

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Henderson, RA; Jarvis, C; Clayton, T; Pocock, SJ; Fox, KA (2015) 10-Year Mortality Outcome of a Routine Invasive Strategy Versus a Selective Invasive Strategy in Non-ST-Segment Elevation Acute Coronary Syndrome: The British Heart Foundation RITA-3 Randomized Trial. *Journal of the American College of Cardiology*, 66 (5). pp. 511-520. ISSN 0735-1097 DOI: <https://doi.org/10.1016/j.jacc.2015.05.051>

Downloaded from: <http://researchonline.lshtm.ac.uk/2255449/>

DOI: [10.1016/j.jacc.2015.05.051](https://doi.org/10.1016/j.jacc.2015.05.051)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

Ten-year mortality outcome of a routine invasive strategy versus a selective invasive strategy in non-ST segment elevation acute coronary syndrome: the British Heart Foundation RITA-3 randomised trial.

ISRCTN 07752711

Running title: Ten-year mortality outcome in the RITA-3 trial.

Word count: 4789

Robert A Henderson ¹

Chris Jarvis ²

Tim Clayton ²

Stuart J Pocock ²

Keith AA Fox ³

¹ Trent Cardiac Centre, Nottingham University Hospitals, Nottingham

² London School of Hygiene and Tropical Medicine, London

³ University of Edinburgh, Edinburgh

Address for correspondence:

Dr R A Henderson
Trent Cardiac Centre
Nottingham University Hospitals
City Campus
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Phone: +44 115 969 1169

Fax: +44 115 962 7968

Email: robert.henderson@nuh.nhs.uk

Abstract

Background

The third Randomised Intervention Treatment of Angina trial (RITA-3) compared a routine early invasive strategy (coronary arteriography and myocardial revascularisation as clinically indicated) with a selective invasive strategy (coronary arteriography only for recurrent ischaemia) in patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS). At a median five years follow-up the routine invasive strategy was associated with a 24% reduction in the odds of all-cause mortality.

Objectives

We report 10 year follow-up of the randomised cohort to determine the impact of a routine invasive strategy on longer-term mortality.

Methods

We randomised 1810 patients with NSTE-ACS to routine invasive and selective invasive strategies. All randomised patients had annual follow-up visits to 5 years and mortality was documented thereafter using data from the Office of National Statistics.

Results

Over 10 years there was no difference in mortality between the two groups (225 [25.1%] versus 232 all-cause deaths [25.4%], $p=0.94$; and 135 [15.1%] versus 147 cardiovascular deaths [16.1%], $p=0.65$ in the routine invasive and selective invasive groups, respectively). Multivariable analysis identified several independent predictors of 10 year mortality: age, previous MI, heart failure, smoking status, diabetes, heart rate, and ST-segment depression. A modified post-discharge GRACE score was used to calculate an individual risk score for each patient and to form low, medium and high risk groups. Risk of death within 10 years varied markedly from 14.4 % in the low risk group to 56.2% in the high risk group. This mortality trend did not depend on the assigned treatment strategy.

Conclusions

The mortality advantage of a routine early invasive strategy seen at 5 years attenuated during later follow-up with no evidence of a difference in outcome at 10 years. Further trials of contemporary intervention strategies in patients with NSTEMI-ACS are warranted.

Keywords

Acute coronary syndrome; unstable angina; NSTEMI; long-term mortality; revascularisation

Abbreviations

CABG = coronary artery bypass graft

CI = confidence interval

GRACE = Global Registry of Acute Coronary Events

GRO = General Register Office

HR = hazard ratio

IQR = interquartile range

NSTE-ACS = non-ST segment elevation acute coronary syndrome

ONS = Office of National Statistics

PCI = percutaneous coronary intervention

RITA = Randomized Intervention Trial of unstable Angina

Introduction

Over recent years two alternative management strategies have evolved for the management of patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS). The routine invasive strategy involves coronary arteriography within 72 hours of an index episode of myocardial ischaemia, and myocardial revascularisation as clinically indicated. The routine invasive strategy defines the coronary anatomy in all patients and facilitates selection of the most appropriate treatment strategy. By contrast, the selective invasive strategy involves continuation of medical therapy, with coronary arteriography and myocardial revascularisation reserved for patients with persistent or recurrent myocardial ischaemia. The selective invasive strategy aims to identify patients most likely to benefit from an invasive procedure, thereby potentially minimizing the risks and costs of routine invasive management.

Several randomised trials have compared routine invasive and selective invasive strategies in patients with NSTE-ACS (1-9). Pooled data from these trials suggest that a routine early invasive strategy reduces the risk of myocardial infarction, severe angina and rehospitalisation (10-12). Moreover in an individual patient data meta-analysis of three trials reporting long term follow-up (FRISC-2, ICTUS, RITA-3) a routine invasive strategy was associated with a lower risk of death or myocardial infarction over 5 years, particularly in patients at increased baseline ischaemic risk (13). These findings have been incorporated into national and international clinical guidelines (14-16).

The third Randomized Intervention Trial of unstable Angina (RITA-3) trial assigned 1810 patients with NSTE-ACS to routine invasive versus selective invasive treatment strategies, and the short and medium term results of the trial have been reported previously (1, 17, 18). During the first year of follow-up the routine invasive strategy approximately halved the risk of refractory angina, relative to the selective invasive strategy (1). At 5 years the routine invasive strategy was associated with an estimated 26% reduction in the odds of cardiovascular death and myocardial infarction and a 24% reduction in the odds of all-cause death (17). Health economic analysis suggested that a routine

invasive strategy be cost-effective, particularly in patients at intermediate or high baseline risk (19). In this report we extend follow-up of the RITA-3 patients to 10 years and assess the impact of baseline risk on long term mortality.

Methods

The methods of the RITA-3 trial have been reported previously (1). In brief, from November 1997 to October 2001 we enrolled 1810 patients with NSTEMI-ACS in an open randomised trial of routine invasive versus selective invasive treatment strategies. Patients were randomised within 48 hours of an index episode of myocardial ischaemia if they had suspected cardiac chest pain at rest and documented evidence of coronary artery disease with at least one of: evidence of ischaemia on an electrocardiogram; pathological Q waves suggesting previous myocardial infarction; or coronary artery disease on a previous arteriogram. In all cases, the participating cardiologist had to be uncertain about the optimal management strategy, and continued medical therapy had to be an acceptable treatment option.

Patients were excluded if coronary arteriography was planned within 72h of the index episode of myocardial ischaemia, or if the ischaemia was thought to be due to an arrhythmia, anaemia, or non-coronary disease. RITA-3 recruited patients before the introduction of serum troponin as a routine biomarker of myocardial necrosis and patients were also excluded if the serum creatine kinase was elevated to twice the upper limit of normal before randomisation.

The trial protocol recommended that all patients were treated during the index hospital admission with aspirin and enoxaparin 1 mg/kg subcutaneously twice daily for 2-8 days. ADP receptor antagonists and glycoprotein IIb/IIIa receptor inhibitors were prescribed as clinically appropriate. Secondary prevention treatment with aspirin, beta blockers, angiotensin converting enzyme inhibitors and statins was encouraged in all patients and was monitored during the first five years of the trial by a member of the RITA-3 Executive Committee.

Patients assigned to the routine invasive strategy underwent coronary arteriography as soon as possible and ideally within 72h of randomisation. The requirement for percutaneous coronary intervention or coronary artery bypass surgery was guided by the arteriographic findings, with no

protocol restriction on the use of intracoronary stents, other interventional devices, or pharmacological treatments. All other aspects of patient management were at the discretion of the supervising clinician.

Patients assigned to the selective invasive strategy were managed with anti-anginal medication with the objective of controlling angina symptoms. Coronary arteriography was only indicated for failure of the selective invasive strategy, defined by recurrence of ischaemic pain at rest or on minimum exertion, with transient or persistent electrocardiographic evidence of ischaemia despite full anti-anginal medication (usually including beta-blockers, nitrates, and antithrombotic treatment in clinically appropriate doses). After discharge from hospital, coronary arteriography could be done for exertional angina despite appropriate anti-anginal medication, or for evidence of ischaemia on functional testing.

Patients had yearly follow-up visits to the hospital to 5 years to document symptoms, cardiac events and vital status. Vital status at 5 years was known for 1802 of 1810 patients (99.6%) and we have previously reported mortality and rates of myocardial infarction and revascularisation procedures at that time-point (17). The trial was not designed or funded to collect information on non-fatal outcomes beyond 5 years but all surviving patients were prospectively registered with the Office of National Statistics (ONS) in England and General Register Office (GRO) in Scotland to ascertain deaths from national mortality data, with 10 year all-cause mortality as a pre-specified secondary outcome. A change in ONS policy prevented collection of mortality information beyond March 2011. Deaths before 5 years were evaluated by an event validation committee and classified as cardiovascular or non-cardiovascular. Deaths between 5 and 10 years were classified as cardiovascular or non-cardiovascular by an investigator blinded to treatment assignment on the basis of the cause of death recorded on the death certificate.

Multicentre national and local ethics committee approvals were obtained. All patients provided written informed consent to participate in the trial before randomisation.

Statistical Analysis

All analyses were done by intention to treat. Kaplan-Meier estimates of 10 year all-cause and cardiovascular mortality were calculated together with risk differences and confidence intervals (CIs) and the treatment effect was assessed with a log rank test. Treatment by time interactions were used to assess whether any impact of treatment differed over follow-up time.

To identify baseline characteristics associated with all-cause mortality, multivariable logistic regression was used; Cox regression was not appropriate because of clear non-proportionality between the treatment groups. In order to allow for the 220 (12%) patients with between 9.4 and 10 years follow-up due to the changes in ONS policy, an adjustment was made by including a covariate of log of total time in the study for each patient, though this had very little impact on the effect estimates of the model. Treatment, age, and gender were included in the model regardless of their statistical significance. Other candidate baseline variables were added in a step-wise manner using $p < 0.01$ as the criterion for inclusion. A Wald test was used to assess overall effect for a three category variable (e.g. smoking). Time updated analyses incorporated myocardial infarction and revascularisation procedures occurring up to 5 years after randomisation into the multivariable model.

In addition, an analysis was undertaken to assess the impact of assigned treatment strategy according to a patient's underlying risk using a risk score developed independently from RITA-3. We used the post-discharge GRACE model, an external validated model that was developed to predict 6-month mortality in patients with acute coronary syndromes who survived to hospital discharge (20). This model was selected as patients enrolled in RITA-3 were randomised in-hospital up to 48h following the index episode of ischaemia and after the very early high risk period for further cardiovascular events. A risk score was calculated for each patient using a modified version of the post-discharge GRACE model nomogram. RITA-3 was designed before the impact of renal function on long-term outcome of patients with acute coronary syndromes was fully recognised and baseline renal function was not recorded routinely in the trial. Renal function was therefore excluded from the risk model and

this approach has been validated previously in a large cohort with acute coronary syndromes in the United Kingdom (21). In addition, we excluded in-hospital percutaneous coronary intervention from the risk model as the procedures occurred after randomisation, were strongly influenced by assigned treatment strategy, and could potentially confound comparison of risk scores between treatment strategy groups. The individual patient risk scores were then used to stratify patients into low, medium and high risk groups such that each group contained approximately one-third of the deaths. Kaplan-Meier estimates of 10 year all-cause mortality were compared between the strategies in each risk group. Interactions between risk groups and treatment were used to formally assess whether the impact of treatment differed in the three groups on the relative or absolute scale. A logistic regression analysis of individual patient risk scores was used to calculate predicted 10 year mortality, which was then plotted against risk score.

Results

Baseline characteristics were well matched between the randomised groups; the mean age at randomisation was 62 years and 38% were female. Electrocardiographic evidence of myocardial ischaemia was present at baseline in 92% and 41% had ST-segment deviation of at least 0.1mV. An elevated level of a serum cardiac biomarker (creatinine kinase, or troponin) was detected in 25%, a history of previous myocardial infarction was recorded in 28%, and 13% had diabetes at baseline (1, 17).

At 1 year 86%, 61%, 29% and 74% of the patients (and at 5 years 80%, 58%, 37% and 82%) were taking aspirin, beta-blocker, ACE inhibitor and statin, respectively. There were no differences between the two treatment strategy groups in the use of any of these medications. Thienopyridines were used routinely in both groups after implantation of a coronary artery stent.

Revascularisation procedures

There was good separation of treatment strategies between the randomised groups and during the index hospital admission coronary arteriography was done in 857 (96%) patients assigned to the routine invasive strategy and 142 (16%) patients assigned to the selective invasive strategy. In the routine invasive strategy group the assigned coronary arteriogram resulted in revascularisation in 397 (55%) patients (PCI 35% [stents inserted in 88% of procedures], CABG 21%). In the selective invasive strategy group myocardial revascularisation during the index hospital admission was done in 94 (10%) patients (PCI 7%, CABG 4%). During subsequent follow-up the rate of revascularisation procedures was slightly lower in the routine invasive group than in the selective invasive group and at five years at least one revascularisation procedure had been done in 546 (61%) and 347 (38%) of the routine invasive and selective invasive strategy groups, respectively (17).

All-cause and cardiovascular mortality

In total 457 deaths (25% of the randomised population) occurred by 10 years (501 over a median of 10.6 years), including 242 deaths (53%) before 5 years and 215 deaths (47%) between 5 and 10 years. Deaths were classified as cardiovascular in 282 cases by 10 years (305 in total) accounting for 62% of all deaths (table 1).

Overall there was no difference in all-cause mortality between the treatment groups (225 deaths [25.1%] in the routine invasive group versus 232 deaths [25.4%] in the selective invasive group, risk difference -0.2%, 95% CI -4.2% to 3.8%, $p=0.94$). Cardiovascular mortality was also similar between the two groups (135 deaths [15.1%] versus 147 deaths [16.1%], respectively, $p=0.65$). The mortality curves diverge over the first 5 years but then progressively converge over the following 5 to 10 years (figures 1 & 2). Rates of all-cause mortality at 2-yearly intervals in the Routine Invasive (RI) and Selective Invasive (SI) arms are shown in the Online Appendix (Online Table 1). The hazard of all-cause mortality in the routine invasive group versus the selective invasive group was lower during years 0-5 (hazard ratio [HR] 0.76, 95%CI 0.59 to 0.98) but higher during years 5-10 (HR 1.28, 95%CI 0.98 to 1.68), $p=0.006$ for treatment time interaction. Similar results were found for cardiovascular mortality (HR 0.70, 95%CI 0.51 to 0.97, and HR 1.29, 95%CI 0.70 to 1.83, for years 0-5 and 5-10, respectively; treatment time interaction $p=0.013$).

Multivariable analysis

Baseline characteristics independently associated with all-cause 10 year mortality are shown in table 2 and a predictive model based on these variables showed good discrimination (c-statistic 0.809).

Variables associated with all-cause mortality at 10 years were also associated with all-cause mortality at five years (Online Table 2). Time updated multivariable analyses suggest that the hazard of all-cause mortality at 10 years was increased by new myocardial infarction within 5 years of randomisation but was not associated with revascularisation procedures (Online Tables 3 and 4).

Risk stratification

A risk score was calculated with the modified post-discharge GRACE score for all 1810 patients. Patients were stratified into risk groups with approximately equal numbers of deaths in each group, resulting in low, intermediate, and high risk categories that included 63.0%, 22.8% and 14.2% of the patients, respectively. The observed 10 year mortality across these risk groups ranged widely from 13.4% in the low risk group to 58.0% in the high risk group (table 3). The median risk score was 82 (IQR 64-97) and the distribution of scores compared with predicted cumulative 10 year mortality for all patients is shown in figure 3. There was close agreement between predicted and observed 10 year mortality in the three risk groups (figure 3).

Cumulative 10 year mortality by assigned treatment strategy for the three risk groups is shown in figure 4. There was no difference in all-cause mortality between the routine invasive and selective invasive strategies in the low and intermediate risk categories (table 3). In the high risk subgroup, patients undergoing a routine invasive strategy appeared to be at lower risk of mortality than patients in the selective invasive group (risk difference at 5 years -11.4% (95% CI -22.8% to -0.1%)) but this difference attenuated later in follow-up because of a low mortality rate in the selective invasive group. At 10 years the absolute risk difference in the high risk group was -0.3% (95% CI -12.4% to 11.7%) and overall there was no evidence for an interaction between risk score and treatment effect on all-cause mortality at 10 years on the relative ($p=0.79$) or absolute scales ($p=0.88$).

Discussion

RITA-3 compared routine invasive versus selective invasive treatment strategies in patients with NSTEMI-ACS and in a previous report the routine invasive strategy was associated with lower all-cause and cardiovascular mortality at 5 years follow-up (17). We now extend follow-up of RITA-3 patients to 10 years and report a progressive diminution of any mortality difference beyond 5 years, suggesting that the differences in revascularisation rates between the routine invasive and selective invasive strategies during the index admission (55% versus 10%, respectively) and sustained over five years (61% versus 34%, respectively) are not associated with longer term survival benefit. It is therefore unclear whether the mortality difference at 5 years in RITA-3 is due to a direct treatment effect that attenuates over time, perhaps due to treatment crossovers, or due to the play of chance.

The relatively low rates of revascularisation in the invasive strategy group in RITA-3 reflect practice in the United Kingdom at the time of enrolment but there was clear separation in revascularisation rates between the two treatment strategies. Moreover in other large trials reporting higher revascularisation rates a routine invasive strategy did not reduce all-cause or cardiovascular mortality at five years (13, 22, 23). In the individual patient data meta-analysis of FRISC-2, ICTUS and RITA-3 there was no difference in five year all-cause mortality and a difference in cardiovascular mortality of borderline statistical significance was driven largely by RITA-3 (13). Hence, definitive evidence for the impact of a routine invasive strategy on longer term mortality is lacking but our report suggests that for most patients with NSTEMI-ACS a major survival benefit over ten years is unlikely.

The multivariable analysis of RITA-3 patients reported in this paper identified several factors that were independently associated with 10-year mortality. For example, a 10 year increment in age was associated with a 4.4-fold increase in the odds of death, while markers of impaired cardiac function (e.g. history of previous myocardial infarction or heart failure), and the severity of underlying coronary artery disease (e.g. ST-segment depression) also had substantial effects on all-cause mortality.

The multivariable model developed from the RITA-3 data showed good discrimination but we preferred a modified post-discharge GRACE score to stratify individual patients by baseline risk, since it was developed independently of RITA-3 to predict 6 month mortality in patients with acute coronary syndrome who survived to hospital discharge, and was validated in an unselected cohort of patients from the large international GRACE registry (20). The post-discharge GRACE score has not been validated in external datasets with longer term follow-up but several of the variables included in the score were also independently associated with 10 year mortality in RITA-3 (e.g. age, history of heart failure, ST segment depression). Moreover the modified post-discharge GRACE score was shown to reliably discriminate those at higher or lower risk of 10 year mortality suggesting that the GRACE score could be used to predict mortality in the longer term.

We used the modified post-discharge GRACE score to stratify patients into low, medium and high risk subgroups. There was no evidence of benefit from routine invasive management in the low and medium risk groups, which comprised over 80% of all patients. We observed a trend towards benefit in the high risk group with a difference in median survival between the routine invasive and selective invasive strategies over 10 years of 1.09 years. If real, the magnitude of this difference in survival is potentially clinically important, but these data should be interpreted cautiously as this post-hoc subgroup analysis is based on relatively small numbers of deaths and lacks statistical power, and at 10 years there was no evidence for an interaction between risk score and treatment. Further investigation of the effect of underlying risk on the impact of a routine invasive strategy on outcome is warranted and an updated individual patient data meta-analysis of the FRISC, ICTUS and RITA-3 trials is planned.

RITA-3 recruited patients considered suitable for either routine invasive or selective invasive strategies and patients in whom early coronary arteriography was considered inappropriate (or mandatory) were excluded. The results of RITA-3 therefore cannot be generalised to the wider unselected population of patients with NSTEMI-ACS. In RITA-3 the observed 6 month mortality in the

low, intermediate and high risk subgroups (defined by the modified version of the post-discharge GRACE score) was 1.8%, 5.6%, and 8.0%, respectively. These mortality rates suggest that the RITA-3 patients were at low to intermediate levels of risk when compared with the spectrum of risk seen in unselected patients with NSTEMI-ACS in the United Kingdom MINAP registry, over half of whom have a six month mortality risk exceeding 9% (24). In the FRISC-2 and ICTUS trials mortality rates in the routine and selective invasive strategy groups at six months were less than 3% (4, 25) and the results of these trials are therefore also not directly relevant to those patients with NSTEMI-ACS at highest risk. These data suggest that the randomised trials of routine invasive versus selective invasive strategies in patients with NSTEMI-ACS have consistently excluded patients at highest risk and the optimal treatment strategy for these patients has not been defined.

The long-term results of RITA-3 have important implications for clinical practice. For most patients with NSTEMI-ACS who are eligible for routine invasive or selective invasive treatment strategies neither strategy confers a prognostic advantage over 10 years. This lack of prognostic benefit must be balanced against the beneficial impact of a routine invasive strategy on other outcomes, (12, 17, 18, 22, 23, 26) but for many patients at lower levels of baseline risk a conservative treatment strategy remains a reasonable treatment option.

Limitations

We relied on national mortality data to determine vital status during follow-up from 5 to 10 years and classified deaths after 5 years as cardiovascular and non-cardiovascular on the basis of certified cause of death. In the United Kingdom there is a legal requirement for all deaths to be registered with ONS or GRO but we cannot exclude the possibility that some deaths were not recorded (for example, amongst patients who emigrate) or that cause of death was not recorded correctly. Nevertheless the Kaplan Meier plots show relatively constant mortality over 10 years, suggesting that substantial underestimation or biased reporting of mortality is unlikely.

The lack of mortality benefit from either treatment strategy at 10 years must be balanced against earlier reductions in the risk of recurrent ischaemia and myocardial infarction with the routine invasive strategy (13, 17). We did not collect information about these end-points or about revascularisation procedures beyond five years and this limits scope for exploratory analyses to examine why any mortality advantage of a routine invasive strategy at 5 years attenuates during longer-term follow-up. Nevertheless in time updated multivariable analysis myocardial infarction during the first 5 years of follow was associated with 10 year all-cause mortality but revascularisation procedures had no substantial impact on outcome.

RITA-3 recruited patients from 1997 to 2001 and before the availability of drug eluting stents and before the routine use of ADP receptor antagonists in patients with NSTEMI-ACS (15). Evidence from mixed treatment comparison meta-analysis suggests that second generation everolimus-eluting stents may reduce mortality relative to bare metal stents, (27) but this benefit has not been demonstrated specifically in patients with NSTEMI-ACS managed by a routine invasive strategy.

Conclusion

In the RITA-3 trial of routine invasive versus selective invasive strategies in patients with NSTEMI-ACS the mortality advantage of a routine early invasive strategy seen at 5 years attenuated during later follow-up. Risk of death within 10 years was influenced by several baseline variables and varied markedly from 14.4 % in the low risk group to 56.2% in the high risk group but this mortality trend did not depend on assigned treatment strategy. Further trials of contemporary intervention strategies in patients with NSTEMI-ACS are warranted.

Acknowledgements

We thank all members of the RITA-3 trial committees; the investigators and coordinators of the RITA 3 trial; the medical and nursing staff in the participating centres responsible for recruitment and follow-up of patients; and most of all, the patients who participated in the trial.

RITA 3 was funded by a competitive grant from the British Heart Foundation, and the British Heart Foundation received a donation from Aventis Pharma. Additional governmental support (Culyer) was obtained to reimburse interventional centres for part of the costs of PCI procedures on trial patients.

References

1. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2002;360:743-51.
2. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *New Engl J Med* 2001;344:1879-87.
3. 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.
4. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;353:1095-104.
5. Spacek R, Widimsky P, Straka Z, et al. Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicenter randomized trial. The VINO Study. *Eur Heart J* 2002;23:230-8.
6. McCullough PA, O'Neill WW, Graham M, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 1998;32:596-605.
7. Michalis LK, Stroumbis CS, Pappas K, et al. Treatment of refractory unstable angina in geographically isolated areas without cardiac surgery. Invasive versus conservative strategy (TRUCS study). *Eur Heart J* 2000;21:1954-9.

8. 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. *New Engl J Med* 1998;338:1785-92.
9. TIMI-III Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and early conservative strategies in unstable angina and non-Q wave myocardial infarction. Results of the TIMI-III trial. *Circulation* 1994;89:1545-56.
10. Mehta SR, Cannon CP, Fox KAA, 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.
11. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;48:1319-1325.
12. 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.
13. Fox KAA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. *J Am Coll Cardiol* 2010;55:2435-45.
14. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2012;126:875-910.

15. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
16. National Institute for Health and Clinical Excellence. Unstable Angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. <http://www.nice.org.uk/nicemedia/pdf/ACSPPCFullGuideline.pdf>.
17. Fox KA, Poole-Wilson P, Clayton TC, Henderson RA, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914-20.
18. Kim J, Henderson RA, Pocock SJ, Clayton T, Sculpher MJ, Fox KA. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). *J Am Coll Cardiol* 2005;45:221-8.
19. Henriksson M, Epstein DM, Palmer SJ, et al. The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial. *Heart* 2008; 94(6):717-23.
20. Eagle KA, Lim MJ, Dabbous OH, et al. A Validated Prediction Model for All Forms of Acute Coronary Syndrome. *JAMA* 2004;291:2727-33.
21. Simms AD, Reynolds S, Pieper K, et al. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the Myocardial Ischaemia National Audit Project (MINAP) 2003-2009: National Institute for Cardiovascular Outcomes Research (NICOR). *Heart* 2013;99:35-40.

22. Lagerqvist B, Husted S, Kontny F, Ståhle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006;368:998-1004.
23. Damman P, Hirsch A, Windhausen F, Tijssen JGP, de Winter RJ. 5-Year Clinical Outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) Trial. A Randomized Comparison of an Early Invasive Versus Selective Invasive Management in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. *J Am Coll Cardiol* 2010;55:858-64.
24. Gray HH, Henderson RA, de Belder MA, Underwood SR, Camm AJ. Early management of unstable angina and non-ST-segment elevation myocardial infarction: summary of NICE guidance. *Heart* 2010;96:1662-8.
25. Wallentin L, Lagerqvist B, Husted S, Kontny F, Ståhle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. *Lancet* 2000;356:9-16.
26. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of Early Invasive Therapy in Acute Coronary Syndromes. A Meta-Analysis of Contemporary Randomized Clinical Trials. *J Am Coll Cardiol* 2006;48:1319-25.
27. Bangalore S, Toklu B, Amoroso N, et al. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ* 2013;347:f6625.

Figure legends

Figure 1. Cumulative all-cause mortality by treatment group. Bars are standard errors.

Figure 2. Cumulative cardiovascular mortality by treatment group. Bars are standard errors.

Figure 3. Histogram showing distribution of modified post-discharge GRACE score (left Y axis) in all patients (N=1810). The red line shows cumulative predicted 10 year mortality (right Y axis) for all patients (N=1810). The blue dots show observed 10 year mortality in the low (risk score <90), medium (risk score 90-107) and high risk (risk score >107) subgroups.

Figure 4. Cumulative all-cause mortality by treatment group stratified by risk group (low, medium and high risk defined by modified pre-discharge GRACE score; see text for details).

Table 1: Long-term mortality by treatment arm (SI=selective invasive; RI=routine invasive; CV=cardiovascular).

| | RI (N=895) | SI (N=915) |
|------------------------------|--------------------|--------------------|
| Deaths at 10 years | 225 (25.1%) | 232 (25.4%) |
| All deaths | 249 (27.8%) | 252 (27.5%) |
| Before 5 years | 104 | 138 |
| 5-10 years | 121 | 94 |
| 10 years+ | 24 | 20 |
| CV deaths at 10 years | 135 (15.1%) | 147 (16.1%) |
| CV deaths | 148 (16.5%) | 157 (17.2%) |
| Before 5 years | 64 | 92 |
| 5-10 years | 71 | 55 |
| 10 years+ | 13 | 10 |
| Median follow up (years) | 10.6 | 10.7 |

Table 2: Multivariable analysis of 10 year mortality (SI=selective invasive; RI=routine invasive; CI=confidence interval; bpm=beats per minute; MI=myocardial infarction).

| Risk Factor | | Deaths | Odds Ratio (95% CI) | P-value |
|----------------------|---------|------------------|----------------------------|----------------|
| | | | N=1808 | |
| Randomised treatment | SI | 232/915 (25.4%) | 1.00 | 0.96 |
| | RI | 225/895 (25.1%) | 1.00 (0.78,1.28) | |
| Age (years) | <60 | 67 /724 (9.3%) | 4.43 (3.63,5.41) | <0.001 |
| | 61-70 | 161/622 (25.9%) | per 10 years | |
| | 71-80 | 201/422 (47.6%) | | |
| | 80+ | 28 /42 (66.7%) | | |
| Heart rate (bpm) | 40-80 | 316/1398 (22.6%) | 1.23 (1.12,1.34) | <0.001 |
| | 81-100 | 122/362 (33.7%) | per 10 bpm | |
| | 101+ | 19/49 (38.8%) | | |
| Smoking status | Non | 78/417 (18.7%) | 1.00 | <0.001 |
| | Ex | 234/806 (29.0%) | 1.56 (1.11,2.18) | |
| | Current | 144/586 (24.6%) | 2.89 (1.99,4.20) | |
| Diabetes | No | 355/1566 (22.7%) | 1.00 | <0.001 |
| | Yes | 102/244 (41.8%) | 2.27 (1.64,3.14) | |
| Previous MI | No | 280/1309 (21.4%) | 1.00 | <0.001 |
| | Yes | 177/501 (35.3%) | 1.75 (1.34,2.28) | |
| ST-depression | No | 238/1150 (20.7%) | 1.00 | <0.001 |
| | Yes | 219/660 (33.2%) | 1.64 (1.28,2.10) | |
| Heart failure | Yes | 401/1702 (23.6%) | 1.00 | 0.005 |
| | No | 56/108 (51.8%) | 1.93 (1.22,3.06) | |
| Gender | Female | 160/682 (23.5%) | 1.00 | 0.051 |
| | Male | 297/1128 (26.3%) | 1.30 (1.00,1.68) | |

Table 3: All-cause mortality by risk group. The risk groups were based on the modified post-discharge GRACE score,(19) which included age, history of congestive heart failure, history of myocardial infarction, resting heart rate (at randomisation), systolic blood pressure (at randomisation), ST-segment depression, and elevated cardiac enzymes. Numbers are number of deaths/number of patients (SI=selective invasive; RI=routine invasive; CI=confidence interval).

| Risk Group | Total (%) | RI (n=895) | SI (n=915) | Odds ratio (95%) | Risk Difference (95% CI) |
|----------------------------|------------------|-----------------|-----------------|---------------------|--------------------------|
| Low (risk score <90) | 153/1140 (13.4%) | 70/554 (12.6%) | 83/586 (14.2%) | 0.88 (0.62 to 1.23) | -1.5% (-5.5% to 2.4%) |
| Medium (risk score 90-107) | 155/413 (37.5%) | 81/213 (38.0%) | 74/200 (37.0%) | 1.04 (0.70 to 1.55) | 1.0% (-8.3% to 10.4%) |
| High (risk score >107) | 149/257 (58.0%) | 74/128 (57.8%) | 75/129 (58.1%) | 0.98 (0.60 to 1.62) | -0.3% (-12.4% to 11.7%) |
| Total | 457/1810 (25.2%) | 225/895 (25.1%) | 232/915 (25.4%) | 0.95 (0.76 to 1.20) | -0.2% (-4.2% to 3.8%) |

Figure 1. Cumulative all-cause mortality by treatment group. Bars are standard errors.

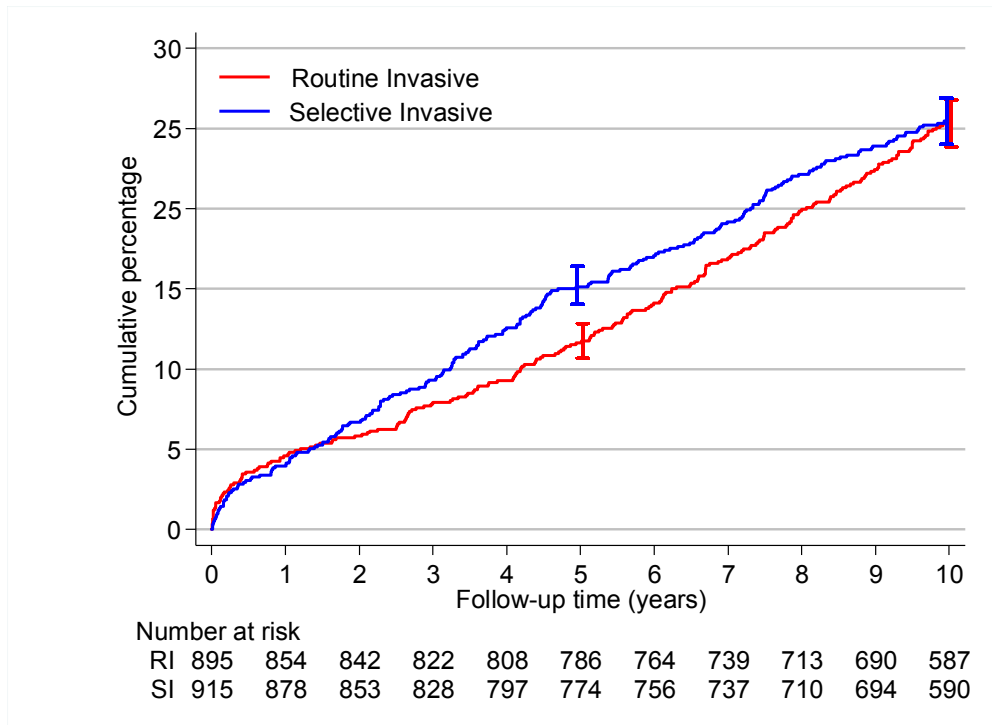


Figure 2. Cumulative cardiovascular mortality by treatment group. Bars are standard errors.

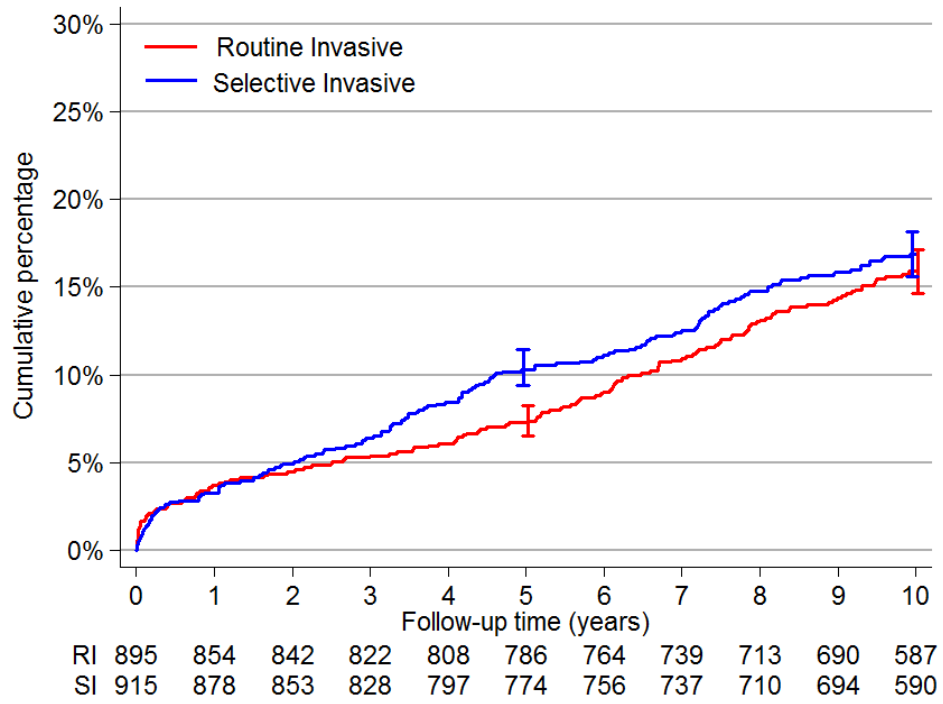


Figure 3. Histogram showing distribution of modified post-discharge GRACE score (left Y axis) in all patients (N=1810). The red line shows cumulative predicted 10 year mortality (right Y axis) for all patients (N=1810). The blue dots show observed 10 year mortality in the low (risk score <90), medium (risk score 90-107) and high risk (risk score >107) subgroups.

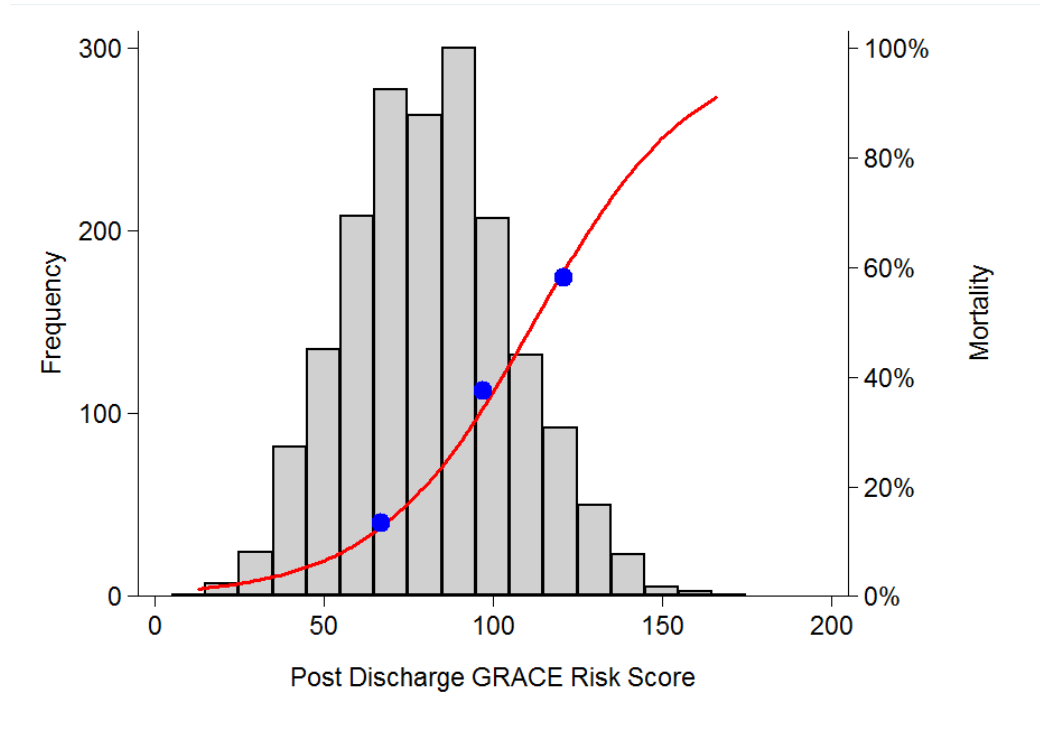


Figure 4. Cumulative all-cause mortality by treatment group stratified by risk group (low, medium and high risk defined by modified pre-discharge GRACE score; see text for details).

