Title: **Microvascular complications in diabetes patients with heart failure and reduced ejection fraction – insights from the Beta-blocker Evaluation of Survival Trial**

Running title Diabetes with complications in HFrEF

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ABSTRACT

Aims: The role of microvascular complications in the risk conferred by diabetes in heart failure with reduced ejection fraction (HFrEF) is unknown.

Methods and results: We studied 2707 HFrEF patients in the Beta-blocker Evaluation of Survival Trial (BEST), stratified into 3 groups: no diabetes and diabetes without or with microvascular complications (neuropathy, nephropathy or retinopathy). The risks of the composite of cardiovascular death or heart failure hospitalization, and all-cause death, were studied using Cox regression analyses adjusted for other prognostic variables. 964 patients had diabetes, of which 313 (32%) had microvascular complications. Patients with microvascular complications had more severe symptoms (New York Heart Association class IV 12% vs. 9% diabetes with no complications and 7% no diabetes), and worse quality of life (Minnesota living with HF median score 60 vs. 54 and 51 points). In patients with diabetes and complications, the rate of the composite outcome was 45 per 100 person-years of follow-up (compared with 34 and 29 in those with diabetes and no microvascular complications and participants without diabetes, respectively). Compared to patients without diabetes, the adjusted hazard ratio (HR) for the composite outcome was 1.44 (95% CI 1.22-1.70) and 1.18 (1.03-1.35) for patients with diabetes with and without complications, respectively. The risk of all-cause mortality was similarly elevated: adjusted HR 1.42 (95% CI 1.16-1.74) and 1.20 (1.01-1.42), respectively.

Conclusion: In HFrEF, diabetes with microvascular complications is associated with worse symptoms and outcomes, than diabetes without microvascular complications. Prevention of microvascular complications has the potential to improve HFrEF outcomes.

Keywords: heart failure, diabetes, microvascular complications

Clinical Trial Registration: URL http://www.clinicaltrials.gov. Unique identifier NCT00000560

INTRODUCTION

It is well known that many patients with heart failure have a concomitant diagnosis of type 2 diabetes and many additional patients have pre-diabetic dysglycemia.[1-3] Heart failure patients with diabetes or pre-diabetic dysglycemia have worse clinical outcomes that those observed in patients with normal glycated hemoglobin.[1-3] How diabetes and dysglycemia confer an excess risk in heart failure is uncertain. In individuals with diabetes, but without heart failure, microvascular disease, manifest as retinopathy, neuropathy and nephropathy, is strongly associated with adverse clinical outcomes. Furthermore, in these individuals, more microvascular complications are associated with greater risk.[4-6] By contrast, the role of microvascular complications in the detrimental consequences of diabetes in heart failure with reduced ejection fraction (HFrEF) is unknown. We have investigated this question further in the Beta-blocker Evaluation of Survival Trial (BEST).

METHODS

BEST was a double-blind, placebo-controlled, randomized trial funded by the National Heart, Lung, and Blood Institute and the Department of Veterans Affairs. The design and results are published.[7-9] The trial was approved by the ethics committee at each study center, and all patients provided written informed consent. We used the de-identified public-use copy of BEST which included all but one participant, in the present analysis available at https://biolincc.nhlbi.nih.gov/studies/best/ upon application.

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Study Patients: Briefly, 2708 patients assessed to be in New York Heart Association (NYHA) functional class III, or IV and with a left ventricular ejection fraction (LVEF) ≤35%, were enrolled in the United States and Canada between 1995 and 1998, and randomly assigned to receive

bucindolol or placebo. They were required to be on optimal medical therapy including the use of angiotensin-converting enzyme inhibitor therapy and before the publication of the Digitalis Investigation Group trial, digoxin was also required but afterwards it became discretionary.[10] Key exclusion criteria included reversible causes of HFrEF, uncorrected primary valve disease, obstructive or hypertrophic cardiomyopathy, amyloidosis, myocarditis or a history of myocardial infarction within the previous six months.

Diabetes and complications of diabetes: In BEST, information about diabetes and the complications of diabetes was collected by means of questions on the trial case report form. Regarding diagnosis, the question was "Does the patient have a documented history of diabetes at baseline (prior to randomization)?" Investigators were asked about microvascular complications as follows: "Does the patient have documented diabetic end organ disease at baseline (prior to randomization)?" If answered yes, there were additional questions (yes/no answers) about retinopathy, nephropathy and neuropathy. In the present analyses, we further defined "macrovascular" complications of diabetes as either evidence of coronary artery disease (prior myocardial infarction; prior coronary artery bypass grafting, prior coronary angioplasty; greater than 70% stenosis with corresponding wall motion abnormality, by coronary angiography; symptoms of angina; a positive stress perfusion study or a positive exercise test with interpretable baseline ECG) or peripheral artery disease. History of stroke/cerebrovascular disease was not collected in BEST.

We divided patients with diabetes according to the presence of microvascular complications and for sensitivity analyses further into 4 groups according to the presence or absence of macrovascular complications. Additionally. we compared the impact of each microvascular complication separately as well as the risk associated with having more than one microvascular complication, and we repeated analyses without African-American patients.

Outcomes: The primary outcome in BEST was all-cause death but in the present manuscript we also examined the composite of cardiovascular death or heart failure hospitalization and each of its components, which were pre-specified secondary endpoints in the trial.

Statistics: Baseline characteristics are presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. Unadjusted event rates are reported per 100 patient years of follow-up according to diabetes status and the presence of microvascular complications. Cox proportional hazard models were applied to calculate hazard ratios (HR) and cumulative event curves according to diabetes status. The adjusted Cox regression models included information on age, sex, treatment, race (Caucasian vs. all other), systolic blood pressure, NYHA class, LVEF, heart rate, body mass index, estimated glomerular filtration rate (eGFR), heart failure duration, ischemic etiology, history of hypertension, atrial fibrillation and presence of a pacemaker or implanted cardioverter defibrillator. Log (-log(survival)) curves were used to evaluate the proportional hazard assumption. The assumption of linearity of continuous variables (age) were tested by including a variable of age squared. All p values are two-sided, and a p value of <0.05 was considered significant. Analyses were performed using Stata version 14 (StataCorp. College Station, Texas, USA), and SAS version 9.4 (SAS Institute, North Carolina, USA).

RESULTS

The present analysis included 2707 patients, of which 963 (36%) had diabetes. Of those with diabetes, 651 (24% of all participants; 68% of those with diabetes) did not have microvascular complications reported whereas 312 (12%; 32%) did. Median follow-up was 2.1 years among patients without diabetes, 2.0 years among patients with diabetes but no microvascular

complications and 1.6 years among patients with diabetes and microvascular complications. Among the 312 patients with microvascular complications, 107 (34%) were reported to have nephropathy, 135 (43%) retinopathy, and 216 (69%) neuropathy. In terms of number of microvascular complications 197 (63%) had one, 85 (27%) had two and 29 (9%) had all three microvascular complications.

Baseline characteristics: As shown in Table 1, individuals without diabetes were, on average, younger (mean age 59.6 years) than both those with diabetes and no complications (61.2 years) and diabetes with microvascular complications (61.8 years). Patients without diabetes had shortest median duration of heart failure (36, 36 and 53 months, respectively) or to be in NYHA class IV (7%, 9% and 12%, respectively); patients without diabetes had the best, and those with diabetes and microvascular complications the worst, disease-related quality of life, evaluated using the Minnesota Living with Heart Failure score (51, 54 and 60 points, respectively). Compared to those without diabetes, kidney function was most markedly reduced (eGFR 70, 70 and 54 ml/min/1.73m^2, respectively) and plasma norepinephrine was lowest (537, 481 and 467 pg/ml, respectively) in patients with microvascular complications. Patients without diabetes were least likely, and those with microvascular complications most likely, to have an ischemic etiology (54%, 65% and 72%, respectively) and history of hypertension (53%, 68% and 73%, respectively). Among patients with diabetes, those with microvascular complications were more likely to be treated with insulin (68% versus 28% in patients with diabetes but without microvascular complications).

Clinical outcomes according to microvascular complication status: The rates of the composite outcome of cardiovascular death or heart failure hospitalization, each of its components and death from any cause were lowest in patients without diabetes, intermediate in individuals with diabetes but without microvascular complications and highest in those with diabetes and microvascular complications (Table 2 and Figure 1).

In adjusted analyses, compared to participants without diabetes, the risk of the composite outcome was significantly higher in those with diabetes and without microvascular complications (HR 1.18 [1.03-1.35]), as well as in individuals with diabetes and complications (HR 1.44 [1.22-1.70]). Quantitatively similar trends were apparent for the components of this composite outcome and for death from any cause, although the higher risks were only statistically significant in patients with diabetes and microvascular complications and not in diabetes patients without microvascular complications (Table 2 and Figure 1). Compared to those without diabetes, the adjusted risk of these adverse clinical outcomes was around 15-20% higher in patients with diabetes and no microvascular complications and approximately 35-50% higher in patients with diabetes and microvascular complications. A direct comparison of outcomes in diabetes patients with and without microvascular complications is listed in the Appendix (Supplementary Table 1). Analyses excluding African-American patients (n=627), yielded results similar to those of the primary analyses (Supplementary Table 2, Appendix).

Clinical outcomes according to individual type of microvascular complication and multiple microvascular complications: The rates of the composite outcome, its components and all-cause mortality for patients with one or more than one microvascular complication, as well as individual types of microvascular complication, are shown in Supplementary Table 3. The rates of all outcomes were higher in patients with more than one microvascular complication compared to those with a single microvascular complication. Compared to patients with no diabetes, the adjusted risk of each outcome was approximately 30% higher in those with one complication and approximately 60-70% higher in individuals with more than one microvascular complication. The elevation in risk for fatal outcomes was similar for each individual type of microvascular

complication, whereas the risk of heart failure hospitalization was numerically higher for nephropathy than for retinopathy or neuropathy (Supplementary Table 3).

Clinical outcomes according to microvascular and macrovascular complication status: When diabetes patients were further stratified according to the absence or presence of both microvascular and macrovascular complications, those with neither type of complication were at lowest risk and those with both types of complications at highest risk, although the number of patients with microvascular complications but without macrovascular disease was small (Supplementary Table 4 and 5; Supplementary Figure 1a and 1b). In adjusted analyses, the greater risk was conferred by microvascular complications, compared with macrovascular disease. Compared to patients without diabetes, diabetes patients without micro- or macrovascular complications had similar risk of the primary endpoint (p=0.212) whereas diabetes patients with micro and/or macrovascular complications had a higher risk (all p-values <0.05)

DISCUSSION

The frequency and significance of microvascular complications in patients with HFrEF and diabetes is unknown. We found that of the 964 participants in BEST with diabetes, 313 patients (32%) had microvascular complications. The commonest microvascular complication among these individuals was neuropathy (69% of those with complications), followed by retinopathy (43%) and nephropathy (34%) and 37% had more than one microvascular complication. In analyses adjusted for other predictors of adverse outcomes, patients with diabetes but *without* microvascular complications were approximately 20% more likely than patients without diabetes to experience a major fatal or non-fatal cardiovascular event. Those *with* microvascular complications were around 40% more likely than patients without diabetes to experience one of these events. Each type of

microvascular complication was associated with a higher risk of adverse outcomes and the risk was greatest in patients with multiple microvascular complications.

The prevalence of microvascular complications in patients with type 2 diabetes is related to adequacy of glycemic control and duration of diabetes.[5,11] The reported prevalence also depends on the patient evaluation employed, with a higher frequency of these microvascular complications identified in studies using high-fidelity investigations such as retinal angiography and sophisticated testing of peripheral and autonomic nervous function.[5]

Prevalence of diabetes with microvascular complications in HFrEF vs. other CV disease: We have been unable to find any other report of the rate of microvascular complications in patients with HFrEF and diabetes. Although there was no major difference in age between the three subgroups of patients examined, patients with diabetes and complications were much more likely to be treated with insulin than those without complications, implying a longer duration of diabetes in the former group. This group (patients with diabetes and complications) also had longer duration heart failure than either patients with diabetes and no complications or those without diabetes. This in turn suggests that diabetes leads to onset of heart failure at an earlier age in patients with diabetes who develop microvascular complications. However, the frequency of these complications in the present study is consistent with other studies using similar reporting methods in patients with cardiovascular disease in approximately the same age range. For example, in the Canagliflozin Cardiovascular Assessment Study (CANVAS), 31% participants had neuropathy, 21% retinopathy and 18% nephropathy (22%, 14% and 11%, respectively, in the present study).[12] In the PROspective pioglitAzone Clinical Trial In macroVascular Events trial (PROACTIVE), 42% of patients with type 2 diabetes and macrovascular disease were reported to have microvascular complications (no breakdown of type of microvascular complication was described).[13]

Microvascular complications in diabetes and HFpEF: Of more interest is a recent study in patients with heart failure and preserved ejection fraction (HFpEF). In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT), 32% of patients were reported to have a microvascular complication (neuropathy in 21%, retinopathy in 15% and nephropathy in 11% of participants with diabetes).[14] Patients in TOPCAT were on average approximately 7 years older than participants in the present study and a similar proportion in the two trials were treated with insulin (38% in TOPCAT versus 41% in BEST). The similar rate of these complications in TOPCAT is perhaps surprising given the older age of the TOPCAT patients and the emerging view that microvascular disease may be a feature of HFpEF itself and play an important role in the pathophysiology of this syndrome.[15]

Risk according to type of microvascular complication: In patients with type 2 diabetes in general, higher HbA1c values is associated with greater risk of microvascular complications which in turn are associated with future cardiovascular risk.[4,16,17] We found the same to be true in HFrEF although the absolute rate of cardiovascular death or heart failure hospitalization in patients with at least one microvascular complication was extraordinarily high at 45 per 100 person-years of follow-up (compared with 34 and 29 in those with diabetes and no microvascular complications and participants without diabetes, respectively). The rate increased to 60 per 100-person years of follow-up in those with more than one complication i.e. more than one in two of these patients suffered a major adverse heart failure-related event annually. While each individual type of complication was associated with a higher risk (compared with no complication), there was a suggestion that neuropathy and retinopathy conferred a greater risk of death whereas nephropathy was more closely associated with risk of heart failure hospitalization. If true, the relationship between nephropathy and heart failure hospitalization is plausible in that renal dysfunction is likely to lead to or accentuate the sodium and water retention that characterises worsening of heart failure.

Similarly, neuropathy, including autonomic neuropathy, can be plausibly linked to cardiovascular death.[5] Indeed, reduced iodine-123 meta-iodobenzylguanidine uptake, indicative of cardiac sympathetic dysregulation, has been demonstrated in patients with diabetes and in patients with HFrEF and diabetes is independently predictive of progression of heart failure.[18] Interestingly, in the present study, we found that diabetes patients with microvascular complications had lower plasma norepinephrine levels than diabetes patients without microvascular complications and patients without diabetes. Why diabetic retinopathy seems to be more closely associated with the risk of death compared with hospital admission is less obvious. This complication is thought to indicate the presence of widespread end-organ microcirculatory damage and investigator-reported retinopathy likely reflects the most advanced stage of this problem.[11] Consequently, retinopathy may simply be a marker of more severe microvascular disease. Alternatively, the development of retinopathy may reflect additional pathophysiologic processes which are also generally more harmful in heart failure. Mechanisms of this type that have been implicated in the development of retinopathy include inflammation, oxidative stress and persistent activation of the renin-angiotensin system.[11] In addition, microvascular disease may particularly affect the myocardium in patients with diabetes which is clearly of greatest danger in patients with already dysfunctional myocardium.[19] Due to the suggestion of less benefit of drug therapy and higher rates of diabetic complications in African-Americans, we repeated analyses without these patients with similar results.[20,21] Another potential risk factor for developing HF in diabetes patients microvascular complications is their presumed more severe diabetes and for this reason intensified glucose-lowering therapy, where some drug classes including pioglitazones have been linked to an increased risk of HF.[22]

Clinical Implications: What are the clinical implications of these findings? Firstly, the diagnosis of microvascular complications identifies patients at extremely high risk of adverse outcomes and physicians should check that disease modifying therapy for heart failure has been maximized and

diabetes treatment likewise optimized. Second, and perhaps more importantly, prevention of microvascular complications seems to be highly desirable, given the prognostic implications of their development, although this association between microvascular complications and worse outcomes could be an epiphenomenon rather than a modifiable risk factor. Clearly, prevention of microvascular complications is a recognized goal of diabetes therapy, although perhaps not always considered a priority by cardiologists.[23,24] Our findings suggest that cardiologists should also have prevention of these complications as a treatment goal, although it has to be acknowledged that the cardiovascular safety of all diabetes drugs in patients with HFrEF has never been established.

Limitations: As with any report of this type, our study has a number of limitations. Glycated hemoglobin levels were not measured. Similarly, duration of diabetes was not documented. Microvascular complications were reported by investigators and not specifically sought using disease-specific questionnaires or specialist testing; both of the latter may have yielded a higher frequency of these complications. For patients without diabetes no information on microvascular complications were available. Finally, it is possible that more contemporary HF treatment with a more effective beta-blocker, MRA and angiotensin-receptor neprilysin inhibitor, as well as use of cardiac devices could improve prognosis in patients with HF and diabetes with microvascular complications.

In summary, we found that about a third of HFrEF patients with diabetes in the BEST trial had microvascular complications and 37% of these had multiple complications. The commonest complication was neuropathy. Patients with diabetes and microvascular complications were around 40% more likely than a patient without diabetes to experience a major adverse cardiovascular event

(which was about twice the incremental risk associated with diabetes and no complications). Each type of microvascular complication was associated with a higher risk of adverse outcomes and the risk was greatest in patients with multiple complications. The resultant absolute rate of adverse cardiovascular outcomes in HFrEF patients with diabetes and multiple microvascular complications was extraordinarily high (rate of cardiovascular death or heart failure hospitalization 60 per 100 person-years of follow-up). Cardiologists need to work in tandem with endocrinologists and primary care practitioners to prevent microvascular complications in their HFrEF patients with diabetes. The presence of microvascular complications should be checked for regularly in order to identify patients at particularly high risk and maximize surveillance and therapy as appropriate.

Conflicts of interest: Drs Kristensen, Lee, Shen and Rørth report no conflict of interests. . Dr Jhund reports consulting and speakers fees from Novartis and research funding from Boehringer Ingelheim. Dr. Køber has received fees for his consulting or trial committee work with Novartis and AstraZeneca. Dr. McMurray´s employer, University of Glasgow has received fees for his consulting or trial committee work with Abbvie, Amgen, AstraZeneca/Medimmune, Bayer, Bristol Myers Squibb, DalCor, GlaxoSmithKline, Merck, Novartis, Resverlogix, Sanofi-Aventis and Stealth Therapeutics.

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Table 1: Baseline characteristics according to diabetes status with or without microvascular complications

		Diabetes		
		Microvascular complications		
	No diabetes	No	Yes	
Patients, no (%)	**1743 (64%)**	**651 (24%)**	**313 (12%)**	**p-value**
Characteristics				
Age, mean	59.6±13.3	61.2±10.7	61.8±9.9	0.0012
Male, n (%)	1364 (78%)	508 (78%)	242 (77%)	0.933
Caucasian, n (%)	1253 (72%)	508 (78%)	242 (77%)	0.0611
HF duration, months	36 (11, 70)	36 (13, 69)	53 (20, 84)	<0.001
NYHA class, n (%)				0.0094
III	1616 (93%)	590 (91%)	275 (88%)	
IV	127 (7%)	61 (9%)	38 (12%)	
LVEF	22.7±7.4	23.3±7.0	23.7±7.2	<0.0001
RVEF	35.1±31.5	34.2±13.9	34.8±12.8	0.4621
Left bundle branch block	448 (26%)	150 (23%)	81 (26%)	0.3857
Right bundle branch block	119 (7%)	39 (6%)	20 (6%)	0.7559
QRS-duration, ms	130±36	124±34	127±31	0.0055
LV hypertrophy	405 (23%)	145 (22%)	66 (21%)	0.6666
Heart rate, bpm	81±13	84±13	83±12	<0.0001
SBP, mmHg	116±17	120±19	120±18	<0.0001
MLHF score	51 (32, 69)	54 (32, 74)	60 (41, 78)	<0.0001
BMI, Kg/m^2	27.3±5.7	29.4±6.2	29.1±5.6	<0.0001
eGFR, $ml/min/1.73m^2$	70 (55, 85)	70 (54, 87)	54 (41, 71)	<0.0001
Plasma norepinephrine, pg/mL	537±351	481±344	467±293	0.0004
Plasma glucose, mmol/L	5.70±1.78	10.22±4.99	11.57±5.57	<0.0001
Medical history, n (%)				
Ischemic etiology	942 (54%)	421 (65%)	224 (72%)	<0.0001
Hypertension	923 (53%)	444 (68%)	228 (73%)	<0.0001
Peripheral artery disease	204 (12%)	112 (17%)	125 (40%)	<0.001
Atrial fibrillation	436 (25%)	143 (22%)	74 (24%)	0.2937
Thromboembolic disease	311 (18%)	118 (18%)	59 (19%)	0.9104
ICD, n (%)	72 (4%)	13 (2%)	5 (2%)	0.0067
Pacemaker, n (%)	154 (9%)	51 (8%)	26 (8%)	0.729
Medication, n (%)				
Loop diuretic	1606 (92%)	622 (96%)	305 (97%)	<0.0001
Digoxin	1613 (93%)	595 (91%)	291 (93%)	0.5804
ACE-I/ARB	1690 (97%)	627 (96%)	300 (96%)	0.5038
MRA	45 (3%)	31 (5%)	16 (5%)	0.0067
Oral antidiabetic agent	0 (0%)	386 (59%)	126 (40%)	<0.0001
Insulin	0 (0%)	185 (28%)	213 (68%)	<0.0001
Diet only	0 (0%)	110 (17%)	7 (2%)	<0.0001
Diabetic retinopathy	0 (0%)	0 (0%)	135 (43%)	<0.0001

Diabetic neuropathy	0 (0%)	0 (0%)	216 (69%)	<0.0001
Diabetic nephropathy	0 (0%)	0 (0%)	107 (34%)	<0.0001

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; HF = heart failure, ARB = angiotensin receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; HF = Heart Failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MLHF = Minnesota Living with Heart Failure questionnaire; MRA = mineralocorticoid-receptor antagonist; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction SBP = systolic blood pressure

Table 2: Risk of various endpoints according to diabetes status with or without microvascular complications at baseline

	No. events	Crude rate per 100py	Unadjusted HR (95% CI)	P	Adjusted* HR (95% CI)	P
Primary comp. (CV death or HFH)						
No diabetes	817	28.7	1.00 (ref.)		1.00 (ref.)	
Diabetes + no complications	340	33.5	1.15 (1.02-1.31)	0.028	1.18 (1.03-1.35)	0.016
Diabetes + complications	197	50.0	1.64 (1.40-1.92)	<0.001	1.44 (1.22-1.70)	<0.001
CV death						
No diabetes	429	12.0	1.00 (ref.)		1.00 (ref.)	
Diabetes + no complications	182	14.0	1.17 (0.98-1.39)	0.080	1.20 (1.00-1.44)	0.054
Diabetes + complications	119	21.2	1.78 (1.45-2.18)	<0.001	1.49 (1.20-1.85)	<0.001
HF hospitalization						
No diabetes	639	22.4	1.00 (ref.)		1.00 (ref.)	
Diabetes + no complications	260	25.6	1.12 (0.97-1.30)	0.112	1.15 (0.99-1.34)	0.077
Diabetes + complications	145	36.8	1.52 (1.27-1.83)	<0.001	1.35 (1.11-1.63)	0.002
All-cause mortality						
No diabetes	512	14.3	1.00 (ref.)		1.00 (ref.)	
Diabetes + no complications	214	16.4	1.15 (0.98-1.35)	0.080	1.20 (1.01-1.42)	0.035
Diabetes + complications	133	23.7	1.68 (1.38-2.03)	<0.001	1.42 (1.16-1.74)	<0.001

*adjusted for age, sex, race, systolic blood pressure, heart rate, BMI, NYHA, LVEF, eGFR, study treatment, ischemic etiology, hx hypertension, hx AF, ICD, pacemaker.

CI = confidence interval; CV = cardiovascular; HFH = heart failure hospitalization; HR = hazard ratio; PY = person years; other abbreviations as footnote to Table 1.

Figure 1a: Cumulative incidence of cardiovascular death or heart failure hospitalization

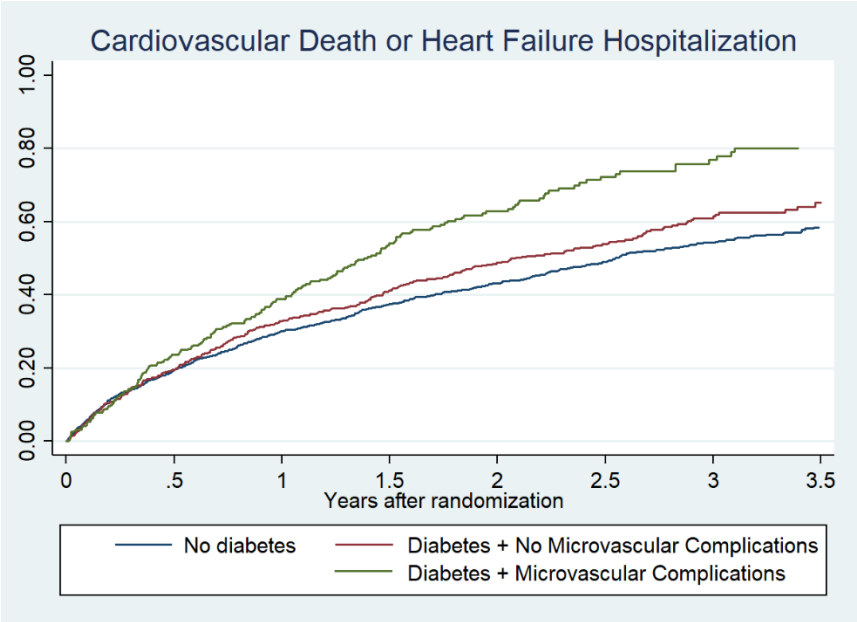

Figure 1b: Cumulative incidence of all cause death