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Evidence-based care in a population with chronic kidney disease and acute coronary syndrome. Findings from the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events.

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ABSTRACT

Background:

Acute coronary syndrome (ACS) guidelines recommend that patients with chronic kidney disease (CKD) be offered the same therapies as other high risk ACS patients with normal renal function. Our objective was to describe the gaps in evidence-based care offered to patients with ACS and concomitant CKD.

Methods:

Patients presenting to 41 Australian hospitals with suspected ACS were stratified by presence of CKD (GFR <60mL/min). Receipt of evidence-based care including, coronary angiography (CA), evidence-based discharge medications (EBM), and cardiac rehabilitation referral (CR), were compared between patients with and without CKD. Hospital and clinical factors that predicted receipt of care were determined using multilevel multivariable stepwise logistic regression models.

Results:

Of the 4778 patients admitted with suspected ACS, 1227 had CKD. On univariate analyses, patients with CKD were less likely to undergo CA (59.1%vs85.0%, P<0.0001), receive EBM (69.4%vs78.7%, p<0.0001) or offered CR (49.5%vs68.0%, p<0.0001). After adjusting for patient characteristics and clustering by hospital, CKD remained an independent predictor of not undergoing CA only (OR=0.48, 95%CI:0.37-0.61). Within the CKD cohort, presenting to a hospital with a catheterisation laboratory was the strongest predictor of undergoing CA (OR=3.07, 95%CI:1.91-4.93).

Conclusion:

The presence of CKD independently predicts failure to undergo CA but not failure to receive EBM or CR which is predicted by comorbidities. Among the CKD population, performance of CA is largely determined by admission to a catheterisation capable hospital. Targeting these patients through standardisation of care across institutions offers opportunities to improve outcomes in this high risk population.

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INTRODUCTION

Patients with chronic kidney disease (CKD) have a significantly increased risk of cardiovascular disease compared to the general population [1]. Ischaemic heart disease is the most common cause of death in patients with CKD and patients presenting with acute coronary syndrome (ACS) commonly have CKD [2,3]. Furthermore, CKD confers poor prognosis in patients presenting with ACS; these patients have higher rates of re-infarction and mortality [3-7].

In recent decades, evidence-based strategies have been developed which improve outcomes in patients with ACS. Such therapies include coronary angiography with view to revascularisation, prognostically important medications commenced during the hospital stay and continued post discharge, and cardiac rehabilitation programs. These strategies result in a consistent relative reduction in cardiovascular events across all degrees of risk, including across all stages of CKD [8,9].

In spite of this, patients with CKD have been consistently found to be less likely to receive evidence-based care, contributing to the poor prognosis in these high risk patients [4,5,8,10-12]. The reasons for this are multiple, but are thought to include a risk adverse attitude of physicians, the perception of a higher risk-benefit ratio and the perceived paucity of evidence in this population [2,4].

In recognition of this, the most recent European Society of Cardiology Guidelines recommend that patients with non ST elevation ACS and CKD should be treated the same way as those patients who do not have renal dysfunction [13]. The recommendation is made acknowledging that this particular population is frequently under-represented in clinical trials.

The aims of the present analysis were to quantify the current under-utilisation of evidence-based ACS therapies in patients with CKD and to characterise both the clinical and hospital factors impacting on the management of these patients. Studies examining the provision of evidence based care at the hospital level have consistently shown significant variations that are, in part, independent of patient level characteristics [14-16]. We analysed a contemporary multicentre Australian database with patient and hospital level data to identify the predictors of under-provision of evidence-based care in this population.

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METHODS

Population and outcomes

The database used was derived from the Australian Co-operative National Registry of Acute Coronary Care, Guideline Adherence and Clinical Events (CONCORDANCE); the design and rationale of this ongoing longitudinal cohort study have been previously described [17]. In brief, CONCORDANCE is an ongoing prospective ACS registry involving 41 sites around Australia which has been enrolling patients since 2009. The hospitals involved are geographically diverse with representation from all states and territories in Australia. 28 (68%) hospitals are located in metropolitan regions and the remainder are in rural locations, 30 (73%) have onsite cardiac catheterisation laboratories.

CONCORDANCE provides continuous real time reporting on the clinical characteristics, management and outcomes of patients hospitalised with suspected ACS. The aims of the clinical initiative are to describe changes in practice patterns over time, document and inform the appropriate use of medications and to provide an understanding of the association between systems of care, delivery and health outcomes.

The first 10 patients older than 18 years of age admitted to each site per month with suspected ACS are recruited. Data regarding pre-hospital assessment and management, patient demographics, co-morbidities, in-hospital investigations and management as well as in-hospital morbidity and mortality are collected prospectively using a standardised electronic case report form. The management of each patient is at the discretion of the treating physicians.

This analysis focused on patients with CKD presenting with suspected ACS. The Glomerular Filtration Rate (GFR) was calculated for all patients using the Cockcroft Gault formula based on the weight and serum creatinine recorded the time of admission. The CKD-EPI formula was not used to determine renal function as not all serum creatinine measurements were calibrated and IDMS traceable. CKD was defined by a GFR <60mL/min [4-6,9,10]. Patients in whom the GFR could not be calculated were excluded from the analysis. Patients who were receiving dialysis were not excluded and constituted less than 1.5% of the total population.

The evidence-based therapies that were examined included coronary angiography during the index admission, (including inter-hospital transfers) (CA), prescription of non-contraindicated evidence

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based medications (EBM) and cardiac rehabilitation referral (CR). Patients were defined as having been discharged on EBM if they were discharged on at least 4 of the following medications: aspirin, $P2Y_{12}$ inhibitor, statin, beta-blocker and angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Information regarding contraindications to medications was collected in the registry and if contraindicated, that medication was coded as being received by that patient. Where contraindications were not documented, relative contraindications were sought from the medical record to minimise the likelihood of ascertainment bias. Peripheral vascular disease was regarded as a contraindication to beta blockers as was high grade heart block in the absence of a pacemaker or defibrillator.

All patients admitted with suspected ACS were included in the analysis of predictors of under-utilisation of CA. Those who died during the index admission or who had a non-ACS diagnosis were excluded from the analysis of predictors of under-treatment with EBM and CR referral on discharge.

Statistical analysis

Patients were dichotomised into two groups based on CKD status (with/without). Demographics, medical history, and in-hospital treatment variables including the receipt of CA, EBM and CR were compared using Chi-Squared test for categorical variables, while continuous variables were analysed using independent samples t-test. Ages were stratified into quartiles, <54, 55-65, 66-75 and >75. Multilevel multivariable stepwise logistic regression models were used to derive the odds ratios (ORs), the corresponding 95% confidence intervals (CIs) and the p-values of the factors associated with the receipt of CA, EBM, and CR across the study population. Candidate variables for the stepwise logistic regression models included variables which were statistically significant at an alpha level of 0.2 on univariate comparisons. CKD was retained in each final model. An additional model was developed predicting the receipt of CA in which patients with CKD were stratified according to Kidney Disease Outcomes Quality Initiative criteria. A final model was constructed limited to the CKD cohort to identify the clinical characteristics and hospital features associated with the receipt of CA. The variables assessed in the multilevel models are listed in Appendix A.

To account for within-hospital clustering, the regression models were built using a logistic generalised estimating equations (GEE) method with exchangeable working correlation matrix, because patients

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at the same hospital are more likely to be similar and have similar responses relative to patients at other hospitals

Data were analysed using Statistical Analysis System (SAS) 9.3 for Windows (SAS Institute Inc. Cary, NC, USA).

Ethics and funding

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and each investigative site has received approval from their ethics committee or institutional review board for participation in the registry. No extramural funding was used to support this work.

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RESULTS

Between May 2009 and March 2014, 5742 patients were admitted with suspected ACS to 41 CONCORDANCE hospitals. Of these 4778 patients had GFR determinable. Of the patients admitted with suspected ACS, 1227 (25.7%) had a GFR <60 mL/min and 250 (5.2%) patients had a GFR <30 mL/min on admission. 69 of these patients were receiving dialysis at the time of admission.

Comparison between CKD and non-CKD populations

Table I outlines the baseline characteristics of patients with CKD and those with preserved renal function admitted with suspected ACS. As expected, patients with CKD were a much higher risk population. They were significantly older, had higher rates of the traditional cardiovascular risk factors as well as a higher prevalence of prior myocardial infarction, heart failure, atrial fibrillation, stroke, significant bleeding and a much higher Global Registry of Acute Coronary Events (GRACE) risk score [18] than those patients without significant CKD. Patients with CKD also had higher rates of dementia and impaired mobility, indicating a more frail population.

Based on univariate analyses, patients with CKD were significantly less likely to be offered CA or to have revascularisation through percutaneous coronary intervention (PCI) than patients with preserved renal function (Table II).

4493 (94.0%) patients survived to hospital discharge with a diagnosis of ACS of whom 1080 (24.0%) had a GFR <60 mL/min and 199 (4.4%) patients had a GFR <30 mL/min at the time of admission. 62 of these patients were receiving dialysis at the time of admission. Table III demonstrates the rates of individual medication prescription on discharge in both patients with CKD and patients with preserved renal function. Patients with CKD were significantly less like to be prescribed a $P2Y_{12}$ inhibitor, specifically the newer agents Ticagrelor or Prasugrel, ACEi / ARB or a statin whereas they were more likely to be prescribed beta blockers than those with preserved renal function.

Amongst patients with CKD, the rates of discharge on EBM (69.4% vs 78.7%) and referral to CR (49.5% vs 68.0%) were significantly lower on univariate analysis than the cohort of patients with preserved renal function.

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Prediction of evidence-based care in patients with ACS

Among patients admitted with suspected ACS, CKD was independently predictive of failure to undergo CA (OR=0.48, 95%CI: 0.37-0.61; p<0.0001) (Figure 1a). In an additional model in which patients were categorised according to severity of CKD (Appendix B), the receipt of CA varied inversely with grade of CKD.

However, among patients with confirmed ACS surviving to discharge, CKD was not independently predictive of failure to receive EBM (OR=1.08, 95%CI: 0.89-1.31; p=0.433) or CR (OR=0.83, 95%CI: 0.68-1.01; p=0.062). Independent predictors of evidence-based therapies are shown in Figure 1a-c.

Prediction of CA in patients with CKD

Of the 1227 patients with CKD admitted with suspected ACS, the strongest independent predictor of coronary angiography was the presence of a catheterisation laboratory at the hospital of presentation (OR=3.07, 95%CI: 1.91-4.93; p<0.0001). A number of patient level factors independently predicted patients with CKD not being offered CA. These are shown in figure 2.

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DISCUSSION

An increasing prevalence of CKD in an aging population means that clinicians are frequently faced with the dilemma of managing ACS patients with impaired renal function. The recognition and treatment of patients with these co-existing issues is challenging due to variation in symptomatology, greater risk of adverse drug reactions and increased frequency of comorbidities, complications, and higher mortality [3]. These differences are exaggerated in patients on dialysis [7,12].

Recognising this, we evaluated both hospital level and patient level determinants of care in patients with CKD presenting with an ACS. We focused on selected, reproducible, widely reported measures of evidence-based care in this analysis [19,20]. The under-provision of this care to patients with CKD is well recognised and confirmed by our observations. We found that the rates of CA, EBM and CR were lower in the CKD cohort than those with preserved renal function.

Coronary angiography with view to revascularisation in patients with CKD and ACS results in reduced ischaemia related events and mortality [4,8,10,21] without an increased risk of dialysis or progression to end stage kidney disease [10]. In our cohort, patients presenting with suspected ACS and CKD were offered coronary angiography less frequently than patients with preserved renal function, an association that persisted after adjusting for coexisting comorbidities and hospital characteristics. The strength of this association was further confirmed by the demonstration of an inverse graded relationship between severity of CKD and likelihood of receiving CA. However, 60% of the CKD population did receive CA, suggesting that under some circumstances, practice did follow the evidence. In further exploring the drivers of this, the most striking observation is the independent powerful effect that lack of a catheterisation laboratory in the admission hospital has on the likelihood of CA in a patient with CKD. This reflects findings in the broader ACS population where underutilisation of guideline recommended investigations and therapies in non-tertiary hospitals has been consistently reported [14-16].

The delivery of evidence-based care in hospitals, to patients presenting with a common clinical condition such as ACS requires a systematic approach where the default position is application of therapy. Where coronary angiography is not available on site, strategies should be in place to afford these patients equitable access to invasive coronary procedures. Our results suggest deficiencies in protocols for transfer from non-CA capable to CA capable sites and highlight a requirement for

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improvement in referral patterns of physicians caring for patients with CKD and ACS in hospitals without catheterisation laboratory facilities.

Within the CKD population, additional predictors of failure to receive CA included a past history of heart failure, or heart failure during the admission, concurrent atrial fibrillation, impaired mobility and dementia. Our findings likely reflected physician perceptions of the patient's overall net benefit with treatment balanced against the risk of adverse outcomes associated with treatment. As comorbidities accrue, risk averse practice increases, paralleling observations in unselected ACS cohorts [22].

We found a lower rate of discharge on EBM in the CKD cohort than in patients with preserved renal function. On descriptive analysis, there was a lower rate of $P2Y_{12}$ antagonist prescription on discharge in patients with CKD than those with preserved renal function, driven by a lower prescription rate of the newer agents Ticagrelor and Prasugrel. This likely reflects a perceived increased bleeding risk among these patients and may be consistent with guideline recommendations [13], although not necessarily congruent with the more recent randomised trial data, showing potent medical therapies such as the newer platelet $P2Y_{12}$ antagonists are beneficial in patients with CKD [9]. Statins were similarly less commonly prescribed among patients with CKD; practice which conflicts with recently available randomised data demonstrating their benefit in this population [23]. CKD has been found to be an independent predictor of early discontinuation of evidence-based medications after ACS so under-prescription of these therapies at the time of discharge is of particular concern [24].

Approximately half of patients with CKD and 68.0% of patients with preserved renal function were referred to CR. Although often overlooked as an important secondary preventative tool after ACS, the beneficial effects of a CR program on life expectancy and quality of life are clearly supported by trials and meta-analyses [25,26]. Our findings reflect published observations that patients who are not referred, or who do not attend or complete CR programs tend to have higher baseline cardiovascular risk and poorer disease knowledge than those who do complete CR [27].

Following multivariable adjustment CKD was not an independent factor determining the likelihood of prescription of EBM and referral to CR in our ACS population. Clinical factors such as the presence of atrial fibrillation (for EBM), dementia or prior stroke (for CR), emerged as the most powerful predictors of failure to offer treatment, reflecting the importance that morbidities accompanying CKD have on treatment decisions in this population. In addition, patients with ACS who were managed

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with PCI were most likely to be discharged on EBM and be referred for CR, practices consistent with prior observations [13,28,29]. While patients undergoing coronary artery bypass grafting (CABG) were readily provided with access to rehabilitation, they were significantly less likely to receive EBM. This has been described before [29], and these patients continue to constitute a readily identifiable cohort for whom specific processes can be put in place to prevent this missed treatment opportunity.

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CONCLUSION

Despite a poor prognosis after a presentation with ACS, patients with CKD are disproportionately under treated with evidence-based therapies. The most striking treatment gap is in the provision of coronary angiography and this is most marked in patients presenting to hospitals without cardiac catheterisation facilities. Optimising delivery of care to these patients requires system-wide strategies to facilitate the provision of better overall access to angiography, together with clinician education to counter overly cautious risk averse behaviour of physicians when treating this population.

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AUTHOR CONTRIBUTIONS

Contribution	Author
Development of original concept	DB, JL
Refining the research question	All authors
Designing and refining study protocol	All authors
Analysis and interpretation of data	DB, JL, KH, BD
Review and critical appraisal of manuscript	All authors

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Table I: Baseline characteristics

Characteristic	CKD (n=1227)	No CKD (n=3551)	p-value
Mean age (yrs)	76.7	60.0	<0.0001
Male (%)	57.3	74.9	<0.0001
Hypertension (%)	76.9	57.2	<0.0001
Diabetes (%)	35.0	24.5	<0.0001
Dyslipidaemia (%)	63.2	54.6	<0.0001
Current smoking (%)	13.4	34.5	<0.0001
Family history of CAD (%)	20.9	39.3	<0.0001
Peripheral vascular disease (%)	14.1	4.4	<0.0001
Prior myocardial infarction (%)	40.9	26.4	<0.0001
Prior coronary angiogram (%)	46.3	32.1	<0.0001
Heart failure (%)	21.1	6.1	<0.0001
Atrial fibrillation (%)	21.9	7.6	<0.0001
Prior stroke (%)	15.4	4.9	<0.0001
Prior major bleeding (%)	4.9	1.8	<0.0001
Dementia (%)	7.5	1.6	<0.0001
Impaired mobility (%)	20.1	4.1	<0.0001
Mean GRACE Risk score	135.3	95.3	<0.0001

CAD- coronary artery disease, GRACE- Global Registry of Acute Coronary Events

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Table II: In hospital angiography and revascularisation

Therapy	**CKD (n=1227)**	**No CKD (n=3551)**	**p-value**
Coronary angiography (%)	59.1	85.0	<0.0001
Percutaneous coronary intervention (%)	26.1	48.0	<0.0001
Coronary artery bypass grafting (%)	7.3	9.1	0.060

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Table III: Medication prescription and cardiac rehabilitation referral on discharge

Discharge Medication	CKD (n=1080)	No CKD (n=3413)	p-value
Aspirin (%)	90.9	92.0	0.278
$P2Y_{12}$ inhibitor (%)	60.5	72.7	<0.0001
Clopidogrel (%)	53.4	54.6	0.505
Clopidogrel/Aspirin combination pill (%)	3.4	6.7	<0.0001
Prasugrel (%)	0.9	5.2	<0.0001
Ticagrelor (%)	3.6	8.5	<0.0001
Statin (%)	86.4	92.4	<0.0001
Beta blocker (%)	85.6	82.6	0.022
ACE inhibitor or ARB (%)	72.6	78.3	0.0001
4 or 5 Evidence-based medications (%)*	69.4	78.7	<0.0001
Cardiac rehabilitation referral (%)	49.5	68.0	<0.0001

*Aspirin, $P2Y_{12}$ inhibitor, statin, beta blocker and ACEi or ARB, ACE- angiotensin converting enzyme, ARB- angiotensin receptor blocker

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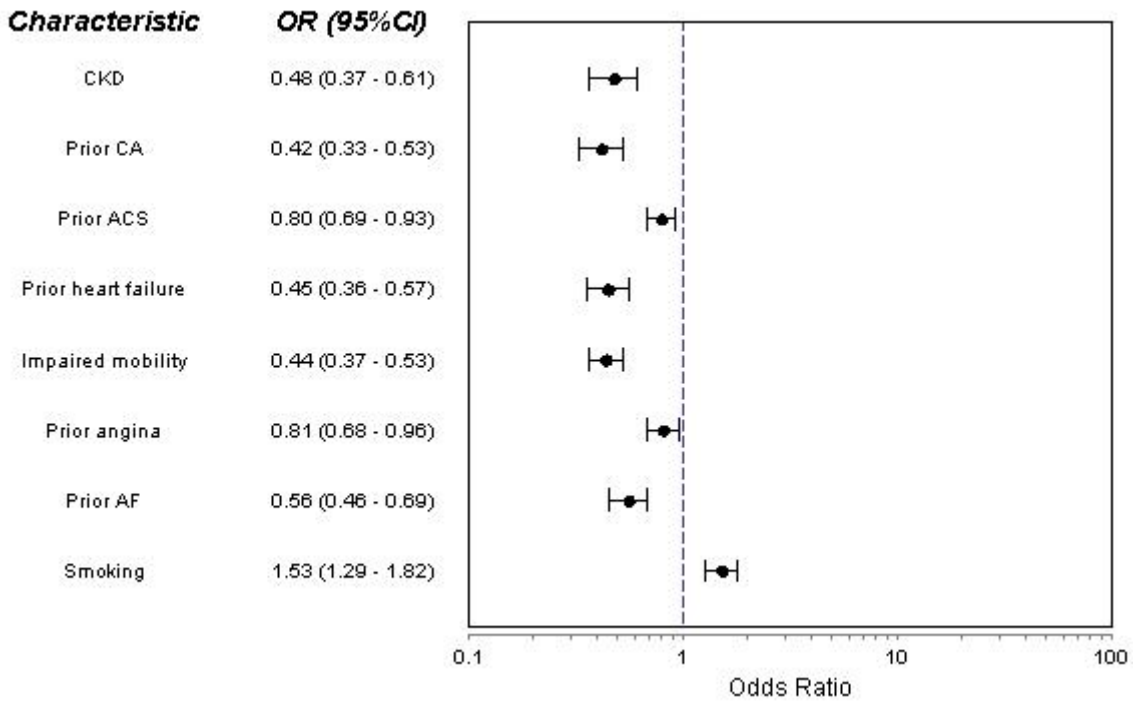

Figure 1a: Predictors of CA in all patients with suspected ACS

Age and sex adjusted multilevel multivariable stepwise logistic regression model. CKD was an independent predictor of patients not undergoing CA. Cardiac comorbidities and markers of frailty such as heart failure, atrial fibrillation and impaired mobility also predicted failure to undergo CA.

CA- coronary angiography, ACS- acute coronary syndrome, OR- odds ratio, CI- confidence interval, CKD- chronic kidney disease, AF- atrial fibrillation

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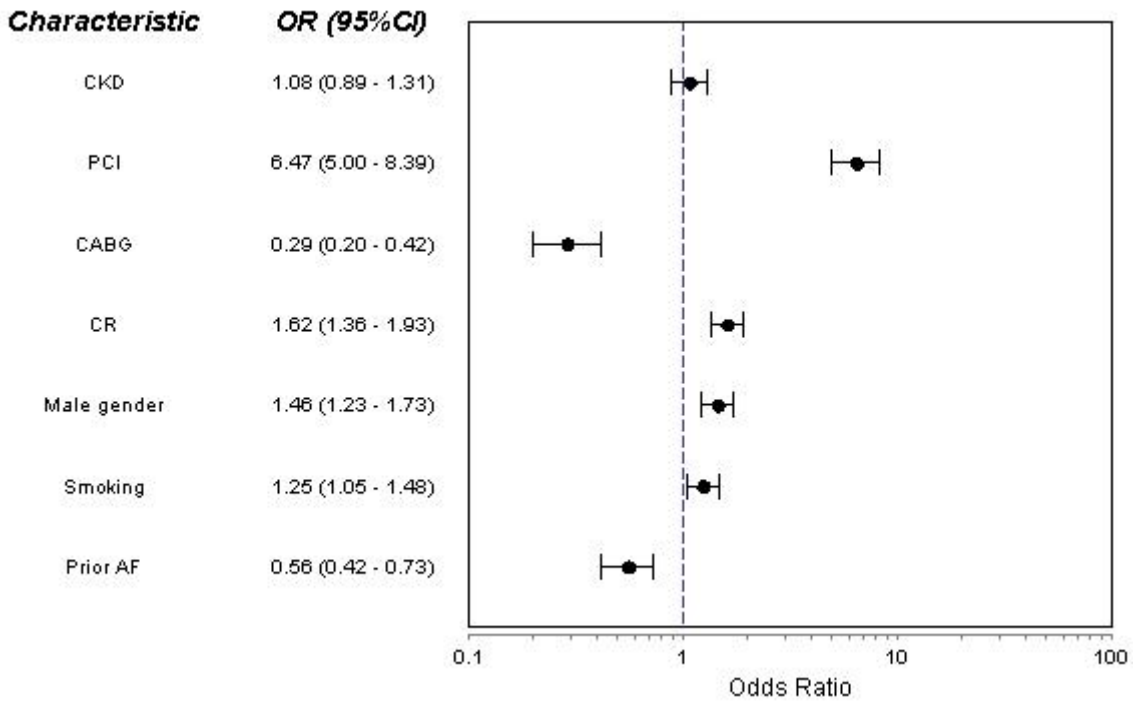

Figure 1b: Predictors of EBM in all ACS patients

Age and sex adjusted multilevel multivariable stepwise logistic regression model. CKD did not independently predict failure to be discharged on EBM, whereas mode of revascularisation had a significant impact on discharge with EBM. Patients undergoing PCI were significantly more likely to be discharged on EBM, whereas those undergoing CABG were significantly less likely to be discharged on EBM.

EBM- evidence based medications, ACS- acute coronary syndrome, OR- odds ratio, CI- confidence interval, CKD- chronic kidney disease, PCI- percutaneous coronary intervention, CABG- coronary artery bypass grafting, CR- cardiac rehabilitation, AF- atrial fibrillation

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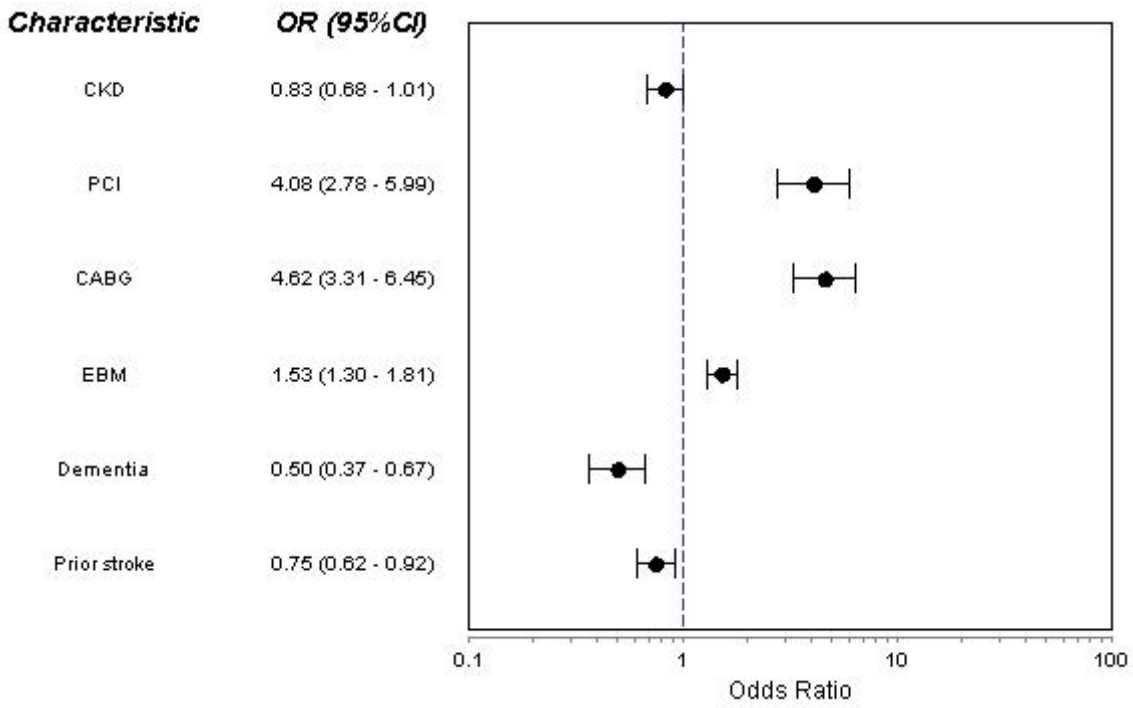

Figure 1c: Predictors of CR in all ACS patients

Age and sex adjusted multilevel multivariable stepwise logistic regression model. Failure to be referred to CR on discharge was not independently predicted by CKD. Patients who underwent revascularisation were significantly more likely to be referred for CR.

CR- cardiac rehabilitation, ACS- acute coronary syndrome, OR- odds ratio, CI- confidence interval, CKD- chronic kidney disease, PCI- percutaneous coronary intervention, CABG- coronary artery bypass grafting, EBM- evidence based medications

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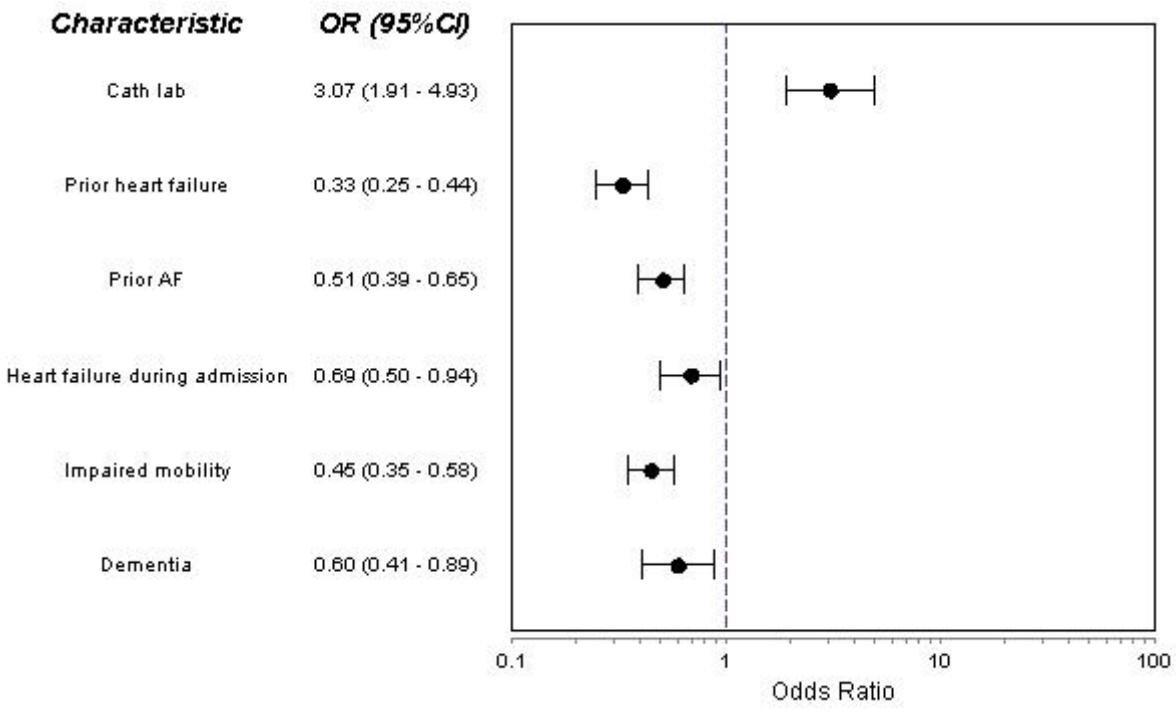

Figure 2: Predictors of CA in patients with CKD

Age and sex adjusted multilevel multivariable stepwise logistic regression model. Amongst patients with CKD, admission to a hospital with a catheterisation laboratory was an independent predictor of CA. Cardiac comorbidities and markers of frailty such as heart failure, atrial fibrillation and impaired mobility also predicted failure to undergo CA in the CKD population.

CA- coronary angiography, CKD- chronic kidney disease, OR- odds ratio, CI- confidence interval, AF- atrial fibrillation

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APPENDIX A- VARIABLES IN MULTILEVEL MODELS

CA multilevel models:

CKD (for the general ACS population model only), age, gender, indigenous status, insurance status, language, prior myocardial infarction (MI), angina, prior heart failure, prior CA, prior PCI, prior atrial fibrillation, prior deep vein thrombosis, prior bleeding, prior valve replacement, pacemaker, defibrillator, prior stroke, diabetes, hypertension, dyslipidaemia, smoking, family history of coronary artery disease, peripheral vascular disease, dementia, impaired mobility, incontinence, liver disease, lung disease, cancer, dialysis, heart failure during admission, cardiogenic shock during admission, recurrent ischaemia, recurrent myocardial infarction, atrial fibrillation during admission, sustained ventricular tachycardia during admission, atrioventricular block during admission, cardiac arrest during admission, stroke during admission, major bleeding during admission and cath lab in admission hospital.

EBM multilevel model:

CKD, age, gender, indigenous status, insurance status, language, prior myocardial infarction (MI), angina, prior heart failure, prior CA, prior PCI, prior atrial fibrillation, prior deep vein thrombosis, prior bleeding, prior valve replacement, pacemaker, defibrillator, prior stroke, diabetes, hypertension, dyslipidaemia, smoking, family history of coronary artery disease, peripheral vascular disease, dementia, impaired mobility, incontinence, liver disease, lung disease, cancer, dialysis, heart failure during admission, cardiogenic shock during admission, recurrent ischaemia, recurrent myocardial infarction, atrial fibrillation during admission, sustained ventricular tachycardia during admission, atrioventricular block during admission, cardiac arrest during admission, stroke during admission, major bleeding during admission, cath lab in admission hospital, PCI during admission, CABG during admission, CA during admission and CR on discharge.

CR multilevel model:

CKD, age, gender, indigenous status, insurance status, language, prior myocardial infarction (MI), angina, prior heart failure, prior CA, prior PCI, prior atrial fibrillation, prior deep vein thrombosis, prior bleeding, prior valve replacement, pacemaker, defibrillator, prior stroke, diabetes, hypertension,

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dyslipidaemia, smoking, family history of coronary artery disease, peripheral vascular disease, dementia, impaired mobility, incontinence, liver disease, lung disease, cancer, dialysis, heart failure during admission, cardiogenic shock during admission, recurrent ischaemia, recurrent myocardial infarction, atrial fibrillation during admission, sustained ventricular tachycardia during admission, atrioventricular block during admission, cardiac arrest during admission, stroke during admission, major bleeding during admission, cath lab in admission hospital, PCI during admission, CABG during admission, CA during admission and EBM on discharge.

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APPENDIX B

Predictors of CA in all patients with suspected ACS (patients with CKD stratified by GFR) (n=4778)*

Characteristic	OR	95% CI	p-value
GFR 30-60mL/min vs GFR ≥60mL/min	0.62	0.47 – 0.80	0.0004
GFR <30mL/min vs GFR ≥60mL/min	0.19	0.14 – 0.26	<0.0001
Prior coronary angiogram	0.42	0.32 – 0.54	<0.0001
Prior acute coronary syndrome	0.82	0.71 – 0.95	0.008
Prior heart failure	0.46	0.37 – 0.58	<0.0001
Impaired mobility	0.48	0.39 – 0.59	<0.0001
Prior angina	0.80	0.68 – 0.95	0.011
Prior atrial fibrillation	0.56	0.46 – 0.69	<0.0001
Smoking	1.51	1.26 – 1.82	<0.0001

* Age and sex adjusted multilevel multivariable stepwise logistic regression model

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