Type 2 diabetes mellitus (T2DM) is a recognised risk factor for heart failure (HF) development, independent of coronary artery disease (CAD) and hypertension. HF development is associated with high mortality, making prevention of HF in T2DM a research and clinical priority.

Glycemic control may influence HF development. Hyperglycemia can exert detrimental effects on the myocardium and has been shown to upregulate the renin–angiotensin–aldosterone system, increase oxidative stress, promote accumulation of advanced glycation end-products, and cause interstitial fibrosis. Hyperglycemia has also been associated with myocardial lipotoxicity, mitochondrial dysfunction, abnormal substrate metabolism and impaired calcium handling. Epidemiological evidence indicated glycosylated hemoglobin (HbA1c), and the risk of HF are related. A cohort study of ≈50000 patients with T2DM showed each 1% increase in HbA1c was associated with an 8% increased risk of HF.

However, large randomized controlled trials, investigating intensive versus standard glycemic control and vascular outcomes, did not show any benefit of intensive glycemic control, and one study found intensive control promoted increased mortality. These studies were not specific to HF and were underpowered to draw conclusions regarding intensive glycemic control and HF development. Meta-analysis of these randomized controlled trials has not shown any reduction in HF risk associated with intensive glycemic control.

In view of these findings, we investigated four principal questions. First, was time-updated HbA1c, a longitudinal measure of glycemic control, associated with HF development in a population with T2DM in Tayside, Scotland? Second, how was HbA1c variability related to HF development because HbA1c variability has previously been linked to incident cardiovascular events? Third, because glycemic control has been associated with CAD and CAD is an accepted risk factor for HF development, was this association dependent on the existence of CAD? Finally, what attributable risk did

**Background**—Type 2 diabetes mellitus is an independent risk factor for heart failure development, but the relationship between incident heart failure and antecedent glycemia has not been evaluated.

**Methods and Results**—The Genetics of Diabetes Audit and Research in Tayside Study study holds data for 8683 individuals with type 2 diabetes mellitus. Dispensed prescribing, hospital admission data, and echocardiography reports were linked to extract incident heart failure cases from December 1998 to August 2011. All available HbA1c measures until heart failure development or end of study were used to model HbA1c time-dependently. Individuals were observed from study enrolment until heart failure development or end of study. Proportional hazard regression calculated heart failure development risk associated with specific HbA1c ranges accounting for comorbidities associated with heart failure, including blood pressure, body mass index, and coronary artery disease. Seven hundred and one individuals with type 2 diabetes mellitus (8%) developed heart failure during follow up (mean 5.5 years, ±2.8 years). Time-updated analysis with longitudinal HbA1c showed that both HbA1c <6% (hazard ratio =1.60; 95% confidence interval, 1.38–1.86; P value <0.0001) and HbA1c >10% (hazard ratio =1.80; 95% confidence interval, 1.60–2.16; P value <0.0001) were independently associated with the risk of heart failure.

**Conclusions**—Both high and low HbA1c predicted heart failure development in our cohort, forming a U-shaped relationship. (Circ Heart Fail. 2015;8:236-242. DOI: 10.1161/CIRCHEARTFAILURE.113.000920.)

**Key Words:** diabetes mellitus ■ echocardiography ■ glucose
specific HbA1c ranges convey and what range defined optimum control?

Methods
We exploited the established regional clinical informatics systems developed by the University of Dundee and NHS Tayside. These systems make use of a unique health record identifier—the Community Health Index (CHI) number—to deterministically link clinical data sets through robust anonymization protocols within the Health Informatics Center (HIC) at an individual level with high accuracy. The clinical data sets include the following:

1. Go-DARTS database

   The Diabetes Audit and Research in Tayside Study (DARTS) is a well-validated, region-wide clinical information system containing data on effectively all patients with diabetes mellitus in the region.20 The DARTS clinical systems facilitated the creation of the Genetics of Diabetes Audit and Research Tayside Scotland (Go-DARTS) database. Population-based recruitment to Go-DARTS, using the data within DARTS, allowed essentially all patients with T2DM in the region to be recruited from 1998, reducing selection bias. All Go-DARTS participants provided written consent for their data to be linked anonymously for research purposes. Many of these individuals were recruited under the auspices of the Wellcome Trust UK Type 2 Diabetes Case Control Consortium.

   We studied 8683 individuals with T2DM recruited to Go-DARTS between December 1998 and May 2009, observing them from recruitment to the end of the study period, August 2011. The Go-DARTS population was described in previous studies.20-22 Collection and analysis of data in DARTS and Go-DARTS was approved by the East of Scotland Research and Ethics Committee.

2. The Tayside echocardiography database

   The Tayside echocardiography database, maintained by the Department of Cardiology, contains data from all clinically requested echocardiograms performed in Ninewells Hospital, Dundee, from September 1993. All echocardiograms were reported by British Society of Echocardiography accredited echocardiographers. This database was linked to the Go-DARTS data to identify echocardiographically defined cases of left ventricular systolic dysfunction. The echocardiography database was previously used to identify structural heart disease for research.23-26

3. Other HIC data sets

   Other data sets used included the dispensed prescribing data set, containing information of drug prescriptions dispensed for all individuals in Tayside over the past 20 years. Hospital discharge data comprised the Scottish Morbidity Record (SMR01) containing ICD 9 and 10 classification codes, mortality data from the General Registrar’s Office, and data containing information on biochemical test results, including HbA1c measurements.

Study Design
To investigate how HbA1c levels predicted incident HF, we performed a retrospective cohort study between December 1998 and August 2011 to ascertain the size of risk of specific levels of HbA1c with respect to the rate of HF development in T2DM, taking into account all risk factors associated with HF.

HF Definition
Incident HF was defined as the first inpatient or outpatient diagnosis of HF according to a previously validated method.23,26-28 All individuals with T2DM and a hospital admission with HF according to ICD codes (ICD 9: 428, ICD10: I50) or an echocardiogram with evidence of left ventricular systolic dysfunction and a prescription for a loop diuretic (British National Formulary code 2.2.2) were regarded as HF cases. A previous case validation exercise found 91% concordance between a clinical diagnosis of HF from case note review and definition of HF based on an echocardiographic evidence of left ventricular systolic dysfunction requiring prescription of loop diuretics.23,25,26 Only incident HF cases were included in the analysis. Individuals who had not been admitted to hospital with HF, had an echocardiogram showing left ventricular systolic dysfunction, nor received a prescription for a loop diuretic were classed as non-HF cases in subsequent analysis.

Time-Updated Analysis With Longitudinal HbA1c
HbA1c was modeled as a time-dependent variable where the follow-up time was split each time the HbA1c category changed. Thus, if subject 1 was in category 6% to 7% HbA1c, the subject would have added person years to the 6% to 7% HbA1c group. If the subject switched to 7% to 8%, the subject would then have also added patient-years to that HbA1c category.

Calculation of HbA1c Variability
To investigate the effects of intrapatient variations of HbA1c on incident HF, we calculated intrapatient mean (HbA1c-MEAN) and standard deviation (HbA1c-SD), respectively. HbA1c values obtained preceding recruitment at the enrolment and until the last recorded value of HbA1c were used. The interindividual difference in the number of HbA1c assessments was adjusted according to the formula: adj-HbA1c-SD=SD√[(n−1)/n] as previously described.29

Statistical Analysis
The chi-squared test of association was used to identify discrete variables, and Student’s t test was used to identify continuous variables associated with HF. Variables showing significant association with HF development were used to model HF by proportional hazard regression.

Covariates
All factors associated with HF contributed to the model, including age, sex, diabetes mellitus duration, number of HbA1c measures, systolic blood pressure, diastolic blood pressure, history of CAD, body mass index, antihyperglycemic medications, and creatinine. Creatinine was categorized in 10 μmol/L increments because of the broad range of values. Age was divided by 10 because of the broad range of values. Values for body mass index, systolic blood pressure, diastolic blood pressure, creatinine, age, and diabetes mellitus duration were taken at baseline.

Diagnosis of CAD was based on hospital admission with corresponding discharge code (ICD 9: 410, 411, 412, 413 or 414 and ICD10: I20, I21, I22, I23, I24 or I25). Existence of CAD was modeled in a time-dependent manner.

Prescriptions for antihyperglycemic medications at study enrolment were analyzed using British National Formulary codes 6.1.2.1 for sulphonylureas, 6.1.2.2 for metformin, 6.1.1.2 for insulin and the approved names pioglitazone and rosiglitazone for thiazolidinediones (TZDs). All participants were assigned to 1 of 5 treatment categories. All participants taking insulin at enrolment were placed in the ‘insulin’ group. Patients taking sulphonylureas at enrolment, who were not taking insulin, were placed in the suphonylureas group. Patients receiving TZDs at enrolment, but not taking insulin or sulphonylureas, were placed in the TZD group. Individuals prescribed metformin only were assigned to the metformin group and those who were not receiving antihyperglycemic agents at enrolment were placed in the diet group.

Treatment category at enrolment was included in the proportional hazard regression model with those receiving diet control as the reference group. In this analysis, time-updated HbA1C was divided into only 3 categories: <6.5, 6.5 to 9, and >9; for simplicity, 6.5% to 9% was used as the reference category.

Statistical analyses were performed using SAS 9.2 for Windows and the R software.30

Results
Out of 8683 individuals, a total of 701 (8%) developed HF during the follow up period (mean 5.5 years, standard deviation 2.8 years; Figure 1). These comprised 196 cases of HF.
based on echocardiography data and 505 based on hospital admission with HF.

**Clinical Features Associated With HF**

Variations in baseline clinical characteristics with HbA1c are shown in Table 1. Simple tests of association showed associations between HF development and number of HbA1c measures, age, sex, diabetes mellitus duration, CAD, systolic blood pressure, diastolic blood pressure, body mass index, creatinine, and HbA1c levels (\(P<0.01\) for all above variables except sex, \(P=0.02\)).

**Time-Updated Analysis With Longitudinal HbA1c**

Time-varying HbA1c analysis (Figure 2 and Table 2) showed an increased risk of HF for HbA1c categories <6%, 7% to 8%, 8% to 9%, and >9% compared with the reference category of 6% to 7%. Risk was significantly increased in the categories <6% (hazard ratio [HR] =1.60, 95% confidence interval [CI], 1.38–1.80; \(P\) value =<0.0001) and >10% groups (HR=1.80, 95% CI, 1.60–2.16; \(P\) value <0.0001). This relationship persisted when baseline antihyperglycemic medications were accounted for (<6.5% HR =1.48, 95% CI, 1.23–1.80; \(P\) value <0.0001; >9% HR =1.31, 95% CI, 1.06–1.61; \(P\) value =0.01; Table 3). Use of insulin and sulphonylureas at baseline were

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**Table 1. Variation in Baseline Clinical Characteristics According to HbA1c Levels and Their Association With HF Development, n=1112 Each Quintile**

<table>
<thead>
<tr>
<th>HbA1c quintile (HbA1c range, %)</th>
<th>First (2.4–6.5)</th>
<th>Second (6.5–7.0)</th>
<th>Third (7.0–7.4)</th>
<th>Fourth (7.4–8.2)</th>
<th>Fifth (8.2–18.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number HbA1c measures (SD)</td>
<td>16.0 (10.4)</td>
<td>20.3 (106)</td>
<td>21.9 (11.3)</td>
<td>24.0 (12.8)</td>
<td>23.4 (12.8)</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>66.9 (11.0)</td>
<td>66.6 (10.4)</td>
<td>64.5 (11.5)</td>
<td>63.3 (11.7)</td>
<td>59.9 (11.9)</td>
</tr>
<tr>
<td>Number male, %</td>
<td>669 (60)</td>
<td>688 (61)</td>
<td>683 (61)</td>
<td>682 (61)</td>
<td>637 (57)</td>
</tr>
<tr>
<td>Duration T2DM, y (SD)</td>
<td>3.8 (5.0)</td>
<td>5.3 (5.1)</td>
<td>5.8 (5.6)</td>
<td>6.9 (5.8)</td>
<td>7.9 (6.6)</td>
</tr>
<tr>
<td>Frequency CAD, %</td>
<td>266 (23)</td>
<td>241 (21)</td>
<td>233 (21)</td>
<td>268 (24)</td>
<td>277 (24)</td>
</tr>
<tr>
<td>SBP, mmHg (SD)</td>
<td>138 (19)</td>
<td>140 (17)</td>
<td>140 (17)</td>
<td>140 (18)</td>
<td>141 (19)</td>
</tr>
<tr>
<td>DBP, mmHg (SD)</td>
<td>76 (11)</td>
<td>77 (10)</td>
<td>77 (10)</td>
<td>78 (10)</td>
<td>79 (10)</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>29.9 (5.8)</td>
<td>30.4 (5.0)</td>
<td>30.8 (5.6)</td>
<td>30.7 (5.4)</td>
<td>31.6 (6.1)</td>
</tr>
<tr>
<td>Creatinine, μmol/L (SD)</td>
<td>92.0 (32.1)</td>
<td>91.1 (22.4)</td>
<td>91.4 (32.5)</td>
<td>90.3 (23.5)</td>
<td>90.1 (27.1)</td>
</tr>
<tr>
<td>Insulin at enrolment, %</td>
<td>26 (2)</td>
<td>36 (3)</td>
<td>80 (7)</td>
<td>185 (16)</td>
<td>469 (42)</td>
</tr>
<tr>
<td>Sulphonylureas at enrolment, %</td>
<td>122 (11)</td>
<td>280 (25)</td>
<td>429 (38)</td>
<td>511 (46)</td>
<td>407 (37)</td>
</tr>
<tr>
<td>Metformin at enrolment, %</td>
<td>182 (16)</td>
<td>350 (32)</td>
<td>356 (32)</td>
<td>264 (24)</td>
<td>122 (1)</td>
</tr>
<tr>
<td>TZDs at enrolment, %</td>
<td>9 (0.8)</td>
<td>30 (3)</td>
<td>40 (4)</td>
<td>42 (4)</td>
<td>25 (2)</td>
</tr>
<tr>
<td>Diet control at enrolment, %</td>
<td>772 (70)</td>
<td>416 (37)</td>
<td>207 (19)</td>
<td>110 (10)</td>
<td>88 (8)</td>
</tr>
<tr>
<td>Frequency HF, %</td>
<td>134 (12)</td>
<td>93 (8)</td>
<td>121 (11)</td>
<td>134 (12)</td>
<td>218 (20)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HF, heart failure; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; and TZDs, thiazolidinediones.
also associated with increased risk of HF development in this cohort.

**HbA1c Variability and Incident HF**

Intra-individual mean (HbA1c-MEAN) and its adjusted standard deviation (HbA1c-SD) were included in the proportional hazard model as above. HbA1c variability (HbA1c-SD) was independently and significantly associated with incident HF (HR=0.80, 95% CI, 0.74–0.85; P value <0.0001), with less variability in HbA1c having a protective effect on incident HF.

**Assumptions of Proportional Hazard Models**

The assumption of proportional hazard with time-dependent covariates were tested by creating interactions of the predictors as a function of survival time and including these values in the model using the function Proporionality test in Proc Phreg in SAS 9.2. Test of proportional hazards did not yield significant P values for any of the covariates in the model or globally, suggesting that the proportional hazard assumptions hold true.

**Discussion**

**U-Shaped Relationship Between HbA1c and HF Development**

Our study generated 3 main findings; first, HbA1c >10% was associated with HF development in a progressive nonlinear relationship even when CAD was accounted for. Second, HbA1c <6% was also associated with an increased HF risk. These findings suggest both high and low HbA1c predicted HF development in our cohort, forming the U-shaped relationship, shown in Figure 2. Third, intraindividual variability in HbA1c was an independent risk factor for development of HF.

Currie et al. previously reported a U-shaped relationship between mean HbA1c and all-cause mortality and cardiac events in a retrospective study of patients with T2DM using the UK General Practice Research Database. They showed HbA1c around 7.5% was associated with the lowest all-cause mortality and lowest progression to large vessel disease events (myocardial infarction, stroke, coronary revascularization, or angina), although they did not look at HF development. Our study extends these findings, showing that the U-shaped relationship between mean HbA1c and cardiovascular risk applies to HF development.

Eight percent of our cohort of patients with T2DM developed HF over 5.5 years, which compares well with previous studies. This is 53% higher than Scotland’s general population (≈0.15%). Echocardiographic and hospital admission data were used in our study, whereas hospital admission data alone generated the Scotland-wide figure quoted.

We identified several risk factors for HF development in T2DM, including increasing age, body mass index, systolic blood pressure, and creatinine at baseline and a history of CAD. These findings are consistent with previous work.

Early observational studies showed raised HbA1c was associated with increased risk of HF development, where HF was identified through hospital admission data, regardless of CAD status. These studies used a single measure of HbA1c, although calculation of the mean of serial HbA1c measures has been shown to better predict diabetic complications.

Lind and colleagues used the Swedish National Diabetes Registry to explore the relationship between mean HbA1c and the risk of HF and reported that individuals with mean HbA1c >7% were at increased risk of developing HF. They reported no further reduction in risk in patients with HbA1c <6% (42 mmol/mol) compared with those with HbA1c 6% to 7%. However, they demonstrated an increased risk of HF hospitalization in patients with mean HbA1c <6% compared with mean HbA1c 6% to 7% in their model accounting for the greatest number of confounding factors. These findings support a U-shaped relationship between HbA1c level and incident HF risk, in-keeping with the UK General Practice Research Database study. This fits with data on mortality and vascular events from recent trials investigating intensive versus standard glycemic control and vascular outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07</td>
<td>1.07–1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration T2DM, y</td>
<td>1.02</td>
<td>1.02–1.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.01</td>
<td>0.90–1.20</td>
<td>0.60</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.63</td>
<td>4.98–5.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine category, μmol/L</td>
<td>1.08</td>
<td>1.07–1.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>0.96</td>
<td>0.94–0.98</td>
<td>0.0003</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>0.91</td>
<td>0.88–0.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c &lt;6%</td>
<td>1.60</td>
<td>1.38–1.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c 7% to 8%</td>
<td>1.04</td>
<td>0.84–1.25</td>
<td>0.68</td>
</tr>
<tr>
<td>HbA1c 8% to 9%</td>
<td>1.07</td>
<td>0.82–1.33</td>
<td>0.57</td>
</tr>
<tr>
<td>HbA1c 9% to 10%</td>
<td>1.18</td>
<td>0.88–1.50</td>
<td>0.27</td>
</tr>
<tr>
<td>HbA1c &gt;10%</td>
<td>1.80</td>
<td>1.60–2.16</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HR, hazard ratio; SBP, systolic blood pressure; and T2DM, type 2 diabetes mellitus.
Table 3. Risk of Heart Failure Development Associated With Varying Levels of Glycemic Control Accounting for Baseline Antihyperglycemic Medications

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.07–1.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration T2DM, y</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.10</td>
</tr>
<tr>
<td>CAD</td>
<td>5.21</td>
<td>4.40–6.17</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.08</td>
<td>1.07–1.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine category, μmol/L</td>
<td>1.10</td>
<td>1.07–1.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>0.97</td>
<td>0.95–0.99</td>
<td>0.0035</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>0.93</td>
<td>0.90–0.97</td>
<td>0.0003</td>
</tr>
<tr>
<td>HbA1c &lt;6.5%</td>
<td>1.48</td>
<td>1.23–1.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c &gt;9%</td>
<td>1.31</td>
<td>1.06–1.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.81</td>
<td>1.43–2.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.17</td>
<td>1.00–1.42</td>
<td>0.11</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.97</td>
<td>0.67–1.39</td>
<td>0.85</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.10</td>
<td>0.93–1.30</td>
<td>0.28</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HR, hazard ratio; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; and TZDs, thiazolidinediones.

The relationship between HF development and HbA1c was not explained by an association between CAD and HbA1c, and HbA1c still predicts HF development independently of CAD. This is consistent with the findings described above.13

Why Was HbA1c <6% Associated With HF Development?
The U-shaped relationship between HbA1c and the risk of developing HF merits discussion. Multiple factors may promote HF development in patients with HbA1c <6%. Adverse off-target drug effects from antihyperglycemic medications may account for some of the incident HF cases in the group of individuals with HbA1c <6%.

Insulin and TZDs have been associated with HF development.35,36 Only 0.9% of individuals with HbA1c <6% were taking TZDs, so we were unable to assess whether their use was associated with increased risk of HF development in this group. Although sulfonylurea use was associated with HF development in our study, previous studies have provided conflicting evidence regarding the risk of HF development with sulfonylurea use. An early study using the General Practice Research Database on 25,690 diabetics showed that the incidence of HF did not differ across oral antidiabetic drug classes.37

However, more recent analyses of observational data have shown an increased risk of HF with sulfonylurea use. McAlister and colleagues reported that users of high-dose sulfonylureas were more likely to develop incident HF than users of high-dose metformin monotherapy (HR 1.38, 95% CI, 1.20–1.60).38 A more recent analysis of the UK General Practice Research Database database of 91,521 patients with diabetes mellitus showed second-generation sulfonylureas were associated with an 18% higher risk of developing HF (HR 1.18, 95% CI, 1.04–1.34; P value 39).

It is impossible to draw firm conclusions regarding the role of antihyperglycemic agents from this observational study. A randomized controlled trial would be required to resolve this issue, which may not be ethically feasible given the data from preceding randomized controlled trials.14–16 Hypoglycemic events may also partially explain the U-shaped relationship because hypoglycemia is an independent cardiovascular risk factor.40 We were unable to analyze the influence of hypoglycemic events from our data, and so discussion regarding their importance is speculative.

Previous reports had linked HbA1c variability to the risk of microvascular complications of both type 139,40 and type 2 diabetes mellitus.41 Retrospective analyses of the Diabetes Control and Complications Trial (DCCT)41,42 showed variation in HbA1c was an independent risk factor for the development of both diabetic retinopathy and nephropathy in individuals with type 1 diabetes mellitus. In the FinnDiane study, HbA1c variability also predicted incident cardiovascular events,18 although the link with cardiovascular events was not a consistent finding.

We looked at the relationship between intraindividual HbA1c variability and incident HF and showed that lower variability in HbA1c had was relatively protective against incident HF. The physiological mechanisms through which HbA1c variability contributes to HF development are not known. However, increased glucose variability has been reported to have promoted cell apoptosis and oxidative stress.43–45 Both these processes can contribute to the pathogenesis of HF.46 The suggestion that HbA1c variability enhances cell apoptosis and oxidative stress in patients with diabetes mellitus remains speculative and cannot be concluded from this study.

Study Limitations
Our study reflects a true population and a real-world scenario. We recognize the inherent limitations that come with a retrospective, nonrandomized observational study. A potential limitation of our study was that we did not model use of antihyperglycemic medication time-dependently and so cannot determine whether the association between antihyperglycemic medications and HF development depended on medication category, medication-dose, or the duration of drug exposure. However, in this observational cohort, modeling the effect of antihyperglycemic treatment category, as well as the inclusion of other cardiovascular protective medication, would have been prohibitively complex, both to analyze and interpret.

Another limitation of our study was that we were unable to take into account hospitalizations occurring outside of Scotland or account for other potential confounding factors, such as atrial fibrillation, smoking status, lipids, and QT interval.

However, our study had multiple strengths. The primary strength of our analysis, relative to the observational studies described earlier, lies in the use of echocardiographic data to identify individuals with incident HF.

Conclusion
Both high and low HbA1c were associated with increased risk of HF development in T2DM, forming a U-shaped relationship. The association between HbA1c and HF development...
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does not depend on the association between HbA1c and CAD. Sulphonlurea drugs and insulin also seem to be associated with HF development when compared with diet control.

Acknowledgments
We acknowledge the support of the Health Informatics Centre, University of Dundee, for managing and supplying the anonymized data and NHS Tayside, the original data owner. We are grateful to all the participants who took part in the Genetics of Diabetes Audit and Research Tayside Scotland (Go-DARTS) study, to the general practitioners, to the Scottish School of Primary Care for their help in recruiting the participants, and to the whole team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

Sources of Funding
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Disclosures
Professor Chim Lang has consulted on saxagliptin (Astra Zeneca). All other authors report no conflicts.

References


Both type 2 diabetes mellitus and heart failure are extremely common. Co-existent type 2 diabetes mellitus and heart failure are associated with high levels of morbidity and mortality. Traditionally, clinicians have aimed to reduce complications in diabetes mellitus through drug therapy to lower HbA1C as much as possible. However, our study shows that this approach may actually be detrimental in the development of heart failure. Our results suggest that metformin has generally been avoided in those with heart disease because of the risk of lactic acidosis. Our results suggest that metformin is relatively protective against heart failure development when compared with drugs, such as sulphonylureas and insulin. These findings may influence clinicians in managing glycemic control in patients with type 2 diabetes mellitus. We acknowledge that clinical practice should not change on the basis of a single, observational study. However, taken in the context of previous results outlined in our article, clinicians may be prompted to approach glycemic control in patients with type 2 diabetes mellitus differently.
Both High and Low HbA1c Predict Incident Heart Failure in Type 2 Diabetes Mellitus


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제2형 당뇨병 환자에서 높거나 낮은 당화혈색소 수치는 심부전 발생을 예측한다

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초록

배경
제2형 당뇨병은 심부전 발생의 독립적인 인자이다. 하지만 심부전과 선행혈당증(antecedent glycemia)과의 관계에 대해서는 연구된 바 없다.

방법 및 결과
Genetics of Diabetes Audit and Research in Tayside Study(Go-DARTS)는 당뇨병에 대한 검증된 임상데이터를 보유하고 있으며, 이 중 8,683명의 제2형 당뇨병 환자들에 대한 연구를 분석하였다. 연구 대상자들의 처방 및 입원기록, 심장초음파 데이터에 연동된 1998년 12월부터 2011년 8월 사이의 심부전 발생 건수를 얻었다. 심부전의 발생 또는 본 연구의 종료 시점까지의 모든 당화혈색소(glycosylated hemoglobin, HbA1c) 수치를 측정하여 시간의존 HbA1c 수치 모델(model HbA1c time-dependently)에 이용하였고, 관찰 기간(평균 5.5년, ±2.8년) 동안, 제2형 당뇨병 환자 701명(8%)에서 심부전이 발생하였다. 추적(longitudinal) HbA1c 수치를 이용한 시간갱신분석(time-updated analysis)에 의하면, 낮은 수치의 HbA1c(HbA1c<6%; HR, 1.60; 95% CI, 1.38-1.86; P<0.0001)와 높은 수치의 HbA1c(HbA1c>10%; HR, 1.80; 95% CI, 1.60-2.16; P<0.0001) 모두 심부전의 위험과 독립적으로 관련이 있었다.

결론
본 연구에서 HbA1c의 높은 수치와 낮은 수치는 U-형 관계를 보이며 심부전의 발생을 예측하였다.