



UNIVERSITY OF LEEDS

This is a repository copy of *Diabetes mellitus is associated with adverse structural and functional cardiac remodelling in chronic heart failure with reduced ejection fraction*.

White Rose Research Online URL for this paper:  
<http://eprints.whiterose.ac.uk/102072/>

Version: Accepted Version

---

**Article:**

Walker, AMN, Patel, PA, Rajwani, A et al. (7 more authors) (2016) Diabetes mellitus is associated with adverse structural and functional cardiac remodelling in chronic heart failure with reduced ejection fraction. *Diabetes and Vascular Disease Research*, 13 (5). pp. 331-340. ISSN 1479-1641

<https://doi.org/10.1177/1479164116653342>

---

© 2016, Author(s). This is an author produced version of a paper published in *Diabetes & vascular disease research*. Uploaded in accordance with the publisher's self-archiving policy.

**Reuse**

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

# **Diabetes mellitus is associated with adverse structural and functional cardiac remodelling in chronic heart failure with reduced ejection fraction**

Andrew MN Walker<sup>1</sup>, Peysh A Patel<sup>1</sup>, Adil Rajwani<sup>1</sup>, David Groves<sup>2,3</sup>,  
Christine Denby<sup>2,3</sup>, Lorraine Kearney<sup>1</sup>, Robert J Sapsford<sup>4</sup>, Klaus K Witte<sup>1</sup>,  
Mark T Kearney<sup>1</sup>, Richard M Cubbon<sup>1</sup>

<sup>1</sup> Leeds Institute of Cardiovascular and Metabolic Medicine, LIGHT laboratories, The University of Leeds, Clarendon Way, LS2 9JT, UK

<sup>2</sup> Department of Medical Physics and Clinical Engineering, Royal Liverpool University Hospital, Prescot St, Liverpool, Merseyside L7 8XP

<sup>3</sup> Department of Physics, University of Liverpool, Oxford Street Liverpool. Merseyside L69 7ZE

<sup>4</sup> Department of Cardiology, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Great George St., Leeds, LS1 3EX, UK

Corresponding author:

Dr Richard M Cubbon<sup>1</sup>

British Heart Foundation Intermediate Clinical Fellow

E-mail: [r.cubbon@leeds.ac.uk](mailto:r.cubbon@leeds.ac.uk)

Tel: +441133430785

Fax: +441133437738

## **Abstract**

Background: Diabetes mellitus (DM) is associated with an increased risk of death and hospitalisation in patients with chronic heart failure (CHF). Better understanding of potential underlying mechanisms may aid the development of DM-specific CHF therapeutic strategies.

Methods: Prospective observational cohort study of 628 patients with CHF associated with left ventricular (LV) systolic dysfunction receiving contemporary evidence-based therapy. Indices of cardiac structure and function, along with symptoms and biochemical parameters, were compared in patients with and without DM at study recruitment and one year later.

Results: Patients with DM (24.2%) experienced higher rates of all-cause (Hazard ratio 2.3 [95% CI 1.8-3.0]) and CHF-specific mortality and hospitalisation despite comparable pharmacological and device-based therapies. At study recruitment, patients with DM were more symptomatic, required greater diuretic doses, and more frequently had radiologic evidence of pulmonary oedema, despite higher LV ejection fraction. They also exhibited echocardiographic evidence of increased LV wall thickness and pulmonary arterial pressure. DM was associated with reduced indices of heart rate variability, and increased heart rate turbulence. During follow-up, patients with DM experienced less beneficial LV remodelling, and greater deterioration in renal function.

Conclusions: DM is associated with features of adverse structural and functional cardiac remodelling in patients with CHF.

### **Key Words:**

Diabetes Mellitus, Chronic Heart Failure, Aetiology, Remodelling

## **Abbreviations and Acronyms**

ACEi – Angiotensin converting enzyme inhibitor

AHRR – Ambulatory heart rate range

ARB - Angiotensin II receptor blocker

CHF – Chronic heart failure

COPD – Chronic obstructive pulmonary disease

CRT – Cardiac resynchronisation therapy

CVA – Cerebrovascular accident

DM – Diabetes mellitus

ECG - Electrocardiogram

ECHO – Echocardiography

eGFR – Estimated glomerular filtration rate

HbA1c – Glycosylated haemoglobin

HRT – Heart rate turbulence

ICD – Implantable cardioverter defibrillator

IHD – Ischaemic heart disease

LV – Left ventricular

LVEDD – Left ventricular end diastolic dimension

LVESD – Left ventricular end systolic dimension

NYHA – New York Heart Association

PA – Pulmonary artery

PVC – Premature ventricular complex

SCD – Sudden cardiac death

SDNN – Standard deviation of normal to normal RR intervals

SEM – Standard error of the mean

WCC – White cell count

## **Introduction**

The prevalence of DM continues to climb at an exponential rate, with current forecasts projecting more than 500 million sufferers by 2035<sup>1</sup>. Given the substantial cardiovascular risk associated with DM, it is likely that co-morbid diabetes will become an increasingly common challenge for all physicians managing cardiovascular disease, and vice versa. Our work<sup>2</sup>, and that of others<sup>3, 4</sup>, has highlighted the significantly increased risk of death and hospitalisation in patients with chronic heart failure and DM. Despite this knowledge, our understanding of what mediates the association between DM and adverse CHF outcomes remains somewhat limited. Previous studies have implicated a diverse array of pathophysiological factors, including unfavourable left ventricular (LV) remodelling<sup>5</sup>, cardiac autonomic dysfunction<sup>6</sup>, and DM-related comorbidity<sup>7</sup>. However, many studies have addressed these issues in isolation, and so we set out to provide a detailed assessment of these factors, along with their change over time, in patients receiving contemporary CHF therapy.

## **Methods**

We conducted a prospective cohort study of 628 unselected patients with CHF associated with LV systolic dysfunction, with the specific aim of examining prognostic factors in patients receiving contemporary therapy. Recruitment was carried out in the cardiology outpatient clinics of 4 United Kingdom hospitals between June 2006 and January 2009 with the ethical approval of Leeds West Research Ethics Committee; all patients provided written informed consent. As previously described<sup>8</sup> patients were eligible for inclusion if they were ambulant outpatients with stable clinical signs and symptoms of CHF for 3 months, with a left ventricular ejection fraction of  $\leq 45\%$  on transthoracic echocardiography.

### Baseline and follow-up assessment

During the study recruitment clinic, details of past medical history were recorded and physical examination was conducted. Functional status was assessed using the New York Heart Association classification. Diabetes was defined at study recruitment on the basis of previous diagnosis and/or

treatment with hypoglycaemic agents. Ischaemic aetiology of CHF was determined by the recruiting physician on the basis of detailed history (of risk factors for atherosclerosis, anginal symptoms or prior myocardial infarction), electrocardiograph (presence of Q waves), echocardiogram (LV regional wall motional abnormalities conforming to a typical coronary distribution), and non-invasive assessment of functionally significant coronary disease or invasive coronary angiography, as clinically indicated. Doses of diuretic therapy, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and beta-blockers were collected at recruitment. As previously reported,<sup>2</sup> doses of loop diuretic, angiotensin converting enzyme inhibitor (or angiotensin receptor blocker), and beta-adrenoreceptor antagonist, were expressed as the equivalent dose of furosemide, ramipril, and bisoprolol, respectively. Receipt of cardiac resynchronisation therapy (CRT) or implantable cardioverter-defibrillator (ICD) was assessed during the 6-month period after recruitment.

All patients underwent resting 12-lead electrocardiographs (ECGs), ambulatory 24-hour ECGs, echocardiography (ECHO), chest radiographs, and blood testing for measurement of full blood count, urea and electrolytes, plasma creatinine and random glucose. All biochemical analyses were conducted in the National Health Service chemical pathology laboratories of the relevant recruiting centres. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease method. HbA1c was measured only in people with known diabetes.

All patients were invited to attend a follow-up clinic approximately 12 months later, where a repeat clinical assessment was made, prior to conducting blood testing, resting and ambulatory electrocardiography, and echocardiography, as outlined above.

### Echocardiography

Two-dimensional transthoracic echocardiography was performed in all patients and reported by local cardiac sonographers, blinded to patient characteristics, according to British Society of Echocardiography

recommendations; left ventricular ejection fraction was calculated according to the Simpson's biplane method.

#### Ambulatory electrocardiography

Twenty-four hour ambulatory ECGs (Lifecard CF, Spacelabs Healthcare Ltd, Hertford, UK) were obtained during normal, unrestricted, out of hospital activity as previously reported<sup>9</sup>. Recordings were analysed with a Spacelabs Sentinel system by independent technical staff blinded to patient characteristics. Non-sustained ventricular tachycardia was defined as the presence of 3 or more consecutive ventricular complexes at a rate of  $\geq 120$  beats per minute, with no evident AV concordance. Atrial arrhythmias (flutter or fibrillation) were defined as present if sustained for  $>30$  seconds.

Each 24 hour ECG recording was manually edited to exclude any incorrectly identified R waves and include any unidentified R waves as determined at the automatic processing stage. Ambulatory heart rate range (AHRR) was defined as maximum minus minimum heart rate during the 24-hour period of analysis, as previously described<sup>9</sup>. For standard deviation of normal to normal (SDNN) analyses, the standard Delmar Reynolds / Spacelabs RR interval exclusion criteria were then applied to the manually edited records. Specifically, RR intervals were excluded if: RR  $>2.0$  seconds; RR  $>3$  standard deviations of the local 20 min interval; RR intervals  $<300$ ms; RR  $>120\%$  of previous RR; RR  $<80\%$  of previous RR. SDNN was then determined using the proprietary Pathfinder software.

Heart rate turbulence was assessed using a Quantec data analysis workstation. The Turbulence analysis followed the method described by Grimm<sup>10</sup> and Schmidt<sup>11</sup> with the mean HRT slope and mean HRT onset calculated from all valid PVCs. The HRT onset was defined as the difference between the mean of the first two sinus RR intervals preceding the PVC and the mean of the subsequent two sinus RR intervals, expressed as a percentage. The HRT slope is defined as the maximum positive value of the slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after PVC.



If more than one positive slope occurred in this period the first positive slope was accepted. The value of HRT slope is expressed in milliseconds per RR interval. PVC were excluded if they failed to satisfy the following criteria: (1) The PVC should occur in isolation with normal sinus beat occurring for at least 12 beats before the PVC and for at least 20 beats after the PVC. (2) The PVC RR maximum and minimum RR intervals should be greater than 20% and less than 20%, respectively, of the mean of the five preceding normal sinus RR intervals. (3) All RR intervals for the 12 beats before the PVC and 20 beats after the PVC should be greater than 300 ms and less than 2000 ms in duration. (4) All normal sinus RR intervals 12 beats before the PVC and 20 beats after the PVC should be within 20% of the mean RR interval of all beats in the 24-h ECG recording. (5) Any change in adjacent normal sinus RR intervals, 12 beats before the PVC and 20 beats after the PVC, should not be greater than 200ms.

#### Classification of mortality and hospitalisation

All patients were registered with the United Kingdom Office of Population Censuses and Surveys, which provided details of any participant death, including location and date; data was available for all participants. All deaths were evaluated by at least two senior physicians, who reviewed death certificates, autopsy findings, and hospital and general practitioners' records; where these physicians felt insufficient information was available, the mode of death was deemed unclassifiable. Mode of death was classified according to our previously published definitions<sup>12</sup>. Briefly, these are: 1) sudden cardiac, if occurring within 1 hour of a change in symptoms or during sleep, or while the patient was unobserved; 2) progressive HF, if death occurred after a documented period of symptomatic or haemodynamic deterioration; 3) other cardiovascular death (e.g. stroke or pulmonary embolism), if not occurring suddenly or in association with progression of HF; and, 4) non-cardiovascular, if none of the above.

Hospitalisation was assessed with the use of institutional clinical event databases detailing all admissions in recruiting centres. Heart failure-related hospitalisation was defined as a new onset or worsening of signs and

symptoms of heart failure, with evidence of fluid overload, requiring at least 24 hours overnight hospitalisation and the use of intravenous diuretics.

### Statistical analysis

Continuous data are presented as mean (and standard error of the mean [SEM]); categorical data are shown as number (percentage). All statistical analyses were performed using IBM SPSS statistics version 21 (IBM Corporation, Armonk, NY, USA). Groups were compared using two-sided Student t-tests for continuous data and two-sided Pearson  $\chi^2$  tests for categorical data. Survival of groups was compared with log-rank tests, and one-year hospitalisation compared using binary logistic regression. Statistical significance was defined as  $p < 0.05$ .

## **Results**

### Clinical Characteristics

628 unselected patients with CHF associated with left ventricular (LV) systolic dysfunction were recruited, of whom 152 (25%) had DM. 148 (97%) of these patients had type 2 diabetes, and diabetes treatment was as follows: diet only in 27.6% (n=42), sulphonylureas in 32.2% (n=49), metformin in 32.9% (n=50), insulin in 28.3% (n=43), and thiazolelidinediones in 3.3% (n=5). The baseline characteristics of these individuals are shown in Table 1. Whilst the age-sex distribution of patients with diabetes was similar to those without, it is clear that ischaemic heart disease, cerebrovascular disease, and systemic hypertension were more commonly associated with DM. The systolic blood pressure and body mass index of patients with DM were also significantly higher. Notably, renal function was worse in patients with DM, and there was a trend toward a greater prevalence of comorbid chronic obstructive pulmonary disease. An adverse haematological and biochemical profile was evident in those with DM, with an elevated white cell count, lower haemoglobin and serum sodium concentration compared to those without the condition. Importantly, those with diabetes had a greater symptom burden at baseline with significantly higher NYHA class than those without the condition. Patients with DM were also more likely to have radiographic evidence of pulmonary oedema.

### Baseline Echocardiographic Findings

Patients with diabetes had a significantly greater LV ejection fraction on transthoracic echocardiography at baseline, despite their poorer NYHA status. Structurally, they had significantly increased LV mean wall thickness versus patients without DM, although the LV end-diastolic dimension (LVEDD) and LV end-systolic dimension (LVESD) were similar in both groups. No differences were noted in Doppler measures of LV inflow (E wave velocity and E/A ratio), but as noted in our discussion of limitations, these are suboptimal indices of LV diastolic function. A higher estimated PA systolic pressure was also seen in those with DM. There was a significant, but weak, correlation between baseline LV wall thickness and systolic blood pressure (SBP) in patients without DM, although there was no such correlation in those with DM (see Figure 1). Furthermore, HbA1c did not correlate with LV mean wall thickness.

### Baseline Electrocardiographic Assessment

Patients with diabetes had a lower resting heart rate at baseline, although other 12-lead ECG parameters did not differ. On 24-hour ECG recording, the prevalence of atrial and ventricular arrhythmias was the same in both groups. In contrast, AHRR and SDNN, along with HRT onset and slope, were lower in patients with diabetes (Table 1). Basal AHRR was calculated from all 574 24-hour ECGs (137 with DM, 437 without DM), and negatively correlated with HbA1c (see Figure 1). As outlined in the methods section, it is not possible to derive SDNN and HRT from ECG recordings with prolonged periods of non-sinus rhythm. SDNN was derived from 202/574 patient 24 hour ECGs in total, (52 with DM, 150 without DM) and 221/574 24 hour ECGs were analysable for HRT (55 with DM, 166 without DM).

### Pharmacological and device therapy

As shown in Table 2, patients with DM were equally likely to receive evidence-based secondary prevention pharmacotherapy for CHF, and the prescribed doses were also similar. Moreover, DM was not associated with altered use of cardiac resynchronisation therapy or implantable cardioverter-defibrillators

(ICDs). However, patients with DM required significantly larger doses of loop diuretic therapy, and were more likely to receive combined loop and thiazide diuretic therapy.

#### One-year follow-up clinical data and hospitalisation

408 of the original 628 patients (65%) were reviewed after one year (mean [SEM] 354 [7.1] days); the remainder either died in the interim or failed to attend their appointment. At one year following enrolment patients with diabetes remained more symptomatic, although there was no widening of the gap in NYHA class. The reduction in heart rate and blood pressure was comparable in both groups, and haematological and biochemical parameters were also equivalent (Table 3). This is in keeping with the data on follow-up pharmacological treatment for CHF (see Table 4) which remained comparable between the two groups, although loop diuretic doses were still higher in those with diabetes (mean 73mg furosemide equivalent dose versus 48mg for those without DM  $P<0.0001$ ). On echocardiography there was significantly less improvement in LVEF in those with diabetes, although the change in other variables was similar.

During the first year of follow-up, 130 patients were hospitalised, of whom 88 had a principal cardiovascular cause of hospitalisation, and 44 a CHF-related hospitalisation. The relative risk associated with DM was: 1.68 (95% confidence interval 1.1-2.57;  $p=0.016$ ) for any hospitalisation, 2.12 (1.32-3.42;  $p=0.002$ ) for cardiovascular hospitalisation, and 2.58 (1.38-4.83;  $p=0.003$ ) for CHF-related hospitalisation.

#### Mortality

After a mean follow-up period of 4.5 (SEM 0.1) years, 250 (39.8%) deaths occurred; of these, there were 95 progressive CHF related deaths, 43 sudden deaths, 14 other cardiovascular deaths, 92 non-cardiovascular deaths, and 6 non-classifiable deaths (Figure 2). In univariate analysis the relative risk associated with DM was: 2.31 (1.78-2.98;  $p<0.001$ ) for overall death, 2.14 (1.4-3.27;  $p<0.001$ ) for progressive CHF death, and 4.16 (2.28-7.57;  $p<0.001$ ) for sudden death. Multivariate analysis (Table 5) showed that DM is an

independent risk factor for all-cause mortality in CHF when other established prognostic factors are included, although with a lower hazard ratio than in univariate analysis.

## **Discussion**

Our investigation provides a number of important and novel insights into how diabetes alters the heart failure phenotype, potentially offering explanations for the increased symptoms, hospitalisation rates and mortality of this group. Firstly, we have shown that diabetes is more frequently associated with radiologic evidence of pulmonary oedema, in spite of greater left ventricular ejection fraction at baseline. This may reflect greater myocardial thickness in those with diabetes, which can increase LV filling pressures, as is supported by greater pulmonary artery systolic blood pressure on echocardiography. After one year of contemporary evidence-based heart failure therapy, improvements in left ventricular ejection fraction were lower in those with diabetes, and they required larger diuretic doses. Secondly, we have shown that 3 distinct measures of heart rate variability all exhibit unfavourable profiles in people with diabetes. Finally, we explored factors underlying our observations, showing HbA1c correlated with some markers of heart rate variability, although neither HbA1c, nor systolic blood pressure correlated with LV wall thickness in those with diabetes..

### CHF phenotype in association with diabetes

Our results provide further evidence that DM has a profound effect on outcomes in patients with CHF. It is associated with a doubling of the risk of cardiovascular and CHF-related hospitalisation and in cardiovascular and all-cause mortality. Moreover, important differences in mode of death were apparent, with a particular excess in the risk of sudden cardiac death in patients with diabetes. These findings are consistent with those from other studies, but we also add important complementary data, documenting associated differences in cardiac structure and function, and poorer response to optimal CHF management. Furthermore, our data demonstrate a higher prevalence of comorbidities in those with DM and CHF, and so the influence of multi-morbidity on the prognosis of these patients may be significant, as

supported by other studies<sup>7, 13</sup>. However, our multivariate analysis supports DM as an independent risk factor for mortality in CHF even when other important comorbidities are taken into account.

Our data also highlight an adverse haematological and biochemical profile of heart failure patients with diabetes, including higher WCC, lower haemoglobin, lower serum sodium concentration, and lower eGFR compared with non-DM patients; all are established adverse prognostic factors in CHF<sup>14</sup>. The elevated WCC may demonstrate the chronic low-grade inflammation known to occur in insulin resistant states<sup>15</sup> whereas low haemoglobin may represent anaemia of chronic disease, or in the context of hyponatraemia may indicate fluid overload.

#### LV structure and function

Interestingly, despite poorer functional capacity at baseline, patients with DM had a significantly greater LV ejection fraction on echocardiography, indicating that LV systolic impairment is less well-tolerated in this group. This may in part be explained by their significantly increased mean LV wall thickness, which is often associated with greater filling pressures. Indeed, this assertion is supported by the elevated PA systolic pressures seen in the group with DM. Given the LVEDD and LVESD were similar in both groups of patients, the increased LV mean wall thickness in those with DM indicates concentric remodelling. Somewhat unexpectedly, LV mean wall thickness did not correlate with systolic blood pressure in people with diabetes, although a weak, but significant correlation was noted in people without diabetes. Furthermore, HbA1c did not correlate with LV mean wall thickness in patients with diabetes. Importantly, we present the novel finding that DM was associated with less favourable LV remodelling after contemporary evidence-based CHF treatment for one year, indicated by significantly less improvement in ejection fraction.

Importantly, there is evidence for abnormal LV remodelling in patients with DM after AMI<sup>16</sup>. Our data further inform the evidence base for adverse structural and functional remodelling as potential contributors to the poor

outcomes seen in patients with DM and CHF. Moreover, our data indicate that current evidence-based treatments for CHF appear not to give comparable benefit to patients with DM in terms of improvement in ejection fraction or in clinical outcomes. The development of DM-specific therapies to limit pathological remodelling in these patients is therefore of considerable importance.

### Electrocardiographic insights

Resting heart rate gives important prognostic information in people with CHF, and its reduction with pharmacotherapy is associated with improved outcomes<sup>17, 18</sup>. As such, it is interesting that the heart rate was lower in those with DM at baseline. Our findings from 24-hour ECG analyses show important differences in heart rate variability and heart rate turbulence in patients with diabetes. These indices reflect autonomic tone, and have been associated with poorer outcomes in patients with CHF<sup>19-21</sup>. The mechanism for this is unclear, although it may indicate a higher predisposition to sudden cardiac death (SCD) in these patients. Previous work from our group<sup>2</sup> has shown that SCD remains a common cause of mortality in DM patients with CHF (reviewed in <sup>22</sup>), in contrast to those without diabetes in whom this outcome has become far less frequent over the last 15 years<sup>12</sup>. In this study we also note an excess of SCD in patients with diabetes, despite comparable use of beta-blockers and ICDs. The usefulness of HRT and SDNN is limited in CHF cohorts, given they cannot be derived in those with non-sinus rhythm, which may affect over 50% of this population<sup>23</sup>. AHRR, which can be derived irrespective of rhythm, provides complementary data, which is associated with mode-specific death and hospitalisation in those with CHF<sup>9</sup>. Interestingly, there was a weak, but significant, inverse correlation between AHRR and HbA1c in patients with diabetes, although the factors underlying this relationship remain unclear. Overall, our data support the presence of significant neurohumoral and electrophysiological abnormalities in patients with DM and CHF, which are likely to contribute to their excess risk of mortality and hospitalisation. Further understanding of the mechanisms which drive these abnormalities, along with improved screening tools to detect those

at risk (particularly of SCD) will aid the development of DM-specific treatment strategies for CHF.

### Limitations

Whilst our work provides important insights into the factors that may contribute to the disparity in outcomes between CHF patients with and without diabetes, it is important to acknowledge its limitations. The cohort size is relatively small in comparison with large scale randomised clinical trial populations. However, this has allowed us to phenotype the study population more extensively than would normally be possible in larger trials, and include data such as HRT and SDNN in our analyses. The observational nature of our study means we are unable to show causation in the associations we have demonstrated, and therefore further work is warranted to define those factors which specifically contribute to poorer outcomes in CHF patients with diabetes. Unfortunately, our data on LV diastolic function is limited as patients were recruited before tissue Doppler imaging techniques were widely available. Although we present data on E wave velocity and E/A ratio, a high proportion of this cohort have atrial fibrillation or pacemakers, meaning these individuals are excluded from this analysis. Moreover, E/A ratio may be misleading in the case of pseudonormalisation noted in some cases of diastolic dysfunction, which may account for the observed lack of difference between patients with and without DM. Thorough characterisation of diastolic function in future studies will be important to investigate its prevalence and impact on mortality in patients with DM and CHF. Finally, as our cohort assessed patients with an ejection fraction of  $\leq 45\%$ , we have no data for those with chronic heart failure with preserved ejection fraction.

### Conclusion

Diabetes mellitus is associated with important differences in the structural and functional remodelling associated with chronic heart failure, which may explain its adverse prognostic impact. Future work is needed to define the mechanisms underlying these observations and guide the development of DM-specific CHF therapies.



## **Funding Acknowledgements and Disclosures**

The authors would like to thank Spacelabs Healthcare Ltd (UK) for the free and unrestricted donation of a development ECG analysis system used to determine the HRV parameters in this project. This study was funded by the British Heart Foundation: project grant PG/08/020/24617. AMNW and PAP are supported by British Heart Foundation (BHF) Clinical Research Training Fellowships. RMC is a BHF Intermediate Clinical Research Fellow and MTK is a BHF Professor of Cardiology. KKW is a National Institute for Health Research Clinician Scientist. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

## References

1. IDF Diabetes Atlas. 2013 ed. Brussels, Belgium: International Diabetes Federation, 2013.
2. Cubbon RM, Adams B, Rajwani A, et al. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology. *Diabetes & vascular disease research : official journal of the International Society of Diabetes and Vascular Disease*. 2013; 10: 330-6.
3. Ushigome R, Sakata Y, Nochioka K, et al. Temporal Trends in Clinical Characteristics, Management and Prognosis of Patients With Symptomatic Heart Failure in Japan- Report From the CHART Studies. *Circulation journal : official journal of the Japanese Circulation Society*. 2015.
4. Cavender MA, Steg PG, Smith SC, Jr., et al. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation*. 2015; 132: 923-31.
5. Shah AM, Hung CL, Shin SH, et al. Cardiac structure and function, remodeling, and clinical outcomes among patients with diabetes after myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both. *American heart journal*. 2011; 162: 685-91.
6. Paolillo S, Rengo G, Pagano G, et al. Impact of diabetes on cardiac sympathetic innervation in patients with heart failure: a 123I meta-iodobenzylguanidine (123I MIBG) scintigraphic study. *Diabetes care*. 2013; 36: 2395-401.
7. Ekundayo OJ, Muchimba M, Aban IB, Ritchie C, Campbell RC and Ahmed A. Multimorbidity due to diabetes mellitus and chronic kidney disease and outcomes in chronic heart failure. *The American journal of cardiology*. 2009; 103: 88-92.
8. Cubbon RM, Woolston A, Adams B, et al. Prospective development and validation of a model to predict heart failure hospitalisation. *Heart*. 2014; 100: 923-9.
9. Cubbon RM, Ruff N, Groves D, et al. Ambulatory heart rate range predicts mode-specific mortality and hospitalisation in chronic heart failure. *Heart*. 2015.
10. Grimm W, Sharkova J, Christ M, Schneider R, Schmidt G and Maisch B. Heart rate turbulence following ventricular premature beats in healthy controls. *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc*. 2003; 8: 127-31.
11. Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet*. 1999; 353: 1390-6.
12. Cubbon RM, Gale CP, Kearney LC, et al. Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras. *Circulation Heart failure*. 2011; 4: 396-403.
13. Ritchie C, Ekundayo OJ, Muchimba M, et al. Effects of diabetes mellitus in patients with heart failure and chronic kidney disease: a propensity-matched study of multimorbidity in chronic heart failure. *International journal of cardiology*. 2009; 134: 330-5.

14. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006; 113: 1424-33.
15. Aroor AR, McKarns S, Demarco VG, Jia G and Sowers JR. Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance. *Metabolism: clinical and experimental*. 2013; 62: 1543-52.
16. Shah AP, Nongthomba U, Kelly Tanaka KK, et al. Cardiac remodeling in *Drosophila* arises from changes in actin gene expression and from a contribution of lymph gland-like cells to the heart musculature. *Mechanisms of development*. 2011; 128: 222-33.
17. Bohm M and Reil JC. Heart rate: surrogate or target in the management of heart failure? *Heart*. 2013; 99: 72-5.
18. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010; 376: 875-85.
19. Stein PK and Deedwania P. Usefulness of abnormal heart rate turbulence to predict cardiovascular mortality in high-risk patients with acute myocardial infarction and left ventricular dysfunction (from the EPHEBUS study). *The American journal of cardiology*. 2009; 103: 1495-9.
20. Moore RK, Groves DG, Barlow PE, et al. Heart rate turbulence and death due to cardiac decompensation in patients with chronic heart failure. *European journal of heart failure*. 2006; 8: 585-90.
21. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation*. 1998; 98: 1510-6.
22. Walker AM and Cubbon RM. Sudden cardiac death in patients with diabetes mellitus and chronic heart failure. *Diabetes & vascular disease research : official journal of the International Society of Diabetes and Vascular Disease*. 2015.
23. Huikuri HV, Makikallio T, Airaksinen KE, Mitrani R, Castellanos A and Myerburg RJ. Measurement of heart rate variability: a clinical tool or a research toy? *Journal of the American College of Cardiology*. 1999; 34: 1878-83.

**Table 1: Baseline Characteristics**

	No DM (n=476)	DM (n=152)	p value
<u>Demographics:</u>			
Age (years)	66.8 (0.6)	68.3 (0.8)	0.15
Male sex (%[n])	72.5 (345)	77.6 (118)	0.21
<u>Medical history:</u>			
Ischaemic aetiology (%[n])	59 (275)	82.6 (123)	<0.001
PMH of CVA (%[n])	6.7 (32)	13.8 (21)	0.006
PMH of COPD (%[n])	10.7 (51)	15.8 (24)	0.093
Active malignancy (%[n])	6.7 (32)	3.3 (5)	0.12
PMH of hypertension (%[n])	26.3 (125)	38.8 (59)	0.003
<u>Symptoms and haemodynamics:</u>			
BMI (Kg/m <sup>2</sup> )	27.5 (0.3)	30.1 (0.6)	<0.001
NYHA class (%[n])			<0.001
I	24.6 (117)	9.3 (14)	
II	41.9 (199)	41.1 (62)	
III	31.2 (148)	46.4 (70)	
IV	2.3 (11)	3.3 (5)	
Systolic BP (mmHg)	120.7 (1)	125.4 (1.9)	0.028
Diastolic BP (mmHg)	72 (0.6)	70.9 (1.1)	0.35
Heart rate (bpm)	74 (0.9)	70.7 (1.3)	0.039
<u>ECG data:</u>			
PR interval (ms)	175.8 (2.6)	182.2 (4.5)	0.22
QRS interval (ms)	121.9 (1.5)	121.2 (2.4)	0.82
QTc interval (ms)	450.3 (1.7)	450.8 (3.1)	0.89
<u>Haematology and biochemistry:</u>			
Haemoglobin (g/dl)	14 (0.1)	13.2 (0.1)	<0.001
White cell count (x10 <sup>9</sup> /l)	8 (0.1)	8.7 (0.4)	0.01
Platelets (x10 <sup>9</sup> /l)	257 (3)	249 (7)	0.27
Sodium (mmol/l)	139.5 (0.2)	138.6 (0.3)	0.008
Potassium (mmol/l)	4.5 (0.02)	4.5 (0.04)	0.22

eGFR (ml/Kg/1.73m <sup>2</sup> )	54.4 (0.7)	50 (1.4)	0.005
ALT (iu/l)	27.6 (1.3)	27.4 (1.5)	0.92
Albumin (g/l)	42.7 (0.2)	42.2 (0.3)	0.11
LDL cholesterol (mmol/l)	2.6 (0.1)	2.1 (0.2)	0.09
<i><u>Imaging data:</u></i>			
Radiologic pulmonary oedema			
(%[n])	21.8 (99)	35 (49)	0.002
LVEDD on echo (mm)	58.8 (0.5)	58.4 (0.8)	0.68
LVESD on echo (mm)	49.3 (0.5)	48.3 (0.9)	0.32
LV ejection fraction on echo (%)	30.7 (0.4)	32.9 (0.7)	0.011
LV mean wall thickness on echo			
(mm)	10.3 (0.1)	10.7 (0.2)	0.031
E wave velocity on echo (m/s)	0.84 (0.02)	0.91 (0.03)	0.09
E/A ratio on echo	1.28 (0.06)	1.39 (0.09)	0.34
PA systolic pressure on echo			
(mmHg)	34 (0.8)	39.3 (1.8)	0.004
<i><u>24hr ECG data:</u></i>			
Any episodes of AF (%[n])	29.6 (131)	27.9 (39)	0.7
Non-sustained VT (%[n])	39.3 (173)	35 (49)	0.36
Heart rate range (bpm)	51.8 (1)	41.8 (1.2)	<0.001
SDNN (ms)	104.8 (2.8)	91.6 (4.3)	0.015
HRT onset (%)	-1.1 (0.2)	-0.2 (0.2)	0.001
HRT slope (ms per RR interval)	9.6 (0.6)	5.9 (0.5)	<0.001

DM: Diabetes mellitus; PMH: previous medical history; CVA: cerebrovascular accident; COPD: chronic obstructive pulmonary disease; BMI: body mass index; NYHA: New York Heart Association; BP: blood pressure; eGFR: estimated glomerular filtration rate; ALT: alanine aminotransferase; LDL: low density lipoprotein; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LV: left ventricle; PA: pulmonary artery; AF: atrial fibrillation; VT: ventricular tachycardia; SDNN: standard deviation of normal to normal; HRT: heart rate turbulence



**Table 2: Baseline Treatment**

	<b>No DM (n=476)</b>	<b>DM (n=152)</b>	<b>p value</b>
ACEi/ARB prescription (%[n])	88.4 (418)	86.8 (131)	0.6
Ramipril equivalent dose (mg)	4.9 (0.2)	5.1 (0.3)	0.63
Beta-blocker prescription (%[n])	80.1 (379)	76.2 (115)	0.3
Bisoprolol equivalent dose (mg)	3.3 (0.1)	3.2 (0.2)	0.76
MRA prescription (%[n])	39.1 (185)	47 (71)	0.085
Furosemide equivalent dose (mg)	49.3 (2.3)	75.5 (4.7)	<0.001
Thiazide and loop diuretic use (%[n])	1.3 (6)	7.9 (12)	<0.001
CRT implant (%[n])*	23.1 (110)	25.7 (39)	0.52
ICD implant (% [n])*	13 (62)	13.8 (21)	0.8

\* Up to 6 months after recruitment

ACEi: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; MRA: mineralocorticoid receptor antagonist; CRT: cardiac resynchronisation therapy; ICD: implantable cardioverter-defibrillator

**Table 3: Change in Clinical Variables at 1 Year**

	No DM (n=310)	DM (n=98)	p value
<u>Symptoms and haemodynamics:</u>			
Worsening NYHA class (%[n])	14.7 (45)	11.3 (11)	0.41
Systolic BP (mmHg)	-1 (1)	-4.6 (1.7)	0.071
Diastolic BP (mmHg)	-0.1 (0.6)	-2.1 (1)	0.085
Heart rate (bpm)	-2.4 (0.7)	-2.7 (1.1)	0.85
<u>Haematology and biochemistry:</u>			
Haemoglobin (g/dl)	-0.4 (0.1)	-0.3 (0.1)	0.44
White cell count (x10 <sup>9</sup> /l)	0.5 (0.7)	-0.1 (0.3)	0.59
Platelets (x10 <sup>9</sup> /l)	1.7 (3.3)	-4.1 (5.5)	0.37
Sodium (mmol/l)	-0.4 (0.2)	0.2 (0.3)	0.078
Potassium (mmol/l)	0.05 (0.03)	0.04 (0.07)	0.91
eGFR (ml/Kg/1.73m <sup>2</sup> )	-1.2 (0.5)	-3 (1.1)	0.11
<u>Imaging data:</u>			
LVEDD on echo (mm)	-2.3 (0.4)	-1.5 (0.7)	0.34
LVESD on echo (mm)	-3.8 (0.5)	-2.1 (0.9)	0.12
LV ejection fraction on echo (%)	7.6 (0.7)	4.1 (1.1)	0.007
LV mean wall thickness on echo (mm)	0.01 (0.13)	-0.12 (0.25)	0.63
<u>24hr ECG data:</u>			
Ambulatory heart rate range (bpm)	-2.4 (0.7)	-2.7 (1.1)	0.85

DM: Diabetes mellitus; NYHA: New York Heart Association; BP: blood pressure; eGFR: estimated glomerular filtration rate; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LV: left ventricle



**Table 4: Change in Treatment at 1 Year**

	<b>No DM</b>	<b>DM</b>	<b>p value</b>
Ramipril equivalent dose (mg)	1.1 (0.2)	1.2 (0.4)	0.9
Bisoprolol equivalent dose (mg)	2 (0.2)	1.2 (0.4)	0.06
Furosemide equivalent dose (mg)	-0.1 (2.6)	0.4 (5.6)	0.94

**Table 5: Multivariate predictors of all-cause mortality**

	HR	95% CI of HR		p value	Wald
		Low	High		
Diabetes	1.64	1.17	2.31	0.005	8
Ischaemic aetiology	1.51	0.98	2.34	0.06	3.5
NYHA class (vs. I)				0.006	12.4
II	2	1.12	3.56		
III	2.51	1.41	4.46		
IV	3.85	1.53	9.73		
Haemoglobin (per g/dl)	0.83	0.75	0.92	<0.001	12.6
Male sex	1.87	1.24	2.81	0.003	9
Age (per year)	1.05	1.03	1.07	<0.001	22.6
eGFR (per ml/Kg/1.73m <sup>2</sup> )	1.009	0.998	1.022	0.12	2.4
Sodium (per mmol/L)	0.97	0.93	1.02	0.2	1.6
Prior CVA	0.8	0.47	1.38	0.43	0.6
Prior hypertension	1.01	0.71	1.44	0.95	0
Heart rate (per bpm)	1.015	1.005	1.025	0.003	9
LVEF (per %)	0.995	0.977	1.014	0.6	0.3
LV mean wall thickness (per mm)	1.02	0.94	1.11	0.64	0.2
Ambulatory heart rate range (per bpm)	0.989	0.979	0.999	0.03	4.6

NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate; CVA: cerebrovascular accident; LVEF: left ventricular ejection fraction; LV: left ventricle