Glycaemic Control & Heart Failure Development
Importance of Health Promotion in the Diabetic Patient

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ABSTRACT

Background
In diabetes, poor glycaemic control is associated with increased risk of cardiovascular events. The relationship between glycaemic control and chronic heart failure (CHF) is less well defined. There is controversy regarding the importance of glycaemic control in patients with type 2 diabetes-mellitus (T2DM) and CHF with recent evidence suggesting that tight glycaemic control may be associated with worse survival.

Aim
The aim of this study was to examine the relationship between HbA1c and the risk of incident CHF and examine the relationship between HbA1c and outcome in T2DM with established CHF.

Methods
This study was carried out in the population (approximately 400,000) of Tayside in Scotland using the Diabetes Audit and Research in Tayside information system. The incidence of new CHF in the DARTS database was determined during the study period (Jan 1994 to Dec 2003). CHF was defined as the presence of a hospital discharge code for CHF or the prescription of CHF medication following a myocardial infarction. A prospective case control study was performed with each case of CHF. Development of CHF was modelled using conditional logistic regression with a proportional hazards model used to consider the impact of HbA1c on survival of the cases.

Results
Out of 3070 diabetic individuals, there were 691 incident cases of CHF (mean age at diagnosis of 70.6±9.8 yrs, 60% males). The adjusted HR of developing CHF for each 1% higher HbA1c was 1.31 (95% CI 1.20-1.44, p=1.43× 10⁻⁹). In the cases there were subsequently 211 deaths. After adjustment the HR of death for each 1% increase in HbA1c was 1.24 (95% CI 1.09-1.42, p=0.0013).

Conclusions
These data suggest that glycaemic control is an independent risk factor for incident CHF in persons with T2DM. In diabetic patients with established CHF, a poor glycaemic control is associated with a worse outcome.

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Introduction
Diabetes is a metabolic condition characterized by constant hyperglycemia; it is well established as a being an independent risk factor for developing cardiovascular events\(^1\). However the exact reason for this association remains unclear; and includes association between diabetes and other cardiovascular risk factors, such as dyslipidemia, hypertension and renal insufficiency. A growing number of epidemiologic studies now implicate chronic hyperglycemia as an important determinant of cardiovascular disease.\(^2\,^3\,^4\,^5\) It is well established that diabetes; a metabolic syndrome that is increasing in prevalence worldwide is a significant risk factor for developing cardiovascular disease and development of heart failure.\(^6\,^7\,^8\)

Epidemiology of Diabetic Heart Failure
Over the previous 2 decades, the prevalence of diabetes, in particular type 2 diabetes, has significantly risen, and has subsequently caused an increase in the incidence of diabetes related complications, including heart failure (HF). Investigations involving subgroup analysis of various randomized clinical studies have proven that a significant number of HF patients are also suffering from diabetes.\(^9\,^10\,^11\) The coexistence of both diabetes and chronic heart failure (CHF) was clearly evident as demonstrated in both the Framingham Study \(^12\) and the UKPDS \(^13\). They can also in most cases coexist as an inter-relationship such that each condition may impact upon the other in terms of aetiology and outcome.\(^12\) The study also concluded that in the presence of diabetes the risk of CHF increases by 2-8 fold.\(^12\) Studies have proven that for every 1% increase in HbA1c was associated with an 12% increased risk of developing CHF independent of age, BMI, BP and presence of any coronary heart disease.\(^14\) Data analyses from the Framingham study demonstrated that diabetes significantly increases the risk for developing CHF by 1.8 times in men and 3.7 times in women.\(^15\)

Pathophysiology of Diabetic Heart Failure
Heart failure development in diabetic patients is associated to abnormal multiple pathophysiologic states. Common comorbidities such as hypertension, renal impairment, dyslipidemia and obesity subsequently lead to both functional and structural abnormalities in the heart; ultimately causing CHF.\(^16\) The United Kingdom Prospective Diabetic Study (UKPDS) showed that hyperglycemia is strongly associated with cardiac abnormalities and dysfunction.\(^14\) The study also concluded that for every 1% rise in HbA1c, the risk of HF was increased by 12%; proving that a significant correlation existed between glycaemic levels and development of HF.

Iribarren et al\(^17\) also demonstrated that in diabetic individuals an HbA1c level ≤10 caused an increase of developing HF by 1.56 fold than an HbA1c level of <7.

There has been much debate about the existence and causation of developing diabetic heart failure as the majority of the studies supporting this concept are based on animal studies.\(^18\) Data suggests that myocardial structure is altered by deposition of collagen and increased fibrosis.\(^19\,^20\,^21\) Di Biello et al were able to prove the presence of early changes of fibrosis in myocardial tissue by using ultrasonic backscatter.\(^22\) Ultrasonic backscatter allows characterization of tissue microstructure
using radio frequency signals that have been backscattered from diseased tissues.\textsuperscript{23}

Heart failure in diabetic patients results from complex interaction involving the sympathetic nervous system, renin angiotensin aldosterone system, increased activity of cytokines and increased oxidative stress. Hyperglycemia leads to activation of protein kinase C at cellular levels that subsequently leads to maladaptive changes in the myocardium.\textsuperscript{24, 25} Activation of protein kinase C leads to malformations in contractile protein functioning and triggering of synthesis of angiotensin converting enzymes (ACE) genes and nitric oxide synthase activity. An increased production and activity of angiotensin converting enzymes leads to apoptosis, necrosis and interstitial fibrosis of myocytes and endothelial cells.\textsuperscript{26} Studies have proven that elevated glycaemic levels lead to glycation of collagen; the final products of glycation lead to stiffening of the myocardium.\textsuperscript{27, 28} Also at the molecular level, calcium hemostasis impairment is also evident in myocytes.

Disruption of calcium hemostasis will tend to lead to decreased uptake and release by the sarcoplasmatic reticulum. Maladaptations at the receptors are mainly due to the decreased number of sarcolemmal sodium calcium exchanger.\textsuperscript{29} Elevated glycaemic levels leads to oxidative stress mainly by production of oxidants from both mitochondrial and non-mitochondrial sources.\textsuperscript{30} Oxidative stress causes damage by interacting with mitochondrial uncoupling as well as direct myocyte death. Disruption in mitochondrial function leads to reduced ATP production and reduced myocardial contractions. Alteration in the utilization of substrate is another factor that contributes to cardiomyocyte damage at the molecular level. Diabetic hearts tend to use fatty acids in preference to glucose or lactate; and over a period of time accumulation of lipids leads to cardiomyocyte death.\textsuperscript{31} Studies in diabetic individuals have been limited to the use of positron emission tomography which confirms the greater use of fatty acids and decreased glucose oxidation in the heart.\textsuperscript{32} Decreasing utilization of fatty acids for oxidation by the heart is an important factor for reduction of cardiomyocyte damage. Therefore evidence demonstrates multiple factors for development of a characteristic diabetic cardiomyopathy independent of other coexisting comorbidities such as hypertension or coronary heart disease.\textsuperscript{31, 32} This concept may also explain why diabetic individuals tend to develop heart failure even in the absence of coronary heart disease. Use of ACE inhibitors suppresses levels of serum aldosterone. Aldosterone causes cardiomyocyte fibrosis that subsequently leads to a dysfunction of the left ventricle. Hence these results are evident for blocking of aldosterone release using ACE inhibitors. Clinical studies have also demonstrated that ACE inhibitors reduce the progression of development of diabetic nephropathy in addition to their blood pressure lowering effect.\textsuperscript{33} ACE inhibitors are also used in prevention of congestive heart failure and prophylaxis of cardiovascular events.\textsuperscript{33}

**Aims of Study**

A potential risk factor that is associated with poor outcomes that is being currently studied is poor glycaemic control. Glycosylated haemoglobin (HbA1c) indicates the ambient plasma glucose concentration over the preceding 2 to 3 months. The HbA1c level is commonly used as an index of average glycaemia and provides a target treatment range in diabetic patients (HbA1c-normal range 6.5%-7%).\textsuperscript{34} Raised HbA1c
levels indicate poor metabolic control and eventually lead to both microvascular and neuropathic complications. Lowering of glycaemia levels in diabetic patients delays the onset and progression of diabetic complications.\textsuperscript{35-36} In addition, raised glycaemic levels are also associated with increased risk of cardiovascular events (CV).\textsuperscript{37} Elevated HbA1c levels have also been proven to be associated with increased risk of heart failure in diabetic patients.\textsuperscript{38} In diabetic individuals with no previous heart failure, elevated HbA1c levels have been associated with an increased risk of incident heart failure and mortality.\textsuperscript{39,40} Despite this evidence, studies investigating the relationship between HbA1c levels and outcomes in diabetic patients have been limited and have reported discrepant results.\textsuperscript{41-42} Therefore, our study aimed to investigate if HbA1c levels could predict outcome in patients with diabetic heart failure.

\textbf{Methods}

\textbf{Data sources}

Our study involved resources from the DARTS (Diabetes Audit and Research in Tayside) and MEMO database (Medicines Monitoring Unit). DARTS is a diabetic population based information system involving patients under the care of NHS Tayside, Scotland (population of approximately 400,000). The DARTS dataset constitutes clinical information for each and every patient being diagnosed with diabetes in Tayside, Scotland since January 1993.\textsuperscript{43} The DARTS database has a 97% sensitivity and is composed of interlinking of patient data sources; record-linking is utilized by way of the patients Community Health Index number (CHI) assigned to each patient at their respective general practice.\textsuperscript{44} Data sources that have been interlinked include date of diagnosis, diabetes type, duration, HbA1c levels, hospital admissions, diabetic medication, diabetic clinic visits, cardiovascular risk factors (BMI, blood pressure, cigarette smoking) and presence of micro or macro vascular complications of diabetes. The database is regularly updated and includes ongoing retrieval and validation of routine data directly from medical records in primary care by a research team of nurses.

The second database used in the study is the MEMO (Medicines Monitoring Unit) database.\textsuperscript{45} MEMO is a University of Dundee based research collaboration that mainly focuses on the effectivity, safety and cost-effective use of drugs and devices on disease. Data primarily involves the Tayside population with linkage to other national datasets also possible.\textsuperscript{46} It contains a detailed list of all prescribed items to patients from community pharmacies. Therefore, for our research purposes we have a detailed record of diabetic medication or insulin prescribed to all diabetic patients within Tayside.

\textbf{Study Population}

The Study population involved all the patients diagnosed with Type 2 diabetes during the study period January 1991 to 30 June 2008 in Tayside, Scotland. The sampling pool obtained from the DARTS database were patients who were diagnosed as type 2 diabetes and had suffered an incidence of new congestive heart failure (CHF) during the above mentioned study period. CHF was defined as the presence of a hospital discharge code for CHF or patients who were on prescription for CHF.
medication (loop diuretic and an ACE inhibitor). In addition, patients were excluded if they were on loop diuretics such as furosemide for renal disease and were on an angiotensin receptor blocker. The overall cohort for this period included 3,070 patients with diabetes out of which 691 incident cases of CHF were reported.

**Statistical Analysis**

HbA1c values recorded during the study period were used to assess glycaemic control for each patient. Individuals were classified into categories based on quintiles of HbA1c. The levels of HbA1c in each quintile were as follows: Q1: HbA1C ≤6.5%; Q2: 6.5% < HbA1C ≤7.2%; Q3: 7.2% < HbA1C ≤7.9%; Q4: 7.9% < HbA1C ≤8.6%, and Q5: HbA1C >8.6%. All HbA1c values available during the observation period were extracted and averaged.

Development of CHF was modeled using conditional logistic regression using the mean HbA1c during the study period. In statistics, conditional logistic regression is used for the prediction of the probability of occurrence of an event by fitting data to an assigned logistical function. Covariates used in the study were number of HbA1c measures taken, mean arterial pressure and if thiazolidinediones were prescribed as diabetic medication. Thiazolidinediones were added as covariates due to their increased risk of causing heart failure. Clinical data included in the study were: risk factors for vascular disease and co morbidities, hypertension, smoking, dyslipidaemia, blood pressure and body mass index were taken into account.

The primary outcome of the entire program was hospital admission for worsening CHF or death due to cardiovascular causes. Deaths were considered to be cardiovascular unless another cause was attributed. Patients who had suffered from a new incidence of CHF were identified and a date of CHF diagnosis was defined for each patient. Division into quintiles was done to ensure that the groups spanned through a wide range of glycaemic values that were inclusive of the normoglycemic range. Univariate and multivariable Cox proportional hazards models were used to assess the relationship between increasing quintiles (Q1 to Q5) of HbA1c and incidence of CHF and outcome in patients with type 2 diabetes and an established diagnosis of CHF. Hazard ratios are presented as per unit 1% increase in HbA1c, and 95% confidence intervals were calculated for hazard ratios.

**Results**

**Key Findings**

- **CHF Incidence**- The adjusted hazard ratio of developing CHF for each 1% increase in HbA1c was 1.31 (95% CI 1.20-1.44, p=1.43×10⁻⁹).
- **Mortality**- Analyses revealed a linear relationship between mortality and increasing HbA1c quintiles in diabetic patients. After adjustment the hazard ratio of death for each 1% increase in HbA1c increased by 1.24 fold (95% CI 1.09-1.42, p=0.0013).
The study cohort was comprised of 3,070 diabetic individuals of that there were 691 incident cases reported of CHF. The cohort comprised of 60% males (mean age of 60.5 years). The mean age at diagnosis of CHF of the diabetic individuals was 70.6±9.8 years (see Table 1). The mean HbA1c level of the cohort was 8.0 ±1.4%. The results showed that as the HbA1c quintiles progressively increased, there was also a simultaneous increase in the prevalence of complications arising due to diabetes, and subsequently individuals were put on a greater number of diabetic medications for better glycaemic control. Diabetic individuals in the higher quintiles were also on higher doses of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers and on tight control of their cholesterol through statins (data not shown).

Table 1. Clinical Characteristics of patients in analysis

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Case</th>
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<td>691</td>
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<tr>
<td>Percentage Males(%)</td>
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<td>60.5</td>
<td>60.3</td>
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</tr>
<tr>
<td>Age at diabetes diagnosis (years)</td>
<td>59.3(12.3)</td>
<td>60.0(12.3)</td>
<td>59.1(12.3)</td>
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<td>-</td>
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<td>Age at CHF diagnosis (years)</td>
<td>67.4(11.2)</td>
<td>70.6(9.8)</td>
<td>66.5(11.4)</td>
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<tr>
<td>Hba1c (%)</td>
<td>7.7(1.3)</td>
<td>8.0(1.4)</td>
<td>7.6(1.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Number of Hba1c measures</td>
<td>18.7(13.7)</td>
<td>21.4(15.2)</td>
<td>18.0(13.1)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetic medication before CHF date:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>% Insulin</td>
<td>19.5</td>
<td>32.8</td>
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<td>% Metformin</td>
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<td>42.4</td>
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<td>% Sulphonylurea</td>
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<td>23.0</td>
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<tr>
<td>% TZD</td>
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<td>7.2</td>
<td>9.7</td>
<td>0.0391</td>
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Data expressed as mean (±SD) or %

CHF Incidence - The incidence of CHF occurring over the 8 years of study increased with subsequent increase in quintiles of HbA1c (see Table 2). On analyses, the adjusted hazard ratio of developing CHF (Q1 used as the reference group) increased progressively with increase in quintiles of HbA1c. On comparison of the quintiles the notable trend was an increase in incidence of CHF as the quintiles increased. The fifth quintile (Q5) had significantly increased incidence of developing CHF (risk adjusted HR: 2.56, 95% CI: 1.78 -3.69, p=3.9×10⁻⁷) and it was 2.5 times higher than in patients with the lowest HbA1c level of 6.5% or less (Q1). The adjusted hazard ratio of developing CHF for each 1% increase in HbA1c was 1.31 (95% CI 1.20-1.44, p=1.43×10⁻⁹).
Table 2: Independent Effect of HbA1c levels on CHF Incidence

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;6.5)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (6.5-&lt;7.2)</td>
<td>0.97</td>
<td>0.69-1.36</td>
<td>0.87</td>
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<tr>
<td>Q3 (7.2-&lt;7.9)</td>
<td>1.60</td>
<td>1.14-2.22</td>
<td>0.01</td>
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<tr>
<td>Q4 (7.9-&lt;8.6)</td>
<td>1.60</td>
<td>1.14-2.25</td>
<td>0.01</td>
</tr>
<tr>
<td>Q5 (≥8.6)</td>
<td>2.60</td>
<td>1.78-3.70</td>
<td>3.90×10⁻⁷</td>
</tr>
<tr>
<td>Number of HbA1c measures</td>
<td>1.04</td>
<td>1.03-1.05</td>
<td>2.95×10⁻²³</td>
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<tr>
<td>HbA1c Standard Deviation</td>
<td>1.04</td>
<td>0.87-1.24</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Quintile 1 is the reference group

**Mortality** - Over a period of 8 years of follow-up 211 patients died. The mean HbA1c level of the cohort was 7.9 ±1.4 % (see Table 3). The adjusted hazard ratios for death are shown in Table 4. Using Q1 as the reference the second quintile (Q2) had a significantly low mortality (risk adjusted HR: 0.96, 95% CI: 0.60 -1.52, p=0.86) when compared to the other 4 quintiles (see Table 4). The fourth quintile (Q4) was significantly the highest in mortality (risk adjusted HR: 1.82, 95% CI: 1.13 -2.95, p=0.01). The results clearly demonstrate a linear relationship between mortality and the quintiles of HbA1C levels. After adjustment the hazard ratio of death for each 1% increase in HbA1c increased by 1.24 fold (95% CI 1.09-1.42, p=0.0013).

Table 3: Clinical Characteristics of patients in analysis

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<th>Survived</th>
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<td>211</td>
<td>402</td>
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</tr>
<tr>
<td>Percentage Males (%)</td>
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<td>57.3</td>
<td>63.2</td>
<td>0.1527</td>
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<tr>
<td>Age at diabetes diagnosis (years)</td>
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<td>61.1(13.0)</td>
<td>58.7(11.6)</td>
<td>0.0210</td>
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<tr>
<td>Age at CHF diagnosis (years)</td>
<td>69.7(9.6)</td>
<td>71.9(9.9)</td>
<td>68.6(9.3)</td>
<td>0.0001</td>
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</tr>
<tr>
<td>Hba1c (%)</td>
<td>7.9(1.4)</td>
<td>7.9(1.4)</td>
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</tr>
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<td>Diabetic medication before CHF date:</td>
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<tr>
<td>% Insulin</td>
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<td>% Metformin</td>
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<td>% Sulphonylurea</td>
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<td>% TZD</td>
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<td>3.3</td>
<td>9.7</td>
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Data expressed as mean (± SD) or %
## Table 4: Independent Effect of HbA1c levels on mortality

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<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
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<tr>
<td>Mean HbA1c:</td>
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<tr>
<td>Q1 (&lt;6.5)</td>
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<tr>
<td>Q2 (6.5-&lt;7.2)</td>
<td>0.97</td>
<td>0.69-1.36</td>
<td>0.87</td>
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<tr>
<td>Q3(7.2-&lt;7.9)</td>
<td>1.60</td>
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<tr>
<td>Q4(7.9-&lt;8.6)</td>
<td>1.60</td>
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<td>0.01</td>
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<tr>
<td>Q5(≥8.6)</td>
<td>2.60</td>
<td>1.78-3.70</td>
<td>3.90×10⁻⁷</td>
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<tr>
<td>Number of HbA1c measures</td>
<td>1.04</td>
<td>1.03-1.05</td>
<td>2.95×10⁻²³</td>
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<tr>
<td>HbA1c Standard Deviation</td>
<td>1.04</td>
<td>0.87-1.24</td>
<td>0.68</td>
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*Quintile 1 is the reference group.

## Discussion

Although increased HbA1c levels have been associated with increased incidence of cardiovascular events in the population\(^{38}\), the association between elevated HbA1c levels and prognosis in diabetic individuals with established HF has been less analyzed. The analysis of HbA1c data collected in our study during the 8 year period showed that in type 2 diabetic individuals who have a diagnosis of symptomatic CHF, the HbA1c levels are strongly associated as independent risk factors for developing CHF and is also a strong independent risk factor for mortality. In this particular population for every 1% increase in HbA1c the risk of developing CHF was increased by 1.31 fold. In the cohort of patients with established CHF who were on treatment for diabetes, the relationship between mortality and increasing HbA1c quintiles was a linear relationship (See Figure 1). Diabetic individuals in the second quintile (Q2) (6.5 %< HbA1c≤7.2%) had the lowest mortality when compared with the other quintiles. Therefore, in this population, for every 1% increase in the level of HbA1c, the risk of CV death increased by 1.24 fold.
The findings from the study extend those from previous analyses of the association between rising HbA1c levels and CV events. The findings are also consistent with analyses in patients with newly diagnosed diabetes, in individuals with established diabetes, and in diabetic individuals with other associated CV risk factors. A study carried out on 2,412 HF patients (907 with diabetes) involved in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) study revealed that the adjusted risks of CV death, HF hospitalization and mortality increased progressively with rising HbA1c. Of note in this study that in both non diabetic and diabetic individuals with CHF; the HbA1c level is an independent risk factor for HF hospitalization, CV death and total mortality. A similar study examined the association between HbA1c and adverse outcomes in 5,815 diabetic individuals with established heart failure. Association between rising quintiles of HbA1c (Q1-Q5) and risk of CHF and death were studied. Of significant note in this study; the association between HbA1c and mortality in diabetic patients with symptomatic HF appeared U-shaped (Figure 2), with patients with a moderate glucose control at the lowest risk of death. (7.1% < HbA1c ≤7.8%). However studies that have been carried out have also shown a paradoxical relationship between HbA1c levels and mortality. In a study involving 123 diabetic individuals with systolic HF an inverse relationship between HbA1c and mortality was identified. In this particular study with advanced systolic HF an HbA1c >7% was associated with a lower mortality than an HbA1c level ≤7%.

Figure 1. Graph represents the proportion of patients who died at 8 year follow-up by HbA1c quintiles (compared to quintile 1): Error bars indicate the 95% confidence intervals.

Figure 2. Graph represents the proportion of patients who died at 2 year follow-up by quintiles (Q) of HbA1c. The graph demonstrates that the association between HbA1c and mortality in diabetic patients with symptomatic HF appears U-shaped, with patients with moderate glucose control at the lowest risk of death. (7.1% < HbA1c ≤7.8%). Global chi-square p=0.001. Error bars indicate the 95% confidence intervals.
The findings of our study adds to the growing body of evidence and confirms the existence of an independent link between increasing glycaemic levels and CV events and supports a complex relationship between HbA1c and mortality in diabetic patients with established HF. Reasons for this relationship however remain unclear.

The increased mortality associated with elevated HbA1c levels is most possibly due to multiple factors and includes both the direct and indirect effects caused by hyperglycemia. Adverse effects of elevated glucose levels include endothelial dysfunction, increased oxidative stress, protein kinase C activation and increased rates of atherosclerosis. Increased glycation end products due to hyperglycemia may also trigger off injurious processes such as myocardial stiffening and activation of cellular receptors for glycation end products that in turn lead to up-regulation of cellular signals subsequently causing cellular dysfunction. Elevated HbA1c levels may also cause an increased resistance to insulin with disturbance in cardiac metabolism, energy utilization in the insulin resistant myocardium and also activation of the sympathetic nervous system. Raised HbA1c levels could also be quite reflective of the individuals poor adherence to medication and in turn associated with poorer outcomes.

Current therapeutic management for HF focus on reduction of neurohumoral activity (e.g., use of ACE inhibitors, angiotensin receptor blockers, Beta blockers and aldosterone antagonists) or by increasing myocardial contractility (digoxin). Our data suggest that for improved clinical management it is worth studying glycaemic control as a method for reducing CHF related morbidity and mortality. However targeting a lower HbA1c level for diabetic patients with established CHF has also its consequences as evident in the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes). Intensive glycaemic control to achieve better HbA1c levels or near normal levels could also be a risk in diabetic individuals with CHF. The ACCORD trial consisted of diabetic patients with established cardiovascular disease being put on an intensive glycaemic control regime to achieve normal levels of HbA1c (<6%) to reduce the incidence of CV events as opposed to being on the standard therapeutic management (a target range of HbA1c from 7.0% to 7.9%). Results in this trial revealed an unexpected rise in mortality in the cohort assigned to intensive glycaemic control with no significant major reduction in CV events compared to mortality of patients assigned to the standard therapy. Future prospective studies are required to investigate the nature of optimum HbA1c levels in diabetic patients with HF as well as to define ideal treatment goals.

**Limitations**

Firstly the study is a retrospective study with the inherent limitations of this type of study design. Multivariable statistical models were used to adjust for heterogeneity amongst the HbA1c quintiles; however residual unmeasured confounding variables may remain. To assess the relationship between HbA1c and mortality; deaths were assumed to be of cardiovascular cause unless another cause was attributed. The relationship between HbA1c and progression of microvascular disease or complications of diabetes were not assessed. This should be the focus of further
studies. Inspite of these limitations, our data has several strengths. The large cohort size allows stratification of data by HbA1c levels to identify the complex relationship between HbA1c, development of CHF and mortality.

Clinical Implications
Our findings may have important clinical and public health implications. Our results suggest that tight glycaemic control may potentially reduce the incidence of heart failure and might be desirable to achieve levels of glycaemia to the normoglycaemic range as possible (i.e. HbA1c 7%). The potential benefit of tight glycaemic control should be weighed against existing barriers such as fear of hypoglycemia. The study of HbA1c variables is of importance for clinicians as both a prognostic tool and in clinical studies. As a prognostic tool it implies a possibility for intensive diabetic care; however the clinician should be aware of HbA1c values from previous encounters in addition to those measured currently when making the prognosis. The clinician should also be aware of the persistent effect of HbA1c on diabetic complications.

Conclusions
Our data suggests that glycaemic control is an independent risk factor for incident CHF in persons with type 2 diabetes. In diabetic patients with established CHF, poor glycaemic control is associated with significantly impaired survival and poorer CV outcomes. Analyses revealed a linear relationship between mortality and increasing HbA1c quintiles in diabetic patients. Our findings certainly have significant public health implications and future prospective studies should be carried out to investigate glucose lowering therapy and optimal HbA1c levels in HF patients.

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