Published in final edited form as:

Expert Rev Cardiovasc Ther. 2015 ; 13(8): 897–906. doi:10.1586/14779072.2015.1059276.

Implantable cardioverter defibrillators in diabetics: efficacy and safety in patients at risk of sudden cardiac death

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Summary

Diabetes mellitus is a major risk factor for arrhythmogenesis and is associated with a 2-fold increase in all-cause mortality and a 4-fold increase in cardiovascular mortality including sudden cardiac death when compared to nondiabetics. Implantable cardioverter defibrillators (ICD) have been shown to effectively reduce arrhythmic death and all-cause mortality in patients with severe myocardial dysfunction. With a high competing risk of nonarrhythmic cardiac and noncardiac death, survival benefit of ICD in patients with diabetes mellitus could be reduced, but the sub-analysis of diabetic patients in randomized clinical trials provides reassurance regarding a similar beneficial survival effect of ICD and cardiac resynchronization therapy in diabetics, as observed in the overall population with advanced heart disease. In this article, the authors highlight some of the clinical issues related to diabetes, summarize the data on the efficacy of ICD in diabetics when compared to nondiabetics and discuss concerns related to ICD implantation in patients with diabetes.

Keywords

ICD; Diabetes mellitus; Sudden death; Survival; Infection; Shocks; Clinical trials

Introduction

Diabetes mellitus (DM) is a major risk factor for increased morbidity and mortality mainly from cardiovascular but also non-cardiovascular causes [1]. Patients with DM are at increased risk of cardiac arrhythmias including atrial fibrillation and ventricular arrhythmias

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Financial and competing interests disclosure

A. Jahangir was supported in part by National Heart, Lung, and Blood Institute grants (R01 HL 101240) and (R01 HL089542). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The authors gratefully acknowledge Susan Nord and Jennifer Pfaff of Aurora Cardiovascular Services for the editorial preparation of the manuscript and Brian J. Miller and Brian Schurrer of Aurora Sinai Medical Center for help with the figures.

that increases predisposition to stroke and sudden cardiac death (SCD), respectively [2–4]. Implantable cardioverter defibrillator (ICD), when compared to antiarrhythmic therapy, has been shown to effectively reduce arrhythmic death and all-cause mortality in the selected population with advanced heart disease, whether used for primary prevention of SCD in patients at risk or those who have already survived an aborted cardiac arrest event [5]. Recent ad hoc analysis of various subpopulations of patients indicates that the survival benefit of ICD in patients is diminished in those with advanced kidney dysfunction, older age or in female patients [6–9]. A similar reduction in survival benefit in patients with DM, a condition associated with multi-organ complications and risk of non-arrhythmic cardiac or non-cardiovascular death is a concern, however sub-analysis of diabetic patients in randomized clinical trials (RCT) provide reassurance regarding beneficial survival effect of ICD and cardiac resynchronization therapy (CRT) similar to what was observed in the overall population with advanced heart disease. This is important because of the rising epidemic of diabetes and metabolic syndrome in the population and the high upfront cost associated with ICD implantation [10], which needs to be justified given early mortality after ICD implantation shown for other subgroups such as class IV heart failure or advanced renal disease [6–9]. In this review we highlight some of the clinical issues related to diabetes, summarize the data on efficacy of ICD and concerns related to ICD implantation in patients with DM.

Search Strategy and Selection Criteria

Clinical studies reported in the English Literature during the period 1 January 1990 to 1st April 2015 were identified through a computerized search using the search terms implantable cardioverter defibrillator, ICD, cardiac resynchronization therapy, CRT, diabetes, sudden death, and arrhythmias using the Medline (PubMed) and Cochrane electronic databases. Reference lists of retrieved articles were scanned for additional reports.

Diabetes mellitus, a rising epidemic

The prevalence of DM is increasing in the United States and elsewhere in the world [201, 11]. More than 29.1 million Americans (9.3% of population) [201] have DM, with about 8.9 million that go undiagnosed [201]. Adding to this high prevalence is the concern of rising incidence of diabetes over time (Figure 1) [202], with the increasing epidemic of obesity and metabolic syndrome that contributes to impaired glucose tolerance in 15% (1 in 6) or 41 million people. In addition, 86 million American adults, or more than 1 out of 3, are prediabetics that if left unattended, 15–30% of these individuals will develop Type 2 diabetes within 5 years. About 1.7 million new cases of DM were detected in 2012 alone [201]. The overall percentage of population with diabetes over two years increased by more than 1%, increasing from 25.8 million (8.3 %) in 2010 to 29.1 million (9.3 %) in 2012 [201]. This is of major public health concern because of significant morbidity and mortality [201] associated with this condition that is the seventh leading cause of death and accounted for \$176 billion direct medical costs and \$245 billion total costs in 2012 [203]. Among patients with type I DM mortality was 5.6 times higher than the general population [12] with cardiovascular disease accounting for 22% deaths [13]. After adjusting for age differences, type II diabetics when compared to nondiabetics had 1.7 fold higher cardiovascular

mortality and 1.8 fold higher hospitalization for non-cardiovascular and cardiovascular adverse outcomes including heart failure and heart attack [201, 14, 15]. A higher incidence of life-threatening cardiac arrhythmias including ventricular fibrillation and SCD is also associated with DM.

Diabetes as a risk factor for life-threatening cardiac arrhythmias

Compared to nondiabetics, patients with DM have a 2 fold increase in all-cause mortality and an almost 4 fold increase in cardiovascular mortality [1]. A substantial proportion of elderly patients hospitalized for acute myocardial infarction have elevated glucose levels, even in the absence of known diabetes that is associated with a greater risk of 30-day mortality [16]. Several studies have identified DM as a risk factor for SCD [4, 17, 18]. In Paris Prospective Study I, after controlling for several other risk factors, DM was associated with significant Sudden Cardiac Death risk (RR 2.21; 95% confidence interval (CI) 1.1 – 4.44) [18]. Though several mechanisms have been hypothesized (Figure 2), precise causes for increased risk of malignant arrhythmias in DM have not been categorically established. Diabetes has both indirect pro-arrhythmic effects, being a risk factor for coronary artery disease, microvascular disease, ischemia-reperfusion injury and dysautonomia as well as direct myocardial effects that contribute to left ventricular dysfunction and electrical instability from metabolic alterations, lipotoxicity, oxidative stress, altered calcium handling and mitochondrial dysfunction increasing susceptibility toward arrhythmogenesis [19,20, 21].

Direct proarrhythmic effects of diabetes

DM has been associated with QT prolongation, which at the cellular level results from increased repolarization duration [15]. QT prolongation is an established risk factor for life-threatening ventricular arrhythmias [22]. Several animal studies have supported the idea that QT prolongation in diabetes could be from reduced repolarization reserve caused by decreased K^+ repolarizing currents [23, 24]. In diabetics, particularly with aging or aging-associated diseases, repolarization is adequate for normal cardiac functioning but under a stressful situation, myocardium is unable to fully compensate, creating a condition that results in prolonged repolarization or inability to shorten action potential that could lead to after-depolarization and triggered activity mediated arrhythmias that can be sustained by re-entry [25]. One of the possible mechanisms for decreased repolarization reserve in DM is the impairment of delayed rectifier K^+ current that contributes to phase II and phase III of cardiac action potential and overall repolarization of the heart [26]. In this background, additional potassium level changes associated with fluctuating insulin levels, osmolar loading and myocardial stretch can create a pro-arrhythmic milieu.

In addition to QT prolongation, myocardial calcium overload also predisposes to arrhythmogenesis [27]. Studies using diabetic animal models demonstrate abnormal cardiomyocyte calcium homeostasis due to alterations in various mechanisms involved in intracellular calcium handling [28–30] and a higher sensitivity to calcium overload induced arrhythmias [31]. A recently published study by Erickson et al. is of particular importance, identifying a novel pathway by which hyperglycemia corresponding to borderline or severe

diabetes induced posttranslational modification (PTM) of Ca^{2+} -Calmodulin-dependent protein kinase II (CaMKII) by O-linked N-acetylglucosamine (O-GlcNAc). CaMKII is a serine/threonine-specific protein kinase that is regulated by the Ca^{2+} /calmodulin complex and involved in various signaling cascades necessary for normal myocardial calcium homeostasis and the hyperglycemia-induced O-GlcNAcylation resulted in autonomous activation of CaMKII and increased calcium release from sarcoplasmic reticulum [32]. This is consistent with previous observations that overexpression of CaMKII leads to myocardial dysfunction including cardiac arrhythmias [33]. Another mechanism through which DM can alter intracellular calcium and potassium homeostasis is by blocking the Na^{+} - K^{+} ATPase pump [34]. This leads to extracellular potassium accumulation and intracellular calcium overload with the later being caused by increased release of calcium from the mitochondria as a consequence of intracellular sodium overload. Extracellular potassium accumulation can potentially lead to diastolic injury currents and delayed repolarization therefore increasing risk of both triggered activity and reentry [34]. Thus QT prolongation and these cellular level electrolyte abnormalities caused by diabetes could act synergistically to further enhance proarrhythmic effect of DM with or without myocardial dysfunction [35]. The risk for life-threatening cardiac arrhythmias in DM is further enhanced by diabetic cardiomyopathy that occur independent of coronary artery disease or hypertension [36]. Myocardial dysfunction, due to cellular hypertrophy and interstitial fibrosis in diabetic cardiomyopathy creates another substrate for life-threatening cardiac arrhythmias [36]. In addition, diabetes-mediated autonomic neuropathy also contributes to QT interval prolongation [38], arrhythmogenesis and SCD [38], particularly in injured hearts after myocardial infarction [40]. Thus, altered regulation of glucose and lipid metabolism, increased production of reactive oxygen species, ionic homeostasis and activation of neurohumoral system all play a role in contributing to the electrical instability in DM [34].

Proarrhythmic effects of hypoglycemia

Independent of the direct pro-arrhythmic effects of DM, there is mounting evidence that hypoglycemia, a common complication associated with tight glycemic control in diabetics [40–42], also contributes to the risk of life-threatening ventricular arrhythmias and sudden cardiac death [19, 20, 43, 44]. The concern that hypoglycemia increases the risk of SCD stems from earlier reports of unexpected deaths in young diabetes patients leading to the term “dead in bed syndrome” [45, 46]. Since initial description, several studies have supported this observation [20]. Hypoglycemia has been linked to arrhythmogenesis through its effect on cardiac repolarization causing QT prolongation [47–51] and enhanced beta-adrenergic stimulation [52] that in turn could result in hypokalemia [53] and cellular calcium overload [54], further aggravating repolarization delay and triggered activity, particularly if frequency of ectopy is increased that can cause long-short activation intervals and polymorphic ventricular tachycardia [43, 44]. Reduced serum potassium level with increased insulin also aggravates QT prolongation and calcium overload [55]. In addition hypoglycemia is linked to bradycardia and aggravation of myocardial energy deficits both from coronary obstruction and cellular effects [19].

The studies on the proarrhythmic effect of hypoglycemia are supported by data from epidemiologic studies and post hoc analysis of clinical trials, which have linked

hypoglycemia with adverse cardiovascular outcomes, including increased cardiovascular and all-cause mortality [40–42, 56–58]. ACCORD [42] trial is one such study that was terminated prematurely because of increased mortality observed in intensive glycemetic control arm (HbA1c goal <6%). In view of results from this and other studies, the American Diabetes Association, the American College of Cardiology Foundation and the American Heart Association [59] all recommend less stringent glycemetic control in diabetic patients with advanced micro or macro vascular complications.

Efficacy of ICD in diabetics

Although, diabetes is known to increase arrhythmogenesis and risk of SCD and overall mortality, and initial retrospective and observational studies indicated a reduced survival benefit in ICD recipients, sub-analysis of RCT indicates a similar survival, functional or hemodynamic benefit from ICD or cardiac resynchronization therapy as nondiabetics in high-risk groups, such as after myocardial infarction or with HF due to ischemic or nonischemic cardiomyopathy [60–74]. Several retrospective studies aimed at mortality risk stratification of ICD recipients by developing clinical algorithms based on varying clinical risk factors [62–68] (Table 1) reported a decreasing ICD survival benefit, resulting from competing causes of death as the comorbidity burden increases. Some of these studies have identified DM as one of the risk stratification parameters associated with increased risk of mortality [65, 67, 68]. The largest among these studies is the study by Bilchick, et al. [68] who analyzed data from >45,000 Medicare beneficiaries who received ICD for primary prevention of SCD, developing and validating a comprehensive risk prediction model called SHOCKED (comprising patients 75 years of age or older, New York Heart Association class III heart failure, out of rhythm attributable to atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, left ventricular ejection fraction (LVEF) 20%, and DM), hence implicating diabetes as one of independent risk factors associated with poor outcomes. In a separate study by Lee et al. [63], although uncomplicated DM was not associated with increased risk of mortality but complicated diabetes with associated microvascular complications was identified as one of the independent predictors of mortality on multivariate analysis. Observational studies in patients with DM and heart failure also reported a relatively poor clinical and echocardiographic response to cardiac resynchronization therapy (CRT) [69] with increased mortality and reduced recovery of left ventricular (LV) function and 6-minute walk [70].

ICD has been shown to be beneficial in preventing SCD in patients with reduced left ventricular ejection fraction and cardiomyopathy [71–74]. Post hoc analysis of the RCT data of diabetic patients provides some reassurance that the beneficial effect of ICD/CRT-D is maintained in patients with diabetes when compared with nondiabetics. A sub-analysis of the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) [60] enrolling patients with severely depressed LVEF (LVEF 30%) more than a month after myocardial infarction randomly assigned to receive either an ICD or conventional medical therapy. Of the 1,232 patients enrolled, 433 (35%) were diabetic (40% were treated with Insulin) and had more advanced heart failure, renal dysfunction and higher blood urea nitrogen, body mass index and more treatment for hypertension. The influence of diabetes on survival in this population, exclusive of an ICD effect was determined from outcomes in

the conventionally treated group and the relative impact of ICDs on survival was determined in the overall study population and subgroups. Diabetics had worse prognosis than nondiabetics with a greater risk of death and heart failure hospitalization. However, the efficacy of ICD in reducing overall mortality in diabetics [Hazard Ratio (HR)] 0.61; 95% CI 0.38 to 0.98) was not significantly different from nondiabetics (HR 0.71; 95% CI 0.49 to 1.05). In another post hoc analysis of the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, the beneficial impact of cardiac resynchronization therapy with a defibrillator (CRT-D) or without a defibrillator (CRT-P) on outcomes among 622 diabetic (41% of the total 1520) patients with advanced HF (class III/IV, LVEF 35%, QRS 120 ms, in sinus rhythm) was demonstrated [75]. A significant reduction in all-cause mortality alone or combined with all-cause hospitalization, cardiovascular hospitalization, or HF hospitalization was demonstrated with CRT (CRT-D and CRT-P combined not alone) compared to optimal pharmacologic therapy group. No significant differences were described between CRT-D and CRT-P group. Procedure-related complications and length of stay were not different in diabetics when compared to non-diabetic patients. In another post hoc analysis of 552 (30%) diabetic and 1,265 non-diabetic patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial with mildly symptomatic heart failure (class I/II, LVEF 30%, QRS 130 ms) with 3:2 randomization to CRT-D vs ICD [76], a similar beneficial effect of CRT-D on survival from death or heart failure event over a mean follow-up of 2.4 years was demonstrated. Although, post hoc analysis, this data provide reassurance of ICD and CRT efficacy in diabetics who otherwise have a higher risk of life-threatening arrhythmias. It is possible that the magnitude of the beneficial effect of ICD is even higher but not fully apparent because of the higher competing risk of noncardiac, non-arrhythmic death resulting in neutral ICD effect on overall survival in diabetics as compared to nondiabetics.

Risk of inappropriate and appropriate ICD therapy in diabetics

Both appropriate and inappropriate ICD therapy has been shown to be associated with increased risk of mortality [77, 78,], however the association between DM and the risk of appropriate and inappropriate ICD therapy has not been adequately investigated. This is of particular relevance with recent demonstrations that hypoglycemia causes post-translational modification of key proteins involved in oxidative stress and calcium handling that increases risk of supraventricular and ventricular arrhythmias that can trigger inappropriate or appropriate therapy [32]. In a post hoc analysis [72] of the MADIT-RIT trial that included 1,500 patients with a primary prevention indication for ICD and resynchronization therapy, the effect of conventional programming was compared to high rate cut-off or delayed ICD programming in diabetic (n=485) and nondiabetic (n=998) patients. A significant overall reduction in inappropriate therapy was seen in both diabetics and nondiabetics, though the effect of high rate cut-off programming in reducing inappropriate ICD therapy was more pronounced in nondiabetic patients. On multivariate analysis, DM was associated with an increased risk of appropriate therapy, which includes both anti-tachycardia pacing and shock therapy and reduced risk of inappropriate therapy. Both appropriate and inappropriate therapies were associated with increased all-cause mortality in diabetics but not in

nondiabetics [72]. Further analysis of this patient group [79], identified increased risk of cardiovascular death over a mean follow-up of 1.4 years with more than 6-fold increase in mortality with appropriate shock and >2-fold increase with inappropriate shock. Appropriate antitachycardia pacing was, however, not associated with increased risk of mortality. DM was an independent risk factor for all-cause mortality along with older age, lower diastolic blood pressure, New York Heart Association (NYHA) class III HF, lower LVEF, ischemic cardiomyopathy and implantation of ICD alone when compared to CRT-D [79]. Increased cardiac mortality after ICD shocks was also recently reported by Proietti et al. [80] after a pooled analysis of 10 studies, demonstrating a hazard ratio (HR) for cardiac death of 2.95 (95% CI, 2.12–4.11; $P < 0.001$) after an appropriate shock compared with an HR of 1.71 (95% CI, 1.45–2.02) for those receiving an inappropriate shock. Information about the impact of diabetes was however not provided. In a recent report from the single-center ICD-registry Ludwigshafen [81], the impact of antitachycardia (ATP)-therapy for VT on mortality in patients implanted with ICD, predominantly (75%) for secondary prevention of SCD, was described. About three-fourths of the 17,827 episodes of ventricular arrhythmias (in 749 patients) documented over a median follow-up of 6 years were terminated by ATP. One-third of patients with first ATP-terminated episode subsequently experienced an ICD shock, which was associated with a four-fold increase in the risk of death. Diabetics had a higher mortality and the occurrence of ATP-terminated episode was also independently associated with increased mortality, even among patients without appropriate ICD shocks [HR 1.92, 95% CI 1.38–2.67].

Other studies however have not found diabetes to be a predictor of increased risk of appropriate or inappropriate ICD therapy. In a post hoc analysis of 1,528 patients enrolled in the INTRINSIC RV [73] trial, a lower risk of inappropriate shocks was described in older diabetics as compared to nondiabetics. The risk of appropriate shocks was similar. In a sub-analysis of 1,520 patients enrolled in the COMPANION trial, DM was not associated with increased risk of ICD therapy in heart failure patients treated with resynchronization therapy [82]. In the MADIT-II trial presence of DM was also not associated with increased risk of appropriate therapy [83]. Further research in this area is required to clarify influence of DM on the risk of appropriate and inappropriate ICD therapy, which could have significant prognostic implications due to overall impact on survival.

Complications associated with ICD implant in diabetics

ICD implantation could be associated with varying complications [84]. Traditionally DM has been associated with increased risk of infections; however, the role of diabetes as a risk factor for ICD infection is not entirely clear, as it has not been consistently implicated as an independent risk factor for CIED (cardiovascular implantable electronic device) infections. In some of these studies, even though patients with CIED infections were more likely to be diabetic, DM was not found to be an independent risk factor for CIED infection [85–87], including device-related infective endocarditis [85]. In a large prospective trial [87] enrolling 6,319 patients at 44 centers in France aimed at examining 1-year incidence and risk factors of infectious complications of pacemaker implantation, diabetes was not found to be predictive of increased incidence of infection on multivariate analysis. This was further supported by a recently published study based on Medicare administrative data on 200,909

implants [88]. DM was not identified as an independent risk factor for CIED infection at 6-month follow-up but generator replacement, re-intervention, prior valvular surgery, re-implantation for device upgrade, malfunction, or manufacturer advisory, renal failure on dialysis, chronic lung disease, cerebrovascular disease and warfarin were independent risk factors on multivariate analysis [88].

In a retrospective study, [89] however, diabetes was identified as one of the 7 independent risk factors contributing to the composite risk score for CIED infections during a 6-month follow-up after use of propylene mesh containing Rifampin and Minocycline. Similarly, in another case control study [90] analyzing data from a registry of 2,496 patients, diabetes was found to be a risk factor for CIED-related infection. In a recent a systematic review and meta-analysis of 60 studies [91], DM, renal insufficiency, chronic obstructive pulmonary disease, malignancy, history of previous device, heart failure, anticoagulant use or skin disorders were identified as significant host-related risk factors for device infection after CIED implantation. Additional longitudinal studies and randomized controlled trials are required to define role of DM and its control in ICD infections. At this point, based on current data there are no additional recommendations on prevention and management of CIED infections in diabetics, other than what is recommended for the overall CIED population [90].

Even though cardiac perforation after an ICD implant is rare, it can have devastating consequences. Data on risk factors associated with cardiac perforation after an ICD implant in diabetic patients and its association with diabetes is limited. In a recently published study from the NCDR registry, DM was associated with a decreased risk of cardiac perforation following ICD implantation [92] that could be a reflection of increased fibrosis that could be protective.

Expert commentary

Patients with DM are at increased risk of cardiac arrhythmias that increases predisposition to sudden cardiac death (SCD) [2–4]. ICD therapy has been shown to be effective in aborting life-threatening ventricular arrhythmias and when compared to antiarrhythmic therapy effectively reduce arrhythmic death and all-cause mortality in patients with advanced heart disease at risk for or following survival from an aborted cardiac arrest event [5]. DM has both direct and indirect effects on cardiac electrophysiology that further increases predisposition to life-threatening arrhythmias. On subgroup analysis of clinical trials in patients with severe LV dysfunction, a similar benefit from ICD implant is described in diabetics compared to the overall study population, providing some evidence for its efficacy. DM can affect several other aspects of ICD implant such as the risk of inappropriate or appropriate shocks or ICD infection, which could be clinically significant. Additional insights into mechanisms underlying diabetes [93] and its impact on myocardial dysfunction, cardiac electrophysiological alterations and arrhythmogenesis may identify new targets for the prevention of cardiac arrhythmias and better risk stratification strategies may improve selection of patients who benefit most from ICD implantation thus improving its cost effectiveness.

Five-year view

The prevalence of diabetes is expected to increase due to aging of the population and increasing prevalence of obesity and metabolic syndrome. This is projected to increase the overall spending on diabetes and its complications from \$176 billion to more than \$220 billion in five years. Ongoing research on the molecular basis of myocardial electrical and mechanical dysfunction is expected to identify novel targets for the prevention of cardiac arrhythmias and heart failure progression that can reduce the need for implantation of implantable cardioverter defibrillators (ICD). In addition, better risk stratification tools that identify individuals for early mortality from nonarrhythmic cardiac and noncardiac death and those who are at the highest risk of arrhythmic death may improve selection of patients who benefit most from ICD implantation and thus improve its cost effectiveness in this high-risk population.

Abbreviations

DM	diabetes mellitus
SCD	sudden cardiac Death
ICD	implantable cardioverter defibrillator
PTM	posttranslational modification
CIED	cardiovascular implantable electronic device
LV	left ventricular
LVEF	left ventricular ejection fraction
RCT	randomized controlled trials
NYHA	New York Heart Association
CRT-D	cardiac resynchronization therapy- defibrillator

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Reference annotations

* = of interest

** = of considerable interest

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Key issues

- The prevalence of diabetes mellitus is increasing with the increasing epidemic of obesity and metabolic syndrome.
- Diabetes mellitus is a major public health concern because of its impact on morbidity, mortality and contribution to rising health care costs.
- Both direct and indirect effects of diabetes on myocardial structure and function contribute to increased risk for cardiac arrhythmias including life-threatening ventricular arrhythmias and sudden cardiac death.
- Both hyperglycemia and hypoglycemia due to inadequate diabetes control can contribute to prolongation of cardiac repolarization, and increased heterogeneity of myocardial refractoriness and electrical conduction that predispose to triggered activity- or re-entry-mediated arrhythmias.
- Although diabetes has been identified as an independent risk factor associated with poor outcomes, sub-analysis of randomized controlled trials (RCT) provides some reassurance regarding the efficacy of ICD in improving overall survival in patients with advanced heart disease.
- Observational studies in patients with heart failure indicate a reduced clinical and echocardiographic response to cardiac resynchronization therapy in those with diabetes mellitus; however, post-hoc analysis of the RCTs indicates maintenance of the beneficial effect.
- Both appropriate and inappropriate therapy are associated with increased all-cause mortality in diabetics however the impact of diabetes on such therapies is not entirely clear and requires further research.
- Traditionally, diabetes has been associated with increased risk of infection; however, its role in increasing the risk of cardiac implantable device infection is not entirely clear.
- Additional research into mechanisms underlying cardiac electrophysiological alterations in diabetics may identify new targets for the prevention of cardiac arrhythmias and better risk stratification strategies may improve selection of patients who benefit most from ICD implantation thus improving its cost effectiveness.

Fig 1. Number and Percentage of U.S. Population with Diagnosed Diabetes

The prevalence of diagnosed diabetes increased from 0.93% in 1958 to 7.18% in 2013. In 2013, 22.3 million people had diagnosed diabetes, compared to only 1.6 million in 1958. (Reproduced from Centers for Disease Control's Division of Diabetes Translation. National Diabetes Surveillance System: Long-term Trends in Diabetes, October 2014. Available at http://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf. [Last accessed May 12, 2015])

Fig 2. Direct and Indirect Proarrhythmic Effects of Diabetes Mellitus

Diabetes Mellitus (DM) and associated complications could be proarrhythmic by causing QT prolongation and abnormalities in intracellular calcium homeostasis. In addition, hypoglycemia could have proarrhythmic effects independent of DM.

Table 1
Studies aiming at identifying risk factors of all-cause mortality in ICD recipients.

Name (publication year)	Objectives	Study design	Predictors identified	Was diabetes associated with increased mortality (Hazard ratio)?
Bilchick et al (2012)	Identify predictors of death within 4 years of ICD placement for primary prevention	Registry based study with more than 45,000 Medicare ICD recipients from 2005 to 2007 were collected. Outcomes data were followed through mid 2010.	"SHOCKED" predictors: Age 75, Heart failure (NYHA III), Out of rhythm because of Afib, COPD, CKD, LVEF 20%, DM.	Yes. HR: 1.43 (95% CI: 1.36 to 1.50).
Lee et al (2007)	Evaluate effect of age, gender and comorbidities on 1 and 2 year mortality rates in ICD recipients.	The frequency of cardiac and non-cardiac comorbidities was examined in 2467 ICD recipients in Ontario, Canada. 1 and 2 year mortality rates were followed-up.	Older age, heart failure, PVD, pulmonary disease, renal disease, micro-vascular complications of DM.	No. However, micro-vascular complications of DM had a HR of 2.33 (95% CI: 1.69–3.21)
Fumagalli et al (2014)	Identify determinants of all-cause mortality in different age groups.	Between 2004 and 2011, 6311 patients with severe left ventricular dysfunction who received ICD in 117 Italian centers were enrolled. Patients were divided into 3 age groups (<65, 65 to 74, 75 yrs). Clinical variables were collected at baseline and during a median follow-up of 27 months.	Older age, CAD, COPD, CKD, DM, complex ventricular arrhythmias, and LVEF.	Yes (age group < 65 yrs. HR 1.57.95 % CI:1.08–2.27) Yes (age group 65–74 yrs. HR 1.48, 95% CI: 1.13–1.9) No (age group 75 yrs. HR 1.15. 95% CI: 0.83–1.59)
Alba et al (2013)	Identify risk factors associated with increased mortality in HF patient receiving ICD.	Meta-analysis included 72 studies evaluating 63 predictors. It was conducted in May 2012.	Independent predictors of mortality with high-evidence: Age, GFR, COPD, DM, PVD, LVEF. Occurrence of appropriate and inappropriate ICD shocks.	Yes HR: 1.56 (95% CI 1.37–1.79)
Cygankiewicz et al (2009)	Assess long term mortality and predictive value of different clinical variables in MADIT II trial patients who received ICD.	655 patients of MADIT II trial who received ICD were followed up to 9 years, averaging 63 months. Different clinical, laboratory and electrocardiographic variables were collected.	age > 65 years, NYHA class 3–4, DM, non– sinus rhythm, high BUN level (>28 mg/Dl)	Yes (Diabetic patients had a mortality rate of 51% during long term follow-up as compared to 35% for non-diabetic patients)
Kramer et al (2014)	Identify predictors of death following ICD generator replacement	111,826 patients from NCDR who received ICD generator replacement between Jan 1, 2005 and March 30, 2010 were eligible. Association between different clinical and procedural factors and 1-, 3-, and 5 year mortality was demonstrated.	Afib, CHF, Older age, chronic lung disease, cerebrovascular disease, DM, low GFR.	YES HR: 1.27(95%CI1.23– 1.30)
Ruwald et al (2014)	Identify factors associated with mortality in MADRIT-RIT population	A post hoc analysis of MADRIT-RIT trial, which included 1500 patients with primary prophylactic indication for ICD/CRT randomized to 3 different ICD programming arms.	ICD-CRT-D, NYHA class III, Ischemic cardiomyopathy, Lower ejection fraction (per 10% reduction), DM, increasing age, lower diastolic BP (per 10 mm Hg)	Yes HR 1.64, 95% CI 1.02 – 2.65, p 0.043

Afib atrial fibrillation; BUN blood urea nitrogen; BPM beats per minute; CAD coronary artery disease; CI confidence interval; CKD chronic kidney disease; COPD chronic obstructive pulmonary disease; DM diabetes mellitus; GFR glomerular filtration rate; HF heart failure; HR hazards ratio; ICD implantable cardioverter defibrillator; LVEF Left ventricular ejection fraction; MADIT II Multicenter Automatic Defibrillator Implantation Trial (MADIT) II; MADIT-RIT Multicenter Automatic Defibrillator Implantation Trial – reduce inappropriate therapy; NCDR national cardiovascular data registry; NYHA New York Heart Association functional classification; PVD peripheral vascular disease;