Cause of Death and the Impact of Implantable Cardioverter Defibrillators Among Patients with Diabetes Mellitus and Heart Failure

by

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ABSTRACT:

Introduction: Diabetes and heart failure (HF) place a large burden on healthcare systems and are associated with increased risk for death, including sudden cardiac death (SCD). However, causes of death have not been fully explored and evidence for primary prevention implantable-cardioverter-defibrillators (ICD) -which reduces the risk of SCD- among patients with co-morbid diabetes and HF have not been well described.

Objective: The objectives of this thesis was to i) describe the causes of death among patients with diabetes and established atherosclerotic cardiovascular disease (ASCVD); ii) describe the causes of death among patients with diabetes and HF with reduced ejection fraction (HFrEF) and iii) describe whether primary prevention ICD placement is associated with a reduction in the risk of all-cause death and sudden death among patients with diabetes and HFrEF.

Research Design and Methods: Data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study were used to describe adjudicated cause of death among patients with type 2 diabetes and ASCVD. The combined Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial and Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) studies were used to describe adjudicated cause of death among patients with diabetes and HFrEF. To evaluate the association with ICD implantation and outcomes the following data was used: i) patient-level combined-analysis from four primary prevention HFrEF ICD trials (MADIT I, MADIT II, DEFINITE, and SCD-HeFT) and ii) real-world data from the Get With The Guidelines - HF registry (GWTG-HF; 2005-2014). The primary outcome was all-cause death and the secondary outcome was SCD.

Results: In TECOS (n=14,671), there were 1084 deaths adjudicated as following: 530 CV (49% of deaths, 1.2 per 100 patient-years [PY]), 338 non-CV (31% of deaths, 0.77 per 100-PY), and

216 unknown (20% of deaths, 0.49 per 100-PY). The most common CV death was sudden death (n=145, 27% of CV death) followed by acute myocardial infarction (MI)/stroke (n=113 [MI n=48; stroke=65], 21% of CV death) and HF death (n=63, 12% of CV death). The most common non-CV death was malignancy (n=154, 46% of non-CV death). Among patients with diabetes and HFrEF in the HF-ACTION/ASIAN-HF cohort (n=2,445 [39.5%, out of 6,182]), there were 527 deaths: 322 (61%; 7.38 per 100-PY) were cardiovascular (CV), 80 (15.1%; 1.83 per 100-PY) were non-CV, and 125 (23.7%; 2.87 per 100-PY) were unknown. Among CV causes of death, sudden death was the most common adjudicated cause of death (n=115, 35.7%), followed by HF death (104, 32.3%), 'Other' CV death (65, 20.2%), and MI/stroke death (38, 11.8%). In the four primary prevention ICD trials, of the 3,359 patients, 996 had diabetes (29.6%). In total, 280 patients with diabetes died. While ICDs were not associated with a reduced risk of all-cause death (hazard ratio [HR] 0.88, 95% CI 0.7-1.12), they were associated with a reduced risk of SCD (adjusted subdistribution HR 0.51 95% CI 0.33-0.81; p=0.004). In the GWTG-HF registry, 663 patients with diabetes received an ICD during the HF hospitalization or were prescribed an ICD at discharge. After propensity matching, ICD use, compared to those without an ICD, was associated with a reduced risk of all-cause death (adjusted HR 0.74, 95% CI 0.65- 0.83; p< 0.0001).

Conclusion: Among patients with diabetes and ASCVD or HFrEF, SCD was the most common subcategory of CV death. The ICD trials demonstrated that in patients with diabetes and HFrEF, ICD implantation was associated with a reduced risk of SCD and observational data suggested an association with a reduced risk of all-cause death. Given the burden of SCD, these findings reinforce the guideline recommendations for ICD implantation in patients with diabetes.

PREFACE

This thesis represents original work by Abhinav Sharma. There are numerous collaborators who have contributed to each chapter as listed below. Components of chapters 1,2,3 and 5 have been published in peer reviewed journals and chapter 6 is currently under peer-review at journal.

Data for this thesis was made available through collaboration with the Duke Clinical Research Institute. The research project, of which this thesis is a part, received research ethics approval from the Duke University Health System Institutional Review Board Protocol # Pro00074594 applied on 3/2/2016 for Chapters 2 and 6. Institutional Review Board waivers were granted for the remaining chapters as data was collected as a part of a randomized controlled trial or registry and patients had already consented to data use for secondary analysis.

The following are the publications associated with the following chapters:

Chapter 1:

Sharma A, Cooper LB, Fiuzat M, Mentz RJ, Ferreira JP, Butler J, Fitchett D, Moses AC, O'Connor C, Zannad F. Anti-hyperglycemic Therapies to Treat Patients With Heart Failure and Diabetes Mellitus. *J Am Coll Cardiol-HF*. 2018 Oct;6(10):813-822.

Chapter 2:

Sharma A, Zhao X, Hammill BG, Hernandez AF, Fonarow GC, Felker GM, Yancy CW, Heidenreich PA, Ezekowitz JA, DeVore AD. Trends in Non-Cardiovascular Comorbidities

among Patients Hospitalized for Heart Failure: Insights from the Get With The Guidelines-Heart Failure Registry. *Circulation Heart Failure.* 2018:11(6):e004646

Chapter 3:

Sharma A, Green A, Dunning A, Lokhnygina Y, Al-Khatib SM, Lopes RD, Buse JB, Lachin JM, Van de Werf F, Armstrong PW, Kaufman KD, Standl E, Chan JCN, Distiller LA, Scott R, Peterson ED, Holman RR. Causes of Death in a Contemporary Cohort of Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease: Insights from the TECOS Trial. *Diabetes Care*. 2017. 40(12):1763-1770.

Chapter 5:

Sharma A, Al-Khatib SM, Ezekowitz JA, Cooper LB, Fordyce CB, Felker GM, Bardy GH, Poole JE, Bigger JT, Buxton AE, Moss AJ, Friedman DJ, Lee KL, Steinman R, Dorian P, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Peterson ED, Inoue LYT, Sanders GD. Implantable Cardioverter-Defibrillators in Patients with Reduced Ejection Fraction and Diabetes. *European Journal of Heart Failure*. 2018; 20(6):1031-1038

For these projects I was responsible for constructing the analysis proposals, data statistical analysis plan, critical revision of the data analysis plan, critical revision of the statistical output, primary manuscript draft creation, and submission for publication.

DEDICATION

I wish to dedicate this thesis to my parents, Omprakash and Rekha Sharma.

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INTRODUCTION

Heart failure (HF) and diabetes mellitus are significant health problems in Canada. Approximately 45,600 patients in 2013 were admitted with HF as the primary diagnosis resulting in a health care cost of $482 million.[1] By 2030, it is estimated that approximately 54,000 patients will be hospitalized for HF and will cost the healthcare system $722 million. When including HF admissions as a secondary diagnosis, healthcare costs are estimated to be $2.8 billion in 2030.[1] Regarding the burden of diabetes, the predicted 10-year risk of developing diabetes in the Canadian population (from 2011) was 10%, which corresponded to 2.16 million new cases.[2] The total health care costs that would be attributed to diabetes during this period were $15.36 billion.[2] In the United States, HF affects more than 5 million adults and costs over $30 billion, while diabetes affects over 29 million adults and costs $176 billion.[3] By 2030, more than 8 million people in the United States (1 in every 33) will have HF with total costs exploding to an estimated $70 billion.[3] The problem for diabetes is even worse with 1 in 3 individuals projected to be affected resulting in total costs of $336 billion by 2030.[4] Combined, the public health and economic consequences of diabetes and HF pose a formidable challenge.

Diabetes is a known independent risk factor for HF, conferring a 2.5 times higher risk for developing HF.[5,6] After HF onset, diabetes increases the risk of cardiovascular death by 38%, all-cause mortality by 40% and hospitalization by 33%.[6] Approximately 91.5% of patients with diabetes have type 2 diabetes mellitus; this proportion increases among those with CV disease.[7] Despite the known health risks, more data is required on the burden of diabetes among patients with HF and whether the incidence is increasing over time. There are overlapping mechanisms contributing to the development of HF among patients with diabetes including the higher

prevalence of traditional HF risk factors (hypertension, coronary disease, and kidney disease), increased microvascular disease, altered energy metabolism (shift in free fatty acid utilization and decreased glucose utilization leading to increased toxic intermediaries), and increased prevalence of structural myocardial dysfunction (**Figure 1**).[8] in addition to diabetes, other non-cardiovascular (CV) comorbidities (such as obesity, renal failure, anemia, depression, and chronic obstructive pulmonary disease (COPD)/asthma) may also influence outcomes among patients with HF.[9]

Historically, trials of either HF or diabetes populations have focused on highly selected populations. Studies rarely consider the complexities of therapeutic management in patients diagnosed with both conditions.[10] For diabetes trials, patients with more severe HF are routinely excluded entirely. To treat diabetes, clinicians have a broad menu of glucose-lowering therapies that includes metformin, sulfonylureas, meglitinides, incretin mimetics, dipeptidyl-dipeptidase 4 (DPP4) inhibitors, sodium glucose cotransporter (SGLT-2) inhibitors and alpha-glucosidase inhibitors. Yet, among the trials, the findings pertaining to CV outcomes, including HF, is often conflicting.[11]

Despite this increasing awareness of HF outcomes among patients with diabetes, there is a paucity of data surrounding the specific causes of death among patients with diabetes and CV disease and specifically those with established HF and reduced ejection fraction (HFrEF). Uncovering the specific causes of death among a patient population enables an understanding of potential therapies that may have maximal CV benefit, can aid in counseling patients regarding future risk of events, and can help guide the design of clinical studies. As an example, the causes of death among patients with impaired-glucose tolerance and CV risk factors in the Nateglinide

And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial were examined.[12] The NAVIGATOR trial enrolled 9,306 participants with impaired glucose tolerance and CV disease or at high CV risk, with a median follow-up of 6.4 years. Investigators reported 244 (39.2%) CV deaths, 313 (50.3%) non-CV deaths, and 65 (10.5%) deaths of unknown cause.[13] Myocardial infarction was the leading cause of investigator-reported death (57/622 [9.2%]). Among non-CV deaths, the most commonly identified cause related to malignancy (177/313 [56.5%]). Despite enrichment for CV events, the primary cause of death was not CV, but non-CV. This may have been a contributing factor to why the therapies, which primarily targets CV outcomes, were not effective in this population.[13] Extending this to patients with diabetes, understanding the causes of death among patients with diabetes and CV disease, specifically HF, remains vital to identify opportunities to optimize outcomes.

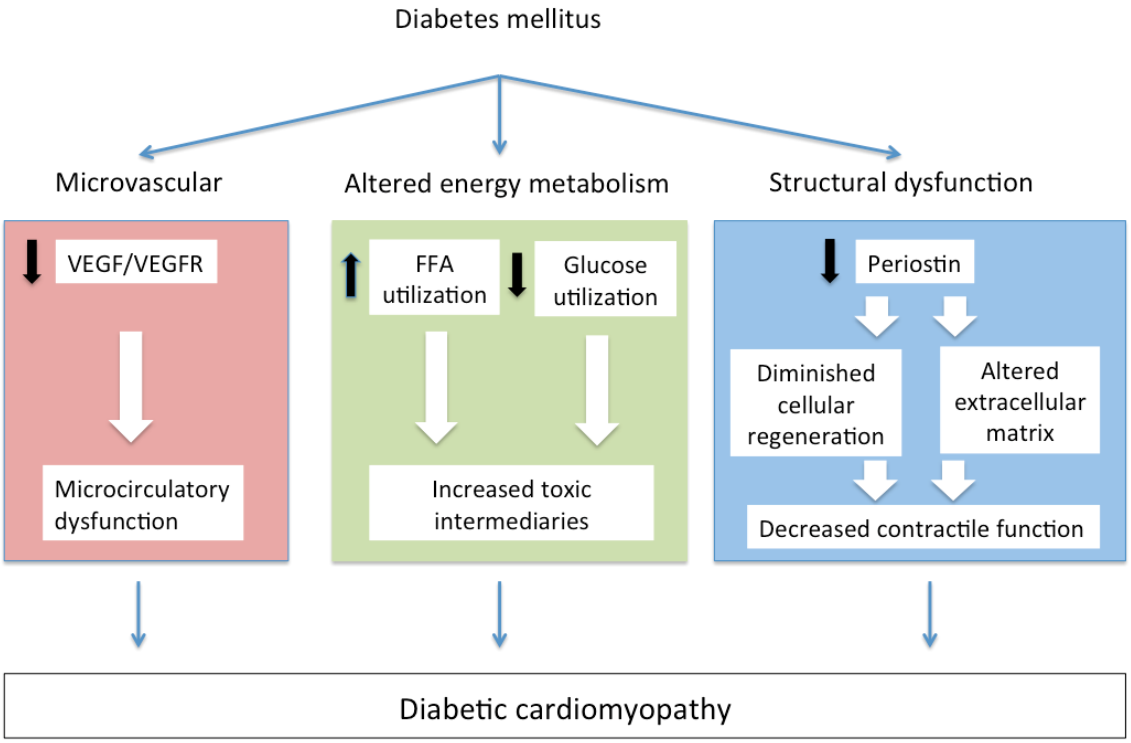
Significant advances in treatment of HF with reduced ejection fraction (HFrEF) including medical therapies (namely angiotensin converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB], mineralocorticoid receptor agonists [MRA], angiotensin receptor neprilysin inhibitors [ARNI], sinoatrial funny current inhibitor) and device therapies (implantable cardioverter defibrillators [ICD], cardiac resynchronization therapy [CRT], and ventricular mechanical assist devices) have revolutionized the treatment of HF.[14] Yet, diabetes is predominantly believed to be an atherothrombotic risk factor in addition to increasing the risk of non-CV events.[4,11] What remains unclear is whether proven HF therapies remain efficacious among patients with HFrEF and diabetes. The presence of diabetes increases the risk of most CV outcomes[4,6,8]; however due to the potential issues of competing risk of morbidity, various therapies that have benefit in a non-diabetic population may not be efficacious among patients

with diabetes and HFrEF. The role of ICDs remains important as this therapy predominantly targets one cause of death: sudden death. Given the costs required to implement these therapies, the significant burden on patients regarding limitation of lifestyle, and the costs on the health care system to continuously monitor and follow these patients over time, the potential impact of ICD on patients with diabetes and HFrEF remains warranted.

The primary aim of this thesis aims to address the following key knowledge gaps: 1) among patient admitted in hospital with HF, what are the major nvon-cardiovascular (CV) comorbidities (including diabetes) and have these comorbidities been increasing over time; 2) what are the specific causes of death among patients with diabetes and established atherosclerotic CV disease; 3) What are the specific causes of death among patients with diabetes and established HF and reduced ejection fraction (HFrEF); and can a therapy such as a primary prevention implantable cardioverter defibrillator (ICD) implantation reduce the risk of all-cause death and specific cause death – namely sudden death - among patients with diabetes and HFrEF. This thesis will be divided into six chapters. The first chapter will focus on a literature review of the efficacy of glucose-lowering therapies and HF therapies in addition to evaluating the literature on cause of death among patients with diabetes and HFrEF. The subsequent chapters will focus on presenting primary data to address the key knowledge gaps.

Figure

Figure 1: Current paradigm in mechanisms leading to the development of heart failure among patients with diabetes



VEGF vascular endothelial growth factor; VEGFR vascular endothelial growth factor receptor;

FFA free fatty acid

CHAPTER 1: Glucose-lowering therapies, heart failure therapies, and cause of death among patients with diabetes and heart failure – a literature review

Recognition of heart failure hospitalization as an important outcome among patients with type 2 diabetes mellitus

In December 2008, the U.S. Food and Drug Administration (FDA) issued guidance to pharmaceutical sponsors setting out updated expectations for on-going development of anti-hyperglycemic drugs.[15] The primary focus of the guidance was to direct sponsors to ensure the cardiovascular (CV) safety of anti-hyperglycemic therapies. Prior to the guidance, approval for anti-hyperglycemic therapies focused on glycemic efficacy, namely the reduction of HbA1c. In addition, safety data was limited to outcomes derived from short-term 6 and 12 months phase 2 and 3 randomized controlled trials. However, two meta-analyses identified CV safety concerns for two classes of anti-hyperglycemic therapies: muraglitazar[16] (the investigational dual peroxisome proliferator-activated receptor (PPAR)-alpha and y agonist and never approved) and the FDA-approved rosiglitazone[17] (a thiazolidinedione; TZD). As a result of these controversial studies, the FDA, and subsequently the European Medicines Agency, mandated long-term CV safety trials as a requirement to obtain approval of new anti-hyperglycemic therapies. The meta-analysis that initially suggested an increased risk of CV outcomes associated with rosiglitazone primarily focused on myocardial infarction [MI] and CV death. The FDA guidance mandated sponsors conduct CV outcome trials to demonstrate that anti-hyperglycemic therapies do not primarily increase the risk of CV MACE events, primarily focusing on composite of CV death, myocardial infarction [MI], or stroke.[15] The guidance indicates that other relevant CV events (hospitalization for acute coronary syndromes or urgent revascularization) could be considered. However, HF as a CV safety events was not suggested in the guidance. Furthermore, while the

guidance mandated that patients at high risk of CV events be enrolled (including patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment), there was no requirement to enroll patients with HF. As a result of the guidance, there has been a significant increase in the number of CV outcome trials for anti-hyperglycemic therapies. HF is a key outcome of interest since the demonstration of an increased risk of HF hospitalization associated with TZDs.[18.] In more recent trials, the possible increased risk of HF hospitalization associated with some dipeptidyl peptidase-4 (DPP-4) inhibitors (saxagliptin and alogliptin but not sitagliptin) has reaffirmed the importance of HF outcomes among anti-hyperglycemic drug trials.[19–22] The emergence of anti-hyperglycemic therapies, namely sodium-glucose co-transporter-2 inhibitors, that may reduce the risk of HF outcomes has resulted in significant interest in how to utilize these therapies as a strategies to reduce the risk of HF hospitalizations.[23,24]

Inclusion of patients with heart failure in anti-hyperglycemic drug trials

Clinical trials of anti-hyperglycemic therapies often excluded patients with HF and 33% of anti-hyperglycemic drug trials did not have a stated definition for HF events.[10] While recent CV safety trials have included more precise HF definition, patients with more severe HF symptoms, typically those with New York Heart Association (NYHA) functional class III-IV, were excluded.[25,26–28] However, more recent anti-hyperglycemic trials typically did not have any specific HF exclusion (except for the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE] trial which excluded patients with NYHA functional class IV).[21] Furthermore, the Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial[29] and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

(LEADER trial)[30] encouraged the inclusion of HF patients by having NYHA II-III and systolic/diastolic dysfunction as enrichment criteria.

Will anti-hyperglycemic therapies increase the likelihood of new onset or recurrent heart failure?

Clinicians have a broad menu of anti-hyperglycemic medications that can be used as first, second or third line therapies. Yet despite the extensive number of drugs available, the optimal therapies for use in patients with diabetes and HF have not been established due to lack of high-quality randomized trial data and conflicting signals of risk and benefit between and within classes antihyperglycemic therapies **(Figure 1).**

Metformin and sulfonylureas

Randomized clinical trials suggest that metformin may reduce macrovascular events and is generally recommended as 1st line treatment among patients with type 2 diabetes.[31,32] There is no prospective randomized trial evaluating whether metformin is the optimal first line agent in patients with diabetes and HF. Cohort and administrative database analyses in patients with diabetes and HF suggest that metformin, alone or in combination, is associated with a lower mortality compared with sulfonylurea therapy.[33]

Sulfonylureas improve glycaemic control by increasing insulin release and unlike other classes of anti-diabetic drugs, they do not cause sodium retention. However, like metformin there are no randomized clinical trials assessing the CV safety of these agents specifically in patients with HF. In patients with newly diagnosed diabetes, the UKPDS trial suggested that the combination of insulin and sulphonylureas versus dietary-based treatment did not increase HF

risk (HR 0.91; 95% CI 0.54–1.52). However, population-based studies have suggested possible increased risk of HF hospitalizations associated with sulfonylureas compared to metformin.[34]

Thiazolidinediones

TZDs work by improving insulin sensitivity, improving blood pressure control, optimizing lipid profiles, and potentially reducing the development of atherosclerosis. While a 2007 meta-analysis suggested that compared to placebo, rosiglitazone increased the odds for myocardial infarction (odds ratio [OR] 1.43; 95% CI 1.03-1.98) and demonstrated a trends towards increased risk of death (OR 1.64; 95% CI 0.98-2.64), subsequent analyses have suggested no increased MI risk associated with rosiglitazone use.[17,35] With regards to HF outcomes, several studies have suggested increased HF risk associated with TZD use. In a small randomized controlled trial of 224 patients with diabetes and HFrEF, rosiglitazone, compared to placebo was associated with an increased risk of new or worsening peripheral edema and an increased use of HF medications associated with rosiglitazone.[36] The PROACTIVE trial demonstrated an increased risk of HF hospitalizations associated with pioglitazone compared to placebo (pioglitazone 6%, placebo 4%; P =0.007).[37] The RECORD trial demonstrated a doubling of fatal and non-fatal HF in patients receiving rosiglitazone (2.7% vs. 1.3%, HR 2.1; 95% CI 1.35–3.27).[38] Furthermore, in RECORD, of the 61 rosiglitazone–treated cases of HF, four patients had the initial HF event as a fatal event and 30% of the surviving patients died during the trial follow-up. This was significantly increased compared to the control group whereby 29 patients had a HF hospitalization – none were fatal initially and 28% of patients subsequently died. These data demonstrated that TZD induced HF carried significant prognostic importance.[39] As a result of these studies, diabetes and HF guidelines recommend not to use TZD in patients

with signs and symptoms of congestive HF and initiation of these therapies is contraindicated in patients with NYHA functional class III-IV HF.[14,40,41] If a new diagnosis of CHF is made or considered likely, even in the absence of prior left ventricular dysfunction, the use of the TZD should be reconsidered.

Insulin

Insulin has a dose dependent antinatriuretic effect and mild fluid retention may be seen with insulin use particularly in individuals with poorly controlled glucose levels at the time of initiation[42]; however, unlike TZDs, it is unclear whether insulin may actually increase the risk of adverse HF events. In the BARI-2D study, insulin therapy did not result in any significant difference in HF outcomes compared with metformin and TZDs.[27] The ORIGIN trial randomized 12 537 patients with dysglycaemia (defined as either impaired glucose tolerance, impaired fasting glucose, or diabetes) to basal insulin glargine or placebo. Overall, insulin was not associated with increased HF risk (HR 0.9, 95% CI 0.77–1.05).[43] More recent data from the ORIGIN trial suggests that insulin does not increase the risk of recurrent HF events.[44] Despite the lack of randomized evidence suggesting harm for HF outcome, guidelines have encouraged caution in the use of insulin in patients with HF.[40]

Dipeptidyl-peptidase 4 inhibitors

There are four placebo controlled randomized controlled clinical trials that have evaluated the safety of dipeptidy-peptidase 4 (DPP-4) inhibitors in patients with type 2 diabetes. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial,[19] 16,492

patients with type 2 diabetes at high risk of CV events were randomized to saxagliptin or placebo. Saxagliptin was associated an increased risk of HF hospitalization (HR 1.27, 95% CI 1.07–1.51 *P* =0.007).[20] The EXAMINE study randomized 5,380 patients within 15-90 days of a myocardial infarction to alogliptin or placebo. Alogliptin had no impact on the composite event of CV death and hospitalization for HF (HR 1.00, 95% CI 0.82–1.21).[21,22] For patients with no baseline HF history, there was a significant increase in HF risk associated with alogliptin (2.2% vs. 1.3%, HR 1.76, 95% CI 1.07–2.90). In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), 14 671 subjects with type 2 diabetes and established atherosclerotic cardiovascular disease were randomized to sitagliptin or placebo.[45,46] Sitagliptin did not increase hospitalization for HF (HR 1.00, 95% CI 0.83–1.20). The recently completed CARMELINA trial evaluated the CV safety of linagliptin versus placebo in patients with high CV risk. Overall, linagliptin was non-inferior to placebo in reducing the risk of three point MACE and did not increase the risk of HF.[47] Recently the U.S FDA released a warning for drugs containing saxagliptin or alogliptin for HF risk.

A small mechanistic study of the DPP-4 inhibitor vildagliptin was conducted in patients with diabetes and HF. The VIVIDD study randomized 254 patients to the DPP-4 inhibitor vildagliptin versus placebo for 52 weeks. The inclusion criteria included an LVEF of <35% and poorly controlled diabetes.[48] The primary outcome (change in LVEF) was similar between groups. The LV systolic and diastolic volumes were increased in the vildagliptin arm compared with placebo groups. Caution should be given in interpreting the findings of increased LV chamber volumes as the clinical relevance remains unclear. In totality, the risk of HF events was balanced between the groups.

GLP-1 receptor agonists

GLP-1 is secreted by cells located in the distal intestine in response to ingestion of food. GLP-1 receptor stimulation in pancreatic beta-cells faciliates glucose-dependent insulin secretion in addition to suppression of glucagon release by alpha-cells.[49] The ELIXA trial evaluated the GLP-1 receptor agonist lixisenatide among patients with type 2 diabetes who had a myocardial infarction in the preceding 180 days.[50] Lixisenatide, compared to placebo, did not significantly reduce the risk of the primary MACE (HR 1.02; 95% confidence interval [CI], 0.89 to 1.17) and had no impact on HF hospitalizations (HR 0.96, 95% CI 0.75–1.23). Similar results were seen in patients with HF and without HF. The LEADER trial evaluated the CV safety of liraglutide in 9340 subjects with established cardiovascular disease or CV risk factors.[30] Liraglutide reduced the risk of the primary MACE outcome of CV death, non-fatal myocardial infarction, and non-fatal stroke (HR 0.87, 95% CI 0.78–0.97). CV mortality was significantly reduced by 22% (HR 0.78, 95% CI 0.66–0.93). Liraglutide was associated with numerically fewer HF hospitalizations but the difference was not statistically significant (218 [4.7%] vs. 248 [5.3%]; HR 0.87, 95% CI 0.73–1.05). The SUSTAIN-6 trial, randomized 3297 patients with diabetes and established CV disease or CV risk factors to semaglutide versus placebo.[29] The trial demonstrated the non-inferiority of semaglutide versus placebo for the primary MACE outcome (HR, 0.74; 95% 95% CI 0.58 to 0.95; p-value for non-inferiority <0.001). Semaglutide did not statistically increase the risk of HF events (vs placebo; 3.6% vs. 3.3%; HR 1.11, 95% CI 0.77-1.61). The EXSCEL trial evaluated the CV safety of exenatide versus placebo in patients with diabetes at high CV risk; overall, the study demonstrated non-inferiority for the primary MACE outcome (HR 0.91 95% CI 0.83-1.00).[51] There was no increased risk of HF seen among patients randomized to exenatide (HR 0.94, 95% CI 0.78-1.13).[51]

Despite the apparent safety of GLP-1 receptor agonists among patients with HF, divergent results arise when GLP-1 receptor agonists are evaluated specifically among patients with established HF. The Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study,[52] randomized 300 patients with and without diabetes with reduced ejection fraction (LVEF ≤ 40%) to liraglutide versus placebo. Patients were also required to have a recent (within 14 days) HF hospitalization and a preadmission oral diuretic dose of at least 40 mg of furosemide or an equivalent. The primary end point was a global rank score across 3 hierarchical tiers: time to death, time to HF rehospitalization, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days. Compared with placebo, liraglutide had no significant effect on the primary end point ($P = 0.31$). However, the point estimates suggested higher risk of death or HF–related events with liraglutide in patients with diabetes (vs placebo; 47% vs. 34%; HR 1.54; 95% CI 0.97-2.46). The LIraglutide on left VEntricular function in chronic heart failure patients (LIVE) study randomized 241 patients with and without diabetes and HFrEF (LVEF ≤45%) to liraglutide or matching placebo for 24 weeks.[53] The primary outcome measure (change in LVEF from randomization to end of follow-up) did not differ between the liraglutide and the placebo group; however increased adverse cardiac events (death caused by ventricular tachycardia (VT), non-fatal VT, atrial fibrillation requiring intervention, aggravation of ischaemic heart disease, and worsening of heart failure) were seen in 12 (10%) patients treated with liraglutide compared with 3 (3%) patients in the placebo group (P =0.04).

The reasons for the divergent signals of risk in patients with HFrEF seen in the FIGHT and LIVE studies compared to the larger LEADER, ELIXA, SUSTAIN-6, and EXSCEL trials remain unclear. A higher risk HF patient population may potentially have differential response to GLP-1 receptor agonist compared to the trial populations enrolled in the CV safety studies. It is unclear whether signals of risk would emerge for patients with HFpEF. Further research will be needed to ascertain the safety of liraglutide and other GLP-1 receptor agonist in patients with established HFrEF. potentially but should be used with caution in patients with a recent HF hospitalization. Despite these results, caution in interpretations across trials should be considered as these trials enrolled different patient populations, endpoints, and trial endpoints.

Sodium Glucose Co-Transporter-2 inhibitors

SGLT facilitates glucose and sodium movement across cell membranes in the proximal renal tubule. Inhibition of SGLT-2 results in insulin independent improvements in glycaemic control due to glycosuria of approximately 70–80 g/day.[54] SGLT-2 inhibitors' ability to optimize volume status through glycosuria and also inhibit sodium-hydrogen exchanger in the kidneys and the heart may result in a cascade of responses including increased natriuresis, decreased myocardial fibrosis, and increased cardiac contractility **(figure 2)**.[55] The EMPA-REG OUTCOME trial was a CV safety trial of the SGLT-2 inhibitor empagliflozin.[56] The trial randomized 7020 patients with type 2 diabetes and established CV disease to receive empagliflozin 10 mg, 25 mg, or placebo. Empagliflozin reduced the primary MACE endpoint compared to placebo (10.5% vs. 12.1%; HR 0.86, 95.02% CI 0.74–0.99). Furthermore, empagliflozin reduced the risk of HF admissions compared to placebo (4.1% vs. 2.7%; HR 0.65, 95% CI 0.50-0.85). Among the patients with a baseline history of HF, empagliflozin was

associated with a numerically lower rate of HF hospitalization (10.4% vs. 12.3%; HR 0.75, 95% CI 0.48–1.19) and CV mortality (8.2% vs. 11.1%; HR 0.71, 95% CI 0.43–1.16).[56] Adverse events consistent with CHF such as edema were reported in a higher proportion of patients treated with placebo [216/2333 (9.3%)] than with empagliflozin (9.3% vs. 4.5%).

The CANVAS program integrated two clinical trials with a total of 10,142 patients with type 2 diabetes and high CV risk. Patients were randomized to canagliflozin or placebo and the trial demonstrated a significant reduction in the risk of CV death, non-fatal MI, or non-fatal stroke (26.9 vs 31.5 per 1000 patient-years; HR 0.86, 95% CI 0.75-0.97).[57] No interaction was seen between patients with and without a baseline history of HF (interaction p=0.51). An unexpected finding of an increased risk of toe or metatarsal amputation was identified (6.3 vs. 3.4 per 1000 patient-years; HR 1.97, 95% CI 1.41-2.75). Randomization to canagliflozin was associated with a reduced risk of HF hospitalization (5.5 vs. 8.7 per 1000 patient-years; HR 0.67, 95% CI 0.52-0.87). Furthermore, patient with a prior history of HF appear to derive a great magnitude of benefit from canagliflozin with regards to reduction in the risk of CV death and HF hospitalization than patients without a prior history of HF.

The DECLARE-TIMI 58 trial randomized 17,160 patients with type 2 diabetes and established ASCVD or multiple CVD risk factors to dapagliflozin versus placebo. The co-primary outcomes were 3-point MACE and CV death or HF hospitalization.[58] After a median follow-up for 4.2 years, dapagliflozin was non-inferior to placebo for the 3-point MACE but demonstrated superiority for CV death or HF hospitalization (HR 0.82; 95% CI 0.73-0.95).[58] Dapagliflozin reduced CV death or HF hospitalization more in patients with HFrEF (HR 0.62; 95% CI 0.45-0.86) than in those without HFrEF (HR 0.88; 95% CI 0.76-1.02)(P-interaction

0.046).[59] Dapagliflozin reduced HF hospitalization in those with (HR 0.64; 95%CI 0.43-0.95) and without HFrEF (HR 0.76; 95%CI 0.62-0.92). However, it only reduced CV death only in patients with HFrEF (HR 0.55, 95% CI 0.34-0.90) but not in those without HFrEF (HR 1.08, 95% CI 0.89-1.31)(P-interaction 0.012).[59]

Implantable Cardioverter Defibrillator use among patients with diabetes and heart failure

There is no currently available meta-analysis data evaluating the efficacy of the interaction between ICDs and diabetes. Four major RCT among patients with chronic stable HFrEF provided evidence of efficacy for ICD on top of medical therapy versus medical therapy alone: Multicenter Automatic Defibrillator Implantation Trial I (MADIT I),[60] MADIT II,[61] Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE),[62] and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[63] In the MADIT 1 trial the hazard ratio for the risk of all-cause death in patients treated with the ICD compared with medical alone therapy was similar among patients with diabetes (HR 0.61; 95% CI 0.38 - 0.98) and nondiabetics (HR 0.71; 95% CI 0.49 to 1.05), with no evidence of interaction.[64] However, within the SCD-HeFT trial, patients with diabetes did not appear to have any benefit of ICD implantation over medical therapy (HR 0.95; 95% CI 0.68-1.33) compared to those without diabetes (HR 0.67; 95% CI 0.50-0.90); no interaction term was provided. Overall, these results suggest a potential mixed benefit for the use of ICD implantation for primary prevention of sudden death among patients with diabetes and HFrEF.

Cause of death among patients with diabetes

Diabetes is an established CV risk factor and is associated with a significant increase in the risk of CV death. As emerging anti-hyperglycemic therapies have demonstrated efficacy in

the ability to reduce the risk of CV death among patient with diabetes at high risk of CV death, there is an unmet need to describe the specific causes of death among patients with diabetes and HF. There are several population and RCT based studies that shed some light onto the cause of death among patients with diabetes across the CV risk spectrum.

Population studies

While there are several population level studies that describe the breakdown of CV and non-CV death, most studies have not specifically assessed the rates of individual CV and non-CV causes of death.[65–67] In general, the majority of studies have aggregated deaths into CV causes of death (such as myocardial infarction, coronary heart disease, HF, atrial fibrillation, and stroke), cancer, and other non-CV-non-cancer death.

Using data from the Swedish National Diabetes Register, cause of death among patients with type 2 diabetes was evaluated from January 1, 1998 until December 31, 2011.[68] Five patients per patient with diabetes was used as a control and matched for age, sex, and county. Cause of death was available from the Swedish Registry for Cause-Specific Mortality. In total there were 435,369 patients with type 2 diabetes and 2,117,483 controls. The crude mortality rate for all-cause death was 38.64 (95% CI 38.37-38.91) per 1000 person-year (PY) among patients with diabetes compared to 30.30 (95% CI 30.19-30.41) per 1000 PY in patients without type 2 diabetes. The rate of CV death was 17.17 (95% CI 16-97-17.34) per 1000 PY in patients with diabetes compared to 12.86 (95% CI 12.79-12.93) per 1000 PY in patients without diabetes. The rate of non-CV death was not aggregated but specific causes of death were described including cancer (diabetes: 8.45 95% CI 8.33-8.58; without diabetes 7.64, 95% CI 7.58-7.69) and diabetes-

related (diabetes: 4.02, 95% CI 3.93-4.11; without diabetes 0.39, 95% CI 0.37-0.40). There was no further breakdown of CV specific causes of death.[68]

The Emerging Risk Factors Collaboration evaluated the distribution of causes of death over 13.6 years (median) follow-up among patients with (n=40,116) and without diabetes (n=674,945) who did not have CV disease at baseline.[69] The contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause), on the basis of coding from the *International Classification of Diseases,* revisions 8 through 10, to at least three digits, or according to study-specific classification systems or ascertainment through death certificates. The crude all-cause mortality risk was 29 per 1000 PY for patients with diabetes and 12 per 1000 PY for patients without diabetes. Among patients with diabetes, the cause-specific rates of death were: CV deaths, 13 versus 5 per 1000 person-years among men and 11 versus 2 per 1000 person-years among women; noncancer, nonvascular deaths, 6 versus 3 per 1000 person-years among men and 6 versus 2 per 1000 person-years among women; and for cancer deaths, 7 versus 4 per 1000 person-years among men and 4 versus 3 per 1000 person-years among women. Individual CV causes of death among patients with diabetes were not described.[69]

The Función de Riesgo ESpañola de acontecimientos Coronarios y Otros (FRESCO) Study was a pooled analysis from 12 population cohorts in 7 Spanish regions.[70] Data was collected between 1991 and 2005 and participants were randomly selected from the general population, did not have incident CV, and were aged 35 to 79 years. All participants were examined at baseline and followed up for a median of 10 years. Diabetes was defined as self-

reported by the participants in all studies. Investigators also considered those participants in whom glycemia >125 mg/dL was observed at the time of baseline examination as having diabetes, regardless of the patient's awareness of the glycemic disorder. Vital status and cause of death was ascertained by examining the corresponding electronic medical record for in-hospital deaths. For out-of-hospital deaths, causes were ascertained by reviewing death certificates from regional and national mortality offices. All deaths were coded according to the ICD-10. The FRESCO cohort included 55,292 individuals (8,627; 15.6% with diabetes). The overall rate of death was 10.9 per 1000 PY in males and 7.6 per 1000 PY in females. The rate of CV death was 3.6 per 1000 PY in males and 2.7 per 1000 PY in females; the rate of cancer death was 3.7 per 1000 PY in males and 2.3 per 1000 PY in females; the rate of other causes were 3.1 per 1000 PY in males, and 2.2 per 1000 PY in females.

Among these population-based studies of patients with diabetes, the risk of non-CV and cancer related mortality can be just as high or exceed CV causes of death. Compared to clinical trial populations of anti-hyperglycemic therapies that enrich for CV disease, these are population-based studies which reflects a more heterogenous population. Furthermore, the Emerging Risk Factor Collaboration evaluated patients without baseline CV disease, thereby selecting for a lower CV risk population.

Clinical trials

Among the numerous anti-hyperglycemic trials that are now being conducted, several have reported the distribution of adjudicated causes of death: SAVOR-TIMI 53, EXAMINE, EXCEL, and EMPA-REG OUTCOME (**Table 1**). The differences in follow-up duration, patient

inclusion criteria, and site selection increase the difficulty in comparison across groups and to the population-based studies.

Cause of death among patients with chronic heart failure and reduced ejection fraction

Among patient in Olmstead County (USA), a HF cohort was evaluated for specific causes of death.[71] The medical records were reviewed under the through the Rochester Epidemiology Project which is a record-linkage system that allows the indexing of all medical records of Olmsted County residents according to the clinical and pathological diagnoses, surgical procedures, and billing information. The Rochester Epidemiology Project indexing system enables the retrieval of all medical records for use in the epidemiological studies and ensures the complete capture of all healthcare-related events occurring in Olmsted County for local residents. Identification of the specific causes of death were obtained through death certificate. This was classified into the following categories: CV death (including coronary heart disease and other cardiovascular), and non-CV cause of death, based on ICD-9 and ICD-10 codes. Data was collected from 1979-2002. Among 1,063 patients with HF, 55% had HFrEF. At a median follow-up of 4.3 years, among subjects with reduced EF, the leading cause of death was coronary heart disease (43%), whereas 36% of deaths were attributed to noncardiac causes. These included deaths most commonly due to cancer (28%) and pulmonary disease (27%), followed by gastrointestinal or genitourinary disease (14%), central nervous system disease (10%), and diabetes mellitus or endocrine disorders (10%).

In comparison, cause of death was evaluated in the Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF) trial, which randomized patients with chronic HF-REF to LCZ696 or

enalapril, and demonstrated that treatment with LCZ696 reduced the composite primary outcome of cardiovascular death or heart failure hospitalization, as well as cardiovascular death and all-cause mortality.[72,73] This sub-study identified that among the 8,399 patients randomized in the trial, there were 1,546 deaths. Overall, sudden death was the most commonly adjudicated cause of death (n=561, 36%), followed by 'other CV deaths' (including all CV death not ascribed to HF or sudden death; n=359, 23%), HF death (n=331, 21%), and non-CV death (n=295, 19%). Follow up was 27 months

Conclusion

Among population level studies among patients with diabetes, non-CV death contributes to a large burden of mortality. However, among clinical trials of patients with type 2 diabetes enriched for CV disease, the burden of death is predominantly CV death; within CV death, sudden death appears to be the primary adjudicated cause of death. There are few studies evaluating cause of death among patients with diabetes and HF.

Tables and Figures

Figure 1: Risk of heart failure events seen in recent anti-hyperglycemic drug trials

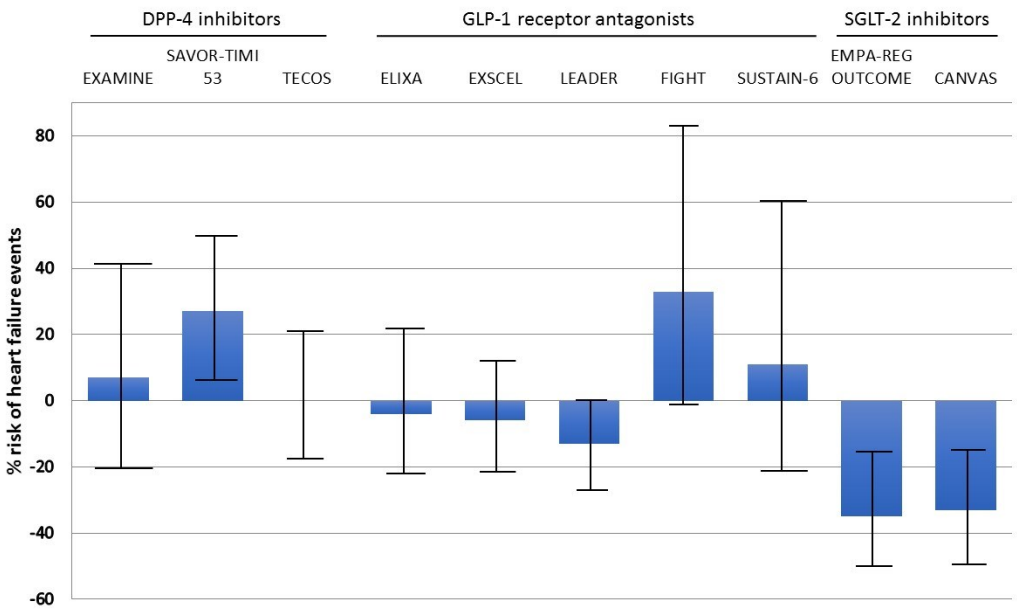
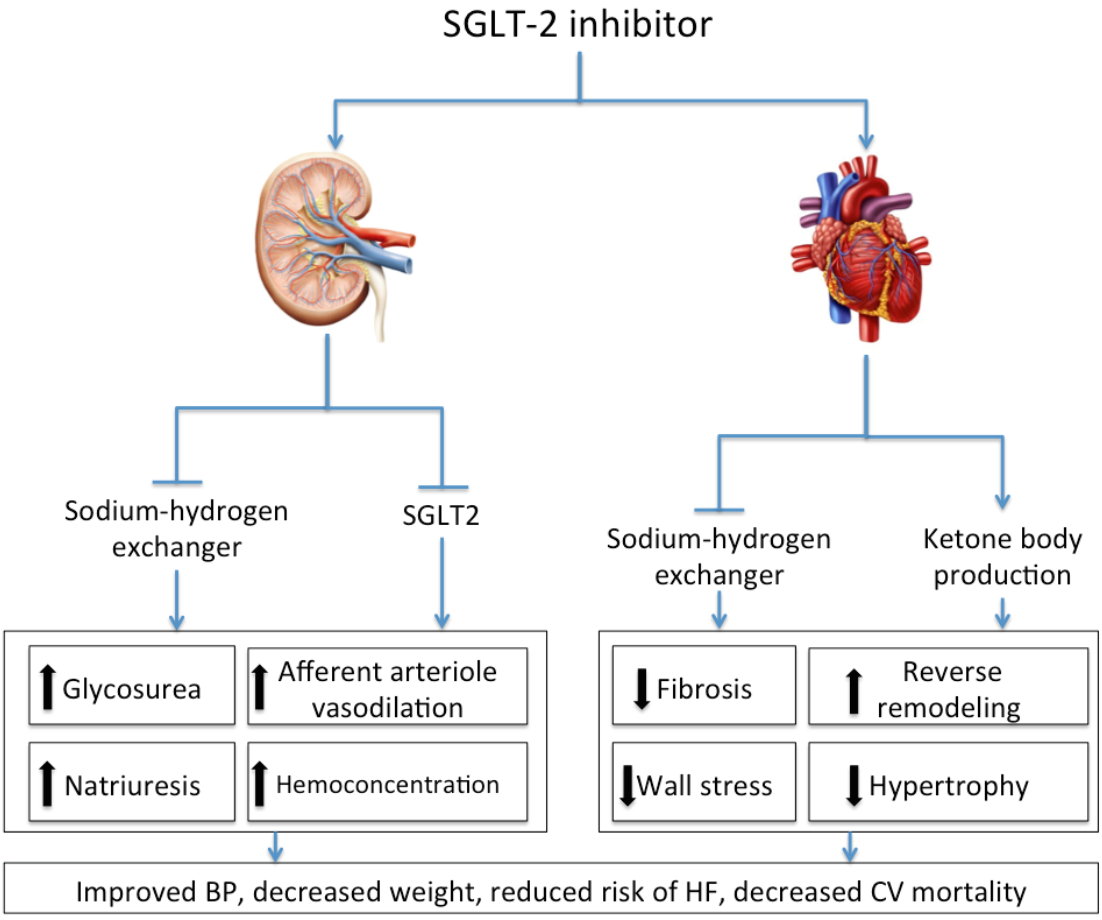


Figure 2: Potential mechanisms of SGLT-2 inhibitors in the heart and kidneys



BP blood pressure, HF heart failure, CV cardiovascular, SGLT2 sodium-glucose cotransporter 2

Table 1: Cause of death among cardiovascular outcome trials of anti-hyperglycemic therapies

Trial (n)	Intervention	Median follow-up	Key inclusion criteria	Cause specific mortality in the placebo arm
DPP-4 inhibitors				
SAVOR-TIMI 53 (16,492)	Saxagliptin vs. placebo	2.1 years	Patients with T2DM (HbA1c ≥6.5%) with an age ≥ 55 years (men) or ≥ 60 years of age (women) with multiple risk factors for CVD or age ≥ 40 years with established ASCVD	Placebo No. (2 years Kaplain Meier %) CV death 260 (2.9) Heart failure 40 (0.5) Acute myocardial infarction 19 (0.2) Cerebrovascular 35 (0.4) Sudden cardiac death 109 (1.3) Other 15 (0.2) Presumed CV 42 (0.4) Non-CV 118 (1.3) Cancer 58 (0.6)
EXAMINE (5,380)	Alogliptin vs. placebo	1.5 years	Patients with T2DM (HbA1c 6.5-11.0% without insulin, 7.0-11.0% with insulin) and ACS within 15–90 days prior to randomization	All-cause mortality 173 (6.5%) CV mortality 130 (4.9%) Sudden cardiac death 72 (2.7%)
GLP-1 receptor agonists				
EXSCEL (14,752)	Weekly exenatide vs. placebo	3.2 years	Patients with T2DM (HbA1c 6.5- 10.0%) and CVD or multiple risk factors for CVD	All-cause mortality n=584 CV death 241 (41.3%) Sudden death 128 (21.9%) Acute myocardial infarction (2.6%) Heart Failure 46 (7.9%) Cardiovascular procedure 8 (1.4%) Stroke 34 (5.8%) Other CV cause 10 (1.7%) Non-CV 201 (34.4.%) Cancer 78 (13.4%)
SGLT2 inhibitors				
EMPA-REG OUTCOME (7,020)	Empagliflozin vs. placebo	3.1 years	Patients with T2DM (HbA1c 7.0-10% on background therapy and 7.0-9.0% for drug naïve) and preexisting CVD, with BMI ≤45 kg/m^2 and eGFR ≥30 mL/min/1.73 m^2	All-cause mortality n=269 CV death 172 (64%) Sudden death n=52 (19%) Acute myocardial infarction n=15 (5.6%) Heart failure n=11 (4%) Stroke n=16 (6%) Cardiogenic shock 3 (1%) Other CV death 74 (28%)

CHAPTER 2: Trends in Non-Cardiovascular Comorbidities among Patients Hospitalized for Heart Failure: Insights from the Get With The Guidelines-Heart Failure Registry

Introduction

Heart failure (HF) is associated with significant morbidity and mortality and places enormous burden on healthcare systems.[40,74] There is growing recognition that patients with HF have a large burden of non-cardiovascular (non-CV) comorbidities which may increase the risk of mortality and decrease quality of life. Among United States (U.S.) Medicare beneficiaries, 40% of patients with HF had over 5 non-CV comorbidities and these patients accounted for the majority of days spent in hospital.[75,76] In the European Society of Cardiology (ESC) HF Pilot survey, among outpatients with chronic HF, 74% had at least one non-CV comorbidity and an increasing number of non-CV comorbidities was associated with a greater risk of mortality.[77]

There is a perception that patients hospitalized for HF are also becoming more medically complex. However, unlike chronic HF, there is limited information on the burden of non-CV comorbidities in patients who are hospitalized for HF. In addition, the temporal trends in the non-CV comorbidity profile and the impact of non-CV comorbidities on outcomes among patients hospitalized with HF remains unexamined. Using data from the Get With The Guidelines-Heart Failure (GWTG-HF) registry, among patients hospitalized for HF we assessed: 1) The prevalence of non-CV comorbidities within the entire GWTG-HF registry cohort; 2) the temporal trends in the prevalence of non-CV comorbidities; 3) the association of non-CV comorbidities with hospital length of stay, in-hospital mortality, and 30-day mortality.

Methods

Study Population

Data for this analysis come from the American Heart Association's GWTG-HF registry and linked Medicare claims available for research from the Centers for Medicare & Medicaid Services (CMS). The GWTG-HF registry is an ongoing quality improvement registry for patients hospitalized with HF in the U.S. Details of the registry have been described previously.[78] Patients are eligible to be included in the GWTG-HF registry if they are admitted or discharged with a diagnosis of HF. Registry patients were linked to Medicare data using indirect identifiers, as described and validated previously.[79] The Medicare data include institutional claims for inpatient hospitalizations and the associated denominator files from 2005 through 2014. The denominator files include information about demographics, Medicare eligibility and enrollment, and mortality. Quintiles, is the data collection coordination center for the American Heart Association/American Stroke Association Get With The Guidelines® programs.

The study population for the present analysis included all patients in the GWTG-HF registry from 01 January 2005 to 31 December 2014. Sites with <75% completeness on medical history panel were excluded. Patients admitted after 2014, missing the medical history panel, or missing body mass index (BMI) were excluded. In 2005, history of prior MI was not captured under the medical history panel. Similarly, a history of coronary artery bypass grafting (CABG) or history of PCI were not captured under the medical history until 2008. Overall, 207,984 patients from 409 hospitals were included in the initial analysis on in-hospital prevalence of non-CV comorbidities and in-hospital outcomes. Medicare fee-for-service beneficiaries aged 65 and older with a linked GWTG-HF hospitalization for HF discharged between January 1, 2005 and December 31, 2014 were used to assess 30-day outcomes. In total 73,878 CMS-linked GWTG-

HF patients were included in the follow-up analysis on post-discharge outcomes. If the patient had multiple hospitalizations in the GWTG-HF registry, the first hospitalization was used for the analysis on post-discharge outcomes.

Definition of non-cardiovascular comorbidities

For the present study, non-CV comorbidities were defined as any of the following: Chronic obstructive pulmonary disorder (COPD) or asthma, anemia, diabetes, chronic kidney disease (CKD)/renal disease, obesity (BMI ≥ 30 kg/m2) and depression. The selection of these co-morbidities are based on the availability of data collected with the GWTG-HF registry and prior analyses that have defined the most clinically relevant non-CV comorbidities among patients with HF.[75–77]

Outcomes

The outcomes assessed were hospital length of stay greater than 4 days, in-hospital mortality, 30-day mortality (from admission), 30-day all-cause readmission (from discharge), and 30-day HF rehospitalization (from discharge).

Statistical analysis

The baseline characteristics of the study population were described by the number of non-CV comorbidities (0, 1, 2, or ≥ 3) using proportions for categorical variables and means with standard deviations or medians with quartiles for continuous variables, testing for differences between groups using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Temporal changes in comorbidities from 2005-2014 were evaluated. In addition, the length of stay > 4 days and mortality differences between groups (with patients who have 0 non-CV comorbidities as the reference) using logistic regression models were assessed.

Covariates used in adjustment models included standard GWTG-HF adjustment variables: age, race, gender, medical history of atrial fibrillation, atrial flutter, hyperlipidemia, hypertension, peripheral vascular disease (PVD), coronary artery disease (CAD), prior myocardial infarction (MI), stroke, history of HF, smoking, hospital characteristics, region, teaching, hospital size, and rural location.

The Generalized Estimating Equation (GEE) method with exchangeable working correlation structure was used to account for within-hospital clustering. Odds ratios and 95% confidence intervals for odds ratio were presented. Most variables had very low rates of missingness. For imputation, after the prior exclusions, missing for all covariates are below 5%. Age and gender have 0 missing. Missing race was imputed to white – most frequent category. Missing medical histories were imputed to "No". Missing hospital characteristics were excluded without imputation.

Cox proportional hazards regression models were performed to evaluate the association between number of non-CV comorbidities and 30-day outcomes. The median LOS in the entire population was 4 days (interquartile range 3-7). We therefore use 4 days as a bench mark in assessing the impact of non-CV comorbidities and LOS. Hazard ratios and 95% CIs for different levels of number of non-CV co-morbidities are provided (0 comorbidity as the reference group). Both unadjusted and adjusted analyses were performed. The standard GWTG-HF adjustment variables were included in the adjusted analysis and included age, white race, gender, history of atrial fibrillation, atrial flutter, hyperlipidemia, hypertension, peripheral vascular disease (PVD), coronary artery disease (CAD), prior myocardial infarction (MI), stroke, prior history of HF, smoking, hospital characters of region, teaching, hospital size, and rural location. Changes in the number of co-morbidities may be attributed to increased capturing of comorbidities in billing

codes. In order to ascertain whether objective measures of disease have been increasing over time, we assessed for changes in the number of people in the different quartiles of BMI and estimated glomerular filtration rate (eGFR) over time. Also, given the overall prevalence of patients with high BMI in the dataset, the relationship between obesity status on 30-day outcomes was assessed by analyzing regression models only adjusting for BMI (BMI ≥30 kg/m^2).

We report 95% confidence intervals and use $\alpha = 0.05$ to establish statistical significance of tests. All tests were two-sided. SAS version 9.4 (SAS Institute Inc, Cary NC) was used for all analyses. The institutional review board of the Duke University Health System approved the study. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Results

Baseline demographics

In the 207,984 patients within the study population, 82% (n=170,717) of patients had at least one non-CV comorbidity. Overall, 18% (n=37,267) had 0 non-CV comorbidities; 30% (n=62,599) had 1 non-CV comorbidity; 27% (n=56,889) had 2 non-CV comorbidities; and 25% (n=51,229) had ≥ 3 non-CV comorbidities. The most common non-CV comorbidity was diabetes (45%, n=93,852) followed by COPD/asthma (32%, n=66,996).

There was a lower median age associated with patients with a greater number of non-CV comorbidities, from 80 years of age in patients with 0 non-CV comorbidities down to 71 years of

age in patients with ≥ 3 non-CV comorbidities (p<0.0001) **(Table 1)**. Patients with more non-CV comorbidities also had more CV comorbidities including hypertension, PVD, CAD, and prior history of HF. Patients had a lower admission brain-natriuretic peptide (BNP) associated with a higher number of non-CV comorbidities. There was a higher median ejection fraction of patients with a greater number of non-CV comorbidities, from 35% in patients with 0 non-CV comorbidities up to 46% in patients with ≥ 3 non-CV comorbidities (p<0.0001). Correspondingly, there was a greater prevalence of HF with preserved ejection fraction (HFpEF; defined as an ejection fraction ≥ 40%) associated with a greater number of non-CV comorbidities: 44% in patients with 0 non-CV comorbidities to 61% in patients with ≥ 3 non-CV comorbidities. Similar trends are seen among Medicare beneficiaries (**Appendix Table 1**).

Temporal trends in the prevalence of non-cardiovascular comorbidities

From 2005 to 2014, there was a decline in patients with 0 non-CV (from 22% in 2005 to 16% in 2014; p<0.0001) and 1 non-CV comorbidity (34% in 2005 to 28% in 2014; p<0.0001); however, there was a corresponding increase in patients with ≥ 3 non-CV comorbidities (from 18% in 2005 to 29% in 2014; p<0.0001) **(Figure 1; Appendix Table 2).** There was an increase in the number of all individual non-CV comorbidities from 2005-2014. The greatest absolute magnitude of increase was for COPD/asthma (9% increase from 2005-2014) and obesity (8% increase from 2005-2014). With regards to temporal trends in CV comorbidities, there were an increase in atrial fibrillation (32% to 37%), hypertension (73% to 84%), and dyslipidemia (35% to 54%). However, history of CAD declined slightly (51% to 49%) and PVD remained relatively unchanged (12% to 13%)**.** As reflected in figure 1, the number of patients with obesity has been

rising while CKD remains unchanged. Depression had the greatest relative increase over time (87%). The number of patients with elevated BMI also increases over time while eGFR remains unchanged (**Appendix Table 3**).

Impact of non-cardiovascular comorbidities and outcomes

Length of stay and in-hospital mortality

There was an increasing length of stay based on the number of non-CV comorbidities (**Table 1**). From 2005 to 2014, the total mean length of stay days declined for all patients, regardless of the number of comorbidities: length of stay in patients with 0 non-CV comorbidities declined from 5.21 days to 4.94 days; length of stay in patients with 1 non-CV comorbidity declined from 5.34 days to 5.03 days; length of stay in patients with 2 non-CV comorbidities declined from 6.18 days to 5.24 days; length of stay in patients with ≥ 3 non-CV comorbidities declined from 6.49 days to 5.49 days (time trend across all groups $p<0.0001$). The unadjusted p-value for continuous LOS between groups using a Kruskal-Wallis test was $p<0.0001$.

Patients with 1, 2, or ≥ 3 non-CV comorbidities, compared to those with 0 non-CV comorbidities, in both unadjusted and adjusted analyses, had an increased risk of having a length of stay > 4 days **(Table 2, Figure 2)**. Furthermore, compared to those with 0 non-CV comorbidities, there was a significantly increased adjusted risk of in-hospital mortality for patients with 1 non-CV comorbidity (odds ratio [OR] 1.09; 95% CI 1.0-1.19; $p=0.04$), 2 non-CV comorbidities (OR 1.32; 95% CI 1.21-1.43; $p<0.0001$), and ≥3 non-CV comorbidities (OR 1.54; 1.39-1.72; $p<0.0001$).

30-day mortality, all-cause rehospitalization, and heart failure rehospitalization

Among Medicare beneficiaries (n=73,878), 9.5% of patients died within 30-days of the index HF hospitalization. Of those with 0, 1, 2, and ≥3 non-CV comorbidities, respectively, 9.2%, 9.5%, 9.5%, and 10.3% of patients died within 30-days of admission from the index HF hospitalization. There was an increased risk of 30-day mortality, compared to patients with 0 non-CV comorbidities, among patients with 1 non-CV comorbidity (adjusted HR [aHR] 1.16; 95% CI 1.09-1.24; p<0.0001), 2 non-CV comorbidities (aHR 1.34; 95% CI 1.25-1.44; p<0.0001), and ≥ 3 non-CV comorbidities (aHR 1.63; 95% CI 1.51-1.75; p<0.0001) **(Table 3, Figure 3)**. Similarly, compared to patients with 0 non-CV comorbidities, the risk of 30-day all-cause and HF readmission increased with an increasing number of non-CV comorbidities **(Table 3).** Patients with ≥ 3 non-CV comorbidities had the highest risk of 30-day all-cause readmission (vs. 0 non-CV comorbidities; aHR 1.44; 1.37-1.52; p<0.0001) and 30-day HF readmission (vs. 0 non-CV comorbidities; aHR 1.38; 95% CI 1.26-1.51; p<0.0001). When adjusting for obesity status alone, there was a decreased risk of 30-day outcomes **(Appendix Table 4)**. The outcomes for a continuous HR based on the number of non-CV comorbidities are presented in **Appendix Table 5**. The risk of 30-day mortality following discharge based on the number of non-CV comorbidities was similar **(Appendix Table 6).** Demographic variable appeared to be the major contributor to the confounding between the number of non-CV comorbidities and in-hospital (**Appendix Table 7**) and 30-day outcomes (**Appendix Table 8**)

Conclusion

Patients admitted in hospital for HF have an increasing number of non-CV comorbidities over time, which are associated with worse outcomes. Diabetes is one of the most common non-CV co-morbidity among patients admitted with HF. Strategies addressing the growing burden of non-CV comorbidities may represent an avenue to improve outcomes and should be included in the delivery of in-hospital HF care.

Tables and Figures

Table 1: Baseline patient characteristics

Variable	Number of non-cardiovascular comorbidities *			
	0 (n=3726)	1 (n=62599)	2 (n=56889)	≥ 3 (n=51229)
Demographics				
Age (median)	80	76	73	71
Gender (female)	48	46	48	53
BMI (median)	24	26	30	33
Race (%)				
White	72	68	66	68
Asian	1.7	1.5	1.3	0.80
American Indian or Alaska Native	0.3	0.40	0.50	0.56
Black or African American	16.0	18.6	19.9	20.1
Hispanic	6.9	8.8	9.3	8.0
Medical History				
Non-cardiovascular co-morbidities				
COPD or Asthma (%)	0	22	36	63
Diabetes (%)	0	27	58	83
Anemia (%)	0	10	21	47
Renal Insufficiency (%)	0	10	23	48
Depression (%)	0	5	11	29
Obesity (BMI ≥ 30 kg/m^2)	0	26	51	72
Cardiovascular co-morbidities				
Chronic or recurrent atrial fibrillation (%)	35	34	33	34
Atrial flutter (%)	2.5	2.5	2.6	3.3
Hyperlipidemia (%)	38	44	51	60
Hypertension (%)	71	77	82	86
PVD (%)	7	10	13	19
CAD (%)	42	46	51	57
Prior MI (%)	17	19	20	24
CVA/TIA (%)	13	14	15	18
Heart failure (%)	55	60	66	75
Prior PCI (%)	10	11	14	18
Prior CABG (%)	13	15	17	20
Valvular Heart Disease (%)	17	16	15	17
CABG/PCI Undetermined (%)	8	8	8	7
Smoking (%)	16	18	18	18
Labs at Admission†				
BNP (pg/mL)	981 (508, 1824)	862 (419-1668)	737 344-1492)	659 (300-1350)
Serum Creatinine (mg/dL)	1.2 (0.9-1.5)	1.2 (1.0-1.6)	1.3 (1.0-1.9)	1.6 (1.1-2.4)
BUN (mg/dL)	22 (16-31)	23 (17-34)	25 (17-39)	31 (20-48)
Ejection Fraction				
HFpEF (Ejection Fraction >/= 40) (%)	44	47	53	61
Ejection Fraction (%)	35	37	40	46
Length of Stay				

Variable	Number of non-cardiovascular comorbidities *			
	0 (n=3726)	1 (n=62599)	2 (n=56889)	≥ 3 (n=51229)
Mean (SD)	5.01 (6.34)	5.24 (5.99)	5.54 (6.83)	5.95 (6.29)
Median (IQR)	4 (2,6)	4 (2,6)	4 (3,7)	4 (3,7)

BMI (body mass index), COPD (chronic obstructive pulmonary disease), PVD (peripheral vascular disease), CAD (coronary artery disease), MI (myocardial infarction), CVA (cerebrovascular accident), TIA (transient ischemic attack), ICD (implantable cardioverter defibrillator), PCI (percutaneous coronary intervention), CABG (Coronary artery bypass grafting), BNP (brain natriuretic peptide), BUN (blood urea nitrogen), HFpEF (heart failure with preserved ejection fraction), SD standard deviation; IQR interquartile range. *All comparisons of baseline characteristics between groups were statistically significant at $p < 0.05$ † reported as median with IQR.

Table 2: In hospital outcomes

Number of Non-CV Comorbidities	Number of patients with event (%)	Unadjusted OR	Unadjusted Lower 95% CI	Unadjusted Upper 95% CI	Unadjusted P-value	Adjusted* OR	Adjusted* Lower 95% CI	Adjusted* Upper 95% CI	Adjusted* P-value
Mortality									
0	959 (2.7%)	1.00		Reference		1.00		Reference	
1	1,595 (2.6%)	0.99	0.91	1.07	0.743	1.09	1.00	1.19	0.040
2	1,578 (2.9%)	1.08	0.99	1.17	0.093	1.32	1.21	1.43	<.0001
≥3	1,549 (3.1%)	1.16	1.04	1.29	0.009	1.54	1.39	1.72	<.0001
LOS>4 Day									
0	12,544 (39.1%)	1.00		Reference		1.00		Reference	
1	22,503 (41.8%)	1.12	1.09	1.15	<.0001	1.16	1.12	1.19	<.0001
2	21,536 (44.2%)	1.24	1.20	1.29	<.0001	1.32	1.27	1.36	<.0001
≥3	20,922 (49.2%)	1.55	1.49	1.63	<.0001	1.67	1.60	1.75	<.0001
Discharge home†									
0	27657 (77.4%)	1.00		Reference				Reference	
1	46516 (77.5%)	0.99	0.95	1.03	0.636	0.83	0.80	0.87	<.0001
2	42360 (77.8%)	1..00	0.96	1.04	0.973	0.73	0.70	0.76	<.0001
≥3	36179 (73.9%)	0.84	0.80	0.88	<.0001	0.54	0.51	0.57	<.0001

CV cardiovascular; LOS length of stay; CI confidence internal

*Adjusted for age, white race, gender, medical histories of atrial fibrillation, atrial flutter, hyperlipidemia, hypertension, peripheral vascular disease, coronary artery disease, prior myocardial infarction, stroke, heart failure, smoking, hospital characters of region, teaching, hospital size, and rural location. † versus other medical facility or nursing facility.

Table 3: Thirty day outcomes among Medicare beneficiaries

		Unadjusted				Adjusted*			
Number of non-CV comorbidities (n)	Number of events at 30-days (%)	Hazard Ratio	Lower CI	Upper CI	P-value	Hazard Ratio	Lower CI	Upper CI	P-value
30 day mortality[+]									
0 (14,676)	1482 (9.2%)	1.00 Reference				1.00 Reference			
1 (21,279)	2224 (9.5%)	1.03	0.97	1.10	0.357	1.16	1.09	1.24	<.0001
2 (17,390)	1829 (9.5%)	1.04	0.97	1.11	0.295	1.34	1.25	1.44	<.0001
≥3 (13,459)	1538 (10.3%)	1.12	1.05	1.21	0.002	1.63	1.51	1.75	<.0001
30-day all-cause readmission†									
0 (15,680)	2666 (17%)	1.00	Reference				Reference		
1 (22,789)	4404 (19.3%)	1.16	1.10	1.21	<.0001	1.15	1.10	1.21	<.0001
2 (18,558)	3770 (20.3%)	1.22	1.16	1.28	<.0001	1.21	1.15	1.28	<.0001
≥3 (14,419)	3422 (23.7%)	1.46	1.39	1.53	<.0001	1.44	1.37	1.52	<.0001
30-day heart failure readmission†									
0 (15,680)	955 (6.1%)	1.00	Reference				Reference		
1 (22,789)	1610 (7.1%)	1.17	1.08	1.27	0.0001	1.14	1.05	1.24	0.0013
2 (18,558)	1324 (7.1%)	1.18	1.08	1.28	0.0001	1.13	1.04	1.23	0.0042
≥3 (14,419)	1260 (8.7%)	1.46	1.35	1.59	<.0001	1.38	1.26	1.51	<.0001

+30-day from admission *Adjusted for age, white race, gender, medical histories of atrial fibrillation, atrial flutter, hyperlipidemia, hypertension, peripheral vascular disease, cornary artery disease, prior myocardial infarction, stroke, heart failure, smoking, hospital characters of region, teaching, hospital size, and rural location. † Among patients discharged alive

Figure 1: Time trends of non-cardiovascular comorbidities among patients admitted with heart failure

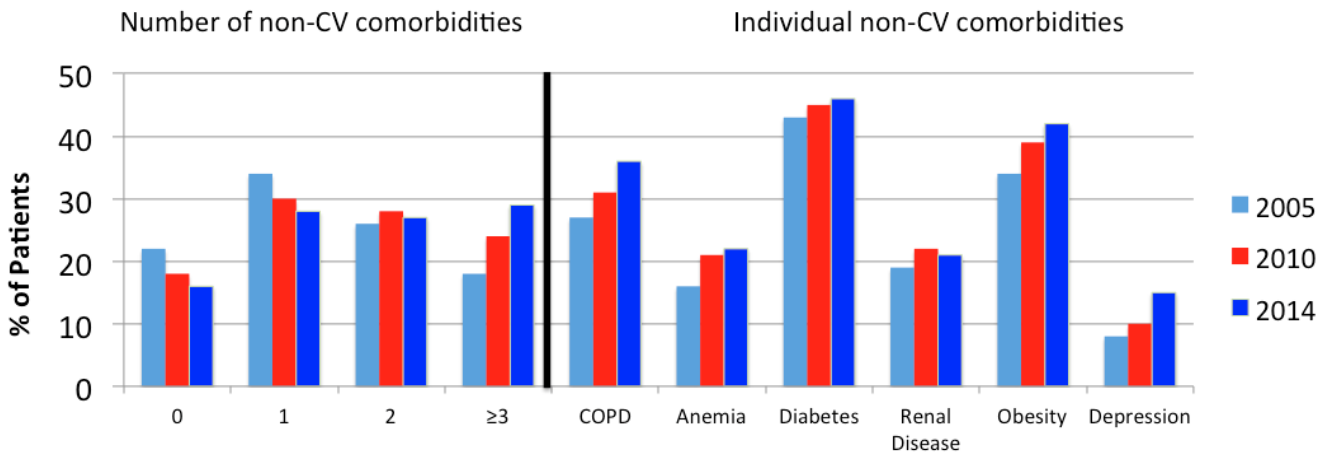
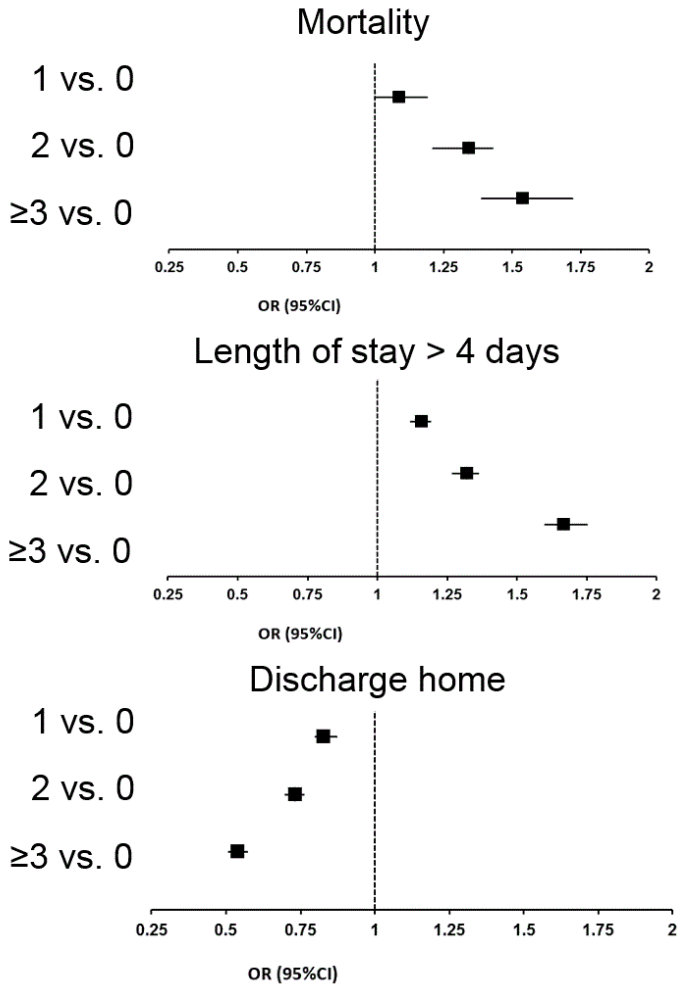
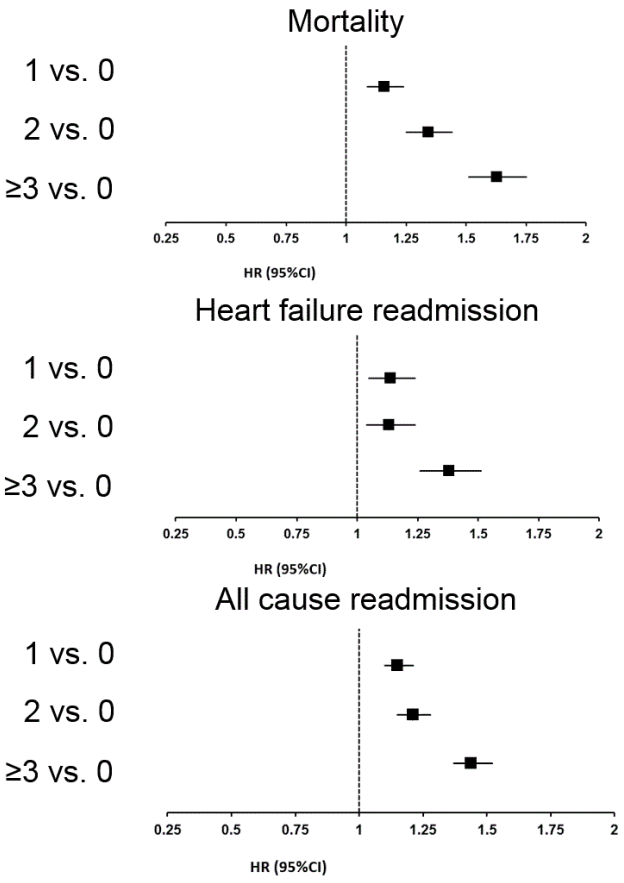


Figure 2: In hospital outcomes associated with number of non-cardiovascular comorbidities



Discharge home is compared to discharge to other health care facility, acute care facility, or hospice.

Figure 3: Thirty day outcomes among CMS patients associated with number of non-cardiovascular comorbidities



CHAPTER 3: Causes of Death in a Contemporary Cohort of Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease: Insights from the TECOS Trial

Introduction

The global burden of diabetes has risen significantly over the past few decades; by 2030, more than 500 million adults will be affected.[80] Diabetes is an established risk factor for cardiovascular (CV) disease,[4] and myocardial infarction (MI) is believed to be the most common cause of death among these patients. However, there is growing recognition that diabetes may increase the risk of other causes of CV death – including sudden death[81] and heart failure (HF) death[11] – and non-CV deaths such as malignancy[82]. Among patients with pre-diabetes and risk factors for CV disease, there is recognition that non-CV deaths, specifically malignancy, contribute to the large burden of all-cause mortality.[13] Since the use of medical therapy to target modifiable CV risk factors has improved and aggressive risk factor management has become more widespread,[4] the distribution of causes of death among a contemporary cohort of patients with diabetes and established atherosclerotic CV disease (ASCVD) should be re-examined. In addition, risk factors associated with specific causes of death should be elucidated to gain an understanding of potentially modifiable risk factors. To help achieve these goals, we used data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). We sought to assess 1) the distribution of specific causes of death, 2) patient demographic profiles associated with specific causes of death, and 3) risk factors associated with causes of death.

Methods

Study population

TECOS was a double-blind, multinational, placebo-controlled CV safety study evaluating the long-term effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), to usual care in patients with type 2 diabetes and established ASCVD. The main methods and results have been reported.[45,83] Briefly, the TECOS study randomized 14,735 patients to the addition of either sitagliptin or placebo to their existing antihyperglycemic therapy in the context of usual care. Eligible patients were at least 50 years of age with type 2 diabetes and established ASCVD, which included a history of major coronary artery disease (CAD), ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease (PAD). Eligible patients had glycosylated hemoglobin (HbA_{1c}) values of 6.5-8.0% (48–64 mmol/mol) on treatment with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or stable treatment with insulin with or without metformin. Patients were excluded from enrollment if they had two or more episodes of severe hypoglycemia in the previous year or if estimated glomerular filtration rate (eGFR) was less than 30 ml/min/1.73m^2 at baseline. The primary CV outcome was a composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

Outcomes

An independent clinical events committee adjudicated causes of death. The committee determinations were used for the purposes of this analysis. Definitions of cause-specific mortality are provided in **Appendix Table 1**. In the primary TECOS results manuscript, deaths adjudicated as due to unknown causes were included as CV deaths, per protocol, in the statistical analysis;[45,83] however, for the present analysis, deaths due to unknown causes were considered

separately from CV death. In addition, deaths due to stroke and MI were combined due to the small number of events.

TECOS adjudication was led by the Duke Clinical Research Institute (DCRI) Clinical Events Classification Committee (CECC). Details of the conduct and organization of the DCRI CECC are located in the appendix of the TECOS primary results article. In brief, DCRI CECC members adjudicated each suspected event using the prespecified endpoint criteria based on the preponderance of the evidence and clinical knowledge and experience. TECOS CECC members adjudicating events were blinded to treatment allocation and did not adjudicate events from their own institutional site.

Statistical analysis

Cox regression modeling was used to determine a list of risk factors for all-cause death and CV death in the intent-to-treat (ITT) TECOS patient population (n=14,671). A combination of backwards and regular stepwise selection methods were used to create a multivariable model of independent risk factors for all-cause mortality and CV death. Linearity assumptions for all continuous baseline characteristics were assessed, and use of transformations such as logarithms (base 10) or linear splines were applied as necessary. Proportional hazards assumptions were assessed, and transformations or time interactions were used as needed. Using a stepwise procedure with criteria of $p<0.10$ for inclusion, a list of covariates for the final multivariable model was generated. These candidate baseline characteristics included: age, ethnicity, geographic region, sex, duration of diabetes, New York Heart Association (NYHA) functional class, history of hypertension, race, history of MI, history of CAD, history of coronary artery bypass graft surgery, history of cerebrovascular disease, prior CV disease, history of percutaneous coronary intervention (PCI), history of PAD, history of HF, smoking status,

weight, BMI, systolic blood pressure, diastolic blood pressure, eGFR, and HbA_{1c}. A sensitivity analysis that included unknown causes of death with CV causes of death was also conducted. For CV death, a further sensitivity analysis using the Fine–Gray method[84] was used to account for the competing risk of non-CV death and unknown cause of death, with results reported based on sub-distributional hazard functions. Multiple imputation via fully conditional specification methods was used for missing baseline covariates; estimates reflect results aggregated over 25 imputations accounting for uncertainty due to missingness. Details of the approach to missing data are presented in the supplemental statistical materials section. All analyses were performed using SAS version 9.4 (Cary, NC; www.sas.com).

Results

Distribution of cause-specific mortality

Among the 14,671 patients in the ITT population of TECOS, 1084 died during a median follow-up period of 3.0 years. Of these, adjudication identified 530 CV deaths (49% of all deaths, 1.20 per 100 patient-years [PY]), 338 non-CV deaths (31% of all deaths, 0.77 per 100-PY), and 216 deaths due to unknown cause (20% of all deaths, 0.49 per 100-PY) **(Figure 1)**. Sudden deaths made up the largest defined subcategory of CV death (n=145, 27% of CV deaths), followed by acute MI or stroke (n=113 [MI n=48; stroke=65], 21% of CV deaths), and HF (n=63, 12% of CV deaths). Among non-CV causes of death, malignancy was the most common (n=154 deaths, 46% of non-CV deaths).

Baseline demographics and causes of mortality

There were differences in baseline demographic variables among the different causes of death **(Table 1)** including age, sex, comorbidities (including smoking, obesity, chronic kidney

disease, hypertension), and history of CV disease (including prior history of HF or cerebrovascular disease). Of all categories of CV death, patients who died of sudden death had the youngest median age (67 years), were most likely to have $HbA_{1c} \geq 7.5\%$ (n=63, 44%), and were most likely to use insulin (n=45, 31%). Patients who died of acute MI/stroke were most likely to be Hispanic/Latino and had the lowest prevalence of aspirin use at baseline (63%). Patients who died of HF had the oldest median age (70 years), longest median duration of diabetes (13.0 years), lowest median eGFR (60 mL/min/1.73 m^2), and highest prevalence of CAD (89%). Relative to other non-CV deaths, patients with deaths adjudicated due to malignancy were least likely to be female (20%), were mostly white (88%), were least likely to have $HbA_{1c} \geq 7.5\%$ (n=46, 31%), and had the highest median BMI (29.5 kg/m^2).

Patients who died from unknown causes had differences in several baseline CV risk factors compared to patients who died of CV causes: history of CAD (76.6% for CV death and 69.4% for unknown cause of death), history of PAD (17.2% for CV death and 21.3% for unknown cause of death), prior MI (50.9% for CV death and 44.9% for unknown cause of death), and prior HF (35.3% for CV death and 30.6% for unknown cause of death) **(Appendix Table 2)**.

Cumulative incidence of causes of death and non-fatal events prior to death

The cumulative incidence of CV mortality (including deaths due to unknown causes) was greater than non-CV mortality over the duration of follow-up **(Appendix Figure 1)**. When CV deaths and deaths of unknown causes were separated, the cumulative incidence of deaths from unknown causes was less than CV deaths **(Appendix Figure 2)**.

Among those who died from CV causes, 17% (n=90) had experienced a non-fatal CV event (MI, stroke, or unstable angina hospitalization) versus 13% (n=43) among those who died

from a non-CV death and 9% (n=20) who died from an unknown cause.

Risk factors associated with specific causes of death

Baseline characteristics associated with increased risk of all-cause death included age (per 5-year increase, hazard ratio [HR] 1.27; p<0.0001), prior MI (HR 1.26; p=0.0005), and HbA_{1c} (per 1% increase, HR 1.23; p=0.0014) **(Table 2)**. Baseline characteristics associated with reduced risk of all-cause mortality included absence of HF (HR 0.59; p<0.0001), female sex (HR 0.69; p<0.0001), history of PCI (HR 0.74; p<0.0001), and higher eGFR (per unit higher log eGFR, HR 0.46; p<0.0001; **Table 2**). For CV mortality specifically **(Table 3)**, similar results were seen. The absence of prior HF was consistently associated with a reduced risk of specific CV causes of death including sudden death (HR 0.40; p=0.0036), HF death (HR 0.29; p=0.0057), and acute MI/stroke death (HR 0.47; p=0.0486); furthermore a higher NYHA class was associated with a higher mortality risk **(Appendix Table 3)**. A higher eGFR was associated with a decreased risk of sudden death (per unit higher log eGFR, HR 0.33; p=0.0001) and HF mortality (per unit higher log eGFR, HR 0.33; p=0.0142) **(Appendix Table 3)**. A 1% higher HbA_{1c} was associated with an increased risk of sudden death (HR 1.41; p=0.0389), while a history of PCI was associated with a decreased risk of sudden death (HR 0.61; p=0.0066). Relatively few significant risk factors were identified for the combined categories of presumed CV and other CV death. Risk of death of unknown causes was similar to those for CV death including age, history of HF, sex, and renal function **(Appendix Table 3)**.

A sensitivity analysis adding deaths from unknown causes to the CV death category yielded similar results **(Appendix Table 4)**. Furthermore, using the Fine–Gray method yielded similar results for the association of risk factors with CV death, adjusting for non-CV or

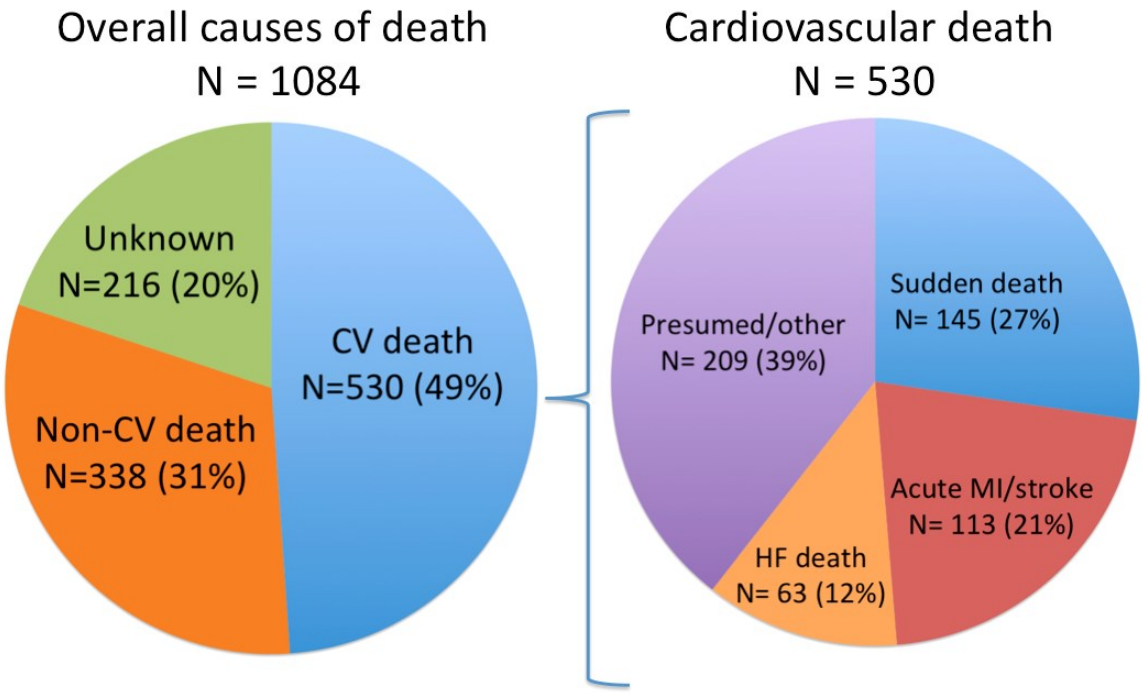
unknown deaths as competing risk **(Appendix Table 5)**.

Conclusions

In this analysis of a contemporary cohort of patients with diabetes and ASCVD, sudden death was the most common subcategory of CV death. HF prevention may represent an avenue to reduce the risk of specific CV death subcategories.

Tables and Figures

Figure 1: Distribution of causes of mortality



CV cardiovascular; MI myocardial infarction; HF heart failure.

Table 1: Baseline demographics and specific cause of mortality

	CV Type of Death				Non-CV Type of Death		
Characteristic	Sudden Death (N=145)	Acute MI/Stroke (N=113)	Heart Failure (N=63)	Presumed and Other CV Cause (N=209)	Malignancy (N=154)	Other (N=184)	Unknown Cause (N=216)
Demographics							
Age, years	67 (62, 73)	69 (63, 75)	70 (65, 77)	68 (61, 74)	69 (65, 74)	71 (65, 77)	70 (62, 76)
Female	36 (25%)	39 (35%)	16 (25%)	49 (23%)	31 (20%)	49 (27%)	59 (27%)
Race groups							
White	88 (61%)	84 (74%)	44 (70%)	127 (61%)	135 (88%)	117 (64%)	141 (65%)
Black	5 (3%)	3 (3%)	3 (5%)	1 (0%)	1 (1%)	5 (3%)	6 (3%)
Asian	39 (27%)	10 (9%)	9 (14%)	56 (27%)	13 (8%)	34 (18%)	46 (21%)
Other	13 (9%)	16 (14%)	7 (11%)	25 (12%)	5 (3%)	28 (15%)	23 (11%)
Not Hispanic or Latino	130 (90%)	94 (83%)	55 (87%)	178 (85%)	143 (93%)	142 (77%)	187 (87%)
Hispanic or Latino	15 (10%)	19 (17%)	8 (13%)	31 (15%)	11 (7%)	42 (23%)	29 (13%)
Medical History and Baseline Labs							
Duration of diabetes, years	11.0 (6.0, 17.0)	11.0 (6.0, 18.0)	13.0 (6.0, 17.0)	11.0 (5.0, 17.0)	11.0 (6.0, 20.0)	12.0 (6.0, 20.0)	11.0 (6.0, 18.5)
Qualifying HbA_{1c}, %	7.3 (6.9, 7.7)	7.2 (6.8, 7.7)	7.1 (6.7, 7.6)	7.3 (6.8, 7.7)	7.2 (6.9, 7.5)	7.3 (6.9, 7.7)	7.3 (6.8, 7.8)
Qualifying HbA1c, mmol/mol	56 (52, 61)	55 (51, 61)	54 (50, 60)	56 (51, 61)	55 (52, 59)	56 (51, 61)	56 (51, 61)
Baseline HbA1c, %	7.4 (6.8, 7.8)	7.2 (6.8, 7.8)	7.2 (6.7, 7.6)	7.3 (6.9, 7.8)	7.2 (6.8, 7.6)	7.2 (6.8, 7.7)	7.3 (6.8, 7.8)
Baseline HbA1c, mmol/mol	57 (51, 62)	55 (51, 62)	55 (50, 60)	56 (52, 62)	55 (51, 60)	55 (51, 61)	56 (51, 62)
Qualifying HbA_{1c} categories							
<7%	42 (30%)	38 (34%)	25 (40%)	64 (31%)	47 (32%)	58 (32%)	73 (34%)
7-7.5%	37 (26%)	28 (25%)	17 (27%)	56 (27%)	56 (38%)	48 (27%)	56 (26%)
≥7.5%	63 (44%)	46 (41%)	21 (33%)	85 (41%)	46 (31%)	75 (41%)	84 (39%)
eGFR, mL/min/1.73 m^2	63.0 (53.6, 80.0)	61.0 (51.0, 81.0)	60.0 (48.0, 78.0)	68.0 (56.0, 90.0)	66.0 (57.0, 82.0)	63.5 (50.0, 79.0)	65.0 (54.8, 82.0)

	CV Type of Death				Non-CV Type of Death		
Characteristic	Sudden Death (N=145)	Acute MI/Stroke (N=113)	Heart Failure (N=63)	Presumed and Other CV Cause (N=209)	Malignancy (N=154)	Other (N=184)	Unknown Cause (N=216)
Log of eGFR, mL/min/1.73 m^2	6.0 (5.7, 6.3)	4.1 (4.0 4.4)	4.1 (3.9 4.4)	4.1 (3.9 4.4)	4.2 (4.0 4.5)	4.2 (4.0 4.4)	4.2 (3.9 4.4)
Serum creatinine, mg/dL	1.10 (0.90, 1.24)	1.04 (0.90, 1.24)	1.12 (0.90, 1.42)	1.02 (0.85, 1.21)	1.05 (0.88, 1.26)	1.10 (0.90, 1.32)	1.05 (0.85, 1.24)
Log of creatinine, mg/dL	0.10 (-0.11 0.22)	0.04 (-0.11 0.22)	0.11 (-0.10 0.35)	0.02 (-0.16 0.19)	0.04 (-0.13 0.23)	0.10 (-0.11 0.28)	0.05 (-0.16 0.22)
History of vascular disease	143 (99%)	113 (100%)	62 (98%)	207 (99%)	154 (100%)	182 (99%)	214 (99%)
History of CAD	114 (79%)	83 (73%)	56 (89%)	153 (73%)	119 (77%)	134 (73%)	150 (69%)
Cerebrovascular disease	35 (24%)	44 (39%)	13 (21%)	69 (33%)	37 (24%)	50 (27%)	66 (31%)
Peripheral artery disease	28 (19%)	18 (16%)	8 (13%)	37 (18%)	29 (19%)	48 (26%)	46 (21%)
Prior MI	74 (51%)	55 (49%)	42 (67%)	99 (47%)	64 (42%)	85 (46%)	97 (45%)
Prior congestive heart failure	52 (36%)	42 (37%)	31 (49%)	62 (30%)	31 (20%)	64 (35%)	66 (31%)
History of hypertension	127 (88%)	103 (91%)	53 (84%)	189 (90%)	137 (89%)	170 (92%)	194 (90%)
NYHA classification at baseline							
I	11 (21%)	7 (17%)	6 (19%)	8 (13%)	8 (26%)	10 (16%)	8 (12%)
II	19 (37%)	16 (38%)	11 (35%)	37 (60%)	16 (52%)	25 (39%)	29 (44%)
III	9 (17%)	12 (29%)	7 (23%)	9 (15%)	1 (3%)	11 (17%)	10 (15%)
IV	2 (4%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	4 (6%)
Not available	11 (21%)	7 (17%)	6 (19%)	8 (13%)	6 (19%)	18 (28%)	15 (23%)
Systolic BP, mmHg	132 (122, 146)	140 (126, 151)	130 (117, 140)	130 (120, 146)	135 (124, 145)	133 (125, 149)	135 (123, 145)
Diastolic BP, mmHg	78 (70, 83)	80 (70, 82)	75 (67, 80)	80 (70, 86)	75 (67, 81)	75 (68, 82)	78 (70, 85)
Baseline weight, kg	84 (68, 98)	80 (69, 95)	85 (72, 95)	81 (69, 98)	86 (77, 98)	80 (67, 91)	78 (66, 93)
Baseline BMI, kg/m^2	29.5 (25.5, 33.5)	28.5 (25.5, 32.4)	29.5 (26.6, 33.5)	28.7 (25.3, 32.9)	29.5 (26.5, 33.7)	28.4 (25.3, 32.1)	28.4 (25.8, 32.5)

	CV Type of Death				Non-CV Type of Death		
Characteristic	Sudden Death (N=145)	Acute MI/Stroke (N=113)	Heart Failure (N=63)	Presumed and Other CV Cause (N=209)	Malignancy (N=154)	Other (N=184)	Unknown Cause (N=216)
Smoking history							
Never	82 (57%)	57 (50%)	32 (51%)	98 (47%)	52 (34%)	84 (46%)	110 (51%)
Current	16 (11%)	12 (11%)	6 (10%)	31 (15%)	23 (15%)	19 (10%)	21 (10%)
Former	47 (32%)	44 (39%)	25 (40%)	80 (38%)	79 (51%)	81 (44%)	85 (39%)
Antihyperglycemic Therapies							
Metformin	117 (81%)	87 (77%)	45 (71%)	159 (76%)	113 (73%)	121 (66%)	150 (69%)
Sulfonylurea	71 (49%)	64 (57%)	33 (52%)	100 (48%)	69 (45%)	78 (42%)	105 (49%)
Pioglitazone/thiazolidinedione	1 (1%)	4 (4%)	4 (6%)	2 (1%)	5 (3%)	3 (2%)	7 (3%)
Insulin	45 (31%)	17 (15%)	16 (25%)	54 (26%)	45 (29%)	66 (36%)	59 (27%)
CV Medications							
Statins	109 (75%)	84 (74%)	46 (73%)	156 (75%)	130 (84%)	129 (70%)	151 (70%)
Aspirin	107 (74%)	71 (63%)	45 (71%)	152 (73%)	110 (71%)	139 (76%)	158 (73%)
ACE inhibitors/angiotensin receptor blockers	126 (87%)	92 (81%)	53 (84%)	158 (76%)	119 (77%)	146 (79%)	167 (77%)
Beta blockers	102 (70%)	77 (68%)	41 (65%)	136 (65%)	98 (64%)	115 (63%)	140 (65%)
Diuretics	94 (65%)	63 (56%)	40 (63%)	113 (54%)	62 (40%)	89 (48%)	114 (53%)

Data are median (IQR) or n (%). CV cardiovascular; CAD coronary artery disease; NYHA New York Heart Association; BP blood pressure; eGFR estimated glomerular filtration rate; MI myocardial infarction; ACE angiotensin-converting enzyme.

Table 2: Risk factors associated with all-cause mortality (Cox proportional hazards model, multivariate analysis)

Risk factor	Adjusted HR with 95% CI	P-value
Age, per 5-year increase	1.27 (1.22-1.32)	<0.0001
Asymptomatic (no CHF) vs. NYHA I	0.59 (0.45-0.76)	<0.0001
NYHA II vs. NYHA I	1.17 (0.87-1.58)	0.3035
NYHA III vs. NYHA I	1.50 (1.04-2.15)	0.0288
NYHA IV vs. NYHA I	3.86 (1.64-9.08)	0.002
History of PCI	0.74 (0.65-0.85)	<0.0001
Female vs. male	0.69 (0.59-0.79)	<0.0001
Log per unit higher eGFR (mL/min/1.73 m^2)	0.46 (0.37-0.58)	<0.0001
Prior myocardial infarction	1.26 (1.10-1.43)	0.0005
HbA_{1c} (%), per 1% increase	1.23 (1.08-1.39)	0.0014
History of PAD	1.28 (1.09-1.49)	0.0024
Current vs. never smoker	1.33 (1.09-1.62)	0.0057
History of cerebrovascular disease	1.22 (1.06-1.40)	0.0064

CHF congestive heart failure; NYHA New York Heart Association; eGFR estimated glomerular filtration rate; PAD peripheral arterial disease; PCI percutaneous coronary intervention. Other variables in the model included history of hypertension (HR 1.18; 95% CI 0.97-1.44; p=0.0968) and former vs. never smoker (HR 0.99; 95% CI 0.87-1.14; p=0.9).

Table 3: Risk factors associated with cardiovascular death (Cox proportional hazards model, multivariate analysis)

Risk factor	Adjusted HR with 95% CI	P-value
Age, per 5-year increase	1.19 (1.12-1.26)	<0.0001
Prior myocardial infarction	1.44 (1.20-1.73)	0.0001
Asymptomatic (no CHF) vs. NYHA I	0.53 (0.37-0.76)	0.0005
NYHA II vs. NYHA I	1.15 (0.77-1.73)	0.49
NYHA III vs. NYHA I	1.64 (1.02-2.63)	0.0042
NYHA IV vs. NYHA I	3.13 (0.94-10.4)	0.064
History of PCI	0.63 (0.51-0.76)	<0.0001
Female vs. male	0.68 (0.55-0.83)	0.0002
Log per unit higher eGFR (mL/min/1.73 m^2)	0.48 (0.35-0.66)	<0.0001
Systolic BP ≤ 135 mmHg, per 5-mmHg increase	0.93 (0.88-0.97)	0.0025
HbA_{1c} (%), per 1% increase	1.29 (1.08-1.54)	0.0046
History of cerebrovascular disease	1.29 (1.06-1.58)	0.0109
BMI ≤ 30 kg/m^2, per 5-unit increase	0.70 (0.59-0.83)	0.0001

NYHA New York Heart Association; eGFR estimated glomerular filtration rate; PAD peripheral arterial disease; PCI percutaneous coronary intervention; BP blood pressure; CHF congestive heart failure. Other variables in the model included: Latin America vs. North America (HR 1.83; 95% CI 1.3-2.6; p=0.0006); Asia Pacific/Other vs. North America (HR 1.40; 95% CI 1.04-1.89; p=0.28); Western Europe vs. North America (HR 1.05; 95% CI 0.73-1.50; p=0.79); Eastern Europe vs. North America (HR 1.50; 95% CI 1.11-2.03; p=0.008); BMI > 30 kg/m^2 (HR 1.13; 95% CI 1.00-1.29; p=0.049); systolic BP > 135 mmHg (HR 1.04; 95% CI 1.00-1.08; p=0.06).

CHAPTER 4: Cause of death among patients with diabetes and heart failure and reduced ejection fraction: Insights from the HF-ACTION and ASIAN-HF studies.

Introduction

Among patients with heart failure (HF), diabetes is one of the most common comorbidity.[3,13] Diabetes significantly increases the risk of mortality and HF hospitalization among patients with established cardiovascular (CV) disease.[6] Furthermore, HF death forms a large component of overall CV death among patients with type 2 diabetes mellitus and established atherosclerotic CV disease.[85] Emerging therapies such as GLP-1 receptor agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors have demonstrated efficacy in reducing the risk of CV death among patients with type 2 diabetes mellitus at high risk for CV events.[30,56–58,86,87] Current practice guidelines recommend the initiation of therapies such as GLP-1 receptor agonists and SGLT-2 inhibitors among patients with type 2 diabetes mellitus and atherosclerotic CV disease with poor glycemic control and currently on metformin (unless contraindicated or not tolerated).[88] Among patients with established HF with reduced ejection fraction (HFrEF), trials evaluating the safety and efficacy of SGLT-2 inhibitors are pending (e.g. NCT 03057977 and NCT03036124).

Despite the emerging interest among patients with HF and diabetes, especially around the optimization of glucose-lowering therapies, the specific causes of death among these patients have not been extensively explored. Understanding the specific causes of death among patients with HF and diabetes will enable a greater understanding of which glucose-lowering therapies to prioritize when attempting to clinically manage these patients. Furthermore, there is significant variation in the clinical heterogeneity,

evidence-based medicine practice patterns, and outcomes among patients with diabetes and HFrEF;[89–92] it is unclear if there is variation in the specific causes of death among various ethnicities. Understanding ethnic variation in cause of death may enable future strategies aimed to reduce the risk of specific causes of death. In order to address this knowledge gap, using adjudicated data from the global cohort of patients from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial and Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry we aimed to describe: 1) the specific causes of death among patients with HFrEF and diabetes; 2) whether patients with diabetes, compared to those without diabetes, are independently at increased risk for specific CV death; and 3) whether there is ethnic variation in cause specific mortality among patients with HFrEF and diabetes.

Methods

The details of the HF-ACTION and ASIAN-HF registry have been previously reported.[93–95] This combined dataset has been used for prior analyses.[89] Both cohorts included patients with chronic stable HFrEF. Briefly, HF- ACTION was a multicentre, randomized, clinical trial of exercise training in patients with chronic and stable HFrEF with left ventricular ejection fraction (LVEF) ≤35%. Overall, 2331 patients from 82 centres in the United States, Canada, and France, were randomized to exercise training plus usual care or usual care alone (2003-2007). The median follow- up was 30 months. The ASIAN- HF registry was a prospective observational registry of patients above 18 years of age, with symptomatic HF and LVEF ≤40%. The main registry enrolled 5276 patients from 46 medical centres across 11 Asian regions (including China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand).

Data variables available to both HF- ACTION and ASIAN- HF (including variables on co- morbidities, HF medication use [i.e. angiotensin- converting enzyme inhibitors/angiotensin II receptor blockers, beta- blockers, mineralocorticoid receptor antagonists, diuretics]) and clinical outcomes were combined. Locally appointed ethics committee approved the research protocol for the HF-ACTION and ASIAN-HF studies and informed consent had been obtained from the subjects.

Study population

This study population includes patients aged 18 years or older in the combined dataset with HFrEF (defined as LVEF ≤35%). Diabetes was defined as the presence of clinical diagnosis (including fasting plasma glucose ≥7 mmol/L or random plasma glucose ≥11.1 mmol/L or glycated haemoglobin ≥6.5%) and/or receiving glucose lowering therapy. In addition, the presence of diabetes was collected at baseline through patient self-reporting and confirmation with a clinician. As previously reported, ethnicity was self- defined (included white, black, Chinese, Malay, Indian, Japanese/Korean).[89,95] An ethnic group could come from different geographic regions. Furthermore, minority groups in HF- ACTION (American Indian, Asian, Pacific Islander, Hispanics, Multiracial and Unknown, combined total n = 142) and ASIAN- HF (Thai, Filipino, Indigenous groups, and Others, combined total n = 327) were excluded for this analysis due to small numbers. Japanese and Korean patients were grouped together due to the small numbers and geographic proximity.[95]

Cause of Death Definition

For both ASIAN- HF and HF-ACTION, cause of death was adjudicated by an event committee using pre- specified criteria (see **Appendix Table 1**). In HF-ACTION, the specific adjudication definition for all causes of death (unknown, non-CV, and MI/stroke death) were not available. In the present analysis, the primary outcome was cause specific mortality at 1 year. The specific categories of death include: CV death, non-CV death, and unknown cause of death. The following categories of death were further included under CV death: sudden death, HF death, Myocardial infarction (MI) or stroke related deaths [combined into one composite], or 'other' CV death. Non-CV death was not further subcategorized.

Statistical analysis

Baseline characteristics for the study population by diabetes status and further by specific causes of death were described using frequencies with percentages for categorical variables and means with standard deviations or medians with interquartile range for continuous variables. We tested for differences between groups using the chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. Cox proportional regression was used to assess the association of diabetes with CV death at 1 year, adjusting for age and sex. Fine-Grey models, adjusted for age and sex were used to assess the association between diabetes and specific causes of death, with all causes of death considered competing outcomes. We assessed whether the following variables modified the relationship between cause of death and diabetes: 1) cohort (HF-ACTION and ASIAN-HF); 2) presence of ischemia; 3) ethnicity. If any interaction was

significant, the individual components of the variables were assessed. In addition, time-to- event analyses using the competing risk approach based on the Fine and Gray model were performed for the secondary outcomes, factoring non- CV deaths as a competing risk. The analysis used a 2- tailed $\alpha = 0.05$ to establish statistical significance and reported 95% confidence intervals (CIs). All statistical analyses were performed with STATA/SE v14.0 (Stata Corp., College Station, TX, USA).

Results

Baseline demographics

The median age was 61.1 years, 21.3% (n=521) were female, and 62.6% (n=1,473) had an ischemic etiology of HF (**Table 1**). Among patients with diabetes, (n=2,445), there were 527 deaths (21.6%). Of these 322 (61.1%) were CV deaths, 80 (15.1%) non-CV deaths, and 125 (23.7%) were unknown causes of death (**Figure 1, Figure 2**). Patients who died of non-CV deaths were older and had a greater burden of CV comorbidities (such as coronary artery disease, hypertension, and atrial fibrillation) compared to other causes of death and survivors (**Table 1**). Similar trends are seen among patients without diabetes (n=3,737) (**Appendix Table 2**).

Distribution of cardiovascular causes of death

Among patients with diabetes, sudden death was the most common cause of death (35.7%, n=115), followed by heart failure death (32.3%, n=104), MI/stroke death (11.8%, 38), and 'Other' CV death (20.2%, n=65). Death per 100 person years are presented in **Table 2**. Patients with diabetes who died from sudden death, compared to other CV deaths, were more likely to be younger (61.7 years of age [sudden death] vs. 65.4 years of

age [HF death] vs. 65.4 years of age [MI/stroke death])(**Appendix Table 3**). Patients who died of sudden death, compared to other causes of CV death, were more likely to be Indian and less likely to be Chinese, have a higher BMI, and are less likely to have CV comorbidities (such as CAD, atrial fibrillation, hypertension)(**Appendix Table 3**). Similar trends were seen among patients without diabetes (**Appendix Table 4**).

Association between diabetes and cardiovascular causes of death

In unadjusted models, diabetes is associated with an increased likelihood of CV death; however, this result was attenuated after multivariable adjustment (HR 1.13; 95% CI 0.90-1.43; p=0.3)(**Table 3**). For CV death, there was no interaction between the presence of diabetes and cohort (ASIAN-HF vs. HF-ACTION) or ethnicity (interaction p value>0.1 for both). However, etiology (ischemic vs. non-ischemic) modified the relationship between diabetes and CV death (interaction p-value 0.02). Patients with ischemic etiology and diabetes had an increased likelihood of CV death (HR 1.47; 95%CI 1.21-1.78; p<0.001) compared to patients with diabetes who had a non-ischemic etiology of HF (HR 1.04; 95% CI 0.8-1.35; p=0.8). Diabetes was not associated with an increased likelihood of sudden death (multivariable adjusted HR 0.87; 95% CI0.60-1.27; p=0.5). Diabetes was not associated with HF death (multivariable adjusted 1.08; 95%CI 0.673-1.59; p=07). However, diabetes was associated with an increased risk of MI/stroke death (multivariable adjusted HR 2.29; 95% CI 1.31-4.0; p=0.004).

Ethnicity, diabetes, and cardiovascular causes of death

Ethnicity modified the relationship between diabetes and sudden death (interaction p-value 0.02)(**Table 3**); patients with diabetes who were Chinese were less likely to die from sudden death (HR 0.44; 95% CI 0.23-0.86). Ethnicity also modified the relationship between diabetes and HF death (interaction p-value 0.01); patients with diabetes who were Japanese/Korean were more likely to die from HF death (HR 3.58; 95% CI 1.32-9.68; p=0.012). Ethnicity did not modify the relationship between diabetes and CV death.

Conclusion

In this global cohort of patients with diabetes and HFrEF, sudden death followed by HF death, are the most common adjudicated causes of death. In addition, ethnic variation was observed regarding the risk of cause specific CV death. Strategies to prioritize prevention of sudden death and HF death are warranted among patients with HF and diabetes.

Tables and Figures

Table 1: Baseline characteristics of patient with diabetes and heart failure with reduced ejection fraction

	Diabetes				
	All	Survivors	CV death	Non-CV death	Unknown
N	2445	1918	322	80	125
Age, years	61.1 (11.1)	60.4 (10.9)	63.7 (11.2)	66.2 (11.3)	62.4 (11.4)
Female sex	521 (21.3%)	413 (21.5%)	71 (22.0%)	17 (21.3%)	20 (16.0%)
Body mass index, kg/m2	27.7 (6.7)	27.9 (6.7)	27.3 (6.9)	25.9 (5.3)	26.6 (5.7)
Systolic blood pressure, mmHg	118.9 (19.7)	119.7 (19.8)	114.9 (19.9)	120.8 (18.8)	116.5 (16.5)
Diastolic blood pressure, mmHg	71.5 (11.8)	72.1 (11.9)	69.2 (11.1)	69.3 (12.9)	69.9 (11.0)
Heart rate, bpm	78.1 (15.3)	78.2 (15.4)	77.5 (14.4)	73.9 (13.2)	81.1 (16.5)
eGFR, mL/min/1.73m2	58.0 (41.4, 77.2)	60.6 (44.4, 80.0)	47.7 (33.5, 64.5)	46.6 (32.2, 66.0)	45.0 (33.0, 73.7)
LVEF, %	25.4 (6.2)	25.7 (6.2)	24.0 (6.7)	25.7 (6.2)	25.0 (5.8)
Ethnicity					
Black	242 (9.9%)	189 (9.9%)	38 (11.8%)	8 (10.0%)	7 (5.6%)
White	388 (15.9%)	311 (16.2%)	52 (16.1%)	16 (20.0%)	9 (7.2%)
Chinese	522 (21.3%)	401 (20.9%)	75 (23.3%)	24 (30.0%)	22 (17.6%)
Malay	329 (13.5%)	245 (12.8%)	50 (15.5%)	10 (12.5%)	24 (19.2%)
Indian	614 (25.1%)	478 (24.9%)	68 (21.1%)	14 (17.5%)	54 (43.2%)
Japanese/Korean	221 (9.0%)	190 (9.9%)	21 (6.5%)	6 (7.5%)	4 (3.2%)
All others	129 (5.3%)	104 (5.4%)	18 (5.6%)	2 (2.5%)	5 (4.0%)
Cohort					
ASIAN-HF	1761 (72.0%)	1376 (71.7%)	221 (68.6%)	56 (70.0%)	108 (86.4%)
HF-ACTION	684 (28.0%)	542 (28.3%)	101 (31.4%)	24 (30.0%)	17 (13.6%)
NYHA class					
Class I/II	1416	1162	151 (48.8%)	44 (57.1%)	59

	(62.4%)	(65.7%)			(53.1%)
Class III	760 (33.5%)	553 (31.2%)	134 (43.4%)	30 (39.0%)	43 (38.7%)
Class IV	92 (4.1%)	56 (3.2%)	24 (7.8%)	3 (3.9%)	9 (8.1%)
Aetiology of HF, ischemic	1473 (62.6%)	1098 (59.7%)	236 (74.2%)	63 (80.8%)	76 (64.4%)
Coronary artery disease, yes	1538 (62.9%)	1176 (61.3%)	223 (69.3%)	63 (78.8%)	76 (60.8%)
Hypertension, yes	1693 (69.4%)	1341 (70.1%)	202 (63.3%)	60 (75.0%)	90 (72.0%)
Atrial fibrillation/flutter, yes	432 (17.7%)	317 (16.5%)	73 (22.7%)	25 (31.3%)	17 (13.6%)
Prior stroke, yes	224 (9.2%)	172 (9.0%)	33 (10.2%)	9 (11.3%)	10 (8.0%)
PVD, yes	152 (6.2%)	97 (5.1%)	38 (11.8%)	9 (11.4%)	8 (6.4%)
COPD, yes	207 (8.5%)	159 (8.3%)	34 (10.6%)	7 (8.8%)	7 (5.6%)
Cancer, yes	91 (3.7%)	66 (3.5%)	12 (3.8%)	8 (10.0%)	5 (4.0%)
Alcohol, ever	750 (30.9%)	600 (31.4%)	99 (31.1%)	22 (27.5%)	29 (23.4%)
Smoking, ever	1239 (50.8%)	970 (50.7%)	166 (51.9%)	48 (60.0%)	55 (44.0%)
Chronic kidney disease (eGFR<60)	1121 (53.5%)	809 (49.3%)	205 (70.4%)	52 (72.2%)	55 (61.1%)
ACEi or ARBs, yes	1908 (78.6%)	1530 (80.4%)	233 (72.4%)	58 (72.5%)	87 (70.7%)
β-blockers, yes	2014 (83.0%)	1603 (84.3%)	259 (80.4%)	64 (80.0%)	88 (71.5%)
Diuretics, yes	2089 (86.1%)	1606 (84.4%)	298 (92.5%)	73 (91.3%)	112 (91.1%)
Aldosterone antagonist, yes	1276 (52.6%)	1006 (52.9%)	169 (52.5%)	31 (38.8%)	70 (56.9%)
Device therapy, vs none					
Any ICD	303 (12.4%)	244 (12.7%)	40 (12.4%)	13 (16.3%)	6 (4.8%)
Any Pacemaker	283 (11.6%)	219 (11.4%)	40 (12.4%)	16 (20.0%)	8 (6.4%)

eGFR estimated glomerular filtration rate; LVEF left ventricular ejection fraction; NYHA New York Heart Association; HF heart failure; PVD peripheral vascular disease; COPD chronic obstructive pulmonary disease; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; ICD implantable cardioverter defibrillator

Table 2: Causes of death per 100-person years among patients with and without diabetes and heart failure with reduced ejection fraction

	Deaths per 100 person years	
	With diabetes	Without diabetes
CV death	7.38 (6.62 - 8.23)	5.21 (4.71 - 5.76)
Non CV death	1.83 (1.47 - 2.28)	1.00 (0.80 - 1.26)
Unknown cause of death	2.87 (2.41 - 3.42)	2.11 (1.80 - 2.47)
Specific causes of CV death		
Sudden death	2.64 (2.20 - 3.17)	2.52 (2.18 - 2.91)
Heart failure death	2.38 (1.97 - 2.89)	2.04 (1.74 - 2.40)
MI/Stroke death	0.87 (0.63 - 1.20)	0.27 (0.18 - 0.42)
Other CV death	1.49 (1.17 - 1.90)	0.37 (0.25 - 0.54)

CV cardiovascular; MI myocardial infarction

Table 3: Risk of cardiovascular and identified specific causes of death

	Age + Sex adjusted		Multivariable adjusted	
Outcomes	HR (95% CI) for diabetes	p-value	HR (95% CI) for diabetes	p-value
CV mortality	1.32 (1.14, 1.54)	<0.001	1.13 (0.90, 1.43)	0.304
	Diabetes x cohort $p_{interaction}$	0.789		
	Diabetes x ethnicity $p_{interaction}$	0.103		
	Diabetes x etiology $p_{interaction}$	0.024		
Stratified by etiology				
Ischemic	1.47 (1.21, 1.78)	<0.001		
Non-ischemic	1.04 (0.80, 1.35)	0.786		
Sudden death	0.98 (0.78, 1.24)	0.884	0.87 (0.60, 1.27)	0.476
	Diabetes x cohort $p_{interaction}$	0.087		
	Diabetes x etiology $p_{interaction}$	0.060		
	Diabetes x ethnicity $p_{interaction}$	0.022		
Stratified by ethnicity				
Blacks	1.18 (0.64, 2.19)	0.594		
Whites	1.15 (0.66, 2.01)	0.631		
Chinese	0.44 (0.23, 0.86)	0.016		
Malay	0.55 (0.25, 1.19)	0.126		
Indian	1.14 (0.73, 1.78)	0.555		
Japanese/Korean	0.79 (0.28, 2.22)	0.658		
Others	1.03 (0.46, 2.32)	0.938		
Heart failure death	1.05 (0.82, 1.34)	0.723	1.08 (0.73, 1.59)	0.694
	Diabetes x cohort $p_{interaction}$	0.958		

	Diabetes x etiology $p_{interaction}$	0.671		
	Diabetes x ethnicity $p_{interaction}$	0.010		
Stratified by ethnicity				
Blacks	0.64 (0.31, 1.35)	0.244		
Whites	1.26 (0.76, 2.08)	0.367		
Chinese	0.74 (0.45, 1.23)	0.247		
Malay	1.18 (0.51, 2.77)	0.696		
Indian	1.73 (0.85, 3.54)	0.130		
Japanese/Korean	3.58 (1.32, 9.68)	0.012		
Others	0.65 (0.24, 1.76)	0.393		
MI/Stroke death	2.78 (1.62, 4.76)	<0.001	2.29 (1.31, 4.00)	0.004
	Diabetes x cohort $p_{interaction}$	0.285		
	Diabetes x etiology $p_{interaction}$	0.544		

CV cardiovascular; MI myocardial infarction; HR hazard ratio; CI confidence interval

Figure 1: Distribution of death based on presence of diabetes in patients with heart failure and reduced ejection fraction

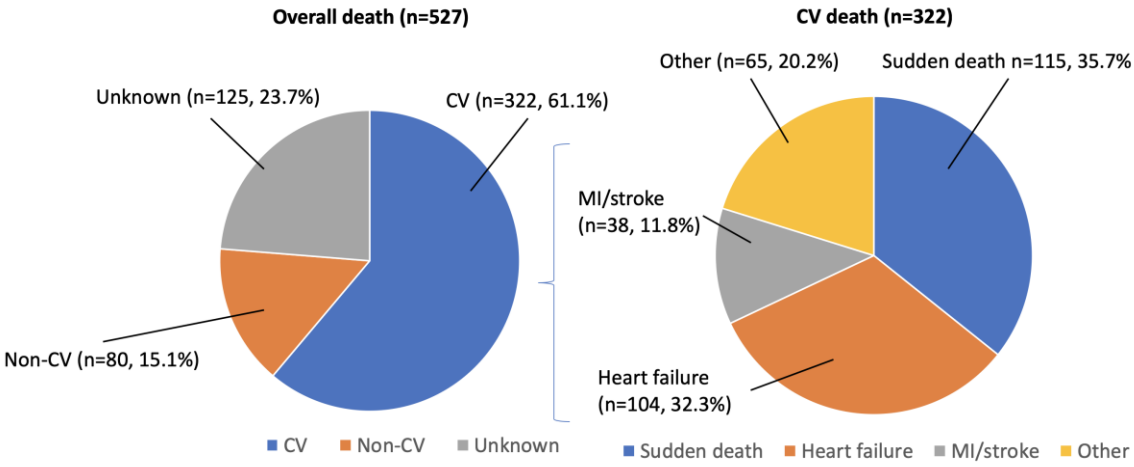


Figure 2A: Kaplan-Meier cause-specific death among patients with diabetes and heart failure with reduced ejection fraction

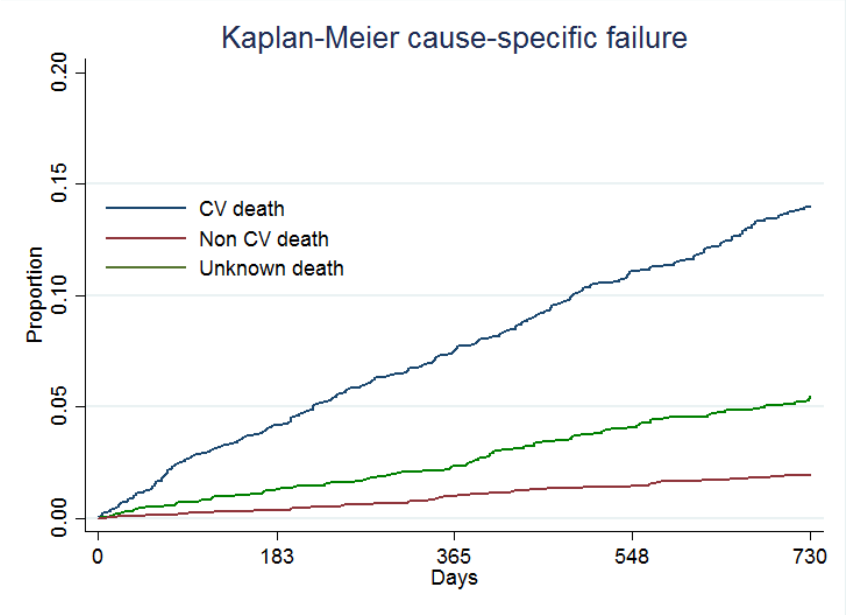
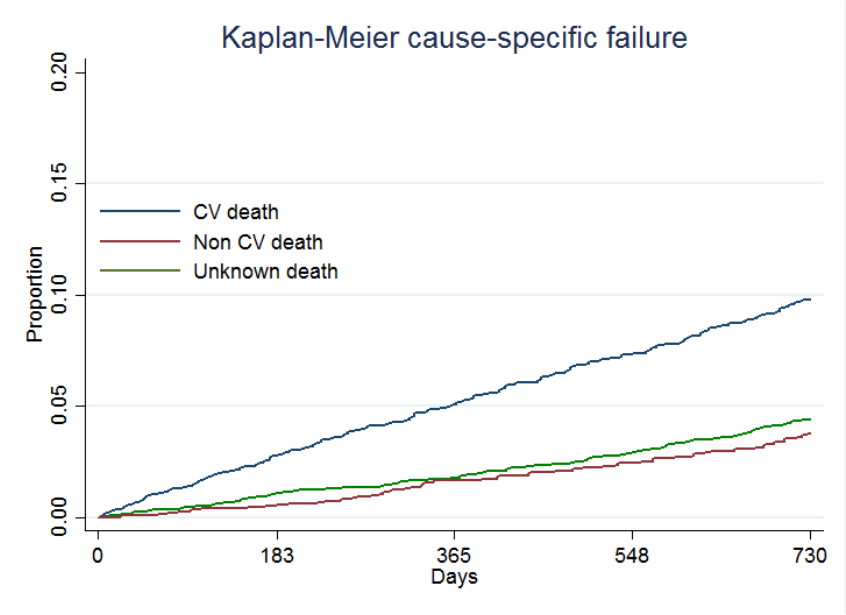


Figure 2B: Kaplan-Meier cause-specific death among patients without diabetes and heart failure with reduced ejection fraction



CHAPTER 5: Implantable Cardioverter-Defibrillators in Patients with Reduced Ejection Fraction and Diabetes

Introduction

As previously shown in this analysis, diabetes is one of the most common co-morbidities among patients with heart failure (HF). Patients with both diabetes and HF, compared to those without diabetes, appear to have significantly different pathophysiologic pathways and a significantly increased risk of HF hospitalization and all-cause death.[6,8,96] HF therapies such as angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, and mineralocorticoid receptor antagonists (MRA) are as effective in patients with diabetes compared with those without diabetes.[97] However, the presence of multiple comorbidities may decrease the survival benefit of implantable cardioverter defibrillator (ICDs).[98,99] Furthermore, while diabetes has been demonstrated to be an independent risk predictor of arrhythmic death and sudden cardiac death (SCD)[81] these patients also have an increased burden of non-arrhythmic death[67,70,82,100,101] which may not be reduced by ICDs. Despite being included in pivotal ICD trials, it is unclear if the presence of diabetes is associated with a reduction in the mortality benefit expected from primary prevention ICD implantation. In addition, diabetes is known to increase the risk of complications such as infections following surgery;[102] however, limited data is available regarding the effect of diabetes on ICD related complications and infections.

To address these knowledge gaps a patient level combined-analysis was conducted of four randomized controlled trials evaluating ICDs for primary prevention in order to assess: 1) outcomes associated with ICDs in addition to medical therapy versus medical

therapy alone among patients with diabetes; 2) the burden of arrhythmic versus non arrhythmic death among patients with diabetes; and 3) whether diabetes is associated with an increased risk of complications associated with ICD implantation.

Methods

Study population

Patient-level data from four major randomized controlled trials of ICDs were analyzed: Multicenter Automatic Defibrillator Implantation Trial I (MADIT I),[60] MADIT II,[61] Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE),[62] and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[63] The amiodarone arm from the SCD-HeFT was excluded. These trials compared ICDs in addition to medical therapy ('ICD group') versus medical therapy alone ('control group'). Inclusion criteria for this analysis were LVEF $\leq$ 35%, time from myocardial infarction to randomization >40 days (where applicable), and availability of data on important covariates. Patients with New York Heart Association (NYHA) functional class IV HF (53 patients in the MADIT II trial) were also excluded. The presence of diabetes was based on the patient and site reported history of diabetes. There were no data available on type of diabetes, duration of diabetes, degree of control of diabetes, or type of anti-diabetic treatment. Trial specific complications included hypotension, syncope, bradycardia or conduction defect, pulmonary embolism, atrial fibrillation, pneumothorax, bleeding, venous thrombosis, problems with a defibrillator lead, defibrillator generator malfunction, myocardial infarction (MI), sustained ventricular tachycardia, ventricular fibrillation, shock (hemodynamic compromise), new or more advanced heart failure, post pericardiotomy syndrome, postoperative infection, renal failure, new or unanticipated

drug therapy, and clinical events requiring surgical correction.

Outcomes

The primary endpoint of this analysis was all-cause death. The secondary endpoints were sudden (arrhythmic) death, non-arrhythmic death, complications of ICD implantation, and appropriate/inappropriate ICD therapies. The definitions of arrhythmic deaths are based on each trial definition of adjudicated arrhythmic death **(Appendix table 1).**

Statistical Methods

Differences in baseline characteristics between patients with and without diabetes were described. Unadjusted all-cause mortality rates were described with Kaplan-Meier survival curves, and differences in survival between patients with ICDs and controls were assessed with log-rank tests for each group (patient with and without diabetes). We fitted Cox-Proportional hazards regression models for all-cause mortality combining data from each trial with a trial-specific random-effect to account for the heterogeneity across trials. In these models, besides including treatment type (ICD versus control) and diabetes status (and an interaction between these two), the following variables were included: age, ejection fraction, sex, NYHA classification, race, QRS duration, presence of coronary artery disease, beta-blocker use, and ACEi use. Twenty-nine patients were removed due to missing variables. In sensitivity analyses we also considered alternative model formulations where trial effects were accounted for with fixed effects model components, but the results were similar and thus were not included in the paper. Appropriate/inappropriate ICD therapies in patients with and without diabetes were

compared using descriptive statistics. We conducted a sensitivity analysis for the outcome of all-cause mortality by including estimated glomerular filtration (eGFR) rate into the adjustment model; this sensitivity analysis did not include the DEFINITE trial as eGFR was not available. Similarly, we also fitted proportional sub-distribution hazard regression models to assess the competing risk of arrhythmic and non-arrhythmic deaths among patients with and without diabetes.[84] We stratified by the presence of ischemia and evaluated the association of diabetes and all-cause mortality. Among patients with ICDs, we also assessed the risk of all-cause death and sudden death (using Cox-proportional hazard models and sub-distribution hazard ratios respectively) among patients with diabetes versus patients without diabetes adjusting for the same variables as described above.

Results

Patient demographics

The final cohort included 3,359 patients **(Figure 1)**. In total, there were 996 patients with diabetes of whom 512 were randomized to ICD with medical therapy and 484 to medical therapy alone. There were also 2,363 patients without diabetes of whom 1,266 were randomized to ICD with medical therapy and 1,097 to medical therapy alone. Compared to those without diabetes (n=2,363), patients with diabetes (n=996), were older, less often white, and had a greater burden of cardiovascular co-morbidities (**Table 1**). Patients with diabetes had higher use of diuretic therapy but equivalent use of ACEi and beta-blockers. Demographics by randomized treatment arm demonstrates similar characteristics **(Appendix table 2).**

Implantable cardioverter defibrillators among patients with diabetes

At 5 years, relative to the number of patients initially enrolled in the study, a greater proportion of patients with diabetes died (46%) compared with those without diabetes (30%). Overall, ICDs were associated with a reduced risk of all-cause death (unadjusted hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.60-0.81; adjusted HR [aHR] 0.68, 95% CI 0.57-0.78). Among patients with diabetes, the ICD was not significantly associated with a reduced risk of all-cause mortality at 5 years (per 100 patient-years; 10.49 with ICD vs. 12.06 without an ICD; unadjusted HR 0.87, 95% CI 0.65-1.18; aHR 0.88, 95% CI 0.69-1.11; **Figure 2A**). In comparison, in patients without diabetes, the ICD significantly reduced the risk of all-cause death (per 100 patient-years; 5.34 with ICD vs 8.78 without an ICD; unadjusted HR 0.61, 95% CI 0.50-0.73; aHR 0.56, 95% CI 0.46-0.67; **Figure 2B**). The presence of diabetes was associated with reduced survival benefit from ICDs (adjusted p-value for interaction between ICD treatment and diabetes in relation to all-cause death: p=0.015). The sensitivity analysis which also adjusted for eGFR did not change these findings (adjusted p-value for interaction between ICD treatment and diabetes in relation to all-cause death: p=0.015).

In the analysis of competing risks of arrhythmic and non-arrhythmic deaths, ICDs were associated with a reduced risk of arrhythmic death among patients with diabetes (per 100 patient-years; 2.34 with ICD vs. 4.36 without an ICD; adjusted subdistribution HR [sHR] 0.51 95% CI 0.33-0.81; p=0.004) as well as those without diabetes (per 100 patient-years; 1.00 with ICD vs. 3.55 without an ICD; adjusted sHR 0.27 95% CI 0.19-0.40; p =0.0001). However, the test for ICD treatment interaction term remained significant (p-value for interaction between ICD treatment and diabetes in relation to

arrhythmic death: p = 0.036). These results indicate a reduced ICD benefit for arrhythmic death among those with diabetes.

The ICD was not associated with a reduced risk of non-arrhythmic death in patients with diabetes (adjusted sHR 1.16 95% CI 0.87-1.53) or without diabetes (adjusted sHR 0.81 95% CI 0.65-1.02). Among patients with ischemic cardiomyopathy, the presence of an ICD was associated with a reduced risk of all-cause mortality in patients without diabetes (aHR 0.59, 95% CI 0.47-0.74) but not among patients with diabetes (aHR 0.76, 95% CI 0.58-1). However, we could not rule out no interaction (p=0.17). A coefficient plot of the variables used in the multivariable analysis is presented as **Figure 3.**

Distribution of arrhythmic and non-arrhythmic death

The rates of deaths from arrhythmic and non-arrhythmic causes were greater in patients with diabetes (**Appendix Figure 1A**) compared with those without diabetes (**Appendix Figure 1B**), across all time points and regardless of the study arm. Overall, among patients with diabetes, 280 patients died (128 [46%] with ICD vs. 152 [54%] with medical therapy alone). Among those without diabetes, 437 died (178 [41%] with ICD vs. 259 [59%] with medical therapy alone). In comparison to patients without diabetes, non-arrhythmic deaths formed a greater proportion of overall death (**Appendix Figure 1A and 1B**). Among patients randomized to receive an ICD, the risk of all-cause death was higher in patients with diabetes compared to patients without diabetes in unadjusted (HR 1.97, 95% CI 1.57-2.47, p<0.001) and adjusted analysis (HR 1.86, 95% CI 1.48-2.34, p<0.001). Similarly, among patients randomized to receive an ICD, the risk of sudden death was higher in patients with diabetes compared to those without diabetes in

unadjusted (sHR 2.16, 95% CI 1.32-3.55, p=0.002) and adjusted analysis (sHR 1.89, 95% CI 1.12-3.16, p=0.016).

Complications of implantable cardioverter defibrillators implantation

Overall, complications related to ICD implantation occurred in 79 (17%) patients with diabetes versus 230 (21%) patients without diabetes. In addition, only 9 patients (2%) with diabetes had an ICD infection compared with 25 patients (2%) without diabetes.

Appropriate and inappropriate implantable cardioverter defibrillator therapies

Data for appropriate and inappropriate shocks were available from the MADIT II and SCD-HeFT. Among patients with diabetes, there were 454 patients with at least 1 shock: of these, 81 (18%) patients had at least one appropriate shock and 373 (82%) patients had at least one inappropriate shock. In patients without diabetes, 1,009 patients had at least 1 shock: of these, 204 (20%) patients had at least one appropriate shocks and 805 (80%) patients had at least one inappropriate shocks. There was no significant difference in the proportion of appropriate and in-appropriate shocks between patients with and those without diabetes (p=0.32). In the MADIT II and SCD-HeFT trials, for patients without diabetes, the average number of appropriate shocks was 1.08 (standard deviation [SD]: 2.75; range: 0 – 33), while for patients with diabetes, the average is 0.83 (SD: 2.39; range: 0-27). For the inappropriate shocks, the average was 0.61 for patients without diabetes (SD: 1.70; range: 0- 16); and among patients with diabetes, the average was 0.52 (SD: 1.55; range 0-11).

Conclusion

Among patients with HF and diabetes, primary prevention ICDs in combination with medical therapy versus medical therapy alone was not significantly associated with a reduced risk of all-cause death but was associated with a reduction in the risk of sudden death. Further studies are needed to evaluate the effectiveness of ICDs among patients with diabetes.

Tables and Figures

Table 1: Baseline characteristics based on randomized treatment.

	No diabetes N= 2,363		Diabetes N=996	
	Control N= 1,097	ICD N= 1,266	Control N=484	ICD N=512
Age. Mean [SD]	60 [12]	61 [12]	62 [10]	62 [12]
Female. n (%)	220 (20)	251 (20)	101 (21)	108 (21)
White. n (%)	878 (80)	1048 (83)	363 (75)	388 (76)
Black. n (%)	161 (15)	173 (14)	79 (16)	92 (18)
Other. n (%)	58 (5)	45 (3)	42 (9)	32 (6)
LVEF %. Mean [SD]	23 [6]	23 [6]	24 [6]	24 [6]
NYHA scores. n (%)				
NYHA 1	184 (17)	257 (20)	64 (13)	79 (16)
NYHA 2	655 (60)	679 (54)	259 (54)	272 (53)
NYHA 3	253 (23)	326 (26)	159 (33)	158 (31)
Comorbidities				
Atrial Fibrillation. n (%)	79 (11)	89 (12)	24 (8)	22 (8)
Ischemic heart disease. n (%)	631 (58)	789 (62)	329 (68)	362 (71)
Prior CABG. n (%)	334 (36)	429 (39)	184 (43)	219 (48)
Prior PCI. n (%)	258 (28)	333 (31)	135 (31)	149 (33)
Hypertension. n (%)	439 (48)	518 (48)	284 (66)	305 (67)
Prior MI. n (%)	595 (54)	751 (59)	305 (63)	338 (66)
Heart failure. n (%)	637 (58)	839 (66)	286 (59)	338 (66)
Smoking. n (%)	895 (82)	979 (78)	378 (78)	399 (78)
Medication				
ACEi. n (%)	960 (88)	1078 (85)	432 (89)	428 (84)
Beta blockers. n (%)	707 (64)	846 (67)	331 (68)	351 (69)
Diuretics. n (%)	858 (78)	961 (76)	420 (87)	445 (87)
Anti-arrhythmic use. n (%)	60 (5)	28 (2)	8 (2)	9 (2)
Laboratory values				
Creatinine (mg/dl) [SD]	1.2 [0.5]	1.2 [0.4]	1.3 [0.5]	1.3 [0.5]
BUN (mg/dl) [SD]	21 [11]	21 [11]	26 [13]	26 [14]
Sodium (mmol/l) [SD]	139 [3]	139 [3]	139 [3]	138 [4]

Electrocardiogram				
LBBB n (%)	181 (20)	219 (21)	80 (19)	85 (19)
QRS Duration (milliseconds) [SD]	119 [30]	121 [32]	120 [31]	119 [31]

(n) denotes %. [n] denotes standard deviation. LVEF left ventricular ejection fraction; NYHA New York Heart Association; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; MI myocardial infarction; ACEi angiotensin converting enzyme inhibitor; BUN blood urea nitrogen; LBBB left bundle branch block.

Figure 1: Study population

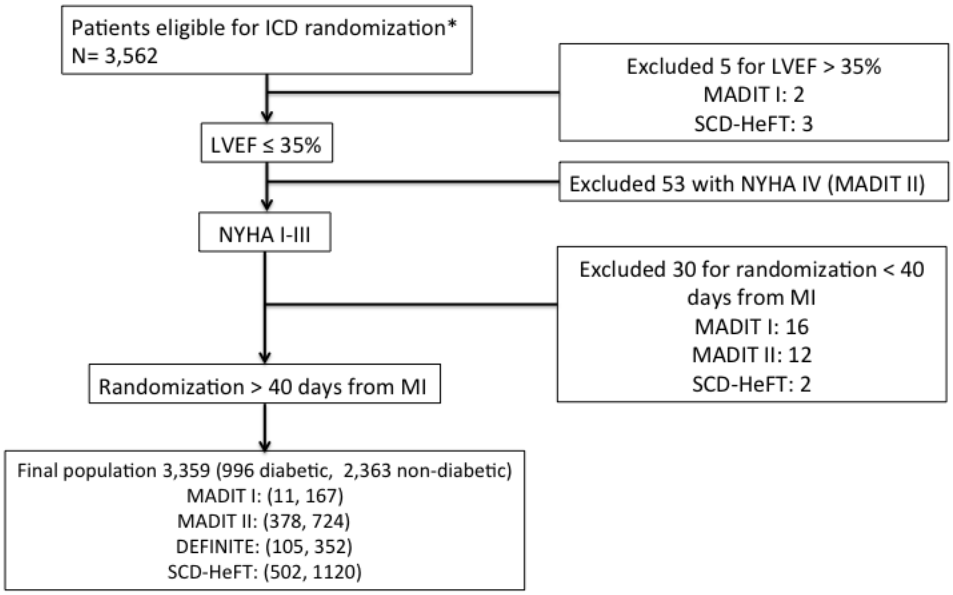
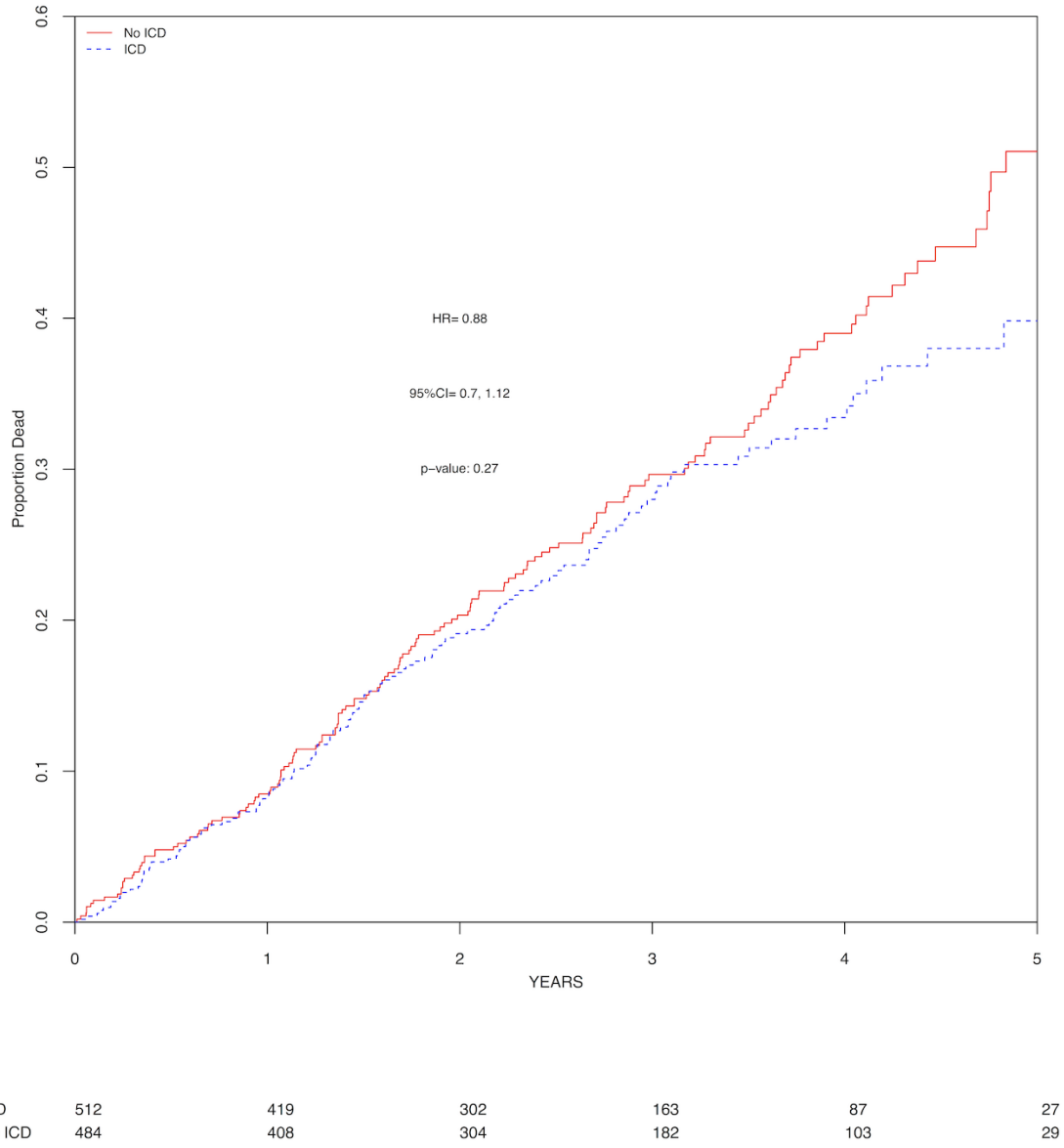
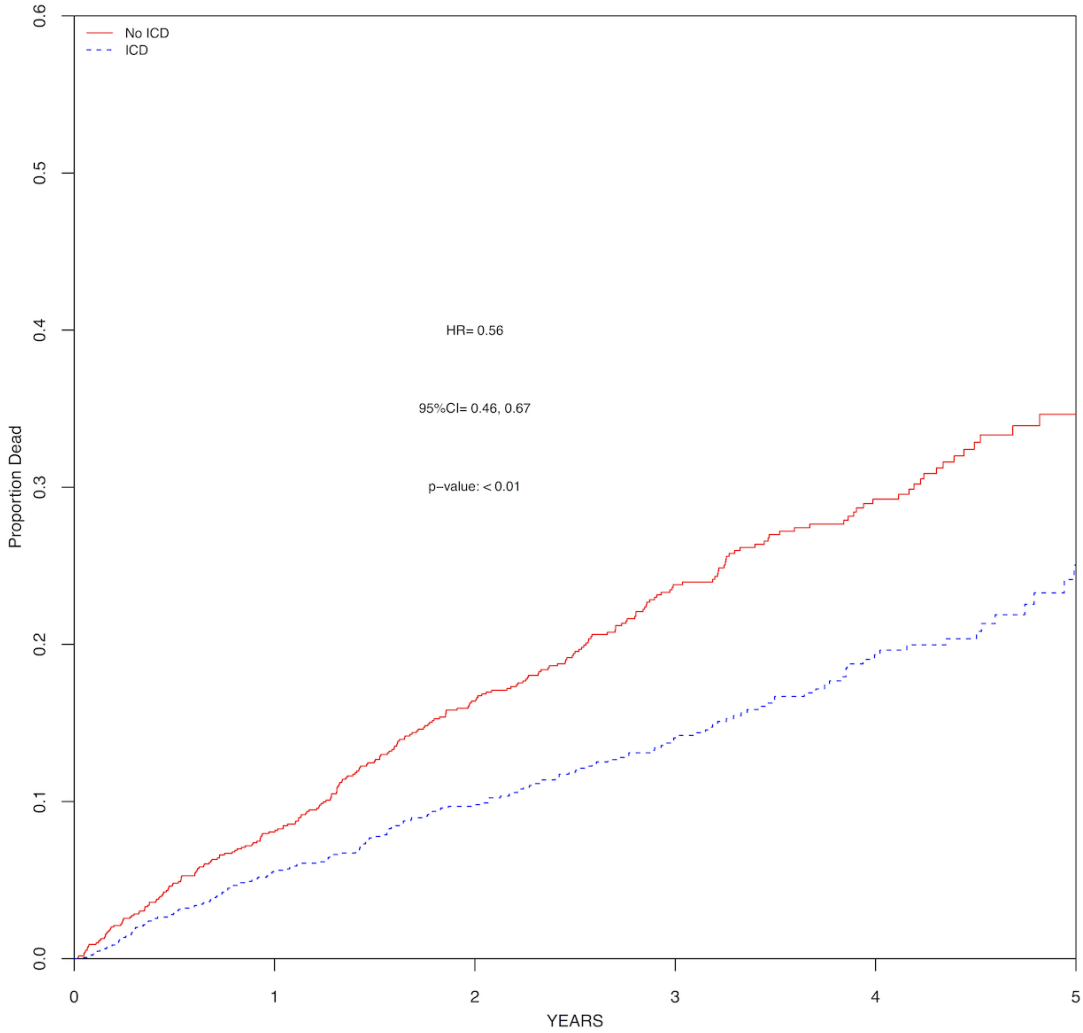


Figure 2A: Association between implantable cardioverter defibrillator randomization and all-cause death among patients with diabetes



Caption: Hazard ratio (HR) represent adjusted hazard ratio; CI confidence interval; ICD implantable cardioverter-defibrillators. Numbers reflects patients at risk.

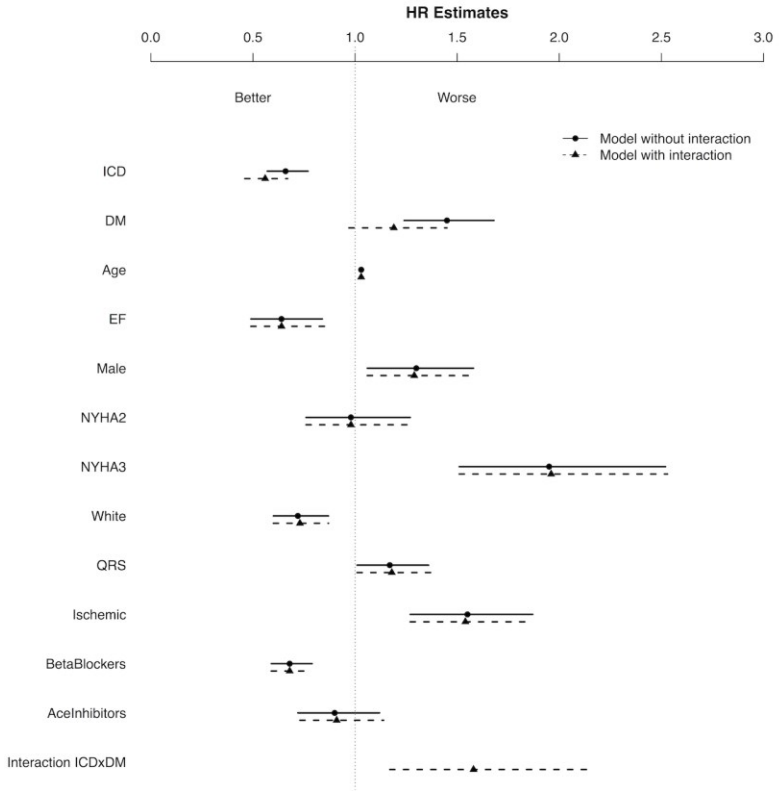
Figure 2B: Association between implantable cardioverter defibrillator randomization and all-cause death among patients without diabetes



ICD	1266	1065	837	526	275	81
No ICD	1097	932	728	463	245	61

Caption: Hazard ratio (HR) represent adjusted hazard ratio; CI confidence interval; ICD implantable cardioverter-defibrillators Numbers reflects patients at risk.

Figure 3: Coefficient plot of variables used in the multivariable analysis for the outcome of all-cause mortality



Caption: ICD implantable cardioverter defibrillator; DM diabetes mellitus; EF ejection fraction; NYHA New York Heart Association functional classification; HR hazard ratio

CHAPTER 6: Comparative effectiveness of primary prevention implantable cardioverter-defibrillators in older heart failure patients with diabetes

Introduction

Among patients with HF and a reduced ejection fraction (HFrEF), diabetes has emerged as one of the most common non-CV comorbidities.[103,74,104] Patients with diabetes and HF, compared to those without diabetes, have a higher risk of all cause and cardiovascular mortality.[6] Among patients with diabetes, HF events including heart failure death form a significant burden of all-cause mortality.[85] There are different underlying pathophysiologic pathways involving inflammation, fibrosis, and that influence disease progression amongst patients with diabetes and HF compared to those without diabetes.[96,87] Patients with diabetes appear to have an increased risk of sudden death which may potentially be modified by the implantation of a primary prevention ICD.[105] HF guidelines recommend the use of primary prevention ICDs among eligible HFrEF patients with comorbidities including diabetes.[106,40] A prior analysis suggested that among those who received an ICD, compared to medical therapy alone, all-cause mortality was not reduced among patients with diabetes and HFrEF.[105] Furthermore there is a high burden of competing risk among patients with HF which may suggests that some patients derive less benefit from primary prevention ICDs.[107,108] A recent study has suggested among patients who have nonischemic HFrEF, an ICD on top of medical therapy, compared to medical therapy alone, may not significantly reduce the risk of all-cause mortality, particularly in the subgroup older than 70 years of age.[109] These results suggest that certain populations of patients with HFrEF may not have significant benefit from an ICD.

We aim to assess the real-world comparative effectiveness of ICD implantation among patients aged 65 years or older with and without diabetes who have HFrEF in the U.S. Get With The Guidelines Heart Failure (GWTG-HF) registry.

Methods

Source of Data

Data for this analysis were obtained from the GWTG-HF registry linked with Centers for Medicare & Medicaid Services (CMS) claims data. Details regarding the GWTG-HF registry have been previously described. Briefly, starting in 2000, the GWTG-HF has been a voluntary U.S. hospital-based quality improvement initiative.[110] All institutions participating in the GWTG-HF registry are required to comply with local regulatory guidelines and, if required, to secure institutional review board approval. Quintiles (Cambridge, MA), serves as the data collection and coordination center for the GWTG-HF registry. The Duke Clinical Research Institute (DCRI, Durham, NC) is the data analysis center. Patient demographic and clinical characteristics including comorbidities, therapies and interventions are collected prospectively through the GWTG-HF registry. Data related to ICD therapy for each hospitalization include whether an ICD was present at admission, implanted during the index hospitalization, or planned post hospital discharge. Data on contraindications to ICD therapy, and any reason documented by a physician for not implanting or prescribing an ICD are also collected. CMS data include Part A inpatient claims and the corresponding denominator files from 2005 through 2014. We linked the registry data to CMS claims data using a validated method that uses combinations of indirect identifiers.[79]

Study Population

For this analysis, the group of interest included patients with and without diabetes in the GWTG-HF registry who were 65 years of age or older and who were linked to CMS data (n = 293,937 from 787 sites). We excluded patients who died during hospital admission (n=4,468); received comfort care only (n=5,897); were not discharged to home (n=4,386); had missing left ventricular ejection fraction (LVEF) data (n= 15,846); had an LVEF >35% (n=61,852); already had ICD at admission (n=5,031); or had a contraindication to ICD [HF diagnosis not predating the current index admission, recent myocardial infarction (MI; within 40 days) or coronary revascularization (percutaneous coronary intervention or CABG within 90 days), class IV HF symptoms, or no reasonable expectation of survival to one year; n=5,534); and those who received cardiac resynchronization therapy (CRT) (n=4,883). Records of subsequent hospitalizations were also excluded (n=716). Patients who received CRT were excluded due to the challenges in distinguishing benefit from ICDs. After these exclusions the final study population included 17,186 patients (6,683 with diabetes; 39%) from 410 hospital sites. Patients were considered to have an ICD if they either received an ICD during the index hospitalization or were prescribed an ICD at discharge. Among the remaining CMS patients, 1,677 patients received or were prescribed an ICD (663 had diabetes; 39%). This group made up the ICD population to whom non-ICD patients were matched.

Endpoints

The primary endpoint of interest was all-cause mortality as determined from the Medicare denominator file. Patients with no record of death in the denominator file were

considered alive as of 12/31/2014 or the date at which the patient was no longer enrolled in Part A & Part B fee-for-service Medicare, whichever came first.

Statistical analysis

Baseline characteristics, comorbidities, laboratory data, were assessed overall and by treatment group. Differences between groups were tested using a chi-square or Fisher's exact test. We presented continuous variables as medians with 25th and 75th percentiles for continuous variables, and difference between groups were tested using the Wilcoxon Rank Sum Test.

We used multivariable Cox proportional hazards models to compare the effectiveness of ICD vs No-ICD on all-cause mortality among patients with diabetes. A similar analysis was conducted among patients without diabetes. The variables selected are based or prior models derived from the GWTG-HF registry.[111,112]

We used a Cox proportional model with propensity score matching approach to control for potential selection bias. First, a logistic regression model was used to assign a propensity of treatment selection to each patient based on the distribution of a defined set of covariate. Case and control were matched in a 1:3 ratio and balance of baseline characteristics before and after matching was checked. A caliper width of 0.25*(standard deviation of the logit) was used. For a given ICD patient, all no-ICD patients were considered whose logit differed from the ICD patient's logit by less than the caliper width; among these patients, the non-ICD patient with the shortest Mahalanobis distance from the ICD patient were selected as the match. Variables used in calculating Mahalanobis distance were all significant predictors from the propensity model. If there were no non-ICD patients that could be matched within the caliper width, the ICD patient

was omitted. After that, the Cox proportional hazard regression was run and hazard ratios (HR) of the two treatment groups were reported, along with its corresponding p-value and 95% confidence interval. Multivariable adjustment of the covariates in the Cox proportional hazards model was conducted using standard patient-level clinical covariates including systolic/diastolic arterial pressure and demographic features, category of HF (preserved EF/depressed EF), serum creatinine, drugs at discharge, composite performance measures (heart failure all or none measure), and hospital-level variables. The impact of age on modifying the association between ICD and mortality was assessed in patients with and without diabetes through an interaction term between ICD and age.

Co-linearity between the predictor variables in the final model was assessed by using variance inflation factors (VIF). Large VIF values (VIF>5) between variables were examined. If there was evidence of strong correlation between two covariates, one was dropped from the model. Multiple imputations were used for missing adjustment values (**Appendix Table 1**). Hospital characteristics were not imputed. If a patient had missing medical history, it was assumed that the medical condition did not occur. If variables have a missing rate of >50%, they were not included in the model. Differences were declared to be statistically significant at $p < .05$, and all statistical tests were 2-sided. For all analyses, SAS version 9.2 (SAS Institute, Cary NC) was used.

Results

Baseline demographics

The unmatched baseline characteristics of patients with diabetes and HFrEF (n=6,540) who have received or were prescribed an ICD (n=646) compared to those

without an ICD (n=5,894) are shown in table 1. Patients with an ICD, compared to those without an ICD, were younger (70.0 versus 78.0 years of age), are more likely to be male (66.3% versus 55.7%), and have a reduced burden of some comorbidities including anemia (11.9% versus 18.3%), prior stroke or TIA (14.9% versus 17.4%), depression (7.0% versus 10.3%), peripheral vascular disease (13.6% versus 16.8%), and renal insufficiency (serum creatinine greater than 2.0 mg per deciliter; 18.6% versus 23.6%). Patients with an ICD were more likely to have a history of coronary artery disease (67.8% vs 60.4%) and prior myocardial infarction (28.6% versus 24.1%). Patients with an ICD also had a lower LVEF (EF 25.0% versus 27.0%). Patients with an ICD were also more likely to be hospitalized at a teaching center (70.3% versus 58.0%). Similar trends are seen for patients without diabetes (**Table 1**). After propensity matching, differences between the 2 groups were balanced (**Table 2, Figure 1**). The absolute standardized difference on all variables was less than 10% in both patients with and without diabetes.

Association of ICD implantation and outcomes

Patients with diabetes

The median follow-up in this analysis amongst patients with diabetes with an ICD was 5.4 years and among patients without an ICD was 4.5 years. Death was censored at five years. The death rate among patients with diabetes and an ICD was 54.4% (cumulative incidence rate 68.1%). The death rate among patients with diabetes who did not have an ICD was 60.0% (cumulative incidence rate 75.1%). After propensity matching, ICD implantation or prescription, compared to those without an ICD, was associated with a reduced risk of all-cause mortality (unadjusted HR 0.77; 95% CI 0.67-

0.85; p <0.0001; **Table 3**). After multivariable adjustment the association remained unchanged (adjusted HR 0.74; 95% CI 0.65- 0.83; p<0.0001; **Figure 2A**).

Patients without diabetes

The median follow-up amongst patients without diabetes with an ICD was 6.0 years and without an ICD was 4.6 years. Death was censored at five years. The death rate among patients without diabetes and an ICD was 47.3% (cumulative incidence rate 57.2%). The death rate among patients without diabetes who did not have an ICD was 57.0% (cumulative incidence rate 70.3%). After propensity matching, ICD implantation or prescription among, compared to those without an ICD, was associated with a reduced risk of all-cause mortality (unadjusted HR 0.67; 95% CI 0.61 to 0.74; p<0.0001; table 3). After multivariable adjustment the association remained unchanged (adjusted HR 0.68; 95% CI 0.61 to 0.75; p<0.0001 **Figure 2B**). An interaction analysis demonstrated that the relationship between an ICD and all-cause mortality was not modified by the presence of diabetes (p=0.28).

Sensitivity analysis

A sensitivity analysis was conducted where patients with an ICD were defined as only those who received an ICD previously or during the index hospitalization, but not those prescribed. Overall, ICDs, compared to those without an ICD, were associated with a reduced risk of all-cause mortality (**Table 4**).

Impact of ischemia and age on the association between ICDs and all-cause mortality

A history of ischemic heart disease did not modify the association between an ICD and all-cause mortality in patients with diabetes (p=0.53) or patients without diabetes (p=0.97). Furthermore, we did not find the interaction effect between age and ICD to be significant in either groups (*p*-value=0.22 in patients with diabetes, *p*-value=0.15 in patients without diabetes).

Conclusion

Primary prevention ICD implantation among older patients with HFrEF and diabetes was associated with a reduced risk of all-cause mortality. This analysis supports current guideline recommendations for implantation of primary prevention ICDs among older patients with diabetes and HFrEF.

Tables and Figures

Table 1: Unmatched baseline characteristics

	With Diabetes			Without Diabetes		
Demographics	Overall (N=6540)	ICD (N=646)	No ICD (N=5894)	Overall (N=10646)	ICD (N=1031)	No ICD (N=9615)
Median Age in years	77.0	74.0	78.0	81.0	76.0	82.0
Male (n, %)	3712 (56.8)	428 (66.3)	3284 (55.7)	5884 (55.3)	704 (68.3)	5180 (53.9)
Race (n, %)						
Asian	314 (4.8)	29 (4.5)	285 (4.8)	437 (4.1)	50 (4.8)	387 (4.0)
Hispanic (any race)	476 (7.3)	47(7.3)	429 (7.3)	427 (4.0)	38 (3.7)	389 (4.0)
Black	925 (14.1)	104(16.1)	8241 (13.9)	1170 (11.0)	109 (10.6)	1061 (11.0)
White	4713 (72.1)	459 (71.1)	4254 (72.2)	8432 (79.2)	823 (79.8)	7609 (79.1)
Missing	1.7	7 (1.1)	105 (1.8)	180 (1.7)	11 (1.1)	169 (1.8)
Median Ejection fraction (%)	27.0	25.0	27.0	25.0	25.0	26.0
Baseline Medical History (n, %)						
Anemia	1155 (17.7)	77 (11.9)	1078 (18.3)	1408 (13.2)	90 (8.7)	1318 (13.7)
Coronary disease	3996 (61.1)	438 (67.8)	3558 (60.4)	5434 (51.0)	584 (56.6)	4850 (50.4)
COPD or asthma	1743 (26.7)	167 (25.9)	1576 (26.7)	25851 (24.2)	241 (23.4)	2340 (24.3)
CVA/TIA	1123 (17.2)	96 (14.9)	1027 (17.4)	1469 (13.8)	126 (12.2)	1343 (14.0)
Depression	652 (10.0)	45 (7.0)	607 (10.3)	810 (7.6)	750 (7.8)	750 (7.8)
Previous MI	1604 (24.5)	185 (28.6)	1419 (24.1)	2121 (19.9)	289 (28.0)	1832 (19.1)
Peripheral vascular	1078 (16.5)	88 (13.6)	990 (16.8)	1059 (9.9)	84 (8.1)	975 (10.1)

disease						
Prior heart failure	3925 (60.0)	395 (61.1)	3530 (59.9)	6046 (56.8)	615 (59.7)	5431 (56.5)
Hyperlipidemia	3606 (55.1)	395 (61.1)	2311 (54.5)	4317 (40.6)	490 (47.5)	3827 (39.8)
Hypertension	5266 (80.5)	517 (80.0)	4749 (80.6)	7307 (68.6)	696 (67.5)	6611 (68.8)
Renal Insufficiency (SCr>2 mg/dl)	1511 (23.1)	120 (18.6)	1391 (23.6)	1626 (15.3)	146 (14.2)	1480 (15.4)
Patient Labs at admission						
Median Sodium (mEq/L)*	138.0	138.0	138.0	138.0	139.0	138.0
Median BUN (mg/dL)*	27.0	25.0	28.0	24.0	23.0	24.0
Median Serum creatinine (mg/dL)	1.4	1.3	1.4	1.3	1.3	1.3
Median BNP (pg/mL)	1130.0	967.5	1150.0	1290.0	1113.0	1306.0
Median Hemoglobin (g/dL	11.9	12.5	11.9	12.4	12.9	12.3
Medications at discharge (n, %)						
ACE inhibitors	3551 (54.3)	395 (61.1)	3156 (53.5)	6010 (56.5)	605(58.7)	5405 (56.2)
ASA	3608 (55.2)	375 (58.0)	3233 (54.9)	5387 (50.6)	584 (56.6)	4803 (50.0)
ARB	1088 (16.6)	132 (20.4)	956 (16.2)	9154 (86.0)	189 (18.3)	1342 (14.0)
Beta Blocker	5723 (87.5)	587 (90.9)	5136 (87.1)	9154 (86.0)	925 (89.7)	8229 (85.6)
Aldosterone Antagonist	1406 (21.5)	172 (26.6)	1234 (20.9)	2251 (21.1)	262 (25.4)	1989 (20.7)
Hospital Characteristics (n, %)						

Hospital type (teaching)	3871 (59.2)	454 (70.3)	3417 (58.0)	6148 (57.7)	738 (71.6)	5410 (56.3)

Table 2: Baseline characteristics after 1:3 matching

	With Diabetes			Without diabetes		
	Overall (N=2562)	ICD (N=649)	No ICD (N=1913)	Overall (N=4158)	ICD (N=1033)	No ICD (N=3125)
Demographics						
Median Age (Years)	2562 (74.0)	649 (74.0)	1913 (73.0)	4158 (76.0)	1033 (76.0)	3125 (76.0)
Male (n, %)	1686 (65.8)	430 (66.3)	1256 (65.7)	2845 (8.4)	705 (8.2)	2140 (68.5)
Race (n, %)						
Asian	119 (4.6)	28 (4.3)	91 (4.8)	172 (4.1)	50 (4.8)	122 (3.9)
Hispanic (any race)	175 (6.8)	47 (7.2)	128 (6.7)	187 (4.5)	38 (3.7)	149 (4.8)
Black	414 (16.2)	104 (16.0)	310 (16.2)	461 (11.1)	109 (10.6)	352 (11.3)
White	1812 (70.7)	463 (71.3)	1349 (70.5)	3279 (78.9)	825 (79.9)	2454(78.5)
Missing	42 (1.6)	7 (1.1)	35 (1.8)	59 (1.4)	11 (1.1)	48 (1.5)
Median Ejection fraction (%)	25.0	25.0	25.0	25.0	25.0	25.0
Baseline Medical History (n, %)						
Anemia	316 (12.3)	77 (11.9)	239 (12.5)	362 (8.7)	90 (8.7)	272 (8.7)
Coronary disease	1695 (66.2)	438 (67.5)	1257 (65.7)	2373 (57.1)	585 (56.6)	1788 (57.2)
COPD or asthma	665 (26.0)	169 (26.0)	496 (25.9)	987 (23.7)	243 (23.5)	744 (23.8)
CVA/TIA	411 (16.0)	98 (15.1)	313 (16.4)	529 (2.7)	127 (12.3)	402 (12.9)
Depression	226 (8.8)	45 (6.9)	181 (9.5)	283 (6.8)	60 (5.8)	223 (7.1)
Previous MI	701 (27.4)	185 (28.5)	516 (27.0)	995 (23.0)	291 (28.2)	664 (21.2)
Peripheral vascular disease	404 (15.8)	89 (13.7)	315 (16.5)	430 (10.3)	84 (8.1)	346 (11.1)
Prior heart failure	1571 (61.3)	399 (61.5)	1172 (61.3)	2453(59.0)	617(59.7)	1836 (58.8)
Hyperlipidemia	1487 (58.0)	396 (61.0)	1091 (57.0)	1787 (43.0)	493 (47.7)	1294 (41.4)

Hypertension	2049 (80.0)	518 (79.8)	1531 ()0.0	2832 (68.1)	701 (67.9)	2131(68.2)
Renal Insufficiency (SCr>2 mg/dL)	502 (19.6)	122 (8.8)	380 (19.9)	624 (15.0)	149 (14.4)	475 (15.2)
Patient Labs at admission						
Median Sodium (mEq/L)	138.0	138.0	138.0	139.0	139.0	139.0
Median BUN (mg/dL)	26.0	25.0	26.0	23.0	23.0	23.0
Median Serum creatinine (mg/dL)	1.3	1.3	1.3	1.3	1.3	1.3
Median BNP (pg/mL)	1037.0	967.5	1047.0	1210.0	1119.5	1220.0
Median Hemoglobin (g/dL)	12.2	12.4	12.1	12.7	12.9	12.6
Median Potassium (mEq/L)	4.2	4.2	4.3	4.1	4.2	4.1
Medications at discharge						
ACE inhibitors	1591 (62.1)	397 (61.2)	1194 (62.4)	2545 (61.)2	604 (58.5)	1941 (62.1)
ASA	1499 (58.5)	378 (58.2)	1121 (58.6)	2329 (56.0)	587 (56.8)	1742 (55.7)
ARB	467 (18.2)	132 (20.3)	335 (17.5)	597 (14.4)	190 (18.4)	407 (3.0)
Beta Blocker	2318 (90.5)	588 (90.6)	1730 (90.4)	3718 (89.4)	926 (89.6)	2792 (89.3)
Aldosterone Antagonist	624 (24.4)	173 (26.7)	451 (23.6)	969 (23.3)	26 3 (25.5)	706 (22.6)
Hospital Characteristics						
Hospital type (teaching)	1794 (70.0)	465 (70.3)	1338 (69.9)	2945 (70.8)	742 (71.8)	2203 (70.5)

Table 3: Risk of all-cause mortality associated with ICD implantation or prescription

Patients With Diabetes					
Raw Mortality Rate (%)		Cumulative Incidence Rate (%)		Unadjusted Hazard Ratio, (95% CI); p value	Adjusted Hazard Ratio, (95% CI); p value
ICD	No-ICD	ICD	No-ICD		
54.4	60.0	68.1	75.1	HR 0.77, (0.67-0.85); p < 0.0001	HR 0.74, (0.65- 0.83); p< 0.0001
Patients Without Diabetes					
Raw Mortality Rate (%)		Cumulative Incidence Rate (%)		Unadjusted Hazard Ratio, (95% CI); p value	Adjusted Hazard Ratio, (95% CI); p value
ICD	No-ICD	ICD	No-ICD		
47.4	57.0	57.2	70.3	HR 0.67, (0.61-0.74); p< 0.0001	HR 0.68, (0.61- 0.75); p< 0.0001
Adjusted interaction p-value between diabetes and ICD implantation for all-cause mortality					P=0.28

Table 4: A sensitivity analysis with ICD defined as previous ICD implantation or implanted during index hospitalization

Patients With Diabetes					
Raw Mortality Rate (%)		Cumulative Incidence Rate (%)		Unadjusted Hazard Ratio, (95% CI); p value	Adjusted Hazard Ratio, (95% CI); p value
ICD	No-ICD	ICD	No-ICD		
54.8	60.0	62.9	75.1	HR 0.65, (0.56-0.76); p<0.0001	HR 0.64 (0.55-0.74); p<0.0001
Patients Without Diabetes					
Raw Mortality Rate (%)		Cumulative Incidence Rate (%)		Unadjusted Hazard Ratio, (95% CI); p value	Adjusted Hazard Ratio, (95% CI); p value
ICD	No-ICD	ICD	No-ICD		
43.7	57.0	51.0	70.3	HR 0.54, (0.47-0.62); p<0.0001	HR 0.58, (0.51-0.66); p<0.0001
Adjusted interaction p-value between diabetes and ICD implantation for all-cause mortality					P=0.28

Figure 1A: Standardized difference of patient characteristics (with diabetes) before and after propensity matching

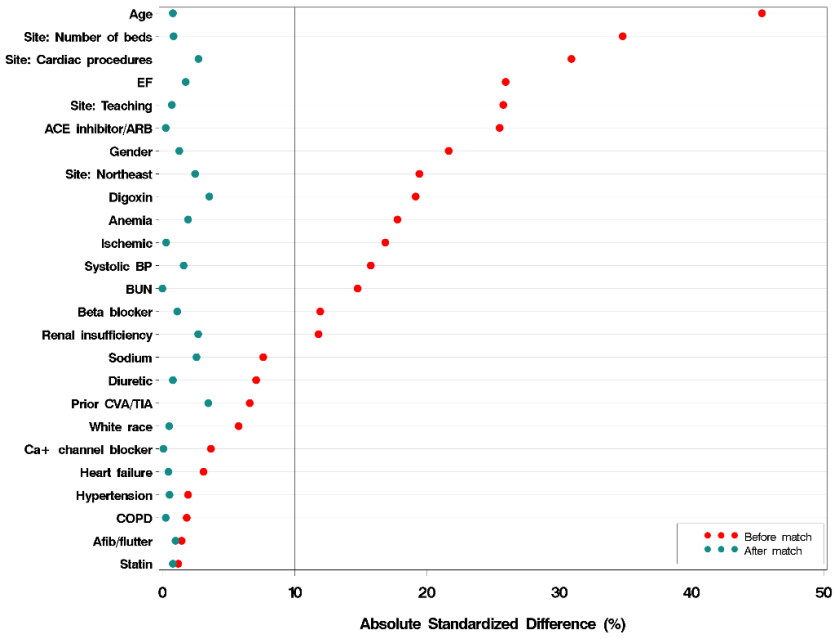


Figure 1B: Standardized difference of patient characteristics (without diabetes) before and after propensity matching

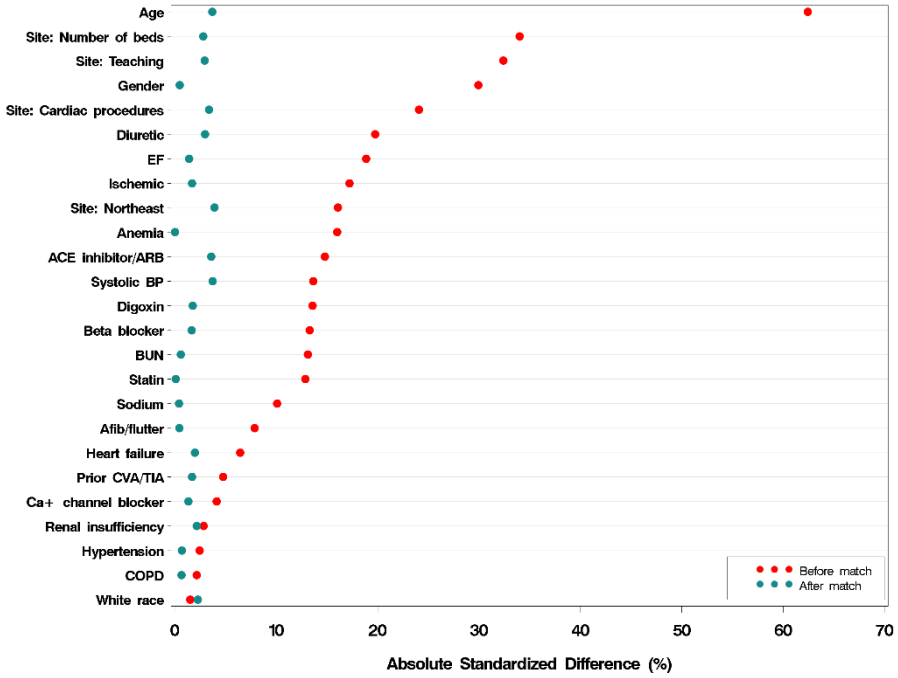


Figure 2A: Kaplan-Meyer curves for the incidences of survival among patients with diabetes

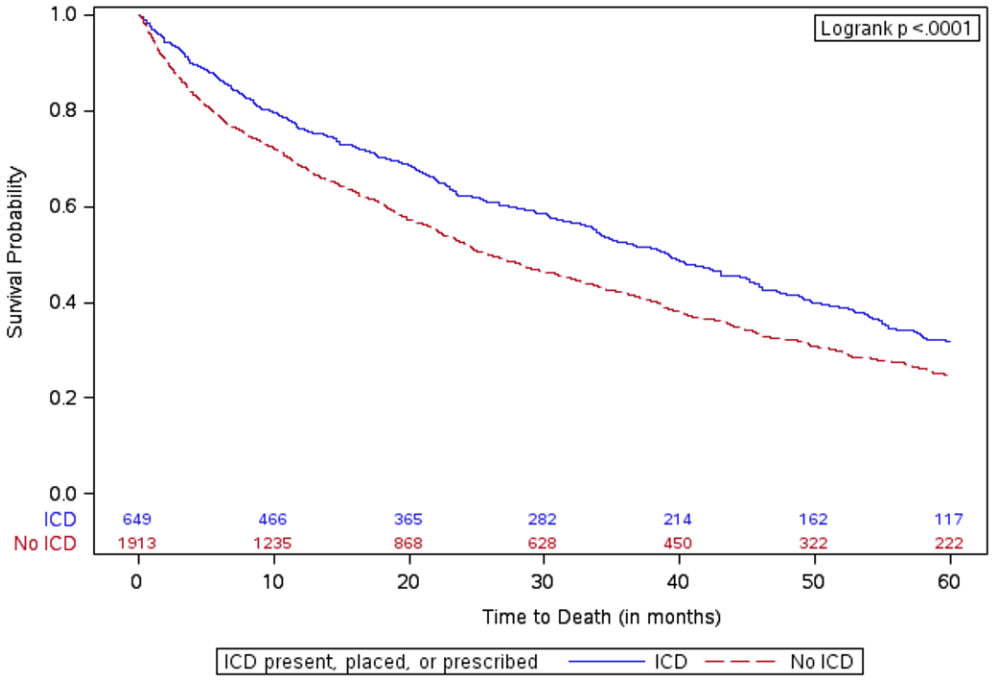
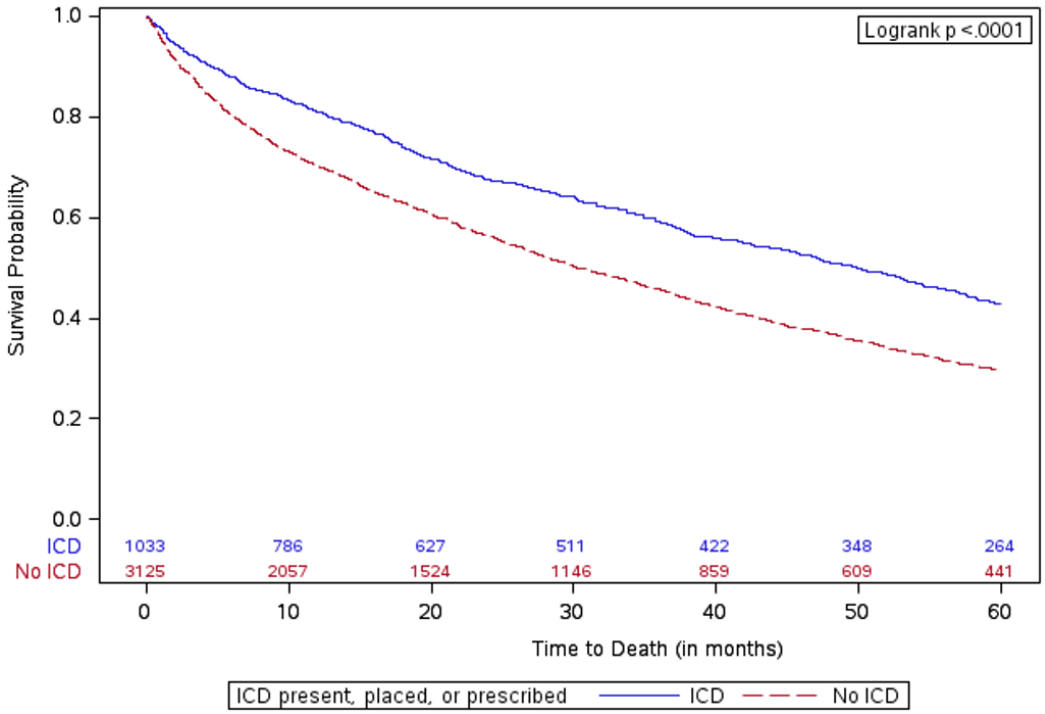


Figure 2B: Kaplan-Meyer curves for the incidences of survival among patients without diabetes



CHAPTER 7: Discussion

The primary aim of this thesis was to address the following knowledge gaps: 1) among patient admitted in hospital with HF, what are the major non-cardiovascular (CV) comorbidities, including diabetes, and have these comorbidities been increasing over time; 2) describe the specific causes of death among patients with diabetes and established atherosclerotic CV disease; 3) describe the specific causes of death among patients with diabetes and established HFrEF; 4) evaluate the comparative effectiveness of implantation of a primary prevention ICD compared to medical therapy to reduce the risk of all-cause death and sudden death among patients with diabetes and HFrEF.

Trends of non-cardiovascular comorbidities including diabetes over time

The prevalence of non-CV comorbidities and the association of number non-CV comorbidities with length of stay, in-hospital mortality, and 30-day mortality among patients enrolled in the GWTG-HF registry who were admitted in hospital for HF was assessed. This analysis identified the following major findings: 1) Patients admitted to hospital with HF have a large burden of non-CV comorbidities; 2) From 2005-2014, there has been a decline in the number of patients with 0 or 1 non-CV comorbidity and an increase in the number of patients with ≥ 3 non-CV comorbidities; 3) patients with a greater number of non-CV comorbidities have increased risk of longer hospital length of stay, in-hospital mortality, and 30-day readmission and mortality.

This analysis aligns with prior studies in chronic stable populations which have identified that patients with HF have a large burden of non-CV comorbidities. In a study using data from 1999 of 122,630 older U.S. Medicare patients, nearly 40% of patients with HF had five or more non-CV comorbidities and over 80% of all in-hospital days are attributed to this patient group.[76] Among 3,226 outpatients with chronic HF in the ESC

HF Pilot Survey, 26% had no co-morbidity, 30% had one co-morbidity, 23% had two co-morbidities, and 43% had two or more co-morbidities.[77] The present analysis extends on prior work evaluating comorbidities in patients with HF by evaluating trends over a decade and across a nationwide sample of hospitals in the US. Utilizing the GWTG-HF registry enables a simultaneous evaluation of both in-hospital and post-discharge outcomes. Among patients with a greater number of non-CV comorbidities, this analysis demonstrated a greater length of stay and decreased risk of being discharged home combined with an increased risk of 30-day all cause rehospitalization, 30-day HF rehospitalization, and 30-day mortality. This evaluation of outcomes across multiple stages of a patients journey, both during and after a HF hospitalization, reflects the how the burden of non-cardiovascular co-morbidities may significantly influence the trajectories of outcomes

The present analysis identified that patients with an increased number of non-CV comorbidities were younger, while prior analysis suggested that chronic stable patients with a greater burden of non-CV comorbidities were older.[75,76,113] This findings likely reflects the study population; younger patients without non-CV comorbidities would have a reduced risk of hospitalization. Furthermore, older patients with multiple non-CV comorbidities may have an increased competing risk of death and thereby would be less likely to be admitted in hospital for HF. A prior analysis of Medicare patients from 1998-1999 also suggested that older patients hospitalized for HF, compared to younger patients, have a reduced incidence of several CV and non-CV comorbidities.[114] In this study, despite the decreasing age seen with an increasing number of non-CV comorbidities, the ejection fraction increased and the proportion of patients with HFpEF

increased. While prior studies in chronic stable HF population demonstrated that patients with HFpEF do not have a significantly increased number of non-CV comorbidities compared to HFrEF,[77] a systematic review identified that overall, patients with HFpEF have an increase burden of many non-CV comorbidities. The finding of reduced NT-proBNP levels with an increased number of non-CV comorbidities may reflect the increased BMI and lower age seen these patients**.**[115] The present analysis identified that diabetes was the most common non-CV comorbidity followed by COPD/asthma, a finding previously seen;[116] these results are not surprising given the strong prognostic association of diabetes and COPD with increased HF hospitalization.[111,117] Conditions such as COPD and anemia may contribute to HF decompensation and ultimately lead to a hospitalization. In addition, several non-CV comorbidities may not be modifiable by HF therapies and may require a multidisciplinary approach to hospitalized HF care.

These results suggest that the comorbidity profile of patients hospitalized with HF has significantly changed over time; more patients have an increased burden of non-CV comorbidities. These finding reflect the observation that patients hospitalized with HF appear to be more medically complex and have multiple comorbid conditions that often complicates management. This increase in complexity among patients over time has been demonstrated across a spectrum of CV disease states.[118,119] In a single tertiary care referral center study of 2,507 outpatients with advanced HF, from 1993 to 2010, there was an increase in the prevalence of non-CV comorbidities such as diabetes (from 26% to 31%) and obesity (as reflected by an increase in BMI from 26 kg/m^2 to 28 kg/m^2) **20**. Despite this increasing complexity of patients, the results suggest that regardless of the number of non-CV comorbidities, over time, the mean length of stay has declined.

Hospitalization represents an ideal time to optimize patient comorbidities **21** ; however, incentives and pressures to decrease length of stay in U.S. hospitals may have resulted in the observed decline in the overall length of stay for patients admitted with HF **22**. As more medically complex patients with multiple non–CV comorbidities are admitted in hospital for HF, the expectation to rapidly discharge these patients may lead to non-optimization of their comorbidities. In this analysis, patients with a higher BMI have a reduced risk of outcomes, which reflects the obesity paradox. These results highlight that the increased risk of outcomes see in patients with increased number of comorbidities is not driven completely by BMI.

Prior analyses of registry data and clinical trials of patients hospitalized with HF have identified that individual non-CV comorbidities such as diabetes, renal impairment, and COPD significantly increase length of stay and in-hospital mortality.[111,120] An increase in the number of non-CV comorbidities was associated with an increase in the prevalence of cardiovascular comorbidities which may have contributed to the worsened outcomes; however, in this analysis the association between in-hospital and 30-day mortality with the number of non-CV comorbidities was present despite multivariable adjustment that included CV comorbidities. As patients with an increasing number of non-CV comorbidities were younger, it is not surprising after adjustment with variables that included age, the risk of outcomes increased. There are likely complex and interdependent mechanisms that contribute to this increased risk of outcomes, including increased activation of renin-angiotensin-aldosterone pathways, requirement of therapies that may increase HF risk (such as thiazolidinedione in patients with diabetes), increased salt/fluid retention (in renal insufficiency), and increased right ventricular strain (in

patients with COPD and obesity).[75] Furthermore, the rates of HF readmission varies from 6.5% to 6.8% based on the number of non-CV comorbidities; in comparison, the all-cause readmission rates ranges from 17% to 23.7%, suggesting that non-HF readmission form the major burden of readmission. Strategies to optimize and treat the growing burden of non-CV comorbidities will be required and should be included in the delivery of in-hospital HF care pathway. Whether such strategies may improve outcomes remains to be determined in prospective trials.

There are a number of limitations to this analysis. The GWTG-HF program is voluntary and may not represent the total population of patients with HF in the U.S. Despite multivariable analyses, residual confounding may account for some of these observations. The comorbidities assessed are limited to those entered into the GWTG HF case report form and likely under-represents the burden of comorbidity in patients with HF. While increased coding of co-morbidities is a possible explanation for the increased number of co-morbidities we are seeing over time, we have also demonstrated an increase in the objective measures of disease severity such as increasing BMI over time. Data on other comorbidities such as sleep apnea were not available and there may have been other non-CV comorbidities that could have been assessed; however, we focused on a limited list of relevant non-CV comorbidities that have been identified in prior literature as being most relevant in patients with HF. The specific causes of death were not available. Potentially, these results may also reflect that the threshold to admit patients may have changed over the years and that patients are more severe disease, and who likely have a greater number of comorbidities, when being admitted. Outcomes for 30-day mortality were limited to Medicare beneficiaries and may not reflect the overall GWTG-HF

population; however, the trends in comorbidities in Medicare patients were similar to the overall population. The large number of patients observed may render some difference in observations as being statistically significant; however, these differences may not be clinically relevant.

What are the specific causes of death among patients with diabetes and established atherosclerotic cardiovascular diseases

In this analysis, the specific causes of death and associated risk factors in an older population of patients with type 2 diabetes and established ASCVD were evaluated in the TECOS study. The main results are notable for the following major findings: 1) sudden death was the most common cause of CV death; 2) patients who experienced sudden death had a distinct profile including being relatively younger and having less well controlled glycemia; 3) non-CV death, specifically malignancy death, contributed to a large burden of overall death; and 4) the preservation of eGFR and absence of prior HF at baseline were consistently associated with a lower risk of multiple causes of death including sudden death, HF death, and acute MI/stroke death.

Sudden death among patients with established ASCVD is of significant clinical interest given the potential for prevention via use of devices such as the implantable cardioverter defibrillator.[121] Sudden death is often presumed to be arrhythmic in nature; however, in the absence of an autopsy, the true underlying mechanism leading to sudden death is often unknown. Diabetes independently increases the risk of sudden death.[100,122] The mechanisms remain unclear but may reflect a combination of microvascular disease (e.g., cardiac autonomic dysfunction) and macrovascular disease.[100] The burden of thrombotic events contributing to sudden death among patients with diabetes also likely

remains underestimated.[123] In the present study, a history of PCI was associated with a significant decrease in the risk of sudden death, suggesting that underlying obstructive coronary atherosclerosis may be a contributor to the mechanism underlying sudden death. Furthermore, these results suggest that poor glycemic control is associated with an increased risk of sudden death. While prospective studies will be needed, these clinical variables may be considered when risk-stratifying patients for therapies that prevent arrhythmic death such as the implantable cardioverter defibrillator. Further research is needed into the underlying mechanism driving sudden death as well as strategies to reduce the risk of sudden death (such as through improved glycemic control).

This analyses also suggest that within TECOS, patients who had sudden death had a different clinical profile than patients who died of other causes. To date, there is limited information from studies evaluating the different profiles of causes of death among patient with diabetes and established ASCVD.[124] Whether differences in clinical profile relate to different underlying mechanisms of disease leading to sudden death over other causes of death remains to be evaluated in future studies.

Other CV outcomes studies evaluating antihyperglycemic therapies have also suggested that the most common cause of CV death is sudden death. In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study,[56] sudden death was the most commonly adjudicated cause of CV death (68 out of 227 CV deaths [29.9%]). In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial, of the patients who died of CV deaths (n=529), 240 (45%) were adjudicated to be sudden death.[19] In the

Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, 54% of CV deaths were adjudicated to be sudden death (132 out of 242 CV deaths). These results may reflect differences in the patient populations and in adjudication definition between the trials.

There is emerging evidence suggesting an association between dysglycemia and cancer-related death.[13,125] In trials of antihyperglycemic agent safety, regulatory agencies often expect that deaths attributed to unknown causes will be combined with CV deaths for the purposes of statistical analysis. This has been considered valid given the likelihood that patients with diabetes will die primarily of CV causes, and because this assumption creates a putative "worst-case" scenario in the assessment of CV safety. This study identified that the rate of cumulative incidence of deaths due to unknown cause was less than that of CV causes of death. The risk factors for deaths of unknown cause are similar to those for CV death; however, the demographic profile of patients who died for unknown causes did not align with that of any specific CV cause death. Furthermore, the distribution of non-fatal events prior to death appears to be different in patients who died from unknown causes compared to CV death.

Compared with older trials, contemporary glucose-lowering drug trials are more likely to enroll patients on therapies that target modifiable CV risk factors: In the United Kingdom Prospective Diabetes Study, only 0.3% of patients were on lipid-lowering agents,[31] compared to the TECOS study where over 70% of patients were on statins. As a result the burden of mortality may be shifting from CV to non-CV mortality. Patients who died of non-CV deaths had similar numbers of non-fatal CV events compared to patients who died of CV death, further highlighting the burden of non-CV death among

patients with type 2 diabetes. Similarly, unknown causes of death may not truly represent CV mortality. These results suggest that the practice of combining CV deaths and deaths due to unknown causes in contemporary clinical trial analyses should be conducted with caution. Furthermore, this finding highlight the need for continued rigorous efforts within trials to collect all available data and accurately adjudicate causes of death to minimize use of the unknown or undetermined categories.

In this analysis, a history of HF and worsening renal function appeared to be the most common risk factors for cause-specific death. Similar results have been seen in other disease states at higher risk for CV events such as atrial fibrillation.[126] Furthermore, as expected, higher eGFR was also associated with a decreased risk of all-cause mortality, CV mortality, sudden cardiac death, and HF death. The association of kidney disease, HF, and diabetes and the increased risk of CV mortality has been previously recognized and may be due to an increased risk of thrombotic events, electrolyte-induced arrhythmias, increased myocardial fibrosis, and autonomic dysfunction.[127] Preserving renal function and optimizing HF care may represent an option to improve outcomes among patients with diabetes and CV disease.

There are several strengths and limitations to this analysis. The large sample size and independent, blinded adjudication processes are some of the major strengths of this analysis; however, these results are subject to the limitations of a post-hoc analysis. In addition, as stated above, an adjudicated cause of death was not obtainable in 20% of cases. Ejection fraction data were not available for the entire cohort, and thus were not included in the analyses. No adjustments were made for multiplicity. As with most clinical trials, the population enrolled in TECOS may not be completely reflective of the

overall diabetes population, and the results of these analyses may not be directly generalizable. In TECOS, 39% of all-cause death (216 adjudicated as unknown and 209 adjudicated as presumed CV deaths out of 1084 all-cause deaths) were non-assessed with regards to specific causes of death. In the EMPA-REG OUTCOMES trial, 28% of events were considered in the 'other' category (129 deaths out of 463 all-cause deaths). These deaths included fatal cases that were not assessable due to a lack of information (reflecting unknown causes of death) and were presumed to be CV deaths as per conventional definition. These differences likely reflect variation in the adjudication definitions for each cause-specific death and the threshold for a death to be considered unknown, presumed, or another category of death.

What are the specific causes of death among patients with diabetes and established heart failure with reduced ejection fraction.

The association between diabetes and adjudicated causes of death among a global cohort of patients with HFrEF in the combined ASIAN-HF and HF-ACTION studies was explored. There are four major findings: 1) CV death, and specifically sudden death, was the most common adjudicated causes of death among patients with and without diabetes; 2) diabetes did not independently increase the risk of CV death, sudden death, or HF death; 3) while the presence of diabetes, compared to those without diabetes, increases the risk of MI/stroke death, this mode of death was the least commonly adjudicated cause of CV death; and 4) ethnic variation in the risk of sudden death and HF death were seen among patients with diabetes.

This analysis highlights the shift in causes of death among causes of death across the spectrum of patients with dysglycemia and CV disease. As previously described, the

NAVIGATOR trial enrolled 9,306 with impaired glucose tolerance at high CV risk;[12,128] among the 7% (n=622) of patients who died, 50.3% were non-CV deaths, 39.2% (n=244) CV deaths, and 10.1 % (n=65) were unknown causes of death.[13] Among the 14,671 patients with type 2 diabetes mellitus and atherosclerotic CV disease in the TECOS trial[45], of the 7.3% (n=1,084) patients who died, 49% (n=530) died from CV death, 31% (n=338) died from non-CV death, and 20% (n=216) died from unknown causes of death.[85] As highlighted with the results of the cause of death analysis in the TECOS study, CV death, was the most common cause of CV death among patients with type 2 diabetes and ASCVD; within CV death, sudden death was the most common cause of death. In the present analysis of patients with diabetes and HFrEF, the burden of mortality was overwhelmingly CV death. Strategies aimed to reduce the potential risk of non-CV death, such as cancer screening, among patients with CV disease are recommend;[129] however, given the high burden of CV death among patients with diabetes and HFrEF, further studies on the utility of such screening strategies are needed.

In this analysis, sudden death and HF death are the most common adjudicated causes of CV death among patients with and without diabetes. However, diabetes does not independently increase the risk of these specific causes of death. This is contrary to prior analyses which have demonstrated that diabetes independently increases the risk of CV death and sudden death.[6,105] In this analysis, the greater use of cardioprotective therapies such as angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists may have contributed to the differences seen compared to other cohorts. While diabetes is independently associated with an increased risk of MI/stroke death, this was the least commonly adjudicated cause of CV death.

Using anticoagulants in patients with stable atherosclerotic vascular disease have demonstrated utility in the secondary prevention of atherothrombotic events;[130] the use of such a strategy is less clear among patients with established coronary heart disease with HFrEF.[131] Potentially, greater clinical emphasis on optimization of antihyperglycemic therapies, such as SGLT-2i, that have demonstrated benefit to reduce CV mortality risk by reducing the risk of HF hospitalization and HF death are warranted.[87,88] Future studies of SGLT-2i in patients with established HFrEF are underway.

This analysis has demonstrated ethnic variation in the risk of specific CV causes of death among patients with diabetes. A prior analysis from the ASIAN-HF has demonstrated the significant ethnic variation regarding patient characteristics and use of HF therapies in Asia among those with HFrEF.[91,94,95] Furthermore, the ASIAN-HF/HF-ACTION cohort has demonstrated marked heterogeneity in the prevalence, comorbidities, and correlates of diabetes among different ethnic groups with HFrEF.[89] Among patients with diabetes and HFrEF there is significant regional variation, both in Asia and when compared to the U.S., in the use of antihyperglycemic and other cardioprotective therapies.[90] The confluence of biologic variability, differences in HF and antihyperglycemic therapies, and regional difference in patterns of care may have all contributed to the results.

This study is subject to the limitations of a retrospective analyses and there are potential unmeasured confounders that may have influenced the results. Specifically, socioeconomic status, health system practice variation, and regional differences in diabetes management were not available in this study. Ethnicity was also self- reported, so these results may not reflect inherent biological or genetic variation between groups.

There are differences in the definitions of specific causes of death in the HF-ACTION and ASIAN-HF studies. Complete definitions for the cause of death among patients within HF-ACTION were not available thereby limiting the comparison of definitions between the cohorts. There was no information about specific diabetic medications or severity of diabetes or other diabetes specific outcomes (such as hypoglycemic events). There was no adjustment for multiple testing and given the smaller sample size, potential differences in the ethnic risk of specific causes of death may have arisen by chance. However, the presence of a well characterized global cohort of patients from two major studies that include adjudicated causes of death significantly strengthen this analysis.

Primary prevention implantable cardioverter defibrillator compared to medical therapy to reduce the risk of all-cause death and sudden death with diabetes and heart failure with reduced ejection fraction in the MADIT I, MADIT II, SCD-HEFT, and DEFINITE trials.

In this analysis, a patient-level combined-analysis of four primary prevention ICD trials was conducted including 3,359 patients to evaluate the comparative effectiveness of ICDs and medical therapy versus medical therapy alone in patients with and without diabetes. This following are the major findings: 1) ICDs with medical therapy versus medical therapy alone was significantly associated with a reduced risk of all-cause death in patients without diabetes but not in patients with diabetes; 2) ICDs are associated with a reduced risk of arrhythmic death in all patients, yet the magnitude of benefit in patients with diabetes is significantly reduced; 3) non-arrhythmic death accounts for the majority of all cause death among patients with diabetes; and 4) patients with diabetes, compared with those without diabetes, did not experience more complications including infection associated with ICD implantations.

A possible explanation of the reduced benefit of ICDs in patients with diabetes seen in the present study relates to competing risk of death; patients with HF who have diabetes may be more likely to die from causes of death that will not be reduced by an ICD. As previously described, dysglycemia is an independent risk factor for sudden death, yet studies have also demonstrated that patients with dysglycemia have a high risk of non-arrhythmic death.[67] Among patients without diabetes, the arrhythmic and non-arrhythmic death rates in patients randomized to medical therapy are similar up to 2 years; this finding suggests a large burden of arrhythmic death relative to the overall death. Among patients with diabetes randomized to medical therapy, the rate of non-arrhythmic death exceeds arrhythmic death earlier suggesting that non-arrhythmic death forms a larger burden of all-cause death. The large competing risk of non-arrhythmic death in patients with diabetes may related to the greater burden of associated co-morbidities; prior studies have demonstrated that patients with a greater burden of co-morbidities increases risk of non-arrhythmic death and decreases in the benefit of ICDs.[98,99]

In addition to competing risk, it is unclear whether the presence of diabetes inherently decreases responsiveness to ICD therapies. Potential additional explanation for the reduced benefit of ICDs in patients with diabetes may relate to hypoglycemia, which may arise from anti-diabetic treatments. Hypoglycemia has been associated with increased risk of arrhythmic deaths and it is unclear if ICD therapies are effective in reducing arrhythmic death in this setting.[132]

In this study, the use of HF medical therapies was lower than those seen in more contemporary HF trials. Among patients with HF, mineralocorticoid receptor antagonists

and sacubitril/valsartan have demonstrated a significant reduction in CV mortality and possibly sudden death.[73,133] A recent analysis has suggested that over time, the risk of sudden death among patients enrolled in heart failure trials has declined.[134] These results emphasize the beneficial impact of evidence based therapies on the risk of sudden death. Furthermore, this analysis demonstrated that patients with diabetes have a higher risk of sudden death compared to those without diabetes; this finding was not seen among the HF-ACTION/ASIAN-HF cohort. The reasons may include the lower use of cardioprotective therapies in the ICD trials, differences in population enrolled, and potentially differences in adjudication strategies.

Empagliflozin, an SGLT-2 inhibitor, has demonstrated a significant reduction in cardiovascular mortality among patients with T2DM and CV risk factors.[56] The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial failed to demonstrate an improvement in the primary outcome of all-cause mortality with ICDs with medical therapy versus medical therapy alone among patients with non-ischemic cardiomyopathy.[109] One speculated reason was the high prevalence of more contemporary HF medical and device therapies. Studies to determine whether greater use of contemporary HF and anti-hyperglycemic drugs among patients with diabetes would further alter the magnitude of ICD benefit are warranted. In this study, a significant benefit in mortality associated with ICD use was seen among patients with ischemic cardiomyopathy. These results support professional guidelines which recommend that appropriate patients with ischemic cardiomyopathy should be considered for ICD placement. Whether patients with diabetes and non-ischemic cardiomyopathy have mortality benefit associated with ICD needs further

evaluation.

A subgroup analysis of DANISH suggested that patients below the age of 70 obtain the most benefit from ICD therapies.[108] This may relate to a reduce burden of comorbidities and potentially a reduced likelihood of competing causes of death. Similarly, patients with diabetes are older and have a larger burden of cardiovascular comorbidities. Strategies to risk stratify patients with diabetes to describe those who have the highest risk of sudden death over other causes of death may identify those who will preferentially benefit from ICD therapies. Despite the increased risk of sudden death among patients with diabetes, the decreased magnitude of benefit of ICD in patients with diabetes compared to patients without diabetes further highlights the importance of competing risk in this population

Across a spectrum of surgical procedures, diabetes has been associated with a significantly increased risk of post-operative complications including wound/incision infections.[102] While the reasons are unclear, multiple mechanisms may be implicated such as vascular changes, impaired wound healing, white blood cell dysfunction, immune suppression, and exogenous intravenous glucose utilization. The present results suggest that there is no increase in post-operative complications including infections among patients with diabetes, but it is important to note the relatively small number of events available for this analysis.

The results presented identified no significant differences in the number of patients who have appropriate or inappropriate shocks among those with and without diabetes. Patients with diabetes may be relatively less mobile, and thereby decreasing the risk of exercise induced tachycardia and inappropriate shock. Furthermore, patients with

diabetes are more likely to be on a statin, which has shown to decrease the incidence of atrial fibrillation and potentially inappropriate shocks.

This analysis was performed on a combined population from several randomized controlled trials which were heterogeneous in their populations. This analysis is subject to the limitations of a post-hoc analysis including being underpowered to detect a difference in all-cause mortality between treatment arms among patients with diabetes; however, the significant interaction term between patients with and without diabetes for all-cause mortality indicates a reduction in the magnitude of ICD benefit among patients with diabetes. Similarly, the reduction in the magnitude of effect of ICD was seen for the outcome of arrhythmic death.

The baseline characteristics between the randomized arms were not balanced in the subgroup of patients with and without diabetes. We evaluated patients with diabetes compared to those without diabetes and adjusted for baseline characteristics and these results remained consistent after multivariable adjustments. There was no consistent definition of diabetes used across the trials. Data on the type of diabetes, duration, or anti-diabetic drug treatment were not available. However, a sensitivity model accounting for renal function did not change the overall results. Data on the exact causes of non-arrhythmic cardiovascular deaths were not consistently available across all trials. Deaths adjudicated as sudden death may not necessarily represent arrhythmic deaths. The analysis of inappropriate shocks would need further validation in a contemporary cohort given that the programming of ICDs is likely different from the time in which these trials were conducted. These data are derived from randomized trials focused on primary prevention and so the findings should not be generalized to patients with eligible for a

secondary prevention ICD; however, this remains one of the largest cohorts of ICD-eligible patients with diabetes and HF for whom adjudicated causes of death is available.

Comparative effectiveness of primary prevention implantable cardioverter defibrillator compared to medical therapy to reduce the risk of all-cause death among patients with diabetes and heart failure with reduced ejection fraction in the Get With The Guidelines – Heart Failure Registry

Extending from the results of the patient level analysis of the MADIT I, MADIT II, DEFINITE, SCD-HEFT trials, this analysis aimed to evaluate the real-world comparative effectiveness of primary prevention ICD implantation versus medical therapy in patients with diabetes and HFrEF. Using data from the GWTG-HF registry, the present analysis assessed the association between primary prevention ICD implantation (defined as receiving an ICD during the index heart failure hospitalization or prescribed an ICD at discharge) and all-cause mortality in patients with and without diabetes. This analysis has multiple key findings. First, patients receiving a primary prevention ICD, compared to those without an ICD, had a lower rate of all-cause mortality regardless of history of diabetes. Second, this relationship was not modified by the presence of ischemic heart disease. Finally, the use of ICDs among eligible patients with and without diabetes remains low even in this very high-risk population. These results reinforce guideline recommendations to consider ICD implantation for primary prevention amongst indicated patients with HFrEF who have diabetes.

As previously described, the prior patient level meta-analysis from MADIT I, MADIT II, DEFINITE, and SCD-HeFT evaluated outcomes after ICD implantation among patients with and without diabetes. ICDs were associated with a reduced risk of all-cause mortality among patients without diabetes (HR 0.56, 95% CI 0.46–0.67) but not

among patients with diabetes (HR 0.88, 95% CI 0.7–1.12; interaction *P*=0.015). Among patients with diabetes, ICDs were associated with a reduced risk of arrhythmic death (adjusted sub-distribution HR, 0.51, 95% CI 0.33–0.81; *P*=0.004); this was also observed in patients without diabetes (sub-distribution HR 0.27, 95% CI 0.19–0.40; *P*=0.0001). Diabetes modified the interaction between ICD implantation and the risk of sudden death, indicating a reduced magnitude of benefit (*P*- value for interaction between ICD treatment and diabetes in relation to arrhythmic death: *P*=0.036). One proposed explanation for these findings was that patients with diabetes have an increased risk of competing causes of death which may not be modified by the presence of an ICD.

These results contrast with the findings from the GWTG-HF analysis and there are several potential reasons. The patient level meta-analysis focused on randomized data from a clinical trial compared to the GWTG-HF results which reflect observational data. While data from randomized studies should be considered the gold-standard, diabetes was not a prespecified as a cohort for randomization, and hence balancing of unmeasured covariates cannot be assumed. In the meta-analysis, while the overall hazard ratios for all-cause mortality crossed one, the directionality of the hazard ratio suggested that potentially there was a reduction of risk associated with ICD implantation in patients with diabetes and HFrEF. but the study was underpower to detect this difference. This is supported by the demonstration of benefit of ICD therapies among patients with diabetes. The other potential difference is in the duration of follow-up. The shorter follow-up from the meta-analysis, reflected by the duration of trials, may not have enabled the differences in the benefit of ICD therapy to become apparent. Indeed, reflecting on the Kaplan-Meier curves, there does appear to be a separation of the survival curves at 2.5

years. These potential reasons may reflect some of the potential causes of why differences in the results of the meta-analysis and the GWTG-HF results are observed. Overall, these results do suggest that eligible patients with diabetes who have an indication for a primary prevention ICD should receive this therapy.

In the DANISH trial, prophylactic ICD implantation in patients with non-ischemic HFrEF was not associated with a reduction in the risk of all-cause mortality compared with usual clinical care, though there appeared to be an interaction by age and the majority of patients had a CRT-P device present at enrollment.[109] These results suggested that the presence or absence of a prior history of ischemic heart disease did not modify the relationship between ICD implantation and all-cause mortality in patients with or without diabetes. While the present findings are non-randomized and are derived from a population-based cohort, they suggest that further research is needed to understand the populations of patients who may maximally derive benefit from an ICD implantation.

Another important finding in this analysis is the overall low use of ICDs in both patients with and without diabetes who are at very high risk of death. Only 11% of eligible patients with diabetes received an ICD. Similar findings have been seen in prior analysis of ICD implantation using the get with the GWTG-HF registry, and other population-based analyses.[135] Several potential explanations may contribute to the low use of ICDs seen in this study. There are well documented gaps, variations, and disparities in the use of guideline-directed medication and device therapies in eligible

patients. In addition, the study population focused on in patients hospitalized with HF. The optimal timing of ICD implantation for such patients is not well established. Clinicians may potentially have opted to consider ICD implantation at another date after further duration or titration of medical therapy. Some patients may have had contraindications or other medical exceptions to ICD placement that were present but not documented.

Further studies will be needed to increase the use of ICDs among eligible patients with HFrEF and diabetes given the high risk of sudden death amongst these patients. Although the causes of death could not be ascertained from this data set, these findings suggest that the mortality rates are still modifiable in these patients through provision of guideline-based care.

The role of ICD implantation among patients with diabetes and HFrEF should also be considered in the context of emerging antihyperglycemic therapies. Trials of Sodium Glucose Cotransporter-2 (SGLT2) Inhibitors have demonstrated a reduction in the risk of heart failure hospitalization among patients with type 2 diabetes who have cardiovascular disease or are at high risk of CV disease.[23,56,57] The benefits of these therapies have been demonstrated in post-hoc analyses of patients with HFrEF; however many of these trials have a very low percentage of individuals with any form of HF[136] Dedicated studies are being conducted among patients with and those without diabetes who have HFrEF or HF with preserved ejection fraction. Among ambulatory patients with HFrEF who were enrolled in clinical trials, the rates of sudden death have declined

substantially over time;[22] this was primarily thought to be resulting from an increase in the use of evidence-based medications on this cause of death. Similarly, as anti-hyperglycemic medical therapies become increasingly used, the role of ICD implantation among patients with diabetes should be further evaluated.[23]

This analysis is subject to the limitation of an observational study in that treatments were not assigned randomly. Propensity matching and subsequent multivariable adjustment may not have completely accounted for residual confounding. This analysis was limited to CMS patients hospitalized with heart failure within the GWTG-HF registry. As a result, these findings may not be generalizable to a younger, healthier patient population or those without medical insurance. The patients who did not receive an ICD may have other considerations that may have precluded them from being eligible for an ICD. For instance, these patients may have appeared too frail or too clinically unwell to have been prescribed an ICD during the hospitalization or at discharge. The use of propensity matching to enable a comparison between the ICD and no ICD group may have also eliminated patients who are too dissimilar to match. Data on the duration of diabetes and glycemic control were not available. Cause specific mortality was also not available. This analysis also primarily evaluated all-cause mortality and not CV death or sudden death which may have impacted the ability to see a relationship between ICD implantation and outcomes. Measures of frailty, such as grip strength and other functional measures (e.g. 6-minute walk test) were not available in the data.

Conclusion

The results identified though this thesis have several thematic conclusions. These findings demonstrate that patients admitted in hospital with HF have become more medical complex over time: patients admitted to the hospital with HF have a large burden of non-cardiovascular comorbidities and the number of patients with multiple non-cardiovascular comorbidities has significantly increased over time. These results have clinical implications as many non-cardiovascular comorbidities contribute to worsening HF but will not be modified by HF specific therapies. Patients with an increased number of non-cardiovascular comorbidities have increased length of hospitalization and an increased risk of in-hospital and 30-day mortality, along with higher risk of 30-day all cause and HF specific readmission. Further research will be needed to evaluate the mechanisms whereby non-cardiovascular comorbidities complicate the management of patients hospitalized with HF. Diabetes was identified as one of the most common non-CV comorbidity thereby highlighting the public health burden of comorbid diabetes and HF. Furthermore, evaluating the specific causes of death among patients with multiple non-cardiovascular comorbidities will be required to identify strategies that may reduce rates of mortality. Optimization of non-cardiovascular comorbidities during HF hospitalization may represent an avenue to improve outcomes and warrants evaluation in prospective studies. These results highlight the need for multi-disciplinary team-based care and improved coordination with primary care and other specialists in order to manage these complex patients.

Regarding causes of death among patients with type 2 diabetes and established ASCVD, sudden death was the most adjudicated cause of CV mortality, and patients with

sudden death had a distinct profile of being relatively younger with less well controlled glycemia. However, given the substantial burden of deaths due to malignancy, deaths attributed to unknown causes may not primarily represent CV causes; caution should be exercised when combining CV and unknown causes of death in clinical trial mortality data. Preserving renal function and prevention or optimization of HF may represent avenues to improve outcomes among patients with diabetes and CV disease; further studies to evaluate such preventative strategies are needed.

Extending of these findings into a population of patients with diabetes and HFrEF, it was identified that among patients with established HFrEF and diabetes, CV death, specifically sudden death followed by HF death, are the most common adjudicated causes of death. While diabetes independently increases the risk of MI/stroke death, this mode of death was the least common adjudicated cause of CV death. In addition, ethnic variation was observed regarding the risk of cause specific CV mortality. Future studies focusing improving risk stratification and prevention of sudden death and HF death should be prioritized among patients with HF and diabetes. Furthermore, studies evaluating the mechanisms of causes specific CV mortality across ethnicities are warranted to identify strategies to improve outcomes.

Given the large burden of sudden death among patients with HFrEF and diabetes, it was surprising to see that a pooled analysis of the major ICD trials failed to demonstrate a reduced risk of all-cause mortality associated with ICDs. While ICDs were associated with a reduced risk of arrhythmic death in all patients, the magnitude of benefit was significantly reduced in patients with diabetes. These findings may be due to the increased burden of competing non-arrhythmic death among patients with diabetes.

However, among older patients with diabetes who were admitted with heart failure, those with a reduced ejection fraction that were implanted with a primary prevention ICD (or were prescribed an ICD upon discharge) had a lower risk of all-cause mortality compared to those without an ICD. This analysis was a non-randomized observational study and there may be unmeasured confounders that have influenced the results. However, this analysis, in addition to the pooled analysis which demonstrated a reduction in the risk of sudden death, provides further evidence for guideline recommendations for the implantation of primary prevention ICDs among eligible patients with diabetes who have heart failure and reduced ejection fraction.

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Supplemental Appendix

Chapter 2:

Appendix table 1: Baseline demographics for CMS patients

	Non-cardiovascular comorbidities*			
Variable	0 (n=16159)	1 (n=23503)	2 (n=19219)	≥3 (n=14997)
Demographics				
Age* (Median)	84.00	82.00	79.00	77.00
Gender (% female)	55.52	53.51	53.03	56.09
BMI* (median)	23.76	25.46	28.90	32.44
	21.10	22.13	24.13	27.76
	26.36	29.01	33.83	37.44
	23.62	26.21	29.81	33.20
	3.49	6.24	7.99	8.35
	0.00	0.00	0.00	0.00
Race				
Native Hawaiian or Pacific Islander	0.16	0.19	0.19	0.11
White	84.36	81.79	79.20	79.18
Asian	1.46	1.31	1.19	0.85
American Indian or Alaska Native	0.14	0.29	0.39	0.56
Black or African American	6.70	8.27	10.43	11.71
Hispanic	4.02	5.31	5.68	5.05
Non-CV Comorbidities				
COPD or Asthma	0.00	24.38	36.89	61.95
Anemia	0.00	11.98	24.58	49.67
Diabetes	0.00	27.79	56.98	81.37
Renal Insufficiency	0.00	10.56	24.00	48.76
Obesity (BMI ≥30 kg/m2)	0.00	19.04	45.07	67.99
Depression	0.00	6.25	12.48	28.68
Medical History				
Atrial Fibrillation (%)	41.24	39.91	38.17	38.73
Atrial Flutter (%)	2.52	2.46	2.55	2.71

	Non-cardiovascular comorbidities*			
Variable	0 (n=16159)	1 (n=23503)	2 (n=19219)	≥3 (n=14997)
Hyperlipidemia (%)	40.36	46.19	52.44	59.58
Hypertension (%)	73.31	76.93	81.25	84.30
Peripheral Vascular Disease (PVD) (%)	8.83	12.29	15.25	20.02
CAD (%)	44.87	49.55	54.31	58.34
Prior MI (%)	16.22	18.52	19.25	21.90
CVA/TIA (%)	14.86	16.21	17.20	19.44
ICD (%)	6.61	6.89	7.46	6.89
Heart failure (%)	49.85	55.06	60.06	67.84
Prior PCI (%)	9.31	11.23	12.98	15.91
Prior CABG (%)	13.89	16.09	17.94	20.06
Valvular Heart Disease (%)	17.87	17.17	15.65	16.62
CABG/PCI Undetermined (%)	9.20	9.56	9.71	8.77
Medical History				
Smoking (%)	6.49	9.19	9.37	10.46
Labs at Admission†				
BNP, pg/mL	882 (479,1650)	798 (408, 1512)	711 (352, 1419)	640 (318, 1293)
Serum Creatinine, mg/dL	1.2 (0.9, 1.5)	1.2 (1.0, 1.6)	1.4 (1.0, 1.9)	1.6 (1.2, 2.3)
BUN, mg/dL	23 (17,32)	24 (18,35)	27 (19,40)	32 (21,48)
Ejection Fraction				
Ejection Fraction ≥ 40%	53.45	56.70	60.75	66.50
Ejection Fraction†	40 (26,55)	45 (29,57)	45 (30,58)	50 (35,60)

BMI (body mass index), COPD (chronic obstructive pulmonary disease), PVD (peripheral vascular disease), CAD (coronary artery disease), MI (myocardial infarction), CVA (cerebrovascular accident), TIA (transient ischemic attack), ICD (implantable cardioverter defibrillator), PCI (percutaneous coronary intervention), CABG (Coronary artery bypass grafting), BNP (brain natriuretic peptide), BUN (blood urea nitrogen), HFpEF (heart failure with preserved ejection fraction), SD standard deviation; IQR interquartile range. *All comparisons of baseline characteristics between groups were statistically significant at $p < 0.05$ † reported as median with IQR.

Appendix table 2: Time trends in comorbidities

Variable	2005 (n=9 140)	2006 (n=17, 104)	2007 (n=17 930)	2008 (n=18, 895)	2009 (n=20, 050)	2010 (n=24, 271)	2011 (n=24, 412)	2012 (n=23, 463)	2013 (n=24, 849)	2014 (n=27, 870)
Demographics										
Age (median)	76.00	75.00	74.00	74.00	74.00	75.00	74.00	74.00	74.00	74.00
Gender (female)	49.70	50.33	49.45	48.50	48.65	49.82	49.22	49.01	48.72	47.80
BMI (median)	26.95	27.34	27.47	27.72	27.80	27.79	27.99	28.04	28.09	28.34
Race (%)										
White	72.74	72.08	69.53	65.79	66.73	65.75	67.35	69.69	67.45	66.96
Asian	0.98	1.08	1.03	1.31	1.83	1.75	1.69	1.07	0.99	1.02
American Indian or Alaska Native	0.46	0.24	0.27	0.21	0.58	0.49	0.57	0.73	0.47	0.41
Black or African American	17.22	18.92	19.47	21.32	18.14	18.66	18.45	17.36	18.46	19.86
Hispanic	4.73	4.67	6.65	8.45	8.77	10.10	8.86	8.50	9.63	9.61
Non-CV Comorbidities										
COPD or Asthma (%)	26.91	28.16	28.64	29.91	31.17	31.33	32.04	34.69	36.48	36.07
Anemia (%)	15.63	16.49	16.93	18.25	19.80	20.92	21.76	22.46	22.92	21.74
Diabetes (%)	43.12	41.23	40.64	43.65	44.02	44.70	44.81	46.29	47.09	46.22
Renal Insufficiency (%)	19.31	18.26	20.16	19.93	22.03	22.01	21.44	21.26	23.33	21.41
Obesity (BMI e 30	33.79	36.61	37.57	38.25	38.80	38.98	40.23	40.47	40.75	42.08

Variable	2005 (n=9 140)	2006 (n=17, 104)	2007 (n=17 930)	2008 (n=18, 895)	2009 (n=20, 050)	2010 (n=24, 271)	2011 (n=24, 412)	2012 (n=23, 463)	2013 (n=24, 849)	2014 (n=27, 870)
kg/m2) (%)										
Depression (%)	8.42	10.18	9.62	10.04	10.14	9.97	11.41	13.09	14.93	15.32
Number of non-CV comorbidities (%)										
≥3	18.09	19.56	20.04	21.72	23.50	24.09	25.45	27.46	29.55	28.61
2	26.39	26.08	26.77	27.46	27.69	27.98	27.88	27.52	27.35	27.38
1	33.60	32.58	32.33	31.06	30.71	30.32	29.40	28.96	27.76	28.36
0	21.93	21.78	20.87	19.76	18.10	17.61	17.27	16.07	15.34	15.64
CV Comorbidities										
Chronic or recurrent Atrial Fib (%)	31.53	29.79	27.75	31.24	32.57	33.89	35.52	36.80	37.30	37.48
Atrial Flutter (%)	1.67	1.55	2.02	2.16	2.08	2.20	3.20	3.77	3.67	3.18
Hyperlipidemia (%)	35.16	38.24	40.80	44.59	47.82	49.49	52.86	54.12	54.18	54.36
Hypertension (%)	72.32	72.71	73.81	78.88	78.38	79.26	80.71	82.00	83.32	84.05
PVD (%)	12.02	12.43	10.83	12.00	12.40	12.59	12.99	13.57	13.47	13.05
CAD (%)	51.12	46.91	47.69	48.87	49.67	49.88	48.57	50.79	50.09	48.91
Prior MI (%)	-	15.42	20.69	23.65	21.70	20.49	21.48	21.44	21.37	20.14
CVA/TIA (%)	13.97	14.57	13.92	15.13	14.97	15.19	15.21	16.37	16.45	16.11

Variable	2005 (n=9 140)	2006 (n=17, 104)	2007 (n=17 930)	2008 (n=18, 895)	2009 (n=20, 050)	2010 (n=24, 271)	2011 (n=24, 412)	2012 (n=23, 463)	2013 (n=24, 849)	2014 (n=27, 870)
Heart failure (%)	1.39	43.39	62.01	67.50	69.79	69.76	71.80	71.47	70.92	71.04
Prior PCI (%)	-	-	-	13.59	16.08	15.41	16.68	17.90	18.19	18.14
Prior CABG (%)	-	-	-	19.14	21.64	20.96	21.12	21.25	21.13	19.96
Valvular Heart Disease (%)	8.18	7.41	7.02	12.12	16.48	18.92	18.95	21.00	20.94	20.34
CABG/PCI Undetermined (%)	29.95	29.99	29.93	3.72	1.93	1.63	1.56	1.21	0.14	0.00

BMI (body mass index), COPD (chronic obstructive pulmonary disease), PVD (peripheral vascular disease), CAD (coronary artery disease), MI (myocardial infarction), CVA (cerebrovascular accident), TIA (transient ischemic attack), ICD (implantable cardioverter defibrillator), PCI (percutaneous coronary intervention), CABG (Coronary artery bypass grafting), BNP (brain natriuretic peptide), BUN (blood urea nitrogen). In 2005, history of prior MI was not captured under the medical history panel. Similarly, a history of coronary artery bypass grafting (CABG) or history of PCI were not captured under the medical history until 2008.

Appendix table 3: Changes in Body mass index and renal function over time

Variable	Level	N (9140)	2005	N (17104)	2006	N (17930)	2007	N (18895)	2008	N (20050)	2009
Measures											
BMI	>=35	1626	17.79	3313	19.37	3585	19.99	3845	20.35	4236	21.13
	>=30 and <35	1462	16.00	2948	17.24	3151	17.57	3382	17.90	3544	17.68
	>=25 and <30	2591	28.35	4638	27.12	4868	27.15	5111	27.05	5465	27.26
	>=18.5 and <25	3023	33.07	5427	31.73	5520	30.79	5766	30.52	5998	29.92
	<18.5	438	4.79	778	4.55	806	4.50	791	4.19	807	4.02
eGFR (missing excluded)	>=90	629	7.50	1378	8.64	1468	8.69	1879	11.19	1731	10.35
	>=60 and <90	2217	26.44	4338	27.21	4652	27.54	4784	28.48	4811	28.77
	>=45 and <60	1838	21.92	3456	21.68	3745	22.17	3515	20.93	3687	22.04
	>=30 and <45	1916	22.85	3511	22.02	3628	21.48	3555	21.16	3653	21.84
	>=20 and <30	941	11.22	1647	10.33	1763	10.44	1611	9.59	1762	10.54
	>=15 and <20	303	3.61	545	3.42	573	3.39	501	2.98	544	3.25
	<15	540	6.44	1066	6.69	1063	6.29	952	5.67	537	3.21

Variable	Level	N (24271)	2010	N (24412)	2011	N (23463)	2012	N (24849)	2013	N (27870)	2014	P-value+
Measures												
BMI	>=35	5312	21.89	5537	22.68	5349	22.80	5747	23.13	6744	24.20	<.0001
	>=30 and <35	4150	17.10	4285	17.55	4146	17.67	4380	17.63	4985	17.89	
	>=25 and <30	6521	26.87	6617	27.11	6321	26.94	6638	26.71	7292	26.16	
	>=18.5 and <25	7266	29.94	7074	28.98	6783	28.91	7151	28.78	7788	27.94	
	<18.5	1022	4.21	899	3.68	864	3.68	933	3.75	1061	3.81	
eGFR	>=90	2453	11.86	2587	12.13	2681	12.07	2919	12.42	3373	12.70	
	>=60 and <90	6036	29.18	6120	28.69	6367	28.67	6832	29.06	7806	29.40	0.0009
	>=45 and <60	4410	21.32	4551	21.33	4848	21.83	4934	20.99	5594	21.07	
	>=30 and <45	4476	21.64	4598	21.55	4769	21.47	4976	21.17	5455	20.54	
	>=20 and <30	2076	10.03	2146	10.06	2259	10.17	2488	10.58	2744	10.33	
	>=15 and <20	623	3.01	679	3.18	701	3.16	672	2.86	770	2.90	

	<15	614	2.97	654	3.07	583	2.63	688	2.93	812	3.06	

Appendix table 4: Outcomes after adjustment with BMI alone

	Unadjusted				Adjusted +			
Outcome	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
30-Day Mortality	0.661	0.618	0.707	<.0001	0.913	0.851	0.979	0.0111
30-Day All-Cause Rehospitalization	0.931	0.899	0.965	<.0001	0.929	0.894	0.964	0.0001
30-Day HF Rehospitalization	0.939	0.885	0.996	0.0366	0.922	0.866	0.981	0.0107

+ for BMI $\geq$ 30 kg/m^2

Appendix table 5: Continuous number of non-CV comorbidities and risk of clinical outcomes.

	Unadjusted				*Adjusted*			
Variable	*Hazard Ratio*	*Lower CI*	*Upper CI*	*P-value*	*Hazard Ratio*	*Lower CI*	*Upper CI*	*P-value*
30-day mortality	1.01	1.00	1.04	0.289	1.14	1.12	1.17	<.0001
30-day all-cause rehospitalization	1.11	1.09	1.12	<.0001	1.11	1.09	1.12	<.0001
30-day heart failure rehospitalization	1.11	1.08	1.13	<.0001	1.09	1.06	1.11	<.0001

Appendix table 6: Risk of 30-day mortality following discharge from the hospital.

	Unadjusted				*Adjusted*			
Variable	*Hazard Ratio*	*Lower CI*	*Upper CI*	*P-value*	*Hazard Ratio*	*Lower CI*	*Upper CI*	*P-value*
Number of Non-CV Comorbidities 1 vs. 0	1.05	0.98	1.13	0.179	1.18	1.10	1.27	<.0001
Number of Non-CV Comorbidities 2 vs. 0	1.01	0.94	1.09	0.824	1.31	1.21	1.41	<.0001
Number of Non-CV Comorbidities >=3 vs. 0	1.11	1.03	1.20	0.010	1.62	1.49	1.76	<.0001

Appendix table 7: Two-step adjusted model for In-hospital mortality

	Unadjusted				*Adjusted for demographics only*				*Adjusted for all covariates*			
Variable	*Odds Ratio*	*Lower CI*	*Upper CI*	*P-value*	*Odds Ratio*	*Lower CI*	*Upper CI*	*P-value*	*Odds Ratio*	*Lower CI*	*Upper CI*	*P-value*
Number of Non-CV Comorbidities 1 vs. 0	0.99	0.91	1.07	0.743	1.09	0.99	1.18	0.068	1.09	1.00	1.19	0.04
Number of Non-CV Comorbidities 2 vs. 0	1.08	0.99	1.17	0.093	1.29	1.19	1.41	<.0001	1.32	1.21	1.43	<.0001
Number of Non-CV Comorbidities >=3 vs. 0	1.16	1.04	1.29	0.009	1.51	1.35	1.69	<.0001	1.54	1.39	1.72	<.0001

Appendix table 8: Two-step adjusted model for 30-day mortality

	Unadjusted				*Adjusted for demographics only*				*Adjusted for all covariates*			
Variable	*Hazard Ratio*	*Lower CI*	*Upper CI*	*P-value*	*Hazard Ratio*	*Lower CI*	*Upper CI*	*P-value*	*Hazard Ratio*	*Lower CI*	*Upper CI*	*P-value*
Number of Non-CV Comorbidities 1 vs. 0	1.03	0.97	1.10	0.357	1.18	1.10	1.27	<.0001	1.16	1.09	1.24	<.0001
Number of Non-CV Comorbidities 2 vs. 0	1.04	0.97	1.11	0.295	1.29	1.20	1.40	<.0001	1.34	1.25	1.44	<.0001
Number of Non-CV Comorbidities >=3 vs. 0	1.12	1.05	1.21	0.001	1.60	1.47	1.73	<.0001	1.63	1.51	1.75	<.0001

Chapter 3:

Appendix table 1: Adjudication definitions of mortality

Cause of death	Definition
Cardiovascular	
Sudden cardiac death	This refers to death that occurs unexpectedly in a previously stable patient and will include the following deaths: i. Witnessed and instantaneous without new or worsening symptoms and also in the absence of progressive circulatory failure, the latter lasting for 60 minutes or more. ii. Witnessed within 60 minutes of the onset of new or worsening symptoms unless a cause other than cardiac is obvious. iii. Witnessed and attributed to an identified arrhythmia (e.g captured on an ECG recording or witnessed on a monitor by either a medic or paramedic). iv. Patients resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, including myocardial infarction, and who die within 24 hours or without gaining consciousness; similar patients who die during an attempted resuscitation. v. Unwitnessed death in the absence of pre-existing progressive circulatory failure or other causes of death (information regarding the patient's clinical status within the week preceding death should be present or the "presumed CV death" classification should be used)
Myocardial infarction death	Death occurring up to 7 days after a documented acute myocardial infarction (verified either by the diagnostic criteria outlined above for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus) and where there is no conclusive evidence of another cause of death. NOTE: If death occurs before biochemical confirmation of myocardial necrosis can be obtained, the CECC will adjudicate based on clinical presentation and ECG evidence. Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause (see definition for death due to other cardiovascular cause, below).
Congestive heart failure	Death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death: Any of the following:

	i. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure. ii. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration. iii. Confinement to bed but only if this is due entirely to heart failure symptoms. iv. Pulmonary oedema sufficient to cause tachypnoea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. v. Cardiogenic shock (defined as hypotension resulting in failure to maintain normal renal or cerebral function for > 60 minutes prior to death) not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. This category will include sudden death occurring during an admission for worsening heart failure.
Stroke	Death occurring within 30 days of a confirmed stroke
Other cardiovascular cause	Death must be due to a fully documented cardiovascular cause not included above (e.g. ruptured aortic aneurysm, pulmonary embolism, or cardiovascular intervention).
Presumed cardiovascular death	All deaths not attributed to the above categories of cardiovascular death and not attributed to a non-cardiovascular cause.
Death from unknown cause	A case will be classified as "unknown" if the circumstances of death are totally unknown and assessment of a cardiovascular or non-cardiovascular cause is not possible. All unknown deaths will be considered to be cardiovascular deaths.
Non-cardiovascular cause of death	A death will be considered non-cardiovascular only if an unequivocal and documented non-cardiovascular cause can be established. This category includes deaths related to non-cardiovascular procedures.

Appendix table 2: Baseline demographics by death status

Characteristic	Survivors (N=13587)	Cardiovascular Death (N=530)	Non-Cardiovascular Death (N=338)	Unknown Cause (N=216)	P-value
Demographics					
Age, years	65 (59, 71)	68 (62, 75)	70 (65, 76)	70 (62, 76)	<0.001
Female	4018 (29.6%)	140 (26.4%)	80 (23.7%)	59 (27.3%)	0.042
Race groups					<0.001
White	9221 (67.9%)	343 (64.7%)	252 (74.6%)	141 (65.3%)	
Black	423 (3.1%)	12 (2.3%)	6 (1.8%)	6 (2.8%)	
Asian	3058 (22.5%)	114 (21.5%)	47 (13.9%)	46 (21.3%)	
Other	885 (6.5%)	61 (11.5%)	33 (9.8%)	23 (10.6%)	
Not Hispanic or Latino	11944 (87.9%)	457 (86.2%)	285 (84.3%)	187 (86.6%)	0.143
Hispanic or Latino	1643 (12.1%)	73 (13.8%)	53 (15.7%)	29 (13.4%)	0.143
Region					<0.001
Latin America	1336 (9.8%)	68 (12.8%)	46 (13.6%)	21 (9.7%)	
Asia Pacific/Other	4267 (31.4%)	160 (30.2%)	76 (22.5%)	62 (28.7%)	
Western Europe	1938 (14.3%)	55 (10.4%)	61 (18.0%)	22 (10.2%)	
Eastern Europe	3638 (26.8%)	173 (32.6%)	80 (23.7%)	74 (34.3%)	
North America	2408 (17.7%)	74 (14.0%)	75 (22.2%)	37 (17.1%)	
Medical History and Baseline Labs					
Duration of diabetes, years	10.0 (5.0, 16.0)	11.0 (6.0, 17.0)	12.0 (6.0, 20.0)	11.0 (6.0, 18.5)	<0.001
Qualifying HbA1c %	7.2 (6.8, 7.6)	7.3 (6.8, 7.7)	7.2 (6.9, 7.6)	7.3 (6.8, 7.8)	0.140
Qualifying HbA1c (mmol/mol)	55 (51, 60)	56 (51, 61)	55 (52, 60)	56 (51, 61)	-
Baseline HbA1c %	7.2 (6.8, 7.7)	7.3 (6.8, 7.8)	7.2 (6.8, 7.7)	7.3 (6.8, 7.8)	0.024
Baseline HbA1c (mmol/mol)	55 (51, 61)	56 (51, 62)	55 (51, 61)	56 (51, 62)	-
Qualifying HbA1c categories					0.063
<7%	4453 (33.8%)	169 (32.4%)	105 (31.8%)	73 (34.3%)	
7–7.5%	4088 (31.0%)	138 (26.4%)	104 (31.5%)	56 (26.3%)	
≥7.5%	4626 (35.1%)	215 (41.2%)	121 (36.7%)	84 (39.4%)	
eGFR, mL/min/1.73 m^2	73.0 (60.0, 88.0)	65.0 (54.0, 83.0)	64.6 (53.0, 80.0)	65.0 (54.8, 82.0)	<0.001
Log of eGFR, mL/min/1.73 m^2	4.3 (4.1 4.5)	4.2 (4.0 4.4)	4.2 (4.0 4.4)	4.2 (4.0 4.4)	<0.001
Serum creatinine, mg/dL	0.98 (0.82, 1.13)	1.06 (0.88, 1.26)	1.06 (0.90, 1.30)	1.05 (0.85, 1.24)	<0.001
Log of creatinine, mg/dL	-0.02 (-0.20 0.12)	0.06 (-0.13 0.23)	0.06 (-0.11 0.26)	0.05 (-0.16 0.22)	<0.001
History of vascular disease	13515 (99.5%)	525 (99.1%)	336 (99.4%)	214 (99.1%)	0.319
History of CAD	10054 (74.0%)	406 (76.6%)	253 (74.9%)	150 (69.4%)	0.229
Cerebrovascular disease	3274 (24.1%)	161 (30.4%)	87 (25.7%)	66 (30.6%)	0.001
Peripheral artery disease	2219 (16.3%)	91 (17.2%)	77 (22.8%)	46 (21.3%)	0.003
Prior myocardial infarction	5739 (42.2%)	270 (50.9%)	149 (44.1%)	97 (44.9%)	<0.001
Prior CABG	3376 (24.8%)	147 (27.7%)	93 (27.5%)	48 (22.2%)	0.223

Characteristic	Survivors (N=13587)	Cardiovascular Death (N=530)	Non-Cardiovascular Death (N=338)	Unknown Cause (N=216)	P-value
Prior congestive heart failure	2295 (16.9%)	187 (35.3%)	95 (28.1%)	66 (30.6%)	<0.001
History of hypertension	11675 (85.9%)	472 (89.1%)	307 (90.8%)	194 (89.8%)	0.005
NYHA classification at baseline					<0.001
I	477 (20.8%)	32 (17.1%)	18 (18.9%)	8 (12.1%)	
II	1159 (50.5%)	83 (44.4%)	41 (43.2%)	29 (43.9%)	
III	301 (13.1%)	37 (19.8%)	12 (12.6%)	10 (15.2%)	
IV	6 (0.3%)	3 (1.6%)	0 (0.0%)	4 (6.1%)	
Not available	352 (15.3%)	32 (17.1%)	24 (25.3%)	15 (22.7%)	
Systolic BP, mmHg	134 (124, 145)	132 (121, 147)	134 (125, 147)	135 (123, 145)	0.947
Diastolic BP, mmHg	79 (70, 84)	79 (70, 84)	75 (68, 82)	78 (70, 85)	<0.001
Baseline weight, kg	83 (72, 97)	82 (69, 96)	83 (70, 94)	78 (66, 93)	0.001
Baseline BMI, kg/m^2	29.6 (26.3, 33.3)	29.0 (25.5, 33.2)	29.0 (25.8, 32.8)	28.4 (25.8, 32.5)	<0.001
Smoking history					0.047
Never	6634 (48.8%)	269 (50.8%)	136 (40.2%)	110 (50.9%)	
Current	1550 (11.4%)	65 (12.3%)	42 (12.4%)	21 (9.7%)	
Former	5403 (39.8%)	196 (37.0%)	160 (47.3%)	85 (39.4%)	
Antihyperglycemic Therapies					
Metformin	11174 (82.2%)	408 (77.0%)	234 (69.2%)	150 (69.4%)	<0.001
Sulfonylurea	6125 (45.1%)	268 (50.6%)	147 (43.5%)	105 (48.6%)	0.055
Pioglitazone/thiazolidinedione	370 (2.7%)	11 (2.1%)	8 (2.4%)	7 (3.2%)	0.753
Insulin	3106 (22.9%)	132 (24.9%)	111 (32.8%)	59 (27.3%)	<0.001
Cardiovascular Medications					
Statins	10914 (80.3%)	395 (74.5%)	259 (76.6%)	151 (69.9%)	<0.001
Aspirin	10736 (79.0%)	375 (70.8%)	249 (73.7%)	158 (73.1%)	<0.001
ACE inhibitors/angiotensin receptor blockers	10694 (78.7%)	429 (80.9%)	265 (78.4%)	167 (77.3%)	0.052
Beta blockers	8613 (63.4%)	356 (67.2%)	213 (63.0%)	140 (64.8%)	0.343
Diuretics	5445 (40.1%)	310 (58.5%)	151 (44.7%)	114 (52.8%)	<0.001

Data are median (IQR) or n (%). CABG coronary artery bypass graft surgery; CAD coronary artery disease; NYHA New York Heart Association; BP blood pressure; eGFR estimated glomerular filtration rate; ACE angiotensin-converting enzyme.

Appendix table 3: Multivariable risk factors associated with cause-specific mortality (Cox proportional hazards model, multivariate analysis)

Risk factor	HR with 95% CI	P-value
Sudden death		
eGFR per $\log_{10}$ (mL/min/1.73 m^2) higher	0.33 (0.18-0.58)	0.0001
Asymptomatic (no CHF) vs. NYHA I	0.40 (0.22-0.74)	0.0036
NYHA II vs. NYHA I	0.93 (0.46-1.88)	0.8338
NYHA III vs NYHA I	1.42 (0.59-3.45)	0.4321
NYHA IV vs. NYHA I	5.43 (1.16-25.5)	0.0318
History of PCI	0.61 (0.43-0.87)	0.0066
Female vs. male	0.65 (0.44-0.95)	0.0265
HbA_{1c} (%), per 1% increase	1.41 (1.02-1.96)	0.0389
Heart failure death		
Age, per 5-year increase	1.39 (1.17-1.64)	<0.0001
Prior MI	2.28 (1.33-3.89)	0.0027
Asymptomatic (no CHF) vs. NYHA I	0.29 (0.12-0.70)	0.0057
NYHA II vs. NYHA I	0.85 (0.31-2.34)	0.7505
NYHA III vs NYHA I	1.50 (0.51-4.45)	0.4612
NYHA IV vs. NYHA I	5.88 (0.68-50.62)	0.1070
eGFR per $\log_{10}$ (mL/min/1.73 m^2) higher	0.33 (0.13-0.80)	0.0142
Systolic BP ≤ 135, per 5-mmHg increase	0.87 (0.77-0.98)	0.0211
Acute MI or stroke death		
Age, per 5-year increase	1.26 (1.12-1.43)	0.0002
History of cerebrovascular disease	1.80 (1.23-2.63)	0.0025
Systolic BP > 135, per 5-mmHg increase	1.11 (1.07-1.43)	0.004
Asymptomatic (no CHF) vs. NYHA I	0.47 (0.22-1.00)	0.0486
NYHA II vs. NYHA I	0.96 (0.40-2.31)	0.9287
NYHA III vs NYHA I	2.19 (0.86-5.58)	0.0989
NYHA IV vs. NYHA I	Not estimable	Not est.
Presumed or other cardiovascular deaths		
Age, per 5-year increase	1.15 (1.06-1.26)	0.0011
History of PCI	0.66 (0.49-0.91)	0.0102
History of cerebrovascular disease	1.35 (1.00-1.82)	0.0502
Unknown causes of death		
Age, per 5-year increase	1.28 (1.17-1.40)	<0.0001
NYHA IV vs. NYHA I	16.48 (4.64-58.5)	<0.0001
NYHA III vs NYHA I	1.94 (0.78-4.84)	0.1556
NYHA II vs. NYHA I	1.57 (0.74-3.35)	0.2413
Asymptomatic (no CHF) vs. NYHA I	0.71 (0.36-1.39)	0.3158
Weight ≤ 90kg, per 5-kg increase	0.87 (0.82-0.93)	<0.0001
Female vs. male	0.64 (0.47-0.89)	0.0071
eGFR per $\log_{10}$ (mL/min/1.73 m^2) higher	0.55 (0.34-0.91)	0.0192

MI myocardial infarction; CHF congestive heart failure; NYHA New York Heart Association; eGFR estimated glomerular filtration rate; PCI percutaneous coronary intervention; BP blood pressure. Other variables in the heart failure death model include: Systolic BP > 135, per 5-mmHg increase (HR 0.99; 95% CI 0.86-1.13; p=0.85). Other variables in the acute MI/stroke death model include: Log of eGFR (mL/min/1.73 m^2) (HR 0.53; 95% CI0.27-1.03; p=0.059); Systolic BP ≤ 135, per 5-mmHg increase (HR 0.94; 95% CI 0.71-1.10; p=0.28). Other variables in the unknown causes of death model include Weight > 90 kg, per 5-kg increase (HR 1.01; 95% CI 0.86-1.19; p=0.88)

Appendix table 4: Sensitivity analysis of risk factors associated with cardiovascular death including unknown deaths

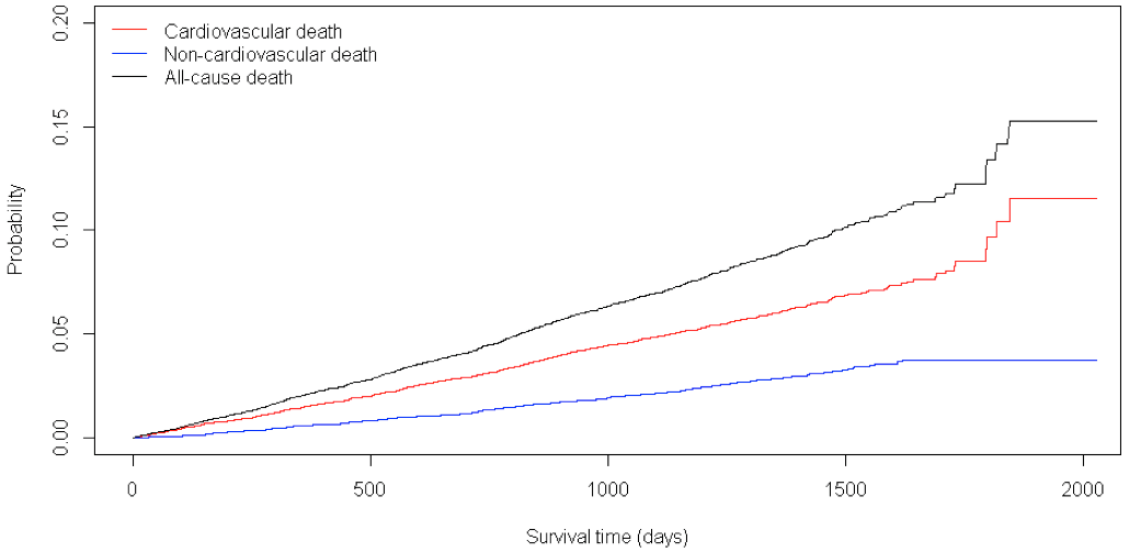
Risk factor	HR (95% CI)	P-Value
Age, per 5-year increase	1.24 (1.18-1.30)	<0.0001
History of cerebrovascular disease	1.28 (1.09-1.52)	0.0033
Prior myocardial infarction	1.37 (1.17-1.60)	0.0001
Asymptomatic (no CHF) vs. NYHA I	0.60 (0.44-0.83)	0.0021
NYHA II vs. NYHA I	1.20 (0.83-1.72)	0.3372
NYHA III vs NYHA I	1.59 (1.03-2.44)	0.0356
NYHA IV vs. NYHA I	5.46 (2.32-12.9)	0.0001
History of PCI	0.65 (0.55-0.76)	<0.0001
White vs. other race	0.53 (0.38-0.76)	0.0004
Black vs. other race	0.70 (0.40-1.21)	0.2039
Asian vs. other race	0.74 (0.49-1.13)	0.1662
Latin America vs. North America	1.22 (0.85-1.74)	0.2872
Asia Pacific/Other vs. North America	1.25 (0.93-1.67)	0.1447
Western Europe vs. North America	1.06 (0.78-1.44)	0.7069
Eastern Europe vs. North America	1.61 (1.24-2.09)	0.0003
Female vs male	0.69 (0.58-0.82)	<0.0001
eGFR per $\log_{10}$ (mL/min/1.73 m^2) higher	0.50 (0.38-0.65)	<0.0001
$qHbA_{1c}$ (%), per 1% increase	1.28 (1.10-1.49)	0.0013
Systolic BP ≤ 135, per 5-mmHg increase	0.93 (0.89-0.97)	0.0004
Systolic BP > 135, per 5-mmHg increase	1.03 (0.99-1.06)	0.1387

Appendix table 5: Fine–Gray Model for cardiovascular death (competing risk adjusted for non-CV and unknown death)

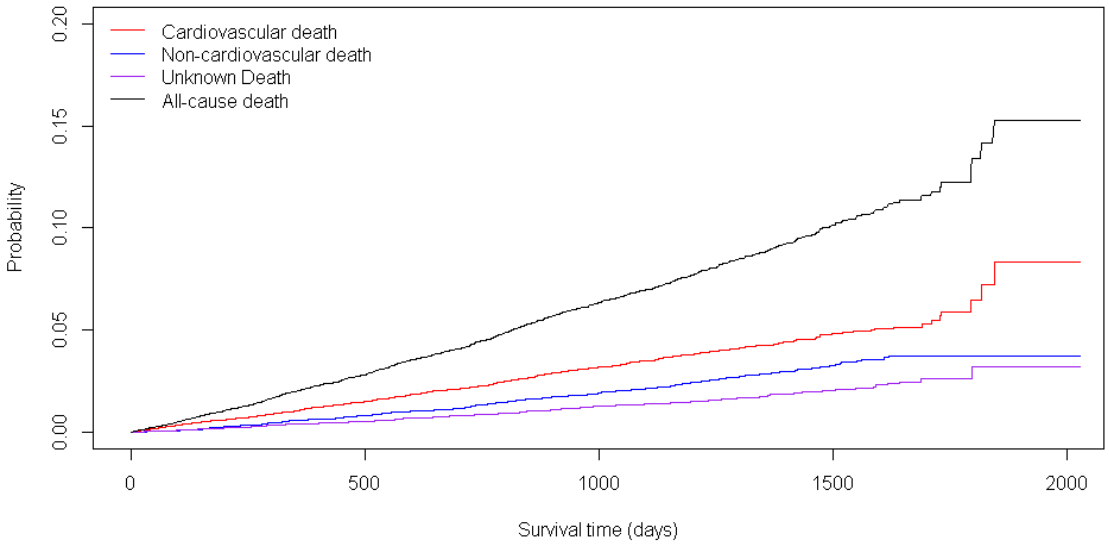
Risk factor	SHR* (95% CI)	P-Value
Age, per 5-year increase	1.17 (1.10-1.25)	<0.0001
History of cerebrovascular disease	1.29 (1.06-1.58)	0.0122
Prior myocardial infarction	1.45 (1.20-1.75)	0.0001
Asymptomatic (no CHF) vs. NYHA I	0.54 (0.37-0.78)	0.0010
NYHA II vs. NYHA I	1.14 (0.76-1.71)	0.5147
NYHA III vs NYHA I	1.61 (1.01-2.58)	0.0467
NYHA IV vs. NYHA I	2.96 (0.90-9.75)	0.0747
History of PCI	0.63 (0.52-0.77)	<0.0001
Latin America vs. North America	1.65 (1.16-2.37)	0.0060
Asia Pacific/Other vs. North America	1.32 (0.98-1.79)	0.0696
Western Europe vs. North America	1.02 (0.72-1.46)	0.8939
Eastern Europe vs. North America	1.49 (1.10-2.03)	0.0103
Female vs. male	0.63 (0.51-0.78)	<0.0001
eGFR per $\log_{10}$ (mL/min/1.73 m^2) higher	0.49 (0.35-0.69)	<0.0001
qHbA_{1c} (%), per 1% increase	1.28 (1.07-1.53)	0.0076
Systolic BP ≤ 135, per 5-mmHg increase	0.93 (0.88-0.97)	0.0028
Systolic BP > 135, per 5-mmHg increase	1.04 (1.00-1.08)	0.0502
Baseline weight ≤ 90 kg, per 5-kg increase	0.92 (0.87-0.96)	0.0007
Baseline weight > 90 kg, per 5-kg increase	1.04 (0.99-1.08)	0.1103

*Sub-distribution hazard ratio.

Appendix figure 1: Cumulative incidence of all-cause, cardiovascular and non-cardiovascular mortality (cardiovascular death includes unknown causes of death)



Appendix figure 2: Cumulative incidence of all-cause, cardiovascular, non-cardiovascular, and unknown mortality



Supplemental Statistical Material

The first table below lists the baseline covariates that were used in the stepwise selection as possible risk factors for each endpoint analysis. Bolded are covariates with missing data. The PROC MI model specifications and Fully Conditional Specification method that were utilized are described. The final table reflects the unique missing data patterns from our dataset for the covariates used in the endpoint analyses; this provides the missing data pattern as well as its frequency within the dataset.

Characteristic	**All Patients (N=14671)**
Demographics	
Age, median (25th percentile, 75th percentile), n	65 (60, 71), 14351
Female	4297/14671 (29%)
Race Groups	
White	9957/14671 (68%)
Black	447/14671 (3%)
Asian	3265/14671 (22%)
Other	1002/14671 (7%)
Not Hispanic or Latino	12873/14671 (88%)
Hispanic or Latino	1798/14671 (12%)
Region Groups	
Latin America	1471/14671 (10%)
Asia Pacific/Other	4565/14671 (31%)
Western Europe	2076/14671 (14%)
Eastern Europe	3965/14671 (27%)
North America	2594/14671 (18%)
Medical History and Baseline Labs	
Duration of Diabetes in yrs, median (25th percentile, 75th percentile), n	10.0 (5.0, 16.0), 14659
Baseline HbA1c (mmol/mol), median (25th percentile, 75th percentile), n	55 (51, 60), 14666
eGFR mL/min/1.73cm2, median (25th percentile, 75th percentile), n	73.0 (60.0 88.0), 14528
Hemoglobin, median (25th percentile, 75th percentile), n	137.00 (127.00 147.00), 9623
Prior Cardiovascular Disease	10863/14671 (74%)
History of CAD	10863/14671 (74%)
Cerebrovascular Disease	3588/14671 (24%)
Peripheral Artery Disease	2433/14671 (17%)
Prior Myocardial Infarction	6255/14671 (43%)
Prior CABG	3664/14671 (25%)

Prior PCI	5714/14468 (39%)
Prior Congestive Heart Failure	2643/14671 (18%)
History of Hypertension	12648/14671 (86%)
NYHA Classification at Baseline	
I	535/2643 (20%)
II	1312/2643 (50%)
III	360/2643 (14%)
IV	13/2643 (0%)
Not Available	423/2643 (16%)
Systolic BP mmHg, median (25th percentile, 75th percentile), n	134 (124 145), 14629
Diastolic BP mmHg, median (25th percentile, 75th percentile), n	79 (70 84), 14629
Baseline Weight kg, median (25th percentile, 75th percentile), n	83 (71 96), 14599
Baseline BMI, median (25th percentile, 75th percentile), n	29.5 (26.3 33.3), 14534
Smoking History	
Never	7149/14671 (49%)
Current	1678/14671 (11%)
Former	5844/14671 (40%)

PROC MI Model Specifications

Data Set	WORK.FORIMP2
Method	FCS
Number of Imputations	25
Number of Burn-in Iterations	20
Seed for random number generator	16218

FCS Model Specification

Method	Imputed Variables
Regression	qhba1c DIABDUR SBPBL DBPBL WGHTBL blgfr AGEIMP blhgb
Logistic Regression	PCIHXFN NYHAGR1N
Discriminant Function	female RACEGR1N REGGR1N hispanic MIHXFN CABHXFN SMOKGR1N CBVHXFN PADHXFN CHFHXFN

Missing Data Patterns

	Covariates										
Group	HbA1c	Duration of Diabetes	Systolic BP	Diastolic BP	Weight	eGFR	History of PCI	Age	Hemoglobin	NYHA Classification	Number of Cases
1	X	X	X	X	X	X	X	X	X	.	2981
2	X	X	X	X	X	X	X	X	.	.	911
3	X	X	X	X	X	X	X	X	X	X	317
4	X	X	X	X	X	X	X	X	.	X	65
5	X	X	X	X	X	X	X	.	X	X	39
6	X	X	X	X	X	X	.	X	X	.	35
7	X	X	X	X	X	X	X	.	X	.	18
8	X	X	X	X	X	X	X	.	.	.	11
9	X	X	X	X	X	X	.	X	.	.	10
10	X	X	X	X	X	.	X	X	X	.	10
11	X	X	X	X	X	X	X	.	.	X	7
12	X	X	X	X	X	.	X	X	.	X	3
13	X	X	X	X	X	.	X	X	.	.	3
14	X	X	X	X	.	X	X	X	X	.	2
15	X	X	X	X	X	X	.	X	.	X	1
16	X	X	X	X	X	X	.	.	.	.	1
17	X	X	X	X	X	.	X	X	X	X	1
18	X	X	X	X	.	X	X	X	.	.	1
19	.	X	X	X	X	X	X	X	X	.	1

Chapter 4:

Appendix table 1: Definition of specific causes of death in the ASIAN-HF and HF-ACTION cohorts

	HF-ACTION	ASIAN-HF (Hicks JACC 2017)
Events		
Cardiovascular	Includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, and death due to other CV causes.	Includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, and death due to other CV causes.
Heart failure	Death from worsening or intractable heart failure that generally occurred during hospitalization but could occur at home during hospice care.	A death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
Sudden cardiac death	Unexpected and otherwise unexplained death in a previously stable patient. This included patients who were comatose and then died after attempted resuscitation. Patients in this category should have had recent human contact before the event.	Refers to a death not following a MI and includes the following: a. Death witnessed and occurring without new or worsening symptoms b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review) d. Death after unsuccessful resuscitation from cardiac arrest (e.g., implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest) e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac

		etiology f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)
MI/Stroke	n/a	MI: Based on 2012 Third Universal Definition of Myocardial Infarction. Stroke: Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction. Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.
Non-cardiovascular death	n/a	Defined as any death with a specific cause that is not thought to be CV in nature.
Unknown cause of death	n/a	Refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few patients in well-run clinical trials.

Appendix table 2: Baseline characteristics of patient without diabetes and heart failure with reduced ejection fraction

	No diabetes				
	All	Survivors	CV death	Non CV death	Presumed CV death
N	3737	3130	380	73	154
Age, years	57.8 (13.8)	57.4 (13.4)	60.0 (14.5)	65.1 (14.3)	59.0 (16.9)
Female sex	889 (23.8%)	783 (25.0%)	60 (15.8%)	10 (13.7%)	36 (23.4%)
Body mass index, kg/m2	26.8 (6.6)	27.0 (6.6)	26.1 (6.5)	25.6 (5.9)	24.3 (6.0)
Systolic blood pressure, mmHg	114.2 (18.7)	115.0 (18.8)	109.8 (17.8)	113.7 (16.8)	109.5 (16.6)
Diastolic blood pressure, mmHg	71.3 (12.2)	71.8 (12.2)	68.9 (12.4)	70.0 (10.8)	68.8 (11.3)
Heart rate, bpm	76.0 (15.1)	75.8 (14.8)	75.9 (15.5)	74.5 (13.6)	80.5 (19.8)
eGFR, mL/min/1.73m2	66.0 (50.9, 81.7)	67.5 (53.4, 82.8)	59.1 (40.5, 73.0)	60.1 (42.2, 75.7)	61.8 (37.5, 74.6)
LVEF, %	24.9 (6.3)	25.1 (6.2)	23.4 (6.5)	23.8 (6.2)	25.0 (6.1)
Ethnicity					
Black	431 (11.5%)	356 (11.4%)	55 (14.5%)	12 (16.4%)	8 (5.2%)
White	935 (25.0%)	799 (25.5%)	94 (24.7%)	22 (30.1%)	20 (13.0%)
Chinese	701 (18.8%)	568 (18.1%)	92 (24.2%)	16 (21.9%)	25 (16.2%)
Malay	245 (6.6%)	196 (6.3%)	26 (6.8%)	7 (9.6%)	16 (10.4%)
Indian	765 (20.5%)	637 (20.4%)	60 (15.8%)	4 (5.5%)	64 (41.6%)
Japanese/Korean	425 (11.4%)	382 (12.2%)	19 (5.0%)	8 (11.0%)	16 (10.4%)
All others	235 (6.3%)	192 (6.1%)	34 (8.9%)	4 (5.5%)	5 (3.2%)
Cohort					
ASIAN-HF	2283 (61.1%)	1902 (60.8%)	218 (57.4%)	38 (52.1%)	125 (81.2%)
HF-ACTION	1454 (38.9%)	1228 (39.2%)	162 (42.6%)	35 (47.9%)	29 (18.8%)
NYHA class					
Class I/II	2317 (65.4%)	2035 (68.7%)	165 (44.2%)	42 (59.1%)	75 (54.3%)
Class III	1067 (30.1%)	826 (27.9%)	163 (43.7%)	23 (32.4%)	55 (39.9%)

Class IV	158 (4.5%)	99 (3.3%)	45 (12.1%)	6 (8.5%)	8 (5.8%)
Aetiology of HF, ischemic	1492 (41.7%)	1210 (40.5%)	181 (48.9%)	38 (56.7%)	63 (42.3%)
Coronary artery disease, yes	1627 (43.7%)	1308 (41.9%)	202 (53.2%)	41 (56.2%)	76 (49.4%)
Hypertension, yes	1632 (43.9%)	1351 (43.4%)	188 (49.5%)	39 (53.4%)	54 (35.3%)
Atrial fibrillation/flutter, yes	734 (19.7%)	555 (17.8%)	116 (30.5%)	25 (34.2%)	38 (24.7%)
Prior stroke, yes	268 (7.2%)	220 (7.1%)	38 (10.0%)	3 (4.1%)	7 (4.5%)
PVD, yes	121 (3.3%)	91 (2.9%)	23 (6.1%)	2 (2.7%)	5 (3.2%)
COPD, yes	343 (9.2%)	268 (8.6%)	51 (13.5%)	14 (19.2%)	10 (6.5%)
Cancer, yes	117 (3.2%)	96 (3.1%)	15 (4.0%)	4 (5.5%)	2 (1.3%)
Alcohol, ever	1314 (35.5%)	1109 (35.8%)	140 (37.2%)	26 (36.6%)	39 (25.3%)
Smoking, ever	1912 (51.4%)	1562 (50.2%)	242 (63.7%)	47 (64.4%)	61 (39.6%)
Chronic kidney disease (eGFR<60)	1180 (38.6%)	920 (36.1%)	172 (51.5%)	31 (49.2%)	57 (49.6%)
ACEi or ARBs, yes	3119 (84.5%)	2664 (85.9%)	284 (75.7%)	59 (83.1%)	112 (76.7%)
β-blockers, yes	3131 (84.8%)	2665 (85.9%)	308 (82.1%)	54 (76.1%)	104 (71.2%)
Diuretics, yes	2929 (79.3%)	2414 (77.8%)	327 (87.2%)	57 (80.3%)	131 (89.7%)
Aldosterone antagonist, yes	2126 (57.6%)	1795 (57.9%)	203 (54.1%)	43 (60.6%)	85 (58.2%)
Device therapy, vs none					
Any ICD	551 (14.8%)	466 (14.9%)	56 (14.7%)	9 (12.3%)	20 (13.0%)
Any Pacemaker	512 (13.7%)	406 (13.0%)	70 (18.4%)	17 (23.3%)	19 (12.3%)

eGFR estimated glomerular filtration rate; LVEF left ventricular ejection fraction; NYHA New York Heart Association; HF heart failure; PVD peripheral vascular disease; COPD chronic obstructive pulmonary disease; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; ICD implantable cardioverter defibrillator

Appendix table 3: Baseline characteristics based on specific causes of cardiovascular death among patients with diabetes and heart failure with reduced ejection fraction

	Sudden death	Heart failure death	Myocardial infarction/stroke death
N	115	104	38
Age, years	61.7 (11.2)	65.4 (12.0)	65.4 (10.6)
Female sex	28 (24.3%)	25 (24.0%)	8 (21%)
Body mass index, kg/m2	28.4 (6.9)	26.5 (7.5)	27.0 (5.9)
Systolic blood pressure, mmHg	118.3 (21.1)	109.3 (17.1)	121.9 (17.7)
Diastolic blood pressure, mmHg	71.5 (12.0)	67.0 (9.7)	70.8 (11.0)
Heart rate, bpm	75.9 (14.2)	79.0 (15.2)	76.8 (13.7)
eGFR, mL/min/1.73m2	45.0 (31.2, 69.0)	47.3 (36.2, 59.5)	46.1 (32.5, 66.4)
LVEF, %	24.9 (6.5)	24.0 (7.1)	24.4 (5.4)
Ethnicity			
Black	19 (16.5%)	10 (9.6%)	6 (16%)
White	18 (15.7%)	23 (22.1%)	1 (3%)
Chinese	12 (10.4%)	25 (24.0%)	12 (32%)
Malay	12 (10.4%)	14 (13.5%)	9 (24%)
Indian	40 (34.8%)	16 (15.4%)	4 (11%)
Japanese/Korean	5 (4.3%)	11 (10.6%)	3 (8%)
All others	9 (7.8%)	5 (4.8%)	3 (8%)
Cohort			
ASIAN-HF	73 (63.5%)	67 (64.4%)	29 (76%)
HF-ACTION	42 (36.5%)	37 (35.6%)	9 (24%)
NYHA class			
Class I/II	53 (47.4%)	38 (40.0%)	21 (56%)
Class III	55 (49.1%)	43 (45.3%)	14 (37%)
Class IV	4 (3.6%)	14 (14.7%)	3 (8%)
Aetiology of HF, ischemic	82 (73.2%)	74 (71.2%)	31 (84%)
Coronary artery disease, yes	77 (67.0%)	73 (70.2%)	28 (74%)
Hypertension, yes	69 (60.5%)	64 (62.1%)	26 (68%)
Atrial fibrillation/flutter, yes	17 (14.8%)	30 (28.8%)	6 (16%)
Prior stroke, yes	14 (12.2%)	6 (5.8%)	9 (24%)
PVD, yes	15 (13.0%)	12 (11.5%)	4 (11%)
COPD, yes	13 (11.3%)	14 (13.5%)	4 (11%)
Cancer, yes	2 (1.7%)	8 (7.7%)	0 (0%)
Alcohol, ever	28 (24.8%)	34 (33.0%)	9 (24%)
Smoking, ever	53 (46.5%)	60 (57.7%)	18 (47%)
Chronic kidney disease	63 (64.9%)	74 (76.3%)	24 (71%)

(eGFR<60)			
ACEi or ARBs, yes	81 (70.4%)	65 (62.5%)	29 (76%)
β-blockers, yes	91 (79.1%)	79 (76.0%)	31 (82%)
Diuretics, yes	101 (87.8%)	96 (92.3%)	36 (95%)
Aldosterone antagonist, yes	60 (52.2%)	49 (47.1%)	21 (55%)
Device therapy, vs none	97 (84.3%)	65 (62.5%)	32 (84%)
Any ICD	6 (5.2%)	22 (21.2%)	3 (8%)
Any Pacemaker	12 (10.4%)	17 (16.3%)	3 (8%)

eGFR estimated glomerular filtration rate; LVEF left ventricular ejection fraction; NYHA New York Heart Association; HF heart failure; PVD peripheral vascular disease; COPD chronic obstructive pulmonary disease; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; ICD implantable cardioverter defibrillator

Appendix table 4: Baseline characteristics based on specific causes of cardiovascular death among patients without diabetes and heart failure with reduced ejection fractions

	Sudden death	**Heart failure death**	**Myocardial infarction/stroke death**
N	184	149	20
Age, years	58.5 (14.2)	61.5 (15.4)	63.4 (12.2)
Female sex	30 (16.3%)	24 (16.1%)	3 (15%)
Body mass index, kg/m2	26.7 (7.1)	25.6 (6.1)	27.2 (5.4)
Systolic blood pressure, mmHg	111.3 (17.1)	107.5 (18.3)	117.3 (17.8)
Diastolic blood pressure, mmHg	69.6 (12.1)	68.0 (12.7)	72.8 (13.3)
Heart rate, bpm	77.2 (16.1)	75.6 (15.0)	73.9 (14.9)
eGFR, mL/min/1.73m2	62.6 (46.0, 79.4)	51.4 (35.8, 66.8)	60.4 (41.8, 82.8)
LVEF, %	23.7 (6.7)	22.6 (6.2)	24.7 (7.1)
Ethnicity			
Black	27 (14.7%)	23 (15.4%)	2 (10%)

White	38 (20.7%)	43 (28.9%)	8 (40%)
Chinese	35 (19.0%)	42 (28.2%)	2 (10%)
Malay	13 (7.1%)	8 (5.4%)	2 (10%)
Indian	44 (23.9%)	12 (8.1%)	3 (15%)
Japanese/Korean	12 (6.5%)	6 (4.0%)	1 (5%)
All others	15 (8.2%)	15 (10.1%)	2 (10%)
Cohort			
ASIAN-HF	112 (60.9%)	77 (51.7%)	10 (50%)
HF-ACTION	72 (39.1%)	72 (48.3%)	10 (50%)
NYHA class			
Class I/II	91 (50.5%)	47 (32.2%)	14 (70%)
Class III	72 (40.0%)	73 (50.0%)	5 (25%)
Class IV	17 (9.4%)	26 (17.8%)	1 (5%)
Aetiology of HF, ischemic	76 (42.9%)	76 (51.7%)	12 (63%)
Coronary artery disease, yes	90 (48.9%)	85 (57.0%)	11 (55%)
Hypertension, yes	89 (48.4%)	80 (53.7%)	7 (35%)
Atrial fibrillation/flutter, yes	47 (25.5%)	53 (35.6%)	9 (45%)
Prior stroke, yes	15 (8.2%)	19 (12.8%)	2 (10%)
PVD, yes	12 (6.5%)	7 (4.7%)	2 (10%)
COPD, yes	22 (12.1%)	27 (18.1%)	0 (0%)
Cancer, yes	7 (3.8%)	7 (4.7%)	1 (5%)
Alcohol, ever	70 (38.3%)	55 (37.4%)	6 (32%)
Smoking, ever	119 (64.7%)	96 (64.4%)	11 (55%)
Chronic kidney disease (eGFR<60)	67 (43.2%)	82 (60.7%)	9 (50%)
ACEi or ARBs, yes	142 (78.5%)	105 (70.5%)	15 (75%)
β-blockers, yes	151 (83.4%)	118	16 (80%)

		(79.2%)	
Diuretics, yes	153 (84.5%)	139 (93.3%)	14 (70%)
Aldosterone antagonist, yes	91 (50.3%)	85 (57.0%)	11 (55%)
Device therapy, vs none	137 (74.5%)	89 (59.7%)	14 (70%)
Any ICD	17 (9.2%)	27 (18.1%)	4 (20%)
Any Pacemaker	30 (16.3%)	33 (22.1%)	2 (10%)

eGFR estimated glomerular filtration rate; LVEF left ventricular ejection fraction; NYHA New York Heart Association; HF heart failure; PVD peripheral vascular disease; COPD chronic obstructive pulmonary disease; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; ICD implantable cardioverter defibrillator

Chapter 5:

Appendix table 1: Definition of sudden cardiac death.

Trial	Definition of sudden death
MADIT I	1) Died suddenly and unexpectedly within 1 h of cardiac symptoms in the absence of progressive cardiac deterioration (this category includes several patients whose time course of death was prolonged by unsuccessful resuscitative measures, as well as patients who died within 1 h of the onset of cardiac symptoms in the setting of stable heart failure [HF]); 2) died unexpectedly in bed during sleep; or 3) died unexpectedly within 24 h after last being seen alive.
MADIT II	1) Died suddenly and unexpectedly within 1 h of cardiac symptoms in the absence of progressive cardiac deterioration (this category includes several patients whose time course of death was prolonged by unsuccessful resuscitative measures, as well as patients who died within 1 h of the onset of cardiac symptoms in the setting of stable heart failure [HF]); 2) died unexpectedly in bed during sleep; or 3)

	died unexpectedly within 24 h after last being seen alive.
SCD-HEFT	1) Deaths resulting from the sequelae of a cardiac arrest; 2) death within 1 hour of the onset of major accelerating symptoms; 3) An instantaneous or nearly instantaneous death in the absence of a clear indication of an alternative mode of death; 4) Death during sleep if the event was unexpected and occurred in the absence of acceleration of HF symptoms; or 5) Deaths within 30 days of and related to a device implantation.
DEFINITE	Death that occurs up to one hour after the onset of symptoms, if a sudden change in symptoms can be defined. A death that occurs after prolonged resuscitation efforts (lasting > 1 hour) is also classified as sudden.

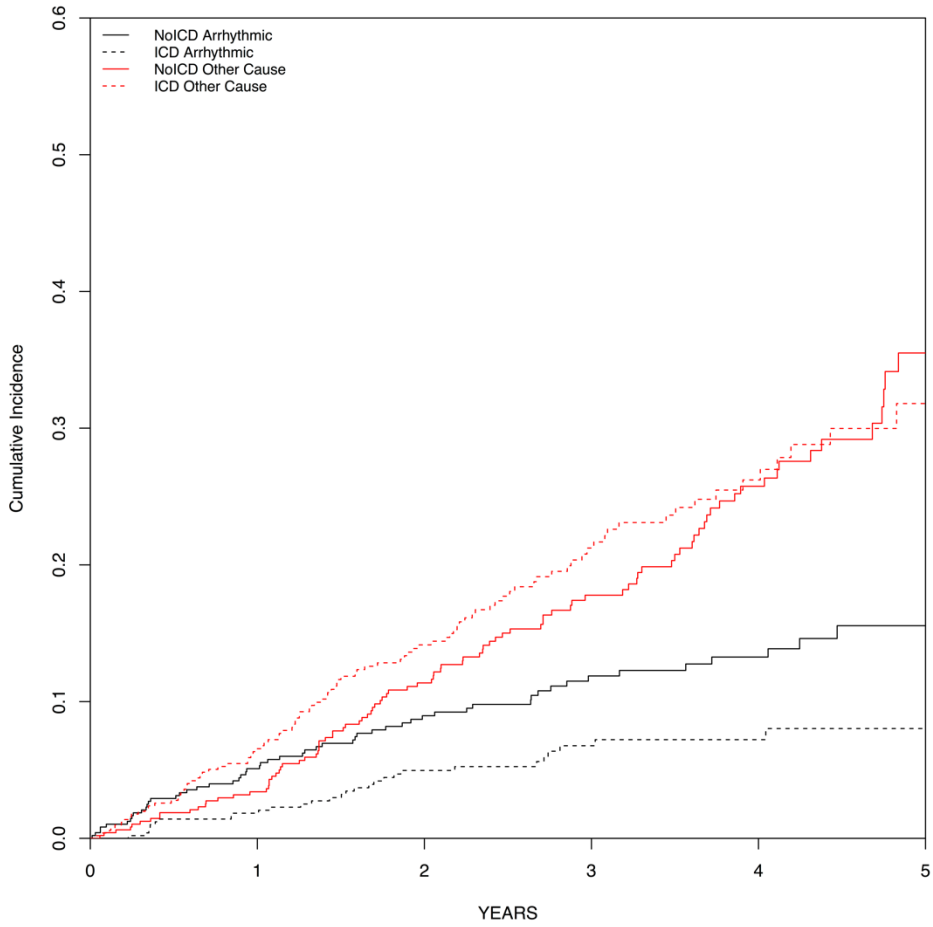
Appendix table 2: Baseline characteristics by diabetic status

	No Diabetes N=2,363	Diabetes N=996	P-value
Age. Mean [SD]	60 [12]	62 [10]	<0.001
Female. n (%)	471 (20)	209 (21)	0.51
White. n (%)	1926 (82)	751 (75)	<0.001
Black. n (%)	334 (14)	171 (12)	
Other. n (%)	103 (4)	74 (7)	
LVEF %. Mean [SD]	23 [6]	23 [6]	0.04
NYHA scores. n (%)			<0.001
NYHA 1	441 (19)	143 (14)	
NYHA 2	1334 (56)	531 (54)	
NYHA 3	579 (25)	317 (32)	
Comorbidities			
Atrial Fibrillation. n (%)	168 (11)	46 (8)	0.01
Ischemic heart disease. n (%)	1420 (60)	691 (69)	<0.001
Prior CABG. n (%)	763 (38)	403 (45)	<0.001
Prior PCI. n (%)	591 (30)	284 (32)	0.19
Hypertension. n (%)	957 (48)	589 (66)	<0.001
Prior MI. n (%)	1346 (57)	643 (65)	<0.001
Heart failure. n (%)	1476 (62)	624 (63)	0.94
Smoking. n (%)	1874 (80)	777 (78)	0.28
Medication			
ACEi. n (%)	2038 (86)	860 (86)	0.96
Beta blockers. n (%)	1553 (66)	682 (68)	0.13
Diuretics. n (%)	1819 (77)	865 (87)	<0.001
Anti-arrhythmic use. n (%)	88 (4)	17 (2)	0.002
Laboratory values			
Creatinine (mg/dl)	1.2 [0.4]	1.3 [0.4]	0.001
BUN (mg/dl)	21.1 [11.1]	25.6 [13.5]	<0.001
Sodium (mmol/l)	139 [3]	139 [4]	<0.001
Electrocardiogram			
LBBB n (%)	400 (20)	165 (19)	0.44
Heart Rate (seconds) [SD]	92 [135]	107 [166]	0.10
QRS Duration (milliseconds) [SD]	120 [32]	119 [31]	0.44

(n) denotes %. [n] denotes standard deviation. LVEF left ventricular ejection fraction; NYHA New York Heart Association; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; MI myocardial infarction; ACEi angiotensin converting enzyme inhibitor; BUN

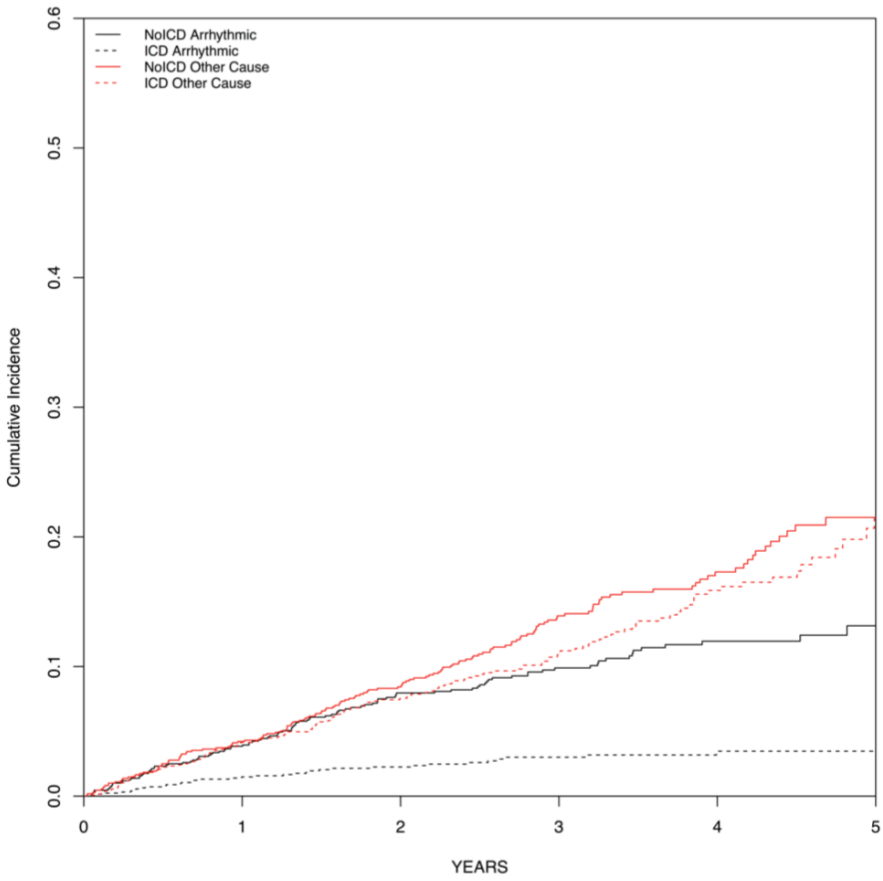
blood urea nitrogen; LBBB left bundle branch block.

Appendix figure 1A: Proportion of death based on arrhythmic and non-arrhythmic deaths in patients with diabetes. Numbers reflects patients at risk.



No ICD Arrhythmic	484	424	353	252	190	126
ICD Arrhythmic	512	451	366	248	181	126
No ICD Other Cause	484	432	344	231	155	84
ICD Other Cause	512	428	324	190	115	56

Appendix figure 1B: Proportion of death based on arrhythmic and non-arrhythmic deaths in patients without diabetes. Numbers reflects patients at risk.



No ICD Arrhythmic	1097	977	813	589	387	214
ICD Arrhythmic	1266	1115	922	638	409	225
No ICD Other Cause	1097	973	808	557	349	167
ICD Other Cause	1266	1083	863	558	309	115

Chapter 6:

Appendix table 1: Percentage missing data of the adjustment variables and the imputation method utilized.

Label	Missing	Imputation
Demographics: Age (18-110)	0.0%	
Black / African-Americans	0.0%	
Ischemic history	0.0%	
Hypertension	0.0%	
Atrial fibrillation or flutter	0.0%	
COPD	0.0%	
Renal insufficiency	0.0%	
CVA/TIA	0.0%	
anemia	0.0%	
Heart failure history	0.0%	
diuretics	25.8%	Multiple imputation
statin	23.7%	Multiple imputation
beta blockers	8.1%	Multiple imputation
digoxin	0.0%	
ACEI/ARB	23.0%	Multiple imputation
Ca channel blocker	0.0%	
Ejection Fraction, %	0.0%	
SBP (50-250), mmHg	15.1%	Multiple imputation
BUN	37.2%	Multiple imputation
Sodium	37.3%	Multiple imputation
Hospital region	0.0%	
Teaching hospitals	0.3%	Not imputed
Number of beds in hospital	0.1%	Not imputed
Site ability to perform PCI, cardiac surgery, or heart transplants	5.1%	Multiple imputation