Coronary revascularisation in stable patients after an acute coronary syndrome: a propensity analysis of early invasive versus conservative management in a register-based cohort study

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ABSTRACT

Objectives: To compare the effectiveness of in-hospital medical therapy versus coronary revascularisation added to medical therapy in patients who stabilised after an acute coronary syndrome (ACS).

Design: Propensity score-matched cohort study from the database of the Tampere ACS registry.

Setting: A single academic hospital in Finland.

Participants: 1149 patients with a recent ACS, but no serious coexisting conditions: recurrent ischaemic episodes despite adequate medical therapy, haemodynamic instability, overt congestive heart failure and serious ventricular arrhythmias.

Primary and secondary outcome measures: The composite endpoint of major acute cardiovascular events (MACEs): unstable angina requiring rehospitalisation, stroke, myocardial infarction and all-cause mortality, at 6-month follow-up.

Results: Compared with standard medical treatment, revascularisation was associated with a lower rate of MACEs at 6 months in patients of the first quintile (HR 0.81; 95% CI 0.66 to 0.99), but a higher rate of MACEs in the fifth quintile (HR 4.74, CI 1.36 to 16.49; p=0.014). There were no significant differences in the rates of MACEs in the remaining three quintiles. Patients of the first quintile were the oldest (79.7 ±8.3 years) and had a more significant (p<0.001) history of prior myocardial infarction (37%) and poor renal function (creatinine, µmol/l: 114.9±70.7). They also showed the highest C reactive protein (7.3±9.5 mg/l) levels.

Conclusions: Our findings suggest that in-hospital coronary revascularisation did not lead to any advantage with signal of possible harm in the great majority of patients who stabilised after an ACS. An early invasive management strategy may be best reserved for elderly patients having high-risk clinical features and biochemical evidence of a strong inflammatory activity.

INTRODUCTION

Within the field of clinical practice, it is common knowledge that patients with acute coronary syndromes (ACS) presenting with recurrent ischaemic episodes despite aggressive medical therapy, haemodynamic instability, overt congestive heart failure or serious ventricular arrhythmias may benefit from early in-hospital coronary revascularisation.1–4 In contrast, it remains uncertain whether patients whose condition can safely be stabilised in the coronary care unit should...
Coronary revascularisation in acute coronary syndromes

ARTICLE SUMMARY

Strengths and limitations of this study

- The strength of the current study was to focus on those patients whose condition can safely be stabilised in the coronary care unit providing key contextual data for identifying patients with poor outcomes likely to benefit from coronary revascularisation therapy, as well as providing initial estimates of the efficacy of therapy.

- Our study should be interpreted in the context of several potential limitations. First, this study has no power to detect differences between treatment groups in the individual components of the primary composite endpoint. Second, this analysis is not a randomised study. Although propensity score helps to adjust for differences between groups, it does not control for unmeasured differences in clinical care. However, as a randomised trial cannot be carried out for every subgroup of patients, an observational database is helpful in providing hypothesis-generating data.

- None of the enrolled patients performed primary pulmonary resuscitation and emergency cardiovascular care. As a result, they were unable to evaluate whether patients who met stabilisation criteria also derived substantial benefit from coronary revascularisation therapy.

- The current study was undertaken to examine the effects of coronary revascularisation therapy in patients who had stabilised after an ACS.

- The decision whether or not to perform coronary revascularisation was left to the discretion of the treating physician.

- The following data were collected for all patients during hospitalisation: demographic characteristics (age and gender), cardiovascular risk factors (smoking, family history of coronary artery disease), coexisting medical condition (hypertension, hyperlipidaemia, diabetes, Canadian Cardiovascular Society functional classification of angina before the acute phase), clinical characteristics at admission (blood pressure, heart rate, ECG findings, troponin I values, C reactive protein, blood lipids, serum creatine), medications (at hospital admission, during hospital stay and at discharge) and in-hospital cardiac procedures (angiography, PCI or CABG).

- The primary measure of outcome was the composite end-point of major acute cardiovascular events (MACEs): unstable angina requiring rehospitalisation, stroke, non-fatal myocardial infarction and all-cause mortality at 6-month follow-up. End-points were mutually exclusive and hierarchical as listed above. The outcomes were assessed from the landmark time. A study nurse contacted all patients alive by telephone to collect follow-up data. Causes of death were registered from official statistics.

- We compare the clinical characteristics and outcome of patients who did and did not undergo in-hospital revascularisation. Results are presented as the mean±SD, or median (IQR) for continuous variables and as the percentage for categorical variables. Categorical data were analysed with between-group comparisons using the χ² test. The Wilcoxon rank sum test and the analysis of variance test were used to compare the two groups on continuous variables.

- A propensity analysis was carried out by use of a logistic regression model for treatment with early-invasive management (in-hospital revascularisation and medical therapy) versus conservative strategy (medical therapy alone). Multiple logistic regression with an in-hospital revascularisation condition as a dependent variable was used in the development of the propensity score.

routine capture of important clinical characteristics like family history of coronary artery disease, diabetes, and gender, cardiovascular risk factors (smoking, coexisting medical condition, and Canadian Cardiovascular Society functional classification of angina before the acute phase), clinical characteristics at admission (blood pressure, heart rate, ECG findings, troponin I values, C reactive protein, blood lipids, serum creatine), medications (at hospital admission, during hospital stay and at discharge) and in-hospital cardiac procedures (angiography, PCI or CABG).

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- A propensity analysis was carried out by use of a logistic regression model for treatment with early-invasive management (in-hospital revascularisation and medical therapy) versus conservative strategy (medical therapy alone). Multiple logistic regression with an in-hospital revascularisation condition as a dependent variable was used in the development of the propensity score.
Covariates were chosen using the approach described by Blackstone.\textsuperscript{10} The final selected model included the following patient variables: age, gender, current or ex-smoking, diabetes, previous myocardial infarction, serum creatinine, systolic and diastolic blood pressure, family history of coronary artery disease, Canadian Cardiovascular Society functional classification of angina before the acute phase (classes 1–4), troponin, C reactive protein and index event (STEMI and NSTACS). The discriminatory power of the logistic regression model was measured by the area under the receiver operating characteristic curve. After fitting the model, we ranked all patients by their estimated propensity score and grouped patients within quintiles. Differences in the selected variables among quintiles were examined using the Wilcoxon rank sum test and the $2\times2$ $\chi^2$ test. We have corrected the $p$ value in multiple comparisons using the Bonferroni procedure.

Event-free survival curves were estimated and plotted on the basis of the Kaplan-Meier estimator. We calculated HR and 95% CI for 6-month MACEs, comparing within each quintile patients who underwent revascularisation and those who did not. The effect of quintile of propensity score and treatment type on all-cause mortality and MACEs was evaluated by a multivariate Cox proportional hazards regression model, which included an interaction term between the two considered covariates. Proportionality in hazard was carefully checked, both with visual analysis of Schoenfeld residuals and with the Grambsch-Therneau test. For the final model, multivariate HRs have been presented along with their 95% CI. Analyses were performed with the STATA V.8 statistical software system.

**RESULTS**

**Characteristics of the study population**

The registry population consisted of 1149 patients (table 1). Of these, 908 (79%) patients were managed only with medical therapy alone and 241 (21%) patients were treated with revascularisation (146 PCI and 95 CABG) and medical therapy. MACEs occurred in 231 of these patients at 6-month follow-up (figure 1). Mortality from any cause occurred in 169 patients, thus representing 73% of the overall MACEs.

**Propensity analysis**

We ranked all patients by their estimated propensity score and grouped patients within quintiles. The median propensity score was 0.197 (IQR, 0.097–0.350). The C-statistic for the propensity score model was 0.77, indicating a good discriminatory power. A sensible match was found in all quintiles with the disappearance of significant baseline differences within quintiles.

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**Table 1** Characteristics of the study population sorted by in-hospital revascularisation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Revascularisation</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Yes (n=241)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>67 (58–74)</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>169 (70)</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>51 (21)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Current or ex-smoking, n (%)</strong></td>
<td>135 (56)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>125 (52)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Family history of CAD, n (%)</strong></td>
<td>67 (28)</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction, n (%)</strong></td>
<td>53 (22)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td>4.7 (4.0–5.5)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>LDL-cholesterol (mmol/l)</strong></td>
<td>2.8 (2.3–3.4)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>HDL-cholesterol (mmol/l)</strong></td>
<td>1.1 (0.9–1.3)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/l)</strong></td>
<td>1.5 (1.0–2.0)</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>146 (127–167)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
<td>80 (70–91)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Creatine (µmol/l)</strong></td>
<td>82 (71–98)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>C reactive protein (mg/l)</strong></td>
<td>9.8 (3.3–32.8)</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td><strong>Troponin I (µmol/l)</strong></td>
<td>10.5 (1.7–35.2)</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td><strong>Canadian Cardiovascular Society, n (%)</strong></td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td><strong>No angina</strong></td>
<td>125 (52)</td>
<td></td>
</tr>
<tr>
<td><strong>Class 1</strong></td>
<td>29 (12)</td>
<td></td>
</tr>
<tr>
<td><strong>Class 2</strong></td>
<td>58 (24)</td>
<td></td>
</tr>
<tr>
<td><strong>Class 3</strong></td>
<td>24 (10)</td>
<td></td>
</tr>
<tr>
<td><strong>Class 4</strong></td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Index event, n (%)</strong></td>
<td>$&lt;$0.001</td>
<td></td>
</tr>
<tr>
<td><strong>ST-elevation myocardial infarction</strong></td>
<td>96 (40)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-ST elevation-acute coronary syndromes</strong></td>
<td>145 (60)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as median (IQR) where otherwise not indicated.
CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
between patients undergoing revascularisation and those receiving medical therapy alone. The rate of revascularisation increased from the first to the fifth quintile: 2.6% (1.3% PCI and 1.3% CABG), 10.3% (4.5% PCI and 5.8% CABG), 12.5% (5% PCI and 7.5% CABG), 24.3% (14.4% PCI and 9.9% CABG) and 50.3% (35.4% PCI and 14.9% CABG), respectively. Conversely, the rate of MACE decreased from the first to the fifth quintile: 52%, 47%, 40%, 29% and 21%, respectively.

Variables within each propensity score quintile are shown in table 2. Propensity scoring by quintile failed to balance a number of covariates across all quintiles. The most striking imbalances in propensity scores occurred in the first and fifth quintiles. The first quintile compared with all other quintiles was characterised by very elderly patients, more comorbid conditions, such as a history of prior myocardial infarction, poor renal function (high creatine levels), high C reactive protein levels and NSTACS. In contrast, the patients of the fifth quintile compared with those of the other quintiles were the youngest. They were prevalently men and showed low C reactive protein levels.

They also had the highest proportions of STEMI (50%) and a family history of coronary artery disease (41.7%).

Table 2  Propensity score quintiles and baseline clinical characteristics

<table>
<thead>
<tr>
<th>Quintile n.1 &lt;0.08377 (n. 230)</th>
<th>Quintile n.2 0.08378–0.15536 (n. 229)</th>
<th>Quintile n.3 0.15537–0.24783 (n. 230)</th>
<th>Quintile n.4 0.24784–0.319149 (n. 230)</th>
<th>Quintile n.5 &gt;0.319150 (n. 230)</th>
<th>p Value for propensity score analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79.7±8.3</td>
<td>74.2±10.4</td>
<td>73.3±9.6</td>
<td>67.3±10.1</td>
<td>58.9±10.9</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>92 (40)</td>
<td>107 (46.7)</td>
<td>117 (50.9)</td>
<td>155 (67.4)</td>
<td>195 (85.2)</td>
</tr>
<tr>
<td>Current or ex-smoking, n (%)</td>
<td>77 (33.4)</td>
<td>104 (45.4)</td>
<td>106 (46.1)</td>
<td>140 (60.8)</td>
<td>137 (59.6)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>81 (35.2)</td>
<td>75 (32.8)</td>
<td>42 (18.3)</td>
<td>59 (25.6)</td>
<td>39 (17)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>103 (44.8)</td>
<td>97 (42.4)</td>
<td>108 (47)</td>
<td>102 (44.3)</td>
<td>124 (53.9)</td>
</tr>
<tr>
<td>Family history CAD, n (%)</td>
<td>17 (7.4)</td>
<td>27 (11.8)</td>
<td>27 (11.7)</td>
<td>45 (19.6)</td>
<td>96 (41.7)</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>85 (37)</td>
<td>53 (23.1)</td>
<td>47 (20.4)</td>
<td>54 (23.5)</td>
<td>41 (17.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>149.0±32.6</td>
<td>148.2±34.0</td>
<td>148.6±30.8</td>
<td>148.1±29.0</td>
<td>144.7±27.8</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.8±0.5</td>
<td>4.6±0.7</td>
<td>4.7±0.6</td>
<td>4.5±0.7</td>
<td>4.6±0.6</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.9±0.2</td>
<td>2.8±0.3</td>
<td>2.7±0.2</td>
<td>2.8±0.2</td>
<td>2.7±0.3</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.1±0.3</td>
<td>1.1±0.3</td>
<td>1.2±0.2</td>
<td>1.1±0.2</td>
<td>1±0.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78.0±19.5</td>
<td>79.4±17.5</td>
<td>80.9±16.8</td>
<td>81.8±17.9</td>
<td>82.4±16.3</td>
</tr>
<tr>
<td>Creatine (µmol/l)</td>
<td>114.9±70.7</td>
<td>97.2±53.0</td>
<td>79.6±26.5</td>
<td>70.7±17.7</td>
<td>70.7±17.7</td>
</tr>
<tr>
<td>C reactive protein (mg/l)</td>
<td>7.3±9.5</td>
<td>5.0±7.0</td>
<td>4.2±5.5</td>
<td>3.1±5.3</td>
<td>2.4±3.7</td>
</tr>
<tr>
<td>Troponin I (µmol/l)</td>
<td>1.2±3.1</td>
<td>2.5±7.2</td>
<td>2.7±5.5</td>
<td>3.9±9.9</td>
<td>9.5±24.9</td>
</tr>
<tr>
<td>No angina, n (%)</td>
<td>113 (49.1)</td>
<td>131 (57.2)</td>
<td>125 (54.4)</td>
<td>129 (56.2)</td>
<td>117 (50.9)</td>
</tr>
<tr>
<td>CCS 1, n (%)</td>
<td>35 (15.2)</td>
<td>20 (8.7)</td>
<td>33 (14.3)</td>
<td>33 (14.3)</td>
<td>21 (9.1)</td>
</tr>
<tr>
<td>CCS 2, n (%)</td>
<td>50 (21.7)</td>
<td>46 (20.1)</td>
<td>46 (20)</td>
<td>50 (21.7)</td>
<td>65 (28.2)</td>
</tr>
<tr>
<td>CCS 3, n (%)</td>
<td>24 (10.4)</td>
<td>25 (10.9)</td>
<td>21 (9.1)</td>
<td>17 (7.4)</td>
<td>25 (10.9)</td>
</tr>
<tr>
<td>CCS 4, n (%)</td>
<td>8 (3.6)</td>
<td>7 (3.1)</td>
<td>5 (2.2)</td>
<td>1 (0.4)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>26 (11.3)</td>
<td>39 (17.0)</td>
<td>70 (30.4)</td>
<td>87 (37.8)</td>
<td>115 (50)</td>
</tr>
<tr>
<td>NSTACS, n (%)</td>
<td>204 (88.7)</td>
<td>190 (83)</td>
<td>160 (69.6)</td>
<td>143 (62.2)</td>
<td>115 (50)</td>
</tr>
<tr>
<td>Medical therapy, n (%)</td>
<td>224 (97.4)</td>
<td>205 (89.7)</td>
<td>201 (87.5)</td>
<td>174 (75.7)</td>
<td>114 (49.6)</td>
</tr>
<tr>
<td>Coronary revascularisation, n (%)</td>
<td>6 (2.6)</td>
<td>24 (10.3)</td>
<td>29 (12.5)</td>
<td>56 (24.3)</td>
<td>116 (50.4)</td>
</tr>
</tbody>
</table>

Values are expressed as medians±SD where not indicated otherwise.

CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSTACS, non-ST elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.
Propensity-stratum-specific effects
For MACEs, gradients across levels of the propensity score for the treated and untreated groups were strong and unexpectedly different. In the first quintile, use of revascularisation was associated with the lowest rates of MACEs as compared with medical therapy (15% vs 28.7%). In contrast, for the fifth quintile, the rates of MACEs were 13.8% and 6.1% in the revascularisation and medical therapy groups, respectively. There were less striking differences in the rates of MACEs in the remaining categories of propensity scores (second quintile: 25% vs 25.3%; third quintile: 35.4% vs 20.3%; fourth quintile: 10.7% vs 13.5%). Table 3 summarises information about the HR of patients who had MACEs during follow-up in the coronary revascularisation group according to percentiles of the propensity score. Compared with standard medical treatment, revascularisation was associated with a lower rate of MACEs at 6 months in patients of the first quintile (HR 0.81; 95% CI 0.66 to 0.99; p=0.041), but a higher rate of MACEs in the fifth quintile (HR 4.94; 95% CI 0.57 to 42.30; p=0.10). No relevant differences were found in the remaining categories of propensity scores (HR of the second quintile: 1.16; 95% CI 0.52 to 2.58; HR of the third quintile: 1.03; 95% CI 0.44 to 2.26 and HR of the fourth quintile: 0.68; 95% CI 0.22 to 2.09).

All-cause mortality
In the first quintile, the 6-month death rate was 0% in the revascularisation group and 24.7% in the medical therapy group. There was a trend towards higher mortality among patients who had undergone revascularisation in the fifth quintile (HR 4.94; 95% CI 0.57 to 42.30; p=0.10). No relevant differences were found in the remaining categories of propensity scores (HR of the second quintile: 2.04).
COURAGE trial included a mixed population of patients with and without prior ACS, but lacked information on time to stabilisation from previous acute episodes to accurately define the boundary between a potentially stable and unstable cohort after an ACS.\(^{3,11}\)

The objective of the current study was to formally test the impact of medical therapy versus coronary revascularisation added to medical therapy on the management of patients with recent ACS who were stable for 48 h after an ACS.

**Methodological strengths of the study**

In this population, we created a propensity score for the likelihood of undergoing in-hospital revascularisation using multiple logistic regressions with in-hospital revascularisation condition as a dependent variable and baseline clinical characteristics of the cohort as covariates including the index event (table 1). The results of the current study were therefore consistent among the two diagnostic groups: STEMI and NSTACS.

**Principal findings**

The principal finding is that selection for in-hospital coronary intervention was not associated with reduced risk compared with medical therapy for the great majority of patients who stabilised after an ACS (the second, third, fourth and fifth quintiles, approximately 80% of the overall study population). Our findings are congruent with previous works that called into question the role of routine revascularisation therapy for prevention of subsequent cardiovascular events among many patients with ACS.\(^{5,12-14}\) With regard to patients with STEMI, the Occluded Artery Trial (OAT) found no discernible benefit at 4-year follow-up among patients with occlusion of the infarct-related artery following a strategy of routine PCI 3–28 days after acute myocardial infarction.\(^{2}\) The findings of the OAT study, however, should not be interpreted as applying to all patients experiencing ACS, but just to a minority of ST-elevation ACS patients: those with no or minimal angina, one-vessel disease and normal ejection fraction. In addition, the OAT study investigated the effect of PCI on a 4-year outcome, so it is not comparable with the results of this study, which looked only at a 6-month outcome. With regard to patients with NSTACS, a TACTICS-TIMI–18 trial post hoc analysis demonstrated that patients with cardiac troponin I levels of less than 0.1 ng/ml had no detectable benefit from early invasive management.\(^{15}\) This study, however, lumped together patients with markedly different clinical characteristics, including those patients with recurrent ischaemic episodes of ischaemia and serious ventricular arrhythmias who were not clearly in a stable phase of their disease. Our results are more representative of the treatment effects of an invasive strategy in patients that can safely be stabilised in the coronary care unit 48 h after an ACS. In these patients, the prognosis is uncertain and the predictive value of troponin determination has not yet been ascertained.

It is interesting that, in our study population, troponin I could not differentiate patients who benefited from coronary revascularisation (first quintile) from those who did not (second, third and fourth quintiles), while C reactive protein levels did so. Although the mechanism underlying the present result cannot be established by our data, previous works could offer a potential explanation for these findings. A post hoc analysis of patients enrolled in the Global Utilisation of Strategies to Open Occluded Coronary Arteries IIb study has indicated that the ‘front-loading’ of major coronary events may be observed within the first 24 h.\(^{16}\) Accordingly, cardiac troponin assay at admission is mainly a predictor of major cardiac events within 48–72 h.\(^{17}\) In our study, we defined a landmark time of 48 h; thus, we missed the earliest occurrence of coronary events and the associated predictor power of troponin. C reactive protein might be a better discriminator of patients who remain at high risk despite apparent stabilisation of their clinical condition, as there is published evidence that elevations in levels of C reactive protein predict the future risk of myocardial infarction even in asymptomatic middle-aged men and women with or without documented ischaemic heart disease.\(^{18}\)

Another important point of the study is that referral to routine in-hospital elective revascularisation is associated with decreased risk of cardiovascular endpoints in approximately 20% of patients, specifically in patients of the lowest-propensity stratum (first quintile). Patients of the first quintile were the oldest, had higher serum creatine levels and had a more significant history of prior myocardial infarction as an index event. They also showed the highest C reactive protein levels. Our results are consistent with previous data. Observational studies and trials of invasive versus medical therapy\(^{19}\) have found that patients 75 years of age benefit more from revascularisation than from optimised medical therapy in terms of symptom relief and quality of life.

Elderly patients have greater disease severity, including prior myocardial infarction and elevated creatinine levels.\(^{19,20}\) It is well established that early revascularisation improves 1-year survival in patients with ACS and renal insufficiency.\(^{19}\) The Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital trial is so far the only trial on treatment according to previous myocardial infarction. It demonstrated the superiority of an early-invasive strategy in patients presenting with ACS and prior myocardial infarction.\(^{21}\)

A further finding of our study was to demonstrate the superiority of freedom from adverse outcomes in the highest-propensity stratum (fifth quintile) managed with medical therapy alone. Patients in the revascularisation group had a significantly higher risk for MACEs (HR 4.74; 95% CI 1.36 to 16.49) and a directionally consistent but non-significantly higher odds of mortality (HR 4.94; 95% CI 0.57 to 42.30). These results clearly call for further investigation. Indeed, there were no significant data from previous works supporting the hypothesis that
selected ACS patients might be harmed more from in-hospital revascularisation. Patients of the fifth quintile were young and prevalently male. They had the highest proportions of ST elevation myocardial infarction as an index event (50%) and a family history of coronary artery disease (41.7%). A previous work has highlighted the importance of male sex and family history in young patients with acute myocardial infarction. We are not aware of previous studies on clinical decision rules for revascularisation in patients with a family history of coronary artery disease. The results that we report herein suggest that the use of revascularisation either with PCI or CABG should be done cautiously. A number of explanations could account for these results. The revascularisation process is intrinsically inflammatory. Both revascularisation strategies may induce a rapid increase in plasma levels of C reactive protein, vascular cell adhesion molecule-1 and chemokines. Patients with a genetic predisposition to coronary disease may be especially vulnerable to these adverse effects as there is increasing evidence that clusters of inflammatory factors and markers of oxidation are associated with a positive parental history of premature coronary heart disease in youths.

An additional explanation for the relatively poor prognosis of patients undergoing revascularisation in the fifth quintile comes from the design of our study. As we defined a landmark time of 2 days, these patients were referred for ‘late’ revascularisation after ACS. The efficacy of late elective PCI in ST elevation myocardial infarction has been assessed in the TAMI-6 (The Thrombolysis and Angioplasty in Myocardial Infarction) and TOAT (Open Artery Trial) trials. None of these trials supported the value of this approach. In TAMI-6, angiography was performed within 30–48 h after symptom onset. PCI was associated with improved left ventricular ejection fraction at 1 month but not at 6 months. In the TOAT trial, angiography was performed at 3 days to 4 weeks after the infarction with PCI having an adverse effect on left ventricular remodelling.

Strengths and limitations of the study

The results of a randomised trial apply only to patients meeting the study entry criteria and given the identical approach. It is simpler to demonstrate that routine in-hospital coronary revascularisation generally works for patients with ACS than it is to define precisely the population that benefits.

The strength of the current study was, therefore, to focus on those patients whose condition can safely be stabilised in the coronary care unit providing key contextual data for identifying patients with poor outcomes likely to benefit from coronary revascularisation therapy, as well as providing initial estimates of the efficacy of therapy.

Our study should be interpreted in the context of several potential limitations. First, this study has no power to detect differences between treatment groups in the individual components of the primary composite endpoint. Second, this analysis is not a randomised study. Although the propensity score helps to adjust for differences between groups, it does not control for unmeasured differences in clinical care. However, as a randomised trial cannot be carried out for every subgroup of patients, an observational database is helpful in providing hypothesis-generating data. Third, the median age was 79.7 years in the first quintile. It is therefore possible that non-cardiovascular mortality contributed to the total deaths, especially in this quintile. However, referral to coronary revascularisation decreased cardiovascular endpoints and mortality as well in these patients; thus, total mortality was most likely driven by mortality from cardiovascular causes. Fourth, the limited duration of follow-up may have obscured the possibility of later benefit. Fifth, the use of observational data from a single centre limits the generalisability of the findings. Sixth, data were not available on the body mass index.

CONCLUSIONS

In summary, we used propensity score analysis and observed a strong and robust heterogeneity in the treatment effects of an invasive strategy, which was associated with a significant reduction in cardiovascular endpoints at 6 months among patients (first quintile) with the oldest age, high-risk clinical features (prior myocardial infarction and renal failure) and biochemical evidence of a strong inflammatory activity (high C reactive protein levels). Conversely, a routine in-hospital elective revascularisation was not associated with reduced risk over medical therapy in the majority of patients (second, third, fourth and fifth quintiles). There was evidence of an increased hazard with an invasive strategy in younger male patients with ST elevation myocardial infarction and a family history of coronary disease. If corroborated by other studies, these findings may have profound clinical implications on the contemporary management of patients whose condition can safely be stabilised after an ACS.

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