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ORIGINAL RESEARCH ARTICLE

Prospective association of serum adipocyte fatty acid-binding protein with heart failure hospitalization in diabetes

Chi Ho Lee[1,2], Andy Ka Chun Kan[1], David Tak Wai Lui[1], Carol Ho Yi Fong[1], Darren Shing Hei Chan[1], Michele Mae Ann Yuen[1], Wing Sun Chow[1], Yu Cho Woo[1], Aimin Xu[1,2] and Karen Siu Ling Lam[1,2]*

[1]*Department of Medicine, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Pokfulam, Hong Kong; and* [2]*State Key Laboratory of Pharmaceutical Biotechnology, University of Hong Kong, Hong Kong*

Abstract

Aims Adipocyte fatty acid-binding protein (AFABP) is associated with cardiovascular diseases in type 2 diabetes. Whether circulating AFABP levels are associated with the risk of heart failure (HF) in type 2 diabetes remains undefined. We investigated the prospective association of circulating AFABP levels with incident HF hospitalization in type 2 diabetes, and its relationship to the use of sodium glucose co-transporter 2 inhibitors (SGLT2i) which reduce HF risk.

Methods and results Baseline serum AFABP level was measured in 3322 Chinese participants without known history of cardiovascular diseases or hospitalization for HF, recruited from the Hong Kong West Diabetes Registry. Its association with incident HF hospitalization was evaluated using multivariable Cox regression analysis. Use of SGLT2i was included as a time-dependent covariate. Among these 3322 participants (52.9% men; mean age 60.0 ± 12.6), 176 (5.3%) developed HF hospitalization over a median follow-up of 8 years. Seven hundred and thirty-one (22%) were started on SGLT2i during the study period (empagliflozin 55.1%, dapagliflozin 44.2%, canagliflozin 0.4%, and ertugliflozin 0.3%). Serum AFABP levels were significantly higher in participants who developed HF hospitalization than those who did not (men: 14.8 vs. 8.3 ng/mL; women: 21.5 vs. 14.6 ng/mL; all: 18.6 vs. 10.9 ng/mL, $P < 0.001$). In multivariable Cox regression analysis, baseline serum AFABP level was significantly associated with incident HF hospitalization [hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.06–1.80, $P = 0.019$] independent of the use of SGLT2i, in a model also consisting of age; sex; body mass index; smoking status; duration of diabetes; hypertension, dyslipidaemia; atrial fibrillation; presence of chronic kidney disease and albuminuria; glycated haemoglobin and high-sensitivity C-reactive protein levels; and use of metformin, insulin, aspirin, furosemide, and beta-blockers at baseline. High cumulative defined daily dose (cDDD) of SGLT2i was protective of incident HF hospitalization (HR 0.10, 95% CI 0.01–0.68, $P = 0.019$). The addition of circulating AFABP level to a clinical model of conventional HF risk factors provided significant improvement in the category-free net reclassification index (11.5%, 95% CI 1.6–22.1, $P = 0.02$) and integrated discrimination improvement (0.3%, 95% CI 0.1–1.7, $P = 0.04$). A dose-dependent reduction in cumulative incidence of HF hospitalization in response to SGLT2i, based on cDDD, was more clearly observed in participants with a higher baseline AFABP level above the sex-specific median (P for trend <0.01).

Conclusions Circulating AFABP level is independently associated with incident HF hospitalization in type 2 diabetes and is potentially helpful in risk stratification for the prevention of HF hospitalization.

Keywords Heart failure; Diabetes mellitus; Adipocyte fatty acid-binding protein; Sodium glucose co-transporter 2 inhibitors

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**Correspondence to: Professor Karen Siu Ling Lam, Department of Medicine, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong. Tel: +852 2255-4783; Fax: +852 2816-2863. Email: ksllam@hku.hk*

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Introduction

Type 2 diabetes is associated with an increased risk of cardiovascular diseases (CVD), including heart failure (HF). Although reductions in cardiovascular deaths due to ischaemic heart disease and stroke have been observed in recent decades, especially among older individuals with type 2 diabetes,[1] mortality related to HF did not change significantly and remained high. In epidemiological studies, type 2 diabetes almost doubled the risk of incident HF hospitalization, regardless of the presence of coronary artery atherosclerosis.[2] Moreover, type 2 diabetes was a significant predictor of adverse outcomes in clinical trials of HF.[3] Both hyperglycaemia and insulin resistance could lead to left ventricular hypertrophy, myocardial fibrosis, and diastolic dysfunction, through various mechanisms including lipotoxicity, inflammation, formation of advanced glycation end products and endoplasmic reticulum stress.[2]

The introduction of sodium glucose co-transporter 2 inhibitors (SGLT2i) has led to a paradigm shift in the management of type 2 diabetes and HF.[4] Canagliflozin, dapagliflozin, and empagliflozin had been consistently shown to reduce the rates of HF hospitalization in several landmark randomized controlled trials.[5–8] The latter two, in particular, were demonstrated to lower the risks of worsening HF and cardiovascular deaths in patients with reduced left ventricular ejection fraction (LVEF), even in patients without diabetes.[9,10] Sotagliflozin, which is a dual inhibitor of SGLT2 and SGLT1, was recently shown to reduce cardiovascular deaths in patients with type 2 diabetes and decompensated HF,[11] as well as HF hospitalization in patients with type 2 diabetes and chronic kidney disease, with and without albuminuria.[12]

Adipocyte fatty acid-binding protein (AFABP) is a lipid chaperone protein that is abundantly secreted by the adipocytes and is also highly expressed in the macrophages and endothelial cells.[13,14] Pre-clinical studies have revealed that AFABP is pro-inflammatory and promotes vascular dysfunction. Our group previously demonstrated that AFABP could perpetuate lipopolysaccharide-induced inflammatory responses in macrophages through its interaction with c-Jun NH2-terminal kinase (JNK) and activator protein-1 forming a positive feedback loop.[15] In mice, the anti-atherogenic effects of adipose-specific JNK inactivation were abolished by the continuous infusion of recombinant AFABP.[16] Moreover, genetic ablation of AFABP protected mice from cardiac dysfunction secondary to diabetes and myocardial ischemia/reperfusion injury. AFABP, on the other hand, reduced endothelial nitric oxide synthase phosphorylation and increased superoxide anions formation. Consequently, endothelial dysfunction ensued which could further induce oxidative stress, cardiac inflammation, hypertrophy, and fibrosis which impaired myocardial contractility.[17] Circulating AFABP level has been shown to have prognostic importance in cardio-renal events and mortality outcomes in patients with and without type 2 diabetes.[18,19] However, with regard to HF, most studies that demonstrated a positive relationship between circulating AFABP levels and ventricular dysfunction were of cross-sectional design.[20,21] Moreover, although circulating AFABP level had been shown in the Cardiovascular Health Study as a modest but independent predictor of incident HF, the study was conducted among older community-dwelling individuals aged 65 years or above, of whom less than 20% had diabetes and was performed during the period when SGLT2i was still not available.[22] Therefore, we conducted this prospective study to investigate the association of circulating AFABP level with HF hospitalization and its relationship to the use of SGLT2i, using an exclusively diabetic population with increased HF risk.

Methods

Study participants

All participants were recruited from the Hong Kong West Diabetes Registry (HKWDR), which comprised patients who had type 2 diabetes and were being followed-up regularly at the medical specialist clinics of the Hong Kong West Cluster since 2008. All Chinese patients were invited during enrolment to the registry to participate in a prospective cohort study that aimed to identify the risk factors, including genetic and serum biomarkers, of diabetic complications as described previously.[19] The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Written informed consent was obtained from all recruited participants prior to any study-related procedures.

In the current study that evaluated the role of circulating AFABP levels and incident HF hospitalization, participants who had history of CVD, HF hospitalization, or structural heart diseases at baseline were excluded. Moreover, participants who were non-Chinese, had end-stage renal disease, on renal replacement therapy or had received a kidney transplant, or had follow-up for less than 1 year were also excluded.

Clinical and biochemical assessments

All participants had regular assessment for the development of chronic diabetic complications every 12 to 18 months, in addition to their usual follow-up for diabetes every 4 to 6 months according to a management protocol. This involved both clinical and laboratory investigations to determine their control of diabetes, its related cardiovascular risk factors, and the presence of chronic diabetic complications.

The participants attended each assessment after an overnight fast of at least 8 h. During the baseline assessment,

demographic data, including age, sex, smoking, and drinking status were obtained. Detailed medical, family, and drug histories were assessed using a standardized questionnaire. Anthropometric parameters, including body weight, height, body mass index (BMI), waist circumference, and blood pressure were measured. Fasting blood was drawn for plasma glucose, lipids, and glycated haemoglobin (HbA1c) levels and stored in aliquots at −70°C for assays of biomarkers of diabetic complications. Serum creatinine level was measured, and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Albuminuria status was assessed using at least two random urine samples on two separate occasions within 6 months, and was categorized accordingly (urine albumin to creatinine ratio $<$ 3 mg/mmol [A1], 3–30 mg/mmol [A2], and $>$30 mg/mmol [A3]). Serum high-sensitivity C-reactive protein (hsCRP) level was measured with a high-sensitivity, particle-enhanced immune-turbidimetric assay (Roche Diagnostics, GmbH, Mannheim, Germany).

Serum AFABP was measured with a monoclonal antibody-based enzyme-linked immunosorbent assay (Antibody and Immunoassay Services, University of Hong Kong) that had been used in other regional and international studies.[23] The intra-assay and inter-assay precision coefficients of variability of the AFABP enzyme-linked immunosorbent assay were $<$4.1% and $<$4.5%, respectively, and the lowest detection limit was 0.39 ng/mL.

Definitions of outcomes and clinical variables

All outcomes were recorded and verified from the Hong Kong Hospital Authority database or their private practitioners as of 30 June 2020. HF hospitalization, the primary outcome of interest in this study, was defined as the first recorded hospitalization with HF as the principle diagnosis coded by a physician based on the Ninth edition of the International Classification of Diseases (ICD). The diagnosis were adjudicated and reviewed by two physicians independently, taking into account a constellation of symptoms (shortness of breath, orthopnoea, and paroxysmal nocturnal dyspnoea), signs (ankle oedema and basal chest crepitations), chest X-ray or transthoracic echocardiography (ECHO) findings (pulmonary congestion and suboptimal LVEF), and treatment of HF (use of intravenous or increased dose of oral diuretics). Disagreements between the two adjudicating physicians were resolved by a third.

Hypertension was defined as blood pressure $\geq$ 140/90 mmHg or the use of anti-hypertensive medications. Dyslipidaemia was defined as fasting triglyceride (TG) $\geq$ 1.69 mmol/L, high-density lipoprotein cholesterol $<$ 1.04 mmol/L in men and $<$1.29 mmol/L in women, low-density lipoprotein cholesterol $\geq$ 2.6 mmol/L or the use of lipid-lowering agents. For the exclusion criteria of the study, known CVD at baseline was defined as any history of myocardial infarction, stroke, transient ischemic attack, HF, and coronary arterial revascularization based on the ICD-9 codes 410–412, 414, 428–429, and 430–438. Moreover, known structural heart disease at baseline was defined as any history of chronic rheumatic heart disease, cardiomyopathy and congenital heart disease based on the ICD-9 codes 393–398, 425, and 745–726.

Sodium glucose co-transporter 2 inhibitors exposure

Since our prospective cohort commenced in 2008 and SGLT2i only became available locally after 2015, use of SGLT2i was treated as a time-dependent covariate in the analysis. In all study participants, prescriptions of SGLT2i including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin were identified. SGLT2i usage was defined by the continuous prescription for at least 90 days during the study period from the initiation of medication to the development of outcome or end of observation, whichever earlier, and classified based on their cumulative daily defined dose (cDDD) as described by the World Health Organization.[24] cDDD reflects the average daily maintenance dose of a drug prescribed for the main indication in an adult. In this study, cDDD was calculated as the sum of dispensed defined daily doses of all prescribed SGLT2i during the study period. One defined daily doses of SGLT2i is equivalent to daily use of canagliflozin 200 mg, dapagliflozin 10 mg, empagliflozin 17.5 mg, or ertugliflozin 10 mg.

Statistical analysis

All data were analysed with IBM SPSS Statistics 26.0 and R Version 3.2.3 (http://www.r-project.org). Data that were not normally distributed as determined using the Kolmogorov–Smirnov test, such as serum AFABP, TG, and hsCRP levels, were log-transformed before analysis. The values were reported as means ± standard deviation, medians with interquartile range if skewed data, or percentages. Comparisons between groups were analysed by χ^2 test for categorical variables, and independent *t*-test or analysis of variance for continuous variables as appropriate. Multivariable Cox regression analysis was performed to evaluate the associations between baseline serum AFABP levels and incident HF hospitalization. The Cox regression analysis was repeated with use of SGLT2i included as a time-dependent covariate. The variables included in the Cox regression models were those that were either biologically relevant or statistically significant in the univariate analysis. The hazard ratio (HR) for circulating AFABP level referred to the risk of

developing HF hospitalization per unit difference in the log-transformed serum AFABP level measured in ng/mL. Proportional hazards assumption was checked and verified using a global goodness-of fit test proposed by Schoenfeld. The predictive performance of the various models was evaluated using *C*-statistics, category-free net reclassification improvement, and integrated discrimination improvement. Furthermore, an exploratory subgroup analysis was performed to evaluate if a dose-dependent association was present between the cumulative incidence of HF hospitalization and use of SGLT2i in participants with baseline AFABP levels above and below the median. In all statistical tests, two-sided *P* values < 0.05 were considered significant.

Results

Baseline serum AFABP levels were significantly higher in participants with incident HF hospitalization than those without

A total of 3322 participants were included in this study, after excluding 1920 with history of CVD, HF hospitalization, or structural heart diseases at baseline. Higher quartiles of serum AFABP levels were significantly associated with older age; longer duration of diabetes; higher BMI; hsCRP levels; prevalence of hypertension; dyslipidaemia; atrial fibrillation; eGFR $<$ 60 mL/min/1.73 m^2; albuminuria; as well as use of multiple medications including metformin, sulphonylurea, glitazones, insulin, aspirin, statin, fibrate, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, furosemide, and beta blockers at baseline (all $P < 0.001$) (*Table 1*).

Over a median follow-up of 8 years, 176 (5.3%) of the 3322 participants developed incident HF hospitalization. Among these 176 participants, 127 (72.2%) had ECHO performed following their admission: 20, 11, and 96 participants had LVEF of $<$40%, 40–49%, and $\geq$50%, respectively. *Table 2* summarizes their baseline characteristics. Participants who had incident HF hospitalization were significantly older, with higher BMI, prevalence of hypertension, atrial fibrillation, and albuminuria at baseline than those without. Moreover, their duration of diabetes was also significantly longer with higher baseline HbA1c, TG and hsCRP, and lower eGFR levels than those without incident HF hospitalization. Furthermore, a significantly higher proportion of participants with HF hospitalization were on insulin, aspirin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, and furosemide at baseline than those who without.

Notably, serum AFABP levels were significantly higher in participants who developed HF hospitalization than those who did not (men: 14.8 vs. 8.3 ng/mL; women: 21.5 vs. 14.6 ng/mL; all: 18.6 vs. 10.9 ng/mL, $P < 0.001$).

Use of SGLT2i during the study period was associated with reduced risk of incident HF hospitalization

All study participants were not on SGLT2i at baseline. However, SGLT2i was started in 731 participants (22%) during the study period (empagliflozin 55.1%, dapagliflozin 44.2%, canagliflozin 0.4%, and ertugliflozin 0.3%). SGLT2i user had a significantly lower risk of incident HF hospitalization than those who did not (HR 0.24, 95% CI 0.04–0.74, $P = 0.014$). Among the SGLT2i users, the cDDD of SGLT2i was significantly lower in those who developed incident HF hospitalization compared with those who did not (139 vs. 686, $P = 0.002$). Moreover, compared with non-users, cDDD of $\geq$180, which was equivalent to the use of dapagliflozin 10 mg daily for 180 days, was significantly associated with a lower risk of incident HF hospitalization (HR 0.08, 95% CI 0.01–0.55, $P = 0.010$). (*Table 3*)

Baseline serum AFABP level was independently associated with incident HF hospitalization in patients with type 2 diabetes

In multivariable Cox regression analysis, serum AFABP level was independently associated with incident HF hospitalization (HR 1.37, 95% CI 1.04–1.79, $P = 0.023$), together with age (HR 1.05, 95% CI 1.03–1.07, $P < 0.001$), duration of diabetes (HR 1.03, 95% CI 1.01–1.05, $P = 0.004$), atrial fibrillation (HR 1.83, 95% CI 1.15–2.92, $P = 0.011$), albuminuria (HR 2.17, 95% CI 1.50–3.15, $P < 0.001$), use of insulin (HR 1.43, 95% CI 1.02–2.00, $P = 0.041$), and furosemide (HR 1.62, 95% CI 1.09–2.41, $P = 0.016$), in a model including also sex; BMI; smoking status; hypertension; dyslipidaemia; eGFR $<$ 60 m/min/1.73 m^2; HbA1c; hsCRP; and use of metformin, beta-blockers, and aspirin at baseline (*Table 4*).

When use of SGLT2i was included in the multivariable Cox regression model as a time-varying covariate, serum AFABP level remained independently associated with a higher risk of incident HF hospitalization (HR 1.38, 95% CI 1.06–1.80, $P = 0.019$), such that each unit increase in the log-transformed serum AFABP level was associated with a 38% increase in the risk of HF hospitalization. On the other hand, use of SGLT2i with cDDD $\geq$ 180 was associated with a significantly lower risk of incident HF hospitalization (HR 0.10, 95% CI 0.01–0.68, $P = 0.019$) (*Table 4*).

Moreover, the addition of circulating AFABP level to the clinical model, which consisted of age; sex; BMI; smoking status; duration of diabetes; hypertension; dyslipidaemia; atrial fibrillation; eGFR $<$ 60 mL/min/1.73m^2; albuminuria; HbA1c; hsCRP levels; and use of metformin, insulin, aspirin, beta-blockers, and furosemide at baseline, provided significant improvement in the net reclassification improvement

Table 1 Associations of baseline clinical variables with increasing quartiles of serum AFABP levels (N = 3322)

Baseline parameter	Quartile 1 M: <5.25 ng/mL; F: <9.35 ng/mL	Quartile 2 M: 5.25–8.53 ng/mL F: 9.35–14.88 ng/mL	Quartile 3 M: 8.54–14.83 ng/mL F: 14.89–25.29 ng/mL	Quartile 4 M: ≥14.84 ng/mL F: ≥25.30 ng/mL	*P* for trend
N	830	832	830	830	—
Clinical characteristics					
Men (%)	52.9	52.8	53.0	52.9	0.974
Age (years)	55.4 ± 11.4	59.5 ± 11.9	61.4 ± 12.6	63.6 ± 13.0	<**0.001**
Ever-smoker (%)	29.2	28.0	30.6	29.3	0.675
Duration of diabetes (years)	10.5 ± 7.62	11.1 ± 8.09	12.0 ± 8.90	13.4 ± 9.31	<**0.001**
BMI (kg/m^2)	23.8 ± 3.49	25.3 ± 3.77	26.8 ± 4.28	28.1 ± 5.20	<**0.001**
Systolic BP (mmHg)	128 ± 17.6	134 ± 18.8	138 ± 19.3	142 ± 20.7	<**0.001**
Diastolic BP (mmHg)	75.9 ± 8.67	76.0 ± 9.59	75.7 ± 10.1	75.6 ± 11.1	0.852
Comorbidities					
Hypertension (%)	62.7	79.1	87.7	94.9	<**0.001**
Dyslipidaemia (%)	82.8	88.9	91.6	93.4	<**0.001**
eGFR < 60 mL/min/1.7 m^2	2.3	6.6	18.9	49.5	<**0.001**
Atrial fibrillation (%)	2.5	4.8	6.3	7.8	<**0.001**
Laboratory values					
HbA1c (%)	7.55 ± 1.37	7.62 ± 1.38	7.70 ± 1.47	7.82 ± 1.54	**0.001**
FG (mmol/L)	7.90 ± 2.51	7.76 ± 2.32	7.92 ± 2.64	8.00 ± 2.74	0.276
TG[a] (mmol/L)	1.04 (0.78–1.52)	1.20 (0.86–1.76)	1.35 (1.00–1.92)	1.46 (1.11–2.10)	<**0.001**
HDL-C (mmol/L)	1.34 ± 0.39	1.27 ± 0.37	1.22 ± 0.37	1.17 ± 0.35	<**0.001**
LDL-C (mmol/L)	2.61 ± 0.79	2.55 ± 0.79	2.55 ± 0.84	2.51 ± 0.82	**0.030**
eGFR (mL/min/1.73 m^2)	94.3 ± 14.8	87.8 ± 16.9	79.9 ± 20.2	61.6 ± 25.8	<**0.001**
Albuminuria ≥ A2 (%)	25.5	33.9	47.6	67.8	<**0.001**
Medications					
Metformin (%)	82.5	85.3	83.9	66.9	<**0.001**
Sulphonylurea (%)	40.6	45.2	48.0	49.8	<**0.001**
Glitazones (%)	0.1	0.7	1.2	3.0	<**0.001**
DPP4-inhibitors (%)	8.8	9.4	11.1	12.3	**0.010**
Insulin (%)	30.7	30.9	31.7	39.5	<**0.001**
Aspirin (%)	12.9	18.1	22.7	25.2	<**0.001**
Statin (%)	22.7	36.4	39.2	46.1	<**0.001**
Fibrates (%)	4.2	4.6	4.3	5.7	0.211
ACEI/ARB (%)	47.2	59.9	69.0	72.4	<**0.001**
Furosemide (%)	3.0	4.6	8.2	20.6	<**0.001**
Spironolactone (%)	0.2	0.5	0.5	1.2	**0.016**
Beta-blockers (%)	14.0	22.7	35.8	46.4	<**0.001**
Biomarkers					
hsCRP[a] (mg/mL)	0.67 (0.29–1.75)	1.02 (0.46–2.29)	1.36 (0.64–3.10)	1.36 (0.65–3.10)	<**0.001**

95% CI, 95% confidence interval; ACEI, angiotensin converting enzyme inhibitors; AFABP, adipocyte fatty acid-binding protein; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FG, fasting glucose; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein-cholesterol; HF, heart failure; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; LDL-C low density lipoprotein-cholesterol; TG, triglyceride.
Data were presented as mean ± standard deviation or median (25th to 75th percentile).
[a]Log-transformed before analysis.

(11.5%, 95% CI 1.6–22.1, P = 0.02) and integrated discrimination improvement (0.3%, 95% CI 0.1–1.7, P = 0.04), although the change in C-statistics was not significant (0.812 vs. 0.808, P = 0.146 with and without serum AFABP, respectively).

Sensitivity analyses

Several sensitivity analyses were performed to further evaluate the association between serum AFABP level and incident HF hospitalization in type 2 diabetes. Among the 3322 study participants, only 1065 (32.1%) had ECHO performed at baseline. However, we identified 57 participants without history of HF hospitalization but with reduced LVEF < 50% at baseline. In a sensitivity analysis excluding these 57 participants, serum AFABP remained independently associated with incident HF hospitalization (HR 1.38, 1.04–1.82; P = 0.026) after multivariable adjustments. (Supporting information, *Table S1*) Next, we conducted a sensitivity analysis including all participants with and without history of CVD and HF hospitalization at baseline (N = 5242). Again, baseline serum AFABP level was independently associated with incident HF hospitalization (HR 1.33, 1.11–1.60, P = 0.002), in a model consisting of age, sex, BMI, ever smoking, duration of diabetes, hypertension, dyslipidaemia, atrial fibrillation, eGFR < 60 mL/min/1.73m^2, presence of albuminuria, HbA1c, use of metformin, insulin, aspirin, furosemide, beta-blockers, spironolactone, hsCRP levels, history of CVD and HF, as well as an interaction term between history of HF and use of furosemide at baseline. Consistently, the association was significant (HR 1.33, 1.10–1.60, P = 0.003) even after further adjustments for the use of SGLT2i (*Table 5*). Since SGLT2i was not available locally until 2015,

Table 2 Baseline characteristics of study participants by incident HF hospitalization

Baseline parameter	No incident HF hospitalization	Incident HF Hospitalization	Unadjusted HR (95% CI)	*P* value
N (%)	3146 (94.7)	176 (5.3)	—	—
Clinical characteristics				
Men (%)	52.9	52.3	0.97 (0.72–1.30)	0.823
Age (years)	59.5 ± 12.5	68.0 ± 12.5	1.07 (1.06–1.09)	<**0.001**
Ever-smoker (%)	29.3	29.0	1.00 (0.72–1.39)	0.986
Duration of diabetes (years)	11.5 ± 8.4	16.9 ± 10.5	1.06 (1.05–1.08)	<**0.001**
BMI (kg/m^2)	25.9 ± 4.5	26.8 ± 4.4	1.04 (1.01–1.07)	**0.017**
Systolic BP (mmHg)	135 ± 20	146 ± 20	1.03 (1.02–1.03)	<**0.001**
Diastolic BP (mmHg)	76 ± 10	72 ± 11	0.96 (0.94–0.97)	<**0.001**
Comorbidities				
Hypertension (%)	80.3	95.5	5.57 (2.74–11.4)	<**0.001**
Dyslipidaemia (%)	88.9	93.8	1.81 (0.98–3.33)	0.057
eGFR < 60 mL/min/1.73 m^2	16.8	46.6	4.87 (3.62–6.56)	<**0.001**
Atrial fibrillation (%)	5.0	12.5	2.98 (1.90–4.67)	<**0.001**
Laboratory values				
HbA1c (%)	7.7 ± 1.4	8.0 ± 1.8	1.13 (1.03–1.24)	**0.010**
FG (mmol/L)	7.87 ± 2.53	8.34 ± 3.06	1.06 (1.004–1.12)	**0.034**
TG[a] (mmol/L)	1.26 (0.90–1.83)	1.44 (1.09–2.14)	1.51 (1.18–1.93)	**0.001**
HDL-C (mmol/L)	1.25 ± 0.38	1.21 ± 0.36	0.77 (0.50–1.17)	0.222
LDL-C (mmol/L)	2.55 ± 0.81	2.58 ± 0.82	0.97 (0.81–1.17	0.772
eGFR (mL/min/1.73 m^2)	81.9 ± 22.8	62.7 ± 25.5	0.966 (0.96–0.97)	<**0.001**
eGFR (%)				<**0.001**
≥90	43.6	17.0	Referent	
60–89	39.5	36.4	2.59 (1.68–4.01)	<**0.001**
30–59	14.3	34.7	7.23 (4.67–11.2)	<**0.001**
15–29	2.5	11.9	16.5 (9.39–29.0)	<**0.001**
Albuminuria ≥ A2 (%)	41.3	75.0	4.52 (3.21–6.37)	<**0.001**
Medications				
Metformin (%)	79.9	75.6	0.69 (0.49–0.98)	**0.038**
Sulphonylurea (%)	46.0	44.3	0.91 (0.68–1.22)	0.530
Glitazones (%)	1.2	2.3	1.53 (0.57–4.12)	0.403
DPP4-inhibitors (%)	10.3	11.4	1.25 (0.79–2.00)	0.345
Insulin (%)	32.3	50.0	2.00 (1.49–2.69)	<**0.001**
Aspirin (%)	19.0	33.0	2.29 (1.67–3.14)	<**0.001**
Statin (%)	35.6	44.9	1.55 (1.15–2.09)	**0.004**
Fibrate (%)	4.7	5.1	1.03 (0.53–2.02)	0.928
ACEI/ARB (%)	61.1	81.3	2.68 (1.83–3.91)	<**0.001**
Furosemide (%)	2.9	10.8	4.54 (2.81–7.32)	<**0.001**
Spironolactone (%)	0.6	0.6	1.09 (0.15–7.81)	0.929
Beta-blocker (%)	29.0	42.0	1.85 (1.37–2.50)	<**0.001**
Biomarkers				
hsCRP[a] (mg/mL)	1.15 (0.48–2.79)	1.41 (0.80–4.14)	1.20 (1.07–1.34)	**0.002**
AFABP[a] (ng/mL)	10.9 (6.5–19.0)	18.6 (11.8–34.0)	2.50 (2.07–3.01)	<**0.001**[b]
Men	8.3 (5.1–14.4)	14.8 (9.0–28.2)		
Women	14.6 (9.2–24.5)	21.5 (14.5–40.8)		

95% CI, 95% confidence interval; ACEI, angiotensin converting enzyme inhibitors; AFABP, adipocyte fatty acid-binding protein; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FG, fasting glucose; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein-cholesterol; HF, heart failure; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; LDL-C low density lipoprotein-cholesterol; TG, triglyceride.
Data were presented as mean ± standard deviation or median (25th to 75th percentile).
[a]Log-transformed before analysis.
[b]Sex-adjusted hazard ratio (95% confidence interval) and *P* value.

a sensitivity analysis was further performed in these 5242 participants but including only participants who survived and remained free of outcome events in 2015. In the remaining 5035 participants, 296 (5.9%) developed HF hospitalization after 2015, (*Table S2*) and serum AFABP level remained significantly associated with incident HF hospitalization (HR 1.26, 1.01–1.56, *P* = 0.037), together with use of SGLT2i with cDDD ≥ 180 (HR 0.51, 0.26–0.98, *P* = 0.042) in multivariable Cox regression analysis (*Table S3*). Lastly, the results were also similar in a sensitivity analysis in which patients with atrial fibrillation at baseline were excluded.

Differences in the cumulative incidence of HF hospitalization among the study participants stratified by their baseline serum AFABP levels and cDDD of SGLT2i

In an exploratory analysis to examine the interactions between the use of SGLT2i and incident HF hospitalization in relation to their baseline serum AFABP level, the study

Table 3 Use of sodium glucose co-transporter 2 inhibitors and incident HF hospitalization

Parameter	Total	No incident HF hospitalization	Incident HF hospitalization	Unadjusted HR (95% CI)	*P*-value
N	3322	3146	176	—	—
Use of SGLT2i	731 (22%)	727 (23.1%)	4 (2.3%)	0.24 (0.04–0.74)	**0.014**
Canagliflozin	3	3	0		
Dapagliflozin	323	320	3		
Empagliflozin	403	402	1		
Ertugliflozin	2	2	0		
cDDD of SGLT2i (n = 731)	681 (298–1159)	686 (299–1163)	139 (124–231)	0.991 (0.985–0.997)	**0.002**
cDDD				0.996 (0.994–0.999)	**<0.001**
No SGLT2i	2591 (78%)	2419 (76.9%)	172 (97.7%)	Referent	—
<180	113 (3.4%)	110 (3.5%)	3 (1.7%)	1.26 (0.40–3.99)	0.690
≥180	618 (18.6%)	617 (19.6%)	1 (0.6%)	0.08 (0.01–0.55)	**0.010**

95% CI, 95% confidence interval; cDDD, cumulative daily defined dose; HF, heart failure; HR, hazard ratio; SGLT2i, sodium-glucose transport protein 2 inhibitors.

Table 4 Multivariable Cox regression analysis showing the associations between baseline circulating AFABP levels and incident HF hospitalization (N = 3322)

Characteristic	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Men	1.43 (0.98–2.09)	0.065	1.44 (0.98–2.11)	0.061
Age (years)	1.05 (1.03–1.07)	**<0.001**	1.05 (1.03–1.07)	**<0.001**
BMI (kg/m^2)	1.05 (0.99–1.07)	0.178	1.03 (0.99–1.07)	0.182
Ever-smoker	0.90 (0.62–1.32)	0.594	0.89 (0.61–1.31)	0.571
Duration of diabetes (years)	1.03 (1.01–1.05)	**0.004**	1.03 (1.01–1.05)	**0.012**
Hypertension	1.41 (0.66–3.01)	0.370	1.38 (0.64–2.93)	0.410
Dyslipidaemia	1.39 (0.74–2.58)	0.305	1.43 (0.75–2.72)	0.272
Atrial fibrillation	1.83 (1.15–2.92)	**0.011**	1.85 (1.13–3.03)	**0.015**
eGFR < 60 mL/min/1.73 m^2	1.39 (0.93–2.07)	0.113	1.38 (0.92–2.05)	0.117
Albuminuria ≥ A2	2.17 (1.50–3.15)	**<0.001**	2.21 (1.52–3.22)	**<0.001**
HbA1c (%)	1.07 (0.96–1.19)	0.219	1.07 (0.94–1.22)	0.302
Metformin	1.46 (0.99–2.17)	0.057	1.56 (1.01–2.42)	**0.045**
SGLT2i[b]	—	—		
No SGLT2i	—	—	Referent	
cDDD < 180	—	—	1.38 (0.43–4.54)	0.578
cDDD ≥ 180	—	—	0.10 (0.01–0.68)	**0.019**
Insulin	1.43 (1.02–2.00)	**0.041**	1.39 (0.98–1.97)	0.060
Aspirin	1.24 (0.89–1.72)	0.206	1.26 (0.90–1.76)	0.185
Furosemide	1.62 (1.09–2.41)	**0.016**	2.26 (1.32–3.87)	**0.003**
Beta-blockers	1.09 (0.80–1.50)	0.577	1.07 (0.77–1.47)	0.698
hsCRP[a] (mg/mL)	1.09 (0.96–1.24)	0.209	1.09 (0.96–1.25)	0.197
AFABP[a] (ng/mL)	1.37 (1.04–1.79)	**0.023**	1.38 (1.06–1.80)	**0.019**

95% CI, 95% confidence interval; ACEI, angiotensin converting enzyme inhibitors; AFABP, adipocyte fatty acid-binding protein; ARB, angiotensin II receptor blockers; BMI, body mass index; cDDD, cumulative defined daily dose; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; SGLT2i, sodium glucose co-transporter 2 inhibitors.
[a]Log-transformed before analysis.
[b]Time-dependent covariate.

participants were divided into two groups with their baseline serum AFABP level above and below the sex-specific median. In each group, the participants were further stratified by their cDDD of SGLT2i. Not surprisingly, participants who had the highest cDDD of SGLT2i had significantly lower cumulative incidence of HF hospitalization compared with those who did not use SGLT2i throughout the study period. This finding was evident in both groups with AFABP above (0.36% vs. 8.44% on no SGLT2i, $P < 0.001$, respectively) or below the sex-specific median (0% vs. 2.98% on no SGLT2i, $P < 0.001$, respectively). On the other hand, a dose-dependent reduction in the cumulative incidence of HF hospitalization in response to SGLT2i, based on cDDD, was more clearly seen in participants with a high baseline AFABP level above the sex-specific median (P for trend < 0.01 and <0.05 for AFABP above and below sex-specific median, respectively) (*Figure 1*).

Discussions

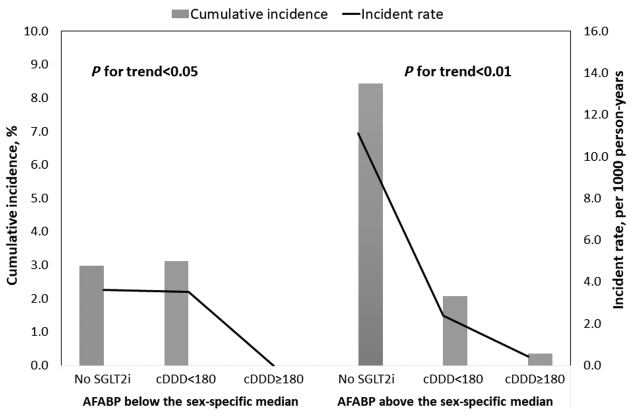
In this study, we observed that serum AFABP level was independently associated with incident HF hospitalization in an exclusively diabetic population with increased HF risk, regardless of the use of SGLT2i during the study period. Moreover, we also explored the potential of employing baseline serum

Table 5 Multivariable Cox regression analysis showing the associations between baseline circulating AFABP levels and incident HF hospitalization in participants with and without history of CVD and HF hospitalization at baseline (N = 5242)

	Model 1		Model 2	
Characteristic	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Men	1.19 (0.91–1.56)	0.216	1.19 (0.90–1.58)	0.226
Age (years)	1.05 (1.04–1.06)	**<0.001**	1.05 (1.04–1.06)	**<0.001**
BMI (kg/m^2)	1.03 (1.003–1.06)	**0.030**	1.03 (1.003–1.06)	0.029
Ever-smoker	1.07 (0.83–1.38)	0.616	1.06 (0.82–1.37)	0.673
Duration of diabetes (years)	1.01 (1.00–1.02)	0.092	1.01 (1.00–1.02)	**0.144**
Hypertension	1.72 (0.86–3.43)	0.127	1.72 (0.87–3.43)	0.121
Dyslipidaemia	1.10 (0.69–1.77)	0.689	1.11 (0.69–1.77)	0.674
Atrial fibrillation	1.81 (1.38–2.38)	**<0.001**	1.77 (1.33–2.36)	**<0.001**
CVD	1.02 (0.79–1.32)	0.872	0.94 (0.71–1.25)	0.658
History of HF hospitalization	1.94 (0.79–4.74)	0.148	1.99 (0.94–4.22)	0.072
eGFR < 60 mL/min/1.73 m^2	1.43 (1.09–1.88)	**0.009**	1.47 (1.12–1.92)	**0.006**
Albuminuria	1.88 (1.47–2.41)	**<0.001**	1.47 (1.12–1.92)	**<0.001**
HbA1c (%)	1.12 (1.04–1.21)	**0.002**	1.12 (1.04–1.21)	**0.004**
Metformin	1.50 (1.16–1.95)	**0.002**	1.55 (1.18–2.03)	**0.002**
SGLT2i[b]	—	—	—	
No SGLT2i	—	—	Referent	—
cDDD < 180	—	—	2.41 (0.87–6.66)	0.091
cDDD ≥ 180	—	—	0.46 (0.24–0.88)	**0.020**
Insulin	1.17 (0.91–1.50)	0.234	1.15 (0.89–1.49)	0.282
Aspirin	1.16 (0.90–1.50)	0.255	1.18 (0.90–1.54)	0.236
Furosemide	1.77 (1.37–2.30)	**<0.001**	1.98 (1.46–2.69)	**<0.001**
History of HF : Furosemide[c]	0.32 (0.12–0.85)	**0.022**	0.29 (0.12–0.67)	**0.004**
Spironolactone	1.53 (0.80–2.97)	0.208	1.55 (0.80–3.00)	0.193
Beta-blocker	1.13 (0.90–1.42)	0.285	1.12 (0.89–1.41)	0.323
hsCRP[a] (mg/mL)	1.04 (0.96–1.14)	0.352	1.04 (0.95–1.14)	0.360
AFABP[a] (ng/mL)	1.33 (1.11–1.60)	**0.002**	1.33 (1.10–1.60)	**0.003**

95% CI, 95% confidence interval; AFABP, adipocyte fatty acid-binding protein; BMI, body mass index; cDDD, cumulative defined daily dose; CVD, cardiovascular diseases; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; SGLT2i, sodium glucose co-transporter 2 inhibitors.
[a]Log-transformed before analysis.
[b]Time-dependent covariate.
[c]Interaction term.

Figure 1 Cumulative incidence of HF hospitalization in study participants stratified by their baseline circulating AFABP levels and use of SGLT2i. AFABP, adipocyte fatty acid-binding protein; cDDD, cumulative daily defined dose; HF, heart failure; SGLT2i, sodium glucose co-transporter 2 inhibitors.



AFABP level as a tool to prioritize patients with type 2 diabetes who might benefit more from the use of SGLT2i in preventing HF hospitalization.

Compared with most previous studies on AFABP and HF, the prospective, contemporary, and homogenous nature of our study cohort is one of its strengths. Although serum AFABP level had been shown to correlate positively with circulating concentrations of N-terminal fragment of pro-B-type natriuretic peptide, an established marker of HF,[21,25,26] the associations between serum AFABP level and left ventricular remodelling is less straight forward. Left ventricular hypertrophy and diastolic dysfunction contribute significantly to the pathogenesis of HF in diabetes, especially in those without known ischaemic heart disease like our study participants.[2] In several cross-sectional studies, high circulating AFABP level was associated with the presence of left ventricular systolic and/or diastolic dysfunction,[20,27,28] as well as increasing severity of clinical HF.[21] However, there were also studies reporting an inverse relationship.[26,29] These conflicting observations could possibly be a result of the inherent limitations of a cross-sectional study design, or differences in the study populations, or both. It was recently shown that the association between circulating AFABP level and left ventricular mass followed a slightly U-shaped curve, with positive association observed only at high circulating AFABP levels,[26] which were commonly found among individuals with type 2 diabetes.[30] Indeed, a recent prospective ECHO study in

patients with type 2 diabetes demonstrated that circulating AFABP level was associated not only with left ventricular remodelling and diastolic dysfunction at baseline but also with the longitudinal increase in left ventricular mass, E/e' ratio, and the development of major adverse cardiovascular events.[31] Therefore, in contrast to our cohort with exclusively individuals with type 2 diabetes, variations in the percentage of patients having type 2 diabetes in the study populations in previous studies could have led to their observed differences in the association between circulating AFABP level and LV remodelling.

Moreover, our findings have extended the understanding of the prospective associations between circulating AFABP level and HF hospitalization, reported previously in the Cardiovascular Health Study.[22] We demonstrated that, despite the beneficial effects of SGLT2i in reducing the risks of HF hospitalization, the longitudinal association between baseline serum AFABP level and incident HF hospitalization remained significant and was independent of the use of SGLT2i in patients with type 2 diabetes. In fact, AFABP, in addition to being a lipid chaperone protein, has also been implicated in endoplasmic reticulum stress, JNK activation, lipotoxicity, and systemic inflammation,[16] which are all key pathways in the pathogenesis of diabetic cardiomyopathy.[2] Moreover, *in vitro* studies had also shown that adipocyte-derived AFABP could exert a negative inotropic effect on rat cardiomyocytes and inhibit their contractility.[32] Together with the clinical data, these preclinical findings provide a mechanistic link that may account for the association between AFABP and the development of HF hospitalization. On the other hand, in our exploratory analysis, we found that the use of SGLT2i appeared to be more effective in reducing the cumulative incidence of HF hospitalization in those with higher HF risk as reflected by their baseline AFABP level. The conclusions from this explorative analysis remained speculative and likely hypothesis generating. However, SGLT2i, beyond glucose-lowering and diuresis, has also been proposed to possess other beneficial effects to the heart, such as reduction of inflammation and oxidative stress, inhibition of sodium-hydrogen exchange, as well as improvement in myocardial remodelling and bioenergetics,[33] which could have offset the detrimental effects of AFABP, with the benefits being more readily observed in those with higher AFABP levels.

There are several limitations in our study. First, the observational study design did not allow for any causal relationship to be inferred between high circulating AFABP level and the development of incident HF hospitalization. Secondly, due to the registry design and the fact that ECHO is not routinely performed in our clinical practice, ECHO data were not available in a significant proportion of participants both at baseline and at the time of HF hospitalization. This rendered it difficult to perform subgroup analysis on the associations of serum AFABP level with different HF phenotypes. Thirdly, neither brain BNP nor N-terminal fragment of pro-BNP level was measured in our study. Furthermore, although some participants might have been managed as outpatients without hospitalization, it is difficult to be certain of the diagnosis of HF based on outpatient records in which the documentation by clinicians can be highly variable. Therefore, in the present study, we have adopted a harder clinical endpoint of HF hospitalization, which is a commonly used outcome in large-scale randomized control trials.[5–8] Lastly, because serum AFABP level was measured only once in all participants, it was possible that changes in serum AFABP level could have occurred during the study period.

Nonetheless, while we previously demonstrated that circulating AFABP had the potential to become a novel prognostic marker of adverse renal and mortality outcomes in diabetes,[19,34] the present study further suggested that it might also be usefully employed for HF risk stratification in patients with type 2 diabetes. Further research is required not only to validate our findings but also to confirm if serum AFABP level can be employed to prioritize the use of SGLT2i in HF prevention. These are important especially in areas where health care resources are limited, and in this era when SGLT2i is increasingly advocated and prescribed in patients with type 2 diabetes for its cardiorenal benefits.

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Conflict of interest

None declared.

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Author contributions

C.H.L. researched the data and wrote the manuscript. D.T.W. L., M.M.A.Y., W.S.C., and Y.C.W. researched the data. A.K.C. K., D.S.H.C., and C.H.Y.F. performed statistical analyses. A.X. and K.S.L.L. critically reviewed and edited the manuscript. K. S.L.L. initiated and supervised the study and is the guarantor of this work and as such had full access to all the data in the

study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interests

All authors declare no conflicts of interest.

Supporting information

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

Table S1. Sensitivity analysis showing the association between baseline circulating AFABP levels and incident HF hospitalization (N=3265 after exclusion of study participants with LVEF <50% at baseline).

Table S2. Use of SGLT2i and incident HF hospitalization in participants who survived and remained free of outcome events in 2015.

Table S3. Sensitivity analysis showing the association between baseline circulating AFABP levels and incident HF hospitalization in participants who survived and remained free of outcome events in 2015 (N=5035).

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