Identification of patients at high risk for adverse coronary events while awaiting routine coronary angioplasty

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Abstract

Background—Identification of patients at risk for progression of coronary stenosis and adverse clinical events while awaiting coronary angioplasty is desirable.

Objective—To determine the standard clinical or angiographic variables, or both, present at initial angiography associated with the development of adverse coronary events (unstable angina, myocardial infarction, and angiographic total coronary occlusion) in patients awaiting routine percutaneous transluminal coronary angioplasty (PTCA).

Patients and methods—Consecutive male patients on a waiting list for routine PTCA. Routine clinical details were obtained at initial angiography. Stenosis severity was measured using computerised angiography.

Outcome measures—Development of one or more of myocardial infarction, unstable angina, or angiographic total coronary occlusion while awaiting PTCA were recorded as an adverse event.

Results—Some 214 of 219 patients underwent a second angiogram. One had a fatal myocardial infarction and four (2%) were lost to follow up. Fifty patients (23%) developed one or more adverse events (myocardial infarction five, unstable angina 35, total coronary occlusion 23) at a median (range) interval of 8 (3-25) months. Twenty (57%) of the 35 patients with unstable angina developed adverse events compared with 30 (17%) of the 180 with stable angina ($P = 0.0001$). Plasma triglyceride concentration was 2.6 (1.2) mmol/l in patients with adverse coronary events compared with 2.2 (1.1) mmol/l in those without such events ($P < 0.05$). Patients with adverse events were younger than those without (54 (9) years *v* 58 (9) years, $P < 0.01$). The relative risk of an adverse event in patients with unstable angina and increased plasma triglyceride concentrations was 6.9 compared with those presenting with stable angina and a normal triglyceride concentration ($P < 0.02$).

Conclusions—The study shows that adverse events are not uncommon in patients awaiting PTCA. Patients at high risk for adverse events may be predicted by the presence of acute coronary syndrome, increased concentration of

plasma triglyceride, and younger age at the time of the first angiogram.

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Waiting lists for non-urgent interventional procedures are an integral part of resource allocation in the National Health Service and are based on clinical assessment of relative risk. The British Cardiac Society survey of waiting times in January 1994 showed that significant numbers of patients were on waiting lists for investigation and interventional procedures for more than 12 months. Moreover, the recent council statement on "demand for services and development of a waiting list strategy" highlights the need for identification of those groups of patients who require urgent fast tracking on cardiac waiting lists. The clinical division of patients, however, into a high risk category (requiring urgent intervention) and a low risk (requiring intervention but at a later unspecified date) may not be ideal. Adverse coronary events, usually in association with disease progression, are well recognised in patients awaiting routine coronary intervention procedures. The incidence of, and mechanisms responsible for, coronary stenosis progression and the development of acute coronary events are incompletely understood, but clearly involve interactions between local coronary and systemic factors.¹ Angiographic stenosis progression is non-linear and largely unpredictable and progression over several years is common.²⁻⁴ Rapid stenosis progression over relatively short periods, however, has also been observed and commonly underlies acute coronary syndrome⁵⁻⁷ and thus may be an important factor in the development of adverse events in patients awaiting coronary intervention. We studied the incidence of, and risk factors associated with, adverse events in such patients. This may help to devise appropriate strategies aimed at minimising adverse events in patients awaiting routine percutaneous transluminal coronary angioplasty (PTCA).

Patients and methods

The patient population consisted of consecutive male patients on a waiting list for routine PTCA between 1 January 1989 and 31

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December 1990 after diagnostic angiography. Subclinical stenosis progression is well recognised in clinical practice and it is therefore our practice to repeat coronary angiography using standardised views before the planned procedure in patients who remain on the waiting list for more than 3 months. All surviving patients therefore underwent a second study, either routinely at the time of PTCA or soon after the development of a clinical adverse event. Patients who were prescribed medical treatment alone, patients referred for surgery, and those who underwent emergency revascularisation without a second angiogram were not included. The clinical management decision to put a patient on the waiting list for coronary intervention was made by a consultant cardiologist and was based on the data available at the time of the first angiogram. Clinical details at initial presentation were obtained and included age, the presence or absence of hypertension, diabetes mellitus, a first degree family history of coronary artery disease, and a history of smoking. A previous history of myocardial infarction required supporting cardiac enzyme, electrocardiographic, or angiographic confirmation. Clinical presentation at study entry and follow up was classified as follows: stable angina: effort induced symptoms unchanged over the previous 3 months; unstable angina: rapidly progressive angina or spontaneous angina at rest with or without electrocardiogram (ECG) changes⁸ any time during the preceding 3 months; or myocardial infarction: based on the presence of a history of prolonged pain, increased cardiac enzymes with ECG changes. Fasting blood was assessed for concentrations of total cholesterol and triglyceride within 3 months of the first angiogram and at least 6 weeks after any acute event. High density lipoprotein (HDL) and low density lipoprotein (LDL) were analysed in a subgroup of patients ($n = 66$).

Over the same period of 3301 male patients who underwent their first coronary angiogram, 2140 received medical treatment in the first instance, 866 were referred for surgery, and 76 underwent emergency PTCA or urgent PTCA within 3 months. Four patients were lost to follow up and are not included in the analysis. The remaining 215 patients on a waiting list for PTCA formed the study group.

CORONARY ANGIOGRAPHY ANALYSIS

Quantitative assessment of stenosis diameter reduction for each lesion $>20\%$ stenosis severity was carried out using a previously validated computer assisted technique (coronary angiography analysis system (CAAS)).⁹⁻¹¹ Briefly, the angiograms were projected blind to the clinical characteristics of the patients and the best views of the lesions of interest were selected for subsequent analysis using an automated edge contour detection system (CAAS; Pie Medical Data, Neptune, New Jersey). The contour of the selected arterial segment was determined automatically by the computerised system. End diastolic frames

were used for measurement of coronary diameters and the projection in which the stenosis was most severe was used for analysis.¹² Absolute minimal luminal diameters were measured in millimetres and the percentage stenosis was derived by comparing the minimal stenotic diameter with an angiographically "normal" (reference) segment. The size of the stem of the coronary catheter was used to calibrate the system and correction was made for pin cushion distortion.

Repeatability

Measurements were repeated blind to the earlier results and the mean value used for analysis. No systematic differences were observed between paired measurements (mean (SD) difference = 0.9 (6)%, t value = 0.8 , $P = 0.5$). Regression of absolute difference between measurements on mean measurement gave $F = 0.14$, $P = 0.7$.

OUTCOME MEASURES

Patients were followed regularly in the outpatient clinic and called in turn for PTCA according to the dynamics of the waiting list, or earlier if their clinical condition deteriorated.

Adverse events

Patients were categorised into two groups, depending on the presence or absence of an adverse event at the time of the second angiogram. The development of a fatal or non-fatal myocardial infarction, unstable angina,⁸ or angiographic new total coronary occlusion (complete obstruction with TIMI (thrombolysis in myocardial infarction) grade 0 flow) were considered as adverse events. The development of one or more of these events in an individual was defined as a single adverse event for the analysis.

STATISTICAL ANALYSIS

Baseline statistical comparisons between groups were performed using the Student's t test or the Wilcoxon test for continuous variables and the χ^2 homogeneity test for categorical variables. The change in stenosis severity between angiograms was analysed using the one sample t test. Triglyceride concentrations were entered as a continuous variable without log transformation and separately as a categorical variable with a 2.3 mmol/l cut off point (equal to >3 SDs above the mean value for our laboratory, normal range 1.5 – 2.1 mmol/l). The potential predictor variables—that is, risk factors assessed at baseline angiography, for adverse events were analysed using the multiple logistic regression model. Variables were entered using stepwise step up logistic regression where variables are added one at a time. This process continues until additional variables give no statistically significant additional predictive ability beyond those already in the model. Each new added variable that contributes significantly ($P < 0.05$) to the prediction displaces (removes) variables in the model that, as a consequence of the new addition, do not.

Table 1 Clinical and angiographic features of 215 men at first diagnostic angiogram

Clinical features	
Mean (SD) age (years)	57 (9.5)
Hypertension	49 (23)
Previous myocardial infarction	85 (40)
Diabetes mellitus	24 (11)
Family history	34 (16)
Smokers	92 (43)
Treatment	
β blockers	157 (73)
Long acting nitrates	121 (56)
Calcium antagonists	140 (65)
More than one medication	210 (98)
Aspirin	206 (96)
Plasma lipid	
Mean (SD) total cholesterol (mmol/l)	6.3 (1.2)
Mean (SD) triglyceride (mmol/l)	2.3 (1.1)
Angiographic findings	
Mean (SD) interval*	8.1 (5.1)
Stenoses >20%†	2.2
Mean (SD) severity (%)	53 (17)
One vessel disease‡	101 (47)
Two vessel disease‡	90 (42)
Three vessel disease‡	24 (11)

Values in parentheses are percentages. *Interval between diagnostic and follow up angiograms in months. †Average number of lesions per patient. ‡Vessels containing a stenosis >50% diameter reduction.

All statistical tests were two tailed and we considered $P < 0.05$ as significant. All results are means (1SD) unless stated otherwise.

Results

Table 1 gives the clinical details, biochemical profile, and angiographic data of the 215 patients at study entry. A further four patients on the waiting list during the same period were lost to follow up. Their outcome is unknown and they were therefore not included in the analysis.

Fifty patients (23%) developed one or more adverse events (median (range) interval 8 (3–25) months) while the remaining 165 (77%) were free of adverse events at follow up (median (range) interval 7 (3–27) months). The adverse events were fatal myocardial

Figure 1 Clinical features at first angiogram and the development of adverse events in 215 patients awaiting percutaneous transluminal coronary angioplasty (PTCA). Patients were grouped according to angina symptoms during the 3 months before the first diagnostic angiogram. An adverse coronary event was defined as the development of myocardial infarction, unstable angina or total coronary occlusion (TIMI 0 flow) while awaiting PTCA. Patients with more than one event were recorded only as single events.

Table 2 Clinical features at initial angiogram and the development of adverse events

Clinical features	No adverse event	Adverse event	p Value
Hypertension	35	14	0.28
Previous myocardial infarction	64	21	0.73
Diabetes mellitus	19	5	0.99
Family history	23	11	0.22
Smoker	67	25	0.26

The development of myocardial infarction, unstable angina, or angiographic new total coronary occlusion were considered as adverse events. Multiple adverse events in an individual were defined as a single event.

infarction (one), non-fatal myocardial infarction (four), unstable angina (35), and new total coronary occlusion (23).

CORONARY EVENTS AND CLINICAL AND ANGIOGRAPHIC FEATURES AT STUDY ENTRY

Multiple logistic regression analysis of the variables (age, interval between angiograms, previous history of myocardial infarction, hypertension, smoking, diabetes mellitus, family history of coronary artery disease, lipid profile, and clinical presentation) revealed that younger age, increased concentration of plasma triglyceride, and instability at presentation were associated with an adverse event at follow up. Table 2 gives univariate comparisons between the development of adverse events and the other clinical risk factors at presentation.

Age

The mean (SD) age of patients with an adverse event was 54 (9) years (median (range) 51 (30–70) years) compared with 58 (9) years (median (range) 59 (35–77) years) for those without an adverse event at follow up ($P < 0.01$, t test and Wilcoxon test).

Stable versus unstable angina

Thirty five patients presented initially with acute coronary syndrome in the three months

Figure 2 Event free probability survival curves at the second angiogram according to clinical presentation. The probability of freedom from adverse coronary events was determined for time on the waiting list. Clinical adverse events could be timed accurately. Accurate timing of the onset of subclinical total coronary occlusion that occurred in 23 patients, however, was not possible and the adverse event was therefore assigned to the date of the second angiogram for the purpose of the analysis. The curve was constructed using the Kaplan-Meier method.

Table 3 Presenting features at initial diagnostic angiography and adverse events while awaiting percutaneous transluminal coronary angioplasty

Presentation	No adverse event	Acute coronary syndrome	Angiographic total coronary occlusion*	Any adverse event
Stable (n = 180)	150 (84)	24 (13)	23 (14)	30 (16)
Unstable (n = 35)	15 (43)	16 (45)	10 (29)	20 (57)
P	0.0001	0.001	0.04	0.0001

Defined angiographically irrespective of whether there were clinical manifestations. Values in parentheses are percentages.

Table 4 Plasma lipids at study entry and incidence of adverse events at follow up

Fasting plasma lipids	No event (n = 165)	Adverse events (n = 50)	p Value
Total cholesterol	6.2 (1.2)	6.3 (1.2)	0.6
Triglyceride	2.2 (1.1)	2.6 (1.2)	<0.05
High density lipoprotein (HDL)	1.03 (0.23) (46)	0.91 (0.17) (20)	0.06
Low density lipoprotein (LDL)	4.9 (0.84) (46)	4.5 (0.89) (20)	0.08

Values are mean (1 SD) in mmol/l. Values in parentheses are HDL and LDL concentrations obtained in a small number of patients.

before the initial angiogram while the remaining 180 presented with stable exertional angina. In each case the patients presenting with unstable angina had settled on standard medical treatment by the time of the first angiographic study and were not considered candidates for urgent or priority coronary intervention by the cardiology consultant in charge. Twenty of the 35 patients (57%) with unstable angina at presentation had an adverse coronary event at follow up compared with 30 of the 180 (17%) who initially presented with stable angina ($P = 0.0001$; fig 1). A significant difference remained between patients presenting with stable and those with unstable angina when adverse events were split into clinically manifest events and angiographic total occlusion (table 3). The majority of angiographic occlusion occurred without the development of acute coronary syndrome. Asymptomatic total coronary occlusion was seen in 17 of the 23 patients with stable angina and in six of the 10 with unstable angina at initial presentation. Figure 2 shows the event free probability survival curves at the second angiogram for patients presenting with stable angina and those presenting with unstable angina.

Table 5 Relative risk of an adverse coronary event while awaiting PTCA according to features at presentation

Variable at presentation	Proportion of patients with adverse event (%)	Relative risk	95% Confidence intervals
Stable angina	17	3.4	1.4-8.3
Unstable angina	57		
Triglyceride concentration <2.3 mmol/l*	15	2.3	1.7-3.2
Triglyceride concentration >2.3 mmol/l	35		
Stable angina and triglyceride concentration <2.3 mmol/l	10	6.7	2.8-17.3
Unstable angina and triglyceride concentration >2.3 mmol/l	67		

*Basal fasting blood was analysed for triglyceride (normal range 1.5-2.3 mmol/l; 2.3 mmol/l >3SDs above normal).

Plasma lipids

Table 4 gives plasma lipid concentrations in patients with and without adverse events. Basal fasting plasma triglyceride concentration was higher in patients with adverse events than in those without (2.6 (1.2) mmol/l v 2.2 (1.1) mmol/l, $P < 0.05$). Patients were dichotomised according to the presence or absence of fasting plasma triglyceride concentration > 2.3 mmol/l. This cut off point was chosen before reviewing the data and was not chosen to maximise posthoc differences between groups. Thirty three of 93 patients (35%) with a triglyceride concentration >2.3 mmol/l had an adverse event compared with 19 of 122 patients (16%) with a triglyceride concentration in the normal range ($P = 0.003$).

Total plasma cholesterol concentration was similar in the two groups. HDL and LDL cholesterol were analysed in a small subgroup of patients ($n = 66$) and were not different in patients with and without adverse events (table 4).

Combined risk factors

Unstable angina and increased plasma triglyceride concentration at initial angiography were recorded in 21 patients of whom 14 (67%) developed an adverse event at follow up. By comparison, of the 106 patients presenting with stable angina and normal triglyceride concentrations only 12 (11%) developed an adverse event ($P < 0.001$). Table 5 gives the risk ratios for the combined risk factors present at initial angiography.

STENOSIS SEVERITY AT INITIAL ANGIOGRAPHY AND ADVERSE EVENTS

The severity of the stenosis intended for angioplasty (target lesion) was not different between patients with and without adverse events (72 (12)% v 73 (12)%) and did not differ significantly at follow up (75 (15)% v 78 (18)%).

Discussion

This study demonstrates that the development of adverse coronary events is not uncommon in patients awaiting routine coronary angioplasty. Moreover, adverse events are independently associated with acute coronary syndrome, an increased concentration of plasma triglyceride, and younger age at initial angiography. Younger patients with coronary disease tend to have a worse prognosis than older patients,^{13 14} and unstable angina is known to be associated with a worse outcome in various circumstances.^{8 15 16} In addition, the role of increased concentration of plasma triglyceride in coronary disease progression has become apparent over recent years.^{17 18} Thus, although our results are not surprising, no study has previously examined these associations in the context of predicting progression of disease in the specific group of patients awaiting routine PTCA.

ADVERSE CORONARY EVENTS AND CLINICAL PRESENTATION

Myocardial infarction and angiographic total coronary occlusion are clear cut and easily defined end points. Subclinical total coronary occlusion with or without angiographic evidence of myocardial damage was included as an adverse coronary event because total coronary occlusion commonly adversely affects the planned procedure and is associated with a less successful course if intervention is attempted.¹⁹ We included unstable angina as an adverse event as it has important clinical and prognostic implications. We used established criteria to define unstable angina at study entry and follow up.⁸

Age

Progression of coronary disease in medically treated young patients with coronary artery disease is more frequent and more pronounced than in older patients.¹³⁻¹⁴ Recent pathological studies have shown that, in contrast to plaques from older patients that tend to have a larger content of fibrous tissue,²⁰ plaques in young patients are characterised by a large amount of lipid containing foam cells and relative lack of acellular scar tissue.²¹ Lipid rich lesions succumb more readily to plaque disruption than lipid poor fibrous plaques,²²⁻²⁴ and might explain our observations.

Unstable angina

There is good evidence that major plaque disruption and thrombus formation¹⁻²⁵⁻²⁶ with or without a degree of coronary spasm²⁷ underlies unstable angina. The ideal strategy for dealing with unstable angina that settles with medical therapy is controversial. Dilatation of unstable coronary stenoses with thrombus is associated with increased risk of early and late complications.²⁸⁻³⁰ Therefore, it is common clinical practice to adopt a policy of "watchful waiting" in patients with unstable angina who settle on conventional medical therapy before proceeding to angioplasty. Our results show that the annual incidence of adverse events in such patients is more than three times greater than in patients presenting with stable angina. This strongly suggests that the potential benefits of a "watchful waiting" policy may have a time limit and this should be weighed against the relatively high risk of rapid stenosis progression in such patients. Recent data presented by Dawkins *et al*³¹ indicates that early intervention in patients with unstable angina is associated with a similar event rate as PTCA in stable angina. Whether this can be extrapolated to our patients with medically settled unstable angina remains to be answered. Although the ideal time interval between the acute coronary event and intervention in patients who settle on medical therapy is not known, our findings demonstrate a clear need to monitor such patients closely.

Plasma triglyceride concentration

The overall correlation between plasma

triglyceride concentration and adverse events was just significant ($P = 0.048$). The division of patients on the basis of high (2.3 mmol/l) and normal triglyceride concentrations showed a highly significant difference between groups ($P = 0.003$). Thus, patients with increased plasma triglyceride concentrations were at 2-3-fold increased likelihood of an adverse event during follow up irrespective of the clinical presentation. Patients with increased triglyceride concentrations and unstable angina at presentation were more than six times more likely to have an adverse event during follow up compared with those presenting with stable angina and normal triglyceride concentrations. Several large scale epidemiological studies have demonstrated strong univariate and multivariate associations between increased plasma triglyceride concentrations and coronary artery disease.¹⁷⁻¹⁸⁻³²⁻³⁶ Whether the association between triglyceride and acute events represents a genuine relation, however, is controversial and a number of important angiographic follow up studies have found no such association.³⁷⁻³⁸ Moreover, while some recent lipid lowering studies have reported an association between triglyceride decrease and a reduction in progression³⁹ others have not.⁴⁰ The controversy has arisen in part because of the observation in some studies that plasma triglyceride is no longer an independent predictor of coronary artery disease when plasma HDL is included in multiple stepwise analysis. This approach may not be appropriate, however, for such closely interdependent variables as HDL and triglyceride, particularly as triglyceride exhibits greater inter-assay and inter-individual variability.⁴¹ Fasting HDL estimation was undertaken in a subgroup of patients in our study and increased plasma triglyceride concentration remained an independent predictor of adverse events when HDL concentrations were included in the regression analysis. These data are consistent with the observations made by the Caerphilly and Speedwell collaborative epidemiological study, in which increased fasting plasma triglyceride was a strong independent risk factor for acute coronary events even after allowance was made for total and HDL cholesterol.¹⁸

As discussed earlier, plaque thrombosis plays a major part in the development of acute coronary events and a strong relation between plasma triglyceride concentration and procoagulant factors has been documented in clinical and laboratory studies.⁴²⁻⁴⁵ Moreover, a recent large scale epidemiological study showed that increased plasma triglyceride is strongly and independently associated with haemostatic factors that have an important part in the pathogenesis of acute coronary events.⁴⁶ Thus, although it is not within the scope of this study to examine the mechanism, it is tempting to speculate that effects on procoagulant status might explain the association between acute coronary events and increased concentrations of plasma triglyceride.

Progression of the target lesion

Overall, the severity of target lesions changed little between angiograms. This is explained partly by the fact that the target lesion was responsible for progression and events in only half of the patients. This has important implications as it re-emphasises the point that the intended target stenosis is not necessarily the most at risk lesion for progression. In addition, although clinical events are associated with angiographic progression at the time of the event, it is not unusual to see little or no apparent change in angiographic appearances particularly following a period of intensive medical therapy. Finally, intraplaque and intraluminal thrombus are likely to have contributed to the severity of some of the unstable lesions at the initial diagnostic angiogram. Thus, it is possible that regression through lysis, organisation, and remodelling in some lesions might have influenced overall progression.

Limitations of the study

This was a registry study in which we systematically collected and analysed a consecutive series of patients who were prospectively placed on a routine waiting list for PTCA over a fixed time interval. The follow up rate was high and only a small group of patients ($n = 4$) were lost to follow up. These four patients represent $< 2\%$ of the total population and therefore their exclusion from the analysis is unlikely to have altered the results. A second important consequence of the retrospective study design is that while the main generally accepted clinical, biochemical, and angiographic risk factors for adverse events were assessed other potentially important variables were not. Nevertheless, the risk factors analysed in our study represent those that are generally available and commonly used in current clinical practice.

The decision to place the patients on the routine waiting list was at the discretion of the consultant cardiologist in charge of the case based on the data available at the time of the first angiogram. This may have introduced clinical bias, but reflects current management practices and therefore such clinical bias is inherent to clinically based follow up studies.

The interval between angiograms was not constant for all patients but varied depending on the dynamics of the waiting list that was determined by clinical events, bed availability, surgical cover, etc. Despite this finding the interval between angiograms was similar for those with and without adverse events.

High and low density lipoprotein fractions were assessed in a relatively small subgroup of patients and therefore these results may not accurately reflect the situation in the population at large. The relation between adverse events and plasma lipid concentrations should be interpreted with caution.

Conclusions

This study suggests that (1) adverse coronary events are relatively frequent in patients

placed on routine waiting lists for PTCA; (2) unstable angina is associated with the development of adverse coronary events even where the patient settles on medical treatment, and (3) the combination of unstable angina at initial presentation and raised fasting plasma triglyceride identifies a subgroup of patients at high risk of adverse events while awaiting coronary intervention.

Our findings have important clinical implications and further larger prospective studies are required to confirm these observations. It remains to be seen whether manipulation of plasma lipids and/or earlier intervention in younger patients who present with unstable angina will result in a more favourable outcome.

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