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Integrating natriuretic peptides and diastolic dysfunction to predict adverse events in high-risk asymptomatic subjects

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Background

Natriuretic peptides and diastolic dysfunction have prognostic value in asymptomatic subjects at risk for heart failure. Their integration might further refine the risk stratification process in this setting. Aim of this paper was to explore the possibility to predict heart failure and death combining diastolic dysfunction and natriuretic peptides in an asymptomatic population at risk for heart failure.

Methods

Among 4047 subjects aged $\geq 55/\leq 80$ years followed by 10 general practitioners in Italy, the DAVID-Berg study prospectively enrolled 623 asymptomatic outpatients at increased risk for heart failure. Baseline evaluation included electrocardiogram, echocardiogram, and natriuretic peptides collection. Based on diastolic dysfunction and natriuretic peptides, subjects were classified in four groups: control group (no diastolic dysfunction/normal natriuretic peptides, 57%), no diastolic dysfunction/high natriuretic peptides (9%), diastolic dysfunction/normal natriuretic peptides (24%), and diastolic dysfunction/high natriuretic peptides (11%). We applied Cox multivariable and Classification and Regression Tree analyses.

Results

The mean age of the population was 69 ± 7 years, 44% were women, mean left ventricular ejection fraction was 61%, and 35% had diastolic dysfunction. During a median follow-up of 5.7 years, 95 heart failure/death events occurred. Overall, diastolic dysfunction and natriuretic peptides were predictive of adverse events (respectively, hazard ratio 1.91, confidence interval 1.19–3.05, $p_{\text{adjusted}} = 0.007$, and hazard ratio 2.25, confidence interval 1.35–3.74, $p_{\text{adjusted}} = 0.002$) with Cox analysis. However, considering the four study subgroups, only the group with diastolic dysfunction/high natriuretic peptides had a significantly worse prognosis compared to the control group (hazard ratio 4.48, confidence interval 2.31–8.70, $p_{\text{adjusted}} < 0.001$). At Classification and Regression Tree analysis, diastolic dysfunction/high natriuretic peptides was the strongest prognostic factor (risk range 24–58%).

Conclusions

The DAVID-Berg data suggest that we look for the quite common combination of diastolic dysfunction/high natriuretic peptides to correctly identify asymptomatic subjects at greater risk for incident heart failure/death, thus more suitable for preventive interventions.

Keywords

Natriuretic peptides • diastolic dysfunction • prognosis • community setting

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Introduction

In a preclinical setting the differentiation between normal and abnormal diastolic function is challenging due to partial overlap of echocardiographic data in healthy individuals and subjects with left ventricular (LV) diastolic dysfunction (DD). Additionally, normal aging is associated with changes in the vascular system and the heart, which may lead to DD.^{1–5} Moreover, apparently healthy older individuals may have subclinical disorders, such as undetected coronary artery disease, that could further complicate the scenario, with wider normal ranges for echocardiographic variables.

Notably, in the case of suspected DD, and a non-diagnostic resting echocardiogram, it has been suggested to perform a diastolic stress test or an invasive right heart catheterization to confirm the presence of DD.⁶ However, the execution of these tests is demanding, they are not widely available, and sometimes are not feasible. A common clinical scenario where it may be cumbersome to make a diagnosis of DD comprises the primary care setting where, typically, elderly people affected by many comorbidities are seen.

A possible alternative solution could be to integrate diastolic function data assessed by resting echocardiography with natriuretic peptide (NP) value.^{7,8} However, despite the well-known prognostic value of NP in symptomatic patients with heart failure (HF), its clinical application in asymptomatic at-risk subjects (stages A and B of HF) is more controversial.^{6,9}

In this context, a combination of DD at rest with NP testing could be useful to correctly risk-stratify stages A and B of HF. Thus, the aim of the present study was to assess whether DD can predict HF or death in an asymptomatic community population at high risk for HF, alone and combined with NP.

Methods

Study population

The characteristics of the Detection of Asymptomatic Ventricular Dysfunction in Bergamo (DAVID-Berg) study have been previously published.^{10–13} Briefly, the DAVID-Berg was a prospective cohort study carried out at three primary care group practices in Bergamo, Italy. In 2008, each primary care physician reviewed the clinical records of all subjects aged 55–80 years ($n = 4047$). Within this age strata, 113 subjects (2.8%) had known or suspected HF, as defined by the European Society of Cardiology (i.e. symptoms and signs of HF associated with objective evidence of a structural or functional abnormality of the heart at rest). Patients without known or suspected HF, without congenital heart disease ($n = 3$) or moderate-to-severe valvular heart disease ($n = 11$) were included. While <1% of subjects were not able to attend the general practice clinic for evaluation, mainly due to personal disabilities or due to unwillingness to participate, from the remaining asymptomatic subjects we selected all individuals with HF risk factors defined as one or more of the following: presence of cardiovascular disease (CVD), diabetes mellitus and hypertension. CVD included ischaemic heart disease, cerebrovascular disease and peripheral vessel disease. Specifically, the following definitions were used.

(1) Ischaemic heart disease, defined as angina pectoris with documented ischaemic changes at stress test, or angiographic evidence of coronary stenosis >70% in at least one epicardial vessel, previous myocardial infarction, previous percutaneous or surgical revascularization.

- (2) Cerebrovascular disease, defined as previous transitory ischaemic attack, or stroke or asymptomatic carotid stenosis >50%.
- (3) Peripheral vessel disease, defined as claudication or asymptomatic iliac/femoral artery stenosis >50%.
- (4) Diabetes mellitus, defined as fasting blood glucose ≥ 126 mg/dl, or two-hour post-challenge serum glucose ≥ 200 mg/dl, or use of insulin, or oral hypoglycaemic agents.
- (5) Hypertension, defined as blood pressure ≥ 140 mm Hg (systolic) or 90 mm Hg (diastolic) or on antihypertensive drugs.

Finally, the DAVID-Berg study population comprised 623 subjects who underwent a protocol consisting of history and physical examination (including height, weight and blood pressure measurement), electrocardiogram (ECG), lipid profile, fasting blood glucose, glycosylated haemoglobin, creatinine, N-terminal fragment of proB-type natriuretic peptide (NT-proBNP), and comprehensive echocardiographic evaluation. Renal function was assessed by the estimated glomerular filtration rate (eGFR) with the simplified Modification of Diet in Renal Disease equation. Renal dysfunction was defined as eGFR <60 ml/min/1.73 m². All patients provided written informed consent to participate in the study, which was approved by the Ethics Committee of the Local Health Authority.

NP assessment

In this study we took into consideration the serum NT-proBNP levels for assessing NP activity. NT-proBNP was measured with a point of care competitive enzyme immunoassay (Cobas h232 Roche Diagnostic). According to the DAVID-Berg study and previous literature,^{13,14} we considered abnormally high NT-proBNP values greater than age-/sex-specific 80th percentiles, as both sex and age significantly impact NT-proBNP plasma values (Supplementary Material Figure). As a sensitivity analysis, we have also used a single cut-point of NT-proBNP equal to 180 ng/l.

Echocardiographic study

The echocardiograms were obtained using a Vivid I GE medical ultrasound machine with a 2.5 MHz transducer (GE Medical System, Horten, Norway). All examinations were performed by cardiologists expert in echocardiography who were blinded to NT-proBNP values. For quality assurance, randomly ($n = 50$) chosen echocardiographic examinations were reviewed by the echo core laboratory at Papa Giovanni XXIII Hospital, Bergamo, Italy, with an intra-class correlation (ICC) of 0.93 for LV ejection fraction (LVEF) and 0.91 for septal mitral annulus E'. All measurements were made in triplicate in patients in sinus rhythm, while in those with atrial fibrillation we averaged measurements over 10 R-R cycles, in accordance with the recommendations of the European/American Society of Echocardiography.¹⁵ LV volumes and LVEF were derived according to the modified biplane Simpson's method in the apical four-chamber and two-chamber views. LV mass (LVM) was calculated from LV linear dimensions and indexed to height^{2,7}. LV hypertrophy (LVH) was defined as LVM indexed to height^{2,7} >44 g/m^{2,7} in women and >48 g/m^{2,7} in men. LVEF was classified as normal ($\geq 53\%$), mildly reduced (40–52%), or reduced (<40%), in accordance with recently updated echocardiography guidelines.¹⁵

The definition of LV DD used in the DAVID-Berg study has been previously reported.¹³ Briefly, we defined DD based on widely accepted diastolic function parameters with validated cut-offs and prognostic relevance, such as left atrial volume index (LAVI) (abnormal >34 ml/m²), septal E' (abnormal <0.07 m/s), and septal E/E' (abnormal >15).¹⁶ To improve diagnostic accuracy, we classified DD presence in the case of two abnormal diastolic parameters out of three.¹³

Participants were divided into four categories according to DD presence and NT-proBNP value as follows: control group (normal diastolic

function and normal NT-proBNP, $n = 353$, 57%), normal diastolic function with abnormal NT-proBNP ($n = 53$, 9%), DD with normal NT-proBNP ($n = 150$, 24%) and DD with high NT-proBNP ($n = 67$, 11%).

Clinical follow-up

Between September 2008–June 2014 data on HF and all-cause death events were prospectively collected. The outcome of interest was a composite of HF events and all-cause death, whichever occurred first. Incident HF was defined as a hospital admission for HF (identified by inpatient first diagnosis of International Classification of Diseases, Ninth Revision code 428.xx), or as a clinical outpatient event in case of appearance of HF signs and symptoms associated with change in diuretic therapy (introduction of loop diuretics or increase in dose of other classes of diuretics).¹⁷ Inpatient and outpatient events were recorded by adequately trained general practitioners during the timeframe of the study and adjudicated by two independent cardiologists in June 2014. If the two cardiologists disagreed, a third cardiologist adjudicated the event.

Statistical analysis

Log transformation was applied to skewed variables (NT-proBNP). Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (25th–75th percentile) if non-parametric, while categorical variables were presented as percentages of observations. Clinical characteristics and cardiovascular structure and function were compared, according to DD or to the four DD-NP groups, with Chi square test, Fisher exact test, t -test, rank sum test or analysis of variance (ANOVA), Kruskal-Wallis test, as determined by variable type and the number of groups to be compared.

Predictors of the composite outcome were assessed via univariate and multivariable Cox regression analyses. Adjusted models were developed with consideration of age, sex and variables having $p < 0.05$ by univariate analysis: heart rate, smoking status, presence of CV disease, total cholesterol, diabetes mellitus, atrial fibrillation and LVEF (modelled as a continuous variable). The risk of the composite outcome was assessed according to DD and abnormal NT-proBNP, or to the four DD-NP groups. Since the evaluation of diastolic function in patients with atrial fibrillation during the echocardiogram may be cumbersome, we have adjusted all our analyses for atrial fibrillation and we have performed a sensitivity analysis excluding subjects with atrial fibrillation ($n = 23$). The assumption of proportional hazards was tested using Schoenfeld residuals and was met for all analyses reported.

We also applied a Classification And Regression Tree (CART) analysis to all the variables included into our multivariable model to identify the optimal risk stratification strategy to predict HF events/death.¹⁸ CART analysis is an empirical, statistical technique based on recursive partitioning of the data space to predict the response.¹⁸ The models are obtained by binary splitting of the data by the value of predictors, and the split variable and split-point are automatically selected from possible predictive values to achieve the best fit. Then, one or both 'child nodes' are split into two or more regions recursively, and the process continues until a stopping rule is applied. Finally, the result of this process is represented as a binary decision tree. Being an automatic statistical analysis, since minor changes in the data can alter some final results, CART was only a confirmatory part of our statistical analysis based on Cox analysis.

Kaplan-Meier survival curves of the four DD-NP groups were plotted and differences were tested for significance using the log-rank test. A two-sided p -value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 13.0 (College Station, Texas, USA).

Results

Overall, the mean age of the study population was 69 years, 56% were men, mostly hypertensive (88%), half had a history of CVD, one-third had diabetes mellitus, and one quarter had renal dysfunction (Table 1). The majority of the population was treated with an angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) (70%). The median NT-proBNP was 180 ng/l, mean septal E' was 0.07 m/s, E/E' was 10.9, and LAVI was 30 ml/m². A third of the population had DD (35%), two thirds had LVH, while the mean LVEF was 61% (Table 1) and LVEF was abnormal ($<53\%$) in one quarter of our cohort (2% had LVEF $<40\%$).

According to the diastolic function, compared to subjects with normal diastole, subjects with DD were older, had a lower heart rate, a higher systolic blood pressure, were less likely to be smokers and had a higher prevalence of atrial fibrillation. While pharmacological therapies did not significantly differ between the two groups, subjects with DD had a higher LVM, lower LVEF, and, by definition, a lower E' , a higher E/E' and greater LAVI. Concomitantly, they had a higher NT-proBNP (Table 1).

Considering the four study subgroups defined according to DD presence and NP values, in comparison with the control group (i.e. no DD and normal NP), patients with isolated high NPs had a higher prevalence of atrial fibrillation, were more often treated with beta-blockers, and had a lower LVEF (Table 2). Conversely, subjects with isolated DD were older, had a lower heart rate, a higher systolic blood pressure, and were less likely to be smokers. Additionally, they had a higher prevalence of LVH, besides diastolic function impairment. Finally, subjects with combined DD and high NPs had a lower BMI, were less likely to be active smokers, had more prevalent atrial fibrillation and were more often treated with beta-blockers. Together with the impairment of the diastolic function parameters, they had more LVH and lower LVEF (Table 2).

Risk of HF and death

During a median follow-up of 5.7 years (25th–75th percentile 5.3–5.9), there were 95 events (38 inpatient HF events, 26 outpatient HF events and 31 deaths), with an overall event rate of 2.8 per 100 person-years. According to DD presence/absence, the event rate was 2.0 per 100 person-years in subjects without DD and 4.5 per 100 person-years in subjects with DD ($p < 0.001$). Similarly, the event rate was 2.1 per 100 person-years in subjects without abnormal NP and 6.2 per 100 person-years in subjects with abnormal NP ($p < 0.001$). Based on the four DD-NP groups (Figure 1), the event rate ranged from 1.7 per 100 person-years (control group, no DD and normal NP) to 3.2 per 100 person-years (normal NP with DD) to 4.2 per 100 person-years (high NP without DD) and 7.9 per 100 person-years (DD and high NP) ($p < 0.001$).

Univariate predictors of the composite outcome were age, heart rate, smoking status, presence of CVD, total cholesterol, diabetes mellitus, atrial fibrillation, LVEF, presence of DD and abnormal NT-proBNP. At multivariable analysis, independent predictors of the composite outcome were age, smoking status, diabetes mellitus, known CVD, LVEF, abnormal NT-proBNP and DD. However, categorising the population according to both DD and NP, only the coexistence of DD and high NP was significantly associated with HF/death events, while the groups with isolated impairment of DD or NP had a

Table 1 Characteristics of the DAVID-Berg population according to diastolic function.

	Overall n = 623	No diastolic dysfunction n = 405, 65%	Diastolic dysfunction n = 218, 35%	p Value
Age	69 ± 7	68 ± 7	70 ± 6	<0.001
Male (%)	349 (56)	234 (58)	115 (53)	0.23
BMI	28.9 ± 5.1	29.0 ± 5.4	28.5 ± 4.5	0.24
Heart rate (bpm)	74 ± 14	75 ± 14	73 ± 14	0.028
SBP (mm Hg)	151 ± 24	149 ± 23	155 ± 25	0.002
Active smoker (%)	79 (13)	64 (16)	15 (7)	0.001
Hypertension (%)	550 (88)	359 (89)	191 (88)	0.91
Diabetes mellitus (%)	219 (35)	141 (35)	78 (36)	0.81
CKD (%)	141 (23)	90 (22)	51 (23)	0.87
Known CVD (%)	321 (52)	215 (53)	106 (49)	0.34
Atrial fib. (%)	23 (4)	3 (1)	20 (9)	<0.001
ACE-i/ARB (%)	437 (70)	279 (69)	158 (72)	0.060
Beta-block. (%)	230 (37)	140 (35)	90 (41)	0.14
Statin (%)	256 (41)	169 (42)	87 (40)	0.19
Diuretics (%)	94 (15)	63 (16)	31 (14)	0.23
Total cholesterol (mg/dl)	202 ± 41	202 ± 41	201 ± 42	0.79
NT-proBNP (ng/l)	180 (90–355)	146 (73–274)	254 (129–612)	<0.001
LVMi (g/m ^{2.7})	55 ± 18	51 ± 14	61 ± 22	<0.001
LVH (%)	417 (67)	241 (60)	176 (81)	<0.001
LVEF (%)	61 ± 9	61 ± 9	59 ± 10	0.016
E/A	0.88 ± 0.43	0.81 ± 0.28	1.02 ± 0.61	<0.001
Deceleration time (ms)	227 ± 67	229 ± 63	225 ± 73	0.48
E'	0.07 ± 0.03	0.07 ± 0.03	0.06 ± 0.02	0.001
E/E'	10.9 ± 4.5	9.5 ± 2.7	13.4 ± 5.8	<0.001
LAVi (ml/m ²)	30 ± 16	23 ± 7	44 ± 19	<0.001

ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; block., blocker; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; fib., fibrillation; LAVi, left atrial volume indexed to BSA; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMi, left ventricular mass indexed to height^{2.7}; NT-proBNP, N-terminal fragment of proB-type natriuretic peptide; SBP, systolic blood pressure. Values of p provided are related to chi-square test (or Fisher's exact test as appropriate) or t-test (or rank sum test for non-normally distributed variables). Known CVD refers to prior transient ischemic attack (TIA), or stroke, or history of peripheral arterial disease or coronary artery disease.

non-significant trend towards higher risk (Table 3, Figure 1). In a sensitivity analysis excluding subjects with atrial fibrillation, we obtained similar results (isolated high NP versus control group: hazard ratio (HR) 1.83, 95% confidence interval (CI) 0.87–3.84, adjusted *p* = 0.11; isolated DD versus control group: HR 1.69, 95% CI 0.94–3.04, adjusted *p* = 0.08; combined DD and high NP versus control group: HR 4.55, 95% CI 2.36–8.79, adjusted *p* < 0.001). Similarly, in a sensitivity analysis considering a single cut-point of NT-proBNP equal to 180 ng/l (median NT-proBNP value of our population) we obtained comparable results, since only the group with combined DD/high NP was associated with a significantly higher risk of adverse events (isolated high NP versus control group: HR 0.93, 95% CI 0.48–1.77, adjusted *p* = 0.82; isolated DD versus control group: HR 1.09, 95% CI 0.46–2.62, adjusted *p* = 0.84; combined DD and high NP versus control group: HR 2.47, 95% CI 1.34–4.54, adjusted *p* = 0.004).

Applying a CART analysis, including all the variables considered in the multivariable Cox regression model, we obtained the risk stratification tree depicted in Figure 2. Specifically, the CART analysis showed that combined DD/high NP was the single strongest prognostic factor in the DAVID-Berg population. Importantly, among

these subjects, the next variable to be considered was LVEF. Indeed, those with abnormal LVEF (<53%) had a risk of HF events/death as high as 58%, while those with preserved LVEF had a risk of 24%. Conversely, the prognostic relevance of isolated impairment of DD or NPs needed to be integrated with the information provided by conventional markers of risk, such as diabetes and age. Indeed, in older subjects without diabetes isolated impairment of DD or NP portends a risk of adverse events as high as 26%, as opposed to 7% in the control group (normal diastole/normal NPs).

Discussion

In a high-risk asymptomatic community setting, DD at rest was a strong predictor of incident adverse events, such as HF and death. However, while subjects with DD and abnormal NPs had a dismal prognosis at long term follow-up, those with DD but normal NPs, as well as those with normal diastole but high NPs, represented lower risk subgroups, with a non-significant trend towards higher event rate, compared to the quite common 'healthy' combination of

Table 2 Characteristics of the DAVID-Berg population according to diastolic function and natriuretic peptides (NPs).

	No DD and normal NPs n = 353, 57%	No DD and high NPs n = 53, 9%	DD and normal NPs n = 150, 24%	DD and high NPs n = 67, 11%	p Value
Age	68 ± 7	68 ± 7	70 ± 6 ^a	70 ± 7	0.002
Male (%)	206 (58)	29 (55)	75 (50)	39 (58)	0.37
BMI	29.2 ± 5.3	28.1 ± 5.9	29.1 ± 4.7	27.4 ± 3.9 ^a	0.040
Heart rate (bpm)	76 ± 14	72 ± 15	72 ± 12 ^a	75 ± 18	0.020
SBP (mm Hg)	149 ± 23	151 ± 23	157 ± 26 ^a	152 ± 24	0.005
Active smoker (%)	54 (15)	10 (19)	13 (9) ^a	2 (3) ^a	0.008
Hypertension (%)	314 (89)	46 (87)	134 (89)	56 (84)	0.83
Diabetes mellitus (%)	123 (35)	19 (36)	56 (37)	21 (31)	0.86
CKD (%)	74 (21)	17 (32)	39 (26)	11 (16)	0.32
Known CVD (%)	182 (52)	34 (64)	68 (45)	37 (55)	0.19
Atrial fib. (%)	1 (0.3)	2 (4) ^a	1 (0.7)	19 (28) ^a	<0.001
ACE-i/ARB (%)	244 (69)	36 (68)	109 (73)	48 (72)	0.35
Beta-block. (%)	113 (32)	27 (51) ^a	53 (35)	37 (55) ^a	0.003
Statin (%)	143 (41)	27 (51)	55 (37)	31 (46)	0.28
Diuretics (%)	57 (16)	6 (11)	21 (14)	10 (15)	0.52
Total cholesterol (mg/dl)	204 ± 41	193 ± 46	204 ± 41	196 ± 43	0.22
NT-proBNP (ng/l)	123 (65–213)	542 (432–892) ^a	169 (103–270)	985 (586–1407) ^a	<0.001
LVMi (g/m ^{2.7})	53 ± 15	56 ± 19	58 ± 14 ^a	63 ± 19 ^a	<0.001
LVH (%)	205 (58)	36 (68)	119 (79) ^a	57 (85) ^a	<0.001
LVEF (%)	62 ± 8	58 ± 11 ^a	62 ± 8	53 ± 13 ^a	<0.001
E/A	0.80 ± 0.27	0.92 ± 0.36	0.92 ± 0.43 ^a	1.34 ± 0.93 ^a	<0.001
Deceleration time (ms)	231 ± 62	218 ± 71	230 ± 64	211 ± 90	0.11
E'	0.072 ± 0.028	0.074 ± 0.024	0.064 ± 0.023 ^a	0.064 ± 0.026 ^a	0.009
E/E'	9.5 ± 2.8	9.8 ± 2.5	12.9 ± 5.4 ^a	14.6 ± 6.8 ^a	<0.001
LAVi (ml/m ²)	22 ± 7	24 ± 8	40 ± 14 ^a	54 ± 25 ^a	<0.001

ACE-i, angiotensin converting enzyme inhibitor; ANOVA, analysis of variance; ARB, angiotensin receptor blocker; block., blocker; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DD, diastolic dysfunction; fib., fibrillation; LAVi, left atrial volume indexed to BSA; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMi, left ventricular mass indexed to height^{2.7}; NP, natriuretic peptide; NT-proBNP, N-terminal fragment of proB-type natriuretic peptide; SBP, systolic blood pressure.

Values of p provided are related to comparison between the four groups of patients by using ANOVA or chi-square test (Fisher's exact test as appropriate).

^ap < 0.05 for comparison with the control group (i.e. no DD and normal NPs).

Figure 1 Probabilities of heart failure (HF)/death according to diastolic dysfunction (DD) and natriuretic peptides (NPs).

Table 3 Cox regression univariate and multivariable analysis for predictors of heart failure (HF) and all-cause death.

	Predictors of HF and all-cause death					
	Univariate analysis			Multivariable analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.04	1.01–1.07	0.011	1.05	1.01–1.08	0.013
Male	1.20	0.80–1.82	0.38	0.86	0.54–1.39	0.55
Heart rate	1.02	1.00–1.03	0.024	1.01	0.99–1.02	0.22
Active smoker	1.99	1.19–3.33	0.009	2.76	1.48–5.15	0.001
Total cholesterol	0.99	0.99–1.00	0.019	0.99	0.99–1.00	0.31
Diabetes mellitus	3.65	2.33–5.71	<0.001	4.01	2.47–6.52	<0.001
Known CVD	1.58	1.02–2.43	0.038	1.70	1.06–2.72	0.027
Atrial fibrillation	2.56	1.24–5.29	0.011	0.99	0.43–2.26	0.98
LVEF	0.95	0.93–0.97	<0.001	0.96	0.94–0.99	0.002
Abnormal NT-proBNP	2.89	1.92–4.36	<0.001	2.25	1.35–3.74	0.002
DD	2.32	1.55–3.47	<0.001	1.91	1.19–3.05	0.007
Control group (no DD, normal NP)	1.00	(Reference)				
No DD, high NP	2.38	1.23–4.63	0.010	1.98	0.97–4.04	0.060
DD, normal NP	1.91	1.13–3.23	0.015	1.75	0.98–3.12	0.057
DD, high NP	4.88	2.90–8.20	<0.001	4.48	2.31–8.70	<0.001

ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; block., blocker; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DD, diastolic dysfunction; fib., fibrillation; HR, hazard ratio; LAVi, left atrial volume indexed to BSA; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass indexed to height^{2.7}; NP, natriuretic peptide; NT-proBNP, N-terminal fragment of proB-type natriuretic peptide; SBP, systolic blood pressure.
HRs and corresponding 95% CIs were adjusted for: age, sex, heart rate, smoking status, presence of CVD, total cholesterol, diabetes mellitus, atrial fibrillation, LVEF, AND presence of DD and abnormal NT-proBNP, OR categorical variable based on DD and NPs.

Figure 2 Risk stratification tree, as obtained by Classification And Regression Tree (CART) analysis. CVD, cardiovascular disease; DD, diastolic dysfunction; HF, heart failure; NP, natriuretic peptide.

normal diastole and normal NPs. These data suggest a need to integrate in clinical practice the information provided by DD and NPs to correctly risk stratify asymptomatic subjects at high risk for HF.

It is well known that the diagnosis of HF with preserved LVEF (HFpEF) may be challenging in clinical practice.^{19–21} Indeed, according to current guidelines, it is important to consider information provided by clinical data, resting ECG and NP.^{9,22} However, the diagnosis of asymptomatic DD in the community is even more challenging, because there are no HF signs or symptoms and functional/structural abnormalities of the myocardium are more likely to be less advanced than in the clinical phase of the disease. Thus, DD estimation should rely on easily obtainable, reliable and reproducible parameters. Notably, DD has been described as a condition that puts asymptomatic patients at risk for incident HF and mortality in community studies, and it has been suggested that even an impaired myocardial relaxation detected with an ECG might be associated with incident death.^{23–27} However, since there are wide normal ranges for echocardiographic variables in different clinical settings, one theoretical approach to improve the diagnostic and prognostic performance of DD could be to use an easily available NP test. Indeed, NP has been used for an early detection of DD in high-risk populations and it has been shown that the inclusion of NT-proBNP into the currently used risk score in HF resulted in significantly better risk stratification.^{28,29}

This biomarker may have a high negative predictive value for elevated filling pressures, even if it should be clarified that, aside the haemodynamic burden, there are several possible causes finally leading to an increased NP. However, independently from the principal mechanism of an increased NP, when abnormal, it might portend an adverse prognosis in a preclinical setting.^{30–32} Furthermore, it has been demonstrated that echocardiography and NPs offer significant HF risk reclassification over a clinical prediction model in older adults.⁷

Importantly, DAVID-Berg data show that subjects with combined DD and high NPs, which was quite a common combination in our population (11%), had a very high incidence of HF and fatal events (7.9%-year risk) during long term follow-up. Compared to the other subgroups, these subjects had a higher prevalence of atrial fibrillation. However, results did not change on excluding the few subjects with this comorbidity, confirming that it is not atrial fibrillation per se that confers the aforementioned greater risk. Noteworthy, among demographic, clinical, laboratory and echocardiographic characteristics, DD combined with abnormal NPs represented the strongest prognostic factor. Hence, according to the DAVID-Berg study, the combination of high NPs and DD could represent the first parameter to be considered for risk stratification purposes, even before LVEF (Figure 2). Thus, these patients might deserve a cardiologist consultation. Conversely, subjects without DD at echo and with normal NPs, approximately 50% of the 'high-risk' DAVID-Berg population, might be managed more conservatively, based on general practitioner follow-up.^{9,22} On the other hand, subjects with DD at echo but with normal NPs and subjects without DD but with elevated NPs represent intermediate risk subgroups, which might need integration of information provided by conventional measures of risk, such as diabetes and age, to adequately risk stratify them (Figure 2).

While it may be argued that in a larger population isolated DD or high NPs might also be associated with a poorer prognosis compared

to subjects with normal NPs and no DD, nowadays the need to properly allocate healthcare resources for a high-cost disease such as HF mandates us to concentrate preventive strategies on higher risk community subjects, such as those with DD and high NPs. Among these strategies we may consider, aside from a cardiologist consultation, are more stringent interventions, aiming at adequate blood pressure, glycaemic, and lipid control, smoking cessation, exercise training and dietetic counselling.^{8,33,34} Of note, the suboptimal blood pressure control in the DAVID-Berg population, which is concordant with widespread unsatisfactory risk factor control,^{35,36} and the encountered independent risk of adverse events associated with diabetes mellitus and smoking habits, further suggest the possibility to improve the outcome of these subjects. Importantly, our results point towards the need for enrolling asymptomatic people with DD and high NPs in clinical trials testing current and novel agents that may reduce the risk of future overt HF, similarly to what is performed nowadays in symptomatic HFpEF patients enrolled in contemporary clinical trials.³⁷

Prior studies suggest the potential clinical utility of NP measurements in subjects without HF. In an Irish outpatient cohort without known HF diagnosis or symptoms it was found that intensification of care based on a screening strategy with NPs reduced the risk for LV dysfunction and HF.³¹ Other contemporary data further underscore the clinical utility of NPs, not only to stratify the individual risk, but also to select appropriate therapy and to guide its optimization. Indeed accelerated up-titration of renin-angiotensin system antagonists and beta-blockers to maximum tolerated dosages was shown to be an effective and safe intervention for the primary prevention of cardiac events in diabetic patients pre-selected using NPs.³⁸ Additionally, in an American community setting, NP level was a stronger predictor of death than traditional risk factors, even among subjects without HF.³⁹ Furthermore, higher LV mass and lower LVEF were strongly associated with higher NP levels. Thus, it was suggested that the common occurrence of an elevated NP level (47% of the study population) may warrant additional investigation, including assessment of cardiac structure and function.³⁹ DAVID-Berg data corroborate and implement these findings, through the integration of NPs and diastolic function data, allowing the identification of the highest risk subjects in the challenging primary care setting. Of note, there is growing evidence to support a possible role in the risk stratification process of asymptomatic populations not only for NPs, but also for a multi-biomarker strategy, including soluble ST2 and high sensitivity troponin.⁴⁰ Further testing is needed to understand whether the integration of DD with this multi-biomarker approach is preferable to the simple association of DD and NPs.

Finally, since subjects with impaired DD and elevated NPs are at higher risk of incident adverse events, these people need to be further studied, aiming to refine the aetiology of their DD, such as hidden cardiomyopathy, amyloidosis, or ischaemic aetiology. At the same time, these subjects might represent the ideal target for novel therapies, such as sodium-glucose co-transporter 2 inhibitors or sacubitril/valsartan, to reduce the likelihood of incident HF. However, this hypothesis needs to be formally tested in an appropriate setting.

The limitations of our analysis should be noted. First, despite multi-variable analyses, residual confounding cannot be excluded. Second,

the inclusion and exclusion criteria of the DAVID-Berg study limit the generalisability of our results to other community settings. In particular, the DAVID-Berg study included only high-risk Caucasian participants with a relatively low prevalence of obese patients. Nonetheless, DAVID-Berg baseline characteristics are similar to those described in other communities, such as in Olmsted County, Minnesota, USA.²³ Third, despite a possibly high prevalence of amyloidosis in our elderly cohort, we were not able to rule out this diagnosis during the timeframe of our study. This might be the focus of novel research in preclinical HF. Fourth, both DD and NPs define a dynamic condition and it would have been ideal to perform a second sampling. Finally, since the DAVID-Berg study comprised quite a small population, the confirmation of these results in larger populations is essential.

In conclusion, in asymptomatic HF stages A and B DAVID-Berg data confirm the prognostic relevance of DD and NPs and suggest that their integration might help to achieve early and correct identification of subjects at greater risk for incident HF and death, thus more suitable for more stringent preventive strategies.

Supplemental material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Author contribution

MG, AGa and MS contributed to the conception or design of the work. MG, AC, PC, AI, AGr, AF and PF contributed to the acquisition of data for the work. MG, CL, ED, AI, AC, PC, GC, RDM, AGr, AI, AGh, AF, PF, GP, AGa and MS contributed to analysis and interpretation of data for the work. MG drafted the manuscript. All critically revised the manuscript and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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