Title

Diabetes and Risk of Sudden Death in Coronary Artery Disease Patients Without Severe Systolic Dysfunction

Journal

JACC Clinical Electrophysiology, 7(12)

ISSN

2405-500X

Authors

Venkateswaran, Ramkumar V
Moorthy, MV
Chatterjee, Neal A
et al.

Publication Date

2021-12-01

DOI

10.1016/j.jacep.2021.05.014

Peer reviewed

HHS Public Access

Author manuscript

JACC Clin Electrophysiol. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

JACC Clin Electrophysiol. 2021 December ; 7(12): 1604–1614. doi:10.1016/j.jacep.2021.05.014.

Diabetes and Risk of Sudden Death in Coronary Artery Disease Patients Without Severe Systolic Dysfunction

Ramkumar V. Venkateswaran, MD[1], **M.V. Moorthy, PhD**[2], **Neal A. Chatterjee, MD, MSc**[3], **Julie Pester, BA**[2], **Alan H. Kadish, MD**[4], **Daniel C. Lee, MD**[5], **Nancy R. Cook, ScD**[2], **Christine M. Albert, MD, MPH**[6]

[1]Division of Cardiology, University of California, San Francisco

[2]Division of Preventive Medicine, Brigham and Women's Hospital

[3]Department of Cardiology, University of Washington

[4]Touro College and University System

[5]Division of Cardiology, Northwestern University Feinberg School of Medicine

[6]Department of Cardiology, Cedars-Sinai Medical Center

Abstract

Objective—To determine absolute and relative associations of diabetes mellitus (DM) and hemoglobin A_{1c} (HbA_{1c}) with sudden and/or arrhythmic death (SAD) versus other modes of death in patients with coronary artery disease (CAD) who do not qualify for implantable cardioverter defibrillators (ICDs).

Background—Patients with CAD and DM are at elevated risk for SAD; however, it is unclear whether these patients would benefit from ICDs given competing causes of death and/or whether HbA_{1c} might augment SAD risk stratification.

Methods—In the PRE-DETERMINE study of 5764 patients with CAD with LVEF >30–35%, competing risk analyses were used to compare absolute and relative risks of SAD versus non-SAD by DM status and HbA_{1c} level and to identify risk factors for SAD among 1,782 patients with DM.

Address for Correspondence: Christine M. Albert MD, MPH, Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, 127 South San Vincente Blvd., AHSP 3100: Los Angeles CA, 90048. Tel 310.423.3869; Fax 310.423.3522 Christine.albert@cshs.org.

Disclosures: Christine M. Albert: Grants from NHLBI, St, Jude, Abbott, and Roche Diagnostics. Consultant for Roche Diagnostics (minor). Daniel Lee: Grants from NHLBI, AHA, and Abbott. All other authors report no disclosures.

Twitter:
Pts with #CAD, LVEF >30–35%, and #DM and/or elevated HbA_{1c} have a heightened risk of #SuddenCardiacDeath. However, they have a higher absolute risk of dying from non-sudden death, suggesting that #ICD therapy may be less effective in this population. (Include Central Illustration as image for tweet)

Results—Over a median follow-up of 6.8 years, DM and HbA_{1c} were significantly associated with SAD and non-SAD ($p < 0.05$ for all comparisons); however, the cumulative incidence of non-SAD (19.2%; CI 17.3–21.2) was almost 4 times higher than SAD (4.8%; CI 3.8–5.9) in DM patients. A similar pattern of absolute risk was observed across categories of HbA_{1c}. In analyses limited to DM patients, HbA_{1c} was not associated with SAD, whereas low LVEF, atrial fibrillation, and ECG measurements were associated with higher SAD risk.

Conclusion—In patients with CAD and LVEF >30–35%, patients with DM and/or elevated HbA_{1c} are at much higher absolute risk of dying from non-SAD than SAD. Clinical risk markers, and not HbA_{1c}, were associated with SAD risk in DM patients.

ClinicalTrials.gov Identifier: NCT01114269.

Condensed Abstract

Patients with coronary artery disease (CAD) and diabetes mellitus (DM) are at elevated risk for sudden and/or arrhythmic death (SAD); however, it is unclear whether these patients would benefit from implantable converter defibrillators (ICDs) given competing causes of death. In the PREDETERMINE study of 5764 patients with CAD and left ventricular ejection fraction >30–35%, the absolute incidence of non-SAD was almost 4 times higher than SAD in the DM population, highlighting the concern that this population may have diminished mortality benefit from ICDs. HbA_{1c} also did not aid with SAD risk stratification within the DM population.

Keywords

Sudden Cardiac Death; Diabetes Mellitus; HbA_{1c}; Risk Stratification

Introduction

Sudden and/or arrhythmic death (SAD) accounts for 230,000 to 350,000 deaths per year in the United States, and usually occurs in the setting of coronary artery disease (CAD). (1,2) While current guidelines recommend implantable cardioverter defibrillators (ICDs) for primary prevention of SAD in patients with a severely reduced left ventricular ejection fraction (LVEF) and symptomatic heart failure (HF), the majority of SADs occur in patients who do not meet these criteria. (3,4) Therefore, there is a pressing need for better SAD risk stratification within this population.

One well established risk factor for SAD is diabetes mellitus (DM). (5–9) In recent studies performed in post-myocardial infarction (MI) or HF patients with preserved LVEF, the presence of DM conferred an absolute risk of SAD comparable to that observed in non-DM patients with reduced LVEF. (8,10) These data provided an impetus to develop ICD trials targeting SAD risk reduction in this high-risk DM patient population. (11) However, patients with DM are also at higher risk of dying from other causes of death (10), and recent data from randomized trials performed in patients with heart failure and reduced ejection fraction (HFrEF) suggest that this competing risk may reduce the benefit of ICDs in patients with DM. (12) Whether these results might differ in high-risk DM patients with lesser degrees of systolic dysfunction is unknown. Also, it is unclear whether severity of DM, as measured

by insulin dependence (13), and/or direct measures of glycemia, such as hemoglobin A_{1c} (HbA_{1c}), might be useful for SAD risk prediction in high risk populations. (14) (15)

When deciding whether to pursue trials of ICD therapy in patient populations thought to be at high risk, it is important to consider both the absolute incidence and relative proportion of SAD versus non-SAD events in that population. In the present study, we examine both the absolute and relative associations of DM and HbA_{1c} with SAD and other modes of death in a prospective cohort of patients with CAD who do not qualify for ICDs on the basis of LVEF and/or New York Heart Association (NYHA) class (PRE-DETERMINE cohort). We also examined whether HbA_{1c} levels and/or other factors might aid in the identification of DM patients at heightened SAD risk.

Methods

Study Population

PRE-DETERMINE (ClinicalTrials.gov identifier: NCT01114269) is a multicenter, prospective, observational study involving 5764 patients with documented CAD or prior myocardial infarction (MI), and either LVEF > 35% or LVEF 30–35% with NYHA class I HF symptoms who did not meet the criteria for ICD implantation for primary prevention of SAD at study enrollment. (16) Patients were excluded if they had a history of metastatic cancer and any other condition that would limit life expectancy to less than six months, history of cardiac arrest not associated with MI, or if ICD implantation was planned. Thorough ascertainment of demographic information, past medical history, cardiovascular risk factors, medication history, and lifestyle choices was done at the time of patient enrollment. The protocol was approved by the institutional review board at Brigham and Women's Hospital and all participants provided consent.

Blood Collection and HbA_{1c} Measurement

Blood samples with HbA_{1c} assays were collected at baseline from 5544 participants (96%) in PREDETERMINE. The staff at the clinical sites performed the venipuncture and then sent the sample by overnight courier in provided chill packs to the Blood Processing Laboratory at Brigham and Women's Hospital. Specimens were received in the laboratory within 24–30 hours of venipuncture. Upon receipt at our laboratory, samples were kept chilled until processed, centrifuged for 20 minutes (2500 rpm, 4°C) and re-aliquoted into 2 ml Nunc vials and stored separately as plasma, buffy coat, and red blood cells at −170° C. Tina-quant Hemoglobin A_{1c} Generation 3 turbidimetric inhibition immunoassays were performed on the Cobas c501 (Roche Diagnostics, Indianapolis, IN).

Ascertainment and Classification of Endpoints

The Clinical Coordinating Center at Brigham and Women's Hospital mailed all study participants questionnaires every six months to assess for interval cardiovascular events, including ICD implantation, and to confirm vital status. If questionnaires were not returned, patients and/or next-of-kin were contacted by telephone. Vital status was also corroborated using contact with postal authorities and searches of obituaries and the National Death Index (NDI). Medical records for all deaths and ICD implantations were pursued to

classify endpoints. Families and witnesses of patients who died outside of the hospital were interviewed regarding details leading up to and including the death.

The primary endpoint was sudden and/or arrhythmic death (SAD). In accordance with prior consensus guidelines, a definite sudden cardiac death was defined as a death and/or witnessed cardiac arrest within one hour of symptom onset, and a probable sudden cardiac death was classified as an unwitnessed death or death during sleep, wherein the subject was noted to be symptom-free within the preceding 24 hours. (17) In both cases, there were no other probable causes of death on history and/or autopsy. An arrhythmic death was defined as a sudden, spontaneous loss of pulse without evidence of prior circulatory impairment or neurologic dysfunction, as per Hinkle and Thaler criteria. (18) Successfully resuscitated out-of-hospital ventricular fibrillation (VF) arrests were also included in the primary endpoint. Deaths were also classified as cardiac, non-cardiac, or due to an unknown cause as outlined previously. (16) Cardiac deaths included SADs, deaths due to MI and progressive HF, and deaths that occurred during CV procedures. Endpoints were adjudicated by three reviewers (R.V.V., N.A.C., C.M.A.).

Statistical Analysis

Baseline characteristics of the population were presented as means with standard deviations, percentages, and compared using t-tests and chi-square tests as appropriate. For all analyses, participants contributed person-time from the date of enrollment to the first occurrence of death, out-of-hospital cardiac arrest, loss to follow-up, or last contact date up to December 2, 2019. Cumulative incidence curves were used to calculate absolute rates of SAD and non-SAD by strata of DM and HbA_{1c} levels (< 5.7%, 5.7–6.4%, ≥ 6.5%), accounting for the corresponding competing outcome. DM status was further classified as non-insulin-dependent DM (nIDDM) and insulin-dependent DM (IDDM) and similar analyses were performed. The Gray test was used to make comparisons of cumulative incidence across these strata.

Subdistribution hazards models (Fine-Gray) were used to examine the association of DM and HbA_{1c} levels with SAD and non-SAD. In these models, individuals who experience the competing mode of death are not censored but remain within the risk sets for the alternative competing outcome. Covariates that were prespecified to be included in these multivariable models were age, race, sex, NYHA class, and LVEF. To determine which other covariates outlined in Table 1 were to be included, a conservative stepwise selection was performed with p-value for entry specified at 0.25 and p-value to stay specified at 0.15. Atrial fibrillation (AF), hypertension, family history of SAD, smoking, BMI, diuretics, and lipid-lowering agents were included in the final models based upon these criteria. For non-normally distributed variables, appropriate transformation to improve normality were performed, and spline modeling was used to determine the linearity of the relationship with SAD. The relationship between age and SAD was nonlinear, thus a squared term was included in the models. DM and HbA_{1c} were initially evaluated in separate Fine-Gray models, and then both covariates were included in a separate model to determine the independent contributions to SAD risk. To explore whether the association between HbA_{1c}

and SAD differed in patients with DM versus those without, an interaction term was added to the latter model.

To directly assess if DM or HbA_{1c} were differentially associated with SAD versus non-SAD, cause-specific hazard ratios based on the Cox model were compared utilizing the method of Lunn-McNeil. (16,19,20) These competing risk models allow individual covariates to have different hazard ratios for SAD and non-SAD in a single multivariable proportional hazards model stratified on event type. This approach can be readily implemented using data augmentation, which requires that each subject has a separate observation for each outcome. To evaluate whether risk factor relationships differed for the SAD and non-SAD outcomes, the likelihood ratio test was used to compare the full competing risk model with a series of reduced models in which one risk factor at a time was forced to have a single effect estimate across both outcomes, while the effects of all other risk factors were allowed to be different.(19,20)

In secondary analyses, both the Fine-Gray and the competing risk Cox proportional hazard models were repeated with secondary outcome endpoints of cardiac and non-cardiac death, as well as SAD and non-SAD cardiac death. In the latter models, non-SAD deaths that were due to non-cardiac causes were not considered a competing outcome and were instead censored in the Fine-Gray models.

To explore whether HbA_{1c} levels and/or other clinical characteristics might serve as potential risk factors for SAD in DM patients, the Fine-Gray models and competing risk Cox regression models for SAD versus non-SAD were repeated after stratifying by DM status. Recently, a composite ECG score accounting for contiguous Q waves, LV hypertrophy, QRS duration, and prolonged JTc was found to selectively predict SAD as opposed to non-SAD events in the entire PRE-DETERMINE cohort. (21) To explore whether this ECG score might be similarly useful within the DM population, this score was included along with the other candidate variables in the stratified analysis.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). A 2-tailed p-value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics and HbA_{1c} Across Spectrum of Diabetes

Baseline characteristics of the 1782 diabetics and 3762 non-diabetics are shown in Table 1. The DM population was older, had a higher proportion of women and minorities, had higher BMIs on average, and were more likely to have certain comorbidities, such as HTN or COPD ($p \leq 0.05$ for all comparisons). Patients with DM were also less likely to exercise or drink alcohol ($p \leq 0.05$ for all comparisons). The DM population had slightly lower mean LVEF compared to the non-DM population (51% vs. 53%, $p \leq 0.001$), and had a higher percentage of patients with NYHA class II-IV symptoms (27.4% vs. 16.3%, $p \leq 0.001$). Patients with DM were also more likely to be treated with beta blockers (85% vs. 81%), renin-angiotensin-aldosterone inhibitors (76% vs. 67%), and diuretics (45% vs. 24%) ($p \leq 0.001$ for all comparisons). As expected, HbA_{1c} levels were higher in patients with DM

(median HbA_{1c} 6.7%) versus those without (median HbA_{1c} 5.6%). As can be seen in Table 2, a higher proportion of patients with IDDM had a HbA_{1c} level ≥ 6.5% as compared to those with nIDDM (82% versus 48%, respectively). The prevalence of undiagnosed DM (HbA_{1c} ≥ 6.5%) was low (3%); however, a significant fraction of patients without DM had HbA_{1c} levels consistent with pre-DM (n = 1338, 36%).

The relationship of DM to SAD and non-SAD

Over a median follow-up time of 6.8 years, there were 184 cases of SAD and 758 cases of non-SAD in the population. The majority of non-SADs were due to non-cardiac causes (n = 561) rather than cardiac causes (n = 142). The absolute risk of SAD was significantly elevated in patients with DM, with an estimated 7-year cumulative incidence of SAD of 4.8% (95% CI 3.8–5.9) as compared to 2.8% (95% CI 2.2–3.3) in those without DM (Figure 1). However, the 7-year cumulative incidence of non-SAD was ~ 4-fold greater than SAD, both in patients with DM (19.2%, 95% CI 17.3–21.2) and in those without (11.5%, 95% CI 10.5–12.6). In Fine-Gray models accounting for multiple confounders and the competing outcome (Table 3), DM was associated with SAD (HR 1.50, 95% CI 1.10–2.04, p = 0.010) and non-SAD (1.65, 95% CI, 1.41–1.93; p<0.001). In a direct test of this difference, in competing risk Cox proportional hazard models the hazard ratios did not significantly differ for SAD versus non-SAD (cause-specific HR for DM [95% CI]: 1.59 [1.17–2.17] vs. 1.72 [1.48–2.00] respectively, p-diff = 0.67).

When patients with DM were further subdivided into patients with and without IDDM, a gradation of absolute and relative risk was observed for SAD and non-SAD (Table 3, Figure 2). The 7-year cumulative incidences of SAD (5.8%, 95% CI 4.1–7.9) and non-SAD (22.4%, 95% CI 19.0–26.0) were highest in patients with IDDM; however, the proportion of deaths that were SAD were similar between the three groups (20.2%, 20.3% and 18.9% in IDDM, nIDDM, no DM, respectively). In multivariable Fine-Gray models, the magnitude of the relative risk elevation associated with IDDM was greater for non-SAD (HR 2.21; 95% CI, 1.77–2.75) than for SAD (HR 1.67; 95% CI, 1.10–2.52); however, confidence intervals overlapped and there was no evidence for a differential association of IDDM with SAD as compared to non-SAD in competing risk Cox proportional hazard models (p-diff = 0.27, data not shown).

The relationship of HbA_{1c} to SAD and non-SAD

Similar to the results for DM, HbA_{1c} levels were significantly associated with SAD. Each 1% increment in HbA_{1c} was associated with a hazard ratio of 1.12 (95% CI 1.01–1.25, p = 0.038) and 1.24 (95% CI 1.16–1.32, p ≤ 0.001) for SAD and non-SAD, respectively. There was also a gradation of absolute risk for both SAD and non-SAD across clinical cut-points of HbA_{1c} (<5.7%, 5.7–6.4%, >6.5%) (Figure 3). In competing risk Cox proportional hazard models, there was again no evidence for a differential association of HbA_{1c} with SAD vs. non-SAD (p-diff = 0.11). When HbA_{1c} was added to the multivariable Fine-Gray model that included DM, both associations were attenuated; however, the association with SAD was attenuated to a greater extent for HbA_{1c} (HR 1.05, 95% CI 0.91–1.20, p = 0.52) than for DM (HR 1.40; 95%, CI 0.98–2.02, p = 0.067). When an interaction term was included to see if

the impact of HbA_{1c} on SAD differed in patients with and without DM, the interaction was non-significant (p = 0.90).

Secondary Outcome Analyses

When non-SAD deaths were limited to cardiac deaths, DM and HbA_{1c} appeared to be more strongly associated with non-SAD cardiac death as compared to SAD both in Fine-Gray analysis (Supplementary Table 1) and in the competing risk Cox proportional hazard models (cause-specific HR for DM [95% CI]: 2.73 [1.92–3.87] vs. 1.59 [1.17–2.17] respectively, p-diff = 0.024); cause-specific HR for HbA_{1c} [95% CI]: 1.39 [1.23–1.56] vs. 1.15 [1.03–1.29] respectively, p-diff = 0.026). In analyses that examined the relationship between DM and HbA_{1c} and cardiac versus non-cardiac death, the cumulative incidence of cardiac versus non-cardiac death followed a pattern similar to that observed for SAD versus non-SAD death, with higher overall incidence of non-cardiac death compared to cardiac death across subtypes of DM and categories of HbA_{1c} (Supplementary Figure 1). In Fine-Gray analysis, DM and HbA_{1c} were strongly associated with both cardiac death and non-cardiac death (Supplementary Table 2). In competing risk Cox proportional hazard models, there was no significant differential association of DM or HbA_{1c} with cardiac death vs. non-cardiac death (cause-specific HR for DM [95% CI]: 1.99 [1.59–2.50] vs. 1.53 [1.28–1.84] respectively, p = 0.077; cause-specific HR for HbA_{1c} [95% CI]: 1.25 [1.15–1.35] vs. 1.25 [1.16–1.34] respectively, p = 0.963).

HbA_{1c} and Risk Factors for SAD versus non-SAD in Patients with DM

In the Fine-Gray analyses limited to DM patients, HbA_{1c} was no longer significantly associated with SAD (HR 1.06, 95% CI 0.91–1.24, p = 0.471), but did remain associated with non-SAD (HR 1.18, 95% CI 1.07–1.29, p < 0.001). Low LVEF (<50%), AF, and high ECG score (3+) were all associated with increased risk for SAD in the DM population ($p \leq 0.05$ for all comparisons) (Table 4). When ECG score was replaced with its individual components in exploratory analyses (Table 4), the magnitude of the association with SAD was greatest for LV hypertrophy and contiguous Q waves (Supplementary Table 3).

In competing risk Cox proportional hazard models within the DM population (Figure 4), HbA_{1c} was not differentially associated with SAD vs. non-SAD (cause-specific HR [95% CI]: 1.11 [0.95–1.30] vs. 1.22 [1.13–1.33]), p-diff = 0.26). The magnitude of the risk elevations associated with BMI, AF, decreasing LVEF, and increasing ECG score were greater for SAD than non-SAD, but these differences were not statistically significant. However, our power to detect such differences within the DM subgroup of the population is limited.

Discussion

In this large, contemporary prospective cohort of at-risk patients with CAD and MI and/or mild-moderate LV dysfunction who do not meet the criteria for ICD implantation, DM and HbA_{1c} levels were positively associated with both SAD and non-SAD, with a much greater absolute risk for non-SAD than SAD in the DM population. When non-SAD events were limited to those due to cardiac causes, the magnitude of the association for non-SAD cardiac

death was greater than that for SAD for both DM and HbA_{1c}. In the DM population, HbA_{1c} levels did not assist in identifying DM patients at higher risk for SAD, whereas decreasing LVEF, AF and selected ECG abnormalities were significantly associated with SAD.

The markedly elevated absolute risk of non-SAD relative to that of SAD in patients with DM demonstrates the challenge that will be faced when designing ICD trials in this high-risk population. Previously, post-hoc analyses of various RCTs, including the MADIT-II trial, have suggested that patients with DM derived the same benefit from ICDs or cardiac resynchronization therapy-defibrillators (CRT-Ds) as patients without DM. (22,23). However, a recent patient level analysis of four primary prevention ICD trials in patients with LVEF <35% found that randomization to ICD implantation was not associated with improved all-cause mortality in patients with DM, whereas, it was strongly associated with reduced mortality in those without. (12,24) These data suggest that either ICD therapy may be less effective in patients with DM and LVEF <35% and/or the risk of non-SAD outweighs the benefits of ICD therapy in this population. (11) Our prospective data, as well as that from prior studies (10), suggest that the risk of non-SAD may similarly outweigh any benefits that the ICD might have on SAD among DM patients who have an LVEF >35%. MADIT S-ICD planned to test the subcutaneous ICD in this exact population; however, the trial was terminated early due to slow enrollment. (11)

Despite the high absolute risk of competing causes of death, the present study, along with several others (7–10), clearly documents that patients with CHD and/or HF with DM are at significantly elevated absolute SAD risk; thus, SAD prevention in this population remains an important unmet need. Our data, taken into context with prior studies, suggest that further risk stratification with markers that specifically associate with SAD rather than non-SAD would be needed before randomized trials of the ICD could be contemplated in patients with DM. In our stratified analysis within the DM population, although trends were seen for BMI and LVEF 40–49%, none of the variables tested were statistically associated with SAD to a greater extent than non-SAD. Low LVEF, AF, and ECG score have been independently associated with SAD in prior studies (21,25) and continued to predict SAD in our DM population. While not statistically significant, the risk of SAD associated with the ECG score was numerically higher than that of non-SAD, and the ECG components of scar and LVH had the strongest associations. Further exploration of these factors as methods to predict SAD in the DM population remains promising.

HbA_{1c} levels and SAD risk

In a previous study that looked at patients without known CAD, HbA_{1c} was associated with increased risk of SAD, even after controlling for DM status. (14) In our population of higher risk patients with known CAD, HbA_{1c} was still associated with SAD, but not after controlling for DM. High glucose levels have been linked to SAD in prior studies (6,14,15,26), and purported hyperglycemia-mediated mechanisms of SAD include, but are not limited to, endothelial dysfunction, inflammation, cardiac dysautonomia, and abnormal repolarization. (5,27) However, hyperglycemia is also linked to other causes of acute and chronic morbidity/mortality (e.g. chronic kidney disease or stroke), and tight glucose control and hypoglycemia might also predispose to SAD in patients with DM. Thus, HbA_{1c} may

not necessarily be the best biomarker to differentiate between risk of SAD and non-SAD in patients with DM. Insulin dependence, another factor which generally reflects poor glucose control, was also highly correlated with SAD in our study and has been shown to be associated with SAD in patients with preserved LVEF. (13) While insulin dependence was also strongly associated with non-SAD in our population, its role in risk prediction warrants further investigation given the arrhythmic effects linked to hypoglycemia. (28)

Future directions

DM is a complicated syndrome that is more than just hyperglycemia, involving insulin resistance, obesity, and lipid metabolism among other things. It is possible that different biomarkers associated with DM, ones that are not necessarily just markers of hyperglycemia, may assist with SAD risk stratification and differentiation from non-SAD. (29) Based upon these and prior analyses in this cohort (16), an ICD trial in CHD patients with DM, even among those with MI and/or mild-moderate LV dysfunction, is unlikely to yield a mortality benefit given the proportional high risk for non-SAD. If trials were to be designed in this population, subgroups with proportionately higher risks of non-SAD as compared to SAD, such as older patients and those with significant HF, may need to be excluded to maximize potential benefit of an ICD. Future ICD trial design will need to consider both the absolute risk and relative proportion of SAD and non-SAD events.

Finally, more work needs to be done to identify medical therapies that reduce SAD in DM. Currently, the pharmacotherapy staples of SAD risk reduction include beta blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, and angiotensin-neprilysin inhibitors, all of which are commonly used in diabetics. (1) However, the recent advent of sodium-glucose cotransporter-2 (SGLT2) inhibitors provides promise. All three of the major SGLT2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) have been shown to reduce CV mortality, and various pleiotropic effects beyond glucose control have been implicated in these findings. (30–32) However, whether these agents specifically reduce SAD in DM and non-DM populations is yet to be determined.

Limitations

This study has some limitations. First, while the 184 cases of SAD represent one of the largest sets of prospectively collected SADs in this at-risk CHD population with LVEF >35%, there is a chance of type II error given the relative infrequency of the endpoint, particularly in the analysis stratified by DM. Second, although we utilized rigorous and widely accepted methods of SAD adjudication, (17,18) the possibility of misclassification cannot be excluded. Third, although efforts were made to specifically recruit women and minorities, the cohort remained predominantly white and male; which limits our ability to generalize the findings to other demographic groups. Fourth, information regarding DM, IDDM, HbA_{1c}, and other risk factors was only ascertained at baseline; thus, some degree of misclassification likely occurred over time due to uncaptured changes in DM status and HbA_{1c}, which could bias our results toward the null. However, the design does mimic that of a randomized trial where patient selection is made on characteristics identified at baseline. Lastly, our study did not control for the use of oral hypoglycemic or non-insulin injectable medications, which would have been informative.

Conclusion

In this prospective study of patients with CAD who do not meet criteria for ICD implantation, DM and HbA_{1c} were associated with increased risk of SAD, but also with a substantially increased absolute risk of non-SAD, suggesting that ICD therapy may not be an ideal therapy for this population. HbA_{1c} was not associated with increased risk of SAD within the DM population. More work is needed to identify DM patients who are specifically at higher risk for SAD to guide more tailored ICD recommendations and advance medical interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding:

The study was supported by research grants from the National Heart, Lung, and Blood Institute (R01HL091069), St Jude Medical Inc. and St Jude Medical Foundation, and Roche Diagnostics.

Abbreviations List

AF	atrial fibrillation
CAD	coronary artery disease
DM	diabetes mellitus
HbA_{1c}	hemoglobin A_{1c}
HF	heart failure
ICD	implantable cardioverter defibrillator
IDDM	insulin-dependent diabetes mellitus
LVEF	left ventricular ejection fraction
nIDDM	non-insulin-dependent diabetes mellitus
NYHA	New York Heart Association
SAD	sudden and/or arrhythmic death

References

1. Al-Khatib SM, Stevenson WG, Ackerman MJ et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2018;15:e190–e252. [PubMed: 29097320]
2. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res 2015;116:1887–906. [PubMed: 26044246]

3. Stecker EC, Vickers C, Waltz J et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. J Am Coll Cardiol 2006;47:1161–6. [PubMed: 16545646]
4. Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry. Eur Heart J 2003;24:1204–9. [PubMed: 12831814]
5. Balkau BJ X; Ducimetière P; Eschwège E Diabetes as a risk factor for sudden cardiac death. Lancet 1999.
6. Jouven X, Lemaitre RN, Rea TD, Sotoodehnia N, Empana JP, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. Eur Heart J 2005;26:2142–7. [PubMed: 15980034]
7. Junttila MJ, Barthel P, Myerburg RJ et al. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. Heart Rhythm 2010;7:1396–403. [PubMed: 20682359]
8. Junttila MJ, Kiviniemi AM, Lepojarvi ES et al. Type 2 diabetes and coronary artery disease: Preserved ejection fraction and sudden cardiac death. Heart Rhythm 2018;15:1450–1456. [PubMed: 30274618]
9. Yeung CY, Lam KS, Li SW, Lam KF, Tse HF, Siu CW. Sudden cardiac death after myocardial infarction in type 2 diabetic patients with no residual myocardial ischemia. Diabetes Care 2012;35:2564–9. [PubMed: 22875229]
10. Coiro S, Girerd N, Sharma A et al. Association of diabetes and kidney function according to age and systolic function with the incidence of sudden cardiac death and non-sudden cardiac death in myocardial infarction survivors with heart failure. Eur J Heart Fail 2019;21:1248–1258. [PubMed: 31476097]
11. Kutyifa V, Beck C, Brown MW et al. Multicenter Automatic Defibrillator Implantation Trial-Subcutaneous Implantable Cardioverter Defibrillator (MADIT S-ICD): Design and clinical protocol. Am Heart J 2017;189:158–166. [PubMed: 28625372]
12. Sharma A, Al-Khatib SM, Ezekowitz JA et al. Implantable cardioverter-defibrillators in heart failure patients with reduced ejection fraction and diabetes. Eur J Heart Fail 2018;20:1031–1038. [PubMed: 29761861]
13. Patel RB, Venkateswaran RV, Singh A et al. The Current Landscape of Atrial Fibrillation and Atrial Flutter Clinical Trials: A Report of 348 Studies Registered With ClinicalTrials.gov. JACC Clin Electrophysiol 2018;4:944–954. [PubMed: 30025696]
14. Patel RB, Moorthy MV, Chiuve SE, Pradhan AD, Cook NR, Albert CM. Hemoglobin A1c levels and risk of sudden cardiac death: A nested case-control study. Heart Rhythm 2017;14:72–78. [PubMed: 27591826]
15. Drechsler C, Krane V, Ritz E, Marz W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. Circulation 2009;120:2421–8. [PubMed: 19948978]
16. Chatterjee NA, Moorthy MV, Pester J et al. Sudden Death in Patients With Coronary Heart Disease Without Severe Systolic Dysfunction. JAMA Cardiol 2018;3:591–600. [PubMed: 29801082]
17. Fishman GI, Chugh SS, Dimarco JP et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation 2010;122:2335–48. [PubMed: 21147730]
18. Hinkle LE Jr., Thaler HT. Clinical classification of cardiac deaths. Circulation 1982;65:457–64. [PubMed: 7055867]
19. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics 1995;51:524–32. [PubMed: 7662841]
20. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. Am J Epidemiol 2005;162:975–82. [PubMed: 16207808]
21. Chatterjee NA, Tikkanen JT, Panicker GK et al. Simple electrocardiographic measures improve sudden arrhythmic death prediction in coronary disease. Eur Heart J 2020.
22. Shahreyar M, Mupiddi V, Choudhuri I, Sra J, Tajik AJ, Jahangir A. Implantable cardioverter defibrillators in diabetics: efficacy and safety in patients at risk of sudden cardiac death. Expert Rev Cardiovasc Ther 2015;13:897–906. [PubMed: 26098816]

23. Wittenberg SM, Cook JR, Hall WJ et al. Comparison of efficacy of implanted cardioverter-defibrillator in patients with versus without diabetes mellitus. Am J Cardiol 2005;96:417–9. [PubMed: 16054472]
24. Rorth R, Dewan P, Kristensen SL et al. Efficacy of an implantable cardioverter-defibrillator in patients with diabetes and heart failure and reduced ejection fraction. Clin Res Cardiol 2019;108:868–877. [PubMed: 30689020]
25. Rattanawong P, Upala S, Riangwiwat T et al. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. J Interv Card Electrophysiol 2018;51:91–104. [PubMed: 29332241]
26. Laukkanen JA, Makikallio TH, Ronkainen K, Karppi J, Kurl S. Impaired fasting plasma glucose and type 2 diabetes are related to the risk of out-of-hospital sudden cardiac death and all-cause mortality. Diabetes Care 2013;36:1166–71. [PubMed: 23248190]
27. Bergner DW, Goldberger JJ. Diabetes mellitus and sudden cardiac death: what are the data? Cardiol J 2010;17:117–29. [PubMed: 20544609]
28. Yakubovich N, Gerstein HC. Serious cardiovascular outcomes in diabetes: the role of hypoglycemia. Circulation 2011;123:342–8. [PubMed: 21263007]
29. Lyons TJ, Basu A. Biomarkers in diabetes: hemoglobin A1c, vascular and tissue markers. Transl Res 2012;159:303–12. [PubMed: 22424433]
30. McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995–2008. [PubMed: 31535829]
31. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644–657. [PubMed: 28605608]
32. Zinman B, Wanner C, Lachin JM et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015;373:2117–28. [PubMed: 26378978]

Perspectives

Competency in Medical Knowledge

Patients with CAD and DM without severe systolic dysfunction are at elevated risk for SAD; however, these patients are 4 times more likely to die from other causes of death, which would diminish any mortality benefit this population might receive from ICDs. HbA_{1c} levels did not augment SAD risk stratification in this CAD population and did not predict SAD among the subset of patients with DM; thus, new markers of risk are needed.

Translational Outlook

These data underscore the need for better SAD risk stratification of patients with DM and CAD, ideally by identifying risk factors and/or biomarkers that can discriminate between SAD and non-SAD risk. Further identification of therapeutics to attenuate SAD risk for this at-risk population beyond ICD therapy is also warranted.

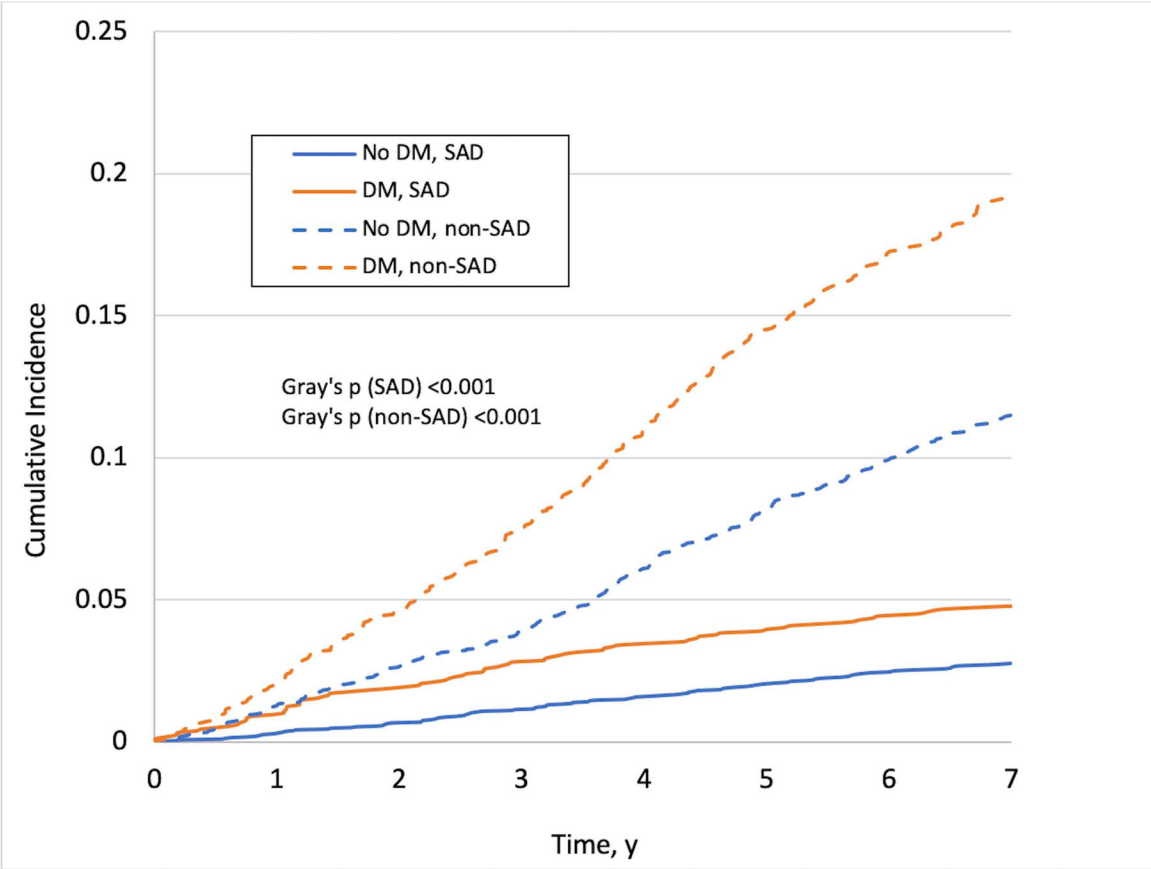


Figure 1. Cumulative Incidence of Sudden and/or Arrhythmic Death (SAD) and Non-SAD in Diabetics and Non-Diabetics

The 7-year cumulative incidence of SAD and non-SAD are shown for diabetics and non-diabetics. The Gray test of equivalence of cumulative incidence functions across strata for each outcome is depicted. Abbreviations: DM, diabetes mellitus; SAD, sudden and/or arrhythmic death.

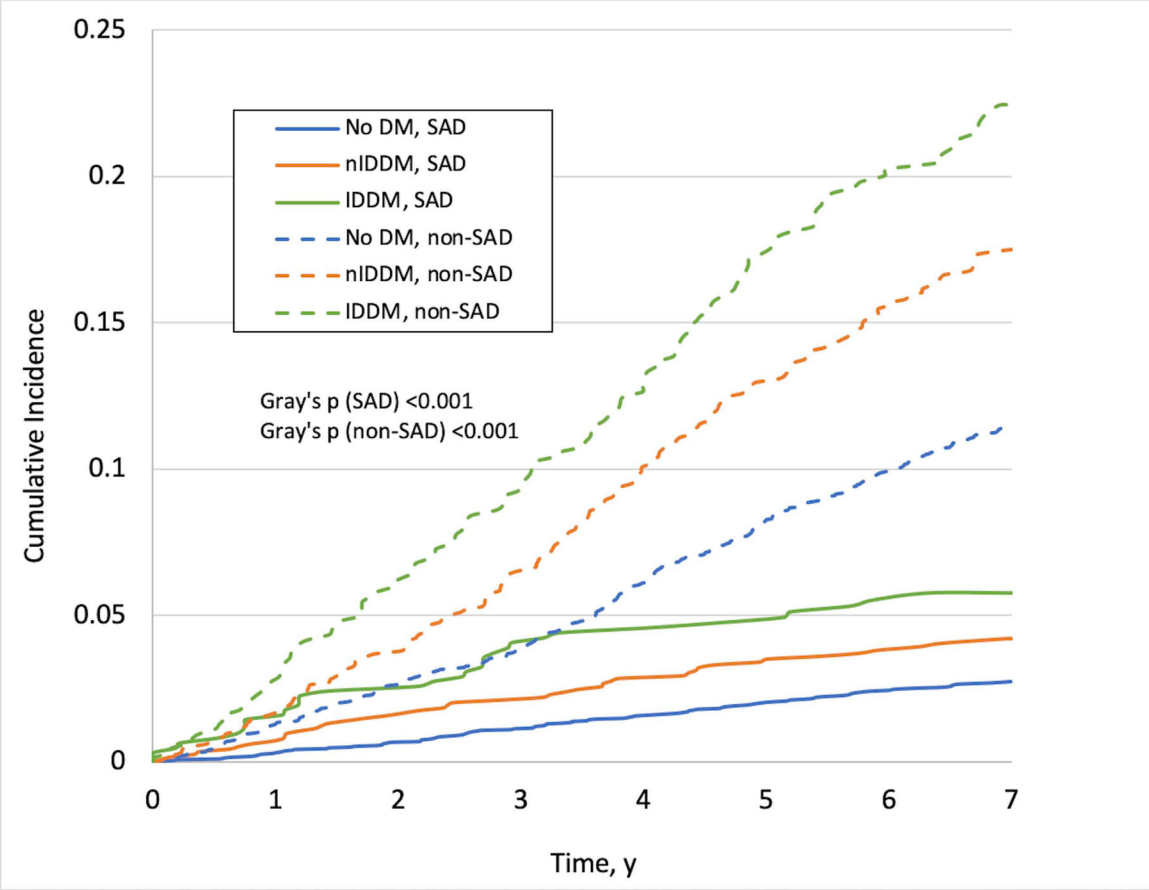


Figure 2. Cumulative Incidence of Sudden and/or Arrhythmic Death (SAD) and Non-SAD Across Subtypes of Diabetes Mellitus

The 7-year cumulative incidence of SAD and non-SAD are shown across subtypes of diabetes mellitus. The Gray test of equivalence of cumulative incidence functions across strata for each outcome is depicted. Abbreviations: DM, diabetes mellitus; nIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; SAD, sudden and/or arrhythmic death.

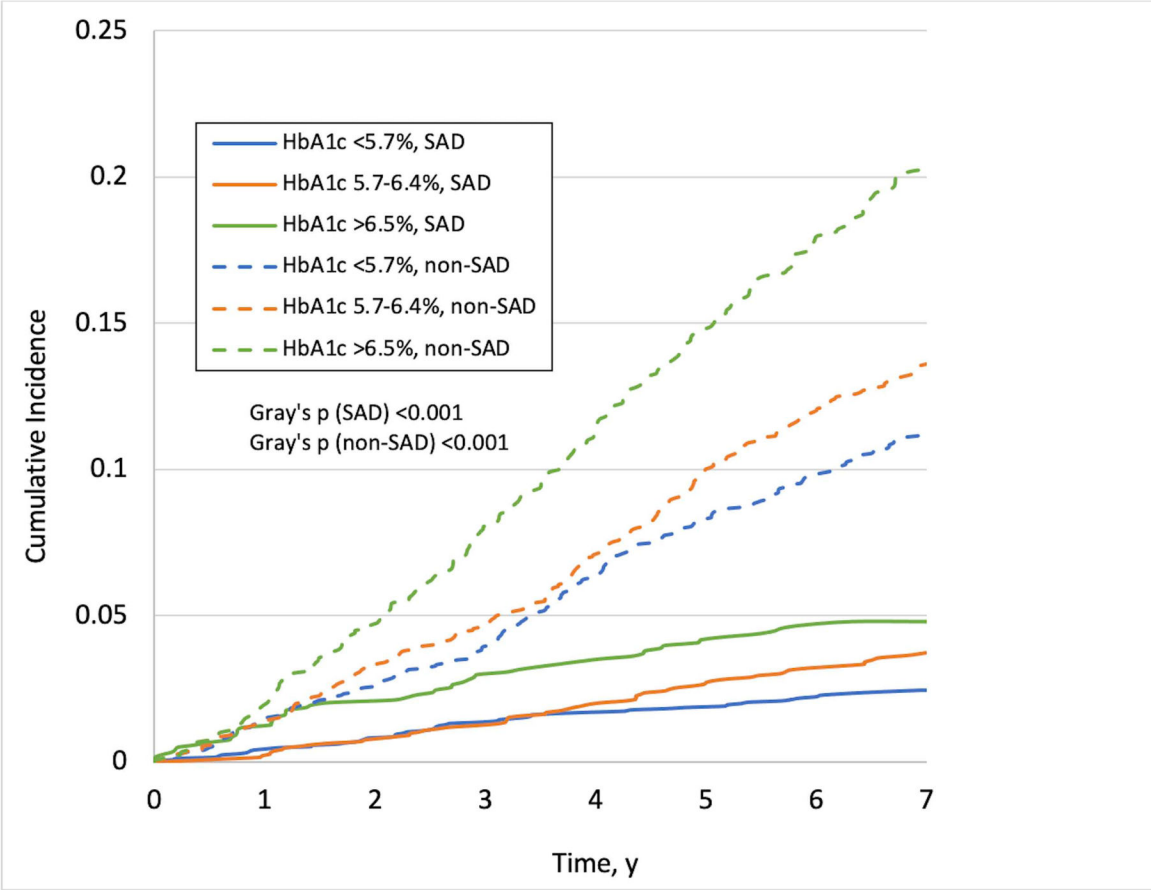


Figure 3. Cumulative Incidence of Sudden and/or Arrhythmic Death (SAD) and Non-SAD Across HbA_{1c}

The 7-year cumulative incidence of SAD and non-SAD are shown across categories of HbA_{1c}. The Gray test of equivalence of cumulative incidence functions across strata for each outcome is depicted. Abbreviations: HbA_{1c}, hemoglobin A_{1c}; SAD, sudden and/or arrhythmic death.

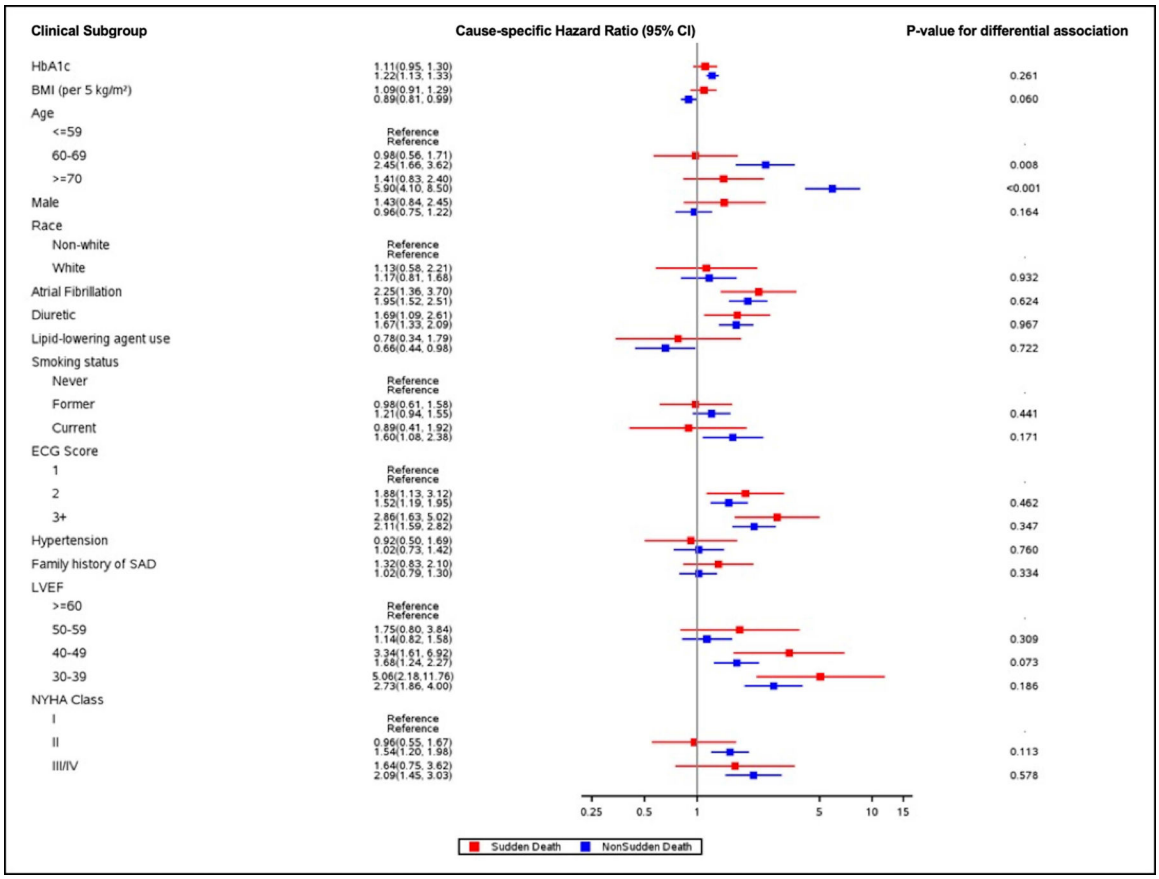
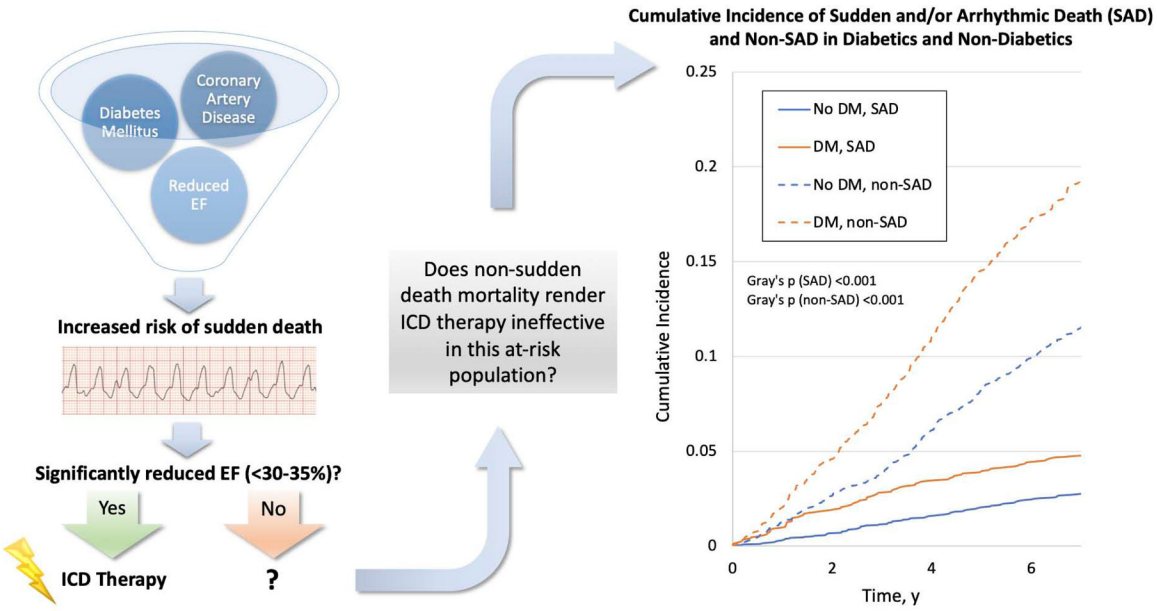


Figure 4. Differential Association of Clinical Risk Factors with Sudden and/or Arrhythmic Death (SAD) vs. Non-SAD in Patients with Diabetes Mellitus

Competing risk Cox proportional hazard models were used in the diabetic population to evaluate the risk of SAD and non-SAD associated with various clinical subgroups. Models were adjusted for age and sex. The p-values depicted reflect the differential association of each clinical subgroup with mode of death. Abbreviations: HbA_{1c}, hemoglobin A_{1c}; BMI, body mass index; SAD, sudden and/or arrhythmic death; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.



Central Illustration. Diabetes and Risk of Sudden Death in Coronary Artery Disease Patients Without Severe Systolic Dysfunction

Patients with CAD, LVEF >30–35%, and DM and/or elevated HbA_{1c} have a heightened risk of sudden cardiac death. However, they have a higher absolute risk of dying from non-sudden death, suggesting that ICD therapy may be less effective in this population.

Table 1.

Baseline Characteristics*

Baseline Characteristic	Diabetes (n= 1782)	No Diabetes (n= 3762)	p-value
Age, years	65 ± 10	64 ± 11	0.013
Male, no.	1302 (73.1)	2926 (77.8)	< 0.001
White	1531 (85.9)	3416 (90.8)	< 0.001
BMI, kg/m^2	31.9 ± 6.3	29.4 ± 5.7	< 0.001
NYHA class			< 0.001
I	1289 (72.6)	3144 (83.8)	
II	378 (21.3)	505 (13.5)	
III	98 (5.5)	94 (2.5)	
IV	11 (0.6)	11 (0.3)	
Canadian anginal class			< 0.001
Asymptomatic	1374 (77.4%)	3205 (85.4%)	
I	192 (10.8%)	298 (7.9%)	
II	112 (6.3%)	146 (3.9%)	
III	72 (4.1%)	70 (1.9%)	
IV	25 (1.4%)	34 (0.9%)	
LVEF, %	51 ± 10	53 ± 9	< 0.001
Hypertension	1553 (87.1)	2669 (70.9)	< 0.001
Hemoglobin A_{1c}, %	6.7 (6.1–7.7)	5.6 (5.3–5.8)	< 0.001
Atrial fibrillation	265 (14.9)	495 (13.2)	0.084
History of myocardial infarction	1571 (88.2)	3466 (92.1)	< 0.001
History of revascularization			
Percutaneous coronary intervention	1385 (77.7)	3051 (81.1)	0.003
Coronary artery bypass surgery	736 (41.3)	1072 (28.5)	< 0.001
COPD	233 (13.1)	392 (10.4)	0.004
Family history of sudden death	469 (26.3)	922 (24.5)	0.146
Smoking status			0.056
Never	594 (33.3)	1270 (33.8)	
Former	955 (53.6)	1916 (50.9)	
Current	233 (13.1)	575 (15.3)	
Alcohol intake			< 0.001
Never	609 (34.2)	1013 (26.9)	
Former	473 (26.6)	749 (19.9)	
Current	698 (39.2)	1999 (53.2)	
Exercise			< 0.001
Rarely/never	983 (55.2)	1553 (41.3)	
1–3×/month	38 (2.1)	123 (3.3)	

Baseline Characteristic	Diabetes (n= 1782)	No Diabetes (n= 3762)	p-value
1–2×/week	242 (13.6)	544 (14.5)	
≥3×/week	517 (29.0)	1537 (40.9)	
Fish consumption			< 0.001
Rarely/never	720 (40.5)	1277 (34.0)	
1–3×/month	320 (18.0)	626 (16.7)	
≥1×/week	738 (41.5)	1850 (49.3)	
Medication use			
Aspirin	1547 (86.8)	3336 (88.7)	0.046
Beta blocker	1522 (85.4)	3064 (81.5)	< 0.001
Lipid-lowering agent	1671 (93.8)	3494 (92.9)	0.218
Renin-angiotensin-aldosterone inhibitors	1358 (76.2)	2501 (66.5)	< 0.001
Diuretic	809 (45.4)	915 (24.3)	< 0.001

* Values are number (percentage) for categorical variables, means ± SD for normally distributed variables, and median (interquartile range) for non-normally distributed variables. Abbreviations: BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

Table 2.

Hemoglobin A_{1c} and Diabetes Status*

Diabetes Status	HbA_{1c} <5.7%, No. (%)	HbA_{1c} 5.7–6.4%, No. (%)	HbA_{1c} ≥6.5%, No. (%)	Total
Insulin-dependent diabetes mellitus (IDDM) (Type I + Type II-insulin-dependent)	26 (4%)	89 (14%)	513 (82%)	628
Non-insulin-dependent diabetes mellitus (nIDDM)	138 (12%)	458 (40%)	558 (48%)	1154
No diabetes mellitus (No DM)	2304 (61%)	1338 (36%)	120 (3%)	3762

* The Jonckheere-Terpstra test confirmed a statistically significant trend between diabetes status and HbA_{1C} when treated as ordinal variables ($p < 0.001$).

Table 3.

The Association between Diabetes Mellitus, Insulin Dependence, and Hemoglobin A_{1c} and Sudden and/or Arrhythmic Death (SAD) and non-SAD Accounting for Competing Outcomes*

Clinical Subgroup	Hazard Ratio for SAD (95% CI)			Hazard Ratio for non-SAD (95% CI)		
Diabetes mellitus						
No	Reference			Reference		
Yes	1.50 (1.10–2.04)	p = 0.010		1.65 (1.41–1.93)	p < 0.001	
Insulin-dependency						
No diabetes mellitus	Reference			Reference		
Non-insulin-dependent diabetes mellitus	1.41 (0.99–2.01)	p = 0.059	p-trend = 0.007	1.42 (1.19–1.70)	p < 0.001	p-trend < 0.001
Insulin-dependent diabetes mellitus	1.67 (1.10–2.52)	p = 0.016		2.21 (1.77–2.75)	p < 0.001	
Hemoglobin A_{1c}						
Continuous variable†	1.12 (1.01–1.25)	p = 0.038		1.24 (1.16–1.32)	p < 0.001	
Categorical variable						
<5.7%	Reference			Reference		
5.7–6.4%	1.29 (0.90–1.85)	p = 0.161		1.01 (0.85–1.20)	p = 0.92	
≥6.5%	1.51 (1.02–2.24)	p = 0.040		1.68 (1.39–2.02)	p < 0.001	

*Four Fine-Gray models were utilized for each of the endpoints (SAD and non-SAD) accounting for the corresponding competing outcomes. The first set of models included DM as a binary variable, the second set included DM categorized by insulin dependency, the third set included HbA_{1c} as a continuous variable, and the final set included HbA_{1c} split by clinical cut points. All models were covariate adjusted and included age, sex, race, NYHA class, LVEF, hypertension, atrial fibrillation, family history of SAD, smoking status, BMI, diuretic use, and lipid-lowering agent use.

†The values depicted in this row are the hazard ratios associated with a 1% increment in hemoglobin A_{1c}.

Table 4.

Risk of Sudden and/or Arrhythmic Death (SAD) and Non-SAD in Patients with Diabetes Mellitus in Fine-Gray Models Accounting for Competing Outcomes

Variable	Hazard Ratio (95% CI)			
	SAD (n = 82)		Non-SAD (n = 325)	
Hemoglobin A_{1c}	**1.06 (0.91–1.24)**	**p = 0.471**	**1.18 (1.07–1.29)**	**p < 0.001**
Age				
≤59	1 (Reference)		1 (Reference)	
60–69	0.93 (0.53–1.63)	p = 0.804	2.74 (1.83–4.12)	p < 0.001
≥70	1.02 (0.56–1.85)	p = 0.949	5.66 (3.82–8.39)	p < 0.001
White	1.03 (0.51–2.08)	p = 0.932	1.22 (0.83–1.79)	p = 0.321
Male	1.39 (0.79–2.45)	p = 0.253	0.96 (0.73–1.26)	p = 0.771
NYHA class				
I	1 (Reference)		1 (Reference)	
II	0.76 (0.42–1.36)	p = 0.350	1.33 (1.02–1.73)	p = 0.036
III/IV	1.01 (0.45–2.30)	p = 0.975	1.73 (1.16–2.57)	p = 0.007
LVEF				
≥60	1 (Reference)		1 (Reference)	
50–59	1.61 (0.74–3.50)	p = 0.230	1.00 (0.72–1.38)	p = 0.984
40–49	2.63 (1.25–5.53)	p = 0.011	1.25 (0.91–1.71)	p = 0.164
30–39	3.51 (1.51–8.14)	p = 0.004	1.82 (1.21–2.73)	p = 0.004
Hypertension	0.89 (0.47–1.69)	p = 0.725	1.01 (0.71–1.43)	p = 0.965
Atrial fibrillation	1.83 (1.04–3.23)	p = 0.036	1.51 (1.15–1.98)	p = 0.003
BMI (kg/m^2)	1.02 (0.98–1.06)	p = 0.283	0.97 (0.95–0.99)	p = 0.008
Family history of SAD	1.28 (0.80–2.04)	p = 0.313	0.98 (0.76–1.26)	p = 0.866
Smoking status				
Never	1 (Reference)		1 (Reference)	
Former	0.89 (0.55–1.43)	p = 0.618	1.16 (0.89–1.51)	p = 0.275
Current	0.82 (0.39–1.72)	p = 0.593	1.65 (1.11–2.46)	p = 0.014

Variable	Hazard Ratio (95% CI)			
	SAD (n = 82)		Non-SAD (n = 325)	
Hemoglobin A_{1c}	**1.06 (0.91–1.24)**	**p = 0.471**	**1.18 (1.07–1.29)**	**p < 0.001**
Lipid-lowering agent use	0.88 (0.38–2.02)	p = 0.754	0.73 (0.47–1.12)	p = 0.148
Diuretic use	1.24 (0.75–2.04)	p = 0.407	1.41 (1.10–1.80)	p = 0.006
ECG score				
1	1 (Reference)		1 (Reference)	
2	1.52 (0.91–2.55)	p = 0.114	1.25 (0.96–1.61)	p = 0.098
3+	2.04 (1.13–3.70)	p = 0.019	1.54 (1.14–2.10)	p = 0.006

*Risk factors for sudden and/or arrhythmic death (SAD) and non-SAD were studied in two separate Fine-Gray models, accounting for the respective competing outcomes. All covariates included in the Fine-Gray models are shown in the table. Abbreviations: BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.