The impact of increased age on outcome from an early invasive strategy in patients with acute coronary syndromes- the ACACIA registry.

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The impact of increased age on outcome from an early invasive strategy in patients with acute coronary syndromes- retrospective analysis from the ACACIA registry.

Running title: ACACIA elderly analysis.

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Keywords

Acute coronary syndrome, elderly, revascularisation, survival.

Word count (excluding title page, abstract, references, figures)

2064

ABSTRACT

Objective

To evaluate the impact of increased age on outcome from invasive management in patients with acute coronary syndromes.

Design

Retrospective analysis of a national Acute Coronary Syndrome registry (ACACIA).

Setting

Multiple Australian (n=39) centres; 25% rural, 52% with onsite cardiac surgery.

Patients

Unselected consecutive patients admitted with confirmed acute coronary syndromes, total n=2559, median 99 per centre.

Interventions

Management was at the discretion of the treating physician. Analysis of outcome based on age>75 was compared using Cox proportional hazard with a propensity model to adjust for baseline covariates.

Main outcome measures

Primary outcome was all cause mortality. Secondary outcome was bleeding and a composite of any vascular event or unplanned readmission.

Results

Elderly patients were more likely to present with high-risk features yet were less likely to receive evidence based medical therapies or receive diagnostic coronary angiography (75% v 49%, p<0.0001) and early revascularisation (50% v 30%, p<0.0001). Multi-variate analysis confirmed the benefit of early revascularisation in the elderly cohort with reductions in 12-month mortality hazard 0.4(0.2-0.7) and

composite outcome 0.6(0.5-0.8). Propensity model suggested a greater absolute benefit in elderly patients compared to others.

Conclusions

Following presentation with ACS elderly patients are less likely to receive evidence based medical therapies, to be considered for an early invasive strategy and be revascularised. Increasing age is a significant barrier to physicians when considering early revascularisation. An early invasive strategy with revascularisation when performed was associated with substantial benefit and the absolute accrued benefit appears to be higher in elderly patients.

Article focus:

To assess the impact of increased age on invasive management in patients with acute coronary syndromes.

Key messages:

Age is a barrier to treatment since elderly patients are less likely to receive evidence based medical therapies and invasive management.

Invasive management, when performed was associated with substantial benefit, greater absolute benefit was demonstrated in elderly patients compared to younger patients.

Strengths and limitations of this study:

The strengths of this study are that the data are large volume and comprise contemporary real world practice.

The limitations of this study are that the reasons and decisions for offering or failing to offer invasive management or evidence based therapy are not fully recorded.

INTRODUCTION

The management of acute coronary syndromes is constantly evolving with new therapies and interventions tested in clinical trials. Subjects with ST elevation myocardial infarction (STEMI) are at very high early risk and timely reperfusion therapy with thrombolysis or primary angioplasty substantially reduces mortality.[1, 2] In patients with non-ST elevation syndromes (NSTEMI) an early invasive strategy with revascularisation where appropriate is recommended by international societies and supported by several prospective trials.[3-5] This strategy is particularly beneficial in patients deemed to be at high risk – specifically those patients with elevated cardiac bio-markers or dynamic ECG changes.[6] Age in isolation has been considered a risk factor for patients presenting with ACS yet a paradox exists that elderly patients >75 years are frequently under-represented in clinical trials whereas in clinical practice they constitute a significant proportion of the patient population.[7, 8] A poor outcome in the elderly population may be associated with more complex coronary disease, increased co-morbidity and higher risk of complication from revascularisation procedures.[9-11] Despite this, recent studies and large international registries have shown the elderly population have substantially improved outcome with early invasive management, yet compared to younger patients an interventional strategy is less likely to be offered.[5, 12-15]

The objective of this study was to assess the management of acute coronary syndromes in an elderly population using data taken from a national registry. Specifically we planned to test the hypothesis that age in isolation does not adversely affect the outcome of patients presenting with ACS who are managed with an early interventional strategy. We also explored the reasons that some elderly patients are not considered appropriate for an early invasive strategy.

METHODS

The Acute Coronary Syndrome Prospective Audit (ACACIA, protocol number PM_L_0051) is a registry of Australian practice collected between 1 November 2005 and 31 July 2007 involving 39 hospitals across all states and territories of Australia. These sites were selected to be representative of rural (25%) and metropolitan (75%) centres, interventional (83%) and non-interventional (17%) centres and 52% of sites reported onsite cardiac surgery. Each site sought consecutive enrolment of between 100 and 150 patients admitted from the local emergency service for suspected ACS (median, 99). Patients presenting with ACS thought to be secondary to major trauma or surgery were excluded. Patients transferred into study centres were excluded if more than 12 hours had passed since their initial presentation, to enable more accurate assessment of immediate care.

Ethics approval was obtained from all sites and written informed consent was obtained from all conscious patients. Access to medical records was permitted.

Funding

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

Definition of ACS and data collection

Patients presenting with suspected STEMI or NSTEMI were eligible for enrolment. The primary discharge diagnosis was determined by the investigators at each site but was confirmed by a central adjudication process. Stratification of data collection diagnoses was also centrally adjudicated to ensure consistency of enrolment from each centre. Allocation to non-cardiac chest pain was made when ACS was excluded or a positive alternative diagnosis was made, data from these patients were not included in the principle analyses. Standard clinical data were recorded including type

and results of all investigations and medications. Early interventional strategy was defined as angiography at any point during the index acute admission including emergency primary PCI for STEMI but excluded outpatient angiography. The use, time and extent of revascularisation by angioplasty (PCI) or surgery (CABG) was recorded. All data was collated by trained research co-ordinators. All cause mortality was determined during the index admission and at 12 months. Any patients lost to follow up were referred as a query to the Australian Institute of Health and Welfare National Death Register to confirm status and cause of death. Data on non-fatal vascular events further revascularisation and unplanned hospital readmissions were recorded from hospital records and discharge codes.

Statistics

Primary outcome was all cause mortality at 12 months. Secondary outcomes were (thrombolysis in myocardial infarction) TIMI bleeding at thirty days and a composite of subsequent myocardial infarction, stroke, death and cardiovascular cause for unplanned hospital readmission at 12 months. We defined the elderly population as those patients older than 75 years, this value was selected since patients of this age and above have frequently been excluded from prospective clinical trials. Categorical outcomes and parameters were analysed with chi-squared analysis or fisher's exact test for 2x2 comparisons. Multi-variate analysis of event free survival and overall survival was performed using Cox proportional hazard. Survival curves were plotted to examine the effect of an early invasive strategy in the aged cohort. Binary logistic regression was used to evaluate time independent outcomes. To evaluate the impact of an early invasive strategy on 12 month mortality in patients >75years and to control for substantial confounding clinical factors associated with increased age, a propensity analysis was performed using a non-parsimonious logistic regression model including

(age>75, gender, indigenous status, Killip class, GRACE score, cardiac arrest, normal ECG, ST segment depression or elevation, shock, pulmonary oedema or arrhythmia; presence of renal replacement therapy, dyslipidaemia, hypertension, diabetes, chronic airways disease, peripheral vascular disease, malignancy or AF; previous history of coronary artery disease, myocardial infarction, PCI, CABG or stroke) (c-index: 0.89). A logistic regression model for survival until 12 months including age, propensity score and early invasive management was then undertaken. This model was used to predict the expected mortality in ascending strata of age groups. These data are presented across the age groups further stratified by use of early invasive management. All data were analysed using commercially available software STATA version 13. Significance was sought at the 5% level.

RESULTS

Baseline characteristics

A total of 3402 patients were enrolled and vital status was available for 3393 at 1 year. Discharge diagnosis of STEMI was recorded in (717), NSTEMI in (1027) and unstable angina in (815) giving a study population of (2559). Elderly patients, >75 years comprised 27% (n=683) of the study population, baseline variables are shown in table 1. The younger group were more likely to be active smokers and to present with cardiac arrest. The elderly group presented more frequently in association with haemodynamic disturbance and other co-morbidity.

Table 1. Baseline characteristics

Variable	<75 years N=1876	%	>75 years N=683	%	Chi (Fishers')
Male	1380	74	372	55	0.001
Dyslipidaemia	1134	60	418	61	0.7
Current Smoker	570	30	34	5	0.001
Known Coronary Disease	851	45	438	64	0.001
Previous MI	479	26	251	37	0.001
Chronic Heart Failure	93	5	121	18	0.001
Previous PCI	356	19	123	18	0.3
Previous CABG	234	12	150	22	0.001
Diabetes	512	27	171	25	0.25
Hypertension	1125	60	510	75	0.001
Atrial Fibrillation	137	7	139	20	0.001
Peripheral Vascular Disease	82	4	80	12	0.001
Malignancy	96	5	84	12	0.001
Elevated Cardiac Bio-markers	1384	74	485	71	0.163
normal ECG	506	27	155	23	0.03
ST segment deviation (including BBB)	894	48	338	50	0.4
ST elevation	577	31	138	20	0.001
ST depression	224	12	123	18	0.001
Left bundle branch block	73	4	72	11	0.001
Killip 1	1589	85	448	66	0.001
Pulmonary oedema	72	4	60	9	0.001
Cardiac Arrest	68	3.6	11	1.6	0.009
Arrhythmia on presentation	115	6	40	6	0.8

In hospital management

During in hospital care the elderly group were less likely to be treated with evidence based medical therapies and were less frequently referred for angiography (79% v 49%, p=0.0001) (table 2). Revascularisation as a whole was therefore less frequently performed in the elderly cohort. The disparity in revascularisation was driven primarily by less frequent referral for diagnostic angiogram. If angiography was performed then the rates of revascularisation were more comparable, (61% v 66%, p=0.04). Logistic regression of the whole cohort identified 13 variables that independently contributed to mortality at 12 months (figure 1). Among these variables an age over 75 increased mortality risk OR 1.7 (1.2-2.6) and early revascularisation reduced risk OR 0.4(0.2-0.7). Division of the data into subjects above the age of 75 found early revascularisation to remain highly protective in terms of risk of all cause mortality OR 0.4(0.2-0.7) and composite outcome 0.6(0.5-0.8). (figures 2, 3). Predicted mortality based on the propensity model confirmed the beneficial effect of early revascularisation with incrementally greater absolute effect in the higher age brackets. (figure 4) We explored the factors associated with for non-referral for angiogram and for not performing revascularisation. Independent variables that appeared to contribute to non referral for angiogram included age over 75, female gender, presence of diabetes and history of previous myocardial infarction.(figure 5) Once an angiogram had been performed fewer variables influenced the decision to perform revascularisation and neither gender nor age over 75 were contributory.

Table 2. In hospital management

Variable	<75years (1876)	%	>75years (683)	%	Chi
Aspirin	1672	89	528	77	0.001
Clopidogrel	1234	66	357	52	0.001
2b3a agent	163	8.7	36	5	0.004
Low molecular weight heparin	1410	75	520	76.1	0.6
ACE-I	1110	59	370	54	0.02
ARA	243	13	116	17	0.009
HMG-CoA enzyme inhibitor	1635	87	537	79	0.001
B-blocker	1346	72	446	65	0.002
Functional test for ischaemia	188	10	43	6.3	0.004
Diagnostic angiography	1401	75	335	49	0.001
Echocardiogram	758	40	293	42	0.26
Angioplasty	808	43	169	25	0.001
Coronary Surgery	154	8.2	46	6.7	0.2
Revascularisation if angiogram	931 from 1401	66	203 from 335	61	0.04
Reperfusion if (STEMI)	420	72	80	60	0.008
Primary PCI	256	44	50	38	0.2
Rescue PCI	33	6	2	1.5	0.05
TIMI bleed	83	4	34	5	.5

TIMI bleeding

There were 123 episodes of TIMI bleeding in the study cohort within 30 days of index presentation. Overall, age >75years was not in isolation a risk for bleeding HR 1.3(0.86-1.9) nor was there excess bleeding in the old versus younger cohorts (5%v4%, p=0.6). Early revascularisation was associated with a substantially higher risk of bleeding in both the young 10.5(5.1-21) and aged 14.9(5.6-40) cohort and this relationship was independent to the use of aspirin, clopidogrel and anti-coagulation at the time of presentation. Comparison limited to the patients who received early revascularisation (n=1134) did reveal excess bleeding in the aged cohort compared to the younger group, 13.2% v 7.6%, p=0.01.

CONCLUSIONS

Elderly patients comprise a large group of the ACS population. Despite having higher baseline risk they are less likely to be offered evidence based medical therapies and substantially less likely to be investigated invasively with a view to early revascularisation. The effect of an early invasive strategy was highly protective with improvements in survival and in the composite outcome of myocardial infarction, stroke, death and cardiovascular cause for readmission; at the expense of a higher incidence of TIMI bleeding. Adjustment for baseline covariates using a propensity model suggested greater absolute benefit in patients at advanced age.

DISCUSSION

The ACACIA dataset provides an outstanding insight into the management of acute coronary syndromes sourcing data from different types of hospital. These data in concordance with other studies show that elderly patients are more often managed conservatively, a particular barrier appears to be at the level of referral for diagnostic

angiogram with less than half of the patients >75years receiving this investigation. This observation is not a new finding; [12, 16]and reflects an obvious referral bias; most young patients are offered an angiogram whereas most elderly patients are not. Our data do not record the reason for this disparity since we do not have data on generalised extreme frailty, patient choice or a positive decision to palliate patients based on extensive co-morbidity. There is no doubt that frailty may influence decision to treat individual patients conservatively[17] but it is extremely unlikely that these factors alone account for the fewer number or elderly patients offered an early invasive strategy and clearly there is a reluctance of clinicians to offer invasive management to some of their elderly patients. An obvious observation is that increased age is associated with mortality, yet the effect of age >75 years was less influential on mortality risk than presence of diabetes, heart failure, and haemodynamic disturbance on presentation. We did observe a higher rate of TIMI bleeding at 30 days in the elderly cohort although this effect did not translate to a change of mortality or composite outcome at 12 months. Furthermore in our adjusted analysis the absolute benefit of early revascularisation was positively associated with increased stratifications of age. This analysis is unsurprising, since those patients at highest risk (such as the elderly) stand to gain most from an early invasive strategy and this fact is consistent with the substantial impact of age on risk in scores such as the GRACE score.[18] The data from the ACACIA registry reinforce the message of these risk scores and other trials demonstrating that age is not a bar to the benefits associated with invasive management and increased age should not be the dominant factor when contemplating management following hospitalisation with ACS. In the real world some patients elect not to pursue an early invasive strategy and this choice may be made more frequently by elderly patients, who may have concerns about their

own frailty and long-term morbidity. Physicians may also judge that a patient has such substantial co-morbidity that a palliative or limited approach should be undertaken.[19] Despite these case specific management decisions, it is clear from our data however that the elderly ACS population are under investigated and under-treated and this may deny these patients the substantial benefit that is seen within 12 months. We encourage all physicians who manage patients with acute coronary syndromes to avoid using advanced age as reason to manage some patients conservatively.

Limitations

The ACACIA data represent a real world registry; individual decisions on patient management such as reasons for not offering an early invasive strategy were not recorded. The geographical challenges of healthcare in Australia are reflected in some of the data such as persisting use of thrombolysis and rescue angioplasty. Transfer from a non-interventional centre to an interventional centre was positively associated with an early invasive strategy. It is possible that further referral bias occurs at this level since cardiologists may pre-select those patients in whom they expect the best outcomes, especially if transfer involves air travel. However our data were carefully selected to be representative of real world cardiology practice including both metropolitan surgical centres and rural district hospitals and evidence of bias in referral based on age or transfer is worthy of discussion.

Data Sharing

The original ACACIA data can be requested by permission from Professor Derek Chew, Flinders Medical Centre, Adelaide, South Australia.

Author Contributions and Declarations

Dr Malkin analysed the data and wrote the first draft of the manuscript

Dr Prakash helped analyse the data and edited the final draft of the manuscript

Professor Chew developed the initial concept and supervised analysis and editing of the final draft of the paper

The authors declare no conflicts of interest

Abbreviations

PCI = Percutaneous Coronary intervention

CABG = coronary artery bypass graft

LBBB = left bundle branch block

ACE-I = angiotensin converting enzyme inhibitor

ARA = Angiotensin receptor antagonist

CHF = Chronic Cardiac Failure

eREVASC = early revascularisation

Legend for Figures and Tables

Table 1. Baseline characteristics of ACS cohort separated by age.

Table 2. In hospital investigation and treatment of ACS cohort separated by age.

Figure 1. Box plot indicating hazard ratio contributing to all cause mortality at 1 year in ACS cohort in multivariate analysis.

Figure 2. Survival curve of elderly ACS cohort with respect to early revascularisation

Figure 3. Freedom from composite outcome in elderly ACS cohort with respect to early revascularisation.

Figure 4. Predicted absolute mortality (error bars are SD) at 1 year calculated from propensity model.

Figure 5. Box plot indicating hazard ratio contributing to likelihood of referral for diagnostic coronary angiography in the ACS cohort.

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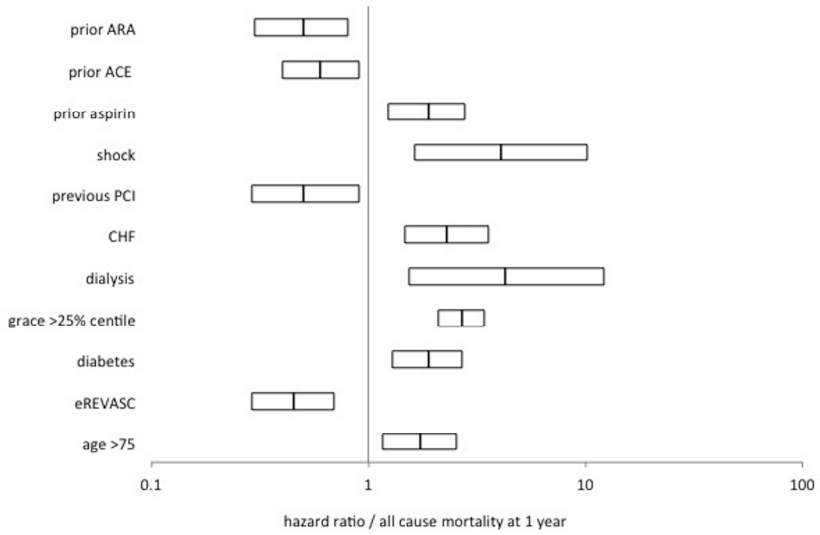

Figure 1. Box plot indicating hazard ratio of mortality at 1 year.
254x190mm (300 x 300 DPI)

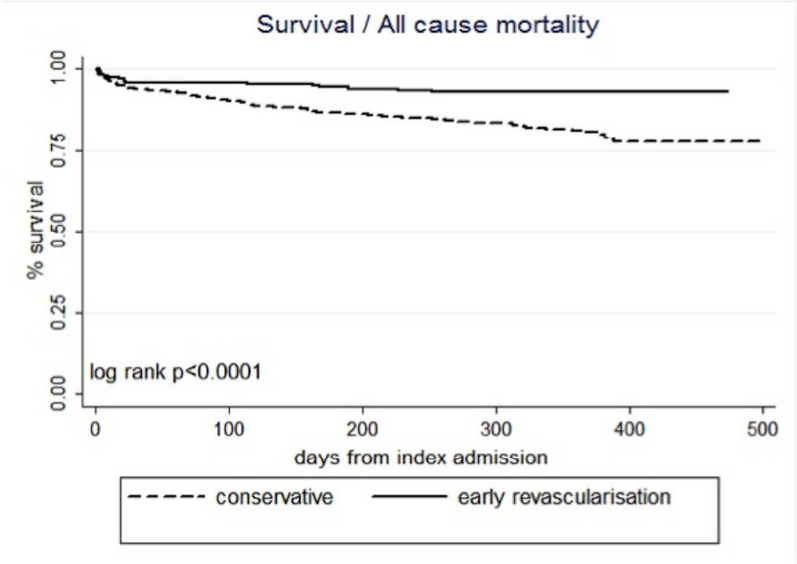

Figure 2. Survival in elderly cohort with respect to early revascularisation
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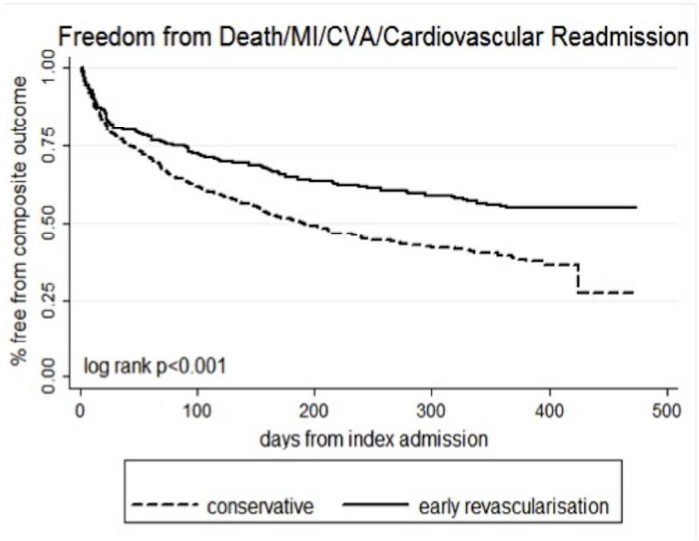

Figure 3. Freedom from composite outcome in elderly cohort with respect to early revascularisation
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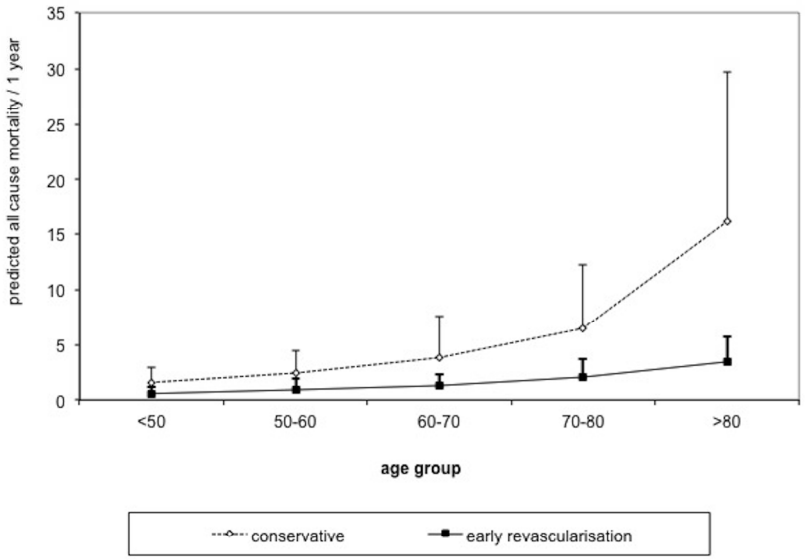

Figure 4. Predicted absolute mortality at 1 year from propensity model
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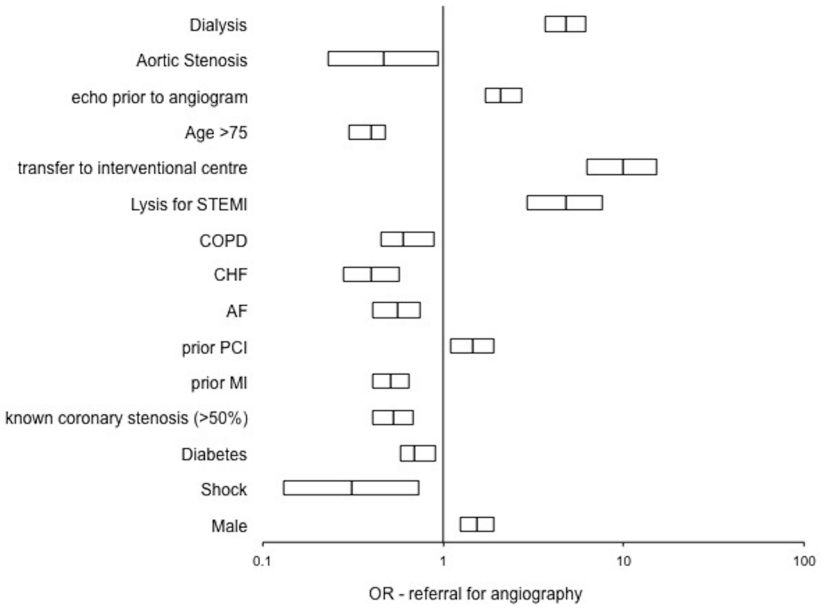

Box plot indicating hazard ratio contributing to likelihood of referral for diagnostic coronary angiography in the ACS cohort.
254x190mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Probably unhelpful
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of increased age on outcome from an early invasive strategy in patients with acute coronary syndromes- retrospective analysis from the ACACIA registry.

Running title: ACACIA elderly analysis.

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Keywords

Acute coronary syndrome, elderly, revascularisation, survival.

Word count (excluding title page, abstract, references, figures)

2064

ABSTRACT

Objective

To evaluate the impact of increased age on outcome from invasive management in patients with acute coronary syndromes.

Design

Retrospective analysis of a national Acute Coronary Syndrome registry (ACACIA).

Setting

Multiple Australian (n=39) centres; 25% rural, 52% with onsite cardiac surgery.

Patients

Unselected consecutive patients admitted with confirmed acute coronary syndromes, total n=2559, median 99 per centre.

Interventions

Management was at the discretion of the treating physician. Analysis of outcome based on age>75 was compared using Cox proportional hazard with a propensity model to adjust for baseline covariates.

Main outcome measures

Primary outcome was all cause mortality. Secondary outcome was bleeding and a composite of any vascular event or unplanned readmission.

Results

Elderly patients were more likely to present with high-risk features yet were less likely to receive evidence based medical therapies or receive diagnostic coronary angiography (75% v 49%, p<0.0001) and early revascularisation (50% v 30%, p<0.0001). Multi-variate analysis confirmed the benefit of early revascularisation in the elderly cohort with reductions in 12-month mortality hazard 0.4(0.2-0.7) and

composite outcome 0.6(0.5-0.8). Propensity model suggested a greater absolute benefit in elderly patients compared to others.

Conclusions

Following presentation with ACS elderly patients are less likely to receive evidence based medical therapies, to be considered for an early invasive strategy and be revascularised. Increasing age is a significant barrier to physicians when considering early revascularisation. An early invasive strategy with revascularisation when performed was associated with substantial benefit and the absolute accrued benefit appears to be higher in elderly patients.

Article focus:

To assess the impact of increased age on invasive management in patients with acute coronary syndromes.

Key messages:

Age is a barrier to treatment since elderly patients are less likely to receive evidence based medical therapies and invasive management.

Invasive management, when performed was associated with substantial benefit, greater absolute benefit was demonstrated in elderly patients compared to younger patients.

Strengths and limitations of this study:

The strengths of this study are that the data are large volume and comprise contemporary real world practice.

The limitations of this study are that the reasons and decisions for offering or failing to offer invasive management or evidence based therapy are not fully recorded.

INTRODUCTION

The management of acute coronary syndromes is constantly evolving with new therapies and interventions tested in clinical trials. Subjects with ST elevation myocardial infarction (STEMI) are at very high early risk and timely reperfusion therapy with thrombolysis or primary angioplasty substantially reduces mortality.[1, 2] In patients with non-ST elevation syndromes (NSTEMI) an early invasive strategy with revascularisation where appropriate is recommended by international societies and supported by several prospective trials.[3-5] This strategy is particularly beneficial in patients deemed to be at high risk – specifically those patients with elevated cardiac bio-markers or dynamic ECG changes.[6] Age in isolation has been considered a risk factor for patients presenting with ACS yet a paradox exists that elderly patients >75 years are frequently under-represented in clinical trials whereas in clinical practice they constitute a significant proportion of the patient population.[7, 8] A poor outcome in the elderly population may be associated with more complex coronary disease, increased co-morbidity and higher risk of complication from revascularisation procedures.[9-11] Despite this, recent studies and large international registries have shown the elderly population have substantially improved outcome with early invasive management, yet compared to younger patients an interventional strategy is less likely to be offered.[5, 12-15]

The objective of this study was to assess the management of acute coronary syndromes in an elderly population using data taken from a national registry. Specifically we planned to test the hypothesis that age in isolation does not adversely affect the outcome of patients presenting with ACS who are managed with an early interventional strategy. We also explored the reasons that some elderly patients are not considered appropriate for an early invasive strategy.

METHODS

The Acute Coronary Syndrome Prospective Audit (ACACIA, protocol number PM_L_0051) is a registry of Australian practice collected between 1 November 2005 and 31 July 2007 involving 39 hospitals across all states and territories of Australia. These sites were selected to be representative of rural (25%) and metropolitan (75%) centres, interventional (83%) and non-interventional (17%) centres and 52% of sites reported onsite cardiac surgery. Each site sought consecutive enrolment of between 100 and 150 patients admitted from the local emergency service for suspected ACS (median, 99). Patients presenting with ACS thought to be secondary to major trauma or surgery were excluded. Patients transferred into study centres were excluded if more than 12 hours had passed since their initial presentation, to enable more accurate assessment of immediate care.

Ethics approval was obtained from all sites and written informed consent was obtained from all conscious patients. Access to medical records was permitted.

Funding

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

Definition of ACS and data collection

Patients presenting with suspected STEMI or NSTEMI were eligible for enrolment. The primary discharge diagnosis was determined by the investigators at each site but was confirmed by a central adjudication process. Stratification of data collection diagnoses was also centrally adjudicated to ensure consistency of enrolment from each centre. Allocation to non-cardiac chest pain was made when ACS was excluded or a positive alternative diagnosis was made, data from these patients were not included in the principle analyses. Standard clinical data were recorded including type

and results of all investigations and medications. Early interventional strategy was defined as angiography at any point during the index acute admission including emergency primary PCI for STEMI but excluded outpatient angiography. The use, time and extent of revascularisation by angioplasty (PCI) or surgery (CABG) was recorded. All data was collated by trained research co-ordinators. All cause mortality was determined during the index admission and at 12 months. Any patients lost to follow up were referred as a query to the Australian Institute of Health and Welfare National Death Register to confirm status and cause of death. Data on non-fatal vascular events further revascularisation and unplanned hospital readmissions were recorded from hospital records and discharge codes.

Statistics

Primary outcome was all cause mortality at 12 months. Secondary outcomes were (thrombolysis in myocardial infarction) TIMI bleeding at thirty days and a composite of subsequent myocardial infarction, stroke, death and cardiovascular cause for unplanned hospital readmission at 12 months. We defined the elderly population as those patients older than 75 years, this value was selected since patients of this age and above have frequently been excluded from prospective clinical trials. Categorical outcomes and parameters were analysed with chi-squared analysis or fisher's exact test for 2x2 comparisons. Multi-variate analysis of event free survival and overall survival was performed using Cox proportional hazard. Survival curves were plotted to examine the effect of an early invasive strategy in the aged cohort. Binary logistic regression was used to evaluate time independent outcomes. To evaluate the impact of an early invasive strategy on 12 month mortality in patients >75years and to control for substantial confounding clinical factors associated with increased age, a propensity analysis was performed using a non-parsimonious logistic regression model including

(age>75, gender, indigenous status, Killip class, GRACE score, cardiac arrest, normal ECG, ST segment depression or elevation, shock, pulmonary oedema or arrhythmia; presence of renal replacement therapy, dyslipidaemia, hypertension, diabetes, chronic airways disease, peripheral vascular disease, malignancy or AF; previous history of coronary artery disease, myocardial infarction, PCI, CABG or stroke) (c-index: 0.89). A logistic regression model for survival until 12 months including age, propensity score and early invasive management was then undertaken. This model was used to predict the expected mortality in ascending strata of age groups. These data are presented across the age groups further stratified by use of early invasive management. All data were analysed using commercially available software STATA version 13. Significance was sought at the 5% level.

RESULTS

Baseline characteristics

A total of 3402 patients were enrolled and vital status was available for 3393 at 1 year. Discharge diagnosis of STEMI was recorded in (717), NSTEMI in (1027) and unstable angina in (815) giving a study population of (2559). Elderly patients, >75 years comprised 27% (n=683) of the study population, baseline variables are shown in table 1. The younger group were more likely to be active smokers and to present with cardiac arrest. The elderly group presented more frequently in association with haemodynamic disturbance and other co-morbidity.

Table 1. Baseline characteristics

Variable	<75 years N=1876	%	>75 years N=683	%	Chi (Fishers')
Male	1380	74	372	55	0.001
Dyslipidaemia	1134	60	418	61	0.7
Current Smoker	570	30	34	5	0.001
Known Coronary Disease	851	45	438	64	0.001
Previous MI	479	26	251	37	0.001
Chronic Heart Failure	93	5	121	18	0.001
Previous PCI	356	19	123	18	0.3
Previous CABG	234	12	150	22	0.001
Diabetes	512	27	171	25	0.25
Hypertension	1125	60	510	75	0.001
Atrial Fibrillation	137	7	139	20	0.001
Peripheral Vascular Disease	82	4	80	12	0.001
Malignancy	96	5	84	12	0.001
Elevated Cardiac Bio-markers	1384	74	485	71	0.163
normal ECG	506	27	155	23	0.03
ST segment deviation (including BBB)	894	48	338	50	0.4
ST elevation	577	31	138	20	0.001
ST depression	224	12	123	18	0.001
Left bundle branch block	73	4	72	11	0.001
Killip 1	1589	85	448	66	0.001
Pulmonary oedema	72	4	60	9	0.001
Cardiac Arrest	68	3.6	11	1.6	0.009
Arrhythmia on presentation	115	6	40	6	0.8

In hospital management

During in hospital care the elderly group were less likely to be treated with evidence based medical therapies and were less frequently referred for angiography (79% v 49%, p=0.0001) (table 2). Revascularisation as a whole was therefore less frequently performed in the elderly cohort. The disparity in revascularisation was driven primarily by less frequent referral for diagnostic angiogram. If angiography was performed then the rates of revascularisation were more comparable, (61% v 66%, p=0.04). Logistic regression of the whole cohort identified 13 variables that independently contributed to mortality at 12 months (figure 1). Among these variables an age over 75 increased mortality risk OR 1.7 (1.2-2.6) and early revascularisation reduced risk OR 0.4(0.2-0.7). Division of the data into subjects above the age of 75 found early revascularisation to remain highly protective in terms of risk of all cause mortality OR 0.4(0.2-0.7) and composite outcome 0.6(0.5-0.8). (figures 2, 3). Predicted mortality based on the propensity model confirmed the beneficial effect of early revascularisation with incrementally greater absolute effect in the higher age brackets. (figure 4) We explored the factors associated with for non-referral for angiogram and for not performing revascularisation. Independent variables that appeared to contribute to non referral for angiogram included age over 75, female gender, presence of diabetes and history of previous myocardial infarction.(figure 5) Once an angiogram had been performed fewer variables influenced the decision to perform revascularisation and neither gender nor age over 75 were contributory.

Table 2. In hospital management

Variable	<75years (1876)	%	>75years (683)	%	Chi
Aspirin	1672	89	528	77	0.001
Clopidogrel	1234	66	357	52	0.001
2b3a agent	163	8.7	36	5	0.004
Low molecular weight heparin	1410	75	520	76.1	0.6
ACE-I	1110	59	370	54	0.02
ARA	243	13	116	17	0.009
HMG-CoA enzyme inhibitor	1635	87	537	79	0.001
B-blocker	1346	72	446	65	0.002
Functional test for ischaemia	188	10	43	6.3	0.004
Diagnostic angiography	1401	75	335	49	0.001
Echocardiogram	758	40	293	42	0.26
Angioplasty	808	43	169	25	0.001
Coronary Surgery	154	8.2	46	6.7	0.2
Revascularisation if angiogram	931 from 1401	66	203 from 335	61	0.04
Reperfusion if (STEMI)	420	72	80	60	0.008
Primary PCI	256	44	50	38	0.2
Rescue PCI	33	6	2	1.5	0.05
TIMI bleed	83	4	34	5	.5

TIMI bleeding

There were 123 episodes of TIMI bleeding in the study cohort within 30 days of index presentation. Overall, age >75years was not in isolation a risk for bleeding HR 1.3(0.86-1.9) nor was there excess bleeding in the old versus younger cohorts (5%v4%, p=0.6). Early revascularisation was associated with a substantially higher risk of bleeding in both the young 10.5(5.1-21) and aged 14.9(5.6-40) cohort and this relationship was independent to the use of aspirin, clopidogrel and anti-coagulation at the time of presentation. Comparison limited to the patients who received early revascularisation (n=1134) did reveal excess bleeding in the aged cohort compared to the younger group, 13.2% v 7.6%, p=0.01.

CONCLUSIONS

Elderly patients comprise a large group of the ACS population. Despite having higher baseline risk they are less likely to be offered evidence based medical therapies and substantially less likely to be investigated invasively with a view to early revascularisation. The effect of an early invasive strategy was highly protective with improvements in survival and in the composite outcome of myocardial infarction, stroke, death and cardiovascular cause for readmission; at the expense of a higher incidence of TIMI bleeding. Adjustment for baseline covariates using a propensity model suggested greater absolute benefit in patients at advanced age.

DISCUSSION

The ACACIA dataset provides an outstanding insight into the management of acute coronary syndromes sourcing data from different types of hospital. These data in concordance with other studies show that elderly patients are more often managed conservatively, a particular barrier appears to be at the level of referral for diagnostic

angiogram with less than half of the patients >75years receiving this investigation. This observation is not a new finding; [12, 16]and reflects an obvious referral bias; most young patients are offered an angiogram whereas most elderly patients are not. Our data do not record the reason for this disparity since we do not have data on generalised extreme frailty, patient choice or a positive decision to palliate patients based on extensive co-morbidity. There is no doubt that frailty may influence decision to treat individual patients conservatively[17] but it is extremely unlikely that these factors alone account for the fewer number or elderly patients offered an early invasive strategy and clearly there is a reluctance of clinicians to offer invasive management to some of their elderly patients. An obvious observation is that increased age is associated with mortality, yet the effect of age >75 years was less influential on mortality risk than presence of diabetes, heart failure, and haemodynamic disturbance on presentation. We did observe a higher rate of TIMI bleeding at 30 days in the elderly cohort although this effect did not translate to a change of mortality or composite outcome at 12 months. Furthermore in our adjusted analysis the absolute benefit of early revascularisation was positively associated with increased stratifications of age. This analysis is unsurprising, since those patients at highest risk (such as the elderly) stand to gain most from an early invasive strategy and this fact is consistent with the substantial impact of age on risk in scores such as the GRACE score.[18] The data from the ACACIA registry reinforce the message of these risk scores and other trials demonstrating that age is not a bar to the benefits associated with invasive management and increased age should not be the dominant factor when contemplating management following hospitalisation with ACS. In the real world some patients elect not to pursue an early invasive strategy and this choice may be made more frequently by elderly patients, who may have concerns about their

own frailty and long-term morbidity. Physicians may also judge that a patient has such substantial co-morbidity that a palliative or limited approach should be undertaken.[19] Despite these case specific management decisions, it is clear from our data however that the elderly ACS population are under investigated and under-treated and this may deny these patients the substantial benefit that is seen within 12 months. We encourage all physicians who manage patients with acute coronary syndromes to avoid using advanced age as reason to manage some patients conservatively.

Limitations

The ACACIA data represent a real world registry; individual decisions on patient management such as reasons for not offering an early invasive strategy were not recorded. The geographical challenges of healthcare in Australia are reflected in some of the data such as persisting use of thrombolysis and rescue angioplasty. Transfer from a non-interventional centre to an interventional centre was positively associated with an early invasive strategy. It is possible that further referral bias occurs at this level since cardiologists may pre-select those patients in whom they expect the best outcomes, especially if transfer involves air travel. However our data were carefully selected to be representative of real world cardiology practice including both metropolitan surgical centres and rural district hospitals and evidence of bias in referral based on age or transfer is worthy of discussion.

Data Sharing

The original ACACIA data can be requested by permission from Professor Derek Chew, Flinders Medical Centre, Adelaide, South Australia.

Author Contributions and Declarations

Dr Malkin analysed the data and wrote the first draft of the manuscript

Dr Prakash helped analyse the data and edited the final draft of the manuscript

Professor Chew developed the initial concept and supervised analysis and editing of the final draft of the paper

The authors declare no conflicts of interest

Abbreviations

PCI = Percutaneous Coronary intervention

CABG = coronary artery bypass graft

LBBB = left bundle branch block

ACE-I = angiotensin converting enzyme inhibitor

ARA = Angiotensin receptor antagonist

CHF = Chronic Cardiac Failure

eREVASC = early revascularisation

Legend for Figures and Tables

Table 1. Baseline characteristics of ACS cohort separated by age.

Table 2. In hospital investigation and treatment of ACS cohort separated by age.

Figure 1. Box plot indicating hazard ratio contributing to all cause mortality at 1 year in ACS cohort in multivariate analysis.

Figure 2. Survival curve of elderly ACS cohort with respect to early revascularisation

Figure 3. Freedom from composite outcome in elderly ACS cohort with respect to early revascularisation.

Figure 4. Predicted absolute mortality (error bars are SD) at 1 year calculated from propensity model.

Figure 5. Box plot indicating hazard ratio contributing to likelihood of referral for diagnostic coronary angiography in the ACS cohort.

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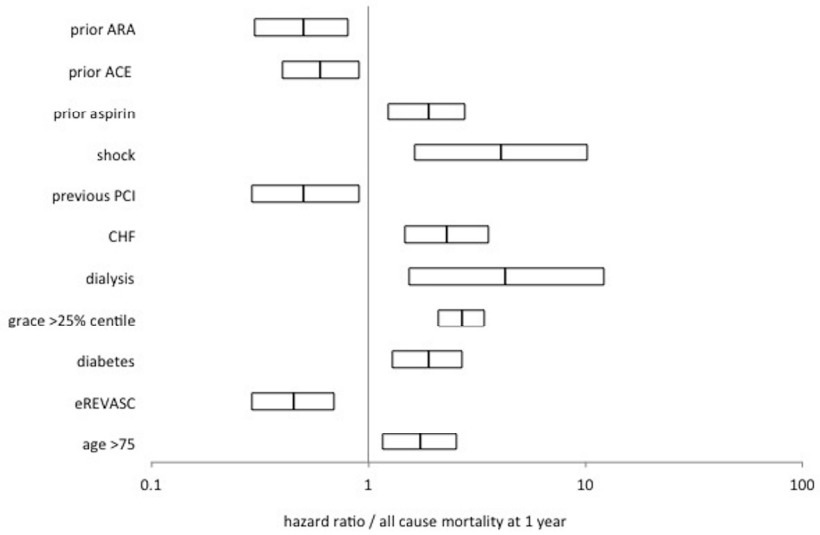

Figure 1. Box plot indicating hazard ratio of mortality at 1 year.
254x190mm (300 x 300 DPI)

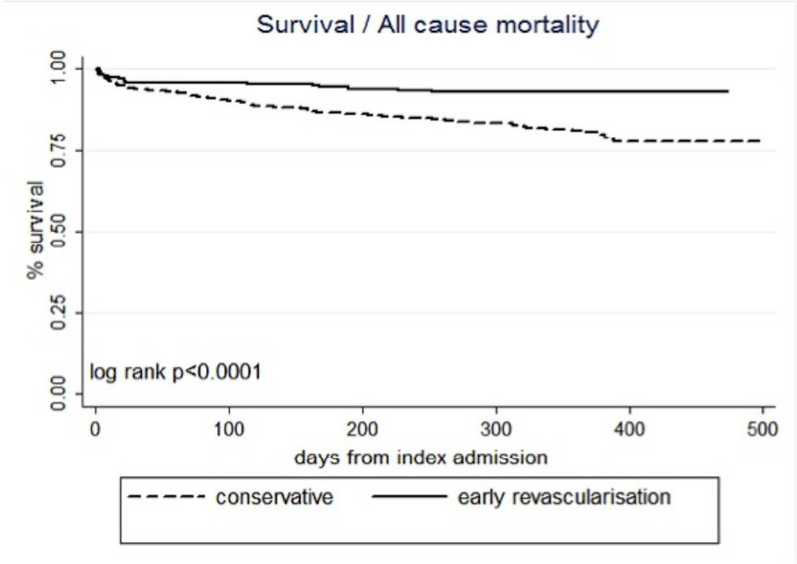

Figure 2. Survival in elderly cohort with respect to early revascularisation
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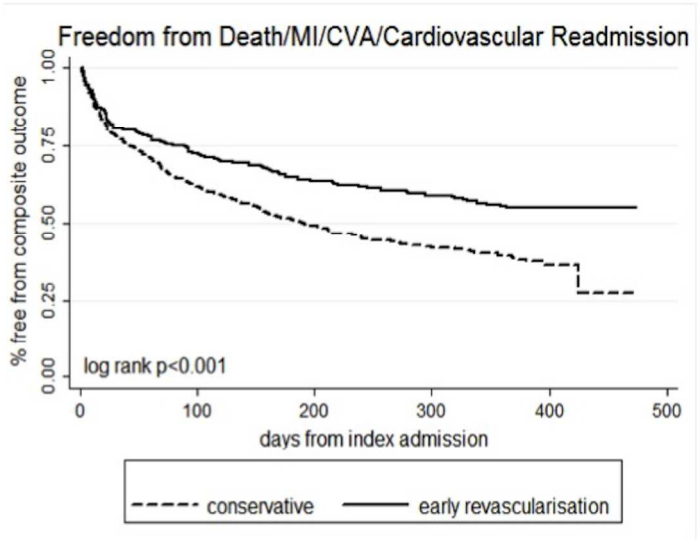

Figure 3. Freedom from composite outcome in elderly cohort with respect to early revascularisation
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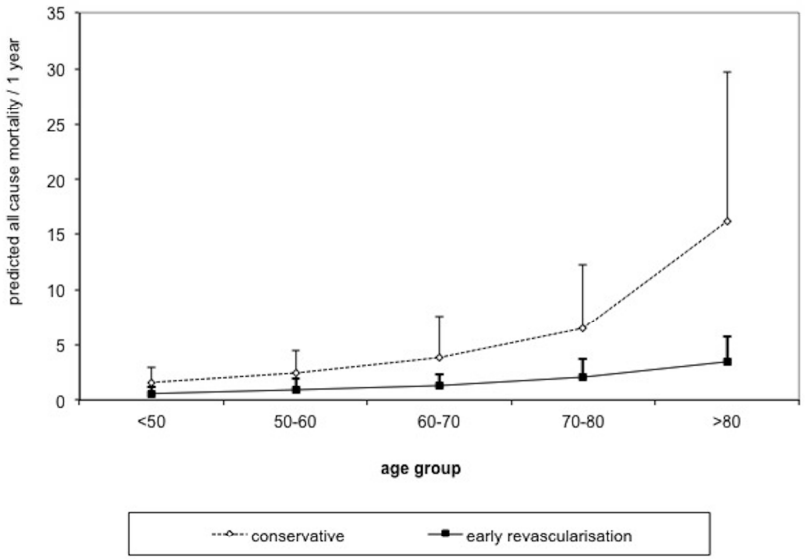

Figure 4. Predicted absolute mortality at 1 year from propensity model
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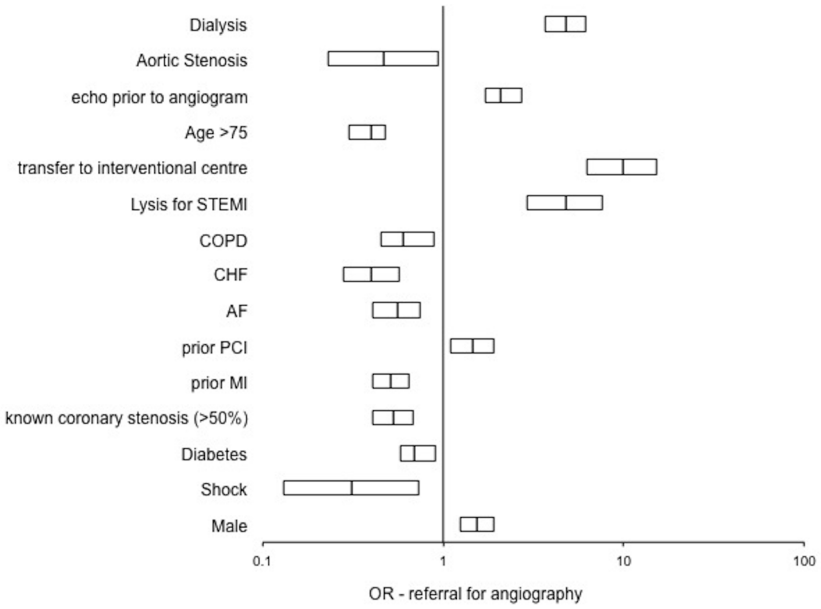

Box plot indicating hazard ratio contributing to likelihood of referral for diagnostic coronary angiography in the ACS cohort.
254x190mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Probably unhelpful
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

The impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes- retrospective analysis study from the ACACIA registry.

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The impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes- retrospective analysis study from the ACACIA registry.

Running title: ACACIA elderly analysis.

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Acute coronary syndrome, elderly, revascularisation, survival.

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ABSTRACT

Objective

To evaluate the impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes.

Design

Retrospective analysis of a national Acute Coronary Syndrome registry (ACACIA).

Setting

Multiple Australian (n=39) centres; 25% rural, 52% with onsite cardiac surgery.

Patients

Unselected consecutive patients admitted with confirmed acute coronary syndromes, total n=2559, median 99 per centre.

Interventions

Management was at the discretion of the treating physician. Analysis of outcome based on age>75 was compared using Cox proportional hazard with a propensity model to adjust for baseline covariates.

Main outcome measures

Primary outcome was all cause mortality. Secondary outcome was bleeding and a composite of any vascular event or unplanned readmission.

Results

Elderly patients were more likely to present with high-risk features yet were less likely to receive evidence based medical therapies or receive diagnostic coronary angiography (75% v 49%, p<0.0001) and early revascularisation (50% v 30%, p<0.0001). Multi-variate analysis found early revascularisation in the elderly cohort to be associated with lower 12-month mortality hazard 0.4(0.2-0.7) and composite

outcome 0.6(0.5-0.8). Propensity model suggested a greater absolute benefit in elderly patients compared to others.

Conclusions

Following presentation with ACS elderly patients are less likely to receive evidence based medical therapies, to be considered for an early invasive strategy and be revascularised. Increasing age is a significant barrier to physicians when considering early revascularisation. An early invasive strategy with revascularisation when performed was associated with substantial benefit and the absolute accrued benefit appears to be higher in elderly patients.

Article focus:

To assess the impact of increased age on invasive management and revascularisation in patients with acute coronary syndromes.

Key messages:

Age is a barrier to treatment since elderly patients are less likely to receive evidence based medical therapies and invasive management.

Invasive management, when performed was associated with substantial benefit, greater absolute benefit was demonstrated in elderly patients compared to younger patients.

Strengths and limitations of this study:

The strengths of this study are that the data are large volume and comprise contemporary real world practice.

The limitations of this study are that the reasons and decisions for offering or failing to offer invasive management or evidence based therapy are not fully recorded.

There is no randomisation process within this registry.

INTRODUCTION

The management of acute coronary syndromes is constantly evolving with new therapies and interventions tested in clinical trials. Subjects with ST elevation myocardial infarction (STEMI) are at very high early risk and timely reperfusion therapy with thrombolysis or primary angioplasty substantially reduces mortality.[1, 2] In patients with non-ST elevation syndromes (NSTEMI) an early invasive strategy with revascularisation where appropriate is recommended by international societies and supported by several prospective trials.[3-5] This strategy is particularly beneficial in patients deemed to be at high risk – specifically those patients with elevated cardiac bio-markers or dynamic ECG changes.[6] Age in isolation has been considered a risk factor for patients presenting with ACS yet a paradox exists that elderly patients >75 years are frequently under-represented in clinical trials whereas in clinical practice they constitute a significant proportion of the patient population.[7, 8] A poor outcome in the elderly population may be associated with more complex coronary disease, increased co-morbidity and higher risk of complication from revascularisation procedures.[9-11] Despite this, recent studies and large international registries have shown the elderly population have substantially improved outcome with early invasive management, yet compared to younger patients an interventional strategy is less likely to be offered.[5, 12-17]

The objective of this study was to assess the management of acute coronary syndromes in an elderly population using data taken from a national registry. Specifically we planned to test the hypothesis that age in isolation does not adversely affect the outcome of patients presenting with ACS who are managed with an early interventional strategy and coronary revascularisation. We also explored the reasons

that some elderly patients are not considered appropriate for an early invasive strategy.

METHODS

The Acute Coronary Syndrome Prospective Audit (ACACIA, protocol number PM_L_0051) is a registry of Australian practice collected between 1 November 2005 and 31 July 2007 involving 39 hospitals across all states and territories of Australia. These sites were selected to be representative of rural (25%) and metropolitan (75%) centres, interventional (83%) and non-interventional (17%) centres and 52% of sites reported onsite cardiac surgery. Each site sought consecutive enrolment of between 100 and 150 patients admitted from the local emergency service for suspected ACS (median, 99). Patients presenting with ACS thought to be secondary to major trauma or surgery were excluded. Patients transferred into study centres were excluded if more than 12 hours had passed since their initial presentation, to enable more accurate assessment of immediate care.

Ethics approval was obtained from all sites and written informed consent was obtained from all conscious patients. Access to medical records was permitted.

Funding

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

Definition of ACS and data collection

Patients presenting with suspected STEMI or NSTEMI were eligible for enrolment. The primary discharge diagnosis was determined by the investigators at each site but was confirmed by a central adjudication process. Stratification of data collection diagnoses was also centrally adjudicated to ensure consistency of enrolment from each centre. Allocation to non-cardiac chest pain was made when ACS was excluded

or a positive alternative diagnosis was made, data from these patients were not included in the principle analyses. Standard clinical data were recorded including type and results of all investigations and medications. Early interventional strategy was defined as angiography at any point during the index acute admission including emergency primary PCI for STEMI but excluded outpatient angiography. The use, time and extent of revascularisation by angioplasty (PCI) or surgery (CABG) was recorded. All data was collated by trained research co-ordinators. All cause mortality was determined during the index admission and at 12 months. Any patients lost to follow up were referred as a query to the Australian Institute of Health and Welfare National Death Register to confirm status and cause of death. Data on non-fatal vascular events further revascularisation and unplanned hospital readmissions were recorded from hospital records and discharge codes.

Statistics

Primary outcome was all cause mortality at 12 months. Secondary outcomes were (thrombolysis in myocardial infarction) TIMI bleeding at thirty days and a composite of subsequent myocardial infarction, stroke, death and cardiovascular cause for unplanned hospital readmission at 12 months. We defined the elderly population as those patients older than 75 years, this value was selected since patients of this age and above have frequently been excluded from prospective clinical trials. Categorical outcomes and parameters were analysed with chi-squared analysis or fisher's exact test for 2x2 comparisons. Multi-variate analysis of event free survival and overall survival was performed using Cox proportional hazard. Survival curves were plotted to examine the effect of an early invasive strategy in the aged cohort. Binary logistic regression was used to evaluate time independent outcomes. To evaluate the impact of an early invasive strategy on 12 month mortality in patients >75years and to control

for substantial confounding clinical factors associated with increased age, a propensity analysis was performed using a non-parsimonious logistic regression model including (age>75, gender, indigenous status, Killip class, GRACE score, cardiac arrest, normal ECG, ST segment depression or elevation, shock, pulmonary oedema or arrhythmia; presence of renal replacement therapy, dyslipidaemia, hypertension, diabetes, chronic airways disease, peripheral vascular disease, malignancy or AF; previous history of coronary artery disease, myocardial infarction, PCI, CABG or stroke) (c-index: 0.89). A logistic regression model for survival until 12 months including age, propensity score and early invasive management was then undertaken. This model was used to predict the expected mortality in ascending strata of age groups. These data are presented across the age groups further stratified by use of early invasive management. All data were analysed using commercially available software STATA version 13. Significance was sought at the 5% level.

RESULTS

Baseline characteristics

A total of 3402 patients were enrolled and vital status was available for 3393 at 1 year. Discharge diagnosis of STEMI was recorded in (717), NSTEMI in (1027) and unstable angina in (815) giving a study population of (2559). Patients excluded from analyses (843) were assigned to a variety of non-ACS diagnoses (including but not exclusive to: musculoskeletal chest pain, pericarditis, respiratory infection and pulmonary embolism) Elderly patients, >75 years comprised 27% (n=683) of the study population, baseline variables are shown in table 1. The younger group were more likely to be active smokers and to present with cardiac arrest. The elderly group

presented more frequently in association with haemodynamic disturbance and other co-morbidity.

Table 1. Baseline characteristics

Variable	<75 years N=1876	%	>75 years N=683	%	Chi (Fishers')
Male	1380	74	372	55	0.001
Dyslipidaemia	1134	60	418	61	0.7
Current Smoker	570	30	34	5	0.001
Known Coronary Disease	851	45	438	64	0.001
Previous MI	479	26	251	37	0.001
Chronic Heart Failure	93	5	121	18	0.001
Previous PCI	356	19	123	18	0.3
Previous CABG	234	12	150	22	0.001
Diabetes	512	27	171	25	0.25
Hypertension	1125	60	510	75	0.001
Atrial Fibrillation	137	7	139	20	0.001
Peripheral Vascular Disease	82	4	80	12	0.001
Malignancy	96	5	84	12	0.001
Elevated Cardiac Bio-markers	1384	74	485	71	0.163
normal ECG	506	27	155	23	0.03
ST segment deviation (including BBB)	894	48	338	50	0.4
ST elevation	577	31	138	20	0.001
ST depression	224	12	123	18	0.001
Left bundle branch block	73	4	72	11	0.001
Killip 1	1589	85	448	66	0.001
Pulmonary oedema	72	4	60	9	0.001
Cardiac Arrest	68	3.6	11	1.6	0.009
Arrhythmia on presentation	115	6	40	6	0.8

In hospital management

During in hospital care the elderly group were less likely to be treated with evidence based medical therapies and were less frequently referred for angiography (79% v 49%, p=0.0001) (table 2). Revascularisation as a whole was therefore less frequently performed in the elderly cohort. The disparity in revascularisation was driven primarily by less frequent referral for diagnostic angiogram. If angiography was performed then the rates of revascularisation were more comparable, (61% v 66%, p=0.04). Logistic regression of the whole cohort identified 13 variables that independently contributed to mortality at 12 months (figure 1). Among these variables an age over 75 increased mortality risk OR 1.7 (1.2-2.6) and early revascularisation reduced risk OR 0.4(0.2-0.7). Division of the data into subjects above the age of 75 found early revascularisation to remain highly protective in terms of risk of all cause mortality OR 0.4(0.2-0.7) and composite outcome 0.6(0.5-0.8). (figures 2, 3). Predicted mortality based on the propensity model suggested further benefit associated with early revascularisation and incrementally greater benefit was projected in the higher age brackets. (figure 4) We explored the factors associated with for non-referral for angiogram and for not performing revascularisation. Independent variables that appeared to contribute to non referral for angiogram included age over 75, female gender, presence of diabetes and history of previous myocardial infarction.(figure 5) Once an angiogram had been performed fewer variables influenced the decision to perform revascularisation and neither gender nor age over 75 were contributory.

Table 2. In hospital management

Variable	<75years (1876)	%	>75years (683)	%	p
Aspirin	1672	89	528	77	0.001
Clopidogrel	1234	66	357	52	0.001
2b3a agent	163	8.7	36	5	0.004
Low molecular weight heparin	1410	75	520	76.1	0.6
Angiotensin Converting Enzyme-Inhibitor	1110	59	370	54	0.02
Angiotensin Receptor Antagonist	243	13	116	17	0.009
HMG-CoA enzyme inhibitor	1635	87	537	79	0.001
B-blocker	1346	72	446	65	0.002
Functional test for ischaemia	188	10	43	6.3	0.004
Diagnostic angiography	1401	75	335	49	0.001
Echocardiogram	758	40	293	42	0.26
Angioplasty	808	43	169	25	0.001
Coronary Surgery	154	8.2	46	6.7	0.2
Revascularisation if angiogram	931 from 1401	66	203 from 335	61	0.04
Reperfusion if (STEMI)	420	72	80	60	0.008
Primary PCI	256	44	50	38	0.2
Rescue PCI	33	6	2	1.5	0.05
TIMI bleed	83	4	34	5	0.5
Time to diagnostic angiogram (days) Excluding primary PCI	1.02 ± 4.5		2.6 ± 4.0		0.5^
Time to primary PCI (minutes)	180.7 ± 42.1		123 ± 61.4		0.3^

Chi-squared statistic unless stated,

^ = unpaired t-test.

TIMI bleeding

There were 123 episodes of TIMI bleeding in the study cohort within 30 days of index presentation. Overall, age >75years was not in isolation a risk for bleeding HR 1.3(0.86-1.9) nor was there excess bleeding in the old versus younger cohorts (5% v 4%, p=0.6). Early revascularisation was associated with a substantially higher risk of bleeding in both the young 10.5(5.1-21) and aged 14.9(5.6-40) cohort and this relationship was independent to the use of aspirin, clopidogrel and anti-coagulation at the time of presentation. Comparison limited to the patients who received early revascularisation (n=1134) did reveal excess bleeding in the aged cohort compared to the younger group, 13.2% v 7.6%, p=0.01.

DISCUSSION

The ACACIA dataset provides an outstanding insight into the management of acute coronary syndromes sourcing data from different types of hospital. These data in concordance with other studies show that elderly patients are more often managed conservatively, a particular barrier appears to be at the level of referral for diagnostic angiogram with less than half of the patients >75years receiving this investigation. This observation is not a new finding; [12, 18]and provides some evidence of referral bias; most young patients are offered an angiogram whereas most elderly patients are not. Unfortunately our data do not record the reason for this disparity since we do not have data on generalised extreme frailty, patient choice or a positive decision to palliate patients based on extensive co-morbidity. There is no doubt that frailty may influence decision to treat individual patients conservatively[19] but it is extremely

unlikely that these factors alone account for the fewer number or elderly patients offered an early invasive strategy. The reason for the apparent reluctance of clinicians to offer invasive management to some of their elderly patients is not clear. An obvious observation is that increased age is associated with mortality, yet the effect of age >75 years was less influential on mortality risk than presence of diabetes, heart failure, and haemodynamic disturbance on presentation. Another possibility is the perceived risk of bleeding, we did observe a higher rate of TIMI bleeding at 30 days in the elderly cohort although this effect did not translate to a change of mortality or composite outcome at 12 months. Furthermore in our adjusted analysis the absolute benefit of early revascularisation was positively associated with increased stratifications of age. This analysis is unsurprising, since those patients at highest risk (such as the elderly) stand to gain most from an early invasive strategy and this fact is consistent with the substantial impact of age on risk in scores such as the GRACE score. [20]The phenomenon of elderly patients deriving a greater absolute benefit than younger patients has previously been reported in subgroup analyses of the TACTICS TIMI 18 trial[16] and from the crusade registry.[17] The data from the ACACIA registry reinforce the message of these trials and other data demonstrating that age is not a bar to the benefits associated with invasive management and increased age should not be the dominant factor when contemplating management following hospitalisation with ACS. In the real world some patients elect not to pursue an early invasive strategy and this choice may be made more frequently by elderly patients, who may have concerns about their own frailty and long-term morbidity. Physicians may also judge that a patient has such substantial co-morbidity that a palliative or limited approach should be undertaken.[21] Despite these case specific management decisions, it is clear from our data however that the elderly ACS population are under investigated and under-

treated and this may deny these patients the substantial benefit that is seen within 12 months. We encourage all physicians who manage patients with acute coronary syndromes to avoid using advanced age as reason to manage some patients conservatively.

CONCLUSIONS

Elderly patients comprise a large group of the ACS population. Despite having higher baseline risk they are less likely to be offered evidence based medical therapies and substantially less likely to be investigated invasively with a view to early revascularisation. The effect of an early invasive strategy with revascularisation was associated with improvements in survival and in the composite outcome of myocardial infarction, stroke, death and cardiovascular cause for readmission; at the expense of a higher incidence of TIMI bleeding. Adjustment for baseline covariates using a propensity model suggested greater absolute benefit in patients at advanced age.

Limitations

The ACACIA data represent a real world registry; individual decisions on patient management such as reasons for not offering an early invasive strategy were not recorded. Hence, the issue of residual selection bias leading to confounding cannot be fully accounted for. While other techniques such as "instrument variable analysis" offer alternative approaches to this problem, determining a viable instrument remains challenging. Nevertheless, these data are consistent with other reported literature. Since there was no randomisation process in this registry data all statistical relationships are reported as associations rather than implied causation.

The geographical challenges of healthcare in Australia are reflected in some of the data such as persisting use of thrombolysis and rescue or convalescent angioplasty.

Our data include all patients diagnosed acute coronary syndromes including those with ST elevation myocardial infarction, we did not exclude these patients from analyses since the main interest of the paper was on the impact on age overall, rather than an analysis of a select population of acute coronary syndromes. Our data, therefore differ from the other major studies of age on outcome that were limited to non ST elevation myocardial infarctions. [5,17,18]

Transfer from a non-interventional centre to an interventional centre was positively associated with an early invasive strategy. It is possible that further referral bias occurs at this level since cardiologists may pre-select those patients in whom they expect the best outcomes, especially if transfer involves air travel. However our data were carefully selected to be representative of real world cardiology practice including both metropolitan surgical centres and rural district hospitals and evidence of bias in referral based on age or transfer is worthy of discussion.

Data Sharing

The original ACACIA data can be requested by permission from Professor Derek Chew, Flinders Medical Centre, Adelaide, South Australia.

Author Contributions and Declarations

Dr Malkin analysed the data and wrote the first draft of the manuscript

Dr Prakash helped analyse the data and edited the final draft of the manuscript

Professor Chew developed the initial concept and supervised analysis and editing of the final draft of the paper.

Professor Chew is the guarantor of this submissions.

The authors declare no conflicts of interest.

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Hospital; Associate Professor Joseph Hung, Sir Charles Gairdner Hos- pital. Tasmania: Dr Philip Roberts-Thomson, Royal Hobart Hospital. Northern Territory: Dr Marcus Iton, Darwin Private Hospital; Dr Alex Brown, Menzies School of Health Research.

Abbreviations

PCI = Percutaneous Coronary intervention

CABG = coronary artery bypass graft

LBBB = left bundle branch block

ACE-I = angiotensin converting enzyme inhibitor

ARA = Angiotensin receptor antagonist

CHF = Chronic Cardiac Failure

eREVASC = early revascularisation

Legend for Figures and Tables

Table 1. Baseline characteristics of ACS cohort separated by age.

Table 2. In hospital investigation and treatment of ACS cohort separated by age.

Figure 1. Box plot indicating hazard ratio contributing to all cause mortality at 1 year in ACS cohort in multivariate analysis.

Figure 2. Survival curve of elderly ACS cohort with respect to early revascularisation

Figure 3. Freedom from composite outcome in elderly ACS cohort with respect to early revascularisation.

Figure 4. Predicted absolute mortality (error bars are SD) at 1 year calculated from propensity model.

Figure 5. Box plot indicating hazard ratio contributing to likelihood of referral for diagnostic coronary angiography in the ACS cohort.

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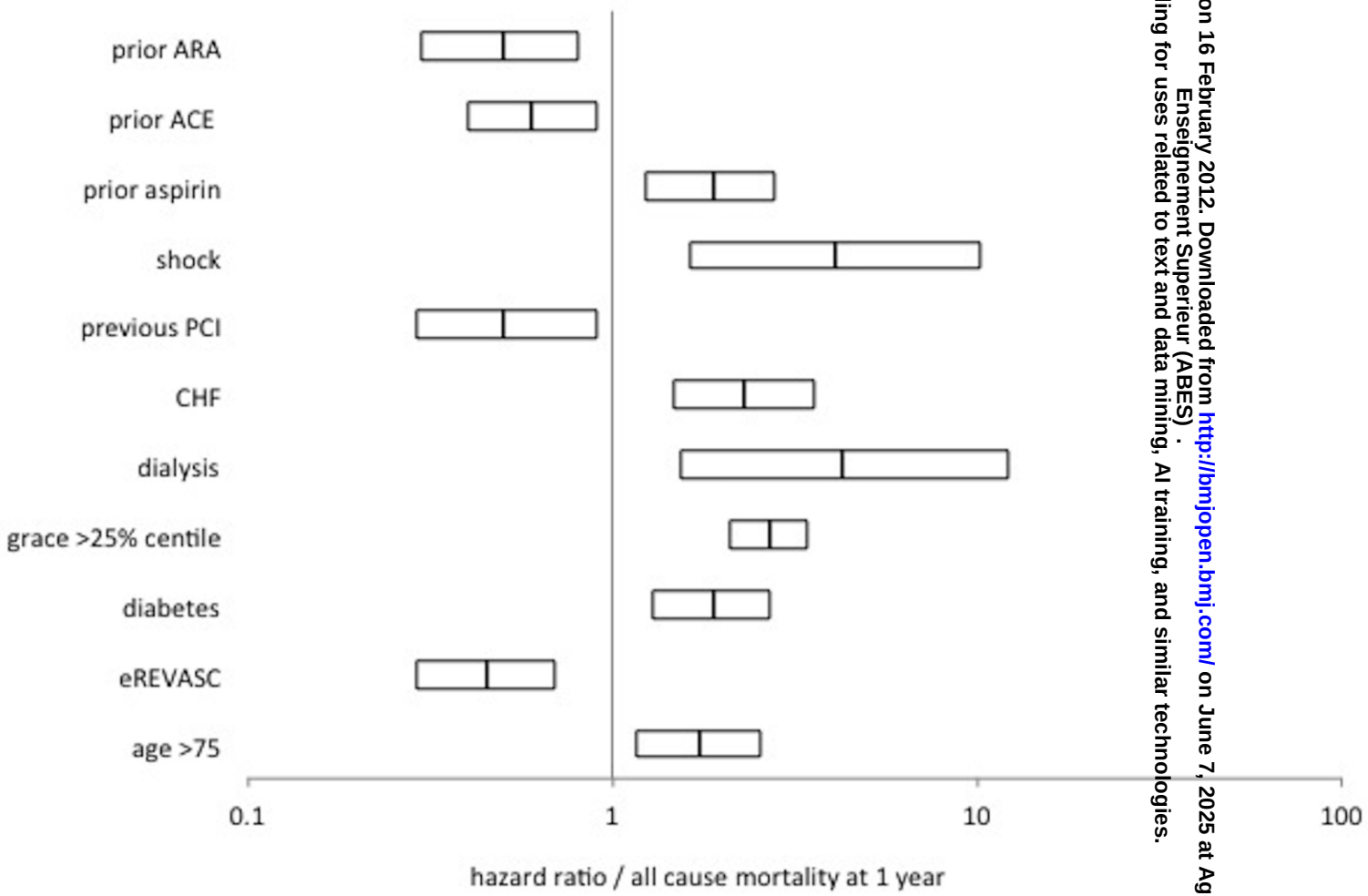

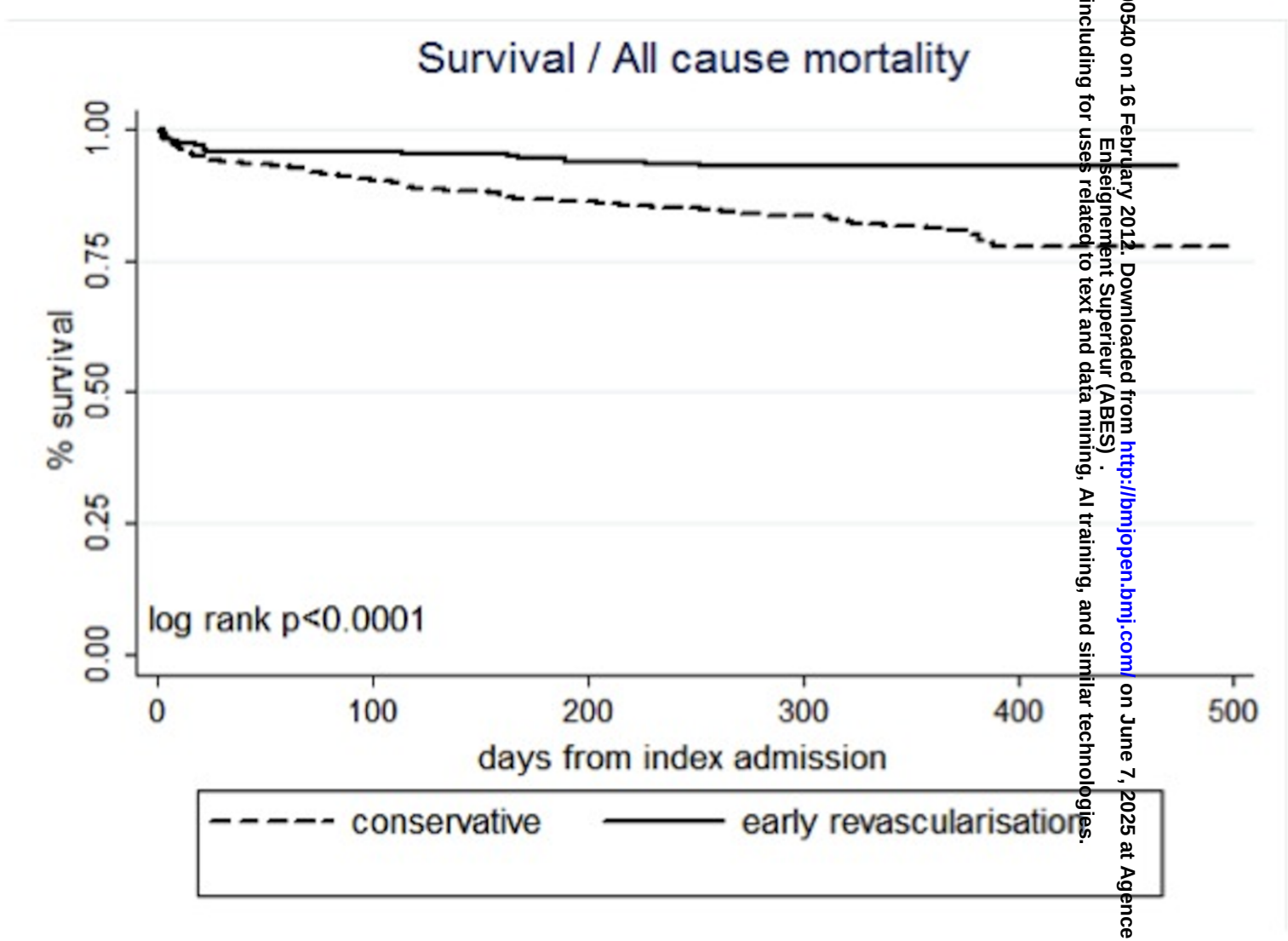

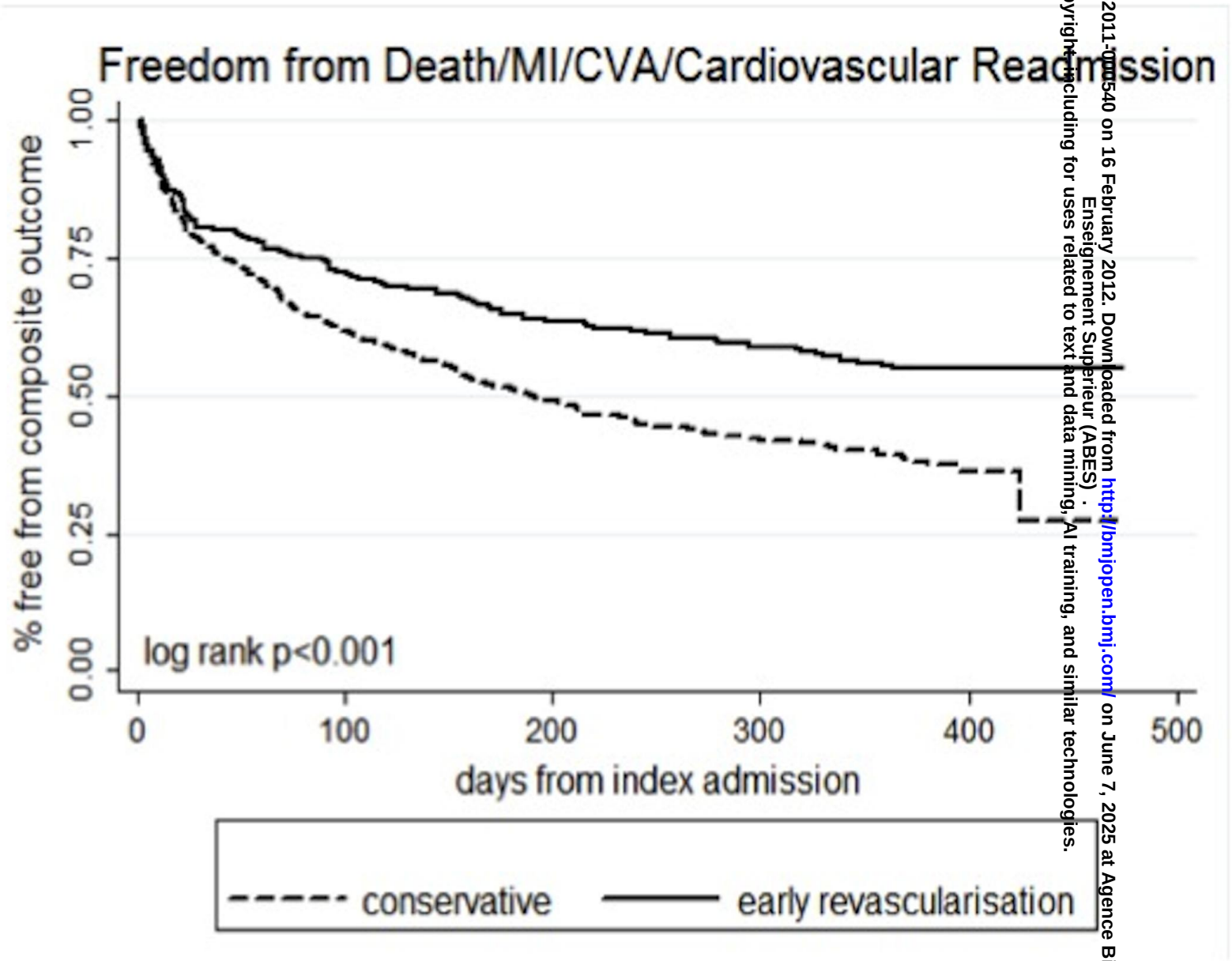

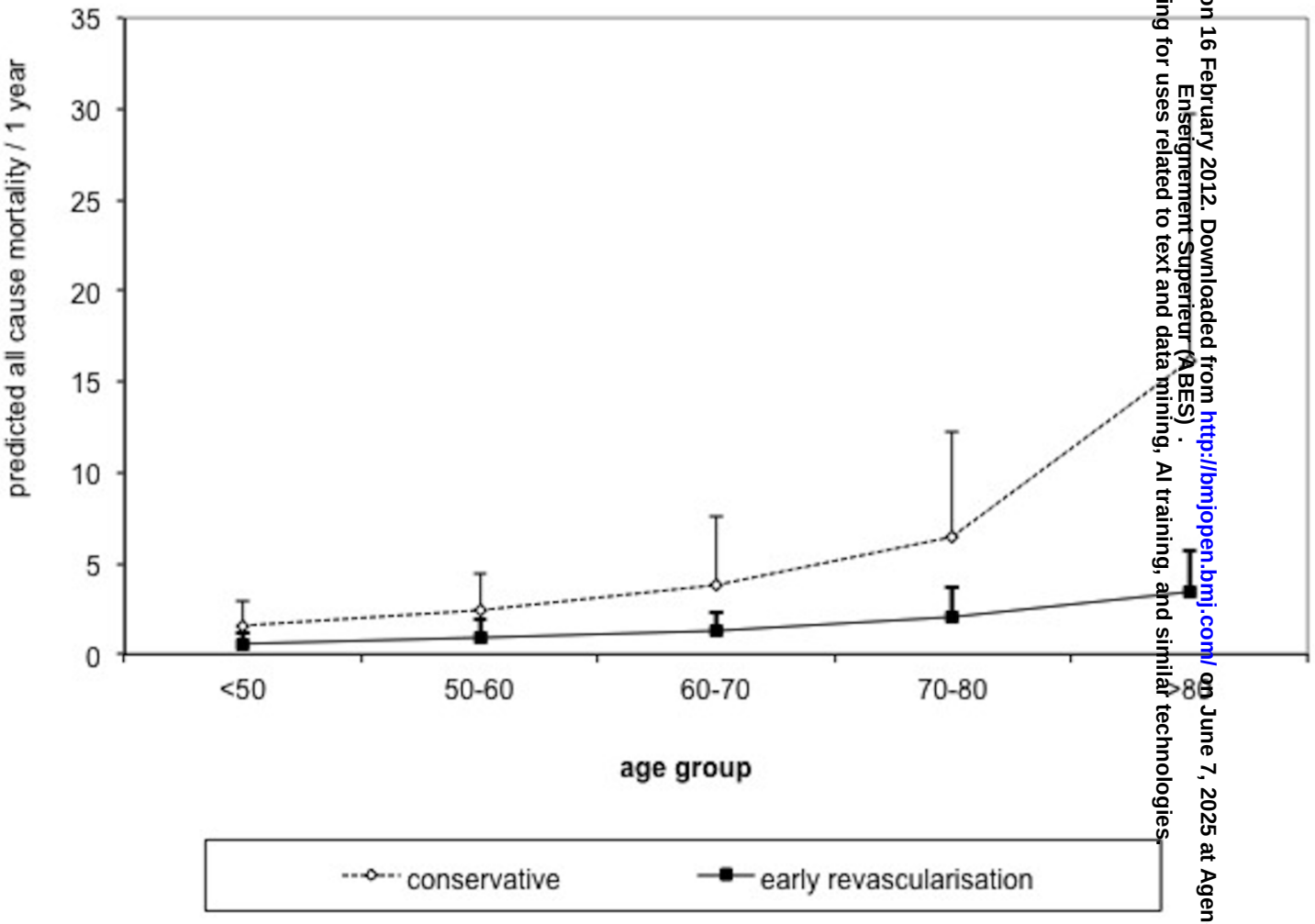

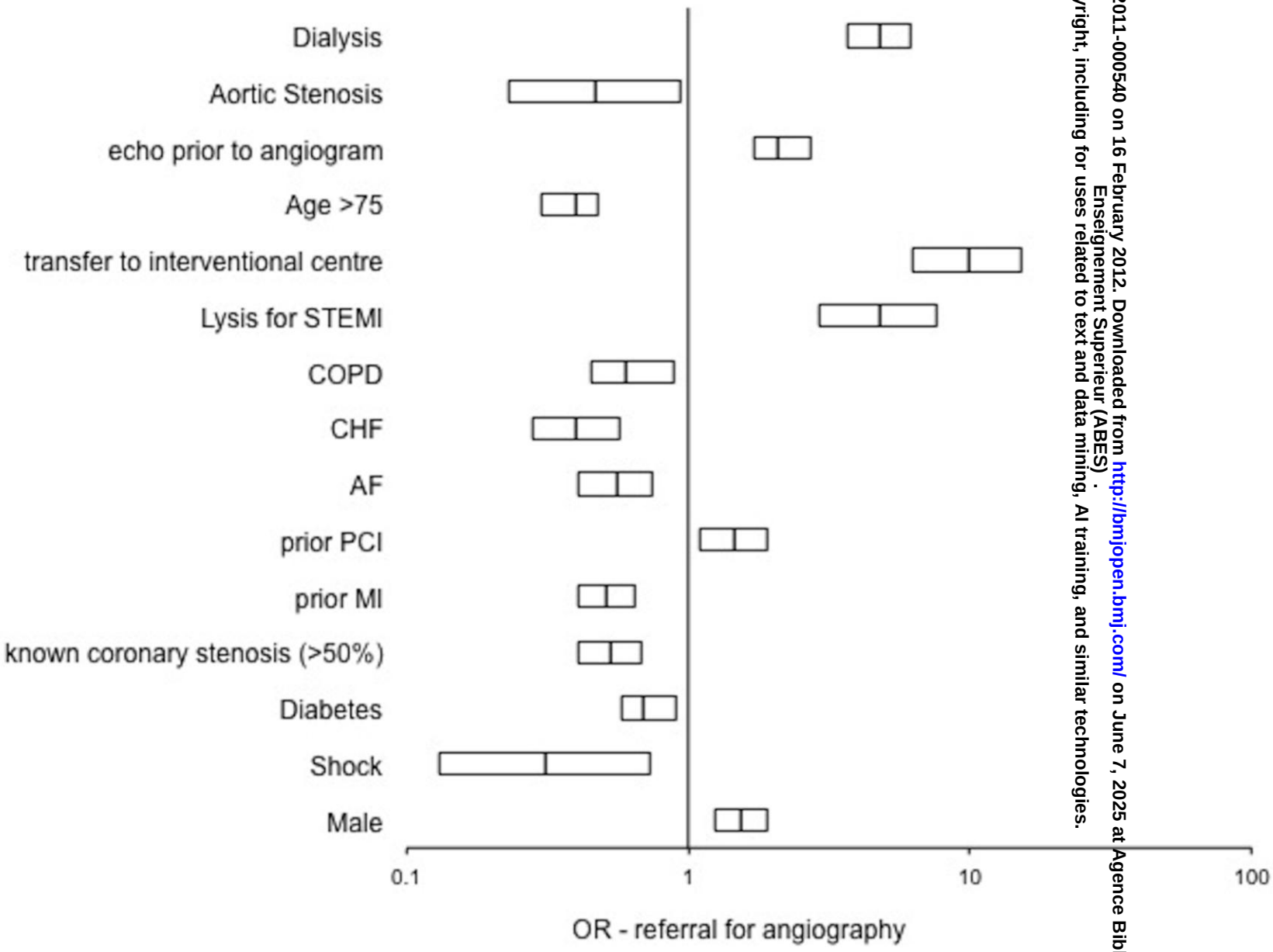

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Probably unhelpful
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.