SUPPLEMENTAL MATERIAL:

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Supplemental Methods:

Bayesian modeling of GUIDELINE-DIRECTED MEDICAL THERAPY (GDMT) goals

For each individual GDMT goal, we modeled longitudinal trajectories over follow-up using Bayesian generalized linear mixed models with a random intercept and random slope to account for unobserved between-participant heterogeneity. To evaluate whether longitudinal GDMT goal trajectories differed between CKD G4-5 versus CKD G5D, each model included visit month, dialysis status at baseline, and their interaction. In addition, we adjusted for baseline participant characteristics, namely, sex, age at randomization, treatment strategy, diabetes status, and ejection fraction. We present the probability of GDMT goal attainment over follow-up by CKD G5D versus CKD G4-5, and the risk difference of GDMT goal attainment at 24 months for CKD G5D versus CKD G4-5. Uncertainty in the predicted trajectories and the risk differences was characterized using 95% credible intervals. By averaging over covariate distributions and random effects, inferences pertain to an average participant. Risk differences at 24 months for baseline characteristics other than dialysis status were also estimated.

We used an analogous analytical framework to assess the relationship of the number of GDMT goals attained with dialysis status at baseline. Using Bayesian ordinal logistic regression, we modeled the probability of attaining more than 0-2 goals, 3 goals, and 4 goals over follow-up as a function of visit month, dialysis status at baseline, and their interaction, in addition to the same participant characteristics adjusted for in the individual GDMT goal attainment analysis. To ease computational burden, we included only a random intercept. We specified a non-proportional

odds model to allow covariate associations to vary by the number of GDMT goals attained. Similar to the analysis of individual GDMT goals, we present the probability of attaining a higher number of GDMT goals over follow-up by CKD G5D versus CKD G4-5, and the risk differences of attaining a higher number of GDMT goals at 24 months for CKD G5D versus CKD G4-5.

Bayesian computation

We conducted the Bayesian analyses using JAGS and R.[23,32] Regression coefficients in each model were assigned mean zero normal prior distributions with a diffuse variance. In the longitudinal analysis of individual GDMT goals, we assigned the hierarchical variance-covariance of the random intercept and random slope an inverse Wishart prior distribution with a prior scale and degrees of freedom to reflect our lack of prior knowledge. For the analysis of the number of GDMT goals attained, we used an inverse gamma prior distribution on the variance of the random intercept. Based on three chains from dispersed initial values, we ran the Gibbs sampler for 200,000 iterations, saving every 20th iteration to reduce autocorrelation in the MCMC sample. The first 100,000 iterations were discarded as burn-in. We assessed model convergence using the Gelman-Rubin diagnostic[33] with convergence indicated by values near 1.

Sensitivity analysis

In the longitudinal data analysis of GDMT goal attainment, the use of generalized linear mixed models implies a missing at random (MAR) mechanism for missed GDMT measurements over follow-up. In other words, we have assumed that the probability of a missed GDMT measurement does not depend on the missing value itself after adjusting for participant characteristics. However, the MAR assumption may not be reasonable in the ISCHEMIA-CKD trial where missing values stem in part from the fact that 192 (25%) participants died before the end of their follow-up. Participants who died may have systematically different longitudinal GDMT profiles compared to surviving participants[34], which would suggest a missing not at random (MNAR) mechanism. For example, if compared to surviving participants, participants who died were sicker at the study start, these participants could have been especially motivated to improve their health -- which may manifest in terms of goal attainment. Alternatively, if participants who died had worse health status, then these participants might have received specialized clinical monitoring that could influence goal attainment. Under an MNAR mechanism, our longitudinal data analysis of GDMT goal attainment would be biased. To assess the sensitivity of our results to the MAR assumption, we extended our analysis into an MNAR framework using pattern mixture models.[35,36] We defined two missingness patterns based on participants who survived to the end of their follow-up versus participants who died before the end of their follow-up. We used the pattern mixture models to examine whether estimated associations were sensitive to an MAR versus MNAR assumption.

Supplemental Figures and Figure Legends:

Figure S1a. Percent individual goal attainment at baseline by chronic kidney disease (CKD) group. The count of non-missing values is provided along the horizontal axis. LDL: low density lipoprotein; SBP: systolic blood pressure.

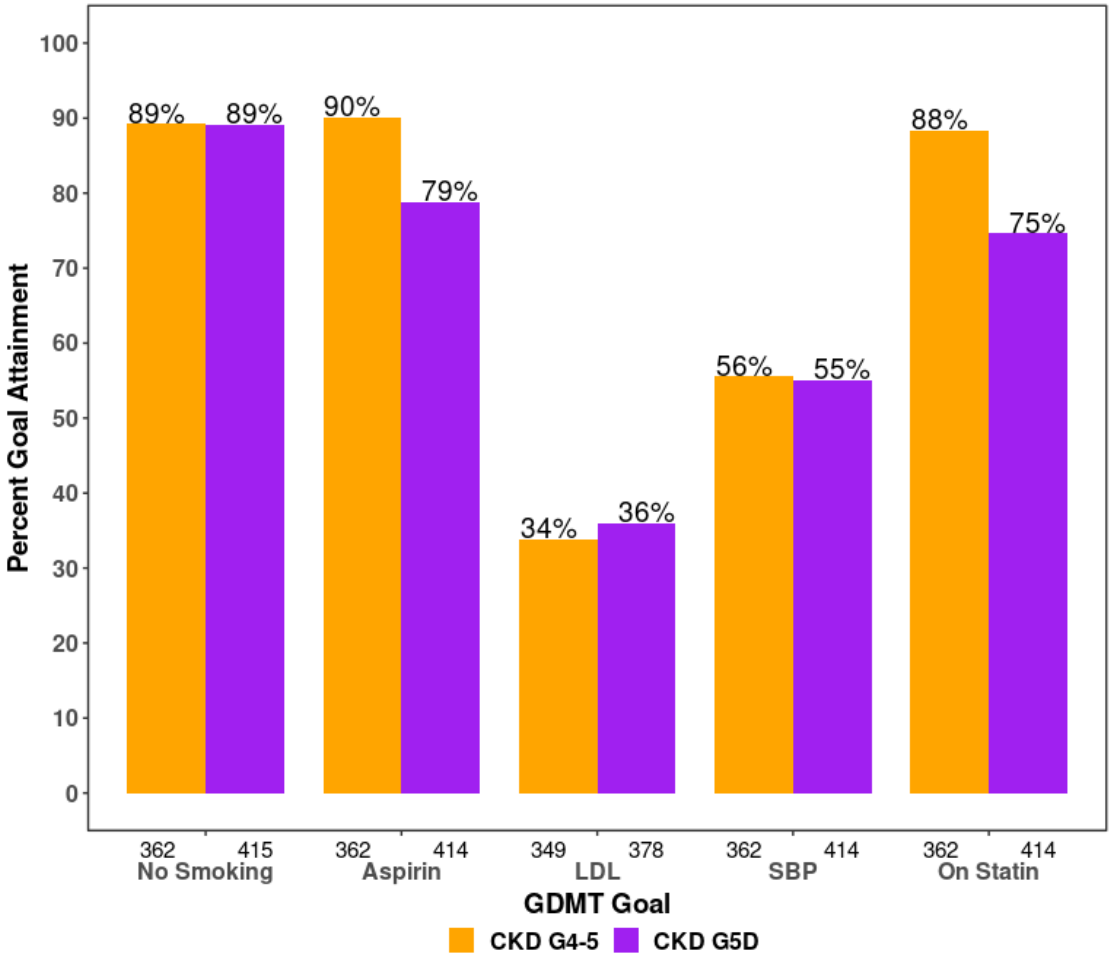


Figure S1b. Percent individual goal attainment at 24 months following randomization by CKD group. The count of non-missing values is provided along the horizontal axis. LDL: low density lipoprotein; SBP: systolic blood pressure.

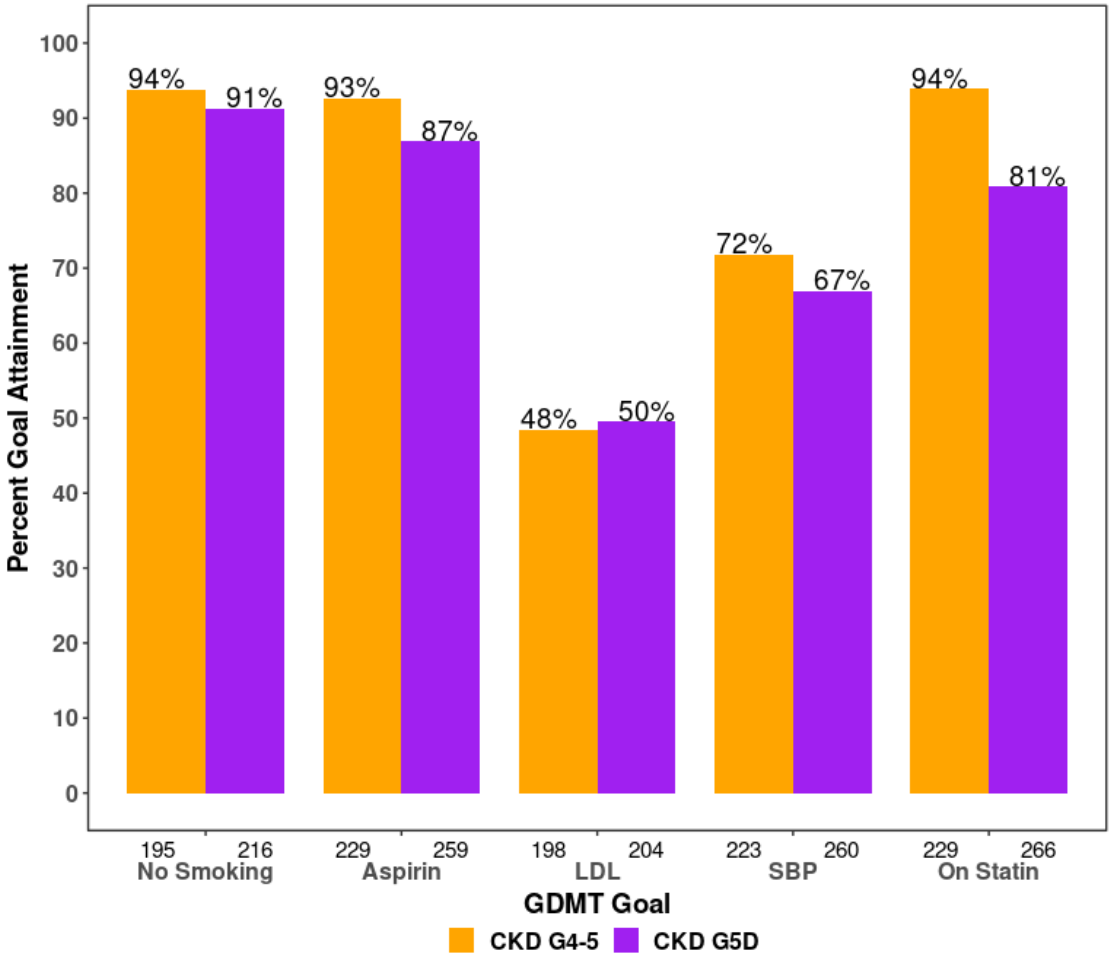


Figure S2: Estimated associations of individual guideline-directed medical therapy (GDMT) goal attainment with participant risk factors. LDL: low density lipoprotein; SBP: systolic blood pressure.

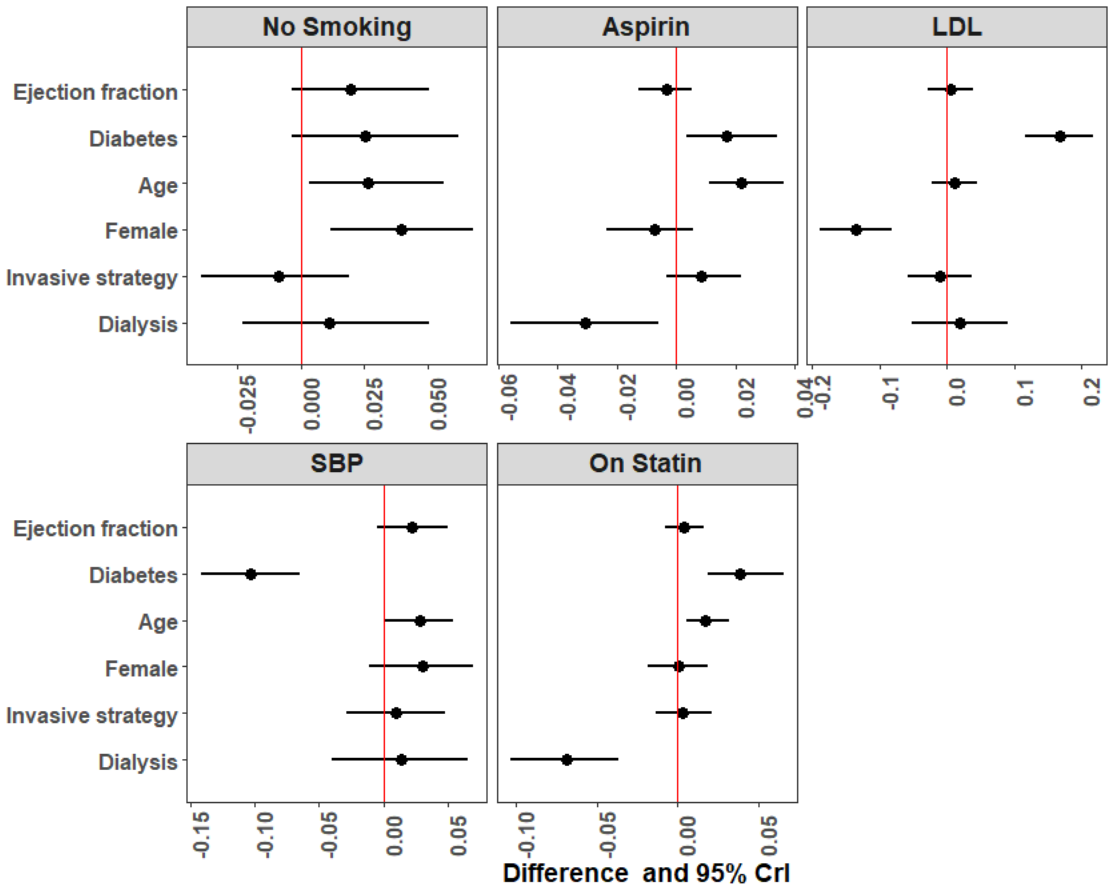


Figure S3a: Forest plot of differences in guideline-directed target achievement by dialysis status, conditional on survival status. 95% CrI: 95% credible interval; CKD: chronic kidney disease; GDMT: guideline directed medical therapy; LDL: low density lipoprotein; SBP: systolic blood pressure.

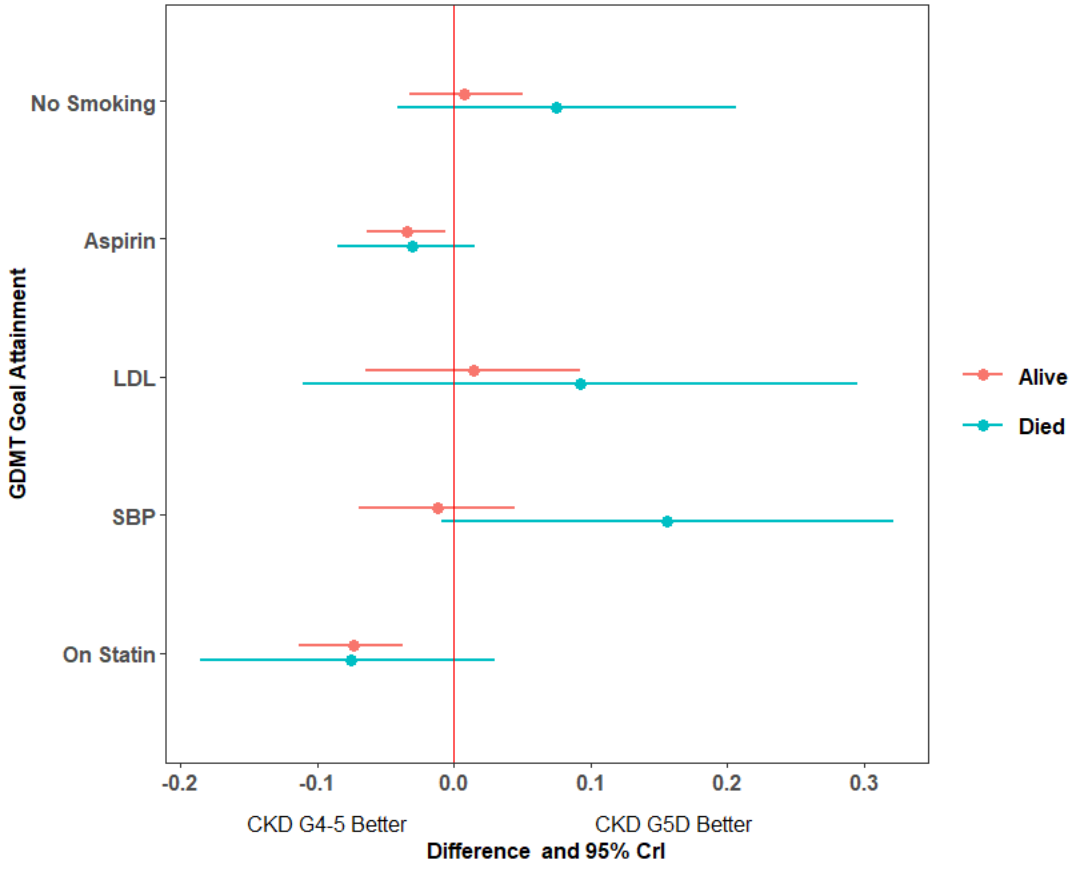


Figure S3b: Predicted probability of guideline-directed medical therapy (GDMT) goal attainment by dialysis status, with credible intervals. Top row presents patients who survived during follow-up and the bottom row those who died during follow up. CKD: chronic kidney disease; LDL: low density lipoprotein; SBP: systolic blood pressure.

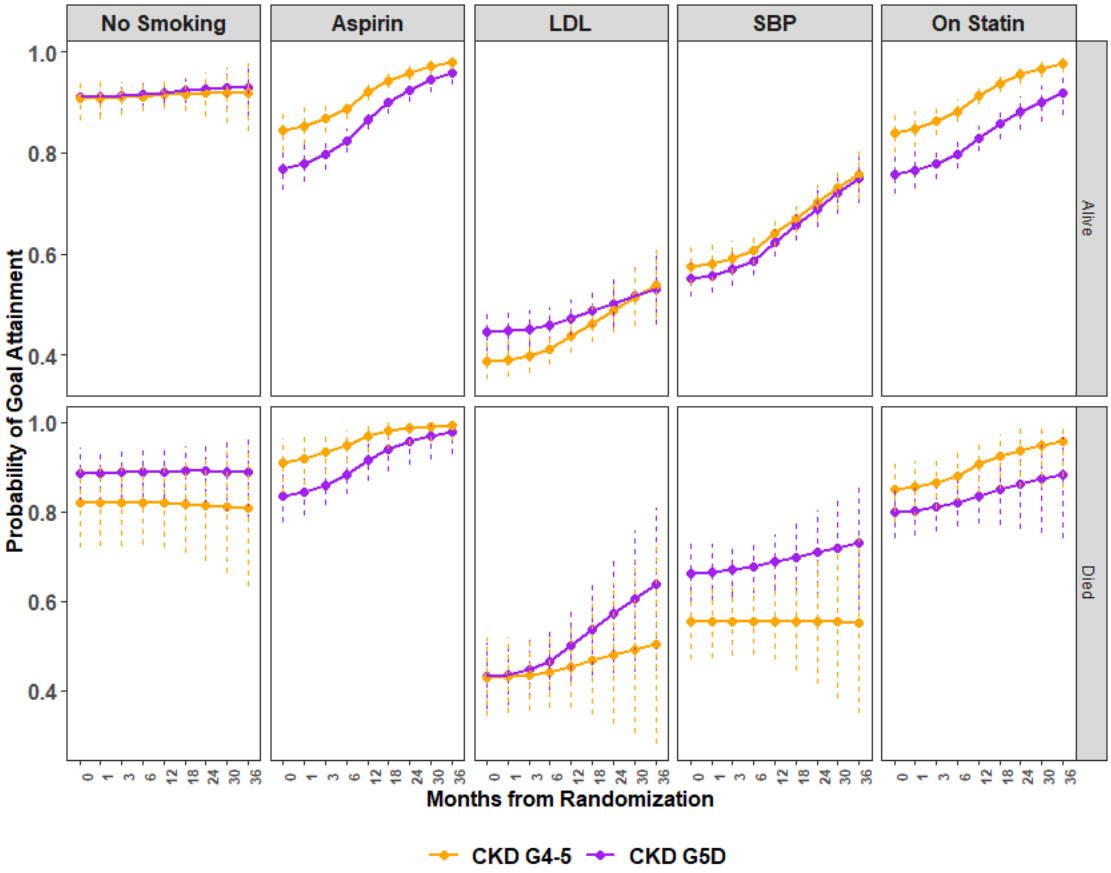
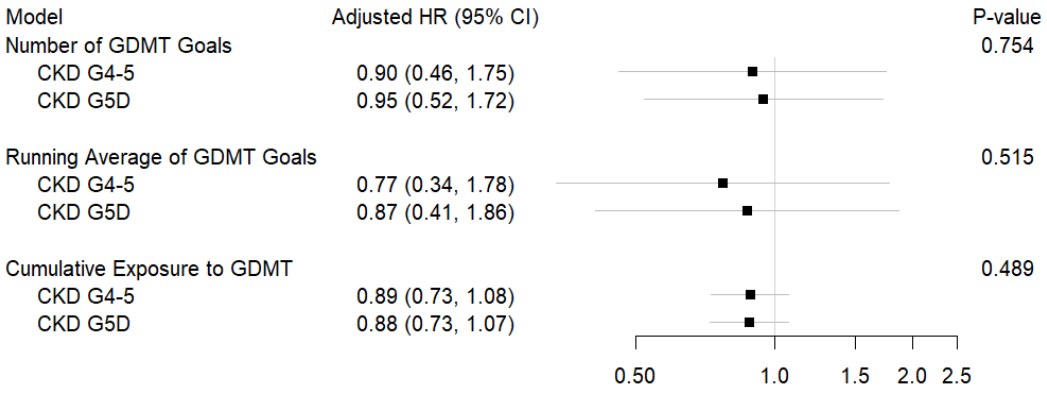


Figure S4: Hazard ratios for guideline-directed medical therapy (GDMT) goal attainment and the primary outcome, by chronic kidney disease (CKD) G4-5 versus CKD G5D. The p-value was obtained from a likelihood ratio test for the interaction term between GDMT goal attainment and dialysis status at baseline. The 5 GDMT goals include: No smoking; aspirin use; LDL-C < 70 mg/dl; SBP < 140 mmHg; being on a statin.



Supplemental Tables:

Table S1: Sensitivity analysis stratifying by dialysis at baseline: chronic kidney disease (CKD) G5D (on dialysis) at baseline. Hazard ratios and 95% confidence intervals for assessing the relationship of all-cause death/MI and number of guideline-directed medical therapy (GDMT) goals attained over follow-up, subsetted to CKD G5D at baseline, Cox regression models with GDMT goals as a time-dependent covariate.

	Number of GDMT Goals	**Running average of GDMT goals**	**Cumulative exposure to GDMT***
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Primary Outcome (all-cause mortality or non-fatal myocardial infarction)	0.93 (0.76, 1.13)	0.89 (0.62, 1.29)	0.89 (0.87, 0.92)
Baseline number of GDMT goals	1.12 (0.94, 1.34)	1.16 (0.88, 1.54)	1.73 (1.42, 2.1)
Female	0.88 (0.6, 1.28)	0.88 (0.61, 1.28)	0.86 (0.59, 1.25)
Age†	1.73 (1.34, 2.22)	1.73 (1.34, 2.23)	2.18 (1.66, 2.88)
INV	1.02 (0.74, 1.42)	1.02 (0.74, 1.42)	1.17 (0.84, 1.65)
Diabetes	2.13 (1.49, 3.05)	2.13 (1.49, 3.05)	2.33 (1.59, 3.4)
Ejection fraction†	0.72 (0.57, 0.9)	0.72 (0.57, 0.9)	0.76 (0.6, 0.96)

CI: confidence interval; GDMT: guideline directed medical therapy; HR: hazard ratio; INV: Initial invasive strategy.

*Per 1 goal increase over 60 days. The 5 GDMT goals include: No smoking; aspirin use; LDL-C < 70 mg/dl; SBP < 140 mmHg; being on a statin.

†Per interquartile increase in variable.

Table S2: Sensitivity analysis stratifying by dialysis at baseline chronic kidney disease (CKD) G4-5 (advanced CKD not on dialysis) at baseline. Hazard ratios and 95% confidence intervals for assessing the relationship of all-cause death/MI and number of guideline-directed medical therapy (GDMT) goals attained over follow-up, subsetted to CKD G4-5 at baseline, Cox regression models with GDMT goals as a time-dependent covariate.

	Number of GDMT Goals	**Running average of GDMT goals**	**Cumulative exposure to GDMT***
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Primary Outcome (all-cause mortality or non-fatal myocardial infarction)	0.9 (0.7, 1.16)	0.71 (0.43, 1.16)	0.86 (0.83, 0.89)
Baseline number of GDMT goals	1.18 (0.94, 1.48)	1.36 (0.96, 1.92)	2.02 (1.56, 2.6)
Female	0.84 (0.54, 1.31)	0.82 (0.53, 1.29)	0.77 (0.48, 1.24)
Age†	1.13 (0.84, 1.54)	1.13 (0.84, 1.53)	1.22 (0.87, 1.72)
INV	1.02 (0.69, 1.5)	1.01 (0.69, 1.49)	0.83 (0.55, 1.26)
Diabetes	1.6 (1.05, 2.44)	1.62 (1.06, 2.48)	1.77 (1.11, 2.82)
Ejection fraction†	0.66 (0.5, 0.86)	0.67 (0.51, 0.87)	0.68 (0.51, 0.92)

CI: confidence interval; GDMT: guideline directed medical therapy; HR: hazard ratio; INV: Initial invasive strategy.

*Per 1 goal increase over 60 days. The 5 GDMT goals include: No smoking; aspirin use; LDL-C < 70 mg/dl; SBP < 140 mmHg; being on a statin.

†Per interquartile increase in variable