SUPPLEMENTAL MATERIALS

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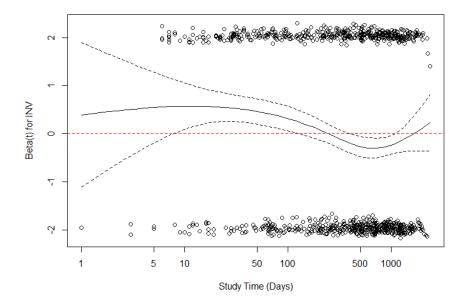
I. Supplemental Methods

Supplement A. Proportional Hazards Assessment for the Association of Death or MI with INV versus CON in the ISCHEMIA Trials

In the ISCHEMIA trial, the assumption of proportional hazards for the effect of INV versus CON was violated. For this combined trial analysis of death or MI, we evaluated whether the proportional hazards assumption held. We fit a Cox proportional hazards regression model of death or MI with treatment strategy, controlling for the same covariates as in the ISCHEMIA-CKD trial primary analysis.

The score test for the null hypothesis of proportional hazards for treatment strategy was rejected (P-value=0.0001). Figure A1 presents the time-varying hazard for INV versus CON. Thus, to assess heterogeneity of treatment effect, we used a Bayesian piecewise exponential model that accommodates non-proportional hazards (see **Supplement B**).

Figure IA. Scaled Schoenfeld residuals for INV versus CON by log-transformed time



Supplement B. Bayesian Modeling of Heterogeneity of Treatment Effect

Statistical model. We adapted the Dixon Simon²⁸ model to a Bayesian piecewise exponential non-proportional hazards ⁴⁸ setting in which the subgroup-specific treatment effects were allowed to vary over follow-up. In the piecewise exponential model, we define j = 1, ..., J time intervals to model the piecewise baseline hazard $h_{0j}(t)$ when follow-up time t belongs to interval j. To allow for non-proportional hazards in the subgroup-specific treatment effects, we define treatment-specific time intervals s = 1, ..., S. We specify the hazard of death or MI for participant i (i = 1, ..., n) at t in time interval j and treatment-specific interval s as

$$h_{iis}(t) = h_{0i}(t)exp(\mu_{is}),$$

where

$$\mu_{is} = \tau_s \mathsf{INV}_{is} + \gamma_{1s} \mathsf{INV}_{is} \times \mathsf{female}_i + \gamma_{2s} \mathsf{INV}_{is} \times \mathsf{diabetes}_i + \gamma_{3s} \mathsf{INV}_{is} \times \mathsf{diabetes}_i \times \mathsf{insulin}_i + \mathbf{w}_i^T \boldsymbol{\alpha}.$$
(1)

In equation (1), $INV_{is} = 1$ if participant *i* belongs to INV and *t* is in time interval *s*; and 0 otherwise. In other words, INV_{is} is the interaction between treatment strategy and the time intervals over which we are interested in characterizing the treatment effect. We have relaxed the assumption of proportional hazards by specifying a time-varying coefficient τ_s on treatment strategy, and time-varying coefficients γ_{rs} on the interactions between treatment strategy and the participant baseline risk factors (r = 1, ..., R) composing the DM-based subgroups. The w_i contains hypothesized confounders of the association between all-cause death/MI and the subgroup-specific treatment effects, with corresponding regression coefficients in α .

Prior distributions. To complete the Bayesian model specification, we assigned the following prior distributions: We assigned independent gamma prior distributions with shape and rate 0.001 for the piecewise baseline hazards h_{0j} ;⁴⁸ and, independent normal prior distributions with mean 0 and variance 100 on τ_s and α . Based on the assumption of exchangeability, for the interaction terms γ_{rs} , we assigned a normal prior distribution with mean 0 and standard deviation σ . For the hierarchical standard deviation σ , we used a truncated normal prior distribution with mean 0 and variance *A*. In sensitivity analysis, we examined values of A = 1 and A = 25.^{23,24} Results were robust to the different choices of *A*. The main text results are based on the more conservative A = 1.

Posterior inferences. Posterior summaries, including posterior means and 95% credible intervals of the hazard ratio for INV versus CON in each of the six subgroups were computed. We used the model coefficients to estimate the overall treatment effect in the No DM and DM subgroups based on a weighted average approach.²⁸ Using the DM subgroup as an example, the treatment effect in DM for time interval *s* is obtained as a weighted average of the:

- 1. Treatment effect for diabetes among females with no insulin usage, $(\tau_s + \gamma_{1s} + \gamma_{2s})$
- 2. Treatment effect for diabetes among females with insulin usage, $(\tau_s + \gamma_{1s} + \gamma_{2s} + \gamma_{3s})$
- 3. Treatment effect for diabetes among males with no insulin usage, $(\tau_s + \gamma_{2s})$
- 4. Treatment effect for diabetes among males with insulin usage, $(\tau_s + \gamma_{2s} + \gamma_{3s})$

The weights are the corresponding relative frequencies of participants with DM who are of a particular sex and insulin status:

- 5. w_{10s} is the proportion of diabetes participants surviving in time interval *s* who are female with no insulin usage.
- 6. w_{11s} is the proportion of diabetes participants surviving in time interval *s* who are female with insulin usage.
- 7. w_{00s} is the proportion of diabetes participants surviving in time interval *s* who are male with no insulin usage.
- 8. w_{01s} is the proportion of diabetes participants surviving in time interval *s* who are male with insulin usage.

Then, we obtain the treatment effect in the DM subgroup as

 $w_{10s}(\tau_s + \gamma_{1s} + \gamma_{2s}) + w_{11s}(\tau_s + \gamma_{1s} + \gamma_{2s} + \gamma_{3s}) + w_{00s}(\tau_s + \gamma_{2s}) + w_{01s}(\tau_s + \gamma_{2s} + \gamma_{3s}),$

which simplifies to

$$(\tau_s + \gamma_{2s}) + (w_{10s} + w_{11s})\gamma_{1s} + (w_{01s} + w_{11s})\gamma_{3s}$$

Covariates in w_i **and time intervals**. In w_i , we included age at randomization, dialysis status at baseline, eGFR among non-dialysis participants only, and ejection fraction, in addition to the main effects for sex, diabetes, and diabetes by insulin usage status. For the *J* piecewise time intervals for the baseline hazards, we followed the main ISCHEMIA trial primary analysis ¹⁰ using 0-14 days; 14-30 days; 30-60 days; 60-90 days; 90-180 days; 180-365 days; 1-1.5 years; 1.5-2 years; 2-2.5 years; 2.5-3 years, 3-3.5 years; 3.5-4 years; 4-5 years, 5-6 years; > 6 years. The *S* time intervals to allow the treatment effect to vary over time in years were: <1, 1-2, 2-3, 3-4, 4-5, >5.

Overall treatment effect in each time interval *s*. To assess whether subgroup-specific treatment effects in each time interval *s* represent HTE, we estimated overall treatment effect in each time interval *s*. We fit a separate Bayesian piecewise exponential non-proportional hazards model with the same *J* piecewise intervals for the baseline hazard and *S* intervals for the time-varying treatment effect. In addition to the time-varying treatment effect, we controlled for participant baseline characteristics including DM, DM by insulin treated, sex, age at randomization, dialysis status at baseline, eGFR among non-dialysis participants only, and ejection fraction.

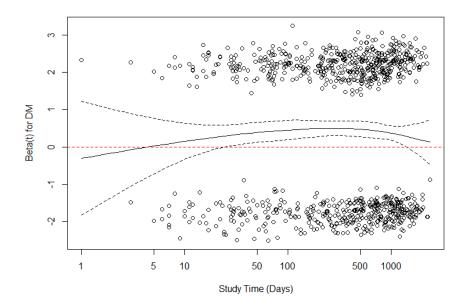
Model fitting. Bayesian models were run with 3 chains from dispersed initial values for 200,000 iterations with a burn-in of 100,000. Every 20th iteration was saved. Model convergence was assessed visually based on traceplots, and using the Gelman-Rubin diagnostic with convergence indicated by values being below the threshold of 1.1.⁴⁹ All analyses were conducted in R⁵⁰ and JAGS⁵¹ software programs using the R package R2jags.⁵²

Supplement C. Proportional Hazards Assessment for the Associations of Death or MI with DM Exposures of Interest

Based on separate multivariable Cox proportional hazards regression models for DM versus No DM status and DM-based subgroups, we assessed the assumption of proportional hazards based on the scaled Schoenfeld residuals for each covariate. Each model adjusted for age, treatment strategy, dialysis, eGFR among non-dialysis patients, and ejection fraction. The Cox model for DM versus No DM additionally adjusted for sex. We used a score test to test the null hypothesis of a zero slope – and thus, proportional hazards – in a regression of the scaled Schoenfeld residuals on log transformed time. We used the plots of the hazard for covariates of interest over time to guide testing interaction terms between time and the DM exposures of interest.

Based on the score test, the null hypothesis of proportional hazards for DM versus No DM was not rejected (p-value=0.4305). Figure C2a shows the time-varying hazard for DM versus now DM by log-transformed time. In the Cox model for DM-based subgroups, the score test rejected the null hypothesis of proportional hazards for non-insulin treated DM Male (p-value=0.0463); and Insulin treated DM Female (p-value=0.0120). For Insulin treated DM Male, the p-value of 0.0643 bordered statistical significance using a five percent significance level. While the plot for the time-varying hazard for non-insulin-treated DM Male appears largely linear, the time-varying hazard plots for Insulin-treated DM Male and Insulin-treated DM Female show some evidence of the magnitude of the hazard distinguished by early versus later follow-up (Figures C2b-d). Therefore, we explore differences using a 180-day cut-off.

Figure IIA. Scaled Schoenfeld residuals for DM versus No DM by log-transformed time



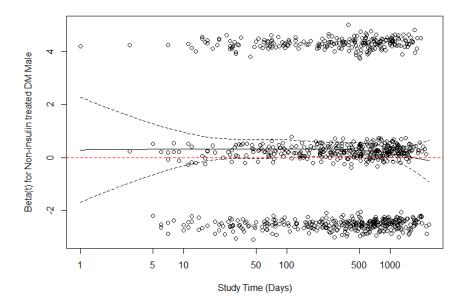


Figure IIB. Scaled Schoenfeld residuals for non-insulin treated DM male by log-transformed time

Figure IIC. Scaled Schoenfeld residuals for insulin treated DM male by log-transformed time

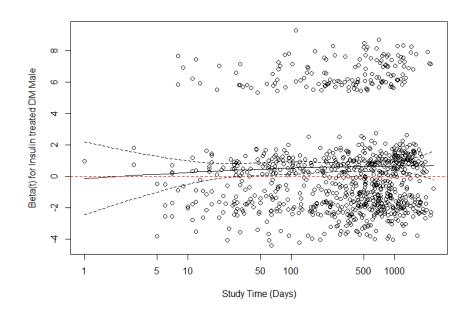


Figure IID. Scaled Schoenfeld residuals for non-insulin treated DM female by log-transformed time

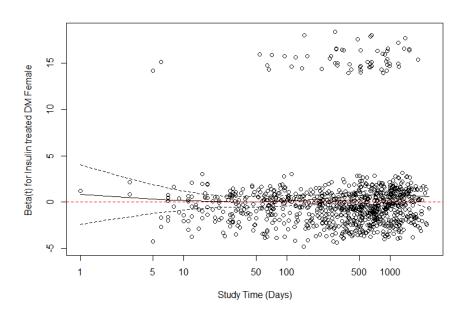


Table I presents the estimated hazard ratios for the DM-based subgroups within time interval defined by the 180 day cut-off. Compared to the reference level of males without DM, both insulin treated DM male and insulin treated DM female appear to have hazard ratios of greater magnitude in the post 180 day period versus the pre 180 day period.

Table I. Adjusted hazard ratios from a Cox non-proportional hazards model for the association of death or MI with DM-based subgroups in time intervals according to a 180-day cut off.^{*,†}

	Cox Model for DM-based subgroups					
	Before 180 days	After 180 days				
	HR (95% CI)	HR (95% CI)				
No DM Male	Ref	Ref				
No DM Female	0.82 (0.53, 1.27)	0.81 (0.61, 1.08)				
Non-insulin treated DM Male	1.39 (1.02, 1.88)	1.23 (1.00, 1.51)				
Non-insulin treated DM Female	1.22 (0.73, 2.02)	1.19 (0.86, 1.65)				
Insulin treated DM Male	1.39 (0.96, 2.02)	2.00 (1.58, 2.52)				
Insulin treated DM Female	0.97 (0.53, 1.77)	2.04 (1.49, 2.78)				

^{*}The Cox non-proportional hazards model adjusted for age, treatment strategy, dialysis, eGFR among non-dialysis patients, and ejection fraction.

[†]The cut-off of 180 days was selected based on Figures C2b-d, which show some evidence of the magnitude of the hazard distinguished by early versus later follow-up.

II. Supplemental Tables

Table I. Comparison of baseline participant characteristic by study inclusion status.

Demographics Ap at Randomization (years) Ap at Randomization (years) Ap at Randomization (years) Median (Q1, Q3) 5556 56 5900 Sender Female 1,410/5,956 (23.7%) 16,66 (28.6%) 1,394/5,900 (2 46 (57, 70) Race American Indian or Alaskan Native 18/5,876 (0.3%) 0/56 (0.0%) 18/5,820 (0.2 45,820 (0.2 45,8	cteristic	All Participants (N=5,956)	Excluded (N=56)	Included (N=5,900)
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White Multiple Races Reported 3,884/5,876 (66.1%) 13/5,876 (0.2%) 23/56 (41.1%) 0/56 (0.0%) 3,861/5,820 (6) 13/5,820 (6) Ethnicity Hispanic or Latino 861/5,550 (15.5%) 3/54 (5.6%) 858/5,496 (15 Diabetes Diabetes 2,608/5,956 (43.8%) 55/56 (98.2%) 2,553/5,900 (4) Diabetes Treatment Insulin Treated 772/2,554 (30.2%) 1/55 (1.8%) 7771/2,553 (3) Non-Insulin Diabetes Medication 1,447/2,554 (56.7%) 0/55 (0.0%) 1.447/2,553 (3) Non-Insulin Diabetes Medication 1,447/2,554 (56.7%) 0/55 (0.0%) 1.447/2,553 (3) Unknown 0/2,554 (0.0%) 54/55 (98.2%) 0/2,553 (0) Cigarette Smoking Never Smoked 2,579/5,951 (43.3%) 24/56 (42.9%) 2,555/5,895 (4) Former Smoker 2,648/5,951 (44.5%) 22/56 (39.3%) 2,626/5,895 (4) Current Smoker 2,648/5,951 (44.5%) 22/56 (39.3%) 2,626/5,895 (4) Baseline Hemoglobin A1c N 3910 54 3856 Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,109/5,882 (1) Prior Myocardial Infarction 1,124/5,338 (18.9%)				16/5,820 (0.3%)
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Former Smoker Current Smoker 2,648/5,951 (44.5%) 22/56 (39.3%) 2,626/5,895 (4 39.3%) Current Smoker 724/5,951 (12.2%) 10/56 (17.9%) 714/5,895 (12 Clinical History Hypertension 4,500/5,934 (75.8%) 38/56 (67.9%) 4,462/5,878 (78) Baseline Hemoglobin A1c N 3910 54 3856 Median (Q1, Q3) 54 3856 Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,266/5,075 (2- Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (12- Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (20- Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (30- On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7. eGFR among Patients not on Dialysis at Baseline 5538 53 5485				
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Clinical History 4,500/5,934 (75.8%) 38/56 (67.9%) 4,462/5,878 (79) Baseline Hemoglobin A1c 3910 54 3856 N 6 (6, 8) 7 (7, 7) 6 (6, 8) Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,266/5,075 (20) Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (11) Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (20) Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3) Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (30) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7) eGFR among Patients not on Dialysis at Baseline 5538 53 5485			· · · · ·	2,626/5,895 (44.5%)
Hypertension 4,500/5,934 (75.8%) 38/56 (67.9%) 4,462/5,878 (74) Baseline Hemoglobin A1c 3910 54 3856 N 6 (6, 8) 7 (7, 7) 6 (6, 8) Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,266/5,075 (24) Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (11) Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (24) Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3.) Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (34) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7.) eGFR among Patients not on Dialysis at Baseline 5538 53 5485	ent Smoker	724/5,951 (12.2%)	10/56 (17.9%)	714/5,895 (12.1%)
Baseline Hemoglobin A1c 3910 54 3856 Median (Q1, Q3) 6 (6, 8) 7 (7, 7) 6 (6, 8) Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,266/5,075 (24) Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (14) Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (24) Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3.) Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (34) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7.) eGFR among Patients not on Dialysis at Baseline 5538 53 5485				
N 3910 54 3856 Median (Q1, Q3) 6 (6, 8) 7 (7, 7) 6 (6, 8) Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,266/5,075 (24) Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (14) Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (24) Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3.) Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (34) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7.) eGFR among Patients not on Dialysis at Baseline 5538 53 5485	ension	4,500/5,934 (75.8%)	38/56 (67.9%)	4,462/5,878 (75.9%)
Median (Q1, Q3) 6 (6, 8) 7 (7, 7) 6 (6, 8) Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,266/5,075 (24) Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (14) Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (24) Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3) Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (34) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7. eGFR among Patients not on Dialysis at Baseline 5538 53 5485	ie Hemoglobin A1c			
Family History of Premature Coronary Heart Disease 1,282/5,127 (25.0%) 16/52 (30.8%) 1,266/5,075 (24) Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (14) Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (24) Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3.) Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (34) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7.) eGFR among Patients not on Dialysis at Baseline 5538 53 5485				
Prior Myocardial Infarction 1,124/5,938 (18.9%) 15/56 (26.8%) 1,109/5,882 (18.9%) Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (24.9%) Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3.9%) Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (34.9%) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7.9%) eGFR among Patients not on Dialysis at Baseline 5538 53 5485	lian (Q1, Q3)	6 (6, 8)	7 (7, 7)	6 (6, 8)
Prior Percutaneous Coronary Intervention (PCI) 1,196/5,952 (20.1%) 13/56 (23.2%) 1,183/5,896 (24 Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3. Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (34 On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7. eGFR among Patients not on Dialysis at Baseline 5538 53 5485	History of Premature Coronary Heart Disease	1,282/5,127 (25.0%)	16/52 (30.8%)	1,266/5,075 (24.9%)
Prior Coronary Artery Bypass Graft (CABG) 231/5,956 (3.9%) 2/56 (3.6%) 229/5,900 (3. Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (30.0%) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7. eGFR among Patients not on Dialysis at Baseline 5538 53 5485	yocardial Infarction	1,124/5,938 (18.9%)	15/56 (26.8%)	1,109/5,882 (18.9%)
Prior MI or Prior PCI or Prior CABG 1,794/5,938 (30.2%) 19/56 (33.9%) 1,775/5,882 (30.2%) On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7.1%) eGFR among Patients not on Dialysis at Baseline 5538 53 5485	ercutaneous Coronary Intervention (PCI)	1,196/5,952 (20.1%)	13/56 (23.2%)	1,183/5,896 (20.1%)
On Dialysis Status at Baseline 416/5,954 (7.0%) 1/54 (1.9%) 415/5,900 (7. eGFR among Patients not on Dialysis at Baseline N 5538 53 5485	oronary Artery Bypass Graft (CABG)	231/5,956 (3.9%)	2/56 (3.6%)	229/5,900 (3.9%)
eGFR among Patients not on Dialysis at Baseline N 5538 53 5485	I or Prior PCI or Prior CABG	1,794/5,938 (30.2%)	19/56 (33.9%)	1,775/5,882 (30.2%)
N 5538 53 5485	lysis Status at Baseline	416/5,954 (7.0%)	1/54 (1.9%)	415/5,900 (7.0%)
	among Patients not on Dialysis at Baseline			
Median (Q1, Q3) 80 (64. 95) 81 (66. 103) 80 (64. 95		5538		
	ian (Q1, Q3)	80 (64, 95)	81 (66, 103)	80 (64, 95)
eGFR ml/min/1.73 m ²	ml/min/1.73 m²			
			44/56 (78.6%)	4,396/5,900 (74.5%)
				735/5,900 (12.5%)
	s than 30 or on dialysis		7/56 (12.5%)	769/5,900 (13.0%)

Non-Cardiac Vascular and Comorbidity History

Characteristic	All Participants (N=5,956)	Excluded (N=56)	Included (N=5,900)
Prior Carotid Artery Surgery or Stent, Stroke, or Transient Ischemic Attack (TIA)	477/5,941 (8.0%)	3/54 (5.6%)	474/5,887 (8.1%)
Prior Stroke	219/5,955 (3.7%)	2/56 (3.6%)	217/5,899 (3.7%)
Prior Peripheral Vascular Disease (PAD) or Surgery or Percutaneous Procedure for PAD	252/5,945 (4.2%)	2/54 (3.7%)	250/5,891 (4.2%)
Angina History			
Baseline Seattle Angina Questionnaire Angina Frequency Scale			
N	5,371	48	5,323
Median (25th, 75th)	90 (70, 100)	90 (75, 100)	90 (70, 100)
Baseline Seattle Angina Questionnaire Angina			
Frequency Scale			
Daily Angina (0-30)	128/5,371 (2.4%)	1/48 (2.1%)	127/5,323 (2.4%)
Weekly Angina (31-60)	906/5,371 (16.9%)	6/48 (12.5%)	900/5,323 (16.9%)
Monthly Angina (61-99)	2,340/5,371 (43.6%)	18/48 (37.5%)	2,322/5,323 (43.6%)
No Angina in Past Month (100)	1,997/5,371 (37.2%)	23/48 (47.9%)	1,974/5,323 (37.1%)
Participant Has Ever Had Angina	5,225/5,956 (87.7%)	46/56 (82.1%)	5,179/5,900 (87.8%)
New Onset of Angina Over the Past 3 Months	976/5,666 (17.2%)	10/56 (17.9%)	966/5,610 (17.2%)
Angina Began or Became More Frequent Over the Past 3 Months	1,500/5,209 (28.8%)	12/46 (26.1%)	1,488/5,163 (28.8%)
Left ventricular systolic dysfunction (35%≤EF<45%)	310/5,951 (5.2%)	4/56 (7%)	306/5,895 (5%)
Ejection Fraction			
N	5,256	50	5,206
Median (25th, 75th)	60 (55, 65)	62 (59, 67)	60 (55, 65)

	All Participants in CON strategy (N=2,955)	No Diabetes at Baseline (n=1,668)	Diabetes at Baseline (n=1,287)	P- value
Overall Revascularization, n (%)	615/2955 (20.8%)	327/1668 (19.6%)	288/1287 (22.4%)	0.0726
PCI	425/615 (69.1%)	228/327 (69.7%)	197/288 (68.4%)	
CABG	190/615 (30.9%)	99/327 (30.3%)	91/288 (31.6%)	
Revascularization not preceded by a Primary event, n (%)	486/2955 (16.4%)	270/1668 (16.2%)	216/1287 (16.8%)	0.7014
PCI	344/486 (70.8%)	190/270 (70.4%)	154/216 (71.3%)	
CABG	142/486 (29.2%)	80/270 (29.6%)	62/216 (28.7%)	
Revascularization preceded by a Primary event, n (%)	129/2955 (4.4%)	57/1668 (3.4%)	72/1287 (5.6%)	0.0054
PCI	81/129 (62.8%)	38/57 (66.7%)	43/72 (59.7%)	
CABG	48/129 (37.2%)	19/57 (33.3%)	29/72 (40.3%)	

Table II. Revascularization in the conservative strategy by diabetes status at baseline

	All Participants without Diabetes at Baseline (N=3,347)			All Participants with Diabetes (N=2,553)			
Characteristic	INV	CON		INV			
	(N=1,679)	(N=1,668)	P-value	(N=1,266)	(N=1,287)	P-value	
Demographics	· _ · _ *	<u> </u>		· · * * * * * *			
Age at Randomization (yrs)			0.437			0.398	
Ν	1679	1668		1266	1287		
Median (Q1, Q3)	64 (57, 71)	64 (57, 71)		64 (58, 70)	64 (58, 70)		
Gender			0.727			0.166	
Female	388/1.679	377/1.668	0.727	327/1,266	302/1,287	0.100	
T emaie	(23.1%)	(22.6%)		(25.8%)	(23.5%)		
Data			0.000			0 507	
Race	7/4 000 (0 40/)	0/4 0 40 (0 40/)	0.603	2/4 2 4 2 (0 20()		0.587	
American Indian or Alaskan Native	7/1,669 (0.4%)	2/1,649 (0.1%)		3/1,242 (0.2%)	6/1,260 (0.5%)		
Asian	424/1,669	413/1,649		399/1,242	411/1,260		
	(25.4%)	(25.0%)		(32.1%)	(32.6%)		
Native Hawaiian or Other Pacific Islander	2/1,669 (0.1%)	4/1,649 (0.2%)		3/1,242 (0.2%)	7/1,260 (0.6%)		
Black or African American	51/1,669 (3.1%)	52/1,649 (3.2%)		77/1,242 (6.2%)	85/1,260 (6.7%)		
White	1,181/1,669	1,175/1,649		756/1,242	749/1,260		
· · · · · · · · · · · · · · · · · · ·	(70.8%)	(71.3%)		(60.9%)	(59.4%)		
Multiple Races Reported	4/1,669 (0.2%)	3/1,649 (0.2%)		4/1,242 (0.3%)	2/1,260 (0.2%)		
Ethnicity			0.189			0.326	
Ethnicity Hispanic or Latino	212/1,582	235/1,563	0.169	212/1,161	199/1,190	0.320	
Thispanic of Latino	(13.4%)	(15.0%)		(18.3%)	(16.7%)		
					, , , , , , , , , , , , , , , , , , ,	0.077	
Diabetes Treatment Insulin Treated				277/1 266	204/4 207	0.877	
Insulin Treated	-	-		377/1,266 (29.8%)	394/1,287 (30.6%)		
Non-Insulin Diabetes	_	_		720/1,266	727/1,287		
Medication				(56.9%)	(56.5%)		
None/Diet Controlled	-	-		169/1,266	166/1,287		
				(13.3%)	(12.9%)		
Cigaratta Smaking						0.241	
Cigarette Smoking Never Smoked	684/1,679	692/1,666		606/1,265	E72/1 20E	0.241	
Never Smoked	(40.7%)	(41.5%)		(47.9%)	573/1,285 (44.6%)		
Former Smoker	754/1,679	746/1,666		540/1,265	586/1,285		
	(44.9%)	(44.8%)		(42.7%)	(45.6%)		
Current Smoker	241/1,679	228/1,666			126/1,285 (9.8%)		
	(14.4%)	(13.7%)					
Clinical History							
Hypertension	1,185/1,671	1,172/1,660	0.842	1,036/1,263	1,069/1,284	0.413	
riypertension	(70.9%)	(70.6%)	0.042	(82.0%)	(83.3%)	0.410	
Depairs Homestatis 0/ At-			0.100			0.040	
Baseline Hemoglobin % A1c	770	756	0.108	1159	1171	0.040	
N Median (Q1, Q3)	6 (6, 6)	6 (5, 6)		7 (7, 8)	7 (7, 8)		
Prior Myocardial Infarction	312/1,675	306/1,663	0.866	238/1,261	253/1,283	0.589	
	(18.6%)	(18.4%)		(18.9%)	(19.7%)		
Prior Percutaneous Coronary	326/1,678	316/1,666	0.735	292/1,265	249/1,287	0.021	
Intervention (PCI)	(19.4%)	(19.0%)		(23.1%)	(19.3%)		
Driar Caropany Artony Dupasa	57/1 670 /2 40/	53/1 669 (2 20/)	0 794	66/1 266 /E 20/)	52/1 297 (4 40/)	0 100	
Prior Coronary Artery Bypass Graft (CABG)	31/1,019 (3.4%)	53/1,668 (3.2%)	0.724	66/1,266 (5.2%)	53/1,287 (4.1%)	0.189	

Table III. Comparison of participant baseline characteristics by treatment strategy, within subgroups defined by diabetes status at baseline

	All Participants without Diabetes at Baseline (N=3,347)				All Participants with Diabetes (N=2,553)		
Characteristic	INV	CON		INV	CON		
	(N=1,679)	(N=1,668)	P-value	(N=1,266)	(N=1,287)	P-value	
Prior MI or Prior PCI or Prior CABG	483/1,675 (28.8%)	483/1,662 (29.1%)	0.886	419/1,261 (33.2%)	390/1,284 (30.4%)	0.122	
eGFR among Patients not on Dialysis at Baseline			0.779			0.736	
N Median (Q1, Q3)	1589 81 (67, 96)	1564 81 (66, 96)		1159 78 (59, 94)	1173 78 (60, 94)		
EGFR ml/min/1.73 m2 Greater than 60	1,319/1,679	1,323/1,668	0.414	864/1,266	890/1,287	0.884	
Between 30 to 59	(78.6%) 198/1,679 (11.8%)	(79.3%) 174/1,668 (10.4%)		(68.2%) 183/1,266 (14.5%)	(69.2%) 180/1,287 (14.0%)		
Less than 30 or on dialysis		(10.478) 171/1,668 (10.3%)		(14.378) 219/1,266 (17.3%)	(14.0%) 217/1,287 (16.9%)		
On Dialysis at Baseline	90/1,679 (5.4%)	104/1,668 (6.2%)	0.279	107/1,266 (8.5%)	114/1,287 (8.9%)	0.715	
Non-Cardiac Vascular and Comorbidity History							
Prior Carotid Artery Surgery or Stent, Stroke, or Transient Ischemic Attack (TIA)	126/1,676 (7.5%)	106/1,664 (6.4%)	0.192	125/1,263 (9.9%)	117/1,284 (9.1%)	0.499	
Prior Stroke	55/1,678 (3.3%)	37/1,668 (2.2%)	0.061	63/1,266 (5.0%)	62/1,287 (4.8%)	0.852	
Prior Surgery or Percutaneous Procedure for PAD	66/1,677 (3.9%)	47/1,666 (2.8%)	0.075	74/1,265 (5.8%)	63/1,283 (4.9%)	0.293	
Angina History Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.197			0.062	
N	1,535	1,544		1,111	1,133		
Median (25th, 75th)	90 (70, 100)	90 (70, 100)		90 (70, 100)	90 (70, 100)		
Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.557			0.255	
Daily Angina (0-30) Weekly Angina (31-60)	39/1,535 (2.5%) 288/1,535 (18.8%)	33/1,544 (2.1%) 265/1,544 (17.2%)		29/1,111 (2.6%) 186/1,111 (16.7%)	26/1,133 (2.3%) 161/1,133 (14.2%)		
Monthly Angina (61-99)	(10.0%) 670/1,535 (43.6%)	(17.27%) 697/1,544 (45.1%)		475/1,111 (42.8%)	480/1,133 (42.4%)		
No Angina in Past Month (100)	538/1,535 (35.0%)	549/1,544 (35.6%)		421/1,111 (37.9%)	466/1,133 (41.1%)		
Participant Has Ever Had Angina	1,508/1,679 (89.8%)	1,476/1,668 (88.5%)	0.180	1,084/1,266 (85.6%)	1,111/1,287 (86.3%)	0.608	
New Onset of Angina Over the Past 3 Months	283/1,593 (17.8%)	287/1,581 (18.2%)	0.776	183/1,203 (15.2%)	213/1,233 (17.3%)	0.168	
Left ventricular systolic dysfunction (35%≤EF<45%)	67/1,678 (4.0%)	82/1,666 (4.9%)	0.223	87/1,265 (6.9%)	70/1,286 (5.4%)	0.154	
Ejection Fraction*			0.307			0.406	
N Median (25th, 75th)	1,490 60 (55, 65)	1,454 60 (55, 65)		1,122 60 (54, 65)	1,140 60 (54, 65)		
Optimal Medical Therapy [†]							

Optimal Medical Therapy[†]

	All Participants without Diabetes at Baseline (N=3,347)			All Participants with Diabetes (N=2,553)		
Characteristic	INV	CON		INV	CON	
	(N=1,679)	(N=1,668)	P-value	(N=1,266)	(N=1,287)	P-value
LDL cholesterol < 70 mg/dL and on any statin	440/1,600 (27.5%)	421/1,601 (26.3%)	0.442	462/1,193 (38.7%)	492/1,221 (40.3%)	0.431
Systolic blood pressure < 140 mmHg	1,108/1,668 (66.4%)	1,132/1,663 (68.1%)	0.312	730/1,261 (57.9%)	783/1,281 (61.1%)	0.097
Aspirin or other anti-platelet o anti-coagulant	r 1,600/1,677 (95.4%)	1,565/1,668 (93.8%)	0.042	1,199/1,266 (94.7%)	1,215/1,286 (94.5%)	0.798
Non smoker	1,438/1,679 (85.6%)	1,438/1,666 (86.3%)	0.578	1,146/1,265 (90.6%)	1,159/1,285 (90.2%)	0.733

		No DM Male (N=2,582)			DM Female (N=765)	
Characteristic	INV	CON		INV	CON	
	(N=1,291)	(N=1,291)	P-value	(N=388)	(N=377)	P-value
Demographics			0.404			0.040
Age at Randomization (yrs) N	1291	1291	0.131	388	377	0.248
Median (Q1, Q3)	64 (57, 71)	63 (56, 70)		64 (59, 71)	65 (58, 72)	
	0+(07,71)	00 (00, 70)		04 (00, 71)	00 (00, 72)	
Race			0.567			0.552
American Indian or	5/1,281 (0.4%)	1/1,280 (0.1%)		2/388 (0.5%)	1/369 (0.3%)	
Alaskan Native						
Asian	339/1,281	344/1,280		85/388 (21.9%)	69/369 (18.7%)	
Native Hawaiian an Othan	(26.5%)	(26.9%)		0/200 (0.00/)	0/077 (0.00/)	
Native Hawaiian or Other Pacific Islander	2/1,281 (0.2%)	4/1,280 (0.3%)		0/388 (0.0%)	0/377 (0.0%)	
Black or African American	35/1,281 (2.7%)	40/1,280 (3.1%)		16/388 (4.1%)	12/369 (3.3%)	
White	896/1,281	888/1,280		· · /	287/369 (77.8%)	
	(69.9%)	(69.4%)		((,	
Multiple Races Reported	4/1,281 (0.3%)	3/1,280 (0.2%)		0/388 (0.0%)	0/377 (0.0%)	
Ethnicity	100/1 010	101/1 010	0.367			0.277
Hispanic or Latino	166/1,216	181/1,212		46/366 (12.6%)	54/351 (15.4%)	
	(13.7%)	(14.9%)				
Cigarette Smoking			0.735			0.850
Never Smoked	449/1,291	459/1,289	0.100	235/388 (60.6%)	233/377 (61.8%)	0.000
	(34.8%)	(35.6%)			(,	
Former Smoker	641/1,291	643/1,289		113/388 (29.1%)	103/377 (27.3%)	
	(49.7%)	(49.9%)				
Current Smoker	201/1,291	187/1,289		40/388 (10.3%)	41/377 (10.9%)	
	(15.6%)	(14.5%)				
Clinical History						
Hypertension	900/1,285	871/1,285	0.216	285/386 (73.8%)	301/375 (80.3%)	0.035
	(70.0%)	(67.8%)			,	
Baseline Hemoglobin % A1c			0.147			0.504
N Madian (04, 02)	617	604		153	152	
Median (Q1, Q3)	6 (6, 6)	6 (5, 6)		6 (6, 6)	6 (6, 6)	
Prior Myocardial Infarction	256/1,288	246/1,286	0.633	56/387 (14.5%)	60/377 (15.9%)	0.578
i noi myööäralai marollon	(19.9%)	(19.1%)	0.000	00,001 (11.070)		0.070
	· · ·					
Prior Percutaneous Coronary	269/1,291	262/1,289	0.748	57/387 (14.7%)	54/377 (14.3%)	0.874
Intervention (PCI)	(20.8%)	(20.3%)				
Prior Coronary Artery Bypass	52/1 201 (1 09/)	10/1 001 (0 00/)	0.202	E/200 (1 20/)	11/377 (2.9%)	0 115
Graft (CABG)	52/1,291 (4.0%)	42/1,291 (3.3%)	0.293	5/388 (1.3%)	11/3/7 (2.9%)	0.115
Prior MI or Prior PCI or Prior	396/1,289	395/1,285	0.992	87/386 (22.5%)	88/377 (23.3%)	0.792
CABG	(30.7%)	(30.7%)		,	· · · · ·	
eGFR among Patients not on			0.754			0.848
Dialysis at Baseline	1005	1210		254	245	
N Median (Q1, Q3)	1235 83 (69, 98)	1219 82 (69, 97)		354 75 (60, 91)	345 76 (59, 91)	
	00 (09, 90)	02 (03, 37)		13 (00, 31)	10 (39, 91)	
EGFR ml/min/1.73 m2			0.059			0.500
Greater than 60	1,047/1,291	1,067/1,291		272/388 (70.1%)	256/377 (67.9%)	
	(81.1%)	(82.6%)		, ,	, ,	
Between 30 to 59	144/1,291	110/1,291 (8.5%)		54/388 (13.9%)	64/377 (17.0%)	
	(11.2%)					

Table IVa. Comparison of participant baseline characteristics by treatment strategy,	
within DM-based subgroups for males and females without DM	

		No DM Male (N=2,582)		No DM Female (N=765)			
Characteristic	INV	CON		INV	CON		
	(N=1,291)	(N=1,291)	P-value	(N=388)	(N=377)	P-value	
Less than 30 or on dialysis	100/1,291 (7.7%)	114/1,291 (8.8%)		62/388 (16.0%)	57/377 (15.1%)		
On Dialysis at Baseline	56/1,291 (4.3%)	72/1,291 (5.6%)	0.147	34/388 (8.8%)	32/377 (8.5%)	0.892	
Non-Cardiac Vascular and Comorbidity History							
Prior Carotid Artery Surgery or Stent, Stroke, or Transient Ischemic Attack (TIA)	100/1,290 (7.8%)	77/1,287 (6.0%)	0.076	26/386 (6.7%)	29/377 (7.7%)	0.610	
Prior Stroke	41/1,290 (3.2%)	25/1,291 (1.9%)	0.046	14/388 (3.6%)	12/377 (3.2%)	0.746	
Prior Surgery or Percutaneous Procedure for PAD	55/1,290 (4.3%)	35/1,289 (2.7%)	0.032	11/387 (2.8%)	12/377 (3.2%)	0.783	
Angina History Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.131			0.943	
N Median (25th, 75th)	1,173 90 (70, 100)	1,179 90 (70, 100)		362 80 (70, 100)	365 80 (70, 100)		
Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.267			0.937	
Daily Angina (0-30) Weekly Angina (31-60)	28/1,173 (2.4%) 224/1,173 (19.1%)	21/1,179 (1.8%) 195/1,179 (16.5%)		11/362 (3.0%) 64/362 (17.7%)	12/365 (3.3%) 70/365 (19.2%)		
Monthly Angina (61-99)	494/1,173 (42.1%)	(10.070) 520/1,179 (44.1%)		176/362 (48.6%)	177/365 (48.5%)		
No Angina in Past Month (100)	(42.176) 427/1,173 (36.4%)	(443/1,179 (37.6%)		111/362 (30.7%)	106/365 (29.0%)		
Participant Has Ever Had Angina	1,163/1,291 (90.1%)	1,135/1,291 (87.9%)	0.069	345/388 (88.9%)	341/377 (90.5%)	0.486	
New Onset of Angina Over the Past 3 Months	(90.1%) 223/1,229 (18.1%)	(87.3%) 226/1,230 (18.4%)	0.883	60/364 (16.5%)	61/351 (17.4%)	0.750	
Left ventricular systolic dysfunction (35%≤EF≤45%)	60/1,290 (4.7%)	63/1,289 (4.9%)	0.850	7/388 (1.8%)	19/377 (5.0%)	0.023	
Ejection Fraction*			0.865			0.117	
N Median (25th, 75th)	1,149 60 (55, 64)	1,126 60 (55, 64)		341 62 (59, 67)	328 62 (56, 68)		
Optimal Medical Therapy [†]							
LDL cholesterol < 70 mg/dL and on any statin	367/1,228 (29.9%)	344/1,235 (27.9%)	0.266	73/372 (19.6%)	77/366 (21.0%)	0.633	
Systolic blood pressure < 140 mmHg	854/1,280 (66.7%)	887/1,287 (68.9%)	0.233	254/388 (65.5%)	245/376 (65.2%)	0.930	
Aspirin or other anti-platelet or anti-coagulant	1,242/1,289 (96.4%)	1,219/1,291 (94.4%)	0.019	358/388 (92.3%)	346/377 (91.8%)	0.802	
Non smoker	1,090/1,291 (84.4%)	1,102/1,289 (85.5%)	0.451	348/388 (89.7%)	336/377 (89.1%)	0.799	
*-reported value, if available. If not TISCHEMIA definition of optimal me		ab entered value. EF,	ejection fraction				

	No	on Insulin DM Ma (N=1,393)	le	Non-Insulin DM Female (N=389)			
Characteristic	INV	CON		INV			
	(N=683)	(N=710)	P-value	(N=206)	CON (N=183)	P-value	
Demographics							
Age at Randomization (yrs)			0.780			0.187	
N	683	710		206	183		
Median (Q1, Q3)	64 (58, 70)	64 (57, 70)		65 (58, 70)	65 (60, 71)		
Race			0.146			0.191	
American Indian or	0/670 (0.0%)	4/698 (0.6%)	0.110	0/201 (0.0%)	1/178 (0.6%)	0.101	
Alaskan Native	0/010 (0.070)	4/000 (0.070)		0/201 (0.070)	1/1/0 (0.070)		
Asian	239/670 (35.7%)	274/698 (39.3%)		76/201 (37.8%)	56/178 (31.5%)		
Native Hawaiian or Other	3/670 (0.4%)	2/698 (0.3%)		0/201 (0.0%)	2/178 (1.1%)		
Pacific Islander	0,010 (0.170)	2/000 (0.070)		0/201 (0.070)	2,110 (11170)		
Black or African American	34/670 (5.1%)	31/698 (4.4%)		7/201 (3.5%)	12/178 (6.7%)		
White	· · · ·	387/698 (55.4%)		· · ·	107/178 (60.1%)		
Multiple Races Reported	2/670 (0.3%)	0/698 (0.0%)		1/201 (0.5%)	0/178 (0.0%)		
Multiple Races Reported	2/0/0 (0.070)	0/030 (0.070)		1/201 (0.070)	0/1/0 (0.070)		
Ethnicity			0.055			0.161	
Hispanic or Latino	115/620 (18.5%)	94/646 (14.6%)	01000	28/191 (14.7%)	35/173 (20.2%)	00.	
				20,101 (11170)	00, 110 (2012,0)		
Diabetes Treatment			0.834			0.942	
Non-Insulin Diabetes	554/683 (81 1%)	579/710 (81.5%)	0.001	166/206 (80.6%)	148/183 (80.9%)	0.012	
Medication	004/000 (01.170)	010/110 (01.070)		100/200 (00.070)	140/100 (00.070)		
None/Diet Controlled	129/683 (18.9%)	131/710 (18.5%)		40/206 (19.4%)	35/183 (19.1%)		
				10/200 (1011/0)			
Cigarette Smoking			0.409			0.435	
Never Smoked	277/682 (40.6%)	272/709 (38.4%)		150/206 (72.8%)	128/182 (70.3%)		
Former Smoker	· · · ·	354/709 (49.9%)		38/206 (18.4%)	42/182 (23.1%)		
Current Smoker	66/682 (9.7%)	83/709 (11.7%)		18/206 (8.7%)	12/182 (6.6%)		
Clinical History							
Hypertension	538/682 (78.9%)	553/707 (78.2%)	0.762	165/206 (80.1%)	159/183 (86.9%)	0.073	
Baseline Hemoglobin % A1c			0.111			0.987	
Ν	628	642		183	163		
Median (Q1, Q3)	7 (6, 8)	7 (6, 8)		7 (6, 8)	7 (6, 8)		
Prior Myocardial Infarction	126/670 (18.6%)	141/708 (19.9%)	0.521	34/205 (16.6%)	30/183 (16.4%)	0.959	
	120/013 (10.070)	141/100 (10.070)	0.021	34/203 (10.070)	30/103 (10.470)	0.000	
Prior Percutaneous Coronary	154/682 (22.6%)	136/710 (19.2%)	0.116	32/206 (15.5%)	23/183 (12.6%)	0.402	
Intervention (PCI)	()						
Prior Coronary Artery Bypass	40/683 (5.9%)	32/710 (4.5%)	0.255	3/206 (1.5%)	4/183 (2.2%)	0.711	
Graft (CABG)							
Prior MI or Prior PCI or Prior	223/679 (32.8%)	214/708 (30.2%)	0.294	50/205 (24.4%)	40/183 (21.9%)	0.555	
CABG							
CFD among Dationts act on			0.074			0.045	
eGFR among Patients not on Dialysis at Baseline			0.974			0.845	
N	657	681		194	174		
	81 (65, 96)	80 (65, 96)			74 (60, 93)		
Median (Q1, Q3)	01 (00, 90)	00 (00, 90)		76 (60, 92)	14 (00, 93)		
ECEP ml/min/1 72 m2			0 504			0 070	
EGFR ml/min/1.73 m2	EAE/600 /70 00/	EC0/740 (70 00/)	0.594	146/006 (70 004)	121/102 /74 00/	0.978	
Greater than 60	545/683 (79.8%)	· · ·		146/206 (70.9%)	131/183 (71.6%)		
Between 30 to 59	77/683 (11.3%)	91/710 (12.8%)		40/206 (19.4%)	34/183 (18.6%)		
Less than 30 or on dialysis	61/683 (8.9%)	57/710 (8.0%)		20/206 (9.7%)	18/183 (9.8%)		
On Dialysis at Readline	26/602 (2 00/)	20/710 (4 40/)	0 700	10/00G (F 00/)	0/102 (1 00/)	0 600	
On Dialysis at Baseline	26/683 (3.8%)	29/710 (4.1%)	0.790	12/206 (5.8%)	9/183 (4.9%)	0.693	

Table IVb. Comparison of participant baseline characteristics by treatment strategy, within DM-based subgroups for males and females with non-insulin treated DM

	-	on Insulin DM Ma (N=1,393)	le	Non-Insulin DM Female (N=389)			
Characteristic	INV (N=683)	CON (N=710)	P-value	INV (N=206)	CON (N=183)	P-value	
Non-Cardiac Vascular and Comorbidity History Prior Carotid Artery Surgery or Stent, Stroke, or Transient Ischemic Attack (TIA)	59/681 (8.7%)	58/709 (8.2%)	0.746	17/206 (8.3%)	10/183 (5.5%)	0.280	
Prior Stroke	24/683 (3.5%)	33/710 (4.6%)	0.286	6/206 (2.9%)	4/183 (2.2%)	0.755	
Prior Surgery or Percutaneous Procedure for PAD	35/683 (5.1%)	32/709 (4.5%)	0.594	10/206 (4.9%)	4/183 (2.2%)	0.158	
Angina History Baseline Seattle Angina Questionnaire Angina Frequency Scale N Median (25th, 75th)	584 90 (70, 100)	602 90 (80, 100)	0.090	178 80 (60, 100)	162 80 (70, 100)	0.119	
Baseline Seattle Angina Questionnaire Angina Frequency Scale Daily Angina (0-30) Weekly Angina (31-60) Monthly Angina (61-99) No Angina in Past Month	12/584 (2.1%) 99/584 (17.0%) 237/584 (40.6%)	13/602 (2.2%) 79/602 (13.1%)	0.290	8/178 (4.5%) 42/178 (23.6%) 82/178 (46.1%) 46/178 (25.8%)	3/162 (1.9%) 31/162 (19.1%) 77/162 (47.5%) 51/162 (31.5%)	0.308	
(100) Participant Has Ever Had Angina	594/683 (87.0%)	615/710 (86.6%)	0.847	189/206 (91.7%)	164/183 (89.6%)	0.469	
New Onset of Angina Over the Past 3 Months	105/646 (16.3%)	116/682 (17.0%)	0.712	28/199 (14.1%)	33/176 (18.8%)	0.220	
Left ventricular systolic dysfunction (35%≤EF≤45%)	56/682 (8.2%)	31/709 (4.4%)	0.004	1/206 (0.5%)	10/183 (5.5%)	0.008	
Ejection Fraction [*] N Median (25th, 75th)	606 60 (53, 64)	636 60 (54, 64)	0.392	178 62 (58, 67)	171 62 (57, 67)	0.172	
Optimal Medical Therapy [†] LDL cholesterol < 70 mg/dL and on any statin	271/649 (41.8%)	299/682 (43.8%)	0.442	51/192 (26.6%)	47/176 (26.7%)	0.975	
Systolic blood pressure < 140 mmHg	407/680 (59.9%)	451/708 (63.7%)	0.140	114/205 (55.6%)	111/183 (60.7%)	0.315	
Aspirin or other anti-platelet or anti-coagulant	650/683 (95.2%)	681/710 (95.9%)	0.499	195/206 (94.7%)	171/182 (94.0%)	0.765	
Non smoker	616/682 (90.3%)	626/709 (88.3%)	0.221	188/206 (91.3%)	170/182 (93.4%)	0.430	
Site-reported value, if available. If ISCHEMIA definition of optimal me		pre-lab entered value.					

		Insulin DM Male (N=531)	Insulin DM Female (N=240)			
Characteristic		CON (NL 275)	D velue		CON (N=110)	Divolue
Demographics	(N=256)	(N=275)	P-value	(N=121)	(N=119)	P-value
Age at Randomization (yrs)			0.940			0.097
Ν	256	275		121	119	
Median (Q1, Q3)	63 (58, 69)	64 (58, 69)		62 (57, 70)	65 (60, 70)	
Race			0.753			0.498
American Indian or Alaskan Native	2/253 (0.8%)	1/268 (0.4%)		1/118 (0.8%)	0/116 (0.0%)	
Asian Native Hawaiian or Other Pacific Islander	63/253 (24.9%) 0/253 (0.0%)	61/268 (22.8%) 1/268 (0.4%)		21/118 (17.8%) 0/118 (0.0%)	20/116 (17.2%) 2/116 (1.7%)	
Black or African American	22/253 (8.7%)	31/268 (11.6%)		14/118 (11.9%)	11/116 (9.5%)	
White	165/253 (65.2%)			82/118 (69.5%)	82/116 (70.7%)	
Multiple Races Reported	1/253 (0.4%)	1/268 (0.4%)		0/118 (0.0%)	1/116 (0.9%)	
Ethnicity			0.448			0.530
Hispanic or Latino	46/237 (19.4%)	44/262 (16.8%)	0.440	23/113 (20.4%)	26/109 (23.9%)	0.000
Diabetes Treatment Insulin Treated	256/256 (100.0%)	275/275 (100.0%)		121/121 (100.0%)	119/119 (100.0%))
Cigarette Smoking			0.709			0.278
Never Smoked	91/256 (35.5%)	90/275 (32.7%)		88/121 (72.7%)	83/119 (69.7%)	
Former Smoker		157/275 (57.1%)		26/121 (21.5%)	33/119 (27.7%)	
Current Smoker	28/256 (10.9%)	28/275 (10.2%)		7/121 (5.8%)	3/119 (2.5%)	
Clinical History						
Hypertension	223/254 (87.8%)	245/275 (89.1%)	0.641	110/121 (90.9%)	112/119 (94.1%)	0.345
Baseline Hemoglobin % A1c			0.058			0.645
Ν	236	252		112	114	
Median (Q1, Q3)	8 (7, 9)	8 (7, 9)		8 (7, 9)	8 (7, 9)	
Prior Myocardial Infarction	59/256 (23.0%)	61/274 (22.3%)	0.829	19/121 (15.7%)	21/118 (17.8%)	0.665
Prior Percutaneous Coronary Intervention (PCI)	76/256 (29.7%)	67/275 (24.4%)	0.167	30/121 (24.8%)	23/119 (19.3%)	0.307
Prior Coronary Artery Bypass Graft (CABG)	15/256 (5.9%)	14/275 (5.1%)	0.697	8/121 (6.6%)	3/119 (2.5%)	0.130
Prior MI or Prior PCI or Prior CABG	107/256 (41.8%)	102/274 (37.2%)	0.282	39/121 (32.2%)	34/119 (28.6%)	0.538
eGFR among Patients not on Dialysis at Baseline			0.070			0.089
Ň	206	220		102	98	
Median (Q1, Q3)	69 (29, 91)	74 (53, 92)		67 (46, 89)	59 (29, 81)	
EGFR ml/min/1.73 m2			0.051			0.246
Greater than 60	112/256 (43.8%)	148/275 (53.8%)	0.001	61/121 (50.4%)	49/119 (41.2%)	0.270
Between 30 to 59	41/256 (16.0%)	31/275 (11.3%)		25/121 (20.7%)	24/119 (20.2%)	
Less than 30 or on dialysis	· · ·	96/275 (34.9%)		35/121 (28.9%)	46/119 (38.7%)	
On Dialysis at Baseline	50/256 (19.5%)	55/275 (20.0%)	0.892	19/121 (15.7%)	21/119 (17.6%)	0.686
Non-Cardiac Vascular and Comorbidity History						

Table IVc. Comparison of participant baseline characteristics by treatment strategy, within DM-based subgroups for males and females with insulin treated DM

		Insulin DM Male (N=531)		Insulin DM Female (N=240)			
Characteristic	INV (N=256)	CON (N=275)	P-value	INV (N=121)	CÓN (N=119)	P-value	
Prior Carotid Artery Surgery or Stent, Stroke, or Transient Ischemic Attack (TIA)	38/255 (14.9%)	29/274 (10.6%)	0.136	11/121 (9.1%)	20/118 (16.9%)	0.071	
Prior Stroke	24/256 (9.4%)	15/275 (5.5%)	0.084	9/121 (7.4%)	10/119 (8.4%)	0.782	
Prior Surgery or Percutaneous Procedure for PAD	20/255 (7.8%)	21/274 (7.7%)	0.939	9/121 (7.4%)	6/117 (5.1%)	0.464	
Angina History Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.727			0.924	
N Median (25th, 75th)	233 90 (80, 100)	252 90 (80, 100)		116 85 (70, 100)	117 80 (70, 100)		
Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.998			0.739	
Daily Angina (0-30) Weekly Angina (31-60) Monthly Angina (61-99) No Angina in Past Month (100)	8/233 (3.4%) 26/233 (11.2%) 97/233 (41.6%) 102/233 (43.8%)	8/252 (3.2%) 29/252 (11.5%) 105/252 (41.7%) 110/252 (43.7%)		1/116 (0.9%) 19/116 (16.4%) 59/116 (50.9%) 37/116 (31.9%)	2/117 (1.7%) 22/117 (18.8%) 52/117 (44.4%) 41/117 (35.0%)		
Participant Has Ever Had Angina	200/256 (78.1%)	231/275 (84.0%)	0.074	101/121 (83.5%)	101/119 (84.9%)	0.766	
New Onset of Angina Over the Past 3 Months	33/243 (13.6%)	50/262 (19.1%)	0.095	17/115 (14.8%)	14/113 (12.4%)	0.598	
Left ventricular systolic dysfunction (35%≤EF<45%)	25/256 (9.8%)	22/275 (8.0%)	0.574	5/121 (4.1%)	7/119 (5.9%)	0.745	
Ejection Fraction			0.079			0.253	
N Median (25th, 75th)	233 57 (51, 61)	235 60 (50, 65)		105 62 (55, 68)	98 60 (55, 65)		
Optimal Medical Therapy [↑] LDL cholesterol < 70 mg/dL and on any statin	99/238 (41.6%)	107/250 (42.8%)	0.788	41/114 (36.0%)	39/113 (34.5%)	0.819	
Systolic blood pressure < 140 mmHg	142/256 (55.5%)	160/272 (58.8%)	0.436	67/120 (55.8%)	61/118 (51.7%)	0.522	
Aspirin or other anti-platelet or anti-coagulant	241/256 (94.1%)	258/275 (93.8%)	0.876	113/121 (93.4%)	105/119 (88.2%)	0.167	
Non smoker	228/256 (89.1%)	247/275 (89.8%)	0.777	114/121 (94.2%)	116/119 (97.5%)	0.333	

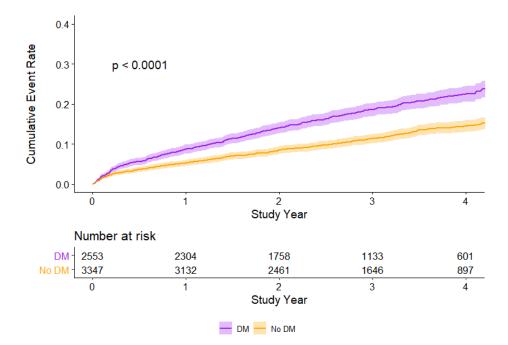


Figure Ia. Kaplan-Meier estimate of cumulative event rates of death or MI by diabetes status

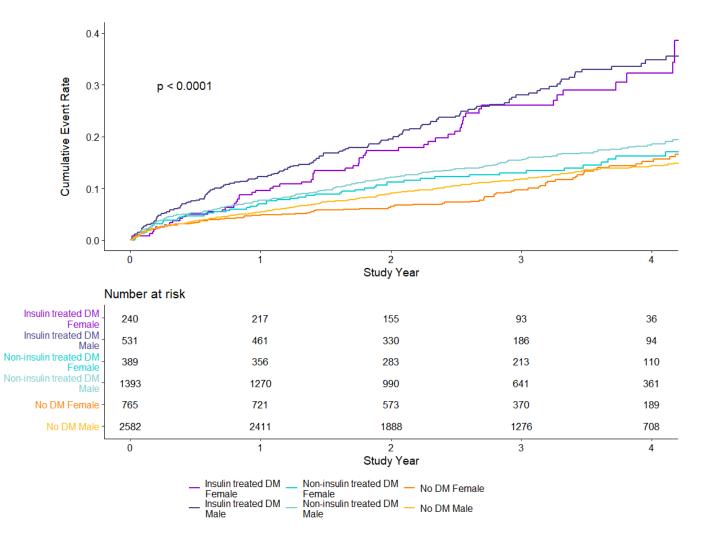


Figure Ib. Kaplan-Meier estimate of cumulative event rates of death or MI by clinical features of diabetes



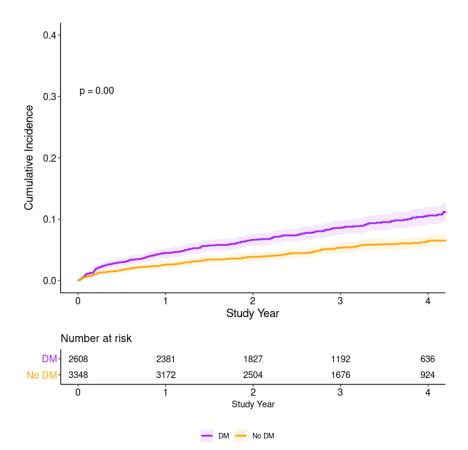


Figure Id. Cumulative incidence of procedural MI (types 4a or 5) (accounting for competing risks) by diabetes status

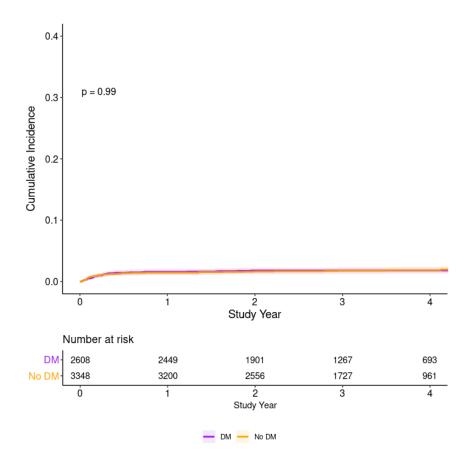


Figure IIa. Comparison of association of death or MI with diabetes status in the ISCHEMIA Trials, ISCHEMIA, and ISCHEMIA-CKD

Group	No. Patients	% Event	Adjusted HR (95% (CI)			F	P-value
ISCHEMIA Trials	;							
No DM	3347	12	Ref					
DM	2553	19	1.49 (1.31, 1.70)					0.000
ISCHEMIA								
No DM	3014	11	Ref					
DM	2116	15	1.37 (1.17, 1.59)					0.000
ISCHEMIA-CKD								
No DM	333	24	Ref					
DM	437	39	1.89 (1.44, 2.49)					0.000
				0.50	1.0	1.5	2.0 2.5	

Figure IIb. Comparison of the association of death or MI with clinical features of diabetes in the ISCHEMIA Trials, ISCHEMIA, and ISCHEMIA-CKD

Group	No. Patients	% Event	Adjusted HR (95% C	CI)	P-value
ISCHEMIA Trials					
No DM Male	2582	13	Ref		
No DM Female	765	11	0.81 (0.64, 1.03)	_	0.092
Non-insulin treated DM Male	1393	16	1.28 (1.08, 1.51)	∎	0.005
Non-insulin treated DM Female	389	16	1.20 (0.91, 1.58)		0.191
Insulin treated DM Male	531	28	1.80 (1.47, 2.20)		0.000
Insulin treated DM Female	240	26	1.69 (1.28, 2.23)		0.000
ISCHEMIA					
No DM Male	2368	12	Ref		
No DM Female	646	10	0.81 (0.61, 1.06)		0.128
Non-insulin treated DM Male	1274	14	1.20 (1.00, 1.45)		0.056
Non-insulin treated DM Female	351	14	1.19 (0.87, 1.61)		0.272
Insulin treated DM Male	332	19	1.58 (1.20, 2.07)	B	0.001
Insulin treated DM Female	159	22	1.87 (1.31, 2.67)	_	0.001
ISCHEMIA-CKD					
No DM Male	214	25	Ref		
No DM Female	119	21	0.90 (0.56, 1.44)		0.653
Non-insulin treated DM Male	119	39	1.74 (1.17, 2.60)	∎	0.006
Non-insulin treated DM Female	38	34	1.39 (0.76, 2.56)		0.285
Insulin treated DM Male	199	43	2.12 (1.50, 2.99)		0.000
Insulin treated DM Female	81	33	1.63 (1.02, 2.59)		0.041
				0.50 1.0 1.5 2.0	2.5

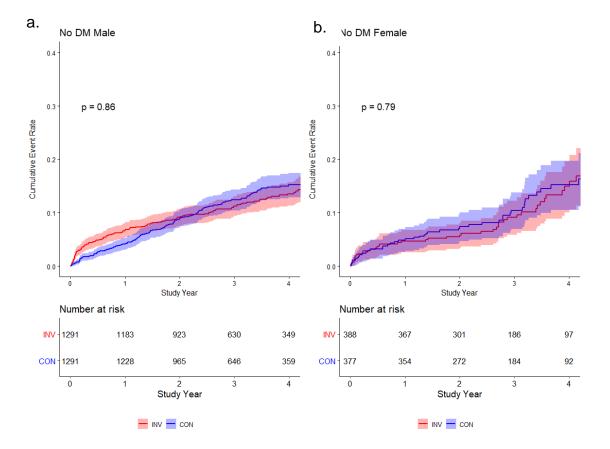
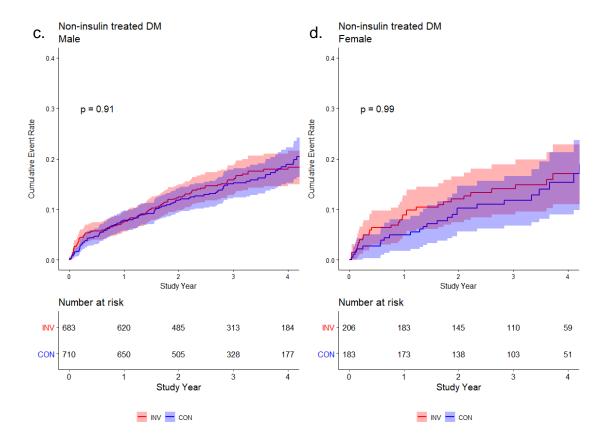


Figure IIIa-f. Kaplan-Meier estimate of cumulative event rates of death or MI by treatment strategy, stratified by clinical features of diabetes



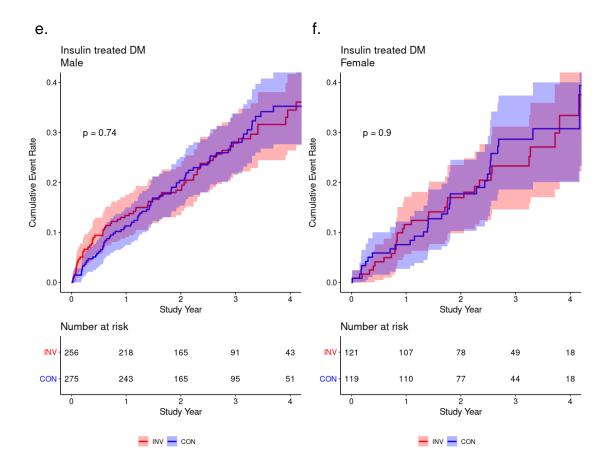


Figure IVa. Diabetes and clinical feature-specific treatment effects over study follow-up in the ISCHEMIA trial. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible area. Vertical dashed red bar is at 1 for reference.

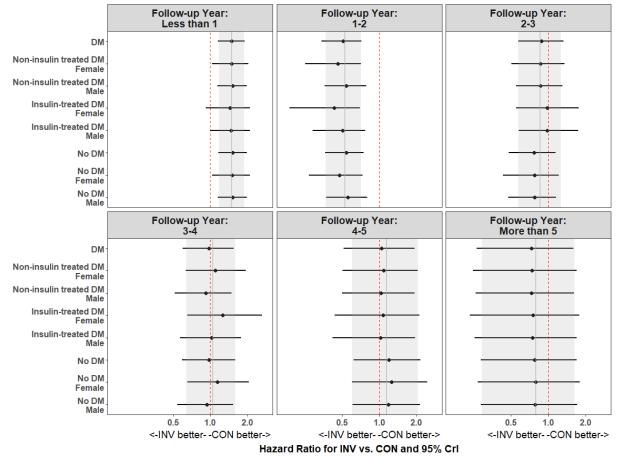


Figure IVb. Diabetes and clinical feature-specific -specific treatment effects over study follow-up in the ISCHEMIA-CKD trial. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible area. Vertical dashed red bar is at 1 for reference.

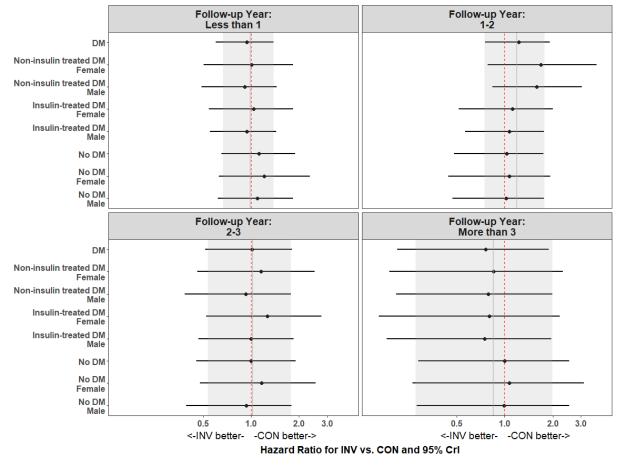
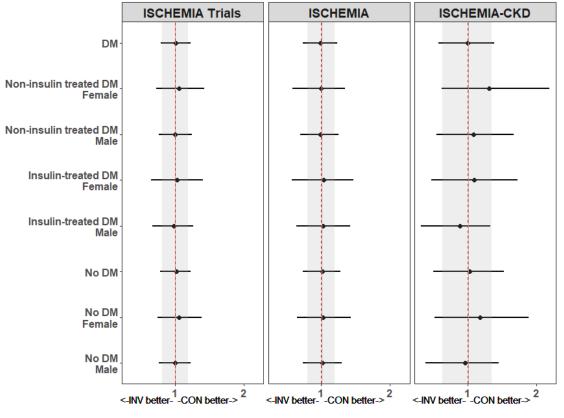
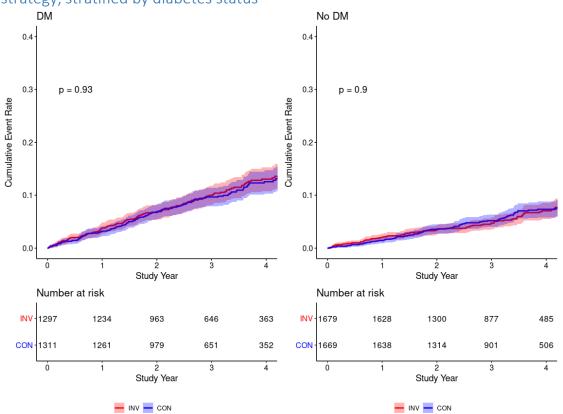


Figure V. Summary diabetes and clinical feature-specific treatment effects based on proportional hazards in the ISCHEMIA Trials, ISCHEMIA, and ISCHEMIA-CKD. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible area. Vertical dashed red bar is at 1 for reference



Hazard Ratio for INV vs. CON and 95% Crl





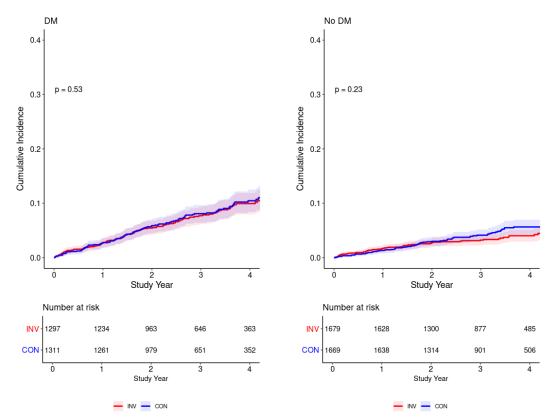


Figure VIb. Cumulative incidence of CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status

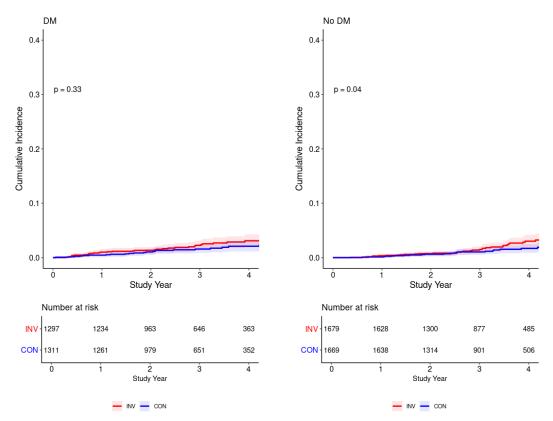
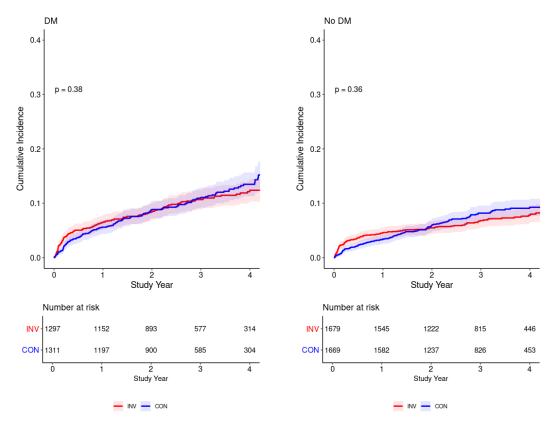
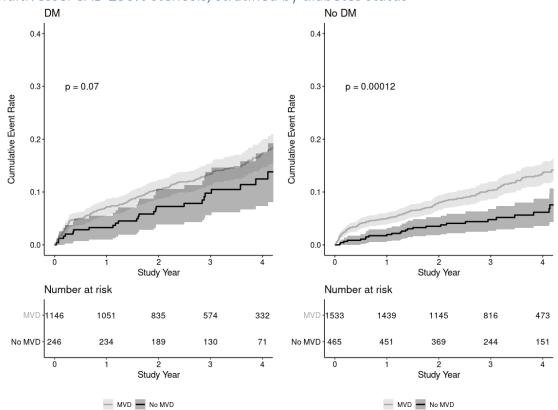


Figure VIc. Cumulative incidence of non-CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status









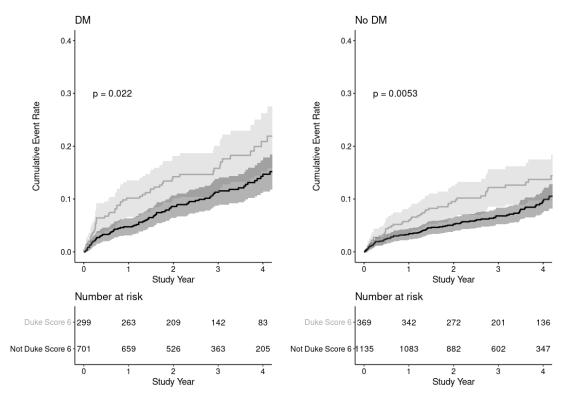
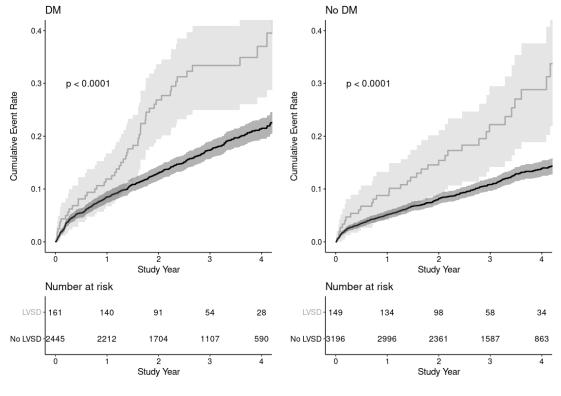


Figure VIIb. Kaplan-Meier estimate of cumulative event rates of death or MI by Duke score 6 severity of CAD, stratified by diabetes status

- Duke Score 6 - Not Duke Score 6

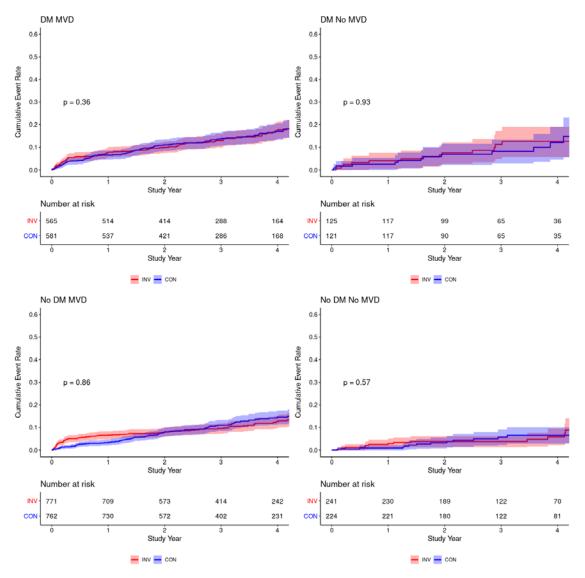
— Duke Score 6 — Not Duke Score 6

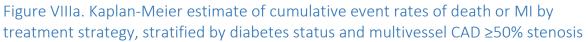




- LVSD - No LVSD

- LVSD - No LVSD





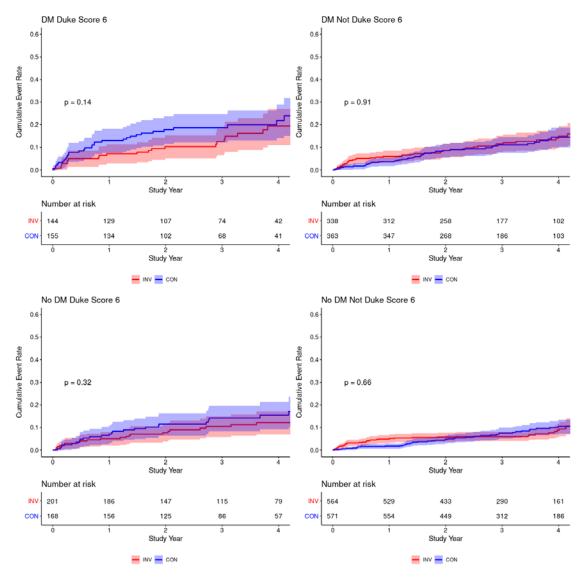


Figure VIIIb. Kaplan-Meier estimate of cumulative event rates of death or MI by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

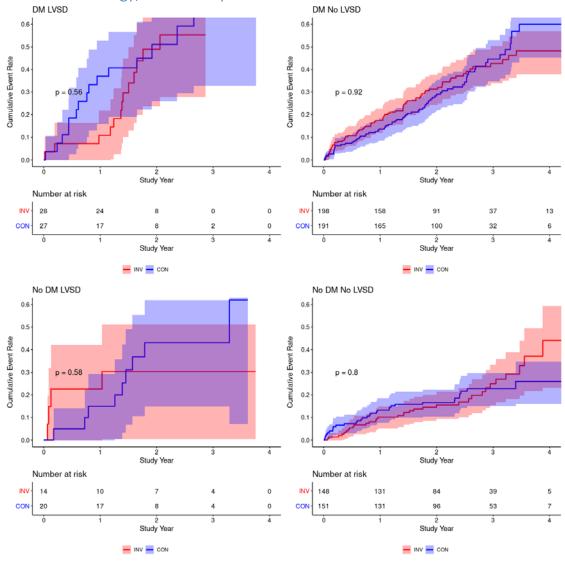


Figure VIIIc. Kaplan-Meier estimate of cumulative event rates of death or MI by treatment strategy, stratified by diabetes status and LVSD

Figure IX. Diabetes anatomic features-specific treatment effects over study follow-up among the subset of ISCHEMIA participants with anatomic features. Color coding is by anatomic feature. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible area. Vertical dashed red bar is at 1 for reference

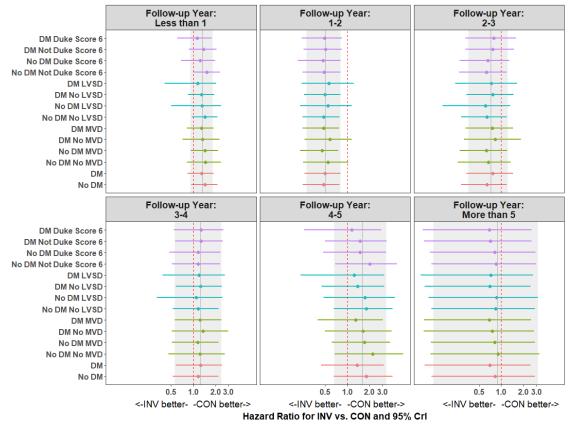
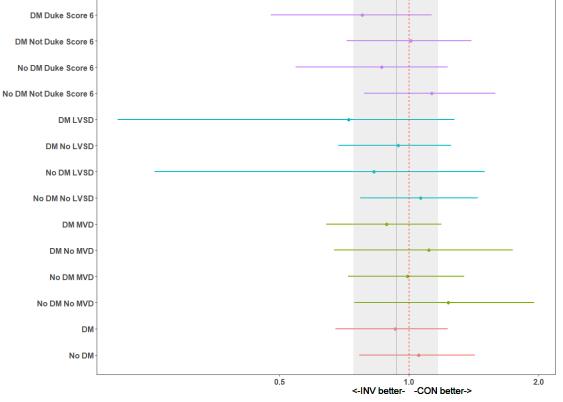
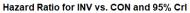


Figure X. Summary diabetes anatomic features-specific treatment effects based on proportional hazards among the subset of ISCHEMIA participants with anatomic features. Color coding is by anatomic feature. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible area. Vertical dashed red bar is at 1 for reference





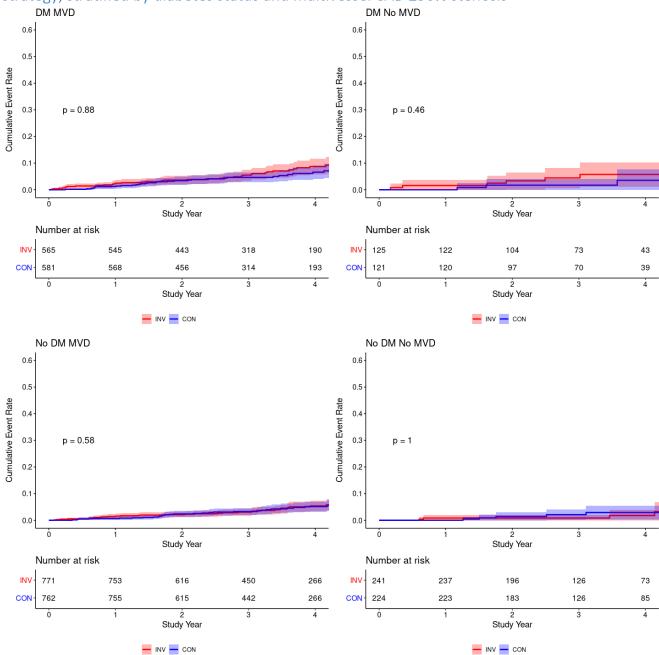


Figure XIa. Kaplan-Meier estimate of cumulative event rates of death by treatment strategy, stratified by diabetes status and multivessel CAD \geq 50% stenosis

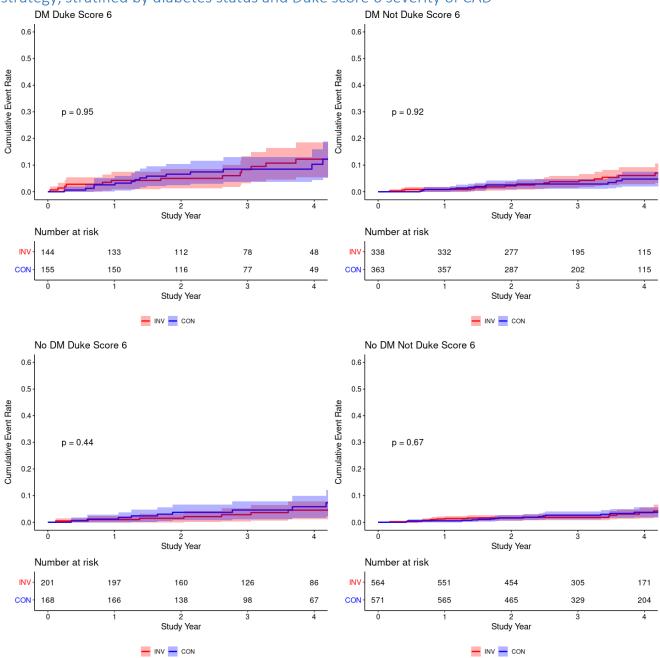


Figure XIb. Kaplan-Meier estimate of cumulative event rates of death by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

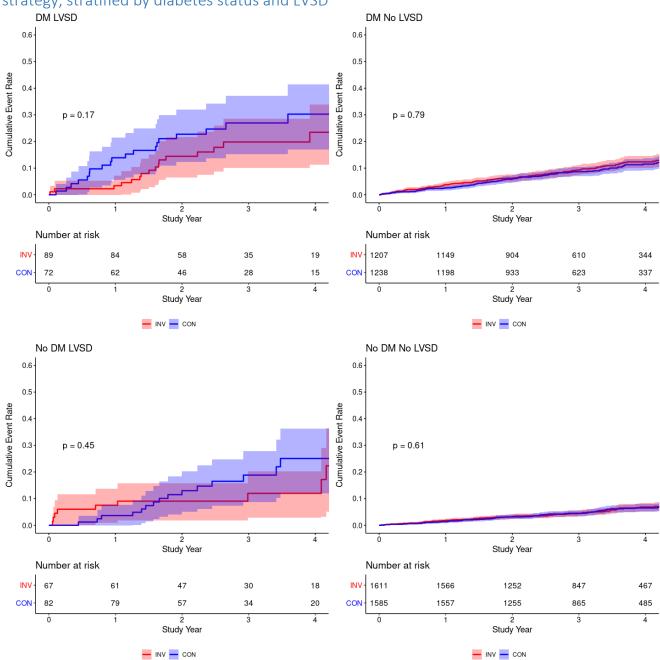
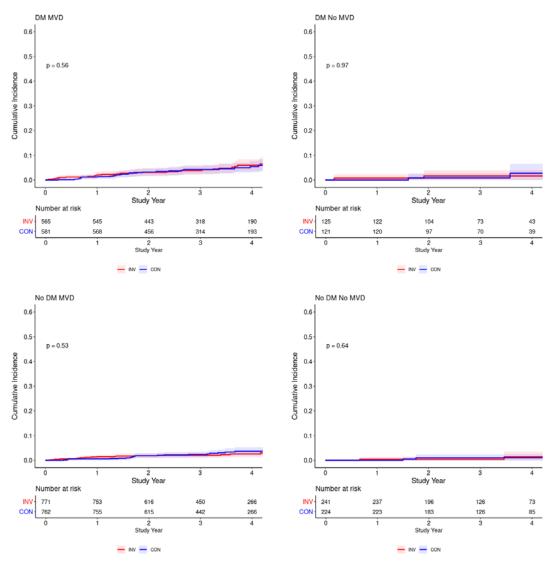
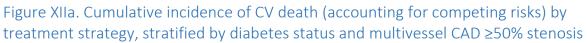


Figure XIc. Kaplan-Meier estimate of cumulative event rates of death by treatment strategy, stratified by diabetes status and LVSD





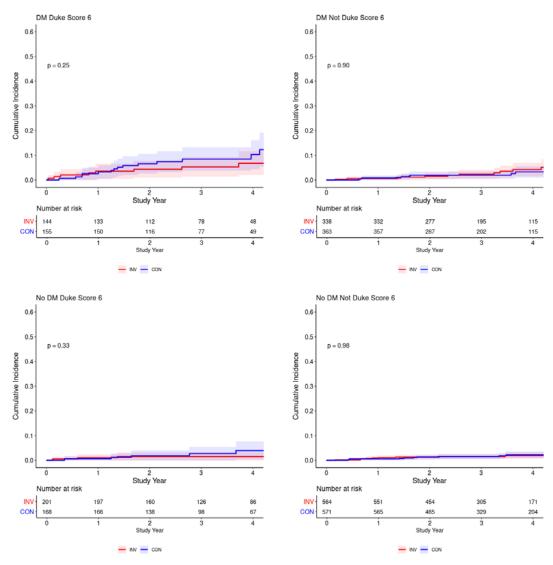


Figure XIIb. Cumulative incidence of CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

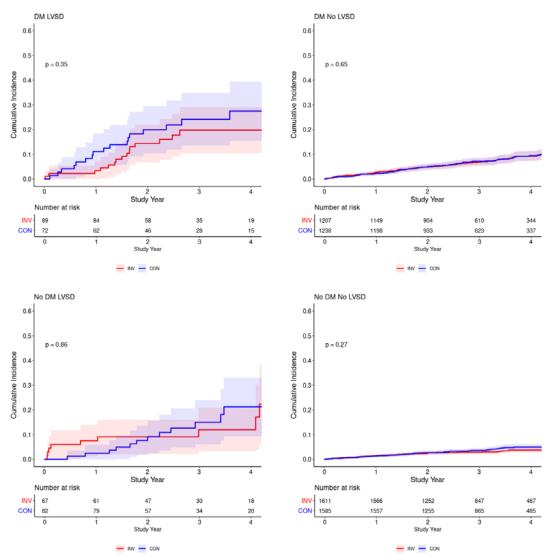


Figure XIIc. Cumulative incidence of CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and LVSD

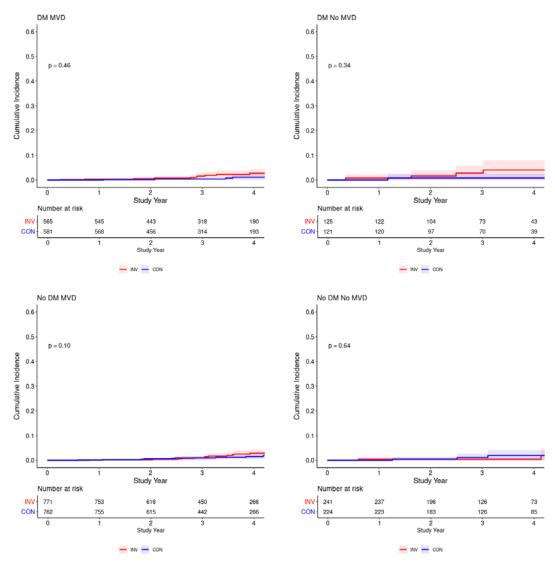
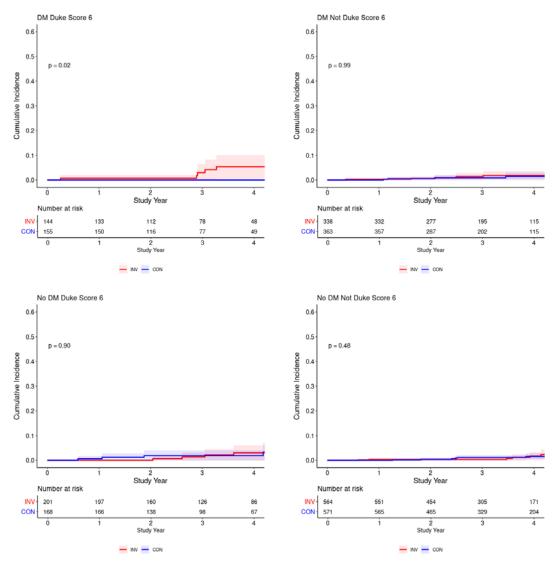
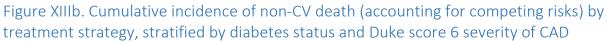
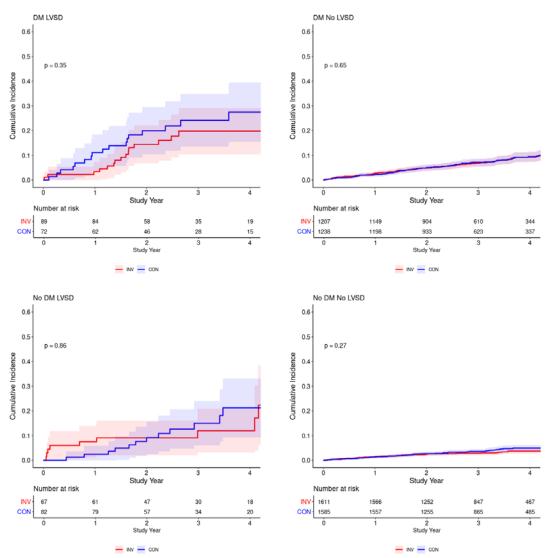
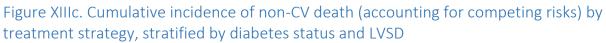


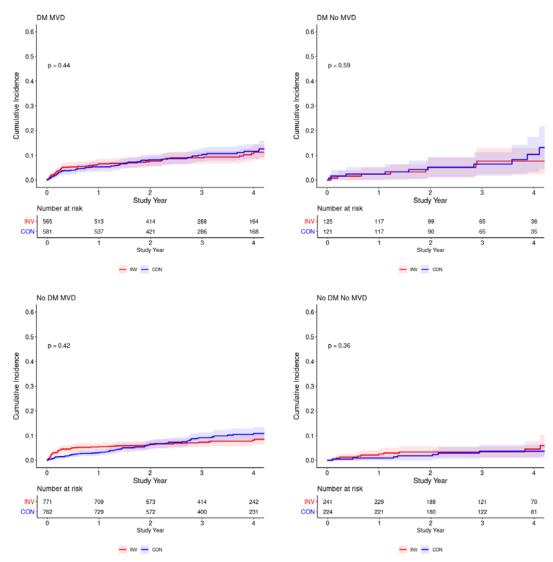
Figure XIIIa. Cumulative incidence of non-CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and multivessel CAD ≥50% stenosis













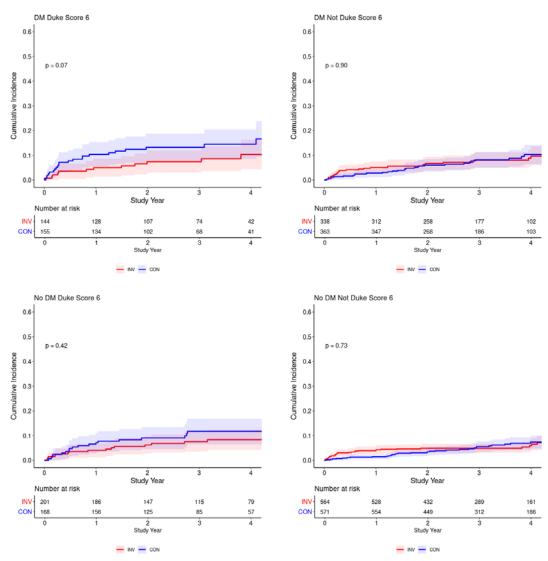


Figure XIVb. Cumulative incidence of MI (accounting for competing risks) by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

