# Hyperglycemia, Ejection Fraction and the Risk of Heart Failure or Cardiovascular Death in Patients with Type 2 Diabetes and a Recent Acute Coronary Syndrome

Sung-Hee Shin, Brian Claggett, Marc A. Pfeffer, Hicham Skali, Jiankang Liu, David Aguilar, Rafael Diaz, Kenneth Dickstein, Hertzel C. Gerstein, Lars V. Køber, Francesca C. Lawson, Eldrin F. Lewis, Aldo P. Maggioni, John J.V. McMurray, Jeffrey L. Probstfield, Matthew C. Riddle, Jean-Claude Tardif, and Scott D. Solomon, for the ELIXA investigators.

From the Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School — both in Boston, MA (S.S, B.C., M.A.P., J.L., E.F.L., S.D.S.); Inha University, Incheon, South Korea (S.S); University of Texas Health Science Center, Houston (D.A), Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); University of Bergen, Stavanger University Hospital, Stavanger, Norway (K.D.); Population Health Research Institute and Department of Medicine, McMaster University and Hamilton Health Sciences, ON, Canada (H.C.G.); Rigshospitalet Copenhagen University Hospital, Copenhagen (L.V.K.); Sanofi U.S., Bridgewater, NJ (F.C.L.); Research Center of the Italian Association of Hospital Cardiologists, Florence (A.P.M.); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); University of Washington Medical Center, Seattle (J.L.P.); Oregon Health and Science University, Portland (M.C.R.); and Montreal Heart Institute, Université de Montréal, Montreal (J.C.T.)

Footnotes: F.C.L.'s Sanofi affiliation is from the time that the research was conducted and the manuscript initiated.

Word count: 4,114

**Corresponding Author**

Scott D Solomon, MD

Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115

E-mail: ssolomon@rics.bwh.harvard.edu.

Telephone: +1-857-307-1960

Fax: +1-857-307-1944

**Aims:** Chronic hyperglycemia, assessed by elevated glycated hemoglobin (A1C), is a known risk factor for heart failure (HF) and cardiovascular (CV) death among subjects with diabetes. Whether this risk varies with left ventricular ejection fraction (LVEF) is unknown. This study evaluated whether A1C influences a composite outcome of either HF hospitalization or CV death differently along the spectrum of LVEF.

**Methods and Results:** We assessed the relationships of baseline A1C and LVEF with a composite outcome of either CV death or HF hospitalization in the 4091 patients with type 2 diabetes and a recent acute coronary syndrome enrolled in the ELIXA trial who had available LVEF. We assessed for interaction between A1C and LVEF as continuous variables with respect to this outcome. During a median follow-up of 25.7 months, 343 patients (8.4%) had HF hospitalization or died of CV causes. In a multivariable model, A1C and LVEF were each associated with an increased risk of HF hospitalization or CV death (adjusted HR=1.11[95% CI 1.01-1.21] per 1% higher A1C and adjusted HR=1.39[95% CI 1.27-1.51] per 10% lower in LVEF). Both A1C and LVEF were independently and incrementally associated with risk without evidence of interaction (p for interaction=0.31). Patients with A1C≥8% and LVEF<40% were at 3-fold higher risk than those with A1C<7% and LVEF≥50% (adjusted HR=3.18[95% CI 2.03-4.98], p<0.001).

C**onclusion:** In a contemporary cohort of patients with type 2 diabetes and acute coronary syndrome, baseline chronic hyperglycemia was associated with an increased risk of HF hospitalization or CV death independently of LVEF.

**Key Words:** Hyperglycemia, Ejection fraction, Cardiovascular outcomes, Diabetes, Acute coronary syndrome

## Introduction

Patients with diabetes are at increased risk for heart failure (HF) and other adverse cardiovascular (CV) outcomes compared with the general population.[1,2,3,4] Diabetes is an independent predictor of CV morbidity and mortality in patients following myocardial infarction.[5,6,7] Glycated hemoglobin (A1C) levels have been shown to relate to the risk of HF and other CV events.[8,9,10] Multiple mechanisms have been proposed for the increased CV risk, including abnormal cardiac structure and function, neuroendocrine dysregulation, and impaired cellular metabolism.[11] Hyperglycemia can also affect endothelial function, inflammation and accelerate progression of atherosclerosis.[12,13,14,15]

Left ventricular ejection fraction (LVEF) provides important prognostic information in patients with myocardial infarction.[16,17] Assessment of LVEF after acute coronary syndrome has both prognostic and therapeutic implications. While the risk of HF or CV death is significantly higher in patients with diabetes compared to patients without diabetes across LVEF range, the effects of diabetes on CV events differs by LVEF. Prior study showed the risk of HF hospitalization or CV death associated with diabetes can be significantly modified by LVEF in a broad range of patients with symptomatic HF.[18] The decrease in risk of HF hospitalization or death associated with higher LVEF was significantly attenuated by diabetes in a high risk patients after myocardial infarction.[19] While diabetes confers a higher risk of sudden cardiac death (SCD) as well as non-SCD in this population, the associations with diabetes and impaired kidney function increased with higher LVEF especially for non-SCD.[20] However, whether glycemic control, measured by A1C, influences outcomes differently along the spectrum of LVEF is not well characterized. Given the association of higher A1C with worse LV diastolic parameters and impairment of LV systolic function determined by global longitudinal strain, the impact of A1C on CV events might be

different across LVEF ranges.[21] In this study, we evaluated the association between chronic hyperglycemia assessed by A1C and LVEF with a composite outcome of either HF hospitalization or CV death in the 4091 patients with type 2 diabetes and a recent acute coronary syndrome enrolled in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial.[22]

## Methods

### Study population

The ELIXA trial included 6068 patients with type 2 diabetes who had had an acute coronary event within 180 days following the hospital admission for the index acute coronary syndrome, but after discharge. Patients were randomly assigned to double-blinded treatment with lixisenatide or placebo in addition to prior glucose-lowering therapy as informed by locally determined standards of care. Details of the trial design, inclusion and exclusion criteria, and the main results have been reported previously.[22,23] Major exclusion criteria were an age of less than 30 years, percutaneous coronary intervention within the previous 15 days, coronary-artery bypass graft surgery for the qualifying event, planned coronary revascularization procedure within 90 days after screening, and estimated glomerular filtration rate (eGFR) of less than 30 mL/min per 1.73 $m^2$ of body-surface area, a A1C level of less than 5.5% or more than 11.0%, or an inability to provide written informed consent. Main ELIXA trial results showed that the addition of lixisenatide had a neutral effect on the rate of major cardiovascular events.

In our analysis, a total of 4,091 patients (67.4%), in whom LVEF was available after index acute coronary syndrome, were included. When available, LVEF was reported by the enrolling sites on an electronic case report form. Median duration from qualifying acute coronary syndrome to

randomization and median duration from LVEF evaluation to randomization were 61 days and 55 days, respectively. Median duration from qualifying acute coronary syndrome to baseline A1C measurement was 61 days.

**Outcomes**

All events of HF hospitalization, CV death, and all-cause death were adjudicated by a centralized and independent adjudication committee according to prespecified definitions.[23] The primary outcome for our analysis was a composite of first occurrence of either hospitalization for HF or CV death. Secondary outcomes included CV mortality, hospitalization for HF and all-cause mortality individually.

**Statistical analysis**

Categorical variables were compared using $\chi^2$ test and continuous variables with trend test across the ordered groups using linear regression. We categorized the patients into three A1C subgroups (<7%, 7-8%, and ≥8%) and three LVEF subgroups (<40%, 40-50% and ≥50%) and compared their baseline characteristics. A1C groups were categorized using the values which are used for a reasonable or less stringent glycemic goals to be achieved and LVEF categories were chosen based on cut-off values commonly referenced in defining HF with reduced, mid-range, and preserved LVEF.[24,25] Spline regression models were used in assessing the continuous relationship of baseline A1C or baseline LVEF with outcomes. Cox proportional hazard models were used to analyze the time to first occurrence of event for the patients and calculate hazard ratios (HRs) and 95% confidence intervals (CI). The assumptions of proportional hazards were tested in Cox models. To

develop the multivariable model for risk of CV outcomes, an initial set of 37 candidate variables reflecting demographic characteristics, medical history and laboratory values was tested for association with CV outcomes in univariate Cox regression model. Twenty-four of these variables with a p-value of less than 0.05 were included for the multivariable Cox model. The final model was made by forward selection method based on a p-value of <0.05, then it was refined to select clinically meaningful covariates. The covariates included in the multivariable models were age, gender, race, duration of diabetes, history of HF, treatment assignment, baseline heart rate, baseline eGFR, and macroalbuminuria. We calculated HR per 1% points of A1C and 10% points of LVEF which could be more interpretable units, given that the standard deviation (SD) of LVEF was 10 times greater than the SD of A1C. In order to assess whether the association between baseline A1C and primary outcome changed during the course of study follow-up, we performed a sensitivity analysis using a Cox model with a time varying coefficient for A1C. An additional sensitivity analysis was performed by including time interval between the acute coronary syndrome event and baseline A1C measurement in the multivariable model, since baseline A1C can be confounded by recent glucose elevations due to the acute coronary syndrome event. To compare relative contribution of A1C and LVEF in predicting clinical outcomes, we tested the difference of the HRs per SD of each variable in the multivariable model. Additionally, we compared the HRs per 1% points of A1C and 10% points of LVEF as well as the HRs of the categorical subgroups.

We assessed interaction between A1C and LVEF with respect to composite outcome and each outcome as continuous variables in regression model. We additionally checked for interaction between A1C and LVEF by stratifying by LVEF <40% (reduced) and ≥40% (preserved). The incidence rates of the categorical subgroups according to A1C and LVEF were calculated by dividing the number of people with a predefined outcome by the person years of follow up within

each category and reported as events per 1000 person-years. The HRs of these defined subgroups were compared. Two-sided p values < 0.05 were considered statistically significant. All analyses were performed using Stata, version 14 (StataCorp).

## Results

### Baseline characteristics of study population

Clinical characteristics of 4091 patients included in our analysis were comparable to the remainder of the ELIXA participants with respect to gender, body mass index, eGFR and A1C. Patients included in this analysis were younger and had a history of atrial fibrillation and HF more frequently than patients in the ELIXA trial not included in this analysis (Table I in the Data Supplement).

Table 1 shows baseline characteristics for the patients according to baseline A1C level and LVEF (mean A1C 7.7±1.3%, mean LVEF 51±12%). Patients with higher A1C levels were younger, more likely to be female, had a longer duration of diabetes and more frequently used insulin at baseline as compared with those with lower A1C. Also, these patients tended to have higher heart rate and more micro- and macroalbuminuria than those with lower A1C. Patients with lower LVEF were more likely to be male and have a history of HF than those with higher LVEF. Systolic blood pressure and eGFR were lower and heart rate was higher in patients with lower LVEF.

### Relationships of baseline A1C and LVEF with CV outcome

During median follow-up of 25.7 months, a total of 289 patients (7.1%) died, 207 patients (5.1%) as a result of a CV cause, 179 patients (4.4%) were hospitalized for HF and 343 patients (8.4%) were hospitalized for HF or died of CV cause. Among the patients who died of CV cause, 85 patients (41%) died of SCD. In 204 patients died of non-SCD, 122 (60%) were as a result of a CV cause, with the following adjudicated reasons: myocardial infarction (n=36, 18%), HF (n=32, 16%), and stroke (n=15, 7%).

The hazard ratios for baseline A1C levels for the composite outcome of HF hospitalization or CV death, CV death, HF hospitalization and all-cause death are shown in Figure 1. As a continuous variable, baseline A1C was associated with higher risk of a composite outcome of HF hospitalization or CV death ($p<0.001$). This relationship remained statistically significant even after adjusting for age, sex, race, duration of diabetes, history of HF, treatment assignment, baseline heart rate, baseline eGFR, macroalbuminuria and LVEF ($p=0.025$). Each 1% higher A1C was associated with 11% higher risk for HF hospitalization or CV death (adjusted hazard ratio [HR]=1.11, 95% confidence interval [CI] 1.01-1.21, p=0.023, Table 2). The relationship of A1C to primary outcome was significantly stronger at the level from 5.5 to 8% than the level from 8 to 11% (p for comparison<0.001). Particularly, each 1% higher A1C was related to a 19% higher risk for CV death (adjusted HR=1.19, 95% CI 1.07-1.34, p =0.002), but not for hospitalization for HF alone (adjusted HR=1.01. 95% CI 0.89-1.14, p=0.86). The relationship of A1C to primary outcome was similar according to the subtype of acute coronary syndrome (p for interaction=0.48, Figure I in the Data Supplement). A1C was related to the composite outcome additionally adjusting for NT-proBNP (adjusted HR=1.12, 95% CI 1.02-1.22, p=0.017). When including time interval between the acute coronary syndrome event and baseline A1C measurement in the multivariable model, A1C was still related to the composite outcome of HF hospitalization or CV death and CV

death alone (adjusted HR=1.11, 95% CI 1.01-1.21, p=0.024 for CV death or HF; adjusted HR=1.19, 95% CI 1.07-1.34, p=0.002 for CV death). There was no statistically significant change in the association between baseline A1C and primary outcome during the course of follow-up (p=0.50). Also, time varying A1C showed similar relationship with clinical outcome as compared with baseline A1C (Table II in the Data Supplement). The change in A1C at 12 weeks was related to primary outcome (unadjusted HR=1.18, 95% CI 1.05-1.32, p=0.005), but was not significant in multivariable analysis (adjusted HR=1.06, 95% CI 0.94-1.19, p=0.37).

Hypoglycemic episodes were reported in 636 patients (16%) during the study and serious hypoglycemic episodes which requires assistance from another person occurred in 28 patients (0.7%). Neither hypoglycemic episodes nor serious hypoglycemic episodes was significantly associated with clinical outcomes (Table III in the Data Supplement).

LVEF was also related to the composite of hospitalization for HF or CV death as was the risk of each component outcome (Figure 2), in univariable and multivariable analyses adjusting for the same model including A1C (p <0.001). A 10% lower LVEF was associated with 39% higher risk of HF hospitalization or CV death (adjusted HR=1.39, 95% CI 1.27-1.51, p<0.001, Table 2). Each 10% lower LVEF was also related to a 44%, 36% and 40% higher risks of CV death, all-cause death and HF hospitalization, respectively. However, when NT-proBNP was included in the multivariable analysis, LVEF was not significantly related to HF hospitalization or CV death (adjusted HR=1.08, 95% CI 0.98-1.19, p=0.11). LVEF assessment by itself did not indicate a worse prognosis, as patients with available LVEF showed comparable primary composite rates to those without available LVEF (*P*=0.61). The association between LVEF and the composite outcome of HF hospitalization or CV death was not influenced by the time between the index event and LVEF assessment (adjusted HR=1.39, 95% CI 1.27-1.52, p<0.001).

When assessing the relationship of A1C and LVEF to primary composite outcome by restricting to the patients with or without history of HF, both A1C and LVEF were independently associated with HF hospitalization or CV death in patients without history of HF whereas only LVEF was related to outcome in those with history of HF (Table IV in the Data Supplement).

Furthermore, the HR per SD of LVEF (adjusted HR=1.48, 95% CI 1.34-1.65) was significantly higher than the HR per SD of A1C (adjusted HR=1.14, 95% CI 1.02-1.28) in predicting HF hospitalization or CV death (p for comparison=0.001). Similarly, 10% lower LVEF was found to be associated with a larger HR of HF or CV death than 1% higher A1C in the multivariable model (p for comparison<0.001). Also, lower LVEF category (<40%) was a stronger predictor of HF hospitalization or CV death than higher A1C category (> 8%) (p for comparison<0.001). When we restricted our analysis to the patients without history of HF, the HR per SD of LVEF was comparable to the HR per SD of A1C (p=0.64).

**Interaction between A1C and LVEF**

The relationship between A1C and a composite outcome of HF hospitalization or CV death was not modified by LVEF (p for interaction=0.31). LVEF did not have any interaction with A1C with respect to each component outcome. A1C had similar relationship with outcomes when LVEF was modelled with reduced or preserved LVEF (Figure II in the Data Supplement).

A1C and LVEF were each independently associated with risk of HF hospitalization or CV death (Table 2, Figure 3). Incidence rates (per 1000 person-years) of HF hospitalization or CV death increased with each lower LVEF category and higher A1C category (Figure III in the Data Supplement). Especially, the incidence rates of HF hospitalization or CV death among patients

with A1C≥8% and LVEF<40% were 6.2-fold higher compared with those with A1C<7% and LVEF≥50%. Even after multivariable adjustment, patients who had A1C≥8% and LVEF<40% were three times more at risk of HF hospitalization or CV death than patients with A1C<7% and LVEF≥50% (adjusted HR=3.18, 95% CI 2.03-4.98, Table 3, Figure 3)

**Relationship of A1C with sudden cardiac death and non-sudden cardiac death**

When dividing the modes of death as CV death and non-CV death, A1C tended to be more related to CV death than non-CV death (Table 4). Among CV death, the relationship of A1C with SCD and non-sudden CV death were similar (adjusted HR 1.18, 95% CI 0.99-1.40 for A1C in predicting SCD; adjusted HR 1.21, 95% CI 1.05-1.40 for A1C in predicting non sudden CV death), whereas LVEF was a stronger predictor of SCD than non-sudden CV death. The relationship of A1C to both SCD and non-sudden CV death in patients who died of a CV cause was not modified by LVEF strata (Figure IV in the Data Supplement).

**Discussion**

In a contemporary cohort of patients with type 2 diabetes and acute coronary syndrome, chronic hyperglycemia assessed by elevated baseline A1C was associated with an increased risk of hospitalization for HF or CV death. This association remained after adjusting for other risk factors, including age, sex, race, duration of diabetes, treatment assignment, history of HF, heart rate, eGFR, macroalbuminuria and LVEF and the association was particularly strong for CV death. While lower LVEF indicated a worse prognosis independently from A1C levels, it did not modify

the relationship between A1C and clinical outcomes. Patients with a higher A1C and a lower LVEF had the highest risk of HF hospitalization or CV death.

There are several potential mechanisms by which type 2 diabetes can contribute to the development of HF and worse CV outcome including by directly affecting myocardial function.[26,27] Previous studies have shown that diabetes can alter cardiac structure and function.[28,29,30] Hyperglycemia has been related to higher LV mass, worse diastolic function, and worse LV systolic function in elderly individuals without prevalent coronary heart disease or HF, in the Athersclerosis Risk in Community (ARIC) study.[21] Sustained hyperglycemia accelerates glycation of interstitial proteins such as collagen, and advanced glycation end products can react with free amino groups on an adjacent protein to form cross-links, which results in increased myocardial stiffness and impaired contractility.[31,32] Impaired calcium homeostasis, activation of the renin-angiotensin system, increased oxidative stress, altered substrate metabolism and mitochondrial dysfunction represent other molecular and pathophysiological mechanisms through which myocardial function may be impaired in diabetes.[33] In contrast to our study, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in patients with type 2 diabetes and acute coronary syndrome trial (EXAMINE) has reported no relationships between A1C category and the risk of major adverse CV events.[34] Our findings cannot be directly compared to this analysis, but heterogeneity across studies is not uncommon and often related to inclusion criteria, participants' characteristics, and outcomes assessment.

In our data, while A1C was significantly related to the composite outcome of HF hospitalization or CV death, its association with this composite outcome was likely driven mostly by CV death than HF hospitalization. A1C was not associated with HF hospitalization alone after adjustment for other risk factors in contrast to LVEF. Death could act as competing events with HF

hospitalization and relatively few events may not provide enough power to clearly estimate this association. Indeed, the HR for the composite outcome was 1.11, and the confidence interval for HF hospitalization was consistent with 1.11 (i.e., that value was contained within confidence interval). So, it could be underpowered to distinguish the separate strengths of associations because of reduced number of events. Also, in our population, the mean A1C was 7.7% and 82% of the population had A1C levels <9%. Therefore, it might be difficult to capture the association with relatively few poorly controlled patients. Diabetic therapy to control hyperglycemia might affect the risk of HF.[35,36] However, the association of A1C with CV mortality was stronger than with HF hospitalization. The combination of other multiple pathophysiologic pathways may explain higher association of A1C with CV death. As shown in prior study on the high-risk myocardial infarction population, the higher risk for CV death in diabetes was predominantly mediated by higher risk for fatal re-infarction.[37] Long term follow-up of UK Prospective Diabetes Study (UKPDS) trial also showed that intensive glycemic control was related to a 15% relative risk reduction in myocardial infarction.[38] Chronic hyperglycemia in diabetic patients can cause vascular damage through molecular mechanism of injury including protein kinase C activity, renin-angiotensin system, superoxide and other reactive oxygen species.[39] Hyperglycemia may lead to arterial inflammation, accelerate atherogenesis and increase atherosclerotic progression and vulnerability.[40] Endothelial dysfunction can be linked to accelerated atherosclerosis and increased CV risk. In addition, long-term hyperglycemia environment can be related to electrical and anatomical remodeling. Suboptimal glycemic control can be related to increased risk of arrythmia through increased sympathetic activity, and increased free radical production, resulting in reduced nitric oxide availability to cells with ensuing increase vasomotor tone and ventricular instability.[41,42] Cardiovascular autonomic neuropathy, which is related to chronic hyperglycemia, can be

linked with higher CV mortality rates.[43] In our data, changes in A1C levels induced by treatment at 12 weeks was not significantly related to primary composite outcome in multivariable analysis. This lack of interaction would suggest A1C may play a role as a marker rather than a mediator of increased CV risk.

Recent studies have shown that the mechanisms by which diabetes affects myocardium may be different according to HF phenotype, with myocardial remodeling driven by microvascular endothelial inflammation in HF with preserved LVEF and by cardiomyocyte cell death and replacement fibrosis in HF with reduced LVEF.[44,45,46] These different myocardial effects of diabetes can be related to different outcomes. An analysis from CHARM showed that diabetes was related to a greater relative risk of CV death or HF hospitalization in patients with preserved LVEF than in patients with reduced LVEF while diabetes was related to a similar increased risk of mortality among them.[18] Another study on the diabatic population after myocardial infarction showed that diabetes attenuate the relationship between higher EF and reduction in HF or mortality.[19] Diabetic patients with the higher LVEF categories after myocardial infarction have a greater mortality risk attributable to diabetes than those with the lower LVEF categories.[47] In our study, lower LVEF was associated with a higher risk of CV outcomes but it did not modify the association of A1C with CV outcomes among patients with diabetes with a recent acute coronary syndrome. Baseline A1C was related to an increased risk of HF hospitalization or CV death independently of LVEF. Even though the mechanism by which diabetes affect the myocardium can be different depending on LVEF status, potential hemodynamic effects of chronic hyperglycemia, assessed by baseline A1C, might be similar regardless of LVEF in this population. Other factors such as insulin resistance and lipotoxicity might have a more important role in these differential effects on adverse outcome in patients with diabetes. In a hyperglycemic milieu, all

the mechanisms can get superimposed and be relevant to alter the myocardium leading to inefficient relaxation and contraction, thus this might lead to have similar effects on CV outcomes.

In addition, LVEF was found to be a stronger prognosticator than A1C in type 2 diabetic patients with recent acute coronary syndrome. This may be largely driven by the observation that A1C and LVEF were similarly prognostic in patients without history of HF, while A1C became less prognostic in patients with history of HF. Metabolic risk factor might need more time to translate into adverse CV outcome as shown in the prior long-term follow-up trials than the risk of depressed pump function which can exert adverse effect on CV outcome more directly.[38,48] Thus, lower LVEF may be associated with more hazard than higher A1C over 2-year follow-up, especially among higher risk patients with history of HF. In addition, the relationship between A1C and outcome in diabetic patients with history of HF might be more complex. A lower A1C may be related to more advanced stage of HF or older age with more comorbid conditions which can contribute to adverse CV outcomes and may complicate the relationship between A1C level and clinical outcome in patients with history of HF. While burden of reduced LV systolic function was stronger than metabolic burden by hyperglycemia in our study, chronic hyperglycemia assessed by elevated A1C was linked to worse CV outcome across the LVEF spectrum and both A1C and LVEF were independently and incrementally associated with risk. Indeed, the patients with higher A1C and lower LVEF are at highest risk for HF or CV death. The patients whose blood sugar levels are not well controlled would be at much higher risk for HF hospitalization or CV death if their LVEF is depressed.

Some limitations of our analysis should be noted. First, we used baseline A1C in our analysis. In the acute setting of acute coronary syndrome, hyperglycemia is common because of an inflammatory and adrenergic response to ischemic stress, and it is known as a predictor of worse

outcomes.[49] Baseline A1C can be affected by this acute hyperglycemia, which also can be related to more frequent use of insulin to control blood sugar at this stage. However, we performed sensitivity analysis by adding time interval between the index acute coronary syndrome event and baseline A1C measurement in the multivariable model and A1C remained as a significant predictor for a composite outcome of CV death or HF hospitalization. Second, our study included only diabetic patients who had had acute coronary syndrome. Prior studies have shown that diabetes may have differential impact on mortality and HF progression according to the etiology of HF and suggest that diabetes and ischemic heart disease interact to accelerate the progression of myocardial dysfunction.[50,51] It should be noted that patients with prior coronary artery bypass graft surgery were excluded from this trial, adding another selection bias, as it is common for patients with diabetes to have more diffuse atherosclerosis, and more likely to be referred for surgical revascularization if their LVEF is lower. Also, we excluded the patients who had eGFR < 30 ml/min/1.73 $m^2$ or a A1C of less than 5.5% or more than 11.0% and our population had a fairly narrow range of A1C level at baseline, which might not reflect real-world population who had more variable levels of chronic hyperglycemia. Our population was relatively young and predominantly white male. Thus, this result cannot be extrapolated to the general population of type 2 diabetic patients and would need to be validated through larger data in the future. Third, we included only HF hospitalization for HF events. It may underestimate the value of A1C on HF in patients who could be managed without hospitalization. Fourth, we excluded 1977 patients who did not have available LVEF in our analysis. However, the patients who were excluded from analysis had similar CV outcome with those with available LVEF. Also, LVEF was not assessed by a core laboratory, rather it was reported from participant sites. The methods which were used at each site to assess LVEF could be different.

## Conclusion

In patients with type 2 diabetes and recent acute coronary syndrome enrolled in the ELIXA trial, chronic hyperglycemia assessed by elevated A1C, and lower LVEF were independently and incrementally related to the composite outcome of HF hospitalization or CV death. Patients with a higher A1C and lower LVEF had the highest risk of this outcome.

**Acknowledgement:** Sanofi funded the ELIXA trial (ELIXA ClinicalTrials.gov number, NCT01147250)

Table 1. Baseline characteristics of the patients according to baseline A1C and LVEF

| | Baseline A1C category (%) | | | P for trend | Baseline LVEF category (%) | | | P for trend |
|---|---|---|---|---|---|---|---|---|
| | A1C<7 | 7≤A1C<8 | A1C≥8 | | EF<40 | 40≤EF<50 | EF≥50 | |
| Number of subjects, no. (%) | 1,432 | 1,103 | 1,556 | | 642 | 1,018 | 2,431 | |
| Age, yr | 61.2±9.7 | 60.2±9.8 | 59.0±9.7 | <0.001 | 60.2±9.5 | 60.4±10.1 | 59.9±9.7 | 0.23 |
| Duration of diabetes, yr | 6.5±7.1 | 9.5±8.4 | 11.5±8.4 | <0.001 | 9.2±8.6 | 9.2 ± 8.1 | 8.9±8.1 | 0.25 |
| Male sex, no. (%) | 1018 (71%) | 788 (71%) | 1021 (66%) | 0.001 | 486 (76%) | 744 (73%) | 1596 (66%) | <0.001 |
| Body mass index, $kg/m^2$ | 30.1 ± 5.4 | 30.3 ± 5.6 | 30.3 ± 6.0 | 0.41 | 29.1±5.6 | 30.0±5.4 | 30.6±5.8 | <0.001 |
| Race, no. (%) | | | | 0.17 | | | | 0.76 |
| Asian | 171 (12%) | 155 (14%) | 205 (13%) | | 83 (13%) | 125 (12%) | 323 (13%) | |
| Black | 58 (4%) | 44 (4%) | 53 (3%) | | 25 (4%) | 31 (3%) | 99 (4%) | |
| Other | 88 (6%) | 69 (6%) | 122 (8%) | | 53 (8%) | 76 (8%) | 150 (6%) | |
| White | 1115 (78%) | 835 (76%) | 1176 (76%) | | 481 (75%) | 789 (77%) | 1858 (77%) | |
| Medical history at randomization, no. (%) | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Hypertension | 1131 (79%) | 837 (76%) | 1136 (73%) | 0.001 | 470 (73%) | 728 (72%) | 1905 (78%) | <0.001 |
| Percutaneous coronary intervention | 925 (65%) | 729 (66%) | 948 (61%) | 0.015 | 373 (58%) | 705 (69%) | 1254 (63%) | <0.001 |
| Heart Failure | 317 (22%) | 289 (26%) | 387 (25%) | 0.09 | 323 (50%) | 242 (24%) | 428 (18%) | <0.001 |
| Atrial fibrillation | 74 (5%) | 64 (6%) | 64 (4%) | 0.17 | 51 (8%) | 75 (7%) | 149 (6%) | 0.17 |
| Systolic blood pressure, mmHg | 129±17 | 130±18 | 128±17 | 0.13 | 123±17 | 128±17 | 131±17 | <0.001 |
| Heart rate, bpm | 69±10 | 70±10 | 72±10 | <0.001 | 72±10 | 71±10 | 70±10 | <0.001 |
| HDL cholesterol, mg/dL | 44±11 | 43±11 | 42±11 | <0.001 | 42±10 | 42±10 | 44±11 | <0.001 |
| LDL cholesterol, mg/dL | 78±34 | 77±35 | 79±36 | <0.001 | 79±35 | 74±32 | 79±36 | 0.13 |
| eGFR, ml/min/1.73 $m^2$ | 75±20 | 76±21 | 77±22 | 0.002 | 71±21 | 76±21 | 78±21 | <0.001 |
| eGFR < 60ml/min/1.73 $m^2$, no. (%) | 328 (23%) | 266 (24%) | 342 (22%) | 0.52 | 211 (33%) | 226 (22%) | 499 (21%) | <0.001 |
| Qualifying ACS event, no. (%) | | | | 0.15 | | | | <0.001 |
| NSTEMI | 563 (39.3%) | 444 (40.3%) | 578 (37.1%) | | 241 (37.5%) | 323 (31.7%) | 1021 (42.0%) | |
| STEMI | 636 (44.4%) | 495 (44.9%) | 736 (47.3%) | | 328 (51.1%) | 586 (57.6%) | 953 (39.2%) | |
| Unstable angina | 232 (16.2%) | 164 (14.9%) | 239 (15.4%) | | 71 (11.1%) | 108 (10.6%) | 456 (18.8%) | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Unclassified | 232 (16.2%) | 164 (14.9%) | 239 (15.4%) | | 2 (0.3%) | 1 (0.1%) | 1 (0.0%) | |
| Albuminuria, no. (%) | | | | <0.001 | | | | 0.22 |
| Normoalbuminuria | 1184 (84%) | 827 (76%) | 1051(68%) | | 459 (73%) | 755 (75%) | 1847(77%) | |
| Microalbuminuria | 193 (14%) | 198 (18%) | 357 (23%) | | 134 (21%) | 190 (19%) | 424 (18%) | |
| Macroalbuminuria | 36 (3%) | 63 (6%) | 128 (8%) | | 39 (6%) | 60 (6%) | 128 (5%) | |
| Median BNP [interquartile range], pg/mL | 107 [49, 223] | 113 [54, 233] | 113 [53, 232] | 0.25 | 265 [135, 512] | 146 [71, 275] | 79 [42, 154] | <0.001 |
| A1C, % | 6.3±0.4 | 7.4±0.3 | 9.0±0.8 | by design | 7.7±1.3 | 7.7±1.2 | 7.6±1.3 | 0.11 |
| LVEF, % | 51±12 | 51±12 | 50±12 | 0.02 | 31±6 | 44±3 | 59±7 | by design |
| Medication at randomization, no. (%) | | | | | | | | |
| Antidiabetic agents | | | | | | | | |
| Insulin | 389 (27%) | 570 (52%) | 1048 (67%) | <0.001 | 323 (50%) | 536 (53%) | 1148(47%) | 0.028 |
| Metformin | 975 (68%) | 765 (67%) | 1064 (68%) | 0.87 | 399 (62%) | 713 (70%) | 1692 (70%) | 0.003 |
| Sulfonylureas | 449 (31%) | 445 (40%) | 628 (40%) | <0.001 | 260 (41%) | 367 (36%) | 895 (37%) | 0.19 |
| Thiazolidinediones | 34 (2%) | 27 (2%) | 26 (2%) | 0.18 | 13 (2%) | 18 (2%) | 56 (2%) | 0.47 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Antiplatelet | 1393 (97%) | 1075 (96%) | 1519 (98%) | 0.82 | 629 (98%) | 991 (97%) | 2367 (97%) | 0.66 |
| Beta blocker | 1228 (86%) | 939 (85%) | 1338 (86%) | 0.82 | 551 (86%) | 886 (87%) | 2068 (85%) | 0.32 |
| Statin | 1345 (94%) | 1048 (95%) | 1446 (93%) | 0.09 | 594 (93%) | 967 (95%) | 2278 (94%) | 0.11 |
| RAS blocking agent | 1227 (86%) | 941 (85%) | 1333 (86%) | 0.96 | 555 (86%) | 881 (87%) | 2065 (85%) | 0.38 |

Plus-minus values are means±SD. Normoalbuminuria was defined as albuminuria <30mg/g, microalbuminuria as ≥30 to <300 mg/g and macroalbuminuria as ≥300mg/g. ACS indicates acute coronary syndrome; A1C, glycated hemoglobin; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; RAS, renin-angiotensin system

Table 2. Estimated hazard ratios for CV outcomes according to A1C and LVEF

| | HF hospitalization or CV death | | CV mortality | | HF hospitalization | | All-cause mortality | |
|---|---|---|---|---|---|---|---|---|
| | Event number = 343 (8.4%) | | Event number = 207 (5.1%) | | Event number = 179 (4.4%) | | Event number = 289 (7.1%) | |
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Univariate analysis | | | | | | | | |
| A1C per 1% points higher | 1.20 (1.11-1.30) | <0.001 | 1.25 (1.13-1.38) | <0.001 | 1.17 (1.04-1.30) | 0.006 | 1.14 (1.04-1.24) | 0.005 |
| LVEF per 10% points lower | 1.64 (1.51-1.78) | <0.001 | 1.65 (1.48-1.83) | <0.001 | 1.71 (1.53-1.92) | <0.001 | 1.52 (1.39-1.66) | <0.001 |
| Bivariate analysis* | | | | | | | | |
| A1C per 1% points higher | 1.18 (1.09-1.28) | <0.001 | 1.23 (1.11-1.36) | <0.001 | 1.15 (1.03-1.28) | 0.015 | 1.12 (1.02-1.23) | 0.014 |
| LVEF per 10% points lower | 1.63 (1.50-1.77) | <0.001 | 1.63 (1.47-1.81) | <0.001 | 1.70 (1.52-1.91) | <0.001 | 1.51 (1.38-1.65) | <0.001 |
| Multivariable model[#] | | | | | | | | |
| A1C per 1% points higher | 1.11 (1.01-1.21) | 0.023 | 1.19 (1.07-1.34) | 0.002 | 1.01 (0.89-1.14) | 0.86 | 1.10 (0.99-1.21) | 0.07 |
| LVEF per 10% points lower | 1.39 (1.27-1.51) | <0.001 | 1.44 (1.29-1.61) | <0.001 | 1.40 (1.24-1.58) | <0.001 | 1.36 (1.24-1.49) | <0.001 |

*Bivariate analysis included both LVEF and A1C, #Multivariable model included age, sex, race, duration of diabetes, history of HF, treatment assignment, baseline heart rate, baseline eGFR, macroalbumiuria, LVEF and A1C

Table 3. Estimated hazard ratios for a composite outcome of HF hospitalization or CV death

| | | A1C<7% | | 7%≤A1C<8% | | A1C≥8% | |
|---|---|---|---|---|---|---|---|
| | | Number of patients | HR [95% CI] | Number of patients | HR [95% CI] | Number of patients | HR [95% CI] |
| EF≥50% | Unadjusted | 888 | Reference | 654 | 1.02 [0.62-1.69] | 888 | 1.76 [1.16-2.67] |
| | Adjusted* | | Reference | | 0.79 [0.47-1.32] | | 1.33 [0.86-2.05] |
| | Adjusted# | | Reference | | 0.74 [0.44-1.25] | | 1.16 [0.73-1.82] |
| 40%≤EF<50% | Unadjusted | 332 | 1.86 [1.10-3.12] | 283 | 2.22 [1.32-3.72] | 403 | 3.54 [2.31-5.43] |
| | Adjusted* | | 1.44 [0.84-2.46] | | 1.43 [0.84-2.44] | | 2.66 [1.72-4.12] |
| | Adjusted# | | 1.43 [0.84-2.44] | | 1.35 [0.79-2.31] | | 2.32 [1.47-3.68] |
| EF<40% | Unadjusted | 211 | 4.84 [3.04-7.71] | 166 | 4.99 [3.05-8.16] | 265 | 6.34 [4.16-9.66] |
| | Adjusted* | | 3.15 [1.96-5.06] | | 2.69 [1.62-4.46] | | 3.18 [2.03-4.98] |
| | Adjusted# | | 3.20 [1.99-5.16] | | 2.55 [1.53-4.26] | | 2.78 [1.72-4.47]) |

*Adjusted for age, sex, race, duration of diabetes, history of HF, treatment assignment, baseline heart rate, baseline eGFR and macroalbuminuria, #Adjusted for age, sex, race, duration of diabetes, history of HF, treatment assignment, baseline heart rate, baseline eGFR, macroalbuminuria and time updated systolic blood pressure

Table 4. Association of A1C and LVEF with sudden cardiac death and non-sudden cardiac death

| | CV death | | | Non-CV death (n=82) |
|---|---|---|---|---|
| | Total (n=207) | SCD (n=85) | Non-SCD (n=122) | |
| | HR [95% CI] | HR [95% CI] | HR [95% CI] | HR [95% CI] |
| Univariate | | | | |
| A1C per 1% point higher | 1.25 [1.13-1.38] | 1.22 [1.04-1.44] | 1.27 [1.11-1.45] | 0.87 [0.72-1.04] |
| LVEF per 10% points lower | 1.65 [1.48-1.83] | 1.88 [1.61-2.22] | 1.49 [1.30-1.72] | 1.23 [1.03-1.46] |
| Multivariable* | | | | |
| A1C per 1% point higher | 1.19 [1.07-1.34] | 1.18 [0.99-1.40] | 1.21 [1.05-1.40] | 0.86 [0.70-1.05] |
| LVEF per 10% points lower | 1.44 [1.29-1.61] | 1.67 [1.40-1.99] | 1.30 [1.12-1.51] | 1.16 [0.97-1.39] |

*Adjusted for age, sex, race, duration of diabetes, history of HF, treatment assignment, baseline heart rate, baseline eGFR, macroalbumiuria, LVEF and A1C

Figure 1. Estimated hazard ratio with baseline A1C and (A) a composite outcome of HF hospitalization or CV death, (B) CV death, (C) HF hospitalization, and (D) all-cause death. Histograms showed the population distribution of A1C. The solid curves indicating unadjusted estimates and dashed curves indicating 95% confidence limits.

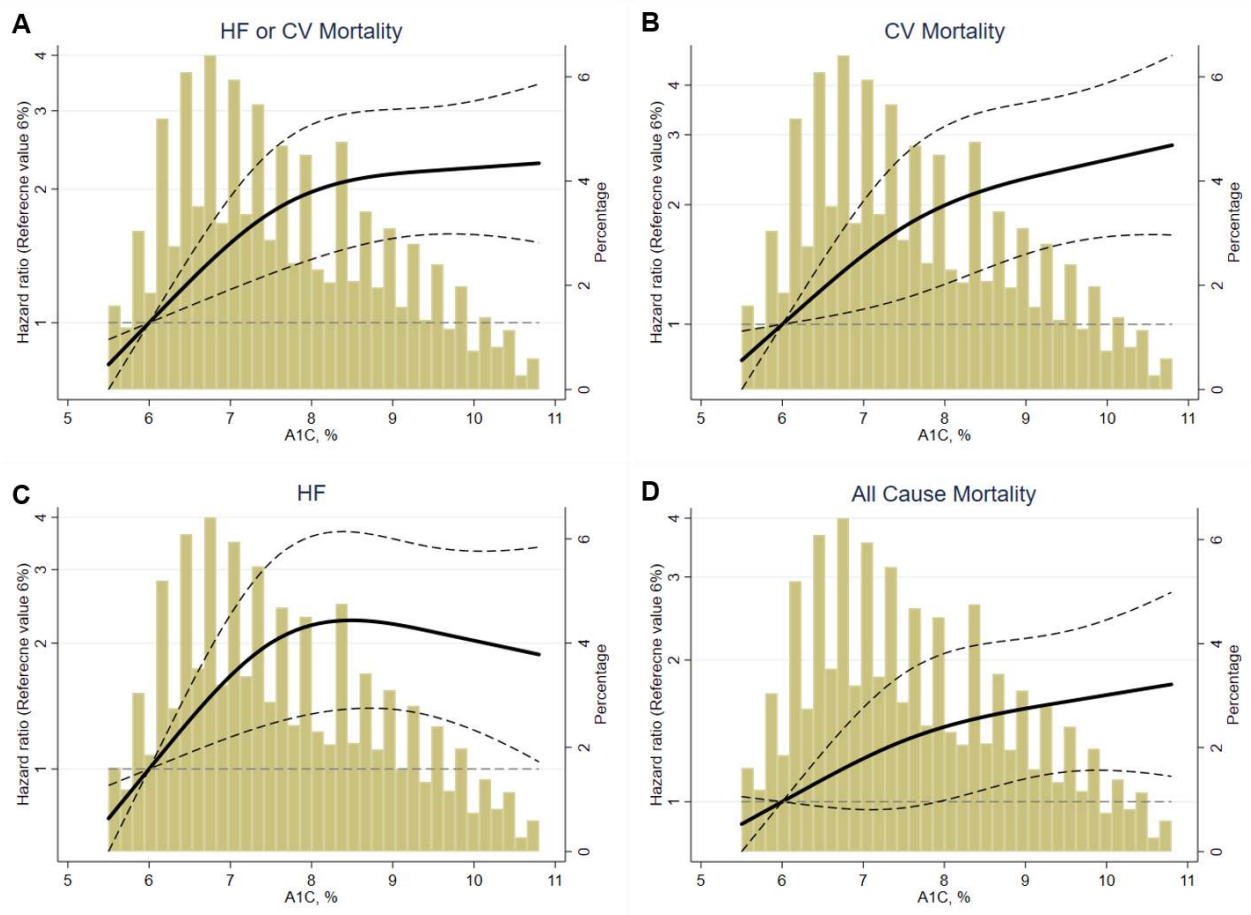


Figure 2. Estimated hazard ratios with LVEF for (A) a composite outcome of HF hospitalization or CV death, (B) CV death, (C) HF hospitalization, and (D) all-cause death. Histograms showed the population distribution of LVEF. The solid curves indicating unadjusted estimates and dashed curves indicating 95% confidence limits.

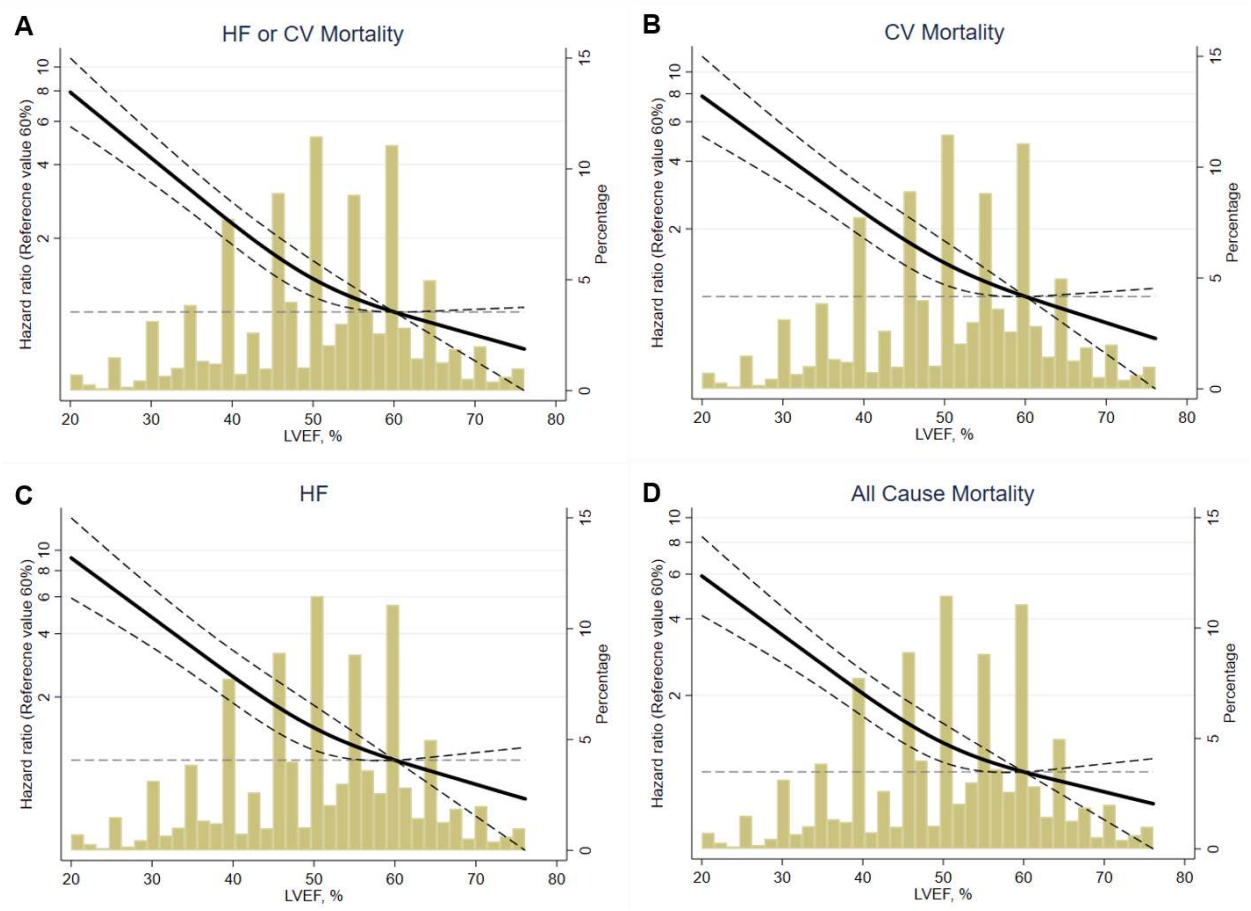
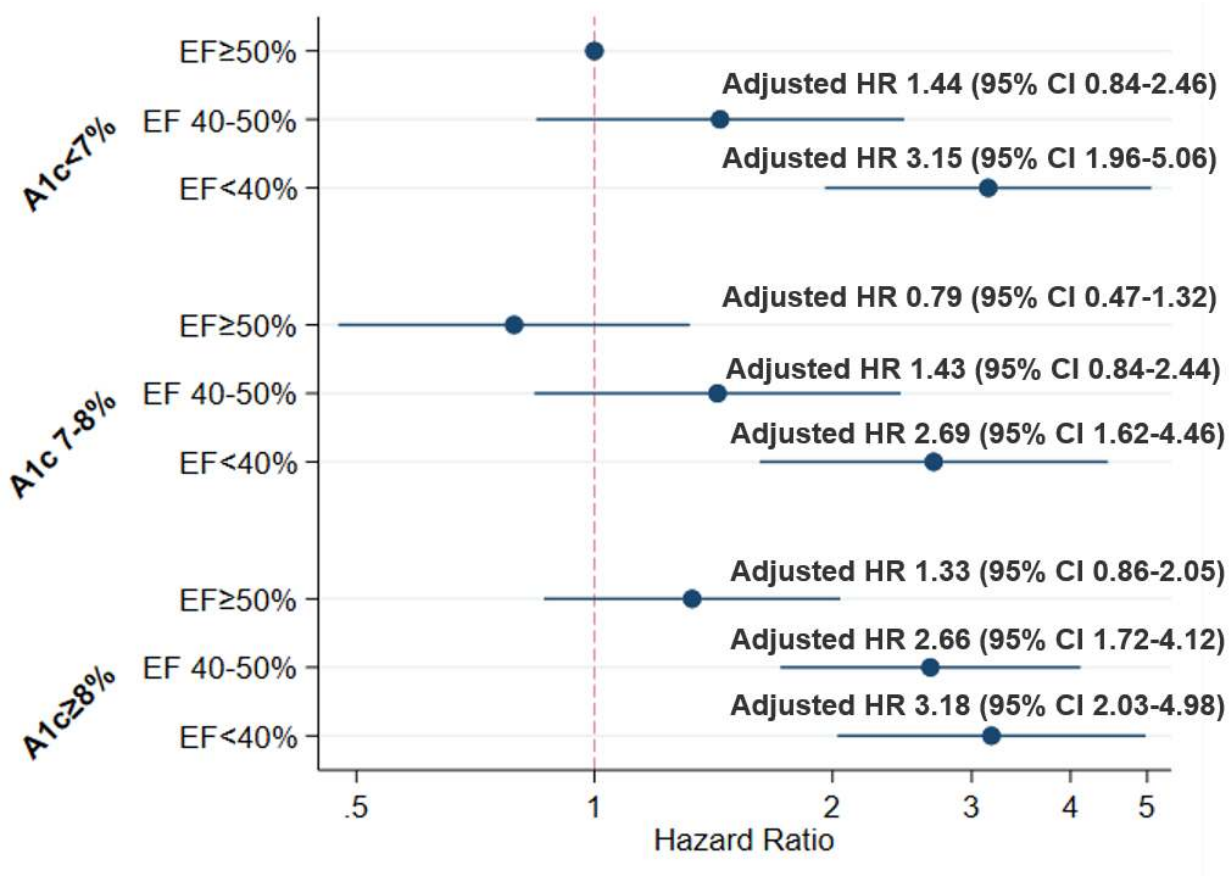


Figure 3. Risk for HF or CV mortality according to subgroup categories of A1C and LVEF.



Supplemental Table I. Clinical characteristics among patients in the ELIXA trial included versus not included in this analysis

| | LVEF (n=4091) | No LVEF (n=1977) | P value |
|---|---|---|---|
| Age, yr | 60.1 ± 9.8 | 60.7 ± 9.5 | 0.013 |
| Duration of diabetes, yr | 9.0 ± 8.2 | 9.8 ± 8.4 | <0.001 |
| Male sex, no. (%) | 2827 (69%) | 1380 (70%) | 0.58 |
| Body mass index, kg/m$^2$ | 30.2 ± 5.7 | 30.0 ± 5.7 | 0.21 |
| Race, no. (%) | | | <0.001 |
| Asian | 531 (13%) | 240 (12%) | |
| Black | 155 (4%) | 66 (3%) | |
| Other | 279 (7%) | 221 (11%) | |
| White | 3126 (76%) | 1450 (73%) | |
| Medical history at randomization, no. (%) | | | |
| Hypertension | 3104 (76%) | 1531 (77%) | 0.18 |
| Percutaneous coronary intervention | 2822 (69%) | 1257 (64%) | <0.001 |
| Heart Failure | 993 (24%) | 365 (19%) | <0.001 |
| Atrial fibrillation | 202 (5%) | 75 (4%) | 0.045 |
| Systolic blood pressure, mmHg | 129 ± 17 | 131 ± 18 | <0.001 |
| Heart rate, bpm | 70 ± 10 | 70 ± 10 | 0.97 |
| HDL cholesterol, mg/dL | 43 ± 11 | 43 ± 11 | 0.89 |
| LDL cholesterol, mg/dL | 78 ± 35 | 80± 36 | 0.13 |
| eGFR, ml/min/1.73 m$^2$ | 76 ± 21 | 76 ± 22 | 0.37 |
| eGFR < 60ml/min/1.73 m$^2$, no. (%) | 936 (23%) | 471 (24%) | 0.40 |
| Albuminuria, no. (%) | | | <0.001 |
| Normoalbuminuria | 3062 (76%) | 1379 (71%) | |
| Microalbuminuria | 748 (19%) | 400 (21 %) | |
| Macroalbuminuria | 227 (6%) | 162 (8%) | |
| Median BNP [interquartile range], pg/mL | 111 [52-228] | 97 [46-199] | <0.001 |

| | | | |
|---|---|---|---|
| A1C, % | 7.7±1.3 | 7.7±1.3 | 0.05 |

Plus-minus values are means±SD. A1C indicates glycated hemoglobin; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction

Supplemental Table II. Estimated hazard ratios for CV outcomes according to time varying A1C and LVEF

| | HF hospitalization or CV death | | CV mortality | | HF hospitalization | | All-cause mortality | |
|---|---|---|---|---|---|---|---|---|
| | Event number = 343 (8.4%) | | Event number = 207 (5.1%) | | Event number = 179 (4.4%) | | Event number = 289 (7.1%) | |
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Univariate analysis | | | | | | | | |
| Time varying A1C per 1% higher | 1.16 (1.09-1.24) | <0.001 | 1.15 (1.06-1.25) | 0.001 | 1.19 (1.09-1.30) | <0.001 | 1.09 (1.01-1.17) | 0.032 |
| LVEF per 10% lower | 1.64 (1.51-1.78) | <0.001 | 1.65 (1.48-1.83) | <0.001 | 1.71 (1.53-1.92) | <0.001 | 1.52 (1.39-1.66) | <0.001 |
| Bivariate analysis* | | | | | | | | |
| Time varying A1C per 1% higher | 1.16 (1.01-1.24) | <0.001 | 1.15 (1.06-1.25) | 0.001 | 1.18 (1.08-1.30) | <0.001 | 1.08 (1.00-1.17) | 0.038 |
| LVEF per 10% lower | 1.63 (1.50-1.78) | <0.001 | 1.64 (1.48-1.82) | <0.001 | 1.71 (1.52-1.92) | <0.001 | 1.52 (1.38-1.66) | <0.001 |
| Multivariable model[#] | | | | | | | | |
| Time varying A1C per 1% higher | 1.11 (1.03-1.19) | 0.005 | 1.13 (1.03-1.24) | 0.009 | 1.09 (0.99-1.24) | 0.08 | 1.08 (0.99-1.17) | 0.08 |
| LVEF per 10% lower | 1.39 (1.27-1.51) | <0.001 | 1.44 (1.29-1.61) | <0.001 | 1.40 (1.24-1.58) | <0.001 | 1.36 (1.24-1.50) | <0.001 |

*Bivariate analysis included both time varying A1C and LVEF, [#]Multivariable model included age, sex, race, duration of diabetes, history of HF, treatment assignment, baseline heart rate, baseline eGFR, macroalbumiuria, LVEF, and time varying A1C

Supplemental Table III. Risk of cardiovascular events and mortality based on reported hypoglycemia.

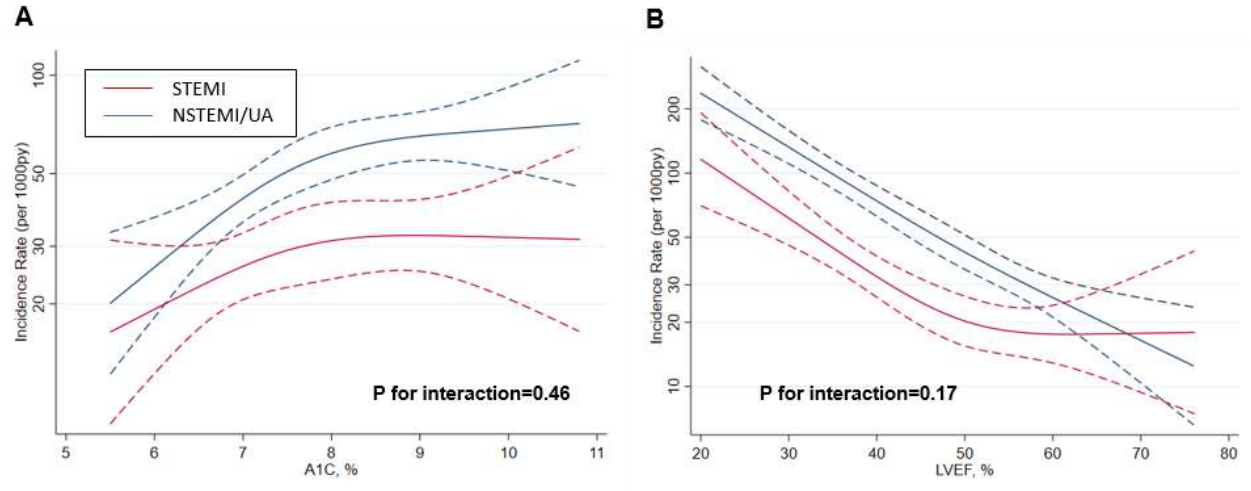
| | Hypoglycemia | | Serious hypoglycemia | |
|---|---|---|---|---|
| | HR [95% CI] | P value | HR [95% CI] | P value |
| HF or CV death | 1.08 [0.82 – 1.43] | 0.58 | 0.82 [0.20-3.28] | 0.77 |
| CV mortality | 0.94 [0.64-1.37] | 0.75 | 1.36 [0.34-5.48] | 0.67 |
| All-cause mortality | 1.02 [0.75-1.39] | 0.91 | 1.45 [0.47-4.53] | 0.52 |

Supplemental Table IV. Risk of A1C and LVEF for HF hospitalization or CV death according to history of HF

| | Patients without history of HF (n=3098) | | Patients with history of HF (n=993) | |
|---|---|---|---|---|
| | Event number=172 (5.5%) | | Event number=171 (17.2%) | |
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Univariate analysis | | | | |
| A1C per 1 point higher | 1.31 (1.17-1.47) | <0.001 | 1.07 (0.95-1.20) | 0.28 |
| LVEF per 10 points lower | 1.37 (1.20-1.57) | <0.001 | 1.54 (1.38-1.73) | <0.001 |
| Bivariate analysis* | | | | |
| A1C per 1 point higher | 1.31 (1.17-1.47) | <0.001 | 1.04 (0.93-1.18) | 0.47 |
| LVEF per 10 points lower | 1.37 (1.19-1.56) | <0.001 | 1.54 (1.38-1.72) | <0.001 |
| Multivariable analysis# | | | | |
| A1C per 1 point higher | 1.24 (1.10-1.40) | 0.001 | 0.99 (0.87-1.12) | 0.84 |
| LVEF per 10 points lower | 1.32 (1.15-1.51) | <0.001 | 1.44 (1.28-1.62) | <0.001 |

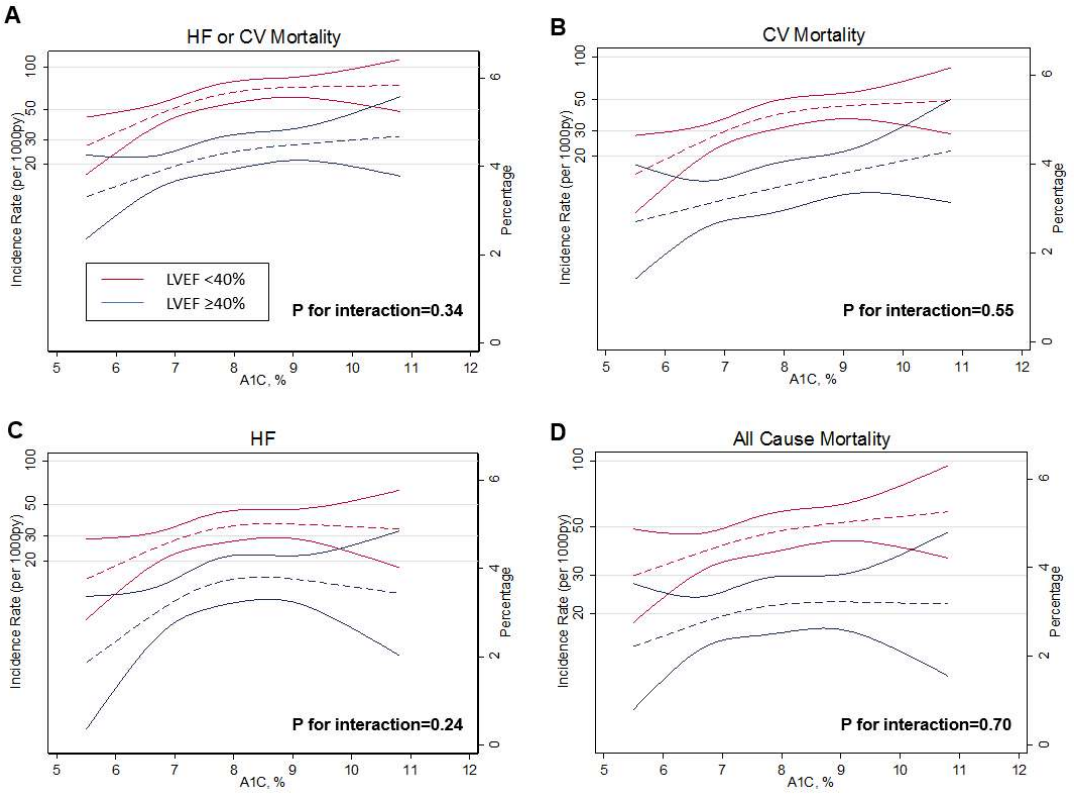
*Bivariate analysis included both LVEF and A1C, #Multivariable model included age, sex, race, duration of diabetes, treatment assignment, baseline heart rate, baseline eGFR, macroalbumiuria, LVEF and A1C

Supplemental Figure I. Incidence rate with (A) baseline A1C or (B) LVEF and a composite outcome of HF hospitalization or CV death according to subtype of index acute coronary syndrome event

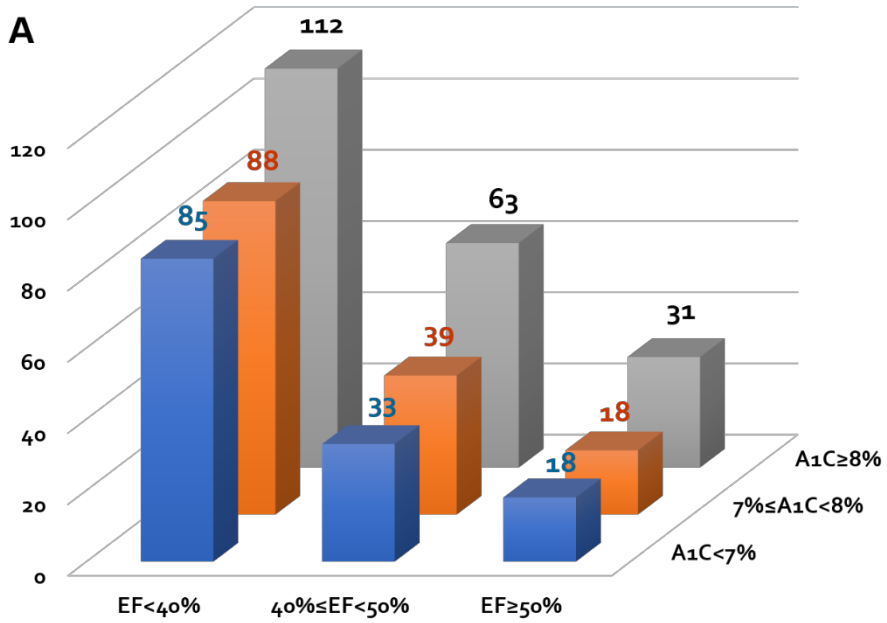


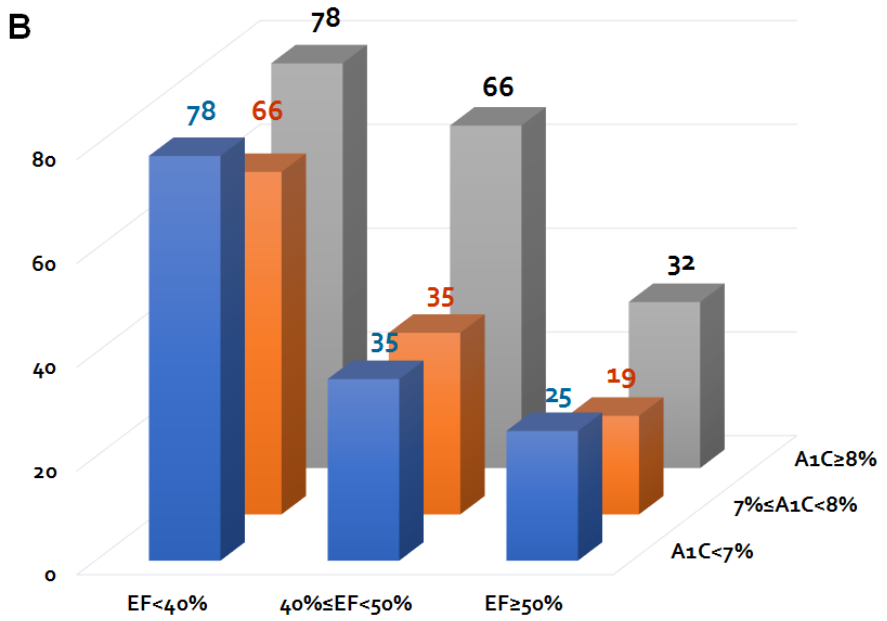

NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina

Supplemental Figure II. Incidence rates for outcomes among patients with reduced and preserved LVEF by baseline A1C.

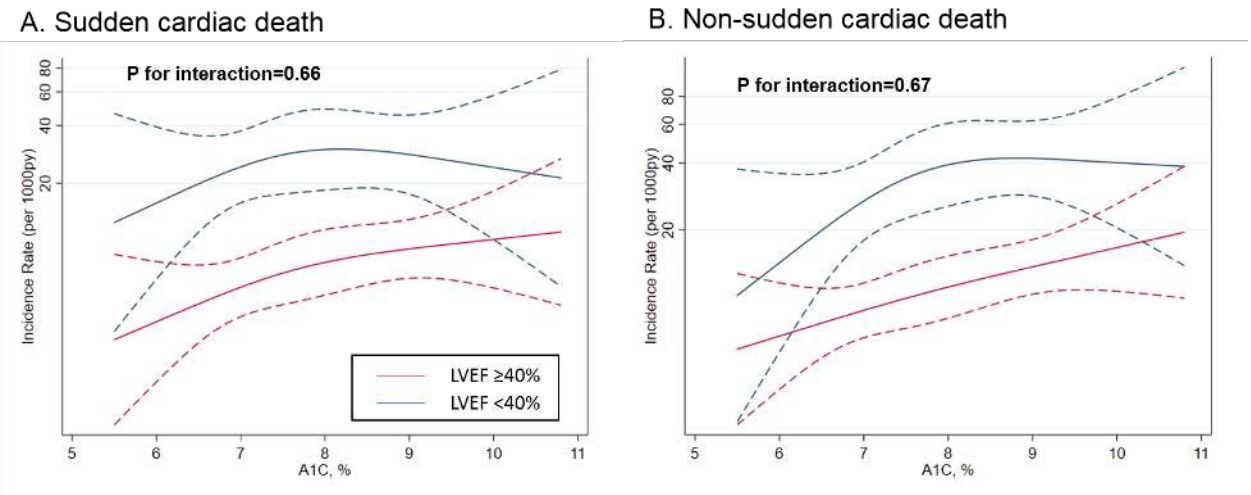


Supplemental Figure III. Incidence rates for HF or CV mortality per 1000 person-years according to subgroup categories of A1C and LVEF. (A) Unadjusted incidence rates and (B) adjusted incidence rates



Supplemental Figure IV. Incidence rates for (A) sudden cardiac death and (B) non-sudden CV death among patients with reduced and preserved LVEF by baseline A1C



## Reference


[1] McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol. 2014;2(10):843-51.

[2] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.

[3] Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, Gheorghiade M, Fonarow GC. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail. 2015;3(2):136-45.

[4] Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105-13.

[5] Murcia AM, Hennekens CH, Lamas GA, Jiménez-Navarro M, Rouleau JL, Flaker GC, Goldman S, Skali H, Braunwald E, Pfeffer MA. Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. Arch Intern Med. 2004;164(20):2273-9.

[6] Aguilar D, Solomon SD, Køber L, Rouleau JL, Skali H, McMurray JJ, Francis GS, Henis M, O'Connor CM, Diaz R, Belenkov YN, Varshavsky S, Leimberger JD, Velazquez EJ, Califf RM, Pfeffer MA. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. Circulation. 2004;110(12):1572-8.

[7] Deedwania PC, Ahmed MI, Feller MA, Aban IB, Love TE, Pitt B, Ahmed A. Impact of diabetes mellitus on outcomes in patients with acute myocardial infarction and systolic heart failure. Eur J Heart Fail. 2011 May;13(5):551-9.

[8] Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, Coresh J. HbA 1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia. 2008;51(12):2197-204.

[9] Gerstein HC, Swedberg K, Carlsson J, McMurray JJ, Michelson EL, Olofsson B, Pfeffer MA, Yusuf S; CHARM Program Investigators. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch Intern Med. 2008;168(15):1699-704.

[10] Erqou S, Lee CT, Suffoletto M, Echouffo-Tcheugui JB, de Boer RA, van Melle JP, Adler AI. Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis. Eur J Heart Fail. 2013;15(2):185-93.

[11] Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. Circulation. 2016;133(24):2459-502.

[12] Ceriello A, Taboga C, Tonutti L, Quagliaro L, Piconi L, Bais B, Da Ros R, Motz E. Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation: effects of short- and long-term simvastatin treatment. Circulation. 2002;106(10):1211-8.

[13] Perkins JM, Joy NG, Tate DB, Davis SN. Acute effects of hyperinsulinemia and hyperglycemia on vascular inflammatory biomarkers and endothelial function in overweight and obese humans. Am J Physiol Endocrinol Metab. 2015;309(2):E168-76

[14] Suzuki LA, Poot M, Gerrity RG, Bornfeldt KE. Diabetes accelerates smooth muscle accumulation in lesions of atherosclerosis: lack of direct growth-promoting effects of high glucose levels. Diabetes. 2001;50(4):851-60.

[15] Bornfeldt KE. 2013 Russell Ross memorial lecture in vascular biology: cellular and molecular mechanisms of diabetes mellitus-accelerated atherosclerosis. Arterioscler Thromb Vasc Biol. 2014;34(4):705-14.

[16] Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, Warnica JW, Khrakovskaya M, Arnold JM, Schwartz Y, Velazquez EJ, Califf RM, McMurray JV, Pfeffer MA. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation. 2005;111(25):3411-9.

[17] Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, Anderson JL, Yusuf S; CORE Study Investigators. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. J Am Coll Cardiol. 2002;39(1):30-6.

[18] MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ; CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J. 2008;29(11):1377-85.

[19] Shah AM, Uno H, Køber L, Velazquez EJ, Maggioni AP, MacDonald MR, Petrie MC, McMurray JJ, Califf RM, Pfeffer MA, Solomon SD. The inter-relationship of diabetes and left ventricular systolic function on outcome after high-risk myocardial infarction. Eur J Heart Fail. 2010;12(11):1229-37.

[20] Coiro S, Girerd N, Sharma A, Rossignol P, Tritto I, Pitt B, Pfeffer MA, McMurray JJV, Ambrosio G, Dickstein K, Moss A, Zannad F. 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(10):1248-1258.

[21] Skali H, Shah A, Gupta DK, Cheng S, Claggett B, Liu J, Bello N, Aguilar D, Vardeny O, Matsushita K, Selvin E, Solomon S. Cardiac structure and function across the glycemic spectrum in elderly men and women free of prevalent heart disease: the Atherosclerosis Risk In the Community study. Circ Heart Fail. 2015;8(3):448-54.

[22] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015;373(23):2247-57.

[23] Bentley-Lewis R, Aguilar D, Riddle MC, Claggett B, Diaz R, Dickstein K, Gerstein HC, Johnston P, Køber LV, Lawson F, Lewis EF, Maggioni AP, McMurray JJ, Ping L, Probstfield JL, Solomon SD, Tardif JC, Wu Y, Pfeffer MA; ELIXA Investigators. Rationale, design, and baseline characteristics in Evaluation of LIXisenatide in Acute Coronary Syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo. Am Heart J 2015;169(5):631-638

[24] American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S61-S70.

[25] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 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

[26] Kenny HC, Abel ED. Heart Failure in Type 2 Diabetes Mellitus. Circ Res. 2019;124(1):121-141.

[27] Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. Circ Res. 2018;122(4):624-638.

[28] Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation. 2000;101(19):2271-6.

[29] Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care. 2001;24(1):5-10.

[30] Shah AM, Shin SH, Takeuchi M, Skali H, Desai AS, Køber L, Maggioni AP, Rouleau JL, Kelly RY, Hester A, Keefe D, McMurray JJ, Pfeffer MA, Solomon SD. Left ventricular systolic and diastolic function, remodelling, and clinical outcomes among patients with diabetes following myocardial infarction and the influence of direct renin inhibition with aliskiren. Eur J Heart Fail. 2012;14(2):185-92.

[31] Avendano GF, Agarwal RK, Bashey RI, Lyons MM, Soni BJ, Jyothirmayi GN, Regan TJ. Effects of glucose intolerance on myocardial function and collagen-linked glycation. Diabetes. 1999;48(7):1443-7.

[32] Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens. 2003;21(1):3-12.

[33] Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007;115(25):3213-23.

[34] Heller SR, Bergenstal RM, White WB, Kupfer S, Bakris GL, Cushman WC, Mehta CR, Nissen SE, Wilson CA, Zannad F, Liu Y, Gourlie NM, Cannon CP; EXAMINE Investigators. Relationship of glycated haemoglobin and reported

hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: The EXAMINE trial. Diabetes Obes Metab. 2017;19(5):664-671.
[35] Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007;370(9593):1129-36.
[36] Cosmi F, Shen L, Magnoli M, Abraham WT, Anand IS, Cleland JG, Cohn JN, Cosmi D, De Berardis G, Dickstein K, Franzosi MG, Gullestad L, Jhund PS, Kjekshus J, Køber L, Lepore V, Lucisano G, Maggioni AP, Masson S, McMurray JJV, Nicolucci A, Petrarolo V, Robusto F, Staszewsky L, Tavazzi L, Teli R, Tognoni G, Wikstrand J, Latini R. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. Eur J Heart Fail. 2018;20(5):888-895.
[37] Tajik AA, Dobre D, Aguilar D, Kjekshus J, Zannad F, Dickstein K; High-Risk MI Database Scientific Committee. A history of diabetes predicts outcomes following myocardial infarction: an analysis of the 28 771 patients in the High-Risk MI Database. Eur J Heart Fail. 2017;19(5):635-642.
[38] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.
[39] Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab. 2013;17(1):20-33.
[40] Renard CB, Kramer F, Johansson F, Lamharzi N, Tannock LR, von Herrath MG, Chait A, Bornfeldt KE. Diabetes and diabetes-associated lipid abnormalities have distinct effects on initiation and progression of atherosclerotic lesions. J Clin Invest. 2004;114(5):659-68.
[41] Chen-Scarabelli C, Scarabelli TM. Suboptimal glycemic control, independently of QT interval duration, is associated with increased risk of ventricular arrhythmias in a high-risk population. Pacing Clin Electrophysiol. 2006;29(1):9-14.
[42] Erickson JR, Pereira L, Wang L, Han G, Ferguson A, Dao K, Copeland RJ, Despa F, Hart GW, Ripplinger CM, Bers DM. Diabetic hyperglycaemia activates CaMKII and arrhythmias by O-linked glycosylation. Nature. 2013;502(7471):372-6.
[43] Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007;115(3):387-97.
[44] Franssen C, Chen S, Unger A, Korkmaz HI, De Keulenaer GW, Tschöpe C, Leite-Moreira AF, Musters R, Niessen HW, Linke WA, Paulus WJ, Hamdani N. Myocardial Microvascular Inflammatory Endothelial Activation in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2016;4(4):312-24.
[45] van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbély A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, Paulus WJ. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation. 2008;117(1):43-51.
[46] Paulus WJ, Dal Canto E. Distinct Myocardial Targets for Diabetes Therapy in Heart Failure With Preserved or Reduced Ejection Fraction. JACC Heart Fail. 2018;6(1):1-7.
[47] Andersson C, Gislason GH, Mérie C, Mogensen UM, Solomon SD, Torp-Pedersen C, Køber L. Long-term prognostic importance of diabetes after a myocardial infarction depends on left ventricular systolic function. Diabetes Care. 2011;34(8):1788-90.
[48] Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, McCarren M, Duckworth WC, Emanuele NV; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;372(23):2197-206
[49] Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, Raskin P; American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2008;117(12):1610-9.
[50] Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. J Am Coll Cardiol. 2001;38(2):421-8.
[51] Domanski M, Krause-Steinrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E, Haffner S, Katz R, Lindenfeld J, Lowes BD, Martin W, McGrew F, Bristow MR; BEST Investigators. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. J Am Coll Cardiol. 2003;42(5):914-22.