Long term outcome after coronary stent implantation: a 10 year single centre experience of 1000 patients

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Abstract

***Objective*—To describe the long term clinical outcome (up to 11 years) after coronary stenting.**

***Design*—A single centre 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*—Up to July 1997 the cumulative incidence of the major adverse cardiac events (MACE) of death, non-fatal acute myocardial infarction, coronary artery bypass grafting, and repeat percutaneous transluminal coronary angioplasty was 8.2%, 12.8%, 13.1%, and 22.4%, respectively. Survival at one, three, and five years was 95%, 91%, and 86%, respectively. Comparison of MACE incidence during the "anticoagulant era" and the "ticlopidine era" revealed significantly improved event free survival with ticlopidine (27% *v* 13%; p < 0.005). Multivariable analyses showed that ejection fraction < 50% (relative risk (RR) 4.1), multivessel disease (RR 3.0), diabetes (RR 2.9), implantation in saphenous vein graft (RR 2.1), indication for unstable angina (RR 1.9), and female sex (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 (versus ticlopidine and aspirin) (RR 1.5), bailout 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 non-diabetic men 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 40% of the patients experienced an adverse cardiac event (mainly repeat intervention) in the long term. New advances in restenosis treatments and in secondary prevention must be directed at this aspect of patient management after stenting.**

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Keywords: stents; percutaneous transluminal coronary angioplasty; follow up; predictors; survival; registry

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The widely heralded results of two simultaneously completed randomised trials,[1 2] showing apparently superior angiographic or clinical outcomes, or both, with stenting in selected patients, in comparison with balloon angioplasty, has led to widespread use of coronary stenting for diverse indications. Although one year and three year follow up studies have suggested sustained benefit of stenting,[3–13] 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 centre between 1986 and 1996. We also investigated the influence of the change from anticoagulation to antiplatelet treatment on long term outcome and predictors of major adverse cardiac events (MACE).

Methods

STUDY PATIENTS

From November 1986 through August 1996, 1000 consecutive patients underwent a first stent implantation. During the follow up period, 46 patients underwent a further separate stent procedure, three patients underwent two additional stent procedures, and one patient underwent four stent procedures. Two or more stents were implanted in 352 patients. Stents were implanted across lesions in saphenous vein grafts in 126 patients. Full systematic anticoagulation treatment was used in 443 patients (from 1986 to July 1995) and antiplatelet treatment 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 ethics committee.

STENT IMPLANTATION PROCEDURE

Angioplasty was performed using mainly 8 French gauge catheters via the femoral route. Heparin 10 000 iu was administered parentally in addition to 250 mg aspirin at the beginning of the procedure; thereafter activated coagulation time was measured hourly and additional

5000 iu heparin given to maintain the activated coagulation time above 300 seconds. All patients were pretreated with aspirin. For planned stent implantation up until the early months of 1995, dextran 500 ml was given intravenously over two hours, beginning before the procedure; for unplanned implantations dextran administration was initiated during the procedure. Also, during that period, intravenous heparin infusion was continued after the procedure until coumadin, administered following the procedure, reached therapeutic concentrations. Coumadin was then continued for three months. From 1995 onward, the use of periprocedural dextran and postprocedural heparin and coumadin was discontinued, and ticlopidine 500 mg per day was started immediately after the procedure or, in the case of elective implantations, during the 24 hours before the procedure where possible and continued for four weeks (2 × 250 mg per day). Intracoronary glyceryl trinitrate was generally used before all contrast injections intended for online or offline quantitative coronary angiography (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 because of microembolisation. The use of abciximab before or during coronary angioplasty in selected patients with unstable angina or high risk candidates was started in mid-1995 and was used according to existing protocols.

In general, monorail dilatation balloon catheters were used for balloon angioplasty, thus guidewires of 175 cm 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 175 cm wire was replaced by a 300 cm or longer wire. The vast majority of stents used during the described study period were hand crimped on the monorail balloon 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 online quantitative angiography using the coronary angiography analysis system), to facilitate stent placement and avoid the risk of unnecessary dissection. In the case of unplanned or emergency stenting, after failed balloon angioplasty, the most technically suitable stent available that could resolve 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 unfavourable morphological circumstances were taken into consideration, as well as the known technical characteristics of the available stents, in the usual way. Before the emergence of the importance of truly "optimal" stent deployment, using a 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, based on online 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 online QCA analysis, with a minimum of two views.

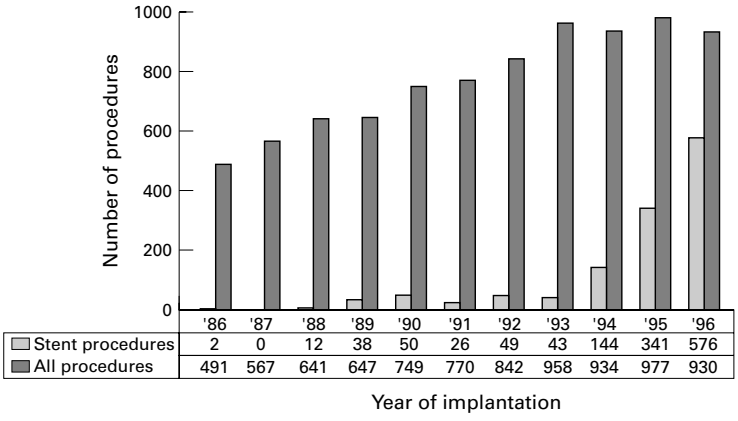

Figure 1 Yearly incidence of stent implantations compared to all angioplasty procedures.

Reference to the "anticoagulant era " and "ticlopidine era" is a means of identifying the change in adjunctive pharmacotherapy as well as the virtually simultaneous application of the concept of optimal stent placement. The identifiable difference could perhaps equally be described in terms of "early stenting practice" and "modern stenting practice".

DATA COLLECTION AND FOLLOW UP

All patients were followed for at least one year post stenting with a median follow up of 29 months. Clinical follow up data were obtained by a combination of review of hospital records for patients who continue to be followed at this institution, and by enquiry to referring cardiologists within the referral area and questionnaires sent to general practitioners. Attention was focused on the occurrence of the hard MACE of death, myocardial infarction, coronary artery bypass surgery (CABG), and repeat percutaneous transluminal coronary angioplasty (PTCA).[14] The diagnosis of myocardial infarction was based upon: an episode of prolonged typical ischaemic pain > 30 minutes unrelieved by vasodilation treatment; a typical serum enzyme pattern; and the development of new pathological Q waves in two or more contiguous ECG leads. All revascularisations were categorised according to whether they involved the target lesion, target vessel, or non-target vessel. Complete clinical follow up was obtained in 990 (99%) 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 1–52 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; sex; diabetes; hypertension; cholesterol; smoking; prior myocardial infarction; prior CABG; prior PTCA; extent of coronary disease; left ventricular function; elective or bailout implantation; indication for unstable angina; post treatment with

Table 1 Baseline clinical characteristics of patients

	n (%)
Number of patients	1000
Vessels treated	1063
Age (range) (years)	59 (28-86)
Male	732 (73)
Diabetes	97 (10)
Hypertension	266 (27)
Smoking	256 (26)
Hypercholesterolaemia	281 (28)
History of MI	391 (39)
History of CABG	160 (16)
History of PTCA	247 (25)
Indication	
Stable angina	500 (50)
Unstable angina	389 (39)
Acute MI	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)
Bailout	375 (37)
Angiographic success	948 (95)
Clinical success*	858 (86)

*Freedom from death, myocardial infarction, CABG or repeat PTCA.
CCS, Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MI, myocardial infarction; RCA, right coronary artery.

anticoagulation or antiplatelet drugs; multivessel stenting; type of stent; use of multiple stents; total length of stent(s) implanted; stent size < 3 mm; stenting in native coronary vessel or saphenous vein graft vessel and at the native coronary target vessel (left anterior descending coronary artery versus right coronary artery versus left circumflex coronary artery).

STATISTICAL ANALYSIS

Survival and event free survival were estimated by Kaplan-Meier curves. Among patient subgroups—for example, native versus bypass, anticoagulation versus ticlopidine—the log rank test was used to compare survival curves. Data are expressed as mean (SD). Continuous variables were compared by Student's *t* test, and 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 comprised 1000 patients with a first stent implantation, who underwent placement of 1560 stents (mean 1.6 stents per patient) in 1063 vessels. Multivessel stenting was performed in 60 patients (6%). Median follow up was 29 months with a range of 12–132 months. The target vessels were the left anterior descending coronary artery (44%), left circumflex coronary artery (16%), right coronary artery (28%), left main coronary artery (< 1% (seven patients)), and saphenous vein grafts (11%). Evolution of stent implantation practice over the years is shown in fig 1.

Baseline characteristics are shown in tables 1 and 2. Mean age was 59 years (range 28–86 years) and 73% of the patients were male. The indication for PTCA was unstable angina in 41% and acute myocardial infarction in 6%. Diabetes mellitus was present in 97 patients (10%). Three hundred and ninety one patients (39%) had a prior myocardial infarction. Previous CABG had been performed in 160 patients (16%) and prior PTCA in 247 patients (25%). Most patients (54%) had one vessel disease. Bailout 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 predominantly performed using the Wallstent (82%). The mean length of implanted stents was 32.7 (19) mm and the maximal balloon diameter used after stenting was 3.6 (0.8) mm.

Table 3 outlines the clinical outcomes in-hospital and long term. Fifteen patients died during the periprocedural in-hospital period (three patients indicated for acute myocardial

Table 2 Stent characteristics

Stent length (mm) (mean (SD))			32.7 (19)			
Balloon size (mm) (mean (SD))			3.6 (0.8)			
Number of implanted stents (mean (SD))			1.6 (0.9)			
Multivessel stenting (n)			58 (5.8%)			
Target vessel	*LAD*	*LCX*	*RCA*	*Left main*	*SVG*	*Total*
Type of stent (n (%))						
Palmaz-Schatz*	288 (41)	76 (32)	107 (24)	2 (33)	20 (12)	493 (32)
Wall stent†	82 (12)	28 (12)	129 (29)	0 (0)	139 (82)	378 (24)
NIR‡	160 (23)	51 (22)	69 (15)	2 (33)	6(4)	288 (18)
AVE§	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)

*Cordis, Johnson & Johnson Interventional Systems; †Schneider Europe; ‡Medinol Boston Scientific Corp; §Arterial Vascular Engineering.
¶Other stent types used were ACS Multilink Guidant (n = 63), Bestent Medtronic (n = 58), Gianturco-Roubin Cook (n = 63), Cordis (n = 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).
LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SVG, saphenous bypass graft.

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	49	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 acute myocardial infarction, bypass surgery, repeat intervention).

infarction, seven patients for unstable angina, and five patients for stable angina), yielding a mortality of 1.5%. Forty nine patients (4.9%) underwent a CABG during the same hospitalisation, of which 21 were truly emergent (directly from the catheterisation laboratory). From 1994 to 1996 this incidence fluctuated around 1.3% per year (fig 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 infarcts 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). Major bleeding complications occurred in 36 patients necessitating blood transfusion (3.6%) or vascular surgery (2.7%). The median hospital stay for the whole study population was four 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.

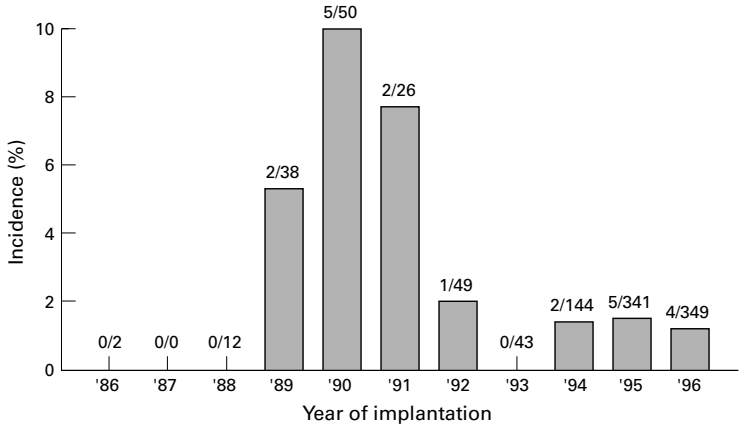

Figure 2 Yearly incidence of true emergency CABG after stent procedure.

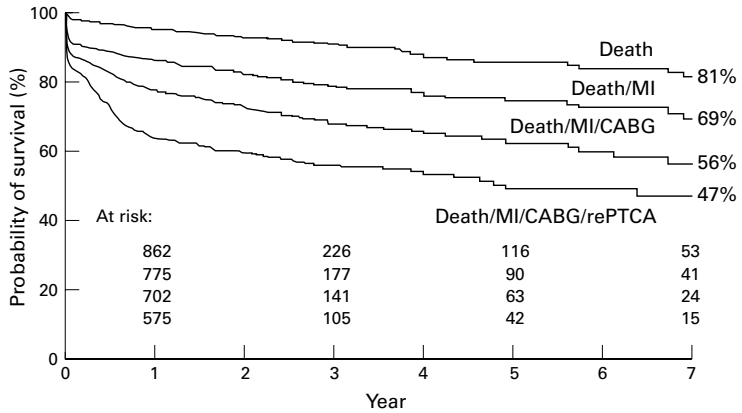

Figure 3 Kaplan-Meier survival curves for death, death or myocardial infarction (MI), death or MI or CABG, and freedom from any MACE event.

During the 11 year late follow up a total of 67 patients (6.7%) died, 60 patients (6%) had a myocardial infarction, 82 patients (8%) underwent CABG, and a repeat angioplasty procedure was performed in 171 patients (17%). Of the 50 patients (5%) who underwent a repeat stent implantation, in 30 they 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 these patients (76%), and this was decreased to 251 patients (40%) at follow up; 250 patients (40%) had no significant coronary lesions at follow up. An increase in vessel disease was reported in 12% of patients at follow up. Of the total of 303 patients who underwent any repeat revascularisation after the index procedure, a target lesion revascularisation was performed in 198 patients (65%) and a target vessel revascularisation was performed in a further 96 patients (32%). Eighty five patients (28%) underwent revascularisation in a new vessel.

Survival and event free survival (freedom from death, myocardial infarction, and revascularisation) curves are shown in fig 3. By Kaplan-Meier estimates, at six months, one year, three years, and five years the cumulative survival rates were 97%, 95%, 91%, and 86%, respectively, and the associated event free survival rates were 72%, 63%, 55%, and 48%, respectively.

Multivariable analysis could be performed in 876 patients with complete data. Independent predictors of mortality (table 4) were ejection fraction < 50% (relative risk (RR) 4.1), diabetes (RR 2.9), multivessel disease (RR 3.0), unstable angina (RR 1.9), saphenous vein graft implantation (RR 2.1), and female sex (RR 1.73). Ejection fraction (RR 2.3), multivessel disease (RR 1.5), use of anticoagulants (versus ticlopidine and aspirin) (RR 2.0), unstable angina (RR 1.4), and diabetes (RR 1.6) 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 (versus ticlopidine and aspirin) (RR 1.5), bailout stenting (RR 1.5), multivessel disease (RR 1.4), and multiple stent implantation (RR 1.4). Predictors of early occurrence of a major cardiac event were use of anticoagulants (RR 3.1), bailout stenting (RR 2.5), use of the largest balloon diameter < 3 mm (RR 2.5), and multiple stent implantation (RR 1.5). Use of anticoagulants (RR 1.4), diabetes (RR 2.0), multivessel disease (RR 1.5), bypass graft stenting (RR 1.5), use of multiple stents (RR 1.9), and prior intervention (RR 1.5) 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 versus

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

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

MACE, mortality, myocardial infarction, CABG, and PTCA; RR, relative risk; CI, confidence interval.

saphenous vein grafting (96% *v* 92% at one year (p = 0.3) and 92% *v* 67% at five years (p < 0.0001)). Event free survival was 69% *v* 49% at one year (p < 0.001) and 57% *v* 25% at five years (p < 0.0001)).

Detailed data on symptomatic status and the use of medication as of July 1997 were available in 679 (68%) patients. Sixty seven per cent were in Canadian Cardiovascular Society (CCS) class 0 or I, 16% were in class II, 13% were in class III, and 4% were in class IV. Seventy one per cent of the patients were taking aspirin, 49% were using β blockers, 31% were taking calcium antagonists, and 19% were using nitrates. Anticoagulant treatment was being used in 9% of the patients, 18% were taking angiotensin converting enzyme inhibitors, and one third of the patients were using cholesterol lowering agents.

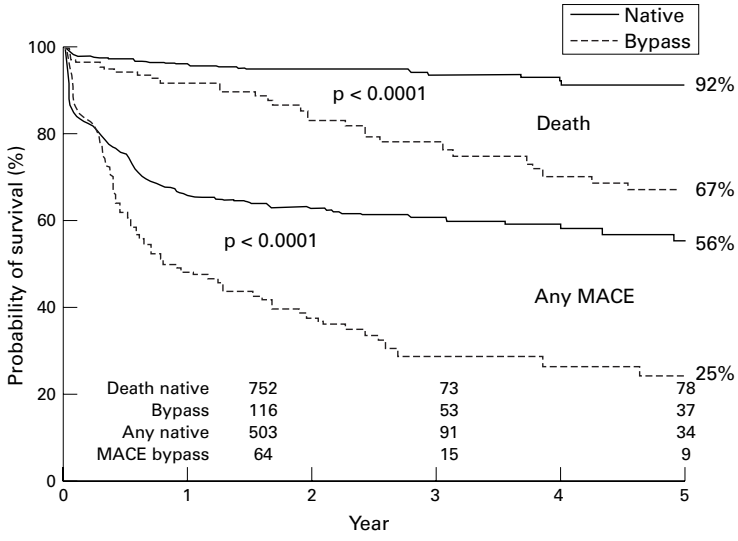

Figure 4 Kaplan-Meier survival curves and event free survival curves (without death, MI, CABG or repeat PTCA) in 880 native coronary grafts and in 120 saphenous bypass grafts.

ANTICOAGULANT COMPARED WITH ANTIPLATELET TREATMENT

Up to July 1995, 443 patients had been treated with conventional anticoagulation; between then and August 1996, 553 patients received ticlopidine and aspirin. Ticlopidine was withdrawn because of severe leucopenia in 0.2% of patients. 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% *v* 9%, p = 0.02), more had prior myocardial infarction (44% *v* 37%), and more were taking antianginal medications (β blockers 58% *v* 39%, nitrates 21% *v* 16%, calcium antagonists 33% *v* 28%). On the other hand fewer patients in the ticlopidine group were smoking (22% *v* 30%), and fewer ticlopidine patients had prior revascularisation (33% *v* 56%). Median hospital stay was seven days (anticoagulants) versus three days (ticlopidine). In the ticlopidine group more stents were implanted per procedure (1.6 *v* 1.4), fewer saphenous vein grafts were stented (6% *v* 19%), and stent procedures were more frequently elective (75% *v* 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 (9%) *v* 15 (3%) patients, p < 0.0001). Emergency coronary bypass was less frequent in the ticlopidine group (1.3% *v* 5.5%, p < 0.001) and early repeat angioplasty was also lower in the ticlopidine group (4% *v* 8%, p < 0.01). Bleeding and vascular

*Table 5 Relation of poststent antithrombotic treatment with occurrence of MACE in-hospital and over the long term**

	In-hospital			*Long term*		
	Anticoagulation	*Antiplatelets†*	*p Value‡*	*Anticoagulation*	*Antiplatelets†*	*p Value‡*
Number of patients	443	553		443	553	
Death	6 (1.4)	7 (1.3)		21 (5.1)	23 (4.1)	
Acute MI	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			

Values are n (%).
*Follow up in both groups truncated on two years; †Antiplatelets were ticlopidine, aspirin, or both; ‡Anticoagulation versus antiplatelets.

complications necessitating blood transfusion or vascular surgery were lower in the ticlopidine group (1.7% *v* 6.2% ($p < 0.001$) and 0.6% *v* 5.7% ($p < 0.0001$), respectively). Mortality after hospitalisation was similar; however, more myocardial infarctions occurred during late follow up in the anticoagulation group (9% *v* 3%, $p = 0.0001$). Also the rate of late CABG was lower in the ticlopidine group (6% *v* 9%, $p = 0.1$), as was the rate for repeat PTCA (14% *v* 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 versus ticlopidine and aspirin.

Discussion

We have described the long term clinical outcome of a heterogeneous patient population undergoing stent implantation in an everyday evolving practice at our centre and according to the prevailing clinical practice between 1986 and 1996. This study cannot be compared to clinical trials, which include only selected patients and only contemporary techniques. The major chronological milestones in evolving stent practice during this decade of coronary stenting were: use of post dilatation to improve acute results of Wallstent implantation (1987); introduction of balloon expandable Palmaz-Schatz stents (1991); appearance of loose crimpable Palmaz-Schatz stents; gradual replacement of anticoagulation by ticlopidine and use of high pressure post dilatation with "oversized" balloons (1994); and appearance of multiplicity of stent designs (1995). The principal observation which can be made on the basis of our findings is that five 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 and stent optimisation 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, because of the simultaneous evolution in stent implant techniques with use of oversized balloons to high pressure (> 14 atm), this apparent benefit of ticlopidine treatment cannot be simply attributed to ticlopidine itself. The decrease in

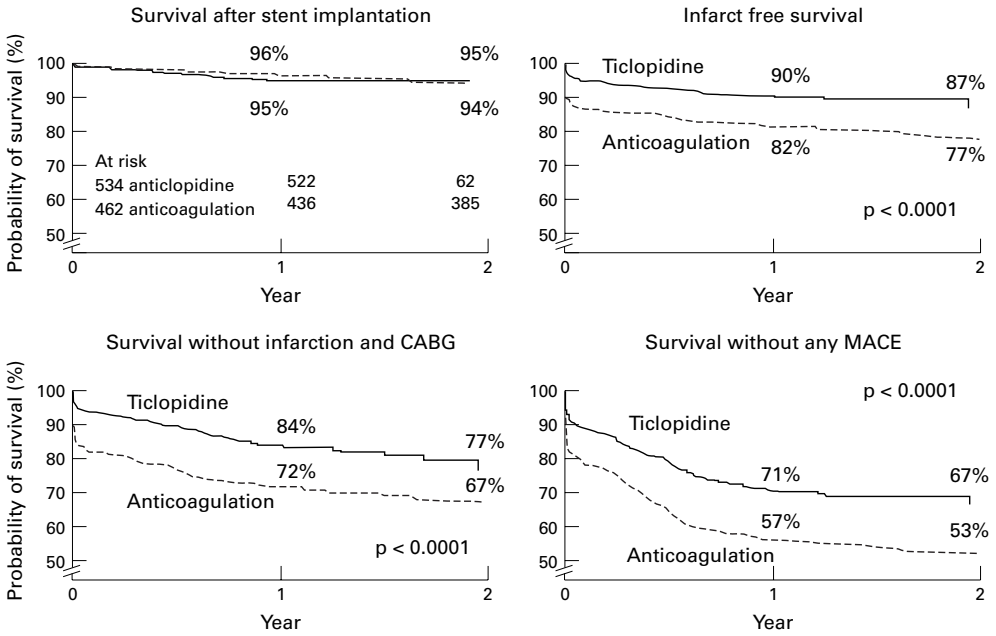

Figure 5 Kaplan-Meier survival curves for death, MI, death or MI or CABG, and freedom from any MACE events in 436 patients treated with anticoagulation and in 522 patients treated with ticlopidine.

bleeding complications can, however, be attributed to the cessation of systematic anticoagulation.

PREDICTORS OF OUTCOME

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

It is noteworthy from the Kaplan-Meier survival curves (fig 3) that the reintervention rate in the second part of the first year after stent implantation was still increasing. This finding is relevant for clinical trials which reported events at six months, and indicates that an extended follow up of nine months or one year, as is becoming standard practice, would be a more honest appraisal of the intermediate incidence of cardiac events related to restenosis.

Although stent implantation has been shown to be as safe and effective in diabetic patients as in non-diabetics in the short term,[15] our data show diabetes to be an independent predictor of reduced long term survival and event free survival, in agreement with a recent three year clinical follow up study of Palmaz-Schatz stent implantation.[6] These findings raise similar issues to the recent revelations from the bypass angioplasty revascularisation investigation (BARI) trial[16] and other studies[17] of diabetics with multivessel disease treated by balloon angioplasty, although poorer outcome in diabetics in this study and indeed in general may be more related to non-target lesion events in the longer term because of progression of disease.

The traditional risk factors, multivessel disease and impaired left ventricular function (ejection fraction < 50%), in agreement with the findings from most other previous stent and angioplasty studies, are associated with significantly reduced long term survival and survival without cardiac events. However, advanced age was not found to be associated with adverse outcome; this indicates that older patients, who are considered to be generally at increased risk for angioplasty[18] and bypass surgery complications,[19] may be effectively treated by 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, as we have previously reported,[20] although some investigators have described results similar to ours as acceptable.[21] Although stenting has been shown to provide superior short term clinical results compared with balloon angioplasty,[22] this patient group continues to present a major therapeutic challenge, apparently because of 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 findings from other studies[23 24] generally reporting an increased risk of angiographic restenosis or clinical events, or both, after six months' follow up, associated with multiple stent placement. However, one single centre study has recently reported no increase in late clinical events of contiguous placement of three or more stents compared with placement of one or two stents.[25]

Improved late outcome in the "ticlopidine era" (even after the six months "restenosis window") compared to the anticoagulation era has not been previously reported. Although the short term advantage of antiplatelet over anticoagulant treatment has been well documented (with[26] or without[27] intravascular ultrasound guidance), especially in high risk patients,[28] no influence on six month angiographic restenosis or target lesion reintervention could be detected in the intracoronary stenting and antithrombotic regimen (ISAR) randomised trial.[29] Accordingly, evolving stent implantation techniques during the study period described here cannot be separated from the changeover to ticlopidine and are likely to be at least partly responsible for the observed long term clinical benefit superficially attributable to treatment with ticlopidine.

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 the first 11 years of stent implantation, with many stent types used 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.

CONCLUSIONS

Long term infarct free survival in our first 1000 patients who underwent stent implantation according to the "best clinical practice of the day" was eminently acceptable. Non-diabetic 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 replacement of anticoagulation by ticlopidine and the adoption of more aggressive stent placement strategies. Certain clinical predictors of increased acute and late risk of adverse events were identified, namely diabetes, multivessel disease, saphenous vein graft stenting, and use of multiple stents. Recent improvements in the acute safety of interventions and possibly long term clinical outcome thereafter, through periprocedural use of platelet glycoprotein IIb/

IIIa receptor antagonists,[30] potential advances in restenosis treatments (for example, brachytherapy,[31] stent coating and seeding,[32] and gene or DNA based treatments[33]), and secondary prevention measures (such as oral antiplatelet agents[34] and statins[35]) may have beneficial effects, especially in these high risk patients but also on a broad basis.

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