Association of Diabetes and Impaired Kidney Function according to Age and LVEF on the Incidence of Sudden Death in Myocardial Infarction Survivors With Heart Failure

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Abstract

Aims: An implantable cardiac defibrillator (ICD) is recommended for reducing the risk of sudden cardiac death (SCD) in myocardial infarction (MI) patients with a left ventricular ejection fraction (LVEF) ≤30%, as well as patients with a LVEF ≤35% and heart failure (HF) symptoms. Diabetes and/or impaired kidney function may confer additional SCD risk. We assessed the association between these two risk factors and SCD, and non-SCD, among MI survivors taking account of age and LVEF**.**

Methods and Results: A total of 17,773 patients from the High-Risk MI Database were evaluated. Overall, diabetes and eGFR<60, individually and together, conferred a higher risk of SCD (adjusted competing risk HR 1.23, 1.23, and 1.32, respectively; all p<0.03) and non-SCD (HR: 1.34, 1.52, and 2.13, respectively; all p<0.0001). Annual SCD rates in patients with LVEF>35% and with diabetes, impaired kidney function, or both (2.0, 2.5 and 2.7%, respectively) were comparable to rates observed in patients with LVEF 30-35% but no such risk factors (1.7%). However, these patients had also similarly higher non-SCD rates, such that the ratio of SCD to non-SCD was not increased. Importantly, this ratio was mostly dependent on age, with higher overall ratios in youngest subgroups (0.89 in patients <55 vs. 0.38 in patients ≥75) , regardless of risk factors.

Conclusion: Although MI survivors with LVEF >35% with diabetes, impaired kidney function, or both are at increased risk of SCD, the risk of non-SCD risk is even higher, suggesting an extension of the current indication for an ICD to them is unlikely to be worthwhile. MI survivors with low LVEF, age below 55 are likely to have the greatest potential benefit from ICD implantation.

Keywords

Diabetes, impaired kidney function, left ventricular dysfunction, sudden cardiac death, high-risk post myocardial infarction patients

Introduction

Current guidelines [1-3] recommend cardiac defibrillator (ICD) implantation in myocardial infarction (MI) patients with left ventricular ejection fraction (LVEF) ≤35% and symptomatic heart failure (HF), or with LVEF ≤30%, even if asymptomatic, when or more 40 days after their index event (≥ 90 days if coronary revascularization occurs). However, reduced LVEF, as a standalone risk-stratifier for guiding ICD implantation, is a relatively poor predictor of sudden cardiac death (SCD)[4] and most SCDs occur in patients with LVEF >35%, i.e. in patients with preserved or only moderately reduced systolic function [4].

Diabetes [5] and impaired kidney function [6], two of the most common comorbidities among patients with MI and are associated with high rates of cardiovascular and all-cause death. There is substantial evidence indicating the association between diabetes and SCD in patients with atherosclerotic coronary artery disease [7] or following MI [8], although little is known regarding its interplay with impaired kidney function, a common condition in diabetic patients. Nevertheless, in a large cohort of HF failure patients, the proportion of overall deaths that were attributable to SCD was lower among individuals with diabetes or impaired kidney function, as compared to those without these comorbidities, suggesting a high level of competing risk of other death modalities in these patients[9].

Recently, the results of the DANISH trial, conducted in patients with non-ischemic cardiomyopathy and low LVEF, emphasized the major impact of age on benefit of ICD treatment [10]. This finding is seemingly the consequence of the higher competing risk of non-SCD in older patients. ICD efficacy may also be reduced among patients with multiple comorbidities and impaired kidney function [11-13]. The interplay between age and diabetes/impaired kidney function, all of which appear as important contributors to the competing risk of non-SCD, has not been investigated in detail.

In the present study, we examined the associations between diabetes and/or impaired kidney function and the risk of SCD and non-SCD and on their relative rates, in survivors of MI complicated by HF, left ventricular dysfunction or both in the pooled population of four large clinical trials [14] conducted before the

era of primary prevention ICD. In addition, these associations were evaluated according to LVEF and age given that these variables could represent major contributors to both the absolute and relative risk of SCD and non-SCD.

Methods

High-risk acute MI trials pooling project

The rationale for selecting and pooling the four trials included in this analysis has been published elsewhere [14]. The High-Risk MI Database Initiative included: the effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left Ventricular Dysfunction trial (CAPRICORN) [15]; the Eplerenone Neurohormonal Efficacy and Survival Study (EPHESUS) [16], the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) [17] and the Valsartan in Acute Myocardial Infarction trial (VALIANT) [18].

Each trial enrolled patients with left ventricular systolic dysfunction (LVEF <40%), HF or both between 12 h and 21 days after acute MI (with the exception of OPTIMAAL[17], which included patients with LVEF <35%, left ventricular enlargement, or new anterior Q-waves if HF was absent). In total, 28,771 patients were enrolled overall (1,959 in CAPRICORN; 6,632 in EPHESUS; 5,477 in OPTIMAAL and 14,703 in VALIANT) with a mean follow-up of 2.7 years. Each trial was randomized and double-blinded. In two trials, patients were assigned equally to placebo or active therapy (carvedilol or eplerenone) [15,16] in addition to usual treatment. In the other two trials, patients were randomized to experimental therapy (losartan or valsartan) or active control (captopril) [17,18]. VALIANT [18] additionally featured a third treatment arm (captopril plus valsartan).

Baseline demographics, risk factors and clinical characteristics at the time of the myocardial infarction were recorded for each trial. An expert endpoint committee adjudicated all events in each of the trials, which had similar definitions of various endpoints [14].

With regard to the studied endpoints, SCD and non-SCD were the pre-specified outcomes in the present analyses. All major clinical trials included in this database had independent blinded endpoint committees that adjudicated the essential primary and secondary study endpoints [15-18]. The definition of SCD varied across studies: depending on the study, SCD referred to witnessed deaths due to an identified

arrhythmia, cardiac arrest or cardiovascular collapse without premonitory heart failure or infarction and/or death during or after successful resuscitation from sudden cardiac arrest.

Definition of history of diabetes and impaired kidney function

Data pertaining to history of diabetes were collected by study investigators at baseline, based on the treating physician's diagnosis of diabetes. Chronic kidney disease was defined by the presence of kidney damage or an estimated Glomerular Filtration Rate (eGFR) less than 60 mL/min/1.73m^2 of body surface area for a period ≥3 months[19]. eGFR was calculated using the four-component Modification of Diet in Renal Disease equation [19].

Statistical methods

Of the 28,771 randomized patients, 1,959 (6.8%) had incomplete data for time-to-event outcomes. LVEF was not reported in 8,857 patients, while eGFR was missing in a further 182 patients. Altogether, 17,773 patients (61.8 %) were available for the present analysis.

Continuous variables are expressed as mean (± standard deviation) and categorical variables as numbers and percentages. Baseline characteristics were defined in the whole sample as well as according to four subgroups characterized by the presence/absence of diabetes and impaired kidney function: 1) no diabetes and no impaired kidney function; 2) diabetes and no impaired kidney function; 3) no diabetes and impaired kidney function; 4) diabetes and impaired kidney function. Differences were evaluated within three LVEF strata (LVEF <30%, LVEF 30-35%, and LVEF >35%) according to current guideline indications for primary prevention ICD therapy after acute MI [1,2], using ANOVA and chi square for trend as appropriate.

Kaplan-Meier survival curves were used to illustrate the distribution of SCD and non-SCD in a follow-up time scale, while a log rank analysis was performed to compare survival curves between groups.

Competing risk regression based on the Fine-Gray proportional sub-hazards model was performed[20] with resulting associations expressed as hazard ratios and their 95% confidence interval (HR, 95% CI). As detailed previously, these models were adjusted for the following three a priori selected models [21]: a) model 1 (age and gender); b) model 2 (age, gender, presence of HF signs/symptoms, LVEF strata, Killip class ≥3, history of angina, myocardial infarction, heart failure, hypertension, renal failure, chronic obstructive pulmonary disease, peripheral artery disease, systolic and diastolic blood pressure, and heart rate); c) model 3: model 2 plus treatment at baseline (digoxin, ACE-I/ARB, beta-blockers, diuretics, aspirin, calcium channel blockers, statin or any lipid lowering agent intake). A possible interaction between risk factor subgroups and LVEF on clinical outcome was assessed by introducing an interaction term (risk factor subgroups*LVEF<30/LVEF 30-35%/LVEF >35%, with LVEF <30% as reference) within models.

In order to adjust Kaplan-Meier survival curves, stabilized inverse probability of treatment weighting methods (sIPTW), a type of propensity score adjustment, were used to address confounding by observed covariates[22]. A multinomial logistic regression model was developed, with diabetes/eGFR as outcome and the aforementioned covariates as predictors. In this model, each subject's weight, called stabilized weight, is equal to the inverse of the probability of being in the group to which the subject belongs (probability predicted from the model), multiplied by the marginal probability of the group in the overall population. The balance between the four diabetes/eGFR groups was assessed by calculating the absolute standardized mean difference (ASMD) before and after weighting. Difference between survivals curves were analyzed using the robust log-rank test.

Annual SCD rates were obtained from these curves during the entire follow-up period after randomization, both in the whole cohort as well as in LVEF and age subsets (<55, 55–64, 65–74, and ≥75 years). A supplementary analysis was performed to assess annual SCD rates during the late phase of MI (i.e. >40 days after the index event, by excluding the timeframe during the course of which ICD demonstrated no beneficial effect)[1].

The subgroup with missing LVEF at baseline and complete follow-up (N=8694, 30.2%) was also investigated in order to investigate outcomes according to diabetic status and eGFR.

A probability value <0.05 was considered significant. Statistical analyses were performed using the SPSS package version 23.0 (Chicago, Illinois) and the R software (The R Foundation for Statistical Computing).

Results

Patient characteristics

The study cohort included 17,773 patients, 3825 with LVEF <30% (21.5%), 7807 with LVEF 30-35% (44%), and 6141 with LVEF >35% (34.5%); mean age was 64±11 years and 70% were male. Compared to patients without diabetes and/or eGFR<60, patients exhibiting both these baseline characteristics were older and had a higher heart rate, systolic blood pressure and Killip class, irrespective of LVEF subgroup. They also were more likely to have prior angina or a previous MI, a previous episode of HF hospitalization or renal insufficiency, and more likely to be on diuretics or digoxin. (*Table 1*).

After applying the sIPTW method, the absolute standardized mean differences were reduced to less than 0.1, thus demonstrating substantial improvement in balance across treatment groups, both in the whole population (*Table S1*) as well as in the LVEF subsets (data not shown).

Impact of diabetes, impaired kidney function, and their interplay on outcomes in the whole cohort.

During a median follow-up of 644 (443-844) days, 1052 patients (5.9%) died of SCD while 2090 patients (11.8%) died of non-SCD. Among non-SCDs, 1642 (78.6%) were of cardiovascular origin, with the following adjudicated causes: HF (N=675, 32.3%), MI (N=248, 11.9%) and stroke (N=142, 6.8%). Using adjusted Kaplan-Meier curves, patients with both diabetes and impaired kidney function (eGFR<60) had higher rates of SCD and non-SCD compared to patients with either diabetes or eGFR<60, or neither of the latter (*Figure 1*). Similar findings were also found using the unadjusted Kaplan-Meier method (*Figure S1*)

In adjusted, competing-risk, survival analysis (model 3 adjustment), diabetes was a significant predictor of SCD (HR=1.23, 1.03 to 1.46, p=0.023) and non-SCD (HR=1.34, 1.17 to 1.53, p<0.0001). Similar associations were also observed for eGFR<60 (HR for SCD =1.23, 1.04 to 1.45, p=0. 014; HR for non-SCD =1.52, 1.35 to 1.71, p<0.0001). Higher risks of each type of death were observed for patients with both comorbidities (HR for SCD=1.32, 1.09 to 1.61, p=0.005 and HR for non-SCD=2.13, 1.87 to 2.43,

p<0.0001). Overall, the risk associated with either comorbidity alone or together was greater for non-SCD than for SCD (*Table 2*).

When considering late phase MI (>40 days after MI), similar results were observed (*Table S2*). In patients whose LVEF was not available at baseline, similar trends were observed although the precision of the estimations was lower given the smaller sample size (*Table S3*).

Impact of diabetes, impaired kidney function, and their interplay according to LVEF

A significant interaction between various combinations of diabetes and eGFR (neither, one or other, both) and LVEF strata was documented for both SCD and non-SCD (respectively 0.024 and 0.008) (*Table S4*). Regarding SCD, this interaction across LVEF strata appeared to be mainly related to the heterogeneity of the respective associations with risk factor subgroups. However the associations for the combined condition of diabetes and eGFR<60 remained stable across LVEF strata (with HRs ranging from 1.29 to 1.34). In contrast, for non-SCD, the associations with this combined condition increased with higher LVEF (HR=1.68, 1.36 to 2.07 for LVEF <30 to HR=2.87, 2.27 to 3.62 for LVEF >35) *(Table S4).*

When calculating the annual SCD rate according to the presence or absence of diabetes and/or of eGFR<60, according to LVEF strata (*Figure 2),* there was an overall annual SCD rate of at least 1% for all subgroups. Patients with LVEF <30% and one or both risk factors had the highest SCD rates. Among patients with LVEF >35% and one or both risk factors, the annual SCD rate was approximately 2% (ranging from 2 to 2.7%), which was comparable or even higher to that documented for patients with LVEF 30-35% and no diabetes or eGFR<60 *(*1.7%, *Figure 2).* However, the SCD/non-SCD ratio tended to be lower in patients with LVEF >35% (0.35 ratio for LVEF>35% versus approximately 0.50 ratio for lower LVEF strata) especially in patients with both diabetes and eGFR<60 *(*ratio 0.28, *Figure 2).*

Similar findings were observed in the late phase analysis (*Table S5)*. Rates of SCD and non-SCD as well as their ratios in patients without available LVEF values at baseline were comparable to the intermediate LVEF stratum (i.e. LVEF 30-35%) *(Table S6.)*

Impact of diabetes, impaired kidney function, and their interplay according to age

When calculating the annual SCD rate according to the presence or absence of diabetes and/or eGFR<60 according to age strata (<55, 55-64, 65-74, > or to 75, *Figure 3*), the overall annual SCD rate was at least 1% for all subgroups. An increase in SCD rates was observed with increasing age categories (1.7 to 3.6%), but this was less substantial than the rise in non-SCD rates (1.9 to 9.4%). As a result, the ratio between risk of SCD (numerator) and risk of non-SCD (denominator) decreased substantially with increasing age, from 0.89 in the youngest patients to 0.38 in patients 75 or older (*Figure 3*). SCD/non-SCD ratios did not appear to be significantly modified by the presence or absence of diabetes and/or eGFR<60 within the various age strata.

Discussion

We evaluated the association between diabetes and/or impaired kidney function and the risk of adjudicated SCD and non-SCD in a cohort of 17,773 MI survivors prior to the era of primary prevention ICD use, and stratified according to the severity of left ventricular dysfunction and age. Overall, our results show that diabetes and/or impaired kidney function independently confer a higher risk of both SCD and non-SCD. However, the most noteworthy result of our analysis is that younger age was the factor most strongly associated with a higher SCD/non-SCD ratio, to a much greater extent than diabetes and/or impaired kidney function. Since a lower SCD/non-SCD ratio is unlikely to identify patients with an overall mortality reduction from ICD treatment, this finding suggests that a pattern of potential age-dependent loss of ICD benefit, similar to that observed in the DANISH trial. Although the latter was performed in patients with non-ischemic cardiomyopathy, it looks like the same outcome might be expected in the older patients after acute MI.

The detailed analysis herein, in a very large dataset of post-MI patients, treated before the era of primary prevention ICD may provide useful insights on risk-stratification in clinical practice based on the complex interplay of diabetes, impaired kidney function, LVEF and age. Indeed, post-MI patients with diabetes and/or impaired kidney function and LVEF >35% have an absolute risk of SCD similar to patients with LVEF 30-35% in the absence of these comorbidities although they display a lower SCD/non-SCD ratio, particularly if both risk factors are present (ratio <0.3), suggesting that the ICD treatment effect may be significantly attenuated in this population. In contrast, post-MI patients aged <55 with diabetes and/or impaired kidney function have a relatively high risk of SCD, irrespective of LVEF, while maintaining a high SCD/non-SCD ratio (close to 1); this implies that there could be an overall mortality benefit from and ICD in younger patients with such comorbidities following MI.

Risk of sudden cardiac death, possible ICD benefits, and competing risk issues in patients with diabetes and/or impaired kidney function beyond left ventricular dysfunction

Currently, the single most widely used criterion for ICD implantation is a severely depressed LVEF (i.e. less than 30% or 35%) [1,2] mainly owing to its ability to predict absolute risk of SCD. However, current mortality rates (including sudden death rates) even without an ICD are lower today in the setting of better medical therapy for systolic HF[23]. This emphasizes the need for the identification of patients currently at higher absolute risk of SCD. In keeping with this line of reasoning, the present results would suggest that there may be a subgroup of patients with a LVEF > 35% and risk factors that are also at a sufficiently increased absolute risk of SCD and thus likely to benefit from ICD implantation. However, the recent results of the DANISH Trial [24] challenged the above concept based on absolute risk and emphasized the importance of competing risk in patients with LVEF≤35% and non-ischemic dilated cardiomyopathy. This concept is also very likely to be highly relevant in ischemic HF.

In line with the present results, data from a cohort of 3,276 MI survivors showed a similar risk of SCD in patients with diabetes and LVEF>35% to that seen in patients without diabetes with LVEF≤35% (4.1% versus 4.9%)[8]. In this previous study, non-SCD risk was disproportionally higher in patients without diabetes and LVEF≤35% when compared to patients with diabetes and LVEF>35% (13.1% versus 4.7%)[8]. In the present cohort, impaired kidney function was found to modify this risk pattern since patients with LVEF >35% with both diabetes and impaired kidney function had a much higher risk of non-SCD (9.7%/year) than patients with only diabetes (3.7%/year) or patients with LVEF <30% but without diabetes/impaired kidney function (6.1%/year). In addition, the risk for non-SCD was found to be systematically higher in patients with impaired kidney function, with or without diabetes (confirmed by survival model results). This is in keeping with an analysis performed in 6,378 HF patients from the SOLVD trial (75% with previous MI) showing a disproportionally increased risk of non-arrhythmic death in patients with more advanced renal dysfunction [25]. Similarly, in the Seattle Proportional Risk Model (derived from a

large ambulatory HF cohort with slightly more than 50% of patients with an ischemic etiology)[9], both diabetes and creatinine levels were associated with a lower proportion of SCD (vs. non-sudden death) (multivariable OR 0.75 and 0.65, respectively; p<0.0001 for both). In addition, a meta-analysis of the MADIT-I[26], MADIT-II[27], and SCD-HeFT[28] trials showed that the ICD treatment effect was significantly greater in patients with eGFR≥60 (adjusted HR= 0.49; 0.24–0.95) than in patients with eGFR <60 (adjusted HR=0.80; 0.40–1.53; p for interaction <0.001).[13] Results from a large ICD Medicare-based registry also suggested the cardinal importance of impaired kidney function in subsequent outcome following ICD implantation [13,29].

Overall, these data strongly suggest that competing risks of non-arrhythmic mortality in patients with impaired kidney function may blunt the potential benefit from prevention of arrhythmic death. Our results further show that the disproportional increase in non-SCD over SCD related to impaired kidney function persists in patients with LVEF > 35% and in patients with diabetes, suggesting that a similarly lesser ICD treatment effect would be observed in these groups.

Competing risk of mode of death and benefit from ICD therapy according to age

Decreasing SCD/nonSCD ratios, according to age, have been reported in an analysis of the Amiodarone Trialists Metanalysis (ATMA), a database including 6252 patients from MI and HF trials[30] and in MI survivors in the TRACE trial [31]. Importantly, in this latter analysis, while absolute SCD rates increased with age (4.8, 7.3, 10.5, and 14.2% in patients <56, 56-65, 66-75, ≥76 years, respectively), likely because the TRACE trial was performed in the early 90s, with less use of effective reperfusion strategies. SCD/non-SCD ratios still decreased with age (1.44, 1.09, 0.76, and 0.55, respectively).

The MADIT II trial did not provide evidence against ICD implantation in patients aged ≥ 75 since no significant interaction with age was identified[32]. However, the SCD-HeFT trial, including patients with ischemic and non-ischemic etiologies, failed to demonstrate a significant treatment effect in patients ≥65

years[28]. Similarly, the more contemporary DANISH trial, assessing the effect of ICD implantation in patients with non-ischemic cardiomyopathy, showed a significantly lower treatment effect in older patients (P for interaction=0.009)[24]. It should be emphasized that people aged >75 are typically poorly represented or even excluded from ICD trials[33]; In our cohort, the subgroup of patients ≥75 years was adequate both in terms of sample size (N=3793) and number of events (293 SCDs and 845 non-SCDs), and much larger than patients included in ICD primary prevention trials.

Future directions

These results refine our understanding of the use of comorbidities such as diabetes and impaired kidney function as risk-stratifiers for SCD following MI. Although these comorbidities confer a high risk of SCD, the risk of non-SCD is even greater; thus, it is likely that additional predictors of SCD should be used to refine risk stratification in these conditions. This is especially true in older individuals, since the ratio of SCD to non-SCD is lower than in younger patients. Consequently, the time has likely come to go beyond the current principal criterion for implantation of ICD, namely LVEF ≤35%. However, in patients <55, since the SCD/non-SCD ratio remains in the vicinity of 1, diabetes and/or impaired kidney function could be useful additional risk-stratifiers. Evidence in this respect may have been provided by The Multicenter Automatic Defibrillator Implantation Trial With Subcutaneous Implantable Cardioverter Defibrillator (MADIT S-ICD) trial (ClinicalTrials.gov Identifier: NCT02787785), which enrolled patients with prior MI, diabetes and a relatively preserved ejection fraction of 36-50%, with the aim of evaluating the survival benefit of receiving a subcutaneous ICD when compared to those receiving conventional medical therapy. Further risk stratifiers such as heart catecholamine uptake using MIBG imaging may help select eligible patients. Accordingly, a strategy trial (The AdreView™ Myocardial Imaging for Risk Evaluation – guiding ICD implantation (ADMIRE-ICD) trial (Clinicaltrials.gov: NCT02656329, EudraCT #: 2015-001464-19) aimed at examining the ability of 123I-mIBG (mIBG) imaging to personalize the need for primary prevention ICD [34].

Unfortunately, both of these trials have recently been terminated due to slow enrollment rates, likely because of the reluctance of investigators to challenge the current (outdated) guidelines. Given the additional results provided in the analysis presented herein, we would suggest that new SCD primary prevention ICD trials are needed and should focus on patients with residual high SCD *vs.* non SCD risk, as conferred by younger age with diabetes and/or impaired kidney comorbidities.

There is an urgent need for new risk-stratification studies following the improvement of HF medication in the past years. Indeed, while all ICD studies have mandated "optimal medical therapy", such therapy has evolved in the last 20 years since the seminal primary prevention ICD studies were published. As recently pointed out[23], during this timeframe SCD rate has almost halved in HF patients with systolic dysfunction enrolled in clinical trials, a finding which can be ascribed to a cumulative benefit of evidence-based medications on this mode of death. These advances may have significantly altered the risk-benefit ratio of ICD implantation since many of these studies were performed prior the introduction of modern drug therapies and prompt revascularization techniques.

The mechanisms behind the increased SCD risk in diabetes and/or renal dysfunction are multiple. Cardiac fibrosis is a hallmark, commonly reported in both conditions[7,12]. Fibrosis is a substrate for malignant arrhythmia[35]. Selective SCD risk enrichment may be provided by cardiac magnetic resonance (CMR) imaging, which can reliably assess ventricular scar and therefore potentially identify a subgroup at increased risk of SCD [36]. The ongoing CMR GUIDE study (Clinicaltrials.gov Identifier: NCT01918215), which is currently testing a CMR-guided ICD insertion strategy for primary prevention in patients with mild-moderate LVEF impairment (i.e. LVEF 36-50%) and evidence of myocardial fibrosis as compared to standard of care, should provide further information on this issue[36]. Ultimately, a multiparametric approach is likely to be the key to success for identifying post-MI patients with mild to moderate LVEF dysfunction who would most benefit from ICD implantation.

Limitations

Our models were adjusted for an extensive number of clinical variables (N=21). However, there may be unknown or other unmeasured confounding variables which were not adjusted for, and which could have affected the observed relationships. Follow-up data on key grouping variables (i.e. diabetes, eGFR, and LVEF) were not available and thus we cannot exclude that a certain percentage of patients crossed over from one group to another, but we believe this is unlikely. Randomized clinical trials included in this analysis were conducted in the late 1990s-early 2000s, with both pharmacological and interventional treatment of MI having evolved since that time. Notwithstanding, our dataset represents a unique opportunity to assess SCD risk before the era of primary prevention ICD. We acknowledge that SCD risk prediction cannot be regarded as an unequivocal substitute for identifying patients most likely to benefit from ICD implantation. However, 70% of SCDs are estimated to be due to lethal arrhythmias[37] (40% of SCD in the early months after the index MI were due to recurrent MI or myocardial rupture in a subgroup of 105 SCDs from the VALIANT trial with available autopsy records[38]) and ICD therapy can effectively treat a large proportion of SCDs (approximately 60% in a RCT meta-analysis report[39]). Nevertheless, the actual benefit derived from ICD implantation may even be more difficult to assess using ICD shock, which can be inappropriate or treat ventricular arrhythmias that could have spontaneously terminated. Lastly, information regarding glycemic control, diabetes duration/type or antidiabetic drugs was not reported in the database.

Conclusions

Among high-risk post-MI patients, diabetes, impaired kidney function or both was found to be independently associated with an increased risk of both SCD and non-SCD. There was a similar absolute risk of SCD among LVEF >35% patients with diabetes and/or impaired kidney function comparatively to patients with LVEF 30-35% and neither of these two risk factors. However, the benefit potentially derived from ICD implantation may be diluted by an excess in non-SCD rates, in particular among LVEF >35% patients with impaired kidney function with or without diabetes. The present findings provide strong

evidence relative to the dominant contribution of age to the competing risk of non-SCD. Major changes in epidemiological characteristics, including ageing and co-morbidities contributions, as well as of pharmacological treatment of acute coronary syndromes and of HF have dramatically have occurred since the time of the seminal ICD trials, on which current guidelines ICD are still based. Modern randomized clinical trials are needed to clarify which patients may benefit most from ICD implantation compared to conventional therapy. These trials should typically use appropriate risk stratification, taking into account, beyond LVEF, etiology, age, diabetes and renal function,

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REFERENCE LIST ("online only".)

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37(27):2129-2200.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. *Circulation.* 2013;128(16):1810-1852.
3. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J.* 2015;36(41):2793-2867.
4. Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? *European Heart Journal.* 2013;34(26):1964-1971.
5. Tajik AA, Dobre D, Aguilar D, Kjekshus J, Zannad F, Dickstein K. A history of diabetes predicts outcomes following myocardial infarction: an analysis of the 28 771 patients in the High-Risk MI Database. *European Journal of Heart Failure.* 2017;19(5):635-642.
6. Fox CS, Muntner P, Chen AY, et al. Use of Evidence-Based Therapies in Short-Term Outcomes of ST-Segment Elevation Myocardial Infarction and Non–ST-Segment Elevation Myocardial Infarction in Patients With Chronic Kidney Disease. *Circulation.* 2010;121(3):357-365.
7. Sharma A, Green JB, Dunning A, et al. Causes of Death in a Contemporary Cohort of Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: Insights From the TECOS Trial. *Diabetes Care.* 2017;40(12):1763-1770.
8. Junttila MJ, Barthel P, Myerburg RJ, et al. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. *Heart Rhythm.* 2010;7(10):1396-1403.
9. Shadman R, Poole JE, Dardas TF, et al. A novel method to predict the proportional risk of sudden cardiac death in heart failure: Derivation of the Seattle Proportional Risk Model. *Heart Rhythm.* 2015;12(10):2069-2077.
10. Kober L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med.* 2016;375(13):1221-1230.
11. Schmidt M, Pedersen SB, Farkas DK, et al. Thirteen-year nationwide trends in use of implantable cardioverter-defibrillators and subsequent long-term survival. *Heart Rhythm.* 2015;12(9):2018-2027.
12. Goldenberg I, Moss AJ, McNitt S, et al. Relations Among Renal Function, Risk of Sudden Cardiac Death, and Benefit of the Implanted Cardiac Defibrillator in Patients With Ischemic Left Ventricular Dysfunction. *The American Journal of Cardiology.* 2006;98(4):485-490.
13. Pun PH, Al-Khatib SM, Han JY, et al. Implantable Cardioverter-Defibrillators for Primary Prevention of Sudden Cardiac Death in CKD: A Meta-analysis of Patient-Level Data From 3 Randomized Trials. *American Journal of Kidney Diseases.* 2014;64(1):32-39.
14. Dickstein K, Bebchuk J, Wittes J. The High-Risk Myocardial Infarction Database Initiative. *Progress in Cardiovascular Diseases.* 2012;54(4):362-366.

15. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *The Lancet.* 2001;357(9266):1385-1390.
16. Pitt B, Remme W, Zannad F, et al. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. *New England Journal of Medicine.* 2003;348(14):1309-1321.
17. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *The Lancet.* 2002;360(9335):752-760.
18. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both. *New England Journal of Medicine.* 2003;349(20):1893-1906.
19. Ferreira JP, Girerd N, Pellicori P, et al. Renal function estimation and Cockcroft–Gault formulas for predicting cardiovascular mortality in population-based, cardiovascular risk, heart failure and post-myocardial infarction cohorts: The Heart 'OMics' in AGEing (HOMAGE) and the high-risk myocardial infarction database initiatives. *BMC Medicine.* 2016;14(1).
20. Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk AU - Fine, Jason P. *Journal of the American Statistical Association.* 1999;94(446):496-509.
21. von Lueder TG, Girerd N, Atar D, et al. Serum uric acid is associated with mortality and heart failure hospitalizations in patients with complicated myocardial infarction: findings from the High-Risk Myocardial Infarction Database Initiative. *European Journal of Heart Failure.* 2015;17(11):1144-1151.
22. Brookhart MA, Wyss R, Layton JB, Stürmer T. Propensity Score Methods for Confounding Control in Nonexperimental Research. *Circulation: Cardiovascular Quality and Outcomes.* 2013;6(5):604-611.
23. Shen L, Jhund PS, Petrie MC, et al. Declining Risk of Sudden Death in Heart Failure. *New England Journal of Medicine.* 2017;377(1):41-51.
24. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *New England Journal of Medicine.* 2016;375(13):1221-1230.
25. Alsheikh-Ali AA, Trikalinos TA, Ruthazer R, et al. Risk of arrhythmic and nonarrhythmic death in patients with heart failure and chronic kidney disease. *American Heart Journal.* 2011;161(1):204-209.e201.
26. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med.* 1996;335(26):1933-1940.
27. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. *New England Journal of Medicine.* 2002;346(12):877-883.
28. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. *New England Journal of Medicine.* 2005;352(3):225-237.
29. Bilchick KC, Stukenborg GJ, Kamath S, Cheng A. Prediction of mortality in clinical practice for medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. *J Am Coll Cardiol.* 2012;60(17):1647-1655.
30. Krahn AD, Connolly SJ, Roberts RS, Gent M, Investigators A. Diminishing proportional risk of sudden death with advancing age: implications for prevention of sudden death. *Am Heart J.* 2004;147(5):837-840.
31. Abildstrom SZ, Rask-Madsen C, Ottesen MM, et al. Impact of age and sex on sudden cardiovascular death following myocardial infarction. *Heart.* 2002;88(6):573-578.
32. Huang DT, Sesselberg HW, McNitt S, et al. Improved survival associated with prophylactic implantable defibrillators in elderly patients with prior myocardial infarction and depressed ventricular function: a MADIT-II substudy. *J Cardiovasc Electrophysiol.* 2007;18(8):833-838.

33. Barra S, Providencia R, Paiva L, Heck P, Agarwal S. Implantable cardioverter-defibrillators in the elderly: rationale and specific age-related considerations. *Europace.* 2015;17(2):174-186.
34. Jacobson AF, Senior R, Cerqueira MD, et al. Myocardial Iodine-123 Meta-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure. *Journal of the American College of Cardiology.* 2010;55(20):2212-2221.
35. Francis Stuart SD, De Jesus NM, Lindsey ML, Ripplinger CM. The crossroads of inflammation, fibrosis, and arrhythmia following myocardial infarction. *Journal of molecular and cellular cardiology.* 2016;91:114-122.
36. Selvanayagam JB, Hartshorne T, Billot L, et al. Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): Study protocol for a randomized controlled trial. *Annals of Noninvasive Electrocardiology.* 2017;22(4):e12420.
37. Greene HL. Sudden arrhythmic cardiac death--mechanisms, resuscitation and classification: the Seattle perspective. *Am J Cardiol.* 1990;65(4):4b-12b.
38. Pouleur AC, Barkoudah E, Uno H, et al. Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *Circulation.* 2010;122(6):597-602.
39. Lee DS, Green LD, Liu PP, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. *J Am Coll Cardiol.* 2003;41(9):1573-1582.

Figure legends

Figure 1. Adjusted Kaplan Meier survival curves in the whole cohort

Sudden cardiac death rate (Panel A) and non-sudden cardiac death (Panel B) among the four subgroups (no diabetes/eGFR≥60, diabetes/eGFR≥60, no diabetes/eGFR<60 and diabetes/eGFR<60) in the whole population.

Figure 2. Annual sudden cardiac death and non-sudden cardiac death rates according to LVEF subgroups

Annual sudden cardiac death and non-sudden cardiac death rates (and their ratio) in the four subgroups according to the degree of left ventricular dysfunction

Figure 3. *Annual sudden cardiac death and non-sudden cardiac death rates according to age categories*

Annual sudden cardiac death and non-sudden cardiac death rates (and their ratio) in the four subgroups according to age categories

Figure S1. Unadjusted Kaplan Meier survival curves in the whole cohort

Sudden cardiac death rate (Panel A) and non-sudden cardiac death (Panel B) among the four subgroups (no diabetes/eGFR≥60, diabetes/eGFR≥60, no diabetes/eGFR<60 and diabetes/eGFR<60) in the whole population.

TABLES

Table 1: Patient characteristics for the Whole study population and subgroups according to degree of left ventricular dysfunction

		LVEF<30% (n=3825)					LVEF 30-35% (n=7807)					LVEF >35% (n=6141)				
Observed frequency	**Whole Sample (17773)**	**No-diabetes EGFR>60 n=1685 (44%)**	**Diabetes EGFR>60 n=660 (17%)**	**No diabetes EGFR<60 n=888 (23%)**	**Diabetes EGFR<60 n=592 (16%)**	**p-value**	**No diabetes EGFR>60 n=4030 (52%)**	**Diabetes EGFR>60 n=1345 (17%)**	**No diabetes EGFR<60 n=1626 (21%)**	**Diabetes EGFR<60 n=806 (10%)**	**p-value**	**No diabetes EGFR>60 n=3139 (51%)**	**Diabetes EGFR>60 n=1080 (18%)**	**No diabetes EGFR<60 n=1306 (21%)**	**Diabetes EGFR<60 n=616 (10%)**	**p-value**
Anthropometry / life style																
Male gender	70%	80%	75%	65%	57%	<0.0001	80%	71%	59%	49%	<0.0001	78%	69%	55%	44%	<0.0001
Age (years)	64±11	61±12	63±11	71±10	70±9	<0.0001	61±12	63±11	70±10	70±9	<0.0001	60±12	63±10	70±10	70±9	<0.0001
Physical examination																
Systolic BP (mmHg)	121±16	117±16	119±16	120±16	124±18	<0.0001	120±16	119±15	122±16	123±18	<0.0001	120±16	124±18	124±18	128±18	<0.0001
Diastolic BP (mmHg)	72±11	71±11	70±11	71±12	70±12	0.180	72±11	72±11	73±11	73±12	0.040	73±11	73±11	73±11	73±11	0.603
Heart rate (bpm)	75±12	78±13	80±14	77±13	78±14	<0.0001	75±12	77±13	74±12	76±13	<0.0001	74±12	76±12	74±12	76±12	<0.0001
e-GFR* (ml/min/1.73m²)	71±43	84±59	82±19	48±9	46±10	<0.0001	84±49	83±34	48±9	47±9	<0.0001	84±58	82±19	49±9	47±9	<0.0001
Killip class ≥ 3	21%	22%	31%	31%	32%	<0.0001	14%	17%	23%	30%	<0.0001	17%	22%	26%	34%	<0.0001
Medical History																
Angina	45%	47%	47%	55%	57%	<0.0001	40%	45%	53%	57%	<0.0001	39%	46%	48%	52%	<0.0001
Previous MI	27%	35%	42%	43%	49%	<0.0001	23%	28%	31%	37%	<0.0001	18%	24%	25%	30%	<0.0001
Heart failure	43%	44%	46%	59%	61%	<0.0001	34%	37%	46%	53%	<0.0001	40%	42%	48%	55%	<0.0001
PAOD	9%	7%	15%	10%	23%	<0.0001	6%	12%	9%	19%	<0.0001	7%	12%	11%	20%	<0.0001
Hypertension	59%	49%	63%	61%	75%	<0.0001	50%	66%	65%	78%	<0.0001	51%	69%	69%	78%	<0.0001
Renal insufficiency	3%	1%	3%	8%	18%	<0.0001	1%	1%	6%	13%	<0.0001	1%	1%	6%	13%	<0.0001
COPD	8%	10%	10%	11%	13%	0.187	7%	8%	10%	10%	0.007	8%	9%	9%	9%	0.297
Concomitant medications																
ACEI/ARB	56%	58%	67%	58%	65%	<0.0001	51%	60%	51%	62%	<0.0001	54%	62%	57%	62%	<0.0001
Aspirin	89%	89%	87%	85%	86%	0.018	91%	92%	88%	87%	<0.0001	91%	91%	88%	88%	0.021
Beta-blockers	71%	72%	70%	62%	61%	<0.0001	77%	74%	68%	65%	<0.0001	74%	72%	67%	66%	<0.0001
Digoxin	13%	20%	26%	25%	28%	<0.0001	8%	16%	14%	19%	<0.0001	6%	10%	11%	14%	<0.0001
Calcium channel blockers	7%	6%	10%	8%	11%	<0.0001	5%	9%	8%	14%	<0.0001	6%	8%	10%	14%	<0.0001

Diuretics	52%	51%	64%	71%	77%	<0.0001	38%	51%	60%	68%	<0.0001	44%	53%	60%	72%	<0.0001
Statins or lipid-lowering drugs	38%	40%	48%	32%	39%	<0.0001	39%	45%	30%	39%	<0.0001	39%	43%	32%	37%	<0.0001

Values are expressed as mean ±standard deviation for all continuous variables and as percentages for categorical variables.
eGFR=estimated glomerular filtration rate; AF: atrial fibrillation; MI=myocardial infarction; COPD=chronic obstructive pulmonary disease; ACE-i= angiotensin converting enzyme inhibitor; ARB= angiotensin II receptor blocker; PAOD=peripheral artery disease; LVEF=left ventricular ejection fraction

Table 2: Association of the interplay of diabetes and impaired kidney function (eGFR<60) with sudden cardiac death and non-sudden cardiac death in univariable and multivariable competing risk model analysis

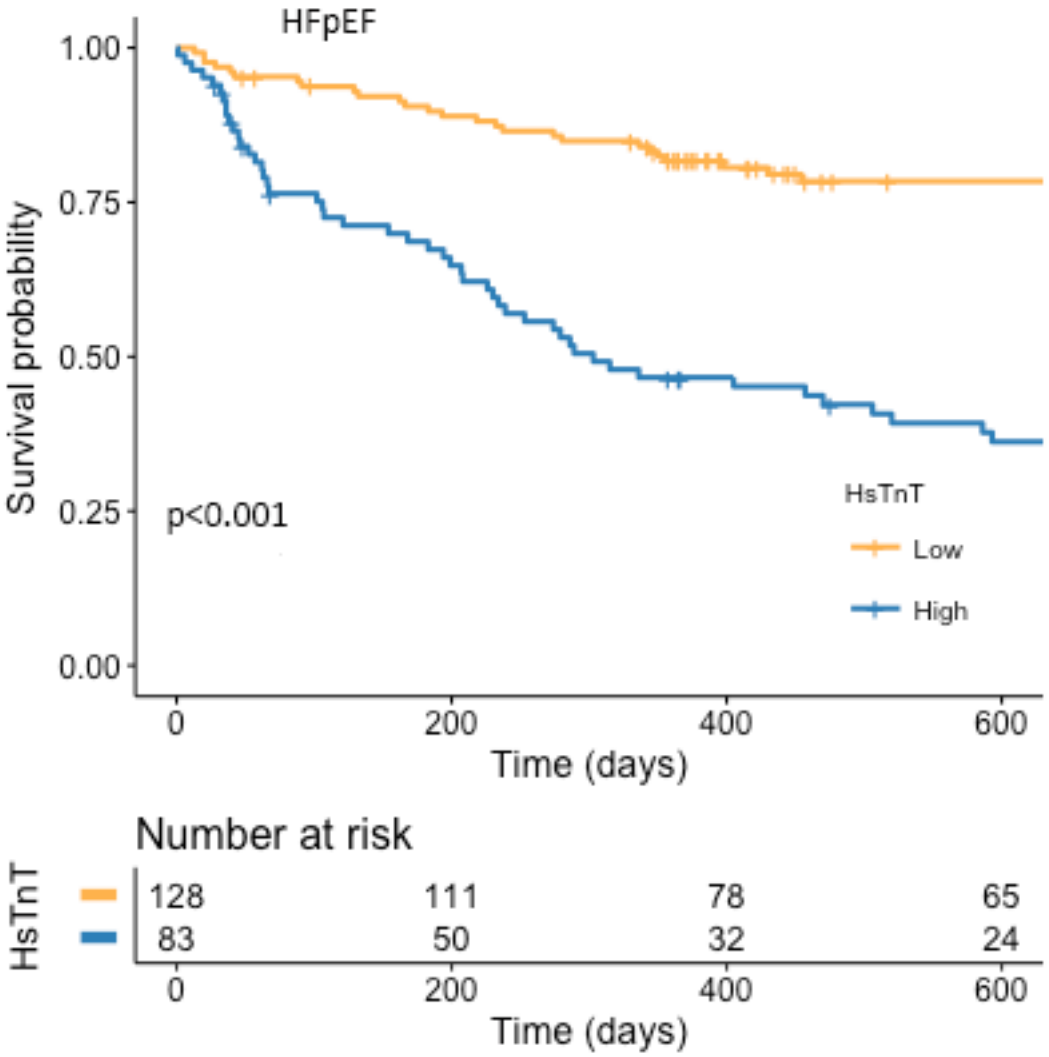
		Competing risk model (sudden cardiac death as outcome, non-sudden death as competing risk event)		Competing risk model (non-sudden death as outcome, sudden cardiac death as competing risk event)	
		HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
Univariable analysis			<0.0001		<0.0001
	No diabetes/eGFR≥60	Reference		Reference	
	Diabetes/eGFR≥60	1.42 (1.19 - 1.68)	<0.0001	1.57 (1.38 - 1.79)	<0.0001
	No Diabetes/eGFR<60	1.67 (1.43 - 1.95)	<0.0001	2.52 (2.26 - 2.82)	<0.0001
	Diabetes/eGFR<60	2.03 (1.70 - 2.42)	<0.0001	3.76 (3.34 - 4.23)	<0.0001
Model 1			<0.0001		<0.0001
	No diabetes/eGFR≥60	Reference		Reference	
	Diabetes/eGFR≥60	1.38 (1.16 - 1.64)	0.0002	1.48 (1.30 - 1.69)	<0.0001
	No Diabetes/eGFR<60	1.45 (1.23 - 1.70)	<0.0001	1.73 (1.54 - 1.94)	<0.0001
	Diabetes/eGFR<60	1.79 (1.49 - 2.16)	<0.0001	2.70 (2.39 - 3.06)	<0.0001
Model 2			0.0009		<0.0001
	No diabetes/eGFR≥60	Reference		Reference	
	Diabetes/eGFR≥60	1.26 (1.06 - 1.50)	0.009	1.36 (1.19 - 1.56)	<0.0001
	No Diabetes/eGFR<60	1.29 (1.10 - 1.53)	0.002	1.58 (1.40 - 1.78)	<0.0001
	Diabetes/eGFR<60	1.42 (1.17 - 1.72)	0.0004	2.21 (1.94 - 2.51)	<0.0001
Model 3			0.013		<0.0001
	No diabetes/eGFR≥60	Reference		Reference	
	Diabetes/eGFR≥60	1.23 (1.03 - 1.46)	0.023	1.34 (1.17 - 1.53)	<0.0001
	No Diabetes/eGFR<60	1.23 (1.04 - 1.45)	0.014	1.52 (1.35 - 1.71)	<0.0001
	Diabetes/eGFR<60	1.32 (1.09 - 1.61)	0.005	2.13 (1.87 - 2.43)	<0.0001

Model 1 is adjusted for age and gender.

Model 2 is adjusted for age, gender, Killip class≥3, HF signs/symptoms, LVEF<30/LVEF 30-35%/LVEF>35%, comorbidities (history of angina, myocardial infarction, heart failure, hypertension, renal failure, COPD, peripheral artery disease), and clinical variables (systolic and diastolic blood pressure, heart rate).

Model 3 is adjusted for age, gender, Killip class≥3, HF signs/symptoms, LVEF<30/LVEF 30-35%/LVEF>35%, co-morbidities (history of angina, myocardial infarction, heart failure, hypertension, renal failure, COPD, peripheral artery disease), clinical variables (systolic and diastolic blood pressure, heart rate), and treatment at baseline (digoxin, ACE-I/ARB, diuretics, aspirin, beta-blockers, calcium channel blockers, statin or any lipid lowering agent intake).

*The present analysis refers to the entire follow-up period starting from randomization.



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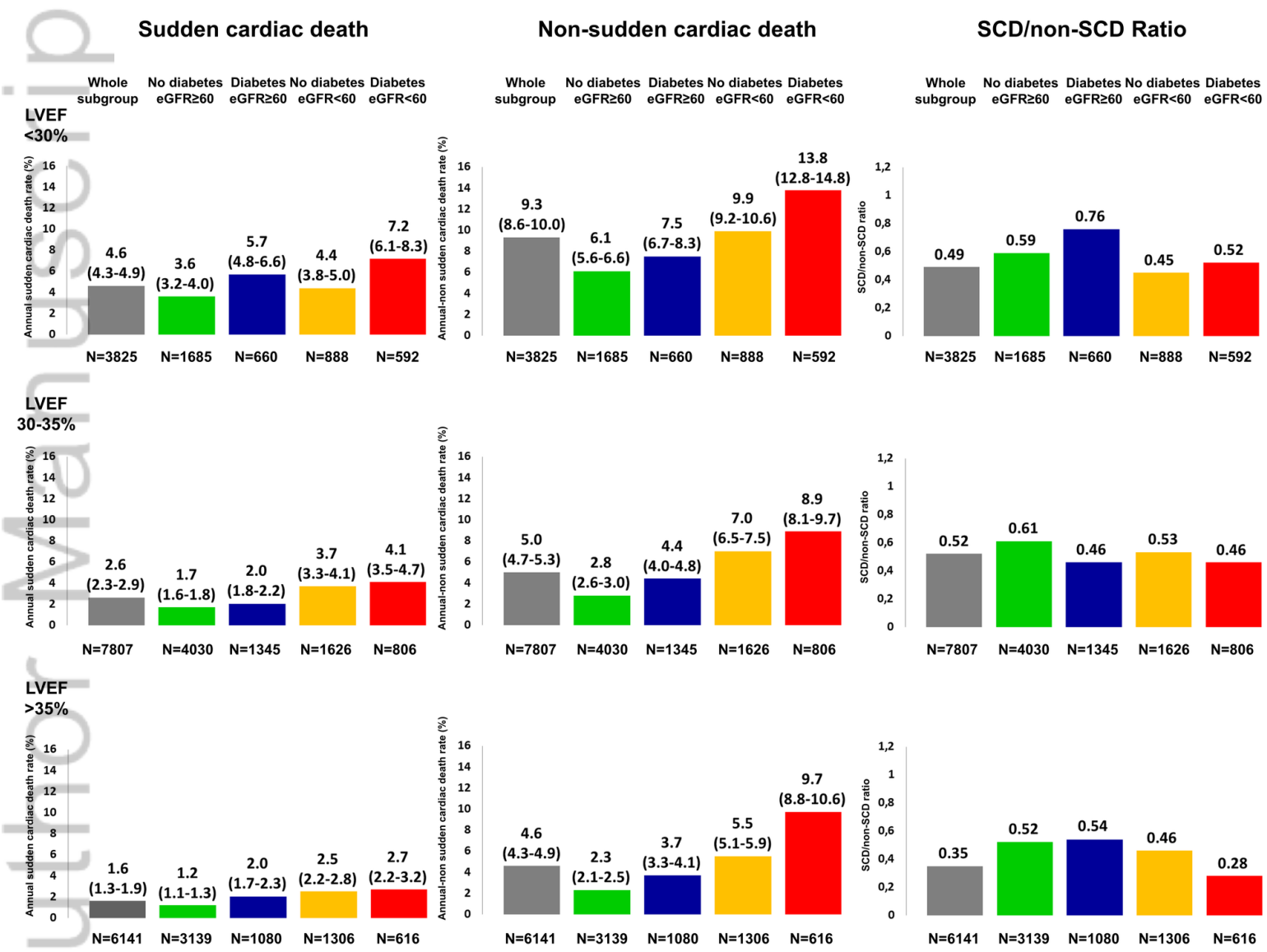

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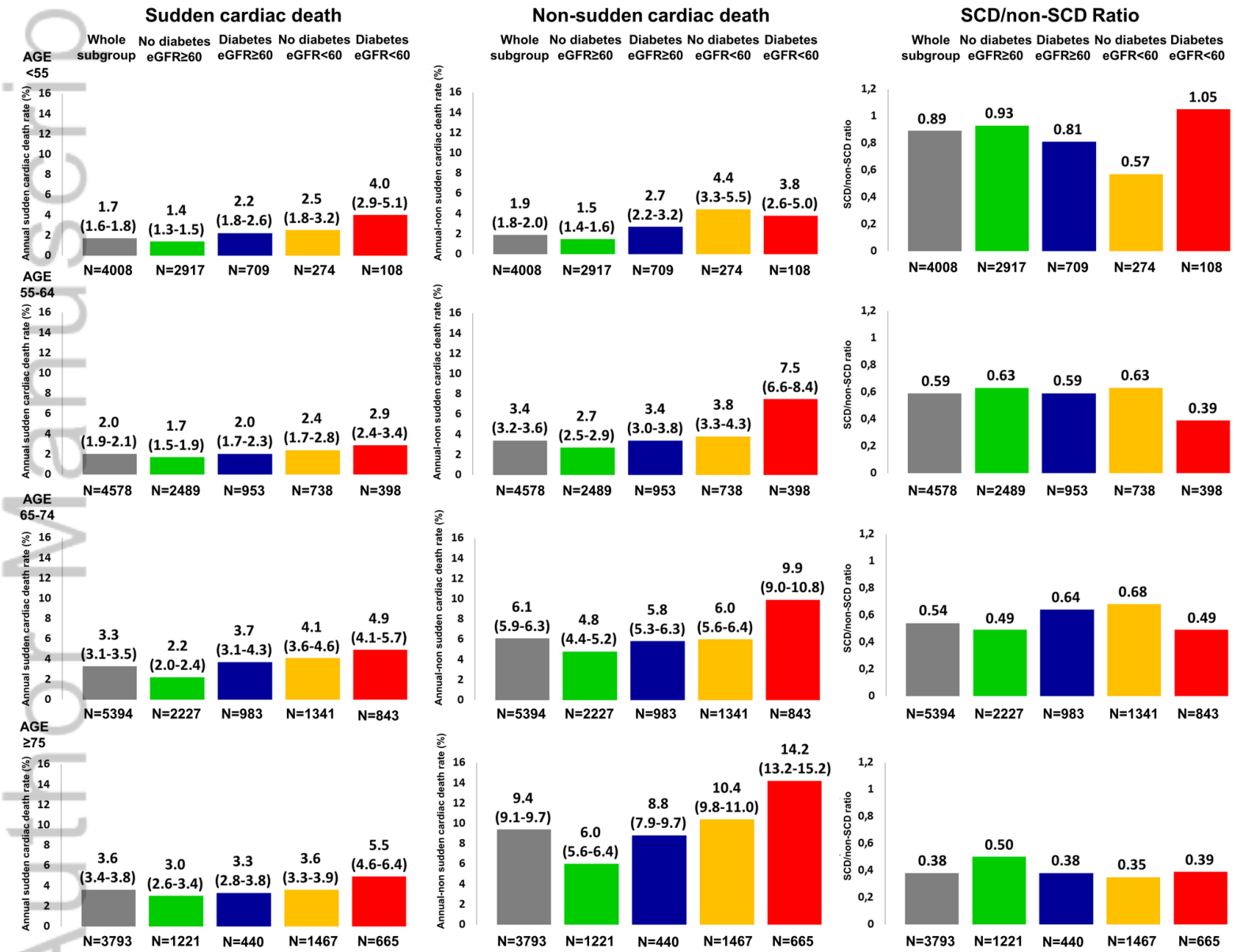

Figure 3 TIF.TIF

All the figures are original to this submission

Total word count: 5462 (including tables); references are “online only”.