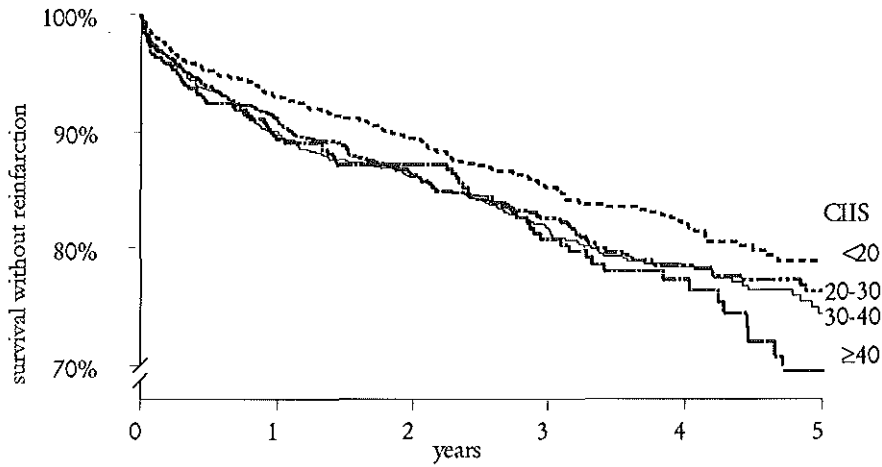

Figure 3. Cumulative survival rates of mortality or myocardial reinfarction in the four CIIS categories <20, 20 to 30, 30 to 40 and >40.

predictors for short- and long-term total mortality with relative risks varying from 1.5 to 2.0, respectively from 1.7 to 2.3 for cardiac mortality. The CIIS category 20-30 was predictive for cardiac mortality at three-years with a relative risk of 1.6 and predictive for total mortality with relative risks of 1.7 (1-year) and 1.5 (3-years). The CIIS was the strongest predictor in the multivariable analyses, even when nine other baseline risk factors were included. The predictive value for 3-year mortality or reinfarction was low with relative risks of 1.31 (95%CI: 1.06-1.62), 1.23 (95%CI: 0.99-1.53) and 1.22 (95%CI: 0.92-1.62) for respectively CIIS categories 20-30, 30-40 and 40 or more.

To evaluate whether the predictive value of the CIIS was independent of the binary ECG abnormalities on the basis of the Minnesota codes, these abnormalities were excluded one category at a time. When patients with any ST segment depression, AV conduction defect, left or right bundle branch block, left ventricular hypertrophy or any arrhythmia's were excluded (data not shown), the relative risks remained significantly higher in the CIIS categories III and IV. When patients with any major Minnesota Codes were excluded, the rates were still 1.5 higher in classes III as that in class I patients; although this was not significant, while the class IV rates remained 2.7 times higher than the class I score (95%CI:1.4-5.3).

The relative contribution of each of the 12 CIIS items were separately analyzed. The amplitudes of R (item 3, see Appendix) and negative T in aVR (item

4) as well as the amplitude of positive T in V1 (item 8) and Q duration in lead III or AVL (item 6) are significant components of the CIIS for total mortality, whereas the same most items were predictive of cardiac mortality (with the negative T amplitude in lead V2 [item 9] replacing item 6). The relative risk for mortality remained unchanged when patients with an anterior infarction or patients with a prior infarction were excluded. Inclusion of other possible confounding factors into the models did not change the associations. Separately analyses were performed on both the anticoagulant group and placebo group with similar results.

DISCUSSION

Infarct size is an important predictor of long-term mortality, whether measured by myocardial enzyme release,[1,2] global or regional left ventricular function or estimated by exercise capacity.[13] The CIIS is a simple and inexpensive measurement of infarct size from the 12-lead ECG. Willems et al[14] related the CIIS with enzymatic infarct size and confirmed that the CIIS reflected myocardial infarct size in acute myocardial infarction patients. The CIIS has been applied in healthy and hypertensive subjects,[4-7] in whom it appeared to be of prognostic value for long-term mortality.

To our knowledge, this report is the first to investigate the prognostic value of the CIIS for mortality in post-myocardial infarction. This analysis of the ASPECT study group confirms that the Cardiac Infarction Injury Score, composed of 12 items from the 12-lead ECG made at discharge in myocardial infarction survivors, is an important predictor of mortality during long-term follow-up. The CIIS has been developed from a well validated database[3] by an extensive statistical search for the best combination of variables and was originally designed to increase the sensitivity of the detection of a recent myocardial infarction (50% infarctions <1 month; 50%: between 1 month and 1-year). Other studies investigated the ECG QRS score system for prediction of an acute or recent infarction.[14,15] However only Bounus et al[16] investigated the predicted value of long-term outcome in patients with coronary artery disease, but he was unable to predict the independent prognostic value of the QRS score. In previous studies,[3-6] high CIIS was associated with increased mortality. In hypertensive men in the MRFIT trial[6] a CIIS of 10 or more was associated with coronary heart disease mortality in the intervention group. Dekker et al[5] reported an association of CIIS >20 with coronary heart disease mortality among apparently healthy middle-age Dutch civil servants. They also

found a CIIS >10 as a predictor of cardiac mortality in apparently healthy men and women. During follow-up in the present study an increasing mortality rate was found with increasing CIIS. The predictive value of the CIIS for mortality was highest after 1-year and decreased with prolonged follow-up. Yet, the CIIS remained a strong predictor for mortality at 3-years. The CIIS had no predictive value for reinfarction (fatal or nonfatal), while only a predictive value of the CIIS≥40 could be shown for short- and long-term prognosis for the combined endpoint of mortality and myocardial reinfarction.

The data indicate that the CIIS, calculated at discharge of post-myocardial infarction patients, is directly related to the risk of subsequent mortality. There was a modest increase in risk associated with a higher score, which was independent of other clinical characteristics and conventional ECG criteria. For this reason, analyses based upon binary ECG criteria based using the Minnesota codes may underestimate the importance of these pathophysiological abnormalities as potential determinants of mortality. The findings suggest that not only the presence but also the severity of abnormalities of cardiac structures and electrophysiological function account, in part, for the increased risk of mortality, observed among post-myocardial infarct patients.

Limitations

The study population was selected, excluding patients with large myocardial infarction.[8] Only 24% of the patients had an anterior myocardial infarction and the mortality rate was low. This resulted in a low-risk group of postinfarct patients. Nevertheless, it is remarkable that even in this study population, risk assessment with the CIIS was successful. Verification and extension of these data in postinfarct patients at similar or higher risk is warranted.

CONCLUSION

The standard 12-lead ECG is an important and basic tool for risk stratification of post-myocardial infarction. By maximizing the prognostic information from the standard ECG in a simple quantitative fashion, the CIIS ECG system appears to be a useful instrument for clinicians who treat long-term post-myocardial infarction patients. The CIIS can easily be automated and by simple quantification, important prognostic risk assessments can be made. The possibility to predict long-term survival or early mortality provides an opportunity for planning adequate

surveillance and diagnostic and interventional programs aimed at future improving programs. Although these results suggest that the CIIS may be a better predictor than the traditional binary ECG criteria that are used to assess myocardial damage, clinicians should be aware that both the sensitivity of the CIIS and the increase in absolute risk remain modest.

Appendix Items in the Cardiac Infarction Injury Score (CIIS).

Component number		Score
(1)	Duration of Q in lead aVL (ms):	
	Q absent	5
	10 ms	1
	20 ms	3
	30 ms	9
	40 ms	10
	50 ms	12
(2a)	Amplitude of positive T in lead aVL	
	≤0.5 mm or >3 mm	3
(2b)	Amplitude of negative T in lead aVL (mm)	mm x 2
(3)	Amplitude of negative R in lead aVR <5 mm	mm x -1
(4)	Amplitude of negative T in lead aVR (mm)	
	absent	6
	1	3
	2	0
	3	-2
	4	-5
	5	-7
	6	-9
	7	-11
	8	-13
(5)	Largest Q/R amplitude ratio in lead II or aVF ≥1/5	12
(6)	Duration of Q in lead III or aVL ≥40 ms	5
(7)	Amplitude if T in lead III >1 mm	5
(8)	Amplitude of positive R lead V1 >2 mm	5
(9)	Amplitude of negative R in lead V2 <3 or ≥14 mm	5
(10)	Amplitude of negative T in lead V2 ≥1/4 mm	5
(11)	Largest Q/R amplitude ratio in lead V3 >1/20	9
(12)	Amplitude of S in lead V5 <2 mm	5

Items 5-12 are dichotomous (yes/no)

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Chapter 4

PROGNOSTIC SIGNIFICANCE OF NONFATAL MYOCARDIAL REINFARCTION IN SURVIVORS OF MYOCARDIAL INFARCTION

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(submitted)

ABSTRACT

Aims
The purpose of this study was to examine the risk of mortality after myocardial *reinfarction* and to determine the independent contribution of nonfatal reinfarction to the risk of subsequent mortality.

Methods and results
The prognostic value of nonfatal reinfarction was assessed in a large series (n=3404) of patients who were enrolled in the ASPECT trial. After adjustment for baseline characteristics the relative risks of nonfatal reinfarction for subsequent cardiac mortality were at 1-month: 2.90 (95%CI: 1.49-5.64), at 1-year: 2.50 (95%CI: 1.47-4.23) and at 3-years 2.87: (95%CI: 1.45-5.35). Rates of death or a second reinfarct in patients who did not undergo a revascularization procedure after a first reinfarct were almost three times higher than in patients who did have PTCA or bypass surgery after a reinfarct (41% versus 15%).

Conclusions
This study population with 3-year follow-up confirms that nonfatal reinfarction carries a strong and independent risk for subsequent mortality. Thus prevention of reinfarction by intensive treatment might contribute in reduction of mortality. In particular, coronary angioplasty or coronary bypass surgery should be considered in all patients after reinfarction to reduce subsequent coronary events and mortality. It is recommended that a prospective trial should be initiated to verify this hypothesis.

INTRODUCTION

In patients who survived one or more previous infarcts, reinfarction may be fatal or otherwise carries an increased risk for subsequent morbidity and mortality.[1-9] The relation between nonfatal reinfarction and subsequent mortality has been evaluated in a few studies performed in the pre-thrombolysis era,[10,11] and in one study in which all patients received thrombolytic therapy.[12] Since thrombolytic therapy decreases initial mortality, but also is associated with an increased rate of recurrent myocardial infarction,[12] reassessment of the impact of reinfarction is appropriate. Therefore, the purpose of this study was to examine the clinical characteristics of fatal and nonfatal reinfarction and to determine the independent contribution of nonfatal reinfarction to the risk of subsequent cardiac death and other events during 3 years follow-up in a large series (n=3404) of patients with recent myocardial infarction, who were enrolled in the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial. The implications of (nonfatal) reinfarction for patient management are discussed.

METHODS

Patients

Patients were enrolled in ASPECT from September 1986 until December 1991. ASPECT was a multicenter, randomised, double-blind clinical trial, with two treatment arms: "active" anticoagulant therapy and matching placebo. All patients had a recent documented myocardial infarction based upon the following criteria: (1) chest pain, (2) typical serum enzyme pattern and (3) evolving ST-T segment changes and/or Q waves. Exclusion criteria included indications for anticoagulant treatment (e.g. left ventricular thrombus or aneurysm, extensive left ventricular dysfunction and chronic atrial fibrillation), use of anticoagulant therapy within six months prior to the index infarction, increased bleeding tendency, anticipated coronary revascularization procedure, and malignant disease with poor prognosis. All patients were followed for 37 (6-67) months. Design, patients, data acquisition, data management and follow-up of the ASPECT trial has been reported previously.[13]

Risk variables

The following variables were collected in each patient: age, sex, prior myocardial

infarction (before the index infarct), cigarette smoking, diabetes mellitus, history of angina, location of the infarct, thrombolytic therapy, left ventricular failure defined as Killip class III or IV on admission, ventricular tachycardia or fibrillation occurring more than 24 hours after entry, heart rate and ST segment depression >0.1 mV at discharge.

Reinfarction and mortality

Three hundred and fifty nine patients died during follow-up. Deaths were classified by a Mortality and Morbidity Classification Committee as sudden (all deaths occurring within 1 hour of onset of symptoms), fatal myocardial infarction, death from progressive heart failure and non-cardiac. A first recurrent nonfatal myocardial infarction was defined in patients who suffered a documented myocardial infarction and survived this event for at least 30 days. The criteria for reinfarction were the same as those for the index infarction.

Statistical analysis

Baseline characteristics of patients experiencing fatal and nonfatal myocardial

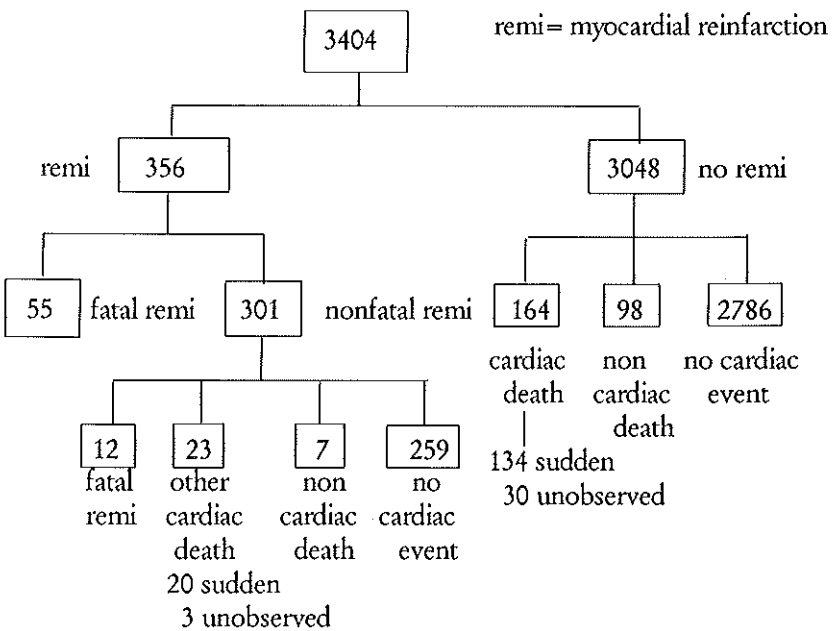

Figure 1. Incidence of cardiac events.

Table 1. Baseline characteristics split up in first cardiac events.

%	no cardiac event	reinfarction			no reinfarction		total
		nonfatal	fatal	fatal or nonfatal	cardiac death	noncardiac death	
Number of patients	2786 (82%)	301 (9%)	55 (2%)	356 (11%)	164 (5%)	98 (3%)	3404
Age≥70 years	19	23	58 *	28 *	41 *	45 *	22
Male	80	82	64 *	79	74 *	82	80
Previous MI	8	16 *	18 *	16 *	17 *	11	9
Diabetes	7	11 *	13	11 *	13 *	10	8
Smoking	53	53	38 *	51	45 *	47	52
History of angina	15	18	44 *	22 *	20	19	16
Anterior infarction	23	26	15	24	36 *	20	24
Thrombolytic therapy	26	28	13 *	25	10 *	19	25
Killip III/IV	5	6	11 *	7	16 *	11 *	6
Heart rate≥70 bpm	11	8	18	10	29 *	11	12
VT/VF>24 hr	2	3	4	3	5 *	7 *	2
ST depression	23	33 *	25	31 *	40 *	31	25

MI=Myocardial infarction; VT/VF=ventricular tachycardia or fibrillation > 24hours after entry. *$p<0.05$ compared to no cardiac event.

infarction were compared using chi-square and Student's t-tests. Cumulative reinfarction rates and mortality rates were described by Kaplan-Meier curves[14] and differences between the curves were assessed by the log-rank test.[15]

A stepwise Cox regression model[16,17] was used to assess clinical predictors for reinfarction (fatal or nonfatal), as well as to identify risk factors for subsequent cardiac mortality after nonfatal reinfarction. A time-dependent Cox proportional hazard model[18] was employed to determine the independent risk of nonfatal reinfarction to subsequent cardiac mortality over time. The basic principle of this analysis is as follows: from enrollment in the study, for each day a separate 2x2 classification was formed for all patients still at risk at that day. The 'horizontal' classification row corresponds to whether a patient had suffered a nonfatal reinfarction before that day or not. The 'vertical' classification column corresponds to cardiac death or not at that day. A relation of cardiac mortality and occurrence of nonfatal reinfarction was constructed at each day during follow-up and a corresponding cardiac death hazard ratio was calculated for nonfatal reinfarction. The Cox survival analysis combines these hazard ratios over time and adjustment of the ratio for differences in the clinical baseline charateristics is possible. This results

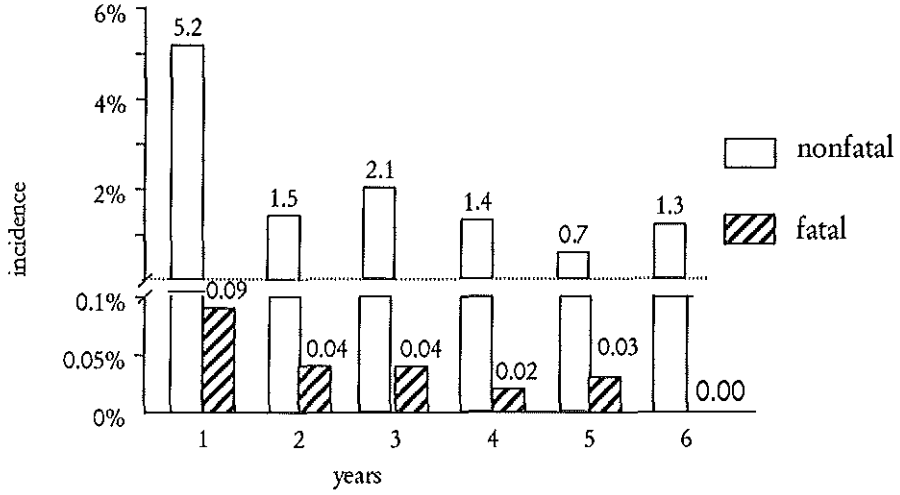

Figure 2. Incidence of recurrent myocardial infarction.

in a hazard ratio for nonfatal reinfarction reflecting the subsequent risk of cardiac mortality for patients with a nonfatal reinfarction as compared with the risk of patients without such nonfatal reinfarction.

All analyses were performed separately on both the 'placebo-assigned' patients and on the anticoagulant treated patients as well as on a combination of both groups, while adjusting for trial treatment.

The mortality rate of patients with nonfatal reinfarction was compared with that of a control group, which consisted of three matched control patients for each patient with a nonfatal reinfarction. Matching was based upon gender, age and time of reinfarction. For each patient with an event a pool of patients was identified who had not experienced an event at that point. A matched control subject for each patient was randomly selected without replacement from the available pool. To avoid retrospective bias, the matching technique allowed selection of patients with later nonfatal reinfarction as control patients for those with early nonfatal reinfarction.

RESULTS

By the end of the 3-year follow-up (range 6-67 months), 359 of the 3404 patients

Table 2. Clinical predictors of mortality or myocardial reinfarction in 3404 post MI patients.

		N	nr of events	(%)	univariate HR	95%CI	multivariable HR	95%CI
Nr of patients		3404	618	(18.2)				
Age ≥70 yr	no	2672	407	(15.2)				
	yes	732	211	(28.8)	2.02	1.72-2.40	1.83	1.54-2.17
Male	no	687	134	(19.5)				
	yes	2717	484	(17.8)	0.92	0.76-1.11		
Previous MI	no	3097	523	(16.9)				
	yes	307	95	(30.9)	1.93	1.55-2.40	1.79	1.44-2.23
History of angina	no	2872	490	(17.1)				
	yes	532	128	(24.1)	1.38	1.13-1.67		
Diabetes	no	3145	547	(17.4)				
	yes	259	71	(27.4)	1.59	1.24-2.03	1.37	1.02-2.14
Anterior infarct	no	2586	453	(17.5)				
	yes	818	165	(20.1)	1.16	0.97-1.39		
Thrombolysis	no	2557	493	(19.3)				
	yes	847	125	(14.8)	0.97	0.79-1.18		
Killip III or IV	no	3213	558	(17.4)				
	yes	189	60	(31.7)	2.00	1.53-2.61	1.66	1.26-2.17
VTVF	no	3330	592	(17.8)				
	yes	74	26	(35.1)	1.95	1.32-2.89		
Heart rate≥70bpm*	no	1454	220	(15.1)				
	yes	1950	398	(20.4)	1.36	1.15-1.60	1.21	1.03-1.44
ST-depression*	no	2554	414	(16.2)				
	yes	850	204	(24.0)	1.42	1.20-1.68	1.23	1.04-1.46

MI=Myocardial infarction; VT/VF=ventricular tachycardia or fibrillation > 24hours after entry.
*at discharge.

had died (11%). Causes of death were sudden (154, 4.5%), myocardial infarction (67, 2.0%), progressive heart failure (30, 0.8%) and non-cardiac (105, 3.1%). The 3-year mortality rate was not different among the placebo (11%) and the anticoagulant group (10%). The reinfarction rate, however, was significantly lower in the anticoagulant group (7% vs 14%; $p<0.0001$). In all analyses of nonfatal reinfarction and subsequent mortality and their risk factors, however, we did not find any differences between both treatment groups. Therefore, the combined analysis on all 3404 ASPECT patients is presented in this report.

A first myocardial reinfarction was documented in 356 patients (11%), of which 55 (16%) were fatal (Figure 1). The occurrence of nonfatal and fatal reinfarction over time is presented in Figure 2. The risk of a reinfarction was 5.2% in the first year. Thereafter, the incidence of a documented reinfarction was low

(0.7%-2.1%). It is likely that part of the 164 patients who died without documented reinfarction (sudden death or unobserved) did in fact suffer from reinfarction. When it would be assumed that all deaths were due to reinfarction, unless otherwise documented, then the total number of (possible) reinfarctions would have been 520 (356+164=15% of the patients) with a mortality rate of 42% (219/520). Of the 301 nonfatal reinfarcts forty seven patients had multiple reinfarctions and 42 patients (14%) died during subsequent follow-up. Causes of subsequent mortality in these patients were fatal myocardial reinfarction (i.e. second or third reinfarction (n=12, 4%), sudden death (n=20, 7%), unobserved death (n=3, 1%) and non-cardiac death (n=7, 2%).

Baseline clinical features and recurrent reinfarction

The baseline characteristics of patients without subsequent cardiac events, those with nonfatal or fatal reinfarction and those with fatal cardiac and noncardiac death are presented in Table 1. Patients with reinfarction were older and more likely to have had a previous infarction (prior to the index infarct), diabetes, previous angina and ST segment depression at hospital discharge than patients without a subsequent cardiac event. Patients who died of cardiac cause had the same characteristics, in addition were more often female, with higher heart rate (≥70 bpm), anterior infarction and more ST-segment depression at hospital discharge and had received

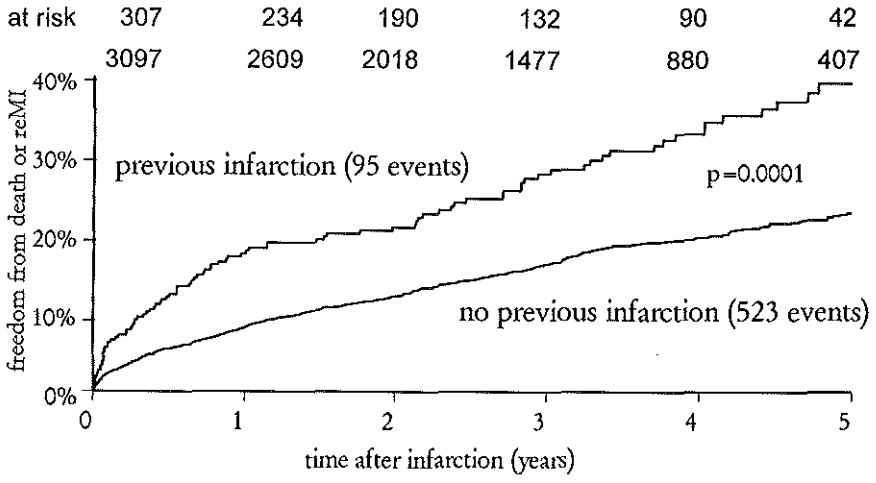

Figure 3. Cumulative survival rates according to patients with and without prior myocardial infarction.

Table 3. Time dependent Cox with nonfatal reinfarction as an independent riskfactor for subsequent cardiac mortality adjusted for preselected clinical characteristics.

	HR	95% CI
Nonfatal reinfarction	2.47	1.77-3.74
Advanced age (≥70 year)	2.07	1.58-2.72
Elevated heart rate ≥70 bpm)	1.92	1.41-2.61
No thrombolytic therapy	1.85	1.22-2.78
Killip class III/IV	1.83	1.25-2.66
Previous infarction	1.76	1.26-2.46
Ineligibility stress test	1.72	1.30-2.27
History of angina	1.52	1.13-2.83

less frequently thrombolytic therapy than patients with a nonfatal reinfarction, or uncomplicated course.

In a multivariable Cox regression analysis the following variables (Table 2) were retained as independent predictors of mortality or reinfarction: age (≥70 years), prior infarction, diabetes, Killip class III/IV, heart rate (≥70bpm) and ST depression >0.1mV. Patient with a prior infarction were likely to have more fatal or nonfatal reinfarctions over time than in patients without prior infarction (Figure 3).

Cardiac mortality after nonfatal reinfarction

The univariable relative risk of nonfatal reinfarction for subsequent cardiac death was 2.88 (95%CI:1.99-4.17). Similar relative risks were found when nonfatal reinfarction was categorized into early (<1 month), medium term (1 month-1 year) and late (1-3 year) reinfarction (respectively 2.90; 1.49-5.64, 2.50; 1.47-4.23 and 2.87; 1.45-5.35). Survival of patients with a nonfatal reinfarction and the matched-control group (matched for age, gender and time after the index infarct) is presented in Figure 4. The cardiac mortality rate was significantly higher in the nonfatal reinfarction group than in the control group. To determine the independent contribution of nonfatal reinfarction to the risk of subsequent cardiac mortality, nonfatal reinfarction was entered into the Cox model as a time-dependent variable along with other pertinent baseline predictors (Table 3). In that model, nonfatal reinfarction was confirmed to be the strongest independent predictor for subsequent cardiac mortality with a relative risk of 2.47 (95%CI: 1.77-3.74).

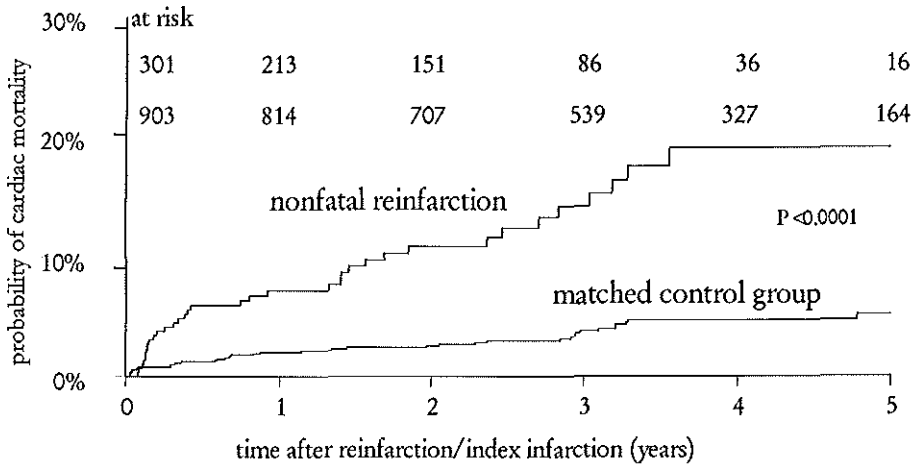

Figure 4. Cumulative survival rates according to patients with nonfatal myocardial infarction and a matched control group.

Medication

Medical therapy was similar in reinfarction (fatal and nonfatal) and reinfarction-free patients. β-blocker agents were used in about 50% of the patients, diuretics were used in one-fifth (23% vs 20%), ace inhibitors in 9%, digitalis was prescribed in 5% and antiarrhythmics in 3% of the patients.

Follow-up revascularization

In the reinfarction-free group 121 patients (4%) underwent angioplasty and 208 patients (7%) had coronary artery bypass graft surgery. After reinfarction the revascularization rates were higher in the 259 patients who were alive at the end of follow-up: 75 patients had thrombolytic therapy and 77 patients underwent an coronary intervention after reinfarction of which 57 within 6 months. Revascularization had been attempted infrequently in patients with subsequent mortality after reinfarction: thrombolytic treatment was performed in only 9 out of 97 patients and 6 patients underwent PTCA or CABG, of which 3 procedures were performed directly after the reinfarction. Of the 110 patients who underwent a revascularization procedure after a reinfarction a subsequent reinfarction or death occurred in 16 patients (15%), of whom in 6 reinfarction occurred as a complication of the procedure and in the other 10 at a later time. In the 246 patients who did not have an intervention after a reinfarct a second reinfarction or mortality was almost

three times higher (102 patients; 41%) (Table 4).

Discussion

The data presented in this report indicate that patients with a first reinfarction are at risk, not only for subsequent death, but also for a second (and third) reinfarction. All 3404 patients in this study were survivors of an infarct (the index infarct). Of those 180 patients (5%) who suffered a reinfarction within one year after the first event, 59 (33%) developed a documented third infarct or death while this was observed in only 8.5% of those without reinfarction within the first year. In patients with an infarction prior to the index infarct 57 patients (19%) developed a third infarct or death. Thus it is apparent that reinfarction begets reinfarction.

As in other studies nonfatal reinfarction is a significant and independent predictor for subsequent cardiac mortality (HR:2.47), even though the risk of nonfatal reinfarction for subsequent cardiac mortality decreased compared with studies of a decade ago.[10,11] The latter may be due to the increased active treatment of acute myocardial infarction with thrombolytic therapy, angioplasty and coronary artery bypass graft surgery.

The worse prognosis of patients with reinfarction in this and other studies[10,11,12] does not only reflect greater cumulative loss of myocardium, resulting in heart failure and death, but also higher rate of subsequent reinfarction with its inherent mortality and other sequellae. These observations, if confirmed by other studies, imply that patients who develop a second infarct should be treated aggressively to try to avoid a third infarct or death. Such treatment should include antiplatelet or anticoagulant therapy[13,19,20], beta-blockers[21], ace inhibitors[22,23], statins[24,25] and probably revascularization by either PTCA or CABG.[26] These measures all reduce the incidence of subsequent myocardial infarction.

Previous studies reported that systematic early intervention after infarction did not improve survival.[27-31] A recent study of the DANAMI group however[26] reported that invasive treatment in post-AMI patients with inducible ischemia results in a reduction in the incidence of mortality (though not significant) and a significant reduction in the incidence of reinfarction and unstable angina.

Rate of nonfatal reinfarction:

The 3-year (0.5-6 year) nonfatal reinfarction rate was 8.8% (6 months:3.4%; 1-year:5.1%). An ~3% to 10% incidence rate of recurrent nonfatal reinfarction one

Table 4. Revascularization after myocardial reinfarction (N=356).

Revascularization	N	%	3rd MI	Death/3rdMI
Yes	110	(31%)	5 (4%)	16 (15%)
No	246	(69%)	28 (11%)	102 (41%)

year after hospital discharge has been reported in post myocardial infarction survivors in the prethrombolytic.[3,4,6,10] In a recent report Volpi et al.[7] found a 2.5 % nonfatal reinfarction rate by 6 months, a figure similar to ours. Also TIMI-II[12] reported a similar rate of 2.7% between 2 weeks and 6 months, and 3.7% between 2 weeks and 1-year. The nonfatal reinfarction rate in patients with a history of prior infarction increased over time, compared to patients without a prior infarction (Figure 2).

Rate of mortality:
Nonfatal reinfarction was followed by subsequent death in 13.6% of which 11.3% was cardiac. These rates are in accordance with previous studies.[10,12] In Figure 3 the continously increasing risk of subsequent cardiac mortality over time in the nonfatal reinfarction patients is evident.

Clinical predictors of mortality or reinfarction:
The association of previous infarction and prior angina pectoris with the occurrence of reinfarction has been reported previously[1,10,19,20] and is related to the fact that both are clinical indicators of more extensive coronary artery disease. In our study prior infarction, diabetes, ST depression, Killip class III/IV and heart rate>70bpm were independent riskfactors of mortality or reinfarction. These findings are in accordance with previous studies.

CONCLUSIONS

This study population with 3-year follow-up demonstrates that nonfatal reinfarction carries a strong and independent risk for subsequent cardiac mortality as well as further infarcts. This result suggest that measures aimed at prevention of reinfarction should be considered in all patients with characteristics associated with an increased reinfarction risk including intensive treatment with ASA or coumadins, statins, beta-blockers and ACE inhibitors and possibly revascularization, might

contribute to a significant mortality reduction in post-myocardial infarction patients. In particularly, a more aggressive treatment such as coronary angioplasty or coronary bypass surgery after a reinfarction might reduce subsequent mortality and coronary events. A prospective study to verify this concept seems warranted.

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Chapter 5

SUSTAINED BENEFIT AT TEN TO FOURTEEN YEARS FOLLOW-UP AFTER THROMBOLYTIC THERAPY IN MYOCARDIAL INFARCTION.

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(submitted)

SUMMARY

Aims

In order to investigate whether the benefit of thrombolytic therapy was sustained beyond the first decade, we report the 10-14 year outcome of 533 patients, who were randomised to either treatment with intracoronary streptokinase or conventional therapy during the years 1980 to 1985.

Methods and findings

Details of survival and cardiac events were obtained from the civil registry, from medical records or from the patient's physician. Patient survival curves were constructed and factors influencing survival were identified. At follow-up, 158 patients (59%) of the 269 patients allocated to thrombolytic treatment and only 129 patients (49%) of the 264 conventionally treated patients were alive. The cumulative 1-, 5- and 10-year survival rates were 91%, 81% and 69% in patients treated with streptokinase and 84%, 71% and 59% in the control group, respectively (P=0.02). Reinfarction during 10-years follow-up was more frequent after thrombolytic therapy, particularly during the first year. Coronary bypass surgery and coronary angioplasty were more frequently performed after thrombolytic therapy. At 10-years approximately 30% of the patients were free from subsequent cardiac events. Significant determinants of mortality in multivariate proportional hazards analysis were elderly age, indicators of impaired residual left ventricular function, multivessel disease and inability to perform an exercise test at the time of hospital discharge.

Conclusions

Improved survival after thrombolytic therapy is maintained beyond the first decade. Age, left ventricular function, multivessel disease and inability to perform a exercise test were independent predictors for long-term mortality, as they are predictors for early mortality.

INTRODUCTION

The introduction of reperfusion therapy has improved outcome of patients with evolving myocardial infarction.[1-9] Hospital survival is improved, and this survival benefit is maintained during follow-up, reported up to 5 years after admission.[10-14] However, final assessment of the value of such therapy requires understanding of the true long term effects, at least through the first decade. Such data are also required to analyse the cost effectiveness of this therapy.[15] The study organised by the Interuniversity Cardiology Institute of The Netherlands consistently showed improved coronary patency, limitation of infarct size, preservation of myocardial function and improved 5 year survival after reperfusion therapy with intracoronary streptokinase and, in some patients, immediate PTCA.[9] In this 10 to 14 years follow-up report the long-term effects of reperfusion therapy are described. Patient characteristics associated with survival and mortality are reported. The data confirm that the salutary effects of early reperfusion therapy are maintained for at least a decade, and that the assumptions in previous cost effect analyses were indeed valid.[15]

METHODS

From May 1981 through March 1985, 533 patients in five participating hospitals

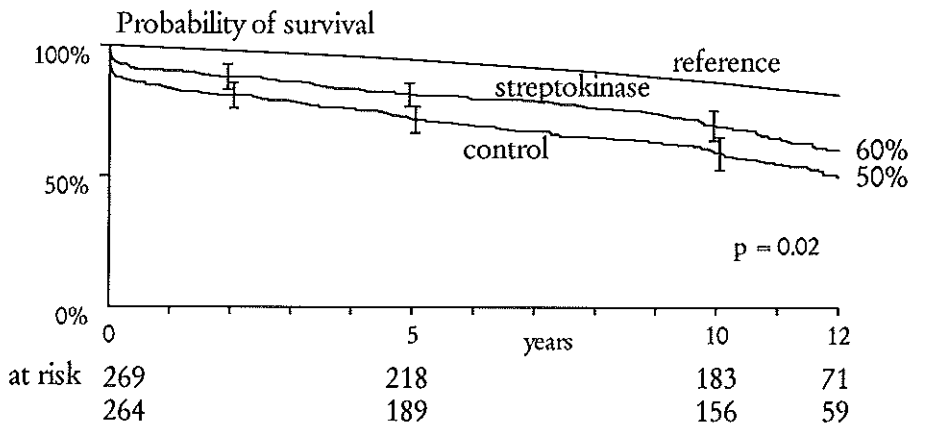

Figure 1. Cumulative survival rates: Comparison with reference Dutch population (matched on age 55 years and gender). The number of patients at risk during various follow-up intervals is presented under the x-axis. Vertical lines represent the 95% confidence intervals.

were randomised to either treatment with intracoronary streptokinase (n=269) or conventional therapy (n=264). The study design, patient characteristics and initial results have been reported previously.[2,16,17] Ninety eight patients received intravenous streptokinase (250,000 U in 1h) preceding angiography followed by treatment with intracoronary streptokinase. Forty six patients underwent immediate coronary angioplasty after thrombolytic therapy. Data analysis was performed according to the 'intention to treat' principle.

Data collection and Follow-up

Survival status was assessed by written inquiries to the Municipal Civil Registration Service. In 4 patients who had moved abroad, survival status could not be retrieved and the last available follow-up data were used, obtained at 3 to 6 years (2 patients allocated to reperfusion therapy and 2 to conventional therapy). Additional follow-up data concerning hospital admissions, recurrent myocardial infarctions and revascularization procedures were obtained by review of hospital records and from the general practitioners. Some patients were contacted by telephone. Their information concerning hospital admissions was checked at the hospital involved. Complete follow-up data,10 years after enrolment, was obtained for 482 (91%) patients. The 51 patients with incomplete data were distributed equally over both treatment groups (27 streptokinase vs 24 conventional). Median follow-up time from randomisation was 12 years (3-14 years).

Survival analysis

Cumulative reinfarction and mortality rates for the two treatment groups were calculated according to the Kaplan-Meier method. The logrank test was used to compare survival and event-free survival among different patient groups. Using age- and gender-specific mortality data from the Netherlands in 1983, the expected survival in a reference population was calculated and compared with survival in patients after myocardial infarction, with and without streptokinase therapy. Mortality risks were weighted according to the sex distribution of the trial population. The standardised mortality ratio, representing the observed mortality / expected mortality was calculated for the two treatment groups. The loss in life expectancy was computed of conventional therapy compared to the reference population and the gain in life expectancy of early thrombolytic therapy.[18]

Statistical analysis

Continuous variables were compared by Student's t-test, categorical variables by χ^2-

Table 1. Univariable analysis of predictors for long-term outcome.

Variable	Placebo	SK	Overall	RR	95%CI
Clinical data					
Age,year					
<55	47/112	30/111	77/223		
>55	85/150	79/156	164/306	1.55	1.26 - 1.91
Gender					
Male	110/220	88/215	198/435		
Female	22/42	21/52	43/94	1.00	0.78 - 1.27
Previous MI					
no	96/202	78/211	174/413		
yes	36/60	31/56	67/116	1.37	1.13 - 1.66
ST-elevation					
>1.2 mV	42/95	35/114	77/209		
< 1.2 mV	76/146	64/129	140/275	1.38	1.12 - 1.71
Killip class III/IV					
no	124/251	100/254	224/505		
yes	8/11	9/12	17/23	1.67	1.28 - 2.17
Anterior MI					
no	66/147	53/139	119/286		
yes	66/115	56/128	112/243	1.21	1.00 - 1.45
VT/VF					
no	77/158	51/147	128/305		
yes	55/104	58/120	113/224	1.20	1.00 - 1.45
Hx of angina					
no	93/188	75/198	168/386		
yes	39/74	34/69	73/143	1.17	0.96 - 1.43
Systolic BP					
≥90 mm Hg	127/252	98/252	225/504		
< 90 mm Hg	5/10	11/15	16/25	1.43	1.05 - 1.95
Atrial fibrillation					
no	123/242	99/249	222/491		
yes	9/20	10/18	19/38	1.11	0.79 - 1.54
Time to treatment					
<2h	98/199	77/191	175/390		
>2h	34/63	32/76	66/139	0.95	0.77 - 1.16
Treatment					
CT	132/262		132/262		
SK i.v.		17/37	17/37	0.91	0.63 - 1.32
SK i.c		42/104	42/104	0.80	0.62 - *1.05*
SK i.v. + i.c.		33/81	33/81	0.81	0.61 - 1.08
SK i.c. + PTCA		17/46	17/46	0.73	0,49 - 1.09
Enzymes					
Infarctsize (HBDH):					
< 1100	47/115	52/158	99/273		
> 1100	53/101	39/70	92/171	1.48	1.20 - 1.83

Variable	CT	SK	Overall	RR	95% - CI
Exercise results					
Exercise test					
no	82/193	66/197	148/390		
yes	50/68	42/69	92/137	1.77	1.49 - 2.10
Angiography					
Vessel disease					
singlevessel	28/83	35/129	63/212		
multivessel	61/113	50/104	111/217	1.72	1.35 - 2.20
Stenosis IRV					
<90%	31/60	44/139	75/199		
>90%	60/143	50/107	110/250	1.17	0.93 - 1.47
LVEF					
>40%	64/163	57/198	121/361		
<40%	47/77	43/56	90/133	2.02	1.67-2.44

CT=conventional treatment; SK=streptokinase; RR=relative risk; CI=confidence interval; MI=myocardial infarction; VTVF=ventricular fibrillation/flutter; BP=blood pressure; IV=intravenous; IC=intracoronary; IRV=infarct related vessel; LVEF=left ventricular ejection fraction.

tests. Patient characteristics were grouped into four categories. Clinical variables represented in the first category were: age, sex, previous myocardial infarction, infarction site, Killip class at admission, time from symptom onset to treatment allocation, sum of ST-elevation at admission, atrial fibrillation and ventricular fibrillation/flutter. In the second category infarct size, as assessed from cardiac enzyme release was added to the first category and in the third model the (in)ability to exercise was added. The fourth category contained variables from the previous categories as well as variables derived from coronary angiography and left ventriculography: the extent and severity of coronary artery disease and left ventricular ejection fraction as measured by contrast angiography or by radionuclide angiography. The Cox proportional hazards model was used to identify independent risk factors for mortality and their relative risk estimates.

RESULTS

A total of 533 patients were enrolled in this study. Baseline characteristics have been described in detail.[9] Mean age was 56 years (28-71 years), 18% were female, 22% had a previous infarction and 46% were admitted with a anterior infarction. At

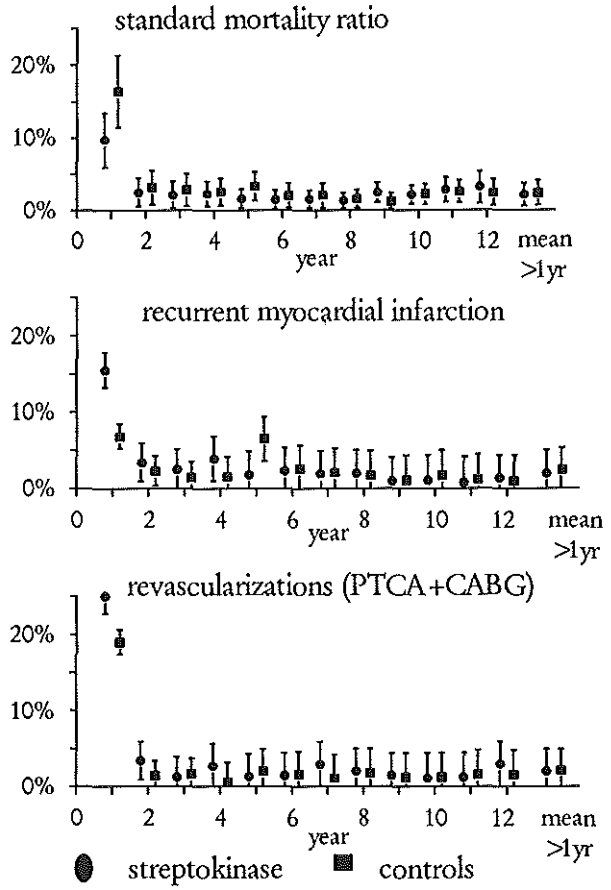

Figure 2. Annual standardised mortality ratio: ratio of the observed mortality and expected mortality of age and gender matched subgroup of the reference Dutch population with 95% confidence intervals. Recurrent myocardial infarction and revascularization rates, corrected for the patients at risk during follow-up.

final follow-up 158 patients (59%) of the 269 patients allocated to thrombolytic treatment were alive and only 129 (49%) of the 264 patients treated with conventional therapy. The cumulative 1-, 5- and 10-year survival rates were 91%, 81% and 69% in patients treated with streptokinase and 84%, 71% and 59% in the control group, respectively. The gain in survival by early reperfusion therapy was highly significant (p=0.02) by logrank analysis. The corresponding expected survival of the reference population was 99%, 95% and 86%, respectively (Figure 1). The loss of life years for myocardial infarction can be computed as the area between the

survival curve of patients receiving conventional therapy and the reference population. The loss corresponded to 28 months at 12 years follow-up.

Extrapolating this would amount to a loss in life expectancy of 65 months. By early reperfusion therapy 32% of the loss in life expectancy was regained. In patients allocated to reperfusion therapy the loss at 12 years follow-up was 17 months and the loss in life expectancy 44 months. The standardised mortality ratios up to 10 years follow-up are shown in Figure 2. The mean standardised mortality in year 2-10 years was 2.1% in patients allocated to streptokinase and 2.4% in patients receiving conventional therapy. This difference is not statistically significant.

Reinfarction

Recurrent infarction occurred more frequently in patients who received thrombolytic treatment than in conventionally treated patients (p=0.03). In particular early reinfarction, within the first year was more frequent after reperfusion therapy, while subsequent reinfarction rates, after the first year, were low in both groups averaging 2% per year (Figure 2). Eighty six (32%) of patients treated with streptokinase had at least one recurrent myocardial infarction at a mean follow-up time of 3.5 year; 39 of these patients had a first reinfarction within 1 year after randomisation. Fifteen patients had a second reinfarction, which was followed by a third reinfarction in 3 patients and a fourth and fifth in 1 patient. In

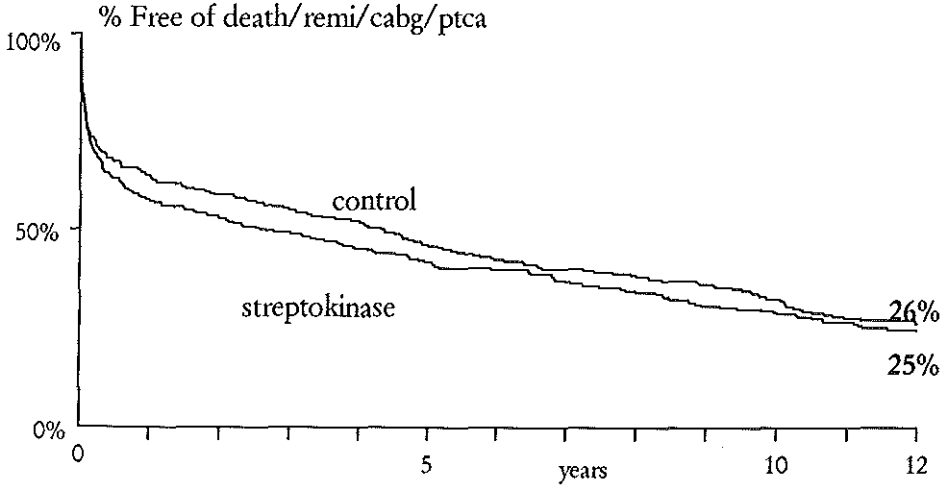

Figure 3. Ten-year freedom from death, recurrent myocardial infarction, CABG and PTCA.

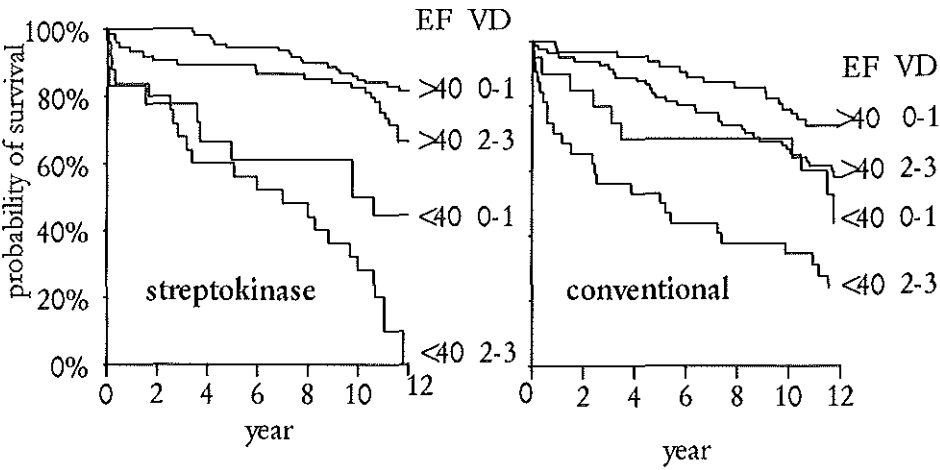

Figure 4. Survival curves after hospital discharge stratified for patients with left ventricular ejection fraction (EF) of ≥40% or <40% combined with none or one diseased vessel versus more than one diseased vessel (VD).

conventionally treated patients 62 (23%) had a recurrent myocardial infarction after a mean of 3.5 years of which 16 occurred within the first year. A second reinfarction was reported in 9 patients and was followed by a third reinfarction in 2 patients.

Revascularization

Forty three (16%) of the patients treated with streptokinase underwent coronary angioplasty and 77 (29%) underwent coronary bypass surgery. In conventionally treated patients the intervention rate was lower ($p<0.001$): only 26 patients (10%) underwent coronary angioplasty and 55 patients (21%) coronary bypass surgery. Revascularization procedures were performed predominantly in the first year, while after the first year were infrequent and not statistically significant between treatment groups, averaging 1.9% and 1.5% per year (Figure 2).

Event free survival

At 1 year, freedom from death, recurrent myocardial infarction, bypass surgery and angioplasty was 57% in patients treated with streptokinase and 64% in conventionally treated patients. Freedom from cardiac events was 42% and 46% at five years and 29% and 32% at 10 years, respectively (Figure 3, p=ns).

Risk assessment

Univariable predictors for increased mortality were the clinical parameters age (≥55 years), Killip class III or IV, extensive infarction identified by total ST-elevation of more than 1.2 mV on the admission ECG; parameters representing residual left ventricular function: enzymatic infarct size, the inability to perform an exercise test and an ejection fraction of less than 40%; and parameters reflecting the extend of coronary artery disease: prior myocardial infarction and the presence of multivessel disease (Table 1).

After multivariable analysis of clinical admission data (model I), five parameters were retained: Killip class III or IV, age (≥55 years), total-ST-elevation > 1.2 mV, prior infarction and an anterior infarct location. When all data available at discharge were added in the multivariable model, age (≥55 years) was retained as a clinical predictor, together with parameters representing left ventricular function and extent of coronary disease. Cumulative survival in patients with multivessel disease and impaired left ventricular function at 1, 5 and 10 year intervals was only 77%, 54% and 33%, respectively as opposed to 99%, 94% and 83% in patients with single vessel coronary artery disease and a well preserved left ventricle (Figure 4). Allocation to streptokinase was a predictor of survival at the time of hospital admission (model I). However, this was no longer apparent when estimates of residual left ventricular function of discharge were included in the analysis (models II,III,IV). This supports the concepts that early reperfusion therapy salvages myocardial tissue which contributes to subsequent survival.

DISCUSSION

Since 1985 a few keypapers demonstrated persistent benefit of fibrinolytic therapy.[1-9] As a result, the use of such treatment has increased rapidly. The results described in the present study show that improved survival in patients treated with early thrombolytic therapy is maintained beyond the first decade. The difference in survival, favouring thrombolytic therapy, was 6% at hospital discharge, 10% at one year and remained 10% at 10 years follow-up. Mortality was high in the first year, particularly in the control group, but subsequently the annual standardised mortality ratio remained stable over the years and did not differ significantly between groups. This is in agreement with reports from other series[11-14], which also show sustained, unchanged benefit during long-term follow-up. Our analysis shows that, in patients surviving their first myocardial infarction for one year, an annual mortality rate of

Table 2 Multivariable analysis and relative risks

Model		I	II	III	IV
Clinical data		+	+	+	+
Infarct size			+	+	+
Exercise test				+	+
Angiogram					+
Age. yr					
< 55	42.1%				
> 55	57.9%	1.90 (1.43 - 2.55)	1.82 (1.32 - 2.50)	1.79 (1.29 - 2.48)	1.62 (1.13 - 2.33)
Rx infarction					
no	79.5%				
yes	20.5%	1.66 (1.22 - 2.26)	1.65 (1.15 - 2.36)		
Anterior infarction					
no	54.8%				
yes	45.2%	1.44 (1.10 - 1.89)			
Killip III/IV					
no	95.7%				
yes	4.3%	2.44 (1.43 - 4.17)			
ST-elevation (mV)					
< 1.2	43.2%				
> 1.2	56.8%	1.70 (1.28 - 2.27	1.43 (1.04-1.97)	1.43 (1.03 - 1.97)	
Infarct size					
< 1100	60.5%				
> 1100	39.5%		1.83 (1.34 - 2.50)	1.67 (1.23 - 2.28)	
No exercise test					
no	75.3%				
yes	24.7%			2.28 (1.63 - 3.18)	1.83 (1.24 - 2.70)
LVEF					
> 40	73.6%				
< 40	26.4%				2.94 (2.10 - 4.13)
Vesseldisease					
Single	50.6%				
multi	49.4%				1.57 (1.11 - 2.22)
Treatment					
CT	49.8%				
SK	50.2%	0.76 (0.58 - 1.00)	0.99 (0.73 - 1.34)	0.96 (0.70 - 1.30)	1.04 (0.74 - 1.46)

Abbreviations as in Table 1. Treatment was forced into the models; 95% confidence intervals are represented between brackets.

about 2.6%-3.3% can be anticipated. This annual mortality rates continues to be about twice as high as the reference population throughout 10 years, which is in agreement with another study.[19]

By multivariate analysis the contribution of thrombolytic therapy was not apparent once parameters of infarct size or residual left ventricular function were included in the model. This supports the notion that survival benefit is established within the initial period, through myocardial salvage and preservation of left

ventricular function. The proposed mechanism of improved survival after thrombolytic therapy through salvation of myocardial tissue and preservation of left ventricular function, implicates that factors determining early survival will also influence long-term survival. Indeed, besides age, left ventricular ejection fraction at the time of discharge and the extend of coronary artery disease appeared to be the main predictive variables influencing short- and long-term mortality.

Two phases can be distinguished in the clinical course of the patients in this study. During the first year events are frequent including reinfarction (15% after streptokinase and 6% in controls) and revascularization procedures (21% and 16% respectively). The course stabilises after the first year with mortality rates of about 3%, reinfarction rates of 3% and revascularization rates of 3%, which were not different among the two treatment groups. The continued instability during the first months after myocardial infarction is in agreement with a recent report indicating rapid progression of coronary artery lesions at different sites shortly after infarction.[20] It is compatible with the suggestion that, at least in some patients, an infectious component may lead to or facilitate a period of instability in patients with coronary artery disease.[21,22].

In the present study, conducted between 1981 and 1985, revascularization procedures were performed in patients with repetitive recurrent ischemia after the initial infarct. A recent study[23] has shown that extensive use of revascularization procedures in patients with symptomatic or silent postinfarct ischemia, may reduce the incidence of early infarction. Thus, a more aggressive intervention regimen might help to avoid part of the excess reinfarction that was observed in the first year after reperfusion therapy.

In the study period as mentioned above, patients after myocardial infarction were treated predominantly with aspirin or coumadin and with beta-blockers (37%). More recently, it has been shown that systematic treatment with cholesterol lowering HMG-CoA reductase inhibitors,[24-26] and treatment with ACE inhibitors[27,28] reduce the incidence of reinfarction. Thus, an improved prognosis with lower myocardial reinfarction rate and lower subsequent mortality may be expected using modern multidrug regimens.

Since prognosis in patients in the current study was related predominantly to the left ventricular function and extend of coronary artery disease, at the time of discharge, the same approach for medical and revascularization therapy should be followed for patients who did and those who did not initially receive reperfusion therapy.

CONCLUSION

This study has provided unique data with respect to long-term outcome after thrombolytic treatment. For the first time, improved survival after thrombolytic therapy has been shown to be maintained beyond a decade. Predictors for early and late mortality were the same. Long-term outcome was related to age, parameters of left ventricular function and to the extend of coronary artery disease.

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Chapter 6

UNSTABLE ANGINA: GOOD LONG-TERM OUTCOME AFTER A COMPLICATED EARLY COURSE

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SUMMARY

Aims
This study was performed to investigate the long-term outcome of patients with unstable angina within subgroups of the Braunwald classification. Long-term follow-up studies of patients with unstable angina are rare and date from more than two decades ago. This study was performed to establish the prognosis of different subgroups of patients with unstable angina (Braunwald criteria) during 7-years follow-up.

Methods and findings
We registered a well-defined group of 417 consecutive patients, hospitalized for suspected unstable angina. In 282 patients (68%) the definite diagnosis was unstable angina; 26 patients had evolving myocardial infarction and in 109 patients (26%) the symptoms were attributed to other or non-specific causes. Patients with definite unstable angina were subdivided according to the Braunwald classification. Survival, survival without infarction and survival without infarction or intervention are reported in each class. After a median follow-up of 94 months mortality rate in the first year was 6% and 2-3% in the following years. Revascularization was particularly frequent in the first year (47%), whereas myocardial infarction rate was 11% in the first year and 1-3% thereafter. The Braunwald classification appeared to be appropriate for risk stratification in the first year. At 7-years however, the event rates in all classes were similar. In particular, the Braunwald classification had no long-term impact on mortality or infarction rates. However, patients with acute angina at rest or postinfarction angina and patients with extensive anginal treatment had high intervention rates.

Conclusions.
This study for the first time demonstrates that, in spite of a complicated course during the first year, current management results in good long-term outcome in patients with unstable angina.

INTRODUCTION

The onset of unstable angina portends a significant risk for the occurrence of major cardiac events including death and myocardial infarction. In previous studies, one-year mortality varied from 2% to 18% and one-year myocardial infarction rates varied from 7% to 21%.[1-3] Long-term follow-up reports of unstable angina patients are rare.[4] We report 7-year follow-up of 282 consecutive patients, who were admitted with unstable angina, to establish the incidence and prognosis of the various subgroups of unstable angina. The Braunwald classification[5] appeared to be an appropriate instrument to identify groups of patients with different levels of risk at 6 months.[6] The validity of this classification for longer term follow-up was assessed.

METHODS

During a 7-month period in 1988 and 1989 a prospective registry was maintained in two hospitals in Rotterdam. 417 consecutive patients suspected of unstable angina, according to the attending physician, were included in the study. The admission diagnosis, *suspected unstable angina*, was based on a history on of chest pain at rest or at minimal exertion, probably of ischemic origin, without signs of acute infarction or other causes of chest pain. Electrocardiographic (ECG) changes were not required for inclusion. Secondary referrals from other hospitals for treatment were excluded. The final diagnosis as registered 24-48 hours after admission was based on evolution of symptoms and on the documentation of objective ECG criteria during observation or elevated enzyme levels. The final diagnoses were classified in 3 groups: acute myocardial infarction, definite unstable angina and atypical chest pain or other disease.[7] The final diagnosis *myocardial infarction* was determined as the occurrence of serum creatine kinase levels above twice the local upper limit of normal. *Definite unstable angina* was based on the assessment of symptoms and on documentation of ECG changes (see data collection). Patients with initial infarction who had recurrent anginal pain after 24 hours were included as postinfarction unstable angina. For patients with definite unstable angina, a final classification was made after 24-48 hours observation according to the definitions of Braunwald's classification of unstable angina[5]:

Severity. New onset of severe or accelerated angina without pain at rest (class I = no rest pain), angina at rest within past month but not within preceding 48 hours (class

Table 1. Univariable and Multivariable Analysis: Dependent and independent predictors of seven-year outcome in 282 patients with unstable angina.

	univariable		multivariable	
	RR†	95% CI‡	RR†	95% CI‡
Mortality				
Age ≥70 years	2.83	1.92-4.19	4.22	2.58-6.89
Male	1.05	0.69-1.60	---	
Diabetes	1.73	1.10-2.72	1.89	1.07-3.36
Braunwald classification:				
Class II§	1.85	0.94-3.61	---	
Class III‖	1.68	0.87-3.26	---	
Class C¶	0.77	0.41-1.42	---	
ECG# abnormalities	0.77	0.51-1.13	---	
Extensive treatment**	1.40	0.94-2.10	---	
Death or infarction				
Age ≥70 years	2.05	1.39-3.01	2.12	1.42-3.17
Male	1.19	0.79-1.78	1.46	0.96-2.21
Diabetes	2.30	1.44-3.65	2.09	1.31-3.34
Braunwald classification:				
Class II§	1.11	0.74-1.66	---	
Class III‖	1.19	0.81-1.74	---	
Class C¶	1.14	0.69-1.89	---	
ECG# abnormalities	0.95	0.64-1.40	---	
Extensive treatment**	1.25	0.84-1.85	---	
Death, infarction or revascularization				
Age ≥70 years	0.83	0.61-1.13	---	
Male	1.95	1.44-2.66	1.66	1.25-2.78
Diabetes	1.08	0.73-1.59	---	
Braunwald classification:				
Class II§	0.60	0.44-0.81	---	
Class III‖	1.70	1.29-2.25	1.66	1.25-2.20
Class C¶	1.62	1.13-2.31	1.62	1.13-2.33
ECG# abnormalities	1.17	0.87-1.55	---	
Extensive treatment**	1.46	1.09-1.94	1.35	1.01-1.81

†RR = Relative Risk; ‡CI = confidence interval; §Class II = subacute angina at rest; ‖Class III = acute angina at rest; ¶Class C = postinfarction angina; #ECG = electrocardiographic; **Extensive treatment = more than one antianginal drug (see Method)

II = subacute angina at rest) or angina at rest within 48 hours (class III = acute angina at rest).

Clinical circumstances. Unstable angina in the absence of extracardiac condition (class B = primary unstable angina) or developed within 2 weeks after acute myocardial

infarction (class C = postinfarction unstable angina). Patients with secondary angina, related to noncardiac problems (class A) were excluded from the analysis.
Electrocardiographic changes was scored as present or absent.
Intensity of treatment was classified as none or one of the major antianginal drugs, β-adrenergic blockers, long acting nitrates and calcium antagonists (minimal therapy); more than one of these drugs (extensive oral therapy) or extensive use of antianginal therapy, including intravenous nitrates (maximal therapy).

Data collection
The data were prospectively collected focusing on the various decision moments during a patient's hospitalisation. Demographic data, history and characteristics of presentation were recorded at admission. During hospitalisation a log was kept of new pain episodes, new infarction or death, and of diagnostic and therapeutic measurements such as ECG's, exercise tests, medication and intervention. The ECG's were coded with respect to the presence or absence of Q waves, signs of left ventricular hypertrophy or intraventricular conduction disturbances. The ST segment was scored as ST elevation or depression ≥ 0.1 mV and/or T wave inversion. The ECG changes were defined as additional ST elevation/depression ≥ 0.1 mV or T wave deviation ≥0.1 mV versus that on the baseline ECG without pain.

Follow-up.
Data after discharge were obtained from the municipal registries, by review of the clinical records, from the general practitioners and from the patients. Patients were followed for 94 months (range, 85-100 months) according to mortality, infarction, revascularization (coronary bypass or angioplasty) and any hospitalisation. Medication at 1, 3, 5 and 7-years was recorded.

Statistical analysis.
Patient groups were compared with a Student's t test for continuous variables and a χ^2 test for categorical data. Endpoints are presented in terms of "survival", "survival without myocardial infarction" and "infarction-free survival without revascularization". Probability of these endpoints is presented as Kaplan-Meier curves.[8] Differences between curves were analysed with log-rank tests.[9] A stepwise Cox proportional hazards model was used to select predictors of (event-free) survival, specifically to relate the various Braunwald classes to prognosis. The following variables were considered: age, gender, history of myocardial infarction,

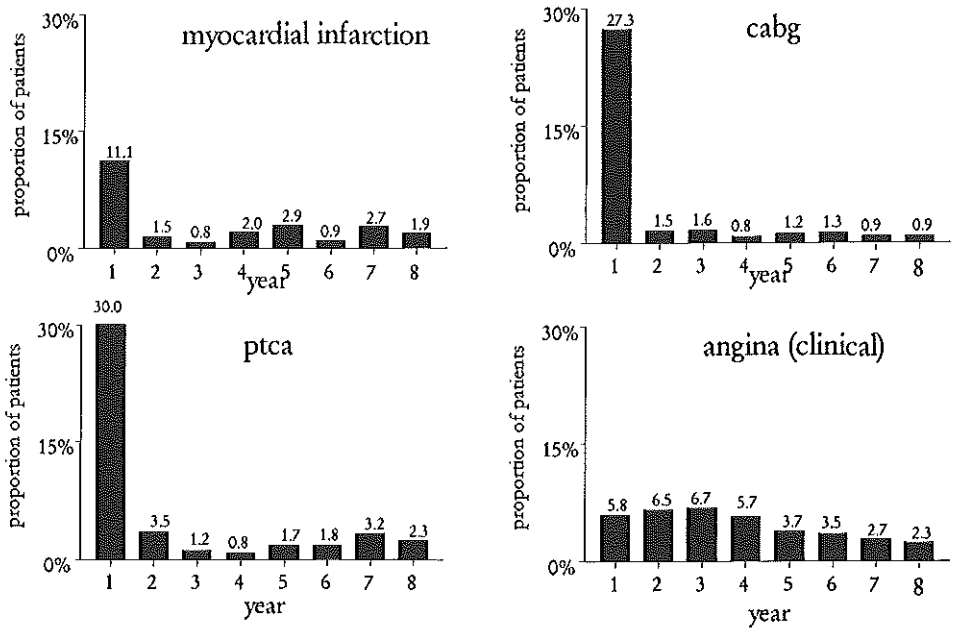

Figure 1. Proportion of events in 282 unstable angina patients

hypertension, Braunwald classes I to III (severity), B and C (clinical circumstances), ECG changes and intensity of medical treatment during hospitalisation. All analyses were performed on the 282 patients with definite unstable angina.

RESULTS

A total of 417 patients were enrolled in an observational study of suspected unstable angina of whom 6 died in hospital.[12] In 282 patients (68%) the definite (final) diagnosis was unstable angina, in 26 patients the definite diagnosis was acute myocardial infarction and in 109 patients (26%) the symptoms were attributed to other or non-specific causes. Median age of patients with unstable angina was 63 years (31 to 89 years), 64% were men, 46% had a previous infarction and 23% had a history of unstable angina. Prior revascularization was performed in 27% of the patients (15% prior coronary bypass surgery, 12% prior coronary angioplasty). Of the 282 patients with a final diagnosis of unstable angina, 20% were categorised in Braunwald class I, 35% in class II, and 45% in class III. A total of 16% were

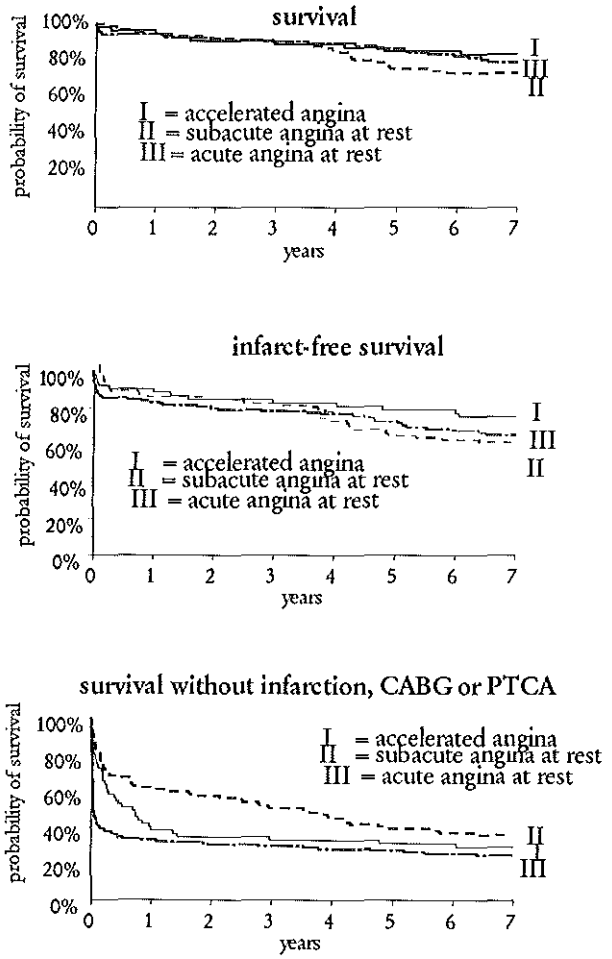

Figure 2. Rates of survival, survival without infarction, and survival without infarction, CABG and PTCA in classes of severity in 282 unstable angina patients.

classified as postinfarction angina (class C) and 6% had ECG changes. Complete 7-year follow-up information could be obtained for 278 patients (99%) with unstable angina. Median follow-up was 94 months, ranging from 6 months to 100 months.

Antianginal treatment (β-blockers, nitrates and/or calcium channel blockers) was prescribed for 87% of the patients at hospital discharge, 65% at the end of the first year and decreased to 51% at 7-years. Extensive treatment (more than one antianginal drug) decreased from 35% at the end of the first year to 26% at 7-years.

Aspirin was routinely prescribed in two-third of the patients, which did not change during follow-up. Long-term oral anticoagulant treatment during follow-up was frequent (13-19%). The use of cholesterol lowering therapy increased from 2% at discharge to 29% at 7-years. After 7-years almost half of the patients (46%) were in CCS class I, 23% were in class II, 20% in class III and 11% were class IV.

The initial course after hospital discharge of the 282 patients was complicated (Figure 1). Myocardial infarction in the first year was observed in 31 patients (11%). After that, yearly infarction rate was low, around 1.9%. Revascularization procedures were performed predominantly during the first year. Coronary angioplasty and/or coronary bypass surgery were performed in 141 patients (50%) at 7 years. Survival rates at 1,3,5 and 7 years were respectively 94%, 88%, 81% and 76%. Mortality between the first and seventh year averaged 3.4% per year which is 1.2% higher than the standardised mortality rate for the general population of the same age. Survival without infarction and infarct-free survival without intervention are shown as Kaplan-Meier curves for the different subgroups (Figure 2). Long-term survival and infarct-free survival were similar with respect to severity (class I to III). Early urgent intervention (<1 month), especially angioplasty, was particularly frequent in class III patients, whereas interventions for patients from class I were performed spread throughout the first year. After one-year follow-up, infarct-free survival without intervention was similar in classes I and III. Class II patients (no angina at rest within 48 hours) had fewer interventions in the first year after hospital discharge. However, in contrast to class I and III, interventions were performed with a constant rate during the total follow-up period. Thus, after 7-years the rates were similar in all severity classes. Survival without infarction or CABG and without PTCA were significantly higher ($P<0.05$) in patients with primary unstable angina (class B) compared with that in postinfarction patients (Figure 3). No significant differences were observed in event-free survival when the patient group was split with respect to the presence or absence of ECG changes during hospitalisation.

Predictors for 7-year mortality by univariable analysis were only age (≥70 years) and diabetes (Table 1). For all three outcomes (death, death or infarction, death or infarction or intervention), the adjusted risk ratios were estimated using the Cox proportional hazard model. Advanced age (≥70 years) and diabetes were retained as independent predictors of mortality. Survival without infarction was related to age, diabetes and male gender. Angina at rest within 48 hours (Class III) and postinfarction angina (Class C) were independent risk factors for the combined endpoint of survival, infarction or intervention, as were the use of two or more

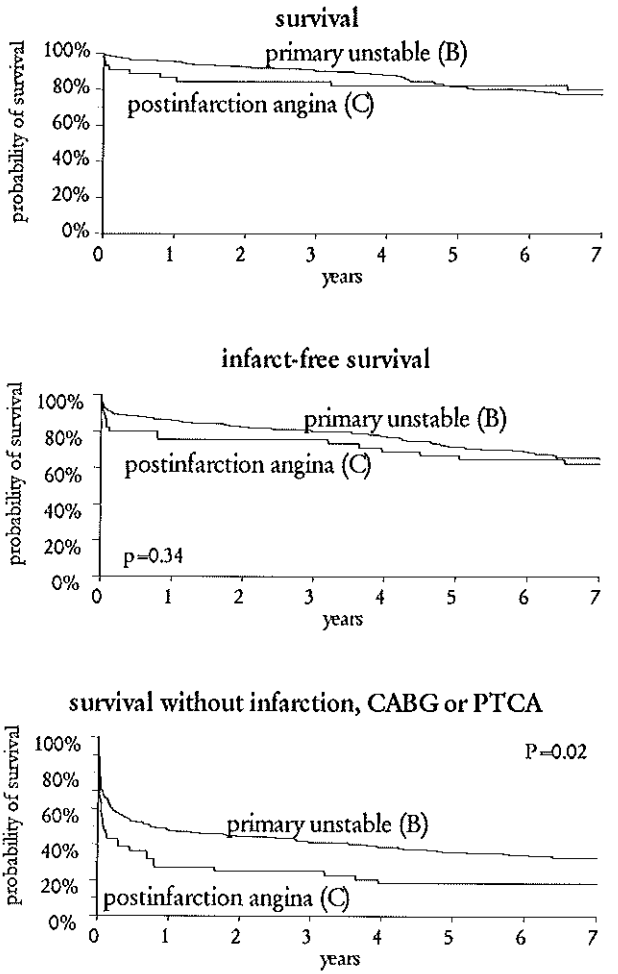

Figure 3. Rates of survival, survival without infarction, and survival without infarction, CABG and PTCA in classes of clinical circumstances in 282 unstable angina patients.

antianginal drugs during hospitalisation and male gender.

DISCUSSION

Long-term follow-up studies of patients with unstable angina are rare and date from more than two decades ago.[1,10] Since then, the practice of cardiology and the

definition of unstable angina have changed. We registered a well-defined group of 282 consecutive patients with unstable angina, out of 417 patients hospitalised for chest pain. The selection of patients immediately after admission ensured that the whole spectrum of unstable angina was included in this registry. This is in contrast with most other studies on unstable angina, which included only selected patients, restricted by age,[11,12] absence of recent myocardial infarction or bypass surgery, duration of pain episodes[19-21] or by the presence of ischemic signs on the ECG[15-17] In most studies, patients were selected 24 to 48 hours after admission, when myocardial infarction had been ruled out by serial enzyme analysis. In contrast, the only exclusion criteria in the present study were evidence of other disease assumed to be causing the chest pain, and referral from other hospitals for further treatment of patients in whom a complete diagnosis already had been established.

Long-term outcome

The present data demonstrate, for the first time, that after a complicated first year course, long-term outcome of patients with unstable angina is good, with low subsequent rates of infarctions and interventions. Mortality rate in the first year was 6% and 2-3% in the following years. Hospitalisation because of chest pain at 1, 3, 5 and 7-years was respectively 5%, 4%, 3% and 2%. This good prognosis is comparable with other reports,[2,12,15,18,19] although these were limited to two-years follow-up, and may be related to the high early intervention rate and to the improved medical therapy of this condition. Revascularization was particularly frequent during hospitalisation and in the subsequent first year, when almost half of the patients (47%) underwent a coronary bypass or an angioplasty procedure. The significant drop in subsequent years is remarkable and reflects the "durability" of current revascularization techniques and effective anti-anginal therapy.

Medication and revascularization

Anti-anginal treatment remained frequent, with a constant group of 25% of the patients taking two or more antianginal drugs (β-blockers, calcium antagonists or nitrates). Most of the patients were taking aspirin (67%) or oral anticoagulants (17%). Most bypass procedures were performed in accelerated angina patients without pain at rest (class I), whereas patients with angina at rest within 48 hours (class III) underwent more coronary angioplasty procedures. Patients with angina at rest without pain within 48 hours (class II) had a lower initial intervention rate than the other subgroups.

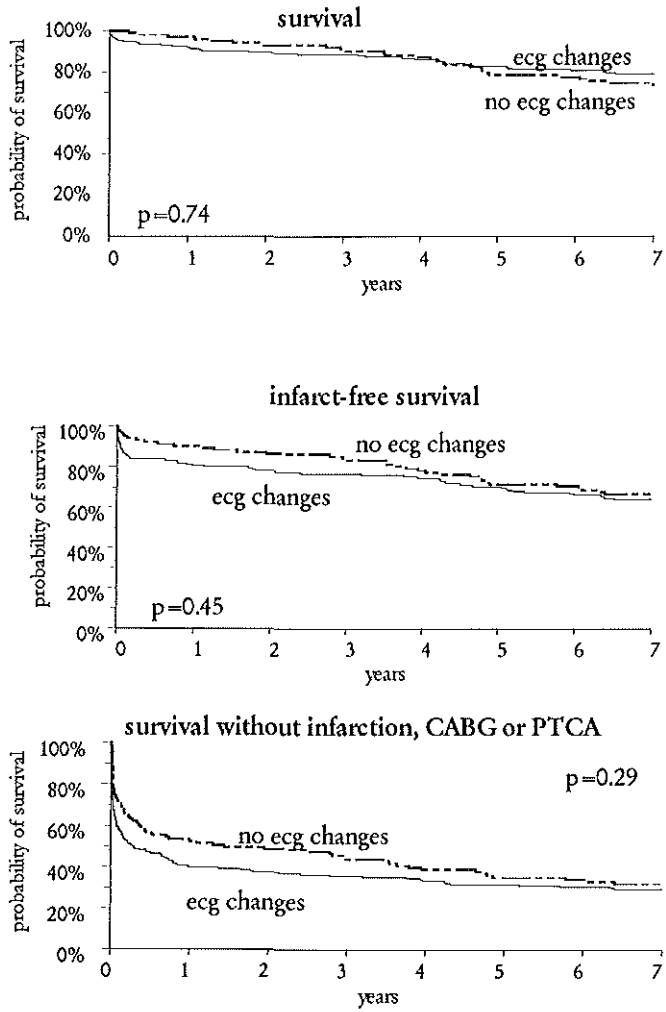

Figure 4. Rates of survival, survival without infarction, and survival without infarction, CABG and PTCA in classes of ECG changes in 282 unstable angina patients.

Braunwald classification

The Braunwald classification of unstable angina has been validated previously, for short-term outcome.[20-23] It appeared to be appropriate for risk stratification in the first year when most of the events occurred. At 7-years however, the event rates in all Braunwald classes were similar. In particular, the Braunwald classification had no long-term impact on mortality or infarction rates. However patients with acute angina at rest (pain within 48 hours, class III), or postinfarction angina (class C) and

patients with extensive antianginal treatment had high intervention rates as might be expected. Quality of life might improve when revascularization would be performed earlier in patients with angina at rest without pain within 48 hours (class II), although it should be appreciated that 30% of all patients survived 7-years without intervention or infarction.

CONCLUSIONS

The definitions by Braunwald, appeared to be appropriate for risk stratification, especially in the first year when most events occurred. However, at 7-years the event rates were similar in all classes of unstable angina. This study demonstrates that, in spite of a complicated course during the first year, long-term outcome is good in patients with unstable angina, with a high early intervention rate and low rates of infarction and intervention thereafter.

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Chapter 7

MORTALITY AND REPEAT INTERVENTIONS UNTIL 20 YEARS AFTER AORTO-CORONARY BYPASS SURGERY: A FOLLOW-UP STUDY OF 1041 PATIENTS.

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(submitted)

SUMMARY

Aims
To determine the very long-term survival and incidence of recurrent interventions following aorto-coronary bypass surgery using venous grafts.

Methods and results
A group of 1041 consecutive patients operated upon between 1971 and 1980 were followed for a median of 19 years (range 13-26). Peri-operative mortality was 1.2%. Survival probability at 5, 10, 15, and 20 years was 92%, 77%, 57%, and 40% respectively. After 5 or more years following operation the mortality was higher than in the matched Dutch population. Age, extent of coronary artery disease, and ejection fraction were independent predictors of mortality. Of the 593 deceased patients at least 63% died of a probable cardiac cause, while cardiovascular mortality was 40% in the general Dutch population. Repeat revascularization procedures (PTCA or CABG) were performed in 343 patients (33%), with an increasing incidence after 7 years.

Conclusions
Aorto-coronary bypass surgery using vein grafts is safe and has a good long-term prognosis for survival. After approximately 7 years both mortality and the need for repeated revascularization increased. Since a majority of patients died of a cardiac cause and a substantial number of patients required repeated revascularization, aorto-coronary bypass surgery is a palliative treatment of a progressive disease.

INTRODUCTION

Aorto-coronary bypass grafting surgery (CABG) is an accepted treatment modality for patients with severe angina pectoris since the seventies.[1] The primary goal of such an operation was and still is relief of anginal symptoms to obtain a better quality of life. Furthermore, it has been shown that subgroups of patients with an intermediate or high mortality risk when maintained on medical therapy may have a better life expectancy after CABG.[2,3] A majority of patients are free of anginal symptoms after operation, while another substantial group has a decrease in symptoms. Only few patients show no improvement at all.[4] Percutaneous transluminal coronary angioplasty (PTCA) is available as an alternative therapy, currently mainly indicated for 1- and 2 vessel disease.[5] Nevertheless, the number of CABG procedures is still increasing,[6] since it is still the treatment of choice for multivessel disease or left main disease, while also a growing number of patients are accepted for surgery despite advanced age or depressed left ventricular function.[7] The number of recurrent operations is also rising, due to progressive native vessel disease and graft atherosclerosis, which is more aggressive and accelerated after the first five postoperative years.[8,9]

Today, several different grafting techniques are used. Originally, only vein grafts were used as bypass material. At present the left internal mammary artery is preferentially anastomosed to the left anterior descending artery.[10] The remaining vessels may be grafted with arterial conduits, like the right internal mammary-, the gastro-epiploic artery and the radial artery. However, venous grafts are still used extensively.

In order to evaluate the very long-term (>20 years) survival and the incidence of recurrent interventions following venous CABG and to identify possible pre-operative risk factors that may predict long-term survival, a group of 1041 patients has been followed who were operated upon between 1971 and 1980 at the Thoraxcenter. Survival probability at 3.5, 7.5, and 11 years of this group of patients have been published previously. [11-13]

METHODS

Patient population

All 1041 consecutive patients who underwent a first CABG procedure

Table 1. Multivariable analysis of risk factors

	Overall mortality		Cardiac mortality	
	RR*	95% CI#	RR*	95% CI#
Age				
<55 years	1.00		1.00	
≥55 years	1.59	1.34-1.87	1.17	0.93-1.46
Vessel disease				
1 vessel	1.00		1.00	
2 vessels	1.32	1.01-1.73	1.83	1.21-2.77
3 vessels	1.99	1.54-2.57	2.87	1.94-4.24
left main	1.76	1.24-2.56	2.34	1.40-3.91
Ejection fraction				
normal (>0.55)	1.00		1.00	
moderate (0.30-0.55)	1.84	1.52-2.22	1.91	1.47-2.47
poor (<0.30)	3.30	2.16-5.04	4.67	2.90-6.53
unknown	1.28	1.02-1.61	1.53	1.13-2.08
Gender				
Male	1.00		1.00	
Female	1.15	0.88-1.49	1.24	0.85-1.80

* RR = Relative Risk; # 95% CI = 95% Confidence interval

between February 1971 and June 1980 at the Thoraxcenter were included in this study. The indication for surgery was based on the findings at catheterization and the fact that the angina pectoris, stable or unstable, was refractory to maximal pharmacological treatment available at that time (mainly a combination of nitrates and beta blockers; calcium antagonists were not yet available). Both elective and emergency surgery procedures were included. Excluded were those patients who needed additional surgery such as valve replacement or aneurysmectomy. The population consisted of 915 males (88%) and 126 females (12%) with a mean age of 53 and 56 years respectively. Single vessel disease was present in 196 patients (19%), 2 vessel disease in 331 (32%), 3 vessel disease in 433 (41%) and left main disease in 81 (8%). A normal ejection fraction was found in 601 patients (58%), a moderately impaired ejection fraction in 246 (24%) and a low ejection fraction in 27 (3%). The ejection fraction was unknown in 167 patients (16%), due to insufficient quality or absence of the ventriculogram.

Coronary angiography

Pre-operatively all patients underwent coronary angiography. A vessel was considered diseased when a luminal diameter narrowing of ≥50 % was seen in

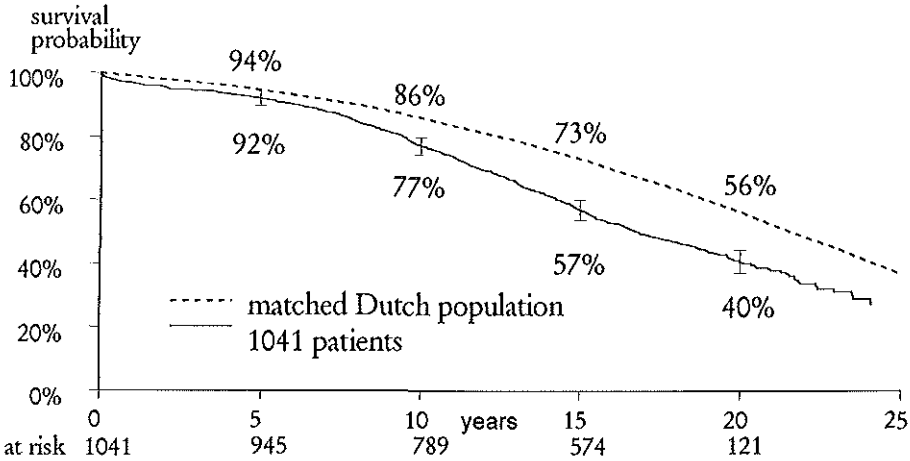

Figure 1. Probability of survival of 1041 patients (solid line) compared to the matched normal Dutch population (dotted line) plotted against time after surgery.

a major coronary artery in more than one projection. This resulted in a classification of 1-, 2- , 3-vessel disease, or left main disease. If left main disease was present, no further specification was made of narrowings present in any of the other segments. During catheterization the ejection fraction was calculated, where possible, using the area length method adjusted for single plane view. Values of ≥0.55 were classified as normal, 0.31-0.55 as moderately impaired, and ≤0.30 as poor.

Table 2. Causes of Death

Cause of death	Patients	%
Peri-operative mortality	12	2.0
Reintervention mortality	25	4.2
Late mortality		
sudden	157	26.5
myocardial infarction	78	13.2
chronic cardiac failure	99	16.7
non-cardiac	143	24.1
unknown	79	13.3
Total	593	100.0

Surgery

All patients underwent CABG surgery using saphenous vein grafts. In our center sequential grafting was introduced in 1976, while internal mammary arteries were used as a graft after 1980. After connecting the patient to the extracorporal circulation, the body temperature was lowered to 28°C. Then the heart was brought into fibrillation by local application of a salt solution of 4°C (external topical cooling). Intermittent aortic cross clamping was used for attachment of the distal graft anastomoses. Crystalloid cardioplegia was not used routinely in the inclusion period. The aim at operation was to bypass all proximal lesions in the major coronary arteries in order to make revascularization as complete as possible. When thought necessary, intimectomy of the artery was performed, most often in the right coronary artery. Over the years the average number of implanted grafts per patient increased from 1.33 in 1971 to 3.04 in 1980, reflecting the increasing experience of the surgical team and technical improvements.

Follow-up

Follow-up vital status was obtained by contacting the civil registry in writing and was complete in 98% at the reference date, February 10, 1997. Eighteen patients were lost to follow-up. Median follow-up was 19 years (range 13-26

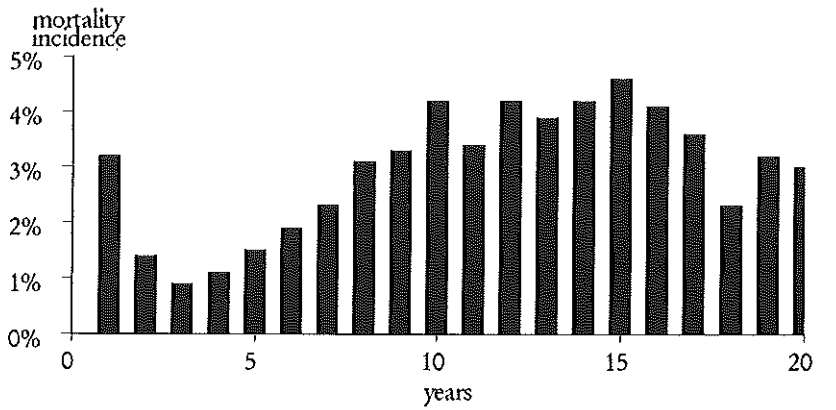

Figure 2. Yearly incidence of mortality of 1041 patients after CABG. The number of deceased patients as a percentage of the number of patients at risk in that year.

years). Mortality was divided into peri-operative mortality (death occurring within 28 days after surgery) and late mortality. The latter was subdivided into: 1) death at re-CABG or PTCA; 2) acute cardiac death (within one hour after beginning of complaints, believed to be of cardiac origin); 3) death caused by myocardial infarction (ascertained by enzyme measurement or ECG); 4) death caused by chronic cardiac failure; 5) death by a non cardiac cause; 6) unknown cause of death. The cause of death was determined by checking our own hospital records, by contacting the referring hospitals (for autopsy reports or letters to the general practitioner) or the treating general practitioner.

Data management and statistics

The acquired information was stored in a database, which also contained information about heart catheterizations, outpatient visits and re-hospitalizations. The survival data were analyzed using the Kaplan Meier method. The log-rank test was used to compare survival curves. A multivariable Cox proportional hazard analysis was performed to weigh factors, potentially influencing survival probability. Pre-selected variables were age, extent of vessel disease, pre-operative ejection fraction, and gender. Significance was defined as $p < 0.05$ and calculated by means of the Student's t-test for continuous data or the χ^2 test for categorical data. The yearly mortality rate was calculated by dividing the number of patients who died in a year by the average number of patients who were at risk in that year.

RESULTS

Survival

Median follow-up for the 1041 patients was 19 years (range 13-26 years). During this period 593 patients (57%) died. Figure 1 shows the Kaplan Meier curve for the survival probability of all 1041 patients and the normal Dutch population matched for gender and age. Estimated survival after CABG was 92% (95% confidence interval 90-94%) at 5 years, 77% (74-80%) at 10 years, 57% (54-60%) at 15 years, and 40% (36-44%) at 20 years. Survival probability for the matched population was 94% at 5 years, 86% at 10 years, 73% at 15 years, and 56% at 20 years. The mortality rate is 3.2% in the first year including peri-operative mortality of 1.2%, and then decreases to 0.9% in the

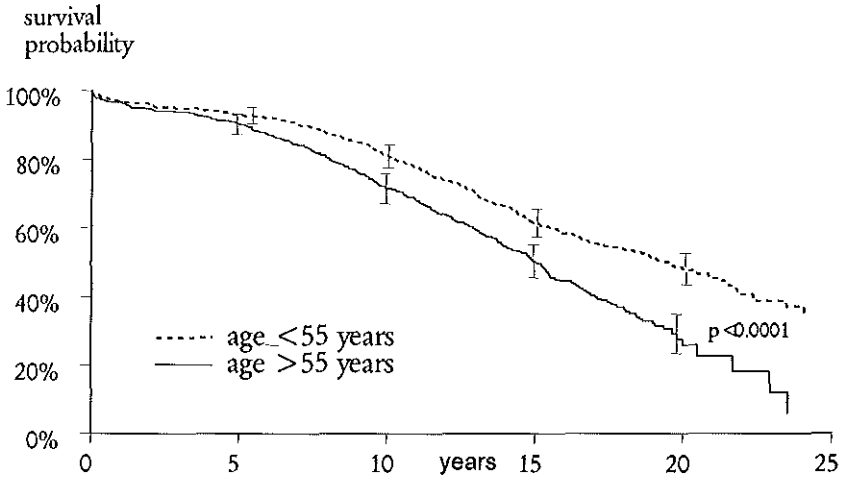

Figure 3. Probability of survival for 1041 patients for age <55 years and age≥55 years plotted against time after surgery.

third year. After that year there is a gradual increase in mortality incidence until approximately 4.6% in the fifteenth year after operation (Figure 2). After the fifteenth year, a trend towards a lower yearly mortality incidence is seen.

Univariable analysis of mortality

By univariable analysis survival appeared to be associated with age at the time of surgery, pre-operative left ventricular ejection fraction and with the extent of coronary artery disease, but not with gender. Survival probability at 20 years for patients younger than 55 years was 48% (95% confidence interval 43-53%). Patients aged 55 years or older had a 26% chance (20-32%) of being alive 20 years after operation. Survival estimates for the two age groups were significantly different ($p < 0.0001$) (Figure 3).

Survival probability according to gender was 39% (35-43%) for male patients at 20 years, and 46% (37-55%) for female patients (Figure 4). No gender difference in survival could be found ($p = 0.3$). Twenty year survival was 58% (50-66%), 47% (41-53%), 28% (23-33%), and 37% (26-48%) for 1-, 2-, 3 vessel disease and left main disease respectively (Figure 5). Survival probabilities in patients with multivessel disease or left main disease were lower compared to patients with single vessel disease (all p values < 0.01). Ten year survival probability for patients with a normal pre-operative ejection

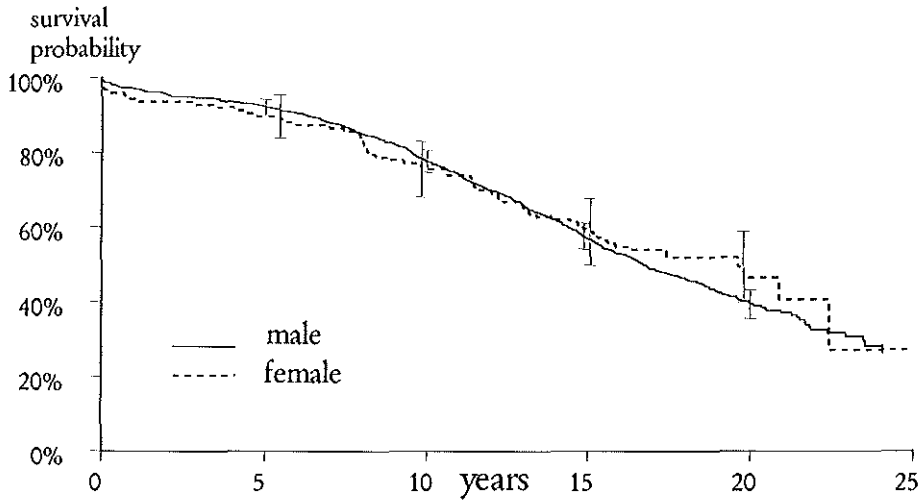

Figure 4. Probability of survival of 1041 patients for gender plotted against time after surgery.

fraction (≥0.55) was 83% (80-86%), and for moderately impaired ejection fraction (0.31-0.55) this was 68% (62 -74%) (Figure 6). Ten year survival probability for patients with a low ejection fraction (<0.30) was 37% (19-55%). For patients with an unknown ejection fraction ten year survival probability was 77% (70-84%). Differences in survival persisted after 10 years. However, in the group with poor ejection fraction, the number of patients at risk after the tenth year is relatively small for accurate interpretation. Survival probability for patients with moderate or poor ejection fraction was significantly different from patients with a normal ejection fraction ($p < 0.0001$). Patients with an unknown ejection fraction had an intermediate survival probability.

Multivariable analysis of mortality

The results of the multivariable analysis for predicting overall and cardiac mortality as presented in Table 1 confirm that in this population, age, vessel disease, and ejection fraction were independent predictors of mortality, while gender was not. Age was not a significant predictor of cardiac mortality. Gender was no independent predictor of cardiac mortality either. Thus, in this analysis ejection fraction and extent of coronary artery disease were the only independent predictors of cardiac mortality.

Cause of death
Cause of death could be ascertained for 514 of the 593 deceased patients (87%) (Table 2). Peri-operative mortality was 1.2% (12 patients) or 2.0% of the deceased patients. A total of 371 patients died of a presumed cardiac cause (63%). This included death at re-CABG or PTCA, sudden death not believed to be of cerebrovascular origin, death by myocardial infarction, or death caused by chronic cardiac failure. A non-cardiac cause of mortality was seen in 143 patients (24%). For 79 patients (13%) the cause of death was unknown.

Reintervention
A total of 411 reinterventions have been performed in 343 out of 1041 patients (33%). In 291 of the cases, the reintervention was re-CABG, in 120 of the cases this was PTCA. Of the 343 patients, 68 had both a re-CABG and a PTCA. Peri-procedural mortality for reintervention was 6.1% (re-CABG: 5.6%, PTCA: 0.5%). In Figure 6 the yearly incidence of re-CABG and PTCA is shown. In the first three years after the initial operation, only re-CABG was performed. Incidence of reintervention was 2.2% in the first year, and remained relatively stable until the seventh year. Thereafter, an increase in incidence up to 4.7% in the tenth year is seen. After the thirteenth year there was a downward trend in reintervention incidence.

DISCUSSION

Mortality
Peri-operative mortality in this study was 1.2%. Compared to other studies in the same period this may be considered as low. Yusuf et al found a 3.2% peri-operative mortality in their overview of 7 randomized trials with 1240 patients.[3]

Until approximately the fifth postoperative year survival is comparable with the matched Dutch population. Later on survival probability in the group of CABG patients decreases at a faster rate. CABG does not seem to provide the patient a normal life expectancy, with the exception of patients with a low-risk profile of single vessel disease and a normal left ventricular ejection fraction. At present these patients with single vessel disease would be referred primarily for angioplasty.

The survival probabilities found in this study correspond well with the 2 other studies that have reported 20 years follow-up,[15-16] despite differences in inclusion criteria and baseline variables and the few number of patients at risk 20 years after CABG in the other reports. A possible reason for the rising mortality after 5-10 years, which has also been reported by others,[17] may be vein graft atherosclerosis, which is accelerated and has been shown to be more aggressive than native vessel disease. Furthermore, progression of coronary artery disease in native vessels may increase the morbidity and mortality.[9] The downward trend in yearly mortality rates which is seen after the fifteenth year may reflect improving treatment possibilities, therapeutic as well as preventive (aspirins, lipid lowering drugs, beta blockers, angiotensin converting enzyme-inhibitors etc). Another reason may be patient selection: patients with poor myocardial function, or with recurrent ischemia may have died earlier and are no longer at risk. Finally, the small number of patients in follow-up after the fifteenth year may result in less accurate predictions of yearly mortality rates.

Predictors of mortality

Univariable and multivariable analysis both show that more advanced age at operation, extensive coronary artery disease, and impaired ejection fraction have an adverse influence on survival. There was no gender difference in survival probability. The latter is in contrast to Weintraub et al. who found

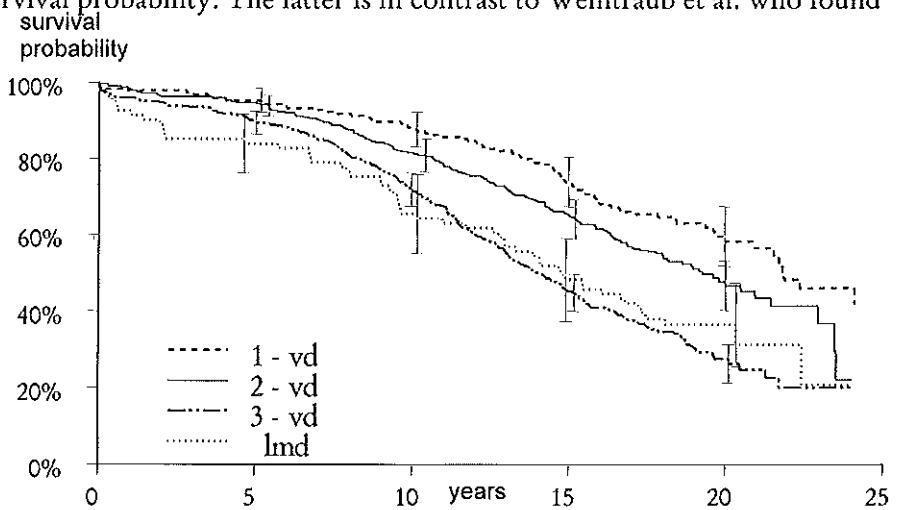

Figure 5. Probability of survival of 1041 patients with 1-, 2-, 3- vessel disease (VD) and left main disease (LMD) plotted against time after surgery.

that female gender is an independent risk factor for death.[7] However, others have also reported that female gender was not an independent risk factor for long term survival.[18]

Cause of death

For the 593 deaths that occurred during 20 years of follow-up, a cause of death could be ascertained for 514 patients (87%). When regarding the long duration of follow-up this can be considered as a high percentage. A presumed cardiac cause was responsible in 63% of the cases. In the Dutch population the possibility of dying from coronary artery disease is 40%.[19] Similarly, Ulicny et al. reported a cardiac cause of death in 60% of their patients[15] and Lawrie et al. in 51% of the patients.[20] Thus, despite surgery for coronary artery disease there still is a greater chance of dying from a cardiac cause. While CABG may improve functional status of the patient, it does not protect against future adverse cardiac events.

Reinterventions

During follow-up, a total of 411 repeat revascularization interventions (either CABG or PTCA) have been performed in 343 patients (33%). Within ten

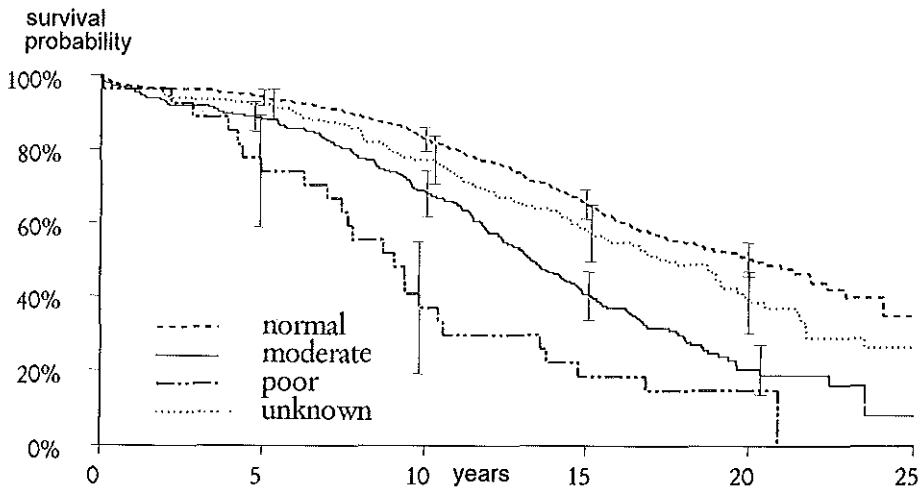

Figure 6. Probability of survival of 1041 patients with normal, moderate, poor, or unknown ejection fraction, plotted against time after surgery.

years after the first operation the cumulative incidence of repeated revascularization intervention was 18%. This corresponds well with a study reported by Rahimtoola.[16] A relatively low number of reinterventions in the first seven years after operation were also reported by Sergeant et al..[21] An increase in reintervention incidence seven years after operation, was also found by van Brussel et al.[17] This phenomenon may be explained by graft atherosclerosis and the progression of native coronary artery disease, which make CABG only a palliative treatment.[9]

LIMITATIONS

The data from a group of 1041 consecutive patients were based on a retrospective study of hospital records and records of general practitioners. When this group was constituted no approval nor support was given by government agencies for a prospectively designed study. Therefore, not all variables at baseline that could have influenced outcomes were available in this study. Only variables already known to influence survival were consistently reported and therefore used for further analysis. Fortunately, data on mortality, cause of death and repeat revascularization procedures where available in a large majority of patients. This is partly due to the availability of a civil registry and the precise record keeping of most co-operating general practitioners. Furthermore, our center has a strong regional function, resulting in a stable patient population over the years.

The follow-up period of this study is very long (26 years for some patients). The endpoints of mortality and recurrent intervention were assessed at irregular intervals of approximately 5 years. While this does not influence the precision of the mortality outcome, it may have reduced the accuracy of assessment of the cause of death. Although physicians in general make notes about the circumstances of death, inaccurate recall of the events may sometimes have influenced the classification of the cause of death. This is also reflected in an unknown cause of death in 13% of the deceased patients. Furthermore, the classification had to be simple and straight forward, allowing the physician to categorize the cause of death without the availability of complex diagnostic assays or autopsies. This may sometimes have lead to incorrect classifications. For instance, the classification sudden death may comprise patients who died of a cerebrovascular attack who could only have

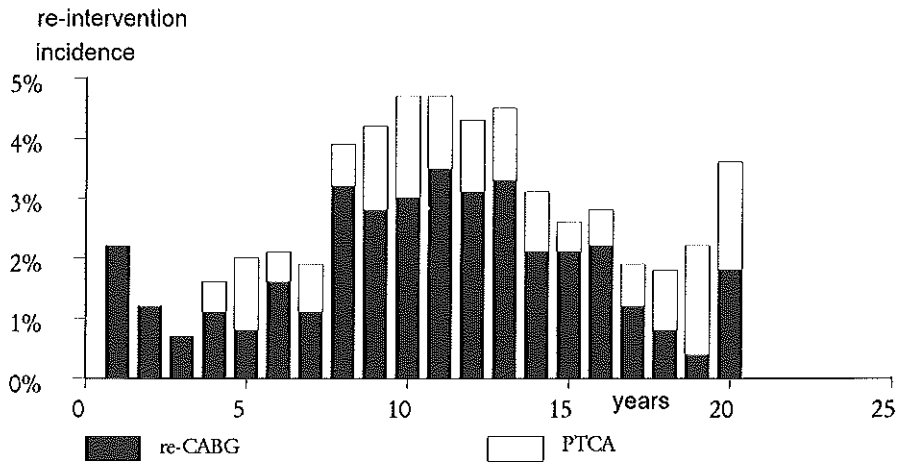

Figure 7. Yearly incidence of re-intervention of 1041 patients after first CABG. The number of re-interventions as percentage of the number of patients at risk in that year.

been correctly classified as non-cardiac cause of death when an autopsy had been performed.

To extrapolate the findings of this study to current practice, it needs to be realized that operation techniques have been changed and present day patient populations are different. Total arterial revascularization is currently propagated to prevent premature death due to graft sclerosis. A beneficial effect of this strategy on late survival has not been proven as yet. Different cardioplegia techniques for myocardial protection have been introduced. Currently more patients with impaired left ventricular function or extensive coronary disease are operated upon, while more patients with one or two vessel disease undergo PTCA instead of CABG. Also, more medical treatment modalities for angina pectoris have been introduced since then, for instance calcium channel blockers. So, at present coronary revascularization may be performed in a later stage of coronary artery disease than 20 years ago. More importantly, the possibilities and awareness of the importance of secondary prevention have increased in the last few years. Aspirin, beta-blockers, lipid-treatment, and life-style changes are now routinely employed following CABG. Therefore, one may hope that the outcomes have improved after CABG performed nowadays. Still, to our knowledge this is one of only few studies addressing the very long-term follow-up of CABG using vein grafts.

CONCLUSION

Aorto-coronary bypass surgery can be regarded as a safe procedure with a low peri-operative mortality. It provides a good long-term survival although less than in the matched normal Dutch population. Survival is negatively influenced by higher age at the time of operation, more extensive vascular involvement, or impaired left ventricular function, even after twenty years of follow-up. The cause of death is more often of cardiac origin than in the normal Dutch population, thus aorto-coronary bypass surgery does not seem to protect the patient from future adverse cardiac events. Furthermore, many of the patients required repeat revascularization by CABG or PTCA, probably due to both progression of native coronary artery disease and vein graft atherosclerosis.

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Chapter 8

CLINICAL OUTCOME 10 YEARS AFTER ATTEMPTED PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN 856 PATIENTS.

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(Journal of the American College of Cardiology 1996;27:1669-77)

ABSTRACT

Objectives. This study reports the 10-year outcome of 856 consecutive patients who underwent attempted coronary angioplasty at the Thoraxcenter during the years 1980 to 1985.

Background. Coronary balloon angioplasty was first performed in 1977, and this procedure was introduced into clinical practice at the Thoraxcenter in 1980. Although advances have been made, extending our knowledge of the long-term outcome in terms of survival and major cardiac events remains of interest and a valuable guide in the treatment of patients with coronary artery disease.

Methods. Details of survival, cardiac events, symptoms and medication were retrospectively obtained from the Dutch civil registry, medical records, by letter, telephone or from their physician, and entered into a dedicated database. Patient survival curves were constructed and factors influencing survival and cardiac events were identified.

Results. The procedural clinical success rate was 82%. Follow-up information was obtained in 837 patients (97.8%). Six hundred and forty-one (77%) patients were alive and of whom 334 (53%) were symptom free and 254 (40%) were taking no anti-anginal medication. The overall 5- and 10-year survival rates were 90% (95% confidence interval [CI] 87.6% to 92.4%) and 78% (95% CI 75.0% to 81.0%), respectively, and the respective freedom from significant cardiac events (death, myocardial infarction, coronary artery bypass surgery and repeat angioplasty) was 57% (95% CI 53.4% to 60.6%) and 36% (95% CI 32.4% to 39.6%). Factors that were found to adversely influence 10-year survival were age $\geq$60 years ($\geq$60 years [67%], 50-59 years [82%], $<$50 years [88%]), multivessel disease (multivessel disease [69%], single vessel disease [82%]), impaired left ventricular function (ejection fraction $<$50% [57%], $\geq$50% [80%]) and a history of previous myocardial infarction (previous myocardial infarction [72%], no previous infarction [83%]). These factors were also found to be independent predictors of death during the follow-up period by a multivariate stepwise logistic regression analysis. Other factors tested, with no influence on survival, were gender, procedural success and stability of angina at the time of intervention.

Conclusions. The long-term prognosis of patients following coronary angioplasty is good, particularly in those $<$60 years old with single-vessel disease and normal left ventricular function. The majority of patients are likely to experience a further cardiac event in the 10 years after their first angioplasty procedure.

INTRODUCTION

Since the introduction of percutaneous transluminal coronary angioplasty into clinical practice by Andreas Gruentzig in 1977,[1,2] the efficacy of this technique in the treatment of coronary artery disease, both native and vein graft vessels, has clearly become established,[3-6] with continuing growth such that the number of angioplasties performed per year equals that of coronary artery bypass operations (coronary artery bypass surgery). The immediate and medium-term outcomes are well described with the problems of abrupt closure and restenosis continuing to elude attempts to reduce their frequency.[7-10] Knowledge of the long-term outcome of angioplasty continues to accumulate over time.[11] Recently King and Schlumpf[12] reported on the 10-year follow-up of Gruentzig's first 169 patients, with an overall 10-year survival rate of 89.5%.

In the present report we describe the 10-year survival and clinical events of the first 856 patients treated by angioplasty at the Thoraxcenter, Rotterdam in the years 1980 to 1985.

METHODS

Patients

Between September 1980 and December 1985, percutaneous transluminal coronary angioplasty was attempted in 856 consecutive patients at the Thoraxcenter, Rotterdam. Patient characteristics are displayed in Table 1. The indication for angioplasty was stable angina in 451 patients, unstable angina in 323, acute myocardial infarction in 76 and other indications in 6. All patients were treated with a combination of beta-adrenergic and calcium channel blocking agents, nitrates and, in patients in unstable condition, intravenous heparin.

Angioplasty technique

At the commencement of the angioplasty procedure, 250 mg acetylsalicylic acid and 100 mg heparin were administered intravenously, with additional boluses of 50 mg given hourly. After completion of the procedure, if the stability of the immediate result was in doubt, a heparin infusion was commenced to achieve an activated partial thromboplastin time of 2.0 to 2.5

Table 1. Clinical characteristics of 856 patients who underwent coronary angioplasty during 1980 to 1985

Male	684	79.9%
Mean age (yr)	56.3	
Range	22-80	
Indication for angioplasty		
Stable angina	451	52.7%
Unstable angina	323	37.7%
MI	76	8.9%
Other	6	0.7%
Previous MI	341	41%
Previous CABG	78	9.1%
No. of vessels diseased		
One	517/817	63.3%
Two	193/817	23.6%
Three	96/817	11.8%
Mainstem	11/817	1.3%
EF < 50%	104/629	16.5%

times control levels for 12 to 24 h. All patients continued to receive nifedipine (40 to 60 mg) and acetylsalicylic acid (500 mg) once daily for a period of at least 6 months. The method of coronary angioplasty changed in February 1983 when the nonsteerable catheter system originally described by Gruentzig (2) was replaced by steerable balloon systems.[13] *Procedural clinical success* was defined as a reduction in the luminal narrowing to <50% of the reference diameter, by visual assessment, with no major complications (death, myocardial infarction, coronary bypass surgery or repeat angioplasty) within 24 h of the procedure. Evidence of myocardial infarction immediately after the procedure was defined by a new Q wave or elevation of myocardial enzyme levels to more than twice the upper limit of normal, or both.

Data collection and follow-up

Procedural details, including complications, were recorded at the time of the procedure and entered into a dedicated data base. Procedure-related events were included in all follow-up analyses. In 1994 all patients who survived the hospital period were initially checked against the civil registry to establish survival or death. This is a reliable and complete source of mortality data in The Netherlands. Primary end points considered at follow-up were death, nonfatal myocardial infarction, recurrent angina pectoris requiring coronary artery bypass surgery or repeat angioplasty and event-free survival. These data

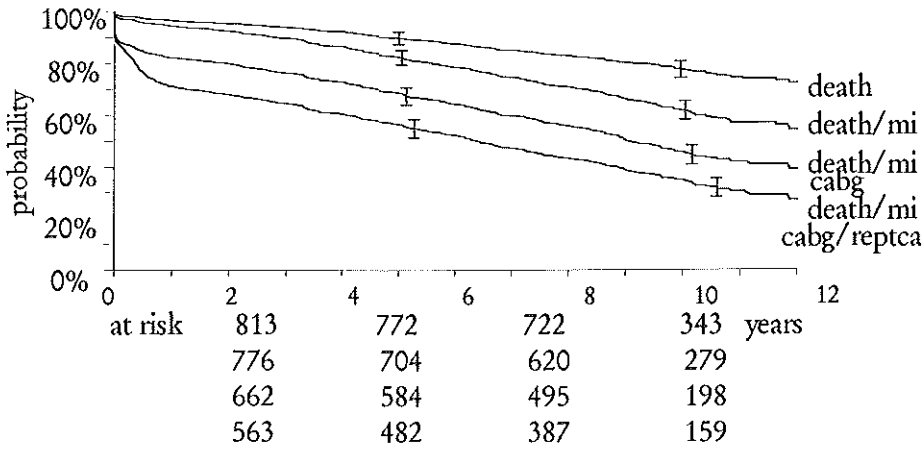

Figure 1. Ten-year survival and event-free survival rates in 856 patients who underwent coronary angioplasty during the years 1980 to 1985. vertical lines =2SE. CABG=coronary bypass surgery. MI =myocardial infarction. reptca =repeat coronary angioplasty.

were retrospectively obtained from the patient by letter or telephone, from family or from the family doctor and checked against hospital records.

Assessment of late myocardial infarction during the follow-up period included a history of prolonged chest pain necessitating hospital admission and documentation of a myocardial infarction by electrocardiographic (ECG) or enzyme criteria. Information on bypass surgery and repeat angioplasty was obtained from the patient and hospital data bases. Additionally, surviving patients were asked for information regarding symptoms of angina pectoris, graded according to the Canadian Cardiovascular Society classification,[14] any resultant limitation in activities and current medication. Follow-up data were obtained for all but 19 (2.2%) patients, the majority of whom had moved abroad. The follow-up period ranged from 0 to 13.3 years (median 9.6 years).

Statistical methods

Patient survival curves were constructed according to the method of Kaplan and Meier.[15] Mean values were calculated for continuous variables and absolute and relative frequencies for discrete variables. Differences between groups were examined for statistical significance by use of a two-sample *t* test for continuous variables and the chi-square test for discrete variables; $p \leq 0.05$ was considered significant. Multivariate logistic regression using a computer

package (BMDP) was performed to identify factors that were related to long-term survival. A forward- and backward-stepping algorithm was used with $p < 0.05$ to identify the variables remaining as independent risk factors for long-term survival. Baseline characteristics tested were age ≥60 years, gender, prior myocardial infarction, unstable angina, multivessel disease, ejection fraction <50% and procedural failure.

RESULTS

During the years 1980 to 1985, 969 consecutive coronary angioplasties were performed on 856 patients. The procedural success rate was 82%. Long-term follow-up information was obtained on 837 (97.8%) patients.

Survival and symptoms

Six-hundred forty-one patients were alive (77%) and 196 dead 8 to 14 years after their initial angioplasty. One hundred and forty-three patients had experienced a myocardial infarction, and 220 (25.7%) had undergone coronary artery bypass surgery, in 62 (7.2%) as an emergency procedure immediately after balloon angioplasty. Two hundred and twenty-one patients underwent

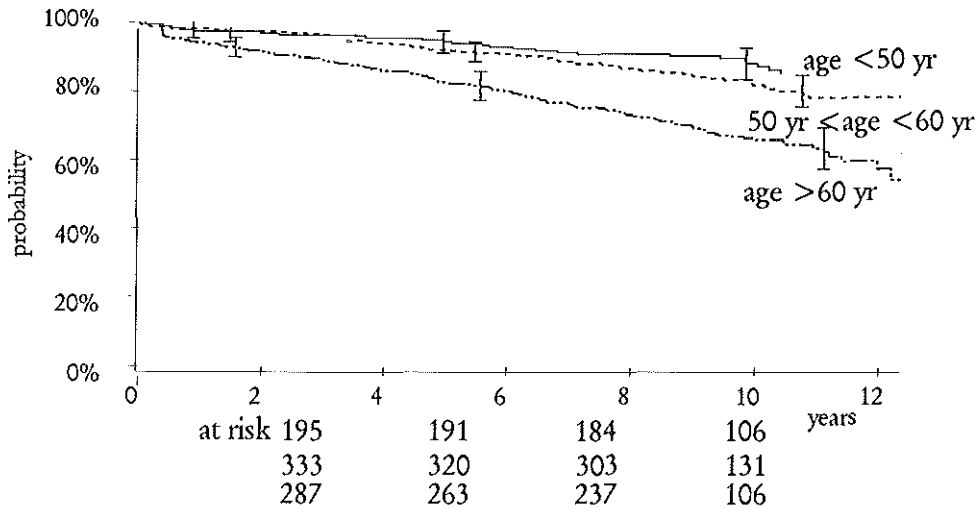

Figure 2. Cumulative survival rate classified into those <50, 50 to 59 and >60 years old at the time of intervention.

Table 2. Symptomatic status and antianginal medication in 630 surviving patients

CCS angina class		
0	334	53%
I	65	10%
II	134	21%
III	97	15%
IV	0	
Limitations of activities (symptomatic patients)		
None	46	40%
Mild	198	68%
Severe	47	16%
Antianginal treatment		
None or aspirin	254	40%
Single therapy*	197	31%
Double therapy	125	20%
Triple therapy	53	8%

*Nitrate, beta-blocker or calcium channel blocker. Data presented are number (%) of patients. CCS = Canadian Cardiovascular Society.

further angioplasty in the follow-up period, 81 (9.5%) within 6 months of the initial procedure. Patient survival and event-free survival curves were calculated using ranked clinical events and are displayed in Figure 1. The overall 5- and 10-year patient survival rates were 90% and 78%, respectively, and the 10-year survival rate for freedom from death, myocardial infarction, bypass surgery and repeat angioplasty was 36% (5-year freedom from cardiac events 57%). When the learning curve taken into consideration, the survival curves were recalculated comparing the first 226 patients who underwent angioplasty with the nonsteerable balloon, prior to March 1983, with the 630 subsequent patients. The 5- and 10-year survivals were identical as was the 10-year freedom from events.

Details of symptomatic status and cardiac medication were obtained for 630 of the 640 survivors (98%). Angina class, the degree of limitation in 293 of 296 patients with angina and number of different antianginal medications (nitrates, beta- and calcium channel blockers), are displayed in Table 2. Fifty three percent of survivors (334 patients) were symptom free, and 40% were taking no anti-anginal medication (254 patients).

Factors influencing cardiac events

The clinical variables age, gender, stability of angina, previous myocardial

Table 3. Factors influencing 5- and 10-year survival.

	Survival rate (%)				
	5-year	95% CI	10-year	95% CI	p value
Overall	90	87.6-92.4	78	75.0-81.0	
Age					
<50 yr	95	91.8-98.2	88	83.4-92.6	
50-59 yr	93	90.2-95.8	82	77.6-86.4	
≥60 yr	84	79.6-88.2	67	61.4-72.6	<0.0005
Male	90	87.4-92.6	78	74.6-81.4	
Female	91	86.6-95.4	79	72.6-85.4	0.97
No previous MI	92	89.4-94.6	83	79.4-86.6	
Previous MI	88	84.4-91.6	72	67.0-77.0	<0.005
Stable angina	92	89.2-94.8	80	76.0-84.0	
Unstable angina	91	87.8-94.2	76	71.0-81.0	0.22
Single-vessel disease	93	90.6-95.4	82	78.4-85.6	
Multivessel disease	84	79.8-88.2	69	63.2-74.8	<0.005
EF ≥50%	91	88.4-93.6	80	76.2-83.8	
EF<50%	79	71.0-87.0	57	47.4-66.6	<0.0005
Procedural success	91	88.8-93.2	77	73.6-80.4	
Procedural failure	87	82.0-92.0	80	73.4-86.6	0.65

CI = confidence interval; other abbreviations as in Table 1.

infarction, multivessel disease and impaired left ventricular function at the time of the index angioplasty and procedural success were tested to see whether they influenced long-term outcome.

Age. When patients were classified into three age groups (<50 years [n=201], 50-59 years [n=342] and ≥60 years [n=313], a clear survival advantage was found in the two younger groups at 5 years after the procedure (Figure 2).

Gender. Survival and event-free survival were tested for the 684 men and 172 women. Women were significantly older than men at the time of initial angioplasty with a mean age of 60.0 compared to 55.3 years in men ($p<0.001$). Additionally, women had suffered fewer myocardial infarctions than men before intervention (34.6% and 43.6%, respectively). There were no significant differences in the other clinical variables, namely, previous bypass surgery, number of vessels diseased and left ventricular impairment. There was no difference in mortality or event rates during the follow-up period (Figure 3). However, surviving women did have significantly more symptoms (41% angina free vs 56% of men, $p<0.05$) and took significantly more antianginal medication (70% at least one antianginal agent compared vs 57% of men).

Stability of angina. Four hundred and fifty-one patients underwent angioplasty

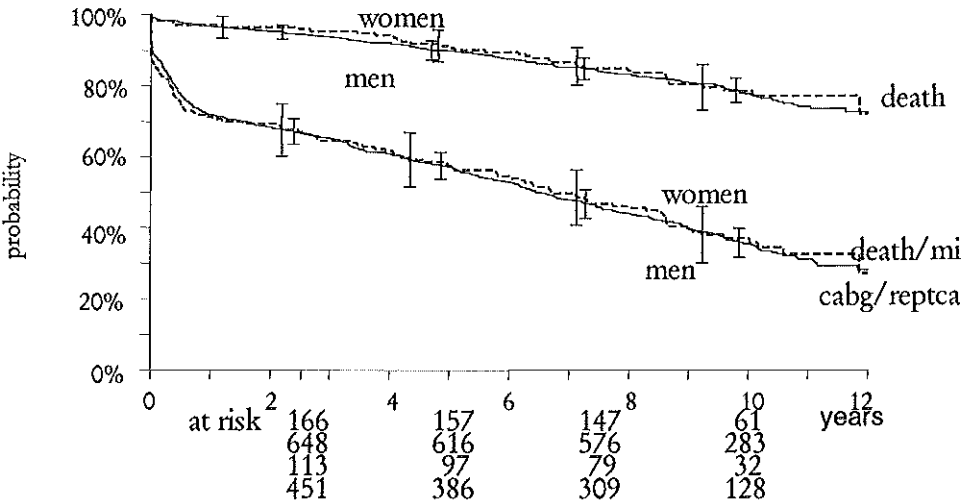

Figure 3. Cumulative survival and event-free survival rates according to gender.

for stable angina, 323 for unstable angina and 76 for an acute myocardial infarction. When survival curves were calculated for patients with stable and unstable angina and compared, there were no differences in long-term survival and cardiac events rates (Figure 4). The two groups were similar with respect to other clinical parameters. There were also no differences in symptoms and the amount of antianginal therapy between the survivors of the two groups at the time of follow-up.

Previous myocardial infarction. Of 833 patients with documented details, 341 patients had a previous myocardial infarction (23 patients unknown). A significant survival benefit for those without a previous myocardial infarction was detectable only 9 years after the index angioplasty (Figure 5).

Multivessel disease. Angioplasty was performed in 517 patients with single vessel disease, 193 with two-vessel disease, 96 with three-vessel disease and 11 with main stem disease (39 not recorded). When patients were classified into 2 groups- those with single-vessel disease and those with multivessel and mainstem disease-and survival curves constructed, a clear survival advantage was detectable for those with one-vessel disease by 1 year after the intervention, with 84% alive at 10-years versus 69% of those with multivessel disease (Figure 6). However, there was no difference in survival or cardiac event rates when patients who underwent single-lesion (n=672) and multiple

Table 4. Long-term outcome after percutaneous transluminal coronary angioplasty.

Study (ref), Year	No of pts	Age yr	mvd %	suc* cess	survival 5yr	survival 10yr	Comment
Weintraub et al,[16] 1994	10,785	58.3	29	90	94	-	1980-1991 infarction excl.; intention to treat
Henderson et al.,[18] 1992	899	54.9	50	81.6	89.2	-	All PTCAs; intention to treat
Kadel et al.,[19] 1992	798	52.8	0	81.2	96		1-vessel disease; single center total occlusions excluded
Talley et al, 1988	427	53.6	14	84	96.3	-	All PTCAs; single center; intention to treat
King and Schlumpf,[12] 1993	169	49.5	42	78.6	-	89.5	All PTCAs; single center; intention to treat
Present study	856	56.3	36.5	82	90	78	All PTCAs; single center; intention to treat

*success = Angiographically successful PTCA (%)

lesion (n = 184) angioplasty were compared.

Left ventricular function. Left ventricular ejection fraction had been calculated in 629 patients: mean [±SD] 59±11%, range 19 to 86%; ≥50% in 525, <50% in 104. Survival and event-free survival curves were constructed for these two groups (Figure 7). There was a clear survival advantage for those with ejection fraction ≥50%, with 80% remaining alive 10 years after angioplasty compared to 57% of those with ejection fraction <50%. However, event-free survival was similar, with less myocardial infarction, coronary artery bypass surgery and repeat angioplasty occurring in the follow-up period in patients impaired left ventricular function.

Procedural success. Angioplasty was successful in 700 patients (82%). When these patients were compared with those with unsuccessful angioplasty with or without a complication, long-term survival was similar. However, significantly more major events occurred in patients with a procedural failure, predominantly about the time angioplasty was performed (Figure 8).

The 5 and 10-year cumulative survival figures for the various subgroups evaluated are shown in Table 3. Univariate analyses were used to test the influence of the previous seven clinical factors on long-term survival. The odds ratios (ORs) for these variables with 95% confidence intervals (CIs) are displayed in Figure 9. Multivariate analysis could be performed on 579 patients complete data. Age ≥60 (OR 2.42, 95% CI 1.62 to 3.63), ejection fraction <50% (OR 2.22, 95% CI 1.33 to 3.70), multivessel disease (OR 1.60, 95% CI

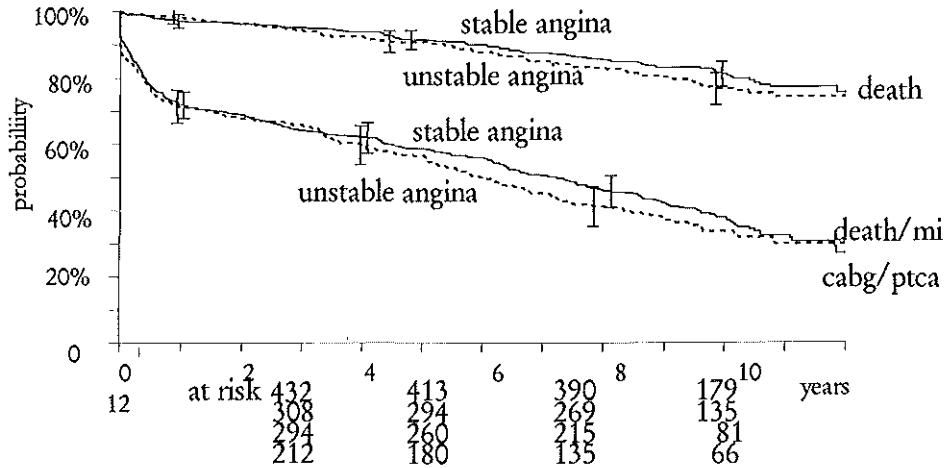

Figure 4. Cumulative survival and event-free survival rates according to stability of angina (stable, unstable).

1.06 to 2.42) and a history of previous myocardial infarction (OR 1.54, 95% CI 1.00 to 2.37) were found to be independent predictors of a diminished long-term survival.

DISCUSSION

In patient management an inevitable question is, What is the prognosis?. The answer can be given only in the light of temporal information gained from similar groups of patients treated by similar means in the past. This also holds true for the management of coronary artery disease by coronary angioplasty. Regardless of an evolving change in patient characteristics, procedural indications, technique and expertise, knowledge of the long-term outcome of early angioplasty practice remains an important source of information and guidance for contemporary cardiologists and patients.

In the present study we examined the late clinical outcome of the first 856 patients who underwent attempted angioplasty in a single center in the years 1980 to 1985. Our patient group included 76 who underwent coronary angioplasty for an evolving acute myocardial infarction and 156 (18%) in whom the procedure was an angiographic failure; thus this was an intention to

treat analysis. Our finding of an overall 5-year survival rate of 90%, although favorable, appears to be lower than previously reported (Table 4). It is recognized that the prognosis of patients with single-vessel disease and good ventricular function is excellent even when managed conservatively (17). When our patients were compared with other studies, we found that our patients were older and more likely to have multivessel disease, both factors associated with a decreased likelihood of event-free survival (18-20). We suggest that the baseline characteristics of our patients more closely resemble those of patients encountered in current angioplasty practice. The 10-year survival of our cohort of patients was 78% and to our knowledge, the only reported data for comparison are from Gruentzig's first 169 patients in whom the 10-year survival was 89.5% (12). His patients were a highly selected group in whom only proximal, discrete, predominantly left anterior descending artery lesions (73%) were treated because of the limitations of the equipment available at the time. Furthermore, his patients were younger and had a mean age of 49.8 years compared to 56.3 years in our study. In our study 543 patients were <60 years old with a 10-year survival rate of 85%.

Only 36% of patients were free from further cardiac events 10 years after the index procedure (57% event-free at 5 years), no doubt a result of our more general patient cohort (myocardial infarction in 41%, prior coronary

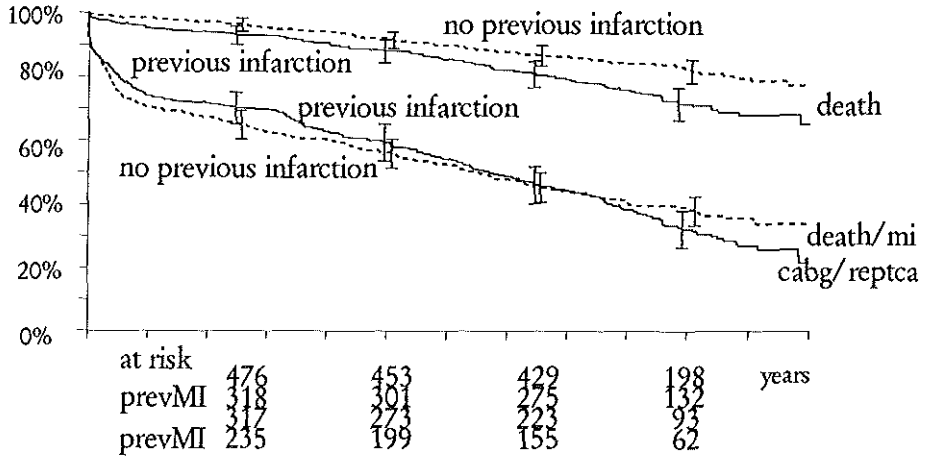

Figure 5. Cumulative survival and event-free survival rates according to a positive or negative history of previous myocardial infarction

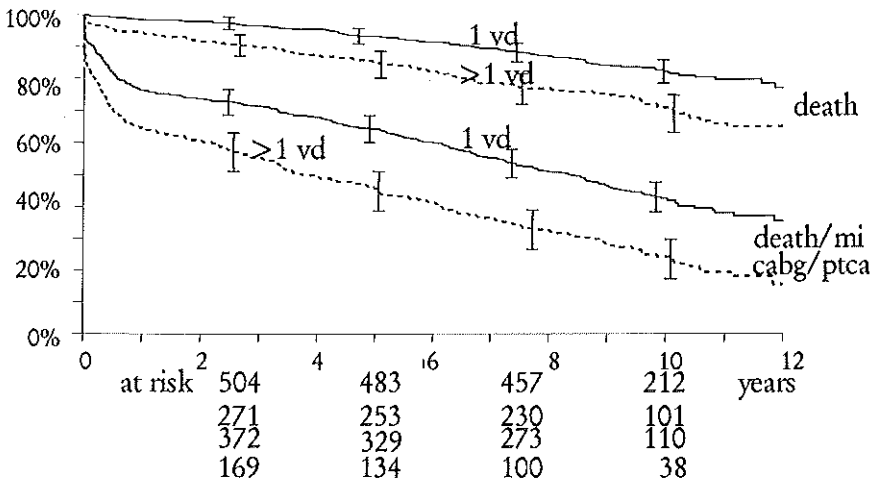

Figure 6. Cumulative survival and event-free survival rates according to the presence of single (1 vd) or multivessel disease (>1 vd).

artery bypass surgery in 9%, multivessel disease in 36.7%, impaired left ventricular function in 16.5%).

Virtually all patients with angiographically unsuccessful angioplasty early in the study period were referred for semiurgent coronary bypass surgery. This tendency decreased as confidence in the technique grew, with an overall rate of 7.2% over the 5-year period. Recent data[21] show that the emergency coronary artery bypass surgery rate is now <1%, and along itwith an improved procedural success rate (now >90%) are most likely the most changed factors when our study patients are compared with those of the present day because the rates of death, myocardial infarction, restenosis and repeat intervention have changed little in the past decade.[21,22] The long-term outcome of patients undergoing contemporary angioplasty may therefore be more comparable to patients in the present study with a successful procedure.

Factors influencing survival

We tested the clinical factors age, gender, previous myocardial infarction, stability of angina, multivessel disease and left ventricular function to assess whether they influenced long-term survival. Although angioplasty has been shown to be a safe and effective in elderly patients with coronary artery disease,[23] our data, in agreement with others, shows a significantly reduced

long-term survival in patients ≥60 years old at the time of their first angioplasty procedure.[24] This may be explained by more extensive coronary artery disease, with possibly less complete revascularization, in this group of patients. Additionally, it is possible that more deaths resulted from other disease processes more likely to manifest with advancing years because our mortality data included deaths from all causes.

The finding that men and women have a similar outcome after angioplasty in the intermediate term[16,25] has been extended to the long-term by our study. The 10-year survival was 78% for men and 79% for women, and the event-free survival rate was identical at 36%. However, there are several important differences in demographic, clinical and angiographic characteristics between these two groups. In our study women were significantly older than men at the time of angioplasty, a factor found to be associated with a less favorable outcome. It is possible that had these two groups been matched for age, women may have had a more favorable outcome than men. This argument is confounded by the development of coronary artery disease at a later age in women than men is related to the protective effect of estrogen. Other important factors not assessed in our study are the increased likelihood of an adverse risk factor profile[16] and smaller coronary vessels, making angioplasty technically more difficult in women. Our finding of significantly

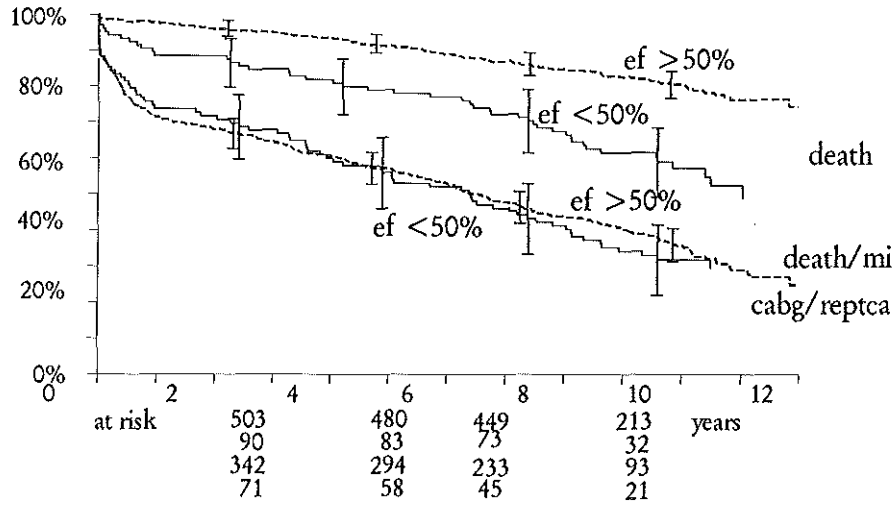

Figure 7. Cumulative survival and event-free survival rates in 629 patients with calculated ejection fraction, classified into ejection fraction <50% and ≥50%.

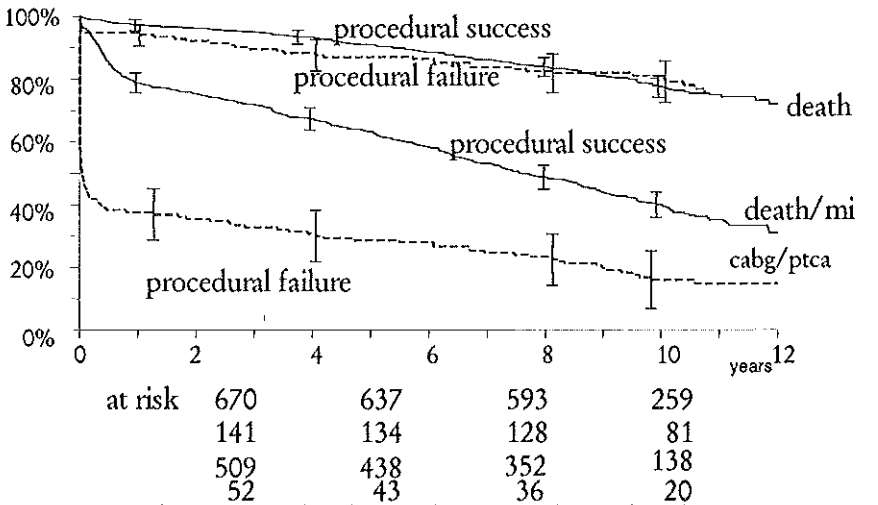

Figure 8. Cumulative survival and event-free survival rates for all patients classified according to whether the procedure was a success or failure. Format and abbreviations as in Figure 1.

more angina in surviving women than in men (59% vs 44%) is consistent with the findings of Kelsey et al[25] who reported angina in 30% of women and 19% of men 4 years after angioplasty.

The detrimental influence of a previous myocardial infarction and related left ventricular impairment on survival has again been demonstrated in the present study. However, those patients with impaired left ventricular function had fewer myocardial infarctions and underwent less bypass surgery and repeat angioplasty in the follow-up period, resulting in 5- and 10-year event-free survival rates nearly identical to those with normal left ventricular function. This finding may be a result of the tendency to manage this higher risk group who often have fewer anginal symptoms, conservatively and that a myocardial infarction is more likely to result in death in these patients with an already compromised myocardium. The negative influence of multivessel disease has been discussed previously. The long-term outcome of patients classified into those with stable and unstable angina syndromes at the time of the initial angioplasty also revealed no significant differences, with 5- and 10-year survival rates of 92% and 91%, and 80% and 76%, respectively. These data support and extend information reported for the intermediate term, with similar survival rate in both groups of patients at 95% to 96% at two and three years after angioplasty[26,27]. Although direct comparison with angioplasty is not

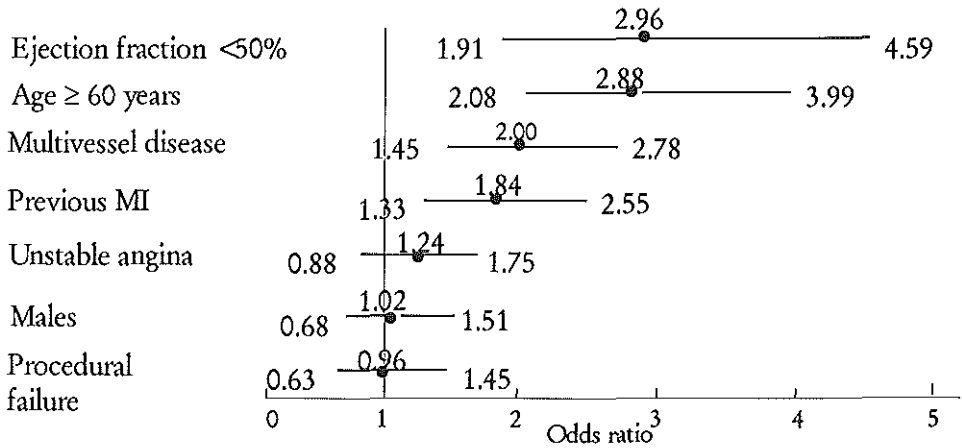

Figure 9. Univariable calculation of the odds ratio for death in the follow-up period, with the 95% confidence intervals for the clinical factors listed. MI =myocardial infarction.

possible without a randomized study, some comment can be made on the results of management of unstable angina by other methods. Luchi et al[28] randomized patients with unstable angina to medical or surgical therapy. The overall 2-year survival rate was 93% and similar for both treatment groups although patients with impaired left ventricular function appeared to benefit from operation. In a large observational study[29] the 10-year survival after coronary artery bypass surgery for unstable angina was found to be 83%.

Comparison with other treatment modalities

The 15 year outcome of patients initially treated by medication or surgery in the Coronary Artery Surgery Study (CASS) trial[30] has recently been reported. The 15-year survival rate was similar for both treatment groups at around 50%. The 10-year survival rates in the same study were 65% and 72% for those initially assigned to medical and surgical therapy, respectively. Between 10 and 15 years there was a 22% mortality rate in the surgical group compared with 15% in the medical group, consistent with advancing vein graft disease[30]. Although this population of patients cannot be directly compared with our study patients, our 10-year survival rate of 78% appears favorable.

The long-term benefit of percutaneous coronary angioplasty compared to coronary artery bypass surgery remains unknown. The intermediate results

of randomized trials of patients with multivessel disease have recently been reported. In the Randomized Intervention Treatment of Angina trial (RITA) trial[31] 1,011 patients with unstable or severe angina were randomized to angioplasty or bypass surgery. The 2.5-year interim analysis showed no differences between these two treatment modalities in the principal endpoint of death or myocardial infarction. However, the prevalence of anginal symptoms was higher in the angioplasty patients of whom almost four times as many required repeat angiography or intervention compared with the coronary artery bypass surgery patients[31]. These findings have been confirmed by the (Emory Angioplasty versus Surgery Trial (EAST)[32] and German Angioplasty Bypass surgery Investigation (GABI)[33]. In both studies, patients who underwent angioplasty required significantly more revascularization procedures in the follow-up period (3 years for EAST, 1 year for GABI), with an increased need for anginal therapy, than those who underwent operation. Continued long-term follow-up of these groups of patients is essential to establish whether those assigned to coronary angioplasty obtain a survival benefit once vein graft disease becomes advanced as is suggested by the CASS registry data, thus perhaps justifying the frequent need for early reintervention.

CONCLUSIONS

Long-term survival in our first 856 patients who underwent attempted coronary angioplasty in the years 1980 to 1985 is good, particularly in those patients aged <60 years old at the time of intervention and those with single-vessel disease and normal left ventricular function. The long-term outcome in terms of survival and freedom from cardiac events was similar in men and women and those with stable and unstable angina. The majority of patients experienced a further cardiac event, most likely a result of procedural failure and restenosis in the early follow-up period and incompleteness of revascularization and progression of atherosclerosis subsequently. Although significant advances have occurred, particularly in improving the immediate success of coronary angioplasty and in the complexity of lesions treated, making comparison with current practice difficult, knowledge of long-term outcome remains essential in planning treatment strategies.

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Chapter 9

LONG-TERM OUTCOME AFTER CORONARY STENT IMPLANTATION: A 10-YEAR SINGLE CENTER EXPERIENCE OF 1000 PATIENTS.

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(submitted)

SUMMARY

Background.
Although 1-year and 3-year follow-up studies have suggested maintained benefit of stenting, long-term follow-up studies in large series of patients have not yet been published. The purpose of this observational study was to describe the long-term clinical outcome up to 11 years after coronary stenting.

Methods.
A single center observational study encompassing 1000 consecutive patients with a first stent implantation (1560 stents) between 1986 and 1996, who were followed for at least one year with a median follow-up of 29 months (range 12-132 months).

Results.
Mean age was 59 years, 73% were male, 10% were diabetic, 39% had prior MI and 41% had prior CABG or PTCA. Stenting was bail-out in 37%, the indication was unstable angina in 41% and AMI in 5%. Angiographic success (diameter stenosis<50% prior to 1995 and <20% after that) was designated by the physician in 95% of the patients. Prior to hospital discharge, 1.5% of patients died, 6.8% experienced non-fatal myocardial infarction (Q or non-Q), 4.9% underwent CABG (of whom 2.1% emergency) and 5.3% repeat PTCA. Up to July 1997 the cumulative incidence of major adverse cardiac events (MACE): death, non-fatal AMI, CABG and repeat PTCA is respectively 8.2%, 12.8%, 13.1% and 22.4%. Survival at 1, 3 and 5 years is respectively 95%, 91% and 86%. Comparison of MACE incidence during the "anticoagulant era" and the "ticlopidine era" revealed significantly improved event-free survival with ticlopidine (27% vs 13%; $p<0.005$). Multivariable analyses demonstrated that ejection fraction <50% (RR: 4.1), multivessel disease (RR: 3.0), diabetes (RR: 2.9), and implantation in saphenous vein graft (RR: 2.1), indication for unstable angina (RR: 1.9) and female gender (RR: 1.7) were independent predictors of increased mortality after stenting. Independent predictors of any MACE were multivessel stenting (RR: 2.0), implantation in saphenous bypass graft (RR: 1.6), diabetes (RR: 1.5), anticoagulant treatment (vs ticlopidine and aspirin) (RR: 1.5), bail-out stenting (RR: 1.5), multivessel disease (RR: 1.4) and multiple stent implantation (RR: 1.5).

Conclusions

Long-term survival and infarct-free survival was good, particularly in nondiabetic males with single vessel disease and good ventricular function, who had a single stent implanted in a native coronary artery. A dramatic improvement was observed in event-free survival, both early and late with the replacement of anticoagulation by ticlopidine. This of course, cannot be separated from improved stent implantation techniques between 1986 and 1995. Ultimately, almost forty percent of the patients experienced an adverse cardiac event in (mainly repeat-intervention) the long-term. New advances in restenosis therapies and in secondary prevention must be directed at this aspect of patient-management after stenting.

INTRODUCTION

The widely heralded outcome of two simultaneously completed randomized trials[1-2] showing apparently superior angiographic and/or clinical outcome with stenting in selected patients, in comparison with balloon angioplasty, has led to widespread use of coronary stenting for diverse indications. Although 1-year and 3-year follow-up studies have suggested sustained benefit of stenting[3-12], long-term follow-up studies of large patient groups have not yet been reported.

To obtain more insights into this aspect of stenting, we investigated the occurrence of major adverse cardiac events up to 11 years after stenting in 1000 patients consecutively treated at a single center between 1986 and 1996. We also investigated the influence of the change from anticoagulation to antiplatelet therapy on long-term outcome and predictors of major adverse cardiac events (death, coronary bypass surgery, or repeat angioplasty [MACE]).

METHODS

Study patients

From November 1986 through August 1996, 1000 consecutive patients underwent a first stent implantation. Two separate stent procedures were performed in 46 patients, 3 patients underwent three and 1 patient 4 stent procedures. Two or more stents were implanted in 352 patients. Stent implantation with saphenous vein grafts as target lesion was performed in 126 patients. Full systematic anticoagulation therapy was used in 443 patients (from 1986 – July 1995) and antiplatelet therapy in 553 patients. Most patients (N=625) received a stent electively. All patients gave informed consent according to the principles of the Declaration of Helsinki and use of new stents was always approved by the Medical Ethical Committee.

Stent Implantation Procedure

Angioplasty was performed using minimum 8 french catheters via the femoral route. Heparin 10,000 units was administered parenterally in addition to 250mg aspirin at the beginning of the procedure thereafter ACT was measured hourly and additional 5000 iu heparin given to maintain ACT above 300 seconds. For planned stent implantation up until the early months of 1995, dextran 500mls was given i.v. over 2 hours, beginning prior to the procedure and for unplanned implantations, dextran was commenced during the procedure. Also, during that period,

Table 1. Baseline clinical characteristics %

	N	(%)
Number of patients	1000	
Vessels treated	1063	
Age (yr.) (range)	59	(28-86)
Male	732	(73%)
Diabetes	97	(10%)
Hypertension	266	(27%)
Smoking	256	(26%)
Hypercholesterolemia	281	(28%)
History of myocardial infarction	391	(39%)
History of CABG	160	(16%)
History of PTCA	247	(25%)
Indication		
Stable angina	500	(50%)
Unstable angina	389	(39%)
AMI	53	(5%)
Unknown	58	(6%)
Function class (CCS)		
I	8	(1%)
II	154	(26%)
III	324	(56%)
IV	98	(17%)
Number of diseased vessels		
1 vessel disease	535	(54%)
2 vessel disease	261	(26%)
3 vessel disease	178	(18%)
Unknown	26	(3%)
Ventricular function		
Good (>50%)	753	(76%)
Moderate (30%-50%)	95	(10%)
Poor (<30%)	31	(3%)
Unknown	121	(12%)
Target vessel		
LAD	468	(44%)
LCX	173	(16%)
RCA	295	(28%)
Left main	7	(1%)
Saphenous bypass graft	120	(11%)
Indication		
elective	625	(63%)
bail-out	375	(37%)
Angiographic success†	948	(95%)
Clinical success*	858	(86%)

† Angio success: 1986-1994 diameter stenosis <50%; 1994 onward diameter stenosis <20%.
*Clinical success: Freedom from death, myocardial infarction, CABG or repeat PTCA.

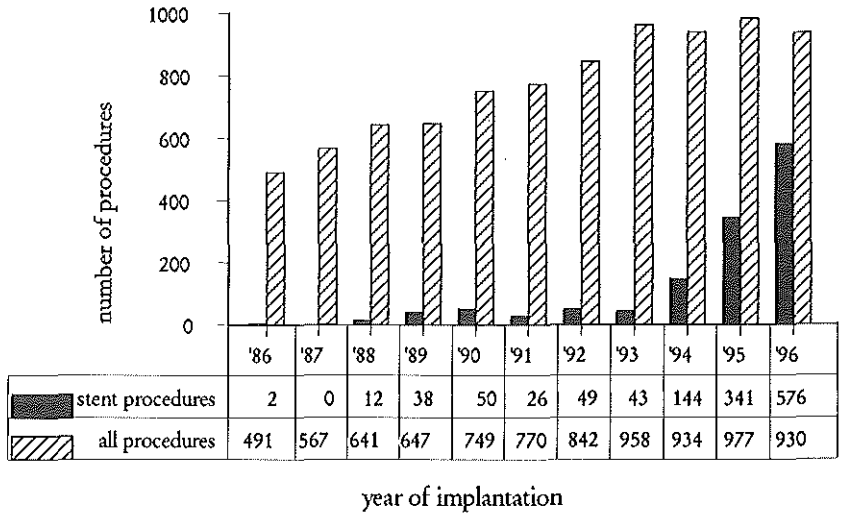

Figure 1. Yearly incidence of stent implantation.

intravenous heparin infusion was continued after the procedure until coumadin, commenced following the procedure, reached therapeutic levels. Coumadin was then continued for 3 months. From 1995 onward, the use of perprocedural dextran and postprocedural heparin and coumadin was discontinued and ticlopidin 500mg per day was commenced immediately after the procedure or during the 24 hours prior to the procedure where possible, in the case of elective implantations. Intracoronary nitroglycerine was generally used prior to all contrast injections intended for on-line or off-line QCA analysis and additionally to treat coronary spasm where necessary. In the case of bypass graft stenting and sometimes for stenting during acute myocardial infarction, intragraft (or intracoronary) verapamil was often administered in the context of poor run-off or "no reflow" considered generally due to micro-embolization. The use of abciximab before or during coronary angioplasty in selected patients with unstable angina or high risk candidates, was commenced in mid 1995 and was used according to existing protocols.

In general, monorail dilatation balloon catheters were used for balloon angioplasty , thus guidewires of 175cm were usually employed. Where over the wire stent delivery systems were required (such as the Palmaz-Schatz, the first generation ACS Multilink and the Wallstent) a 175cm wire was replaced by a 300 cm or longer wire. The vast majority of stents used were hand-crimped on the monorail balloon

Table 2. Stent characteristics

Mean stent length (mm)	32.7	(± 19)
Mean balloon size (mm)	3.6	(± 0.8)
Mean number of implanted stents	1.6	(± 0.9)
Multivessel stenting, N (%)	58	(5.8%)

Target vessel	LAD	LCX	RCA	LM	SVG*	Total
Type of stent						
Palmaz-Schatz[1]	288 (41%)	76 (32%)	107 (24%)	2 (33%)	20 (12%)	493 (32%)
Wall stent[2]	82 (12%)	28 (12%)	129 ((29%)	0 (0%)	139 (82%)	378 (24%)
NIR[3]	160 (23%)	51 (22%)	69 (15%)	2 (33%)	6 (4%)	288 (18%)
AVE[4]	47 (7%)	20 (9%)	47 (11%)	0 (0%)	3 (2%)	117 (8%)
Other stent types†	125 (18%)	60 (26%)	95 (6%)	2 (33%)	2 (1%)	284 (18%)

*SVG=saphenous bypass graft
[1]Cordis, Johnson&Johnson Interventional Systems. [2]Schneider Europe. [3]Medinol Boston Scientific Corp. [4]Arterial Vascular Engineering. †Other stent types used were ACS Multilink Guidant (n=63), Bestent Medtronic (n=58), Gianturco-Roubin Cook (n=63), Cordis (43), Wiktor Medtronic (n=26), Radius Scimed Boston Scientific Corp. (n=9), Crown Johnson&Johnson Interventional Systems (n=9), ACT-one Progressive Angioplasty Systems Inc (n=6) and Freedom Global Therapeutics (n=5).

used for lesion dilatation. In the case of elective stent placement, adequate but not aggressive predilatation was generally performed using a balloon matched 1:1 to the reference vessel diameter, (measured routinely by on-line quantitative angiography by the CAAS system), to facilitate stent placement and avoid the risk of dissection. In the case of unplanned or emergency stenting, after failed balloon angioplasty, whatever stent available in the department at the time which was considered to be capable of resolving the problem in the safest and most efficient manner was chosen. Thus the length of segment to be covered, the diameter of the vessel and the presence of unfavorable morphological circumstances were taken into consideration, as well as the known technical characteristics of the available stents, in the usual way. Post dilatation of balloon expandable stents was generally performed to safely achieve an optimal result. Prior to the emergence of the motto of high pressure postdilatation with oversized balloons, in late 1994, post dilatation after stent deployment was only performed if the angiographic result after deployment was unsatisfactory, in the opinion of the operator, using on-line QCA analysis. Generally the appearance of a "step up/step down" in the stented area was considered satisfactory and in the absence of that, a diameter stenosis $< 30\%$ by on-line QCA analysis, in a minimum of 2 views.

Table 3 Major cardiac events in 1000 patients

	In-hospital		Out-hospital		Total	
	All†	Ranking*	All†	Ranking*	All†	Ranking*
Death	15	15	67	67	82	82
MI	68	66	60	46	128	104
CABG	48	35	82	63	131	87
Repeat PTCA	55	26	171	110	224	114
Subacute thrombosis	30					

†All: all events non-mutually exclusive analysis.
*Ranking: frequency of events in descending order of severity (death worst outcome, followed in order of ranking by AMI, bypass surgery, repeat intervention)

In the case of the Wallstent, the initial experience began in 1986 with the first generation of the device. Since then a second generation has been introduced with the same basic structure but improved visibility characteristics, with addition of cobalt and reduced shortening on expansion, due to decrease in the braiding angle of the mesh (a third generation Magic Wallstent is now available but was not employed in the patients described in this study). A long (>300cm) guidewire, ideally with support characteristics, is required to deliver the over the wire stent delivery system. Adequate but conservative predilatation of the target lesion was generally performed, to ensure complete stenosis dilatation but avoid unnecessary dissection and retain some stenosis as a marker and possible anchor for Wallstent deployment. The Wallstent was chosen based on on-line quantitative angiographic measurements of maximal target segment diameter and total segmental length to be covered. Generally, up until 1995, the diameter chosen was at least 1.5mm larger in diameter than the target segment and the unconstrained length 8mm longer than the target lesion to allow adequate anchorage proximal and distal and to allow for foreshortening after deployment and subsequent postdilatation. Since 1995, the diameter sizing has become more conservative, with ideally 0.5-1mm oversizing compared to the maximal segmental lumen diameter. The Wallstent requires special preparation, different from balloon expandable stents, to vent the polyurethane tube restraining the stent. This was performed by infusing X-ray contrast at 4-5 atmospheres of pressure, using the balloon indeflator device, until all air was visibly expelled, confirmed by visualizing the appearance of contrast emerging from the catheter tip immersed in water. The Wallstent was deployed by first placing the distal tip of the delivery system 4-5mm distal of the target lesion in a relatively disease free coronary site; after demonstrating a satisfactory position for stent

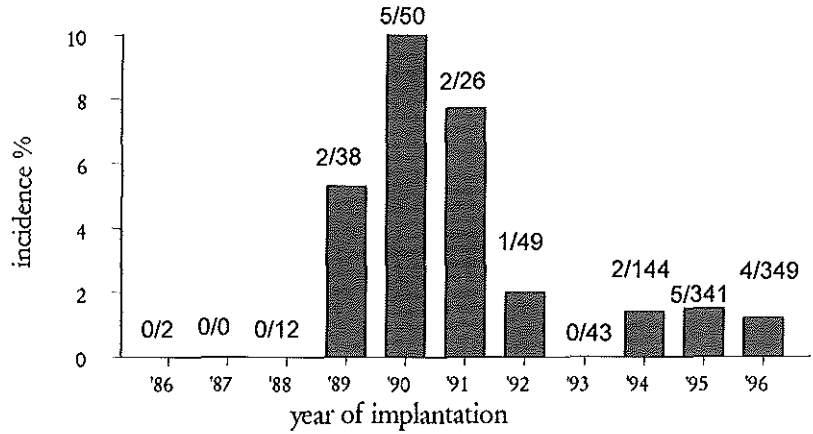

Figure 2. Incidence of truly emergency CABG after stent implantation.

release by contrast injections, the inflator was turned to 4 atmospheres and if properly vented this pressure is self-maintained, then the rolling membrane was retracted by firmly holding the steel rod handle of the delivery device and gently withdrawing the outer catheter membrane. Once the membrane begins to retract and the stent begins to open from distal to proximal in a flaring motion, it can no longer be replaced and the stent must be deployed, or can be dragged more proximally, if necessary. After the stent has been released, it expands to conform to the artery diameter, exerting additional radial force because of the use of a stent which is larger than artery lumen diameter. The delivery catheter must be removed before post-dilatation can be performed. In the early years, after stent release, the procedure was considered completed but because of the occurrence of up to 21% incidence of stent thrombosis[13] the concept of routine post dilatation or "swiss-kiss" was introduced to improve the luminal geometry. From 1991 post dilatation became routine. The only difference in technical approach, compared with balloon expandable stents was less aggressive or no post-dilatation of the distal portion of the Wallstent, because of the over-sizing, self-expanding nature and greater length of Wallstents and thus greater over-sizing distally compared to proximally – so that more often than not a "step-down" could be seen distally without any further action after deployment.

Data collection and follow-up

All patients were followed for at least one year and were thus at least one year post-stenting with a median follow-up of 29 months. Clinical follow-up data were obtained by review of hospital records and by questionnaires sent to general practitioners. Attention was focussed on the occurrence of the hard clinical endpoints of death, myocardial infarction, coronary bypass surgery and repeat angioplasty.[14] The diagnosis of myocardial infarction was based upon (1) episode of prolonged typical ischemic pain>30 minutes unrelieved by vasodilation therapy, (2) typical serum enzyme pattern and (3) development of new pathological Q waves in 2 or more contiguous ECG leads. All revascularizations were categorized according to whether they involved the target lesion (TLR), target vessel (TVR) or non TVR. Complete clinical follow-up was obtained in 990 patients (99%) of the patients. In 10 patients who had moved abroad, survival status could not be retrieved and the last available follow-up data were used, obtained at 1 month to 52 months after stenting.

For the purpose of examining predictors of long-term outcome in multivariable analyses, the following characteristics were selected as being of relevance: age, gender, diabetes, hypertension, cholesterol, smoking, prior myocardial infarction, prior bypass surgery, prior angioplasty, extent of coronary disease, left ventricular function, elective or bailout implantation, indication for unstable angina, post treatment with anticoagulation or antiplatelets, multivessel stenting, type of stent, use of multiple stents, total length of stent(s) implanted, stent size < 3mm, stenting in native coronary vessel or saphenous-vein graft vessel and at the native coronary target vessel (LAD vs RCA vs LCX).

Statistical analysis

Survival and event-free survival were estimated by Kaplan-Meier curves. Among patient subgroups (e.g. native vs bypass, anticoagulation vs ticlopidine) the logrank test was used to compare survival curves. Data are expressed as mean value ± SD. Continuous variables were compared by Student's t-test, categorical variables by χ^2-tests. The independent association of the clinical characteristics with long-term mortality, mortality or infarction and any major cardiac event was tested by using the Cox proportional hazard model. Logistic regression was used for the in-hospital outcome.

RESULTS

The study cohort consisted of 1000 patients with a first stent implantation, who underwent placement of 1560 stents (mean 1.6) in 1063 vessels. Multivessel stenting was performed in 60 patients (6%). Median follow-up post stenting was 29 months with a range of 12 to 132 months. The target vessels were left anterior descending coronary artery (44%), left circumflex coronary artery (16%), right coronary artery (28%), left main coronary artery (6 patients) and saphenous vein grafts (SVG) (11%). Evolution of stent implantation practice over the years is shown in Figure 1.

Baseline characteristics are shown in Tables 1 and 2. Mean age was 59 years (range 28-86) and 73% of the patients were male. The indication for PTCA was unstable angina in 41% and AMI in 6%. Diabetes mellitus was present in 97 patients (10%). Three hundred ninety one patients (39%) had a prior myocardial infarction. Previous coronary artery bypass grafting had been performed in 160 patients (16%) and prior PTCA in 247 patients (25%). Most patients (54%) had one vessel disease. Bail-out stenting (acute or threatened vessel closure) occurred in 27% of the patients. The majority of the stents used were Palmaz-Schatz (32%), Wallstent (24%), NIR stent (18%) and AVE stent (8%). A total of 10 other stent types were used in the remaining 18%. Saphenous vein graft stenting was

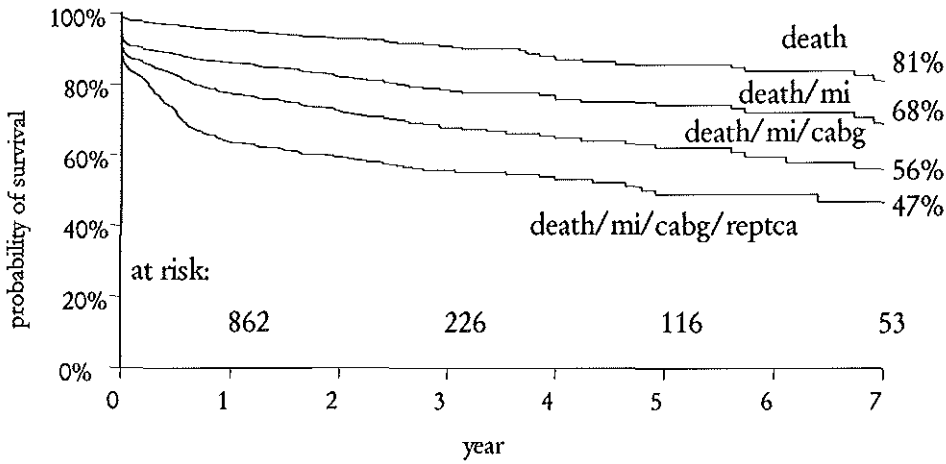

Figure 3. Seven-year cumulative survival and event-free survival rates in 1000 patients who underwent stent implantion during the years 1986-1996.

Table 4. Multivariable analysis: Independent predictors of mortality, mortality and myocardial infarction and any MACE.

	In-hospital		Out-hospital		All	
	RR[ζ]	95%CI[ζ]	RR[ζ]	95%CI[ζ]	RR[ζ]	95%CI[ζ]
Mortality						
Diabetes	-		2.96	1.56-5.71	2.85	1.56-5.20
Ejection Fraction<50%	7.53	1.97-28.8	4.02	2.23-6.79	4.05	2.39-6.86
Multivessel disease	-		3.03	1.29-6.07	2.95	1.42-6.13
Bypass graft	-		2.06	1.23-4.21	2.09	1.16-3.74
Females	5.29	1.29-21.6	-		1.73	1.01-2.94
Unstable angina	-		2.14	1.22-3.76	1.88	1.11-3.20
Mortality/Myocardial infarction						
Diabetes	-		1.81	1.09-3.29	1.64	1.05-2.56
Ejection fraction<50%	-		3.01	1.95-4.65	2.33	1.61-3.35
Multivessel disease	-		1.64	1.00-2.71	1.52	1.08-2.13
Bypass graft	-		2.34	1.45-3.80	-	
Anticoagulation	2.59	1.47-4.56	-		1.98	1.38-2.86
Bail-out stenting	2.28	1.31-3.96	-		-	
Unstable angina	-		-		1.41	1.02-1.96
Diameter<3mm	2.52	1.17-5.43	-		-	
Multiple stents	1.75	1.03-2.98	-		-	
Any MACE[*]						
Diabetes	-		1.98	1.41-2.79	1.51	1.11-2.07
Prior intervention	-		1.52	1.13-2.64	-	
Ejection fraction<50%	-		-		-	
Multivessel disease	-		1.47	1.10-1.97	1.44	1.12-1.84
Bypass graft	-		1.46	1.00-2.14	1.62	1.17-2.23
Anticoagulation	3.07	1.91-4.94	1.41	1.07-1.86	1.50	1.17-1.92
Bail-out stenting	2.54	1.63-3.94	-		1.47	1.16-1.87
Multiple stents	1.55	1.01-2.39	1.86	1.43-2.42	1.38	1.38-2.16
Diameter balloon<3mm	2.55	1.33-4.89	-		-	
Multivessel stenting	-		1.91	1.00-3.65	2.02	1.09-3.73
Unstable angina	1.73	1.12-2.66	-		-	

[*] MACE = mortality, myocardial infarction, CABG and PTCA
[ζ]RR = Relative Risk; CI = Confidence Interval

predominantly performed using the Wallstent (82%). The mean length of implanted stents was 32.7 mm (± 19) and the maximal balloon diameter used after stenting was 3.6 mm (± 0.8).

Table 3 outlines the clinical outcomes in-hospital and long-term. Fifteen patients died during the peri-procedural in-hospital period, yielding a mortality of 1.5%.

Forty-nine patients (4.9%) underwent a CABG during the same hospitalization, of which 21 were truly emergent (directly from the cathlab). From 1994 to 1996 this incidence fluctuated around 1.3% per year (Figure 2). Fifty five patients (5.5%) underwent repeat angioplasty during the same hospital admission, (35 patients in the anticoagulant era and 18 patients in the ticlopidine era) Acute myocardial infarct occurred in 68 patients (6.8%) and subacute thrombosis occurred in 30 patients (16 patients in the anticoagulant era and 14 patients in the ticlopidine era). A major bleeding complication occurred in 36 patients necessitating bloodtransfusion (3.6%) or vascular surgery (2.7%). The median hospital stay for the whole study population was 4 days. Our study group included 53 patients (5%) who underwent a stent implantation for evolving acute myocardial infarction and 52 patients (5%) in whom the procedure was an angiographic failure.

During 11 year late follow-up a total of 67 patients (6.7%) died, 60 patients (6%) had a myocardial infarction, 82 patients (8%) underwent coronary artery bypass grafting and a repeat angioplasty procedure was performed in 171 patients (17%). Of the fifty patients (5%) who underwent a repeat stent implantation, 30 were performed in the same vessel.

Routine follow-up angiography was performed in 630 patients (63%). At baseline significant one-vessel disease had been reported in 477 of the patients (76%) and in 251 patients (40%) at follow-up with 250 patients (40%) reported as having no significant coronary lesions at follow-up. In 12% of patients an increase in vessel disease was reported at follow-up. Of the total of 303 patients who underwent any repeat revascularization after the index procedure, a target lesion revascularization was performed in 198 patients (65%) and a target vessel revascularization was performed in a further 96 patients (32%). Eighty five patients (28%) underwent a revascularization in a new vessel.

Survival and event-free survival (freedom from death, myocardial infarction and revascularization) curves are shown in Figure 3. By Kaplan-Meier estimates, the cumulative survival rate was 97%, 95%, 91% and 86% at respectively 6 months, 1-, 3- and 5-years and the associated event-free survival was 72%, 63%, 55% and 48%.

Multivariable analysis could be performed in 876 patients with complete data. Independent predictors of mortality (Table 4) were ejection fraction <50% (Relative Risk [RR]: 4.2), diabetes (RR: 2.9), multivessel disease (RR: 2.9), saphenous vein graft implantation (RR: 2.3) and female gender (RR: 2.0). Ejection fraction (RR: 2.3), multivessel disease (RR: 1.6), use of anticoagulants (vs ticlopidine and

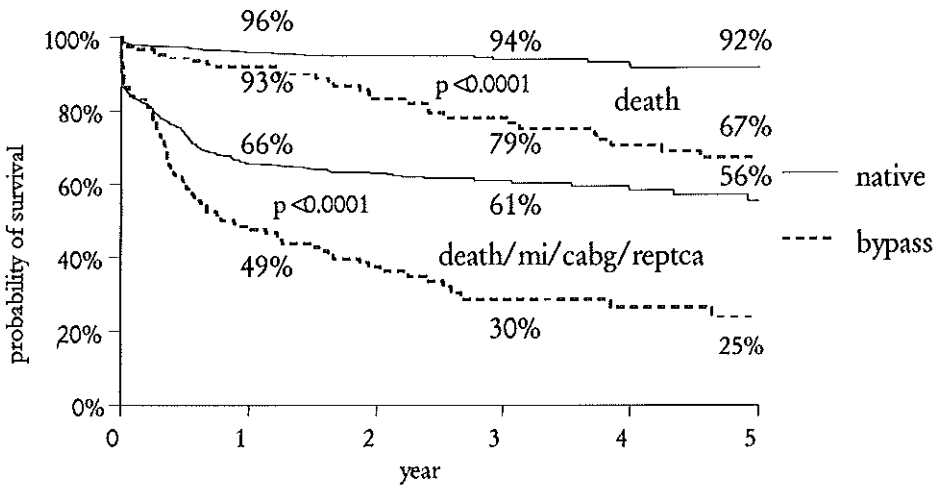

Figure 4. Cumulative survival and event-free survival rates in native grafts and saphenous vein grafts (bypass).

aspirin) (RR: 1.9) and diabetes (RR: 1.7) were independent predictors of death or myocardial infarction. Predictors of any MACE were multivessel stenting (RR: 2.0), implantation in saphenous bypass graft (RR: 1.6), diabetes (RR: 1.5), anticoagulant treatment (vs ticlopidine and aspirin) (RR: 1.5), bail-out stenting (RR: 1.5), multivessel disease (RR: 1.4) and multiple stent implantation (RR: 1.5). Predictors of early occurrence of a major cardiac event were use of anticoagulants (RR:2.7), bail-out stenting (RR: 2.7), use of a largest balloon diameter < 3mm (RR: 2.3) and multiple stent implantation (RR:1.7). Use of anticoagulants (RR: 1.5), diabetes (RR: 2.1), multivessel disease (RR:1.4), bypass graft stenting (RR:1.5), use of multiple stents (RR:1.8) and prior intervention (RR: 1.6) were predictors of a late event (>6 months). The type of stent was of no predictive value of mortality or any MACE.

Figure 4 shows significantly better survival for native coronary artery stenting vs saphenous vein grafting (96% vs 92% at 1 year [p=0.3] and 92% vs 67% at 5 years [p<0.0001]). Event-free survival was 69% vs 49% at 1 year [p<0.001] and 57% vs 25% at 5 years [p<0.0001]).

Detailed data on symptomatic status and the use of medication as of July 1997 were available in 679 of the 933 survivors (74%). Sixty seven percent were in CCS class 0 or I, 16% were in class II, 13% were in class III and 4% were in class IV. Seventy one percent of the patients were taking aspirin, 49% were using β-blockers, 31% a calcium-antagonist and 19% were using nitrates. Anticoagulant

therapy was being used in 9% of the patients, 18% were taking ace-inhibitors and one-third of the patients (35%) were using cholesterol-lowering agents.

Anticoagulant compared with antiplatelet treatment

Up to July 1995 443 patients had been treated with conventional anticoagulation and between then and august 1996 553 patients received ticlopidine and aspirin. Ticlopidine was withdrawn for severe leukopenia in 0.2%. To adjust for differences in follow-up duration, follow-up was truncated to two years. Differences were found in the baseline characteristics between the two groups. Age was similar, but in the ticlopidine group more patients had diabetes (11% vs 9%; p=0.02), more prior myocardial infarction (44% vs 37%), more anti-anginal medication was being taken (β-blockers: 58% vs 39%, nitrates: 21% vs 16% and calcium antagonists: 33% vs 28%). On the other hand less patients in the ticlopidine group were smoking (22% vs 30%), and less ticlopidine patients had prior revascularization (33% vs 56%). Median hospital stay was 7 days (anticoagulants) vs 3 days (ticlopidine). In the ticlopidine group more stents were implanted per procedure (1.6 vs 1.4), less SVG were stented (6% vs 19%) and stent procedures were more frequently elective (75% vs 50%). During the in-hospital period MACE occurred in 24.1% in the anticoagulation group and in 9.0% in the ticlopidine group with similar mortality (Table 5). However acute myocardial infarction occurred more often in the anticoagulation group (39 patients [9%] vs 15 [3%]; p<0.0001). Emergency coronary bypass was less frequent in the ticlopidine group (1.3% vs 5.5%; p<0.001) and early repeat angioplasty was also lower in the ticlopidine group (4% vs 8%; p<0.01). Bleeding and vascular complications necessitating blood transfusion or vascular surgery were lower in the ticlopidine group (respectively 1.7% vs 6.2% [p<0.001] and 0.6% vs 5.7% [p<0.0001]). Mortality after hospitalization was similar, however, more myocardial infarctions occurred during late follow-up in the anticoagulation group (9% vs 3%; p=0.0001). Also rate of late coronary bypass surgery was lower in the ticlopidine group (6% vs 9%; p=0.1) and the same was found for repeat angioplasty (14% vs 23%; p<0.001). Figure 5 shows the cumulative survival rates, freedom from death or myocardial infarction and event-free survival of patients who were treated with anticoagulation vs ticlopidine and aspirin.

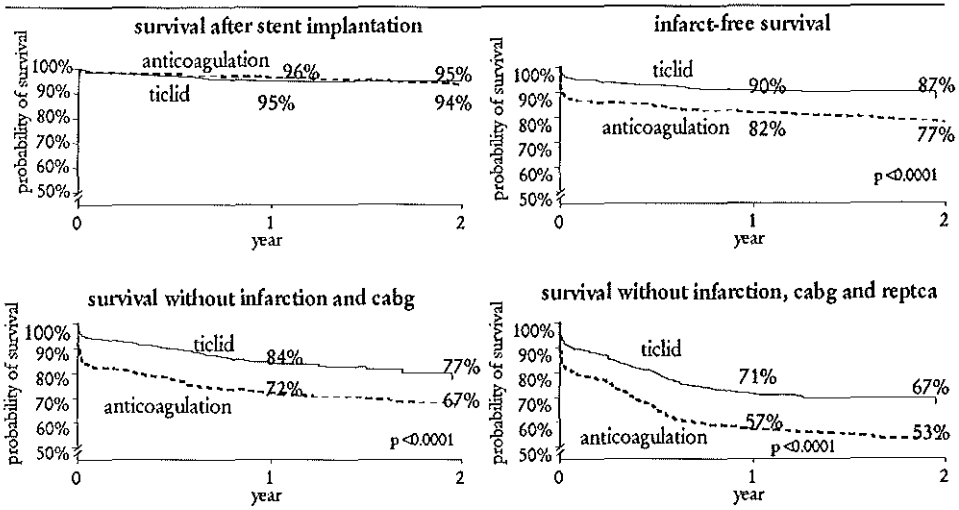

Figure 5. Cumulative survival and event-free survival rates according to ticlopidine and anticoagulation.

DISCUSSION

We describe the long-term clinical outcome of a heterogeneous patient population undergoing stent implantation in everyday evolving practice at our center and according to the prevailing clinical practice between 1986 and 1996. This study cannot be compared to clinical trials, including only selected patients and only contemporary techniques. The major milestones in evolving stent practice during this decade of coronary stenting were chronologically (1) use of post dilatation to improve acute results of Wallstent implantation (1987), (2) introduction of balloon expandable Palmaz-Schatz stents (1991), (3) appearance of loose crimpable Palmaz-Schatz stents, (4) gradual replacement of anticoagulation by ticlopidine and use of high pressure post dilatation with "oversized" balloons (1994) and (5) appearance of multiplicity of stent designs (1995). The principle observation which can be made on the basis of our findings are first, that 5-year survival after stent implantation in unselected " all comers" including the earliest experiences is an impressive 86%, which can be expected to be even higher in the post ticlopidine era. Striking differences in the occurrence of myocardial infarction and need for CABG or repeat PTCA were found between the patient groups treated with anticoagulants and ticlopidine both in-hospital and late outcome. However due to the simultaneous evolution in stent implant techniques with use of oversized balloons

to high pressure (>14ATM) this apparent benefit of ticlopidine therapy cannot of course be simply attributed to ticlopidine itself. The decrease in bleeding complications can however be attributed to the cessation of systematic anticoagulation.

The prognosis of nondiabetic patients with single vessel disease, unimpaired ventricular function, who had a single stent implanted in native arteries (n=299) is excellent (survival: 95% at 5-years). Poor left ventricular function was associated with greater risk of death in-hospital (RR:7.5) and late outcome (RR:3.9). Females had 5 times higher risk of in-hospital death and 2 times overall increased risk than males. Use of anticoagulants was associated with two times risk of death or MI and also 50% higher risk of any MACE. Bypass graft stenting has two times increased risk of death than native vessel stenting. Also implantation of multiple stents in the same procedure was associated with higher risk of any MACE, as was stenting in multiple vessels.

It is noteworthy that the reintervention rate in the second part of the first year after stent implantation is still increasing. This finding is relevant for clinical trials who report events at 6 months and indicates that an extended follow-up to 9 months or 1-year would include a higher percentage of cardiac events.

Although stent implantation has been shown to be safe and effective in diabetes patients on the short-term, our data show diabetes to be an independent predictor of reduced long-term survival and event-free survival.

The traditional risk factors multivessel disease and impaired left ventricular function (ejection fraction < 50%), in agreement with most other previous stent and angioplasty studies, show significantly reduced long-term survival, and survival without cardiac events. However, advanced age was not found to be associated with adverse outcome indicating that older patients are eminently suitable for stenting, especially with the reduced bleeding risks with antiplatelet agents.

In-hospital outcome of stent implantation in saphenous vein grafts is highly acceptable, but long-term outcome is poor. Although stenting provides superior short-term results compared with balloon angioplasty[15], this patient group continuous to present a major challenge apparently due to the indolent nature of advanced coronary and graft disease post CABG.

The increased risk of reinterventions after implantation of multiple stents is in agreement with a prior recent study[16] who reported an increased restenosis rate after 6-months follow-up.

Improved late outcome in the ticlopidine era (even after the 6-months "restenosis window") compared to the anticoagulation era has not been previously

Table 5. Relationship of post stent antithrombotic therapy with occurrence of MACE in-hospital and on the long-term†.

	In-hospital					Long-term				
	Anticoagulation		Antiplatelets§		Pvalue	Anticoagulation		Antiplatelets§		Pvalue
Number of patients	443		553			443		553		
Death	6	(1.4%)	7	(1.3%)		21	(5.1%)	23	(4.1%)	
AMI	39	(9.3%)	15	(2.8%)	0.0001	33	(8.7%)	14	(2.7%)	0.001
Repeat intervention										
CABG	23	(5.5%)	7	(1.3%)		36	(8.6%)	33	(6.2%)	
Angioplasty	33	(7.9%)	19	(3.6%)	0.0001	88	(22.9%)	70	(13.6%)	0.001
Complications										
Bleeding	26	(6.2%)	9	(1.7%)	0.001					
Vascular	24	(5.7%)	3	(0.6%)	0.0001					

†Follow-up in both groups truncated on 2-years.
§Antiplatelets: ticlopidine and/or aspirin
*: p-value: anticoagulation vs antiplatelets

reported. Evolving stent implantation techniques obviously cannot be separated from the change over to ticlopidine and are likely to be at least partly responsible for the benefit.

Since follow-up of the ticlopidine era is still less than 3-years, long-term clinical follow-up must continue in order to document continued benefit of stenting and lack of any late adverse effects. This data certainly suggests that long-term outcome is good considering the influence of the learning curve and the problems of thrombosis in the first years.

Continued critical clinical follow-up era must continue and be documented to provide the key prognostic data required to facilitate informed clinical decision making for optimal patient care.

Study limitations

This study has several important limitations. It is an observational study of daily clinical practice with both prospective and retrospective data collection during 11-years of stent implantation with several types of stent types used and in diverse clinical circumstances. The entire evolution of stent practice over the past decade is

covered in this study and the patient group is truly heterogeneous, so the results must be interpreted with these considerations in mind.

CONCLUSION

Long-term survival and infarct-free survival in our first 1000 patients who underwent a stent implantation according to the "best clinical practice of the day" was eminently acceptable, considering the earliest clinical experience of 21% acute or subacute thrombosis reported in 1991. Nondiabetic patients with single vessel disease and normal ventricular function, who had a single stent implanted in a native coronary artery had particularly good clinical outcome. There was a dramatic improvement in event-free survival, both early and late with the gradual replacement of anticoagulation by ticlopidine and the adoption of more aggressive stent placement strategies. On the debit side however, 40% of patients experienced major adverse cardiac events in the long-term. Recent advances in new restenosis therapy (for example brachy therapy) and secondary prevention (such as antiplatelet agents and statins) must be directed at this aspect of post intervention management.

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Chapter 10

LONG-TERM CLINICAL OUTCOME AFTER STENT IMPLANTATION IN SAPHENOUS VEIN GRAFTS

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SUMMARY

Objectives
We sought to determine the role of stent implantation in vein grafts by evaluating the long-term clinical outcome and estimated event-free survival at 5 years in 62 patients and by comparing these data with those of other treatment modalities reported.

Background
Patients with recurrent angina after coronary artery bypass surgery pose a problem. Stent implantation has been advocated in an effort to avoid repeat operation and to address the limitations of balloon angioplasty.

Methods
Patients undergoing stenting of a vein graft were entered in a dedicated data base. They were screened for death, infarction, bypass surgery and repeat angioplasty. Procedure related events were included in the follow-up analysis. Survival and event-free survival curves were constructed by the Kaplan-Meier method.

Results
A total of 93 stents (84 Wallstent and 9 Palmaz-Schatz) were implanted in 62 patients. During the in-hospital period, seven patients (11%) sustained a major cardiac event: two deaths (3%), two myocardial infarctions (3%), three urgent bypass surgeries (5%). The clinical success rate, therefore, was 89%. During the follow-up period (median 2.5 years, range: 0 to 5.9) another five patients (8%) died, 14 (23%) sustained a myocardial infarction, 12 (20%) underwent bypass surgery and 14 (23%) underwent angioplasty. The estimated 5-year survival and event-free survival rates (free from infarction, repeat surgery and repeat angioplasty) was (mean ± SD) 83 ± 5% (95% confidence interval [CI]: 73% to 93%) and 30 ± 7% (95% CI: 16 to 44%), respectively.

Conclusions
The in-hospital outcome of patients who underwent stent implantation in a vein graft is acceptable but the long-term clinical outcome is poor. It is unlikely that mechanical intervention alone will provide a satisfactory or definite answer for the patient with graft sclerosis over the long-term.

INTRODUCTION

Coronary artery bypass surgery effectively relieves angina in patients with obstructive coronary artery disease and may prolong life in a selected group of patients.[1,2] Recurrence of angina, however, occurs in 5% to 10% of the patients each year and is mainly due to graft failure or a combination of graft failure and progression of coronary atherosclerosis.[3-5] Serial angiographic studies revealed that 15% to 30% of the grafts are stenosed at 1 year after surgery and that nearly 50% of the grafts are closed at 10 years after surgery.[6-8]

As the number of patients who undergo surgery increases, the number of patients with recurrent angina due to graft failure will also increase.[9,10] Optimal management of these patients remains a subject of debate. In addition to pharmacological treatment, other therapeutic options are repeat surgery or percutaneous revascularization. In general, repeat surgery is associated with an increased morbidity and mortality and less symptomatic relief in comparison with a first operation.[10-12] Balloon angioplasty of vein grafts may successfully be performed in selected patients but is plagued by a high restenosis rate.[3] Patients with old, diffusely diseased or totally occluded grafts are at an increased risk of major cardiac complications owing to the risk of embolization of friable graft tissue into the coronary circulation.[3] As a result, the use of stents is advocated to treat such patients. This is not only based on the fact that stents can be easily implanted in such large vessels but and may contain friable graft tissue and thus reduce the risk of embolisation, but also on the assumption that the superior angiographic outcome immediately after implantation will be translated into a superior long-term clinical outcome.[13,14] Clinical benefit, however, is largely based on anecdotal experience and a number of case studies with special emphasis on technical success rates and short-term rather than long-term clinical outcome Randomised clinical trials are now underway to address this issue.[15] They may, however, fail to give a definite answer due to stringent inclusion and exclusion criteria. To reinforce the debate on the role of stent implantation in vein grafts and while awaiting the results of randomised trials, we report the immediate and long-term clinical outcome in a series of 62 patients who underwent stent implantation in a vein graft. All patients gave written informed consent before stent implantation, and the study was approved by the Medical Ethical Committee of our institution.

Table 1: Baseline clinical and angiographic characteristics of 62 study patients.

Median age (range)	65	(43-78)
Men	52	(84)
Previous AMI	37	(60)
Previous PTCA	17	(27)
Risk factors:		
smoking	12	(19)
hypercholesterolemia	32	(52)
hypertension	17	(27)
diabetes	7	(11)
Functional class (NYHA)		
I	2	(3)
II	7	(11)
III	31	(50)
IV	22	(36)
Vessel disease		
one-vessel	1	(2)
two-vessels	12	(19)
three-vessels	49	(79)
Ejection fraction:		
>50%	17	(27)
30-50%	40	(65)
≤30%	3	(5)
Unknown	2	(3)
Angiographic indication		
Primary lesion	51	(82)
Restenosis	8	(13)
Rescue angioplasty	3	(5)
Median graft age (range)	7.7	(1-20)

AMI = acute myocardial infarction, NYHA = New York Heart Association, PTCA = percutaneous transluminal coronary angioplasty.

METHODS

Patients

Between November 1986 and June 1994, 62 patients underwent stent implantation in a vein graft. They constitute 1.2% of the 5,340 patients who underwent coronary angioplasty in our institution during the same period. Baseline clinical and angiographic characteristics are shown in Table 1. The majority of patients underwent stent implantation because of severe angina pectoris (NYHA class III and IV, 86%) and as a treatment of a de novo graft

lesion (82%). Most of the grafts were old (median age 7.7 years) and were, in general, diffusely diseased. Detailed baseline angiographic data were available in 57 patients and are shown in Table 2.

Stent implantation

Stent implantation was performed by standard techniques using the femoral approach, as previously described.[16] The target lesion was first dilated with a balloon catheter to facilitate stent delivery. At variance with current standards of stent implantation, additional balloon dilatation after stenting was performed in only 44 patients (71%). This was done with semicompliant balloons equal in size to or 0.5 mm larger than the interpolated reference diameter of the bypass graft (on-line quantitative coronary angiographic measurement) and by using pressures ranging from 10 to 14 atmospheres. The total number, type and size of stents implanted is shown in Table 2. In almost all patients (90%) a Wallstent was used.

The postoperative treatment changed throughout the study period. While all patients were treated with a combination of acetylsalicylic acid, dipyridamole, heparin and acenocoumarol immediately after implantation, the first 26 patients also received 100,000 to 250,000 U of intravenous urokinase which was infused through the guiding catheter into the vein graft. Thrombolytic therapy was later withheld from the postoperative treatment because of a high frequency of major bleeding complications, particularly at the vascular access site.

Stent implantation was regarded to be angiographically successful when there was no residual stenosis within the stented segment by visual assessment. A clinically successful stent implantation was defined as an angiographically successful implantation free of procedure-related complications leading to death, myocardial infarction, bypass surgery or repeat angioplasty. A peri-procedural infarction was determined by the development of new Q-waves or an increase in the serum cardiac enzymes to more than twice the upper limit of normal.

Data collection and follow-up

Procedural details, including complications, were prospectively entered into a dedicated database at the time of implantation. Procedure-related events were included in the follow-up analyses. All patients who survived their hospital stay were checked against the civil registry to establish survival or death.

Table 2: Number, type and size of stents implanted, quantitative and qualitative angiographic data.

Number of stents	93	(100%)
Stents per patient	1.5	
Type:		
Wallstent	84	(90%)
Palmaz-Schatz	9	(10%)
Nominal Size		
3.0	5	(5%)
3.5	25	(27%)
4.0	38	(41%)
4.5	14	(15%)
5.0	8	(7%)
5.5	1	(1%)
6.0	2	(2%)
Quantitative Angiographic data (57 patients)		
Before	3.3±1.8	
After stenting	3.5±1.0	
Minimal Lumen diameter (mm)		
Before stenting	1.4 ± 0.5	
After stenting	2.7 ± 3.1	
Diameter stenosis (%)		
Before stenting	58 ± 2.0	
After stenting	23 ±0 9	
Lesion length (mm)		
Before stenting	16.5 ± 8.3	
After stenting	-	
Qualitative Angiographic data (n=62 patients)		
Chronically occluded graft	0	
Presence of thrombus	3	(1%)
Long lesions (> 15 mm)	32	(52%)
Tandem lesions	23	(37%)
Lesion containing ulcus	25	(40%)

Data presented are mean value ± SD or number (%) of patients (pts).

Patients were screened for the occurrence of death, acute myocardial infarction, recurrent angina necessitating repeat percutaneous revascularization or repeat bypass surgery. Clinical follow-up information was obtained retrospectively through an interview during outpatient clinic visits or from the patient or family by telephone or from the referring physician. Two patients were lost to follow-up. As a result, follow-up was complete for 60 patients (98%). The median period of follow-up was 2.5 years, ranging from 0 to 5.9 years. Patient survival curves and event-free plots were constructed by

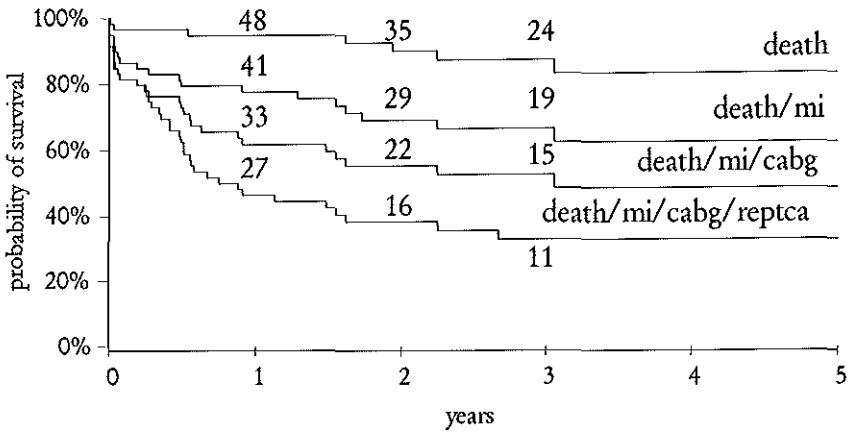

Figure 1. Survival and event-free survival curves (Kaplan-Meier) of patients who underwent stent implantation in a vein graft. cabg=coronary artery bypass graft surgery; mi=myocardial infarction; reptca=repeat percutaneous transluminal coronary angioplasty.

the Kaplan-Meier method. Repeat angiography 6 months after stent implantation was performed in only 43 patients (69%).

RESULTS

In-hospital outcome

A total of 93 stents were implanted (Table 2). In one patient, stent implantation was unsuccessful. Therefore, the implantation or angiographic success rate was 98%. In seven patients, a total of nine major cardiac events occurred during the hospital period (Table 3). As a result, the overall clinical success rate was 89%. Two patients (3.2%) died after stent implantation. Both of them received thrombolytic therapy-one patient because of protocol requirements during the initial study period and the other patient because of an acute myocardial infarction that was treated with balloon angioplasty and subsequent stent implantation, in addition to thrombolysis. In this patient, embolization of the graft material was noted during the procedure, which resulted in a creatine kinase (CK) elevation to 640 U/liter. A computed tomographic scan confirmed intracranial haemorrhage in both patients. Two other patients (3.2%) developed an acute myocardial infarction during hospital

Table 3: Major cardiac events during hospital stay and after discharge.

	In-hospital (n=62)		After discharge (n=60)*		Total (n=62)	
	Total	Ranking	Total	Ranking	Total	Ranking
Event						
Death	2 (3%)	2 (3%)	5 (8%)	5 (8%)	7 (11%)	7 (11%)
AMI	3 (5%)	2 (3%)	14 (23%)	14 (23%)	17 (27%)	16 (26%)
CABG	3 (5%)	3 (5%)	12 (20%)	12 (20%)	15 (24%)	15 (24%)
Re-PTCA	1 (2%)	0	18 (30%)	14 (23%)	19 (31%)	14 (23%)
Total	9 (15%)	7 (11%)	49 (82%)	45 (75%)	58 (94%)	52 (84%)

* Two patients lost to follow-up. Data presented are number (%) of patients. Ranking = frequency of events in descending order of severity (death [worst outcome], followed in order of rank by acute myocardial infarction [AMI], bypass surgery [CAB], repeat intervention [Re-PTCA]). Total = total count of all events (non-mutually exclusive analysis

stay with a CK elevation to 706 and 1,100 IU/l. One of these two patients was admitted because of an acute inferior infarction and was treated with balloon angioplasty and stent implantation into the graft supplying the right coronary artery. The other patient developed an antero-lateral infarction with a CK elevation to 706 IU/liter 4 days after stent implantation. Although the infarction was mainly caused by a subacute stent thrombosis, the exact cause was not documented. Another three patients (4.8%) were referred for urgent bypass surgery; one patient because of recurrent angina 11 days after stent implantation and two other patients because of a documented subacute stent thrombosis. In one of these two patients, anticoagulation was stopped because of a gastro-intestinal bleeding (Mallory-Weiss syndrome).

In addition, a major bleeding complication necessitating blood transfusion occurred in six patients-(9.8%), two groin (3.2%), three gastrointestinal (4.8%), one retroperitoneal (1.6%)-and a vascular access site complication necessitating surgery or blood transfusion, or both, in another eight patients (12.9%). The median hospital stay for the total study cohort was 9 days (range 5 to 53).

Clinical events after hospital discharge

Table 3 lists the occurrence of major events after hospital discharge. There were five deaths (8%) two of which were cardiac, one noncardiac and two of

unknown aetiology. Fourteen patients (23%) sustained a nonfatal myocardial infarction. In 2 of these 14 patients, myocardial infarction was associated with a repeat balloon angioplasty during the follow-up period. Twelve patients (20%) underwent repeat bypass surgery at a median interval of 7 months (range 1 to 43). In all but one of these patients, the indication of repeat surgery was angina pectoris in association with restenosis of the stented graft segment. Repeat angioplasty was performed in 18 other patients (30%) at a medium interval of 6 months (range 1 to 32). As for the patients who underwent repeat bypass surgery, in all but one, the angiographic indication to perform angioplasty was restenosis in or adjacent to the stented graft segment. Repeat angioplasty was successful in 16 patients but was complicated by a myocardial infarction in two. Repeat angiography 6 months after stent implantation was performed in 43 patients (69%). Restenosis (50% diameter stenosis criterion) was documented in 23 patients (53%), 7 of whom underwent repeat angioplasty and 6 bypass surgery. During the further follow-up, another seven and six patients underwent repeat angioplasty and bypass surgery, respectively, because graft failure at the stented site in all but two patients.

Survival and event-free survival

The mean ± SD estimated survival at 5 years after stent implantation was 83 ± 5% (95% confidence interval [CI] 73% to 93%) (Figure 1). Survival free from myocardial infarction at 5 years was 61 ± 6 % (95% CI 49% to 73%) and event-free survival at 5 years free from myocardial infarction, bypass surgery and angioplasty was 30 ± 7% (95% CI 16 to 44%).

DISCUSSION

The present study describes the immediate and long-term clinical outcome of 62 patients with angina pectoris who underwent stent implantation in a vein graft. The angiographic indication was a de novo lesion in the majority of patients (82%) and a restenotic lesion in 13%. Taking into account the limitations of this study-on the one hand, the design and therefore the potential shortcomings in the accuracy of data collection, and, on the other hand, the fact that it concerns of a series of non-consecutive patients with, in general, advanced graft failure-the main message of the present study is that stent implantation in vein grafts can safely be performed but that the long-

Table 4.In-hospital events after balloon angioplasty of saphenous vein grafts.

Author		ref no.	Study period	no of pts	Age (yr)	Graft age (yr)	Death (%)	AMI (%)	CABG (%)
Ford	1981	18	'78-'79	9	51	0.3-4.7	0	0	0
Jones	1983	19	'78-'82	37	54	2	0	5	5
Douglas	1983	20	'78-'92	62	54	<1->5	0	0	2
El-Gamal	1984	21	'80-'82	31	nr	0.3-4.7	0	5	0
Block	1984	22	'79-'82	44	56	0.2-9	0	0	2
Corbelli	1985	23	'81-'84	35	51	<0.5->5	0	0	2
Reeder	1986	24	'79-'84	19	60	3	5	5	10
Cote	1987	25	'81-'85	82	60	4	0	4	1
Ernst	1987	26	'80-'85	33	59	nr	0	6	0
Dorros	1988	27	'79-'86	53	58	7	4	1	1
Reed	1989	28	'83-'86	54	58	3	0	0	0
Platko	1989	29	'81-'87	101	60	4	2	6	2
Webb	1990	30	'78-'88	140	nr	nr	0	4	1
Jost	1991	31	'78-'83	41	57	3	0	0	0
Reeves	1991	32	'81-'87	57	58	5	2	9	2
Plokker	1991	33	'80-'89	454	60	6	1	3	1
Meester	1991	34	'81-'88	84	60	5	4	8	2
White	1993	35	nr	21	65	10	0	0	0
Morrison	1994	36	'86-'93	75	62	8	3	3	1
Total/Weighted average				1,408			1	6	2

nr = not reported; ref = reference; other abbreviations as in Tables 1 to 3.

term clinical outcome is poor. This should be interpreted when taking into account that in the majority of the patients a Wallstent was implanted and that high pressure balloon dilations according to current standards were not performed. Changes in stent design and, especially, implantation and deployment technique may beneficially have influenced acute and late outcome.[13,15]

In-hospital results

With respect to safety, the frequency of in-hospital events is acceptable despite advancing graft age and the complications one could anticipate from such a graft based on underlying histopathologic substrate described by Sabre et al.[17] The reported frequency of in-hospital events compare favourably with that after balloon angioplasty of vein graft lesions and with that after repeat bypass

Table 5. In-hospital events after repeat bypass surgery.

Author	year	ref	Study Period	N of pts	Age (yr)	Graft age (yr)	Death (%)	AMI (%)	Retho-racotomy(%)	Other (%)
Norwood	1977	37	'70-'75	26	49	0.5	8	12	nr	nr
Reul	1979	38	'68-'78	168	51	nr	5	2	2	≥2
Schaff	1983	39	'69-'80	106	49	nr	3	8	nr	11
Foster	1984	11	'76-'79	283	52	3	5	6	5	5
Cameron	1988	40	'70-'73	64	58	8	5	nr	nr	nr
Brenovitz	1988	41	'73-'86	150	56	8	12	5	7	23
Osaka	1988	42	'70-'83	119	52	4	3	9	3	3
Verkkala	1989	43	'70-'88	71	54	4	10	nr	nr	nr
Nair	1989	44	'80-'86	73	51	3	4	nr	nr	nr
Loop	1990	45	'67-'87	2509	57	6	4	7	8	9
Verheul	1991	46	'79-'87	200	58	5	8	4	6	7
Galbut	1991	47	'82-'88	88	62	9	7	8	6	21
Akl	1992	48	'81-'90	115	54	0.5	5	4	nr	7
Horton	1992	49	'81-'90	172	59	3-7	1	0	2	nr
Noyez	1994	50	'87-'92	16	50	11	0	3	13	13
Total/ Weighted averag				4,160			5	6	7	9

Other = total sum of reported complications such as cerebrovascular accidents, pulmonary and renal failure, bleeding and wound infection; other abbreviations as in Tables 1,2 and 4.

surgery (Table 4 and 5).[18-50] It is however, inferior to the frequency after stent implantation in vein grafts reported by other investigators (Table 6).[51-63] Again, one should account for the type of patients treated in this study. In most other reported studies shown in Table 6, 70 to 80% of the patients had a discrete lesion less than 10 to 13 mm long and, thus, they may represent a more favorable group of patients. Furthermore, it should be recognised that two patients died because of an intracranial haemorrhage after thrombolytic therapy and that two other patients received a stent in the setting of an acute myocardial infarction. Fine tuning of the indication for stent implantation and of the periprocedural and postprocedural pharmacological treatment by systematic use of high pressure balloon dilatations may have resulted in a better immediate outcome. It is noteworthy, that despite the above observations, the frequency of in-hospital major cardiac events compare favourably with that after stent implantation in coronary arteries. The

reported frequencies of death, acute myocardial infarction, emergency bypass surgery in 1,191 patients treated with a stent in a coronary artery between 1989 and 1992 were 2.0, 3.3 and 1.9%, respectively.[64]

Long-term results

The long-term clinical outcome is disturbing. This is not so much because of the estimated 5-year survival rate which was 83% in this study. The long-term survival does not differ from the 5-year survival in patients who underwent balloon angioplasty of a vein graft lesion or who underwent repeat bypass surgery, which have been reported to vary between 70% and 89% and 76% and 94%, respectively (Table 7).[65-67] Rather, It is mainly because of a high incidence of myocardial infarction and a very strong need for repeat revascularization during the follow-up period. Almost 25% of the patients sustained an acute myocardial infarction at a median time of 6 months (range 1 to 21) after the index procedure, and almost 50% of the patients underwent repeat revascularization by means of either repeat bypass surgery (22%) or repeat angioplasty (23%) at a median of 7 (range 1 to 43) and 6 (range 1 to 32) months, respectively. In all these patients, apart from two, the indication for repeat revascularization was failure of the graft at the site of the stented segment. As mentioned above, the use of high pressure balloon dilation after stenting may have resulted in a lower restenosis rate and, less need for subsequent revascularization.

Yet, although half of the major cardiac events occurred within the first 6 months after stent implantation, these data and the configuration of the Kaplan-Meier plots indicate a continuous and progressive clinical deterioration beyond this period. Given the limitations of comparing those data with other studies reported to date, the 1- and 5-year survival rates do not differ between the various treatment modalities for recurrence of angina due to graft failure (Table 7). The 5-year event-free survival, however, appears to be significantly inferior after balloon angioplasty or stent implantation, when compared with repeat surgery. This is largely based on the stronger need of repeat revascularization after catheter-based interventions. It is, however, important to point out that the decision to proceed with another revascularization is not only patient but also physician related. The threshold for performing a third or fourth repeat bypass operation is obviously much higher than for another angioplasty. If repeat surgery and angioplasty are excluded from the survival

Table 6. In-hospital events after stent implantation in saphenous vein grafts.

First Author	Year	Ref nr.	Study Period	No.of Pts	Age (yr)	Graft age(yr)	No.of Stents	Death (%)	AMI (%)	CABG (%)	PTCA (%)	Bleeding Vas
Urban	1989	51	'86-'88	13	63	5	20	0	0	0	nr	15
De Scheerder	1992	52	'88-'90	69	63	7	136	4	7	6	3	33
Strumpf	1992	53	'90-'91	26	68	9	30	0	4	0	4	19
Pomerantz	1992	54	'88-'91	69	66	9	84	0	10	0	nr	7
White	1993	55	nr	11	64	nr	16	0	0	0	0	0
Wong	1994	56	'90-'92	589	66	9	nr	2	0.3	1	nr	16
Eeckhout	1994	57	'86-'93	40	63	8	58	0	2	2	nr	14
Fenton	1994	58	'90-'91	198	66	8	nr	0.5	0.5	0.5	0.5	26
Nordrehaug	1994	59	nr	19	60	nr	nr	0	11	0	6	16
Keane	1994	60	'91-'93	29	63	10	35	0	0	0	0	17
Piana	1994	61	'88-'93	150	66	9	200	1	0	0	0	27
Rocha-Sing	1995	62	'89-'92	22	66	nr	nr	5	0	0	0	<7
Wong	1995	63	'90-'91	231	66	8	305	1	1	0.4	0.4	1
Total weighted average				1,466				1	1	1	1	16
Present study			'86-'94	62	65	8	93	3	5	5	1	23

Vas = vascular complications; other abbreviations as in Tables 1 to 4.

analysis, the 5-year survival free from myocardial infarction is 61 ± 6% (95% CI 49% to 73%). Nevertheless, patients who have had previous bypass surgery represent a select and difficult-to-manage subgroup of patients with ischemic heart disease. This is illustrated by the work of Lytle et al. from The Cleveland Clinic Foundation.[68] They found that patients who have had previous bypass surgery do less well in terms of survival and event-free survival, irrespective of the presence or absence of graft stenoses, in comparison with patients with obstructive coronary artery disease but without previous bypass operation. Furthermore, it needs to be emphasised that the prognosis of patients who have had previous bypass surgery is determined not only by the extent of coronary artery disease and the degree of graft failure but also by other clinical and anatomic factors such as age, coexisting disorders, ventricular function and type of conduit used. Furthermore, it is of noteworthy that the Cholesterol Lowering Atherosclerosis Study, in which male patients who have had previous bypass surgery were randomised into a placebo group and a group receiving lipid-modifying drugs, revealed a significantly lower rate of

Table 7. Survival and event-free survival after balloon angioplasty, repeat surgery or stent implantation in saphenous vein grafts.

	Survival				Event-free survival			
Treatment	Ref.No	No.of pts	1 year	5 years	Ref	No.of pts	1 year	5 years
Balloon Angioplasty	27,29,30, 33,34,66	915	90-94%	70-89%	33,34,66	621	50-60%	26%
Repeat surgery	39-42,65	1,939	---	76-94%	65,67	2,000	---	63-76%
Stent implantation	54,61	219	90-91%	---	54,56,58	1006	56-80%	---
This study		62	95%	83%		62	46%	30%

--- = not available

progression and a significantly higher rate of regression in the active treatment group (39% vs 61% and 16% vs 2.4%, respectively).[69] Therefore, risk factor modification may play a role in the improvement of the late outcome.

Study Limitations

A number of limitations have been briefly mentioned above. In addition to the design, the major drawback of the present study is that the population does not compromise a series of consecutive patients. Therefore, the possibility of an important selection bias cannot be neglected. In addition, we have basically reserved stent implantation for patients with advanced graft failure. This is not only because of our own philosophy with respect to the management of these patients but also because our center is a tertiary referral center. Forty-three percent of the patients are referred because of this top referral function. The small number of patients did not allow us to stratify patients into subgroups in order to explore which patient may benefit more from this treatment than the other. Therefore, we are unable to give guidelines with respect to improvement in patient selection and indications. In addition, the results reported herein need to be challenged by other investigators with larger series and, if possible, consecutive patients. Learning curve, more strict indications, improvements in stent design, changes in periprocedural procedures such as in-stent high pressure balloon dilations which affects not only the postprocedural pharmacological treatment but also potentially the clinical outcome and ,finally, more attention to risk factor modifications may contribute to superior results.

CONCLUSION

The management of patients with recurrent angina and graft failure is complex. In this historical series of non-consecutive patients in which the self-expanding Wallstent was predominantly used according previous standards of stenting, stent implantation was associated with a poor long-term clinical outcome. These observations needs to be challenged by more recent studies. It may well be that changes in stent design and the systematic use of in-stent high pressure balloon dilations, may result in a better long-term outcome. In addition, attention needs to be paid to risk factor modification to reduce long-term graft failure.

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Chapter 11

SUMMARY AND DISCUSSION

This thesis summarizes the long-term outcome of patients after a major cardiac event, such as myocardial infarction (MI), unstable angina pectoris (UAP), coronary bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty procedure (PTCA). The purpose of this chapter is to review the results and to investigate whether there are similarities or differences among these patients. We also investigated which risk factors are of predictive value for mortality or coronary heart disease (CHD) and try to give an advice how to deal with these risk factors in order to reduce future cardiac events.

The course of events in patients with MI or UAP is characterized by a period of instability, particularly in the first months up to 1-year, followed by stability, albeit with continued risk for (re)infarction or mortality. Patients after PTCA or CABG have similar risk for (re)infarction or mortality during follow-up. In addition, after PTCA (including stent) an increased early reintervention rate is observed due to restenosis.

It is remarkable that in patients with CHD the disease may be stable for years up to a point at which it becomes unstable with accelerated progression of the disease, resulting in (a series of) major cardiac events. The continuation of instability during the first month after myocardial infarction is in agreement with a recent report indicating rapid progression of coronary artery lesions at different sites shortly after infarction.[1] It is compatible with the suggestion that, at least in some patients, an infectious component may lead to or facilitate a period of instability in patients with coronary heart disease (CHD).[2,3]. In patients with acute myocardial infarction and unstable angina, this unstable period is a hallmark of such systematic atherosclerotic activity. After a period with high activity with rapid progression of CHD and a high rate of cardiac events and coronary interventions, the patient ultimately becomes stable again.

A typical example is male born in 1944 who had a first myocardial infarction in 1980. Thereafter a second infarct occurred in 1982 with subsequent three coronary angioplasty procedures because of recurrent severe angina in '82,'83 and '84, and coronary bypass surgery in '83. After that unstable period however, this patient remained free of anginal pain for years and had no other sequellae of this disease and resumed his job.

Another example is a female born in 1942 who underwent coronary bypass surgery in 1980. Thereafter a period followed with extensive and severe peripheral disease at different locations, requiring several operations between 1981 and 1986. She underwent twice a blockade of the ganglion stellatum in '87 and '90 because of otherwise intolerable angina. Angiography showed

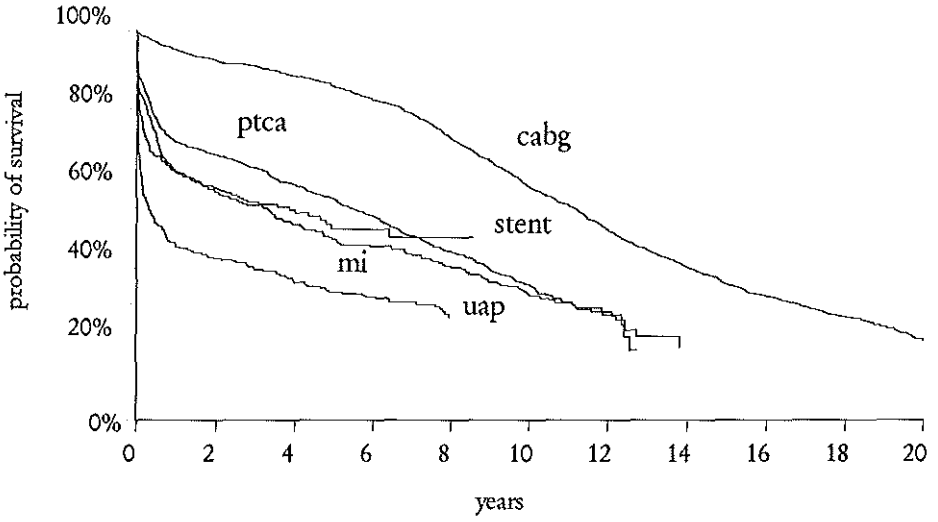

Figure 1. Event-free (freedom from death, (re)MI, CABG or PTCA) survival rates.

a 100% stenosis in the right coronary artery and circumflex, which was judged inoperable. Subsequently, her situation became stable again with little anginal pain since 1991.

These patient histories support the notion of multifocal activity of atherosclerotic disease during some time, resulting in myocardial infarction or unstable angina often followed by coronary intervention. Thereafter however, the disease seems stabilized. This process is shown in Figure 1 which combines the event-free survival (freedom from death, myocardial infarction, CABG or PTCA) of different groups of patients, as described in this thesis. In patients with MI or UAP coronary events were frequent, especially in the first year. After the first year however, the event rate was low. This also shown in Figure 2 where the yearly incidence of mortality and MI of the different groups is presented.

Prognosis of CHD and risk assessment

The concept of risk assessment has become an integral part of clinical assessment and decision-making in patients with CHD. In all studies summarized in Chapter 1 of this thesis this risk appeared related to age, the degree of impairment of left ventricular function and the extend of the coronary disease, measured either by angiography (left ventricular ejection fraction, multivessel disease) or by clinical parameters such as Killip Class, inability to perform an exercise test, heart rate, prior MI and a history of angina pectoris.

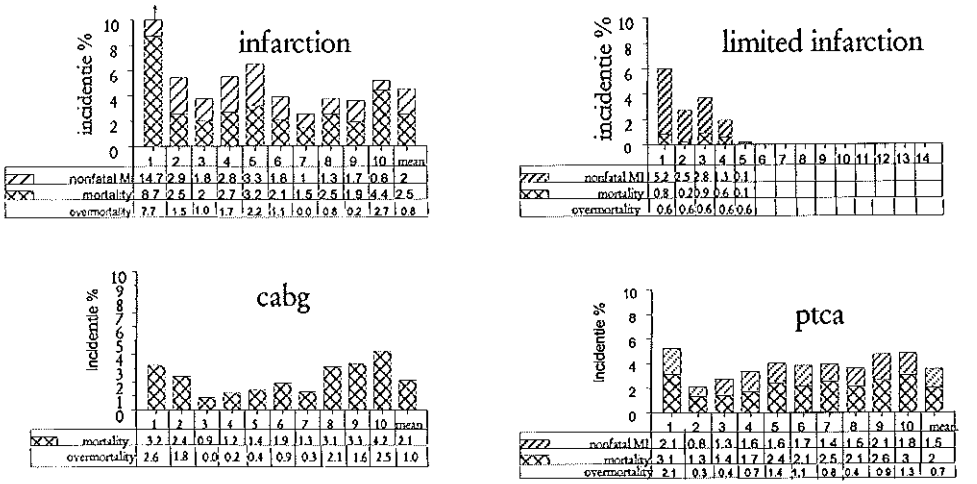

Figure 2. Yearly incidence of mortality and nonfatal myocardial infarction. Overmortality=difference between mortality and mortality in the general populaion.

At certain stages of the development of CHD specific measures may be taken to reduce the risk. For example PTCA or CABG reduce not so much the true extend of coronary disease, but the consequences of extensive disease through removal (PTCA) or bypassing stenosis, while early reperfusion therapy in acute myocardial infarction salvages myocardial function.

Reducing plaque progression

As mentioned previously, progression of plaque may be rapid. This process is explained by de Feyter et al.[4] (Figure 3). The possible relationship between focal and diffuse coronary atherosclerosis and clinical coronary events is illustrated here. Reduction of this progression or even regression may be achieved with statins. The 4S and the CARE trials[5,6] have consistently shown the benificial effect of predominantly LDL-cholesterol lowering in patients with established CHD with average or moderately elevated cholesterol levels. When prevention with lipid-lowering drugs is being considered, these findings indicate that treatment with a statin should be considered in all patients with established coronary artery disease. Perhaps that in low-risk (young) patients with limited disease and none or only one risk factor (Chapter 2) this treatment with statins may be omitted. For every individual patient the treating physician should make a rational choice which (combination of) medication should be described, depending on side effects, heart

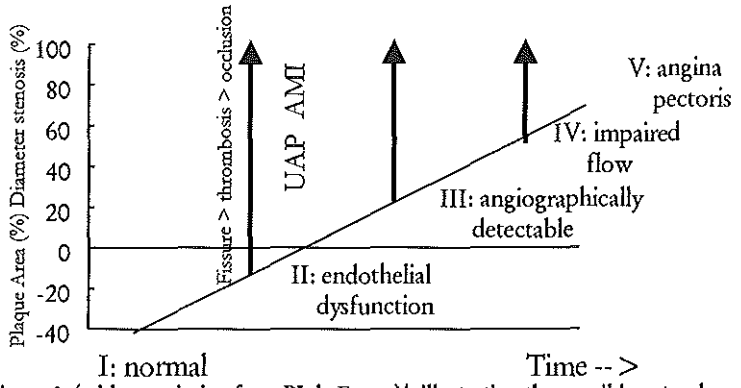

Figure 3. (with permission from PJ de Feyter)[4], illustrating the possible natural course of focal coronary atherosclerosis, plaque progression, plaque fissure, thrombosis and ensuing clinical events. Phase 1: no abnormalities. Phase 2: a focal atherosclerotic lesion is present. Phase 3: the plaque occupies more than 40% of area of the internal elastic lamina. Phase 4: Plaque grow occurs, which may be still clinically silent. Phase 5: plaque growth to an obstruction >50% causes angina pectoris. Plaque rupture may occur.

rate, blood pressure and cholesterol level.

Secondary prevention and reducing plaque rupture

Either secondary prevention of plaque rupture or reduction of thrombosis can be achieved with lipid lowering agents, ACE inhibitors, beta-blockers and ASA or coumadins. The improved long-term outcome through use of beta-blockers has been shown in postMI patients,[7] in patients with stable or unstable angina and hypertension.[8] Therapy with antiplatelets or coumadins may reduce the occurrence of thrombosis when plaque rupture suddenly occurs. Although there are multiple trials examining the use of aspirin for the secondary prevention in CHD, no single study has provided definitive results. A meta-analysis of 18,000 patients revealed that platelet inhibitor therapy reduced cardiovascular mortality by 13% and nonfatal myocardial infarction by 31%.[9] The ASPECT and WARIS trials used coumadins and found a significant reduction in reinfarction in survivors of an infarction. The WARIS trial also found a significant reduction in mortality in patients using oral anticoagulants.[10,11] The CARS trial[12] reported no significant difference in reinfarction, nonfatal ischemic stroke or vascular death between monotherapy with aspirin and a combination of coumadin and aspirin. These findings indicate that aspirin and anticoagulants for secondary prevention in survivors of a myocardial infarction convey protection against death and reinfarction. The advantage of

aspirin over anticoagulant agents is lower cost (Fl 10,- per year for aspirin), ease of administration and less need for monitoring, but is probably somewhat less effective.

Reduction of extend of vessel disease

The extend of coronary vessel disease is expressed as (recurrent) ischemia and diagnosed with coronary angiography. This extent of coronary vessel disease may be relieved by PTCA or CABG. The choice between both procedures is a difficult one. In an editorial, Simoons[10] has summarized the advantages and disadvantages of both procedures. CABG surgery is a large operation with long period of recovery compared to PTCA, which is less invasive, less radical and has fast recovery. However, the reintervention rate after PTCA is much higher than after CABG. In our study (Chapter 8) only 57% respectively 35% of the patients were free from death, MI or reintervention at 5- and 10-years after PTCA. After CABG surgery 85%, respectively 60% were free from death, MI or reintervention at 5 and 10 years. Important to note is that both procedures are not without danger: 1 to 2 patients out of 100 patients die during the procedure, while 5% to 10% had experienced an infarct at the time of the procedure (depending on the definition for infarction used). The long-term outcome is good. Our studies report 5-, 10-, 15- and 20-year survival rates of respectively 92%, 77%, 57% and 40% after CABG and similar 90% and 78% respectively at 5- and 10 year after PTCA. The 5-year outcome of mortality of the randomized BARI trial[14] who compared CABG and PTCA, reported a non-significant difference in survival (7.0% versus 7.8%). In 1986 stent implantation was introduced as an addition to PTCA and since 1994 the BENESTENT and STRESS trials showed an improved benefit of stent implantation, stents are now widely used, although long-term outcome is still unknown.[15,16] In Chapter 9 we reported the largest and the longest follow-up study up to now of the first 1000 stent implantations in our center. Mean follow-up was 2.5 years (range 1-11 years). Overall survival rate was good: at 1, 3 5- and 7 years 95%, 91%, 86% and 81% respectively. The choice between CABG or PTCA with or without stenting however is still difficult and often subjective.

Management of acute myocardial infarction

Immediate benefit with thrombolytic therapy is achieved in certain subgroups of patients with evolving MI. Chapter 5 describes the 10 to 14 year outcome after thrombolytic therapy. In this randomized trial the benefit of thrombolytic therapy, compared to conventional therapy, was 10% at one year and was sustained during

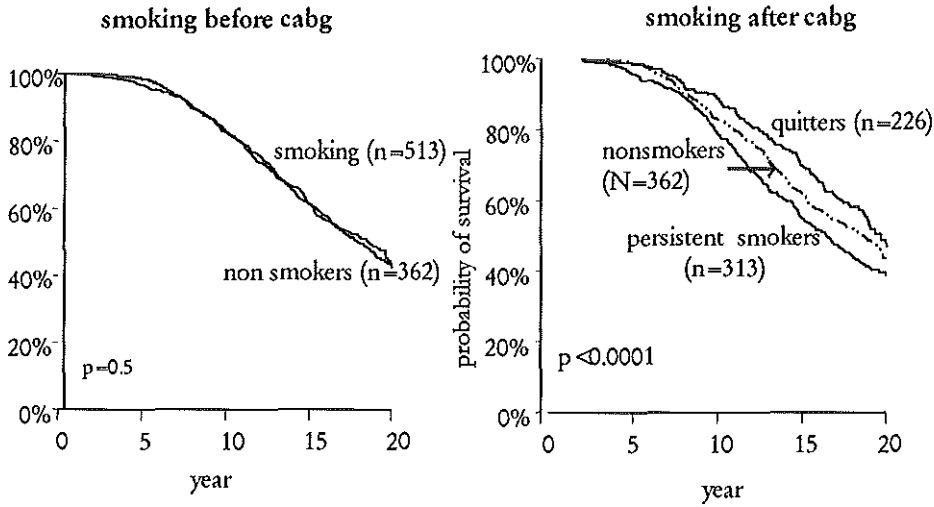

Figure 4. Smoking before and after coronary artery bypass graft surgery.

the first decade. Thrombolytic therapy is now probably performed in 30%-50% of the patients with an acute MI and is indicated in particular for the larger early infarcts (elevated ST segment at admissions) to salvage myocardial function.

Improvement of left ventricular function

Various studies, such as AIRE, SAVE, SOLVD and CATS[17-20] have shown that ACE inhibitors may improve left ventricular function in postMI patients by prevention of 'remodeling" of the heart. In the AIRE study a reduction in mortality was achieved of 27%; approximately 40 lives might be expected to be saved for every 1000 patients treated for one year. Benefit was apparent within weeks of starting treatment. This benefit was similar in the other studies, which included high risk patients.

Modification of risk factors

Apart from the mentioned medical and interventional management, several other risk factors of progression of the disease in CHD patients, that can be influenced, have been identified. Among these, tobacco smoking, diabetes, hypertension, obesity, a sedentary lifestyle and a diet rich of calories and unsaturated fat are most prominant.[18] Reduction of all these factors is desirable and life style changes should always be advised.

The most important modifiable risk factor for cardiac death is smoking and this risk can be reduced 'easily' by smoking cessation. Paradoxically, all studies in this thesis, as well as in another study[22] have found no increased risk or even a beneficial effect of smoking. A typical example is shown in Figure 4 where patients from our study, after coronary bypass surgery, were divided in current smokers (just before CABG) and nonsmokers with similar survival rates up to 20 years after CABG. Important to note is that smokers were younger with lesser underlying atherosclerosis at the time of the acute event than nonsmokers. However *smoking cessation* after coronary bypass surgery is associated with a twofold decrease in the relative risk of death as is clearly seen in Figure 5. Other studies reported similar results after myocardial infarction and coronary angioplasty.[23,24]

CONCLUSION

It is remarkable that patients with MI or UAP often suffer a period with high atherosclerotic activity and rapid progression of coronary artery disease. After such period of high risk which may vary from a few months to one year, most patients become stable again with a low rate of recurrent episodes of unstable angina or reinfarctions. Thus, we conclude that there is a need for early and close supervision of patients after myocardial infarction or unstable angina, especially in the first year. Clinicians should focus more closely on the possibility to perform early intervention after myocardial infarction or unstable angina. In particular, after a recurrent infarct we have shown that patients are at high risk for mortality, a more aggressive therapeutic intervention, such as PTCA or CABG, might reduce subsequent mortality and coronary events. It is recommended that a prospective trial should be initiated to verify this hypothesis.

In patients who had bypass surgery, reintervention rate was rare up to 7-8 years. Thereafter both mortality and the need for repeat revascularization increased. After PTCA however, the need for early repeat revascularization was much higher (restenosis) and only 35% of the patients were free from an cardiac event at 10-years follow-up.

As in previous studies, our studies confirmed that impaired left ventricular function and the extend of coronary disease, together with age, are the most important risk factors of mortality and coronary heart disease. To further improve outcome of patients with different manifestations of CAD, a combined approach is warranted with PTCA or CABG to reduce the extend of coronary disease, in

selected patients. In addition, adequate pharmacologic management with antiplatelets, ace inhibitors, beta-blockers and statins, in most patients and particularly modification of "classifical" risk factors for progression of CAD such as smoking, diabetes, hypertension, obesity, a sedentary lifestyle and adverse dietary habits, where appropriate.

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SAMENVATTING

Dit proefschrift beschrijft de lange-termijn uitkomsten van verschillende groepen hartpatiënten. Dit betreft in het bijzonder patiënten die opgenomen zijn geweest wegens een myocard infarct (MI) of wegens onstabiele angina pectoris (OAP) en patiënten die een coronaire bypass operatie (CABG) of een Dotter procedure (PTCA) hebben ondergaan. Voor al deze groepen patiënten is nagegaan welke factoren van invloed zijn op een verhoogd sterfte risico en het (opnieuw) optreden van cardiale gebeurtenissen zoal sterfte, MI, CABG of PTCA.

In hoofdstuk 1 wordt een literatuur overzicht gegeven van andere studies die gedurende langere tijd patiënten, zoals zojuist beschreven, hebben vervolgd. Er is onderscheid gemaakt in de volgende 6 groepen: (1) patiënten die tijdens een zich ontwikkeld hartinfarct werden behandeld met het stolsel-oplossende medicament trombolyse, (2) patiënten die een infarct hebben overleefd, (3) patiënten die werden opgenomen wegens onstabiele angina pectoris, (4) patiënten die een coronaire bypass operatie hebben ondergaan, (5) patiënten die een Dotter procedure ondergingen en (6) patiënten waarbij naast een Dotter procedure ook één of meerdere stents werden ingebracht in het zieke vat. De diverse karakteristieken van deze studies worden beschreven. Tot slot worden de sterfte percentages en, indien bekend, de kans op een nieuw hartinfarct, CABG of PTCA gedurende verschillende follow-up jaren gepresenteerd.

De hoofdstukken 2, 3 en 4 zijn gebaseerd op de gegevens van de ASPECT studie. Dit was een studie van 1986-1991, waarbij 3404 patiënten met een (veelal) beperkt hartinfarct, na ontslag uit het ziekenhuis werden gerandomiseerd naar antistolling of placebo (een nepmiddel). Hoofdstuk 2 beschrijft een risico stratificatie van sterfte. Het bleek mogelijk te zijn om een subgroep van 40% te selecteren met hooguit één risicofactor, die een uitstekende prognose had met betrekking op overleving. Dit risico was zelfs identiek met een vergelijkbare, niet-zieke, groep personen uit de Nederlandse bevolking.

De 'Cardiac Infarction Injury Score' (CIIS) is een eenvoudige methode om uit het ECG (hartfilmpje) een score te bepalen, die een maat is voor de grootte van het hartinfarct (hoofdstuk 3). Deze CIIS is gemeten bij patiënten met een hartinfarct vlak voor ontslag uit het ziekenhuis. Het blijkt dat een hoge score is gerelateerd aan een hogere kans op sterfte op de lange-termijn (binnen 5-jaar). Ook na correctie van andere risicofactoren bleek deze relatie stand te houden.

Hoewel het logisch lijkt dat het optreden van een tweede, niet-fataal, hartinfarct de kans op latere sterfte hoger lijkt te maken, is dit wetenschappelijk nog nog maar weinig aangetoond. Hoofdstuk 4 beschrijft patiënten die een tweede hartinfarct hebben overleefd. Onze studie bevestigt onze vermoedens dat een niet-

fataal tweede hartinfarct een sterk verhoogd risico met zich meebrengt op latere sterfte. Dit betekent dat preventie van een nieuw hartinfarct door middel van therapeutische behandeling, deze sterfte zou kunnen verminderen. In het bijzonder, zou bij alle patiënten met een tweede hartinfarct een Dotter procedure of een bypass operatie zeer sterk moeten worden overwogen om hiermee latere sterfte te kunnen reduceren. Een prospectieve studie zou kunnen bevestigen of deze hypothese klopt.

Behandeling met een stolsel-oplossend geneesmiddel (trombolyse) bij patiënten tijdens een zich ontwikkelend hartinfarct, blijkt, vergeleken met patiënten die conventioneel werden behandeld, een 10% sterfte reductie op te leveren. In hoofdstuk 5 blijkt dat dit gunstige effect zelfs na 12 tot 14 jaar nog herkenbaar is.

In hoofdstuk 6 wordt de 7-jaars follow-up van 417 patiënten beschreven die in de periode 1988-1989 werden opgenomen vanwege onstabiele angina pectoris. Deze studie toont, voor het eerst, aan dat er vooral in het eerste jaar de ziekte nogal gecompliceerd verloopt met een snelle progressie, resulterend in een relatief grote kans op hartinfarct, Dotter procedure of bypass operatie. Na het eerste jaar wordt de situatie stabiel, mede dankzij een optimale behandeling met o.a. anti-angineuze medicatie, met als gevolg een goede prognose op de lange-termijn (tot 7-jaar).

Hoofdstuk 7 beschrijft 1041 patiënten die in de periode 1970-1980 een coronaire bypass operatie hebben ondergaan. Bij alle patiënten werd een ader uit het onderbeen als omleiding gebruikt. De uitkomsten na een zeer lange-termijn (17-27 jaar) worden hier beschreven. Het blijkt dat deze operatietechniek veilig is met een uitstekende prognose met vooral in de eerste 7-8 jaar weinig sterfte, hartinfarct of noodzaak tot een nieuwe operatie of Dotter procedure. Nadien neemt de incidentie van deze cardiale gebeurtenissen toe, wat niet weg neemt dat na 10-, respectievelijk 20-jaar follow-up, 77%, respectievelijk 40% van alle patiënten nog steeds in leven is.

De 10-jaars follow-up van patiënten die een Dotter procedure ondergingen in de periode 1980-1985, wordt beschreven in hoofdstuk 8. Het blijkt dat de lange-termijn prognose van deze patiënten goed te noemen is, vooral in jonge (<60 jaar) mannen met een één-vatslijden en een normale hartfunctie. De 5-, respectievelijk 10-jaars overlevings percentages zijn 90%, respectievelijk 78%. Tweederde van alle Dotter patiënten blijkt echter na 10-jaar een cardiale gebeurtenis (hartinfarct, bypass operatie of Dotter procedure) te hebben doorgemaakt.

In hoofdstuk 9 wordt de lange-termijn uitkomsten van de eerste 1000 patiënten beschreven, waarbij naast een Dotter procedure ook een stent werd ingebracht. Gemiddeld werden deze patiënten 29 maanden vervolgd (12-132

maanden). De lange-termijn prognose op overleving is goed, vooral in niet-diabetische mannen met een één-vatslijden en een normale hartfunctie, en waarbij slechts één stent werd ingebracht in een kransslagader. Het 5-jaars overlevings percentage was 86%. Vooral de overgang van uitgebreide antistolling naar behandeling met ticlopidine en een verbeterde implantie techniek in 1995 zorgde voor een belangrijke vermindering van ziekenhuis complicaties (bloedingen, hartinfarct, bypass operatie, of hernieuwde Dotter procedure).

Hoofdstuk 10 beschrijft patiënten, waarbij van 1986 tot 1994 een stent werd ingebracht in een omleidings vat van een eerdere bypass operatie. De prognose, vlak na implantatie, is acceptabel in deze zieke groep patiënten, maar de lange-termijn uitkomsten zijn matig. Na 5-jaar was nog maar slechts 30% vrij van sterfte, hartinfarct, bypass operatie of een nieuwe Dotter procedure.

Tot slot worden in hoofdstuk 11 de verschillende series patiënten samengevat en wordt gezocht naar de overeenkomsten en verschillen van de boven genoemde groepen patiënten. Alle risicofactoren voor een verhoogde kans op sterfte worden nog eens samengevat en er wordt geprobeerd om tot een advies te komen hoe om te gaan met deze risicofactoren om zo een nieuw cardiale gebeurtenis te voorkomen bij patiënten, waarbij reeds een hartziekte is geconstateerd.

NAWOORD

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CURRICULUM VITAE

Ron van Domburg werd geboren op 25 maart 1951 te Bergen op Zoom.

In 1979 is hij getrouwd met Ellen Griffioen. Samen hebben zij twee kinderen: Marlous (1981) en Vincent (1984). Hij woont in Nieuwerkerk aan den IJssel.

In 1969 behaalde hij het HBS-B diploma aan het Stevin Lyceum te 's Gravenhage.

Hij was student assistent aan de Technische Universiteit Delft, afdeling Wiskunde, van 1974 tot 1979. Van 1969 tot 1979 studeerde hij Wiskunde en deze studie werd afgerond bij de afdeling Mathematische Statistiek onder leiding van Prof. dr ir J.W. Sieben.

Sinds 1980 is hij werkzaam als statisticus/epidemioloog en automatiseerder bij het Academisch Ziekenhuis Dijkzigt Rotterdam, op de afdelingen klinische en experimentele informatieverwerking en klinische epidemiologie van het Thoraxcentrum.

Op het gebied van de automatisering heeft hij zich voornamelijk bezig gehouden met het Thoraxcenter Utility System TUS, de patiënten database van het Thoraxcentrum. In dat kader heeft hij een computerprogramma ontwikkeld, dat reeds sinds de beginjaren '80 alle (poli)klinische patiëntenbrieven verzorgt, meestal in combinatie met de opslag van patiëntgegevens ten behoeve van wetenschappelijk onderzoek. Daarnaast heeft hij een poliklinisch Afspraken programma gerealiseerd dat 10 jaar lang tot volle tevredenheid heeft gefunctioneerd. Ook ontwikkelde hij diverse programma's voor de harttransplantatie afdeling (wachtlijst, follow-up).

Daarnaast ondersteunt hij de invoer, onderhoud en statistische analyse van projecten ten behoeve van wetenschappelijk onderzoek. In dit kader ontwikkelde hij onder andere het Clinical Trial (CLINT) database management pakket.

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