Title

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ORIGINAL RESEARCH

Dialysis Initiation in Patients With Chronic Coronary Disease and Advanced Chronic Kidney Disease in ISCHEMIA-CKD

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BACKGROUND: In participants with concomitant chronic coronary disease and advanced chronic kidney disease (CKD), the effect of treatment strategies on the timing of dialysis initiation is not well characterized.

METHODS AND RESULTS: In ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches–Chronic Kidney Disease), 777 participants with advanced CKD and moderate or severe ischemia were randomized to either an initial invasive or conservative management strategy. Herein, we compare the proportion of randomized participants with non–dialysis-requiring CKD at baseline (n=362) who initiated dialysis and compare the time to dialysis initiation between invasive versus conservative management arms. Using multivariable Cox regression analysis, we also sought to identify the effect of invasive versus conservative chronic coronary disease management strategies on dialysis initiation. At a median follow-up of 23 months (25th–75th interquartile range, 14–32 months), dialysis was initiated in 18.9% of participants (36/190) in the invasive strategy and 16.9% of participants (29/172) in the conservative strategy *(P*=0.22). The median time to dialysis initiation was 6.0 months (interquartile range, 3.0–16.0 months) in the invasive group and 18.2 months (interquartile range, 12.2–25.0 months) in the conservative group *(P*=0.004), with no difference in procedural acute kidney injury rates between the groups (7.8% versus 5.4%; *P*=0.26). Baseline clinical factors associated with earlier dialysis initiation were lower baseline estimated glomerular filtration rate (hazard ratio [HR] associated with 5-unit decrease, 2.08 [95% CI, 1.72–2.56]; *P*<0.001), diabetes (HR, 2.30 [95% CI, 1.28–4.13]; *P*=0.005), hypertension (HR, 7.97 [95% CI, 1.09–58.21]; *P*=0.041), and Hispanic ethnicity (HR, 2.34 [95% CI, 1.22–4.47]; *P*=0.010).

CONCLUSIONS: In participants with non–dialysis-requiring CKD in ISCHEMIA-CKD, randomization to an invasive chronic coronary disease management strategy (relative to a conservative chronic coronary disease management strategy) is associated with an accelerated time to initiation of maintenance dialysis for kidney failure.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01985360.

Key Words: chronic coronary disease ■ chronic kidney disease ■ dialysis ■ guideline-directed medical therapy

In the United States, ≈125 000 patients annually transition from advanced non–dialysis-requiring chronic kidney disease (CKD) to end-stage kidney disease requiring maintenance dialysis treatment, which translates to an unadjusted dialysis incidence rate of 373.4 per million/year.[1,2] Factors associated with CKD

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CLINICAL PERSPECTIVE

What Is New?

- In patients with concomitant chronic coronary disease and advanced chronic kidney disease, an initial strategy including invasive cardiovascular procedures was associated with a significantly earlier initiation of dialysis compared with an initial conservative strategy.

What Are the Clinical Implications?

- In ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches–Chronic Kidney Disease), although there was no significant difference in procedure-related acute kidney injury between the treatment groups, invasive management was associated with earlier initiation of dialysis.
- This association should be explored in future studies.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
CCD	chronic coronary disease
ISCHEMIA-CKD	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches–Chronic Kidney Disease

progression to kidney failure include older age, higher body mass index, diabetes, cardiovascular disease, proteinuria, and hypertension.[3] Although maintenance dialysis prevents death from uremia, mortality among patients with end-stage kidney disease remains high.[4] Furthermore, individuals with end-stage kidney disease have poorer quality of life than the general population.[5]

In patients with concomitant chronic coronary disease (CCD) and advanced CKD, the effects of CCD treatment strategies on CKD progression are not well characterized. The ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches–Chronic Kidney Disease) demonstrated that in participants with advanced CKD and moderate or severe myocardial ischemia, an initial invasive strategy did not reduce the risk of death or nonfatal myocardial infarction compared with an initial conservative strategy.[6] In the current study, we examined the incidence and timing of dialysis initiation among those participants not on dialysis at baseline according to the randomized CCD management strategy.

METHODS

Design

The design of ISCHEMIA-CKD has been previously reported.[7] Briefly, ISCHEMIA-CKD was an investigator-initiated, international, randomized clinical study designed to determine whether an initial invasive strategy of coronary angiography and revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), if suitable, in addition to guideline-directed medical therapy, would reduce cardiovascular events in participants with advanced CKD and moderate or severe myocardial ischemia, compared with a conservative strategy of guideline-directed medical therapy alone, with coronary angiography and revascularization reserved if guideline-directed medical therapy is ineffective. The study was funded by the National Heart, Lung, and Blood Institute. The corresponding health authorities and ethics boards/institutional review boards overseeing the participating center approved the study. The data were assembled and analyzed by the Statistical and Data Coordinating Center located at Duke Clinical Research Institute. The data that support the findings of this study are available from the corresponding author on reasonable request.

Procedures

Participants who met eligibility criteria and gave informed written consent were randomized 1:1 to an initial invasive or conservative ischemia treatment strategy. Advanced CKD was defined as estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m^2 or on dialysis. Participants not on dialysis were defined as having stage 4 CKD if their baseline eGFR was between 15 and 29 mL/min per 1.73 m^2, and stage 5 CKD with a baseline eGFR <15 mL/min per 1.73 m^2.[8]

Participants randomized to the invasive strategy were expected to undergo cardiac catheterization within 30 days after randomization, with revascularization (PCI or CABG) as soon thereafter as clinically appropriate. The selection of PCI versus CABG (or medical therapy, in cases of nonobstructive coronary artery disease or otherwise unfavorable coronary anatomy) was left to the discretion of the treating "heart-kidney" team per local standards and expertise. Strategies to reduce the risk of acute kidney injury (AKI) included a customized hydration protocol[9] and a contrast volume threshold, which was calculated on the basis of the individual participant's eGFR and body weight, along with protocols for ultra-low-volume[10] and zero-contrast PCI techniques.[11]

Guideline-directed medical therapy consisted of intensive, comprehensive secondary prevention, with lifestyle and pharmacologic interventions recommended equally to both groups using individualized treatment regimens based on treat-to-target algorithms. Dose adjustments were recommended for medications that are renally excreted or dialyzed. Medication adherence was tracked using the Morisky-Green-Levine medication adherence survey.[12]

Participants were followed up at 1.5, 3, 6, and 12 months after randomization during the first year and every 6 months thereafter. Participant data were collected on electronic case report forms.

Primary Outcomes

The primary purpose of the current analysis was to compare, among the participants who were not on dialysis at baseline, the proportion of participants within each management strategy (invasive versus conservative) who initiated dialysis and the time to dialysis initiation by randomized treatment group. Time to dialysis initiation was calculated from the date of randomization to the study visit date when maintenance dialysis initiation was documented. Treating cardiologists and nephrologists elected to start dialysis in accordance with local practices and guidelines.[13–15] The eGFR at the time of dialysis initiation was not collected. AKI was defined as serum creatinine increase ≥25% and/or ≥0.5 mg/dL from baseline within 7 days of any invasive treatment.

Statistical Analysis

The analysis cohort includes subjects who were not on dialysis at baseline. For descriptive analyses, categorical variables were presented as frequencies and proportions, and continuous variables were summarized with medians and 25th to 75th interquartile ranges. Cumulative event probabilities for dialysis initiation by CCD treatment strategies and postrandomization procedure status at various time points during the follow-up were estimated by a nonparametric cumulative-incidence function estimator with death as a competing risk.[16] The Fine-Gray test was used to compare cumulative incidence functions at a certain time point. We assessed the effect of the randomized treatment strategy on initiation of dialysis through a multivariable Cox model, with the adjustment of baseline covariates. We estimated hazard ratios and 95% CIs. The assumption of proportional hazards during the entire follow-up period for randomized treatment strategies in the Cox model was violated; therefore, we created a piece-wise hazard function representing the 3 follow-up periods that were reflective of the progression of study treatment and follow-up: from randomization to 6 months, 6 months to 2 years, and over 2 years. Treatment effects in each of the 3 periods were calculated. The list of baseline covariates was selected from those included in the Table using backward and forward selection process with an inclusion criterion of $P<0.05$. We assessed the linearity of continuous variables using restricted cubic splines.[17] The linearity assumption was confirmed for all baseline continuous variables; hence, the original form of the data was used in the model.

We considered 2-tailed $P<0.05$ to be significant, without adjustment for multiple comparisons. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

Baseline Characteristics

Between April 29, 2014, and January 31, 2018, a total of 802 participants were enrolled for consideration of randomization in the study. Of these participants, 777 (96.9%) from 118 sites in 30 countries were randomized: 388 to the invasive group and 389 to the conservative group. Of the 777 participants, 362 (46.6%) had advanced (stage 4 or 5), non–dialysis-requiring CKD at baseline, and constitute the analytic cohort for this study. The characteristics of these 362 patients are reported in the Table; 190 participants were randomized to the invasive group, and 172 participants were randomized to the conservative group. The median age of the 362 participants was 66 years, 68.2% were men, 91.4% had hypertension, and 61.6% had diabetes. Baseline eGFR was 23 mL/min per 1.73 m^2 (interquartile range, 17–27 mL/min per 1.73 m^2) in the total cohort and was similar in the 2 treatment strategies. Among the 190 invasive group participants, 154 (81.1%) underwent coronary angiography, 84 (44.2%) underwent PCI, and 16 (8.4%) underwent CABG. The most common reasons that coronary angiography was not performed in the invasive strategy group were death and illness that occurred before the procedure and patient preference. Among the 172 participants in the conservative strategy group, coronary angiography was performed in 37 (21.5%), 15 (8.7%) underwent PCI, and 9 (5.2%) underwent CABG. The reasons for coronary angiography in participants randomized to conservative strategy were most often a confirmed or suspected clinical event and nonadherence to protocol. The median duration of follow-up among survivors (146 in the invasive group, and 134 in the conservative group) was 23 months (interquartile range, 14–32 months).

Outcomes

Among participants who were not requiring dialysis at baseline, dialysis was initiated in 36 of 190 (18.9%) in the invasive strategy group and 29 of 172 (16.9%) in the conservative strategy group ($P=0.22$). Among

Table. Baseline Characteristics by Randomized Treatment in Participants Not on Dialysis at Study Entry

Characteristic	Invasive (n=190)	Conservative (n=172)	All (n=362)	*P* value
Demographics				
Age at randomization, y				0.065
No.	190	172	362	
Median (25th–75th percentile)	65 (58–71)	67 (59–75)	66 (59–73)	
Male sex	135/190 (71.1)	112/172 (65.1)	247/362 (68.2)	0.226
Region				0.430
Asia	69/190 (36.3)	68/172 (39.5)	137/362 (37.8)	
Europe	71/190 (37.4)	60/172 (34.9)	131/362 (36.2)	
Latin America	11/190 (5.8)	4/172 (2.3)	15/362 (4.1)	
North America	36/190 (18.9)	35/172 (20.3)	71/362 (19.6)	
Other	3/190 (1.6)	5/172 (2.9)	8/362 (2.2)	
Race				0.951
White	129/184 (70.1)	116/170 (68.2)	245/354 (69.2)	
Black	11/184 (6.0)	9/170 (5.3)	20/354 (5.6)	
Asian	42/184 (22.8)	43/170 (25.3)	85/354 (24.0)	
Other*	2/184 (1.1)	2/170 (1.2)	4/354 (1.1)	
Ethnicity				0.755
Hispanic or Latino	19/183 (10.4)	15/160 (9.4)	34/343 (9.9)	
Not Hispanic or Latino	164/183 (89.6)	145/160 (90.6)	309/343 (90.1)	
Vital signs				
Body mass index, kg/m^2				0.428
No.	190	172	362	
Median (25th–75th percentile)	28 (25–31)	28 (25–33)	28 (25–32)	
Systolic blood pressure, mm Hg				0.991
No.	190	172	362	
Median (25th–75th percentile)	136 (120–150)	133 (125–150)	135 (125–150)	
Diastolic blood pressure, mm Hg				0.383
No.	190	172	362	
Median (25th–75th percentile)	79 (70–84)	76 (70–85)	78 (70–85)	
Clinical history				
Hypertension	171/190 (90.0)	159/171 (93.0)	330/361 (91.4)	0.313
Diabetes	118/190 (62.1)	105/172 (61.0)	223/362 (61.6)	0.836
Prior myocardial infarction	33/190 (17.4)	36/172 (20.9)	69/362 (19.1)	0.389
Cigarette smoking				0.881
Never smoked	94/190 (49.5)	83/172 (48.3)	177/362 (48.9)	
Former smoker	77/190 (40.5)	69/172 (40.1)	146/362 (40.3)	
Current smoker	19/190 (10.0)	20/172 (11.6)	39/362 (10.8)	
Prior PCI	39/190 (20.5)	29/172 (16.9)	68/362 (18.8)	0.373
Prior CABG	8/190 (4.2)	7/172 (4.1)	15/362 (4.1)	0.946
Noncardiac vascular and comorbidity history				
Prior stroke	21/190 (11.1)	9/172 (5.2)	30/362 (8.3)	0.045
Prior peripheral artery disease	8/190 (4.2)	15/172 (8.7)	23/362 (6.4)	0.079
Prior liver disease	6/190 (3.2)	8/172 (4.7)	14/362 (3.9)	0.462
Dyslipidemia (LDL-C >70 mg/dL)	115/179 (64.2)	109/170 (64.1)	224/349 (64.2)	0.980
Hyperglycemia (fasting glucose >126 mg/dL)	40/121 (33.1)	38/114 (33.3)	78/235 (33.2)	0.964

(*Continued*)

Table. Continued

Characteristic	Invasive (n=190)	Conservative (n=172)	All (n=362)	*P* value
Angina and heart failure history				
Ejection fraction (%)				0.485
No.	160	137	297	
Median (25th–75th percentile)	58 (50–63)	58 (50–64)	58 (50–64)	
Laboratory values				
Estimated GFR from enrollment, mL/min				0.678
No.	190	172	362	
Median (25th–75th percentile)	23 (16–27)	23 (17–27)	23 (17–27)	
Medications				
Anticoagulant medications	18/186 (9.7)	19/171 (11.1)	37/357 (10.4)	0.657
Statins	165/190 (86.8)	155/172 (90.1)	320/362 (88.4)	0.331
High-intensity statin				0.988
Yes	62/190 (32.6)	56/172 (32.6)	118/362 (32.6)	
No/unknown dose	128/190 (67.4)	116/172 (67.4)	244/362 (67.4)	
Ezetimibe	9/190 (4.7)	7/172 (4.1)	16/362 (4.4)	0.758
Fibrate	11/190 (5.8)	3/172 (1.7)	14/362 (3.9)	0.046
Other lipid-lowering medication	1/190 (0.5)	1/172 (0.6)	2/362 (0.6)	1.000
Antihypertensive and anti-ischemic/ anginal medications	188/190 (98.9)	169/172 (98.3)	357/362 (98.6)	0.672
β-Blocker	154/190 (81.1)	131/172 (76.2)	285/362 (78.7)	0.256
Calcium channel blocker	106/190 (55.8)	97/172 (56.4)	203/362 (56.1)	0.908
ACEI/ARB	97/190 (51.1)	95/172 (55.2)	192/362 (53.0)	0.426
Diuretic	106/190 (55.8)	104/172 (60.5)	210/362 (58.0)	0.368
Ranolazine	3/190 (1.6)	9/172 (5.2)	12/362 (3.3)	0.052
Ivabradine	1/190 (0.5)	1/172 (0.6)	2/362 (0.6)	1.000

Data are given as number/total (percentage), unless otherwise indicated. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; and PCI, percutaneous coronary intervention.
*Other race categories included are: American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander, and multi-race.

participants who initiated dialysis, the median time to dialysis initiation was 6.0 months (interquartile range, 3.0–16.0 months) in the invasive strategy group and 18.2 months (interquartile range, 12.2–25.0 months) in the conservative strategy group (*P*=0.004). The cumulative incidence of dialysis initiation at 1 year was higher in the invasive strategy group (12.5% [95% CI, 8.1%–17.9%]) than the conservative strategy group (4.3% [95% CI, 1.9%–8.3%]; *P*=0.006). At 2 years, however, there was no difference between the treatment strategies in the rate of dialysis initiation (Figure 1).

Among the 362 participants not on dialysis at baseline, 191 underwent coronary angiography with or without PCI or CABG (154 invasive, and 37 conservative; Table S1). The 3-year cumulative incidence rate of new dialysis among participants with and without procedures was 27.6% (95% CI, 20.0%–35.8%) and 22.2% (95% CI, 14.2%–31.4%), respectively (*P*=0.372; Figure 2). The number of those initiating dialysis and the cumulative incidence at various time points are reported in Table S2. To further explore timing of dialysis initiation, we analyzed dialysis initiation in patients who had or did not have an invasive procedure in both arms. As shown in Figure 3A, the initiation of dialysis following the invasive procedure was earlier among those in the invasive arm who underwent a procedure than those in the conservative arm who underwent a procedure. Furthermore, these results were confirmed after excluding patients who underwent CABG after randomization (Figure S1). Procedural AKI occurred in 12 of 154 (7.8%) with the invasive strategy and 2 of 37 (5.4%) with the conservative strategy (*P*=0.26).

Baseline Factors Associated With Time-to-Dialysis Initiation

Lower eGFR at baseline was associated with a higher risk for starting dialysis (Figure 4A and 4B). By multivariable Cox regression analysis, shorter time to dialysis initiation was associated with lower baseline eGFR (5-unit decrease in eGFR: hazard ratio [HR], 2.07 [95% CI, 1.70–2.52]; *P*<0.001), diabetes (HR, 2.29 [95% CI,

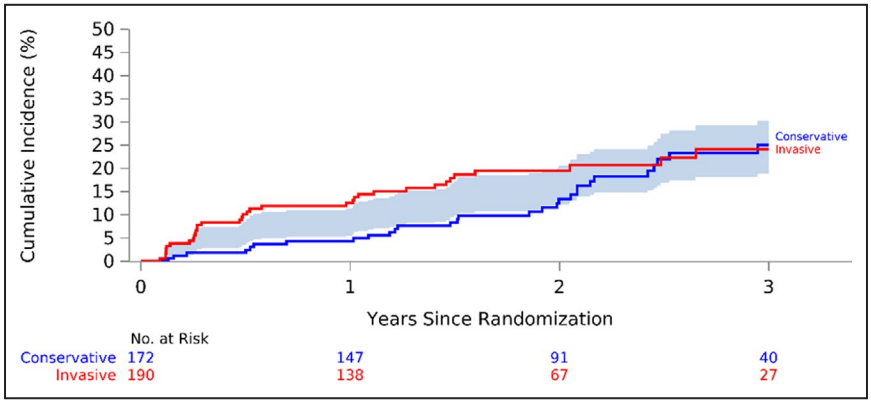

Figure 1. Cumulative incidence plot of new dialysis over time, by randomized treatment group among subjects not on dialysis at baseline.
At 3 years of follow-up, incidence of dialysis initiation was similar between participants in the invasive strategy and conservative strategy groups (*P*=0.879). However, median time to dialysis initiation was 6.0 months (interquartile range [IQR], 3.0–16.0 months) in the invasive strategy group and 18.2 months (IQR, 12.2–25.0 months) in the conservative strategy group (*P*=0.004). The shading displays the half width of the CI for the difference between treatment strategies. Overlap of the lines and shading indicates that the 95% CI for the difference includes 0.

1.28–4.10]; *P*=0.005), hypertension (HR, 7.83 [95% CI, 1.07–57.20]; *P*=0.043), and Hispanic ethnicity (HR, 2.30 [95% CI, 1.20–4.40]; *P*=0.012) (Figure 5). As anticipated, those in stage 5 CKD had a significantly higher risk of dialysis initiation than those in stage 4 CKD (HR, 3.86 [95% CI, 2.24–6.66]; *P*=0.001; Table S3). The proportional hazard assumption was violated for the timing of dialysis initiation between treatment arms. The HR comparing the invasive with the conservative treatment group was 5.26 (95% CI, 1.55–17.92; *P*=0.008) from randomization to 6 months, 1.17 (95% CI, 0.56–2.48; *P*=0.68) from 6 months to 2 years, and 0.53 (95% CI, 0.17–1.66; *P*=0.28) from 2 years to the end of follow-up. When we did not take the nonproportionality into consideration, the HR for starting dialysis comparing the invasive versus the conservative strategy for the entire follow-up period was 1.44 (95% CI, 0.87–2.38; *P*=0.152) (Figure S2).

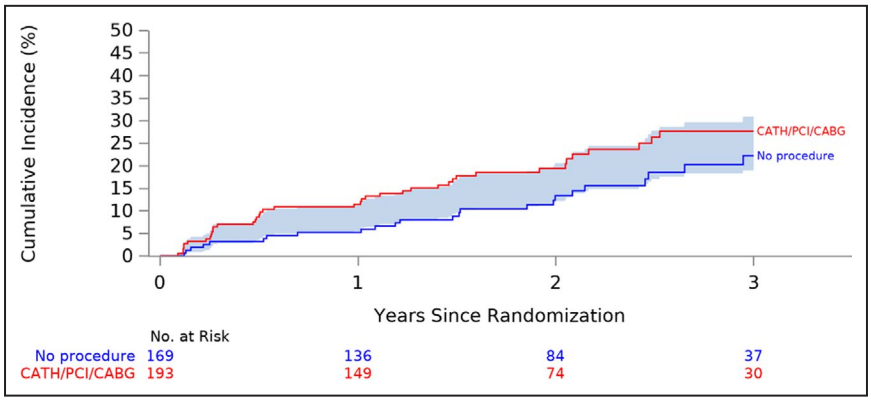

Figure 2. Cumulative incidence plot of new dialysis over time among subjects with and without procedures after randomization.
The 3-year cumulative incidence rate of new dialysis among subjects with and without procedures was 27.6% (95% CI, 20.0%–35.8%) and 22.2% (95% CI, 14.2%–31.4%), respectively (*P*=0.372). Median time to dialysis initiation was 9.3 months (interquartile range [IQR], 3.2–17.8 months) among subjects with procedures and 17.7 months (IQR, 6.5–25.0 months) among subjects without procedures (*P*=0.057). The shading displays the half width of the CI for the difference between treatment strategies. Overlap of the lines and shading indicates that the 95% CI for the difference includes 0. CATH/PCI/CABG indicates catheterization/percutaneous coronary intervention/coronary artery bypass grafting.

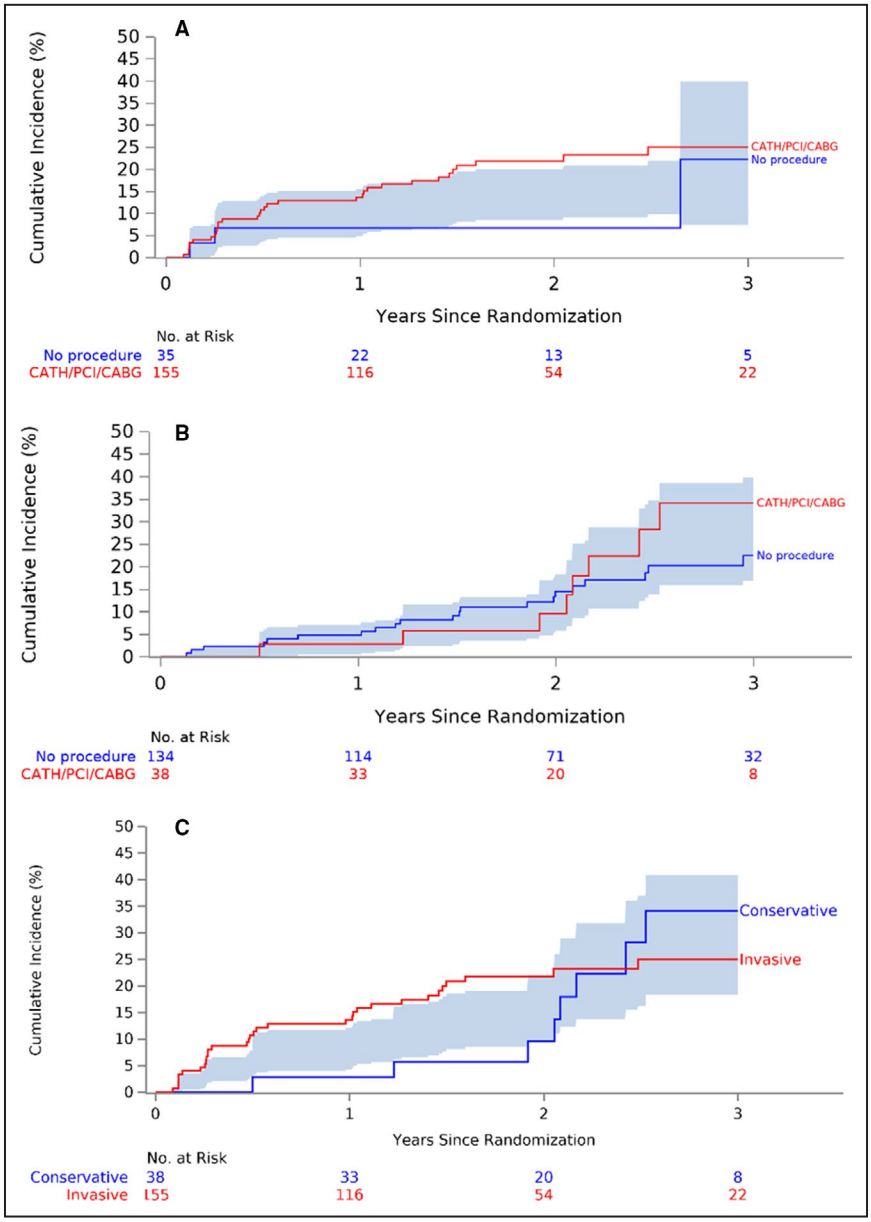

Figure 3. Time to dialysis initiation from randomization among selected subgroups. **A**, Between those who underwent catheterization/percutaneous coronary intervention/coronary artery bypass grafting (CATH/PCI/CABG) (red line) vs those who did not undergo CATH/PCI/CABG (blue line), among those randomized to the invasive strategy (Invasive). **B**, Between those who underwent CATH/PCI/CABG (red line) vs those who did not undergo CATH/PCI/CABG (blue line), among those randomized to the conservative strategy (Conservative). **C**, Between those randomized to Invasive (red line) vs Conservative (blue line) strategy, but only those participants undergoing CATH/PCI/CABG after randomization and during study follow-up.

DISCUSSION

In this post hoc analysis of data from ISCHEMIA-CKD, although the overall incidence of dialysis initiation was similar in patients with CCD managed with an initial invasive and conservative strategy, the time to initiation of maintenance dialysis was accelerated in patients randomized to the invasive strategy.

The observed dialysis initiation rate in this study was similar to that reported in the literature in patients with advanced CKD.[18] For example, in a contemporaneous clinical study, the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) study,[19] kidney failure requiring dialysis initiation occurred in 40 of 174 (23%) of patients with eGFR <30 mL/min per 1.73 m^2 at baseline at a

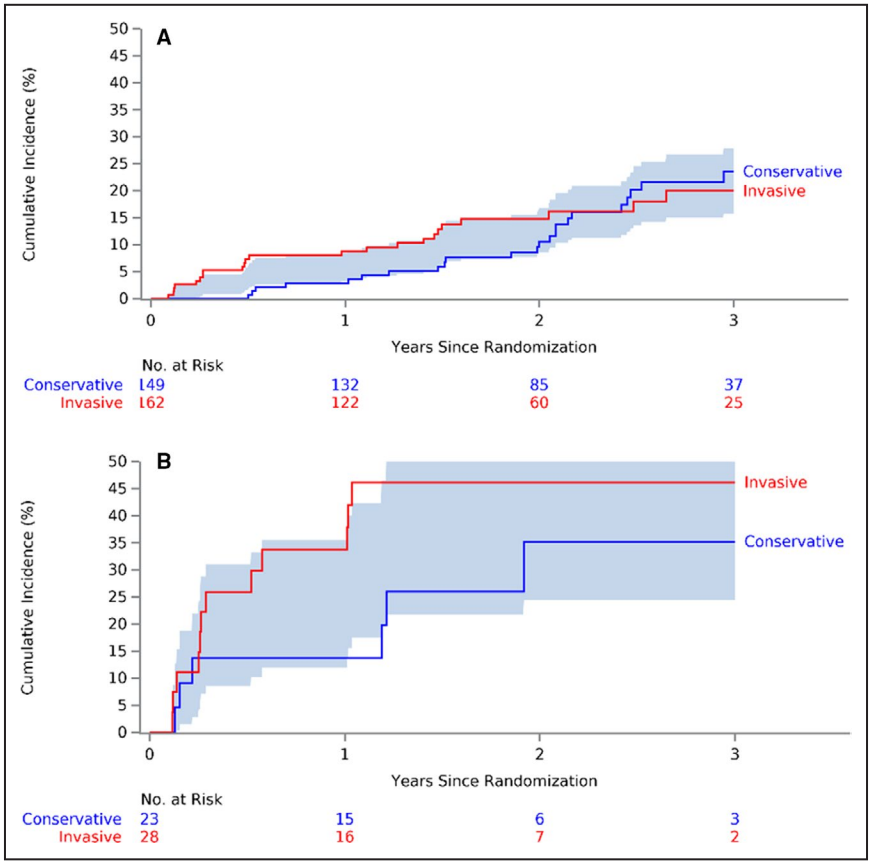

Figure 4. Cumulative incidence plot of new dialysis over time among people with stage 4 chronic kidney disease (CKD; A) and stage 5 CKD (B) at baseline by randomized treatment.
A statistically significant association with lower estimated glomerular filtration rate and risk for starting dialysis was observed.

median follow-up duration of 2.62 years.[20] Despite the implementation of low-contrast exposure protocols in our study, procedure-related AKI may have contributed in part to the earlier initiation of dialysis in the invasively managed participants. Potential mechanisms for CKD progression following postprocedural AKI include the following: (1) acute tubular necrosis from direct toxicity of the contrast medium or (2) atheroembolic disease from angiography itself or from subsequent procedures, including PCI and CABG.[21] Although the serum creatinine concentration often returns to baseline after an episode of AKI, reductions in muscle mass or hyperfiltration of remnant nephrons may mask damage already done. This may also occur after CABG, and recent evidence has suggested that these events may promote progression in the longer term.[22,23] However, the rates of procedure-related AKI were low and similar between the 2 arms. Moreover, our analysis showed that the initiation of dialysis was earlier among those in the invasive arm who underwent a procedure than those in the conservative arm who underwent a procedure, which suggests lack of a causal relationship and the potential for residual confounding. It is plausible that anticipation anxiety and enhanced vigilance among the treating team resulted in early initiation of dialysis selectively in the invasive strategy in which the coronary procedures were elective and planned, whereas the procedures in the conservative strategy were more likely in the setting of an urgent/emergent cardiovascular event, possibly at a different hospital.

In the current study, lower baseline eGFR, diabetes, hypertension, and Hispanic ethnicity were significant predictors of dialysis initiation. The eGFR value at the time of dialysis initiation was not available. In ISCHEMIA-CKD, the timing of dialysis initiation was left to the treating physicians according to guideline recommendations and local standard of care, although an element of anticipation anxiety and enhanced vigilance could have played a role. There is no minimum eGFR that provides an absolute indication to begin dialysis in the absence of signs or symptoms attributable to kidney failure.[13–15] However, eGFR of <5 mL/min per 1.73 m^2 represents a critical cutoff for dialysis

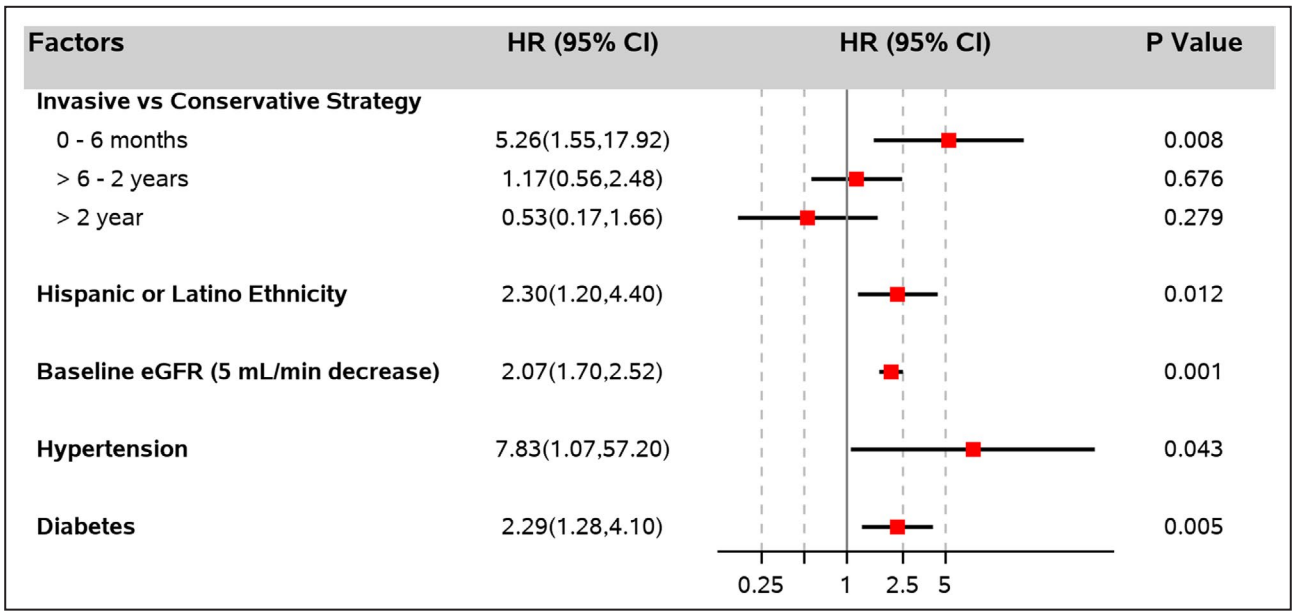

Figure 5. Factors associated with dialysis initiation.
eGFR indicates estimated glomerular filtration rate; and HR, hazard ratio.

start. The IDEAL (Initiating Dialysis Early and Late) study, which is the only randomized, controlled study that examined mortality related to the time of dialysis initiation, found no difference in survival between early (eGFR 8–13 mL/min per 1.73 m^2) or late (eGFR 3–5 mL/min per 1.73 m^2) initiation of dialysis.[24] In that study, the median time to dialysis initiation was 1.8 versus 7.4 months in the early- and late-start groups, respectively. Contributing factors for dialysis initiation are as follows: (1) comorbid conditions, such as diabetes and cardiovascular disease[24,25]; (2) older age; (3) timing of referral of patients with CKD to a nephrologist; and (4) the preference of the nephrologist, as there is large variability in individual practices.[26–28] Finally, we found variations in progression to dialysis initiation by racial/ethnic background.[29]

The current analysis has several strengths. Results were derived from a large, randomized clinical study, thereby reducing unmeasured confounding. The population was diverse in terms of age, sex, race and ethnicity, geographic region, and other cardiovascular (including stroke and peripheral artery disease) and noncardiovascular diseases. Few cardiovascular clinical studies have enrolled participants with advanced CKD, including participants with end-stage kidney disease and those with non–dialysis-requiring CKD. Baseline therapy for CCD was excellent, with the large majority of randomized participants treated with β-blockers and statins. There are, however, several limitations. Neither participants nor clinicians were blinded to the invasive versus conservative strategy. In this open-label study, there may have been a bias to earlier dialysis initiation after invasive procedures compared with conservative care because of either more frequent creatinine assessment or concerns for more rapid deterioration. Follow-up serum creatinine concentrations were not mandated by protocol and were not obtained at prespecified time intervals. However, among the 362 participants not on dialysis at baseline, 341 (94%) had ≥1 serum creatinine determinations performed 1 to 54 months after randomization. We did not collect some variables related to dialysis initiation, including the following: the reason for initiation of dialysis, whether dialysis was permanently required, or the exact time of dialysis initiation. Detailed data on other risk factors for CKD progression, including proteinuria and CKD cause, were obtained. Finally, the results of the present study do not apply to participants excluded from randomization, including those with unacceptable angina, recent acute coronary syndromes, left ventricular dysfunction, or heart failure.

In conclusion, in participants with advanced non–dialysis-requiring CKD and CCD in ISCHEMIA-CKD, randomization to an invasive strategy for coronary disease management resulted in a similar incidence but shorter time to dialysis initiation compared with a conservative strategy. These findings should be evaluated in future studies.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics by post randomization angiography status among subjects who are not on dialysis at baseline

Characteristic	Angiography: Yes (N=191)	Angiography: No (N=171)	All (N=362)	P value
Demographics				
Age at Randomization (yrs.)				0.734
N	191	171	362	
Median (25th, 75th)	65 (59, 72)	67 (58, 74)	66 (59, 73)	
Male Sex	141/191 (73.8%)	106/171 (62.0%)	247/362 (68.2%)	0.016
Region				<.001
Asia	53/191 (27.7%)	84/171 (49.1%)	137/362 (37.8%)	
Europe	81/191 (42.4%)	50/171 (29.2%)	131/362 (36.2%)	
Latin America	11/191 (5.8%)	4/171 (2.3%)	15/362 (4.1%)	
North America	42/191 (22.0%)	29/171 (17.0%)	71/362 (19.6%)	
Other	4/191 (2.1%)	4/171 (2.3%)	8/362 (2.2%)	
Race				<.001
White	145/185 (78.4%)	100/169 (59.2%)	245/354 (69.2%)	
Black or African American	11/185 (5.9%)	9/169 (5.3%)	20/354 (5.6%)	
Asian	28/185 (15.1%)	57/169 (33.7%)	85/354 (24.0%)	
Other	1/185 (0.5%)	3/169 (1.8%)	4/354 (1.1%)	
Vital Signs				
BMI(Kg/m2)				0.015
N	191	171	362	
Median (25th, 75th)	28 (25, 33)	27 (24, 31)	28 (25, 32)	
Systolic Blood Pressure (mmHg)				0.685
N	191	171	362	
Median (25th, 75th)	136 (120, 150)	133 (125, 150)	135 (125, 150)	
Diastolic Blood Pressure (mmHg)				0.059
N	191	171	362	
Median (25th, 75th)	76 (70, 80)	80 (70, 90)	78 (70, 85)	
Clinical History				
Hypertension	172/190 (90.5%)	158/171 (92.4%)	330/361 (91.4%)	0.526
Diabetes	124/191 (64.9%)	99/171 (57.9%)	223/362 (61.6%)	0.170
Prior Myocardial Infarction	38/191 (19.9%)	31/171 (18.1%)	69/362 (19.1%)	0.669
Cigarette Smoking				0.121
Never Smoked	84/191 (44.0%)	93/171 (54.4%)	177/362 (48.9%)	
Former Smoker	86/191 (45.0%)	60/171 (35.1%)	146/362 (40.3%)	
Current Smoker	21/191 (11.0%)	18/171 (10.5%)	39/362 (10.8%)	
Prior PCI	41/191 (21.5%)	27/171 (15.8%)	68/362 (18.8%)	0.167
Prior CABG	8/191 (4.2%)	7/171 (4.1%)	15/362 (4.1%)	0.964
Non-Cardiac Vascular and Comorbidity History				
Prior Stroke	18/191 (9.4%)	12/171 (7.0%)	30/362 (8.3%)	0.407
Prior Peripheral Artery Disease (PAD)	13/191 (6.8%)	10/171 (5.8%)	23/362 (6.4%)	0.709
Prior Liver Disease	6/191 (3.1%)	8/171 (4.7%)	14/362 (3.9%)	0.449
Dyslipidemia (LDL-C >70 mg/dL)	113/182 (62.1%)	111/167 (66.5%)	224/349 (64.2%)	0.394
Hyperglycemia (Fasting Glucose > 126 mg/dL)	44/119 (37.0%)	34/116 (29.3%)	78/235 (33.2%)	0.212

Characteristic	Angiography: Yes (N=191)	Angiography: No (N=171)	All (N=362)	P value
Angina and Heart Failure History				
Ejection Fraction				0.011
N	159	138	297	
Median (25th, 75th)	56 (50, 61)	60 (51, 65)	58 (50, 64)	
Lab values				
Estimated GFR from Enrollment (mL/min)				0.681
N	191	171	362	
Median (25th, 75th)	22 (17, 27)	23 (17, 27)	23 (17, 27)	
Medications				
Anticoagulant Medications	22/188 (11.7%)	15/169 (8.9%)	37/357 (10.4%)	0.382
Statins	166/191 (86.9%)	154/171 (90.1%)	320/362 (88.4%)	0.351
High-Intensity Statin				0.401
Yes	66/191 (34.6%)	52/171 (30.4%)	118/362 (32.6%)	
No/Unknown Dose	125/191 (65.4%)	119/171 (69.6%)	244/362 (67.4%)	
Ezetimibe	11/191 (5.8%)	5/171 (2.9%)	16/362 (4.4%)	0.190
Fibrate	12/191 (6.3%)	2/171 (1.2%)	14/362 (3.9%)	0.012
Other Lipid Lowering Medication	1/191 (0.5%)	1/171 (0.6%)	2/362 (0.6%)	1.000
Anti-Hypertensive and Anti-Ischemic/Anginal Medications	189/191 (99.0%)	168/171 (98.2%)	357/362 (98.6%)	0.670
Beta Blocker	157/191 (82.2%)	128/171 (74.9%)	285/362 (78.7%)	0.088
Calcium Channel Blocker	101/191 (52.9%)	102/171 (59.6%)	203/362 (56.1%)	0.195
ACE/ARB	109/191 (57.1%)	83/171 (48.5%)	192/362 (53.0%)	0.104
Angiotensin Receptor Blocker (ARB)	53/191 (27.7%)	43/171 (25.1%)	96/362 (26.5%)	0.575
Diuretic	120/191 (62.8%)	90/171 (52.6%)	210/362 (58.0%)	0.050
Ranolazine	5/191 (2.6%)	7/171 (4.1%)	12/362 (3.3%)	0.434
Ivabradine	2/191 (1.0%)	0/171 (0.0%)	2/362 (0.6%)	0.500

Table S2. Cumulative number of subjects with dialysis initiation and cumulative incidence (95% CI) post randomization among subjects not on dialysis at baseline

	Invasive strategy (N = 190)	**Conservative strategy (N = 172)**	**P value**
6 Month	18 10.1%(6.2%,15.0%)	3 1.8%(0.5%,4.8%)	0.001
12 Month	22 12.5%(8.1%,17.9%)	7 4.3%(1.9%,8.3%)	0.006
24 Month	32 19.5%(13.7%,26.0%)	19 13.4%(8.3%,19.6%)	0.154
36 Month	35 24.1%(16.8%,32.2%)	29 25.0%(17.0%,33.9%)	0.879

Table S3. Multivariable Cox model of new dialysis with randomized treatment and baseline risk factors with eGFR as a binary covariate (< 15 [stage 5 CKD] vs ≥ 15 [(stage 4 CKD])

	HR (95% CI)	P value Association with new dialysis
Invasive vs Conservative strategy 0 - 6 months	5.68(1.67,19.33)	0.005
>6 months – 2 years	1.18(0.56,2.48)	0.670
>2 years	0.48(0.15,1.51)	0.211
Ethnicity: Hispanic/Latino vs non-Hispanic/Latino	2.36(1.23,4.51)	0.010
Ethnicity not reported vs Non-Hispanic/Latino	1.49(0.58,3.84)	0.528
Stage 5 CKD at baseline vs stage 4 CKD	3.86(2.24,6.66)	0.001
Hypertension	6.22(0.86,44.99)	0.070
Diabetes mellitus	2.19(1.23,3.93)	0.008

Figure S1. Cumulative incidence curves of new dialysis over time after excluding subjects with CABG post randomization.

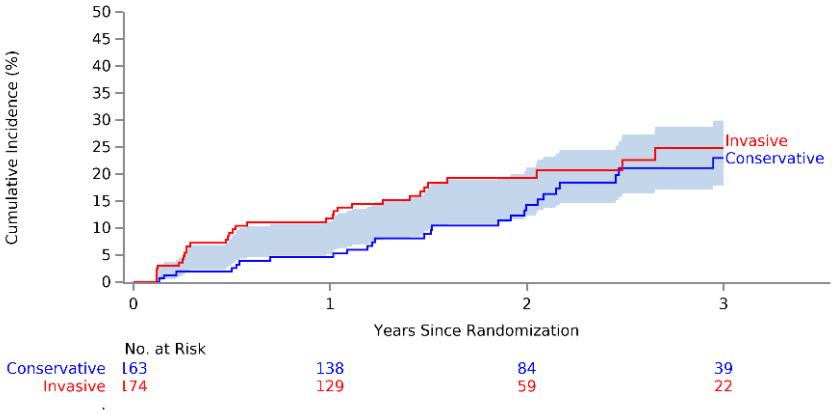

Figure S2. Factors associated with dialysis initiation ignoring non-proportional hazard of randomized treatment strategies