ORIGINAL ARTICLE

Disease progression and adverse events in patients listed for elective percutaneous coronary intervention

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Objective: To record disease progression and the timing of adverse events in patients on a waiting list for elective percutaneous coronary intervention (PCI).

Design: Observational prospective study.

Settings: A UK tertiary cardiothoracic centre, at a time when waiting lists for PCI were up to 18 months.

Patients: 145 patients (116 men, median age 59.5 years) placed on an elective waiting list for PCI between October 1998 and September 1999.

Main outcome measures: Adverse events recorded were death, myocardial infarction, need for urgent hospital admission because of unstable angina, and need for emergency revascularisation while waiting for PCI.

Results: During a median follow up of 10 months (range 1–18 months), nine (6.2%) patients experienced an adverse event. Eight (5.52%) patients were admitted with unstable angina as emergencies. One was admitted with a myocardial infarction. Twenty nine (20.0%) patients had significant disease progression at the time of the repeat angiogram before PCI. In 10 (7%), disease had progressed so that PCI was no longer feasible and patients were referred for coronary artery bypass graft. Sixteen (11%) were removed from the PCI waiting list because of almost complete resolution of their anginal symptoms.

Conclusion: Adverse coronary events and clinically significant disease progression occur commonly in patients waiting for PCI. Despite the presence of severe coronary lesions, myocardial infarction was rare and no patients died while on the waiting list. Resolution of anginal symptoms was also comparatively common. The pathophysiology of disease progression frequently necessitates a change in the treatment of patients waiting for PCI.

The most important indication for elective percutaneous coronary intervention (PCI) is chest pain adversely affecting quality of life despite optimal medical treatment. There is some information on adverse event (AE) rates in patients waiting for elective PCI for up to a mean follow up of 24 months in the pre-secondary prevention/statin era.¹ Some data are also available from trials where patients were randomised to medical treatment or PCI.² However, with advances in PCI techniques more complex lesions and multi-vessel disease patients are being listed for elective PCI. In the past a higher proportion of such patients were treated with coronary artery bypass grafting (CABG) (Regional Audit Data 1997–2003 South West Cardiothoracic Centre, Plymouth, UK, unpublished data). Waiting times are of particular concern in these patients because adverse cardiac events and excess deaths have been reported on waiting lists for revascularisation by CABG.^{3–7}

It is also important when advising patients on the risks and benefits of PCI to know the natural history in the medium term of treating such patients with medical therapy only. The chances of symptoms resolving on medical treatment over the following year, compared with the risks of a delay in PCI resulting in the need for CABG because of disease progression are of key importance.

This study aimed to assess the incidence and time points of adverse events in a representative cohort of patients from a UK elective PCI waiting list where the relative frequency of elective revascularisation by PCI compared with CABG is about 4:1 (Regional Audit Data 1997–2003 South West Cardiothoracic Centre, Plymouth, UK, unpublished data). Because of local factors operating in the south west of England in 1998–2000, the time these patients spent on the

waiting list in the secondary prevention/statin era was longer than has been reported previously in the literature.

METHODS

The study group comprised 145 consecutive patients placed on the combined waiting list for elective PCI at the cardiothoracic centre in Plymouth, UK between 1 October 1998 and 30 September 2000. Patients were studied prospectively.

Demographic details, vessel distributions, severity of disease, and drug therapy at the time of listing for PCI were recorded. All patients were followed up from their initial presentation to the time of their PCI.

AEs recorded were: death, myocardial infarction (MI), the need for urgent or emergency hospital admission because of unstable angina (UA), and the need for ischaemia driven revascularisation because of significant angiographic disease progression related to the target lesion while on the waiting list. The time from the date patients were placed on the waiting list to the time AEs occurred was also recorded.

All statistical analysis was done using MINITAB (USA). Data are expressed as medians (ranges) or percentages, where appropriate. Pearson's correlation and logistic regression were performed. Significance was defined as $p < 0.05$.

RESULTS

The observational cohort was composed of 145 outpatients (116 men, median age 59.5 years (range 31–79 years)). Tables 1 and 2 summarise demographic details and vessel

Abbreviations: AE, adverse event; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; UA, unstable angina

Table 1 Demographic data of the patient cohort

Total number of patients	145
Age (median (range) years)	59.5 (31–79)
Male (%)	79.6
Smoker/former smoker (%)	65.3
History of angina (%)	95.2
History of myocardial infarction (%)	38.7
History of hypertension (%)	25.2
History of diabetes mellitus (%)	9.5
History of peripheral vascular disease (%)	6.1
History of stroke (%)	4.1
Family history of coronary disease (%)	30.6
Past history of PCI (%)	10.2
Past history of CABG (%)	6.1
Exercise tolerance test performed (%)	63.9
Exercise tolerance test positive (%)	46.9
Myocardial perfusion scans performed (%)	8.2
Creatinine (median (range) $\mu\text{mol/l}$)	100 (65–1047)
Cholesterol (median (range) mmol/l)	5 (4–8)
Number of vessels diseased (mean (range))	1.45 (1–3)
Waiting time for PCI (median (range) months)	10 (1–18)

distributions of disease at the time of listing for PCI. Ninety per cent of the study population were treated with aspirin or an alternative antiplatelet agent, 67% received a β blocker, 53% received a calcium channel antagonist, and 69% received a statin. Some 4.6% of the patients were not taking any antianginal drugs, while 68.2% took one to two antianginals and 27.2% took three to four antianginals.

During a median follow up of 10 months (range 1–18 months), nine (6.2%) patients experienced an AE. One patient (0.7%) was admitted with an MI and eight (5.5%) were admitted with UA as emergencies, of which five (3.5%) patients underwent emergency PCI. Six of these patients had progression of the target lesion and the remainder had angiographic evidence of new disease. The events are all summarised in table 3. The median time from referral date to unplanned hospital admission was 11 months (range 3–16).

Of the study population, 29 (20.0%) patients had angiographic progression of coronary disease at the time of their check angiogram before PCI. Of these patients, 14 (9.7% of the total cohort) had progression of their target lesion to the extent of total or subtotal occlusion. Fifteen (51.7%) patients, had disease progression to cause a new significant flow limiting stenosis separate to the target lesion. Of the 29 patients who had disease progression, only eight were admitted with UA/MI while on the waiting list, three had increasing anginal symptoms, one of which had to be transferred to the priority list. Two patients developed a sub-acute occlusion requiring rotablation and 10 were referred for CABG.

In 16 (11.0%) patients, anginal symptoms significantly improved while waiting for PCI. Their names were removed from the PCI waiting list. A further three (2.1%) had developed angiographic regression of their coronary disease at the time of the repeat angiogram and did not require PCI.

There was a positive correlation between the frequency of adverse events and the number of vessels diseased ($r = 0.16$, $p = 0.057$). On stepwise logistical analysis in the whole population, history of a MI ($p = 0.03$) and left ventricular function ($p = 0.003$) were independently associated with an AE ($R^2 = 7.3\%$, $p < 0.05$).

DISCUSSION

As would be anticipated, the data show that waiting for elective PCI is not without risk. However, given the severity of the angiographic disease in the patients studied, the most striking feature is the absence of death and the rarity of MI (0.7%). The most frequent clinical risk was emergency

Table 2 Coronary anatomy (%) of angiographic disease in the study population

Left main stem	0.68
Proximal LAD	19.2
1 Vessel disease—proximal LAD	50.7
2/3 Vessel disease—proximal LAD	20.5
2/3 Vessel disease + proximal LAD	8.9

unplanned admission with a suspected acute coronary syndrome, but none of these admissions progressed to death or Q wave MI.

In contrast with the low risk of progression to a severe clinical event, 20% had significant angiographic disease progression while waiting. This correlates well with previous data.^{8–11} The highest risk group was patients with a previous MI or impaired left ventricular function. Events in these patients accounted for 69% of all events that occurred during the study. Absence of these two features therefore had a high negative predictive value of 80% for the prediction of AEs. The positive predictive value of these features was low at 20%. Both history of MI and left ventricular function were independently associated with AEs, although the R^2 was only 7.3%. Therefore, although clinically significant it will not prove to be useful clinically because it only accounts for 7.3% of the variance in the model. Our data therefore fail to provide a means to identify which patients are likely to go on to experience an AE while waiting for PCI.

Of the patients who had coronary disease progression, very few of them had worsening symptoms or required hospitalisation. Stable symptoms, where commonly associated with “silent” disease progression, even to the extent of total occlusion, making PCI less effective and more challenging.¹² Despite evidence of disease progression there was little change in the severity of target lesions between angiograms. This finding is consistent with previous studies and emphasises the fact that the stenosis in the intended target lesion is not necessarily the lesion most at risk for progression.¹³

In total, 16 patients (11%) had improvement of their symptoms while on the waiting list and were thus removed, and three patients had angiographic evidence of disease regression at repeat angiography on admission. This comparatively frequent improvement in patients clinical status shows that patients who go onto PCI waiting lists should be reassessed before admission and informed at the time they are placed on the waiting list that there is a chance their symptoms may resolve and that elective PCI may cease to be indicated.

Hospitalisation while on the waiting list occurred during a period of 92 to 488 days. Although this may show that waiting lists of less than three months may be associated with low rates of progression to emergency hospital admission, it is not possible to comment on a “safety period” for being on the waiting list, as silent progression of coronary lesions to untreatable occlusions may have occurred early without being indicated by clinical signs. Patient 9 in table 3 was admitted to hospital as an emergency after being on the waiting list for 339 days. The repeat angiogram showed progression of the initial RCA target lesion to total occlusion, not amenable to angioplasty. However, there was new significant disease in the left anterior descending artery (LAD) and had this patient received angioplasty after waiting a short period of time on the waiting list, it is quite possible that they still would have been admitted as an emergency because of the progression of separate disease in the LAD.

Opinion in the USA has suggested that patients should not wait any longer than one to two weeks after a cardiac event

Table 3 Major adverse events while on waiting list

Patient number	Age	Sex	Diabetic	Previous MI	LV Fx	Clinical end point	Procedure	Time on waiting list to clinical event (days)
1	74	M	No	Yes, CABG	Mild impairment	MI on waiting list	PCI to Cx and RCA	396
2	58	F	No	No	Good	UA on waiting list	PCI to Cx and RCA	92
3	59	F	No	Yes	Good	UA on waiting list	PCI to RCA	488
4	73	M	No	Yes	Mild impairment	UA on waiting list	PCI to D2	177
5	59	M	No	Yes	Mild impairment	UA on waiting list	PCI to RCA and LAD	147
6	69	M	No	No	Good	UA on waiting list	PCI to RCA and LAD	479
7	73	M	No	Yes	Good	UA on waiting list	PCI to LAD and D1	177
8	48	M	No	No	Good	UA on waiting list	*	135
9	78	F	No	Yes	Mild impairment	UA on waiting list	†	339

*Admitted as an emergency for PCI to RCA, but patient declined any intervention and self discharged. †Referred for PCI to RCA, but disease progression while on the waiting list resulted in complete total occlusion to the RCA and new significant disease to the LAD and was therefore referred for CABG. M, male; F, female; UA, unstable angina; MI, myocardial infarction; LV Fx, left ventricular function; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery; D1/2, first/second diagonal of LAD.

before undergoing PCI.¹⁴ In the population reported by these authors there was a high rate of early acute MI. However, our data differ from these findings. This may be because of a longer time period between onset of presenting symptoms such as chest pain and patients undergoing coronary angiography in the UK. This may result in most patients on UK waiting lists being in a more chronic phase of clinically apparent coronary disease. National service framework guidelines on waiting times for PCI suggest that patients should not have to wait longer than six months at present, with an aim to improve the waiting time to three months by 2005.¹⁵ Ideally the time interval between coronary angiography and elective PCI should be no longer than is required for the patient, patient's family, and physician to have what ever time they feel is required for gaining adequate informed consent for the revascularisation procedure. This would reduce the comparatively high frequency of adverse events that we observed to a minimum. It is, however, somewhat

reassuring that despite the excessively long waiting times in our study, there was a complete absence of death or major MI.

Pathogenesis

Adverse cardiac events are attributed to the process of coronary artery disease progression over time.¹⁶ Risk factors and disease severity contribute to disease progression. However, progression of coronary disease is a non-linear process and follows an unpredictable course over several years.¹⁷⁻²² The process can lead to total occlusion of a vessel or new stenoses developing in areas of the coronary circulation that were found to be normal at previous investigation.²³ Furthermore, rapid stenosis progression occurring over shorter periods of time is thought to be the process underlying acute coronary syndrome.²⁴ Large plaques are at a higher risk of rupture than small plaques. Nevertheless, it has been hypothesised that the risk of a MI arising from a small plaque is greater overall, as small plaques are far more

Figure 1 Filling of coronary collaterals in a normal postmortem human heart by immersion radiography. The arrow shows ligation of a proximal branch of the circumflex with back filling of the distal vessel by collaterals. Reproduced with permission (Fulton WFM. Immersion radiography of injected specimens. *Br J Radiol* 1963;**36**:687).

Figure 2 Filling of coronary collaterals in a postmortem human heart by immersion radiography. Extensive enlargement and recruitment of small calibre collaterals in a patient with chronic coronary artery disease. Reproduced with permission from Georg Theine, Stuttgart. (Fulton WFM. Intercoronary anastomoses studied by post-mortem stereoradiography. In: Kattenbach JP, et al, eds. *Coronary heart disease* 1978).

common than large plaques.²⁵ The absence of symptomatic deterioration despite vessel occlusion may well be dependent on the development of coronary collaterals, which have been shown to develop over a time course of 6–12 months in humans (see figs 1 and 2).²⁶

The neovascularisation process occurs by growth from both the adventitia and the arterial lumen and extends into the intima of advanced plaques. The intra-plaque neovasculature is fragile and has an increased susceptibility to rupture. When the process of plaque rupture and healing occurs repeatedly, there is a layering effect of the plaque, which may account for the intermittent step-wise pattern of growth in the plaque.²⁵

Limitations

The study has its limitations. Firstly, it does not measure mortality or morbidity in patients earlier in the care pathway, for instance, when they were waiting for coronary angiography. This is an important phase in the natural history of coronary disease in these patients as many had waited for several months for coronary angiography. Secondly, the low number of women in this study as in other reports has prevented assessment of potentially important sex differences with regards to AEs. Thirdly, as death and MI are clearly infrequent events in this population, a larger study would be required to give an accurate assessment of the small number of patients at risk for these most serious adverse events.

CONCLUSION

The benefits of PCI in reducing symptoms and improving quality of life are established. A long waiting time before receiving definitive treatment not only leaves patients suffering from symptoms that significantly impair quality of life, but in some may also result in a reduced probability of overall benefit from PCI because of silent disease progression. Fortunately, death and major cardiac damage from MI seem to be uncommon. The complexity of the pathogenetic processes underlying coronary artery disease result in a wide range of changes that occur in stable angina patients over a 10 month median period and, in this series, resulted in PCI no longer being the most appropriate treatment in 18%.

These findings provide the most extended study of the natural history of patients with chronic stable angina in the secondary prevention/statin era listed for PCI.

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