SUPPLEMENTAL MATERIALS

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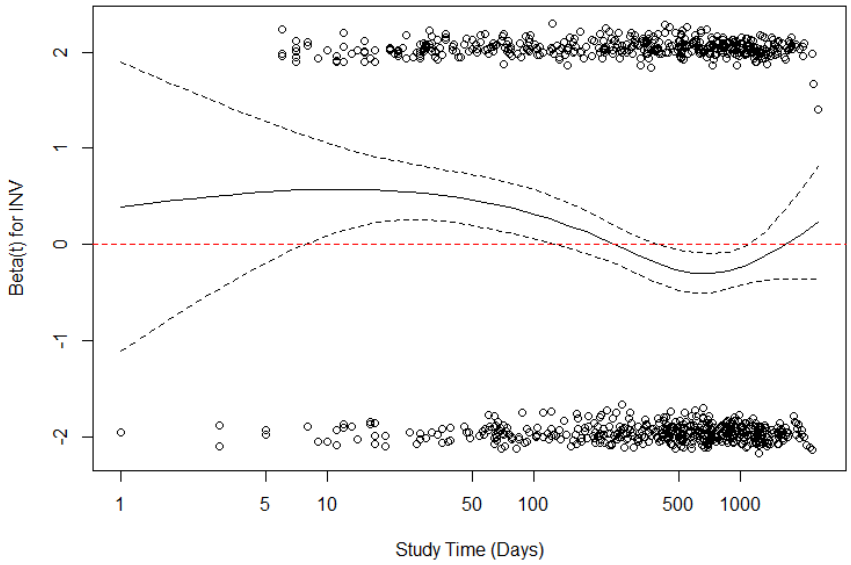
I. Supplemental Methods

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 Simon[28] 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 $j = 1, \ldots, J$ 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 $s = 1, \ldots, S$. We specify the hazard of death or MI for participant i ($i = 1, \ldots, n$) at t in time interval j and treatment-specific interval s as

$$h_{ijs}(t) = h_{0j}(t)exp(\mu_{is}),$$

where

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

In equation (1), $\text{INV}_{is} = 1$ 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 ($r = 1, \ldots, R$) composing the DM-based subgroups. The $\mathbf{w}_i$ contains hypothesized confounders of the association between all-cause death/MI and the subgroup-specific treatment effects, with corresponding regression coefficients in $\boldsymbol{\alpha}$.

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 $\boldsymbol{\alpha}$. 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 $\mathbf{w}_i$ and time intervals. In $\mathbf{w}_i$, 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 20^{th} 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 R[50] and JAGS[51] 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

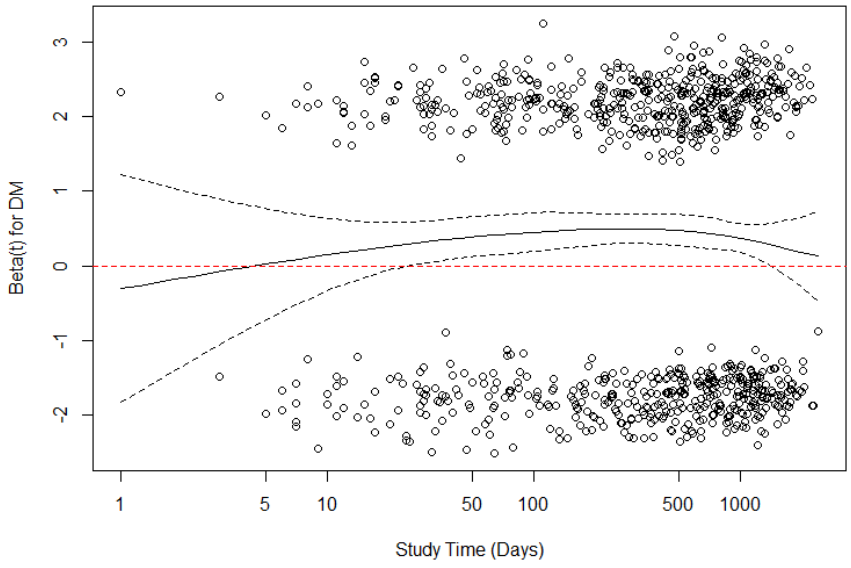


Figure IIB. Scaled Schoenfeld residuals for non-insulin treated DM male by log-transformed time

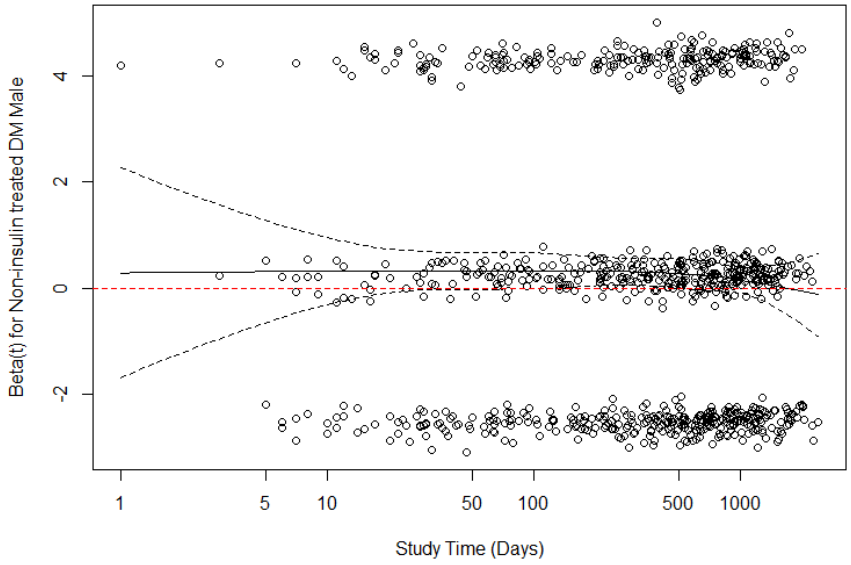


Figure IIC. Scaled Schoenfeld residuals for insulin treated DM male by log-transformed time

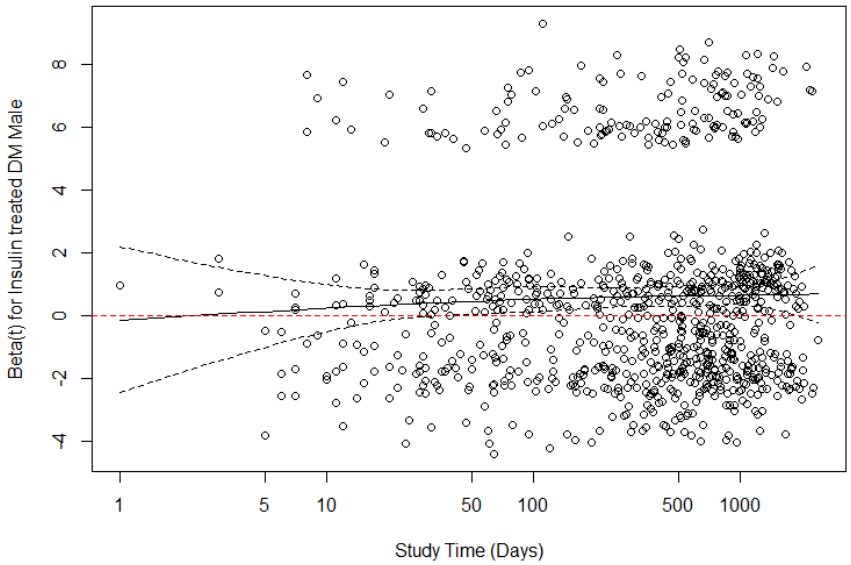


Figure IID. Scaled Schoenfeld residuals for non-insulin treated DM female by log-transformed time

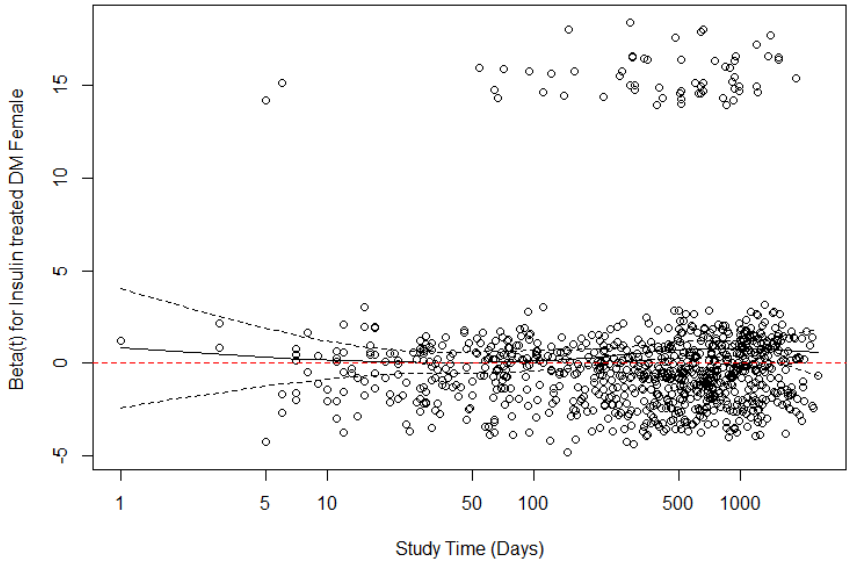


Table I presents the estimated hazard ratios for the DM-based subgroups within time interval defined by the 180 day cut-off. Compared to the reference level of males without DM, both insulin treated DM male and insulin treated DM female appear to have hazard ratios of greater magnitude in the post 180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

Characteristic	All Participants (N=5,956)	Excluded (N=56)	Included (N=5,900)
Demographics			
Age at Randomization (years)			
N	5956	56	5900
Median (Q1, Q3)	64 (57, 70)	63 (54, 69)	64 (57, 70)
Gender			
Female	1,410/5,956 (23.7%)	16/56 (28.6%)	1,394/5,900 (23.6%)
Race			
American Indian or Alaskan Native	18/5,876 (0.3%)	0/56 (0.0%)	18/5,820 (0.3%)
Asian	1,676/5,876 (28.5%)	29/56 (51.8%)	1,647/5,820 (28.3%)
Native Hawaiian or Other Pacific Islander	18/5,876 (0.3%)	2/56 (3.6%)	16/5,820 (0.3%)
Black or African American	267/5,876 (4.5%)	2/56 (3.6%)	265/5,820 (4.6%)
White	3,884/5,876 (66.1%)	23/56 (41.1%)	3,861/5,820 (66.3%)
Multiple Races Reported	13/5,876 (0.2%)	0/56 (0.0%)	13/5,820 (0.2%)
Ethnicity			
Hispanic or Latino	861/5,550 (15.5%)	3/54 (5.6%)	858/5,496 (15.6%)
Diabetes	2,608/5,956 (43.8%)	55/56 (98.2%)	2,553/5,900 (43.3%)
Diabetes Treatment			
Insulin Treated	772/2,554 (30.2%)	1/55 (1.8%)	771/2,553 (30.2%)
Non-Insulin Diabetes Medication	1,447/2,554 (56.7%)	0/55 (0.0%)	1,447/2,553 (56.7%)
None/Diet Controlled	335/2,554 (13.1%)	0/55 (0.0%)	335/2,553 (13.1%)
Unknown	0/2,554 (0.0%)	54/55 (98.2%)	0/2,553 (0.0%)
Cigarette Smoking			
Never Smoked	2,579/5,951 (43.3%)	24/56 (42.9%)	2,555/5,895 (43.3%)
Former Smoker	2,648/5,951 (44.5%)	22/56 (39.3%)	2,626/5,895 (44.5%)
Current Smoker	724/5,951 (12.2%)	10/56 (17.9%)	714/5,895 (12.1%)
Clinical History			
Hypertension	4,500/5,934 (75.8%)	38/56 (67.9%)	4,462/5,878 (75.9%)
Baseline Hemoglobin A1c			
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 (24.9%)
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 (20.1%)
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 (30.2%)
On Dialysis Status at Baseline	416/5,954 (7.0%)	1/54 (1.9%)	415/5,900 (7.0%)
eGFR among Patients not on Dialysis at Baseline			
N	5538	53	5485
Median (Q1, Q3)	80 (64, 95)	81 (66, 103)	80 (64, 95)
eGFR ml/min/1.73 m^2			
≥60	4,440/5,956 (74.5%)	44/56 (78.6%)	4,396/5,900 (74.5%)
Between 30 to 59	740/5,956 (12.4%)	5/56 (8.9%)	735/5,900 (12.5%)
Less than 30 or on dialysis	776/5,956 (13.0%)	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)

*Site-reported value, if available. If not available, then core-lab entered value. EF, ejection fraction

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

	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 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 (N=1,679)**	**CON (N=1,668)**	**P-value**	**INV (N=1,266)**	**CON (N=1,287)**	**P-value**
Demographics						
Age at Randomization (yrs)			0.437			0.398
N	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 (23.1%)	377/1,668 (22.6%)		327/1,266 (25.8%)	302/1,287 (23.5%)	
Race			0.603			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 (25.4%)	413/1,649 (25.0%)		399/1,242 (32.1%)	411/1,260 (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 (70.8%)	1,175/1,649 (71.3%)		756/1,242 (60.9%)	749/1,260 (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
Hispanic or Latino	212/1,582 (13.4%)	235/1,563 (15.0%)		212/1,161 (18.3%)	199/1,190 (16.7%)	
Diabetes Treatment						0.877
Insulin Treated	-	-		377/1,266 (29.8%)	394/1,287 (30.6%)	
Non-Insulin Diabetes Medication	-	-		720/1,266 (56.9%)	727/1,287 (56.5%)	
None/Diet Controlled	-	-		169/1,266 (13.3%)	166/1,287 (12.9%)	
Cigarette Smoking						0.241
Never Smoked	684/1,679 (40.7%)	692/1,666 (41.5%)		606/1,265 (47.9%)	573/1,285 (44.6%)	
Former Smoker	754/1,679 (44.9%)	746/1,666 (44.8%)		540/1,265 (42.7%)	586/1,285 (45.6%)	
Current Smoker	241/1,679 (14.4%)	228/1,666 (13.7%)		119/1,265 (9.4%)	126/1,285 (9.8%)	
Clinical History						
Hypertension	1,185/1,671 (70.9%)	1,172/1,660 (70.6%)	0.842	1,036/1,263 (82.0%)	1,069/1,284 (83.3%)	0.413
Baseline Hemoglobin % A1c			0.108			0.040
N	770	756		1159	1171	
Median (Q1, Q3)	6 (6, 6)	6 (5, 6)		7 (7, 8)	7 (7, 8)	
Prior Myocardial Infarction	312/1,675 (18.6%)	306/1,663 (18.4%)	0.866	238/1,261 (18.9%)	253/1,283 (19.7%)	0.589
Prior Percutaneous Coronary Intervention (PCI)	326/1,678 (19.4%)	316/1,666 (19.0%)	0.735	292/1,265 (23.1%)	249/1,287 (19.3%)	0.021
Prior Coronary Artery Bypass Graft (CABG)	57/1,679 (3.4%)	53/1,668 (3.2%)	0.724	66/1,266 (5.2%)	53/1,287 (4.1%)	0.189

Characteristic	All Participants without Diabetes at Baseline (N=3,347)			All Participants with Diabetes (N=2,553)		
	INV (N=1,679)	CON (N=1,668)	P-value	INV (N=1,266)	CON (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	1589	1564		1159	1173	
Median (Q1, Q3)	81 (67, 96)	81 (66, 96)		78 (59, 94)	78 (60, 94)	
EGFR ml/min/1.73 m2			0.414			0.884
Greater than 60	1,319/1,679 (78.6%)	1,323/1,668 (79.3%)		864/1,266 (68.2%)	890/1,287 (69.2%)	
Between 30 to 59	198/1,679 (11.8%)	174/1,668 (10.4%)		183/1,266 (14.5%)	180/1,287 (14.0%)	
Less than 30 or on dialysis	162/1,679 (9.6%)	171/1,668 (10.3%)		219/1,266 (17.3%)	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)	39/1,535 (2.5%)	33/1,544 (2.1%)		29/1,111 (2.6%)	26/1,133 (2.3%)	
Weekly Angina (31-60)	288/1,535 (18.8%)	265/1,544 (17.2%)		186/1,111 (16.7%)	161/1,133 (14.2%)	
Monthly Angina (61-99)	670/1,535 (43.6%)	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	1,490	1,454		1,122	1,140	
Median (25th, 75th)	60 (55, 65)	60 (55, 65)		60 (54, 65)	60 (54, 65)	
Optimal Medical Therapy†						

	All Participants without Diabetes at Baseline (N=3,347)			All Participants with Diabetes (N=2,553)		
Characteristic	**INV (N=1,679)**	**CON (N=1,668)**	**P-value**	**INV (N=1,266)**	**CON (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 or anti-coagulant	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

*Site-reported value, if available. If not available, then core-lab entered value. EF, ejection fraction
†ISCHEMIA definition of optimal medical therapy[11]

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 (N=1,291)**	**CON (N=1,291)**	**P-value**	**INV (N=388)**	**CON (N=377)**	**P-value**
Demographics						
Age at Randomization (yrs)			0.131			0.248
N	1291	1291		388	377	
Median (Q1, Q3)	64 (57, 71)	63 (56, 70)		64 (59, 71)	65 (58, 72)	
Race			0.567			0.552
American Indian or Alaskan Native	5/1,281 (0.4%)	1/1,280 (0.1%)		2/388 (0.5%)	1/369 (0.3%)	
Asian	339/1,281 (26.5%)	344/1,280 (26.9%)		85/388 (21.9%)	69/369 (18.7%)	
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 (69.9%)	888/1,280 (69.4%)		285/388 (73.5%)	287/369 (77.8%)	
Multiple Races Reported	4/1,281 (0.3%)	3/1,280 (0.2%)		0/388 (0.0%)	0/377 (0.0%)	
Ethnicity			0.367			0.277
Hispanic or Latino	166/1,216 (13.7%)	181/1,212 (14.9%)		46/366 (12.6%)	54/351 (15.4%)	
Cigarette Smoking			0.735			0.850
Never Smoked	449/1,291 (34.8%)	459/1,289 (35.6%)		235/388 (60.6%)	233/377 (61.8%)	
Former Smoker	641/1,291 (49.7%)	643/1,289 (49.9%)		113/388 (29.1%)	103/377 (27.3%)	
Current Smoker	201/1,291 (15.6%)	187/1,289 (14.5%)		40/388 (10.3%)	41/377 (10.9%)	
Clinical History						
Hypertension	900/1,285 (70.0%)	871/1,285 (67.8%)	0.216	285/386 (73.8%)	301/375 (80.3%)	0.035
Baseline Hemoglobin % A1c			0.147			0.504
N	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 (19.9%)	246/1,286 (19.1%)	0.633	56/387 (14.5%)	60/377 (15.9%)	0.578
Prior Percutaneous Coronary Intervention (PCI)	269/1,291 (20.8%)	262/1,289 (20.3%)	0.748	57/387 (14.7%)	54/377 (14.3%)	0.874
Prior Coronary Artery Bypass Graft (CABG)	52/1,291 (4.0%)	42/1,291 (3.3%)	0.293	5/388 (1.3%)	11/377 (2.9%)	0.115
Prior MI or Prior PCI or Prior CABG	396/1,289 (30.7%)	395/1,285 (30.7%)	0.992	87/386 (22.5%)	88/377 (23.3%)	0.792
eGFR among Patients not on Dialysis at Baseline			0.754			0.848
N	1235	1219		354	345	
Median (Q1, Q3)	83 (69, 98)	82 (69, 97)		75 (60, 91)	76 (59, 91)	
EGFR ml/min/1.73 m2			0.059			0.500
Greater than 60	1,047/1,291 (81.1%)	1,067/1,291 (82.6%)		272/388 (70.1%)	256/377 (67.9%)	
Between 30 to 59	144/1,291 (11.2%)	110/1,291 (8.5%)		54/388 (13.9%)	64/377 (17.0%)	

	No DM Male (N=2,582)			No DM Female (N=765)		
Characteristic	**INV (N=1,291)**	**CON (N=1,291)**	**P-value**	**INV (N=388)**	**CON (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	1,173	1,179		362	365	
Median (25th, 75th)	90 (70, 100)	90 (70, 100)		80 (70, 100)	80 (70, 100)	
Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.267			0.937
Daily Angina (0-30)	28/1,173 (2.4%)	21/1,179 (1.8%)		11/362 (3.0%)	12/365 (3.3%)	
Weekly Angina (31-60)	224/1,173 (19.1%)	195/1,179 (16.5%)		64/362 (17.7%)	70/365 (19.2%)	
Monthly Angina (61-99)	494/1,173 (42.1%)	520/1,179 (44.1%)		176/362 (48.6%)	177/365 (48.5%)	
No Angina in Past Month (100)	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	223/1,229 (18.1%)	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	1,149	1,126		341	328	
Median (25th, 75th)	60 (55, 64)	60 (55, 64)		62 (59, 67)	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 available, then core-lab entered value. EF, ejection fraction
†ISCHEMIA definition of optimal medical therapy[11]

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

	Non Insulin DM Male (N=1,393)			Non-Insulin DM Female (N=389)		
Characteristic	**INV (N=683)**	**CON (N=710)**	**P-value**	**INV (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 Alaskan Native	0/670 (0.0%)	4/698 (0.6%)		0/201 (0.0%)	1/178 (0.6%)	
Asian	239/670 (35.7%)	274/698 (39.3%)		76/201 (37.8%)	56/178 (31.5%)	
Native Hawaiian or Other Pacific Islander	3/670 (0.4%)	2/698 (0.3%)		0/201 (0.0%)	2/178 (1.1%)	
Black or African American	34/670 (5.1%)	31/698 (4.4%)		7/201 (3.5%)	12/178 (6.7%)	
White	392/670 (58.5%)	387/698 (55.4%)		117/201 (58.2%)	107/178 (60.1%)	
Multiple Races Reported	2/670 (0.3%)	0/698 (0.0%)		1/201 (0.5%)	0/178 (0.0%)	
Ethnicity			0.055			0.161
Hispanic or Latino	115/620 (18.5%)	94/646 (14.6%)		28/191 (14.7%)	35/173 (20.2%)	
Diabetes Treatment			0.834			0.942
Non-Insulin Diabetes Medication	554/683 (81.1%)	579/710 (81.5%)		166/206 (80.6%)	148/183 (80.9%)	
None/Diet Controlled	129/683 (18.9%)	131/710 (18.5%)		40/206 (19.4%)	35/183 (19.1%)	
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	339/682 (49.7%)	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
N	628	642		183	163	
Median (Q1, Q3)	7 (6, 8)	7 (6, 8)		7 (6, 8)	7 (6, 8)	
Prior Myocardial Infarction	126/679 (18.6%)	141/708 (19.9%)	0.521	34/205 (16.6%)	30/183 (16.4%)	0.959
Prior Percutaneous Coronary Intervention (PCI)	154/682 (22.6%)	136/710 (19.2%)	0.116	32/206 (15.5%)	23/183 (12.6%)	0.402
Prior Coronary Artery Bypass Graft (CABG)	40/683 (5.9%)	32/710 (4.5%)	0.255	3/206 (1.5%)	4/183 (2.2%)	0.711
Prior MI or Prior PCI or Prior CABG	223/679 (32.8%)	214/708 (30.2%)	0.294	50/205 (24.4%)	40/183 (21.9%)	0.555
eGFR among Patients not on Dialysis at Baseline			0.974			0.845
N	657	681		194	174	
Median (Q1, Q3)	81 (65, 96)	80 (65, 96)		76 (60, 92)	74 (60, 93)	
EGFR ml/min/1.73 m2			0.594			0.978
Greater than 60	545/683 (79.8%)	562/710 (79.2%)		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 Baseline	26/683 (3.8%)	29/710 (4.1%)	0.790	12/206 (5.8%)	9/183 (4.9%)	0.693

Characteristic	Non Insulin DM Male (N=1,393)			Non-Insulin DM Female (N=389)		
	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			0.090			0.119
N	584	602		178	162	
Median (25th, 75th)	90 (70, 100)	90 (80, 100)		80 (60, 100)	80 (70, 100)	
Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.290			0.308
Daily Angina (0-30)	12/584 (2.1%)	13/602 (2.2%)		8/178 (4.5%)	3/162 (1.9%)	
Weekly Angina (31-60)	99/584 (17.0%)	79/602 (13.1%)		42/178 (23.6%)	31/162 (19.1%)	
Monthly Angina (61-99)	237/584 (40.6%)	246/602 (40.9%)		82/178 (46.1%)	77/162 (47.5%)	
No Angina in Past Month (100)	236/584 (40.4%)	264/602 (43.9%)		46/178 (25.8%)	51/162 (31.5%)	
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*			0.392			0.172
N	606	636		178	171	
Median (25th, 75th)	60 (53, 64)	60 (54, 64)		62 (58, 67)	62 (57, 67)	
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 not available, then core-lab entered value.
†ISCHEMIA definition of optimal medical therapy[11]

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)**	**CON (N=119)**	**P-value**
Demographics						
Age at Randomization (yrs)			0.940			0.097
N	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	63/253 (24.9%)	61/268 (22.8%)		21/118 (17.8%)	20/116 (17.2%)	
Native Hawaiian or Other Pacific Islander	0/253 (0.0%)	1/268 (0.4%)		0/118 (0.0%)	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%)	173/268 (64.6%)		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%)		23/113 (20.4%)	26/109 (23.9%)	
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	137/256 (53.5%)	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
N	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
N	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%)		61/121 (50.4%)	49/119 (41.2%)	
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	103/256 (40.2%)	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						

Characteristic	Insulin DM Male (N=531)			Insulin DM Female (N=240)		
	INV (N=256)	CON (N=275)	P-value	INV (N=121)	CON (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	233	252		116	117	
Median (25th, 75th)	90 (80, 100)	90 (80, 100)		85 (70, 100)	80 (70, 100)	
Baseline Seattle Angina Questionnaire Angina Frequency Scale			0.998			0.739
Daily Angina (0-30)	8/233 (3.4%)	8/252 (3.2%)		1/116 (0.9%)	2/117 (1.7%)	
Weekly Angina (31-60)	26/233 (11.2%)	29/252 (11.5%)		19/116 (16.4%)	22/117 (18.8%)	
Monthly Angina (61-99)	97/233 (41.6%)	105/252 (41.7%)		59/116 (50.9%)	52/117 (44.4%)	
No Angina in Past Month (100)	102/233 (43.8%)	110/252 (43.7%)		37/116 (31.9%)	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	233	235		105	98	
Median (25th, 75th)	57 (51, 61)	60 (50, 65)		62 (55, 68)	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

*Site-reported value, if available. If not available, then core-lab entered value. EF, ejection fraction
†ISCHEMIA definition of optimal medical therapy[11]

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

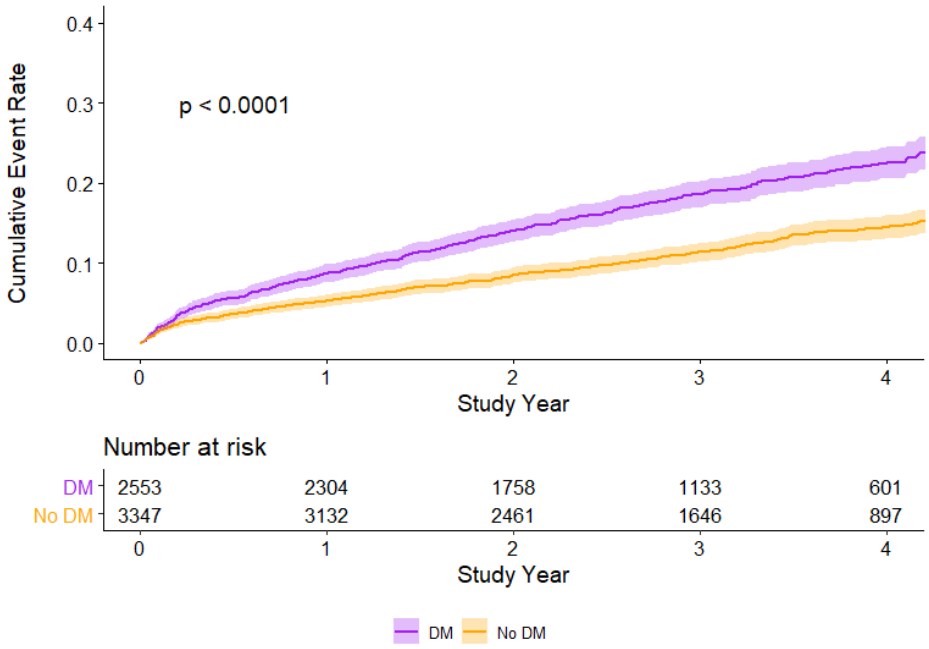


Figure Ib. Kaplan-Meier estimate of cumulative event rates of death or MI by clinical features of diabetes

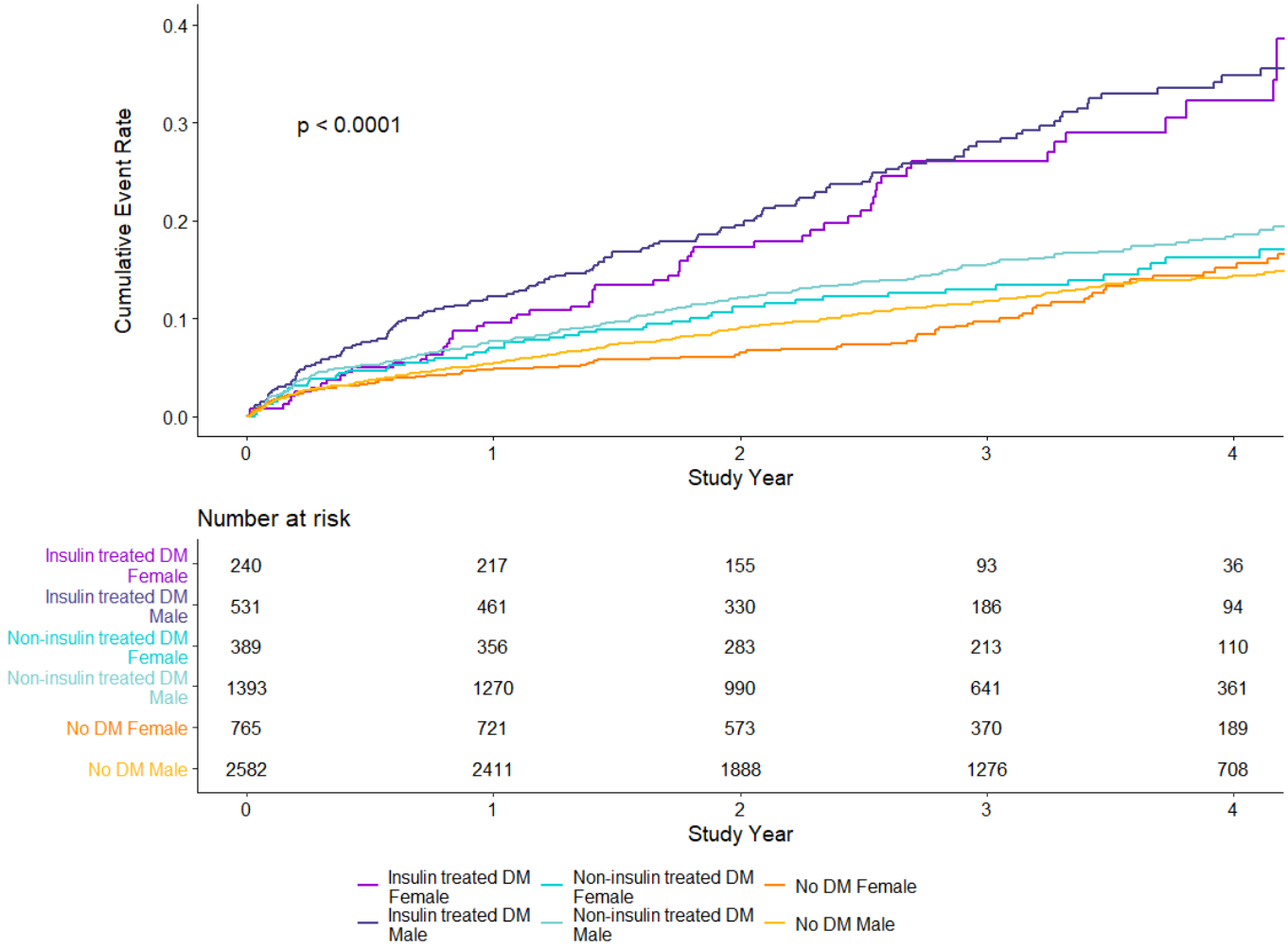


Figure Ic. Cumulative incidence of nonprocedural MI (types 1, 2, 4b or 4c) (accounting for competing risks) by diabetes status

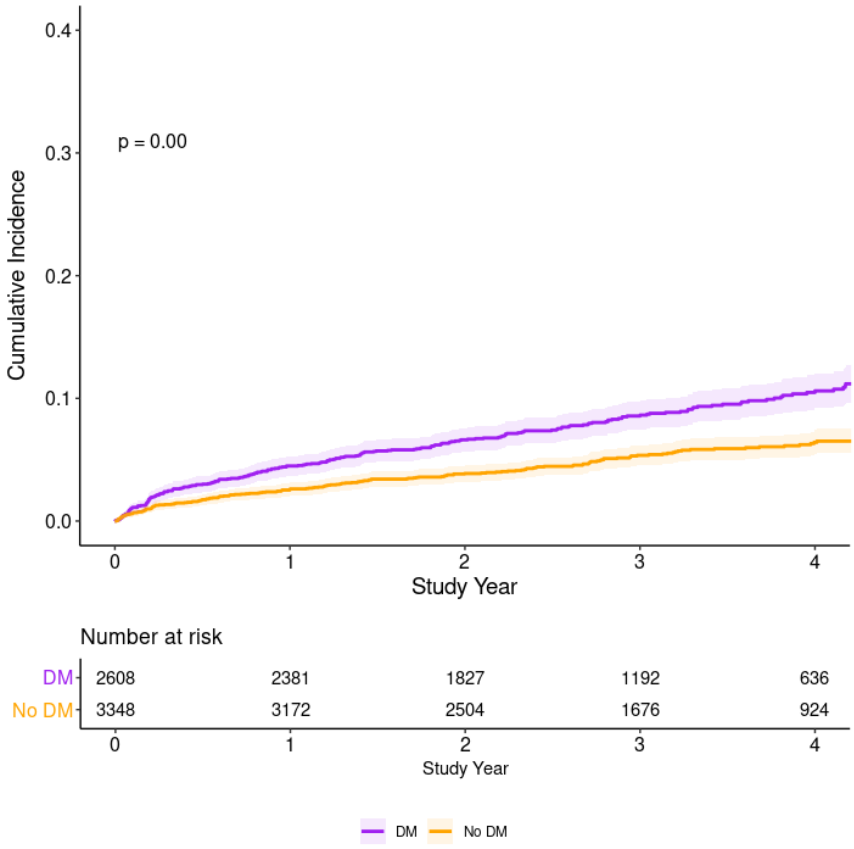


Figure Id. Cumulative incidence of procedural MI (types 4a or 5) (accounting for competing risks) by diabetes status

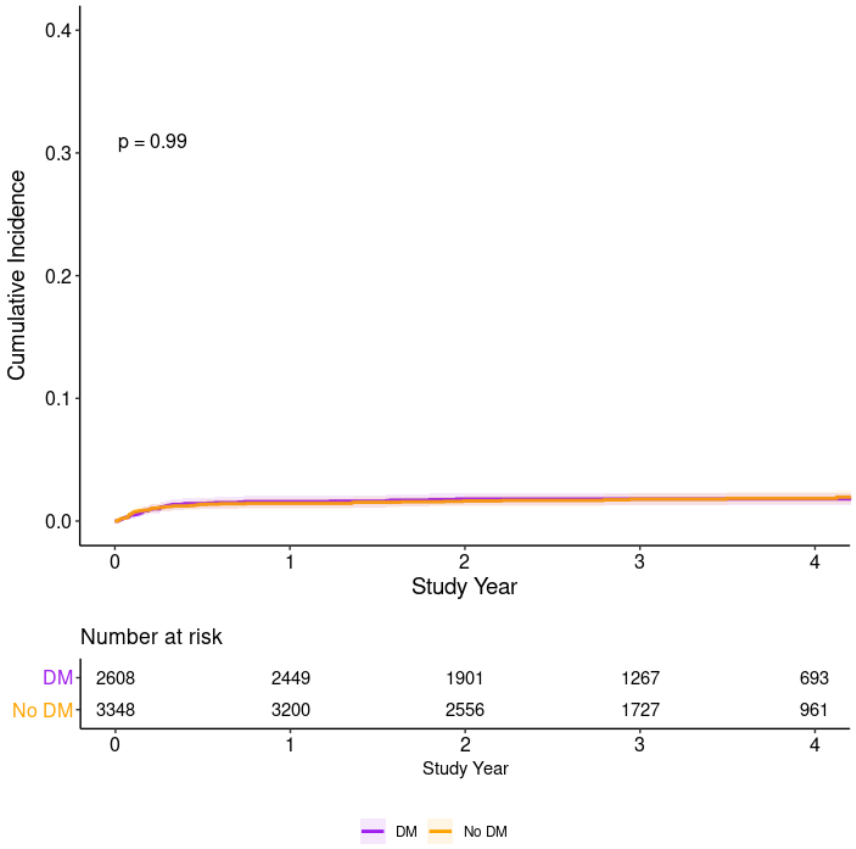


Figure IIa. Comparison of association of death or MI with diabetes status in the ISCHEMIA Trials, ISCHEMIA, and ISCHEMIA-CKD

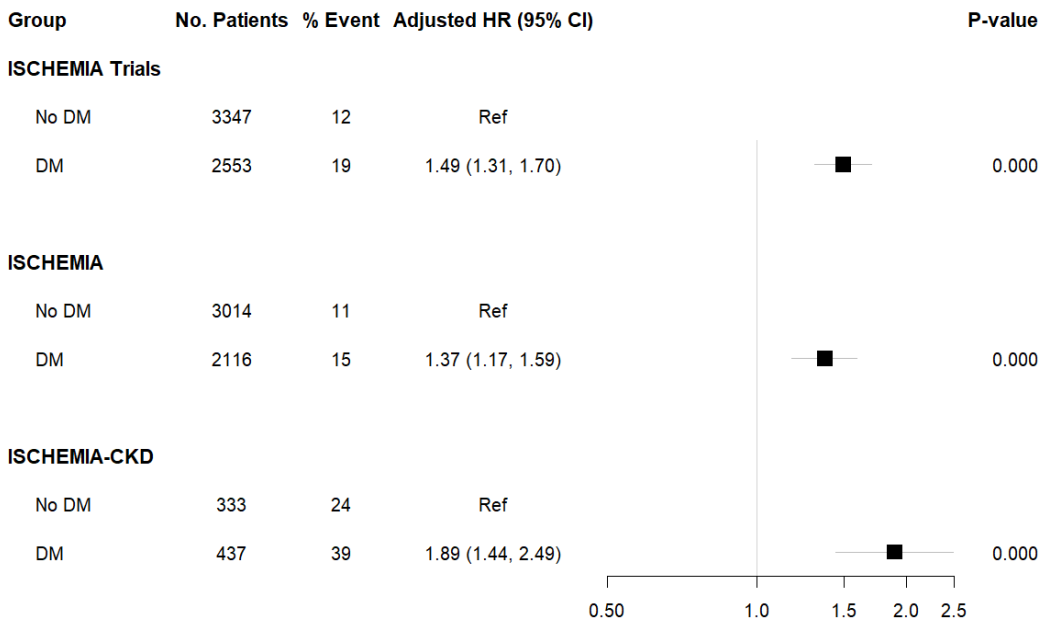


Figure IIb. Comparison of the association of death or MI with clinical features of diabetes in the ISCHEMIA Trials, ISCHEMIA, and ISCHEMIA-CKD

Group	No. Patients	% Event	Adjusted HR (95% 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)	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

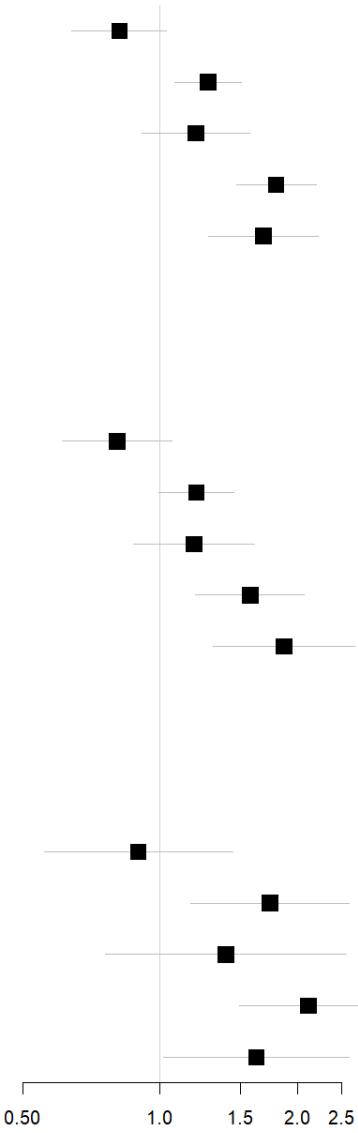
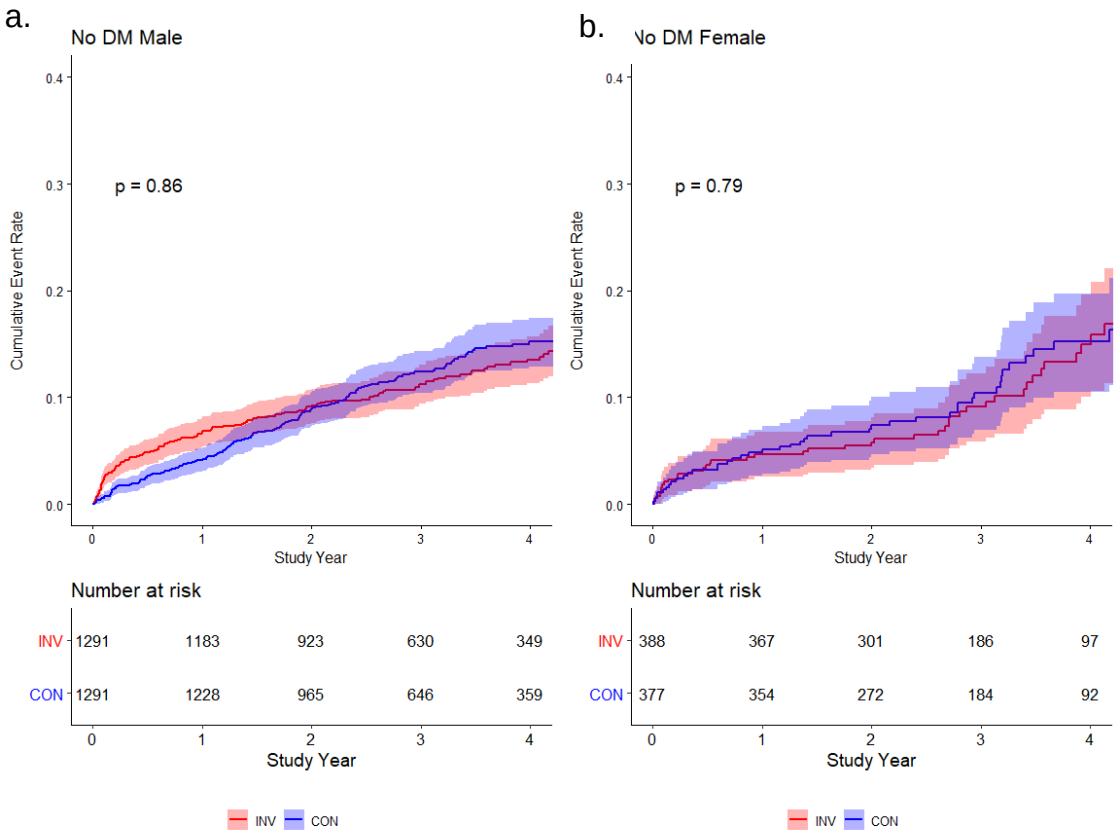
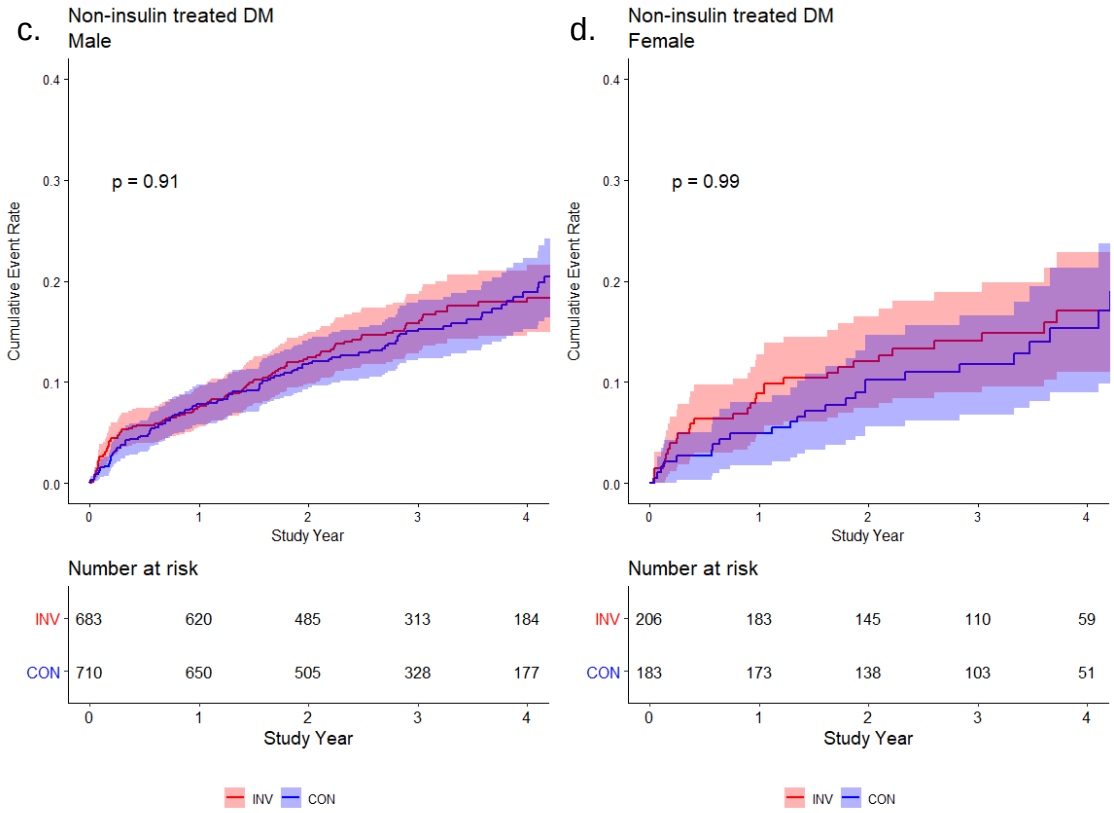
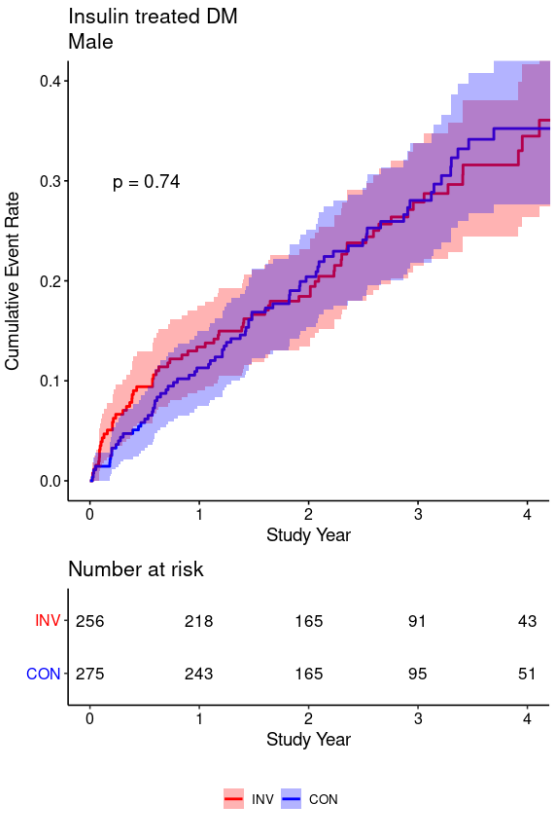


Figure IIIa-f. Kaplan-Meier estimate of cumulative event rates of death or MI by treatment strategy, stratified by clinical features of diabetes




c.
Non-insulin treated DM
Male
p = 0.91
Cumulative Event Rate
0.0
0.1
0.2
0.3
0.4
0
1
2
3
4
Study Year
Number at risk
INV 683 620 485 313 184
CON 710 650 505 328 177
Study Year
INV CON
d.
Non-insulin treated DM
Female
p = 0.99
Cumulative Event Rate
Study Year
Number at risk
INV 206 183 145 110 59
CON 183 173 138 103 51
Study Year
INV CON

e.


Insulin treated DM
Male
p = 0.74
Cumulative Event Rate
0.0
0.1
0.2
0.3
0.4
0
1
2
3
4
Study Year
Number at risk
INV 256 218 165 91 43
CON 275 243 165 95 51
Study Year
INV CON

f.

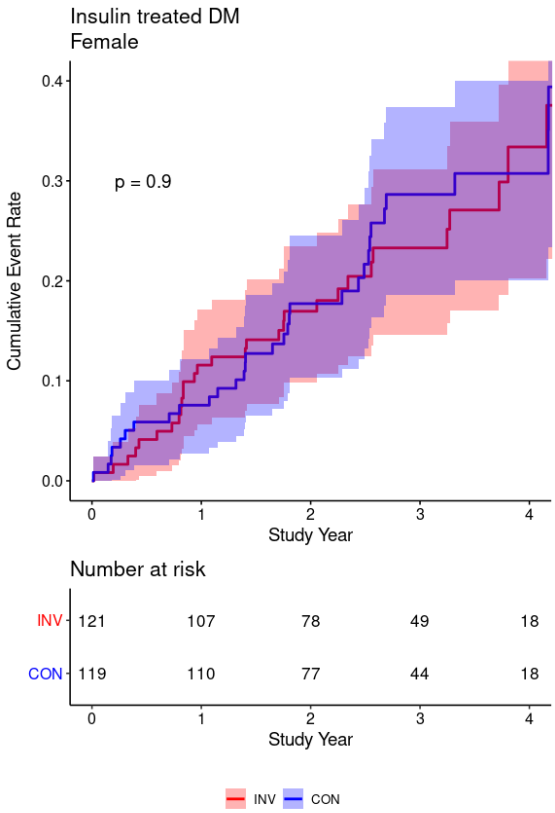

Insulin treated DM
Female
p = 0.9
Cumulative Event Rate
0.0
0.1
0.2
0.3
0.4
0
1
2
3
4
Study Year
Number at risk
INV 121 107 78 49 18
CON 119 110 77 44 18
Study Year
INV CON

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.

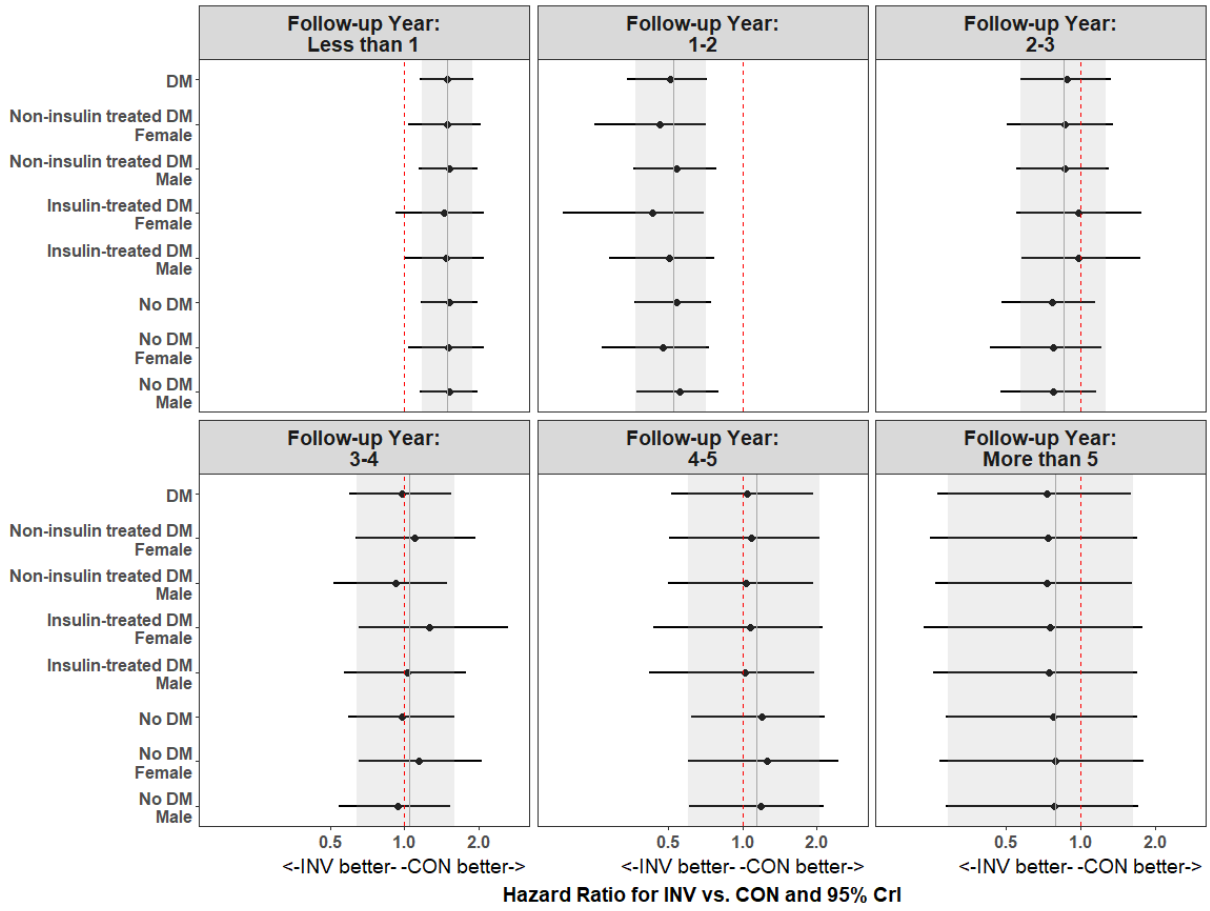


Figure IVb. Diabetes and clinical feature-specific -specific treatment effects over study follow-up in the ISCHEMIA-CKD trial. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible area. Vertical dashed red bar is at 1 for reference.

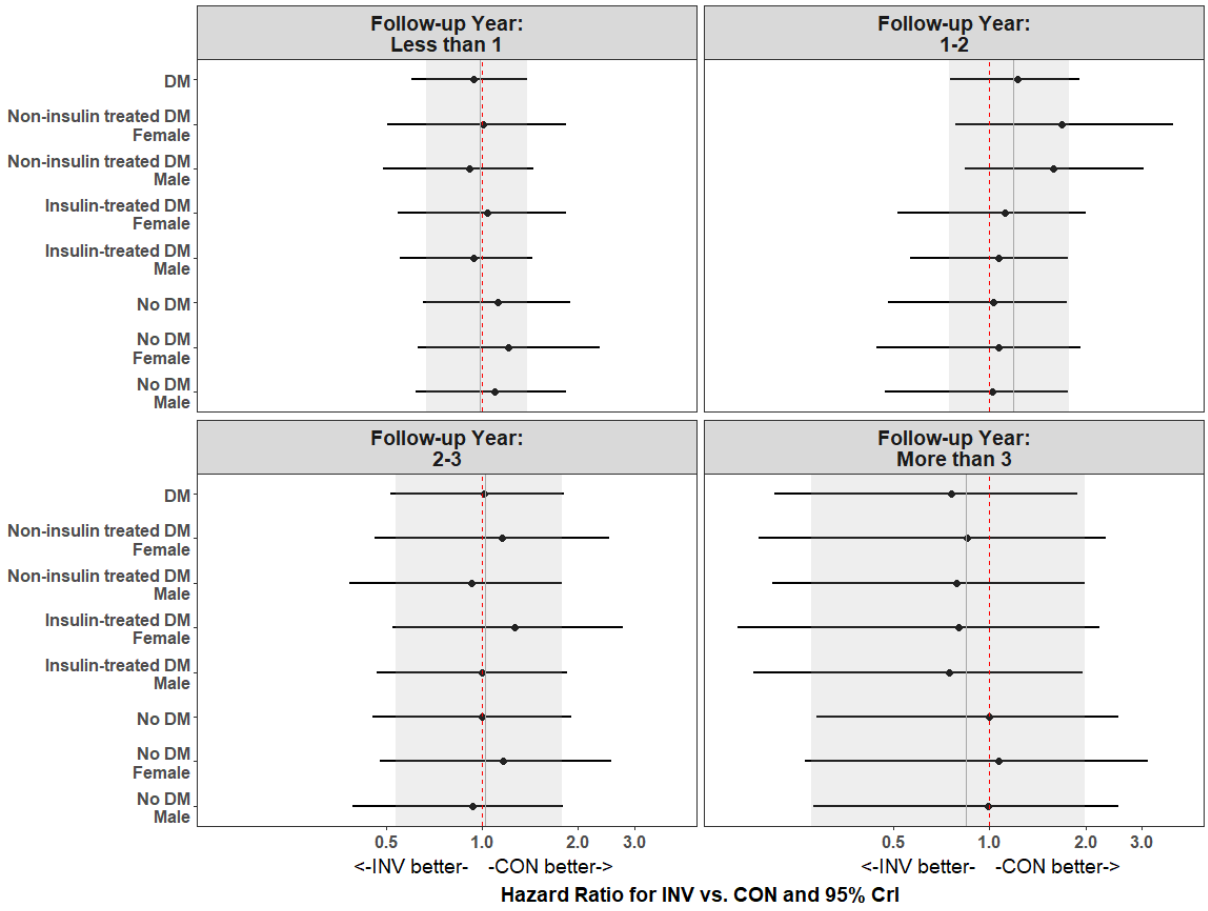


Figure V. Summary diabetes and clinical feature-specific treatment effects based on proportional hazards in the ISCHEMIA Trials, ISCHEMIA, and ISCHEMIA-CKD. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible area. Vertical dashed red bar is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

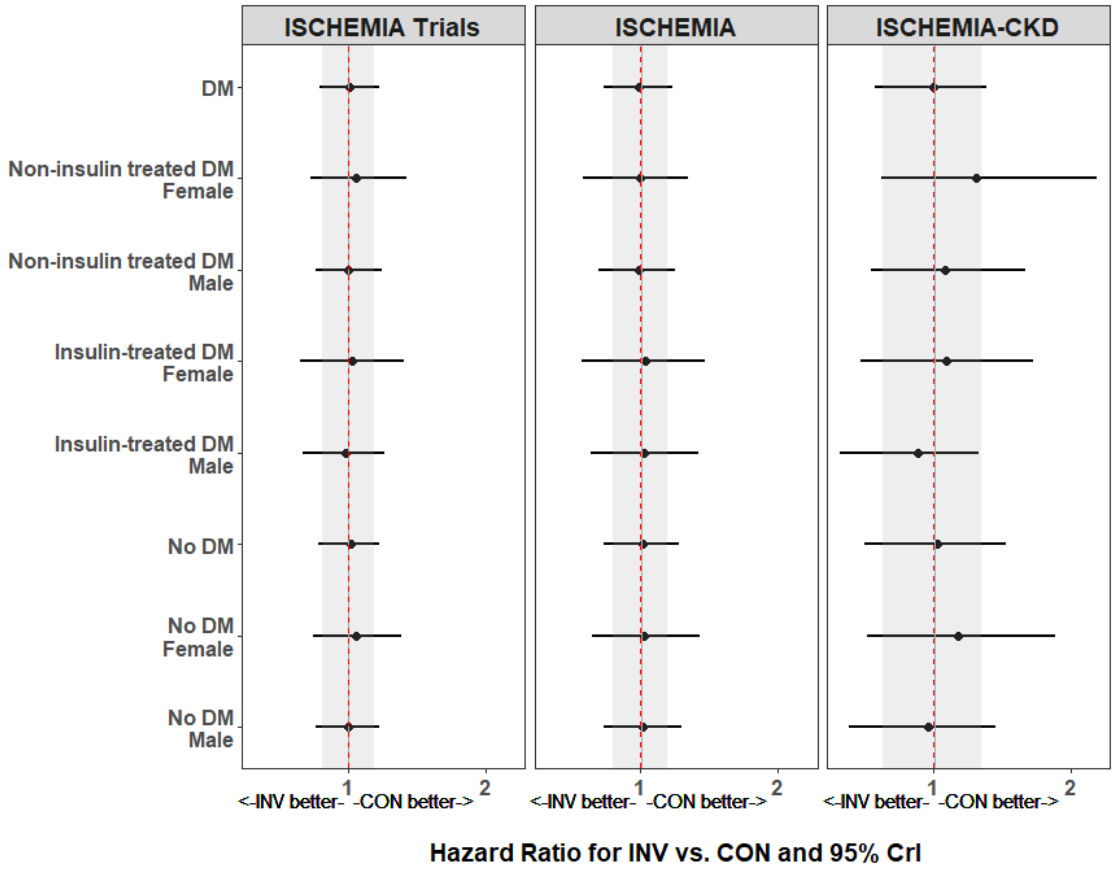


Figure VIa. Kaplan-Meier estimate of cumulative event rates of death by treatment strategy, stratified by diabetes status

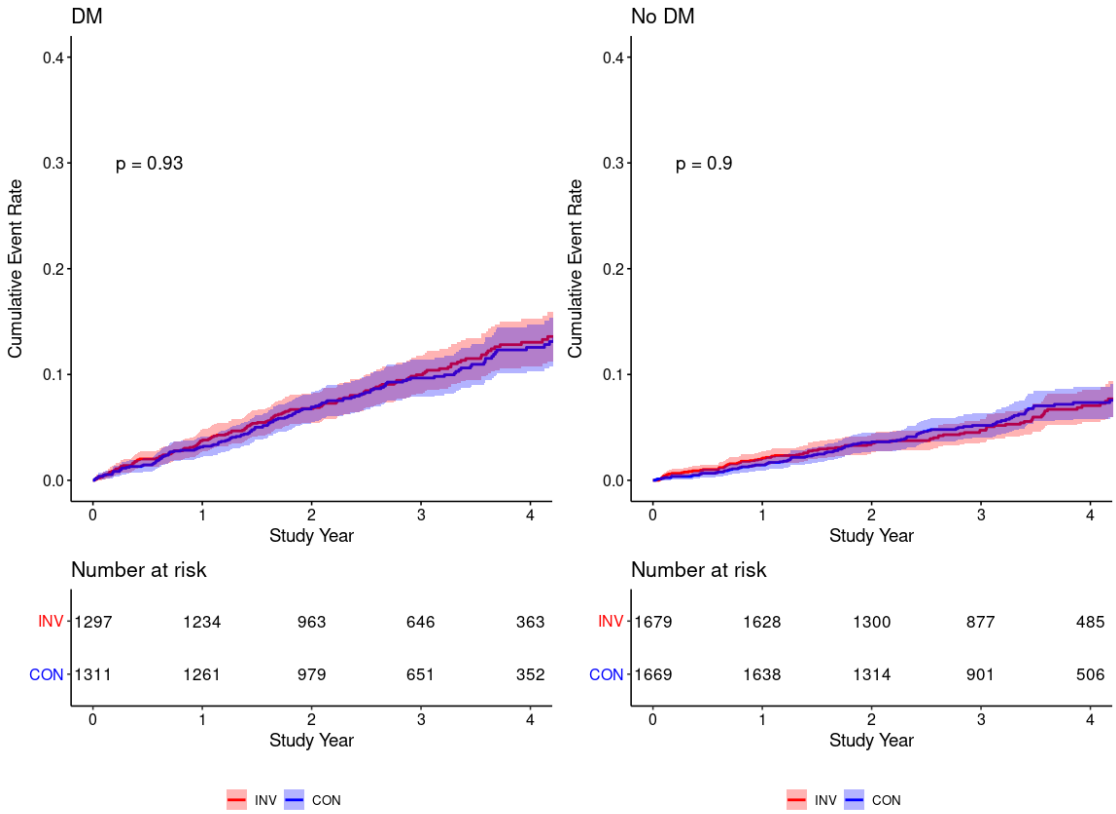


Figure VIb. Cumulative incidence of CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status

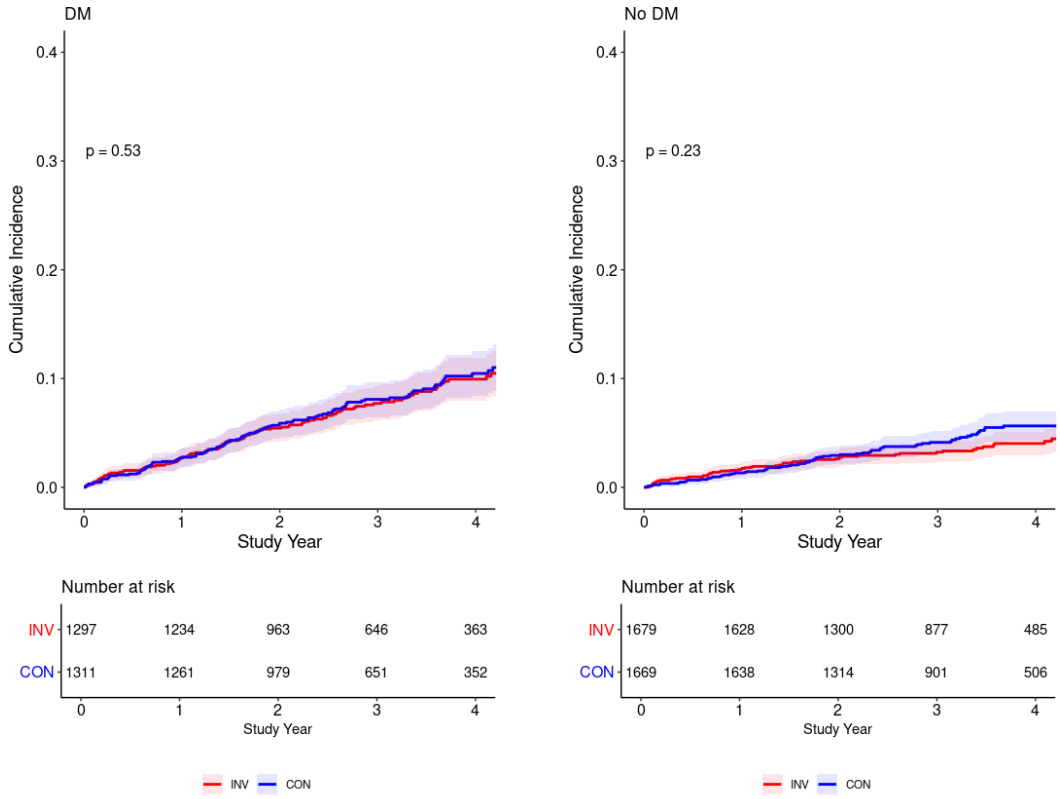


Figure VIc. Cumulative incidence of non-CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status

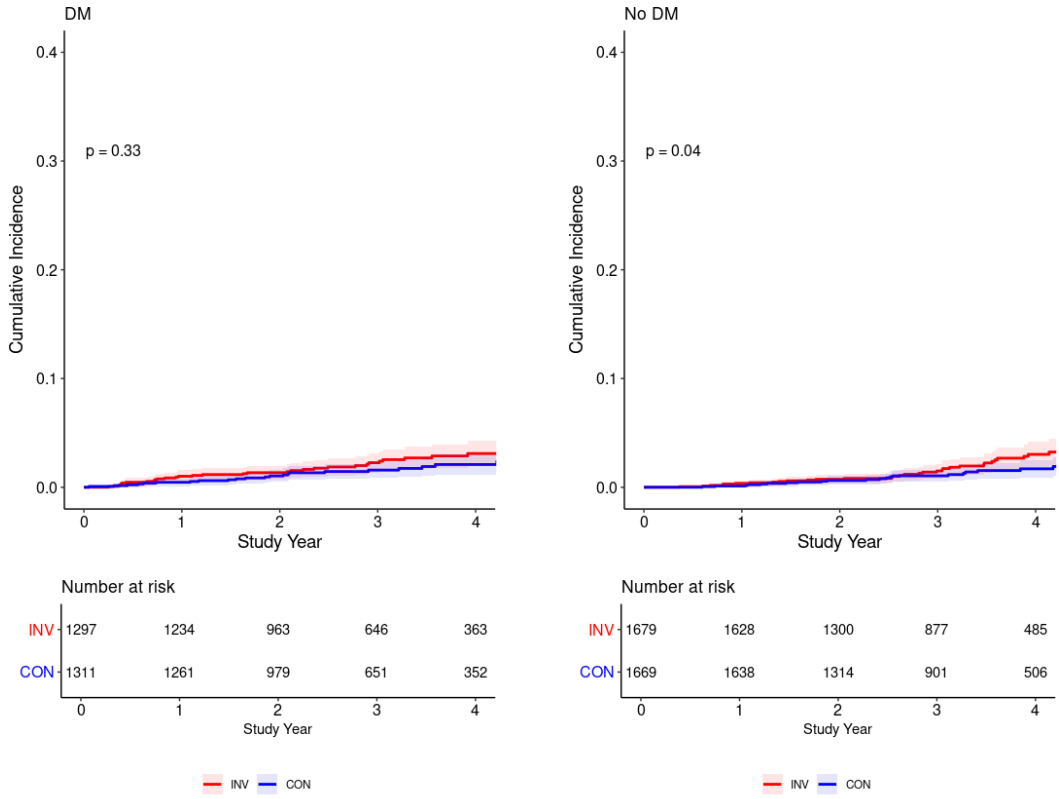


Figure VId. Cumulative incidence of fatal and non-fatal MI (accounting for competing risks) by treatment strategy, stratified by diabetes status

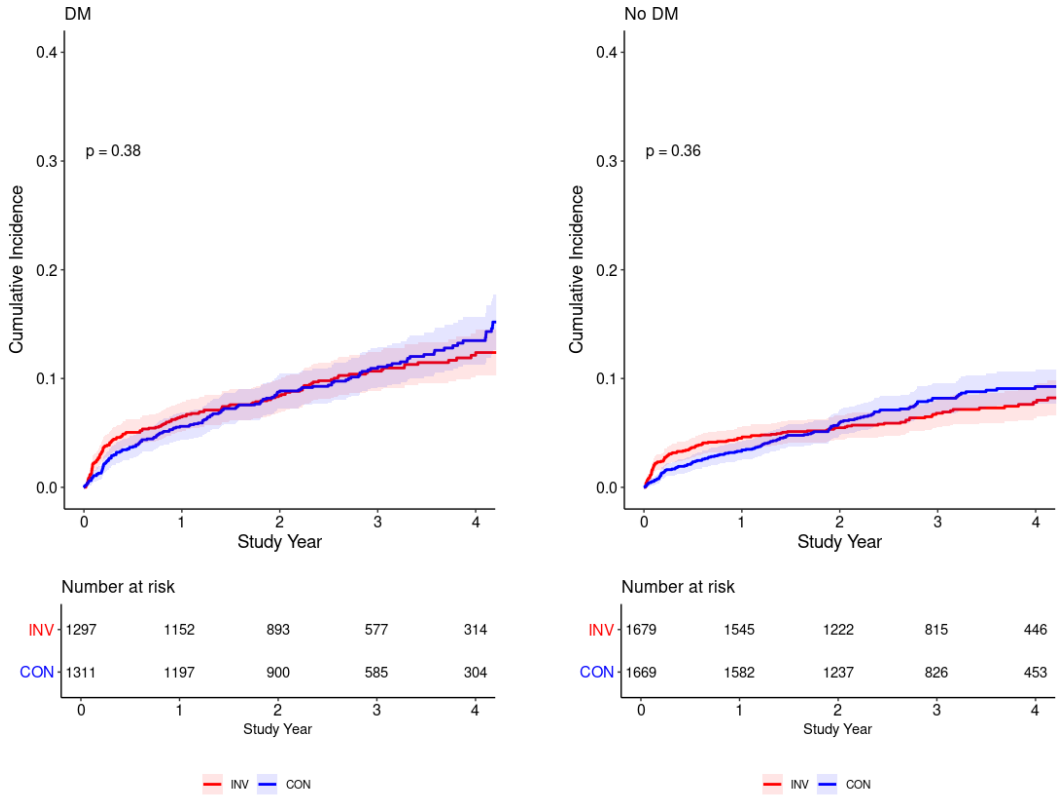


Figure VIIa. Kaplan-Meier estimate of cumulative event rates of death or MI by multivessel CAD ≥50% stenosis, stratified by diabetes status

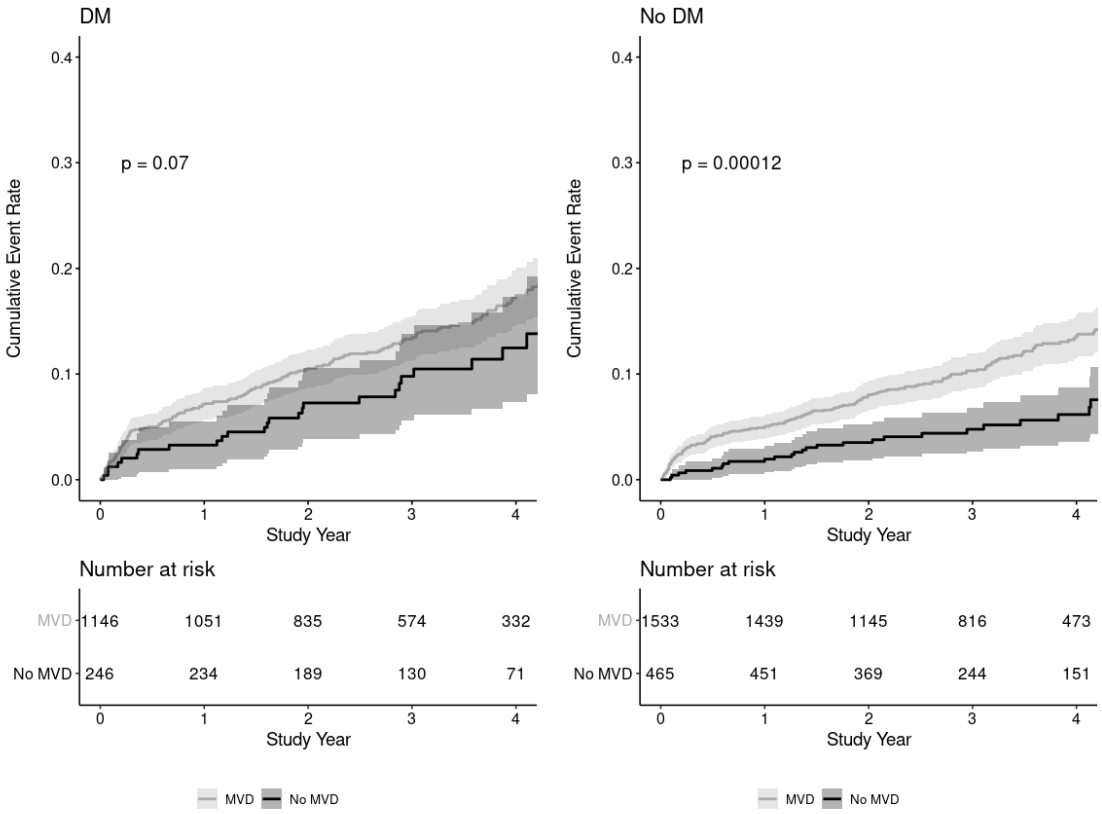


Figure VIIb. Kaplan-Meier estimate of cumulative event rates of death or MI by Duke score 6 severity of CAD, stratified by diabetes status

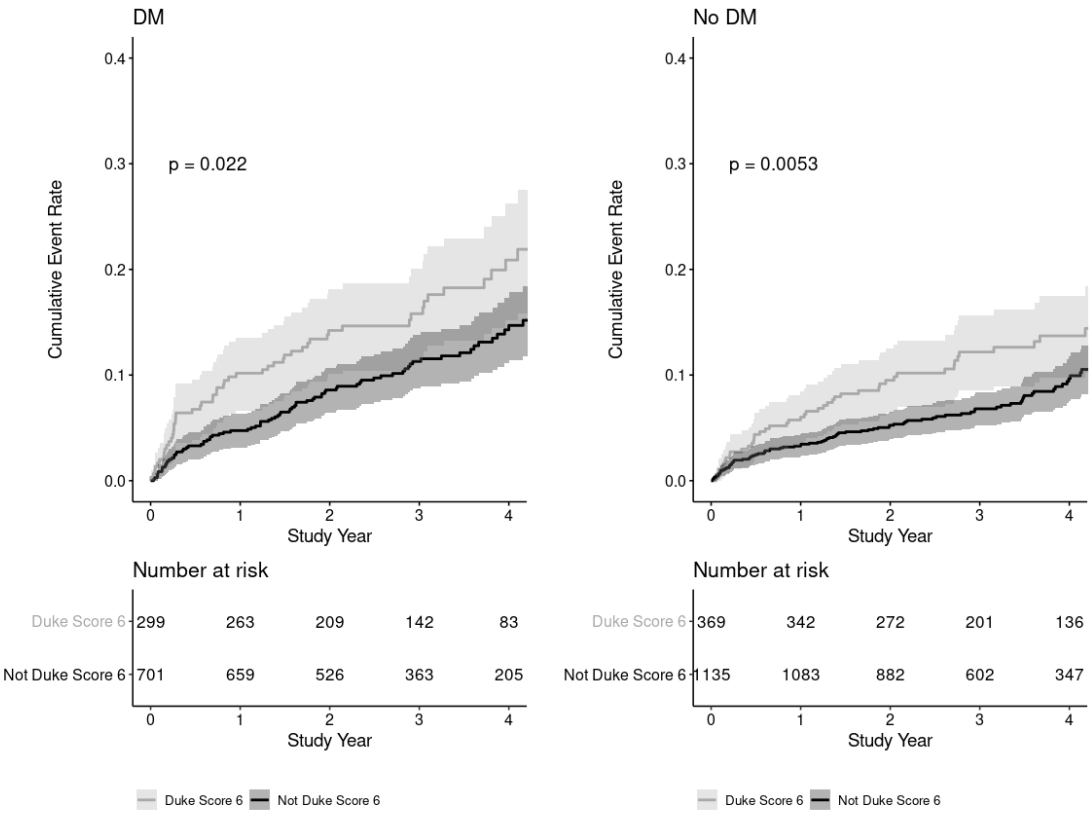


Figure VIIc. Kaplan-Meier estimate of cumulative event rates of death or MI by LVSD, stratified by diabetes status

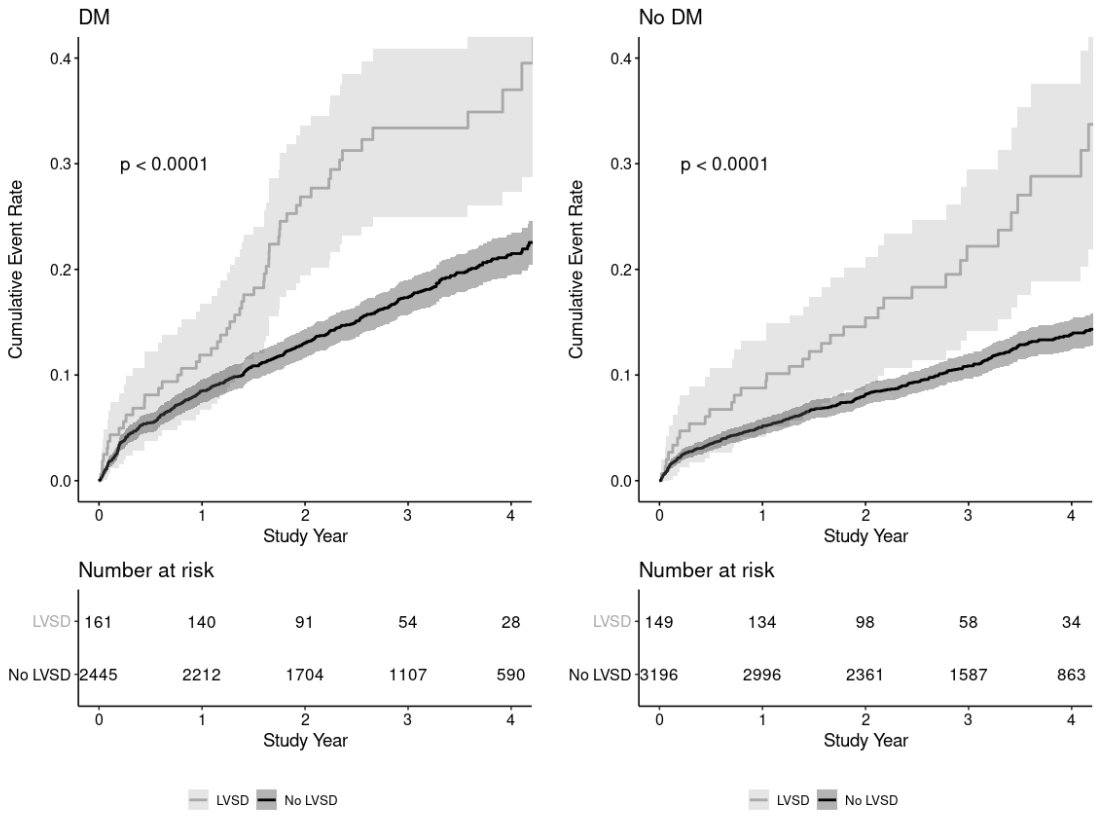


Figure VIIIa. Kaplan-Meier estimate of cumulative event rates of death or MI by treatment strategy, stratified by diabetes status and multivessel CAD ≥50% stenosis

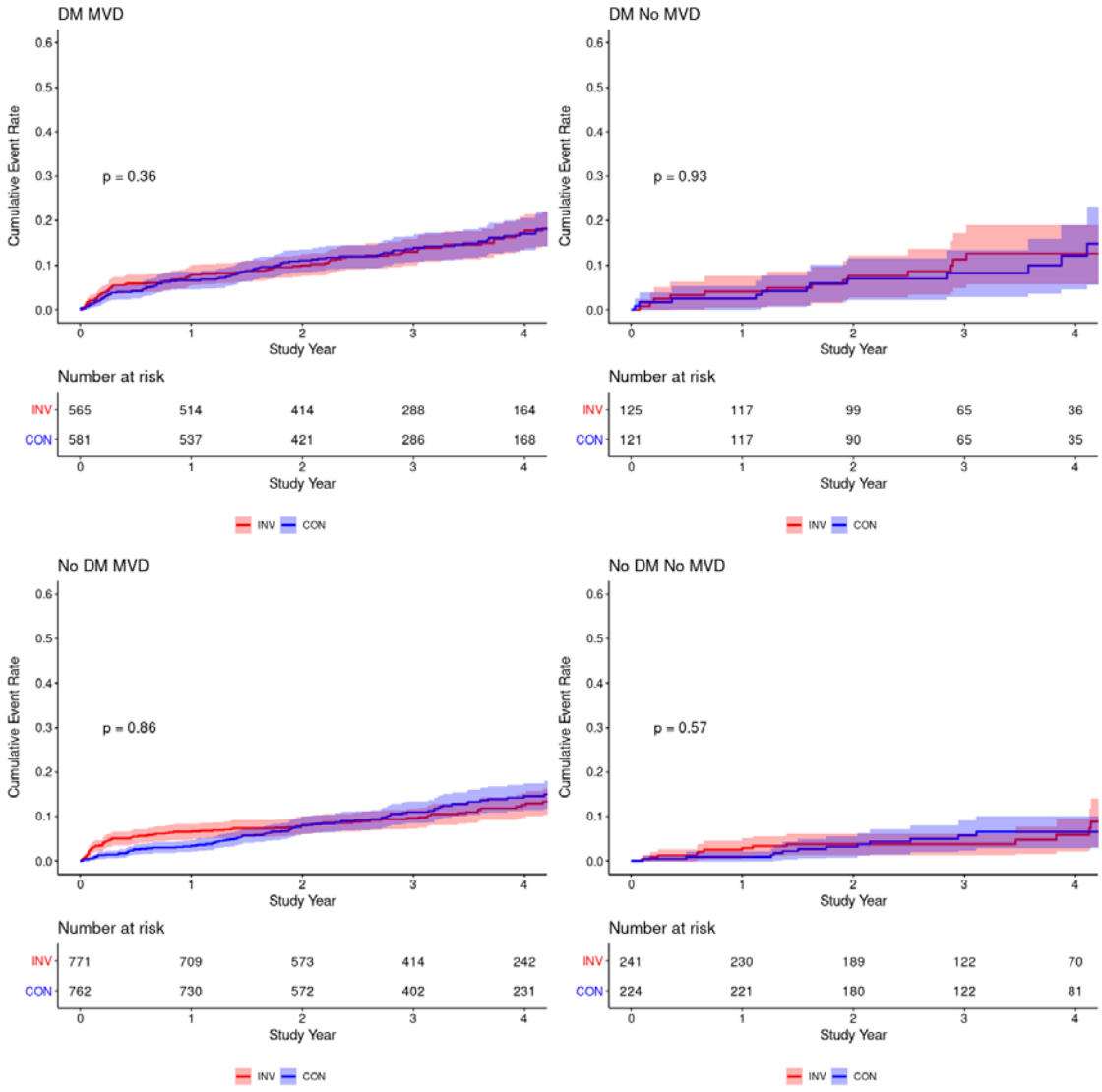


Figure VIIIb. Kaplan-Meier estimate of cumulative event rates of death or MI by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

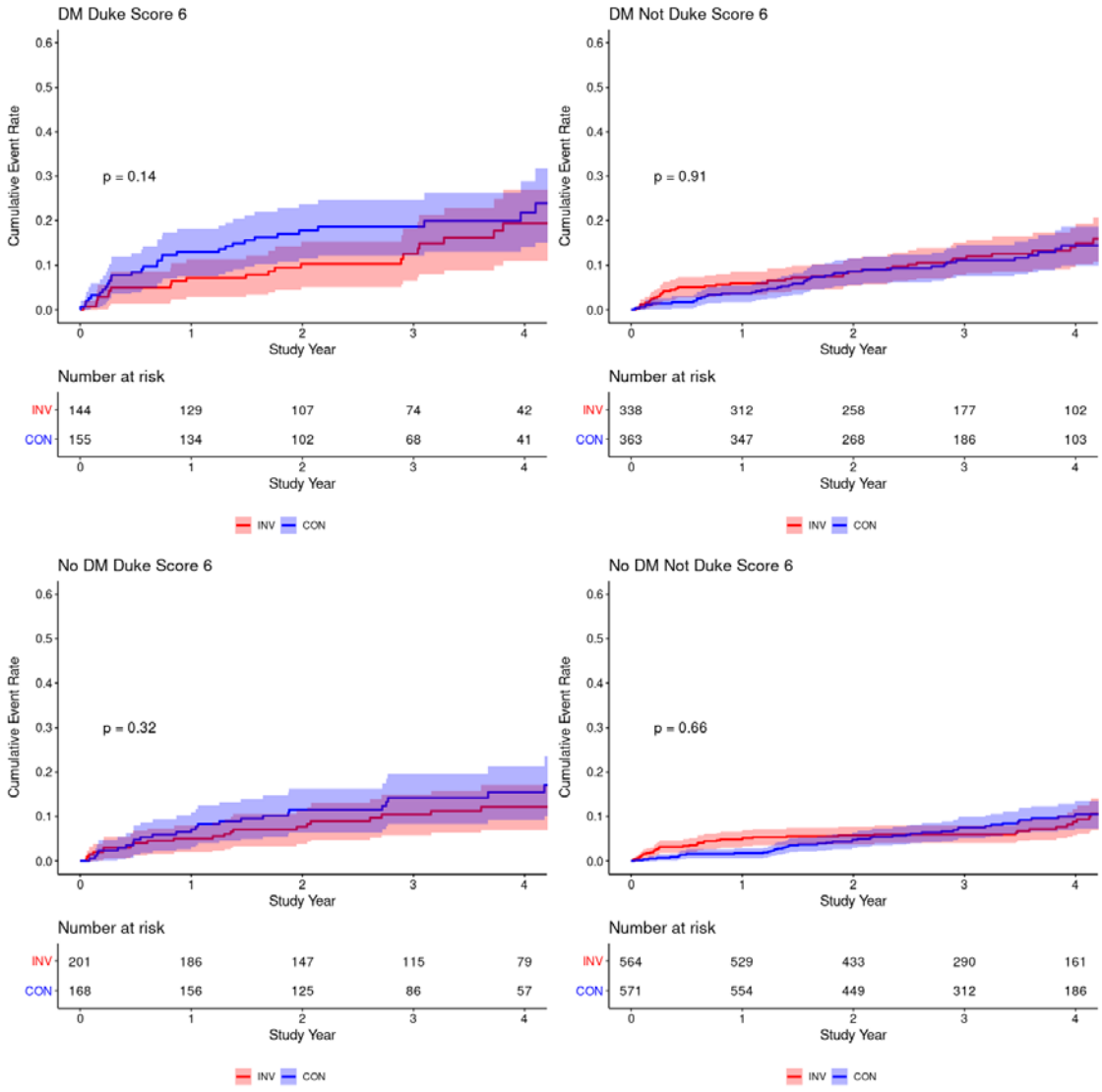


Figure VIIIc. Kaplan-Meier estimate of cumulative event rates of death or MI by treatment strategy, stratified by diabetes status and LVSD

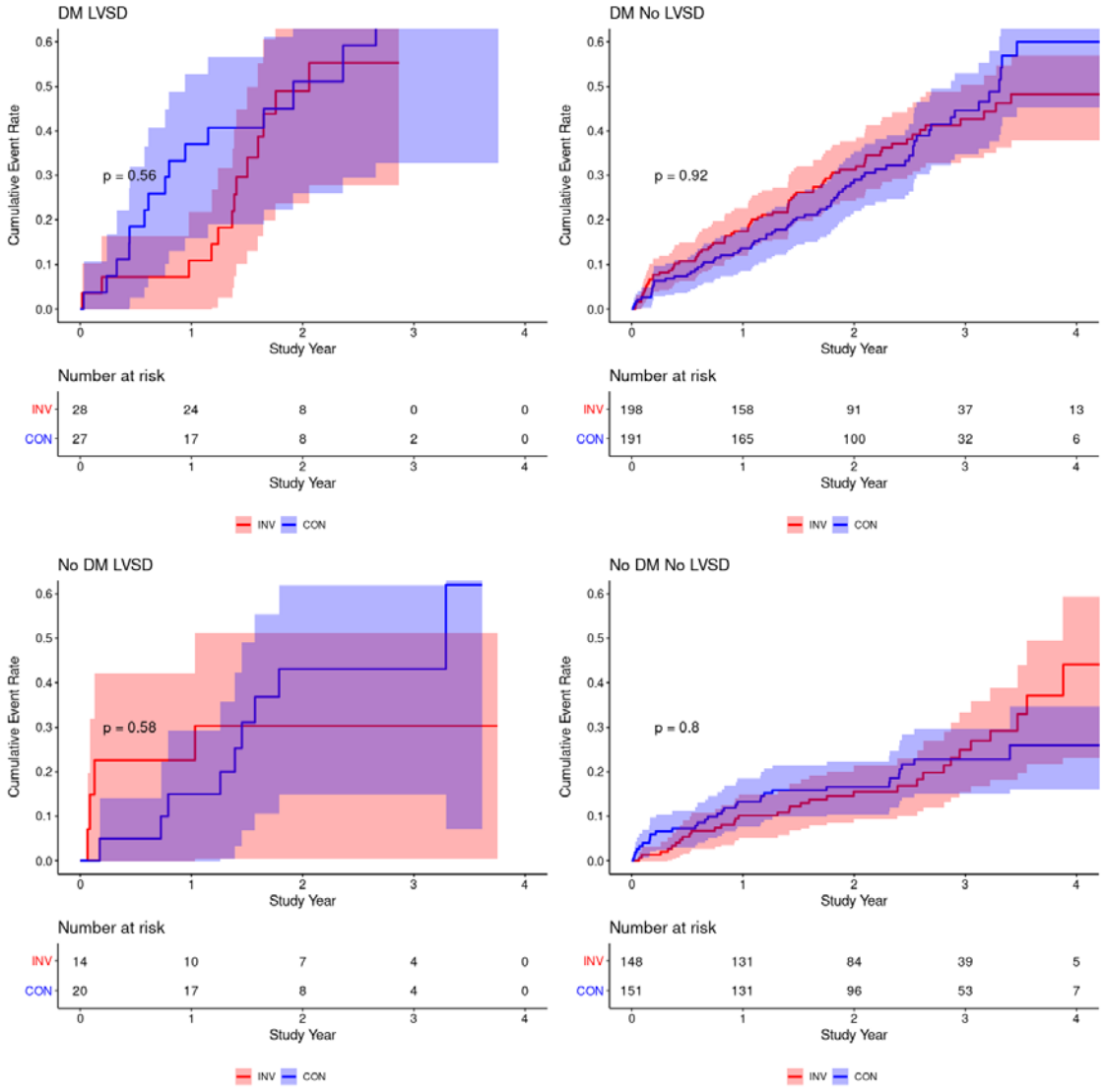


Figure IX. Diabetes anatomic features-specific treatment effects over study follow-up among the subset of ISCHEMIA participants with anatomic features. Color coding is by anatomic feature. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to the 95% credible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

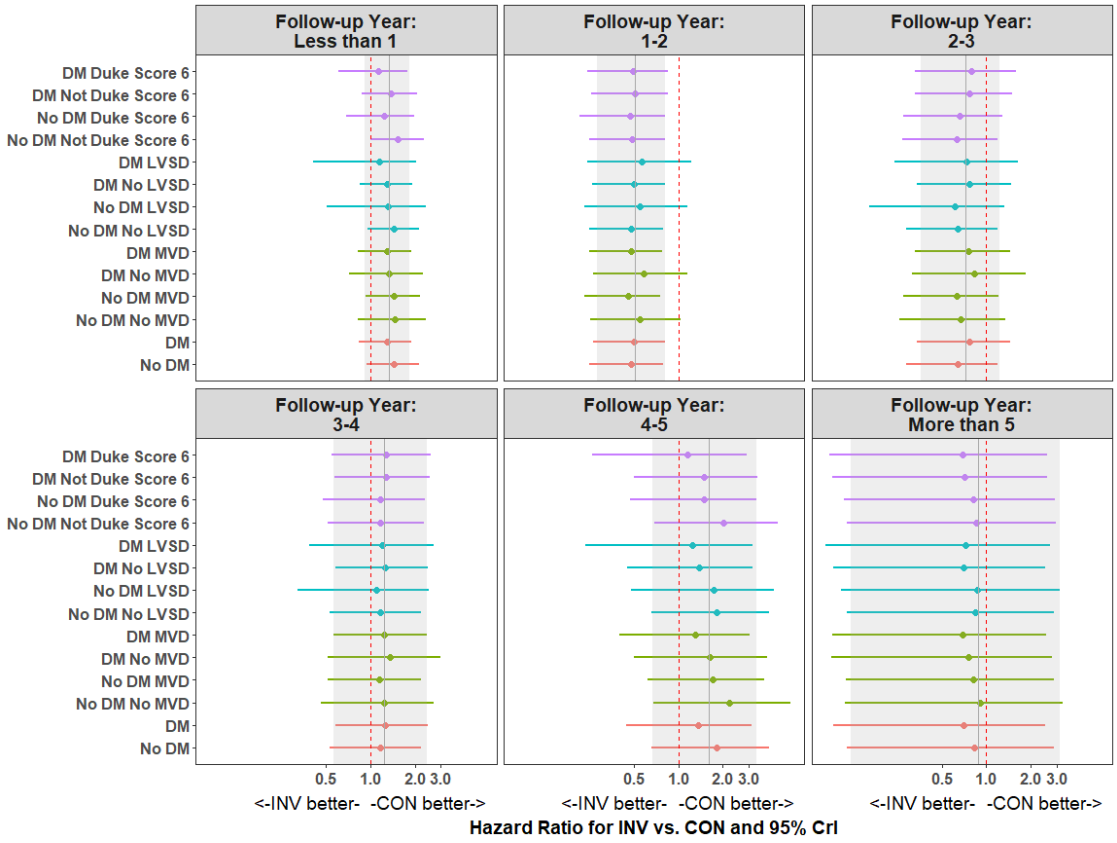


Figure X. Summary diabetes anatomic features-specific treatment effects based on proportional hazards among the subset of ISCHEMIA participants with anatomic features. Color coding is by anatomic feature. Vertical gray bar is the overall treatment effect and the associated gray shading correspond to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

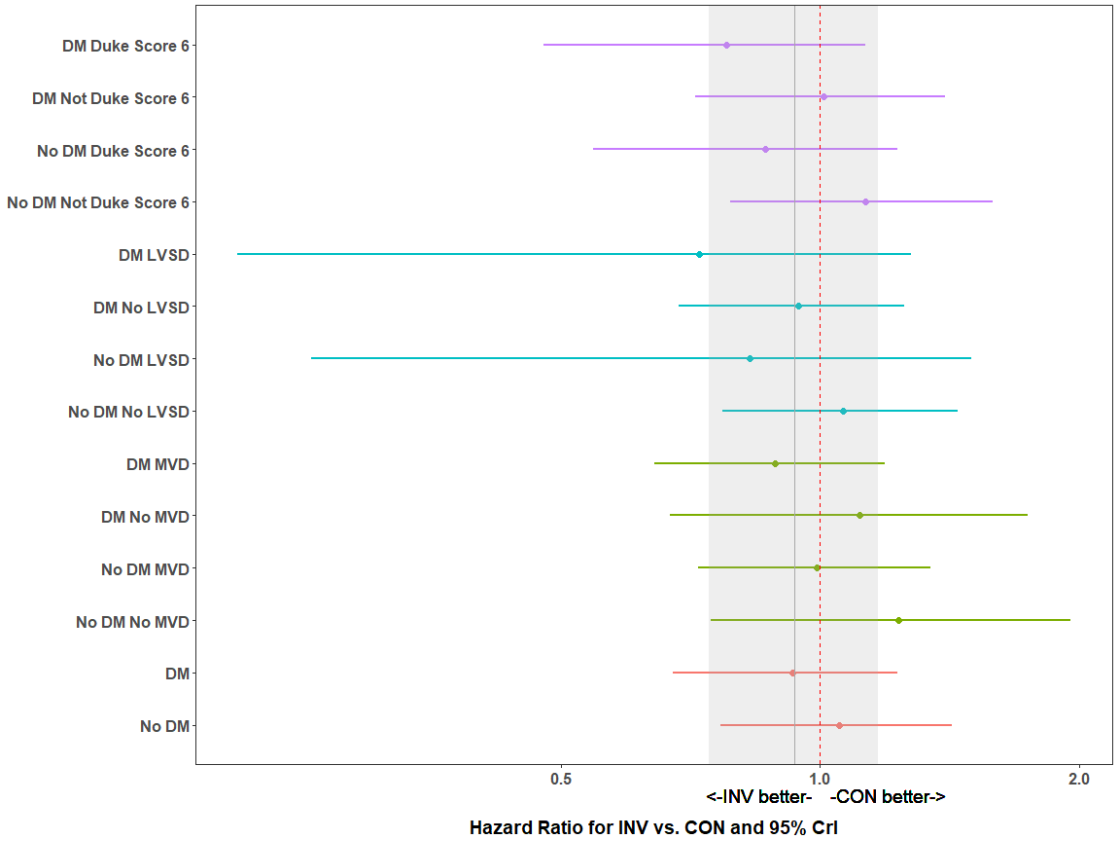


Figure XIa. Kaplan-Meier estimate of cumulative event rates of death by treatment strategy, stratified by diabetes status and multivessel CAD ≥50% stenosis

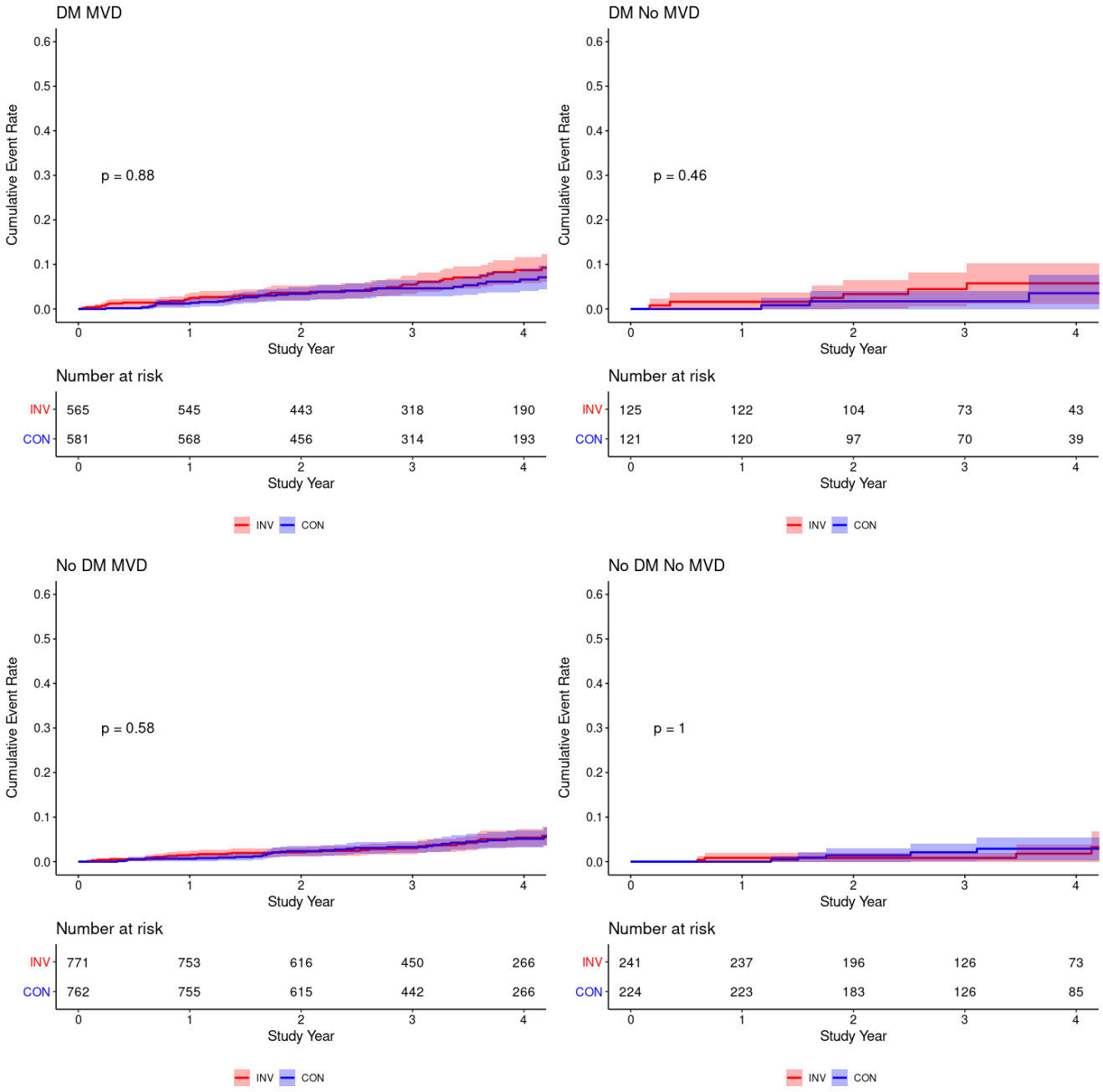


Figure XIb. Kaplan-Meier estimate of cumulative event rates of death by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

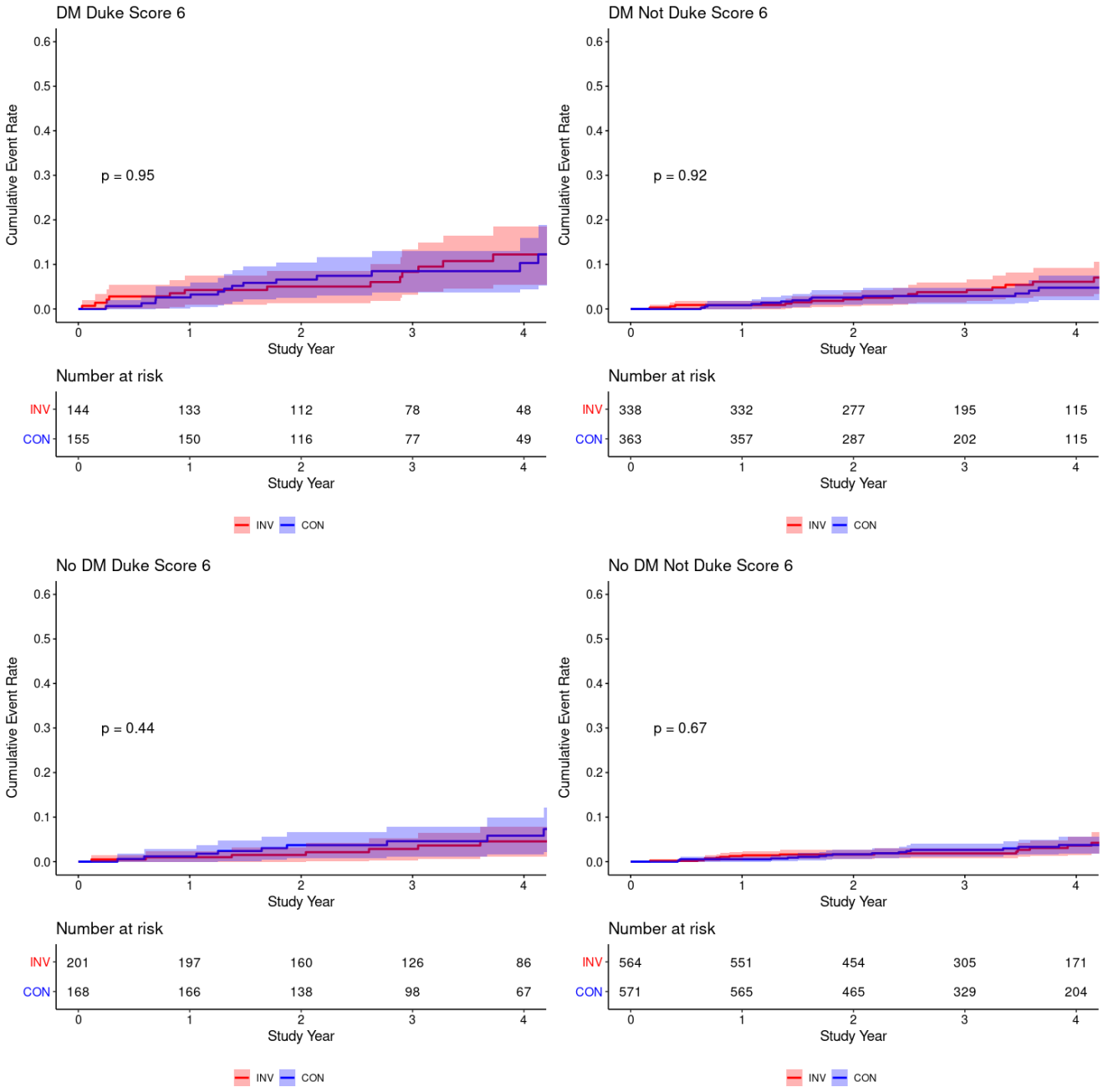


Figure XIc. Kaplan-Meier estimate of cumulative event rates of death by treatment strategy, stratified by diabetes status and LVSD

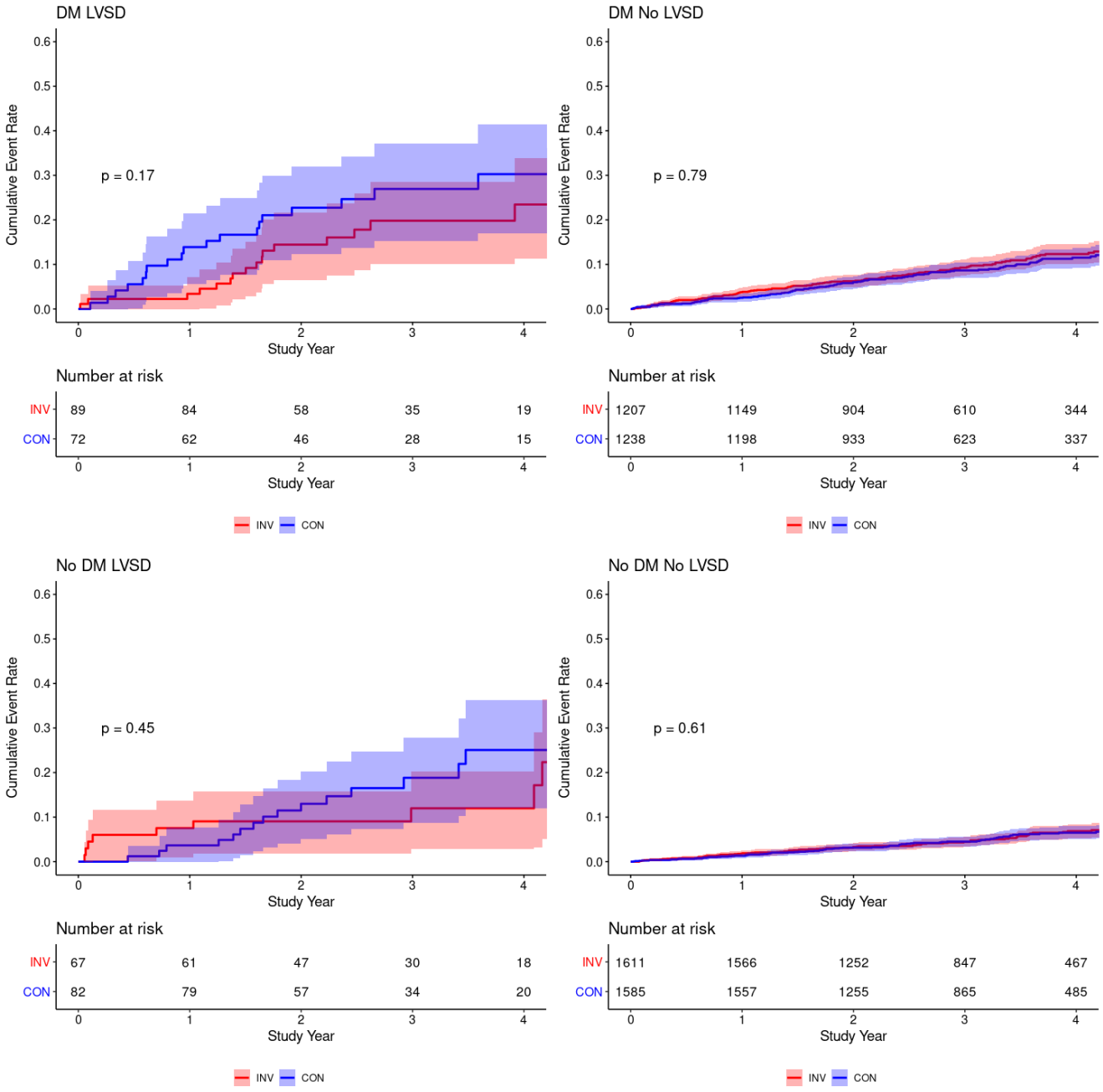


Figure XIIa. Cumulative incidence of CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and multivessel CAD ≥50% stenosis

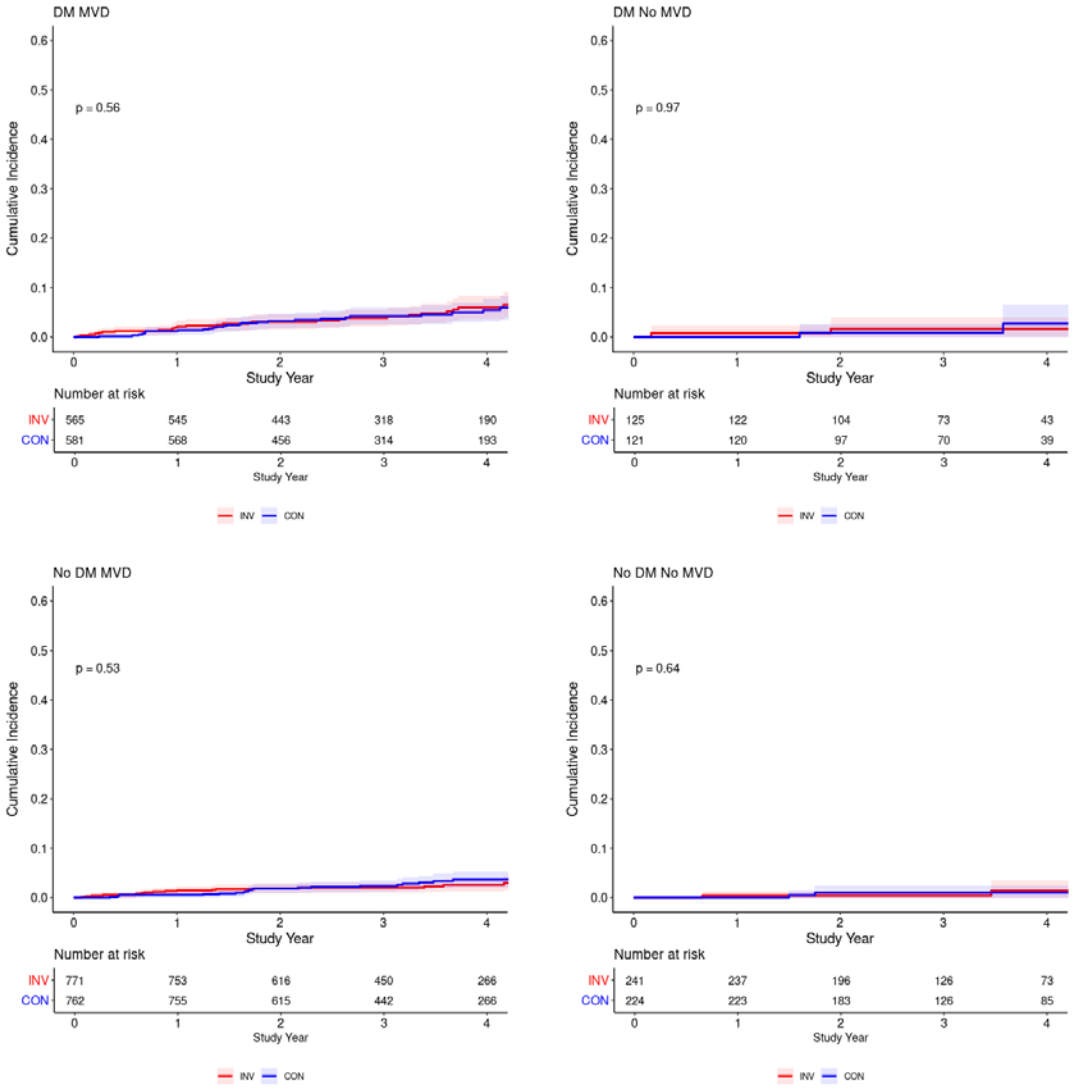


Figure XIIb. Cumulative incidence of CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

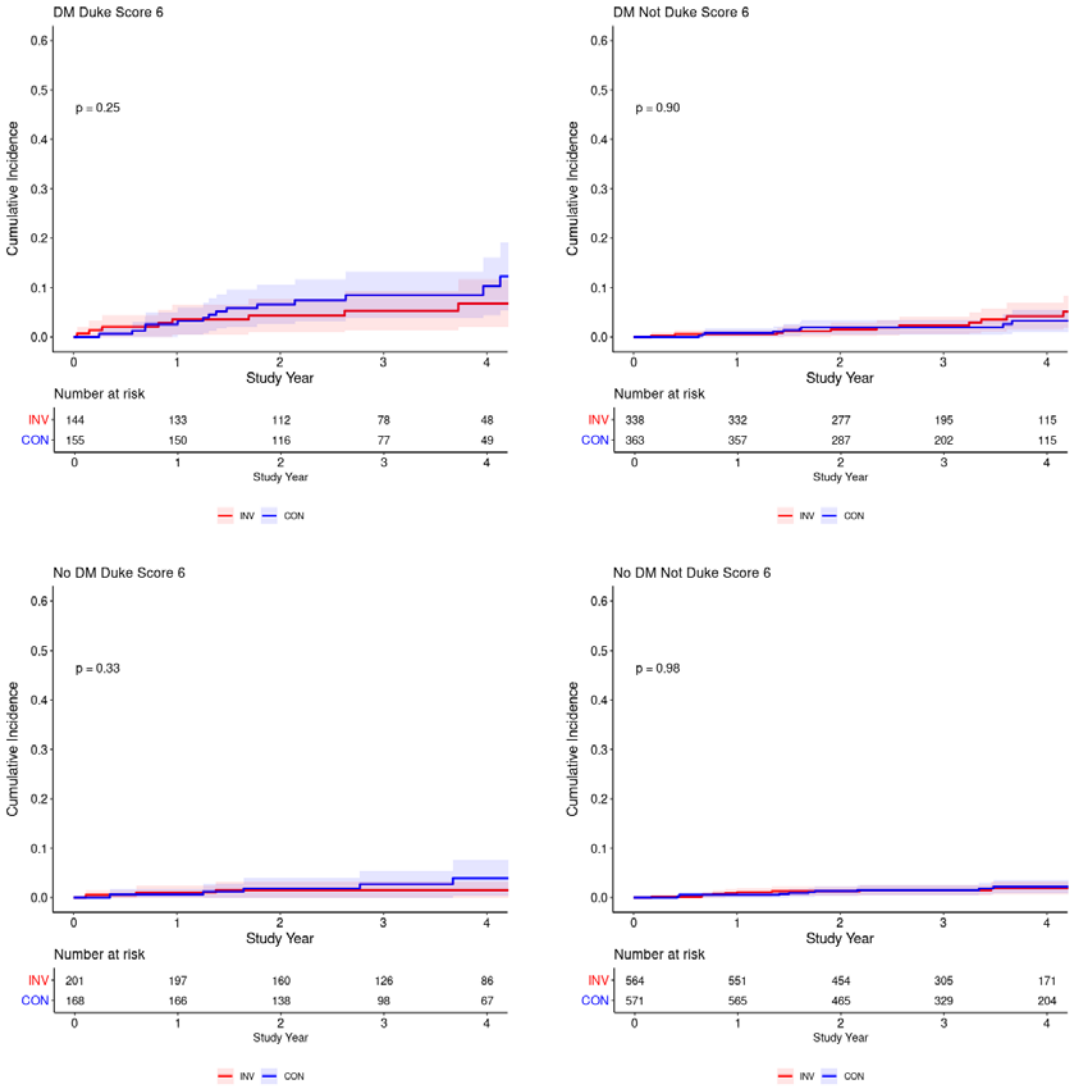


Figure XIIc. Cumulative incidence of CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and LVSD

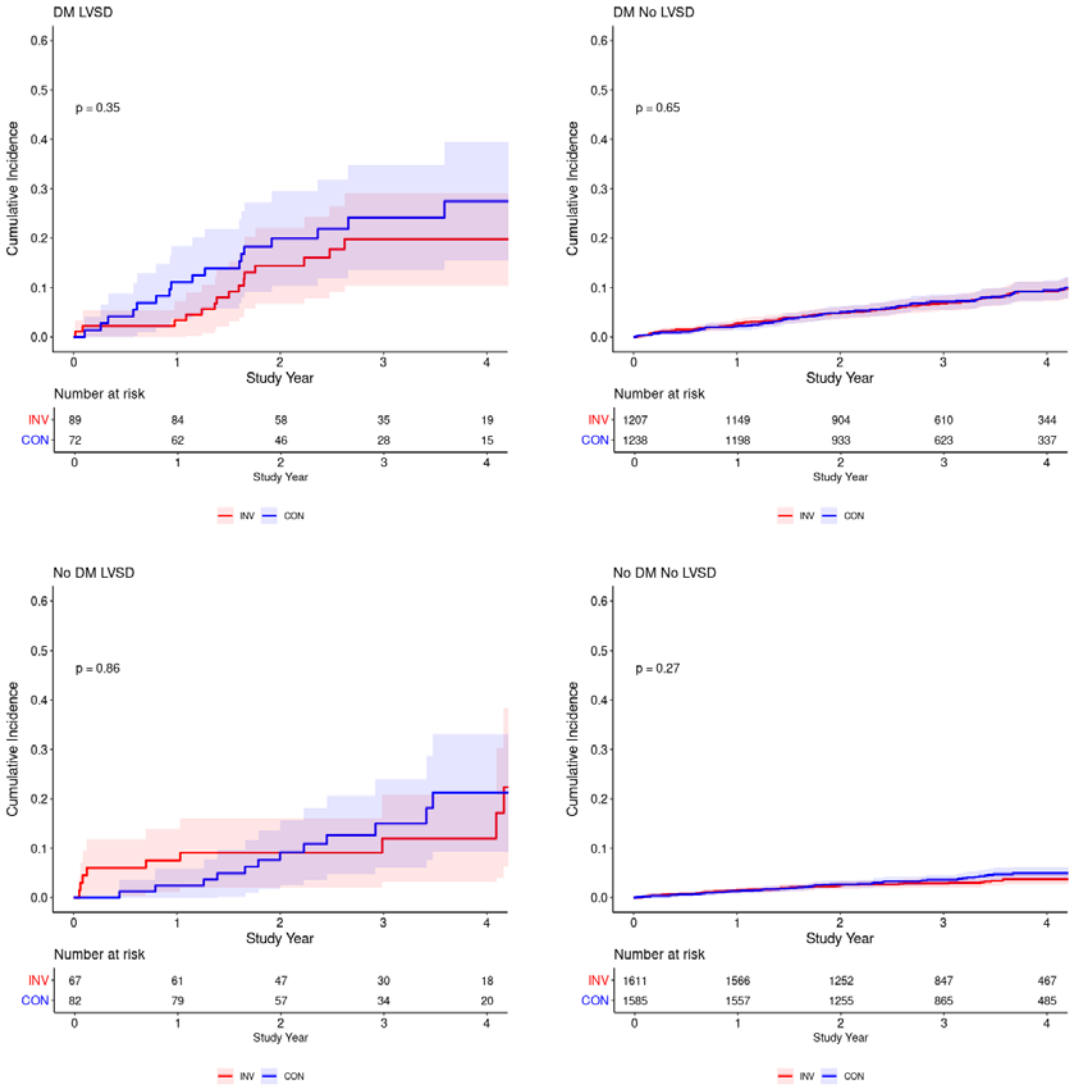


Figure XIIIa. Cumulative incidence of non-CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and multivessel CAD ≥50% stenosis

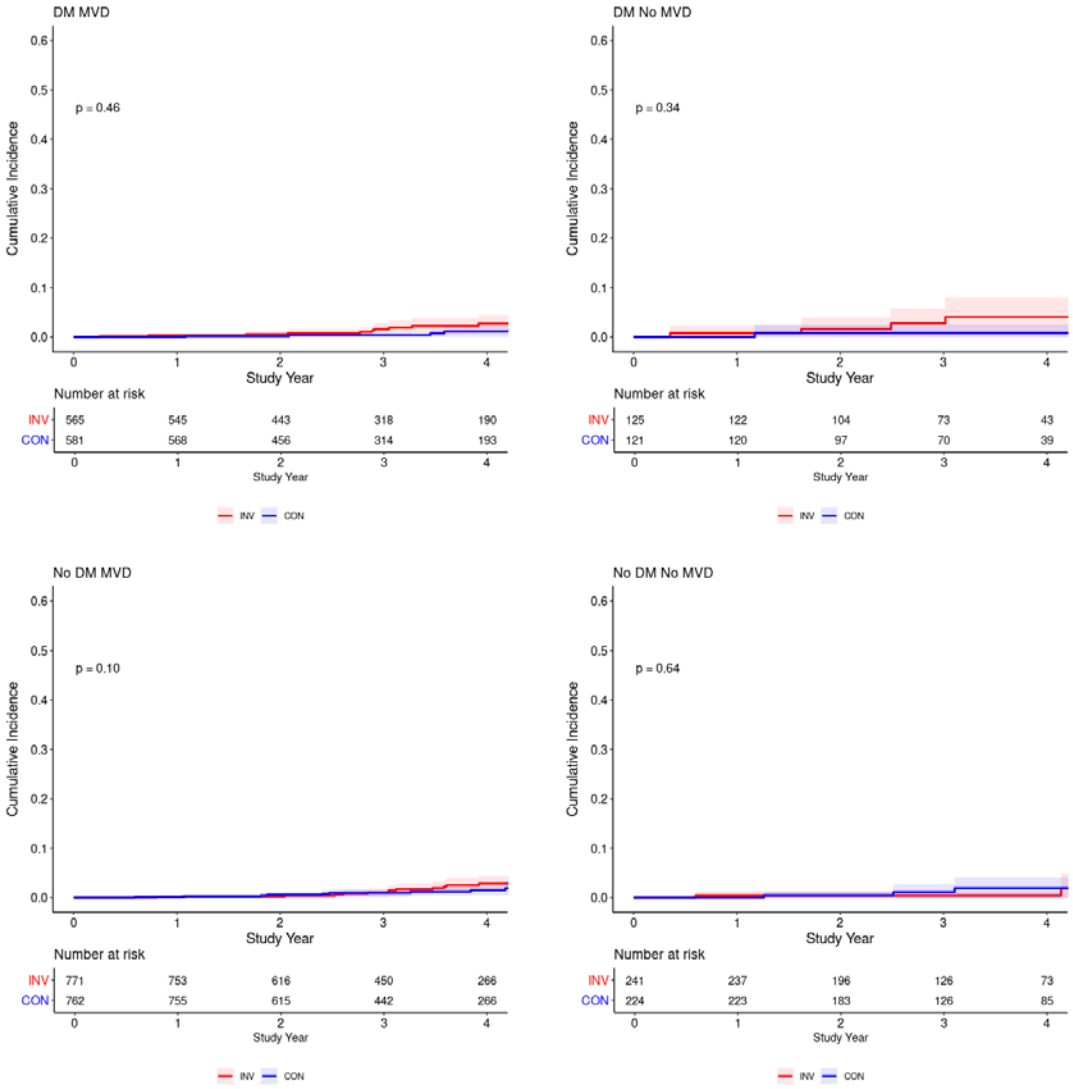


Figure XIIIb. Cumulative incidence of non-CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

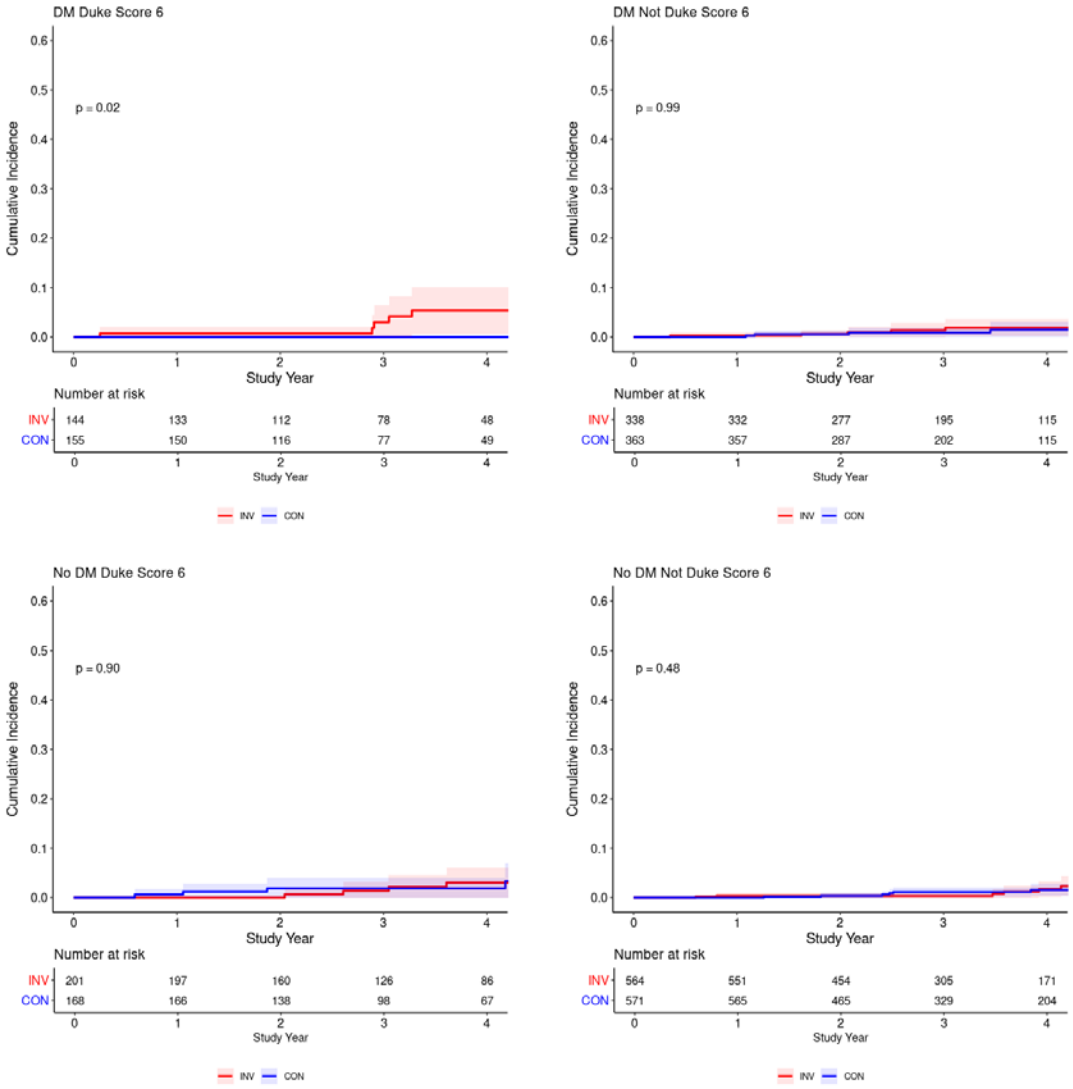


Figure XIIIc. Cumulative incidence of non-CV death (accounting for competing risks) by treatment strategy, stratified by diabetes status and LVSD

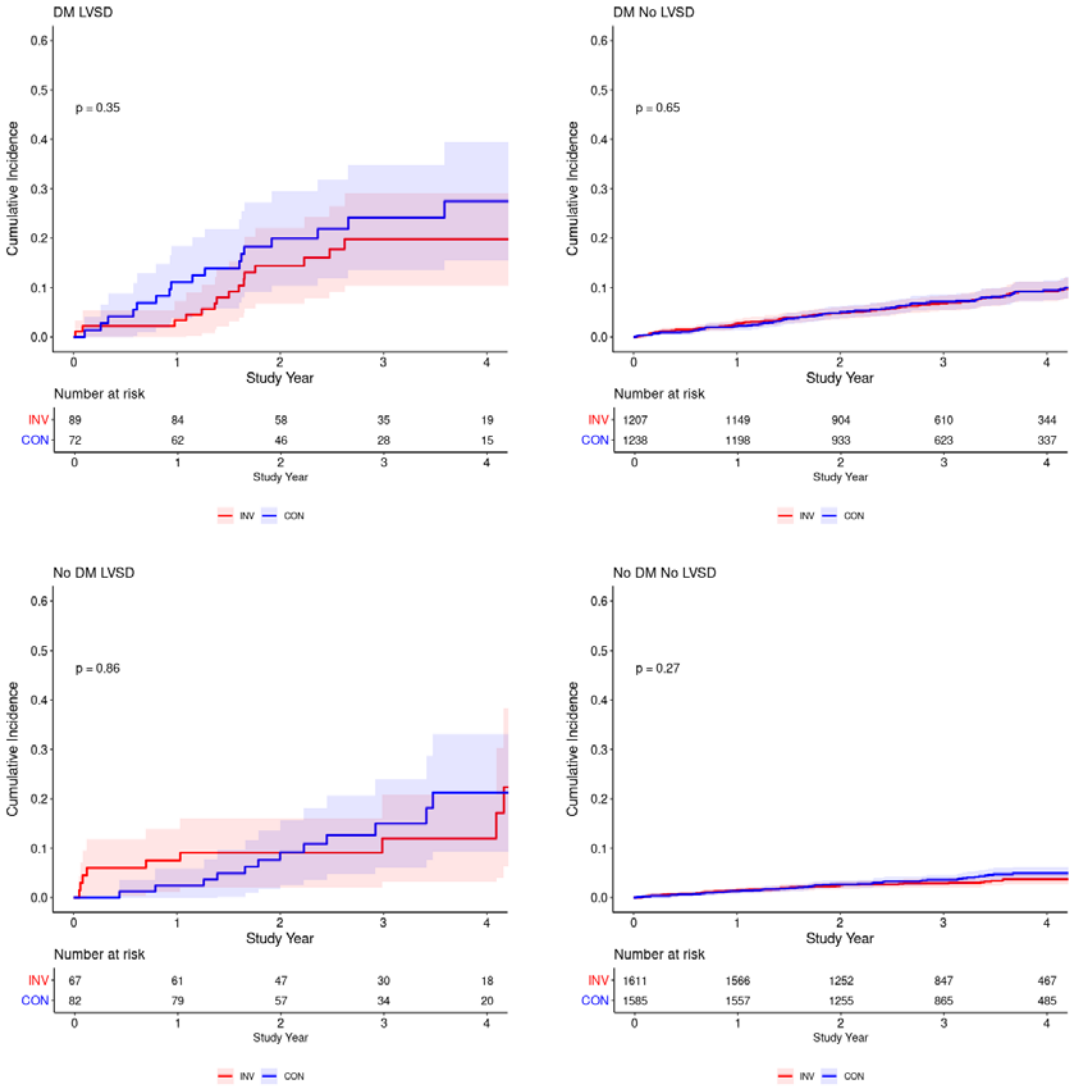


Figure XIVa. Cumulative incidence of MI (accounting for competing risks) by treatment strategy, stratified by diabetes status and multivessel CAD ≥50% stenosis

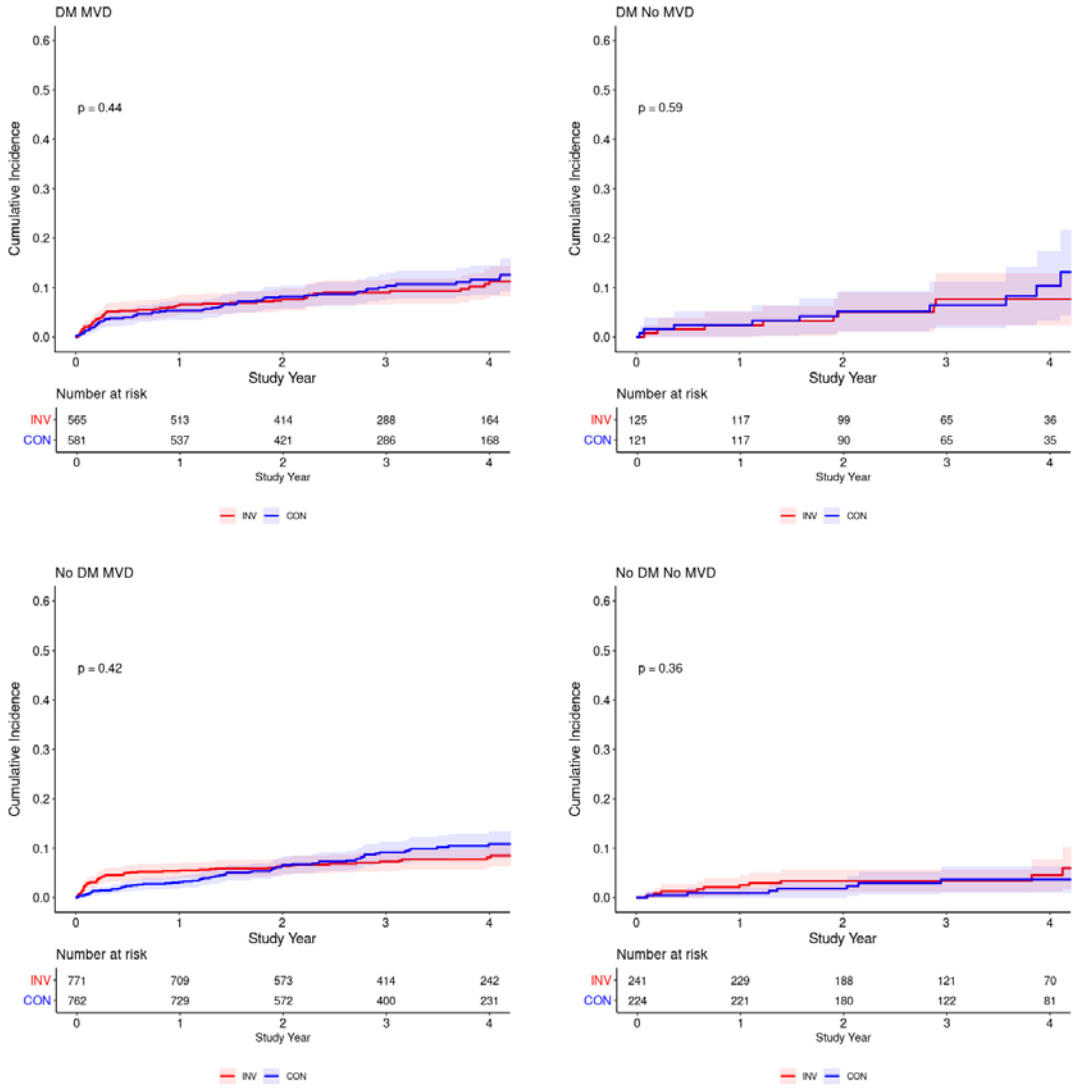


Figure XIVb. Cumulative incidence of MI (accounting for competing risks) by treatment strategy, stratified by diabetes status and Duke score 6 severity of CAD

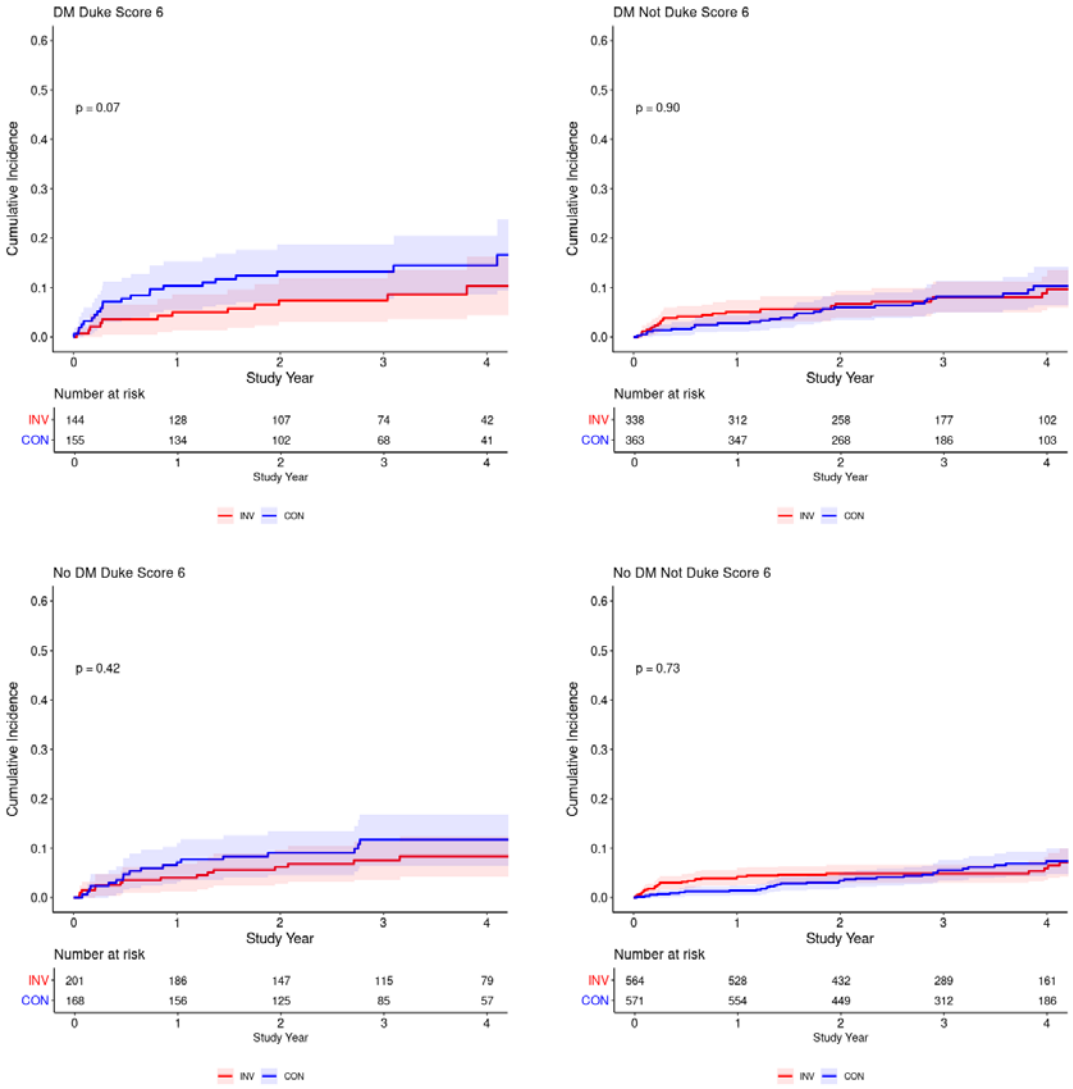


Figure XIVc. Cumulative incidence of MI (accounting for competing risks) by treatment strategy, stratified by diabetes status and LVSD