Predictors of 90-day outcome in patients stabilized after acute coronary syndromes


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Aims We investigated predictors of 90-day risk among patients surviving the early period after an acute coronary syndrome (ACS).

Methods and Results The study population included 15,904 stabilized ST-segment elevation or non-ST-segment elevation ACS patients randomized in SYMPHONY and 2nd SYMPHONY. We developed risk models for death, death or myocardial infarction (MI), and death, MI, or severe recurrent ischaemia (SRI) using Cox proportional-hazards techniques. Demographic, history, and pre-randomization clinical and medication variables were tested. Validation techniques included development of individual trial models, backward elimination and bootstrapping. Of 118 variables, 17 independently predicted mortality. The strongest associations included greater age ($\chi^2 = 31.1$), higher randomization heart rate ($\chi^2 = 27.4$), and heart failure (HF) variables (HF between qualifying event and randomization, $\chi^2 = 21.8$; history of HF, $\chi^2 = 12.2$). Higher creatinine clearance ($\chi^2 = 17.7$) and percutaneous coronary intervention between qualifying event and randomization ($\chi^2 = 11.1$) most strongly predicted lower risk. Similar characteristics entered the double and triple composite models, but HF variables and age less strongly predicted these end-points.

Conclusions In patients stabilized after ACS, those at highest risk over the next 90 days can be identified. Typical clinical markers are better at identifying risk of death than non-fatal MI or SRI. Novel risk markers are needed for these outcomes.

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KEYWORDS
Acute coronary syndromes; risk models; outcomes; risk stratification

Introduction
Quantification of subsequent risk in stabilized patients after acute coronary syndromes (ACS) could improve clinical management and also facilitate designing clinical trials of strategies targeted at preventing recurrent ischaemic events. Although models have been developed that identify demographic, historical and clinical characteristics associated with short-term outcomes after both ST-segment elevation acute myocardial infarction (MI) and non-ST-segment elevation ACS, the clinical trial populations used have generally been randomized within 6–24 h of symptom onset. Thus, these models are limited by reflecting the high early hazard of ACS patients. For example, among ST-segment elevation MI patients in Global
Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) I, 39% of 30-day deaths occurred within 24 h; 55% within 48 h. Similarly, among non-ST-segment elevation ACS patients randomized in Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), 56% of death or MI end-points occurred within 96 h. Less is known about the characteristics associated with outcome among patients stable for several days or how clinical management during that time affects later outcome.

To identify characteristics associated with outcomes in patients stabilized after an ACS, we developed predictive models for 90-day death, death or MI, and death, MI or severe recurrent ischaemia leading to unplanned revascularization (SRI) using the 15 904 patients randomized in the Sibrafiban versus aspirin to Yield Maximum Protection from ischaemic Heart events post-acute cOrOrynS Syndromes (SYMPHONY) and 2nd SYMPHONY trials.

Methods

Patient population

Between August 1997 and August 1999, 15 904 patients from 931 clinical centres in 37 countries were randomized in SYMPHONY and 2nd SYMPHONY to evaluate sibrafiban, an oral platelet glycoprotein IIb/IIIa inhibitor, for secondary prevention. Complete methods and results of these trials have been published. Patients with both ST-segment elevation MI and non-ST-segment elevation ACS were eligible if they presented with ≥20 min of chest pain or anginal-equivalent symptoms and met electrocardiographic or cardiac marker criteria. Randomization occurred within 7 days, and patients were stable for ≥12 h (without recurrent ischaemia or haemodynamic instability and with Killip class <II) at randomization.

SYMPHONY randomized 9233 patients a median of 3.6 (interquartile range 2.2–5.1) days after ACS to 90-day treatment with either aspirin 80 mg twice-daily or one of two dosing strategies (high or low) of sibrafiban twice-daily without background aspirin. The 2nd SYMPHONY randomized 6671 patients at a median of 3.7 (2.6–5.5) days to either aspirin 80 mg twice-daily, aspirin 80 mg plus low-dose sibrafiban twice-daily, or high-dose sibrafiban alone twice-daily. Median treatment duration was 90 (35–138) days.

End-points

The SYMPHONY primary end-point was the 90-day incidence of a composite of death, MI, or SRI (death/MI/SRI). The time to this composite was the 2nd SYMPHONY primary end-point. The occurrence of MI and SRI was determined by a blinded Clinical Events Classification Committee for each trial using prespecified criteria. SRI was defined as recurrent ischaemic symptoms for ≥20 min resulting in unplanned or unscheduled revascularization. The MI end-point required elevation of CK-MB > upper limit of normal (ULN) for clinical events, >3×ULN post-percutaneous coronary intervention (PCI) and >5×ULN post-bypass surgery, or the development of new Q-waves in ≥2 contiguous ECG leads.

Statistical methods

General

Extensive information on demographics and history, clinical characteristics and complications, procedure and concomitant medication use, and outcomes was collected in each study. Variables collected and database structure were common to SYMPHONY and 2nd SYMPHONY. Baseline characteristics in each study have been previously published. After verifying the similarity of the two populations and ensuring common variable definitions, the databases were merged to form a single, combined database. Descriptive statistics (medians [interquartile ranges] and percentages) were generated to summarize data.

Modelling

Because 2nd SYMPHONY was terminated early, duration of follow-up varied widely, median 94 (64–157) days. Therefore, for development of the outcomes models using the individual or combined databases, we used Cox proportional-hazards modelling with censoring at 90 days. We developed predictive models for death, death or MI (death/MI), and death/MI/SRI.

For each model, univariable associations with outcomes were assessed for each potential covariate shown in Appendix 1. Continuous variables that were nonlinear with respect to outcome were transformed using restricted cubic spline techniques. All variables for which there were fewer than 200 patients missing data, were entered into an initial multivariable model using a stepwise selection process. If a variable with more than 200 patients missing was strongly predictive or considered clinically important it was added into the initial candidate variables. After initial stepwise model development, other variables were tested one at a time in addition to those in the initial model. Variables were retained if \( P < 0.05 \). Satisfaction of the proportional-hazards assumption was verified for each retained variable.
The final death model included 14,970 patients and 268 events, the death/MI model, 14,805 patients and 1,024 events, and the death/MI/SRI model, 14,906 patients and 1,398 events. There were only small differences in crude event rates between the modelled groups and those excluded from the models due to missing information. Among patients excluded from the death model, mortality was 1.71% vs 1.80% in the modelled group. The difference was slightly larger for death/MI; 8.11% in the group not included vs 6.92% in the modelled group. For death/MI/SRI, the event rate was 9.43% among patients not included compared with 9.38% among those modelled.

Several strategies were used to validate the models. First, individual models were developed for each trial (SYMPHONY and 2nd SYMPHONY) separately and compared for similarity prior to the decision to use a final combined-group model. Further, for models developed in both the separate trials and the combined database, backward elimination was performed. Finally, bootstrapping (20 samples with replacement per model developed) was also performed.

Results

The 15,904 patients in SYMPHONY and 2nd SYMPHONY survived a median 3.6 (2.5–5.4) days after their qualifying event and prior to randomization. The qualifying event was MI for 73.4% (63.7% ST-segment elevation and 36.3% non-ST-segment elevation) and for 26.6%, unstable angina.

Figure 1 displays event-free survival (a) and hazard function (b) curves for death, death/MI, and death/MI/SRI for the combined trial populations. Previous trials of acute ST-segment elevation MI have demonstrated three phases to these curves, a high-risk acute period over the first 24–48 h, a more modest-risk subacute period from 2–10 days, and a subacute to chronic phase to 30 days. The curves for each end-point in the current study population support that the population was enrolled beyond the initial high-risk period and that the modelling reflects events occurring in the second and third risk phases.

Mortality

Baseline characteristics by mortality status and univariable and multivariable associations between pre-randomization characteristics and mortality for the 17 independently associated variables are shown in Table 1. Age and creatinine clearance (CrCl) had the strongest univariable associations, followed by a history of heart failure, heart failure between qualifying event and randomization, and diuretic use.

Among the 17 variables independently associated with mortality, greater age, higher randomization heart rate, heart failure between qualifying event and randomization, history of heart failure, lower qualifying event systolic blood pressure, qualifying event MI, and angiotensin converting enzyme inhibitor use prior to randomization were most strongly associated with increased 90-day mortality risk. Better renal function and PCI prior to randomization were most strongly associated with reduced 90-day mortality risk. As shown in Fig. 2, better renal function was associated with lower mortality to a creatinine clearance of 70 cc·min⁻¹, above which risk remained constant.

The full model likelihood ratio $\chi^2$ was 367. A model with age alone had a likelihood ratio $\chi^2$ of
165, suggesting that age contributed approximately 45% of the full model’s prognostic information. Together, the six strongest predictors in Table 1 accounted for approximately 81% of the model’s prognostic information. The mortality model equation is shown in Appendix 2. Run as a logistic regression, the model c-index was 0.80.

Death or myocardial infarction

Covariates in the 90-day death/MI model are displayed by strength of association in Table 2, and the model equation in Appendix 2. Age and variables describing heart failure were less strong predictors of the double composite than death alone. Elevated cardiac marker levels at qualifying event, greater age, diuretic use, and recent anginal symptoms were most strongly associated with increased risk, while increasing time between qualifying event and randomization and PCI prior to randomization were most strongly associated with lower 90-day death/MI risk. In a pattern similar to that for 90-day mortality, higher creatinine clearance was associated with lower 90-day death/MI. Run as a logistic regression, the model c-index was 0.68.

**Death/MI/SRI**

The triple composite multivariable model (Table 3, Appendix 2) was similar to the double composite
model. Factors most strongly associated with 90-day occurrence of death/MI/SRI included age, recurrent ischaemia between qualifying event and randomization, diuretic use, and elevated qualifying event cardiac markers. Longer time from qualifying event to randomization, PCI between qualifying event and randomization, and higher creatinine clearance were most strongly associated with lower risk. Run as a logistic regression, the model c-index was 0.64.

**Table 2** Pre-randomization characteristics associated with death/MI

<table>
<thead>
<tr>
<th></th>
<th>Death/MI</th>
<th>No death/MI</th>
<th>Wald ( \chi^2 )</th>
<th>Univariable</th>
<th>Multivariable</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours from QE to treatment</td>
<td>84 (56,122)</td>
<td>92 (61,131)</td>
<td>31.6</td>
<td>34.4</td>
<td>0.995 (0.994–0.996)</td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention between QE and randomization</td>
<td>17.6%</td>
<td>26.0%</td>
<td>10.1</td>
<td>27.3</td>
<td>1.64 (1.36–1.97)</td>
<td></td>
</tr>
<tr>
<td>Elevated cardiac markers at QE</td>
<td>85.8%</td>
<td>82.1%</td>
<td>89.1</td>
<td>16.1</td>
<td>1.01 (1.007–1.020)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (54, 73)</td>
<td>59 (51, 68)</td>
<td>52.6</td>
<td>15.1</td>
<td>0.985 (0.978–0.993)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (cc . min(^{-1}))</td>
<td>79 (60,104)</td>
<td>88 (68,110)</td>
<td>85.4</td>
<td>13.0</td>
<td>1.32 (1.14–1.54)</td>
<td></td>
</tr>
<tr>
<td>Pre-randomization diuretic use</td>
<td>29.2%</td>
<td>17.8%</td>
<td>13.3</td>
<td>11.4</td>
<td>1.24 (1.10–1.41)</td>
<td></td>
</tr>
<tr>
<td>Anginal symptoms in 6 weeks before QE</td>
<td>49.5%</td>
<td>43.6%</td>
<td>8.9</td>
<td>10.6</td>
<td>1.06 (0.53–0.85)</td>
<td></td>
</tr>
<tr>
<td>Streptokinase for QE</td>
<td>7.5%</td>
<td>10.4%</td>
<td>33.7</td>
<td>9.4</td>
<td>1.22 (1.08–1.39)</td>
<td></td>
</tr>
<tr>
<td>Heart failure between QE and randomization</td>
<td>5.6%</td>
<td>2.2%</td>
<td>33.5</td>
<td>9.3</td>
<td>1.56 (1.17–2.08)</td>
<td></td>
</tr>
<tr>
<td>Randomization heart rate (beats . min(^{-1}))</td>
<td>70 (62, 80)</td>
<td>70 (61, 78)</td>
<td>19.9</td>
<td>8.9</td>
<td>1.008 (1.003–1.013)</td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>28.6%</td>
<td>19.5%</td>
<td>36.2</td>
<td>7.9</td>
<td>1.23 (1.07–1.42)</td>
<td></td>
</tr>
<tr>
<td>High-dose sibrafiban</td>
<td>36.5%</td>
<td>32.5%</td>
<td>8.0</td>
<td>7.2</td>
<td>1.19 (1.05–1.35)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus with end organ damage</td>
<td>2.8%</td>
<td>1.3%</td>
<td>26.1</td>
<td>6.7</td>
<td>1.62 (1.13–2.33)</td>
<td></td>
</tr>
<tr>
<td>QE Killip class ≥II</td>
<td>17.4%</td>
<td>10.3%</td>
<td>50.2</td>
<td>6.3</td>
<td>1.25 (1.05–1.49)</td>
<td></td>
</tr>
<tr>
<td>Lateral electrocardiographic changes at QE</td>
<td>53.5%</td>
<td>47.8%</td>
<td>14.4</td>
<td>5.9</td>
<td>1.17 (1.03–1.32)</td>
<td></td>
</tr>
<tr>
<td>Asian race</td>
<td>5.8%</td>
<td>4.4%</td>
<td>3.9</td>
<td>5.7</td>
<td>1.39 (1.06–1.82)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>30.2%</td>
<td>30.1%</td>
<td>0.00</td>
<td>4.7</td>
<td>0.86 (0.75–0.99)</td>
<td></td>
</tr>
<tr>
<td>Pre-randomization heparin</td>
<td>71.0%</td>
<td>68.3%</td>
<td>2.90</td>
<td>4.5</td>
<td>1.17 (1.01–1.34)</td>
<td></td>
</tr>
<tr>
<td>History of heart failure</td>
<td>9.4%</td>
<td>3.9%</td>
<td>68.0</td>
<td>4.4</td>
<td>1.28 (1.02–1.62)</td>
<td></td>
</tr>
<tr>
<td>Recurrent ischaemia between QE and randomization</td>
<td>9.2%</td>
<td>7.7%</td>
<td>4.8</td>
<td>4.1</td>
<td>1.25 (1.01–1.54)</td>
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</table>

QE = qualifying event.

**Mortality**

As in previous risk models, age was most strongly associated with mortality in this cohort, contributing about 45% of the total prognostic information. Age remained strongly predictive despite co-linearity with other model variables such as creatinine clearance, not included in modelling in previous studies. When creatinine clearance entered the model, the \( \chi^2 \) for age was decreased by 63.

Consistent with previous reports of high cardiac event rates and cardiovascular mortality in post-ACS patients with renal impairment,\(^7\)–\(^10\) the observed strength of association of renal function with clinical outcomes highlights the high-risk nature of renal impairment. Importantly, there was no interaction of sibrafiban treatment with renal function on the relationship with outcome. Patients were excluded from the SYMPHONY trials for serum creatinine \( >1.5 \text{ mg} \cdot \text{dl}^{-1} \), yet median creatinine clearance was only 87 cc . min\(^{-1}\), and in approximately 25% it was \(<70 \text{ cc} \cdot \text{min}^{-1} \). In the patients who died, median creatinine clearance was 64...
Thus, serum creatinine is a sub-optimal surrogate for renal function, and it is clear that even modest degrees of renal dysfunction are associated with adverse outcomes among ACS patients.

The association of renal dysfunction with worse outcome may be due to renal insufficiency itself or related co-morbidities, but other factors may also contribute. The Centers for Education and Research on Therapeutics (CERTs) investigators have shown failures to prescribe or adjust medications appropriately for renal dysfunction (Donal Reddan, personal communication) which could contribute to adverse events. Thus, the association of renal dysfunction with worse outcomes should serve to highlight the need for both aggressive risk factor modification and careful monitoring of prescription patterns and medication dosing in these patients. The tendency to exclude this high-risk group from cardiovascular clinical trials should be carefully re-examined.

Because most previous MI and ACS studies used for modelling have randomized patients early after presentation, it has been difficult to model the association of early revascularization with mortality. Our results suggest a significant independent relationship of early PCI with lower 90-day mortality, as well as the double and triple composite end-points, observations that are consistent with the findings of recent randomized trials of early invasive strategies in ACS patients.11,12 Although a mechanism for this association is not clear, an antiinflammatory effect of PCI, as suggested by enhanced benefit of an early invasive strategy among patients with elevated baseline interleukin-6 levels in the FRISC II study, could be operative.13 Other studies have suggested that PCI may mitigate mortality risk associated with an elevated WBC count (a potential proxy for inflammation).14 Alternatively, given that the hazard for ischaemic events after PCI occurs largely within the first 6–9 h after the procedure,15 rather than early

<table>
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<th>Predictors of outcome in stable post-ACS patients</th>
<th>177</th>
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</table>

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PCI resulting in lower risk, these patients may simply have incurred that risk prior to being randomized. Therefore, as suggested by Langer, rather than PCI protecting from events, the association of PCI with reduced risk may simply reflect a lower-risk population at randomization.16

Similar to models developed in patients randomized early in acute MI and ACS trials, new heart failure after the qualifying event and higher heart rate several days out from it predicted higher mortality risk. Such characteristics among ‘stable’ post-ACS patients may identify those relatively less stable for whom longer hospital stays and more aggressive inpatient treatment and outpatient secondary prevention are warranted.

Death/MI and the triple composite

Creating models for the risk of death/MI or other composite end-points has been more difficult, and models have had lower discriminative ability and performed less well across populations than mortality models. In part this may be due to the heterogeneous MI end-point in clinical trials, which includes both spontaneous and procedural MI.2 In addition, factors other than demographic and clinical characteristics directly attributable to patients or that occur after randomization, which may be subject to variations in practice pattern, may be more important in predicting non-fatal outcomes.

As in previous studies, age and heart failure were less strongly associated with death/MI or the triple composite than with death alone. Time from qualifying event to randomization was most strongly associated with death/MI risk and was nearly as strongly associated with the triple composite. As more time elapsed, a subsequent event was less likely. This is consistent with previous observations on event timing after MI in which the majority of cardiac complications occurred within the first 24-48 h and were uncommon after 3 days.17 This observation may reflect stabilization or healing of ruptured plaque, use of therapeutic or procedural interventions during this time, and/or simply a survivor effect bias.

Diabetes mellitus with end organ damage—a marker of severe or long-standing diabetes—was weakly associated with 90-day death/MI and the triple composite end-point although diabetes mellitus overall was not. This may reflect that other variables such as creatinine clearance or age carry much of the prognostic information explained by diabetes. Regardless, the association of diabetes with higher likelihood of recurrent ischaemic events emphasizes that this group should be targeted for more aggressive use of proven secondary prevention measures, and warrants specific study of this group in future clinical trials.

Presentation with elevated cardiac markers, unstable symptoms prior to presentation, and prior MI were among the strongest associations with death/MI, predicting higher-risk even after stabilization for several days. Targeting these patients may be particularly important in designing clinical trials of secondary prevention strategies and in improving use of proven therapies. However, to do this most effectively will require development of better predictive models than those currently available. Similar to previous studies, the c-indices of the double and triple composite models in this study were only 0.68 and 0.64, respectively.

In addition to clinical risk predictors, incorporation of biochemical risk markers or the results of continuous electrocardiographic ischaemia monitoring may provide additional information to more effectively identify those at risk for non-fatal recurrent ischaemic events. In the current models, presentation marker status added prognostic information to clinical variables even in a selected population stabilized for several days. Although serial marker testing over the first 24 h provides incremental prognostic information to baseline testing,18 it is unclear if adding later measures of these markers in patients who are stable after several days would provide further useful information.

Markers of inflammation may provide incremental risk stratification above that of clinical variables. Other studies have suggested that WBC count at presentation may provide prognostic information.14,19 Less is known about WBC count measured several days after presentation in stable patients. In our database, 9006 patients had a WBC count measured at randomization. When forced into our models, it was an independent predictor of mortality, but not of the double or triple composite end-points. In previous studies, C-reactive protein (CRP), a marker of inflammatory system activation, has also been shown to be predictive of short- and long-term mortality after ACS,20,21 but like WBC in our study, the incremental prognostic utility of CRP for non-fatal events, is less clear.22–24

Several studies have shown that silent ischaemia detected by continuous electrocardiographic ST-segment trend monitoring also predicts cardiac risk after ACS and may be complementary to cardiac marker testing.25–28 Therefore, like serum risk markers, incorporating the results of continuous ECG monitoring for recurrent ischaemia into
non-fatal ischaemic event risk models may also improve prognostic ability.

**Strengths and limitations**

Overall, the models developed from the SYMPHONY databases performed similarly to those developed in other MI and ACS populations. A strength of our modelling is that we investigated factors associated with outcome in ACS patients stable for a median of 3.6 days after the index event. Thus, the models reflect the characteristics and factors associated with later risk in ACS patients. Also, available for modelling were clinical, procedural, and medication use variables collected during the period from qualifying event to randomization that in clinical trial models have previously not been evaluated for association with outcome. Many of the same covariates were also found to predict longer-term outcome following discharge among Nottingham Heart Attack Register patients who had been admitted for suspected MI, but in whom the diagnosis was not confirmed. Application of these models may be uniquely suited to risk assessment at or near the time of discharge to guide further evaluation and treatment and to counsel patients regarding prognosis.

A potential limitation of our modelling is that our population included only patients enrolled in clinical trials who, by selection, may not mirror the breadth of risk in the general population. Only future validation of our model in registries or other unselected populations can confirm its broad generalizability. We also did not prespecify covariates for inclusion in the modelling. This allowed us to investigate associations of previously untested variables with outcomes, but testing of a large number of candidate variables may have resulted in some associations due to chance. Use of backward elimination and bootstrapping to assess the stability of variables included in the initial model and cross-validation between models from the individual trial databases should reduce this likelihood, but variables with weaker associations could reflect spurious associations related to multiple testing. Further investigation of these variables and their associations with outcomes in other populations may be helpful.

**Conclusion**

Among patients’ stable 3–4 days after an ACS, multivariable models can identify patients at risk for death or non-fatal recurrent ischaemic events. However, typical clinical markers are better at identifying risk of death than non-fatal MI or SRI. Further investigation into incorporation of novel laboratory markers of risk may refine the ability to predict risk for non-fatal ischaemic outcomes. Application of these risk models should be useful both in clinical care and in designing clinical trials to test new strategies for preventing recurrent ischaemic events after ACS.

**Acknowledgements**

SYMPHONY and 2nd SYMPHONY were funded by research grants from F. Hoffmann-La Roche, Ltd, Basel, Switzerland.

**Appendix 1**

**Candidate variables for multivariable models**

**Demographics**

Age, height, weight, body mass index, male sex, race/ethnicity (white, black, Asian, Hispanic, American Indian).

**Risk factors and clinical history**

Family history of coronary artery disease, history of heart failure, hypertension, hypercholesterolaemia, history of angina, diabetes mellitus, diabetes mellitus with end-organ damage, insulin-treated diabetes mellitus, prior stroke, prior transient ischaemic attack, prior myocardial infarction, prior angiography, prior coronary artery bypass grafting, severe chronic obstructive pulmonary disease, cancer, abnormal liver enzymes, chronic renal insufficiency, peripheral arterial disease, history of atrial fibrillation, history of supraventricular tachycardia, history of ventricular dysrhythmias, history of heart block, current smoker, never smoker, past smoker, angina within 6 weeks before qualifying event, multiple episodes of angina before qualifying event.

**Clinical characteristics**

Qualifying event diastolic blood pressure, randomization diastolic blood pressure, qualifying event systolic blood pressure, randomization systolic blood pressure, qualifying event heart rate, randomization heart rate, qualifying event Killip class >II, qualifying event Killip class >III, qualifying event mitral regurgitation, qualifying event S3 gallop, randomization mitral regurgitation, randomization S3 gallop.

**Qualifying event characteristics**

Qualifying event myocardial infarction, qualifying event ECG abnormalities (left bundle branch
block, paced rhythm, T-wave pseudonormalization, Q wave, ST-segment depression, ST-segment elevation, T-wave inversion), location of ECG changes (inferior, lateral, posterior, anterior), abnormal qualifying event ECG, elevated cardiac markers at qualifying event.

Clinical events between qualifying event and randomization
Acute mitral regurgitation, atrial fibrillation, heart failure, shock, pulmonary oedema, recurrent ischaemia, heart block, supraventricular tachycardia, ventricular fibrillation.

Study treatment characteristics
Time from qualifying event to treatment, treatment assignment (control group, low-dose sibrafiban, high-dose sibrafiban).

Laboratory measures
Serum creatinine, creatinine clearance (CrCl = [(140-age) × weight in kilograms/serum creatinine × 72] × 0.85 if female)

Medication use
Baseline medications (angiotensin converting enzyme inhibitor, antiarrhythmic, aspirin, beta-blocker, calcium channel blocker, coumadin, digitalis, diuretic, heparin, intravenous glycoprotein IIb/IIIa inhibitor, lipid-lowering therapy, low-molecular-weight heparin, nitrates, nonsteroidal antiinflammatory agents, oral antiplatelet therapy, statin, vitamins), pre-randomization thrombolysis, thrombolysis for qualifying event, streptokinase for qualifying event, rPA for qualifying event, APSAC for qualifying event.

Procedure use
Any pre-randomization angiography, angiography between qualifying event and randomization, emergency percutaneous coronary intervention, any pre-randomization stent, stent between the qualifying event and randomization, any pre-randomization percutaneous coronary intervention, percutaneous coronary intervention between qualifying event and randomization, any pre-randomization coronary artery bypass grafting, coronary artery bypass grafting between qualifying event and randomization.

Appendix 2
Equations for 90-day models
Mortality
Hazard = \exp (−0.00716 × QE SBP) + (−0.64652 × prior coronary bypass surgery) + (0.02453 × randomization heart rate) + (0.25094 × lateral ECG changes at QE) + (0.03995 × age) + (−0.02595 × creatinine clearance) + (0.48715 × qualifying event MI) + (0.25938 × angina in prior 6 weeks) + (0.39708 × pre-randomization angiotensin converting enzyme inhibitor) + (0.94527 × CHF between QE and randomization) + (0.32533 × hypertension) + (0.67301 × prior transient ischaemic attack) + (0.33639 × prior MI) + (0.47536 × chronic obstructive pulmonary disease) + (−0.65614 × pre-randomization PCI) + (−0.51245 × pre-randomization thrombolysis).

Death or myocardial infarction
Hazard = \exp (0.01356 × age) + (0.00770 × randomization heart rate) + (0.49418 × elevated QE cardiac markers) + (0.48121 × diabetes mellitus with end-organ damage) + (0.22424 × QE Killip class ≥II) + (0.15448 × lateral ECG changes at QE) + (−0.00500 × hours from QE to treatment start) + (−0.01472 × creatinine clearance) + (0.17464 × high-dose sibrafiban) + (0.33010 × Asian race) + (0.21542 × angina in prior 6 weeks) + (0.27811 × pre-randomization diuretic) + (0.15235 × pre-randomization heparin) + (0.44746 × CHF between QE and randomization) + (0.21958 × recurrent ischaemia between QE and randomization) + (0.24772 × history of CHF) + (0.20136 × hypertension) + (0.20742 × prior MI) + (−0.46333 × pre-randomization PCI) + (−0.39597 × streptokinase for QE) + (−0.15394 × never smoked).

Death, myocardial infarction, or severe recurrent ischaemia
Hazard = \exp (0.25604 × elevated QE cardiac markers) + (0.42182 × diabetes mellitus with end-organ damage) + (0.14207 × angina in prior 6 weeks) + (0.01201 × age) + (0.16519 × QE Killip class ≥II) + (0.00745 × randomization heart rate) + (−0.00390 × h from QE to randomization) + (0.22873 × pre-randomization diuretic) + (0.12881 × pre-randomization heparin) + (0.40749 × CHF between QE and randomization) + (0.35451 × recurrent ischaemia between QE and randomization) + (0.15931 × hypertension) + (0.17923 × prior MI) + (0.21671 × prior PCI) + (−0.16702 × never smoked) + (−0.34560 × PCI between QE and randomization) + (−0.25631 × streptokinase for QE) + (0.23795 × randomization SBP) + (−0.00191 × randomization SBP squared) + (5.01 × 10^{-6} × randomization SBP cubed)]

Abbreviations: QE = qualifying event; SBP = systolic blood pressure; MI = myocardial infarction; PCI = percutaneous coronary intervention; CHF = congestive heart failure; ECG = electrocardiogram
References


