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SHORT COMMUNICATION

Type 2 diabetes and heart failure: insights from the global DISCOVER study

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Abstract

Aims Heart failure (HF) is increasingly recognized as a major cause of morbidity and mortality in patients with type 2 diabetes (T2D), but the global epidemiology and treatment of HF in T2D are not well defined. This study aimed to examine the global prevalence of HF and the incidence of HF over 3 years of follow-up in patients with T2D [by presence and absence of co-existing coronary artery disease (CAD)].

Methods and results DISCOVER was a 3 year, prospective, observational study of T2D patients enrolled at initiation of second-line glucose-lowering therapy. Among 14 057 patients with T2D from 36 countries, 289 (2.1%) had a diagnosis of HF at enrolment; median prevalence across countries was 2.0% (inter-quartile range 1.0–3.1%). Patients with HF at baseline were more likely to be older [HF vs. no HF: 67 ± 12 vs. 57 ± 12 years, standardized difference (StDiff) = 84%] and have longer duration of T2D (8.1 ± 7.2 vs. 5.6 ± 5.2 years, StDiff = 40%), CAD (44% vs. 6%, StDiff = 97%), atrial fibrillation (21% vs. 1%, StDiff = 66%), and kidney disease (23% vs. 4%, StDiff = 55%). Patients with HF were less likely to be on metformin (66% vs. 79%, StDiff = 28%) and thiazolidinediones (5.5% vs. 10.6%, StDiff = 19%) but had similar use of other glucose-lowering medications. Among 9313 patients with follow-up data, there were 70 incident cases of HF, which translates to an incidence of 2.6 cases per 1000 person years. Of these incident HF cases, 60% occurred in the absence of pre-existing or concomitant CAD, and 73% were diagnosed in the outpatient setting.

Conclusions In a large, global cohort of patients with T2D, the majority of incident cases of HF occurred in outpatients and in the absence of known CAD. These findings highlight the need for greater awareness of HF risk in patients with T2D.

Keywords Heart failure; Diabetes mellitus; Epidemiology

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Background

Heart failure (HF) is increasingly being recognized as a substantial cause of morbidity and mortality in patients with type 2 diabetes (T2D).[1] While the development of HF in T2D has traditionally been attributed mostly to common risk factors [e.g. hypertension and coronary artery disease (CAD)], both systolic and diastolic dysfunction may develop in patients with T2D regardless of these typical risk factors.[2] Furthermore, although HF in patients with T2D is most commonly observed in a setting of preserved ejection fraction (EF),[3] diabetes increases the risk of cardiovascular morbidity and

mortality in patients with HF regardless of EF, with perhaps even greater associated risk in patients with HF and preserved EF.[4,5] Despite increasing recognition—with HF now included as an essential outcome in many cardiovascular outcomes trials of glucose-lowering medications—the risk of developing HF and contributing factors are still not fully documented. A key limitation of these cardiovascular outcomes trials is that they used extensive inclusion and exclusion criteria and included mostly patients with established cardiovascular disease (i.e. high risk for HF) and only examined HF hospitalizations. Prior epidemiological studies that primarily used administrative data within narrow geographical regions (e.g. California and UK) found HF prevalence of 5–12% in people with T2D and incidence rates of 2–10 events per 1000 patient years[6–8] (with one outlier study showing an incidence rate of 33 per 1000 patient years[9]). We sought to fill that gap by examining the prevalence and incidence of HF in a global cohort of patients with primarily early-stage T2D.

Aims

We used DISCOVER—a prospective observational study of patients with T2D—to examine the prevalence of HF at enrolment and the incidence of HF over 3 years of follow-up in subjects by presence or absence of CAD.

Methods

DISCOVER was a 3 year, prospective, observational study of patients with T2D enrolled between 2014 and 2016 from 38 countries at the initiation of second-line glucose-lowering therapy.[10] Data were collected at 0, 6, 12, 24, and 36 months using a standardized case report form. In line with the observational nature of the study, data were measured according to routine clinical practice, and the occurrence of events was not adjudicated. The diagnosis of HF (and other events) was determined by hospitalization or emergency room records (diagnosis codes) or evaluation by the local physician. Study protocols were approved by each country's clinical research ethics committees and each site's institutional review board, and all patients provided written informed consent.

Data from China (n = 1292) had to be excluded because of new regulations released after study completion. Data from Russia were excluded because it was a notable outlier concerning HF prevalence/incidence (Supporting Information, *Table S1*). Follow-up data from Canada, Denmark, Japan, and Norway (n = 2293) were excluded because of missing data on hospitalizations. Incidence of HF over time (reported per 1000 patient years) was examined in the overall population and by presence or absence of CAD diagnosed before or concurrently with HF. Characteristics of patients with and without HF at baseline were compared using standardized differences (>10% considered clinically meaningful[11]). The association of patient factors with incidence of HF was examined with a hierarchical modified Poisson regression model (given the low number of HF events).

Results

Of the 14 057 patients with T2D from 36 countries, 289 (2.1%) had a diagnosis of HF at enrolment. Median (interquartile range) baseline prevalence across the 36 countries was 2.0% (1.0–3.1%). EF was documented in only 37% of patients with HF (mean EF 49.5 ± 12.9%). Patients with HF were more likely to be older and have a longer duration of T2D, hypertension, CAD, atrial fibrillation, prior stroke, and chronic kidney disease (*Table 1*). Patients with HF were more likely to be on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and diuretics. In terms of glucose-lowering medications, patients with HF were less likely to be on metformin and thiazolidinediones; otherwise, there were no significant differences in use of other classes of glucose-lowering medications.

Among the 9300 patients from 32 countries with follow-up data (Supporting Information, *Table S2*), there were 70 documented incident cases of HF over the 3 years of follow-up for an incidence rate of 2.6 cases per 1000 patient years and a cumulative prevalence of 2.8% (*Figure 1*). At the time of HF diagnosis, 60% of patients had no known CAD, and 73% of incident HF diagnoses were made in the outpatient setting. In the multivariable model, older age, CAD, atrial fibrillation, kidney disease, and hypertension were each associated with increased risk of incident HF (*Table 2*). The median rate ratio was 2.5, however, indicating substantial variability in the diagnosis of incident HF across countries independent of patient factors.

Discussion

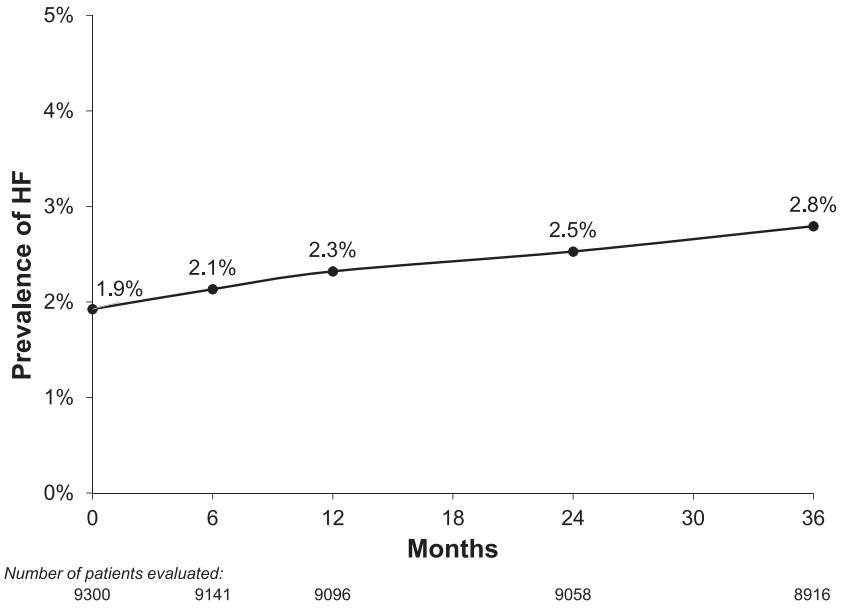
In a large, global, prospective cohort of patients with mostly early-stage T2D, we found that both the prevalence and incidence of HF were not particularly high, although a diagnosis of HF was notably more common in older patients and those with vascular or kidney disease—all known risk factors for HF in T2D.[12] Our rates were notably lower than prior estimates using administrative data,[6–9] which may reflect the younger age and lower co-morbidity burden in our cohort. Despite this low event rate, we believe there are three important insights from our study. First, over half of patients did not have clinically evident CAD at the time of HF diagnosis. While ischaemic heart disease is a common cause of HF, patients with

Table 1 Characteristics of T2D patients with vs. without HF

	HF n = 289	No HF n = 13 768	Absolute standardized differences[a]
Age (years)	67.0 ± 11.6	57.1 ± 12.0	84%
Male sex	162 (56.1%)	7516 (54.6%)	2.9%
Body mass index (kg/m^2)	31.0 ± 6.4	29.2 ± 5.9	30%
Diabetes duration (years)	8.1 ± 7.2	5.6 ± 5.2	40%
HbA1c (%)	8.0 ± 1.7	8.3 ± 1.7	19%
Hypertension	242 (84.0%)	7035 (51.1%)	75%
Coronary artery disease	128 (44.3%)	888 (6.4%)	97%
Prior stroke	32 (11.1%)	241 (1.8%)	39%
Peripheral artery disease	15 (5.2%)	117 (0.8%)	26%
Atrial fibrillation	61 (21.1%)	176 (1.3%)	66%
Chronic kidney disease	65 (22.6%)	607 (4.4%)	55%
Glucose-lowering medications			
Metformin	192 (66.4%)	10 856 (78.8%)	28%
DPP-4 inhibitors	146 (50.5%)	6712 (48.8%)	3.5%
Sulphonylureas	127 (43.9%)	6171 (44.8%)	1.8%
SGLT2 inhibitors	25 (8.7%)	1297 (9.4%)	2.7%
Thiazolidinediones	16 (5.5%)	1461 (10.6%)	19%
Alpha-glucosidase	19 (6.6%)	934 (6.8%)	0.8%
Meglitinides	9 (3.1%)	371 (2.7%)	2.5%
GLP-1 receptor agonists	7 (2.4%)	294 (2.1%)	1.9%
Insulin	20 (6.9%)	851 (6.2%)	3.0%
Cardiac medications			
Diuretic	125 (43.3%)	1544 (11.2%)	77%
ACE-I/ARB	202 (69.9%)	5090 (37.0%)	70%
Beta-blockers	144 (49.8%)	1738 (12.6%)	88%

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; SGLT2, sodium–glucose cotransporter 2; T2D, type 2 diabetes.
[a]>10% considered clinically meaningful.

Figure 1 Cumulative prevalence of heart failure (HF) over time in patients with type 2 diabetes. Patients from Canada, Denmark, Japan, and Norway excluded from these calculations.



T2D have an increased risk of non-ischaemic HF—both with and without systolic dysfunction—likely due to common concomitant risk factors (e.g. obesity, hypertension, and sleep apnoea) and direct effects of diabetes (microvascular endothelial dysfunction, inflammation, increased myocardial fibrosis, and increased oxidative stress).[13]

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Table 2 Factors associated with incident heart failure

	HR (95% CI)	*P*-value
Age (per 5 years)	1.29 (1.12–1.48)	0.003
Male sex	1.31 (0.80–2.13)	0.124
Diabetes duration (per 5 years)	1.13 (0.94–1.36)	0.404
Coronary artery disease	2.71 (1.54–4.78)	0.007
Chronic kidney disease	2.45 (1.21–4.95)	0.043
Hypertension	2.11 (1.13–3.96)	0.003
Atrial fibrillation	3.42 (1.51–7.74)	0.002

CI, confidence interval; HR, hazard ratio.

Second, treatment of T2D can impact the risk of HF.[1] While a strategy of intensive glucose control has no benefit for reduction of HF (and possible risk when HbA1c $< 7\%$),[14] choice of glucose-lowering medications can significantly impact risk. Metformin and sodium–glucose cotransporter 2 inhibitors improve HF outcomes, whereas sulphonylureas, insulin, and thiazolidinediones likely increase HF risk.[1,14] Similar to other studies,[3] we observed a lack of targeted glucose-lowering medication selection in patients with HF—with low use of sodium–glucose cotransporter 2 inhibitors (no more than in those without HF), paradoxically lower use of metformin, and similar use of high-risk medications such as sulfonylureas and insulin. Ideally, as patients in DISCOVER were enrolled at the time of initiation of second-line glucose-lowering medication, we would have observed higher use of medications with cardiovascular risk reduction across the board. A greater awareness of the risk of incident HF in patients with T2D may increase not only recognition and resultant appropriate treatment but also greater use of prevention strategies.

Third, the majority of HF diagnoses in patients with T2D in our study were made in an outpatient setting. As opposed to myocardial infarctions or strokes, which manifest as acute events, HF is a slowly progressive disease with symptoms such as fatigue and dyspnoea that could be attributed to other conditions and thus requires acute awareness of the risk and surveillance for subtle signs of volume overload. Efforts to better identify patients with T2D who are at high risk for HF and screening strategies to recognize HF when it occurs are needed, especially in primary care settings where most patients with T2D are seen. These data also suggest that trials where only HF hospitalizations are assessed may underestimate the true incidence of HF in patients with T2D.

In terms of limitations, as DISCOVER was an observational study designed to capture real-world care, reporting of complications relied on investigators' clinical judgement with no standardized screening protocol or adjudication of HF diagnoses. Second, as there was no mandatory testing in DISCOVER, EF data were missing in most patients. Third, six countries were excluded from the follow-up analyses for various administrative reasons, which reduced our cohort size—particularly among patients in the Western Pacific Region—and limited our ability to compare incidence rates across countries. Because of these exclusions, we have likely underestimated the burden of chronic kidney disease in patients with HF. Fourth, the low number of incident HF cases limited the number of variables we could investigate in the multivariable model. Future studies should explore not only the role of patient co-morbidities but also medications and cardiovascular risk factors in development of incident HF. Finally, despite enrolling a large number of diverse patients with T2D from multiple countries—many of which have rarely been studied before—it is unclear if our findings are generalizable to those not included.

In conclusion, in a large multinational cohort of patients with relatively early-stage T2D, most diagnoses of HF occurred in the absence of known CAD and in the outpatient setting. These findings highlight the need for greater awareness of indolent HF in outpatients with T2D, and a deeper understanding of how to prevent, diagnose, and optimally manage patients with T2D and HF—particularly with targeted selection of glucose-lowering medications and glycaemic goals.

Conflict of interest

K.K., F.B., B.C., M.B.G., L.J., A.N., M.V.S., I.S., J.V., H.W., and M.K. are members of the DISCOVER Scientific Committee and received financial support from AstraZeneca to attend DISCOVER planning and update meetings. S.V.A., F.T., and M.K. are employees of Saint Luke's Mid America Heart Institute, which has received research funding from AstraZeneca for participation in DISCOVER. H.C., A.C., P.F., G.L.-S., J.M., L.R., and F.S. are employees of AstraZeneca. N.H. and J.V. are former employees of AstraZeneca. J.C.-R. is an employee of Evidera. In addition, K.K. has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda, Servier, and Pfizer and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, and Pfizer and also acknowledges support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care—East Midlands (NIHR CLAHRC—EM) and the National Institute of Health Research (NIHR) Leicester Biomedical Research Centre. B.C. has received honoraria from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharpe & Dohme, Novartis, Novo Nordisk, Sanofi, and Takeda. M.B.G. has received honoraria from Merck Serono. M.K. has received honoraria from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, GlaxoSmithKline, Glytec Systems, Intarcia, Janssen, Merck (Diabetes), Novartis, Novo Nordisk, and Sanofi and research support from AstraZeneca and Boehringer Ingelheim. L.J. has received honoraria from AstraZeneca, Bayer, Boehringer

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of patients from Russia versus other countries.

Table S2. Characteristics of patients in the analytic cohort versus those excluded.

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