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RESEARCH

Renal outcomes associated with invasive versus conservative management of acute coronary syndrome: propensity matched cohort study

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Abstract

Objectives To examine the association of early invasive management of acute coronary syndrome with adverse renal outcomes and survival, and to determine whether the risks or benefits of early invasive management differ in people with pre-existing chronic kidney disease.

Design Propensity score matched cohort study.

Setting Acute care hospitals in Alberta, Canada, 2004-09.

Participants 10 516 adults with non-ST elevation acute coronary syndrome.

Interventions Participants were stratified by baseline estimated glomerular filtration rate and matched 1:1 on their propensity score for early invasive management (coronary catheterisation within two days of hospital admission).

Main outcome measures Risks of acute kidney injury, kidney injury requiring dialysis, progression to end stage renal disease, and all cause mortality were compared between those who received early invasive treatment versus conservative treatment.

Results Of 10 516 included participants, 4276 (40.7%) received early invasive management. After using propensity score methods to assemble a matched cohort of conservative management participants with characteristics similar to those who received early invasive management (n=6768), early invasive management was associated with an increased risk of acute kidney injury (10.3% *v* 8.7%, risk ratio 1.18, 95% confidence interval 1.03 to 1.36; P=0.019), but no difference in the risk of acute kidney injury requiring dialysis (0.4% *v* 0.3%, 1.20, 0.52 to 2.78; P=0.670). Over a median follow-up of 2.5 years, the risk of progression to end stage renal disease did not differ between the groups (0.3 *v* 0.4 events per 100 person years, hazard ratio 0.91, 95% confidence interval 0.55 to 1.49; P=0.712); however, early invasive management was associated with reduced long term mortality (2.4 *v* 3.4 events per 100 person years, 0.69, 0.58 to 0.82; P<0.001). These associations were consistent among people with pre-existing reduced estimated glomerular filtration rate and with alternate definitions for early invasive management.

Conclusions Compared with conservative management, early invasive management of acute coronary syndrome is associated with a small increase in risk of acute kidney injury but not dialysis or long term progression to end stage renal disease.

Introduction

Approximately 40% of people with acute coronary syndromes receive early invasive management involving coronary angiography and percutaneous coronary intervention within 48 hours of hospital admission.[1] Randomised trials show that this approach reduces recurrent angina, readmission to hospital, and myocardial infarction and improves long term survival in appropriately selected high risk people compared with conservative management (employing medical treatments and reserving invasive procedures only for people with signs of ongoing ischaemia despite medical management) for non-ST elevation acute coronary syndrome.[2-6] Accordingly, current guidelines recommend early invasive management for high risk people with non-ST elevation acute coronary syndrome,[7] although observational studies suggest that not all eligible people receive these interventions.[1 8 9]

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Supplementary tables 1-5

Acute kidney injury complicates 6-13% of invasive coronary procedures[10 11] and is associated with adverse outcomes, including prolonged hospital stay, recurrent cardiovascular events, end stage renal disease, and mortality.[12-14] Fear of precipitating acute kidney injury as a result of radiocontrast nephropathy possibly contributes to underuse of invasive treatment in people at high risk of acute kidney injury (particularly those with pre-existing chronic kidney disease),[1 8 9] despite the higher risk of adverse cardiovascular outcomes and death, as well as the potential for greater absolute benefit in this population.[15] Although several studies have identified the risks of acute kidney injury in people receiving invasive coronary procedures,[12 13 16 17] acute kidney injury can also develop in people with an acute coronary syndrome who do not receive invasive coronary procedures. However, little is known about the comparative risks of acute kidney injury in people with acute coronary syndromes who are treated with an invasive versus conservative approach. Furthermore, since studies suggest that people with acute kidney injury are at a higher risk of chronic kidney disease progression,[18 19] the risks of end stage renal disease associated with an invasive management approach (compared with conservative management), among people with and without pre-existing chronic kidney disease, deserve further investigation.

Given these knowledge gaps in evidence from clinical trials and the importance of this information to help inform clinical decision making, we did a cohort study of people receiving early invasive versus conservative management of acute coronary syndrome. We compared the risks of acute kidney injury, kidney injury requiring dialysis, end stage renal disease, and survival between early invasive and conservative management strategies. We also determined whether associations between treatment strategies and these outcomes varied by baseline levels of kidney function.

Methods

We did a cohort study linking data from a comprehensive clinical registry of people admitted to hospital for acute coronary syndrome with provincial administrative healthcare and laboratory data in Alberta, Canada. The study cohort was derived from the Heart Alert Registry of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH).[20] Heart Alert prospectively collects data on personal characteristics; clinical characteristics, including physiological variables at admission; management strategies; processes of care; and outcomes for all people admitted with a primary diagnosis of acute coronary syndrome to any of six acute care hospitals in southern Alberta, Canada. Cardiac catheterisation was performed at one of these hospitals (the referral center for these six hospitals) during the study period.

The study cohort consisted of all Alberta residents aged 18 or more years and admitted to a Heart Alert registry hospital with non-ST segment acute coronary syndrome between 1 January 2004 and 31 October 2009. We included people with an admitting diagnosis of unstable angina or non-ST elevation myocardial infarction and excluded those with ST elevation myocardial infarction, as regional practices at the time of this study included emergent primary angioplasty as the principal treatment approach. Eligible participants required at least one inpatient serum creatinine measurement within the first two days of hospital admission to establish kidney function. We excluded patients receiving chronic dialysis before admission.[21]

Measurement of exposure

For the primary analysis we excluded patients who died within the first two days of hospital admission, then defined participants as receiving early invasive management if they received coronary angiography (with or without percutaneous coronary intervention) within two days of hospital admission; we classified all other participants as receiving conservative management.

We also conducted secondary analyses after excluding patients who died during the index hospital admission and used an alternative definition of early invasive management in which we compared patients who received invasive management at any time during their hospital admission with those who only received medical treatment during the hospital stay. In further sensitivity analyses we compared patients who received revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) with those who only received medical treatment during their hospital stay.

Measurement of covariates

From the Heart Alert registry of the APPROACH database we determined information at admission on personal characteristics, comorbidities, vital signs, electrocardiography, cardiac enzymes, and TIMI (thrombolysis in myocardial infarction) risk score.[22] We enhanced missing data on medical comorbidities by linking to provincial healthcare administrative records as previously described.[20 23 24] Cardiac enzymes were considered increased if the concentration of troponin T or I or creatine kinase (CK-MB) on the day of admission was above the reference range. We obtained information on subsequent use and timing of coronary angiography, percutaneous coronary intervention, coronary artery bypass grafting, drugs, complications, and length of stay during the index hospital admission from the Heart Alert registry of the APPROACH database, and obtained data on all serum creatinine measurements, albuminuria, and haemoglobin concentration from the Alberta Kidney Disease Network repository of laboratory data.[25 26] We determined the estimated glomerular filtration rate at admission using the first serum creatinine measurement obtained in hospital and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[27]

Measurement of outcomes

Short term outcomes during the index hospital admission were acute kidney injury, acute kidney injury treated with dialysis, new myocardial infarction or reinfarction, congestive heart failure, stroke, blood transfusion, and all cause mortality. Acute kidney injury was defined according to the Acute Kidney Injury (AKI) Network criteria based on a more than 50% or 0.3 mg/dL (26 μmol/L) increase in serum creatinine concentration during hospital stay using the value obtained at the time of admission as the baseline measurement.[28] Acute kidney injury requiring dialysis was identified using a validated administrative data coding approach.[29] Long term outcomes were progression to end stage renal disease (defined as chronic dialysis or kidney transplantation within one of the Alberta renal programmes[21]) and all cause mortality (determined by linkage to provincial vital statistics records) with follow-up until 31 December 2009.

Statistical analyses

We used a propensity score approach to account for baseline differences at admission between treatment groups. To estimate the odds of receiving early invasive management we developed a non-parsimonious multivariable logistic regression model.

Covariates included in the model were age, sex, coronary risk factors (diabetes mellitus, hypertension, hyperlipidaemia, cigarette smoking, family history of coronary artery disease), additional comorbidities (previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, heart failure, peripheral vascular disease, cerebrovascular disease), Charlson comorbidity score, estimated glomerular filtration rate at admission, albuminuria, anaemia, electrocardiographic evidence of ischaemia (dynamic ST changes or T wave inversion), thrombolysis in myocardial infarction score, increased cardiac enzyme levels (CK-MB, troponin T or I above reference range), hypotension, tachycardia, and presenting hospital.

For the initial matched cohort we matched people who received early invasive management to those who received conservative management on the basis of their propensity scores, while simultaneously forcing an exact match within strata of estimated glomerular filtration rate (categorised as ≥60, 30-59, and <30 mL/min/1.73 m^2).[30] We used one-to-one matching without replacement, with a caliper width of 0.2 of the standard deviation of the logit of the propensity score. We compared the balance in covariates before and after matching using standardised differences.[31] Using statistical methods for paired data we compared continuous and categorical variables in the matched pairs. We compared the relative risks of processes of care and short term outcomes in participants who received early invasive versus conservative management using generalised estimating equations. To account for correlation between matched pairs we used stratified Cox proportional hazards models to compared long term outcomes, including end stage renal disease and survival. To determine if findings were consistent across different severities of chronic kidney disease, we also performed analyses stratified on the basis of the estimated glomerular filtration rate at admission. To carry out these stratified analyses, we performed the propensity score matching process while simultaneously forcing an exact match within strata of estimated glomerular filtration rate, and we compared outcomes within estimated glomerular filtration rate stratum specific matched pairs. We included interaction terms between estimated glomerular filtration rate and treatment strategy in regression models to test for modification of the treatment effect by baseline estimated glomerular filtration rate.

For analyses using the alternative definition of invasive management based on coronary angiography (with or without percutaneous coronary intervention) performed at any time during hospital admission, we created separate propensity score matched cohorts using a similar approach as described but instead defined treatment based on an invasive coronary procedure performed at any time during the index hospital stay. In sensitivity analyses we also compared outcomes in a separate propensity score matched cohort in which we compared patients who received coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) at any time during the index hospital stay with those who received only medical management. We followed the same approaches to those described previously to compare outcomes between these propensity score matched pairs. All statistical analyses were conducted using STATA (version 11.0).

Results

A total of 10 697 Alberta residents aged 18 or more years with an admission diagnosis of non-ST segment elevation acute coronary syndrome were eligible for inclusion. After excluding people receiving dialysis at admission, those without a measure of kidney function during hospital stay, and those who died within the first two days of admission (fig 1⇓), the final study cohort included 10 516 participants, of whom 4276 (40.7%) received early invasive management (coronary angiography) within two days of hospital admission. At admission the characteristics of participants who received early invasive management differed from those who received a conservative approach (table 1⇓). Participants who received early invasive management were more likely to be men and to present to a hospital with cardiac catheterisation facilities. Those with older age, greater comorbidity, albuminuria, anaemia, and lower estimated glomerular filtration rate were less likely to receive early invasive management (table 1). Participants with lower estimated glomerular filtration rates were less likely to receive early invasive than conservative management, even though the thrombolysis in myocardial infarction risk scores were higher at lower estimated glomerular filtration rates, with a mean of 2.5 (SD 1.3), 3.0 (1.3), and 3.5 (1.5) for those with an estimated glomerular filtration rate of ≥60, 30-59, and <30 mL/min/1.73 m^2, respectively (see supplementary tables 1 and 2).

Comparisons with early invasive versus conservative treatment in propensity matched pairs

From the final cohort, 3384 (79.1%) participants who received an early invasive strategy were matched on their propensity score to 3384 (54.2%) patients who received conservative management (fig 1). The balance of characteristics at admission between the two groups was improved after matching on the propensity score (table 1). The mean standardised difference in covariates between the two groups decreased from 15.2% (range 0.3-48.1%) before matching to 1.7% (range 0-8.2%) after matching.

Table 2⇓ shows the processes of care during the index hospital admission for the two treatment groups. Among the matched patients those who received early invasive management were more likely to receive coronary angiography (100% *v* 57.4%), percutaneous coronary intervention (56.3% *v* 30.0%, risk ratio 1.88, 95% confidence interval 1.78 to 1.99), and coronary artery bypass grafting (12.6% *v* 5.3%, 2.38, 2.01 to 2.81) during the index hospital admission. The median number of days from admission to coronary angiography was 1 (interquartile range 0-2) in the early invasive group and 5 (4-7) among those in the conservative management group who subsequently received invasive management later in the admission. Participants who received early invasive management were more likely to receive antiplatelet agents, β blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and statins or lipid lowering drugs, but less likely to receive diuretics (table 2). The median number of serum creatinine measurements during the hospital stay was similar between the groups; however, participants who received early invasive management had a longer hospital stay than those managed conservatively (table 2).

The risk of acute kidney injury was higher among matched participants who received early invasive management (10.3% *v* 8.7%, risk ratio 1.18, 95% confidence interval 1.03 to 1.36; P=0.019) (table 3⇓), corresponding to one additional episode of acute kidney injury for every 62 participants treated with an early invasive approach instead of a conservative approach. However, the risk of acute kidney injury requiring dialysis did not differ significantly between the two treatment groups, nor did the risk of reinfarction, congestive heart failure, stroke, blood transfusion, or death during the index admission (table 3). During long term follow-up (median 2.5 years) there was

no significant difference in risk of end stage renal disease (0.3 *v* 0.4 events per 100 person years, risk ratio 0.91, 95% confidence interval 0.55 to 1.49; P=0.712). However, the long term adjusted risk of death was lower in matched participants who received early invasive management (2.4 *v* 3.4 events per 100 person years, 0.69, 0.58 to 0.82; P<0.001).

Figure 2⇓ shows the risks of acute kidney injury, progression to end stage renal disease, and long term mortality, stratified by baseline estimated glomerular filtration rate. The absolute risks of these outcomes were higher in participants with a lower estimated glomerular filtration rate; however, the relative risks of these outcomes associated with early invasive versus conservative management did not differ according to baseline estimated glomerular filtration rate (P interaction >0.10 for all outcomes, fig 2).

Sensitivity analyses for invasive management and revascularisation versus medical management in propensity matched pairs

Results from analyses using an alternative definition of invasive management (comparing invasive management at any time during the index hospital admission versus medical management alone) were similar to the primary analysis. The admission characteristics of the 4292 participants included in this analysis were well balanced between the two treatment groups after matching on the propensity score (table 4⇓). Among the matched patients who received invasive management, 49.3% (n=1058) received percutaneous coronary intervention and 11.2% (n=241) received coronary artery bypass grafting (table 5⇓). Participants who received invasive management during the index admission were also more likely to receive antiplatelet agents, β blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and statins or lipid lowering drugs but less likely to receive diuretics. Participants who received invasive management had a longer hospital stay than those managed medically and had a small but statistically significant greater number of serum creatinine measurements during the index hospital admission.

The associations between invasive management at any time during the index admission to hospital and outcomes were similar to those of the primary analysis (table 6⇓). Compared with participants who received medical therapy alone, matched participants who received invasive management had a higher risk of acute kidney injury (18.4% *v* 14.0%, risk ratio 1.31, 95% confidence interval 1.16 to 1.48; P<0.001), corresponding to one additional episode of acute kidney injury for every 23 participants who received invasive management. There were no significant differences between treatment groups in the risk of acute kidney injury requiring dialysis, other complications during admission to hospital, or long term risk of progression to end stage renal disease, whereas those who received an invasive procedure at any time during hospital stay were at lower risk of long term mortality (5.7 *v* 3.5 events per 100 person years, hazard ratio 0.62, 95% confidence interval 0.52 to 0.74; P<0.001). The relative risks of these outcomes were again consistent across all levels of admission estimated glomerular filtration rate when invasive management at any time during the index hospital admission was compared with medical management alone (fig 3⇓).

Results from additional sensitivity analyses comparing those who received coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) at any time during the index hospital admission versus medical management alone again showed a higher risk of acute kidney injury in those who received revascularisation, no difference in the risk of end stage renal disease, and a lower risk of long term mortality in those who received revascularisation (see supplementary tables 3-5).

Discussion

In this cohort study, compared with people managed conservatively, people with otherwise similar characteristics who received early invasive management for non-ST segment elevation acute coronary syndrome were modestly more likely to develop acute kidney injury during admission to hospital. Despite this finding, early invasive management was not associated with a significant increase in short term risk of acute kidney injury requiring dialysis, or long term risk of end stage renal disease, but was associated with better long term survival. Similar findings were observed when people who received invasive procedures at any time during admission to hospital were compared with those managed medically, and when those who received coronary revascularisation were compared with those who received medical management alone. Although patients with lower estimated glomerular filtration rate at admission were less likely to receive invasive management and were at higher risk of adverse outcomes, the associations between invasive management and clinical outcomes remained consistent across varying levels of baseline estimated glomerular filtration rate. These finds suggest that the additional short term risks of acute kidney injury associated with invasive coronary procedures are fairly small and, when considered alongside other clinical outcomes, should not act as a deterrent to their use.

Data on the risk of adverse renal events from randomised trials of early invasive versus conservative treatment for acute coronary syndrome are limited, in part due to the exclusion of patients with moderate to severe renal insufficiency from trials. Among people with baseline serum creatinine concentrations <1.7 mg/dL (150 µmol/L) enrolled in the Fast Revascularization during InStability in Coronay artery disease (FRISC) trial, estimated glomerular filtration rate declined similarly in the early invasive and conservative management arms; however, the incidence of acute kidney injury, acute dialysis, and end stage renal disease was not reported.[32] Several previous observational studies have shown a high incidence of acute kidney injury after coronary angiography and percutaneous coronary intervention in people with chronic kidney disease,[10 11] and strong associations between acute kidney injury and death, major adverse cardiovascular events, and kidney failure requiring dialysis in this setting.[12-14 16] Although other studies have examined the links between acute kidney injury and mortality and end stage renal disease in people admitted to hospital with myocardial infarction treated with either invasive or medical management,[18 33] these studies have not compared renal outcomes on the basis of treatment strategies.

Our findings show that acute kidney injury is a relatively common complication in people with non-ST elevation acute coronary syndrome and chronic kidney disease and increases substantially with lower baseline estimated glomerular filtration rate. However, the difference in the incidence of acute kidney injury between people who receive early invasive management and similar patients treated conservatively is relatively small. Importantly, despite the modestly higher risk of acute kidney injury associated with early invasive management at all levels of estimated glomerular filtration rate, our findings suggest that this strategy is not associated with higher risks of more clinically relevant renal outcomes (including acute dialysis or progression

to end stage renal disease), which occurred much less often at all levels of baseline estimated glomerular filtration rate, regardless of treatment strategy. Since early invasive management seemed to be consistently associated with a long term survival advantage at all levels of baseline estimated glomerular filtration rate, these findings (interpreted in light of their consistency with results from randomised trials showing that early invasive management improves long term survival in high risk patients[3 4]) suggest that restricting or delaying access to invasive coronary procedures may not avoid most cases of clinically relevant acute kidney injury and could deny high risk individuals (including those with pre-existing chronic kidney disease) important benefits.

There are several potential mechanisms for the higher risk of acute kidney injury associated with early invasive management. People who received early invasive management were more likely to receive coronary angiography, percutaneous coronary intervention, coronary artery bypass grafting surgery, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers, placing them at risk of acute kidney injury from contrast exposure, perioperative ischaemia, and haemodynamic effects. Furthermore, patients who received invasive management had a longer hospital stay and more measurements of creatinine during follow-up, which may have increased the probability that acute kidney injury would be ascertained. However, the magnitude of the increased risk associated with invasive management strategies was small, suggesting that patients' characteristics such as age, comorbidity, pre-existing chronic kidney disease, drug use (including diuretics and inhibitors of the renin angiotensin system), and haemodynamic instability are more important contributors to the risk of acute kidney injury in patients with acute coronary syndrome than whether or not they are managed invasively or medically.

The better survival associated with early invasive management of non-ST elevation acute coronary syndrome in this cohort are in keeping with the clinical benefits of angiography and revascularisation reported in clinical trials, including subgroups with pre-existing chronic kidney disease.[2-4] Although episodes of acute kidney injury have been linked to an increased risk of end stage renal disease,[18 19 34] we did not observe a higher risk of end stage renal disease in people with otherwise similar characteristics who received early angiography despite the higher risk of acute kidney injury, even among strata with lower baseline estimated glomerular filtration rate. Radiocontrast associated acute kidney injury is typically manifested by a small change in serum creatinine levels, rarely leads to acute dialysis, and is usually reversible.[10] Our findings suggest that the majority of such additional episodes of acute kidney injury associated with invasive procedures may confer relatively low risks of progression to end stage renal disease, although further studies are needed to help predict those at risk of progressive chronic kidney disease after acute kidney injury.

Strengths and limitations of this study

Our study has several strengths. Firstly, unlike previous observational studies examining the risk of acute kidney injury and subsequent clinical outcomes in the setting of percutaneous coronary intervention, our study enrolled all people with acute coronary syndrome within a geographical region. We also included a control group treated with conservative management, allowing us to determine the additional risks of events related to management relative to the risks that may occur as a result of individual comorbidities or other predisposing factors. Secondly, we used prospectively collected data to minimise misclassification and adjusted for important prognostic variables, including laboratory data, to reduce the potential for confounding. Finally, we used a propensity score matching approach to minimise treatment by indication bias.

Our study also has some limitations. Firstly, our study was observational in design and thus, unlike a randomised trial, does not prove a causal relation between treatment strategy and outcomes. However, the renal outcomes we examined have not been studied in trials of early invasive versus conservative treatment for non-ST elevation acute coronary syndrome, despite multiple observational studies linking acute kidney injury to adverse outcomes after coronary angiography and percutaneous coronary intervention. Furthermore, although we used a propensity score analysis to limit the potential for bias, residual confounding remains possible owing to unmeasured variables such as frailty, which may influence both treatment selection and outcomes. However, the strength of the treatment effect of early invasive treatment that we observed was similar to that observed in randomised trials of early invasive treatment for high risk patients, suggesting that propensity score matching possibly mitigated much of the treatment-selection bias.

Secondly, our study was conducted in a single geographical region in Canada, thus the availability and utilisation of cardiac catheterisation and rates of revascularisation (percutaneous coronary intervention and coronary artery bypass grafting) after non-ST acute coronary syndrome may differ in other settings. However, similar findings have been reported elsewhere, including the observation that patients with chronic kidney disease are less likely to receive invasive management despite better survival associated with these procedures irrespective of baseline estimated glomerular filtration rate.[35] Thirdly, relatively few people in our study had admission estimated glomerular filtration rates <30 mL/min/1.73 m^2, nor did we have sufficient study size to further stratify outcomes based on albuminuria. The higher risk of acute kidney injury in these subgroups could have a larger implication on the absolute risk of acute dialysis and end stage renal disease, particularly in these high risk people.[8 36 37] Finally, few patients developed acute kidney injury requiring dialysis or end stage renal disease, limiting the power of our study to exclude small differences in the risk of these outcomes between treatment strategies. Therefore, despite our findings, further trials remain necessary to examine renal outcomes, quality of life, and survival with early invasive treatments in people with moderate to advanced chronic kidney disease.

Conclusion

In conclusion, early invasive management of non-ST elevation acute coronary syndrome is associated with a small increase in the risk of acute kidney injury compared with a conservative management approach but is not associated with higher risks of in-hospital acute kidney injury requiring dialysis or long term risk of end stage renal disease. Given the improvement in cardiovascular outcomes and long term survival observed with early invasive management, these results suggest that invasive treatments should not be withheld solely because of concern they might increase the risk of kidney injury.

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What is already known on this topic

Acute kidney injury after invasive coronary procedures is associated with adverse outcomes, including end stage renal disease and death

Fear of precipitating contrast induced acute kidney injury possibly contributes to underuse of invasive treatments for acute coronary syndrome in people at high risk of kidney disease

Comparisons of renal outcomes between people treated with invasive versus conservative management are lacking

What this study adds

People who received early invasive management for non-ST segment elevation acute coronary syndrome were modestly more likely to develop acute kidney injury

After early invasive management the risks of requiring dialysis and long term risk of end stage renal disease were similar, and patients had better long term survival than those treated conservatively

These findings were consistent across varying levels of baseline kidney function, suggesting similar relative risks and benefits of early invasive management in people with and without pre-existing kidney disease

submit the article for publication. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All researchers acted independently of funders.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) was initially funded with a grant from the W Garfield Weston Foundation; the ongoing operation of the APPROACH project has been made possible by support from Alberta Health Services (Calgary Zone, Edmonton Zone), Libin Cardiovascular Institute of Alberta and Mazankowski Alberta Heart Institute; the APPROACH initiative has also received contributions from Alberta Health and Wellness, and the following industry sponsors—Merck Frosst Canada, Eli Lily Canada, Roche Canada, Bristol-Myers Squibb, and Philips Medical Systems Canada to support the basic infrastructure of this cardiac registry initiative; MTJ was supported by a KRESCENT fellowship (funded by the Canadian Institutes for Health Research, Kidney Foundation of Canada, and Canadian Society of Nephrology) and an Alberta Innovates-Health Solutions award; MT and BJM were supported by Health Scholar and BRH by a population health investigator award from Alberta Innovates-Health Solutions; WAG was supported by a senior health scholar award from Alberta Innovates-Health Solutions; MLK received part support from the Libin Trust Fund and has received honorariums for presentations from the Canadian Cardiovascular Society and Medtronic; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the Conjoint Health Research Ethics Board of the University of Calgary.

Data sharing: No additional data available.

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Tables

Table 1| Admission characteristics of patients admitted to hospital for non-ST elevation acute coronary syndrome by treatment strategy in entire cohort and after propensity score matching*. Values are numbers (percentages) unless stated otherwise

	Entire cohort			After propensity score matching		
Characteristics	Early invasive (n=4276)	Conservative (n=6240)	Standardised difference (%)	Early invasive (n=3384)	Conservative (n=3384)	Standardised difference (%)
Mean (SD) age (years)	62.6 (11.8)	68.7 (13.0)	–48.1	63.4 (12.0)	64.2 (12.0)	–6.7
Men	3160 (73.9)	4018 (64.4)	20.7	2433 (71.9)	2372 (70.1)	3.8
Risk factors:						
Diabetes mellitus	924 (21.6)	1741 (27.9)	–14.6	761 (22.5)	785 (23.2)	–1.6
Hypertension	2685 (62.8)	4162 (66.7)	–8.3	2135 (63.1)	2156 (63.7)	–1.4
Hyperlipidaemia	3224 (75.4)	4356 (69.8)	12.6	2501 (73.9)	251 (74.1)	–0.3
Cigarette smoker	1107 (25.9)	1142 (18.3)	18.3	826 (24.4)	772 (22.8)	3.9
Family history coronary artery disease	1753 (41.0)	1866 (29.9)	23.4	1320 (39.0)	1255 (37.1)	4.0
Comorbidities						
Previous myocardial infarction	894 (20.9)	1735 (27.8)	–15.9	734 (21.7)	748 (22.1)	–1.0
Previous percutaneous coronary intervention	894 (20.9)	1248 (20.0)	2.3	690 (20.4)	653 (19.3)	2.6
Previous coronary artery bypass grafting	252 (5.9)	786 (12.6)	–23.1	220 (6.5)	254 (7.5)	–3.6
Heart failure	145 (3.4)	674 (10.8)	–29.3	129 (3.8)	135 (4.0)	–0.8
Peripheral vascular disease	137 (3.2)	381 (6.1)	–14.0	115 (3.4)	132 (3.9)	–2.5
Cerebrovascular disease	261 (6.1)	562 (9.0)	–10.6	213 (6.3)	230 (6.8)	–1.7
Mean (SD) Charlson comorbidity score(range 0-35)	1.6 (1.9)	2.4 (2.4)	–37.8	1.7 (1.9)	1.7 (2.4)	–1.7
Admission characteristics:						
Mean (SD) eGFR (mL/min/1.73 m^2)	66.9 (20.4)	61.3 (23.6)	25.2	66.4 (20.8)	67.0 (21.5)	–2.6
eGFR ≥60	2518 (58.9)	3089 (49.5)	18.8	1949 (57.6)	1949 (57.6)	0
eGFR 30-59	1676 (39.2)	2558 (41.0)	–3.7	1364 (40.3)	1364 (40.3)	0
eGFR <30	81 (1.9)	587 (9.4)	–33.0	74 (2.2)	74 (2.2)	0
Albuminuria†	842 (19.7)	1704 (27.3)	–17.8	694 (20.5)	724 (21.4)	–2.2
Anaemia‡	487 (11.4)	1429 (22.9)	–30.8	426 (12.6)	437 (12.9)	–0.9
Increased cardiac enzyme levels	1030 (24.1)	1186 (19.0)	12.5	761 (22.5)	670 (19.8)	6.5
Hypotension§	38 (0.9)	87 (1.4)	–4.7	30 (0.9)	27 (0.8)	1.4
Tachycardia¶	445 (10.4)	880 (14.1)	–11.3	376 (11.1)	376 (11.1)	–0.1
ST deviation	282 (6.6)	412 (6.6)	–0.3	213 (6.3)	203 (6.0)	1.1
T wave inversion	77 (1.8)	62 (1.0)	6.8	54 (1.6)	37 (1.1)	1.1
Mean (SD) TIMI score (range 0-7)	2.7 (1.3)	2.8 (1.4)	–6.2	2.7 (1.3)	2.7 (1.3)	0.6
Hospital characteristics:						
Catheterisation facility	1950 (45.6)	1872 (30.0)	32.6	1394 (41.2)	1262 (37.3)	8.2

eGFR=estimated glomerular filtration rate; TIMI=thrombolysis in myocardial infarction.

*Propensity score matched using 1-to-1 caliper matching without replacement (caliper width of 0.2 of log odds of propensity score).

†Semiquantitative urine dipstick measurement ≥+ or urine albumin:creatinine ratio >3 mg/dL within six months before admission.

‡Haemoglobin concentration <11.0 g/dL for men and <10.0 g/dL for women at time of admission.

§Presenting systolic blood pressure <90 mm Hg.

¶Presenting heart rate >100 beats per minute.

Table 2| Processes of care with early invasive versus conservative management among propensity score matched patients admitted to hospital for non-ST elevation acute coronary syndrome. Values are numbers (percentages) of participants unless stated otherwise

Processes of care	Early invasive (n=3384)	Conservative (n=3384)	Risk ratio 95% (CI)	P value
Percutaneous coronary intervention	1906 (56.3)	1012 (30.0)	1.88 (1.78 to 1.99)	<0.001
Coronary artery bypass grafting	428 (12.6)	180 (5.3)	2.38 (2.01 to 2.81)	<0.001
Aspirin	3131 (92.5)	3074 (90.8)	1.02 (1.00 to 1.03)	0.012
Ticlopidine or clopidogrel	2636 (77.9)	2289 (67.6)	1.15 (1.12 to 1.18)	<0.001
β blocker	2748 (81.2)	2637 (77.9)	1.04 (1.02 to 1.07)	<0.001
ACE inhibitor or angiotensin receptor blocker	2523 (74.5)	2371 (70.0)	1.06 (1.03 to 1.10)	<0.001
Statin or lipid lowering drug	2800 (82.7)	2556 (75.5)	1.10 (1.07 to 1.12)	<0.001
Diuretic	431 (12.7)	489 (14.4)	0.88 (0.78 to 0.99)	0.035
Median (intequartile range) creatinine measurements	3 (1-4)	3 (2-4)	—	0.339*
Median (interquartile range) No of days in hospital	6 (4-8)	4 (2-8)	—	<0.001*

ACE=angiotensin converting enzyme.

*Wilcoxon paired signed rank test.

Table 3| Outcomes with early invasive versus conservative management among propensity score matched patients admitted to hospital for non-ST elevation acute coronary syndrome. Values are numbers (percentages) of participants unless stated otherwise

Variables	Early invasive (n=3384)	Conservative (n=3384)	Risk ratio (95% CI)	P value
In-hospital outcomes:				
Acute kidney injury	349 (10.3)	295 (8.7)	1.18 (1.03 to 1.36)	0.019
Acute kidney injury requiring dialysis	12 (0.4)	10 (0.3)	1.20 (0.52 to .2.78)	0.670
Myocardial infarction or reinfarction	13 (0.4)	10 (0.3)	1.30 (0.57 to 2.96)	0.533
Congestive heart failure	45 (1.3)	56 (1.6)	0.80 (0.54 to 1.19)	0.275
Stroke	7 (0.2)	3 (0.1)	2.33 (0.60 to 9.02)	0.220
Blood transfusion	27 (0.8)	26 (0.8)	1.03 (0.61 to 1.76)	0.889
Mortality	51 (1.5)	73 (2.1)	0.77 (0.47 to 1.27)	0.311
Long term outcomes:				
End stage renal disease, No (events/100 person years)	28 (0.3)	31 (0.4)	0.91 (0.55 to 1.49)*	0.712
Mortality, No (events/100 person years)	196 (2.4)	286 (3.4)	0.69 (0.58 to 0.82)*	<0.001

*Hazard ratio (95% confidence interval).

Table 4| Admission characteristics of patients admitted to hospital for non-ST elevation acute coronary syndrome by treatment strategy in entire cohort and after propensity score matching*. Values are numbers (percentages) of participants unless stated otherwise

	Entire cohort			After propensity score matching		
Characteristics	Invasive† (n=7032)	Medical (n=3185)	Standardised difference (%)	Invasive (n=2146)	Medical (n=2146)	Standardised difference (%)
Personal:						
Mean (SD) age (years)	64.1 (11.8)	70.5 (13.8)	–50.8	67.5 (12.9)	68.6 (13.0)	–9.3
Men	5098 (72.5)	1838 (57.7)	31.4	1358 (63.3)	1290 (60.1)	6.8
Risk factors:						
Diabetes mellitus	1667 (23.7)	880 (27.9)	–9.6	569 (26.5)	573 (26.7)	–0.5
Hypertension	4536 (64.5)	2105 (66.1)	–3.5	1378 (64.6)	1408 (65.6)	–2.2
Hyperlipidaemia	5344 (76.0)	2038 (64.0)	26.4	1496 (69.7)	1438 (67.0)	5.9
Cigarette smoker	1716 (24.4)	462 (14.5)	25.2	395 (18.4)	343 (16.0)	6.2
Family history of coronary artery disease	2757 (39.2)	777 (24.4)	32.3	659 (30.7)	564 (26.3)	9.6
Comorbidities:						
Previous myocardial infarction	1589 (22.6)	959 (30.1)	–17.0	582 (27.1)	607 (28.3)	–2.8
Previous percutaneous coronary intervention	1435 (20.4)	666 (20.9)	–1.1	474 (22.1)	455 (21.2)	2.3
Previous coronary artery bypass grafting	548 (7.8)	462 (14.5)	–21.3	247 (11.5)	277 (12.9)	–4.5
Heart failure	345 (4.9)	411 (12.9)	–28.2	189 (8.8)	215 (10.0)	–4.3
Peripheral vascular disease	281 (4.0)	197 (6.2)	–9.6	122 (5.7)	118 (5.5)	0.8
Cerebrovascular disease	464 (6.6)	319 (10.0)	–12.4	182 (8.5)	206 (9.6)	–4.1
Mean (SD) Charlson comorbidity score (range 0-35)	1.8 (1.8)	2.8 (2.5)	–40.3	2.3 (2.3)	2.5 (2.5)	–9.1
Admission characteristics:						
Mean (SD) eGFR (mL/min/1.73 m^2)	65.6 (20.9)	60.5 (24.8)	21.9	63.0 (23.4)	63.3 (24.7)	–1.2
eGFR ≥60	3966 (56.4)	1557 (48.9)	15.0	1131 (52.7)	1131 (52.7)	0.0
eGFR 30-59	2855 (40.6)	1239 (38.9)	3.5	835 (38.9)	835 (38.9)	0.0
eGFR <30	211 (3.0)	385 (12.1)	–35.2	180 (8.4)	180 (8.4)	0.0
Albuminuria‡	1554 (22.1)	854 (26.8)	–10.9	532 (24.8)	545 (25.4)	–1.5
Anaemia§	928 (13.2)	879 (27.6)	–36.2	464 (21.6)	494 (23.0)	–3.4
Increased cardiac enzyme levels	1624 (23.1)	497 (15.6)	18.9	363 (16.9)	346 (16.1)	1.9
Hypotension¶	63 (0.9)	54 (1.7)	–6.9	30 (1.4)	34 (1.6)	–1.2
Tachycardia**	774 (11.0)	519 (16.3)	–15.6	281 (13.1)	339 (15.8)	–7.8
ST deviation	464 (6.6)	191 (6.0)	2.4	120 (5.6)	127 (5.9)	–1.0
T wave inversion	105 (1.5)	25 (0.8)	6.7	24 (1.1)	19 (0.9)	2.2
TIMI score (range 0-7)	2.9 (1.3)	2.7 (1.3)	3.8	2.7 (1.4)	2.7 (1.4)	2.8
Hospital characteristics:						
Catheterisation facility	2539 (36.1)	1229 (38.6)	–5.1	781 (36.4)	846 (39.4)	–6.1

eGFR=estimated glomerular filtration rate; TIMI=thrombolysis in myocardial infarction.

*Propensity score matched using 1-to-1 caliper matching without replacement (caliper width of 0.2 of log odds of propensity score).

†Occurring anytime during index hospital admission versus medical management only during index hospital admission.

‡Semiquantitative urine dipstick measurement ≥+ or urine albumin:creatinine ratio >3 mg/dL within six months before admission.

§Haemoglobin concentration <11.0 g/dL for men and <10.0 g/dL for women at time of admission.

¶Presenting systolic blood pressure <90 mm Hg.

**Presenting heart rate >100 beats per minute.

Table 5| **Processes of care with invasive management at any time during index hospital admission versus medical management alone among propensity score matched patients admitted to hospital for non-ST elevation acute coronary syndrome. Values are numbers (percentages) of participants unless stated otherwise**

Processes of care	Invasive (n=2146)	Medical (n=2146)	Risk ratio (95% CI)	P value
Percutaneous coronary intervention	1058 (49.3)	0 (0)	—	—
Coronary artery bypass grafting	241 (11.2)	0 (0)	—	—
Aspirin	1931 (90.0)	1842 (85.8)	1.04 (1.02 to 1.07)	<0.001
Ticlopidine or clopidogrel	1582 (73.7)	1096 (51.1)	1.44 (1.37 to 1.51)	<0.001
β blocker	1697 (79.1)	1486 (69.2)	1.14 (1.10 to 1.18)	<0.001
ACE inhibitor or angiotensin receptor blocker	1551 (72.3)	1348 (62.8)	1.15 (1.10 to 1.20)	<0.001
Statin or lipid lowering drug	1685 (78.5)	1424 (66.3)	1.18 (1.14 to 1.23)	<0.001
Diuretic	408 (19.0)	481 (22.4)	0.85 (0.76 to 0.95)	<0.001
Median (interquartile range) serum creatinine measurements	3 (2-6)	3 (1-4)	—	<0.001*
Median (interquartile range) No of days in hospital	7 (4-9)	5 (3-8)	—	<0.001*

ACE=angiotensin converting enzyme.

*Wilcoxon paired signed rank test.

Table 6| **Outcomes with invasive management at any time during index hospital admission versus medical management alone among propensity score matched patients admitted to hospital for non-ST elevation acute coronary syndrome. Values are numbers (percentages) of participants unless stated otherwise**

Variables	Invasive (n=2146)	Medical (n=2146)	Risk ratio (95% CI)	P value
In-hospital outcomes:				
Acute kidney injury	394 (18.4)	300 (14.0)	1.31 (1.16 to 1.48)	<0.001
Acute kidney injury requiring dialysis	14 (0.6)	9 (0.4)	1.56 (0.70 to 3.46)	0.279
Myocardial infarction or reinfarction	8 (0.4)	5 (0.2)	1.60 (0.52 to 4.89)	0.410
Congestive heart failure	57 (2.6)	67 (3.1)	0.85 (0.60 to 1.20)	0.354
Stroke	3 (0.1)	2 (0.09)	1.50 (0.25 to 8.98)	0.657
Blood transfusion	25 (1.2)	33 (1.5)	0.76 (0.45 to 1.27)	0.295
Long term outcomes:				
End stage renal disease, No (events/100 person years)	52 (1.0)	48 (1.0)	1.06 (0.75 to 1.50)*	0.721
Mortality, No (events/100 person years)	184 (5.7)	284 (3.5)	0.62 (0.52 to 0.74)*	<0.001

*Hazard ratio (95% confidence interval).

Figures

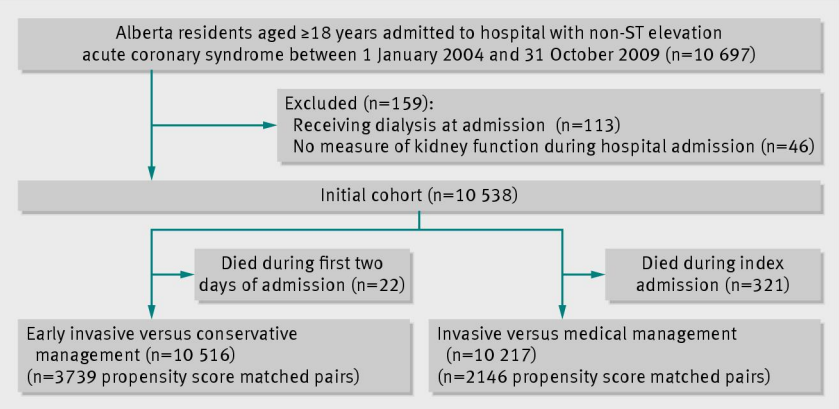

Fig 1 Formation of cohort

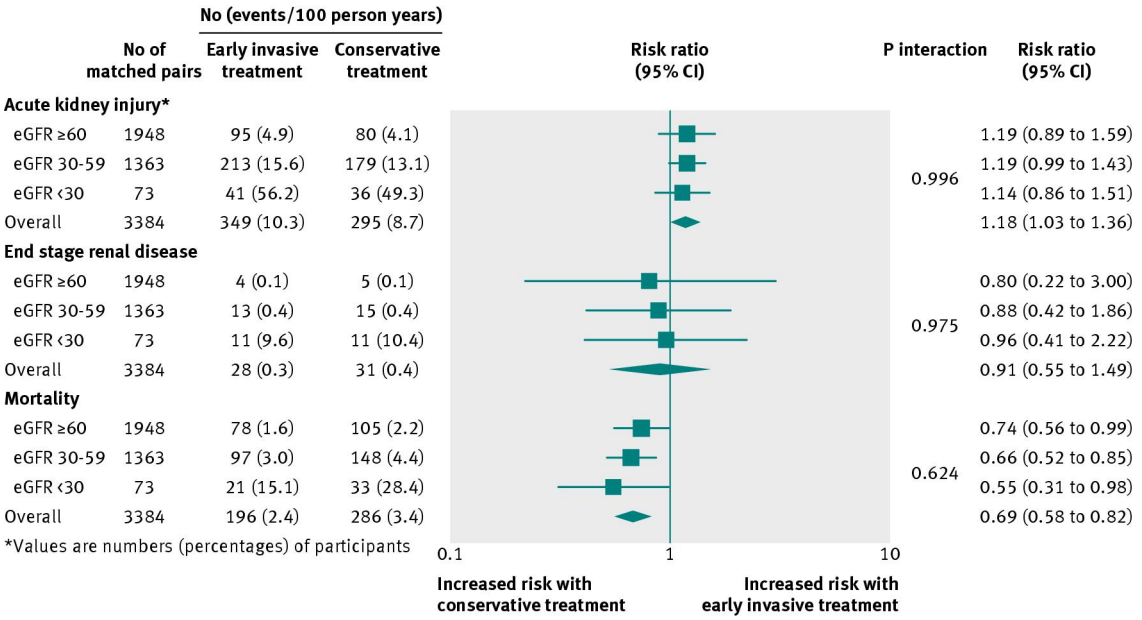

Fig 2 Outcomes with early invasive versus conservative management among propensity score matched patients admitted to hospital for non-ST elevation acute coronary syndrome, stratified by baseline estimated glomerular filtration rate (eGFR)

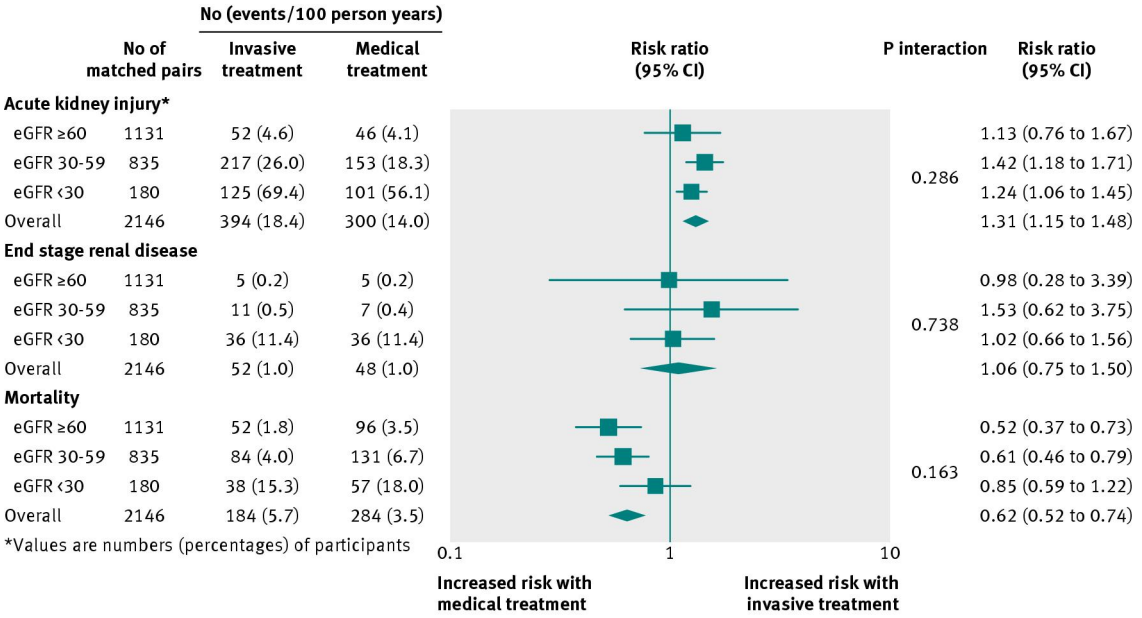

Fig 3 Outcomes with invasive management at any time during index hospital admission versus medical management alone among propensity score matched patients admitted to hospital for non-ST elevation acute coronary syndrome, stratified by admission estimated glomerular filtration rate (eGFR)