

Opportunistic Screening for Asymptomatic Left Ventricular Dysfunction in Type 2 Diabetes Mellitus

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Abstract

BACKGROUND Prevention of heart failure (HF) has been recognized as an urgent public health need. International guidelines recommend natriuretic peptide biomarker-based screening for patients at high HF risk to allow early detection and intervention to delay HF progression and mortality. Little has been reported the incorporation of screening procedure to existing clinical practice. The objective of the study was to describe the opportunistic screening of left ventricular dysfunction in patients with type 2 diabetes mellitus (DM). **METHOD** This was a prospective screening study at the DM complication screening center. **RESULTS** Between 2018 and 2019, 1,132 consecutive DM patients with no prior history of HF or atrial fibrillation (AF) attending regular complication screening were invited to participate. Of these, 89 patients refused or failed to complete the screening. The final analysis included 1,043 patients (age: 63.7 ± 12.4 years; male: 56.3%). The mean HbA1c was $7.25 \pm 1.34\%$. There were 81.8% patients with concomitant hypertension, 31.1% with coronary artery disease, 8.0% with previous stroke, and 5.5% with peripheral artery disease. Furthermore, 45.7% patients had diabetic retinopathy, 33.6% had peripheral neuropathy, and 30.7% had chronic kidney disease (CKD) stage 3-5. At the screening session, 43 patients (4.1%) had an elevated NT-proBNP concentration above the age-specific diagnostic thresholds for HF, and 43 patients (4.1%) had newly detected AF. The prevalence of elevated NT-proBNP concentration increased with age from 0.85% in patients aged <50 years to 7.14% in those aged 70-79 years and worsening kidney function from 0.43% in patients with CKD stage 1 to 42.86% in CKD stage 5. In multivariate logistic regression, male gender (OR: 3.67 (1.47-9.16), $p = 0.005^*$), prior stroke (OR: 3.26 (1.38-7.69), $p = 0.007^*$), CKD ($p < 0.001^*$), and newly detected AF (OR: 7.02 (2.65-18.57), $p < 0.001^*$) were significantly associated with elevated NT-proBNP concentration. Amongst patients with elevated NT-proBNP concentration, their mean left ventricular ejection fraction (LVEF) was $51.4 \pm 14.7\%$, and 45% patients had a LVEF <50%. **CONCLUSION** Both NT-proBNP and ECG screening could be easily implemented. Our findings demonstrate systemic screening allows detection of early phase HF and asymptomatic AF in patients with DM, thereby facilitating the implementation of preventive measure to improve the long-term outcomes.

Research In Context

What is already known about this subject?

- Patients with Diabetes Mellitus (DM) have a higher risk of developing heart failure (HF) than those without.
- Plasma natriuretic peptides is useful in screening early HF and/or asymptomatic left ventricular dysfunction amongst patients at risk of developing HF.

What is the key question?

- Is incorporating serum N-terminal-B-type natriuretic peptide (NT-proBNP) measurement into the DM complication screening program effective in identifying patients with early HF?

What are the new findings?

- In a tertiary center of patients with type 2 DM, the prevalence of elevated NT-proBNP concentration was 4.1%.
- Amongst patients with elevated NT-proBNP concentration, their mean left ventricular ejection fraction (LVEF) was $51.4 \pm 14.7\%$, and 45% patients had a LVEF below 50%.
- Prevalence of raised NT-proBNP increased with age and chronic kidney disease (CKD) stage.

How might this impact on clinical practice in the foreseeable future?

- Targeted screening of early HF with NT-proBNP in DM patients should be considered, particularly those with advanced age and CKD stages.

Background

Heart failure (HF) is a cardiovascular disease epidemic affecting 26 million people worldwide.¹ The incidence and prevalence of HF appear to be on a rising trend, particularly in developing countries due to the rapidly aging population and the high prevalence of cardiovascular risk factors. In Asian countries, the prevalence of HF reportedly ranges between 1.3% and 6.7%.² In China, there are 4.2 million people living with HF.^{3,4} Over the past few decades, advances in pharmacological therapy including angiotensin converting enzyme inhibitors,^{5,6} angiotensin II receptor blockers, beta-adrenergic blockers,⁷⁻⁹ mineralocorticoid receptor antagonists,^{10,11} ivabradine,¹² and more recently sacubitril/valsartan,¹³ as well as various device therapies have been shown in randomized controlled trials to significantly improve patient outcomes particularly in those with reduced left ventricular ejection fraction (LVEF). Nonetheless, due to the progressive nature of the condition, the prognosis of HF in real-world practice remains poor. In a recent European study, the 1-year mortality rate in patients with newly diagnosed HF was as high as 16.4%;¹⁴ likewise, the reported 1-year mortality in Asia ranged between 8.9% and 19.5%.¹⁵⁻¹⁷ Therefore, prevention of HF has turned into the priority of HF management at the public health level.

Diabetes mellitus (DM) is a well-recognized risk factor of cardiovascular diseases and HF.¹⁸ Patients with DM have a 2- to 4-fold higher risk of HF compared with those without,¹⁹ and up to 27.7% of DM patients had concomitant HF.²⁰⁻²⁴ In 2001, the American College of Cardiology (ACC) and the American Heart Association (AHA) introduced a new HF classification system including individuals who have not had clinical HF, but are at high risk of developing HF due to either concomitant comorbidities such as DM (Stage A), or underlying cardiac structural abnormalities (Stage B).²⁵ The initial intention to include these so-called “pre-HF” patients into the classification is merely to help healthcare providers with the early identification of patients who are at risk of developing HF. Recently, sodium–glucose cotransporter-2 (SGLT2) inhibitors have been shown in pivotal studies to substantially reduce hospitalization of HF

and/or cardiovascular mortality in patients with DM, even amongst those without pre-existing HF or established cardiovascular disease,^{26,27} providing a genuine therapeutic option to prevent HF. Early identification of patients with DM at high risk of developing HF before the occurrence of clinical HF, followed by aggressive preventive measure appears to be a logical strategy. Nonetheless, amongst patients with newly diagnosed HF, the prevalence of DM was as high as 36%,¹⁷ precluding any form of primary preventive measure. In fact, the latest ACC/AHA/HFSA guideline for the management of HF has recommended natriuretic peptide biomarker-based screening for patients at risk of developing HF (Class IIa, B-R),²⁸ which could help early identification of individuals at high-risk to prevent the development of HF. Despite this, clinical literatures describing the incorporation of NT-proBNP measurement as a screening tool to routine DM complication screening program is scarce. In the present study, we explored the possibility of incorporating NT-proBNP measurement into the DM complication screening program in order to identify individuals at high risk of developing HF.

Methods

Study Design and Patients

This prospective screening study was coordinated by the Division of Cardiology, and the Division of Endocrinology and Metabolism, the Department of Medicine, The University of Hong Kong. The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. All participants were recruited from the Diabetic Complication Screening Center, Queen Mary Hospital. Patients with type 2 DM scheduled for their regular diabetic complication screening were invited to participate to the study. Patients were excluded if they were under 18 years of age, had history of heart failure and/or atrial fibrillation (AF). Written informed consent was obtained from all recruited participants.

Patients attended their regular diabetic complication screening visit every 1.5 to 2 years. At the first visit, demographic data, detailed medical and drug histories were obtained using a standardized questionnaire and the territory-wide computerized medical system. During each visit, anthropometric parameters including body weight, height, body mass index, and blood pressure were measured. After an overnight fast of at least 8 hours, fasting blood was drawn for plasma glucose, lipids and glycated hemoglobin (HbA1c). Serum creatinine was measured and estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as described previously.²⁹ Albuminuria status was assessed using at least two random urine samples. All patients, except those who were being followed up regularly by ophthalmologists at the public sector had retinal photographs captured and graded systemically by trained optometrists and ophthalmologists according to the United Kingdom National Screening Committee guidelines.³⁰

In this study, individuals who agreed to participate, after their written informed consent, would have serum N-terminal-B-type natriuretic peptide (NT-proBNP) assayed (Roche Diagnostics, GmbH), and a

frontal plane (6-lead) 10-second electrocardiogram (ECG) performed at a seated-position for the detection of AF. Patients with an elevated serum NT-proBNP concentration above the age-specific diagnostic threshold for HF, according to the manufacturer's instruction, were invited for a transthoracic echocardiography within 1 week. Two independent cardiologists reviewed all the ECG tracings recorded to provide a rhythm diagnosis using standard criteria.³¹

Statistical Analysis

Continuous and discrete variables were expressed as mean \pm standard deviation and percentages, respectively. Chi-square test or Fisher's exact test was used to compare categorical variables between groups. Student's t test was performed to compare continuous variables. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) of each variable to predict elevated NT-proBNP concentration and AF were determined by univariate logistic regression and with multivariate logistic regression model for variable with p -value < 0.1 . All statistical analyses were performed using the Statistical Package for the Social Sciences software version 21.0 for Mac (SPSS, Chicago, IL).

Results

Between November 2018 and October 2019, 1,132 patients who fulfilled the inclusion criteria of the present study were invited to participate, of which 30 patients declined. The response rate was 97.3%. In addition, 59 patients consented for the study (5.2%) did not complete all screening procedures and were excluded from the final analysis. As a result, 1,043 patients with type 2 DM were included in this final analysis (Fig. 1). Table 1 summarizes the characteristics of the study population. The mean age was 63.7 ± 12.4 years; 587 patients (56.3%) were male. The mean body mass index was 26.0 ± 4.6 Kg/m², and the mean Hba1c was $7.25 \pm 1.34\%$. 846 patients (81.8%) had concomitant hypertension, and 337 patients (32.3%) had positive smoking history. In addition, 477 patients (45.7%) had diabetic retinopathy, 350 patients (33.6%) had peripheral neuropathy, and 320 patients (30.7%) had CKD stage 3–5. For macrovascular complications, there were 324 patients (31.1%) with coronary artery disease, 83 patients (8.0%) with previous stroke, and 57 patients (5.5%) with documented peripheral artery disease.

Table 1
Demographics and clinical characteristics

	Total (n = 1,043)
Demographics and co-morbidities	
Age, years	65
Male, n (%)	587 (56.3)
Hypertension, n (%)	846 (81.1)
Smoking status, n (%)	
Never smoker, n (%)	706 (67.7)
Ex-smoker, n (%)	237 (22.7)
Current smoker, n (%)	100 (9.6)
Diabetic retinopathy, n (%)	488 (46.2)
Peripheral neuropathy, n (%)	350 (33.6)
Chronic kidney disease	
CKD Stage 3–5, n (%)	320 (30.7)
Dialysis, n (%)	13(1.2)
Renal transplant, n (%)	10 (1.0)
Coronary artery disease, n (%)	324 (31.1)
Stroke, n (%)	83 (8.0)
Peripheral artery disease, n (%)	57 (5.5)
Anthropometric and physical parameters	
Weight, kg	67.3 ± 13.8
Height, m	1.60 ± 0.09
BMI, kg/m ²	26.0 ± 4.6
Systolic BP, mmHg	133.6 ± 17.0
Diastolic BP, mmHg	71.8 ± 11.7
Biochemical measurements	

Abbreviations: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; LDL; and NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

	Total (n = 1,043)
Hba1c, %	7.25 ± 1.34
NT-proBNP, pg/ml	328 ± 2,175
eGFR, ml/min/1.73m ²	70.5 ± 25.2
Proteinuria, n (%)	501 (48)
Albumin, d/L	44.2 ± 3.6
Hb, g/dL	13.2 ± 1.7
Abbreviations: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; LDL; and NT-proBNP: N-terminal prohormone of brain natriuretic peptide.	

Forty-three patients (4.1%) had an elevated NT-proBNP concentration above the age-specific diagnostic threshold for heart failure during the screening procedure. At the same time, 43 patients (4.1%) were newly detected to have AF. 10 patients (1.0%) had both an elevated NT-proBNP concentration and newly detected AF. The prevalence of elevated NT-proBNP concentration increased with age from 0.85% in patients aged < 50 years to 7.14% in those aged 70–79 years and with worsening kidney function from 0.43% in patients with CKD stage 1 to 42.86% in CKD stage 5. (Fig. 2). Table 2 summarizes the prevalence of elevated NT-proBNP concentration in these 1,043 patients stratified according to their age and CKD stage. Likewise, the prevalence of newly detected AF increased with age, as well as worsening kidney function. (Fig. 3)

Table 2
The prevalence of elevated NT-proBNP concentration in 1,043 patients with type 2 diabetes mellitus stratified according to age and chronic kidney disease stage

	CKD stage 1	CKD stage 2	CKD stage 3–5
Age < 60 years	0.0%	0.6%	9.5%
Age 60–69 years	0.0%	1.0%	14.3%
Age ≥ 70 years	5.9%	3.1%	9.6%
Abbreviations: CKD: chronic kidney disease			

Table 3 summarizes factors predictive of an elevated NT-proBNP concentration above the age-specific diagnostic threshold of heart failure in patients with type 2 DM, together with their corresponding ORs based on logistic regression and 95% CIs. On univariate analysis, increasing age, male gender, hypertension, coronary artery disease, prior stroke, peripheral arterial disease, proteinuria, CKD, peripheral neuropathy, and newly detected AF were associated the increasing risk of elevated NT-proBNP

concentration. On multivariate analysis, only male gender (OR: 3.67 (1.47–9.16), $p = 0.005^*$), prior stroke (OR: 3.26 (1.38–7.69), $p = 0.007^*$), CKD ($p < 0.001^*$), and newly detected AF (OR: 7.02 (2.65–18.57), $p < 0.001^*$) remained significantly associated elevated NT-proBNP concentration (Table 3). All patients with an elevated NT-proBNP concentration above the diagnostic threshold of HF were invited for transthoracic echocardiogram, of which 42 patients participated and 1 patient refused. The mean left ventricular ejection fraction (LVEF) was $51.4 \pm 14.7\%$; 19 out of 42 patients (45%) had a LVEF below 50%, 13 patients with LVEF $> 50\%$ (31.0%) had left ventricular hypertrophy and diastolic dysfunction, and 1 patient had moderate-to-severe mitral regurgitation. 12 patients with LVEF below 50% were in sinus rhythm and 7 were in AF.

Table 3

Univariate and multivariate analyses showing the predictors of elevated NT-proBNP concentration in 1,043 patients with type 2 diabetes mellitus

	Number	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age			0.026*		0.734
< 50	1	Reference		Reference	
50–59	4	2.05 (0.28–18.58)	0.522	0.74 (0.57–9.46)	0.814
60–69	15	4.99 (0.65–38.15)	0.122	1.33 (0.12–14.61)	0.815
70–79	16	8.92 (1.17–68.14)	0.035*	1.41 (0.13–15.89)	0.782
≥80	7	8.04 (0.97–66.45)	0.053	0.77 (0.06–9.87)	0.838
Male	35	3.55 (1.63–7.73)	0.018*	3.67 (1.47–9.16)	0.005*
Smoker	5	1.25 (0.48–3.26)	0.643		
Hypertension	42	10.24 (1.40–74.85)	0.022*	1.04 (0.12–9.26)	0.969
Atrial fibrillation	10	8.89 (4.04–19.53)	< 0.001*	7.02 (2.65–18.57)	< 0.001*
CAD	23	2.87 (1.44–4.94)	0.002*	2.10 (0.96–4.58)	0.063
PAD	10	4.67 (2.20–9.91)	0.001*	1.70 (0.63–4.56)	0.294
Stroke	14	6.51 (3.29–12.90)	< 0.001*	3.26 (1.38–7.69)	0.007*
Diabetic retinopathy	23	1.38 (0.75–2.55)	0.299		
Peripheral neuropathy	25	2.89 (1.55–5.36)	0.001*	1.14 (0.50–2.60)	0.749
CKD					< 0.001*
Stage 1	1	Reference		Reference	
Stage 2	7	3.36 (0.41–27.49)	0.258	1.83 (0.21–16.28)	0.586
Stage 3	14	13.64 (1.78–104.61)	0.012*	5.64 (0.66–48.61)	0.115
Stage 4	12	79.54 (10.03–630.82)	< 0.001*	37.21 (3.97–348.84)	0.002*
Stage 5	9	174.00 (20.4–1487.7)	< 0.001*	168.6 (16.5–1,727.7)	< 0.001*

Abbreviations: BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; CKD: Chronic kidney disease; and PAD: Peripheral artery disease.

	Number	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Proteinuria	34	4.31 (2.05–9.08)	< 0.001*	1.28 (0.52–3.15)	0.595
BMI			0.611		
< 22.9	14	Reference			
23.0-24.9	9	0.96 (0.41–2.25)	0.921		
≥25	20	0.722 (0.36–1.45)	0.361		
Hba1c		1.02 (0.82–1.28)	0.861		
Systolic BP		0.99 (0.98–1.01)	0.451		
Abbreviations: BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; CKD: Chronic kidney disease; and PAD: Peripheral artery disease.					

Table 4 summarizes factors predictive of newly detected AF in patients with type 2 DM, together with their corresponding ORs based on logistic regression and 95% CIs. On univariate analysis, increasing age, male gender, coronary artery disease, prior stroke, and CKD, were associated newly detected AF. On multivariate analysis, only increasing age, male gender, and prior stroke remained significantly associated newly detected AF (Table 4). Non-vitamin K oral anti-coagulants and warfarin were initiated in 39 patients (90.7%) and 4 patients (9.3%) respectively.

Table 4
Univariate and multivariate predictors of newly detected atrial fibrillation in 1,043 patients with type 2 diabetes mellitus

	Number	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age			0.006*		0.095
< 60	3	Reference		Reference	
60–69	18	5.97 (1.74–20.44)	0.004*	2.94 (1.06–8.18)	0.019*
70–79	13	7.07 (1.99–25.08)	0.002*	5.26 (1.90–14.58)	0.040*
≥80	9	10.42 (2.77–39.24)	0.001*	4.74 (1.47–15.26)	0.017*
Male	33	2.66 (1.30–5.45)	0.008*	2.13 (1.09–4.90)	0.029*
Smoker	7	1.90 (0.82–4.38)	0.134		
Hypertension	40	3.21 (0.98–10.48)	0.054*	1.13 (0.31–4.03)	0.856
Elevated NT-proBNP	10	8.88 (4.04–19.53)	< 0.001*		
CAD	21	2.20 (1.19–4.05)	0.012*	1.22 (0.63–2.34)	0.553
PAD	6	2.33 (0.95–5.73)	0.065	1.40 (0.52–3.82)	0.506
Stroke	11	4.43 (2.14–9.16)	< 0.001*	3.24 (1.50–7.01)	0.003*
Diabetic retinopathy	15	0.59 (0.31–1.12)	0.104		
Peripheral neuropathy	20	1.77 (0.96–3.27)	0.069	1.01 (0.50–2.07)	0.970
CKD					0.640
Stage 1	2	Reference		Reference	
Stage 2	20	4.92 (1.14–21.21)	0.033*	3.01 (0.68–13.34)	0.146
Stage 3	17	8.36 (1.91–36.57)	0.005*	3.23 (0.68–15.27)	0.139
Stage 4	3	7.88 (1.28–48.51)	0.026*	2.23 (0.32–15.38)	0.416
Stage 5	1	5.78 (0.50–66.49)	0.160	2.67 (0.21–33.70)	0.448
Proteinuria	27	1.87 (1.00–3.52)	0.051	1.28 (0.63–2.61)	0.491
BMI			0.530		
< 22.9		Reference			
23.0–24.9		1.50 (0.61–3.67)	0.379		

Abbreviations: BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; CKD: Chronic kidney disease; and PAD: Peripheral artery disease.

	Number	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
≥25		1.50 (0.72–3.12)	0.274		
Hba1c		0.99 (0.79–1.25)	0.935		
Systolic BP		0.98 (0.96–0.99)	0.040*		

Abbreviations: BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; CKD: Chronic kidney disease; and PAD: Peripheral artery disease.

Discussion

In the present study, we incorporated NT-proBNP measurement together with ECG screening into the DM complication screening program. We identified the prevalence and predictors of elevated NT-proBNP concentration, which is indicative of a higher risk of developing HF and therefore could inform further clinical management. First, in our cohort of 1,043 consecutive DM patients without prior history of HF or AF, we showed that the prevalence of elevated NT-proBNP concentration, defined as above the age-specific diagnostic threshold of HF, was relatively high at 4.1%. The prevalence increased progressively with age (from 0.85% in patients aged < 50 years to 7.14% in those aged 70–79 years), as well as with worsening kidney function (from 0.43% in patients with CKD stage 1 to 42.86% in CKD stage 5). Second, in multivariate logistic regression, male gender (OR: 3.67 (1.47–9.16), $p = 0.005^*$), prior stroke (OR: 3.26 (1.38–7.69), $p = 0.007^*$), CKD ($p < 0.001^*$), and newly detected AF (OR: 7.02 (2.65–18.57), $p < 0.001^*$) were associated with elevated NT-proBNP concentration. Third, amongst DM patients with elevated NT-proBNP concentration, 45% of them had an LVEF below 50%, and 31% of them had diastolic dysfunction with left ventricular hypertrophy. Last but not least, AF was newly detected in 4.1% of the current study population.

DM is associated with macrovascular and microvascular complications that can go unnoticed and be left untreated until irreversible damage ensues. The American Diabetes Association (ADA) has recommended a comprehensive list of medical evaluations to detect complications, which has been widely incorporated into DM complication screening programs worldwide.³² On the other hand, despite the high prevalence of HF (~ 28%) amongst DM patients,^{20–24} early detection or screening of HF and/or asymptomatic left ventricular dysfunction has not been recommended or routinely practiced. This may be partly related to the difficulty to detect HF particularly non-acute HF in primary care setting.³³ Plasma natriuretic peptides including NT-proBNP and BNP which have high positive predictive value for HF, are established tests for HF diagnosis,^{34–36} as well as prognostication.^{37–39} More recently, the use of plasma natriuretic peptides has been extended for screening of early HF and/or asymptomatic left ventricular dysfunction amongst patients at risk of developing HF.^{28, 40–42} The screening yield depends on the prevalence of HF and/or asymptomatic left ventricular dysfunction in specific screened population. In the present study involving patients with DM but without prior history of HF and AF, the overall prevalence of elevated NT-proBNP

concentration was relatively high at 4.1%, compared with ~ 1% prevalence of HF in the general population. Although NT-proBNP assay has a high positive predictive value to detect early HF and/or asymptomatic left ventricular dysfunction, it is not widely available due to cost. Nonetheless, the prevalence increased disproportionately with age and CKD stage, two independent predictors of elevated NT-proBNP concentration and asymptomatic left ventricular dysfunction in patients with DM. For instance, while the prevalence of elevated NT-proBNP concentration in DM patients aged < 70 years and with CKD stage 1 is negligible and may not justify screening, for those with CKD stage 3–5, the prevalence of elevated NT-proBNP concentration could range from 9.5–14.3%, giving a very high screening yield. Therefore, an age- and kidney function-based screening would be a more efficient strategy to identify patients with early HF or asymptomatic left ventricular dysfunction.

As the purpose to detect early HF and/or asymptomatic left ventricular dysfunction is to prevent HF, there should be a therapeutic intervention effective at this early phase to modify the disease course. In the STOP-HF trial involving 1,374 patients aged 40 years or older with at least one high-risk factor for HF but without HF and/or asymptomatic left ventricular dysfunction,⁴⁰ a BNP based screening program, together with the collaborative care between primary care physician and cardiovascular specialist, reduced the combined rates of left ventricular dysfunction and HF, which confirmed the role of plasma natriuretic peptides as a HF risk identifier. Furthermore, in the PONTIAC study,⁴¹ accelerated up-titration of renin-angiotensin system antagonists and beta-adrenergic blockers amongst DM patients with an elevated NT-proBNP concentration reduced hospitalization or death due to cardiac disease by 64% in 2 years. More recently, in EMPA-REG,²⁶ and CANVAS trials that randomized patients with type 2 DM and history of cardiovascular disease to SGLT2 inhibitors (empagliflozin and canagliflozin, respectively) or placebo, SGLT2 inhibitors substantially reduced cardiovascular mortality and hospitalization for HF. Furthermore, subgroup analyses of these landmark randomized controlled trials revealed that SGLT2 inhibitors reduced HF hospitalization regardless of the presence of documented HF at baseline, suggesting the possibility of utilizing SGLT2 inhibitors to improve HF outcome in DM patients with subclinical HF^{43, 44}. These further strengthens the armamentarium to prevent DM related HF.

Limitations

There are several limitations in our study. First, the presented data are collected from a single center, therefore local patient characteristics and medical practice may limit the generalizability of the results. Second, since the current study is a single-arm observational study instead of a randomized controlled trial, it remains uncertain whether incorporation of NT-proBNP measurement and ECG to DM complication screening program could reduce the risks of incident HF, hospitalization for HF, and/or mortality. Nonetheless, identification of these at-risk patients by systematic screening is the critical first step that would allow further prospective assessment of whether early intervention is associated with improved clinical outcome.

Conclusion

In a tertiary center of patients with type 2 DM, the prevalence of elevated NT-proBNP concentration and AF were both 4.1%. As the prevalence of raised NT-proBNP increased with age and CKD stage, targeted screening in these patient subgroups may result in a higher yield than universal screening. Identification of DM patients at risk of developing HF by systematic screening may allow early intervention to improve clinical outcome.

Abbreviations

AF

Atrial Fibrillation

CKD

Chronic Kidney Disease

DM

Diabetes Mellitus

ECG

Electrocardiogram

HbA1c

Glycated hemoglobin

HF

Heart Failure

LVEF

Left Ventricular Ejection Fraction

NT-proBNP

N-terminal-B-type Natriuretic Peptide

OR

Odds Ratio

SGLT2

Sodium–glucose Cotransporter-2

Declarations

Ethics approval and consent to participate: The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB number: UW 14-380). Informed written consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions: CWS is the principal investigator of the whole study responsible for study design, study execution, manuscript drafting, and study site recruitment. CKW and DH are major contributor in writing the manuscript. MZ, YML, WHL, YML, JJH, CPL, and EWC are the investigator of a local site and is responsible for the study design and study execution. WSY, MLZ, LXY, YQF, NT, JYC, XLL, HFT, CHL, and WSC made contribution to data collection. All authors read and approved the final manuscript.

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Figures

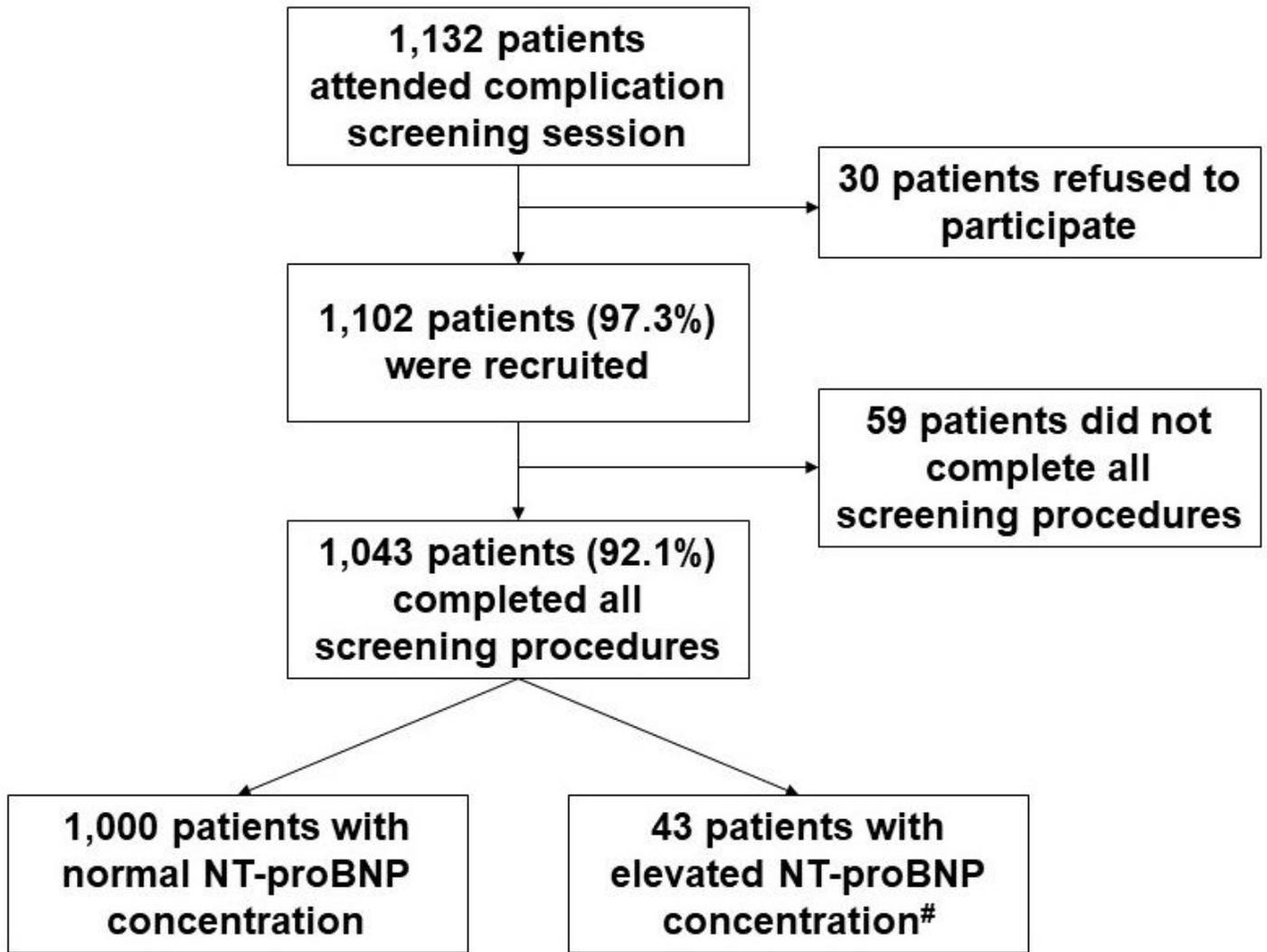
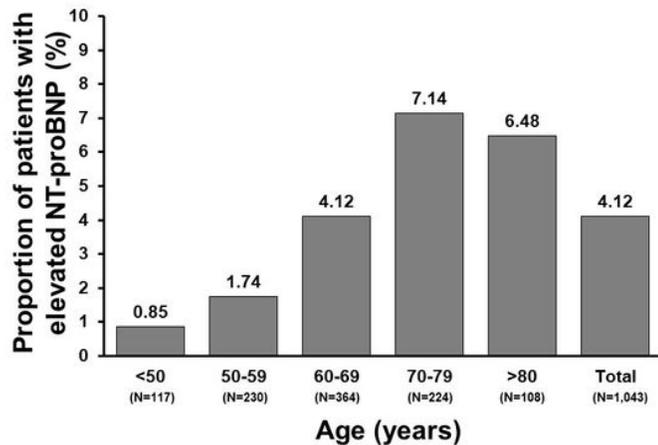
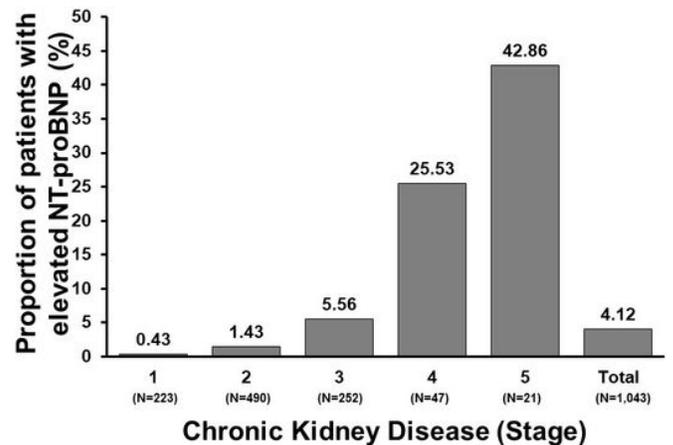
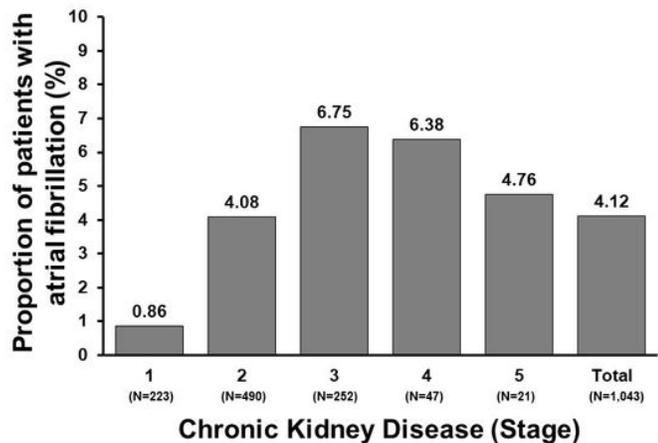
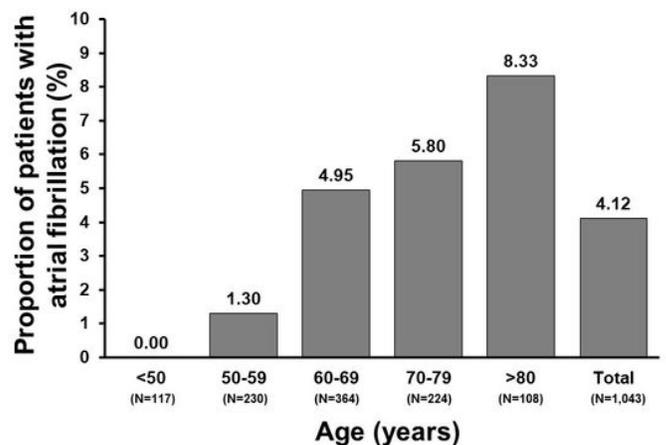


Figure 1

Study population

A**B****Figure 2**

Prevalence of elevated NT-proBNP concentration above the diagnostic threshold for heart failure across (1) age groups and (2) chronic kidney disease stages

A**B****Figure 3**

Prevalence of newly detected atrial fibrillation across (1) age groups and (2) chronic kidney disease stages