The value of routine non-invasive tests to predict clinical outcome in stable angina

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Received 20 November 2002; accepted 20 November 2002

Background Chronic stable angina is a common condition, but considerable differences exist in the likelihood of acute coronary events such as CHD death, non-fatal myocardial infarction (MI) and unstable angina between individual patients. Effective risk prediction is necessary for optimum management. The aim of this study was to identify clinical features and non-invasive test parameters associated with high risk of these coronary events in stable angina and compose a clinically useful model to predict adverse outcomes in this population.

Methods Six hundred and eighty-two patients with stable angina and a positive exercise test (1 mm ST depression) from the Total Ischaemic Burden European Trial (TIBET) study, were studied. Resting ECG, exercise tolerance testing and echocardiography were performed at baseline, off anti-anginal therapy. The patients were then randomised to treatment with atenolol, nifedipine or a combination of both. Clinical follow up continued for an average of 2 years (range 1–3 years).

Results and conclusions Prior MI or prior CABG were the clinical parameters associated with adverse outcome in patients with stable angina and a positive exercise test. On the ECG, left ventricular hypertrophy was predictive, and on echocardiogram, increased left ventricular dimensions were predictive of adverse events. When combined with time to ischaemia on exercise testing in a simple clinically applicable table these factors could be used to predict of 2 year probability of events for an individual patient.

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KEYWORDS
Stable angina; Non-invasive testing; Echocardiography; Exercise testing; Prognosis

Introduction

The ability to predict, and potentially intervene to avert adverse future events is an extremely desirable goal. The prospect of achieving this goal, combined with current advances in medical knowledge, information processing and rigorous statistical analysis have led to the development of risk prediction techniques based on probabilities rather than intuition. In many situations, and keenly so in the setting of coronary disease, prediction of future events is of tremendous importance to a range of interested parties, from the individual patient, to health care providers, to
medical insurers, yet accurate risk prediction remains a challenge.

Left ventricular function and the severity and extent of coronary disease exert a profound influence on outcome in patients with angina, yet the most definitive means to obtain detailed information concerning the coronary plaque burden and left ventricular function remains cardiac catheterisation. However, considerable information concerning prognosis may be gleaned by non-invasive methods. This information may be used to facilitate triage of cardiac catheterisation referrals, and also to add to the predictive value of the coronary anatomy to allow more complete risk assessment. Clinical history, in particular heart failure or prior myocardial infarction (MI) or revascularisation, measures of functional capacity and evidence of inducible ischaemia all provide useful prognostic information, individually and in combination.

Given the considerable adverse impact of poor ventricular function at ventriculography on survival, the addition of echocardiographic assessment of left ventricular dimensions and function would be expected to add significant incremental prognostic information to that obtained from clinical evaluation and exercise testing.

The objective of this study was to assess the cumulative prognostic information obtained from routinely performed non-invasive testing including non-invasive assessment of left ventricular function by echocardiography. Using this information, it was then possible to derive a simple, easy to use table for estimating the probability of future fatal and non-fatal cardiac events. The data are extracted from the TIBET (Total Ischaemic Burden European Trial). This was a multicentre study which investigated the prognostic importance of the total ischaemic burden in patients with chronic stable angina, and compared the anti-anginal efficacy of atenolol 50 mg bd, nifedipine sustained-release and their combination using standardised protocols for exercise tolerance testing and ambulatory ECG monitoring. Analyses of the primary and secondary endpoints have been reported elsewhere. In summary, the presence, frequency and duration of ischaemic events on ambulatory Holter monitoring, on or off treatment, were not predictive of outcome. There was no evidence of significant difference between the three treatments with regard to their effects on exercise performance, or on the frequency or duration of ambulatory ischaemia. For the purposes of assessing cardiac risk, clinical, exercise and echocardiographic variables at baseline, before treatment were examined to determine their influence on prognosis.

**Methods**

**Patients**

Six hundred and eighty-two patients were randomised in the TIBET study. The mean age was 59 years, range 36–81 years. Eighty-six percent of the patients were male. All patients gave a history consistent with stable angina for at least 3 months before entering the study, and demonstrated objective evidence of ischaemia on exercise testing. None of the patients were under consideration for coronary artery bypass grafting at the time of inclusion into the study. Thirty-five patients had previously undergone CABG. The vast majority of patients were free of clinical heart failure, with only three patients with clinically diagnosed heart failure during pre-randomisation assessment. Patients were excluded from the study if they had any other important clinical disease in particular, renal impairment as defined as serum creatinine >200 µmol/l; hepatic impairment; uncontrolled hypertension, defined as systolic BP >200 mmHg or diastolic BP >105 mmHg on placebo, or contraindications to beta-blockade and/or nifedipine.

**Measurements**

The TIBET study design has been described previously. Resting ECG, blood pressure measurement, exercise tolerance testing and echocardiography were performed at baseline before active therapy.

**Clinical information**

The following clinical and demographic data were recorded: age, gender, occurrence of previous MI, history of hypertension, diagnosis of diabetes, smoking status and whether or not the patient had undergone coronary angiography, percutaneous trans coronary angioplasty or coronary artery bypass grafting. Blood pressure was measured with a standard sphygmomanometer using Karotkov sound V to record diastolic pressure after 3 min sitting and 1 min standing. Standing heart rate was also recorded.

**Resting ECG**

Measurements recorded on the resting ECG comprised ventricular ectopics, left ventricular hypertrophy (LVH), occurrence of 1 mm ST depression, Q waves, T wave inversion, conduction abnormalities, R wave and ECG heart rate.
Echocardiography

All patients underwent echocardiographic assessment of left ventricular dimensions at baseline. End-systolic and end-diastolic dimensions were measured in a long axis parasternal view according to American Society of Echocardiography criteria and fractional shortening calculated.

Exercise tolerance testing

To assess suitability for inclusion in the study, patients underwent symptom limited exercise testing during a 2 week placebo run in phase. To be randomised to one of the treatment arms the patients were required to have at least 1.5 mm ST depression during a symptom limited exercise test at a workload of <10 METS. Although central analysis was performed at a later date to ensure uniformity in reporting, randomisation occurred on the basis of the investigator's own interpretation of the exercise ECG. When subjected to central analysis after randomisation, some patients (56 in total, <10% of the total group) were found to have had less than 1 mm of ST depression during exercise before treatment. Only centrally analysed data have been used for the purposes of statistical analysis, but it is important that these patients all had a positive exercise test in the opinion of the investigators. Each centre consistently used either a treadmill or bicycle exercise test. The Bruce protocol was used for the treadmill tests and the bicycle protocol started at 30 W and increased by 30 W every 3 min. All exercise times were standardised to allow pooling of the bicycle and the treadmill exercise times.

Clinical follow up

Follow up was for a period of 1–3 years. It was felt that beyond this time period medical interventions, including revascularisation were more likely to have occurred, which have the potential to influence the clinical outcome. Therefore risk assessment involving clinical history, exercise and echocardiographic testing would be most useful in predicting risk over the short- to mid-term period chosen, rather than over a prolonged period of time with constantly evolving patterns of treatment in the interim which could not be controlled for in the analysis. The combined endpoint comprised time to the first major adverse cardiac events of unstable angina, MI or cardiac mortality, as defined below. Unstable angina was included as an endpoint as it is an important cause of morbidity in this population, with its own attendant mortality. It is likely that if the new European Society of Cardiology definition of MI, on the basis of troponin, was applied to the unstable angina events in this study a considerable number would in fact be re-classified as MIs.

Unstable angina

This was defined as chest pain of increasing frequency and severity or at rest requiring hospitalisation of the patient and not associated with the development of new Q waves or a rise in cardiac enzymes.

Myocardial infarction; silent or symptomatic

A silent MI was defined as the presence of pathological Q waves in the ECG without a history of chest pain.

A symptomatic MI was defined according to the following criteria, at least two of which must be fulfilled:

(a) Chest pain of more than 30 min duration with onset during the previous 48 h or pulmonary oedema in the absence of valve disease or shock without hypovolaemia.
(b) Transient elevation of aspartate transaminase (AST) to values above the normal limits of the laboratory with a maximum approximately 24 h after the estimated onset of the infarction and/or transient elevation of creatinine kinase (CK) to values above the limits of the laboratory with a maximum approximately 24 h after the onset of the infarction.
(c) ECG series with the development of pathological Q waves and/or the development or disappearance of localised ST segment elevation combined with the development of T wave inversion in at least two of the routine 12 standard leads.

Cardiac mortality

For a diagnosis of acute fatal MI to be recorded, this diagnosis had to be stated on the death certificate or if the death certificate diagnosis was uncertain, evidence of recent MI had to be present at post-mortem examination. Sudden cardiac death was recorded if the patient died within 24 h of the onset of symptoms and extra-coronary causes of death were lacking.

Statistical methods

Response and modelling

The data were analysed as time to first event of the combined endpoint of cardiac mortality, non-fatal
MI or unstable angina, with follow up of 1–3 years. Variables within clinical history, baseline echocardiography, resting and exercise ECGs were investigated univariately, and then jointly within a class using stepwise selection, in Cox proportional hazards (CPH) models. Then composite models were fitted across the classes of variables using stepwise selection on variables found to be significant within each class. All p values reported are for the Wald statistic from the CPH model. In the univariate analysis Fisher's exact test was used if the number of subjects with an event was very low in any category when a binary outcome was being studied. Forwards selection was used with a Wald p value to stay at 0.05.

Figures and tables

Continuous data are presented as mean [standard deviation], for subjects with and without a hard endpoint. Categorical data are given as number [percent] of subjects with and without the variable, for subjects with and without an endpoint (Tables 1–3). Estimated hazard ratios with approximate 95% confidence intervals (CI) are given for the univariate analysis, but only the results for the echocardiogram and exercise tests are tabulated. For binary variables the hazard ratio is that associated with the presence or absence of the risk factor, while for continuous variables it is for the given increment (for example, an increase of 0.5 cm of end-diastolic dimension). For the composite models, estimated hazard ratios and 95% CIs are given for each variable conditional on all other variables in the model (Table 4).

Estimated 2 year probabilities of the endpoints of cardiac death, non-fatal MI or unstable angina were calculated from a version of the composite CPH model for the various combinations of the levels of the risk predictors previous CABG, LVH on

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<th>Table 1 Univariate analysis of echocardiographic data (baseline data on 612 cases (of whom 68 suffered endpoints))</th>
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<td>Variable</td>
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<td>ESD (cm)</td>
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<td>Fractional shortening (%)</td>
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Hazard ratio quoted is for a 0.5 cm increase in either end-diastolic or end-systolic dimension or 10% increase in fractional shortening.

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Data available on 569 patients who underwent exercise testing at baseline.

⁴ Number of subjects with/without the stated risk factor.
⁵ Fisher’s exact test.

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<th>Table 3 Univariate analysis of baseline exercise ECG continuous covariates (off treatment)</th>
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<td>Peak log rate pressure</td>
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Data available on 569 patients who underwent exercise testing at baseline.
resting ECG, end-diastolic dimension on echocardiogram and time to 1 mm ST depression on exercise testing (Table 5).

Variable definitions and transformations

Fractional shortening is \[100 \times \frac{\text{end diastolic} - \text{end systolic}}{\text{end diastolic}}\] dimensions. Log rate pressure product is the natural logarithm of heart rate\(\times\)systolic blood pressure. To allow the combination of bicycle and treadmill exercise tests, bicycle data were standardised to the mean and standard deviation of the treadmill. All times are reported on the scale of the Bruce protocol treadmill.

Other statistical issues

There were data missing for almost all variables. Each analysis was done with the maximum complete data within that class. No adjustment has been made for the multiple tests of significance. Models derived from stepwise procedures should be interpreted with caution. The non-inclusion of a variable does not mean that it does not have predictive capacity in this data set, only that it does not provide additional predictive capacity in the presence of variables already in the model. In addition there may well be models which would perform almost as well as the model given. For example, end-systolic and end-diastolic dimensions are probably interchangeable in any model.

Results

Clinical data

Univariate analysis of all the clinical and demographic assessments described in the clinical information section revealed the most statistically significant determinants of outcome in the clinical history to be previous MI (hazard ratio 1.69, 95% CI [1.06–2.69], \(p=0.027\)) and previous CABG (hazard ratio 2.40 [1.15–5.02], \(p=0.019\)). Of the 72 patients who suffered the combined endpoint (and who had a complete set of clinical data), 10 had cardiac death as their first event, 36 had an initial...
MI and 26 had unstable angina. Thirty-two had a history of previous MI and eight had previous CABG.

**Resting ECG**

Of the individual parameters listed above from the baseline ECG, ECG evidence of LVH was found, using univariate analysis, to be predictive of the combined endpoint of death, MI or unstable angina. Endpoints occurred significantly more frequently in patients with LVH on the baseline ECG. Of the 66 patients with complete ECG data who suffered a major cardiac adverse event, 14 had ECG–LVH (hazard ratio 2.92 [95% CI 1.62–5.28], p<0.001). No other ECG variable achieved statistical significance at p<0.05.

**Echocardiography**

Of the echocardiographic parameters, the most significant predictors of outcome were left ventricular dimensions measured as described (Table 1). Endpoints were more frequent in patients with larger end-systolic dimensions (hazard ratio for a 0.5 cm increase 1.29 [95% CI 1.14–1.46], p<0.001) and end-diastolic dimensions (hazard ratio for a 0.5 cm increase 1.33 [95% CI 1.15–1.53], p<0.001). Fractional shortening just failed to reach statistical significance (p=0.055).

**Exercise tolerance test variables**

The univariate analysis of the exercise tolerance test variables are shown in Table 2 (categorical covariates) and Table 3 (continuous covariates). On the exercise test, occurrence of ≥1 mm ST depression and time to occurrence of ≥1 mm ST segment depression were individually related to outcome. Of the 69 patients with complete exercise data who experienced a major adverse cardiac event, all but one had 1 mm ST depression during exercise, yielding a hazard ratio of 6.21 [95% CI 0.86–44.7], Fisher’s exact test p value 0.022. It must be acknowledged that the selection criteria for the study included ST depression and only relatively small number of patients, who were in violation of the protocol. This small number is reflected in the wide confidence interval which includes unity. However, time to ST depression was also predictive, with every 30 s quicker to 1 mm ST depression associated with an increased hazard ratio of 1.06 [95% CI 1.00–1.11], p=0.049.

**Multivariate analysis**

After stepwise fitting, previous CABG, and to a lesser extent previous MI (p=0.07), baseline LVH, time to 1 mm ST depression and end-diastolic dimensions were jointly predictive of the combined endpoint of cardiac death, non-fatal MI or unstable angina shown in Table 4. Although previous MI is of borderline statistical significance it was considerably more frequent in the population studied, and as such, still likely to be of clinical importance.

**Two year probability of events**

Estimated 2 year probabilities of the combined endpoint of cardiac death, non-fatal MI or unstable angina were calculated from the composite CPH model for various combinations of the levels of risk predictors including baseline ECG–LVH, echocardiographic ventricular dimensions, prior CABG and time to ST depression (Table 5). The estimated probabilities of an event within 2 years range from 3% to almost 80% according to the individual’s risk as measured by the stated risk factors.

**Discussion**

The usefulness of clinical information and non-invasive data in assessment of prognosis in stable angina, specifically in those patients with stable angina and a positive exercise test, has been illustrated clearly in this study. Previous studies have demonstrated the usefulness of clinical features, in particular symptoms of heart failure or a previous MI in prediction of adverse outcome in coronary disease patients even when exercise variables and coronary anatomy are taken into account. Pryor et al. showed that clinical history was at least as good as if not superior to exercise testing in isolation in predicting future risk of cardiovascular death. However, our study is unique in that it has selected patients with stable angina, without overt heart failure, and has combined clinical and exercise data with non-invasive assessment of left ventricular function in assessing prognosis.

**Clinical features**

In this population a prior history of MI is a significant predictor of subsequent outcome, HR 1.69, but when subjected to multivariate analysis this predictive value is attenuated, and is of borderline statistical significance. On the other hand, ventricular size remains an important and statistically significant predictor of outcome even in multivariate analysis. This confirms the important contribution of left ventricular damage at the time of MI (seen as an increase in ventricular dimensions on subsequent echo) to subsequent cardiac event rates.
The significant adverse effect of a prior history of CABG on prognosis is also noteworthy. It must be taken into consideration that the population under study all had positive exercise tests, and so the finding that previous CABG is associated with more frequent adverse events must be qualified. We have found that patients with angina and a positive exercise test post-CABG fare worse in terms of future death or infarction, or hospitalisation for unstable angina, than their counterparts who have not been previously surgically revascularised. There are several possible explanations. Firstly, this group of individuals are likely to have more severe disease to have been selected for coronary artery bypass in the first instance. Secondly, even with the routine use of aspirin, thrombotic occlusion of venous grafts is not uncommon, and atherosclerotic disease progresses more rapidly than in native coronary arteries or arterial conduits. Further revascularisation in such patients is performed, at higher procedural risk, primarily for symptomatic control, but has not been shown to offer improved prognosis.

Resting ECG

This study re-enforces the benefits of performing a resting ECG in assessment of the patient with angina and identifies the presence of ECG–LVH as an important prognostic indicator. ECG–LVH is well known to be a strong indicator of adverse prognosis in the general population, hypertensives and the elderly, and has been shown to be closely associated with the development of coronary disease in population studies. However, this study confirms the independent effect of LVH on prognosis even in a population with angina. The presence of ECG–LVH was associated with an almost trebling of the risk of future adverse events. This is in keeping with a previous study which showed ECG–LVH to be predictive of death in subjects both with and without documented coronary disease. In our study ECG–LVH continued to add incremental predictive information when combined with clinical, exercise and echocardiographica data. So, the simple resting ECG, far from being relegated, retains its place in the investigative hierarchy for stable angina.

Exercise test

In patients with stable angina and objective evidence of ischaemia during exercise testing, the time to ischaemia (1 mm ST depression) was predictive of subsequent cardiac events, with a HR of 1.06 for every 30 s less on the treadmill. This result is in keeping with the findings of previous investigators who have shown that the time to ST depression, and reduced exercise capacity are more closely associated with outcome than the presence or magnitude of ST change. In this study the magnitude of ST depression was not an independent predictor of outcome. This contrasts with the findings of the APSIS study, a similar study of stable angina patients treated with either verapamil or metoprolol, where the investigators found that maximal ST change as well as exercise duration independently predicted cardiovascular death or infarction.

Echocardiographic assessment of the left ventricle

The fundamental importance of left ventricular function, determined at catheterisation, to prognosis, across all levels of the extent of coronary disease, is well recognised. During the 4 year follow up of medically treated patients in the CASS study the survival in subjects with poor left ventricular function was 58% compared to 92% in the normal left ventricular function group, with a marked difference in survival regardless of whether the patients had one, two or three vessel disease. It may seem difficult to extrapolate these results to the current population with stable angina, due to increased rates of revascularisation and the introduction and routine prescription of prognosis modifying drugs such as aspirin and statins. However, although the absolute mortality rates observed in trials of coronary surgery versus medical therapy in the 1970s and 1980s may have been reduced, analysis of the results of these trials using decision analysis and incorporating current recommendations for treatment estimate that improvements in infarct free survival would apply to both medical and surgical patients, so that conclusions of the trials remain valid. Also the potential reduction in events which would be expected from the introduction of ACE inhibitors would be limited to those patients with heart failure or post-MI, as aside for prescription for concomitant hypertension, these were the evidence based indications for ACE inhibitor therapy in coronary artery disease until the publication of the HOPE trial. The data we have presented, relating to echocardiographic assessment of the left ventricle, have confirmed our expectation, based on CASS and other angiographic studies, that left ventricular function has a
profound effect on prognosis in the stable angina population. It should be emphasised that in the population studied, only three patients had clinically diagnosed heart failure. Yet, non-invasive assessment of left ventricular function was found to be a significant and powerful predictor of subsequent adverse events, with a graded increase in risk as ventricular dimensions increased, highlighting the fact that ventricular dysfunction is often sub-clinical, and must be actively investigated. In this case the aphorism ‘more is missed by not looking than by not knowing’, is proven true.

The important contribution of non-invasive assessment of left ventricular function in determining prognosis in coronary disease and added yield from exercise testing have been demonstrated in the post-MI population in the GISSI—Prevenzione Study. However, this is the first large scale study to combine echo with clinical and exercise data in assessing prognosis in the stable angina population. M-mode measurement of end-systolic and end-diastolic diameters were found to complement clinical and exercise data, and appeared in all the composite models as significant prognostic variables, reflecting the strong and independent impact of poor left ventricular function on outcome. In this population, standard trans-thoracic echocardiography, a relatively inexpensive and non-invasive technique, which does not incur the risk of radiation exposure, affords not only important prognostic information with regard to outcome, but also incremental prognostic information when combined with exercise and clinical data.

Prognostic assessment combining clinical ECG, echo and exercise data

The tables combining clinical, ECG, echo and exercise test data provide a clinically relevant and easy to use assessment of risk. From these data it is possible to estimate the 2 year probability of events. This has the advantage of not only allowing effective separation of very high and very low risk (for example, a patient who presents with angina who has had previous CABG, with LVH on the ECG, a dilated ventricle and ST depression within 2 min on the treadmill, who has a 79% probability of death MI or unstable angina over 2 years versus a patient without prior CABG, no LVH, a normal sized ventricle and ST depression after 8 min on the treadmill who has a 3% probability of an event within 2 years) but also, very importantly, allows effective discrimination of the levels of intermediate risk between these extremes. The format of the table is simple and easy to read, and does not require the clinician to utilise complex scoring systems to calculate the probabilities. The information gained is not only of importance in clinical practice, but also in the planning of clinical trials, as selection of a high-risk population in this manner has been shown to be useful in creating an appropriate population for investigation with a predictable number of outcome events.

The study is not without limitations. Although over 680 patients were randomised in the study, the number of endpoints was relatively small. However, this frequency reflects that of a low-risk stable population which is clinically relevant. The algorithm devised to predict 2 year outcome has not yet been prospectively validated as a means to estimate the probability of events, although this project may be undertaken in the future.

The importance of left ventricular damage in determining the prognosis in coronary artery disease has been confirmed in a low-risk population with stable angina, with progressive deterioration in ventricular dimensions associated with a graded increase in risk. The study has demonstrated the incremental prognostic information obtained by combining echocardiographic assessment of the left ventricle with clinical and exercise parameters. The risk prediction model allows easily performed, clinically relevant estimation of cardiac risk using routinely performed non-invasive tests.

References


