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Early invasive strategy in senior patients with non-ST-segment elevation myocardial infarction: is it cost-effective? - a decision-analytic model and value of information analysis

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ABSTRACT

Background Non-ST-elevation myocardial infarction (NSTEMI) is the most common type of heart attack in the UK and it is becoming increasingly prevalent among older people. An early invasive treatment strategy may be effective and cost-effective for treating NSTEMI but evidence is currently unclear.

Objectives To assess the cost-effectiveness of the early invasive strategy versus medical management in elderly patients with NSTEMI and to provide guidance for future research in this area.

Methods A long-term Markov state transition model was developed. Model inputs were systematically derived from a number of sources most appropriate to a UK relevant analysis, such as published studies and national routine data. Costs were estimated from the perspective of National Health Service and Personal Social Services. The model was developed using TreeAge Pro software. Based on a probabilistic sensitivity analysis, a value of information analysis was carried out to establish the value of decision uncertainty both overall and for specific input parameters.

Results In 2017 UK £, the incremental cost-effectiveness ratio of the early invasive strategy was £46 916 for each additional quality-adjusted life-year (QALY) gained, with a probability of being cost-effective of 23% at a cost-effectiveness threshold of £20 000/QALY. There was a considerable decision uncertainty with these results. The value of removing all this uncertainty was up to £1 920 000 annually. Most uncertainty related to clinical effectiveness parameters and the optimal study design to remove this uncertainty would be a randomised controlled trial.

Conclusion Based on current evidence, the early invasive strategy is not likely to be cost-effective for elderly patients with NSTEMI. This conclusion should be interpreted with caution mainly due to the absence of NSTEMI-specific data and long-term clinical effectiveness estimates.

Strengths and limitations of this study

- The main strength and contribution of this study is the identification of critical parameters for establishing cost-effectiveness of the early invasive strategy in elderly non-ST-elevation myocardial infarction (NSTEMI) patients.
- The model utilised data from a variety of sources. These included large published studies, previous economic evaluations and national surveillance data.
- Uncertainty was incorporated in multiple input parameters by using a second-order Monte Carlo probabilistic sensitivity analysis and numerous scenarios were assessed in sensitivity analysis.
- The main limitations of the analysis stemmed from paucity of NSTEMI-specific and long-term data.

INTRODUCTION

Acute coronary syndrome (ACS) is a major cause of mortality and morbidity in the UK and worldwide.[1] It is comprised of three life-threatening conditions including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA). While STEMI is considered to be the most acute form of heart attack,[2] NSTEMI and UA are less obstructive, characterised by partial rather than complete blockage of coronary artery. For this reason, recommended management is the same and the conditions are commonly grouped as non-ST-ACS (NSTEACS). Out of the three types of ACS, NSTEMI is the most common, causing a significant burden to the National Health Service (NHS) and society in terms of mortality, morbidity and economic losses.[3]

The recommended treatments for NSTEACS include conservative management (ie, by medication only) and early invasive strategy. An early invasive strategy can be defined as angiography followed by revascularisation, if appropriate. This latter procedure includes percutaneous coronary intervention (PCI) or coronary artery bypass

graft (CABG). Evidence increasingly shows that the early invasive strategy results in better clinical outcomes for higher risk patients with NSTEACS both in the short-term and long-term.[4–6] The largest improvements are reported in the highest risk groups (ie, those with a thrombolysis in myocardial infarction[7] (TIMI) score >2).[5] Out of all potential risk-factors, older age poses one of the greatest risks for NSTEMI. According to an analysis of a national registry containing 616 011 ACS events, in-hospital mortality is 10 times higher for those aged between 75 to 84 and 18 times higher for patients aged 85+ compared with those younger than 55.[8] Even though older patients are 30% to 40% of the NSTEMI population, and have the greatest potential to benefit from an invasive therapy,[9] they are often denied coronary revascularisation due to the perceived high risk of in-hospital mortality and bleeding complications.[10] Such decisions may not be best for patients and may be waste of scarce healthcare resources, if invasive therapy were shown to be cost-effective.

To address this, a comparison of the costs, effects and cost-effectiveness of the early invasive strategy is necessary.[11] This paper reports the first evaluation of the cost-effectiveness of early invasive strategy compared with conservative management in elderly patients with NSTEMI and also aims to determine what research is still needed to provide definitive guidance to practitioners, patients and the public.

METHODS

A long-term Markov state transition model was developed to estimate the long-term cost-effectiveness of the early invasive versus the conservative strategy. The cycle length was 1 year. The modelling process was carried out using TreeAge Pro R2.1 (Williamstown, Massachusetts, USA)[12] software and in accordance with the National Institute for Health and Care Excellence (NICE) reference case for economic evaluations.[13] The perspective of the analysis was NHS and Personal Social Services. Costs were expressed in pound sterling at a 2016 to 2017 price base, and benefits were reported as quality-adjusted life-years (QALYs). Both costs and benefits were discounted at an annual rate of 3.5%, based on the NICE guidance.[14] This article is reported in accordance with Consolidated Health Economic Evaluation Reporting Standards.[15]

Target population

The model was based on a hypothetical cohort of elderly people, with equal proportions of males and females, undergoing either conservative management or invasive treatment therapy. The mean starting age was 75 years.

Model structure

The model consisted of five mutually exclusive states 'stable', 'post-MI', 'post-stroke', 'post-MI post-stroke' and 'death'. A diagrammatical representation of the model is illustrated in figure 1 and the full structure, as used in the modelling software, is included in the online supplementary file 1.

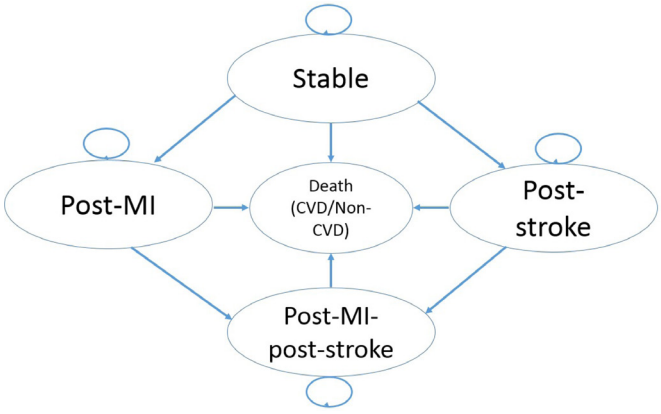

Figure 1 Markov model structure (where Post-MI refers to post myocardial infarction; Post-MI-Post-Stroke is post-myocardial infarction and post-stroke; Death CVD/Non-CVD is death from cardiovascular causes/non-cardiovascular causes).

All patients entered the model immediately after the post-index NSTEMI event health state ('stable'). An individual could remain in this health state, die from other causes, experience a fatal or non-fatal stroke or myocardial infarction (MI). Depending on the events experienced an individual could move to the subsequent health states 'post-MI' after a non-fatal MI, 'post-stroke' after a non-fatal stroke, 'dead' for those patients dying or remained in the 'stable' state. Once in a 'post-MI' or 'post-stroke' health state, the individual could either remain in the states (by either experiencing no event or a recurrent event) or progress to the combined 'post-MI post-stroke' state (by experiencing a different type of event, for example, MI for post-stroke patients or vice versa) or die.

Model inputs

Baseline event rates

The two key events that could be experienced in each non-death state of the model were MI and stroke. For MI, the baseline event rates were derived from a large UK-based Third Randomised Intervention Treatment of Angina trial (RITA-3).[6] For stroke, the average baseline event probability was calculated using a cardiovascular disease risk calculator QRISK2 in which age-specific UK general population characteristics,[16] derived from Health Survey England,[17] were applied, starting from the age of 75 (our target population). In order to derive the annual probability of stroke in population with heart disease, the 10-year risks were converted to annual risks and inflated by the hazard ratio of stroke in ACS patients relative to the general population.

The model structure also allowed the possibility of recurrent events of MI and stroke (excluding the index NSTEMI event). These were derived from Smolina *et al*[18] with the sample size of nearly 390 000 individuals. Similarly, the annual rate of recurrent stroke was a based on a

large national General Practice Research Database study[19] which reported the long-term risks of stroke recurrence in the UK setting.

Mortality

UK national life tables were used to determine the probability of all-cause death for all ages with standardised mortality ratios (SMRs) of NSTEACS, MI and stroke used to adjust mortality for the 'stable', 'post-MI' and 'post-stroke' states, respectively. For the combined 'post-MI post-stroke' state the SMR was estimated using the additive method.[20]

The model also included the possibility of operation related mortality following revascularisation. Based on national registries for cardiac surgery,[21 22] a risk of 1.1% of death within 30 days after PCI or CABG was used. This was calculated as the weighted average of in-hospital mortality using the ratio of PCI to CABG which is approximately 11:1, and which represents the current practice for the NSTEMI population in the UK.[23]

Effectiveness

The clinical benefits of the early invasive strategy were evaluated in terms of its effects on MI and stroke. In order to estimate the difference in MIs between the two arms, we used the results of a large, most recent and nationally representative RITA-3 trial[6] comparing early invasive strategy to conservative management (mean age=63 years).[24] The trial reported incidence of MI for 1 and up to 5 years. Having two data points (at 1 and 5 years) in both conservative and invasive arms, and given that the survival curves were not parallel (as illustrated in RITA-3 results[25]) meaning that proportional hazards could not be applied, resulted in the decision to extrapolate the rates in each arm by applying Weibull survival functions.[26] The MI incidence curves and the values used for extrapolation and the resulting parameters are illustrated in the online supplementary files 2 and 3, respectively. The relative risk of stroke was obtained from a meta-analysis conducted as a part of Cochrane review comparing routine invasive versus conservative strategies (mean age=67 years, so slightly younger that our modelled cohort).[27]

Resource use and costs

Annual costs in pound sterling were estimated for each state in the Markov model. The main sources of data were national routine sources, such as the NHS reference costs 2016 to 2017,[28] British National Formulary[29] and the unit costs of health and social care[30] and previous economic evaluations.[31 32] Where necessary, the costs were inflated to 2017 price level.

Model state costs

For the 'stable' state, a micro-costing exercise was undertaken to estimate the annual cost of medications and general practitioner (GP) visits. Based on a previous economic evaluation, three visits were assumed.[19]

The cost for the 'post-MI' was based on event rates from the Myocardial Ischaemia National Audit Project (MINAP) data set multiplied by their respective unit costs from NHS reference costs and included the costs of secondary prevention medication; the cost of acute MI was derived from the study by Palmer *et al*,[31] as it is the most commonly referenced cost for MI.[33]

The cost of both acute stroke and the 'post-stroke' state were obtained from the Sentinel Stroke National Audit Programme which was judged to be the most reliable source of costs for this condition.[34]

In relation to fatal events, the costs of fatal MI and stroke were estimated from a range of UK-specific burden-of-illness papers. These estimates have been used by other health technology assessments in cardiovascular disease area.[35]

Intervention costs

The costs of revascularisation (ie, PCI and CABG) were derived from the NHS reference costs.[28] Since the unit cost of angiogram was not available in the NHS reference costs, this estimate was based on a survey of five hospitals in the UK, conducted as a part of the RITA-2 trial.[36]

Utilities

In order to calculate QALYs, each of the health states included in the Markov model had a utility value associated with it. The utility values for 'stable' and 'post-MI' states were sourced from a recent NICE technology appraisal focusing on ACS management.[33] This source was chosen because the authors of the technology appraisal had conducted a literature review of health-related quality of life data that are applicable to NSTEACS population in the UK. Utilities for stroke were calculated based on a utility mapping study.[37] The utilities for 'post-stroke' and 'post-MI' states were combined by the multiplicative method. This method for combining utilities was recommended by NICE.[38]

Table 1 illustrates all input parameters used in the model. It is important to note that, since standard errors were unavailable for most of the parameters, the majority of the values were fixed.

Utility decrements due to negative treatment effects such as bleeding were not modelled explicitly. This is because for all state costs and utilities average values for the patient population were used, which accounted for the proportion of patients who experienced adverse events associated with the treatment. Decrements by age were considered in a sensitivity analysis.

Patient and public involvement

Additional patient and public involvement (PPI) was not sought for this work but we built on PPI work in the SENIOR-RITA trial. PPI in this trial was included through VOICENorth - an internal partner organisation comprising a network of citizens who contribute to research at Newcastle University. The lay summary of the SENIOR-RITA protocol was presented to the VOICENorth Research Support Group. One member of

Table 1 Model inputs

State/event/procedure	Probability (SE)	Distribution used in PSA	Source
MI (control)	0.05 (age-dependent)	–	Fox *et al*[6 25]
MI (intervention)	0.04 (age-dependent)	–	Fox *et al*[6 25]
Stroke	0.02 (age- and sex –dependent)	–	Craig *et al*[17] NICE[33]
Recurrent MI	0.03(0.0006)	Normal	Smolina *et al*[18]
Recurrent stroke	0.11 (age-dependent)	–	Mohan *et al*[42]
Relative risk (RR)			
RR (stroke)	0.83 (0.52)	Log-normal	Fanning *et al*[27]
Mortality			
Baseline probability of death	0.03	None as based on population level data	Office for National Statistics[43]
SMR for NSTEMI ► Year 1 ► Subsequent years	5.21 1.97	None as based on population level data	NICE[33]
SMR for post-MI ► Year 1 ► Subsequent years	5.84 2.21	As above	NICE[33]
SMR for post-stroke	2.3 (0.20)	Log-normal	Hankey[44]
SMR for post-MI post-stroke ► Year 1 ► Subsequent years	8.67 5.51	– –	NICE[33] Hankey[44]
Probability of fatal MI	0.38 (increases with age)	–	Smolina *et al*[18]
Probability of fatal recurrent MI	0.34 (increases with age)	–	Smolina *et al*[18]
Probability of fatal stroke	0.13	Beta (n=9710; n=74 307)*	Bray *et al*[45]
Probability of fatal recurrent stroke	0.16	–	Lee *et al*[19]
Operative mortality	0.01†	–	NICOR[21 22]
State/procedure	**Cost (£) (SE)**		
Stable	220	–	NICE[46] BNF[29] PSSRU[30]
Post-MI	280	–	NICE[46]
Post-stroke	5800	–	SSNAP[34]
Post-MI post-stroke	6080	–	NICE[46] SSNAP[34]
Acute MI	6236 (2495)	Gamma	Palmer *et al*[31]
Acute stroke	22 000	–	SSNAP[34]
Fatal MI	1200	–	Greenhalgh *et al*[32]
Fatal stroke	2200	–	Greenhalgh *et al*[32]
Angiogram	1053 (256)	Gamma	RITA-2[36]
PCI	1992 (618)	Gamma	NHS reference costs[28]
CABG	9752 (2977)	Gamma	NHS reference costs[28]
Revascularisation (PCI/CABG)	4033	–	NHS reference costs[28]
State/Event	**Utility (SE)**	**Distribution used in PSA**	**Source**
Stable	0.842 (0.002)	Beta	NICE[33]
Post-MI	0.821 (0.038)	Beta	NICE[33]
Post-stroke	0.702 (0.014)	Beta	Whynes *et al*[37] Kalra *et al*[47]
Post-MI and post-stroke	0.576(0.014)	Beta	NICE[33] Whynes *et al*[37] Kalra *et al*[47]

Continued

Table 1 Continued

State/event/procedure	Probability (SE)	Distribution used in PSA	Source

*Where n=the number of events; n=total sample.
†As these data relate to a younger age group (average age of operative mortality is 66 years for CABG and 65 years for PCI), we have conducted a sensitivity analysis where the operative mortality is an illustrative 10%.
BNF, British National Formulary; CABG, coronary artery bypass graft; MI, myocardial infarction; NICE, National Institute for Clinical Excellence; NICOR, National Institute for Cardiovascular Outcomes Research; PCI, percutaneous coronary intervention; PSA, Probabilistic Sensitivity Analysis; PSSRU, Personal and Social Services Research Unit; SMR, standardised mortality ratio; SSNAP, Sentinel Stroke National Audit Programme; STEMI, ST-elevation myocardial infarction.

the group was invited to participate as a Trial Steering Committee lay member.

Link to the PPI group: https://www.ncl.ac.uk/ageing/partners/internal_ageing/voice/

ANALYSIS

The joint estimates of costs and effects were combined in an incremental analysis between two strategies, and presented as the point estimate of mean incremental cost-effectiveness ratio (ICER) for early invasive versus conservative management. The ICER was calculated as difference in costs divided by difference in effects (QALYs) between the two interventions.

Both probabilistic (with 10 000 iterations) and deterministic sensitivity analyses were used to explore parameter and other forms of uncertainty surrounding estimates of cost-effectiveness. Six one-way sensitivity analyses were conducted to investigate the impact of varying key assumptions and/or parameter values used in the base-case analysis. Additionally, a series of deterministic sensitivity analyses using low values of −25% and high values of +25% were also undertaken for all variables without prespecified distributions in order to investigate their relative impact on the results. The results of the analyses were presented in a Tornado diagram.

Threshold analyses were also conducted for the effectiveness parameters, relative risk (RR) of stroke, probability of MI in the invasive arm and RR of MI (used in sensitivity analysis), in order to identify the values they would need to take in order for the invasive strategy to be cost-effective.

Finally, a value of information analysis was conducted in order to determine the value of future research overall as well as for specific parameters or groups of parameters. The resulting estimates were expressed as expected value of perfect information (EVPI) and the expected value of partial perfect information (EVPPI), respectively. The analysis was carried out using an online tool, Sheffield Accelerated Value of Information.[39]

RESULTS

The model predicted mean life time costs of £8799 (95% credible interval (Crl) £7,934 to £9,790) and £9478 (95% Crl £8,331 to £10,773) and QALYs were 5.14 (95% Crl 5.09 to 5.18) and 5.15 (95% Crl 5.10 to 5.20) for the conservative and early invasive strategies, respectively. Thus, the resulting incremental cost per QALY for the early invasive strategy compared with conservative management was £46 916 per QALY gained. According to the probabilistic sensitivity analysis, the conservative management has a 77% chance of being cost-effective when society is willing to pay £20 000 per QALY, as illustrated by the cost-effectiveness acceptability curve in figure 2. These results appear to be robust based on the one way sensitivity analyses which tested the importance of varying the key drivers of the model results. These included the relative risks of stroke and MI, length of treatment effectiveness, stroke-related mortality, rates of revascularisation and utilities. In every alternative scenario the invasive strategy was less cost-effective than in the base case analysis. Thus, none of these changes were found to affect the optimal treatment decision. Results of the deterministic sensitivity analyses can be found in the online supplementary file 4.

According to the additional sensitivity analyses which investigated the impact of varying the variables without predefined distributions, model results are most sensitive to varying the probabilities of MI in both the control and the intervention arms (ie, variables relating to intervention effectiveness). The impact of varying other variables is relatively minor. This is illustrated in the Tornado diagram (figure 3).

In the threshold analyses we identified the values which the effectiveness variables would need to take at the point when the intervention just becomes cost-effective (assuming a value of £20 000 for society's willingness to pay for a QALY). For the threshold analyses, the values that the probability of MI in the invasive arm, RR stroke and RR MI would need to take are implausible (equal to 0.01 and 0.53 and 0.40, respectively).

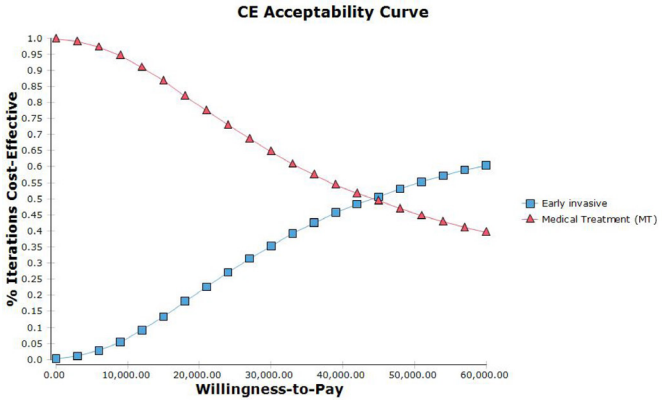

Figure 2 Cost-effectiveness acceptability curves.

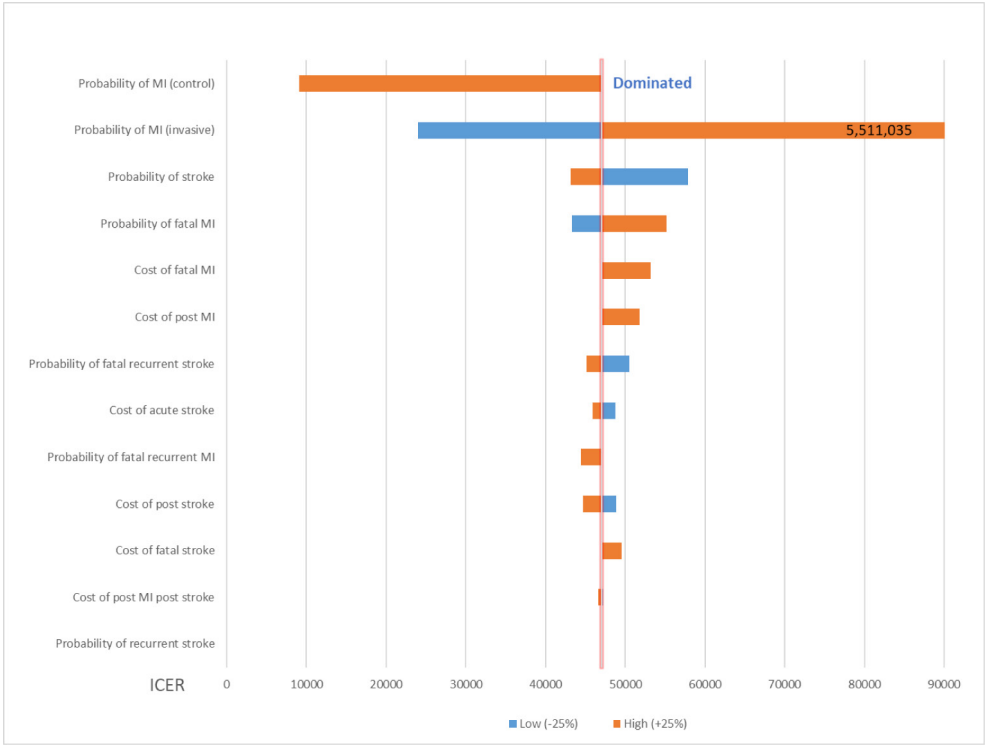

Figure 3 Tornado diagram. ICER, incremental cost-effectiveness ratio; MI, myocardial infarction.

Value of information analysis

Assuming that the number of people affected by the decision about the early invasive versus conservative strategy per year in the UK is 49 071 (the reported annual incidence of NSTEMI,[40]) then the total EVPI per year is £1.92 million for the UK. Assuming these technologies will be used for the next 20 years, the EVPI is £38.30 million. This is the value of removing all decision uncertainty about which treatment is cost-effective. Results from the EVPPI showed that the most important areas were those relating to the relative effectiveness of interventions. This is illustrated in table 2.

DISCUSSION

One of the aims of this study was to evaluate the cost-effectiveness of the early invasive strategy in elderly patients with NSTEMI. The data for this model came from the best available sources and were rigorously assembled.

Table 2 Value of information analysis results

Groups of parameters	Per person EVPPI per year (£)	EVPPI for UK per year (£)	EVPPI for UK over 20 years (£)
Clinical effectiveness (RR stroke)	30.70	1 506 359	3 012 715
Costs	0.08	4333	86 667
Utilities	0	0	0

EVPPI, expected value of partial perfect information; RR, relative risk.

Using these data, the early invasive strategy was not cost-effective when compared with the conservative management. Nevertheless, the probabilistic sensitivity analysis results showed that, at the NICE willingness to pay threshold is £20,000, the early invasive strategy has a 23% chance of being cost-effective when compared with the conservative management. The total value of information over 20 years is £38.3 million and the main source of the uncertainty is around relative effectiveness of the two treatments. The optimal type of study to provide that data would be a randomised controlled trial comparing early invasive strategy to conservative management for elderly individuals with NSTEMI.

Our results are consistent with the clinical conclusions of a recent Cochrane review[27] comparing the two treatment strategies in patients with NSTEACS. The Cochrane review did not stratify patients based on their risk profiles but a previous economic evaluation by Henriksson *et al* has suggested that the invasive strategy was cost-effective only for those patients in the highest risk group.[9]

In terms of this study, there are several potential explanations for the early invasive strategy being inferior to conservative management in terms of the cost-effectiveness. First, only a fraction of patients received the additional benefits of the early invasive strategy due to the high baseline rates of angiography and revascularisation currently in the UK. Second, additional clinical effectiveness in terms of reductions in MI and stroke were small on average, although CIs were wide (risk ratio 0.83, 95% CI 0.34 to 1.86) indicating the considerable uncertainty in rates of MI and stroke. A further reason that the early invasive strategy was not cost-effective was the

high background mortality in the 'stable' state (whereby patients had an initial NSTEMI but no subsequent events). This meant that a high proportion of people incurred the treatment costs but did not survive long enough to gain benefits of invasive treatment.

Strengths and limitations

Strengths

To our knowledge, this was the first economic evaluation comparing the early invasive versus conservative management in the area of NSTEMI. The main contribution of the study is that, with rigorous attempts to structure the decision problem and to identify data, it has identified the critical parameters and thus the type of future research required to establish the cost-effective strategy for treating elderly patients with NSTEMI.

Another strength of this study is that almost all the input parameters that were used in the model were informed by the local evidence and results of this economic analysis should therefore be generalisable across the UK NHS. Furthermore, the analysis was conducted using best practice methods[41] and used a comprehensive range of sensitivity analyses to explore and characterise uncertainty. Our results remained robust in each of the explored scenarios.

Finally, model validation was ensured by carrying out a number of internal and external validation exercises in this way further reinforcing its conclusions. This process followed recommended best practice.[41] A detailed summary of model validation and the overall modelling methodology is available online (online supplementary file 5).

Limitations

The model attempted to focus on NSTEMI population. However, despite extensive efforts to obtain data specific to this population relevant data for key model inputs were not available. For example, some model estimates came from studies which included people with UA. UA is a lower risk patient group, with less capacity to benefit from the invasive intervention.[9] This may have biased our results against the early invasive intervention. Also, few data were available for longer term outcomes. Therefore, data on short-term effectiveness (5 years or less) were used as the basis of extrapolations. These shorter term data may have not fully reflected the benefits of the invasive intervention and may have thus biased the results against this strategy. A further potential bias against the invasive strategy may have arisen from the fact that the RITA-3 trial[6] from which the effectiveness data were obtained was conducted nearly 20 years ago, and as such we may have overestimated the adverse outcomes in contemporary NSTEMI care.

In terms of biases favouring the invasive strategy, such bias might have arisen from the fact that patients in the conservative arm in RITA-3 trial had very low rates of dual-antiplatelet therapy (DAPT) compared with those in the invasive arm. Thus, any improvements in the invasive arm could arguably be attributed to the higher rates of DAPT.

Another limitation relating to the data used in the model is that measures of variance were only available for some of the parameters. The implication of this is that the EVPI is underestimated as the value of removing uncertainty around parameters, such as the state costs and baseline probabilities, was not considered. For example, we could not explore the uncertainty around the probabilities of MI in each arm. This is because RITA-3 trial data suitable for constructing distributions was only available for the composite outcomes (MI or death). Thus, we were restricted in our ability to incorporate information into the probabilistic sensitivity analysis. Despite this limitation, the value of information analysis still showed considerable value in further research on the clinical effectiveness of treatments. Had we been able to incorporate the uncertainty surrounding these events, then we anticipate that the EVPI and EVPPI would be no less and possibly greater.

Finally, due to paucity of data, the model structure itself was limited. Specifically, it did not reflect the short-term treatment phase which was a common practice in other modelling studies. However, we attempted to address this limitation by incorporating the risk of operative mortality after undergoing revascularisation. This resulted in more conservative estimate of cost-effectiveness.

Overall, it is possible that the value of further research has been underestimated but given the uncertainties it remains most likely that further evidence on the relative effectiveness of treatments would be desirable.

CONCLUSION

This study has presented the first cost-effectiveness analysis evaluating the early invasive strategy in elderly patients with NSTEMI. The results indicate that, in the long-term, the early invasive strategy is more costly but only marginally more effective than conservative management and is therefore not cost-effective. However, given restrictions in the current evidence base, coupled with the results of our value of information analysis argue for a well-designed randomised controlled trial comparing the early invasive strategy to conservative management with a follow-up long enough to estimate longer term impacts.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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