

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

Raffaele Bugiardini,¹ Markku Eskola,² Heini Huhtala,³ Kari Niemelä,² Pekka Karhunen,⁴ Rossella Miglio,⁵ Olivia Manfrini,¹ Carmine Pizzi,¹ Kjell Nikus²

To cite: Bugiardini R, Eskola M, Huhtala H, *et al.* 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. *BMJ Open* 2013;**3**:e002559. doi:10.1136/bmjopen-2013-002559

► Prepublication history for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-002559>).

Received 4 January 2013
Revised 25 March 2013
Accepted 26 March 2013

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

For numbered affiliations see end of article.

Correspondence to

Dr Raffaele Bugiardini;
raffaele.bugiardini@unibo.it

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 \pm 8.3 years) and had a more significant ($p<0.001$) history of prior myocardial infarction (37%) and poor renal function (creatinine, $\mu\text{mol/l}$: 114.9 \pm 70.7). They also showed the highest C reactive protein (7.3 \pm 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.

ARTICLE SUMMARY

Articles focus

■ To examine the effects of coronary revascularisation therapy in patients who have stabilised after an acute coronary syndrome (ACS), we used a propensity score analysis^{6 7} based on the likelihood of undergoing revascularisation after stabilisation. Propensity-stratum-specific analyses were then used to evaluate the association of in-hospital coronary revascularisation and major acute cardiovascular events.

Key message

■ The principal finding is that routine in-hospital coronary intervention adds no benefit to medical therapy for the great majority of patients. Moreover, we found a significant reduction in cardiovascular endpoints associated with revascularisation, compared with medical treatment in patients with oldest age prior to myocardial infarction and renal failure and an increased hazard in younger male patients with ST elevation myocardial infarction and a family history of coronary disease

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

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.

routinely receive an interventional approach before hospital discharge.

Previous studies lumped together patients with such markedly different clinical characteristics.^{2 5–7} 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.

METHODS**Study population and data collection**

The Tampere University Hospital registry enrolment region encompasses the city of Tampere and 11 neighbouring municipalities. Between January 2002 and March 2003, 1188 consecutives were included in the Tampere University Hospital Registry. In February 2005, the vital status was known for 1186 patients up to 302 days after recruitment.

The ethics committee at Tampere University Hospital approved the study protocol. The patients gave their written informed consent for participation. The diagnosis of ACS was based on symptoms, troponin I values and ECG findings at admission. Troponin I values were collected at baseline and after 6–12 h. Patients were categorised as ST segment elevation myocardial infarction (STEMI) and Non-ST elevation acute coronary syndrome (NSTACS). The definition of clinical stabilisation met the criteria of the 2005 AHA Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.⁸ None of the enrolled patients performed primary or rescue percutaneous coronary intervention (PCI).

Patients were excluded from the analysis if they had recurrent ischaemic episodes despite adequate medical therapy, haemodynamic instability, overt congestive heart failure (Killip class III or IV) or serious ventricular

arrhythmias.⁹ To avoid survival bias—as patients who were selected for the study would have to survive enough to have the procedure—a landmark time was used. We defined the landmark time as 2 days, based on the fact that in the study cohort coronary revascularisation (PCI or coronary artery bypass grafting (CABG)) was performed 3–6 days after admission. After excluding 37 patients for the above reasons, the final analysis population was 1149 participants whose symptoms had resolved by the time of evaluation.

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).

Treatment decisions

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

End-points

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.

Statistical analysis

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 χ^2 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.

Covariates were chosen using the approach described by Blackstone.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 2×2 χ^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

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

Variable Number (n=908)	Revascularisation	
	Yes (n=241)	p-Value
Age (years)	75 (65–81)	67 (58–74) <0.001
Male, n (%)	499 (55)	169 (70) <0.001
Diabetes, n (%)	245 (27)	51 (21) 0.07
Current or ex-smoking, n (%)	417 (46)	135 (56) 0.003
Hypertension, n (%)	490 (54)	125 (52) 0.46
Family history of CAD, n (%)	145 (16)	67 (28) <0.001
Previous myocardial infarction, n (%)	236 (26)	53 (22) 0.17
Total cholesterol (mmol/l)	4.6 (3.9–5.4)	4.7 (4.0–5.5) 0.19
LDL-cholesterol (mmol/l)	2.8 (2.1–3.3)	2.8 (2.3–3.4) 0.14
HDL-cholesterol (mmol/l)	1.1 (0.9–1.4)	1.1 (0.9–1.3) 0.08
Triglycerides (mmol/l)	1.3 (1.0–1.7)	1.5 (1.0–2.0) <0.001
Systolic blood pressure (mm Hg)	145 (125–167)	146 (127–167) 0.84
Diastolic blood pressure (mm Hg)	79 (68–90)	80 (70–91) 0.19
Creatine (μ mol/l)	89 (73–113)	82 (71–98) 0.001
C reactive protein (mg/l)	13.3 (3.4–63.9)	9.8 (3.3–32.8) <0.001
Troponin I (μ mol/l)	3.6 (0.5–21.7)	10.5 (1.7–35.2) <0.001
Canadian Cardiovascular Society, n (%)		0.77
No angina	490 (54)	125 (52)
Class 1	118 (13)	29 (12)
Class 2	200 (22)	58 (24)
Class 3	91(10)	24 (10)
Class 4	18 (2)	2 (1)
Index event, n (%)		<0.001
ST-elevation myocardial infarction	236 (26)	96 (40)
Non-ST elevation-acute coronary syndromes	672 (74)	145 (60)

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

	Quintile n.1 ≤ 0.08377 (n. 230)	Quintile n.2 0.08378– 0.15536 (n. 229)	Quintile n.3 0.15537– 0.24783 (n. 230)	Quintile n.4 0.24784– 0.39149 (n. 230)	Quintile n.5 >0.39150 (n. 230)	p Value for propensity score analysis
Age (years)	79.7±8.3	74.2±10.4	73.3±9.6	67.3±10.1	58.9±10.9	<0.001
Male, n (%)	92 (40)	107 (46.7)	117 (50.9)	155 (67.4)	195 (85.2)	<0.001
Current or ex-smoking, n (%)	77 (33.4)	104 (45.4)	106 (46.1)	140 (60.8)	137 (59.6)	<0.001
History of diabetes, n (%)	81 (35.2)	75 (32.8)	42 (18.3)	59 (25.6)	39 (17)	<0.001
History of hypertension, n (%)	103 (44.8)	97 (42.4)	108 (47)	102 (44.3)	124 (53.9)	0.05
Family history CAD, n (%)	17 (7.4)	27 (11.8)	27 (11.7)	45 (19.6)	96 (41.7)	<0.001
Prior myocardial infarction, n (%)	85 (37)	53 (23.1)	47 (20.4)	54 (23.5)	41 (17.8)	<0.001
Systolic blood pressure (mm Hg)	149.0±32.6	148.2±34.0	148.6±30.8	148.1±29.0	144.7±27.8	0.6
Total cholesterol (mmol/l)	4.8±0.5	4.6±0.7	4.7±0.6	4.5±0.7	4.6±0.6	0.09
LDL-cholesterol (mmol/l)	2.9±0.2	2.8±0.3	2.7±0.2	2.8±0.2	2.7±0.3	0.1
HDL-cholesterol (mmol/l)	1.1±0.3	1.1±0.3	1.2±0.2	1.1±0.2	1±0.3	0.09
Diastolic blood pressure (mm Hg)	78.0±19.5	79.4±17.5	80.9±16.8	81.8±17.9	82.4±16.3	0.06
Creatine (µmol/l)	114.9±70.7	97.2±53.0	79.6±26.5	70.7±17.7	70.7±17.7	<0.001
C reactive protein (mg/l)	7.3±9.5	5.0±7.0	4.2±5.5	3.1±5.3	2.4±3.7	<0.001
Troponin I (µmol/l)	1.2±3.1	2.5±7.2	2.7±5.5	3.9±9.9	9.5±24.9	<0.01
No angina, n (%)	113 (49.1)	131 (57.2)	125 (54.4)	129 (56.2)	117 (50.9)	0.7
CCS 1, n (%)	35 (15.2)	20 (8.7)	33 (14.3)	33 (14.3)	21 (9.1)	
CCS 2, n (%)	50 (21.7)	46 (20.1)	46 (20)	50 (21.7)	65 (28.2)	
CCS 3, n (%)	24 (10.4)	25 (10.9)	21 (9.1)	17 (7.4)	25 (10.9)	
CCS 4, n (%)	8 (3.6)	7 (3.1)	5 (2.2)	1 (0.4)	2 (0.9)	
STEMI, n (%)	26 (11.3)	39 (17.0)	70 (30.4)	87 (37.8)	115 (50)	<0.001
NSTACS, n (%)	204 (88.7)	190 (83)	160 (69.6)	143 (62.2)	115 (50)	<0.001
Medical therapy, n (%)	224 (97.4)	205 (89.7)	201 (87.5)	174 (75.7)	114 (49.6)	
Coronary revascularisation, n (%)	6 (2.6)	24 (10.3)	29 (12.5)	56 (24.3)	116 (50.4)	

Values are expressed as median±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.

Table 3 Subgroups analysis with Cox regression model according to percentiles of the propensity score

Quintile	Patients in the medical therapy group are the referent category		
	HR	95% CI	p Value
First	0.81	0.66 to 0.99	0.041
Second	1.13	0.52 to 2.56	NS
Third	1.70	0.91 to 3.17	NS
Fourth	0.96	0.42 to 2.24	NS
Fifth	4.73	1.36 to 16.49	0.014

NS, non-significant.

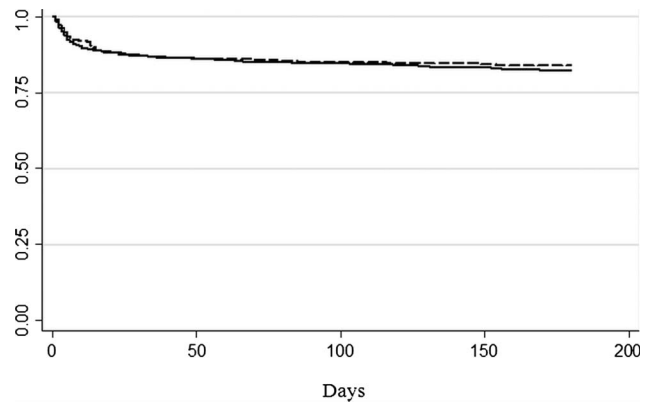
Propensity-stratum-specific effects

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 4.74; 95% CI 1.36 to 16.49; $p=0.014$). There were no significant differences in the HRs of MACEs in the remaining three quintiles.

Multivariate Cox regression analysis was used to confirm these results. There was a significant interaction ($p<0.001$) between the quintiles of propensity score and treatment. The treatment covariates for MACEs resulted in a significant effect of revascularisation methods, mainly in the first and fifth quintiles. Interaction analysis showed heterogeneities of the effects of treatment depending on the revascularisation methods. This model was used to test whether the HRs of each quintile were significantly different from each other with respect to the effect of revascularisation. There was a significant interaction ($p<0.001$) between the first and the fifth quintiles and treatment

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

**Figure 1** Kaplan-Meier estimates of the cumulative event rates (major acute cardiovascular events): in-hospital coronary revascularisation group (—); medical therapy group (---). The rate of the primary endpoint (unstable angina requiring rehospitalisation, stroke, non-fatal myocardial infarction and all-cause mortality) at 6 months was not significantly different between the two groups (adjusted HR 1.41, 95% CI 0.98 to 2.04).

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).

DISCUSSION

This study provides insights on real-life treatment of patients who stabilised 48 h after an ACS. The research question is relevant, as in a substantial number of patients control of anginal symptoms, ECG changes and haemodynamics are achieved with medical treatment within the first 24 h. The use of propensity score as a stratification method yielded new information on how clinical variables may influence 6-month outcomes. The principal finding is that outcomes in the great majority of patients appear to be unaffected by treatment with in-hospital coronary intervention.

Moreover, we found a significant reduction in cardiovascular endpoints associated with revascularisation, compared with medical treatment in patients with oldest age prior to myocardial infarction and renal failure and an increased hazard in younger male patients with ST elevation myocardial infarction and a family history of coronary disease. There is, therefore, a strong and robust heterogeneity in the treatment effects of an invasive strategy in patients who have stabilised after an ACS.

Meaning of the study

The Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial found that optimal medical therapy was just as good at preventing future events as receiving coronary revascularisation added to optimal medical therapy in patients with stable angina.¹¹ However, the results of randomised trials do not necessarily apply to other populations. The

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.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.^{2 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 creatinine 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 therapy¹⁹ 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.¹⁹ 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.^{22–24} 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.^{25–27}

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)²⁸ and TOAT (Open Artery Trial) trials.²⁹ None of these trials supported the value of this approach.^{28–29} In TAMI-6, angiography was performed within 30–48 h after symptom onset.²⁸ 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.²⁹

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 treatment. It is without empirical evidence to expand the results of a trial into a broad therapeutic principle. 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.

Author affiliations

¹Experimental, Diagnostic and Speciality Medicine, University of Bologna, Bologna, Italy

²Heart Center, Pirkanmaa Hospital District, Tampere, Finland

³School of Public Health, University of Tampere, Tampere, Finland

⁴Medical School, University of Tampere, and Research Unit of Laboratory Centre, Tampere, Finland

⁵Statistical Sciences “Paolo Fortunati”, University of Bologna, Bologna, Italy

Contributors RB and KN had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RB, KN, CP and OM participated in the study concept and design. ME, KM, PK and KN participated in the acquisition of data. RB, RM, OM and CP participated in the analysis and interpretation of data. RB, OM and CP participated in the drafting of the manuscript. RM, ME, KM, PK and KN

participated in the critical revision of the manuscript for important intellectual content. RB, RM and OM participated in the statistical analysis.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Patient consent Obtained.

Ethics approval Tampere University Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

- FRagmin and Fast Revascularisation during Instability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:708–15.
- Hochman JS, Lamas GA, Buller CE, *et al.* Occluded Artery Trial Investigators. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006;355:2395–407.
- Weintraub WS, Grau-Sepulveda MV, Weiss JM, *et al.* Prediction of long-term mortality after percutaneous coronary intervention in older adults: results from the National Cardiovascular Data Registry. *Circulation* 2012;125:1501–10.
- Brugada J, Aguinaga L, Mont L, *et al.* Coronary artery revascularization in patients with sustained ventricular arrhythmias in the chronic phase of a myocardial infarction: effects on the electrophysiologic substrate and outcome. *J Am Coll Cardiol* 2001;37:529–33.
- O'Donoghue M, Boden WE, Braunwald E, *et al.* Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;300:71–80.
- Mehta SR, Cannon CP, Fox KA, *et al.* Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908–17.
- Schomig A, Mehilli J, De Waha A, *et al.* A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol* 2008;52:894–904.
- 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. ECC Committee, Subcommittees and Task Forces of the American Heart Association. *Circulation* 2005;112(Suppl 24):IV1–203.
- Scanlon PJ, Faxon DP, Audet AM, *et al.* ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 1999;33:1756–824.
- Blackstone EH. Comparing apples and oranges. *J Thorac Cardiovasc Surg* 2002;123:8–15.
- Boden WE, O'Rourke RA, Teo KK, *et al.* COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–16.
- Wright RS, Anderson JL, Adams CD, *et al.* American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;57:19, e215–367.
- Smith SC Jr, Feldman TE, Hirshfeld JW Jr, *et al.* American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 Guideline update for Percutaneous Coronary Intervention—Summary Article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2006;47:216–35.
- Cantor WJ, Goodman SG, Cannon CP, *et al.* Early cardiac catheterization is associated with lower mortality only among high-risk patients with ST- and non-ST-elevation acute coronary syndromes: observations from the OPUS-TIMI 16 trial. *Am Heart J* 2005;149:275–83.
- Morrow DA, Cannon CP, Rifai N, *et al.* TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction—results from a randomized trial. *JAMA* 2001;286:2405–12.
- Cho L, Bhatt DL, Marso SP, *et al.* An invasive strategy is associated with decreased mortality in patients with unstable angina and non-ST-elevation myocardial infarction: GUSTO IIb trial. *Am J Med* 2003;114:106–11.
- McAlister FA, Oreopoulos A, Norris CM, *et al.* Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Exploring the treatment-risk paradox in coronary disease. *Arch Intern Med* 2007;167:1019–25.
- Ridker PM, Danielson E, Fonseca FA, *et al.* JUPITER Study Group; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.
- Pfisterer M. Trial of Invasive versus Medical therapy in Elderly patients Investigators. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation* 2004;110:1213–18.
- Lee CH, Tan M, Yan AT, *et al.* Canadian Acute Coronary Syndromes (ACS) Registry II Investigators. Use of cardiac catheterization for non-ST-segment elevation acute coronary syndromes according to initial risk: reasons why physicians choose not to refer their patients. *Arch Intern Med* 2008;168:291–6.
- Boden WE, O'Rourke RA, Crawford MH, *et al.* Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;338:1785–92.
- Saleh N, Tornvall P. Serum C-reactive protein response to percutaneous coronary intervention in patients with unstable or stable angina pectoris is associated with the risk of clinical restenosis. *Atherosclerosis* 2007;195:374–8.
- Angioi M, Abdelmouttaleb I, Rodriguez RM, *et al.* Increased C-reactive protein levels in patients with in-stent. *Am J Cardiol* 2001;87:1189–93.
- Vallely MP, Bannon PG, Bayfield MS, *et al.* Endothelial activation after coronary artery bypass surgery: comparison between on-pump and off-pump techniques. *Heart Lung Circ* 2010;19:445–52.
- Schnabel RB, Lunetta KL, Larson MG, *et al.* The relation of genetic and environmental factors to systemic inflammatory biomarker concentrations. *Circ Cardiovasc Genet* 2009;2:229–37.
- Dehghan A, Dupuis J, Barbalic M, *et al.* Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. *Circulation* 2011;123:731–8.
- Chu Y, Alwahdani A, Iida S, *et al.* Vascular effects of the human extracellular superoxide dismutase R213G variant. *Circulation* 2005;112:1047–53.
- Topol EJ, Califf RM, Vandormael M, *et al.* TAMI 6 A randomized trial of late reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction-6 Study Group. *Circulation* 1992;85:2090.
- Yousef ZR, Redwood SR, Bucknall CA, *et al.* Late intervention after anterior myocardial infarction: effects on left ventricular size, function, quality of life, and exercise tolerance: results of the Open Artery Trial (TOAT Study). *J Am Coll Cardiol* 2002;40:869–76.