# Association between Decreasing Estimated Glomerular Filtration Rate and Risk of Cardiac Conduction Defects in Patients with Type 2 Diabetes

**Running Title:** Cardiac conduction defects and CKD in diabetes.

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**LIST OF ABBREVIATIONS**

AV, atrio-ventricular

BMI, body mass index

CKD, chronic kidney disease

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

COPD, chronic obstructive pulmonary disease

ECG, electrocardiograms

eGFR, estimated glomerular filtration rate

HbA1c, hemoglobin A1c

IHD, ischemic heart disease

LAH, left anterior hemi-block

LBBB, left bundle branch block

LPH, left posterior hemi-block

MDRD, Modification of Diet in Renal Disease

RBBB, right bundle branch block

T2DM, type 2 diabetes

VHD, valvular heart disease

**ABSTRACT**

**Aim**: We aimed to assess the association between decreasing estimated glomerular filtration rate (eGFR) or abnormal albuminuria and the risk of certain cardiac conduction defects in patients with type 2 diabetes mellitus (T2DM).

**Methods**: We examined a hospital-based sample of 923 patients with T2DM discharged from our Division of Endocrinology over the years 2007-2014. Standard electrocardiograms (ECGs) were performed in all patients. eGFR was estimated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, whilst albuminuria was measured by an immuno-nephelometric method on morning spot urine samples.

**Results:** A total of 253 (27.4%) patients had some type of cardiac conduction defects on ECGs (defined as at least one heart block among first-degree atrio-ventricular block, second-degree block, third-degree block, left bundle branch block, right bundle branch block, left anterior hemi-block or left posterior hemi-block). Prevalences of patients with $eGFR_{CKD\text{-}EPI}$<30 ml/min/1.73 $m^2$, $eGFR_{CKD\text{-}EPI}$ 59-30 ml/min/1.73 $m^2$ or abnormal albuminuria (i.e. urinary albumin-to-creatinine ratio ≥30 mg/g) were 7.0%, 29.4% and 41.3%, respectively. After adjustment for known cardiovascular risk factors, diabetes-related variables and potential confounders, there was a significant, graded association between decreasing eGFR values and risk of cardiac conduction defects (adjusted-odds ratios of 2.05 [95% CI 1.2-3.5], 2.85 [95% CI 1.6-5.1] and 3.62 [95% CI 1.6-8.1] for $eGFR_{CKD\text{-}EPI}$ 89-60, $eGFR_{CKD\text{-}EPI}$ 59-30 and $eGFR_{CKD\text{-}EPI}$ <30 ml/min/1.73$m^2$, respectively). Conversely, abnormal albuminuria was not associated with an increased risk of conduction defects (adjusted-odds ratio 1.09, 95% CI 0.7-1.6).

**Conclusion:** Decreasing eGFR is independently associated with an increased risk of cardiac conduction defects in patients with T2DM.

**Key words:** chronic kidney disease; kidney dysfunction; cardiac conduction defects; diabetes

## INTRODUCTION

Cardiac conduction defects are unusual in healthy individuals but they become more common with ageing, presence of hypertension and ischemic heart disease (IHD) [1]. There are also a few observational studies reporting an increased prevalence of certain cardiac conduction defects, such as bundle branch blocks, bi-fascicular block and high-degree atrio-ventricular (AV) block, in patients with type 2 diabetes mellitus (T2DM) [2-4]. Most clinicians overlook this association, and the causes of cardiac conduction defects among patients with T2DM are not fully known. Notably, although it is well known that second-degree AV block and third-degree AV block are closely associated with an increased risk of fatal and nonfatal cardiovascular events, accumulating evidence now suggests that prolonged PR interval, first-degree AV block or bundle branch blocks are also associated with poor cardiac prognosis, independent of traditional cardiovascular risk factors [**5-7**].

Chronic kidney disease (CKD) is a common pathologic condition worldwide; e.g. in 2010 the age-standardized global prevalence of CKD stages 1-5 in adults was nearly 10% in men and 12% in women, respectively [**8,9**]. Several prospective studies showed that decreasing estimated glomerular filtration rate (eGFR) and abnormal albuminuria are associated with an increased risk of all-cause and cardiovascular mortality both in the general adult population and in 'high-risk' patient groups, including patients with T2DM [**10-15**]. To date, emerging evidence also suggests a significant association between the severity of CKD and certain cardiac conduction defects in patients with advanced CKD or in hypertensive patients without overt cardiovascular disease [**16,17**].

To our knowledge, it is currently uncertain whether decreasing eGFR values (*even* within the near-normal range) or raising albuminuria also increase the risk of cardiac conduction defects in patients with T2DM. We think this topic deserves in-depth investigation, as the presence of certain cardiac conduction abnormalities might contribute to explain, at least in part, the increased risk of cardiovascular morbidity and mortality observed in patients with coexistent T2DM and CKD.

Therefore, the aim of this cross-sectional study was to establish whether decreasing eGFR values and abnormal albuminuria are significantly associated with an increased prevalence of certain cardiac conduction defects in a large hospital-based sample of patients with T2DM.

## METHODS

### Patients

We retrospectively identified all patients with established T2DM, who were discharged from our Division of Diabetes and Endocrinology at the Verona University hospital during the years 2007-2014. Where a patient had had multiple discharges in 2007-2014 the first discharge with complete data was considered for statistical analyses. Most of these patients were admitted to the hospital for the following main clinical reasons: persistent poorly controlled diabetes or diabetic foot ulcers.

A total of 1,252 patients with established T2DM were initially identified in our electronic database. We subsequently excluded 329 patients (26% of total) with pacemakers/implantable cardioverter defibrillators, pre-existing atrial fibrillation or flutter, congestive heart failure, severe valvular heart disease (VHD), acute myocardial infarction or other important comorbidities (including

**hyperosmolar hyperglycemic syndrome, acute kidney injury**, acute electrolyte disturbances, thyroid dysfunction, cirrhosis, end-stage renal disease and malignancy), as well as patients taking any anti-arrhythmic agents (except the use of beta-blockers), which are all conditions known to induce cardiac conduction defects. As a result of this selection, 923 (74%) patients were included in the final analysis.

The local ethics committee approved the study protocol. The ethics committee exempted such kind of research from the informed consent requirement because we only accessed retrospectively a de-identified database for the purpose of data analysis.

**Clinical and laboratory data**

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Patients were considered to have hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any anti-hypertensive agents. Detailed information on comorbid conditions and use of medications was acquired in all patients by interviews during medical visits.

Venous blood samples were collected in the morning after an overnight fast of at least 8 hours. Complete blood count, creatinine (measured using a Jaffé rate-blanked and compensated assay), thyroid-stimulating hormone, electrolytes, lipids and other biochemical blood measurements were determined using standard laboratory procedures. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald's formula. Hemoglobin A1c (HbA1c) was measured by a high-performance liquid chromatography analyzer on Tosoh-G7 automated analyzer (Tosoh Bioscience Inc., Tokyo, Japan).

Glomerular filtration rate (eGFR) was estimated from calibrated serum creatinine values using the four-variable Modification of Diet in Renal Disease (MDRD) study equation [**18**] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [**19**]. However, the CKD-EPI equation, which uses the same four variables as the MDRD study equation, has been shown to be more accurate than the MDRD study equation for estimating GFR in different populations [**19**], as well as for predicting the risk of mortality in patients with T2DM [**20**]. Urinary albumin excretion was measured by an immuno-nephelometric method on a morning spot urine sample and expressed as the albumin/creatinine ratio (ACR) on Beckman-Coulter IMMAGE (Beckman-Coulter Instruments, Fullerton, CA; USA); **abnormal albuminuria was defined as a urinary ACR ≥30 mg/g creatinine**.

Presence of IHD was defined as a documented history of myocardial infarction, angina pectoris or coronary revascularization procedures. Pre-existing history of mild-to-moderate VHD was confirmed by reviewing hospital medical records, including diagnostic symptoms patterns and echocardiograms (patients with prosthetic heart valves or severe VHD were excluded from the study). The pre-existing history of peripheral artery disease was based on medical history and examination (e.g., intermittent claudication, rest pain or lower-extremity revascularization procedures) and was then confirmed by reviewing hospital medical records of patients, including radiologic imaging results. The pre-existing history of chronic obstructive pulmonary disease (COPD) was confirmed by reviewing medical records of the hospital, including diagnostic symptoms patterns, and results of lung function tests. In most patients, the presence of microvascular diabetic complications, such as diabetic retinopathy (diagnosed with fundoscopy after pupillary dilation) and lower-extremity sensory neuropathy (assessed by biothesiometer or 5.07/10-gm monofilament) were also recorded.

**Standard electrocardiograms**

A standard 12-lead electrocardiogram (ECG) was usually performed in all patients during the first 1-2 days of hospital stay and then repeated before discharge from the hospital in all patients who had abnormal ECGs. A 24-hour ECG Holter monitoring or a conventional echocardiography were not routinely performed in these patients. The diagnosis of **persistent** cardiac conduction defects was made on the basis of automatic interpretation of standard ECGs (**and confirmed on at least two ECGs during the hospital stay**) that was subsequently validated by an expert cardiologist, who was blinded to patient's clinical data. In particular, the first-degree AV block was defined as a PR interval duration of 200 ms or more with no variation [**21**]. The diagnosis of second-degree AV block was performed in accordance with progressive prolongation of PR interval, culminating in a non-conducted P wave [**21**]. Second-degree AV block was subsequently classified in Mobitz type I or Mobitz type II. A third-degree AV block was diagnosed when the P waves were not followed by QRS complexes [**21**]. Similarly, the presence of complete right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior hemi-block (LAH) or left posterior hemi-block (LPH) were also diagnosed by an expert cardiologist according to standard ECG criteria [**21**].

**Statistical analysis**

Data are reported as means±SD, medians and inter-quartile ranges (IQR) or percentages. Cross-sectional associations between increasing CKD stages (i.e. $eGFR_{CKD\text{-}EPI}$ ≥90 [CKD stage 1], $eGFR_{CKD\text{-}EPI}$ 89-60 [CKD stage 2], $eGFR_{CKD\text{-}EPI}$ 59-30 [CKD stage 3] and $eGFR_{CKD\text{-}EPI}$ <30 [CKD stages 4 to 5] ml/min/1.73 $m^2$) and clinical, biochemical and electrocardiographic characteristics of patients were assessed using the one-way analysis of variance for normally distributed variables and the Kruskal-Wallis test for non-normally distributed variables (i.e., diabetes duration, serum

triglyceride and alanine aminotransferase levels). The chi-squared test was used to test for between-group differences among the categorical variables. Logistic regression analysis was used to examine the association between decreasing $eGFR_{CKD\text{-}EPI}$ (included either as categorical or as continuous measure) or abnormal albuminuria and the risk of either any cardiac conduction defects on ECGs (i.e., **the primary outcome measure of the study**, which was defined as presence of at least one heart block among first-degree AV block, second-degree AV block, third-degree AV block, LBBB, RBBB, LAH or LPH), or any AV block (i.e., at least one among first-degree AV block, second-degree AV block or third-degree AV block), or any bundle branch block (i.e., at least one among LBBB, RBBB, LAH or LPH), **which were the secondary outcome measures of the study**. We performed four forced-entry logistic regression models: the first model was unadjusted (unadjusted model); the second model was adjusted for age, sex, BMI, duration of diabetes and HbA1c (adjusted model 1); the third model was further adjusted for serum electrolytes (potassium, calcium), uric acid, hypertension (i.e. blood pressure ≥140/90 mmHg and/or drug treatment, *including* the use of ACE-inhibitors, angiotensin receptor blockers, diuretics, dihydropyridine calcium-channel blockers or beta-blockers), prior history of IHD, mild-to-moderate VHD, peripheral artery disease, and use of statins, fibrates, allopurinol, anti-platelets drugs, anti-coagulants or nitrates (adjusted model 2). Lastly, the fourth multivariable regression model was further adjusted for abnormal albuminuria and other microvascular diabetic complications (i.e., diabetic retinopathy and peripheral sensory neuropathy) (adjusted model 3). We also repeated these multivariable logistic regression analyses using $eGFR_{MDRD}$, instead of $eGFR_{CKD\text{-}EPI.}$ The same aforementioned multivariable regression models were also performed for examining the association between abnormal albuminuria and the risk of any cardiac conduction defect; in such case, in the fully adjusted model 3 the results were also adjusted for $eGFR_{CKD\text{-}EPI}$ included as a continuous measure. Covariates included in these multivariable logistic regression models were

selected as potential confounding factors based on their significance in univariate analyses or based on their biological plausibility. A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using STATA software, version 14.2 (STATA, College Station, Texas, USA).

**RESULTS**

Among the 923 patients with established T2DM that were included in the study (56% men, mean age of 65 years, median diabetes duration of 12 years), 248 (26.9%) patients had an $eGFR_{CKD\text{-}EPI}$ ≥90 ml/min/1.73 $m^2$ (CKD stage 1), 339 (36.7%) patients had an $eGFR_{CKD\text{-}EPI}$ 89-60 ml/min/1.73 $m^2$ (CKD stage 2), 271 (29.4%) patients had an $eGFR_{CKD\text{-}EPI}$ 59-30 ml/min/1.73 $m^2$ (CKD stage 3), and 65 (7%) had an $eGFR_{CKD\text{-}EPI}$ <30 ml/min/1.73 $m^2$ (CKD stages 4-5). In addition, 381 (41.3% of total) had abnormal albuminuria. Overall, there were 300 total cardiac conduction defects among 253 (27.4%) patients, who had some type of **persistent** conduction defects, detected by standard ECGs during the hospital stay. In particular, 111 patients had a first-degree AV block, 3 had a second-degree AV block (2 of whom had Mobitz type I and 1 had Mobitz type II), 1 had a third-degree AV block, 89 had RBBB, 25 had LBBB, 69 had LAH and 2 patients had LPH. Because of the study design, no patients were treated with amiodarone, propafenone, digitalis, non-dihydropyridine calcium-channel blockers or other anti-arrhythmic agents, except beta-blockers.

**Table 1** shows the clinical, biochemical and electrocardiographic characteristics of patients stratified by increasing CKD stages. Compared to those with CKD stage 1 (i.e. $eGFR_{CKD\text{-}EPI}$ ≥90 ml/min/1.73 $m^2$), patients with increasing CKD stages (i.e. decreasing $eGFR_{CKD\text{-}EPI}$ values) were older, more likely to be female, had a longer duration of diabetes, higher levels of serum

creatinine, potassium and uric acid, and lower levels of total cholesterol, LDL cholesterol, HDL-cholesterol and alanine aminotransferase (ALT). The prevalence of abnormal albuminuria, hypertension, mild-to-moderate VHD, IHD, peripheral artery disease, diabetic retinopathy and peripheral sensory neuropathy also increased significantly across increasing stages of CKD, whereas the prevalence of smoking history decreased. The proportion of patients treated with insulin, allopurinol, diuretics, dihydropyridine calcium-channel blockers, beta-blockers, angiotensin receptor blockers, antiplatelet drugs, anticoagulants or nitrates significantly increased across increasing stages of CKD. Conversely, the proportion of those treated with metformin or ACE-inhibitors decreased across CKD stages. No significant differences were observed in BMI, fasting glucose, HbA1c, triglycerides, calcium, prior COPD, and use of sulfonylureas, incretin mimetics or fibrates. With regards to the electrocardiographic findings, PR, QRS and QTc intervals progressively increased across increasing CKD stages.

**Supplementary Table 1 shows the clinical, biochemical and electrocardiogram characteristics of patients stratified by presence or absence of any persistent cardiac conduction defect on ECGs. Patients with cardiac conduction defects were older, more likely to be male, had longer duration of diabetes, higher serum uric acid, higher serum creatinine, lower eGFR values (including also more severe stages of CKD), and longer PR, QRS and QTc intervals on ECGs compared to those without cardiac conduction defects. Moreover, they also had lower HbA1c, total and LDL-cholesterol levels. Additionally, the prevalence of abnormal albuminuria, IHD, mild-to-moderate VHD, diabetic retinopathy, peripheral artery disease as well as the proportion using dihydropyridine calcium channel blockers, diuretics, nitrates, statins, anti-platelet agents or anticoagulants were greater in patients with cardiac conduction defects than in those without. No significant differences were found in BMI, smoking history, COPD, hypertension, peripheral**

**sensory neuropathy, serum electrolytes, use of beta-blockers, ACE-inhibitors or angiotensin receptor blockers and treatment for diabetes between the two groups of patients.**

As shown in **Figure 1**, the prevalence of **persistent** cardiac conduction defects on standard ECGs (i.e. any heart block, any AV block, or any bundle branch block) sharply increased across increasing CKD stages. Specifically, among the different types of cardiac conduction defects, the prevalence of first-degree AV block and LBBB increased significantly across increasing CKD stages.

**Figure 2** shows the prevalence of cardiac conduction defects (singly or in combination) stratified by presence or absence of abnormal albuminuria. Patients with abnormal albuminuria had a higher prevalence of any AV block, any bundle branch block or any heart block compared to their counterparts with normal albuminuria. Among the specific types of cardiac conduction defects, patients with abnormal albuminuria had a higher prevalence of first-degree AV block, and tended also to have an unsignificant increase in LPH.

**Table 2** shows the effect of adjustment for multiple clinical risk factors and potential confounders on the associations between increasing CKD stages (Panel A), $eGFR_{CKD\text{-}EPI}$ (included as a continuous measure; Panel B) or abnormal albuminuria (Panel C) and the risk of any cardiac conduction defect. In univariate logistic regression analysis (unadjusted model), there was a stepwise increase in the risk of any conduction defect across increasing CKD stages, which was found to be more evident among individuals with CKD stages 4-5 (i.e., $eGFR_{CKD\text{-}EPI}$ <30 ml/min/1.73 $m^2$). Notably, this association was only slightly attenuated after adjustment age, sex, BMI, HbA1c and duration of diabetes (Panel A, adjusted model 1). Results remained essentially unchanged even after additional adjustment for serum electrolytes, uric acid, hypertension, prior IHD, mild-to-moderate

VHD, peripheral artery disease, abnormal albuminuria, diabetic retinopathy, peripheral sensory neuropathy, and use of various medications (Panel A, adjusted models 2 and 3). Notably, other risk factors (together with increasing CKD stages) that were independently associated with the risk of any cardiac conduction defect were older age, male sex, a longer duration of diabetes, and the presence of mild-to-moderate VHD or IHD ($p$<0.05-0.001). When we repeated the same multivariable regression models using $eGFR_{CKD\text{-}EPI}$ values as a continuous measure (**Table 2,** Panel B), we found that a 1-SD decrement (i.e., 26.5 ml/min/1.73 $m^2$) in $eGFR_{CKD\text{-}EPI}$ was significantly associated with a 45% increase in the risk of any cardiac conduction defect even after adjusting for multiple risk factors and potential confounders (Panel B, adjusted model 3). Again, when we included abnormal albuminuria in all the aforementioned multivariable regression models (**Table 2,** Panel C), we found that abnormal albuminuria was significantly associated with the risk of any cardiac conduction defect in the unadjusted model, and even after adjusting for age, sex, BMI, HbA1c and diabetes duration (adjusted model 1). However, this association became statistically not significant after further adjustment for $eGFR_{CKD\text{-}EPI,}$ comorbidities and other relevant cardiovascular risk factors (Panel C, adjusted models 2 and 3). Almost identical results were observed when patients who took beta-blockers (n=276) or those with a prior history of IHD (n=185) were excluded from statistical analyses, or when all the aforementioned logistic regression models were repeated using $eGFR_{MDRD}$ for staging CKD (data not shown).

We undertook some sensitivity analyses to evaluate the robustness of our findings. **Supplementary Figure 1** shows the association between decreasing $eGFR_{CKD\text{-}EPI}$ (for each SD decrement) and risk of any cardiac conduction defect in patients stratified by sex, duration of diabetes (by median values), HbA1c level (by median values), hypertension, presence of prior IHD, mild-moderate VHD or use of beta-blockers. Notably, the significant association between

decreasing $eGFR_{CKD\text{-}EPI}$ values and risk of any cardiac conduction defect was consistent in all subgroups examined.

We also performed separate logistic regression analyses for examining the associations between CKD stages (Panel A), $eGFR_{CKD\text{-}EPI}$ (included as a continuous measure; Panel B) or abnormal albuminuria (Panel C) and the risk of either any AV block (**Table 3**) or any bundle branch block (**Table 4**). Also in such case, we observed a stepwise increase in the risk of either AV blocks or bundle branch blocks across increasing CKD stages that remained significant even after adjusting for potential confounding factors (adjusted model 3; Panel A). Almost identical results were found when $eGFR_{CKD\text{-}EPI}$ was included as a continuous measure in the aforementioned logistic regression models (Panel B). Conversely, abnormal albuminuria was not independently associated with the risk of either AV blocks or bundle branch blocks (adjusted models 2 and 3, Panel C). Finally, the results remained essentially unchanged even when we excluded patients with fascicular blocks (i.e., LAH and LPH) and restricted our statistical analyses to examine the association between increasing CKD stages (or abnormal albuminuria) with the risk of having LBBB and/or RBBB (data not shown).

**DISCUSSION**

To our knowledge, this cross-sectional study is the first to examine the association between increasing stages of CKD or abnormal albuminuria and the risk of **persistent** cardiac conduction defects on standard ECGs in patients with T2DM. The novel results of our study provide significant evidence that (*i*) patients with T2DM and decreasing $eGFR_{CKD\text{-}EPI}$ values (*even* in the near-normal range, i.e., CKD stage 2) have a markedly higher prevalence of any cardiac conduction defect

(mostly due to first-degree AV block and LBBB) compared to those with normal $eGFR_{CKD\text{-}EPI}$ (CKD stage 1); (*ii*) the strong association between increasing CKD stages and the risk of any cardiac conduction defect remained statistically significant even after adjustment for traditional cardiovascular risk factors, prior IHD, mild-to-moderate VHD, diabetes-related variables, serum electrolytes, abnormal albuminuria and use of certain medications; (*iii*) the aforementioned results were also observed for the association between decreasing $eGFR_{CKD\text{-}EPI}$ values and the risk of either any AV block or any bundle branch block; and (*iv*) the presence of abnormal albuminuria was not independently associated with risk of any cardiac conduction defect after adjustment for multiple potential confounding factors, including also $eGFR_{CKD\text{-}EPI}$.

Collectively, these findings confirm the presence of a high prevalence of certain cardiac conduction defects (~27%) in patients with T2DM [2-4], and expand the results of some recent cross-sectional studies that examined the association between increasing CKD stages and presence of cardiac conduction defects in 'high-risk' patient populations [**16,17**]. In a small observational study, involving 50 CKD patients undergoing hemodialysis with an implantable cardiac monitor inserted, Wong *et al.* reported a total of 7,686 cardiac arrhythmia events in 43 of these patients (including bradycardia, second-degree AV block, non-sustained ventricular tachyarrhythmias or paroxysmal atrial fibrillation) during the period between hemodialysis sessions [**16**]. This suggests that the risk of sudden cardiac death and significant arrhythmias is greatest during the long inter-dialytic period. In a cross-sectional study of nearly 4,000 hypertensive patients without overt cardiovascular disease, Sciarretta *et al.* reported that CKD (defined either by decreased eGFR or by abnormal albuminuria) was significantly associated with ECG abnormalities such as intra-ventricular conduction defects, ventricular repolarization alterations, and left-axis deviation, independent of traditional cardiovascular risk factors [**17**].

We believe that the strong and graded associations we observed between decreasing $eGFR_{CKD\text{-}EPI}$ values (*even* in the near-normal range) and the risk of any cardiac conduction defect (or any AV block or any bundle branch block) may have important clinical implications. Indeed, our findings can partly explain the increased risk of cardiovascular morbidity and mortality observed in patients with coexistent T2DM and CKD. However, it is known that a number of other pathophysiological derangements associated with more advanced stages of CKD, including disordered sodium, potassium, and water homeostasis, renin-angiotensin-aldosterone and sympathetic activity, anemia, bone and mineral metabolism, uremia, and toxin accumulation can also contribute to progression of cardiovascular disease and adverse survival outcomes [**22,23**]. Further larger studies are needed to better elucidate if lower eGFR and/or higher albuminuria may have differential effects on the risk of cardiac conduction defects in patients with T2DM.

The underlying mechanisms for the increased risk of cardiac conduction defects seen among T2DM patients with decreasing eGFR values (*even* within the near-normal range) that we have observed are not fully understood. However, it is plausible that endothelial dysfunction, coagulation-fibrinolytic system abnormalities, low-grade inflammation, increased oxidative stress and hyperuricemia may contribute to promoting important derangements in the structural and electrophysiological substrates of both the myocardium and the His-Purkinje system, thus inducing an increased vulnerability to cardiac arrhythmias [**24-26**]. Hence, it is reasonable to assume that several of these pathophysiological factors, which are also frequently present in T2DM patients with CKD stages 2 to 5, might be actively involved in the development (and persistence) of certain cardiac conduction defects [**24-27**]. However, more research is needed to

dissect out the underlying mechanisms involved in each specific group of cardiac conduction abnormalities.

Our study has some important limitations that should be mentioned. First, this is a retrospective analysis of a single-center registry of hospitalized patients with T2DM. Second, the cross-sectional design of the study limits our ability to establish causal or temporal relationships. Third, **although we excluded most patients with cardiac and noncardiac related pathologic conditions known to induce cardiac conduction defects or marked reductions in eGFR values, and we confirmed the presence of cardiac conduction defects on the basis of at least two ECGs during the hospital stay (see Methods section),** a selection bias of including a hospital-based sample of individuals with T2DM (most of whom hospitalized for poorly controlled diabetes or diabetic foot ulcers) cannot be definitely excluded. Thus, our results might not necessarily be generalizable to other populations with T2DM. Fourth, we used an estimated GFR instead of a directly measured GFR to define and stage CKD. However, current GFR estimates facilitate the screening, evaluation and management of CKD, and many scientific organizations recommend the use of the CKD-EPI study equation for estimating kidney function in clinical practice [**28**]. **Fifth, we had only a single measurement of albuminuria, so we cannot exclude that urinary ACR values could be falsely high in some of these patients hospitalized for poorly controlled diabetes or diabetic foot ulcers (especially when ACR was in the range of 30-300 mg/g, i.e., microalbuminuria)**. Sixth, in our sample there were relatively few patients with CKD stages 4-5. Hence, the results of this study should not be extrapolated to more advanced stages of CKD. Finally, although our multivariable logistic regression models were extensive, we cannot rule out the eventuality of residual confounding or confounding from unmeasured factors (e.g., cardiac autonomic neuropathy and conventional

echocardiographic parameters, such the left atrial and ventricular volumes and left ventricular ejection fraction) that might, at least in part, explain these results.

Notwithstanding these limitations, our study has also important strengths, including the large sample size, the complete nature of the dataset, the ability to adjust for multiple potential confounding factors and the exclusion of patients with pacemakers or implantable cardioverter defibrillators, patients treated with anti-arrhythmic drugs or those with serious comorbidities, such as pre-existing atrial fibrillation/flutter, congestive heart failure, severe VHD or prosthetic valves, acute kidney injury, acute electrolyte disturbances, thyroid dysfunction, end-stage renal disease, decompensated cirrhosis or malignancies. We believe that inclusion of patients with these severe comorbidities might have confounded the interpretation of data.

In conclusion, the results of this cross-sectional study show for the first time that decreasing $eGFR_{CKD\text{-}EPI}$ values (*even* in the near-normal range), but not abnormal albuminuria, are independently associated with a higher prevalence of **persistent** cardiac conduction defects (mostly due to first-degree AV block and LBBB) in a large hospital-based sample of patients with T2DM. Further research is required to corroborate these findings in larger samples and better elucidate the underlying mechanisms responsible for this association.

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**Authors Contributions:** AM and GT conceived and designed the study. RR, TT, AF, IP and AR researched data and reviewed/edited the manuscript. SB, PLT, GL, GZ, EB and CDB contributed to discussion and reviewed/edited the manuscript. AM and GT analyzed the data and wrote the manuscript draft. All authors have approved the submitted version of the manuscript.

**REFERENCES**

1. Braunwald's Heart Disease. A textbook of cardiovascular medicine. 9th Ed, 2012, p. 818-24.

2. Movahed MR. Diabetes as a risk factor for cardiac conduction defects: a review. Diabetes Obes Metab 2007; 9: 276-81.

3. Pfister R, Cairns R, Erdmann E, Schneider CA; PROACTIVE investigators. Prognostic impact of electrocardiographic signs in patients with Type 2 diabetes and cardiovascular disease: results from the PROactive study. Diabet Med 2011; 28: 1206-12.

4. Gupta S, Gupta RK, Kulshrestha M, Chaudhary RR. Evaluation of ECG abnormalities in patients with asymptomatic type 2 diabetes mellitus. J Clin Diagn Res 2017; 11: OC39-41.

5. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA 2009; 301: 2571-7.

6. Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. Eur Heart J 2013; 34: 138-46.

7. Kwok CS, Rashid M, Beynon R, Barker D, Patwala A, Morley-Davies A, et al. Prolonged PR interval, first-degree heart block and adverse cardiovascular outcomes: a systematic review and meta-analysis. Heart 2016; 102: 672-80.

8. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Rev Nephrol 2017; 13: 104-14.

9. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015; 88: 950-7.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296-305.
11. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol 2004; 15: 1307-15.
12. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286: 421-6.
13. Targher G, Zoppini G, Chonchol M, Negri C, Stoico V, Perrone F, et al. Glomerular filtration rate, albuminuria and risk of cardiovascular and all-cause mortality in type 2 diabetic individuals. Nutr Metab Cardiovasc Dis 2011; 21: 294-301.
14. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013; 24: 302-8.
15. Penno G, Solini A, Bonora E, Orsi E, Fondelli C, Zerbini G, et al; Renal Insufficiency and Cardiovascular Events (RIACE) Study Group. Defining the contribution of chronic kidney disease to all-cause mortality in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study. Acta Diabetol 2018; 55: 603-12.
16. Wong MC, Kalman JM, Pedagogos E, Toussaint N, Vohra JK, Sparks PB, et al. Temporal distribution of arrhythmic events in chronic kidney disease: highest incidence in the long interdialytic period. Heart Rhythm 2015; 12: 2047-55.
17. Sciarretta S, Pontremoli R, Rosei EA, Ambrosioni E, Costa V, Leonetti G, et al. Independent association of ECG abnormalities with microalbuminuria and renal damage in hypertensive patients without overt cardiovascular disease: data from Italy-Developing Education and awareness on MicroAlbuminuria in patients with hypertensive Disease study. J Hypertens 2009; 27: 410-7.
18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999; 130: 461-70.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604-12.
20. Targher G, Zoppini G, Mantovani W, Chonchol M, Negri C, Stoico V, et al. Comparison of two creatinine-based estimating equations in predicting all-cause and cardiovascular mortality in patients with type 2 diabetes. Diabetes Care 2012; 35: 2347-53.

21. The Minnesota code manual of electrocardiographic findings: standards and procedures for ECG measurement in epidemiologic and clinical trials. Prineas RJ, Crow RS, Zhang ZM, Eds. 2nd Edition. London: Springer-Verlag, 2010.
22. Tomey MI, Winston JA. Cardiovascular pathophysiology in chronic kidney disease: opportunities to transition from disease to health. Ann Glob Health 2014; 80: 69-76.
23. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost 2010; 36: 34-40.
24. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015; 12: 230-43.
25. Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. Int J Cardiol 2013; 169: 62-72.
26. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation 2003; 108: 2154-69.
27. Mantovani A, Rigolon R, Pichiri I, Morani G, Bonapace S, Dugo C, et al. Relation of elevated serum uric acid levels to first-degree heart block and other cardiac conduction defects in hospitalized patients with type 2 diabetes. J Diabetes Complications 2017; 31: 1691-7.
28. Levey AS, Inker LA. Assessment of glomerular filtration rate in health and disease: a state of the art review. Clin Pharmacol Ther 2017; 102: 405-19.

**Table 1.** Clinical, biochemical and electrocardiographic characteristics of patients with type 2 diabetes, stratified by increasing CKD stages (by using the $eGFR_{CKD\text{-}EPI}$ equation).

| | **CKD Stage 1 ($eGFR_{CKD\text{-}EPI}$ ≥90 ml/min/1.73 $m^2$) (*n*=248; 26.9%)** | **CKD Stage 2 ($eGFR_{CKD\text{-}EPI}$ 89-60 ml/min/1.73 $m^2$) (*n*=339; 36.7%)** | **CKD Stage 3 ($eGFR_{CKD\text{-}EPI}$ 59-30 ml/min/1.73 $m^2$) (*n*=271; 29.4%)** | **CKD Stages 4-5 ($eGFR_{CKD\text{-}EPI}$ <30 ml/min/1.73 $m^2$) (*n*=65; 7%)** | ***P* value** |
|---|---|---|---|---|---|
| Age (years) | 54.5 ± 11 | 66.0 ± 11 | 71.2 ± 10 | 73.9 ± 12 | <0.001 |
| Sex (male) (%) | 65.7 | 58.7 | 45.4 | 52.3 | <0.001 |
| Weight (kg) | 86 ± 23 | 82 ± 21 | 82 ± 20 | 83 ± 20 | 0.53 |
| BMI (kg/$m^2$) | 30.5 ± 7.1 | 29.9 ± 7.1 | 30.7 ± 6.7 | 30.0 ± 6.6 | 0.52 |
| Current smokers (%), n=282 | 66.7 | 56.0 | 29.2 | 19.1 | <0.001 |
| Duration of diabetes (years) | 9 (5-15) | 10 (5-20) | 17 (10-26) | 15 (7-25) | <0.001 |
| Systolic blood pressure (mmHg) | 140 ± 18 | 141 ± 19 | 141 ± 20 | 144 ± 26 | 0.46 |
| Diastolic blood pressure (mmHg) | 83 ± 11 | 80 ± 11 | 78 ± 11 | 79 ± 13 | <0.001 |
| Hypertension (%) | 68.6 | 78.5 | 87.8 | 87.7 | <0.001 |
| Fasting glucose (mg/dl) | 200 ± 107 | 194 ± 112 | 203 ± 140 | 196 ± 179 | 0.82 |
| HbA1c (%) | 10.1 ± 2.7 | 9.7 ± 2.5 | 9.6 ± 2.6 | 9.2 ± 2.9 | <0.05 |
| Total cholesterol (mg/dl) | 184 ± 50 | 172.7 ± 51 | 170 ± 51 | 160 ± 55 | <0.01 |
| LDL-cholesterol (mg/dl) | 110 ± 43 | 96 ± 39 | 90 ± 39 | 83 ± 40 | <0.001 |
| HDL-cholesterol (mg/dl) | 41 ± 13 | 42 ± 15 | 42 ± 16 | 36 ± 13 | <0.05 |
| Triglycerides (mg/dl) | 137 (92-186) | 141 (99-199) | 152 (111-220) | 167 (115-228) | 0.412 |
| ALT (U/l) | 27 (18-44) | 22 (16-36) | 20 (15-30) | 16 (10-23) | <0.001 |
| Sodium (mmol/l) | 138 ± 3 | 139 ± 3 | 138 ± 4 | 138 ± 4 | 0.06 |
| Potassium (mmol/l) | 3.9 ± 0.4 | 4.0 ± 0.4 | 4.1 ± 0.6 | 4.3 ± 0.7 | <0.001 |
| Calcium (mg/dl) | 9.0 ± 0.4 | 9.1 ± 0.5 | 9.1 ± 0.5 | 8.9 ± 0.6 | 0.11 |
| Uric Acid (mg/dl) | 4.5 ± 1.6 | 4.8 ± 1.5 | 5.8 ± 1.8 | 6.9 ± 2.1 | <0.001 |
| Creatinine (mg/dl) | 0.74 ± 0.14 | 0.94 ± 0.16 | 1.37 ± 0.29 | 2.94 ± 1.38 | <0.001 |
| $eGFR_{CKD\text{-}EPI}$ (ml/min/1.72 $m^2$) | 101.8 ± 10 | 76.4 ± 9 | 46.1 ± 8 | 20.2 ± 6 | ND |
| Abnormal albuminuria (%) | 30.2 | 35.7 | 48.7 | 81.5 | <0.001 |
| IHD (%) | 12.5 | 19.2 | 25.1 | 32.3 | <0.001 |
| Mild-moderate VHD (%) | 2.8 | 6.8 | 11.8 | 15.4 | <0.001 |
| COPD (%) | 3.6 | 5.6 | 5.9 | 9.2 | 0.32 |
| Diabetic retinopathy (%), any degree | 28.7 | 38.6 | 51.5 | 67.7 | <0.001 |
| Peripheral sensory neuropathy (%) | 20.2 | 27.6 | 35.5 | 38.1 | <0.001 |
| Peripheral artery disease (%) | 37.0 | 49.1 | 61.6 | 73.0 | <0.001 |
| Insulin users (%) | 64.1 | 64.9 | 80.8 | 86.2 | <0.001 |
| Metformin users (%) | 49.6 | 48.1 | 23.9 | 6.2 | <0.001 |
| Sulfonylurea users (%) | 18.1 | 20.3 | 23.3 | 15.4 | 0.26 |
| Incretin users (%) | 6.4 | 9.4 | 8.1 | 6.1 | 0.56 |
| ACE-inhibitor users (%) | 50.4 | 55.2 | 51.6 | 27.7 | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| ARB users (%) | 16.5 | 19.5 | 26.9 | 26.1 | <0.05 |
| Beta-blocker users (%) | 16.9 | 28.6 | 38.7 | 49.2 | <0.001 |
| Dihydropyridine CCB users (%) | 21.4 | 29.5 | 42.1 | 46.2 | <0.001 |
| Diuretic users (%) | 24.2 | 39.2 | 70.8 | 78.5 | <0.001 |
| Antiplatelet drug users (%) | 42.7 | 60.2 | 74.5 | 76.9 | <0.001 |
| Anticoagulant drug users (%) | 0.4 | 6.2 | 8.9 | 10.8 | <0.01 |
| Nitrate drug users (%) | 5.3 | 9.7 | 15.9 | 23.1 | <0.001 |
| Statin users (%) | 45.9 | 59.3 | 61.9 | 60.0 | <0.01 |
| Fibrate users (%) | 2.4 | 4.4 | 3.3 | 4.6 | 0.59 |
| Allopurinol (%) | 4.6 | 6.4 | 16.8 | 18.8 | <0.001 |
| **Electrocardiographic findings** | | | | | |
| Heart rate (bpm) | 75.9 ± 12 | 76.0 ± 14 | 75.3 ± 13 | 75.6 ± 14 | 0.92 |
| PR interval (ms) | 160.1 ± 26 | 166.7 ± 33 | 176.2 ± 37 | 182.8 ± 46 | <0.001 |
| QRS interval (ms) | 93.9 ± 16 | 97.4 ± 20 | 99.7 ± 23 | 99.2 ± 25 | <0.05 |
| QTc interval (ms) | 429.6 ± 30 | 436.5 ± 31 | 441.4 ± 31 | 437.2 ± 63 | <0.01 |

Sample size, *n*=923 except where indicated. Data are expressed as means±SD, medians and IQR (in parenthesis) or percentages.

Differences among the four groups were tested by the chi-squared test for categorical variables, the one-way ANOVA for normally distributed continuous variables and the Kruskal-Wallis test for non-normally distributed variables (*i.e.* diabetes duration, serum triglyceride and ALT levels). Abnormal albuminuria was defined as urinary ACR ≥30 mg/g. Hypertension was defined as blood pressure ≥140/90 mmHg or use of any anti-hypertensive agents.

Abbreviations: ACE, angiotensin-converting-enzyme; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; ND, not determinate; VHD, valvular heart disease.

**Table 2**. Associations between increasing CKD stages (Panel A), $eGFR_{CKD\text{-}EPI}$ (included as a continuous measure; Panel B) or abnormal albuminuria (Panel C) and the risk of any **persistent** cardiac conduction defect in patients with type 2 diabetes.

| **(Panel A) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI** | **Odds Ratio(s) ± 95% CI** | **Odds Ratio(s) ± 95% CI** | ***P* value for trend** |
|---|---|---|---|---|---|
| **CKD Stages** | **Stage 1 ($eGFR_{CKD\text{-}EPI}$ ≥90 ml/min/1.73 $m^2$) (*n*=248)** | **Stage 2 ($eGFR_{CKD\text{-}EPI}$ 89-60 ml/min/1.73 $m^2$) (*n*=339)** | **Stage 3 ($eGFR_{CKD\text{-}EPI}$ 59-30 ml/min/1.73 $m^2$) (n=271)** | **Stages 4-5 ($eGFR_{CKD\text{-}EPI}$ <30 ml/min/1.73 $m^2$) (n=65)** | |
| Unadjusted model | *Ref.* | 1.91 (1.2-2.9) | 3.13 (2.0-4.8) | 4.81 (2.6-8.6) | <0.001 |
| Adjusted model 1 | *Ref.* | 1.69 (1.0-2.8) | 2.79 (1.7-4.6) | 4.22 (2.2-8.1) | <0.001 |
| Adjusted model 2 | *Ref.* | 1.83 (1.1-3.1) | 2.60 (1.5-4.6) | 3.51 (1.6-7.6) | <0.001 |
| Adjusted model 3 | *Ref.* | 2.05 (1.2-3.5) | 2.85 (1.6-5.1) | 3.62 (1.6-8.1) | <0.001 |
| **(Panel B) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI(s)** | ***P* value** | | |
| **$eGFR_{CKD\text{-}EPI}$ for 1-SD decrement (*i.e.* 26.5 ml/min/1.73 $m^2$)** | | | | | |
| Unadjusted model | | 1.61 (1.4-2.0) | <0.001 | | |
| Adjusted model 1 | | 1.56 (1.2-2.0) | <0.001 | | |
| Adjusted model 2 | | 1.47 (1.2-1.7) | <0.001 | | |
| Adjusted model 3 | | 1.45 (1.1-1.7) | <0.001 | | |
| **(Panel C) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI(s)** | ***P* value** | | |
| **Abnormal albuminuria (ACR ≥30 mg/g; yes *vs*. no)** | | | | | |
| Unadjusted model | | 1.57 (1.2-2.1) | <0.005 | | |
| Adjusted model 1 | | 1.39 (1.0-1.9) | <0.05 | | |
| Adjusted model 2 | | 1.27 (0.9-1.9) | =0.19 | | |
| Adjusted model 3 | | 1.09 (0.7-1.6) | =0.64 | | |

Sample size, *n*=923. Data are expressed as odds ratios ± 95% confidence intervals (CI) as assessed by either univariable (unadjusted) or multivariable logistic regression analyses. The presence of any cardiac conduction defect (n=253; defined as presence of at least one of the following heart blocks: first-degree AV block, second-degree AV block, third-degree AV block, LBBB, RBBB, LAH or LPH) was included as the dependent variable. CKD stage 1 was the reference category (*Ref*.) in all logistic regression models including CKD stages.

Other covariates included in these multivariable regression models were as follows: *model 1*: adjusted for age, sex, BMI, HbA1c, diabetes duration; *model 2*: the same covariates included in model 1 *plus* potassium, calcium, uric acid, hypertension (i.e. blood pressure ≥140/90 mmHg or use of any anti-hypertensive drugs, including also beta-blockers), prior history of IHD, prior history of VHD, peripheral artery disease, and current use of statins, fibrates, allopurinol, anti-platelets drugs, anti-coagulants or nitrates; *model 3*: the same covariates included in model 2 *plus* presence of diabetic retinopathy, peripheral sensory neuropathy, and abnormal albuminuria (i.e. urinary ACR ≥30 mg/g). NB: in adjusted model 3 of panel C the results were also adjusted for $eGFR_{CKD\text{-}EPI}$ included as a continuous measure.

**Table 3**. Associations between increasing CKD stages (Panel A), $eGFR_{CKD\text{-}EPI}$ (included as a continuous measure; Panel B) or abnormal albuminuria (Panel C) and the risk of any **persistent** atrio-ventricular block in patients with type 2 diabetes.

| **(A) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI** | **Odds Ratio(s) ± 95% CI** | **Odds Ratio(s) ± 95% CI** | ***P* value for trend** |
|---|---|---|---|---|---|
| **CKD Stages** | **Stage 1 ($eGFR_{CKD\text{-}EPI}$ ≥90 ml/min/1.73 $m^2$) (*n*=248)** | **Stage 2 ($eGFR_{CKD\text{-}EPI}$ 89-60 ml/min/1.73 $m^2$) (*n*=339)** | **Stage 3 ($eGFR_{CKD\text{-}EPI}$ 59-30 ml/min/1.73 $m^2$) (n=271)** | **Stages 4-5 ($eGFR_{CKD\text{-}EPI}$<30 ml/min/1.73 $m^2$) (n=65)** | |
| Unadjusted model | *Ref.* | 2.12 (1.1-4-2) | 4.67 (2.4-8.9) | 6.40 (2.9-14.4) | <0.001 |
| Adjusted model 1 | *Ref.* | 1.58 (0.8-3.2) | 3.21 (1.6-6.4) | 4.44 (1.9-10.3) | <0.001 |
| Adjusted model 2 | *Ref.* | 1.31 (0.6-2.7) | 2.25 (1.1-4.8) | 2.88 (1.1-7.5) | <0.01 |
| Adjusted model 3 | *Ref.* | 1.30 (0.6-2.7) | 2.20 (1.1-4.7) | 2.74 (1.1-7.5) | <0.01 |
| **(B) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI(s)** | ***P* value** | | |
| **$eGFR_{CKD\text{-}EPI}$ for 1-SD decrement (*i.e.,* 26.5 ml/min/1.73 $m^2$)** | | | | | |
| Unadjusted model | | 1.89 (1.7-2.5) | <0.001 | | |
| Adjusted model 1 | | 1.69 (1.4-2.0) | <0.001 | | |
| Adjusted model 2 | | 1.47 (1.1-2.0) | <0.001 | | |
| Adjusted model 3 | | 1.45 (1.1-2.0) | <0.001 | | |
| **(C) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI(s)** | ***P* value** | | |
| **Abnormal albuminuria (yes *vs*. no)** | | | | | |
| Unadjusted model | | 1.58 (1.1-2.4) | <0.05 | | |
| Adjusted model 1 | | 1.32 (0.9-2.0) | 0.19 | | |
| Adjusted model 2 | | 1.29 (0.8-2.0) | 0.27 | | |
| Adjusted model 3 | | 0.90 (0.5-1.5) | 0.69 | | |

Sample size, *n*=923. Data are expressed as odds ratios ± 95% confidence intervals (CI) as assessed by either univariable (unadjusted) or multivariable logistic regression analyses. The presence of any electrocardiographic AV block (defined as at least one among first-degree AV block, second-degree AV block or third-degree AV block) was included as the dependent variable. CKD stage 1 was the reference category (*Ref*.) in all logistic regression models including CKD stages.

Other covariates included in these multivariable regression models were as follows: *model 1*: adjusted for age, sex, BMI, HbA1c, diabetes duration; *model 2*: the same covariates included in model 1 *plus* potassium, calcium, uric acid, hypertension (i.e. blood pressure ≥140/90 mmHg or use of any anti-hypertensive drugs, including also beta-blockers), prior history of IHD, prior history of VHD, peripheral artery disease, and current use of statins, fibrates, allopurinol, anti-platelets drugs, anti-coagulants or nitrates; *model 3*: the same covariates included in model 2 *plus* presence of diabetic retinopathy, peripheral sensory neuropathy, and abnormal albuminuria (i.e. urinary ACR ≥30 mg/g). NB: in adjusted model 3 of panel C the results were also adjusted for $eGFR_{CKD\text{-}EPI}$ included as a continuous measure.

**Table 4**. Associations between increasing CKD stages (Panel A), $eGFR_{CKD\text{-}EPI}$ (included as a continuous measure; Panel B) or abnormal albuminuria (Panel C) and the risk of any **persistent** bundle branch block in patients with type 2 diabetes.

| **(A) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI** | **Odds Ratio(s) ± 95% CI** | **Odds Ratio(s) ± 95% CI** | ***P* value for trend** |
|---|---|---|---|---|---|
| **CKD Stages** | **Stage 1 ($eGFR_{CKD\text{-}EPI}$ ≥90 ml/min/1.73 $m^2$) (*n*=248)** | **Stage 2 ($eGFR_{CKD\text{-}EPI}$ 89-60 ml/min/1.73 $m^2$) (*n*=339)** | **Stage 3 ($eGFR_{CKD\text{-}EPI}$ 59-30 ml/min/1.73 $m^2$) (n=271)** | **Stages 4-5 ($eGFR_{CKD\text{-}EPI}$<30 ml/min/1.73 $m^2$) (n=65)** | |
| Unadjusted model | *Ref.* | 1.56 (0.9-2.5) | 2.05 (1.3-3.3) | 2.45 (1.2-4.9) | <0.001 |
| Adjusted model 1 | *Ref.* | 1.47 (0.8-2.6) | 2.10 (1.2-3.7) | 2.51 (1.2-5.4) | <0.005 |
| Adjusted model 2 | *Ref.* | 1.87 (0.9-3.5) | 2.48 (1.3-4.9) | 2.80 (1.1-6.9) | <0.01 |
| Adjusted model 3 | *Ref.* | 2.20 (1.1-4.2) | 2.89 (1.4-5.8) | 2.78 (1.1-7.3) | <0.01 |
| **(B) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI(s)** | **P value** | | |
| **$eGFR_{CKD\text{-}EPI}$ for 1-SD decrement (*i.e,* 26.5 ml/min/1.73 $m^2$)** | | | | | |
| Unadjusted model | | 1.35 (1.2-1.6) | <0.001 | | |
| Adjusted model 1 | | 1.33 (1.1-1.6) | <0.01 | | |
| Adjusted model 2 | | 1.39 (1.1-1.6) | <0.01 | | |
| Adjusted model 3 | | 1.37 (1.1-1.6) | <0.01 | | |
| **(C) Logistic Regression Models** | | **Odds Ratio(s) ± 95% CI(s)** | ***P* value** | | |
| **Abnormal albuminuria (yes *vs*. no)** | | | | | |
| Unadjusted model | | 1.37 (1.0-1.9) | <0.05 | | |
| Adjusted model 1 | | 1.29 (0.9-1.9) | 0.19 | | |
| Adjusted model 2 | | 1.23 (0.8-1.9) | 0.33 | | |
| Adjusted model 3 | | 1.17 (0.7-1.8) | 0.49 | | |

Sample size, *n*=923. Data are expressed as odds ratios ± 95% confidence intervals (CI) as assessed by either univariable (unadjusted) or multivariable logistic regression analyses. The presence of any bundle branch block (defined as at least one among LBBB, RBBB, LAH or LPH) was included as the dependent variable. CKD stage 1 was the reference category (*Ref*.) in all logistic regression models including CKD stages.

Other covariates included in these multivariable regression models were as follows: *model 1*: adjusted for age, sex, BMI, HbA1c, diabetes duration; *model 2*: the same covariates included in model 1 *plus* potassium, calcium, uric acid, hypertension (i.e. blood pressure ≥140/90 mmHg or use of any anti-hypertensive drugs, including also beta-blockers), prior history of IHD, prior history of VHD, peripheral artery disease, and current use of statins, fibrates, allopurinol, anti-platelets drugs, anti-coagulants or nitrates; *model 3*: the same covariates included in model 2 *plus* presence of diabetic retinopathy, peripheral sensory neuropathy, and abnormal albuminuria (i.e. urinary ACR ≥30 mg/g). NB: in adjusted model 3 of panel C the results were also adjusted for $eGFR_{CKD\text{-}EPI}$ included as a continuous measure.

**FIGURE LEGENDS**

**Figure 1**. Prevalence of different types of **persistent** cardiac conduction defects (singly or in combination, i.e. any AV block, any bundle branch block or any heart block) on standard electrocardiograms in 923 patients with type 2 diabetes stratified by increasing stages of CKD (i.e., stage 1 [$eGFR_{CKD\text{-}EPI}$ ≥90 ml/min/1.73 $m^2$], stage 2 [$eGFR_{CKD\text{-}EPI}$ 89-60 ml/min/1.73 $m^2$], stage 3 [59-30 ml/min/1.73 $m^2$] and stages 4-5 [<60 ml/min/1.73 $m^2$]).

**Figure 2**. Prevalence of different types of **persistent** cardiac conduction defects (singly or in combination, i.e. any AV block, any bundle branch block or any heart block) on standard electrocardiograms in 923 patients with type 2 diabetes stratified by abnormal albuminuria (urinary albumin-to-creatinine ratio ≥30 mg/g).

**Supplementary Figure 1**. Association between decreasing $eGFR_{CKD\text{-}EPI}$ (for each SD decrement, i.e. 26.5 ml/min/1.73 $m^2$) and the risk of any cardiac conduction defect in different subgroups patients with type 2 diabetes. Results are expressed as unadjusted odds ratios and 95% confidence intervals. All p-values ($p$ ≥0.10) for interaction are not statistically significant.