

# Impaired glucose tolerance and albuminuria in patients with chronic heart failure: a subanalysis of the SUPPORT trial

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## Abstract

**Aims** The study aims to evaluate the prognostic significance of impaired glucose tolerance (IGT) with reference to albuminuria in patients with chronic heart failure (CHF).

**Methods and results** We examined 535 CHF patients (mean 66 years, women 25%) in the control arm of our SUPPORT trial, in which we examined additive impact of olmesartan in hypertensive patients with symptomatic CHF treated with  $\beta$ -blockers and/or angiotensin-converting enzyme inhibitors. We examined the association between glycaemic abnormality (assessed by 75 g of oral glucose tolerance test) and albuminuria for a composite outcome of all-cause death, myocardial infarction, stroke, and HF hospitalization. IGT patients ( $N=113$ , mean 67.2 years) were older and more frequently treated with  $\beta$ -blockers compared with those with normal glucose regulation ( $N=142$ , mean 64.0 years) and those with diabetes mellitus ( $N=280$ , mean 65.7 years). Multivariable Cox proportional hazard models revealed that, as compared with normal glucose regulation (NGR), IGT was associated with increased risk of the outcome when complicated by albuminuria [hazard ratio (HR) 2.25; 95% confidence interval (CI) 1.14–4.42;  $P=0.019$ ] but not when uncomplicated by albuminuria (HR 0.76; 95% CI 0.35–1.60,  $P=0.47$ ) ( $P$  for interaction = 0.041). This was also the case for diabetes mellitus and albuminuria (HR 2.06; 95% CI 1.17–3.61;  $P=0.012$ ). Among IGT patients without albuminuria, 21 (29%) developed albuminuria at 1-year visit, which was again associated with poor prognosis (HR 7.36; 95% CI 1.39–38.98,  $P=0.019$ ).

**Conclusions** These results indicate that IGT is associated with poor prognosis when complicated by albuminuria in CHF patients, demonstrating the importance of combined early stages of glucose intolerance and renal dysfunction in the management of CHF.

**Keywords** Chronic heart failure; Impaired glucose tolerance; Diabetes mellitus; Albuminuria

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## Introduction

Glucose regulation abnormalities, including impaired glucose tolerance (IGT), are commonly noted in non-diabetic patients with chronic heart failure (CHF).<sup>1–5</sup> However, it remains unknown whether IGT itself is associated with poor prognosis, although a previous study suggested the correlation between IGT and HF severity.<sup>6</sup> Furthermore, IGT is usually assessed by baseline serum glucose,<sup>4,7</sup> insulin,<sup>6</sup> and haemoglobin A1c (HbA1c) levels<sup>8</sup> but not necessarily by oral glucose tolerance test (OGTT), which has advantages for accurate assessment of glucose regulation.<sup>8</sup>

Accumulating evidence also indicates that albuminuria is associated with insulin resistance in patients with Types I<sup>9</sup> and II<sup>10</sup> diabetes mellitus (DM) as well as in non-DM subjects,<sup>11</sup> suggesting that it is also the case in patients with IGT. However, it is still unclear whether IGT contributes to the development for albuminuria. This issue is clinically important in the management of CHF patients with IGT, because we found that not only macroalbuminuria but also microalbuminuria is significantly associated with increased mortality in CHF patients.<sup>12</sup> Furthermore, it has been recently shown that in Type I DM patients, myocardial deformation assessed by echocardiography was primarily associated with the presence of albuminuria,<sup>13</sup> suggesting that combination of abnormalities of glucose regulation and renal function

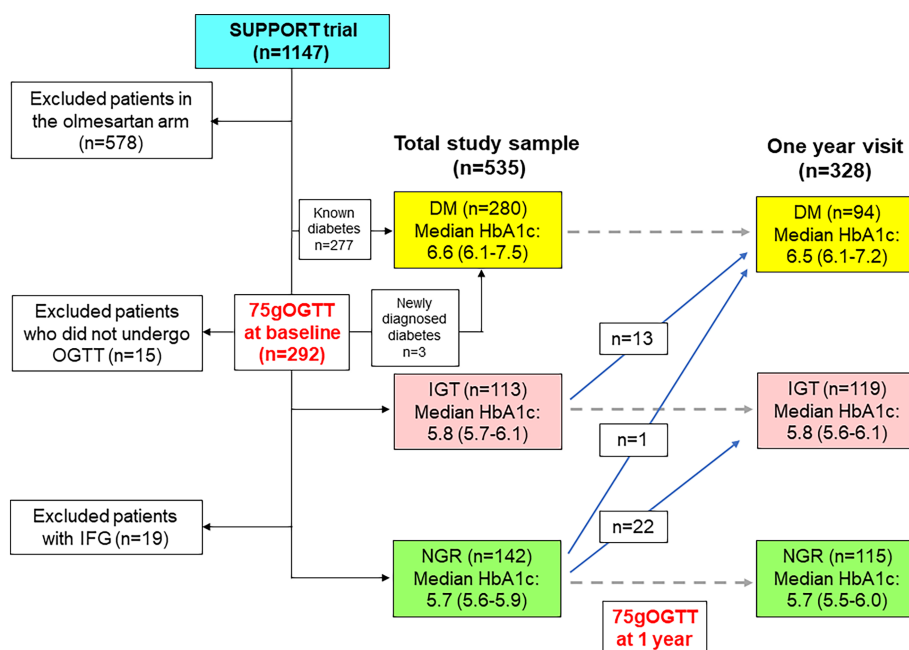
may impair cardiac function in CHF patients. However, the prognostic value of combined IGT and albuminuria remains to be examined. In the present study, we thus aimed to evaluate the prognostic significance of IGT in relation with albuminuria in CHF patients, as a subanalysis study of our SUPPORT (supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan) trial.<sup>15,16</sup>

## Methods

### Study subjects

The present study is a post hoc, exploratory analysis, using the dataset of our SUPPORT trial.<sup>15,16</sup> The trial demonstrated that additive use of olmesartan did not improve clinical outcomes and that addition of olmesartan to the combination therapy with angiotensin-converting enzyme inhibitors and  $\beta$ -blockers was associated with increased adverse cardiac events in CHF patients.<sup>14</sup> Thus, among 1147 patients of our SUPPORT trial, we enrolled 569 patients in the control arm in the present study. Of the 569 patients enrolled, we excluded 19 patients with impaired fasting glucose and finally enrolled 142 with normal glucose regulation (NGR), 113 with IGT, 280 with DM (277 known DM and three newly diagnosed DM) (*Figure 1*).

**Figure 1** Study diagram. DM, diabetes mellitus; HbA1c, haemoglobin A1c; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGR, normal glucose regulation; OGTT, oral glucose tolerance test.



## The SUPPORT trial

The SUPPORT trial (NCT00417222) was a randomized clinical trial that evaluated the efficacy and safety of olmesartan in stable CHF patients with a history of hypertension who had been treated with angiotensin-converting enzyme inhibitors and/or  $\beta$ -blockers or both at enrolment.<sup>14,15</sup> In the SUPPORT trial, patients were eligible if they met all the following criteria: (i) New York Heart Association (NYHA) Classes II to IV CHF, (ii) history of hypertension or treated with anti-hypertensive medications, (iii) aged 20 to <80 years, (iv) stable with angiotensin-converting enzyme inhibitors and/or  $\beta$ -blockers, and (v) not treated with angiotensin II receptor blockers. Exclusion criteria were (i) patients with renal dysfunction (serum creatinine  $\geq 3.0$  mg/dL) or those who were under chronic haemodialysis, (ii) drug hypersensitivity to olmesartan, (iii) severe liver dysfunction, (iv) history of angioedema, (v) history of malignant tumour or life-threatening illness of poor prognosis, (vi) pregnant or possibly pregnant patients, (vii) cardiovascular surgery within 6 months prior to the date of the entry, (viii) acute myocardial infarction within 6 months prior to the date of the entry, and (ix) percutaneous coronary intervention with or without stent implantation within 6 months prior to the date of the entry.<sup>14,15</sup>

The trial was approved by institutional review boards at each institution, and all participants provided written informed consent. The trial was conducted according to the Declaration of Helsinki. The primary objective of the trial was to examine whether an additive treatment with an angiotensin II receptor blocker, olmesartan, would reduce the mortality and morbidity of chronic HF patients with a history of hypertension. Between October 2006 and March 2010, a total of 1147 CHF patients with a history of hypertension were assigned to either the olmesartan or the control group (standard care), according to a 1:1 ratio of olmesartan to control and were followed up until the study ended on 31 March 2013.

## Definitions of impaired glucose tolerance, diabetes mellitus, and albuminuria

In the SUPPORT trial, patients without known DM underwent a standardized procedure of 75 g of OGTT twice at enrolment [median (IQR) 5 (0–33) days from randomization] and 1-year follow-up visit [median (IQR) 364 (339–399) days after randomization] (*Figure 1*).<sup>16</sup> The abnormalities in glucose tolerance were defined according to the 2006 WHO criteria<sup>8</sup>; newly diagnosed DM as fasting plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L) or 2 h plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L); IGT as fasting plasma glucose <126 mg/dL (7.0 mmol/L) and 2 h plasma glucose  $\geq 140$  mg/dL but <200 mg/dL (7.8 and 11.1 mmol/L); impaired fasting glucose as fasting plasma glucose 110–125 mg/dL (6.1–6.9 mmol/L) and 2 h plasma glucose <140 mg/dL (7.8 mmol/L). In the morning after a 9 h fast,

blood and urine samples were collected at each participating site. Blood samples were centrifuged within 30 min at 4°C and were stored at –20°C until assay. Urine samples were stored at 4°C until assay. Urine and blood samples were measured in a central laboratory (SRL, Tokyo, Japan), and urinary albumin-to-creatinine ratio (UACR) was calculated to compensate for variations in urine concentration in spot-check samples. Albuminuria was defined as UACR  $>30$  mg/g to describe urine albumin levels not detected by a dipstick test.<sup>17</sup>

## Outcome

The study outcome was a composite of all-cause death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for worsening HF, which was identical to the SUPPORT trial.<sup>15,16</sup> All-cause death was adjudicated by the death certificate and/or the medical records. The definitions of MI and stroke were based on the 2001 ACC key data elements and definitions.<sup>18</sup> A hospitalization for worsening HF was defined as an admission to a hospital necessitated by HF and primarily for its treatment or when HF became a major component of the patient's hospitalization.<sup>19</sup> A patient hospitalized for HF had to show signs and symptoms of worsening HF and require treatment with intravenous diuretics. Evidence of worsening HF included at least one of the following items: increasing dyspnoea on exertion, orthopnoea, nocturnal dyspnoea, pulmonary oedema, increasing peripheral oedema, increasing fatigue or decreasing exercise tolerance, renal hypoperfusion (e.g. worsening renal function), raised jugular venous pressure, and radiological signs of HF.<sup>19</sup> The independent events committee adjudicated all events for all-cause death, non-fatal MI, non-fatal stroke, and hospitalization for worsening HF in a blinded fashion (SI, NI, and YM) in the SUPPORT trial.

## Statistical methods

Clinical characteristics are described stratified by NGR, IGT, and DM. For comparing two groups, we used *t*-test for normally distributed and Wilcoxon rank sum for non-normally distributed data. For three or more groups, we used ANOVA for normally distributed and Kruskal–Wallis for non-normally distributed data. We examined determinants of albuminuria or IGT by multivariable logistic regression models with comparison of backward and forward selection methods considering the following variables at baseline as candidate: IGT (for the determinant of albuminuria), diabetes, albuminuria (for the determinant of IGT), age, sex, NYHA class, systolic and diastolic blood pressure (BP), heart rate, body mass index (BMI), smoking, ischaemic aetiology, history of HF hospitalization, atrial fibrillation, history of cancer, haemoglobin, estimated glomerular filtration rate, left ventricular ejection

**Table 1** Baseline characteristics

	Overall (N = 535)	NGR (N = 142)	IGT (N = 113)	DM (N = 280)	P value
Age, years	65.6 ± 10.0	64.0 ± 11.8	67.2 ± 8.0*	65.7 ± 9.7	0.035
Women, n (%)	136 (25%)	41 (29%)	34 (30%)	61 (22%)	0.13
NYHA, n (%)					0.37
II	499 (93%)	130 (92%)	105 (93%)	264 (95%)	
III	33 (6%)	12 (9%)	8 (7%)	13 (5%)	
Systolic BP, mmHg	127 ± 18	124 ± 18	129 ± 19*	128 ± 18	0.02
Diastolic BP, mmHg	74 ± 12	73 ± 11	75 ± 11	74 ± 12	0.32
Heart rate, bpm	71 ± 15	71 ± 14	71 ± 14	72 ± 15	0.83
BMI, kg/m <sup>2</sup>	24.6 ± 4.1	23.7 ± 3.8	24.3 ± 3.7**	25.3 ± 4.3	<0.001
Smoking (past or current), n (%)	272 (48%)	74 (52%)	51 (45%)	147 (53%)	0.64
Ischaemic heart disease, n (%)	249 (47%)	47 (33%)	47 (42%)**	155 (55%)	<0.001
History of HF hospitalization, n (%)	269 (50%)	69 (49%)	59 (52%)	141 (50%)	0.85
Atrial fibrillation, n (%)	226 (42%)	64 (45%)	52 (46%)	110 (39%)	0.34
Cancer, n (%)	59 (11%)	19 (13%)	10 (9%)	30 (11%)	0.50
LVEF, %	53.7 ± 14.5	53.9 ± 15.0	50.9 ± 14.8**	54.7 ± 14.1	0.06
LVEF categories					0.015
EF ≥ 50%, n (%)	310 (62%)	85 (60%)	60 (53%)	184 (66%)	
EF 40–49%, n (%)	110 (21%)	35 (25%)	21 (19%)	54 (19%)	
EF < 40%, n (%)	96 (18%)	22 (16%)	32 (28%)	42 (15%)	
LV mass index, g/m <sup>2</sup>	137.0 ± 43.8	141.4 ± 47.0	143.6 ± 44.1**	132.0 ± 41.3	0.024
LV geometry					
Normal LV, n (%)	35 (7%)	9 (6%)	8 (7%)	18 (7%)	0.95
Eccentric LVH, n (%)	216 (41%)	56 (39%)	47 (43%)	113 (41%)	0.84
Concentric LV remodelling, n (%)	14 (3%)	3 (2%)	0	11 (4%)	0.08
Concentric LVH, n (%)	134 (25%)	33 (23%)	24 (21%)	77 (28%)	0.36
LA dimension, mm	43.0 ± 8.6	42.6 ± 9.4	43.6 ± 8.4	43.0 ± 8.1	0.68
E/A ratio	1.0 ± 0.7	1.1 ± 0.7	1.0 ± 0.9	0.9 ± 0.5	0.21
Haemoglobin, g/dL	13.7 ± 1.8	13.5 ± 1.8	13.7 ± 1.9	13.8 ± 1.9	0.61
HbA1c, median (IQR), %	6.1 (5.7, 6.8)	5.7 (5.6, 5.9)	5.8 (5.7, 6.1)	6.6 (6.1, 7.5)	<0.001
eGFR	74.7 ± 33.5	80.3 ± 40.5	75.9 ± 33.7	71.4 ± 29.0	0.034
CKD stage					0.42
G1	115 (22%)	39 (28%)	26 (23%)	50 (18%)	
G2	241 (45%)	59 (42%)	49 (43%)	133 (48%)	
G3a	103 (19%)	26 (18%)	22 (20%)	55 (20%)	
G3b	50 (9%)	15 (11%)	10 (9%)	25 (9%)	
G4	25 (5%)	3 (2%)	6 (5%)	16 (6%)	
BNP, median (IQR)	78.2 (38.1, 174.0)	73.3 (36.8, 198.5)	92.7 (52.6, 237.0)**	70.9 (32.1, 159.0)	0.011
UACR, median (IQR)	20.9 (8.4, 65.6)	12.6 (6.2, 42.9)	14.9 (8.7, 46.1)**	26.8 (10.9, 93.0)	<0.001
Albuminuria, n (%)	222 (42%)	47 (33%)	41 (36%)**	134 (48%)	0.007
ACEI, n (%)	431 (81%)	122 (86%)	90 (80%)	219 (78%)	0.16
β-blocker, n (%)	394 (74%)	102 (72%)	95 (84%)***	197 (70%)	0.017
Ca channel blocker, n (%)	201 (38%)	46 (32%)	42 (37%)	113 (40%)	0.28
Loop diuretics, n (%)	275 (51%)	66 (47%)	62 (55%)	147 (53%)	0.36
Spironolactone, n (%)	145 (27%)	37 (26%)	33 (29%)	75 (27%)	0.84
Thiazide, n (%)	22 (4%)	4 (3%)	4 (4%)	14 (5%)	0.53
Statin, n (%)	262 (49%)	53 (37%)	52 (46%)	157 (56%)	0.001
Oral diabetes medication, n (%)	132 (25%)	—	—	132 (47%)	—
Insulin use, n (%)	28 (5%)	—	—	28 (10%)	—
Aspirin, n (%)	289 (60%)	76 (62%)	62 (61%)	151 (58%)	0.73
Warfarin, n (%)	162 (33%)	39 (32%)	33 (32%)	90 (35%)	0.84

Two patients are missing information on NYHA functional class. Left ventricular dimensions and mass were indexed to body surface area as per European Association of Cardiovascular Imaging (EACI) guidelines.<sup>34</sup> Left ventricular hypertrophy (LVH) was defined as LV mass index (LVMI) >115 g/m<sup>2</sup> in men or >95 g/m<sup>2</sup> in women. Left ventricular geometry was categorized as normal, concentric remodelling (RWT > 0.42, normal LVMI), concentric hypertrophy (RWT > 0.42, elevated LVMI), or eccentric hypertrophy (RWT < 0.42, elevated LVMI). CKD stage was classified by the recommendation of Kidney Disease: Improving Global Outcomes (KDIGO).<sup>35</sup> Baseline characteristics stratified by NGR, IGT, and diabetes, and albuminuria are provided in Supporting Information, Table S1.

ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; BMI, body mass index; BNP, brain natriuretic peptide; DM, diabetes mellitus; HbA1c, haemoglobin A1c; HF, heart failure; LA, left atrium; LVEF, left ventricular ejection fraction; LV, left ventricular; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

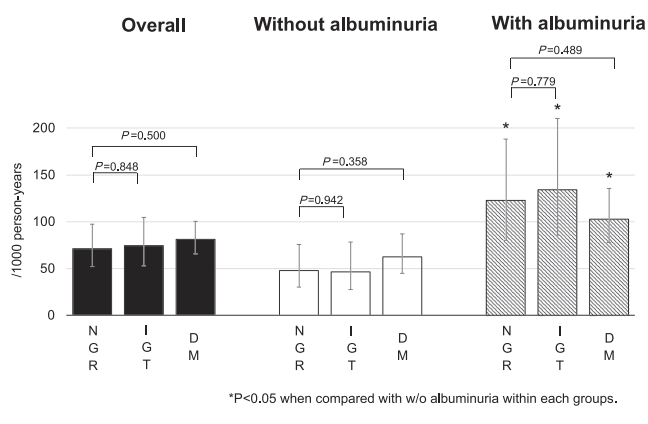
\*P < 0.05 between the NGR and IGT subgroups.

\*\*P < 0.05 between the IGT and DM subgroups.

fraction (LVEF), left ventricular mass index (LVMI), and brain natriuretic peptide (BNP). The final model was determined by the lowest value of Akaike information criterion. Event rates (per 1000 person-years) were calculated for the

composite of all-cause death, non-fatal MI, non-fatal stroke, and hospitalization for worsening HF. Event rates were analysed with the exact probability test. For time to first event analysis, we plotted Kaplan–Meier survival curves and

**Figure 2** Event rates (per 1000 person-years) for the composite of all-cause death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for worsening HF. Event rates were analysed with the exact probability test.



employed multivariable Cox proportional hazard models adjusted for age, sex, ischaemic aetiology, NYHA functional class, systolic BP, heart rate, BMI, LVEF, history of HF hospitalization, and BNP.<sup>20,21</sup> We compared the risk between NGR and DM patients, without considering the presence or absence of albuminuria. Then, we examined the risk of DM considering the presence or absence of albuminuria, where NGR without albuminuria served as a reference. We also assessed the prognostic impact of combined glycaemic status and albuminuria stratified by baseline LVEF ( $\geq 50\%$ , preserved;  $\geq 40$  to  $< 50\%$ , mid-range; and  $< 40\%$ , reduced).

**Table 2** (A) Prognostic significance of glycaemic status, haemoglobin A1c, and albuminuria in the overall samples. (B) Prognostic significance of glycaemic status with and without albuminuria in the overall samples

(A) Variable	HR (95% CI)	P value	Z score
NGR	Reference		
IGT	1.00 (0.61–1.64)	0.99	0.00
DM	1.27 (0.84–1.93)	0.24	1.14
HbA1c (per 1% increase) <sup>a</sup>	1.18 (1.05–1.33)	0.007	2.70
Albuminuria	1.74 (1.22–2.47)	0.002	3.09
(B) Variable (overall, n = 535)	HR (95% CI)	P value	Z score
NGR without albuminuria	Reference		
NGR with albuminuria	1.77 (0.91–3.45)	0.09	1.6
IGT without albuminuria	0.76 (0.36–1.60)	0.47	-0.72
IGT with albuminuria	2.25 (1.14–4.42)	0.019	2.34
DM without albuminuria	1.45 (0.81–2.60)	0.213	1.24
DM with albuminuria	2.06 (1.17–3.61)	0.012	2.51

DM, diabetes mellitus; HbA1c, haemoglobin A1c; HR, hazard ratio; IGT, impaired glucose tolerance; NGR, normal glucose regulation. DM, diabetes mellitus; HR, hazard ratio; IGT, impaired glucose tolerance; NGR, normal glucose regulation.

<sup>a</sup>Adjusted for age, sex, ischaemic aetiology, NYHA functional class, systolic blood pressure, heart rate, body mass index, LVEF, history of HF hospitalization, BNP, and albuminuria.

To estimate the survival probabilities in unbiased way, we performed landmark analysis stratified by status of albuminuria at 1-year visit evaluated by second urinalysis, setting date at 1-year visit as observation Time 0.<sup>22</sup> A two-sided *P* value of  $< 0.05$  was considered to be statistically significant. All analyses were performed with STATA 15 (College Station, TX).

## Results

### Baseline characteristics

Of 535 patients, the mean age was  $65.6 \pm 10.0$  years, 25% were women, 93% had NYHA Class II, and 82% LVEF  $> 40\%$  (Table 1). The median (IQR) BNP level was 78.2 (38–174) pg/mL. Median (IQR) HbA1c levels (%) were 5.7 (5.6, 5.9) in NGR, 5.8 (5.7, 6.1) in IGT, and 6.6 (6.1, 7.5) % in DM (Table 1). Patients with IGT, as compared with those with NGR and DM, were older and more likely to be treated with  $\beta$ -blockers (Table 1). Median (IQR) UACR levels (mg/g) were 12.6 (6.2, 42.9) in NGR, 14.9 (8.7, 46.1) in IGT, and 26.8 (10.9, 93.0) in DM ( $P < 0.001$ ). Albuminuria was noted in 47 (33%), 41 (36%), and 134 (48%) in NGR, IGT, and diabetes, respectively ( $P = 0.007$ ) (Table 1 and Supporting Information, Table S1). Patients with DM and albuminuria had higher UACR [median (IQR): 103.0 (53.0, 294.0)] than those with IGT and albuminuria [77.5 (45.8, 165.0),  $P = 0.11$ ] (Supporting Information, Table S1). Across the categories, patients with albuminuria had higher prevalence of atrial fibrillation, larger left atrial dimension, and higher BNP levels.

**Table 3** Relationships between abnormalities in glucose regulation and albuminuria at baseline and 1-year follow-up by multivariable logistic regression models

Variables	Odds ratio (95% CI)	P value	Z score
Albuminuria at baseline			
IGT	0.94 (0.54–1.63)	0.816	-0.23
Diabetes	1.75 (1.11–2.75)	0.016	2.41
Systolic BP (per 5 mmHg increase)	1.12 (1.07–1.19)	$< 0.001$	4.27
BNP (log)	1.40 (1.18–1.66)	$< 0.001$	3.82
Atrial fibrillation	1.66 (1.13–2.44)	0.010	2.41
BMI	1.06 (1.01–1.11)	0.017	2.38
Albuminuria at 1 year			
IGT	0.96 (0.47–1.96)	0.916	2.38
Diabetes	1.33 (0.74–2.40)	0.338	2.57
History of HF hospitalization	1.94 (1.17–3.22)	0.010	2.57
NYHA class	3.28 (1.23–8.75)	0.017	2.38

We used backward and forward selection methods. The final model was determined as the one using backward selection by the lowest value of Akaike information criterion (AIC).

BP, blood pressure; BMI, body mass index; BNP, brain natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction.



## Association between abnormality in glycaemic status, albuminuria and outcome

During the median follow-up of 4.1 years (IQR: 3.1–5.0 years), 151 patients experienced the composite outcome. *Figure 2* shows event rates (per 1000 person-years) stratified by NGR, IGT, and DM. Patients with DM had numerically, but insignificantly, higher event rate [81.1 (65.5–100.3) per 1000 person-years] followed by IGT [74.3 (52.8–104.5)] and NGR [71.1 (51.0–97.3)]. When stratified by the presence of albuminuria, event rates were significantly higher in patients with albuminuria compared with those without albuminuria in all the three groups. HRs (95% CI) for the outcome in patients with albuminuria over those without it were 1.00 (0.61–1.64;  $P=0.99$ ) in IGT and 1.27 (0.84–1.93;  $P=0.24$ ) in DM at baseline after adjustment for potential confounders, including age, sex, ischaemic aetiology, NYHA functional class, systolic BP, heart rate, BMI, LVEF, history of HF hospitalization, and BNP (*Table 2A*). Every 1% increase in HbA1c was associated with a 18% increase in the outcome (HR 1.18; 95% CI 1.05–1.33,  $P=0.007$ ) after adjustment for age, sex, ischaemic aetiology, NYHA functional class, systolic BP, heart rate, BMI, LVEF, history of HF hospitalization, BNP, and albuminuria (*Table 2A*).

Albuminuria at baseline was significantly associated with the outcome (HR 1.74; 95% CI 1.22–2.47;  $P=0.002$ ) after adjustment for age, sex, ischaemic aetiology, NYHA functional class, systolic BP, heart rate, BMI, LVEF, history of HF hospitalization, and BNP (*Table 2A*). In addition, as compared with NGR without albuminuria, HRs of NGR, IGT, and DM with albuminuria were 1.77 (0.91–3.45,  $P=0.09$ ), 2.25 (1.14–4.42,  $P=0.019$ ), and 2.06 (1.17–3.61,  $P=0.012$ ), respectively, whereas there was no significant association between NGR, IGT, and DM without albuminuria (*Table 2B*). We also noted significant interaction for the impact on the incidence of the composite endpoint between albuminuria and IGT ( $P$  for interaction=0.041) or DM ( $P$  for interaction=0.001) at baseline.

When stratifying by baseline LVEF ( $\geq 50\%$ , preserved;  $< 50\%$ , mid-range; and  $< 40\%$ , reduced), in reduced LVEF but not in mid-range and preserved LVEF subgroups, patients with diabetes and albuminuria and those with IGT and albuminuria tended to be associated with poor prognosis (Supporting Information, *Table S3*).

Of 328 patients, 14 (4.3%, 13 in IGT and one in NGR) and 22 patients (6.7%, all in NGR) were newly diagnosed as having DM [11.2 (6.6–18.8)/1000 person-years] and IGT [16.7 (95% CI 10.9–25.7)/1000 person-years], respectively, at 1-year visit [median (IQR) 364 (339–399) days from randomization] (*Figure 1*). At 1-year follow-up, 90 patients [25 (19.5%) in NGR, 19 (17.8%) in IGT, and 46 (18.0%) in DM] developed to albuminuria. In overall cohort, patients who developed albuminuria at 1 year had similar incidence of the composite outcome compared with those with known

albuminuria at baseline (Supporting Information, *Figure S1A*). When stratified by the presence of albuminuria at 1 year, NGR, IGT, and DM were associated with poor prognosis in patients with NGR (2.97; 95% CI 1.02–8.64;  $P=0.045$ ) and IGT (3.59; 95% CI 1.04–12.46;  $P=0.044$ ), but not in DM (2.13; 95% CI 0.62–7.34;  $P=0.230$ ) (Supporting Information, *Figure S1B–D*).

## Determinant factors of impaired glucose tolerance or albuminuria in chronic heart failure

Determinants of IGT were identified as systolic BP (per 5 mmHg increase, 1.09; 1.02–1.17;  $P=0.016$ ), age (per 5 years increase, 1.16; 1.02–1.32;  $P=0.025$ ), and LVEF (per 5% decrease, 1.10; 1.01–1.20;  $P=0.037$ ) (Supporting Information, *Table S2*). *Table 3* shows the determinant factors of albuminuria by multivariable logistic models, including systolic BP, BNP, AF, and BMI. Of note, DM was also associated with albuminuria (odds ratio, 1.75; 95% CI 1.11–2.75;  $P=0.016$ ) but IGT was not (0.94; 0.54–1.63;  $P=0.816$ ). When we evaluated the association between abnormalities of glycaemic status and development of albuminuria, IGT and DM had numerically, but not statistically, higher odds ratios, while advanced NYHA class and history of HF hospitalization were associated with development of albuminuria (*Table 3*).

## Discussion

The novel findings of the present study are as follows: (i) although IGT itself was not associated with poor prognosis, it was a significant prognostic factor in CHF patients when complicated with albuminuria. (ii) Newly developed albuminuria was associated with poor prognosis in CHF patients with NGR or IGT. To the best of our knowledge, this is the first study that demonstrates the clinical significance of combined early stages of IGT and renal dysfunction in CHF patients. The present study also indicates the clinical importance of combined tests of OGTT and urinalysis to more accurately assess long-term prognosis of CHF patients.

## Prevalence and incidence of impaired glucose tolerance and diabetes mellitus in chronic heart failure patients

By repeating OGTT and urinalysis, we confirmed higher prevalence of IGT in CHF patients.<sup>1–5</sup> Indeed, 23% of our CHF patients had IGT, a higher prevalence than in Japanese general population (14.6%).<sup>3</sup> A previous study with OGTT showed that in outpatients with HF and LVEF  $\leq 45\%$ , the prevalence of IGT was 23%,<sup>5</sup> a consistent finding with our present finding. In the present study, IGT was related with age, systolic

**Table 4** Comparison of patients, measurements, and outcomes with previous heart failure studies

Reference	Number of patients	Study patients	Measurements	Outcomes
<b>Prevalence of IGT or diabetes</b>				
Suskin <i>et al.</i> <sup>1</sup>	663	NYHA II–IV, EF <40%	Fasting plasma glucose and insulin levels	27%, diabetes; 8%, newly diagnosed diabetes; 9%, elevated glucose levels
Witteles <i>et al.</i> <sup>2</sup>	43	Idiopathic dilated cardiomyopathy	OGTT	49%, IGT
Kim <i>et al.</i> <sup>3</sup>	56	Dilated cardiomyopathy	OGTT	50%, IGT; 26.8%, newly diagnosed diabetes
Berry <i>et al.</i> <sup>4</sup>	454	Acute HF	Plasma glucose level	13%, IGT
Egstrup <i>et al.</i> <sup>5</sup>	413	Outpatients with HF and LVEF ≤45%	OGTT	23%, IGT; 18%, newly diagnosed diabetes
Present study	535	Chronic HF with a history of hypertension (82%; LVEF >40%)	OGTT	<At enrolment>23%, IGT; 0.5%, newly diagnosed diabetes <At 1 year>5%, newly diagnosed IGT; 2.5%, newly diagnosed diabetes
<b>Prognostic significance of abnormalities in glucose regulation</b>				
Doehner <i>et al.</i> <sup>6</sup>	105 (male)	Chronic HF	ivGTT	HR 0.28 (0.14–0.55, <i>P</i> =0.0003) of insulin sensitivity <sup>a</sup> for all-cause death
Gerstein <i>et al.</i> <sup>25</sup>	2412	Chronic HF	HbA1c	HR 1.22 (1.16–1.29, <i>P</i> <0.001) per 1% HbA1c increase for all-cause death
Berry <i>et al.</i> <sup>4</sup>	454	Acute HF	Plasma glucose level	HR 1.41 (0.92–2.16, <i>P</i> =0.12) of IGT for all-cause death
Kosiborod <i>et al.</i> <sup>7</sup>	50532	Post discharge after acute HF, Age >65 years (retrospective)	Plasma glucose level	HR 1.00 (0.99–1.01, <i>P</i> =0.75) for all-cause mortality (per 10 mg/dL admission serum glucose increase)
Present study	535	Chronic HF with a history of hypertension (82%; LVEF >40%)	OGTT	HR 1.18 (1.05–1.33, <i>P</i> =0.007) per 1% HbA1c increase for composite outcome HR 1.00 (0.61–1.64, <i>P</i> =0.99) for IGT HR 2.25 (1.14–4.42, <i>P</i> =0.019) for IGT complicated with albuminuria

EF, ejection fraction; HbA1c, haemoglobin A1c; HF, heart failure; HR, hazard ratio; IGT, impaired glucose tolerance; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OGTT, oral glucose tolerance test.

<sup>a</sup>Insulin sensitivity—the inverse of insulin resistance—is defined as the fraction of the glucose distribution space cleared per minute by insulin-dependent glucose disposal relative to the concentration of insulin and is expressed in min/μU/mL.

BP, and LVEF in the logistic regression analysis. These results suggest that insulin resistance is associated with severity of HF, a consistent finding with the previous study that insulin resistance was associated with exercise intolerance partly through reduced coronary flow reserve.<sup>23</sup> In the present study, we have extended the clinical relevance of IGT and DM by repeated evaluation of glucose regulation; in CHF, the incidence rate of newly diagnosed IGT and DM was 16.7 (95% CI 10.9–25.7)/1000 person-years and 11.2 (6.6–18.8)/1000 person-years, respectively. This incident rate of newly diagnosed DM was higher than in Japanese general population (age 19–82 years) with 8.8/1000 person-years,<sup>24</sup> although no report is yet available for the incidence of IGT. Thus, it is important to continuously monitor glucose tolerance in CHF patients.

### Prognostic implications of impaired glucose tolerance and diabetes mellitus in chronic heart failure

In terms of the prognostic importance of IGT and DM in CHF patients, our findings extend on the previous studies

assessing the prognostic significance of combined glucose intolerance and albuminuria. In the previous studies, IGT was assessed in relation to baseline serum glucose,<sup>4,7</sup> insulin,<sup>6</sup> and HbA1c<sup>25</sup> levels. In the present study, we employed OGTT as a gold standard to evaluate IGT and DM. A recent study with OGTT at baseline showed an association of known or newly diagnosed DM and prognosis in CHF patients.<sup>5</sup> In this study with 413 CHF patients, the mortality rate was almost two-fold higher in DM patients than in those without it,<sup>5</sup> although prognostic impact of IGT was not examined. In the present study, for the first time, we evaluated the prognostic significance of IGT in CHF patients by OGTT. In the present study, IGT was associated with systolic BP and LVEF, whereas no association was noted between IGT and long-term prognosis, suggesting that IGT is related to the severity of HF, but a longer period would be needed for future adverse effects.

In terms of the prognostic impact of DM in CHF, the adjusted HR of DM was numerically higher but statistically insignificant. In contrast, elevated HbA1c was significantly associated with higher event rate, as in the previous report.<sup>25</sup> In the present study, HbA1c levels were lower (mean 6.6%) compared with the previous study (7.7%),<sup>8</sup> suggesting that

DM was well controlled and thus adverse prognostic impacts of DM were not so evident.

### Prognostic significance of albuminuria in chronic heart failure with references to normal glucose regulation, impaired glucose tolerance, and diabetes mellitus

In the present study, we first demonstrated the prognostic significance of the combined early stages of glycaemic abnormality (IGT) and renal dysfunction (albuminuria) in CHF patients by repeating OGTT and urinalysis. In fact, patients with NGR and albuminuria had higher event rate than in those with IGT or DM without albuminuria, suggesting that albuminuria has more prognostic impact than glycaemic abnormalities in CHF patients.

We and others have previously shown the prognostic impacts of DM and albuminuria in CHF patients<sup>12,26–29</sup> (Table 4). A previous study showed that albuminuria was associated with poor prognosis in CHF patients.<sup>28</sup> The present findings have extended this observation by demonstrating the prognostic interaction between glycaemic abnormalities and albuminuria in CHF patients. In the present study, newly developed albuminuria had similar prognostic significance to known albuminuria in patients with NGR and IGT, suggesting usefulness of repeating urinalysis to assess the prognostic risk of renal dysfunction in this population. Furthermore, after adjusting confounders, we noted a 125% increase in the prognostic risk of albuminuria in HF patients with IGT. A recent study by echocardiography has shown that in patients with Type I DM, myocardial deformation was associated primarily with the presence of microalbuminuria.<sup>17</sup> We also previously demonstrated that combined abnormalities of glycaemic regulation and albuminuria impair cardiac function, especially diastolic function, and influence the prognosis in CHF patients.<sup>13</sup> Indeed, in the present study, NGR and IGT patients with newly developed albuminuria had similar prognosis compared with those with known albuminuria, and severity of CHF was associated with progression of albuminuria, suggesting that reduction in albuminuria may be beneficial for CHF patients with NGR and IGT. However, it is still controversial whether albuminuria is a therapeutic target. This question may be answered by the ongoing clinical trials in HF patients with any glycaemic status to evaluate the effects of sodium-glucose co-transporter 2 inhibitors (empagliflozin/dapagliflozin), which are known to reduce UACR and renal events in Type II DM.<sup>30,31</sup>

### Study limitations

Several limitations should be mentioned for the present study. First, as our patient population is relatively homogeneous with Japanese patients, external validation studies should be

conducted. Second, in the present study, we enrolled CHF patients with hypertension based on the study design, majority of them had preserved EF, which limits the data on clinical significance of IGT and albuminuria in patients with reduced EF. Third, timing of follow-up OGTT (approximately 1 year) may be relatively short to fully evaluate the impact of IGT or DM. Finally, because we excluded 19 patients with IGF, we were unable to evaluate the association between IGF and prognosis. However, IGF has been shown to be less significantly associated with cardiovascular events and mortality.<sup>32,33</sup>

## Conclusions

In the present study, we were able to demonstrate that IGT is associated with poor prognosis when complicated by albuminuria in CHF patients, demonstrating the importance of combined early stages of glucose intolerance and renal dysfunction in the management of HF.

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## Conflict of interest

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## Supporting information

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

**Table S1.** Baseline characteristics stratified by glycemic control condition and albuminuria.

**Table S2.** Determinants of IGT in HF patients by multivariable logistic regression model.

**Table S3.** Prognostic significance of glycemic status and

albuminuria after adjusting for age, sex, and BNP levels stratified by preserved, mid-range, and reduced LVEF subgroups.

**Figure S1.** Kaplan–Meier survival curves in (A) CHF patients in overall, (B) those with NGR, (C) those with IGT, and (D) those with DM stratified by the status of albuminuria at 1-year visit; without albuminuria or developed albuminuria at 1 year, and known albuminuria., setting date at 1-year visit as observation time 0. HRs are adjusted for age, sex and BNP at 1 year. Abbreviations; w/o, without.

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