PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of increased age on outcome from an early invasive strategy in patients with acute coronary syndromes- the ACACIA registry.
AUTHORS	CJ Malkin, Prakash R and DP Chew

VERSION 1 - REVIEW

REVIEWER	Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI Chief of Cardiology, VA Boston Healthcare System Disclosures: Dr. Bhatt receives research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, sanofi aventis, and The Medicines Company.
REVIEW RETURNED	24/11/2011

GENERAL COMMENTS	This is an outstanding analysis on an important topic. I have only two minor comments: 1. In the abstract results, it would be better to write 'lower' mortality than 'reduction' in mortality - as the study was not randomized, it is better not to imply causation, but rather just state association. 2. A prior large analysis from the US ACS registry CRUSADE had also documented underutilization of angiography in older patients. This paper could be referenced: Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC Jr, Pollack CV Jr, Gibler WB, Ohman EM for the CRUSADE Investigators. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Journal of the American Medical Association 2004;292(17):2096-104.

REVIEWER	Richard G. Bach, MD Associate Professor of Medicine Washington University School of Medicine
REVIEW RETURNED	30/11/2011

THE STUDY	This manuscript is a report of a study examining the effect of increased age on management and outcome for patients hospitalized with acute coronary syndrome (ACS). It involves a retrospective analysis of an Australian multicenter registry. Outcomes were analyzed for 2559 patients enrolled at 39 hospitals between November 2005 and July 2007 using Cox proportional hazards modeling with propensity model adjustment for covariates.

	The primary outcome was all cause mortality with secondary outcomes of bleeding and the composite of death, myocardial infarction, stroke or unplanned CV readmission. The authors report that patients older than 75 years were more likely to present with high-risk features yet less likely to receive evidence based medical therapies or to receive diagnostic coronary angiography and early revascularisation. Early revascularisation in the elderly cohort was associated with lower 12-month mortality and lower composite outcome. The authors concluded that elderly patients with ACS are less likely to receive evidence based medical therapies, to be considered for an early invasive strategy and undergo revascularisation, and that an early invasive strategy with revascularisation was associated with substantial benefit and the absolute accrued benefit appears to be higher in elderly patients. Comments: 1 The results described in this manuscript are similar to several previous analyses that have documented higher risk but lower use of evidence-based therapies including early invasive management for ACS among the elderly. The benefit of an early invasive strategy for the elderly has been observed in previous studies. The authors should cite and discuss in the Discussion the previously published subgroup analysis relevant to this topic from the prospective, randomized, controlled TACTICS-TIMI 18 study (Ann Intern Med 2004;141:186-195). 2 The authors describe analyses of the association between early revascularization and outcome among the elderly, but do not show analyses specifically examining outcomes according to the early invasive strategy per se, and this may be misleading for the reader. An analysis directed at examining the impact of the early invasive strategy -- as the manuscript title suggests -- should also include those ACS patients invasively managed but who do not undergo revascularization. The observation that early revascularization is associated with lower mortality in the elderly cohort itself may be notable, but given that those undergoing revascularization represent a highly select group (from an already select group referred for diagnostic angiography), there is a high likelihood of significant bias and residual confounding, despite attempted propensity adjustment, that should be recognized and discussed in the discussion of the results. 3 The investigators included STEMI patients who underwent emergency primary PCI in the analysis. Since early management of STEMI with the paradigm of rapid reperfusion (and the well documented and dramatic effect of time to reperfusion on outcome for STEMI patients) may differ substantially from early management of NSTE ACS, mixing these together seems inappropriate when considering the goal of examining the effect of early invasive management on outcome for the elderly. The analyses of this registry for this paper would be better restricted to patients with NSTE ACS. 4 The authors report that 3402 patients were enrolled in the registry and vital status was available for 3393, yet the study population was 2559. The authors should account specifically for those 834 patients from the registry group not included in the analysis and provide justification.
RESULTS & CONCLUSIONS	1. The authors describe analyses of the association between early revascularization and outcome among the elderly, but do not show analyses specifically examining outcomes according to the early invasive strategy per se, and this may be misleading for the reader. An analysis directed at examining the impact of the early invasive

	strategy -- as the manuscript title suggests -- should also include those ACS patients invasively managed but who do not undergo revascularization. The observation that early revascularization is associated with lower mortality in the elderly cohort itself may be notable, but given that those undergoing revascularization represent a highly select group (from an already select group referred for diagnostic angiography), there is a high likelihood of significant bias and residual confounding, despite attempted propensity adjustment, that should be recognized and discussed in the discussion of the results. 2. In the context of the study design, the confidence in cause and effect is overstated in the paper, where the authors seem to state that early revascularization "reduced" adverse outcomes. For example, the abstract states "…the benefit of early revascularization in the elderly cohort with reductions in 12 month mortality hazard…"; the Results (p. 10) state "early revascularization reduced risk OR 0.4…"; and the Conclusions (p. 12) state "…the effect of an early invasive strategy was highly protective with improvements in survival…" Although this retrospective observational registry analysis may provide interesting and informative observations, it cannot provide cause and effect and the results would be better described as associations. 3. The benefit of an early invasive strategy for the elderly has been observed in previous studies. The authors should cite and discuss in the Discussion the previously published subgroup analysis relevant to this topic from the prospective, randomized, controlled TACTICS-TIMI 18 study (Ann Intern Med 2004;141:186-195). 4. The registry did not provide data on the actual reasons patients did not undergo early invasive management. This important limitation should temper the author's statements in the Discussion (p. 13) that "…elderly patients are more often managed conservatively…and [this] reflects an obvious referral bias..." and that "…clearly there is a reluctance of clinicians to offer invasive management to some of their elderly patients." These statements are more speculation than fact and the reasons may not be so clear or obvious without any objective data. 5. The Conclusions (p. 12) appear out of place and would be better if relocated to the end of the Discussion.
GENERAL COMMENTS	The observations in this study are very interesting although not entirely novel. The study does represent an analysis of new independent registry data with a relatively recent perspective and significant observations. The investigators appear to have analyzed and reported the association between outcome and the restricted use of early revascularization rather than the more inclusive early invasive management strategy, and so the title may be misleading to the reader. The lack of data on detailed comorbidities, functional status, and the actual reasons that elderly patients were less likely to undergo invasive management represents an important limitation on the interpretation and conclusions common to the available studies on this topic.

REVIEWER	Dr Eliano Pio Navarese, Interventional cardiologist and clinical researcher Nicolaus Copernicus University, Poland. I do not have conflict of interest to disclose.
REVIEW RETURNED	09/12/2011

GENERAL COMMENTS	The manuscripts sounds interesting and it adds an important piece of information to the current available literature for timing in NSTEMI;

	the paper is well written; These are my minor comments: 1) Throughout the manuscript there is no mention at all about timing of interventional approach (the paper is focused on early timing approach of invasive approach in patients > 75 years; for example, The specific question of optimal timing was addressed for the first time in the ISAR-COOL trial,16 in which 410 patients with ischemic symptoms conversely, events while waiting for angiography.ST-segment depression or positive troponin were randomized to a very early (median = 2.4 h) versus a delayed (median = 86 h) invasive strategy; in ABROAD trial as early invasive approach was used primary PCI like approach; 2) The authors should comment more on the potential advantages to treat high risk patients very early in light of the subgroup analysis of TIMACS study where high GRACE risk scores were found to benefit from an early invasive approach (the authors should report the results for the overall population in the TIMACS study where conversely there were no clear benefits of early approach in the overall population as also recently demonstrated in a recent meta-analysis that should be considered in discussion because it addresses the available evidence of timing in NSTEMI: Early vs. delayed invasive strategy in patients with acute coronary syndromes without ST-segment elevation: a meta-analysis of randomized studie: QJM. 2011 Mar;104(3):193-200.

VERSION 1 – AUTHOR RESPONSE

Two reviewers, Professor Bhatt and Professor Bach have commented that this paper is based on retrospective analyses of registry data and there was no randomisation process. We have changed the text to reflect this subtle change of analysis. The use of the words or text implying 'causation' when applied to statistical relationships has been changed to 'association' in both the abstract and main paper.
The same reviewers have also identified significant contributions from themselves and others to the literature in this area and we have acknowledged and cited these papers in the paper.

Dr Navarese has questioned the timing of interventional approach. In the paper we define early invasive approach as being within the timeframe of the index admission. We have added the data of time to invasive management in the baseline data to allow comparison of this 'real world' data to other published trials. The significant geographical challenges of delivering emergency cardiology within Australia would limit the provision of very early intervention such as described in the ISAR-COOL trial and this is the reason that thrombolysis for ST elevation myocardial infarction is still used in some remote centres in Australia. Other than adding the baseline data we have not added substantially to the analysis. We take the view that the prospective clinical trials (summarized in Dr Navarese's recently published meta-analysis) have failed to demonstrate unequivocal benefit of offering very early invasive management to most patients with acute coronary syndromes (excluding STEMIs). Furthermore most health case systems either because of cost, or geography are unable to offer this service; therefore such discussion is rather academic.

Professor Bach has made raised other issues that require clarification and in some cases alterations in the paper.
Our analysis is of an early invasive strategy and revascularisation rather than of just an invasive strategy, this has been clarified in the text and we have amended the title. A number of patients were

invasively managed but not revascularised; this has been clarified in the results.
The number of patients enrolled, studied and excluded is more clearly defined in methods section.
We have improved other components of the conclusions in line with points raised in this review. Specifically, previous literature are cited and discussed and the limitations of the data are more thoroughly described

We have included STEMIs within our data series since this is a registry analysis of an early invasive strategy for all acute coronary syndromes. We have attempted to maximise the data to permit meaningful analysis of outcome in elderly patients. Furthermore invasive angiography performed after thrombolysis for ST elevation myocardial infarction is practiced in centres serving remote communities in Australia and therefore excluding ST elevation myocardial infarctions would exclude potentially important data.

The revised paper has been uploaded and new changes are indicated by red text.

Thank you in advance for a further review of this manuscript

Yours sincerely

Chris malkin

VERSION 2 – REVIEW

REVIEWER	Richard G. Bach, MD Associate Professor of Medicine Washington University School of Medicine
REVIEW RETURNED	06/01/2012

THE STUDY	1. In response to my earlier comment that there appeared to be potentially misplaced attribution of cause and effect to these observations, and that they rather represented associations, there were some minor changes to the text but I continue to feel that the changes in the text are at times inadequate. The statement in the abstract that "…Multi-variate analysis confirmed the benefit of early revascularisation in the elderly cohort 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…" continues to explicitly attribute the benefit to the early revascularization, which I believe overstates confidence in cause and effect. Likewise, in the Conclusions on page 14, I believe the statement "…The effect of an early invasive strategy was highly protective with improvements in survival etc…" continues to strongly overstate causality. This may be subtle, but I believe the language conveying the results remains important for valid interpretation for the reader. Perhaps this limited ability to attribute cause and effect could be explicitly discussed under Limitations. 2. The authors have made some modifications to address my earlier concern that their analyses did not test "the early invasive strategy" per se but rather focused on the association between early revascularization and outcome among elderly patients managed invasively, but the changes leave some ambiguity and this may remain misleading for the reader. The statement on page 5 that "…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…" does

	not explicitly admit that the analyses tested an effect of early revascularization, not invasive management. Similarly, in the Conclusions it is stated that "The effect of an early invasive strategy was highly protective with improvements in survival etc…" while the data in the manuscript tests the association between early revascularization and improved outcomes. I think this remains an issue with the revised version, additional clarifications should be made, and this should be explicitly discussed under Limitations. 3. The investigators continue to include STEMI patients who underwent emergency primary PCI in the analysis, which differs from most previous studies. Although I continue to believe that the analyses would be more relevant if restricted to patients with NSTE ACS and that the inclusion of STEMI patients may bias or confound the interpretation of the results for patients with NSTE ACS, at least if they remain included a statement alerting the reader to this fact would be helpful in the Discussion or Limitations.

VERSION 2 – AUTHOR RESPONSE

We welcome further review from Professor Bach and have agreed to the changes suggested.

Point 1, we have refrained from attributing cause and effect with respect to the impact of an early invasive strategy and revascularisation on outcome. This is an observational study and we have now made a consistent effort to limit statistical relationships to association. This concept is stated within the limitations section.

Point 2, we have clarified the hypothesis. Our analysis was on the effect of age on outcome from an early invasive strategy and revascularisation not invasive strategy alone.

Point 3, we have retained the data on ST elevation myocardial infarction. We do accept that this makes out data more heterogenous than previously published studies on this theme (most now cited within the paper) that have limited their analyses to Non ST elevation myocardial infarction. However, we feel that the issue of age, invasive management and revascularisation is relevant in both non-ST elevation and ST elevation infarction. This issue is particularly relevant in Australia and other centres serving large geographical areas since persisting use of thrombolysis with rescue and so called 'convalescent' angiography is still prevalent. With all respect to the reviewer we feel that excluding this data from the analysis weakens the paper rather than strengthens it. As suggested we have specifically stated the presence of all acute coronary syndromes including ST elevation myocardial infarction within the limitations section.

We trust the paper is now acceptable for publication and look forward to hearing from you.

Yours sincerely,

Chris malkin.