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Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction

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Aims To examine: (i) the temporal changes in the management pattern; (ii) the reasons for any treatment disparities; (iii) the relationship between invasive treatment and outcome, among acute coronary syndrome (ACS) patients with vs. without kidney dysfunction.

Methods and results Canadian ACS I, ACS II registries and Global Registry of Acute Coronary Events (GRACE) were prospective, multicentre, observational studies of patients with ACS. From 1999 to 2007, non-ST elevation (NSTE) ACS patients were recruited in ACS I ($n = 3295$; 1999–2001), ACS II ($n = 1956$; 2002–2003), and GRACE ($n = 6491$; 2004–2007) in Canada. Using the four-variable Modified Diet in Renal Disease equation, we stratified the study population ($n = 11\,377$) into three groups based on their estimated glomerular filtration rate (eGFR), and examined their treatment and outcome. While in-hospital use of coronary angiography and revascularization increased over time in all groups ($P < 0.001$), patients with kidney dysfunction were less likely to undergo invasive management ($P < 0.001$). Unadjusted 1 year mortality was lower among patients receiving in-hospital coronary angiography within all eGFR categories ($\geq$60 mL/min/1.73 m^2: 2.5 vs. 7.6%, $P < 0.001$; 30–59 mL/min/1.73 m^2: 8.0 vs. 14.6%, $P < 0.001$; $<$30 mL/min/1.73 m^2: 27.5 vs. 41.5%, $P = 0.043$). In-hospital revascularization was independently associated with lower 1-year mortality (adjusted OR = 0.52, 95% CI 0.36–0.77, $P = 0.001$), irrespective of eGFR (P for heterogeneity = 0.39). Underestimation of patient risk was the most common barrier to an invasive treatment strategy.

Conclusion Despite temporal increases in invasive management of NSTE-ACS, patients with kidney dysfunction are more commonly treated conservatively, with an associated worse outcome. In-hospital revascularization was independently associated with improved survival, irrespective of eGFR. Randomized controlled trials involving patients with kidney dysfunction are needed to confirm whether more aggressive treatment will improve their poor outcome.

Keywords Kidney dysfunction • Acute coronary syndrome • Treatment • Coronary angiography • Outcome

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Introduction

Kidney dysfunction is associated with a worse outcome after acute coronary syndromes (ACSs).[1–5] With diabetes and hypertension on the rise in an ageing population, the prevalence of chronic kidney disease (CKD) is expected to increase.[6] The expansion of this high-risk population necessitates the evolution of evidence-based therapies to optimize outcomes after ACS.

Clinical trial evidence has led to important changes in the management of non-ST elevation (NSTE) ACS over the past decade.[7] In particular, current guidelines emphasize the use of an early-invasive approach in moderate- to high-risk NSTE-ACS patients.[7–10] However, patients with CKD were vastly underrepresented in these pivotal randomized clinical trials.[11] Furthermore, previous observational studies based on data from the 1990s have documented the under-utilization of evidence-based therapies in ACS patients with kidney dysfunction despite their higher risk for adverse outcomes.[12–16] It is unclear whether such treatment disparities persist in the current era. If they do, it would be important to elucidate the reasons underlying these disparities.

To gain a better understanding of the contemporary 'real world' management of NSTE-ACS patients with kidney dysfunction, we examined the temporal trends in their treatment and outcomes across three registries in Canada [Canadian ACS I and ACS II registries, and Global Registry of Acute Coronary Events (GRACE)] spanning the years 1999 through 2007, in comparison with patients with preserved kidney function. Furthermore, we explored physicians' rationale for management decisions, which may account for the observed treatment disparities. Finally, we examined the independent association between invasive management and 1 year outcome.

Methods

Registry design and patients

The Canadian ACS I, ACS II registries and Canadian GRACE were prospective, multi-centre, observational studies of patients with ACS. The design of the ACS I, ACS II, and GRACE projects have been described previously.[17,18] Briefly, in ACS I and II registries, patients $\geq$18 years of age with suspected acute cardiac ischaemia of onset $<$24 h were eligible for inclusion. In GRACE, inclusion criteria were age $\geq$18 years and admission to hospital for suspected ACS with at least one of the following: abnormal cardiac biomarkers, ECG changes, and/or documented history of coronary artery disease. In all three registries, patients with ACS secondary to serious comorbidity, surgery, or trauma were excluded. These liberal eligibility criteria, as well as instructions to study centres to enrol consecutive patients when feasible, aimed to minimize selection bias. In ACS II, only patients with suspected NSTE-ACS were recruited. All data were recorded on standardized reporting forms by the local study coordinator or the most responsible physician. In-hospital management included all cardiac procedures performed during index admission, regardless of any subsequent inter-hospital transfers. Standardized definitions of outcomes and adverse events were used, and central data checks were executed with queries forwarded to participating centres for clarification. Local institutional review boards approved study protocols and all patients provided informed consent. The present study included only patients with NSTE-ACS. Thus, patients with $\geq$0.1 mV of ST-segment elevation in at least two contiguous leads, and those with a final diagnosis other than ACS were excluded from the analysis.

From 1999 to 2007, a total of 11 742 patients with NSTE-ACS were recruited from 51 centres in ACS I (n = 3295; 1999–2001), 36 centres in ACS II (n = 1956; 2002–2003), and 48 centres in Canadian GRACE (n = 6491; 2004–2007). On-site coronary angiography was available in 29.4, 33.3, and 38.3% of the participating hospitals in ACS I, ACS II, and GRACE, respectively. Cardiologists were the most responsible physicians in the majority of patients (60.8%) in the ACS I and ACS II registries. Patients with end-stage kidney disease requiring renal replacement therapy were not excluded from the registries. Glomerular filtration rate was estimated using the four-variable modified diet in renal disease (MDRD) formula.[19] Since ACS I and GRACE did not capture ethnicity data, and African-Canadians comprised a small proportion of the study population in ACS II, correction for race was not used when calculating estimated glomerular filtration rate (eGFR). Following the National Kidney Foundation guidelines, we stratified the study population into three groups: eGFR $\geq$60, 30–59, and $<$30 mL/min/1.73 m^2, corresponding to normal-to-mildly, moderately, and severely impaired renal function, respectively.[6] Chronic kidney disease was defined as eGFR $<$60 mL/min/1.73 m.[2,6] Data were unavailable for determining eGFR using the MDRD equation in 365 patients, who were excluded from the study. The final study population thus comprised of 11 377 patients.

In ACS I and II registries, patients were contacted by the designated study coordinator at the admitting hospital or centrally by the Canadian Heart Research Centre via telephone interview to ascertain their 1 year outcome. Follow-up data were not available for 390 patients (7.4%). In ACS II registry, the most responsible physician completed an additional page of the case report form, indicating the reason(s) for not referring the patient to cardiac catheterization if a conservative management approach was undertaken.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), whereas categorical variables are expressed as percentages. Trends were examined by Kendall τ-b test for continuous variables and Mantel–Haenszel χ^2 test (for trend) for categorical variables. To evaluate the independent prognostic significance of kidney dysfunction, we adjusted for other confounders[17,20] in a multivariable logistic regression model. The primary endpoint was all-cause mortality at 1 year (available for patients in the ACS I and ACS II registries). Confounders entered into the model included elements comprising the GRACE risk score.[17,21] To determine the relationship between treatment and 1 year outcome, we entered in-hospital revascularization as a predictor, and tested for its interaction with eGFR categories in the multivariable model. We used generalized estimating equations to control for the clustering of patients within hospitals. Model discrimination and calibration were assessed by the c-statistic and Hosmer–Lemeshow goodness-of-fit test, respectively. Because patients who died shortly after admission may not have had a chance to undergo cardiac catheterization, we also conducted a sensitivity analysis excluding all in-hospital deaths.

To confirm the robustness of our results, we performed a stratified (by quintiles) propensity score analysis.[22] We constructed a multivariable logistic regression model to predict in-hospital revascularization using patient, hospital, and physician characteristics as predictor variables. This non-parsimonious model included a total of 26 covariates and 2 interaction terms known from previous analyses to be associated with invasive management. The propensity score model demonstrated good discrimination (c-statistic = 0.79) and adequate fit with the data

Table 1 Patient demographics in ACS I, ACS II and GRACE stratified by estimated glomerular filtration rate

eGFR, *n* = 11 377 (mL/min/1.73 m^2)	ACS I (*n* = 3242)				ACS II (*n* = 1923)				GRACE (*n* = 6212)			
	≥60 (*n* = 2060)	30–59 (*n* = 1021)	<30 (*n* = 161)	*P* for trend	≥60 (*n* = 1234)	30–59 (*n* = 578)	<30 (*n* = 111)	*P* for trend	≥60 (*n* = 3672)	30–59 (*n* = 2173)	<30 (*n* = 367)	*P* for trend
Age[a]	63 (54–71)	74 (67–79)	75 (69–80)	<0.001	62 (53–71)	73 (65–80)	74 (68–82)	<0.001	62 (54–72)	75 (67–82)	77 (69–84)	<0.001
Male (%)	72.6	56.0	55.3	<0.001	74.7	53.8	51.4	<0.001	72.2	54.6	50.7	<0.001
Current smoker (%)	30.3	14.6	12.1	<0.001	26.5	14.0	16.2	<0.001	27.8	12.8	7.6	<0.001
Hypertension (%)	46.8	62.2	71.1	<0.001	51.4	70.8	84.7	<0.001	56.8	75.1	84.9	<0.001
Diabetes (%)	23.6	31.3	47.2	<0.001	23.1	30.8	54.1	<0.001	23.9	34.3	50.3	<0.001
Dyslipidaemia (%)	49.0	45.6	47.2	0.092	54.8	58.0	60.4	0.12	56.1	58.5	64.6	0.003
Prior angina (%)	56.6	70.6	78.6	<0.001	51.1	63.3	75.7	<0.001	45.3	53.5	56.0	<0.001
Prior MI (%)	32.0	46.8	56.6	<0.001	29.7	40.7	53.2	<0.001	29.1	42.9	56.3	<0.001
Prior CABG (%)	13.9	18.1	18.9	0.002	12.1	17.8	26.1	<0.001	11.5	18.1	21.0	<0.001
Prior PCI (%)	16.9	16.2	17.1	0.71	20.1	23.5	24.3	0.072	19.2	20.8	19.2	0.23
Prior heart failure (%)	6.8	20.2	44.3	<0.001	4.5	14.7	30.6	<0.001	5.2	16.2	35.5	<0.001
Prior stroke (%)	6.2	13.2	17.5	<0.001	6.7	13.0	22.5	<0.001	6.4	13.8	20.3	<0.001
SBP at presentation (mm Hg)[a]	148 (130–166)	148 (130–170)	146 (127–170)	0.52	147 (130–167)	148 (127–170)	152 (130–173)	0.41	146 (130–164)	144 (124–165)	136 (116–158)	<0.001
DBP at presentation (mm Hg)[a]	82 (72–94)	80 (69–92)	76 (68–90)	<0.001	82 (72–93)	79 (69–90)	76 (66–86)	<0.001	81 (71–92)	76 (65–88)	70 (59–83)	<0.001
HR at presentation[a]	71 (61–84)	74 (63–90)	79 (67–98)	<0.001	76 (65–89)	76 (65–90)	81 (70–94)	0.038	77 (66–90)	80 (67–96)	82 (70–97)	<0.001
Killip class I (%)	87.9	74.2	66.9	<0.001	89.6	78.1	57.6	<0.001	91.1	78.6	58.1	<0.001
Killip class II (%)	10.3	20.2	25.2		8.4	15.5	21.2		6.1	13.1	24.0	
Killip class III/IV (%)	1.8	5.6	7.9		2.0	6.4	21.2		2.8	8.4	17.9	
Cardiac arrest (%)	0.6	1.2	0.6	0.21	0.6	0.5	0	0.59	0.3	0.8	1.1	0.006
ST deviation (%)	17.0	19.5	28.6	0.004	22.0	29.1	33.3	<0.001	28.0	37.2	45.2	<0.001
Abnormal initial biomarker (%)	38.3	40.6	43.5	0.11	53.4	52.2	63.1	0.56	40.9	45.5	54.1	<0.001
Abnormal biomarker within 24 h (%)	57.6	60.1	62.7	0.08	70.2	68.7	80.2	0.30	61.4	67.2	77.5	<0.001
Initial creatinine (μmol/L)[a]	81 (72–92)	114 (99–129)	249 (197–352)	<0.001	83 (73–93)	114 (102–129)	229 (199–350)	<0.001	81 (72–93)	116 (100–132)	233 (196–338)	<0.001
eGFR (mL/min/1.73 m^2)[a]	76 (68–87)	50 (43–55)	20 (13–25)	—	76 (67–87)	49 (42–55)	20 (15–26)	—	76 (67–87)	49 (41–55)	21 (14–26)	—
GRACE risk score[a]	104 (87–126)	129 (107–155)	156 (129–181)	<0.001	109 (90–129)	131 (111–160)	156 (136–190)	<0.001	109 (89–132)	140 (117–170)	169 (140–194)	<0.001

GRACE risk score: low risk ≤108; intermediate risk 109–140; high risk ≥141.
CABG, coronary artery bypass graft surgery; DBP, diastolic blood pressure; HR, heart rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
[a]Median (interquartile range).

(Hosmer–Lemeshow goodness-of-fit *P*-value = 0.25). There was an adequate overlap in the distribution of propensity scores between the groups with and without in-hospital revascularization. Stratification by quintiles of propensity score achieved adequate balance in the covariates. All analyses were performed using SPSS (version 15.0, SPSS Inc., Chicago, IL, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Study population

Of the 11 377 study patients, 61.2%, 33.2%, and 5.6% had an eGFR $\geq$60, 30–59, and $<$30 mL/min/1.73 m^2, respectively. Patient demographic data stratified by eGFR within each registry are shown in *Table 1*. Overall, patients with eGFR of $\geq$60, 30–59, and $<$30 mL/min/1.73 m^2 had median GRACE risk scores of 107 (IQR: 88–129), 136 (IQR: 113–165), and 163 (IQR: 137–190), respectively (*P* for trend <0.001).

In-hospital medical management

Table 2 summarizes the in-hospital use of antiplatelet and antithrombotic agents within the first 24 h of presentation. The use of aspirin and heparin was lower in patients with decreased eGFR in all registries, and remained largely unchanged across the three registries. Overall, thienopyridine use increased from ACS I to ACS II to GRACE, but it remained lower in patients with reduced eGFR (*P* for trend <0.001).

In-hospital invasive management

Figure 1 illustrates the in-hospital use of coronary angiography and revascularization stratified by eGFR. Rates of coronary angiography increased significantly in all groups between ACS I and II, and stabilized in GRACE. The per cent increase between ACS I and GRACE was highest for eGFR $\geq$60 mL/min/1.73 m^2 patients (22%) and lowest for the eGFR $<$30 mL/min/1.73 m^2 group (7.5%). In all registries, coronary angiography was used less frequently in patients with decreased eGFR (*P* for trend <0.001). Similar results were obtained after stratifying by hospitals with and without on-site cardiac catheterization facilities.

PCI rate doubled between ACS I and ACS II, but again plateaued in GRACE; the exception was a continued increase of 5.8% seen in the eGFR $<$30 mL/min/1.73 m^2 group. Despite this finding, the greatest overall change from ACS I to GRACE was again seen in the eGFR $\geq$60 mL/min/1.73 m^2 group, which experienced a 17.9% increase, compared with 10.2% increase in eGFR $<$30 mL/min/1.73 m^2 stratum. CABG rate showed a sharp rise from ACS I to ACS II, followed by a decline in GRACE. As seen with coronary angiography, PCI and CABG rates were lower in patients with worse kidney dysfunction in all registries and, taken together, patients with reduced eGFR were less likely to receive any revascularization procedure ($P < 0.001$). When considering only patients referred for coronary angiography, the rate of revascularization (PCI/CABG) increased across the three registries from 50.5 to 56.2%, 44.4 to 53.5%, and 32.6 to 49.2%, in the eGFR $\geq$60, 30–59, and $<$30 mL/min/1.73 m^2 groups, respectively.

Table 2 In-hospital (<24 h) use of antiplatelet/antithrombin therapy stratified by estimated glomerular filtration rate in ACS I, ACS II, and GRACE

eGFR (mL/min/1.73 m^2)	ACS I (n = 3242)				ACS II (n = 1923)				GRACE (n = 6212)				All patients (n = 11377)			
	≥60	30–59	<30	*P* for trend	≥60	30–59	<30	*P* for trend	≥60	30–59	<30	*P* for trend	≥60	30–59	<30	*P* for trend
ASA (%)	92.4	88.2	84.9	<0.001	94.7	91.3	88.3	0.002	93.6	90.8	83.7	<0.001	93.4	90.2	84.8	<0.001
Thienopyridine (%)	9.1	8.4	8.2	0.46	60.0	49.0	49.5	<0.001	68.5	60.7	52.5	<0.001	49.4	44.7	40.8	<0.001
Heparin (%)	91.2	88.1	79.2	<0.001	92.3	87.0	86.5	<0.001	89.5	85.2	77.6	<0.001	90.5	86.3	79.6	<0.001
Glycoprotein IIb/IIIa inhibitor (%)	6.1	4.6	0.6	0.003	13.8	8.5	4.5	<0.001	7.0	6.0	3.6	0.012	8.0	6.0	3.0	<0.001

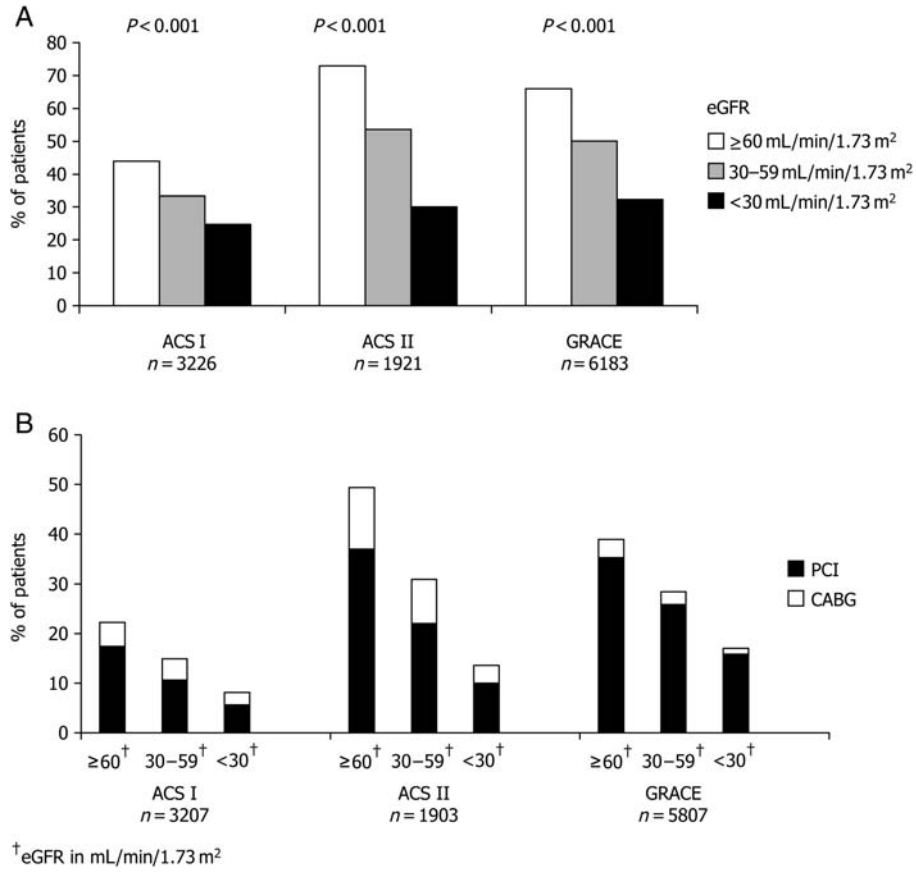

Figure 1 Rates of in-hospital coronary angiography (*A*) and revascularization (*B*) stratified by estimated glomerular filtration rate. In (B), *P* for trend <0.001 in each registry for PCI and ≤0.002 in ACS II and GRACE for CABG.

Patient outcomes

Figure 2 shows the rates of in-hospital mortality, re-infarction, and bleeding, stratified by eGFR. In all registries, patients with decreased kidney function had higher in-hospital and 1 year mortality rates (1 year mortality data not available for GRACE). Of note, the eGFR <30 mL/min/1.73 m^2 group in GRACE had a higher median GRACE risk score than in other registries, representing a sicker cohort. Both in-hospital death/re-infarction rate and major bleeding rate showed an inverse relationship with eGFR. In ACS I and II, the unadjusted 1 year mortality rate was lower among patients receiving in-hospital coronary angiography for all levels of kidney dysfunction (*Figure 2E*).

In multivariable analysis (*Table 3*), in-hospital revascularization was independently associated with lower 1 year mortality (adjusted OR = 0.52, 95% CI 0.36–0.77, *P* = 0.001), irrespective of eGFR (*P* for interaction = 0.39). The c-statistic was 0.83 and the Hosmer–Lemeshow goodness-of-fit *P*-value was 0.33, indicating good model discrimination and calibration, respectively. The results were similar when eGFR was analysed as a continuous variable. Propensity score analysis also yielded similar results (adjusted OR = 0.53, 95% CI 0.38–0.75, *P* < 0.001; *P* for interaction with CKD = 0.86). In a sensitivity analysis excluding in-hospital deaths, in-hospital revascularization remained a strong predictor of lower 1 year mortality (adjusted OR = 0.58, 95% CI 0.38–0.87, *P* = 0.008).

Reported reasons for not pursuing an invasive approach

In ACS II, 679 of 1956 patients were not referred for in-hospital coronary angiography. *Table 4* lists the physician-reported reasons for not pursuing an invasive approach in these patients. The most commonly cited reason for not pursuing an invasive strategy in these patients was insufficient patient risk (37.7%). In those patients deemed 'not high risk', the calculated GRACE risk scores were 110 (IQR: 88–134) and 140 (IQR: 119–163) for patients without and with CKD, respectively (*P* < 0.001).

Discussion

Our key findings in this multi-centre, observational study of the management of NSTE-ACS patients were: (i) the rates of in-hospital coronary angiography and revascularization increased with time across all strata of kidney dysfunction; (ii) patients with CKD continue to be treated more conservatively compared to their counterparts, despite their higher inherent risk; (iii) there was an association between an invasive management approach

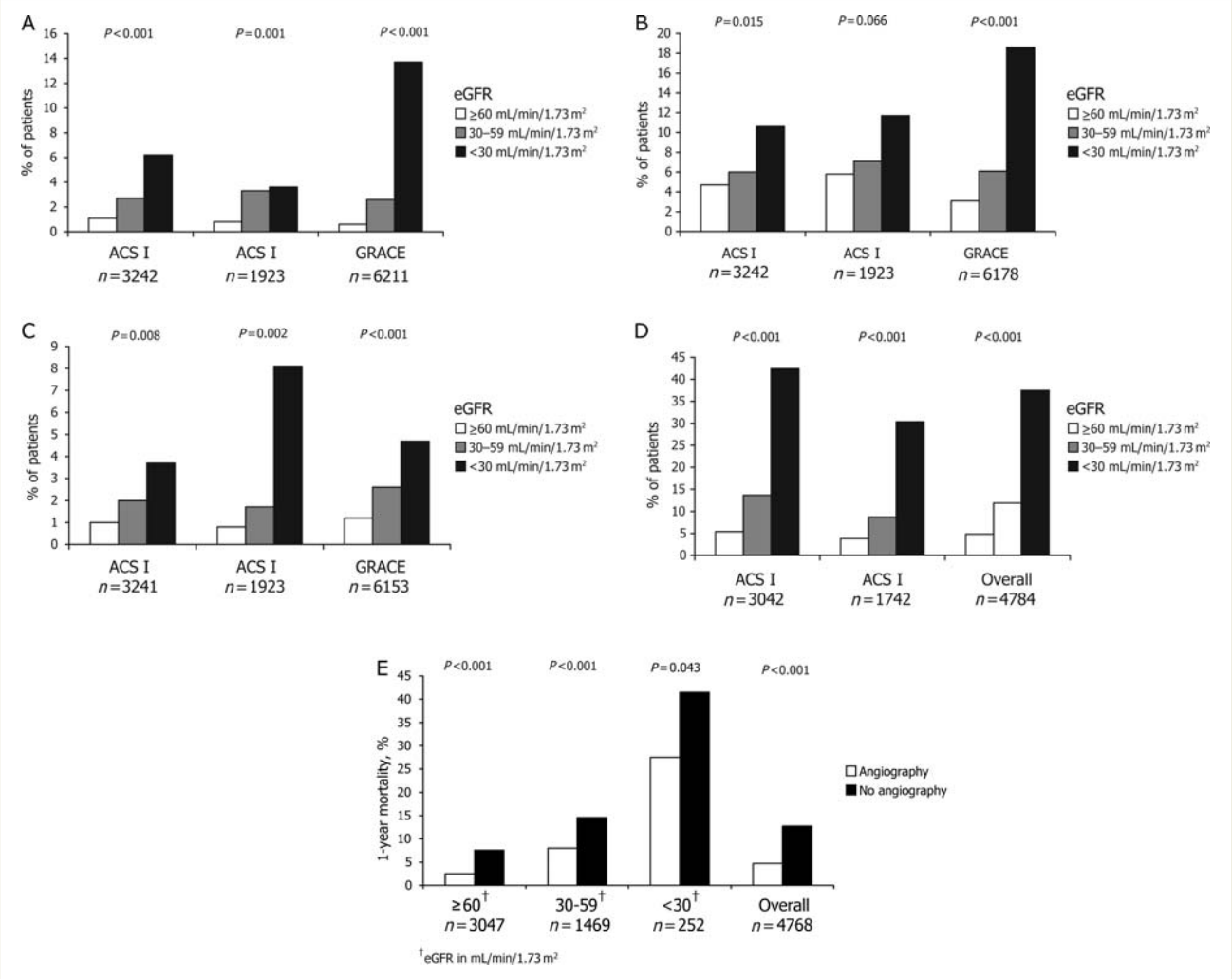

Figure 2 In-hospital mortality (*A*), death or non-fatal re-infarction (B), major bleeding (*C*), 1 year all-cause mortality (*D*), and relationship between coronary angiography and 1 year mortality (*E*) in ACS I, ACS II, and GRACE, stratified by estimated glomerular filtration rate.

and improved 1 year survival across all strata of renal dysfunction, which was maintained after controlling for potential confounders; (iv) misperception of patient risk was the most commonly cited reason for not referring patients with renal dysfunction to coronary angiography.

Chronic kidney disease is a well-established coronary artery disease risk factor and is a powerful predictor of mortality after NSTE-ACS.[1–3] Data primarily from the 1990s showed that evidence-based treatments of NSTE-ACS were generally underutilized in these patients, despite their higher mortality risk.[12–16] Yet, in all of these studies, use of ASA,[14,15] beta-blockers,[14,15] reperfusion,[15] and glycoprotein IIb/IIIa antagonists[23] in patients with kidney dysfunction were associated with better outcomes. Conceivably, a primary contributor to the observed underutilization of contemporary treatments of NSTE-ACS in patients with kidney dysfunction has been their under-representation in most randomized clinical trials.[11] Indeed, only limited clinical trial data on the management of NSTE-ACS in patients with kidney dysfunction exist.[11,24,25] In subgroup analyses of the TACTICS-TIMI 18 and FRISC-II trials, patients with kidney insufficiency undergoing early invasive treatment had a decreased incidence of adverse cardiovascular events.[24,25] Current American College of Cardiology/American Heart Association guidelines support an early-invasive approach in the management of NSTE-ACS in moderate to high-risk patients.[7] In view of important changes in the management of NSTE-ACS over the past decade and a general paucity of data in the current era management of NSTE-ACS in patients with kidney dysfunction, examination of more recent management trends and their impact on survival in this subgroup of patients appears warranted.

In the present study, we found increased rates of in-hospital coronary angiography and revascularization over time across strata of kidney dysfunction, consistent with clinical trials supporting an early-invasive strategy in NSTE-ACS.[7–10] More importantly, we observed an independent association between in-hospital coronary revascularization and improvement in 1 year survival, irrespective of eGFR. These results complement the single-centre long-term follow-up study by Keeley *et al.*[26] All in all, these observations

Table 3 Multivariable logistic regression model for 1 year mortality in NSTE-ACS patients in the ACS I and II registries

Independent predictor	Adjusted odds ratio	95% Confidence interval	*P*-value
Age (per 10-year increase)	1.78	1.54–2.05	<0.001
Heart rate (per 10 bpm increase)	1.11	1.07–1.16	<0.001
Systolic blood pressure (per 10 mm Hg increase)	0.93	0.89–0.97	0.001
Previous MI	1.46	1.12–1.90	0.006
Previous CHF	1.88	1.38–2.55	<0.001
Killip			
I	Reference		
II	1.57	1.17 –2.11	0.003
III/IV	2.52	1.77–3.57	<0.001
ST deviation	1.4	1.00–1.95	0.047
Abnormal initial biomarker	1.75	1.40–2.18	<0.001
eGFR (mL/min/1.73 m^2)*			
>60	Reference		
30–59	1.09	0.85–1.4	0.51
<30	4.34	3.00–6.27	<0.001
In-hospital revascularization*	0.52	0.36–0.77	0.001

**P* for interaction between in-hospital revascularization and eGFR categories = 0.39; this interaction term was eliminated from the final model.

are consistent with previous, albeit limited, randomized trial data supporting an early invasive strategy in NSTE-ACS patients with renal dysfunction,[24] as well as with studies in the general population suggesting that high-risk patients may benefit the most from an early-invasive approach.[27–29] Of note, cardiovascular disease remains the principal cause of death in patients with kidney dysfunction,[6] and these patients are more likely to die from cardiovascular causes than to progress to an end-stage renal disease.[6,30] Therefore, while the risk of complications with an early invasive strategy may be increased in patients with kidney insufficiency,[28] the overall risk-benefit ratio may be favourable, at least among carefully selected patients.[24,25]

Despite these encouraging findings, patients with kidney dysfunction continue to be treated more conservatively, with an associated worse outcome. Interestingly, over time, as evidenced by our most recent data, rates of revascularization following coronary angiography have become very similar across all strata of kidney dysfunction, indicating that the major roadblock to revascularization was the lack of initial referral to angiography. Previous research has highlighted the important observation that higher-risk NSTE-ACS patients are paradoxically treated conservatively despite current recommendations.[20,29,31,32] A similar treatment-risk paradox seems to be present among patients with kidney dysfunction. This treatment gap needs to be addressed, if we are to improve outcomes in this high-risk population.

Management decisions in patients with renal dysfunction are complex and the reasons for the observed undertreatment are likely multifactorial. Various factors, such as overestimation of treatment-associated mortality and morbidity (e.g. contrast nephropathy and bleeding), concerns over co-morbidities, lack of definitive clinical trial data, under-recognition of patient's poor prognosis, and underestimation of treatment benefit likely all play

Table 4 Physician-reported reasons for not pursuing an invasive approach stratified by estimated glomerular filtration rate

	Overall (*n* = 679)	eGFR ≥60 mL/min/1.73 m^2 (*n* = 334)	eGFR <60 mL/min/1.73 m^2 (*n* = 345)	*P*-value
Patient not high risk (%)	42.1	46.7	37.7	0.02
Not supported by evidence (%)	7.1	6.3	7.8	0.46
Not high enough risk or not supported by evidence (%)	48.9	52.7	45.2	0.055
Renal insufficiency (%)	2.1	0.3	3.8	0.002
Significant comorbidity (%)	8.5	4.5	12.5	<0.001
Patient/family refused (%)	6.6	5.1	8.1	0.12
Previously defined anatomy unsuitable (%)	13.1	14.4	11.9	0.36
Previously defined anatomy and revascularization already planned (%)	5.6	7.5	3.8	0.044
Bleeding or other safety concerns (%)	4.4	1.5	7.2	<0.001
No reason given (%)	14.4	15.9	13.0	0.33
GRACE score of patients who were not considered high risk and did not undergo angiography[a]	n/a	110 (88–134)	140 (119–163)	<0.001

[a]Median (interquartile range).

a role. Moreover, in-hospital mortality and treatment-associated complications may be higher with an early-invasive approach in these patients.[28] These immediate risks may be more evident than the potential for improvement in long-term outcomes,[28] and therefore have a greater impact on clinical decision-making.

Elimination of treatment disparities in patients with kidney dysfunction requires a clear understanding of the underlying barriers to treatment. To the best of our knowledge, no study has yet specifically addressed this important issue, and there is no contemporary prospective study in the literature that has examined the treating physician's rationale for not referring patients with kidney dysfunction to coronary angiography. Importantly, in this study, the most commonly cited reason for foregoing an early-invasive management strategy in the eGFR <60 mL/min/1.73 m^2 group was insufficient risk (37.7%), while concerns over comorbidity (12.5%) and bleeding (7.2%) were minor in comparison. Furthermore, the median GRACE score of those patients deemed 'low risk' was paradoxically high. Thus, misrepresentation of the actual risk and subsequent denial of early-invasive management may have contributed to worse outcomes in this group of patients. Not only are these findings in agreement with previous studies that suggest undertreatment of high-risk populations,[20,31–33] but they may also advocate for the more widespread use of risk scores to assist in the optimal management of NSTE-ACS patients.[34,35] In particular, this study highlights for the first time the important finding that part of the treatment gap in the management of NSTE-ACS patients with kidney dysfunction may be mediated by the physician's misperception of patient risk. Our observational data also suggest that invasive therapy may be beneficial for high-risk ACS patients, including those with kidney dysfunction.

This study has several limitations. Sites participating in the ACS I, ACS II, and GRACE registries were not randomly recruited and, while the enrolment of consecutive patients was encouraged, it was not verified. Furthermore, need for informed consent may have limited inclusion of patients who died before or shortly after admission, potentially reducing the generalizability of our findings. Second, eGFR was calculated using the MDRD formula without correcting for ethnicity since ACS I and GRACE did not capture this information. Furthermore, we did not collect data on acute kidney injury requiring renal replacement therapy and serial creatinine measurements during hospitalization. eGFR calculation was based on creatinine on presentation, which may not have been at a steady state, and thus, may not represent a true estimation of patients' baseline kidney function. Despite these limitations, our study is unique in that it reflects current management patterns of NSTE-ACS in patients with kidney dysfunction based on large unselected cohorts, and reveals, for the first time, some of the key reasons that underlie the treatment barriers faced by this high-risk population. Finally, due to possible unmeasured confounders, this observational study cannot establish the efficacy of coronary revascularization—rather, we demonstrate that the benefits of invasive management also seem to extend to ACS patients with kidney dysfunction, who were under-represented or excluded in randomized clinical trials.

In conclusion, despite temporal increases in invasive management of NSTE-ACS, patients with kidney dysfunction continue to be treated more conservatively, with an associated worse outcome. Coronary revascularization was independently associated with improved 1 year survival across all strata of kidney dysfunction. Underestimation of patient risk was the most common barrier to pursuing an early-invasive strategy in this high-risk group. Better risk stratification and randomized controlled trial data are needed to guide optimal management of this rapidly expanding patient population.

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