Title: Association between type 2 diabetes and all-cause hospitalization and mortality in the UK general heart failure population: stratification by diabetic glycemic control and medication intensification.

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<td>BMI</td>
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Abstract

Objectives: To investigate in the general heart failure (HF) population, whether the associations between type 2 diabetes (T2D) and risk of hospitalization and death, are modified by changing glycemic or drug treatment intensity.

Background: In the general HF population, T2D confers a higher risk of poor outcomes, but whether this risk is modified by the diabetes status is unknown.

Methods: A nested case-control study in an incident HF database cohort (2002-2014) comparing patients with T2D to those without, for risk of first hospitalization and all-cause death. The T2D group was stratified by categories of HbA1c or drug treatments measured 6-months before hospitalization and 1-year before death and compared to the same reference group without T2D.

Results: In HF, T2D was associated with risk of first hospitalization (adjusted odds ratio 1.29; 95%CI 1.24-1.34) and mortality(1.24,1.29-1.40). Stratification of the T2D group by HbA1c and compared to the same HF reference group without T2D, showed U-shaped associations with both outcomes. Highest risk categories were HbA1c >9.5%(hospitalization:1.75; 95%CI 1.52-2.02, mortality:1.30,1.24-1.47) and <5.5%(1.42,1.12-1.80; 1.29,1.10-1.51 respectively). T2D group with change in HbA1c of >1% decrease was associated with hospitalization(1.33,1.18-1.49) and mortality(1.36,1.24-1.48). T2D drug group associations with hospitalization were: ‘no medication’(1.12,1.04-1.19), ‘oral anti-hyperglycemic only’(1.34,1.27-1.41), ‘oral anti-hyperglycemic+insulin’(1.36,1.21-1.52), ‘insulin only’(1.61,1.43-1.81) and with mortality:1.31(1.23-1.39), 1.16(1.11-1.22), 1.19(1.06-1.34), 1.43(1.31-1.57). T2D group with reducing drug treatments were associated with hospitalization(2.13,1.68-2.69) and mortality(2.09,1.81-2.41).

Conclusions: In the general HF population, T2D stratified by glycemic control and drug treatments showed differential risks. Routine measures of dynamic diabetes status provide important prognostic indication of poor outcomes in HF.
Introduction

In heart failure (HF) populations, prognosis is poor and optimization of HF treatment and common comorbidities are fundamental to improving prognostic outcomes such as hospitalization and death. Type-2 diabetes (T2D) is one of the most common comorbidities in HF impacting approximately a third of all patients (1). Despite early promise from new ‘add-on’ pharmacotherapies for T2D such as sodium-glucose cotransporter 2 (SGLT2) inhibitors (2), T2D is associated with a significantly high risk of adverse outcomes in HF (3). Management of T2D is centred around three key metabolic markers; haemoglobin A1C (HbA1c), blood pressure and low density lipoprotein (4) and guidelines advocate target-based individualised treatment (i.e. reducing HbA1c to below a specific concentration) (5) often necessitating the addition of further glucose-lowering therapies over time and the attendant risk of hypoglycemia (6). Treatment of HF patients with T2D can therefore be compounded by polypharmacy and uncertainty about the safety of some glucose lowering drug therapies particularly where renal dysfunction also exists (7).

Current evidence on T2D in HF is predominantly from trials or hospital based registries (8-10) and there is extremely limited evidence on T2D in the general unselected HF population. Furthermore evidence has included the ‘presence or absence’ of T2D as a single baseline measure which treats HF patients with diabetes as a homogenous group and ignores the potential importance of levels of glycemic control and anti-diabetic treatment that vary over time. These measures are captured in routine management of HF patients with T2D and may provide important indication of differential prognostic risk in the larger general population where most of the chronic disease management is carried out.

We used two case control studies nested within an incident cohort of general population HF patients from the UK Clinical Practice Research Datalink (CPRD), to investigate the association between T2D and subsequent risk of all-cause first hospitalization and mortality, compared to HF.
patients without T2D. T2D patients were stratified by measures of glycemic control and anti-diabetic
drugs and by change in these measures recent to the chosen outcomes.

**Methods**

**Study population**

We conducted two case-control studies nested within the prospective CPRD database cohort
which covers approximately 10% of the UK general population\(^\text{(11)}\). Anonymised data included
population demographic and lifestyle factors, clinical data on diagnoses, prescribed drugs and
laboratory tests, and linked to hospital admissions data based on Hospital Episode Statistics (HES) and
mortality data. Data was available for the time-period between 1\(^\text{st}\) January 2002 and 1\(^\text{st}\) January 2014
and CPRD permission for data access was under licence (protocol 12_162) with approval granted from
the Independent Scientific Advisory Committee.

We chose a nested case-control design to establish a specific temporal link between T2D
measures and their short term association with outcomes and to account for the varying nature of
glycemic control and drug treatments over time. Patients aged over 40 years were selected by a first
diagnostic HF code applied to clinical records in the 10 year time-period from 1\(^\text{st}\) January 2002 to 1\(^\text{st}\)
January 2012. Time for follow-up for each patient was from the date of the first HF code to either the
date of the patient transferring out of practice, the outcome event or the study end (1\(^\text{st}\) January 2014).

Presence of T2D in the HF population, after exclusion of T1D was based on clinical or drug codes
applied prior to the outcome event date and all patients had minimum 3-years of up to standard CPRD
data before study entry. The HF and T2D code sets were validated by clinicians and other CPRD
strategies\(^\text{(12,13)}\)(Supplementary file).

**Selection of cases and matched controls**

For the CPRD sample with linked hospitalization data \((n=27,283)\), the outcome event date was
defined by the first all-cause hospitalization after, but not including the HF diagnosis date. All-cause
mortality data was available for the whole cohort \((n=48,978)\) and the outcome event date was defined as the date of all-cause death. For both analyses, all cases were matched on the outcome event date with up to four controls randomly sampled from the HF cohort still at risk of the event. Matching was by the HF diagnosis date \((\pm 1 \text{ month})\) and duration of follow-up. Using this approach controls are eligible to be selected multiple times and later as a case, approximating the situation in Cox-regression and unbiased estimates of rate ratio, comparable to other cohort analyses can be calculated\(^{(14)}\).

**Measurement of diabetes status and change**

T2D status was defined by glycemic control and separately by drug treatment intensity. Glycemic control was measured by the most recent HbA1c level recorded on or before the outcome date, but values were excluded if they were recorded more than 6-months before the outcome date for first hospitalization and 12-months for mortality. T2D patients were stratified into six HbA1c categories; \(<5.5\%\), \(5.5-6.4\%\), \(6.5-7.5\%\), \(7.6-8.5\%\), \(8.6-9.5\%\) and \(>9.5\%\). Change in glycemic control was measured using two HbA1c values (the most recent value as outlined above and a previous value separated by at least 3 months). For hospitalization analyses, previous values were excluded if they were more than 12 months before the recent value. For mortality analyses values were excluded if they were more than three years before the recent value. The difference between the two values was then adjusted for the interval time to calculate change in HbA1c over the 6-months for hospitalization and 12-months for all-cause mortality. Patients with T2D were categorised into the following change groups; an absolute increase in HbA1c of \(>1\%\), decrease of \(>1\%\) or minimal change \(\leq 1\%\).

T2D patients were separately stratified by four a priori ordinal categories of drug treatment intensity and three categories of drug treatment change. Drug treatment intensity levels were (i) none, (ii) oral anti-hyperglycemic only, (iii) oral anti-hyperglycemic plus insulin and (iv) insulin only. GLP-1 receptor agonists were only prescribed in very low numbers (248 patients in total) so for simplicity were included in the oral group. Treatment status was based on drug prescribing recorded in the 4-months
period before the outcome date. The change categories were measured in two four month time-windows separated by an interval of 6 months for hospitalization or 12 months for all-cause mortality. Change was based on an increase in at least one of the defined drug treatment categories, or a decrease in at least one of the defined drug categories or no change of treatment in the defined change windows.

**Measurement of confounding**

Confounders were selected using current evidence which included age, sex, body mass index (BMI), smoking, alcohol, cholesterol, Hemoglobin, blood pressure (BP), estimated glomerular filtration rate (eGFR), hypertension, ischaemic heart disease (IHD), previous myocardial infarction, atrial fibrillation and chronic obstructive pulmonary disease. The Index of Multiple Deprivation was also included which is a score relating to the individual patient postcode that combines seven weighted indicators covering economic, health, social and housing domains into a single deprivation score.

For these confounders the most recent measure before the outcome date was used. Drug measures for aspirin, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers and diuretics were also extracted in a 4-month time window before the outcome date.

**Statistical analysis**

For each outcome analysis, the case and control status is first presented to compare patient and clinical characteristics. To build the multivariable models, linearity was investigated using likelihood ratio tests and quadratic terms were added for continuous variables where necessary. For correlated variables with coefficient >0.5, the most clinically relevant one was selected. First order interactions terms were included in a full multivariable model to examine the relationship between diabetes and age, sex and renal function for both outcomes. Then, for the two outcomes, multiple imputation was performed for the missing confounder data (<20%) using matching variables and full-conditional specification in StataMP 13 and analyses were combined using Rubin’s rules.
Next, conditional logistic regression was used to compute odds ratios comparing HF patients with T2D to HF patients without, adjusting for all selected confounders. The T2D group was then stratified into sub-groups by measures of recent HbA1c, drug treatment intensity and their change. The T2D sub-groups were then compared to the same HF patients without T2D reference group, for both outcomes. All estimates are presented as adjusted odds ratios (aOR) with 95% confidence intervals. Significant stratified effects among T2D groups by HbA1c or drug treatments and change were indicated where confidence intervals for estimates did not overlap (17).

Four sensitivity analyses were carried out. First the adjusted all-cause mortality models were further adjusted for the Index of Multiple Deprivation. Second, given the potential prognostic implications of different drug types, the oral anti-hyperglycemic group was further categorised by drug type. Third, to account for diabetes duration, the T2D group were differentiated by patients who had diabetes occurring before or after their HF. Fourth, to account for baseline and finishing HbA1c level, the change in HbA1c associations with both outcomes were stratified by start and end HbA1c level.

Results

Of the 27,283 HF sample with linked hospitalization data, 23,701 (87%) experienced a first hospitalization over a median follow-up of 99 days [IQR 14-482]. Of the 48,978 CPRD patients from the total incident HF cohort, 26,021 (53%) died over a median follow-up of 2.6 years [IQR 0.8-5.0]. For hospitalization cases, 4,969 (21%) had T2D compared to 14,023 (16.9%) of controls. For all-cause mortality cases, 6,008 (25.3%) had T2D compared to 22,212 (21.8%) of controls. Cases for both outcomes were older with more comorbidities, less prescribed HF-related drugs (Table 1), and had a lower BMI, cholesterol, Hemoglobin, eGFR and blood pressure. The proportion of women was higher for all-cause mortality cases but lower for hospitalization cases compared to controls.

HF and T2D and outcomes
Presence of T2D in HF patients was significantly associated with first hospitalization (aOR 1.29, 1.24-1.34) (Table 2) and this risk was higher in older than younger groups and in females than males (Supplementary Table 1). Presence of T2D in HF patients was also significantly associated with all-cause mortality (aOR 1.24,1.29-1.40) (Table 3) which was higher in the younger (1.35,1.25-1.45) than the older group (1.20,1.14-1.28) (Supplementary Table 2).

T2D status and hospitalization

A recent HbA1c within 6 months of the first hospitalization was recorded in 69% of the matched sample. When the T2D patients were stratified by levels of HbA1c, comparing to the HF group without T2D, there was a U-shaped relationship with risk of first hospitalization (Figure 1). The highest risk was in the HbA1c >9.5% group with an aOR of 1.75 (1.52-2.02) which was significantly higher than the lowest risk HbA1c groups which were 5.5-6.4% (1.13,1.03-1.24) and 6.5-7.5% (1.13,1.05-1.22) (Table 2).

In categories of drug treatment intensity, there was incremental significant association of increased risk of first hospitalization, from the T2D group without medications (1.12,1.04-1.19) to the oral anti-hyperglycemic group (1.34,1.27-1.41), oral anti-hyperglycemic and insulin (1.36,1.21-1.52) to the insulin only group (1.61,1.43-1.81) (Table 2).

T2D status and all-cause mortality

A recent HbA1c measure within 12 months of mortality was recorded in 83% of the matched sample. In strata of HbA1c, T2D patients also showed a U-shaped relationship with mortality compared to the HF group without T2D (Table 3 and Figure 2). The estimate for HbA1c group <5.5% was aOR 1.29 (1.10-1.51) and the HbA1c group >9.5% was 1.30 (1.24-1.47) for mortality. This was significantly higher than the lowest risk HbA1c 6.5-7.5% group, 1.10 (1.03-1.17).
In terms of drug treatment intensity, the strongest associations with mortality were for T2D patients without drug treatment (aOR 1.31, 1.23-1.39) and insulin only (1.43, 1.31-1.57) which were significantly higher than the oral anti-hyperglycemic group (1.16, 1.11-1.22). The oral anti-hyperglycemic plus insulin group was similar (1.19, 1.06-1.34).

**T2D change and hospitalization**

Two HbA1c measures to indicate change over a 6-month time-period were available for 58% of T2D patients in the hospitalization matched sample. Of this group, 12% experienced an increase and 17% a decrease in HbA1c level of >1% and the other 79% experienced ≤1% change. Compared to the HF group without T2D, the T2D groups with >1% change in HbA1c were associated with higher risk of hospitalization than the ≤1% change group (1.16, 1.09-1.23). The estimate for the HbA1c >1% increase was (1.30, 1.14-1.48) and >1% decrease was (1.33, 1.18-1.49).

Drug treatment intensity increase over 6-months before hospitalization occurred in 6% of T2D patients and decrease in at least one drug category in 2% of T2D patients (Table 2). The significantly stratified estimates of association with hospitalization were: no change (aOR 1.26, 1.21-1.31), intensity increase (1.53, 1.34-1.76) and intensity decrease (2.13, 1.68-2.69).

**T2D change and all-cause mortality**

Two HbA1c measures to indicate change over a 12-month time-period were available for 76% of T2D patients in the matched mortality sample. Of this group, 17% experienced an increase or 19% a decrease in HbA1c of >1% and 64% experienced ≤1% change. Compared to the HF group without T2D, the T2D group with >1% decrease in HbA1c conveyed the greatest risk (1.36, 1.24-1.48) which significantly differed to the ≤1% change group (1.12, 1.06-1.18). HbA1c group with >1% increase was similar (1.15; 1.05-1.27).
Increase in drug treatment intensity over 12-months occurred in 10% of T2D patients and decrease in 4% with 86% experiencing no change (Table 3). Compared to the HF group without T2D, the T2D group with intensity decrease was associated with the highest risk (2.09, 1.81-2.41) which significantly differed to the no change group (1.20, 1.16-1.25) or intensity increase group (1.25, 1.12-1.38).

Finally, all sensitivity analyses are presented in supplementary tables 3 to 5. Adjustment of the mortality models with Index Multiple Deprivation had minimal non-significant influence on effect estimates. When the oral T2D group was categorised by different drug types, those prescribed metformin were associated with less risk of both outcomes than those prescribed other anti-diabetic drugs which was significant for all-cause mortality. The risk association between increased HbA1c level and hospitalization was greater in patients with a high start and end HbA1c value. The high risk association between decreasing HbA1c level and all-cause mortality was not influenced by the start or end HbA1c value. In terms of T2D duration, risk of both outcomes was significantly higher for those with T2D onset before HF than for T2D onset after HF.

Discussion

This is the first study to investigate in the incident HF general population, the comorbid effect of T2D status and change on first hospitalization and all-cause mortality. Our national population-based study of over 48,000 general HF patients has shown that distinct levels of glycemic control and related drug treatment intensity significantly stratify the risk associated with T2D for first hospitalization and all-cause death, compared to HF patients without T2D. Changes in level of glycemic control and drug treatment intensity also show stratified associations in the recent time-periods before the outcomes. HF duration, socio-demographic factors, CVD status and other drug treatments did not explain these associations.
The highest risk of hospitalization and all-cause death was associated with the T2D group on insulin, consistent with previous hospital HF studies (20,21). This group tends to indicate patients with poor control in T2D with more severe metabolic disturbances and increased severity (22). However, an elevated risk of all-cause mortality was also associated with the T2D without drug treatment. Diabetes studies have shown diet-controlled diabetics have better glycemic control and less complications (23) and in HF that T2D treated with metformin can be protective compared to no drug treatments (24). The high risk in the no-medications group in this study in the 4-months prior to death likely reflects end-stage HF severity where de-prescribing may occur (25).

T2D patients grouped by levels of HbA1c showed a U-shaped relationship with outcomes with the lowest and highest HbA1c groups associated with the highest risk of first hospitalization and all-cause mortality. Previous evidence on HbA1c and outcomes in HF has been inconsistent. In the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trial (10) a linear association was found between increasing HbA1c and increasing mortality risk but in other non-trial HF populations a similar U-shaped association has been reported (6,26,27). The prior non-trial studies were based on small select samples but patients were generally older with a higher proportion of people with more advanced HF disease than in the CHARM trial. By studying a large sample of the general HF population our data adds to and supports a more complex relationship between HbA1c and outcomes in HF. Whilst our study sample was from the general HF population, measurement of HbA1c was in the imminent time-period prior to admission or death and the associated risk likely reflects the more severe HF group which is congruent with the prior evidence in more advanced disease (26). This ‘reverse epidemiology’ where known risk factors improve survival in HF has been related previously to more advanced disease (31). Whilst the study findings point to the importance of low as well as high HbA1c for outcome risk we did not include individual or repeated hypoglycemic events in our analyses which have previously been shown to be associated with increased risk of cardiovascular events and
death in T2D patients(32). Future investigation of the relationship between low HbA1c, rate of hypoglycemic events and outcomes would further delineate these associations. We found the lowest risk HbA1c level for all-cause mortality reflected current international diabetic guidelines(5), but the level was even lower for first hospitalization. A shift to the right in the U curve has been found previously in more advanced disease suggesting a lower threshold for hypoglycemia(28). The different HbA1c levels of risk for the two outcomes in part reflects that HF severity may be higher for patients close to death compared to those at risk of the first hospitalization(29). This implies that the target for HbA1c control needs to be guided by the severity of the HF with higher level targets in more severe disease and with more scope for intensive glucose lowering therapy in less severe HF. In the general HF population, around a quarter of T2D patients experienced a HbA1c level change >1% in both directions and this conferred a higher prognostic risk than the HF patient ≤1% change. Changing levels therefore becomes an important modifiable marker of risk, which is easily identifiable in routine practice and a >1% decrease in the HbA1c level(30) suggests that guideline-recommended tighter control is paradoxically associated with increased prognostic risk in HF.

The study strengths included the incorporation of HF duration, socio-demographic, clinical and drug treatment factors. The HF population was derived from a national UK database with high validity of newly diagnosed patients linked to both hospitalization and all-cause mortality data over a 12-year time-period. Measurements of T2D were based on two routinely collected and well coded measures of prescribing and physiological change. Both HF and T2D register in the UK are supported by performance incentives which include annual reviews in primary care. The hospitalizations and mortality are also part of UK mechanisms for collecting comprehensive and regular data. The nested case control design with risk set sampling provided the method to take account of the time varying nature of T2D status and patient factors and to measure recent change and virtually minimises the potential for selection bias.
The study was retrospective and observational in nature so measurements were based on routine practice and HF diagnosis from the general population. Routine data can be subject to misclassification leading to over-ascertainment of HF or under-ascertainment of DM. However, accuracy of diagnosis within the CPRD has been found to be valid for a range of morbidities (11) including HF and T2D (12, 14). The definitions provide the real world context for the general HF population and any misclassification would likely bias the results towards the null value. The clinical diagnosis of T2D was based on drug and clinical codes to improve identification but cardiac imaging data was not available so we were unable to further phenotype HF or provide specific risk estimates for preserved or reduced ejection fraction status. Similarly, indicators of HF severity were not available so we were not able to investigate the influence of HF severity on the associations between T2D measures and outcomes. Instead the study provides the comorbid effects of T2D stratified by status and change when compared to the HF sample without diabetes, who will also include comparable phenotypes. Over the 12-year study time frame, HF and T2D management has changed, but case and controls were matched on calendar time and the time varying measures of HF and T2D drugs were measured during follow-up immediately prior to the match dates.

Conclusions

Our study showed that measures of T2D status and treatments were associated with differential risk of 6-month first all-cause hospitalization and 1-year mortality. Routine measures of diabetes status provide important prognostic indication of imminent poor outcomes in HF.

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Clinical Perspectives

• This is the first and largest study in the general population of unselected HF patients to show
differential risk associations according to T2D guideline-driven glycemic control and drug
treatments.

• Glycaemic control and drug treatments are routinely recorded in the general HF population with
T2D and provide important risk indicators of imminent hospitalization and all-cause death.

Translational outlook

• This study showed important prognostic associations but the observational design precluded
causal relationships. Further investigation into the temporal relationships between (i) drug
titration and glycemic control and (ii) change in diabetes status and HF severity, is important for
guiding tailored comorbidity monitoring and intervention targets in quality HF guideline care.

Figure 1: HbA1c adjusted associations with all-cause first hospitalization.
The T2D group was stratified by categories of HbA1c and compared to HF patients without T2D for occurrence of a first ‘any-
cause’ hospitalization after the HF incidence date.

Figure 2: HbA1c adjusted associations with all-cause mortality
The T2D group was stratified by categories of HbA1c and compared to HF patients without T2D for ‘any-cause’ death after
the HF incidence date.

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