ORIGINAL ARTICLE

Prevalence and non-invasive predictors of left main or three-vessel coronary disease: evidence from a collaborative international meta-analysis including 22 740 patients

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ABSTRACT

Background Left main disease (LMD) and three-vessel disease (3VD) have important prognostic value in patients with coronary artery disease. However, uncertainties still exist about their prevalence and predictors in patients with acute coronary syndrome (ACS) and also in patients with stable coronary disease. Thus the aim of this study was to perform an international collaborative systematic review and meta-analysis to appraise the prevalence and predictors of LMD and 3VD.

Methods Medline/PubMed were systematically searched for eligible studies published up to 2010, reporting multivariate predictors of LMD or 3VD. Study features, patient characteristics, and prevalence and predictors of LMD and 3VD were abstracted and pooled with random-effect methods (95% CIs).

Results 17 studies (22 740 patients) were included, 11 focusing on ACS (17 896 patients) and six on stable coronary disease (4844 patients). In the ACS subgroup, LMD or 3VD occurred in 20% (95% CI 7.2% to 33.4%), LMD in 12% (95% CI 10.5% to 13.5%), and 3VD in 25% (95% CI 23.1% to 27.0%). Heart failure at admission and extent of ST-segment elevation in lead aVR on 12-lead ECG were the most powerful predictors of LMD or 3VD. In the stable disease subgroup, LMD or 3VD was found in 36% (95% CI 18.5% to 48.8%), with the most powerful predictors being transient ischaemic dilation during the imaging stress test, extent of ST-segment elevation in aVR and V1 during the stress test, and hyperlipidaemia.

Conclusions This meta-analysis demonstrated that severe coronary disease—that is, LMD or 3VD—is more common in patients with ACS or stable coronary disease than generally perceived, and that simple and low-cost tools may help in the selection of the most appropriate therapeutic approach.

INTRODUCTION

Left main coronary disease (LMD) and three-vessel coronary disease (3VD) carry a high risk of death and adverse events in both stable and unstable

clinical settings.^{1 2} This poor prognosis may be improved in selected patients by percutaneous or surgical revascularisation,^{1–3} but invasive interventions are often not carried out because of underestimation and poor definition of patient risk. For example, in a large contemporary registry, percutaneous coronary intervention was performed in only 70% of patients with acute myocardial infarction and 35% of patients with unstable angina.⁴

Clearly, reliable and independent predictors of LMD and/or 3VD could be helpful in order to focus resources and aggressive therapies to this high-risk subset of patients.

A few studies have addressed these issues in various populations,^{5 6} but, to our knowledge, no meta-analyses have been performed to globally assess them. We therefore performed a systematic review focusing on (1) the incidence of LMD or 3VD, and (2) their non-invasive predictors.

METHODS

The main objective of this study was to identify multivariate predictors of LMD or 3VD using a meta-analytical approach. Current guidelines were followed during the course of the present research, in particular the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, and recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE).^{7–11 14}

Search strategy and study selection

Medline, Cochrane Library and Biomed Central were systematically appraised in keeping with established methods¹² with highly specific terms 'left main* OR multivessel disease* and predictor (NOT (review(pt) OR editorial(pt) OR letter(pt)))'.

Two independent reviewers (GB-Z, FDA) first analysed selected citations at the title and/or abstract level, with disagreements resolved after

consensus. If potentially pertinent, studies were then appraised as complete reports according to the following explicit selection criteria. Inclusion criteria were (all had to be met for inclusion) studies that (1) investigated patients presenting with acute coronary syndrome (ACS) or patients with stable angina or instrumental ischaemia, (2) reported predictors of LMD or 3VD identified through multivariate analysis, and (3) defined 3VD as a significant stenosis in all three main epicardial coronary arteries. Exclusion criteria were non-human studies and duplicate reporting (in which case the article reporting on the largest sample was retained).

Data extraction

The same two investigators independently and in a blinded fashion tabulated the data of all studies qualifying for the meta-analysis and also contacted the corresponding authors for additional information.¹³ Data collected included authorship, journal and year of publication, country of origin, baseline demographic and clinical features (eg, risk factors, previous percutaneous or surgical revascularisation, indication for angiography), and independent predictors of LMD or 3VD. They were reported both as frequencies in different studies and with their power of prediction, evaluated as OR.

Internal validity and quality appraisal

The quality of each manuscript was graded using a modified MOOSE code taking into account the specific features of each study,⁹ with regard to design, setting, data source, statistical approach to multivariate analysis. A score of zero was assigned to retrospective and single-centre studies, and a score of one to prospective and multicentre studies. Studies with potential study bias in selection, adjudication, detection and attrition were ascertained as low with no bias identified, moderate with one identified, and high with two identified or when bias could not be assessed. An overall credibility index was built on all these parameters, with a score of 10 implying a very high credibility index, and 7–9, 4–6, 1–3 and 0 indicating high, moderate, low and very low indices, respectively.

Data analysis and synthesis

Continuous variables are reported as mean (SD) or median (range). Categorical variables are expressed as n/N (%). Statistical pooling was performed according to a random-effects model with generic inverse-variance weighting, computing risk estimates with 95% CIs, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). Fixed effect was also appraised, and reported only if different results from random were found. Independent predictors were reported according to the number of studies in which they were evaluated and weighted according to their OR. Small-study bias was appraised by graphical inspection of funnel plots. Standard hypothesis testing was set at the two-tailed 0.05 level.

Figure 1 Review profile.

Table 1 Key patient characteristics

Characteristic	ACS studies (n=17 896)	Stable patients (n=4844)
Age (years)	65 (60–66)	62 (60–65)
Male gender	64% (60–71)	70% (65–73)
Diabetes	34% (27–36)	35% (20–39)
Hypertension	66% (57–76)	62% (60–70)
Dyslipidaemia	49% (46–57)	52% (40–64)
Prior cardiac events (both myocardial ischaemia and revascularisation*)	47.5% (40–58)	20% (18–26)
Admitted with unstable angina	58% (40–309)	—
Admitted with acute myocardial infarction	80% (54–150)	—
Admitted with non-ST segment elevation myocardial infarction	65% (30–250)	—
Admitted with ST segment elevation myocardial infarction	71% (61–87)	—
Admitted with chest pain with positive stress test	—	10% (9–12)
Consecutive patients undergoing percutaneous coronary revascularisation, with documented angina or positive ischaemia test	—	80% (70–87)
Asymptomatic diabetic patients (a research protocol)	—	10%

Values are % or median (1st–3rd quartile).

*Including previous acute myocardial infarction, surgical and percutaneous revascularisation.

ACS, acute coronary syndrome.

RESULTS

Figure 1 summarises the 17 studies that were found by the search and retained for analysis with a total of 22740 patients^{15–31}; 11 focused on ACS (n=17896)^{15–25} and six on stable coronary disease (n=4844).^{26–31}

Baseline features of patients with ACS and stable coronary disease are reported in table 1. Most of the patients were older than 60 years, and were male in almost two-thirds of the cases. Rates of cardiovascular risk factors were similar for patients with stable and unstable coronary disease, while previous cardiovascular events were more commonly reported in patients with ACS (48% vs 20%). The latter were more often admitted for acute myocardial infarction, especially ST elevation myocardial infarction (up to 70%), while patients with stable disease most often underwent coronary angiography because of symptoms (80%) or laboratory evidence of ischaemia (10%).

In 68% of the studies, physicians appraising the ECG were blinded to the angiography results. The definition of coronary vessel stenosis, other than LMD stenosis, was more than 75% in 57% of the studies.

Among patients with ACS, the prevalence of LM or 3V disease was 20% (95% CI 7.2% to 33.4%), the prevalence of LM disease alone was 12% (95% CI 10.45% to 13.5%), and the prevalence of

Figure 2 Prevalence of left main (LM) and three-vessel disease (reported as percentages) in stable patients and patients with acute coronary syndrome.

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Table 2 Most common non-invasive predictors of left main and three-vessel disease in patients presenting with acute coronary syndrome

Predictor	No of overall studies (N=11) (%)	No of studies reporting both LMD and 3VD predictors (N=3) (%)	No of studies reporting only multivessel predictors (N=6) (%)	No of studies reporting only LMD predictors (N=2) (%)
Age (per decade increase)	3 (27)	1 (33)	2 (33)	—
ST elevation in aVR	3 (27)	1 (33)	1 (17)	1 (50)
Male gender	3 (27)	1 (33)	1 (17)	1 (50)
Positive biomarkers (troponins)	1 (20)	—	—	1 (50)
History of coronary artery disease	3 (27)	1 (33)	1 (17)	1 (50)
Signs of left heart failure detected at the time of hospital admittance	2 (18)	—	1 (17)	1 (50)
Peripheral artery disease	2 (18)	1 (33)	1 (17)	—
Diabetes mellitus	2 (18)	1 (33)	1 (17)	—
Heart rate (per 10 beats/min increase)	2 (18)	1 (33)	1 (17)	—
TIMI risk score (for points increase)	1 (9)	1 (33)	—	—
Pro-BNP	1 (9)	—	1 (17)	—
Previous use of aspirin	1 (9)	1 (9)	—	1 (50)
ST segment depression	1 (9)	—	—	1 (50)

3VD, three-vessel disease; BNP, B-type natriuretic peptide; LMD, left main disease; TIMI, Thrombolysis In Myocardial Infarction risk score.

3V disease alone was 25% (95% CI 23.1% to 27.0%) (figure 2). The most common predictors are reported in table 2. Heart failure at clinical presentation (reported in 18% of studies) and degree of ST elevation in lead aVR (reported in 27% of cases) were the most powerful predictors (figure 3).

In stable patients, as reported in figure 2, the overall incidence of LMD or 3VD was 36% (95% CI 18.5% to 48.8%), with the most powerful predictors being transient ischaemic dilation (TID) during myocardial perfusion imaging, lead aVR and V1 elevation during the stress test, and hyperlipidaemia (all reported in 9% of studies: table 3, figure 4).

The most important methodological features of these studies, and their internal validity, are reported in tables A and B (online appendix). Briefly, most were single-centre studies performed more commonly in North America and Asia, used a logistic regression model, and were assessed as having moderate overall credibility by our criteria.

DISCUSSION

The key findings of our study are: (a) LMD and 3VD are common clinical conditions, more common than generally expected, in both stable and unstable coronary disease; (b) simple, inexpensive and readily available clinical and laboratory tests may be helpful for screening patients with these high-risk conditions to enable them to receive optimal treatment.

Patients with 3VD and LMD have been the subject of several investigations to assess the best revascularisation procedure³². For this reason, it is useful to know of tools that could quickly identify this condition or raise a strong clinical suspicion.

Our meta-analysis provides interesting information from an epidemiological point of view, revealing the most powerful predictors of LMD and 3VD in patients with ACS and stable angina. In ACS, the prevalence of LMD and 3VD was 20.13%, the prevalence of LMD alone was 12%, and the prevalence of 3VD alone was 25.7% among patients who underwent coronary angiography. In this group, the most powerful predictors of LMD or 3VD were degree of ST elevation in lead aVR and heart failure. In patients with stable coronary disease, the prevalence of LMD and 3VD was 33.5%, and the most powerful predictor of these conditions was TID during myocardial perfusion imaging. Our percentage of LMD is slightly higher than literature data. In fact, although there are no specific studies on incidence and prevalence of LMD and ACS, in retrospective analysis including all subjects who underwent angiography for suspected coronary artery disease, this condition was found in 4.7–9%.^{36–38} In our meta-analysis, one in four patients with ACS was affected by 3VD; this rate is higher than reported in data extrapolated from CADILLAC (15.6%) and Stent-PAMI I (13.18%) (two studies on primary percutaneous coronary intervention), but similar to other trials.^{39–40} These differences may

Figure 3 Most powerful predictors of left main disease/three-vessel disease in patients with acute coronary syndrome (reported as OR). *Obtained in study reporting only left main disease predictors. **Obtained in study reporting left main and three-vessel disease predictors. Thrombolysis In Myocardial Infarction risk score (TIMI).

Table 3 Most common non-invasive predictors of left main and three-vessel disease in stable patients (reported as percentages and absolute values)

Predictor	No (%) (N=6)
Age (per decade)	2 (18)
Lead aVR ST elevation during stress test	1 (9)
Lead V1 ST elevation during stress test	1 (9)
Leads V4, V5, V6, II, III, aVF depression during stress test	1 (9)
Transient ischaemic dilation during myocardial perfusion imaging	1 (9)
Pregnancy-associated plasma protein-A levels	1 (9)
Coronary artery calcification score	1 (9)
Male gender	1 (9)

be related to the absence of a uniform definition of 3VD which would allow a precise comparison between different studies. In the stable patients, one in three had either LMD or 3VD. Baseline characteristics of patients in the COURAGE study show a slightly lower percentage (25%) with 3VD. However, it should be remembered that, in this trial, patients with unprotected LMD were excluded.³⁹ A more accurate comparison can be performed with the analysis of the subgroup of patients with high-risk coronary disease in the CASS registry, which reported that 8% of women and 27% of men with stable chest pain and no history of myocardial infarction had LMD or 3VD.⁴⁰

Another important aspect to consider is that we found the most powerful predictors of 3VD and LMD to be ST elevation in lead aVR and a clinical finding of heart failure. It is important to emphasise this finding because it means that clinical examination and the 'plain old 12-lead ECG' are still among the top predictors in the evaluation of ACS, even though new technologies are assuming an increasing role.^{41–44} Moreover, this could be very useful in the clinical evaluation of unstable disease: if LMD is suspected, ergometric tests should be avoided because of potential risk, and an invasive diagnostic study should be performed.

Several editorials have suggested that lead aVR was of little help in ECG analysis, as it provides only reciprocal information from the left lateral side, whereas its original purpose was to explore the outflow tract of the right ventricle and the basal part of the septum located in the upper right side of the heart.^{45–46} In contrast, several clinical studies have shown that ST elevation in lead aVR was not only helpful in identifying severe coronary artery disease, but could also be a predictor of adverse outcome in ACS.^{46–48} Assessment of baseline ECG and an eventual stress test can provide useful prognostic information.⁴⁹ For this reason, they are both taken into account in current clinical practice,^{50–51} despite their unclear predictive value, which goes beyond the aim of the present study.

Figure 4 Most powerful predictors of left main disease/three-vessel disease in stable patients (reported as OR). *Transient ischaemic dilation during myocardial perfusion imaging.

Similar considerations can be made about heart failure and ACS. In fact, the GRACE study group has amply shown that Killip class is a powerful predictor of in-hospital and 6-month mortality in ACS.⁵² In 2005, the CADILLAC group documented that heart failure was a predictor of 1-year mortality among patients with ST elevation myocardial infarction; this study also showed that the presence of 3VD was also a powerful prognostic factor.³⁹ A correlation between extent of coronary artery disease and heart failure was underlined by Haim *et al*⁴² in a large European survey of outcome of 2529 patients with ACS complicated by symptomatic heart failure. In fact, prevalence of 3VD and LMD in these subjects was significantly higher than in other patients.

Finally, with regard to stable patients, we found that the most powerful predictor of LMD or 3VD was TID during myocardial perfusion imaging. Our result confirms medical literature data that consider TID to be an important marker of both 3VD and LMD,⁵² and it is interesting that similar observations were obtained in patients undergoing stress echocardiography.⁵³ However, Valdiviezo *et al* reported that TID does not increase the likelihood or severity of coronary artery disease in patients with otherwise normal SPECT (Single-photon emission computed tomography) radionuclide myocardial perfusion images.^{54–56}

Our work has several limitations. First, the prevalence data were limited to a small subset of patients, because of our strategy to include studies that used multivariate analyses to define predictors. Second, no pooling was made of predictors, and, as the most common predictors are not necessarily the most powerful ones, a bias was created in selecting the ones that were most often reported.^{57–59} Prospective studies would give a different perspective, as they would use predefined parameters; however, the present approach gives a wider perspective across the existing literature. Another important limitation is that we could not obtain discrete data on the relative incidence of LMD versus 3VD in patients with stable angina, and therefore could not distinguish between predictors of LMD and 3VD. However, the data remain clinically useful, as these two groups of patients can generally benefit from angiography with a view towards interventional therapy. Finally, the epidemiological data were obtained from analysis of cohorts of prospective and retrospective studies, which may be influenced by recruitment bias. This may lead to some differences compared with the 'real world'. The funnel plot (figure 5) is skewed in showing only the more precise larger studies. A final limitation was that patient-level data were not used.

Figure 5 Funnel plot.

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Contributors FDA conceived and designed the study and wrote the paper. GBZ and IS supervised the conduct of the trial and data collection. GBZ, IS and FDA provided statistical advice on study design and analysed the data; all authors contributed substantially to its revision. FDA takes responsibility for the paper as a whole. FDA, GBZ and IS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors were involved in the writing and approved the manuscript.

Competing interests None.

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