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Invasive versus Conservative Management in Patients ≥85 years presenting with Non-ST Elevation Myocardial Infarction

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Introduction

There are well documented therapeutic challenges in the invasive management of elderly patients presenting with acute coronary syndromes due to the clinical complexity, frailty and high-risk coronary lesions observed in the this population.[1, 2] Accordingly, the decision to undertake invasive management of these patients is becoming increasingly relevant. While the use of coronary angiography (CA) and percutaneous coronary intervention (PCI) have revolutionised the treatment of patients with acute coronary syndrome (ACS), there is a paucity of evidence to guide management in those ≥85 years with non-ST elevation myocardial infarction (NSTEMI). [3, 4]

The 2015 European Society of Cardiology [5] guidelines recommend high-risk patients with NSTEMI be treated with guideline-directed medical therapy and an early invasive strategy. Despite being a higher risk cohort, elderly patients are less likely than their younger counterparts to be treated according to these guidelines.[6, 7] Reasons for this "treatment-risk" paradox include, but not limited to, perceived poorer outcome, higher risk of complications and end-organ dysfunction.[8] Moreover, clinical trials to date have not evaluated other key indicators of health status including functional and cognitive status, that can more accurately characterise patient risk, as opposed to just chronological age.[8] Accordingly, our primary aim was to evaluate the safety, efficacy and long-term outcomes of invasive management in very elderly patients aged ≥85 years with

NSTEMI. Additionally, we sought to assess predictors of invasive management in this patient population.

Methods

Study Design and Population

Patients ≥85 years of age presenting with a NSTEMI to a tertiary referral hospital between January 2008 and June 2018 were included in this retrospective cohort study. Hospitalisation records were searched based on the International Classification of Diseases Tenth Edition (ICD-10). Patients were included if they had a primary diagnosis of NSTEMI (code I21.4). In accordance with the Fourth Universal Definition of Myocardial Infarction (MI), NSTEMI was defined as a (1) rise and/or fall of troponins with at least one value above the 99th percentile, with either (2) ECG changes without ST-segment elevation and/or (3) symptoms of ischemia. [9]

All patient records were individually assessed by two physician researchers (PK, GM) for confirmation of the ICD-10 diagnosis, recording co-morbidities, medications and outcomes. Any discrepancies in patient records were verified by two cardiologists (MBY, ANK). Patients were excluded if the primary diagnosis was not met or when the system recorded duplicate entries or had incomplete patient records. Ethics approval was obtained from the Human Research Ethics Committee (Approval number: LNR/15/Austin/408).

Study variables

Inpatient progress notes, discharge summaries, laboratory results, procedure reports and operative reports were obtained from the electronic medical records system. Baseline demographic data, medication use, cardiovascular risk factors

and clinical status on presentation were recorded. Additionally, specific data on functional status (independent, partially independent/low level care facility, fully dependent/high level care), mobility (no gait aids, single-point stick, four-wheel frame, wheelchair), and cognitive status (no cognitive impairment, mild cognitive impairment, dementia) were also recorded.

Invasive management was defined as in-hospital coronary angiography with a view to PCI, or coronary artery bypass grafting (CABG). Type I MI was defined as MI presumed to be caused by atherosclerotic coronary artery disease usually precipitated by plaque rupture and Type II MI diagnosed as ischaemia in the context of myocardial oxygen supply and demand mismatch.[9] Chronic kidney disease was defined as stage IV or V as per the KDIGO guidelines.[10]

Primary Study Outcomes: Efficacy and Safety

The primary study outcome was all-cause mortality on longest follow-up. Secondary outcomes included in-hospital bleeding and stroke. Hospital readmissions due to a cardiac cause were also recorded. In-hospital bleeding was defined as any bleeding requiring transfusion and/or medical intervention and/or leading to or prolonging hospitalisation and/or a drop in haemoglobin of > 3g/dL. Stroke was defined as development of an acute focal neurological deficit for >24hours either associated with bleeding on computed tomography (CT) scan (haemorrhagic stroke) or without bleeding on CT scan (ischaemic stroke). Readmissions for a primary cardiac aetiology included recurrent MI, congestive heart failure, cardiac rhythm disturbance, cerebrovascular event, unplanned revascularisation or bleeding complication.

Statistical Analysis

Results were presented as mean ± standard deviation or median with interquartile range (IQR) for non-normally distributed data. Comparisons between groups were performed with the chi-square test for categorical data and the student t-test or Mann-Whitney U test as appropriate for continuous data. Multivariate logistical regression analysis was used to determine the predictors of patients undergoing invasive management [odds ratio (OR); 95% confidence intervals (CIs)]. Survival curves were generated using Kaplan-Meier method and compared using the log-rank test. Cox-proportional hazard modelling was used to determine independent predictors for survival. Pre-specified variables included baseline demographics, cardiovascular risk factors, mobility, living status and cognition. Univariable predictors yielding $p<0.1$ were entered into the multivariable model as covariates. The Cox proportional hazard models were then used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for those independent variables. To avoid multicollinearity between univariable predictors, a correlation coefficient of <0.7 was set. All reported p values are two-tailed, with $p<0.05$ considered significant. Statistical analysis was performed using STATA 13/MP (Statacorp, College station, TX, USA).

Results

Overall, 7,591 admission records of patients presenting with NSTEMI were identified over the ten-year period. Of these 1,939 (25.5%) were ≥85 years and were included in the study analysis. On individual review, 887 records were excluded on the basis of readmissions or due to patient data that pre-dated the inception of electronic medical records at our centre and 1,052 patients were included in the final analysis (Supplementary Figure 1).

Baseline and presentation characteristics are presented in Supplementary Table 1. The mean age of the cohort was 89.0 ± 3 years and 43.6% were male. Overall, 25.7% of exhibited at least mild cognitive impairment, 39.5% were in residential care and 62.0% required mobility aids. In this cohort, 953 patients (90.6%) were managed conservatively and 99 (9.4%) received invasive management. Of those who received invasive CA, 45 (45.4%) received revascularisation with PCI and 9 (9.1%) with CABG. Six (6.1%) patients managed invasively had in-hospital bleeding while 2 (2.0%) had in-hospital stroke.

Predictors of Invasive management

Patients undergoing invasive management were younger, more likely to be male, with preserved cognition and physical function (all p<0.001). They were also more likely to suffer from a Type 1 myocardial infarction (MI) (86% VS 46.9%, p<0.001) or have received inpatient cardiology consultation (91% vs 41.4%, p<0.001). On multivariate logistic regression, preserved cognition (OR, 4.44; 95%CI, 1.67-11.72; p=0.003), independent living status (OR, 3.80; 95%CI, 1.53-9.47;

p=0.004), independent mobility (OR, 2.64; 95%CI, 1.55-4.49; p=0.008) and younger age (OR 0.64, 95% CI 0.56-0.73; p<0.001) were independent predictors of invasive management (Table 1).

In-hospital management

Prescription of guideline-directed medical therapy (GDMT) is illustrated in Figure 1. Adherence to GDMT, with prescription of aspirin, dual anti-platelet therapy (DAPT), beta-blocker, statin and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, was greater in those receiving invasive management (p value for all <0.001).

Clinical outcomes: Invasive vs Conservative management (Table 2).

There was a trend to increased in-hospital bleeding (6.1% vs 2.6%, p=0.054) in patients managed invasively. However, there was no difference in the rates of in-hospital stroke (2.0% invasive vs 3.8% conservative, p=0.37). Cardiac rehospitalisation was noted in 305 patients (28.9%) with no significant difference between groups (34.3% vs 28.3%, p=0.21).

Overall, 495 deaths (47.1%) occurred over a mean follow-up of 1.3 ± 1 years. Invasive management was associated with lower in-hospital (1.0% vs 19.6%, p<0.001) and long-term mortality (20.2% vs 49.7%, p<0.001) (Figure 2). On Cox proportional hazards modelling, after adjusting for cardiovascular risk factors, living, cognitive and mobility status, invasive management remained the strongest independent predictor of improved survival (HR, 0.47; 95% CI, 0.26-

0.85; p=0.01). Independent mobility status on presentation was a favourable multivariate predictor of long-term survival while advancing age and male gender conferred an adverse prognosis (p value for all <0.01) (Figure 3).

Discussion

In this single-centre study evaluating outcomes in patients aged ≥ 85 years with NSTEMI, four key findings merit attention. First, less than 1 in 10 patients aged ≥85 years presenting with NSTEMI received invasive management. Second, patients with clinical factors not accounted for in risk calculators such preserved cognition, independent mobility and independent living status were more likely to receive invasive management. Third, a mortality rate approaching 50% at a mean follow-up of 1.3 years highlights the substantial risk conferred by NSTEMI in this population. Lastly, invasive management is generally safe with low rates of in-hospital mortality and is the strongest independent predictor of long-term survival.

Despite current guidelines highlighting the elderly as a high-risk patient population, only a minority (9.9%) of patients aged ≥85 years presenting with NSTEMI underwent coronary angiography. Similar findings were highlighted in The Global Registry of Acute Coronary Events (GRACE) where invasive angiography was performed only in 33% of patients aged >80 years compared to 67% in those aged <70 years.[11] Often, these clinical decisions are influenced by cognitive biases.[12] Further, it is also unclear whether survival benefit observed in younger, healthier patient populations undergoing invasive management could be translated to very elderly population. In fact, we also noted a statistically

significant greater adherence to GDMT in those receiving invasive management compared to those receiving conservative management which may have also confounded study results. However, this "treatment-risk" paradox in this cohort of very elderly patients is a finding of considerable importance given our ageing population and the substantial risk of long-term mortality in patients who are not treated as per guideline recommendations.[6, 7] Undoubtedly, other factors of consideration reflective of the advanced age including functional status, quality of life, frailty as well as patient preferences need to be balanced when a management strategy is considered. Notwithstanding, age alone should not preclude patients from an invasive management strategy.[8]

In our cohort of elderly patients presenting with NSTEMI, the absence of frailty, as determined by cognitive status, independent living status and mobility were the strongest predictors of invasive management. These findings, whilst not frequently reported in contemporary registry studies,[11, 13] are clinically relevant and appear to help clinicians in assessing suitability for invasive management. Indeed conventional prognostic scales for ACS include the consideration of chronological age but do not consider biological vulnerability.[14] Given the apparent reliance on physician guided assessment of frailty, it is plausible that validated frailty tools may systematically enhance risk stratification of elderly patients that may benefit from an invasive management strategy.[15, 16] While formal frailty scores like Katz[17], Edmonton[15, 18] or Barthel Index([19] were not available for this patient cohort, future studies could consider incorporating these scores to further risk stratify their patients.

Periprocedural safety of invasive management is an important consideration, especially in a multimorbidity cohort of elderly patients. Most importantly, in-hospital mortality in patients with NSTEMI in our study is very low at a 1%, which is similar to the rates seen in young patients from our region.[20] This is very encouraging given the comparable rates of periprocedural complications seen in well selected elderly patients who undergo invasive management. Although there were no differences in the rate of in-hospital stroke, patients managed invasively demonstrated a trend to higher rates of bleeding. Similar findings were demonstrated in a meta-analysis where a higher rate of major bleeding was seen in elderly patients receiving invasive management.[21] With appropriate patient selection, routine radial access angiography, and minimisation of pre-treatment with dual antiplatelet therapy prior to coronary visualisation there is potential for further reduction in the rates of periprocedural bleeding in the elderly. [22]

Prior studies evaluating the efficacy of an invasive strategy in the elderly with NSTEMI have reported discrepant results. While observational studies such as GRACE, CRUSADE and SENIOR-NSTEMI [6, 23, 24] consistently report improved outcomes in patients managed invasively, randomised trials have demonstrated no significant differences.[25] This may be due to significant selection bias in observational studies whereby patients managed invasively represent a healthier cohort with a reduced burden of both measured and unmeasured comorbidities. Furthermore, there is a paucity of evidence in patients ≥85 years. Importantly, our study demonstrated that an invasive management strategy was associated with

very low rates of in-hospital mortality and significantly lower long-term mortality. In fact, after adjusting for important clinical and functional covariates pertinent in this patient population, invasive management strategy was the strongest predictor of improved long-term survival with early separation of the Kaplan Meier curves. Randomised trials of elderly patients are grossly underpowered and notoriously difficult to recruit due to significant clinician preference for one treatment over another.[25] Patients recruited for RCTs also tend to be highly selected with high exclusion rates which may not be applicable to daily practice. This highlights the importance of an adequately powered randomised clinical trial with broad inclusion criteria to clearly ascertain the benefit of invasive management in very elderly patients.

Implications

First, this study importantly highlights the substantial mortality rate in very elderly patients presenting with NSTEMI. While prior studies have evaluated outcomes in the elderly, they focused primarily on patients ≥65 years with some studies reporting outcomes in those ≥75 years.[26] Given the ageing population, it is imperative we continue to pursue the best management strategy for those over 85 years of age without offering futile treatments. Secondly, our relatively long-term follow up is also advantageous as other have predominantly focused on short-term mortality and in-hospital outcomes.[11] Third, as very elderly patients with NSTEMI are at highest risk, it is conceivable they have the most to gain from an invasive strategy. Thus, our very low in-hospital mortality, stroke and bleeding complications can reassure clinicians that modern invasive procedures in

appropriately selected patients are safe, even in the very elderly. Lastly, we identified clinical predictors of invasive management and mortality that are not routinely captured in risk calculators, emphasising the value of multidisciplinary team involvement ensuring individualised, patient-centred decision making.

Limitations

Given the retrospective nature of this study there are inherent limitations. The improvements in outcomes with an invasive strategy is an association and does not infer causation. Confounding by indication is a major concern whereby patients with poorer prognosis would tend to be managed medically. To account for this, statistical adjustments in the multivariate model included both biological comorbidities as well as key measures of frailty. Secondly as the study is single centre, generalisability may be limited however our large size and inclusion of consecutive patients is advantageous. Thirdly, the documentation of cognitive function was based on medical records rather than objective testing thus we may have misclassified some patients, particularly those without a formal diagnosis of cognitive impairment. Moreover, of the 1,939 patient records studied, 480 of them had to be excluded from the analysis due to incomplete records. Notwithstanding, we believe that our large cohort size (1052 patients) still allows for generalisability and interpretation of the date. Forth, due to low numbers of patients with type II MI referred for an invasive strategy, we refrained from comparative analysis across MI types. Lastly, data regarding whether death was cardiac or non-cardiac was not available. However, given the subjective nature of this determination and the overall high number of

deaths observed in our population, assessment of all-cause mortality would reduce any potential bias related to this outcome.

Conclusion

Only one in ten very elderly patients with NSTEMI underwent invasive management with a view to revascularisation and this was an independent predictor of long-term survival. Careful multidisciplinary and geriatric assessment is required and age alone should not be considered a barrier to invasive management. Randomised controlled trials are essential to guide clinical practice in this high-risk population.

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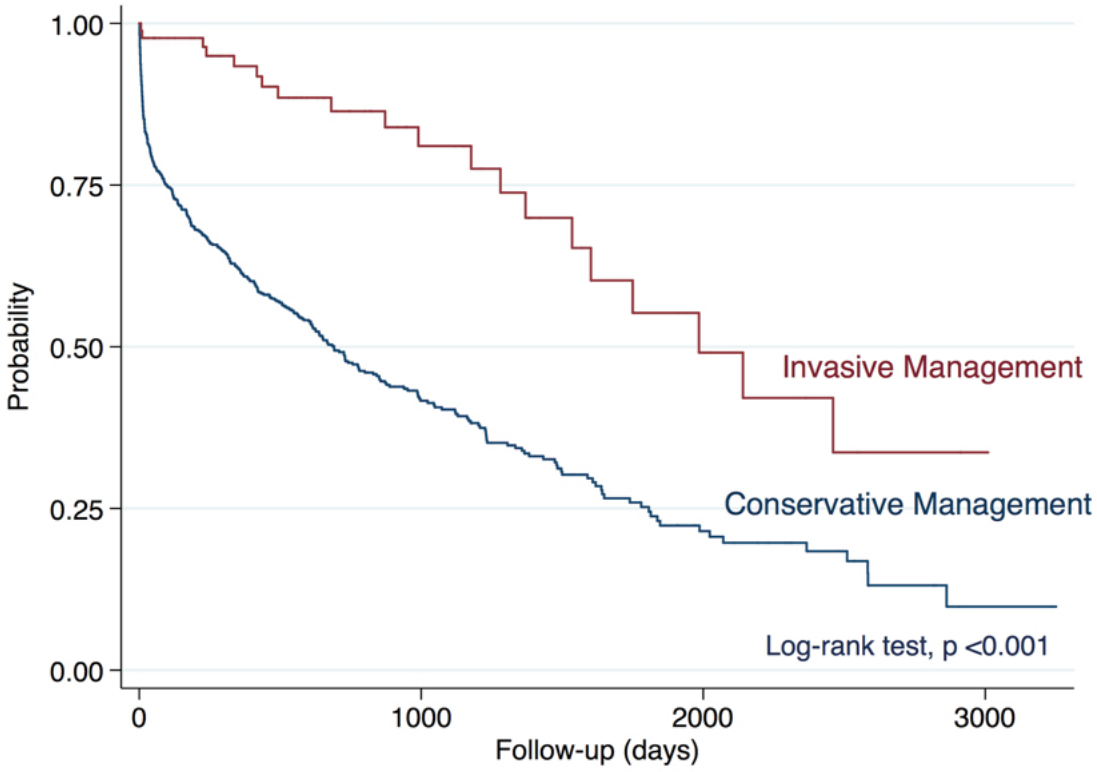

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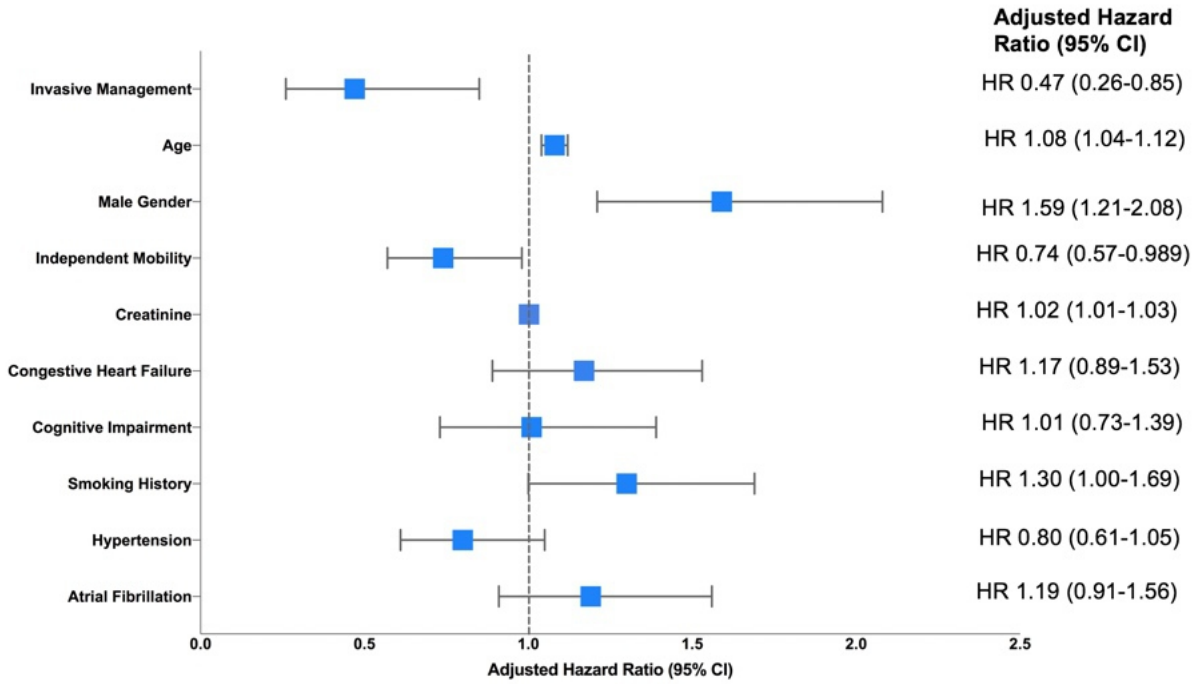

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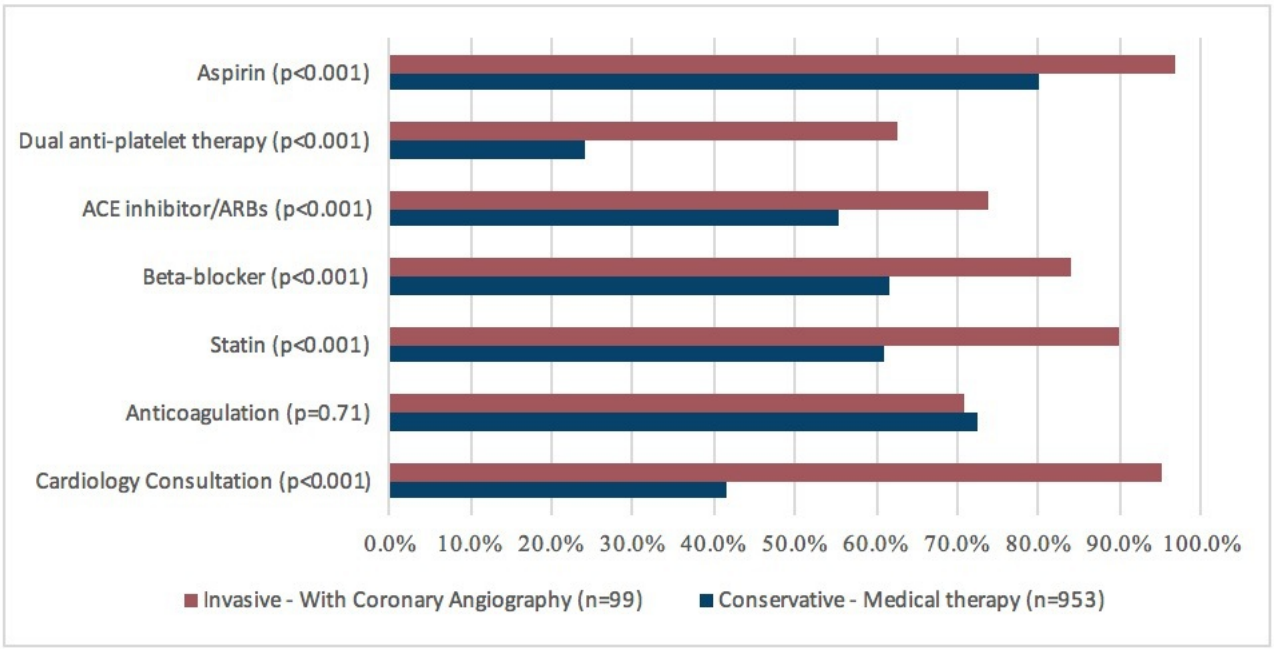

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Abstract

Background: Guidelines recommend early coronary angiography (CA) in patients with non-ST-elevation myocardial infarction (NSTEMI), irrespective of age. However, elderly patients are less likely to be treated according to these guidelines due to their perceived high risk and medical comorbidities. Whether an invasive strategy is associated with improved survival in patients aged ≥85 years remains uncertain due to their exclusion from randomised trials.

Methods: Consecutive patients aged ≥85 years presenting to a tertiary centre with NSTEMI between 2008-18 were included in this retrospective cohort study. Patients were stratified based on whether they underwent invasive management with CA with a view to revascularisation versus conservative management. The primary outcome was long-term mortality.

Results: Of 7,591 patients with NSTEMI, 1052 patients ≥85years were included. 99(9.4%) patients underwent CA. Those undergoing CA were more likely to be younger, male, live independently, without mobility or cognitive issues (all p<0.01). Overall, 495(47%) patients died during a mean follow-up of 1.3±1 year. On Cox regression, after adjusting for age, pre-morbid functional status, cognition and cardiovascular risk factors, invasive management was the strongest predictor for survival (HR 0.47; 95%CI 0.26-0.85; p=0.01). Invasive management was associated with a trend to increased risk of in-hospital bleeding (6.1% vs 2.6%, p=0.054) with no significant difference in stroke (2.0% vs 3.8%, p=0.37).

Conclusion: In patients aged ≥85 years who presented with NSTEMI, invasive management was associated with improved survival without significant differences in bleeding or stroke. A randomised controlled study assessing the efficacy and safety of invasive management in very elderly patients with NSTEMI is warranted.

Keywords: Non-ST-elevation myocardial infarction (NSTEMI), Elderly, invasive management, conservative management

	Odds Ratio	95% CI	p-value
Age	0.64	0.56-0.73	<0.001
Male Sex	1.6	0.98-2.64	0.06
Diabetes	0.72	0.41-1.25	0.25
Heart failure	0.64	0.32-1.27	0.2
Any cognitive impairment	0.24	0.09-0.63	0.004
Independent mobility	2.33	1.33-3.90	0.003
Independent living	4.00	1.60-9.89	0.003
AF	0.62	0.33-1.13	0.12
History Stroke/TIA	0.89	0.47-1.70	0.73
Chronic kidney disease	0.5	0.26-0.97	0.04

CI; confidence interval; AF, atrial fibrillation; TIA, transient ischaemic attack

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	Conservative Management (n=953)	Invasive Management (n=99)	p-value
In-hospital mortality	187 (19.6%)	1 (1.0%)	<0.001
Long-term mortality	474 (49.7%)	20 (20.2%)	<0.001
In-hospital stroke	36 (3.8%)	2 (2.0%)	0.37
In-hospital bleeding	25 (2.6%)	6 (6.1%)	0.054

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