Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction

Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial

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Background—The prevalence of pre–diabetes mellitus and its consequences in patients with heart failure and reduced ejection fraction are not known. We investigated these in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.

Methods and Results—We examined clinical outcomes in 8399 patients with heart failure and reduced ejection fraction according to history of diabetes mellitus and glycemic status (baseline hemoglobin A1c [HbA1c] <6.0% [<42 mmol/mol], 6.0%–6.4% [42–47 mmol/mol; pre–diabetes mellitus], and ≥6.5% [≥48 mmol/mol; diabetes mellitus]), in Cox regression models adjusted for known predictors of poor outcome. Patients with a history of diabetes mellitus (n=2907 [35%]) had a higher risk of the primary composite outcome of heart failure hospitalization or cardiovascular mortality compared with those without a history of diabetes mellitus: adjusted hazard ratio, 1.38; 95% confidence interval, 1.25 to 1.52; P<0.001. HbA1c measurement showed that an additional 1106 (13% of total) patients had undiagnosed diabetes mellitus and 2103 (25%) had pre–diabetes mellitus. The hazard ratio for patients with undiagnosed diabetes mellitus (HbA1c ≥6.5%) and known diabetes mellitus compared with those with HbA1c<6.0% was 1.39 (1.17–1.64); P<0.001 and 1.64 (1.43–1.87); P<0.001, respectively. Patients with pre–diabetes mellitus were also at higher risk (hazard ratio, 1.27 [1.10–1.47]; P<0.001) compared with those with HbA1c<6.0%. The benefit of LCZ696 (sacubitril/valsartan) compared with enalapril was consistent across the range of HbA1c in the trial.

Conclusions—In patients with heart failure and reduced ejection fraction, dysglycemia is common and pre–diabetes mellitus is associated with a higher risk of adverse cardiovascular outcomes (compared with patients with no diabetes mellitus and HbA1c <6.0%). LCZ696 was beneficial compared with enalapril, irrespective of glycemic status.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01035255.

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Key Words: clinical trial ■ diabetes mellitus ■ heart failure ■ prognosis ■ treatment outcome

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* A list of all PARADIGM-HF Investigators and Committees is given in the Appendix.

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H
o2
or type 2 diabetes mellitus are 2 of the great
epidemics of modern times.1,2 Although each begets
the other, the links between the 2 conditions are not fully elucidated.3
Although it is widely acknowledged that diabetes mellitus is a risk
marker for the development of heart failure and greatly height-
ens the risk of worse outcomes once heart failure develops,4,6 the
relationship between heart failure and the development of diabetes
mellitus is less well understood. Although heart failure seems to
be a state of insulin resistance, the mechanisms underlying this
are not clear. Few studies have investigated the prevalence of
pre–diabetic dysglycemia in patients with heart failure and even
fewer its clinical consequences (and with conflicting findings).8,9
Identification of an association, if any, between pre–diabetes
mellitus and adverse clinical outcomes is of clinical importance
from 2 contrasting perspectives. There has been recent concern
that hypoglycemic agents might contribute to the poor cardiovas-
cular outcomes, including heart failure, in patients with diabetes
mellitus.3 Demonstration that patients with pre–diabetes mellitus,
untreated with hypoglycemic agents, have worse outcomes than
normoglycemic patients would support the view that dysglycemia
per se is harmful in heart failure. If so, treatment of such patients
with hypoglycemic agents might prevent the development of dia-
betes mellitus and improve heart failure outcomes. We, therefore,
investigated the prevalence of diabetes mellitus and pre–diabetes
mellitus in patients with heart failure and reduced ejection frac-
tion (HF–REF) who participated in the Prospective Comparison of
ARNI With ACEI to Determine Impact on Global Mortality and
Morbidity in Heart Failure (PARADIGM-HF) trial10 and examined
the relationship between glycemic status and clinical outcomes
in this trial. We also compared the effect of sacubitril/valsartan
(LCZ696) with enalapril in patients in the PARADIGM-HF trial
according to glycemic status.

Methods
The design and primary results of the PARADIGM-HF trial have been
described in detail.10–12
The trial was approved by the ethics committee at each study cen-
ter. All the patients provided written informed consent.

Study Patients
The inclusion criteria for the PARADIGM-HF trial included New York
Heart Association class II–IV symptoms, EF ≤40% (changed to ≤35%
by amendment), and a plasma B-type natriuretic peptide (BNP) ≥150
pg/mL (or N-terminal pro-BNP ≥200 pg/mL). Patients who had been
hospitalized for heart failure within the preceding 12 months could
be enrolled with a lower natriuretic peptide concentration (BNP, ≥100 pg/
ml or N-terminal pro-BNP, ≥400 pg/mL). Patients were required to
be taking an angiotensin-converting enzyme inhibitor or angiotensin
receptor blocker at a dose equivalent to enalapril 10 mg daily for at
least 4 weeks before screening, along with a stable dose of a β-blocker
(unless contraindicated or not tolerated) and a mineralocorticoid recep-
tor antagonist, if indicated. The exclusion criteria included history of
intolerance of an angiotensin-converting enzyme inhibitor or angio-
tensin receptor blocker, symptomatic hypotension (or a systolic blood
pressure <100 mm Hg at screening/≤95 mm Hg at randomization),
an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73
m², a serum potassium concentration >5.2 mmol/L at screening (>5.4
mmol/L at randomization), or a history of angioedema.

Study Procedures
On trial entry, existing treatment with an angiotensin-converting
enzyme inhibitor or angiotensin receptor blocker was stopped, but
other treatments for heart failure were continued. Patients first re-
ceived enalapril 10 mg twice daily for 2 weeks (single-blind) and then
LCZ696 (single-blind) for an additional 4 to 6 weeks, initially at 100
mg twice daily and then 200 mg twice daily. Patients tolerating both
drugs at target doses were randomly assigned in a 1:1 ratio to double-
blind treatment with either enalapril 10 mg twice daily or LCZ696
200 mg twice daily. The dose of enalapril was selected based on its ef-
fect to reduce the risk of death compared with placebo in the Studies
of Left Ventricular Dysfunction (SOLVD) treatment trial.11 LCZ696
200 mg twice daily delivers the equivalent of valsartan 160 mg twice
daily and significant and sustained neprilysin inhibition.

Definition of Pre–Diabetes Mellitus, Undiagnosed
Diabetes Mellitus, and Diabetes Mellitus
For the purposes of this study, patients without a previous diagno-
sis of diabetes mellitus were divided into 3 categories according to
the hemoglobin A1c (HbA1c) level using the International Diabetes
Expert Committee criteria14,15: (1) normal, <6.0% (<42 mmol/mol); (2)
pre–diabetes mellitus, 6.0% to 6.4% (42–47 mmol/mol); and (3)
undiagnosed diabetes mellitus, 6.5% to 7.9% (>48 mmol/mol). Patients
with a previous diagnosis of diabetes mellitus (irrespective of HbA1c
level) were considered to have diabetes mellitus.

Study Outcomes
The PARADIGM-HF trial was designed to recruit ≥8400 patients and
continue until 1229 patients experienced cardiovascular deaths and 2410
patients experienced either a first hospitalization for heart failure or car-
diovascular death (primary outcome). However, an independent data
and safety monitoring board recommended early termination of the study
when the prespecified boundary for overwhelming benefit for both car-
diovascular mortality and the primary outcome had been crossed. The
primary outcome of this analysis was a composite of death from cardio-
vascular causes or a first hospitalization for heart failure. The secondary
outcomes of the PARADIGM-HF trial were the time to death from any
cause, the change from baseline to 8 months in the clinical summary
score on the Kansas City Cardiomyopathy Questionnaire (KCCQ; on a
scale from 0 to 100, with higher scores indicating fewer symptoms and
physical limitations associated with heart failure), the time to a new
onset of atrial fibrillation, and the time to the first occurrence of a decline
in renal function (which was defined as end-stage renal disease or as a
decrease in the eGFR of at least 50% or a decrease of >30 mL/min per
1.73 m² from randomization to <60 mL/min per 1.73 m²); there were too
few patients with new onset atrial fibrillation and decline in renal func-
tion for meaningful analysis in the current study of HbA1c subgroups.
Adjudication of these outcomes was carried out in a blinded fashion by
a clinical end point committee according to pre–specified criteria. Safety
outcomes included hypotension, elevation of serum creatinine, hyperka-
lemia, cough, and angioedema, as previously reported.11

Statistical Analysis
Baseline characteristics are presented as mean with SDs for con-
tinuous variables and frequencies and percentages for categorical
variables. Unadjusted event rates are reported per 100 patient-years of
follow-up according to diabetic status. Cox proportional hazard
models were applied to calculate hazard ratios (HRs) for the out-
comes in patients with pre–diabetes mellitus, undiagnosed diabe-
etes mellitus, and diabetes mellitus with normoglycemic patients as
reference, as well as treatment effect of LCZ696 for the outcomes
according to glycemic status. Event-free survival curves (Figure 1)
were calculated using Kaplan–Meier estimates. In additional Cox
models were applied to calculate hazard ratios (HRs) for the outcomes
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Kristensen et al. Pre–Diabetes Mellitus and Diabetes Mellitus in PARADIGM-HF

at 8-month follow-up according to diabetes mellitus status and used logistic regression to calculate odds ratios for this reduction in patients with diabetes mellitus and pre–diabetes mellitus compared with normoglycemic patients. We applied a cubic spline model to assess the relationship between HbA1c and the primary composite outcome in patients not treated with glucose-lowering drugs. All P values are 2-sided, and a P value of <0.05 was considered significant. Analyses were performed using Stata version 13 (Stata Corp, College Station, TX), and SAS version 9.4 (SAS Institute, Cary, NC).

Results

Overall, 8274 patients had known diabetes mellitus or a measurement of HbA1c at baseline. Of these, 2907 (35%) had a history of diabetes mellitus. Of the 5367 (65%) patients with no history of diabetes mellitus, 2160 (40% [26% of total]) had HbA1c <6.0%, 2103 (39% [25% of total]) had HbA1c 6.0% to <6.5%, and 1106 (21% [13% of total]) had HbA1c ≥6.5% (“undiagnosed diabetes mellitus”). A total of 4013 (49%) patients were, therefore, defined as having diabetes mellitus based on history (n=2907) or HbA1c ≥6.5% (n=1106). The median follow-up in patients with normal HbA1c was 26 months, and it was 27 months in both patients with pre–diabetes mellitus and diabetes mellitus.

Baseline Characteristics

Patients with pre–diabetes mellitus and diabetes mellitus were older, more often whites, had longer heart failure duration, a higher body mass index (and more obesity), and evidence of overall worse heart failure status (Table 1). Manifestations of worse heart failure status included higher New York Heart Association class and BNP levels, lower KCCQ score and eGFR, more edema, and greater use of diuretics (Table 1). The exception to this was EF, which was marginally although insignificantly higher in patients with pre–diabetes mellitus and diabetes mellitus compared with those with normal HbA1c. Patients with pre–diabetes mellitus and diabetes mellitus also more commonly had a history of myocardial infarction and atrial fibrillation. Generally, the trends identified were most marked in patients with diabetes mellitus and intermediate between diabetes mellitus and normoglycemia in individuals with pre–diabetes mellitus. Patients in Latin America had the lowest prevalence of pre–diabetes mellitus/diabetes mellitus and the highest proportion of normoglycemia. The prevalence of diabetes mellitus was most prevalent in North America and the Asia-Pacific region. However, when both diabetes mellitus and pre–diabetes mellitus were taken into account, the rate of dysglycemia was similar in Western/Central Europe and the Asia-Pacific region and less in North America, compared with these other regions.

Clinical Outcomes According to HbA1c Category and Diabetes Mellitus Status

The clinical outcomes of interest according to the predefined glycemia categories are summarized in Table 2 and illustrated by Figure 1. Kaplan–Meier curves for the primary composite end point of cardiovascular death or heart failure (HF) hospitalization, each of the components separately, and all-cause mortality according to history of diabetes mellitus and glycemic status. HbA1c indicates hemoglobin A1c.
The rates of both the primary composite outcome and all-cause death were the lowest in the normal HbA1c group, significantly higher in the pre–diabetes mellitus category, and the highest in individuals with undiagnosed and known diabetes mellitus (Table 2; Figure 1). Patients with a history of diabetes mellitus were at higher risk of the primary composite outcome of heart failure hospitalization and cardiovascular mortality compared with those with normal HbA1c: adjusted HR, 1.64; 95% confidence interval, 1.44 to 1.88; P<0.001. The HR for patients with undiagnosed
Table 1. Baseline Characteristics According to the Presence of Diabetes Mellitus, Defined by Previous Diagnosis, Undiagnosed Diabetes Mellitus (HbA1c, ≥6.5), Pre–Diabetes Mellitus (HbA1c, 6.0–6.4), or Normoglycemia (HbA1c, <6.0)

<table>
<thead>
<tr>
<th></th>
<th>Any HbA1c</th>
<th>HbA1c, 6.0–6.4</th>
<th>HbA1c, 6.0–6.4</th>
<th>HbA1c, &gt;6.0</th>
<th>HbA1c, &lt;6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, n (%)</strong></td>
<td>2907 (35)</td>
<td>2103 (26)</td>
<td>1106 (13)</td>
<td>2158 (26)</td>
<td>2103 (26)</td>
</tr>
<tr>
<td><strong>Age, mean</strong></td>
<td>65±10</td>
<td>63±12</td>
<td>64±12</td>
<td>62±12</td>
<td>64±12</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>613 (21)</td>
<td>258 (23)</td>
<td>470 (22)</td>
<td>474 (22)</td>
<td>470 (22)</td>
</tr>
<tr>
<td><strong>White, n (%)</strong></td>
<td>2010 (69)</td>
<td>688 (62)</td>
<td>1424 (68)</td>
<td>1333 (62)</td>
<td>1424 (68)</td>
</tr>
<tr>
<td><strong>LCZ696 treatment, n (%)</strong></td>
<td>1451 (50)</td>
<td>549 (50)</td>
<td>1040 (50)</td>
<td>1087 (50)</td>
<td>1040 (50)</td>
</tr>
<tr>
<td><strong>HbA1c, median (Q1–Q3)</strong></td>
<td>7.2 (6.5–8.4)</td>
<td>6.6 (6.5–6.9)</td>
<td>6.1 (6.0–6.2)</td>
<td>5.6 (5.4–5.7)</td>
<td>7.2 (6.5–8.4)</td>
</tr>
<tr>
<td><strong>HF duration, y, n (%)</strong></td>
<td>765 (26)</td>
<td>379 (34)</td>
<td>629 (30)</td>
<td>707 (33)</td>
<td>629 (30)</td>
</tr>
<tr>
<td><strong>NYHA class, n (%)</strong></td>
<td>115 (4)</td>
<td>56 (5)</td>
<td>102 (5)</td>
<td>109 (5)</td>
<td>102 (5)</td>
</tr>
<tr>
<td><strong>Geographical region, n (%)</strong></td>
<td>291 (10)</td>
<td>120 (11)</td>
<td>199 (10)</td>
<td>199 (9)</td>
<td>199 (9)</td>
</tr>
<tr>
<td><strong>Edema, n (%)</strong></td>
<td>688 (24)</td>
<td>234 (21)</td>
<td>444 (21)</td>
<td>363 (17)</td>
<td>444 (21)</td>
</tr>
<tr>
<td><strong>Rales, n (%)</strong></td>
<td>252 (9)</td>
<td>92 (8)</td>
<td>170 (8)</td>
<td>139 (6)</td>
<td>170 (8)</td>
</tr>
<tr>
<td><strong>Third heart sound, n (%)</strong></td>
<td>290 (10)</td>
<td>121 (11)</td>
<td>176 (8)</td>
<td>199 (9)</td>
<td>176 (8)</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td>0.30±0.06</td>
<td>0.29±0.06</td>
<td>0.30±0.06</td>
<td>0.29±0.06</td>
<td>0.29±0.06</td>
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<tr>
<td><strong>Heart rate, beats per min</strong></td>
<td>74±12</td>
<td>73±13</td>
<td>72±12</td>
<td>71±12</td>
<td>72±12</td>
</tr>
<tr>
<td><strong>SBP, mmHg</strong></td>
<td>123±16</td>
<td>120±14</td>
<td>120±15</td>
<td>121±15</td>
<td>120±15</td>
</tr>
<tr>
<td><strong>KCCQ score</strong></td>
<td>71±20</td>
<td>72±19</td>
<td>73±19</td>
<td>76±18</td>
<td>73±19</td>
</tr>
<tr>
<td><strong>BMI, kg/m², n (%)</strong></td>
<td>9 (0)</td>
<td>18 (1)</td>
<td>10 (1)</td>
<td>9 (0)</td>
<td>18 (1)</td>
</tr>
<tr>
<td><strong>18–24.9</strong></td>
<td>433 (15)</td>
<td>220 (20)</td>
<td>502 (31)</td>
<td>607 (28)</td>
<td>502 (31)</td>
</tr>
<tr>
<td><strong>25–29.9</strong></td>
<td>1040 (36)</td>
<td>447 (40)</td>
<td>833 (40)</td>
<td>935 (43)</td>
<td>833 (40)</td>
</tr>
<tr>
<td><strong>30</strong></td>
<td>1425 (49)</td>
<td>429 (39)</td>
<td>750 (36)</td>
<td>607 (28)</td>
<td>750 (36)</td>
</tr>
<tr>
<td><strong>eGFR, mL/min per 1.73 m²</strong></td>
<td>64 (52–78)</td>
<td>66 (54–80)</td>
<td>66 (54–78)</td>
<td>69 (56–82)</td>
<td>66 (54–78)</td>
</tr>
<tr>
<td><strong>CKD (eGFR&lt;60), n (%)</strong></td>
<td>1183 (41)</td>
<td>401 (36)</td>
<td>753 (36)</td>
<td>686 (32)</td>
<td>753 (36)</td>
</tr>
<tr>
<td><strong>BNP, pg/mL</strong></td>
<td>247 (154–449)</td>
<td>291 (172–582)</td>
<td>251 (157–496)</td>
<td>240 (143–443)</td>
<td>251 (157–496)</td>
</tr>
<tr>
<td><strong>NT-proBNP, pg/mL</strong></td>
<td>1549 (854–3103)</td>
<td>1838 (954–3758)</td>
<td>1664 (906–3326)</td>
<td>1582 (878–3036)</td>
<td>1664 (906–3326)</td>
</tr>
<tr>
<td><strong>ICD/CRT-D, n (%)</strong></td>
<td>501 (17)</td>
<td>113 (10)</td>
<td>292 (14)</td>
<td>321 (15)</td>
<td>292 (14)</td>
</tr>
<tr>
<td><strong>CRT-P+D, n (%)</strong></td>
<td>232 (8)</td>
<td>54 (5)</td>
<td>129 (6)</td>
<td>152 (7)</td>
<td>129 (6)</td>
</tr>
<tr>
<td><strong>Medical history, n (%)</strong></td>
<td>1980 (68)</td>
<td>659 (60)</td>
<td>1207 (57)</td>
<td>1117 (52)</td>
<td>1207 (57)</td>
</tr>
<tr>
<td><strong>Ischemic cause</strong></td>
<td>1459 (50)</td>
<td>454 (41)</td>
<td>848 (40)</td>
<td>814 (38)</td>
<td>848 (40)</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td>1459 (50)</td>
<td>454 (41)</td>
<td>848 (40)</td>
<td>814 (38)</td>
<td>848 (40)</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
<td>286 (10)</td>
<td>69 (6)</td>
<td>178 (9)</td>
<td>180 (8)</td>
<td>178 (9)</td>
</tr>
<tr>
<td><strong>Previous AF</strong></td>
<td>1072 (37)</td>
<td>436 (39)</td>
<td>827 (39)</td>
<td>697 (32)</td>
<td>827 (39)</td>
</tr>
<tr>
<td><strong>Medication, n (%)</strong></td>
<td>2434 (84)</td>
<td>933 (84)</td>
<td>1644 (78)</td>
<td>1628 (75)</td>
<td>1644 (78)</td>
</tr>
<tr>
<td><strong>Loop diuretic</strong></td>
<td>2010 (69)</td>
<td>688 (62)</td>
<td>1424 (68)</td>
<td>1333 (62)</td>
<td>1424 (68)</td>
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<td><strong>Continued</strong></td>
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</tbody>
</table>
diabetes mellitus (HbA1c, >6.5%) compared with those with HbA1c <6.0% was 1.39 (1.18–1.64); P<0.001. The elevation in risk related to dysglycemia seemed more marked for heart failure hospitalization than for cardiovascular death or all-cause death. These differences in risk persisted after adjusting for other prognostic variables. In particular, the elevated

<table>
<thead>
<tr>
<th>Table 2. Event Rates and Risks of the Primary End Point (CV Death or Heart Failure Hospitalization), CV Death, Heart Failure Hospitalization, All-Cause Mortality, and Worsening KCCQ Score, According to History of DM and Glycemic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Patients</strong></td>
</tr>
<tr>
<td>Primary composite end point</td>
</tr>
<tr>
<td>No DM and HbA1c, &lt;6.0</td>
</tr>
<tr>
<td>No DM and HbA1c, 6.0–6.4</td>
</tr>
<tr>
<td>No DM and HbA1c, &gt;6.5</td>
</tr>
<tr>
<td>DM and any HbA1c</td>
</tr>
<tr>
<td>CV death</td>
</tr>
<tr>
<td>No DM and HbA1c, &lt;6.0</td>
</tr>
<tr>
<td>No DM and HbA1c, 6.0–6.4</td>
</tr>
<tr>
<td>No DM and HbA1c, &gt;6.5</td>
</tr>
<tr>
<td>DM and any HbA1c</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
</tr>
<tr>
<td>No DM and HbA1c, &lt;6.0</td>
</tr>
<tr>
<td>No DM and HbA1c, 6.0–6.4</td>
</tr>
<tr>
<td>No DM and HbA1c, &gt;6.5</td>
</tr>
<tr>
<td>DM and any HbA1c</td>
</tr>
<tr>
<td>All-cause mortality</td>
</tr>
<tr>
<td>No DM and HbA1c, &lt;6.0</td>
</tr>
<tr>
<td>No DM and HbA1c, 6.0–6.4</td>
</tr>
<tr>
<td>No DM and HbA1c, &gt;6.5</td>
</tr>
<tr>
<td>DM and any HbA1c</td>
</tr>
<tr>
<td>Significant worsening in KCCQ clinical score (≥5) at 8 mo†</td>
</tr>
<tr>
<td>No DM and HbA1c, &lt; 6.0</td>
</tr>
<tr>
<td>No DM and HbA1c, 6.0–6.4</td>
</tr>
<tr>
<td>No DM and HbA1c, &gt;6.5</td>
</tr>
<tr>
<td>DM and any HbA1c</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular; DM, diabetes mellitus; HbA1c, hemoglobin A1c; and KCCQ, Kansas City Cardiomyopathy Questionnaire.

*Adjusted for age, sex, race (white vs all other), geographical region, heart failure duration, New York Heart Association class, left ventricular ejection fraction, heart rate, KCCQ score, body mass index, estimated glomerular filtration rate, N-terminal pro–B-type natriuretic peptide, ischemic cause, previous myocardial infarction, previous stroke, and previous atrial fibrillation.

†Scores on the KCCQ range from 0 to 100 (higher scores indicating fewer symptoms).

‡Effect of diabetes mellitus/dysglycemia on worsening KCCQ clinical score (≥5) at 8 mo was estimated by logistic regression and is shown as odds ratios. Information on KCCQ score was only available for 7623 (92%) patients. 

AF indicates atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CRT-P+D, cardiac resynchronization therapy, pacemaker + defibrillator; HbA1c, hemoglobin A1c; HF, heart failure; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; MRA, magnetic resonance angiogram; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; and SBP, systolic blood pressure.

AF indicates atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CRT-P+D, cardiac resynchronization therapy, pacemaker + defibrillator; HbA1c, hemoglobin A1c; HF, heart failure; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; MRA, magnetic resonance angiogram; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; and SBP, systolic blood pressure.

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risk related to pre–diabetes mellitus and diabetes mellitus was apparent across the spectrum of EF, although nonsignificantly so in patients with EF ≥35% and tended to be accentuated at lower EF (Figure 2). A similar pattern was observed when we assessed the risk related to diabetes mellitus and pre–diabetes mellitus according to kidney function (Figure 3). In a cubic spline analysis restricted to patients not on glucose-lowering drugs (n=6069), we found a correlation between increasing HbA1c and elevated risk of the primary outcome (Figure 4).

At 8 months after randomization, more patients with known diabetes mellitus (35%) and undiagnosed diabetes mellitus (32%) had a decline of ≥5 points in KCCQ score, compared with patients with pre–diabetes mellitus (30%) and those with normal HbA1c (29%); P value for difference is 0.0002. Compared with the group with normal HbA1c, the adjusted odds ratios for a 5-point reduction were 1.23 (1.07–1.40) for patients with known diabetes mellitus, 1.12 (0.95–1.33) for those with undiagnosed diabetes mellitus, and 1.04 (0.91–1.20) for patients with pre–diabetes mellitus (Table 2).

**Effect of LCZ696 (Sacubitril/Valsartan) According to Diabetes Mellitus Status**

The effect of LCZ696 on the different outcomes is shown in Table 3. In each of the 3 predefined glycemia categories, LCZ696 reduced the occurrence of the primary composite outcome compared with enalapril. Fewer patients treated with LCZ696 considered themselves worse 8 months into the study (defined by a reduction in KCCQ score of ≥5 points) (0.91–1.20) for patients with pre–diabetes mellitus (30%) and intermediate glycemia (HbA1c =0.14).

**Prespecified Safety Assessments**

Adverse events causing drug discontinuation were overall rare, although more prevalent in patients with diabetes mellitus, compared with patients with normal HbA1c, and intermediate in the pre–diabetes mellitus group (Table 4). Renal impairment and hyperkalemia were more prevalent adverse events in patients with diabetes mellitus. We found no interaction with LCZ696 treatment, except for a higher likelihood of increase in serum creatinine ≥3.0 mg/dL, but importantly, this did not lead to more study drug discontinuation. Angioedema was very rare, regardless of diabetic status and assigned treatment.

**Patients With Previously Known Diabetes Mellitus Versus Undiagnosed Diabetes Mellitus**

Notable differences between these 2 groups included older age, longer duration of heart failure, lower eGFR, and more frequent ischemic cause (and previous myocardial infarction), in patients with known diabetes mellitus (Table 1). In terms of medication, patients with known diabetes mellitus were more likely to be treated with antiplatelet agents and statins. The risk of the primary outcome was higher in patients with known diabetes mellitus (P=0.025), primarily because of a higher risk of heart failure hospitalization (P=0.032), whereas the risk of cardiovascular death was similar in those with known and undiagnosed diabetes mellitus (P=0.205). Finally, the risk of all-cause mortality seemed higher in patients with known diabetes mellitus, compared with patients with HbA1c ≥6.5%, and more so in adjusted analyses (HR, 1.46 [1.26–1.70] versus HR, 1.25 [1.03–1.51]; P=0.07).

**Discussion**

This study has 3 key findings. First, although it is known that the prevalence of diabetes mellitus is high in patients with HF-REF, it seems that both pre–diabetes mellitus and undiagnosed diabetes mellitus are also common in these patients. Second, non–diabetic dysglycemia (pre–diabetes mellitus) is associated with a substantially increased risk of adverse outcomes in HF-REF. Finally, LCZ696 (sacubitril/valsartan) is superior to enalapril, irrespective of glycemic status.

The first of our findings shows that a patient with HF-REF without a history of diabetes mellitus has approximately a 1-in-5 chance of actually having the condition (but not yet diagnosed) and a >1-in-3 chance of having pre–diabetes mellitus, based on HbA1c testing. Few previous studies have reported the prevalence of non–diabetic dysglycemia (pre–diabetes mellitus) is associated with a substantially increased risk of adverse outcomes in HF-REF. Finally, LCZ696 (sacubitril/valsartan) is superior to enalapril, irrespective of glycemic status.

![Figure 4. Risk of the primary composite outcome according to hemoglobin A1c (HbA1c) in patients not receiving glucose-lowering drugs.](Image)
of dysglycemia and patients in the Asia-Pacific region and Europe the highest. This contrasts strikingly with the prevalence of diabetes mellitus in the general population. For example, using similar HbA1c diagnostic thresholds, the prevalence of diagnosed diabetes mellitus, undiagnosed diabetes mellitus, and pre–diabetes mellitus in US residents aged \( \geq 65 \) years was 17.7% (95% confidence interval, 15.6–19.8), 3.5% (2.6–4.4), and 8.1% (6.6–9.6), respectively, giving a total of 29.3% individuals with diabetes mellitus or pre–diabetes mellitus, an overall prevalence considerably less than half of that observed in our patients with HF-REF.18

The significance of this finding is related to the worse clinical status and substantially elevated risk of adverse clinical outcomes conferred by both pre–diabetes mellitus and diabetes mellitus. In 1 study, pre–diabetes mellitus and insulin resistance were correlated with worse symptom status, reduced exercise tolerance, and neurohumoral activation, and another study showed that elevated HbA1c was associated with increased mortality in nondiabetic patients referred for suspected heart failure.19,20 Our findings confirm and extend these previous observations from RESOLVD pilot study, particularly with the demonstration of a worse KCCQ score, more edema and

### Table 3. Treatment Effects of LCZ696 (Sacubitril/Valsartan) According to History of Diabetes Mellitus and Glycemic Status

<table>
<thead>
<tr>
<th></th>
<th>Normal HbA1c, n=2158</th>
<th>Pre–Diabetes Mellitus, n=2103</th>
<th>Undiagnosed Diabetes Mellitus, n=1106</th>
<th>Diabetes Mellitus, n=2907</th>
<th>( P ) Values of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td></td>
</tr>
<tr>
<td>HF hospitalization or cardiovascular death</td>
<td>0.80 (0.73–0.87)</td>
<td>0.88 (0.85–0.92)</td>
<td>0.97 (0.92–1.03)</td>
<td>0.97 (0.87–0.98)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.80 (0.71–0.89)</td>
<td>0.85 (0.85–0.95)</td>
<td>0.91 (0.89–0.93)</td>
<td>0.97 (0.83–1.14)</td>
<td>0.06</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.80 (0.71–0.89)</td>
<td>0.85 (0.65–1.12)</td>
<td>0.73 (0.57–0.93)</td>
<td>0.97 (0.71–1.21)</td>
<td>0.14</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.84 (0.76–0.93)</td>
<td>0.68 (0.55–0.85)</td>
<td>0.77 (0.63–0.95)</td>
<td>0.86 (0.74–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Significant worsening in KCCQ clinical score (( \geq 5 )) at 8 mo†</td>
<td>0.83 (0.76–0.92)‡</td>
<td>0.73 (0.60–0.89)‡</td>
<td>0.86 (0.71–1.04)‡</td>
<td>0.93 (0.71–1.21)‡</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HF, heart failure; HR, heart rate; and KCCQ, Kansas City Cardiomyopathy Questionnaire.

†Scores on the KCCQ range from 0 to 100 (higher scores indicating fewer symptoms).
‡Treatment effect of LCZ696 (sacubitril/valsartan) on worsening KCCQ clinical score (\( \geq 5 \)) at 8 mo was estimated by logistic regression and is shown as odds ratios.

Information on KCCQ score was only available for 7623 (92%) patients.

### Table 4. Prespecified Safety Assessments According to History of Diabetes Mellitus and Glycemic Status

<table>
<thead>
<tr>
<th></th>
<th>Normal HbA1c, n=2158</th>
<th>Pre–Diabetes Mellitus, n=2103</th>
<th>Undiagnosed Diabetes Mellitus, n=1106</th>
<th>Diabetes Mellitus, n=2907</th>
<th>( P ) Values of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension, n (%)</strong></td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td></td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>98 (9)</td>
<td>160 (15)</td>
<td>88 (8)</td>
<td>173 (17)</td>
<td>46 (8)</td>
</tr>
<tr>
<td>Symptomatic hypotension with SBP &lt;90 mmHg</td>
<td>15 (1)</td>
<td>28 (3)</td>
<td>12 (11)</td>
<td>37 (4)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Leading to study drug discontinuation</td>
<td>5 (1)</td>
<td>10 (1)</td>
<td>7 (1)</td>
<td>9 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Renal impairment, n (%)</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, ( \geq 2.5 ) mg/dL</td>
<td>29 (3)</td>
<td>28 (3)</td>
<td>35 (3)</td>
<td>29 (3)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Serum creatinine, ( \geq 3.0 ) mg/dL</td>
<td>13 (1)</td>
<td>15 (1)</td>
<td>8 (1)</td>
<td>15 (1)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Leading to study drug discontinuation</td>
<td>9 (1)</td>
<td>5 (1)</td>
<td>12 (1)</td>
<td>2 (0)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Hyperkalemia, n (%)</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td></td>
</tr>
<tr>
<td>Serum potassium, &gt;5.5 mmol/L</td>
<td>149 (14)</td>
<td>151 (14)</td>
<td>167 (16)</td>
<td>143 (14)</td>
<td>83 (15)</td>
</tr>
<tr>
<td>Serum potassium, &gt;6.0 mmol/L</td>
<td>54 (5)</td>
<td>40 (4)</td>
<td>54 (5)</td>
<td>38 (4)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>Leading to study drug discontinuation</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Cough, n (%)</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td></td>
</tr>
<tr>
<td>Any cough</td>
<td>143 (13)</td>
<td>116 (11)</td>
<td>150 (14)</td>
<td>121 (12)</td>
<td>82 (15)</td>
</tr>
<tr>
<td>Leading to study drug discontinuation</td>
<td>5 (1)</td>
<td>1 (0)</td>
<td>9 (1)</td>
<td>3 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Angioedema (adjudicated), n (%)</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td>Enalapril LCZ696</td>
<td></td>
</tr>
<tr>
<td>No treatment or antihistamines only</td>
<td>4 (0)</td>
<td>4 (0)</td>
<td>2 (0)</td>
<td>3 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Catecholamines or corticosteroids without hospitalization</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>3 (0)</td>
<td>3 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hospitalized without airway compromise</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>2 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any adverse event leading to study drug discontinuation, n (%)</td>
<td>21 (2)</td>
<td>15 (1)</td>
<td>30 (3)</td>
<td>15 (1)</td>
<td>16 (3)</td>
</tr>
</tbody>
</table>

HbA1c indicates hemoglobin A1c; and SBP, systolic blood pressure.
higher natriuretic peptide levels in patients with pre–diabetes mellitus compared with those with normal HbA1c. The finding that lower HbA1c in patients without known diabetes mellitus corresponded to a better prognosis is in contrast with the observed U-shaped relationship between HbA1c and adverse outcomes in patients with known and treated diabetes mellitus. We also found, as previously, that these manifestations of worse clinical status were apparent despite a similar or even higher EF than in the group with normal HbA1c, which is an unexplained and perhaps paradoxical finding.

Although the heightened risk related to diabetes mellitus is well known, the risk associated with pre–diabetes mellitus is not. This finding is important for many reasons. Most significantly, it shows that dysglycemia itself, rather than the use of hypoglycemic drugs, is a risk factor for adverse outcomes. Recently, there has been concern that the agents used to lower blood glucose may be harmful in patients with heart failure. As our patients with pre–diabetes mellitus were not receiving these treatments, hypoglycemic agents cannot account for the worse outcomes in this group compared with subjects with normal HbA1c. However, patients with diabetes mellitus also did worse than patients with pre–diabetes mellitus (and those with known diabetes mellitus did worse than those with undiagnosed diabetes mellitus), still leaving open the possibility of harm related to hypoglycemic drugs (although there are other reasons why the more severe and probably longer duration of hyperglycemia in diabetes mellitus might be associated with worse outcomes than pre–diabetes mellitus).

Second, these findings are important as they emphasize the need to better understand the effect of treatments for dysglycemia on outcomes in patients with heart failure. If hypoglycemic treatments were shown to improve outcomes across the range of dysglycemia, including both pre–diabetes mellitus and diabetes mellitus, potentially a large proportion of patients would be eligible for such treatment. Although the relationship between dysglycemia and adverse events in heart failure is clear and strong, it is only an association and a clear cause-and-effect mechanistic pathway has not been confirmed. Moreover, as alluded to above, there has been concern that at least some hypoglycemic agents may increase rather than decrease the risk of heart failure–related events.

As anticipated, renal dysfunction and hyperkalemia were more common among patients with diabetes mellitus (compared with those with normoglycemia) in the enalapril group; however, both these adverse effects were numerically (but statistically insignificantly) less common in the LCZ696 group, compared with the enalapril group, across all glycemia categories. Renal dysfunction was also more frequent in angiotensin-converting enzyme inhibitor–treated patients with diabetes mellitus than in those without diabetes mellitus. Marked renal dysfunction (serum creatinine, ≥3.0 mg/dL) was less frequent with LCZ696 than with enalapril, irrespective of glycemia status. Hypotension was more common overall with LCZ696 compared with enalapril; the increment in hypotension with LCZ696 was smaller in patients with diabetes mellitus than in the other glycemia groups.

This study has many limitations. It is a retrospective analysis. Our dysglycemia categorization is based on 1 set of criteria, and other slightly different criteria exist. Our patients had only 1 measurement of HbA1c and not at least 2 measurements or supplementary analyses of fasting glucose and oral glucose tolerance, as recommended in guidelines.

In summary, we have shown that in patients with chronic HF-REF, dysglycemia is common and pre–diabetes mellitus, as well as diabetes mellitus, is associated with worse clinical status and a significantly increased risk of adverse cardiovascular outcomes compared with normoglycemic patients. LCZ696 was beneficial, irrespective of HbA1c concentration and diabetes mellitus status.

Appendix

Ahmed F, Baben L, Badat A, Basson D, Bester F, Bruning A, Delport E, Dindar F, Foccart J, Gani M, Gerntholtz T, Haidar A, Halpern S, Hargrove J, Harris J, Hart T, Hass G, Grazette L, Laufer N, Lefkowitz D, Rouleau, Shi, Solomon, Swedberg, Zile, McMurray, and Packer and A.R. Rizkala have consulted for or received research support from Novartis, sponsor of the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. Dr Packer has consulted for Novartis, Pfizer, Sanofi, Cytokinetics, Cardiokinetics, BioControl, Janssen, Amgen, CardioMEMS, and Cardiorentis. Dr McMurray’s employer, University of Glasgow, was paid by Novartis for Dr McMurray’s time spent as cochairman of the PARADIGM-HF trial. Dr Desai consulted for Novartis, Relypsa and St. Jude Medical. Drs Lefkowitz and Shi are employees of Novartis. Drs Swedberg and Zile have received honoraria from Novartis for sponsored lectures. Dr Martinez are on the speaker’s bureau of Novartis. Dr Squire received honoraria from Novartis for participating in various activities. Drs Kristensen and Preis report no conflicts.

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7. Swan JW, Anker SD, Walton C, Gudsland IF, Clark AL, Leyva F, Stevenson JC, Coats AJ. Insulin resistance in chronic heart failure:...
Clinical Perspective

In this study, we examined the prevalence of pre–diabetes mellitus and diabetes mellitus in patients with heart failure and reduced ejection fraction in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial and their relationship with clinical outcomes. We also examined whether dysglycemia modified the benefit of sacubitril/valsartan compared with enalapril. Pre–diabetes mellitus (25% of patients), undiagnosed diabetes mellitus (13%), and known diabetes mellitus (35%) were common and associated with worse symptoms, more edema, and higher natriuretic peptide levels than normoglycemia. Patients with dysglycemia had a higher risk of cardiovascular death and heart failure hospitalization. The benefit of sacubitril/valsartan was consistent irrespective of glycemic status. These findings confirm and extend previous observations that patients with pre–diabetes mellitus and diabetes mellitus have worse clinical status and outcomes than normoglycemic patients, despite similar or higher ejection fraction. In particular, the observation that untreated dysglycemia is associated with adverse outcomes is notable. The potential mechanistic pathway(s) linking dysglycemia to adverse outcomes in heart failure and reduced ejection fraction remain to be elucidated, as do the effects of hypoglycemic agents in the large segment of these patients with pre–diabetic dysglycemia.
Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial


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