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Lipoprotein(a) as a risk predictor for cardiac mortality in patients with acute coronary syndromes

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Aims Raised lipoprotein(a) concentrations are considered to be a risk factor for atherothrombotic diseases. We examined whether baseline concentrations were a risk factor for an adverse outcome in patients admitted with acute coronary syndromes.

Methods and Results Five hundred and nineteen patients admitted with suspected acute coronary syndromes were studied and followed prospectively for a median of 3 years. The prognostic significance of a baseline lipoprotein(a) concentration of ≥ 30 mg . dl^{-1} or lower for subsequent cardiac death was assessed in patients with myocardial infarction (266) and unstable angina (197) and compared with other variables in regression models. In patients with myocardial infarction, a baseline lipoprotein(a) concentration of ≥ 30 mg . dl^{-1} was associated with a 62% increase in subsequent cardiac death compared to the lower concentration group (29·8% vs 18·6%, Log rank $P = 0{\cdot}04$). In a multivariate regression model a baseline lipoprotein(a) concentration of ≥ 30 mg . dl^{-1} retained its significance as an independent predictor of cardiac death ($P = 0{\cdot}037$). In patients with unstable angina, baseline concentrations of $\geq 7{\cdot}9$ mg . dl^{-1} were found to be significant predictors of cardiac death in univariate ($P = 0{\cdot}021$) and multivariate ($P = 0{\cdot}035$) regression models.

Conclusion Baseline lipoprotein(a) concentrations in patients admitted with acute coronary syndromes are associated with an increased risk of cardiac death. For patients with myocardial infarction a concentration of ≥ 30 mg . dl^{-1} appears appropriate as a risk discriminator; for patients admitted with unstable angina, however, much lower concentrations of lipoprotein(a) appear to be prognostically important.
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Key Words: Lipoprotein(a), unstable angina, myocardial infarction, prognosis, risk stratification.

Introduction

Lipoprotein(a) is an enigmatic lipoprotein. Initially discovered by Berg[1,2], it resembles low density lipoproteins, being rich in cholesterol and apolipoprotein B-100, but in addition contains a glycoprotein called apolipoprotein (a)[3–5]. DNA sequencing of this glycoprotein moiety established that it has a close structural homology with plasminogen and other coagulation zymogen proteases[6–9], and so lipoprotein(a) may have both pro-thrombotic and pro-atherogenic potential. A wealth of elegant basic research both in vitro[10–22] and in vivo[23–28], has subsequently explored, and for the most part supported, this hypothesis.

Clinical studies however, have yielded less clear cut results. Primary epidemiological studies examining the role of lipoprotein(a) concentrations of ≥ 30 mg . dl^{-1} as an independent risk factor for myocardial infarction have mostly reported positive results[29–32], but with notable exceptions[33,34]. Definitive explanations for the differences in these well conducted observational studies remains elusive, and so at present there is no clear consensus on the role of lipoprotein(a) as a primary risk factor for myocardial infarction or that its routine measurement for risk stratification is justified. Treatment options for lowering raised lipoprotein(a) concentrations remain limited, with no effect of diet or treatment with standard lipid lowering agents[35,36] except nicotinic acid[37,38] and in post menopausal women the use of hormone replacement therapy[39,40]. One therapeutic option suggested is that lowering the low density lipoprotein cholesterol may attenuate the pathological actions of lipoprotein(a)[41].

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More recently, clinical cardiology studies have examined the role of lipids and coagulation markers as risk factors for a subsequent adverse cardiac outcome in patients who have sustained myocardial damage[42–45]. Whether the atherothrombotic potential of raised lipoprotein(a) concentrations confers an increased risk for an adverse outcome in this population with confirmed coronary disease who have sustained a prothrombotic event remains to be determined. We have therefore examined the prognostic significance of baseline lipoprotein(a) concentration on cardiac mortality in a cohort of patients admitted with acute coronary syndromes.

Methods

This was a single centre study of patients admitted with chest pain to a hospital coronary care unit. Management decisions were based on clinical, electrocardiographic (ECG) and routine biochemical marker results by physicians unaware of the admission lipoprotein(a) results. Patients admitted to the coronary care unit underwent daily sampling for 3 days for the routine cardiac enzyme protocol in the hospital and the daily creatine kinase, aspartate transaminase and hydroxybutyrate dehydrogenase estimations were used for the final World Health Organisation (WHO)[46] biochemical diagnostic coding of the admissions. Patients also underwent multiple timed sampling for research purposes approved by the local ethical committee during their hospital stay which included samples taken on admission to the coronary care unit prior to the initiation of antithrombotic therapy. These coded samples were centrifuged and separated on the coronary care unit and the aliquotted supernatants immediately frozen in liquid nitrogen before storage in a -80 °C freezer.

Clinical data

Full clinical details were recorded on all patients by pro-forma. Particular attention was paid to previous cardiac history, classification of chest pain before entry, admission clinical findings, inpatient clinical course and management, discharge drug management and subsequent investigations and treatment. As part of the standard coronary care unit protocol, all patients received dietary and lifestyle modification advice, but subsequent managements were at the discretion of the admitting physician. Follow up for survival, interventions and mortality was by examination of hospital records, post-mortem results where available, death certificates, general practitioner questionnaire, patient or next of kin questionnaire, with follow-up telephone contact if required. Survival status and cause of death were established for all patients. Cause of death was classified according to American Heart Association criteria[47].

Diagnostic classifications

Myocardial infarction was diagnosed retrospectively if at least two of the following WHO criteria were met: typical chest pain, diagnostic ECG changes, cardiac enzymes at least twice their upper reference limit within the first 48 h from admission.

Unstable angina was retrospectively diagnosed if the WHO criteria for myocardial infarction were not met; all enzyme measurements (creatine kinase, aspartate transaminase, hydroxybutyrate dehydrogenase) were less than twice their upper reference range throughout the routine sampling period with evidence of proven ischaemic heart disease defined on the basis of a further cardiac event (death, coronary revascularization or myocardial infarction), a positive coronary angiogram (at least a 50% stenosis in a major coronary segment), a positive exercise treadmill test (>0·1 mV ST segment depression 80 ms after the J point), or demonstration of ischaemia on Thallium radio-isotope study.

Analytical methods

Aspartate transaminase and hydroxybutyrate dehydrogenase were measured at 37 °C by optimized methods on a PERSPECTIVE analyser (American Monitor, Burgess Hill, West Sussex, U.K.) by the manufacturer's recommended methods. The manufacturer's reagents were used for aspartate transaminase (reference interval: 11–55 u . l^{-1}) and commercially supplied reagents used for hydroxybutyrate dehydrogenase (reference interval: 90–180 u . l^{-1}) (Merckotest HBDH, BDH Diagnostics, Poole, Dorset, U.K.). Total creatine kinase was measured at 30 °C by optimized methods, using commercially supplied reagents (creatine kinase NAC opt., BCL, Lewes, Sussex, U.K.) (reference interval <120 u . l^{-1}). All determinations were made using an RA 1000 analyser (Bayer Technicon, Basingstoke, U.K.). Troponin T was determined by ELISA using an ES-300 Immunoassay analyzer (Boehringer Mannheim, Lewes, Sussex, U.K.) as previously described[48] (diagnostic cut-off 0·1 ng . ml^{-1}).

Lipid variables

Admission lipoprotein(a) concentrations were determined by ELISA using sheep polyclonal monospecific antibodies against purified human lipoprotein(a) (Biopool AB, Umea, Sweden). The standard calibration curve was linear in the range 0–60 mg . dl^{-1}. If serum samples were of higher concentration separate aliquots were diluted with sample buffer and analysed. The within-run coefficient of variation was 3·2%, and the between-run coefficient of variation was 6%. The reference median lipoprotein(a) concentration for our laboratory is 7·9 mg . dl^{-1}. All samples were batch assayed in duplicate with the mean value reported, within

Table 1 Baseline demographics. Variables are expressed as percentages or mean values with standard errors unless otherwise stated

Variable	Myocardial infarction	Unstable angina
Number	266	197
Age (years)	63 (0·66)	60·8 (0·81)
Male sex	77%	70%
Time from worst pain to admission (h)	4·55	4·83
Previous angina	11%	17%
Current smoker	36%	30%
Family history of premature cardiac disease	20%	17%
Diabetes mellitus	15%	15%
Hypertension	27%	27%
Previous myocardial infarction	17·5%	36%
Admission mean cholesterol (mmol . l^{-1})	6·29 (0·1)	6·27 (0·12)
Admission median triglyceride (mmol . l^{-1})	1·4 (0·4–9·1)	1·6 (0·4–6·6)
Admission median lipoprotein(a) (mg . dl^{-1})	12·6 (0–103)	9·6 (0–98)
Admission lipoprotein(a) $\geq$30 mg . dl^{-1}	25%	23%
Thrombolysis	77%	—
Heparin on CCU	57%	50%
Aspirin therapy	78%	72%
Beta-blocker therapy	26%	25%
Subsequent revascularization	27%	27%

6 months of the entry admission, by a single experienced operator blinded to the clinical data.

Although lipoprotein(a) concentrations were originally thought to increase from the baseline value within the first few hours following myocardial infarction[49], larger studies have shown that no significant rise in lipoprotein(a) concentrations occurs within the first 24–48 h from admission in both myocardial infarction[50,51] and unstable angina[51]. Comparison of paired plasma and serum samples for lipoprotein(a) concentration (n = 20) showed a linear correlation (Rank Spearman correlation coefficient = 0·96).

Cholesterol (reference interval 3·5–6·5 mmol . l^{-1}) was measured by a cholesterol oxidase method on a Technicon Axon (Bayer Technicon, Basingstoke, Hampshire, U.K.) by the manufacturers' recommended method (within-run coefficient of variation 2·2%, between-run coefficient of variation 5%). Triglycerides (reference interval 0·9–2·0 mmol . l^{-1}) were measured by a lipoprotein lipase/glycerol kinase/glycerol phosphate oxidase reaction on a Technicon Axon by the manufacturers recommended method (within-run coefficient of variation 3·0%, between-run coefficient of variation 5%).

Statistical analyses

Baseline demographics were expressed as percentages, means with standard errors or medians with interquartile ranges where appropriate. Correlations were tested by the Rank Spearman statistical test (r_S). Cumulative hazard function plots were generated using the Kaplan–Meier method with differences examined using the Log rank statistical test. Univariate and multivariate regression analysis for survival used the Cox regression statistical model. For all statistical evaluations, a two-sided *P* value of 0·05 or less was considered to be statistically significant. The endpoint studied was cardiac death as first event. Non cardiac deaths were treated as censored observations.

Results

Admission lipoprotein(a) concentrations were available for 519 patients on their index admission with chest pain. By the criteria defined above, the admission was classified as myocardial infarction in 266 patients and unstable angina in 197 patients. Fifty-six patients had a final diagnosis of non cardiac chest pain and were excluded from the subsequent analysis. The cohort have been followed for a median of 965 days (lower quartile 838, upper quartile 1292). The baseline demographics for the acute coronary syndrome cohort are shown in Table 1. Overall, 21% (57/266) of the myocardial infarction group and 15·7% (31/197) of the unstable angina group have died a cardiac death.

Myocardial infarction group

The demographics for this group are shown in Table 1. Twenty five per cent (67/266) of the patients had a baseline lipoprotein(a) concentration of $\geq$30 mg . dl^{-1}. There was no correlation between baseline lipoprotein(a) concentration and age, time from worst pain to admission sample, peak values of the biochemical markers of myocyte damage and admission triglyceride concentrations. No difference was observed between the

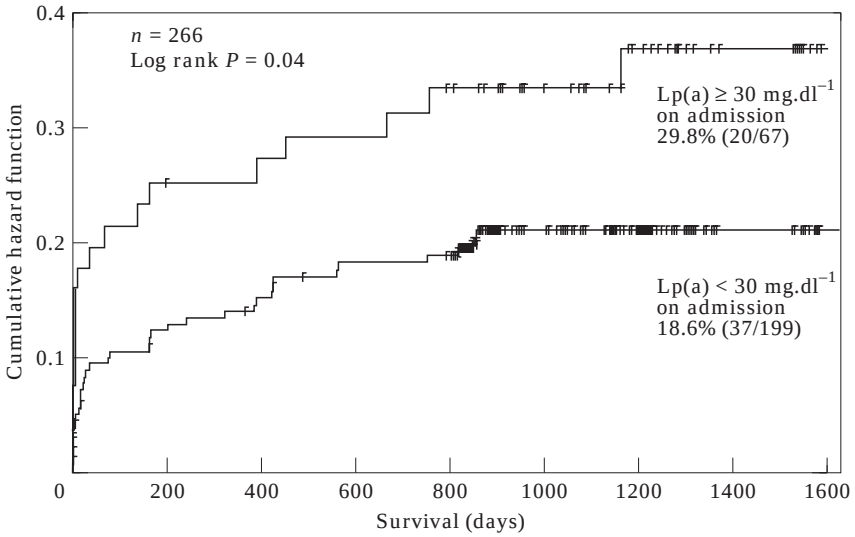

Figure 1 **Kaplan–Meier cumulative hazard function curves for subsequent cardiac death in 266 myocardial infarction patients according to entry lipoprotein(a) concentration. A baseline lipoprotein(a) concentration of $\geq$30 mg . dl^{-1} was associated with a significant 62% increase in cardiac death compared to myocardial infarction patients with a lower baseline lipoprotein(a) concentration.**

incidence of successful reperfusion following thrombolysis assessed non-invasively[52,53], in the high or low baseline lipoprotein(a) groups or in the subsequent revascularization rates. There was no difference between baseline lipoprotein(a) concentrations in those with or without a history of previous angina or myocardial infarction[54]. Baseline lipoprotein(a) concentrations correlated significantly with admission total cholesterol concentrations (r_S=0·273, P=0·0009). On follow-up 29·8% (20/67) of the patients with a baseline lipoprotein(a) concentration $\geq$30 mg . dl^{-1} died compared to 18·6% (37/199) of the remainder, Log rank P=0·04. The Kaplan–Meier cumulative hazard function plot is shown in Fig. 1. Whether the lipoprotein(a) level of 30 mg . dl^{-1} proposed as the risk discriminant in primary studies was appropriate for patients with proven heart disease who had sustained a thrombotic event was then examined.

The baseline lipoprotein(a) concentrations were divided into low, medium or high with high concentrations defined as $\geq$30 mg . dl^{-1} and medium and low concentrations defined as being below 30 mg . dl^{-1} and above (medium) or below (low) the median normal lipoprotein(a) concentration for our laboratory of 7·9 mg . dl^{-1}. The cumulative hazard function plots for subsequent cardiac death for these three groups are shown in Fig. 2. This analysis shows that a baseline lipoprotein(a) concentration of $\geq$30 mg . dl^{-1} appears to be appropriate as a risk predictor for patients admitted with myocardial infarction. Independent predictors for subsequent cardiac mortality from the variables in Table 1 were examined in a Cox univariate regression model and are summarized in Table 2. The five significant independent positive predictors of subsequent cardiac death were entered in a one step multivariate Cox regression model, the results of which are shown in Table 3. All retained their independence as risk factors.

Unstable angina group

The demographics for this group are shown in Table 1. Twenty three percent (46/197) of the patients had a baseline lipoprotein(a) concentration $\geq$30 mg . dl^{-1}. The baseline lipoprotein(a) concentration did not correlate with age, time from worst pain to baseline sample, admission total cholesterol or triglyceride. On follow-up 23·9% (11/46) of the patients with an admission lipoprotein(a) concentration $\geq$30 mg . dl^{-1} have died, compared to 13·2% (20/151) of the remainder, Log rank P=0·08. The Kaplan–Meier cumulative hazard function plot is shown in Fig. 3.

The baseline lipoprotein(a) concentrations were then divided into high, medium and low lipoprotein(a) groups as defined above, and their cumulative hazard function plots for cardiac death are shown in Fig. 4. This analysis shows that much lower concentrations of lipoprotein(a) than 30 mg . dl^{-1} may be important as risk predictors in patients admitted with unstable angina. The univariate Cox regression model (Table 2) identified aspirin usage (P=0·002) and subsequent revascularization (P=0·029) as independent negative predictors of subsequent cardiac death and only age (P=0·003) as an independent positive predictor of subsequent cardiac death. A baseline lipoprotein(a) of $\geq$30 mg . dl^{-1} did not achieve significance in this analysis (Table 2). Due to the Kaplan–Meier hazard function results shown in Fig. 4, the much lower discriminant lipoprotein(a) concentration of $\geq$7·9 mg . dl^{-1} was then examined. This lipoprotein(a) concentration was a significant

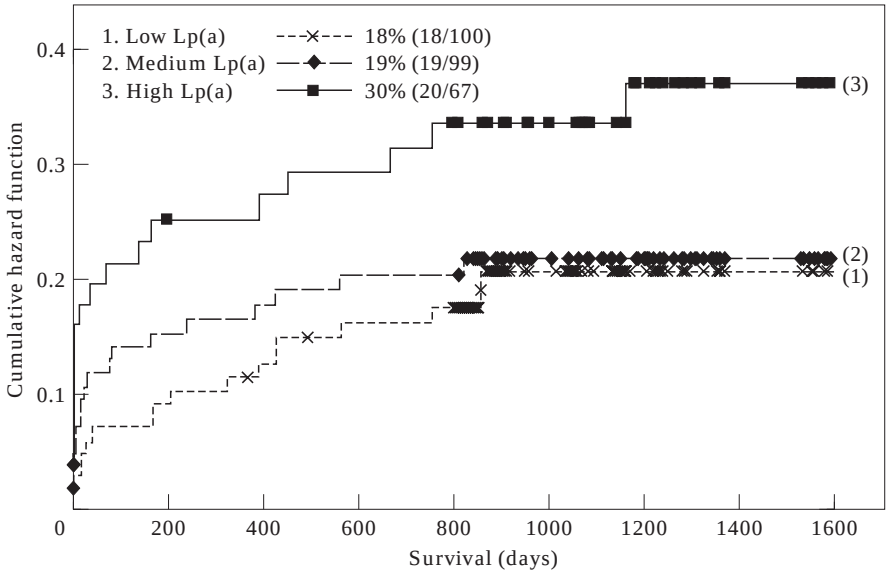

Figure 2 **Kaplan–Meier cumulative hazard function curves for subsequent cardiac death in 266 myocardial infarction patients according to varying entry lipoprotein(a) concentrations. The baseline lipoprotein(a) concentrations were divided into low (Group 1), medium (Group 2) or high (Group 3) with high concentrations defined as $\geq$30 mg . dl^{-1} and medium and low concentrations defined as being below 30 mg . dl^{-1} and above (medium) or below (low) the median normal lipoprotein(a) concentration for our laboratory of 7·9 mg . dl^{-1}. This analysis shows that a baseline lipoprotein(a) concentration of $\geq$30 mg . dl^{-1} appears to be appropriate as a risk predictor for patients admitted with myocardial infarction (high vs low, log rank *P* = 0·07, high versus medium, log rank *P* = 0·12, medium vs low, log rank *P* = 0·75).**

predictor of cardiac death in both the univariate (Table 2) and in a one step multivariate model with age ($P = 0{\cdot}035$). To further test this lower discriminant as a risk predictor in unstable angina, a baseline lipoprotein(a) concentration of $\geq 7{\cdot}9$ mg . dl^{-1} was examined in a one step multivariate regression model with a number of conventional risk predictors for this acute coronary syndrome namely, rest pain on admission[55], the presence of ST depression or T wave inversion on the admission electrocardiogram[56] and increasing angina in the 48 h prior to entry (accelerated angina)[57]. A baseline lipoprotein(a) concentration of $\geq 7{\cdot}9$ mg . dl^{-1} was superior to these variables as a risk predictor for subsequent cardiac death (Table 3).

Pathophysiological sub-studies

Lipoprotein(a) appears to induce foam cell formation and significant lipid accumulation in atherosclerotic lesions which may lead to a softer plaque[22]. When these plaques rupture in acute coronary syndromes, a more severe plaque injury may result. One would predict therefore that if this was true one might be able to identify a more aggressive prothrombotic response. This was studied by examining for correlations between the baseline lipoprotein(a) concentrations and the admission coagulation factor concentrations of fibrinogen and prothrombin fragment 1+2 (F_{1+2}) which defines in vivo thrombin activation[58,59]. No significant correlations were seen between these factors in either the myocardial infarction group (n = 88) (lipoprotein(a) and F_{1+2}, $r_s = 0{\cdot}01$, $P = 0{\cdot}94$ and lipoprotein(a) and fibrinogen $r_s = -0{\cdot}07$, $P = 0{\cdot}52$) or in the unstable angina cohort (n = 79) (lipoprotein(a) and F_{1+2}, $r_s = -0{\cdot}06$, $P = 0{\cdot}60$ and lipoprotein(a) and fibrinogen $r_s = -0{\cdot}001$, $P = 0{\cdot}97$).

As the presence of the cardiac specific protein Troponin T identifies high risk subgroups in patients admitted with acute coronary syndromes[60–62], the association with baseline lipoprotein(a) concentrations was studied. In the myocardial infarction group (n = 240), 57% were Troponin T positive on admission (>0·1 ng . ml^{-1})[62]. Whilst the median baseline lipoprotein(a) concentrations were higher in the positive compared to the negative group (medians 15 mg . dl^{-1} vs 10·7 mg . dl^{-1} respectively) this did not reach conventional significance ($P = 0{\cdot}12$) nor was there any significant correlation between the baseline lipoprotein(a) concentration and admission Troponin T concentration ($r_s = 0{\cdot}099$, $P = 0{\cdot}132$). The association between admission lipoprotein(a) concentrations and Troponin T in unstable angina patients has already been reported[63].

Discussion

This prospective study shows that raised baseline lipoprotein(a) concentrations are associated with

Table 2 The variables identified in Univariate Cox Regression analysis as independent predictors of subsequent cardiac death. The baseline variables from Table 1 were entered into a univariate Cox regression analysis for the end point cardiac death

Variable	Significance	Relative risk	95% Confidence intervals
Myocardial infarction			
Age*	0·0001	1·1	1·06–1·14
Previous MI*	0·0002	3·0	1·70–5·38
Infarct size*	0·0017	1·0	1·01–1·05
Hypertension*	0·033	1·8	1·05–3·10
Lipoprotein(a) $\geq$30 mg . dl^{-1}*	0·042	1·8	1·02–3·10
Thrombolysis†	0·0001	0·30	0·18–0·51
Revascularization†	0·001	0·18	0·07–0·51
Beta-blocker†	0·002	0·20	0·07–0·55
Aspirin (150 mg)†	0·01	0·50	0·28–0·84
i.v. Heparin on CCU†	0·048	0·59	0·35–0·99
Unstable angina			
Age*	0·003	1·10	1·02–1·11
Lipoprotein(a) $\geq$30 mg . dl^{-1}*	0·090	1·89	0·90–3·90
Lipoprotein(a) $\geq$7·9 mg . dl^{-1}*	0·021	2·56	1·15–5·74
Aspirin (150 mg)†	0·002	0·33	0·16–0·66
Revascularization†	0·029	0·27	0·08–0·87

*Significant positive predictors in both acute coronary syndromes; †significant negative predictors for subsequent cardiac death. In the unstable angina group, the lower lipoprotein(a) discriminant of $\geq$7·9 mg . dl^{-1} was also analysed because of the significant hazard function results shown in Fig. 4.

Table 3 Variables examined in a Cox Multivariate Regression analysis as predictors of subsequent cardiac death

Variable	Significance	Relative risk	95% Confidence intervals
Myocardial infarction			
Age	0·0001	1·1	1·05–1·16
Previous MI	0·0004	3·6	1·80–7·20
Infarct size	0·013	1·03	1·02–1·06
Hypertension	0·021	2·18	1·10–4·20
Lipoprotein(a) $\geq$30 mg . dl^{-1}	0·037	2·16	1·05–4·46
Unstable angina			
Lipoprotein(a) $\geq$7·9 mg . dl^{-1}	0·021	2·48	1·11–5·56
Rest pain on admission	0·757	0·87	0·37–2·04
ECG ST or T changes	0·366	0·72	0·35–1·47
Accelerated angina	0·420	0·70	0·29–1·66

For myocardial infarction, the five positive predictors of cardiac death identified in Table 2 were examined in a one-step multivariate regression model. All retained their independence as risk factors for subsequent cardiac death. For unstable angina, the lipoprotein discriminant of $\geq$7·9 mg . dl^{-1} was examined in a one-step multivariate regression model with conventional risk factors for this syndrome, including the presence of ST depression or T wave inversion on the admission electrocardiogram (ECG ST or T changes) and increasing angina in the 48 h prior to entry (accelerated angina)

increased cardiac mortality on follow-up in patients admitted with acute coronary syndromes. At an lipoprotein(a) discriminant of $\geq$30 mg . dl^{-1}, the hazard function curves separate very early in the myocardial infarction group and continue to slowly separate further over time (Fig. 1). These early deaths were mainly readmissions with fatal myocardial reinfarctions and may be related to the prothrombotic properties of lipoprotein(a). Examining the effect of differing lipoprotein(a) discriminant concentrations (Fig. 2) shows that this hazard is mainly seen with admission lipoprotein(a) concentrations of $\geq$30 mg . dl^{-1} and so this concentration appears appropriate as a risk predictor for subsequent cardiac death in

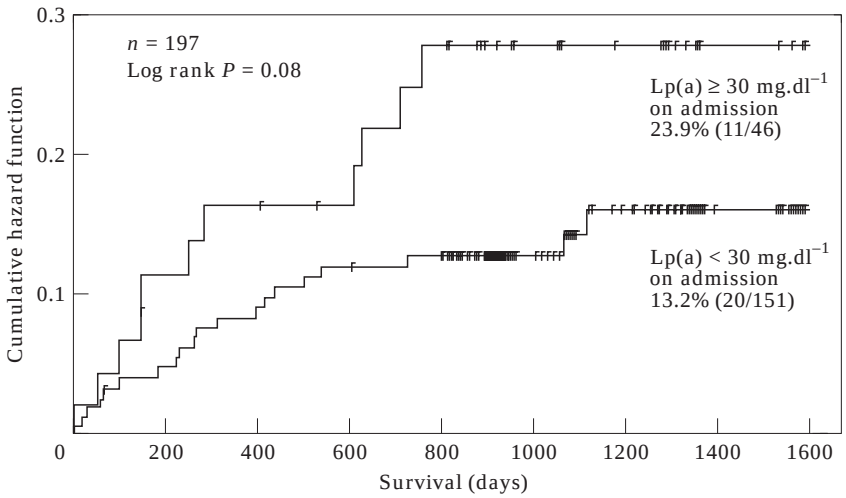

Figure 3 **Kaplan–Meier cumulative hazard function curves for subsequent cardiac death in 197 unstable angina patients according to entry lipoprotein(a) concentration. A baseline lipoprotein(a) concentration of ≥ 30 mg . dl^{-1} was associated with an 80% increase in cardiac death compared to unstable angina patients with a lower baseline lipoprotein(a) concentration, which did not reach conventional significance.**

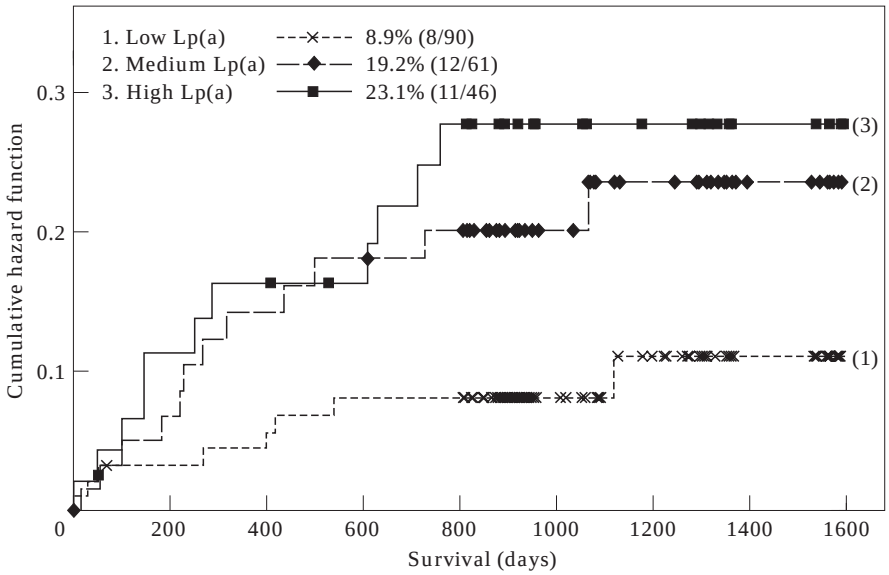

Figure 4 **Kaplan–Meier cumulative hazard function curves for subsequent cardiac death in 197 unstable angina patients according to varying entry lipoprotein(a) concentrations. The baseline lipoprotein(a) concentrations were divided into low (Group 1), medium (Group 2) or high (Group 3) as defined in Fig. 2. This analysis shows that both medium and high baseline lipoprotein(a) concentrations are associated with similar adverse outcomes (high vs low, log rank $P = 0{\cdot}017$, high vs medium, log rank $P = 0{\cdot}61$, medium vs low, log rank $P = 0{\cdot}06$) and suggests that much lower concentrations of lipoprotein(a) than 30 mg . dl^{-1} may be important as risk predictors for subsequent cardiac death in patients admitted with unstable angina.**

patients admitted with myocardial infarction carrying a two-fold increase in risk which is roughly equivalent to that of hypertension[64].

The significant correlation between the admission total cholesterol and the baseline lipoprotein(a) concentrations in the myocardial infarction group lends credence to the hypothesis from primary epidemiological studies[29–31] that patients with high lipoprotein(a) concentrations and raised cholesterol concentrations act as combined risk factors for myocardial infarction. There was however, no correlation between the admission lipoprotein(a) concentration and the

coagulation variable concentrations measured. It may be that the differences are too small to be detected on peripheral sampling and coronary sinus sampling is required to accurately study differences in coagulation activation, or that the effect of lipoprotein(a) on the degree of plaque rupture and subsequent variations in the amount of thrombus generated in the coronary artery maybe too small to significantly elevate markers of coagulation activation. In agreement with other studies[65], however, baseline lipoprotein(a) concentrations did not affect patency following thrombolysis and did not correlate with infarct size assessed by peak concentrations of biochemical markers of myocyte damage.

Examination of the role of lipoprotein(a) in the group of patients with unstable angina produced a very different pattern of results. At a lipoprotein(a) discriminant of ≥ 30 mg . dl^{-1}, the hazard function curves separate much more slowly over time than in the myocardial infarction group (Fig. 3). The pro-atherogenic properties of lipoprotein(a) may be more important in this patient group. Examining the effect of differing lipoprotein(a) discriminant concentrations (Fig. 4) however, shows that baseline lipoprotein(a) concentrations lower than ≥ 30 mg . dl^{-1} appear to be prognostically important.

Some 10% of the patients studied received pharmacological lipid lowering therapy during follow-up. This low treatment rate is in accord with the recently reported results of a U.K. National Survey[66]. Of interest, however, was the finding in our study that the total admission cholesterol, when entered into the regression model either as a continuous variable or as categorical variables with cut offs of 5·2 or 6·5 mmol . l^{-1}, either alone or combined with either admission lipoprotein(a) ≥ 30 mg . dl^{-1} or $\geq 7{\cdot}9$ mg . dl^{-1} was not a predictor of subsequent cardiac death in either acute coronary syndrome. These findings suggest that lipoprotein(a) may be acting independently from the cholesterol with regard to outcome in this patient group and challenges the view that aggressive lowering of low density lipoprotein cholesterol may attenuate the pathological actions of lipoprotein(a)[41]. This question should be answered by analyses with respect to lipoprotein(a) concentrations in the different treatment arms of the large post infarct lipid lowering trials[42,43]. If the results concur with our findings then it raises the question as to whether focusing studies on treating the prothrombotic potential of lipoprotein(a) may prove to be more beneficial in reducing subsequent cardiac events.

In conclusion, this study has shown that baseline lipoprotein(a) concentrations in patients admitted with acute coronary syndromes are associated with an increased risk of cardiac death. For patients with myocardial infarction a concentration of ≥ 30 mg . dl^{-1} appears appropriate as a risk discriminator; for patients admitted with unstable angina however, much lower concentrations of lipoprotein(a) appear to be prognostically important.

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