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Every obstruction does not need a stent: an important lesson from the ISCHEMIA-CKD trial for kidney-transplant surgeons

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Revascularization either with percutaneous coronary intervention (PCI) or with coronary artery bypass grafting (CABG), as appropriate, is the guideline-based therapy for patients presenting with acute coronary syndromes [1]. In contrast, the optimal management of stable ischaemic heart disease (ISHD) remains uncertain. Prior randomized trials among patients with stable ISHD have suggested no benefit of an invasive strategy over optimal medical treatment (OMT) [2, 3]. These trials have been criticized because a large proportion of participants had minimal symptom burden and low-to-moderate myocardial ischaemia, and therefore the rates of revascularization were low in the group assigned to interventional therapy [2, 3]. Furthermore, patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² or those on dialysis were either underrepresented or excluded from these trials (Table 1). Thus, the management of stable ISHD, particularly in patients with advanced chronic kidney disease (CKD), is based on low-quality evidence provided by small *post hoc* analyses of randomized trials [6] or on observational data [7].

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches-Chronic Kidney Disease (ISCHEMIA-CKD) trial [5] addresses this unmet need. ISCHEMIA-CKD was conducted in parallel at most of the same sites with the much larger ISCHEMIA trial [4]. These two trials share several similarities in their design. Both recruited patients with stable ISHD and moderate-to-severe myocardial ischaemia detected via non-invasive screening tests, and implemented the same intervention. Both randomized patients to an initial invasive strategy in addition to

OMT or to conservative management of stable ISHD that required OMT alone. The invasive strategy included routine cardiac catheterization followed by revascularization (PCI or CABG, as appropriate) plus OMT. The conservative strategy was based on OMT alone; coronary angiography and revascularization were options but only when OMT had failed.

ISCHEMIA-CKD and ISCHEMIA [6, 7] also have some methodological differences that merit our attention: (i) patients with eGFR <30 mL/min/1.73 m² were excluded in ISCHEMIA and (ii) the use of computed tomographic (CT) imaging of coronary anatomy as a screening procedure to rule out left main coronary artery disease or non-obstructive disease was not performed in ISCHEMIA-CKD. This was because of an elevated risk of contrast-induced acute kidney injury (AKI) in such patients.

ISCHEMIA-CKD enrolled 777 patients with advanced CKD (defined as those with eGFR <30 mL/min/1.73 m² or those on dialysis, approximately half and half) (Figure 1) [5]. Contrary to the original expectation that invasive strategy would confer cardioprotective benefits, the primary composite outcome of all-cause death or non-fatal myocardial infarction (MI) did not differ between the invasive- and conservative-strategy groups [hazard ratio (HR): 1.01; 95% confidence interval (CI): 0.79–1.29]. The invasive strategy did not improve the secondary composite outcome of death, non-fatal MI or hospitalization for unstable angina, heart failure (HF) or resuscitated cardiac arrest (HR: 1.02; 95% CI: 0.79–1.29). Not only did the invasive strategy in ISCHEMIA-CKD show no cardioprotective benefit, but it was also associated with a 3.76-fold higher hazard of

Table 1.. Major randomized trials comparing an early invasive strategy versus conservative treatment in patients with stable ISHD

Trial	Patient characteristics	Patients with CKD at baseline			Intervention	Follow-up	Primary outcome	Overall effect
		eGFR <60	eGFR <30	Dialysis				
COURAGE [2]	2287 patients with stable ISHD	320 (13.9%)	16 (0.7%)	None	PCI plus OMT versus OMT alone	4.6 years	All-cause death or non-fatal MI	Neutral
BARI-2D [3]	2368 patients with diabetes mellitus and stable ISHD	494 (20.9%)	None ^a	None	Revascularization (PCI or CABG) plus OMT versus OMT alone	4.37 years	All-cause death, non-fatal MI or stroke	Neutral
ISCHEMIA [4]	5179 patients moderate-to-severe myocardial ischaemia	568 (11.0%)	None ^b	None	Revascularization (PCI or CABG) when feasible plus OMT versus OMT alone and angiography if OMT failed	3.2 years	Cardiovascular death, non-fatal MI or hospitalization for unstable angina, HF or resuscitated cardiac arrest	Neutral
ISCHEMIA-CKD [5]	777 patients with advanced CKD and moderate-to-severe myocardial ischaemia	None	366 (47.1%)	411 (52.9%)	Revascularization (PCI or CABG) when feasible plus OMT versus OMT alone and angiography if OMT failed	2.2 years	All-cause death or non-fatal MI	No difference in the primary outcome; higher risk of stroke and new-onset dialysis

^aPatients with serum creatinine >2 mg/dL were not eligible in the BARI-2D trial.

^bPatients with eGFR <30 mL/min/1.73 m² were not eligible in the ISCHEMIA trial.

BARI-2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation.

FIGURE 1: The design and main findings of the ISCHEMIA-CKD trial.

stroke (HR: 3.76; 95% CI: 1.52–9.52); of note, these events were not common during the periprocedural period but occurred several months or years later. Although the nature of strokes is not reported, it is possible that dual anti-platelet therapy following deployment of a coronary stent increased the risk for haemorrhagic stroke; worsening of kidney failure, and therefore hypertension, could be another reason (indeed dialysis was more common in the intervention group and dialysis itself may increase the risk of strokes). Among participants not on dialysis at baseline, compared with OMT, invasive strategy raised by 48% the hazard of death or initiation of dialysis (HR: 1.48; 95% CI: 1.04–2.11); this increase in risk was predominantly driven by the increased risk for dialysis. In a prespecified secondary analysis of ISCHEMIA-CKD, the invasive strategy was similarly effective as OMT in improving angina-associated health-related quality of life [8]; the lack of sustained benefit on symptom burden was irrespective of the severity of angina at baseline.

In ISCHEMIA-CKD, the revascularization rate among participants in invasive strategy was lower than that seen in the ISCHEMIA (where patients did not have advanced CKD). Over a median follow-up of 2.2 years, the cumulative incidence of cardiac catheterization and revascularization in the invasive-strategy group were 85.2% and 50.2%, respectively [5]. In contrast, in ISCHEMIA, substantially higher rates of coronary catheterization and revascularization were observed (96% and 79% in the invasive-strategy group, respectively) [4]. The presence of microvascular heart disease could be one reason for this difference, but this stark difference in rates is better explained by the study design. Specifically, CT imaging had not been implemented as a preprocedural screening test in ISCHEMIA-CKD; thus, more patients could have non-obstructive coronary disease. Indeed, no coronary disease was present in 26.5% of patients in ISCHEMIA-CKD versus only 6.1% in ISCHEMIA. In the majority (75.4%) of patients who were not revascularized in ISCHEMIA-CKD, the reason was that they did not have obstructive coronary disease. In fact, only 14.2% in ISCHEMIA-CKD did not undergo revascularization because of lack of suitable arteries; this proportion was higher in ISCHEMIA (26.4%).

In the OMT arm, the 3-year cumulative incidence of angiograms was 31.6%—the majority of these were due to either a confirmed or suspected coronary event. Likewise, the 3-year cumulative incidence of revascularizations was 19.6%. The >50% difference in angiograms and >30% difference in revascularizations between assigned groups provide reassurance that the protocol was closely adhered to despite being a worldwide study. Furthermore, despite the exclusion of patients with non-obstructive disease and the higher revascularization rate, the larger ISCHEMIA trial also failed to show a cardioprotective benefit with invasive therapy [4]. Thus, the ISCHEMIA and ISCHEMIA-CKD results are consistent.

OPTIMIZING GUIDELINE-BASED MEDICAL THERAPY FOR CORONARY CARE

Participants in the ISCHEMIA-CKD trial received guideline-based therapy aiming at improved risk-factor management. Types of medications and attainment of risk-factor goals were adequately balanced in the intensive- and conservative-strategy arms [5], providing reassurance that the treatment effect of revascularization was not biased by between-group differences in OMT. Overall, this intervention resulted in a significant increase in the proportion of ISCHEMIA-CKD participants with controlled systolic blood pressure (from 55.3% at baseline to 68.6% at study end). A similar improvement was noted in the proportion of participants with controlled low-density lipoprotein cholesterol (from 34.9% to 49.4%). These results emphasize the need for optimization of medical management—over interventional procedures—as a cardioprotective strategy in advanced CKD.

ACUTE CORONARY SYNDROME: INVASIVE MANAGEMENT STILL STANDARD OF CARE

Although among patients with stable ISHD every blocked coronary does not need a stent, some may require revascularization. The ISCHEMIA-CKD trial excluded patients with recent acute coronary syndromes or recent revascularization, symptomatic

patients with unacceptable angina despite OMT, as well as those with severe HF and left ventricular ejection fraction <35% [5]. In these patients, invasive therapy may be essential; at least, it should not be denied based on the results of ISCHEMIA-CKD.

Subgroup analyses of the ISCHEMIA-CKD trial revealed also some potential sources of heterogeneity with respect to the treatment effect of invasive therapy. The severity of myocardial ischaemia was a determinant of primary outcome; those with severe ischaemia appeared to derive greater benefit from invasive therapy ($P = 0.02$) [5]. Similarly, patients with lower eGFR and those with a lower ejection fraction appeared to benefit more from invasive therapy (there were significant interaction effects). Interaction effects can be statistically significant by chance alone, nonetheless, therapy may need to be individualized.

HEART-KIDNEY TEAMS—A LESSON IN COLLABORATION

Despite a high risk for contrast-induced nephropathy among ISCHEMIA-CKD participants, the overall incidence of AKI after coronary angiography or PCI was only 7.9% in the invasive-strategy group versus 0% in the conservative-strategy group. The periprocedural initiation of dialysis occurred in 2.1% of invasively treated versus 0.6% of conservatively managed participants [5]. These incidence rates are sharply lower than the 26.6% incidence of post-PCI AKI among 27 980 patients with eGFR <30 mL/min/1.73 m² enrolled in a large registry during 2009–11; the incidence of new-onset dialysis was 4.6% [9]. The provenance of these discrepant results may lie in the trial design. The design of ISCHEMIA-CKD prespecified the implementation of a customized volume-repletion protocol based on haemodynamic-guided fluid administration for the prevention of AKI. Invasive procedures were performed by well-trained interventional personnel at investigator sites with experience in the use of novel ultra-low volume and zero contrast PCI techniques, and each site required a collaborating nephrologist [5].

The successful implementation of a strategy to minimize the incidence of contrast-induced nephropathy within the framework of the ISCHEMIA-CKD trial is a call-to-action to form ‘heart-kidney teams’ as done by the trial. Owing to the fear of contrast-induced AKI and the associated risk of in-hospital morbidity and mortality, a high proportion of patients with moderate-to-severe CKD are denied the optimal invasive therapy after an acute coronary syndrome—this phenomenon has been termed ‘renalism’ [10]. As an example, analysis of 57 284 elderly participants in the Cooperative Cardiovascular Project [10] showed that the proportion of patients after an acute MI that were invasively treated was lower in those with than in those without CKD (25.2% versus 46.8%, respectively). However, the proportion of participants who fulfilled the criteria of appropriateness for invasive management was similar in both subgroups (50.9% versus 50.4%, respectively). CKD patients who were considered appropriate and underwent revascularization had significantly lower 1-year mortality risk than those who were also appropriate for revascularization but received conservative treatment [10]. Even though the ISCHEMIA-CKD trial showed that

an invasive strategy is not superior to OMT in patients with advanced CKD and stable ISHD, the promising results for AKI call for interventional therapy when indicated, such as in the management of acute coronary syndrome. Implementing a protocol as in the ISCHEMIA-CKD trial for AKI prophylaxis may save kidneys while saving the heart.

A MESSAGE FOR THE KIDNEY TRANSPLANT SURGEONS

An important lesson from ISCHEMIA-CKD concerns patients who are screened for coronary disease prior to kidney transplant. Based on a small trial published in 1992 in 26 patients with insulin-dependent diabetes and advanced CKD who were candidates for kidney transplantation, many transplant surgeons require that a blocked coronary be stented [11]. In this trial, compared with conservative management (based on the administration of a calcium channel blocker and aspirin), revascularization lowered the incidence of cardiovascular events (10 events in 13 patients in a medically managed group versus 2 events in 13 patients in the revascularization group) over a median follow-up of 8.4 months [11]. The much larger 777-patient ISCHEMIA-CKD trial does not support these findings. The evidence of harm (strokes and death/dialysis) is real; the overall evidence of benefit to favour revascularization is absent (Figure 1). Thus, we should stop demanding that every blocked coronary be stented. In fact, the ISCHEMIA-CKD trial suggests no revascularization is required for most patients with stable ISHD. In fact, about one in eight will go on dialysis after CABG. For the surgeon who may be reluctant to adopt this view, clinical-trial evidence from other high-risk surgical populations showed no benefit of coronary revascularization before surgery as prophylaxis for post-operative cardiovascular complications [12, 13]. The Coronary Artery Revascularization Prophylaxis (CARP) trial [13] randomized 510 veterans with stable ISHD waiting for elective vascular surgery to either pre-operative revascularization or conservative management and found no difference in the risk of post-operative MI; revascularization had no benefit on survival over a follow-up of 2.7 years. In the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE-V) trial [12], 101 patients with severe ischaemia at myocardial stress testing were randomized to revascularization or medical treatment before elective vascular surgery. Once again, revascularization did not improve the composite outcome of all-cause death or MI at 30 days and >1-year long follow-up. ISCHEMIA-CKD extends these data to patients with advanced CKD and demonstrates the harms of interventional coronary procedures. Taken together, clinical-trial evidence supports the notion that not every blocked coronary needs a stent. Perhaps this is the most important lesson for all of us treating those with advanced CKD—particularly the transplant surgeons screening patients for a prospective kidney transplant.

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

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CONFLICT OF INTEREST STATEMENT

R.A. has the following disclosures: member data safety monitoring committees are Astra Zeneca and Ironwood Pharmaceuticals. Member steering committees of randomized trials are Akebia, Bayer, Janssen, Glaxo Smith Cline, Reata, Relypsa, Sanofi and Genzyme US Companies. Member adjudication committees are Bayer, Boehringer Ingelheim and Janssen. Member scientific advisory board or consultant are Celgene, Daiichi Sankyo, Inc., Eli Lilly, Relypsa, Reata, Takeda Pharmaceuticals USA, ZS Pharma and Merck. P.I.G. has nothing to disclose.

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COVID-19 and policy changes for kidney disease: the need for a ‘decade of the kidney’

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In this issue of *Nephrology Dialysis Transplantation*, a timely analysis and call to action by the Council of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and the European Renal Association COVID-19 Database (ERACODA) working group [1] highlights the extremely high burden of coronavirus disease 2019 (COVID-19) infection in chronic kidney disease (CKD) patients, who, compared with patients suffering from other major disorders, are at

the highest risk to develop severe COVID-19 and to die from it [2].

Although it could be anticipated that the pandemic would take a heavy toll on the CKD population, as COVID-19 caused severe problems in populations with notorious CKD risk factors like diabetes and cardiovascular disease, the initial publications from China reported a prevalence of CKD below 1% in hospitalized COVID-19 patients [3], and it took some time before