Clinical research

Association of revascularisation with low mortality in non-ST elevation acute coronary syndrome, a report from GUSTO IV-ACS

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Background Immediate, as well as early, revascularisation is of benefit in patients with acute coronary syndromes (ACS) presenting with ST elevation. However, trials comparing invasive versus medical treatment in patients with an acute coronary syndrome without ST elevation do not consistently show improvement in survival after revascularisation. Accordingly, additional data are warranted.

Methods The effect of revascularisation within 30 days on one-year survival in the GUSTO IV ACS trial was investigated. A total of 7800 patients were included with an acute coronary syndrome without ST elevation, documented by either elevated cardiac troponin or transient or persistent ST-segment depression. In this trial, comparing abciximab versus placebo as initial medical therapy, coronary angiography within 60 h after randomisation was discouraged. In 30-day survivors, those who underwent revascularisation were compared with 30-day survivors without revascularisation. Adjustments were made for patient characteristics, and for a propensity score that was adjusted for covariates associated with the likelihood of early revascularisation.

Findings Of the 7496 patients who survived at least 30 days, 2265 (30%) underwent coronary revascularisation within 30 days: 789 patients CABG, 1450 PCI and 26 both CABG and PCI. Procedure-related mortality was low at 1.8%. Patients with revascularisation had a lower one-year mortality compared to medically treated patients (2.3% vs. 5.6%, p < 0.001). After multivariable analyses, patients with revascularisation had a relative risk of subsequent mortality within 1 year of 0.53 (95% CI 0.37–0.77) compared to patients without revascularisation.

KEYWORDS
Non-ST elevation myocardial infarction; Acute coronary syndrome; Revascularisation

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Conclusions

Revascularisation within 30 days is associated with an improved prognosis in ACS without ST-segment elevation. The relative high mortality in medically treated patients may be related in part to patient selection, but warrants further studies to improve outcome of these patients.

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Introduction

The early prognosis of patients who present with an acute coronary syndrome (ACS) without ST elevation is generally good. Nevertheless, 10–15% of these patients develop myocardial infarction or die within one year after admission. Current medical therapy includes heparin, antiplatelet agents and anti-ischaemic agents. Coronary revascularisation by either percutaneous coronary intervention (PCI) or coronary bypass surgery (CABG) is recommended in patients with recurrent ischaemia or other high-risk characteristics. However, in clinical practice revascularisation is often offered when facilities are available (“local routine”). There are several randomised studies addressing the routine use of an invasive approach in the treatment of non-ST elevation acute coronary syndromes. Although part of the results support benefit of a systematic invasive approach, mortality at 6–12 months follow-up is not significantly different for revascularisation versus medical therapy in the majority of these trials (Table 1).

We investigated the association of revascularisation and outcome in GUSTO IV-ACS, a large randomised trial evaluating the GP IIb/IIIa inhibitor abciximab administered during 24 or 48 h in patients with an ACS without ST-segment elevation. In this trial, coronary angiography was discouraged within 60 h after randomisation unless the patient had recurrent or continuing ischaemia at rest associated with ischaemic ST-T changes that were unresponsive to intensive medical therapy. Subsequent revascularisation was at the discretion of the hospital physician.

Methods

Patients, study procedures

Design, methods, and main results of GUSTO IV-ACS have been described previously. In short, it was a multi-centre, randomised trial of patients with ACS without persistent ST-segment elevation. Eligible patients were aged at least 21 years and had experienced one or more episodes of angina lasting at least 5 min within 24 h before admission. They had either an abnormal cardiac troponin T or I test or at least 0.5 mm of transient or persistent ST-segment depression.

Patients were randomly assigned to one of three treatment groups: abciximab for 24 h (0.25 mg/kg bolus followed by a 0.125 lg/kg per min infusion up to a maximum of 10 lg/min for 24 h) followed by 24 h of placebo infusion; abciximab for 48 h (same bolus and infusion for total duration of 48 h); or matching placebo (bolus and 48 h infusion). All patients were to receive aspirin for at least 30 days if not contraindicated. Furthermore, all patients received unfractionated heparin as bolus and infusion for 48 h or low molecular weight heparin (dalteparin) subcutaneously every 12 h for 5–7 days or until a revascularisation procedure or discharge. Continuation of anti-thrombin therapy with unfractionated or low molecular weight heparin was left at the discretion of the investigator. Concomitant therapy with b-blockers was strongly recommended. Use of all other cardiac medications (e.g., nitrates, calcium-channel blockers, angiotensin-converting-enzyme inhibitors) was left at the discretion of the investigator. Venous blood samples were collected at baseline and 8, 16, 24, 36 and 48 h after randomisation for assessment of CK-MB. An elevated troponin was defined as a cardiac troponin T or I above the upper limit of normal for the local qualitative or quantitative assay. In addition, quantitative levels of troponin T were also determined centrally by a third generation assay on an Elecsys (Roche diagnostics) with the detection limit 0.01 lg/l. Also levels of C-reactive protein (CRP) were determined at baseline. An elevated CRP was defined as a CRP value > 10 mg/l.

Table 1 Randomised trials comparing conservative with invasive treatment in acute coronary syndromes without ST elevation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Total included</th>
<th>Revascularisation (%)</th>
<th>Long-term mortality</th>
<th>Invasive</th>
<th>Conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI-IIIB</td>
<td>1994</td>
<td>1473</td>
<td>60</td>
<td>40</td>
<td>30 (4.1%)</td>
<td>32 (4.4%)</td>
</tr>
<tr>
<td>VANQWISH</td>
<td>1998</td>
<td>920</td>
<td>44</td>
<td>33</td>
<td>58 (7.8%)</td>
<td>36 (4.9%)</td>
</tr>
<tr>
<td>FRISC-II</td>
<td>1999</td>
<td>2457</td>
<td>78</td>
<td>37</td>
<td>27 (2.2%)</td>
<td>48 (3.9%)</td>
</tr>
<tr>
<td>TIM-I-18</td>
<td>2001</td>
<td>2220</td>
<td>61</td>
<td>37</td>
<td>37 (3.3%)</td>
<td>39 (3.5%)</td>
</tr>
<tr>
<td>TRUCS</td>
<td>2000</td>
<td>148</td>
<td>53</td>
<td>32</td>
<td>3 (3.9%)</td>
<td>9 (12.5%)</td>
</tr>
<tr>
<td>VINO</td>
<td>2002</td>
<td>131</td>
<td>73</td>
<td>39</td>
<td>2 (3.1%)</td>
<td>9(13.4%)</td>
</tr>
<tr>
<td>RITA 3</td>
<td>2002</td>
<td>1810</td>
<td>44</td>
<td>10</td>
<td>41 (4.6%)</td>
<td>36 (3.9%)</td>
</tr>
</tbody>
</table>

Total 9159

198 (4.3%) 209 (4.6%) *

*p = 0.6.

a TIMI-IIIB, VANQWISH, FRISC-II, TRUCS, RITA three one-year follow-up, TIMI 18 and VINO 6-months follow-up.
The primary endpoint in the trial was the occurrence, within 30 days after randomisation, of death (from any cause) or myocardial infarction, adjudicated by the Clinical Endpoint Committee.11 Follow-up data were obtained on the vital status up to one year after randomisation.12 Deaths were reported by the investigator at each site. Follow-up data were collected via the register office, the General Practitioner, or via a direct contact with the patient or his relatives by telephone. Death related to revascularisation was defined as death within 2 days after the procedure.

Statistical analysis

Patients who underwent revascularisation within 30 days after enrolment were compared with those not undergoing the procedure. Because patients undergoing revascularisation within 30 days were selected and survived at least until their revascularisation, which may introduce bias, all analyses, including potential beneficial effect of revascularisation, were restricted to 30-day survivors.

Because of the differences in revascularisation rates among participating hospitals, and the significant differences in baseline characteristics between patients with and without revascularisation, a propensity score method was applied.13 Firstly, factors associated with revascularisation were identified. Thereafter, a multivariable logistic regression analysis was performed to identify independent predictors of revascularisation. On the basis of the results of the logistic regression analysis, a propensity score was calculated for each patient. So, the propensity score represents the probability that a patient received revascularisation.

Differences between group means were tested by the two-tailed Student’s t test. A χ² statistic was calculated to test differences between proportions. Survival functions were calculated, using the Kaplan–Meier product limit method.14 Mantel–Cox (or log-rank) test was applied to evaluate the differences between survival functions.15 Categories for subgroup analyses include age, gender, diabetes, elevated troponin, ST depression and CRP status. Four groups were determined that underwent revascularisation before day 7, at 8–14 days, at 15–21 days, or between 22 and 30 days after inclusion.

Multivariable Cox proportional-hazards regression analysis was applied to describe the relation between revascularisation and one-year survival after adjustment for differences in baseline characteristics between revascularised and non-revascularised patients. The follow-up period was divided into different time periods to assess whether the hazard ratios were constant across time for the different variables. In the multivariable model, apart from revascularisation, age, gender and the propensity score, all baseline variables were included with significant association with one-year mortality in univariate analysis. To assess whether there was a U- or J-shape association between continuous variables and mortality, stratified analyses were performed. The 95% confidence intervals were calculated by standard techniques, using beta-coefficients and standard errors. Statistical significance was defined as a p-value of less than 0.05.

Results

Baseline characteristics

Between July 17, 1998 and April 21, 2000 a total of 7800 patients were randomised. Follow-up data up to 365 days after randomisation were available for 7746 patients (99.3%). At 30 days follow-up, mortality was 3.9% (304 patients), so the current analyses concerned 7496 patients. Western European hospitals enrolled 3538 (47%) of these patients, Eastern Europe 2340 (31%), North America 1059 (14%), and other countries 559 (7%). Local troponin was available in 6630 patients (88%), with a total of 3864 patients (58%) with positive local troponin. The central measured quantitative troponin T-levels ranged from 0.01 to 17.3 lg/l and the quartile limits were 0.01, 0.12 and 0.44 lg/l.

Revascularisation

Within 30 days after inclusion, coronary angiography was performed in 3685 patients (49%). A total of 2265 (30%) patients underwent revascularisation: 789 patients CABG, 1450 patients PCI and 26 both CABG and PCI. PCI was performed after a median of 7 days, whereas CABG was performed after a median of 12 days. Very few patients (147, 2%) underwent coronary revascularisation within 48 h, while on study treatment: 1.6% PCI and 0.3% CABG. Differences in baseline characteristics between patients with and without revascularisation within 30 days were summarized in Table 2. Patients with positive local troponin had revascularisation performed more often and earlier compared to patients with negative local troponin. Compared to patients with PCI, patients who underwent CABG were older: 62.4 ± 11.0 vs. 65.1 ± 10.0 years, respectively (p < 0.001).

The proportion of patients undergoing revascularisation within 30 days varied substantially among the different hospitals, from 0% to 100%, with a median of 32%. A total of 1460 patients (19.5%) were admitted to hospitals in the highest quartile of revascularisation (50% or more revascularisation in that specific hospital), whereas 2243 patients (29.9%) were admitted in hospitals in the lowest quartile of revascularisation (less than 15% revascularisation in that specific hospital). Revascularisation was less common in Eastern Europe (11.5%) compared to Western Europe (36.8%) or North America (42.6%).

The likelihood of revascularisation by multivariable analyses was independently associated with increasing age, male gender, previous PCI, elevated troponin, admission in a hospital with a high revascularisation rate, and no diabetes, no increased CRP, no previous heart failure and no admission in Eastern Europe. These variables were included in the propensity score of revascularisation. Of the patients with a propensity score in the lowest quartile, 9.8% had revascularisation within 30 days. Of the patients with a propensity score in the highest quartile, 56% had revascularisation within 30 days. We assessed the goodness of fit of the propensity score with the c-statistic (area under the receiver operating characteristic curve, 0.76) and the Hosmer–Lemeshow test (p < 0.05).

One-year mortality

In the 7496 30-day survivors, after one-year follow-up a total of 649 patients had died (8.7%). Unadjusted predictors of one-year mortality were assessed. One-year mor-
Mortality and revascularisation

Among the 2340 patients who underwent coronary revascularisation within 30 days, procedure-related mortality, defined as death within 2 days after revascularisation, was 1.8%: 1.3% for PCI (19 patients) and 2.6% for CABG (22 patients, p < 0.001).

In patients who survived at least 30 days, one-year mortality was lower in those with (2.3%) than those without (5.6%) revascularisation (adjusted survival curves in Fig. 1, p < 0.001). A similar pattern was apparent in the analysis of all patients enrolled: 5.5% vs. 9.5% one-year mortality, respectively (p < 0.001%). The propensity score for revascularisation was significantly associated with one-year mortality (p < 0.001), which was 1.1% in the lowest quartile and 10.1% in the highest quartile. Multivariable analysis was performed including the propensity score, age, gender and all other variables with significant association with one-year mortality in univariate analysis. After multivariable analyses in 30-day survivors, mortality remained significantly associated with lack of revascularisation, increasing age, elevated troponin, elevated CRP, diabetes, previous MI and a history of heart failure. The propensity score was not significantly associated with one-year mortality after multivariable analyses (p = 0.21). Patients with revascularisation had a relative risk of one-year mortality of 0.53 (95% CI 0.37–0.77) compared to patients without revascularisation. When the type of revascularisation was entered into the analysis, survival appeared to be particularly improved after PCI, whereas the results after CABG were less clear. Patients with PCI had a relative risk of 0.44 (95% CI 0.28–0.72) for one-year mortality compared to patients without PCI. Patients with CABG had a relative risk of 0.83 (95% CI 0.53–1.33) for one-year mortality compared to patients without CABG.

In patients who underwent PCI, the timing of the procedure was not associated with one-year mortality. However, in patients after CABG, those who had surgery within the first week had a higher one-year mortality (12%) than those operated between day 8 and 30 (6.8%, p = 0.02).

Table 2 Differences between patients with and without revascularisation within 30 days in those who survived at least 30 days

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With revascularisation (N = 2265)</th>
<th>Without revascularisation (N = 5231)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1645 (73%)</td>
<td>3045 (58%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>63 (±11)</td>
<td>66 (±11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight at admission (kg)</td>
<td>79 (±14)</td>
<td>77 (±14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>669 (30%)</td>
<td>1595 (31%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes</td>
<td>440 (19%)</td>
<td>1135 (22%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1058 (47%)</td>
<td>2797 (54%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>745 (33%)</td>
<td>1479 (28%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>353 (16%)</td>
<td>386 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>211 (9%)</td>
<td>478 (9%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>43 (2%)</td>
<td>138 (3%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart failure</td>
<td>90 (4%)</td>
<td>434 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin use previous 7 days</td>
<td>1915 (85%)</td>
<td>4356 (83%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>268 (12%)</td>
<td>2072 (40%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Raised troponin*</td>
<td>1265 (56%)</td>
<td>2599 (50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Raised baseline CK-MB</td>
<td>932 (45%)</td>
<td>1836 (38%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean baseline CK-MB (U/l)</td>
<td>26.8 ± 47</td>
<td>24.9 ± 48</td>
<td>0.14</td>
</tr>
<tr>
<td>ST-depression</td>
<td>1772 (78%)</td>
<td>4216 (81%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Elevated CRP*</td>
<td>457 (20%)</td>
<td>1145 (22%)</td>
<td>0.10</td>
</tr>
<tr>
<td>MI within 48 h</td>
<td>46 (2.0%)</td>
<td>34 (0.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinolytics within 48 h</td>
<td>9 (0.4%)</td>
<td>8 (0.2%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Cardiac troponin T or I above the upper limit of normal for the local qualitative or quantitative assay.

* CRP value >10 mg/l.
Subgroup analyses

In the patients who survived for 30 days, after univariate analyses, patients selected to undergo revascularisation consistently showed improved survival in all subgroups. The association between revascularisation and one-year mortality after multivariable analyses in several subgroups is depicted in Fig. 2. In all subgroups a survival benefit of revascularisation was apparent, although in younger patients, and in those without ST depression, this association was not statistically significant.

Abciximab

No significant differences were apparent between patients randomised to placebo, 24 h abciximab or 48 h abciximab who did, or did not undergo revascularisation. Also in patients undergoing PCI within 30 days there were no differences between the three treatment groups.

Discussion

In patients hospitalised with an acute coronary syndrome and ST-segment elevation, immediate revascularisation by PCI improves outcome and is the recommended therapy. Furthermore, survival is improved in patients with myocardial infarction undergoing early revascularisation. Our analysis provides evidence that in ACS patients without ST-segment elevation, coronary revascularisation within 30 days after admission is also associated with a favourable one-year survival.

In the Swedish registry of over 21,000 patients surviving 14 days after a first myocardial infarction, one-year mortality was 4.0% without and 3.3% with revascularisation within 14 days. After multivariable analysis, accounting for baseline characteristics and the propensity for revascularisation, the relative risk was 0.47 (95% CI 0.37–0.60), which is similar to the relative risk of 0.53 (0.37–0.77) in the present study. The similar benefit of early revascularisation in patients admitted with or without ST elevation is consistent with the current notion that these represent subsets of the continuous spectrum of acute coronary syndromes.

Registry data and randomised trials

Data of registries of the effects of revascularisation in patients with non-ST elevation myocardial infarction (non-STEMI) show conflicting results. For example, in the OASIS registry, evaluating approximately 8000 patients with suspected non-STEMI from six countries, a reduction in refractory ischaemia and need for hospitalisation was observed after revascularisation, but not a decrease of mortality. Randomised trials comparing an invasive with a conservative approach show a favouring of invasive treatment, without statistical significance (p = 0.6, Table 1). In FRISC II and in TACTICS-TIMI 18 a benefit of invasive treatment was apparent, particularly in patients with positive troponin.

In GUSTO IV-ACS and the Swedish registry benefits of early revascularisation appeared much larger than in the randomized trials, even after adjustment for other patient and hospital characteristics. It should be appreciated, nevertheless, that such multivariable adjustments may not correct for all patient characteristics, and do not fully compensate the effect of careful selection of patients who are candidates for revascularisation, and those who are not! Similarly, the results of the randomised trials of invasive versus medical approach should be interpreted with caution. In these trials, many patients in the conservative treatment groups crossed-over to invasive treatment, and many patients allocated to invasive treatment did not undergo such therapy (Table 1). Thus the true benefit of revascularisation is, most likely, overestimated by the registries and underestimated by the trials.

Revascularisation in practice

Recent European and American guidelines for clinical practice advise an invasive strategy in patients with ACS and failed medical therapy as well in high risk patients. This is in agreement with observations from
FRISC II and TACTICS-TIMI 18 demonstrating that a reduction of death or subsequent myocardial infarction can be expected only in high-risk groups. In our analyses, however, survival benefit after revascularisation was shown in every subgroup, independent of early risk stratification.

Timing of revascularisation

Patients with non-STEMI have the highest risk of an unfavourable event within the first 48 h after admission. Nevertheless, the appropriate timing of coronary angiography and revascularisation remains controversial. In an early invasive approach, the risk of peri-procedural complications may be increased. Therefore, a period of ‘cooling off’ has been recommended, in which patients are medically stabilised. This allows partial resolution of the initially strong inflammatory response with liberation of cytokines, increased generation of free radicals, and enhanced activity of the coagulation system. On the other hand, early angiography and subsequent revascularisation may prevent myocardial infarction or death in a high risk period, whereas prognosis after PCI in these patients has improved with the use of stents and GP IIb/IIIa inhibitors. Although we found an increased mortality in patients with early CABG, this can be due to confounding as very unstable patients will undergo early CABG. In PURSUIT, early PCI (within 24 h) in patients receiving a GP IIb/IIIa inhibitor had the lowest event rate after 30 days. Possibly, when indicated, PCI should be performed as soon as possible after admission for ACS while CABG should be deferred. However, until now, there are few randomised data available which compared an early with a later invasive approach, and these give conflicting results.

Angioplasty or surgery

In the randomised trials of invasive versus conservative management in ACS, there are different findings with regard to mortality after CABG. In FRISC II, the in-hospital and 30-day mortality after CABG in the invasive group was, respectively, 1.2% and 2.1%. Similar low rates were observed in TACTICS TIMI 18, and outcome was comparable between patients undergoing CABG and PCI. In VANQWISH, however, there was a very high mortality in the CABG group. In recent randomised trials comparing stented angioplasty and bypass surgery, which included patients with non-STEMI, the incidence of death or myocardial infarction during follow-up of two years were similar between the two groups. The less favourable outcome after CABG in our study is most likely related to the selection of patients with more extensive disease to undergo surgery.

GP IIb/IIIa inhibitors

A number of previous studies have demonstrated beneficial effects of GP IIb/IIIa inhibitors in patients with ACS without ST-elevation, in particular in patients undergoing PCI. In the guidelines of management of patients with non-STEMI, use of GP IIb/IIIa inhibitors are recommended, in addition to standard treatment (aspirin and unfractionated heparin or low molecular weight heparins) for patients with high risk features such as elevated troponin, ST-segment changes, or recurrent ischaemia. GP IIb/IIIa inhibitors are particularly effective in patients with non-STEMI when early PCI is performed. GUSTO IV-ACS does not provide additional information on this issue, as only 128 patients (1.6%) had PCI within 48 h, while on study medication.

Limitations

We present post hoc analyses, evaluating treatment strategies that were not randomised. Because coronary angiography and revascularisation were left at the discretion of the investigator, the decision for angiography may have introduced both confounding by indication and confounding by contraindication. Although the complications of coronary angiography are uncommon, several subgroups may have an increased risk, and patient characteristics may have influenced the decision not to perform angiography. It is therefore not surprising that in GUSTO IV-ACS significant differences could be observed between patients with and without revascularisation (Table 2). Nevertheless, after multivariable analyses including the known risk factors for impaired outcome, and a propensity score for revascularisation, a significantly lower one-year mortality was again demonstrated in patients with revascularisation. A statistical limitation was that the c-statistic of our propensity score was 0.76, whereas a c-statistic between 0.8 and 0.9 would have been more appropriate.

The fact that in the inclusion criteria of GUSTO IV-ACS coronary angiography was discouraged during or within 12 h after the completion of the study agent infusion, could have introduced selection bias. Unfortunately, no detailed information was recorded in the trial about the findings of angiography. There was also no information about the cause of death, additional revascularisation or re-admissions for other reasons between 30 days and one year. We had no data on use of medication during follow-up. Particularly in patients who had PCI, more patients may have used clopidogrel.

Conclusions

Our observations support other reports indicating that in patients with acute coronary syndromes early revascularisation is associated with a lower mortality. However, in most patients with acute coronary syndromes, early revascularisation was not performed, and the relatively high risk of one-year mortality in these patients remains a concern. This emphasizes the need for studies to improve management of medically treated patients. Also the optimal timing of angiography and subsequent
revascularisation if appropriate remains uncertain. We recommend angiography and revascularisation to be considered during the initial hospitalisation of patients with an acute coronary syndrome without ST-elevation.

Expression of interests

Dr. Barnathan and J.S. Cooper are employees of Centocor Inc. Drs. Armstrong, Wallentin, and Simoons have received grant support from Lilly, and Dr. Barnathan and J.S. Cooper are employees of Centocor Inc. Drs. Armstrong, Wallentin, and Simoons have received grant support from Lilly, and Dr. Armstrong has received grant support from Zillig.

References


