

## Original Investigation

# Natriuretic Peptide–Based Screening and Collaborative Care for Heart Failure

## The STOP-HF Randomized Trial

Mark Ledwidge, PhD; Joseph Gallagher, MB; Carmel Conlon, PhD; Elaine Tallon, PGDip; Eoin O'Connell, MLitt; Ian Dawkins, DPhil; Chris Watson, PhD; Rory O'Hanlon, MD; Margaret Bermingham, BSc(Pharm); Anil Patle, MBA; Mallikarjuna R. Badabhagni, RDCS; Gillian Murtagh, MD; Victor Voon, MB; Leslie Tilson, PhD; Michael Barry, MD; Laura McDonald; Brian Maurer, MD; Kenneth McDonald, MD

**IMPORTANCE** Prevention strategies for heart failure are needed.

**OBJECTIVE** To determine the efficacy of a screening program using brain-type natriuretic peptide (BNP) and collaborative care in an at-risk population in reducing newly diagnosed heart failure and prevalence of significant left ventricular (LV) systolic and/or diastolic dysfunction.

**DESIGN, SETTING, AND PARTICIPANTS** The St Vincent's Screening to Prevent Heart Failure Study, a parallel-group randomized trial involving 1374 participants with cardiovascular risk factors (mean age, 64.8 [SD, 10.2] years) recruited from 39 primary care practices in Ireland between January 2005 and December 2009 and followed up until December 2011 (mean follow-up, 4.2 [SD, 1.2] years).

**INTERVENTION** Patients were randomly assigned to receive usual primary care (control condition; n=677) or screening with BNP testing (n=697). Intervention-group participants with BNP levels of 50 pg/mL or higher underwent echocardiography and collaborative care between their primary care physician and specialist cardiovascular service.

**MAIN OUTCOMES AND MEASURES** The primary end point was prevalence of asymptomatic LV dysfunction with or without newly diagnosed heart failure. Secondary end points included emergency hospitalization for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure.

**RESULTS** A total of 263 patients (41.6%) in the intervention group had at least 1 BNP reading of 50 pg/mL or higher. The intervention group underwent more cardiovascular investigations (control, 496 per 1000 patient-years vs intervention, 850 per 1000 patient-years; incidence rate ratio, 1.71; 95% CI, 1.61-1.83;  $P < .001$ ) and received more renin-angiotensin-aldosterone system-based therapy at follow-up (control, 49.6%; intervention, 56.5%;  $P = .01$ ). The primary end point of LV dysfunction with or without heart failure was met in 59 (8.7%) of 677 in the control group and 37 (5.3%) of 697 in the intervention group (odds ratio [OR], 0.55; 95% CI, 0.37-0.82;  $P = .003$ ). Asymptomatic LV dysfunction was found in 45 (6.6%) of 677 control-group patients and 30 (4.3%) of 697 intervention-group patients (OR, 0.57; 95% CI, 0.37-0.88;  $P = .01$ ). Heart failure occurred in 14 (2.1%) of 677 control-group patients and 7 (1.0%) of 697 intervention-group patients (OR, 0.48; 95% CI, 0.20-1.20;  $P = .12$ ). The incidence rates of emergency hospitalization for major cardiovascular events were 40.4 per 1000 patient-years in the control group vs 22.3 per 1000 patient-years in the intervention group (incidence rate ratio, 0.60; 95% CI, 0.45-0.81;  $P = .002$ ).

**CONCLUSION AND RELEVANCE** Among patients at risk of heart failure, BNP-based screening and collaborative care reduced the combined rates of LV systolic dysfunction, diastolic dysfunction, and heart failure.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00921960

JAMA. 2013;310(1):66-74.

◀ Editorial page 44

+ Supplemental content at [jama.com](http://jama.com)

**Author Affiliations:** Chronic Cardiovascular Disease Management Unit, St Vincent's Healthcare Group/St Michael's Hospital, Dublin, Ireland (Ledwidge, Gallagher, Conlon, Tallon, O'Connell, Dawkins, Watson, O'Hanlon, Bermingham, Patle, Badabhagni, Murtagh, Voon, McDonald L, Maurer, McDonald K); School of Medicine and Medical Science, University College, Dublin, Ireland (Ledwidge, Gallagher, Tallon, O'Connell, Watson, O'Hanlon, Bermingham, Voon, McDonald); National Centre for Pharmacoeconomics, St James's Hospital, Dublin, Ireland (Tilson, Barry).

**Corresponding Author:** Kenneth McDonald, MD, Chronic Cardiovascular Disease Management Unit, St Vincent's Healthcare Group, Dun Laoghaire, Dublin, Dublin 4, Ireland ([kenneth.mcdonald@ucd.ie](mailto:kenneth.mcdonald@ucd.ie)).

The increasing prevalence of heart failure (HF) remains a major public health concern underlining the need for an effective prevention strategy.<sup>1</sup> Present-day approaches, focusing mainly on risk factor intervention, have brought about some reduction in new-onset HF.<sup>2–4</sup> However, recent major reports in the United States and the European Union underline difficulties in achieving adequate risk factor control and show that present strategies will not be as effective as desired.<sup>5,6</sup> This, in turn, may in part be explained by the uniform direction of resources to a population containing predominantly lower-risk patients and the lack of risk stratification beyond that calculated from standard risk factors.

Refining risk prediction may be aided by the use of brain-type natriuretic peptide (BNP), which has been shown in large general and American College of Cardiology Foundation/American Heart Association stag A/B (asymptomatic) populations to identify those at highest risk of cardiovascular events and, more specifically, of newly diagnosed HF.<sup>7,8</sup> Studies have shown advantages of using this peptide in this regard over conventional risk indicators.<sup>8,9</sup> This may reflect the fact that BNP is a response to established cardiovascular damage whereas other conventional risk indicators reflect the potential for cardiovascular insult. New data suggest that more targeted surveillance using a combination of risk factors and BNP may improve identification of those at greatest risk of newly diagnosed HF.<sup>10</sup>

Therefore, we hypothesized that BNP-based screening and intervention would target management to those at highest risk of HF and asymptomatic ventricular dysfunction, providing an approach to prevention of HF and cardiovascular disease that would be superior to standard care. The St Vincent's Screening to Prevent Heart Failure (STOP-HF) study was designed as a pragmatic, prospective randomized trial in a broad community population characterized by collaborative care intervention between cardiovascular specialists and primary care physicians.

## Methods

### Patient Population

All primary care physicians in the catchment area of St Vincent's University Hospital, Dublin, Ireland, participating in the Community Programme for Cardiovascular Risk Evaluation (COMPARE) study were invited to participate by mail and then at an initiation meeting. COMPARE was a nurse-provided primary care cardiovascular risk screening program. Patients were referred by their primary care physicians to the STOP-HF program between 2005 and 2009, with 39 participating practices.

Patients from COMPARE were eligible to participate in the STOP-HF study if they were older than 40 years and had a history of 1 or more of the following: (1) hypertension (medicated for  $\geq 1$  month); (2) hypercholesterolemia, defined as total cholesterol greater than 193 mg/dL (5.0 mmol/L) (174 mg/dL [4.5 mmol/L] in high-risk patients) and/or low-density lipoprotein cholesterol greater than 116 mg/dL (3.0 mmol/L) (97 mg/dL [2.5 mmol/L] in high-risk patients) or receiving lipid-

lowering therapy; (3) obesity, defined as body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 30; (4) vascular disease, including coronary artery disease (confirmed by angiography or history of myocardial infarction), cerebrovascular disease, and peripheral vascular disease; (5) diabetes mellitus; (6) arrhythmia requiring therapy; or (7) moderate to severe valvular disease. We excluded those who refused to provide informed consent, had established evidence of left ventricular systolic dysfunction, had evidence or a history of symptomatic HF, or had a diagnosis compromising survival over the study period.

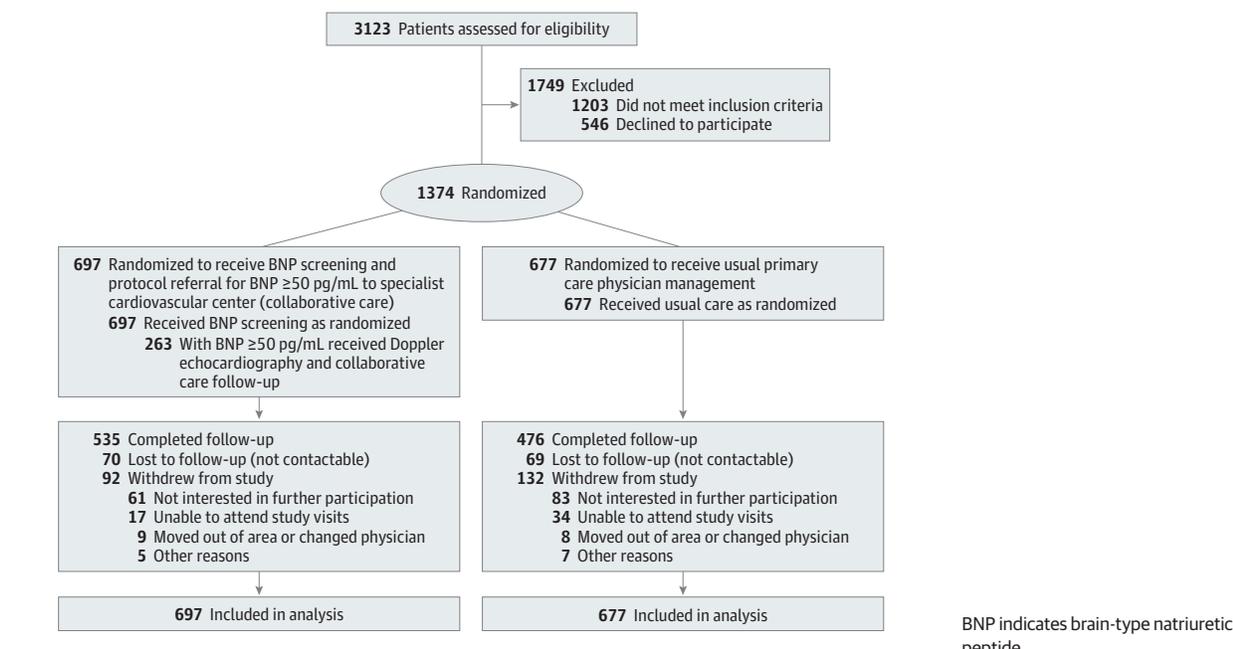
### Study Procedures

The study protocol was approved by the St Vincent's University Hospital Ethics Committee and conformed to the principles of the Declaration of Helsinki. The study nurse enrolled consecutive consenting patients and obtained written consent. Study group was assigned by the STOP-HF center according to a computer-generated random number list created by the study statistician. An administrator in the study center allocated patients consecutively to intervention or control group. The allocation sequence was concealed from the investigators until individuals were assigned. The randomization process assigned patients 1:1 to control group (receiving routine primary care physician management) or BNP-driven collaborative care between the primary care physician and specialist cardiovascular center. It was not possible to blind participants or clinical investigators to group assignment. All patients in the study underwent BNP blood testing (Triage, Biosite) at study commencement and annually thereafter. Primary care physicians did not have access to BNP testing outside of the study protocol. Enrollment commenced in January 2005 and ended in December 2009. Follow-up was completed in December 2011 (Figure 1).

In the control group, patient care continued with advice on lifestyle modification and risk factor intervention as determined by primary care physicians without knowledge of BNP results and with at least an annual patient visit. At the annual review, the study nurse performed blinded BNP testing on all control-group patients as part of a structured cardiovascular risk and lifestyle review. Patients in the control group received specialist cardiologist care only if requested by the primary care physician as part of their usual care.

In the intervention group, BNP results were made available to primary care physicians with protocol referral of all patients with a value of 50 pg/mL or higher (50 ng/L) to the specialist cardiovascular service. Those with BNP values less than 50 pg/mL received the same care as provided in the control group, albeit with disclosure of BNP values to patients and primary care physicians. Participants with a BNP level of 50 pg/mL or higher underwent Doppler echocardiography (see eAppendix in the Supplement) and review by a cardiologist at the study center, who decided on further investigation and management. In addition to disclosure of BNP values to patients and the primary care physicians, the focus of the specialist intervention for those with elevated BNP was multidimensional. This approach included optimal risk factor management with the most appropriate therapy and complete investigation and

Figure 1. Participant Flow



treatment of abnormalities defined on examination or on Doppler echocardiography. In addition, all patients received further coaching by a specialist nurse who emphasized individual risk status and the importance of adherence to medication and healthy lifestyle behaviors.

Patients with an initial BNP level of 50 pg/mL or higher also received ongoing collaborative care with at least an annual specialized cardiovascular review, including repeat Doppler echocardiography, BNP measurement, and other investigations as appropriate. In all patients with an initial BNP of less than 50 pg/mL, annual BNP testing by their primary care physician resulted in specialist referral with management as outlined above if the value increased to 50 pg/mL or higher. Participants' primary care physicians were informed of all clinical investigations performed by the specialist cardiovascular center and were involved in any change in management strategy.

At study termination, all control and intervention participants underwent clinical assessment by a cardiologist including Doppler echocardiography; the technician and reporting cardiologist were blinded to study group allocation.

### End Points

The original protocol version from June 2004 specified newly diagnosed HF or left ventricular systolic dysfunction as the primary end point. However, slower-than-expected recruitment rates resulted in an extension of the study in April 2009 and the redefinition of the primary end point to include significant left ventricular diastolic dysfunction as determined by a ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E') greater than 15. This change in the study primary end point was approved by the institutional review board and occurred before completion of recruitment in December 2009. The change was approved and imple-

mented before the assessment of the study primary end point, which began in 2010, and prior to any data analysis occurring. Therefore, the primary end point of the study as reported herein is the prevalence of left ventricular dysfunction (asymptomatic left ventricular systolic dysfunction or asymptomatic left ventricular diastolic dysfunction) with or without newly diagnosed HF at study completion.

The inclusion of asymptomatic left ventricular systolic dysfunction or significant diastolic dysfunction as a component of the primary end point reflects the heightened risk status of these abnormalities, specifically to the later development of HF. Left ventricular dysfunction was defined as any combination of (1) left ventricular ejection fraction less than 50% or (2) E/E' ratio greater than 15 in the setting of normal left ventricular ejection fraction on Doppler echocardiography. The presence of HF was defined as symptoms of HF requiring emergency admission to the hospital, confirmed by hospital discharge summary.

Secondary end points reported herein include emergency hospitalizations for any of the following major adverse cardiovascular events: arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or HF. All major adverse cardiovascular events were classified based on the discharge summary from the hospitalization event, and the STOP-HF investigators did not have any influence in the decision to admit. All clinical end points were assessed by a member of the study team by reviewing the primary care physician's records and confirmed by hospital discharge summary. This process was carried out by the same specialist nurse for consistency of reporting over the study duration. The nurse who reviewed records to determine outcomes was blinded to participant allocation. Finally, we also evaluated change in BNP over time. Other end points included in

the study protocol were evaluation of the relationship between BNP and severity of left ventricular dysfunction, hospital admissions and death, quality-of-life and cost-effectiveness analyses, and evaluation of the clinical, demographic, biochemical, pharmacological, genomic, proteomic, and metabolomic determinants of BNP. These will be reported in future analyses.

### Sample Size Calculation

Sample size calculations were originally based on the primary end point of HF and/or left ventricular systolic dysfunction, the prevalence of which was assumed to be 9.6% in the control group and 5.9% in the treatment group. This yields an odds ratio (OR) of approximately 0.59. Using an OR of 0.59, an  $\alpha = .05$  (2-tailed), and power level of 80%, the total required sample size was  $n = 1644$ .

Sample size calculations were later adjusted when the primary end point was changed. The calculations were then based on a prevalence of left ventricular dysfunction (systolic and diastolic) with or without HF expected to be 19.6% in the control group at study end. The treatment effect was expected to be similar to that observed at 1 year with antihypertensive intervention in the LIFE study.<sup>11</sup> This implies a prevalence of 13.4% in the intervention group and an absolute reduction of 6.2%.

With an OR of 0.63, an  $\alpha = .05$  (2-tailed), and a power level of 80%, the revised total required sample size was 1129. The principal investigators agreed that the study would continue until a sufficient number of patients were followed up for at least 1 year (accounting for known patient withdrawals) to exceed the numbers in the power calculation. Further assumptions were that allocation to control or intervention group was even and unbiased (ie, group membership was an independent random binomial variable with  $P = .50$ ) and that covariates account for 0% of the variation in probability of HF or left ventricular dysfunction.

### Statistical Analysis

All analyses were carried out on an intention-to-treat basis using R software, version 2.7.2 (CRAN Project). Analyses were performed by a statistician employed by the St Vincent's University Hospital, the Heartbeat Trust, and the School of Medicine and Medical Science at University College (E.O.). The analyses included all 1374 patients as randomized. Missing data were handled as follows. Study group, age, and sex were available for all patients. Multiple imputation using chained equations was then carried out (using R software's "mice" package) with 10 imputations and 10 iterations per imputation. Predictive mean matching was used for all variables and the variables entered were E/E', ejection fraction, major adverse cardiovascular events (HF, myocardial infarction, arrhythmia, stroke, transient ischemic attack, and peripheral or pulmonary thrombosis/embolus), years in study, study group, age, sex, comorbidities (hypercholesterolemia, diabetes, hypertension, and ischemic heart disease), baseline blood levels (BNP, low-density lipoprotein cholesterol, and triglycerides), baseline anthropometric measures (body mass index, systolic and diastolic blood pressure, and heart rate), and baseline medication use ( $\beta$ -blockers, diuretics, antiplatelet therapy, statins, calcium channel block-

ers, angiotensin-converting enzyme inhibitors,  $\alpha$ -blockers, and angiotensin II receptor blockers). The results presented herein (primary and secondary end points) are pooled results from the multiple imputed data sets with results using a last-observation-carried-forward analysis (eTables 6 and 7 in the Supplement).

Primary and secondary outcomes were analyzed using generalized linear modeling with a binomial outcome distribution for prevalence and a Poisson outcome distribution for incidence rate (adjusted for patient-years). Analyses were performed both with and without adjustment for the effects of age, sex, diabetes, hypertension, obesity, and vascular disease. The effects of the intervention on these outcomes in the intervention group vs the control group are expressed as odds ratios (prevalence) and incidence rate ratios (IRRs) herein.

The significance threshold was defined as  $P < .05$  and all tests are 2-sided.

## Results

### Participants

From the participating practices, 1374 patients were randomized (Figure 1) and followed up for a mean of mean of 4.2 (SD, 1.2) years (Table 1 and eAppendix in the Supplement). Hypertension was the most prevalent risk factor, and most participants had at least 2 risk factors in addition to age. There were 37 deaths (5.5%) in the control group and 36 (5.2%) deaths in the intervention group. There were 309 all-cause emergency hospitalizations in the control group (106.6 per 1000 patient-years) and 269 all-cause emergency hospitalizations in the intervention group (92.2 per 1000 patient-years) (eTable 9 in the Supplement). The IRR was 0.85 (95% CI, 0.72-1.00;  $P = .05$ ). A full list of the cardiovascular and noncardiovascular emergency and elective admissions and outpatient visits is presented in eTables 11 and 12 in the Supplement.

### Primary End Point

The primary end point of left ventricular dysfunction and HF was met in 59 (8.7%) of 677 control-group patients and 37 (5.3%) of 697 intervention-group patients (OR, 0.55; 95% CI, 0.37-0.82;  $P = .003$ ). Asymptomatic left ventricular dysfunction was found in 45 (6.6%) of 677 control-group patients and 30 (4.3%) of 697 intervention-group patients (OR, 0.57; 95% CI, 0.37-0.88;  $P = .01$ ). Heart failure occurred in 14 (2.1%) of 677 control-group patients and 7 (1.0%) of 697 intervention-group patients (OR, 0.48; 95% CI, 0.20-1.20;  $P = .12$ ) (Table 2 and eTable 4 in the Supplement). The unadjusted analyses and the covariate-adjusted analyses were similar for the primary outcome measure (OR, 0.57; 95% CI, 0.38-0.86;  $P = .007$ ).

Twenty-one cases of new-onset HF requiring hospitalization (14 in the control group and 7 in the intervention group) were identified, the majority of which had preserved ejection fraction. Ten of those in the control group were admitted once and 6 of those in the intervention group were admitted once. The remainder in both groups were admitted on 2 occasions. Seventeen of the 21 admissions occurred in patients with at least 1 BNP measurement result of 50 pg/mL or higher before diagnosis (eTable 8 in the Supplement).

Table 1. Baseline Participant Characteristics

Characteristics	All Participants		Participants With BNP $\geq$ 50 pg/mL	
	Control (n=677)	Intervention (n=697)	Control (n=235)	Intervention (n=263)
Age, mean (SD), y	65.4 (10.3)	64.1 (10.1)	70.8 (8.5)	67.9 (9.0)
Male, No. (%)	300 (44.3)	323 (46.3)	104 (44.3)	104 (44.9)
Hypertension, No. (%)	419 (61.9)	433 (62.1)	164 (69.8)	205 (78.0)
Diabetes mellitus, No. (%)	123 (18.2)	127 (18.2)	47 (20.0)	54 (20.5)
Obesity, No. (%)	193 (28.5)	180 (25.8)	69 (29.4)	63 (24.0)
Arrhythmia, No. (%)	54 (8.0)	48 (6.9)	32 (13.6)	31 (11.8)
Valvular disease, No. (%)	3 (0.44)	7 (1.0)	2 (0.85)	5 (1.9)
Lipid disorders, No. (%)	376 (55.5)	355 (50.9)	144 (61.3)	132 (50.2)
Vascular disease, No. (%)	23 (3.4)	32 (4.6)	13 (5.5)	21 (8.0)
Myocardial infarction, No. (%)	56 (8.3)	73 (10.5)	37 (15.7)	46 (17.5)
No. of risk factors, No. (%)				
1	204 (30.1)	204 (29.3)	62 (26.4)	65 (24.7)
2	242 (35.8)	241 (34.6)	86 (36.6)	99 (37.6)
$\geq$ 3	180 (26.6)	188 (27.0)	83 (35.3)	97 (36.9)
BNP, mean (SD), pg/mL	44.8 (57.5)	48.2 (84.9)	86.6 (73.2)	91.6 (118.0)
Cholesterol, mean (SD), mg/dL				
Total	182.1 (40.6)	182.7 (39.9)	174.9 (42.3)	180.1 (40.4)
Low-density lipoprotein	101.4 (34.3)	103.1 (36.4)	95.7 (32.0)	100.1 (35.0)
High-density lipoprotein	50.5 (16.1)	49.3 (15.7)	50.6 (15.3)	48.9 (15.3)
Non-high-density lipoprotein	131.6 (38.4)	133.4 (38.2)	124.3 (39.8)	131.2 (36.6)
Triglycerides	150.4 (78.8)	156.7 (82.6)	140.2 (72.0)	152.7 (82.9)
Glucose, mean (SD), mg/dL	109.6 (37.6)	109.8 (37.8)	110.5 (40.2)	108.8 (28.41)
Creatinine, mean (SD), mg/dL	0.95 (0.22)	0.95 (0.23)	1.01 (0.27)	0.97 (0.25)
Body mass index <sup>a</sup>	28.0 (5.5)	27.7 (5.0)	27.9 (6.1)	27.4 (4.5)
Heart rate, mean (SD), /min	70 (12)	70 (12)	67 (12)	67 (12)
Blood pressure, mean (SD), mm Hg				
Systolic	147.0 (22.5)	144.7 (20.9)	148.7 (23.7)	147.1 (23.7)
Diastolic	80.5 (11.9)	81.1 (12.0)	77.6 (12.3)	79.0 (12.1)

Abbreviation: BNP, brain-type natriuretic peptide.

SI conversions: To convert BNP to ng/L, multiply by 1.0. To convert total, low-density lipoprotein, high-density lipoprotein, and non-high-density lipoprotein cholesterol to mmol/L, multiply by 0.0259. To convert triglycerides to mmol/L, multiply by 0.0113. To convert glucose to mmol/L, multiply by 0.0555. To convert creatinine to  $\mu$ mol/L, multiply by 88.4.

<sup>a</sup> Calculated as weight in kilograms divided by height in meters squared.

## Secondary End Points

### Major Adverse Cardiovascular Events

Seventy-one patients (10.5%) were admitted for major adverse cardiovascular events in the control group and 51 (7.3%) were admitted in the intervention group (OR, 0.69; 95% CI, 0.49-0.98;  $P = .04$ ) (Table 2 and Figure 2). The incidence rates of emergency hospitalization for major cardiovascular events were 40.4 per 1000 patient-years in the control group vs 22.3 per 1000 patient-years in the intervention group (IRR, 0.60; 95% CI, 0.45-0.81;  $P = .002$ ). In the group with BNP levels of 50 pg/mL or higher, the incidence rates of emergency hospitalization for major adverse cardiovascular events were 78 per 1000 patient-years in the control group and 40 per 1000 patient-years in the intervention group (IRR, 0.54; 95% CI, 0.37-0.77;  $P = .002$ ) (Table 3). Results for the group with BNP levels of less than 50 pg/mL are presented in eTable 5 in the Supplement. The most frequently observed clinical events were arrhythmia (90% atrial fibrillation), transient ischemic attack, and stroke (Table 2 and eTable 10 in the Supplement).

### Diagnostic Investigations

Electrocardiography, cardiac imaging, ambulatory blood pressure monitoring, and stress testing were more likely to be per-

formed in the intervention group, with more marked differences in the group with BNP levels of 50 pg/mL or higher (496 vs 850 cardiovascular investigations per 1000 person-years in the control and intervention groups, respectively; IRR, 1.71; 95% CI, 1.61-1.83;  $P < .001$ ) (eTable 2 in the Supplement).

### Pharmacotherapy

At baseline, pharmacotherapy was well matched between the groups, with approximately half of the total population receiving statins, antiplatelet therapy, and agents that modify the renin-angiotensin-aldosterone system (RAAS). Diuretics were prescribed in approximately one-fifth of patients in both groups as therapy for hypertension. There was an increase in RAAS-modifying therapies in the intervention group, driven predominantly by increased use of angiotensin receptor blockers (eTable 3 in the Supplement).

### BNP and Risk Factor Control

Levels of BNP increased in both groups over the duration of the study, consistent with the increasing age of the population. In the subgroup with BNP levels of 50 pg/mL or higher, the increase in BNP levels in the intervention group was approximately half of that observed in the control group (mean,

Table 2. End-Point Prevalence Analysis

End-Point Events	No. (%) of Participants		Unadjusted Multiple Imputation, OR (95% CI)	P Value	Adjusted Multiple Imputation, OR (95% CI)	P Value
	Control	Intervention				
All patients	n=677	n=697				
Heart failure or LVD	59 (8.7)	37 (5.3)	0.55 (0.37-0.82)	.003	0.57 (0.38-0.86)	.007
Heart failure or LVSD	33 (4.9)	23 (3.3)	0.63 (0.38-1.04)	.07	0.65 (0.38-1.09)	.10
Asymptomatic LVSD	19 (2.8)	16 (2.3)	0.73 (0.38-1.40)	.34	0.70 (0.37-1.31)	.26
Asymptomatic LVDD	26 (3.8)	14 (2.0)	0.51 (0.28-0.92)	.03	0.58 (0.32-1.06)	.08
Asymptomatic LVD	45 (6.6)	30 (4.3)	0.57 (0.37-0.88)	.01	0.60 (0.39-0.93)	.02
Arrhythmia	29 (4.3)	21 (3.0)	0.72 (0.43-1.23)	.23	0.77 (0.45-1.32)	.35
Heart failure	14 (2.1)	7 (1.0)	0.48 (0.20-1.20)	.12	0.52 (0.21-1.32)	.17
Myocardial infarction	11 (1.6)	8 (1.1)	0.71 (0.30-1.72)	.45	0.71 (0.29-1.74)	.46
Pulmonary embolism/deep vein thrombosis	10 (1.5)	4 (0.6)	0.51 (0.18-1.44)	.21	0.47 (0.16-1.40)	.18
Stroke/transient ischemic attack	28 (4.1)	13 (1.9)	0.48 (0.26-0.91)	.02	0.51 (0.27-0.96)	.04
Major adverse cardiovascular events <sup>a</sup>	71 (10.5)	51 (7.3)	0.69 (0.49-0.98)	.04	0.72 (0.50-1.03)	.08
Participants with BNP ≥50 pg/mL	n=235	n=263				
Heart failure or LVD	44 (18.7)	25 (9.5)	0.44 (0.26-0.73)	.002	0.46 (0.27-0.79)	.005
Heart failure or LVSD	29 (12.3)	17 (6.5)	0.46 (0.24-0.90)	.03	0.48 (0.24-0.97)	.04
Asymptomatic LVSD	17 (7.2)	12 (4.6)	0.52 (0.24-1.14)	.11	0.51 (0.24-1.06)	.07
Asymptomatic LVDD	15 (6.4)	8 (3.0)	0.48 (0.21-1.07)	.08	0.58 (0.26-1.30)	.19
Asymptomatic LVD	32 (13.6)	20 (7.6)	0.47 (0.27-0.83)	.01	0.50 (0.28-0.90)	.02
Arrhythmia	23 (9.8)	18 (6.8)	0.69 (0.36-1.31)	.26	0.71 (0.37-1.36)	.30
Heart failure	12 (5.1)	5 (1.9)	0.43 (0.15-1.19)	.11	0.47 (0.16-1.33)	.15
Myocardial infarction	6 (2.6)	2 (0.8)	0.31 (0.06-1.65)	.17	0.29 (0.05-1.53)	.15
Pulmonary embolism/deep vein thrombosis	5 (2.1)	2 (0.8)	0.30 (0.06-1.50)	.14	0.30 (0.05-1.62)	.16
Stroke/transient ischemic attack	14 (6)	9 (3.4)	0.57 (0.25-1.31)	.19	0.67 (0.28-1.57)	.36
Major adverse cardiovascular events <sup>a</sup>	45 (19.1)	35 (13.3)	0.65 (0.40-1.05)	.08	0.68 (0.41-1.11)	.13

Abbreviations: BNP, brain-type natriuretic peptide; LVD, left ventricular dysfunction; LVDD, left ventricular diastolic dysfunction; LVSD, left ventricular systolic dysfunction; OR, odds ratio.

<sup>a</sup> Major adverse cardiovascular events included arrhythmia, heart failure, myocardial infarction, pulmonary embolism/deep vein thrombosis, stroke, and transient ischemic attack.

12.5 vs 23.5 pg/mL;  $P = .24$ ). In the subgroup with BNP levels less than 50 pg/mL, there was no change in BNP levels in either group or between groups over the follow-up period; absolute mean changes were 0.4 pg/mL in the control group compared with 0.5 pg/mL in the intervention group, respectively ( $P = .90$ ). The details of cardiovascular risk factor control at baseline and follow-up are presented in eTable 1 in the Supplement.

## Discussion

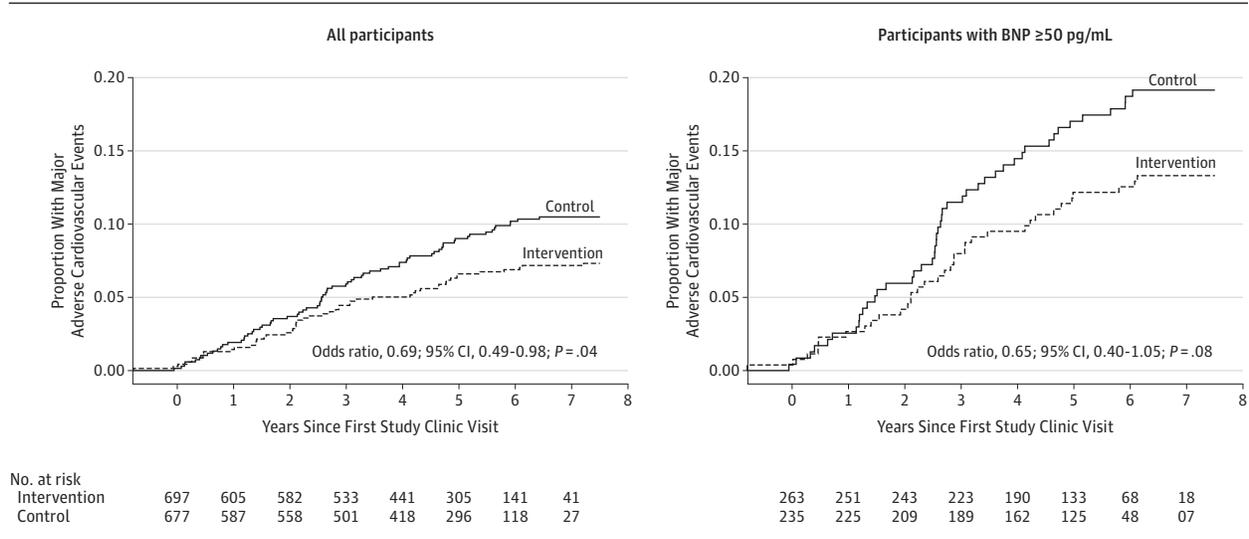
STOP-HF is the first prospective, randomized study, to our knowledge, to demonstrate a reduction in newly diagnosed HF, asymptomatic left ventricular dysfunction, and emergency cardiovascular hospitalizations using BNP-guided collaborative care in a broad community cohort. It confirms BNP as a risk identifier for HF and cardiovascular events and provides unique data on the potential benefit of using levels of this peptide as a guide for care. The positive clinical effect of this intervention was associated with improved risk factor control, increased use of agents that modulate the RAAS targeted at those with elevated BNP levels, and increased use of some cardiovascular diagnostics. These data suggest that a targeted strat-

egy for HF prevention using BNP and collaborative care in a community population may be effective and that benefits extend beyond prevention of HF to an overall reduction in emergency cardiovascular admissions.

We observed a divergence in patient prevalence and incident rate analyses of the secondary end point of major adverse cardiovascular events. While unadjusted patient prevalence analysis showed significant reductions in the intervention vs control groups, a covariate-adjusted analysis of the secondary end point of patient prevalence of major adverse cardiovascular events showed no difference. However, all the incident rate analyses of major adverse cardiovascular events demonstrated significant results (all  $P < .001$ ).

The need for an effective prevention approach to HF is underlined by epidemiological trends,<sup>12</sup> with HF prevalence expected to increase by 30% in the United States by 2030.<sup>1</sup> Present strategies have focused on at-risk cohorts, especially those in middle age with established risk factors. However, the results of NHANES<sup>4</sup> and EUROASPIRE III<sup>3</sup> continue to show disappointing risk factor control, and on current trends, the 2020 American College of Cardiology Foundation/American Heart Association goals of ideal cardiovascular health in the US population are not achievable.<sup>6</sup>

Figure 2. Kaplan-Meier Analysis of Major Adverse Cardiovascular Events in the Full Study Sample and in Participants With BNP ≥50 pg/mL



BNP indicates brain-type natriuretic peptide. Major adverse cardiovascular events included arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure. In the full sample, 51 (7.3%) of 697 patients were admitted for major adverse

cardiovascular events in the intervention group and 71 (10.5%) of 677 were admitted in the control group. In participants with BNP ≥50 pg/mL, 35 (13.3%) of 263 were admitted for major adverse cardiovascular events in the intervention group and 45 (19.1%) of 235 were admitted in the control group.

Table 3. Event Rate Analysis

Events	No. of Events		No. of Person-Years		Events per 1000 Person-Years		Unadjusted Multiple Imputation, IRR (95% CI)	P Value	Adjusted Multiple Imputation, IRR (95% CI)	P Value
	Control	Intervention	Control	Intervention	Control	Intervention				
All patients										
Arrhythmia	45	29	2898.26	2917.16	15.5	9.9	0.69 (0.43-1.12)	.13	0.74 (0.45-1.21)	.19
Heart failure	18	8	2898.26	2917.16	6.2	2.7	0.47 (0.20-1.09)	.09	0.52 (0.22-1.23)	.13
Myocardial infarction	11	8	2898.26	2917.16	3.8	2.7	0.73 (0.31-1.75)	.31	0.73 (0.30-1.75)	.31
Pulmonary embolism/deep vein thrombosis	11	4	2898.26	2917.16	3.8	1.4	0.50 (0.18-1.39)	.17	0.48 (0.17-1.36)	.15
Stroke/transient ischemic attack	32	16	2898.26	2917.16	11	5.5	0.53 (0.29-0.96)	.05	0.58 (0.32-1.06)	.09
Major adverse cardiovascular events <sup>a</sup>	117	65	2898.26	2917.16	40.4	22.3	0.60 (0.45-0.81)	.002	0.64 (0.48-0.86)	.006
Participants with BNP ≥50 pg/mL										
Arrhythmia	38	25	1051.17	1150.29	36.2	21.7	0.63 (0.38-1.06)	.09	0.62 (0.37-1.04)	.08
Heart failure	16	5	1051.17	1150.29	15.2	4.3	0.35 (0.13-0.98)	.06	0.38 (0.14-1.05)	.07
Myocardial infarction	6	2	1051.17	1150.29	5.7	1.7	0.32 (0.06-1.68)	.16	0.29 (0.06-1.48)	.13
Pulmonary embolism/deep vein thrombosis	5	2	1051.17	1150.29	4.8	1.7	0.31 (0.06-1.55)	.14	0.34 (0.06-1.83)	.18
Stroke/transient ischemic attack	17	12	1051.17	1150.29	16.2	10.4	0.64 (0.31-1.34)	.2	0.78 (0.37-1.63)	.32
Major adverse cardiovascular events <sup>a</sup>	82	46	1051.17	1150.29	78	40	0.54 (0.37-0.77)	.002	0.56 (0.39-0.81)	.004

Abbreviations: BNP, brain-type natriuretic peptide; IRR, incidence rate ratio.

<sup>a</sup> Major adverse cardiovascular events included arrhythmia, heart failure,

myocardial infarction, pulmonary embolism/deep vein thrombosis, stroke, and transient ischemic attack.

A separate HF prevention evidence base comes from specific pharmacological interventions directed mainly at hypertension, hyperlipidemia, and proven vascular disease in selected clinical trial populations.<sup>3,4,13-15</sup> However, the translation

of these results into routine community populations is challenging.<sup>16</sup> Also, the same intervention is applied across a population regardless of individual risk assessment or change in risk profile over time. This results in effort being equally di-

rected at lower- and higher-risk cohorts with resultant resource implications.<sup>17-19</sup>

Several data sets indicate that BNP may be effective in refining risk prediction for HF and cardiovascular disease and that it adds predictive power to conventional risk factors.<sup>8</sup> Conventional risk indicators reflect potential for cardiovascular insult and later development of HF, whereas BNP responds to established cardiovascular damage. In addition to standard signals for BNP release,<sup>20-22</sup> other work has demonstrated that this peptide responds to fibroinflammation,<sup>23</sup> a fundamental pathophysiological signal present from the outset of many cardiovascular diseases.

The independent association of baseline BNP level with outcome in this study suggests the potential value of this peptide in risk stratification of American College of Cardiology Foundation/American Heart Association stage A/B HF. The intervention strategy of referral for specialist cardiovascular review if BNP was 50 pg/mL or higher was based on an initial observation from our unit demonstrating a 3-fold increase in events in those with BNP levels of 50 pg/mL or higher,<sup>24</sup> a finding supported by other data sets. However, in the present and other studies,<sup>8</sup> evidence exists of increased risk at BNP levels below 50 pg/mL, and further work is required to clarify the most clinically effective and cost-effective cutoff. Nonetheless, in STOP-HF, the benefit of the intervention was more marked in the population with any BNP measurements of 50 pg/mL or higher, and the number needed to treat for this intervention to prevent 1 major adverse cardiovascular event requiring hospitalization over 1 year was 48, comparing favorably with other prevention strategies in cardiovascular disease.<sup>3-5</sup>

In the setting of improved risk stratification and collaborative care as a result of rapid, near-patient BNP testing, the mechanisms explaining the benefits observed in the intervention group are likely multifactorial. They include facilitating targeted therapy changes, in particular increased use of angiotensin receptor blockers and increased use of diagnostic tests. Although blood pressure reduction in both groups was similar, the targeted use of RAAS-modifying therapy may have contributed to the reduction in end points through mechanisms other than blood pressure reduction.<sup>25</sup> Patient adherence to therapy and lifestyle advice may have been encouraged by communicating risk status to patients. Overall, the multiple and varied mechanisms of the intervention suggests the importance of the disease management approach to this population.

Future modifications of this strategy may bring further clinical benefits. For example, applying this strategy only to patients older than 60 years may be more effective. Alternatively, further evaluation of BNP level to trigger intervention

or combining BNP with other biomarkers reflective of early target organ damage could allow for even more effective risk stratification.

This study has a number of limitations. First, this trial was carried out in a single region within the Irish health care system (described in the eAppendix in the Supplement), and the overall prevalence of HF was low in the studied population. Therefore, results may not be generalizable to other health care settings. Second, inherent in pragmatic trials, nonblinding of patients and practices can bias toward a finding of equivalence because of the influence of treatment recommendations in intervention patients on clinicians' management of the control group. This may explain the improvement in blood pressure seen in both the control and intervention groups. However, this strengthens the conclusion of an added benefit of BNP stratification above conventional risk factor control. Third, it is not possible to determine precisely what components within the multifactorial intervention may have led to improvement, but this design provides real world evidence for the effectiveness of the strategy. Fourth, the event rate was lower than expected and the trial included a heterogeneous group of patients, resulting in wide confidence intervals around the primary end point. Furthermore, while the intervention was directed at cardiovascular care, with reductions in cardiovascular hospitalizations, the absolute difference in all-cause hospitalizations was small. The study was underpowered for determination of mortality and all-cause hospitalization outcomes, and further larger trials will help clarify this. Fifth, the study did not demonstrate that BNP screening had an effect on other clinical outcomes, such as symptomatic HF. Sixth, although every effort in the study design and covariate analysis was made to minimize the possibility of selection bias, it needs to be considered for both practices and patients. Seventh, we defined new-onset HF and major adverse cardiovascular events based on those requiring emergency hospitalization with confirmation of the diagnosis in the discharge summary, as this provides a more robust end point.<sup>26</sup> Therefore, because outpatient diagnoses were not assessed as part of this study, we cannot exclude the possibility that differences in such diagnoses exist. Finally, a full cost-effectiveness analysis of this strategy and data on quality-of-life indexes for participants have not been reported herein and are the subject of ongoing analyses.

In conclusion, among patients at risk of HF, BNP-based screening and collaborative care reduced the combined rates of left ventricular systolic dysfunction, diastolic dysfunction, and HF as well as emergency hospitalizations for major adverse cardiovascular events.

#### ARTICLE INFORMATION

**Author Contributions:** Dr K. McDonald had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ledwidge and K. McDonald served as co-principal investigators. *Study concept and design:* Ledwidge, Conlon, Tallon, Maurer, K. McDonald. *Acquisition of data:* Ledwidge, Conlon, Tallon, Patle,

Badabhaghi, Tilson, Barry, L. McDonald, K. McDonald.

*Analysis and interpretation of data:* Ledwidge, Gallagher, Conlon, O'Connell, Dawkins, Watson, O'Hanlon, Birmingham, Patle, Murtagh, Voon, Tilson, Maurer, K. McDonald.

*Drafting of the manuscript:* Ledwidge, Gallagher, Tallon, O'Connell, Dawkins, Badabhaghi, Murtagh, Voon, L. McDonald, K. McDonald.

*Critical revision of the manuscript for important intellectual content:* Ledwidge, Gallagher, Conlon, Tallon, Dawkins, Watson, O'Hanlon, Birmingham, Patle, Tilson, Barry, L. McDonald, Maurer, K. McDonald.

*Statistical analysis:* Ledwidge, Conlon, O'Connell, Dawkins, Voon.

*Obtained funding:* Ledwidge, Maurer, K. McDonald.

**Administrative, technical, or material support:**

Ledwidge, Gallagher, Conlon, Tallon, Watson, Bermingham, Patle, Badabhagani, Murtagh, Barry, L. McDonald, K. McDonald.

**Study supervision:** Ledwidge, Conlon, Watson, O'Hanlon, Maurer, K. McDonald.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ledwidge reports board membership and shares in Solvotrin Therapeutics and is a named inventor on several patents relating to superspirin effects of isosorbide prodrugs, weight monitoring in heart failure, and novel biomarkers of cardiovascular disease. He is also funded by an EU FP7 grant investigating biomarkers of cardiovascular disease and a Health Research Board, Ireland, project grant. Dr Gallagher received payment for lectures from Merck, Servier Laboratories, Pfizer, and Grunenthal and travel expenses to meetings from Merck. Dr Conlon was funded by a grant from the Health Research Board, Ireland. Dr Bermingham received funding for lectures and development of educational materials from the Health Service Executive in Ireland and travel expenses for meetings from A. Menarini. Mr O'Connell received consultancy fees from Deakin University, Australia, for programming work relating to accelerometer processing tools. Dr Murtagh received a training grant and travel grant from A. Menarini. Dr Kenneth McDonald is a named inventor on several patents relating weight monitoring in heart failure and novel biomarkers of cardiovascular disease. He is also funded by an EU FP7 grant investigating biomarkers of cardiovascular disease and by the Health Research Board of Ireland. He had received honoraria from Pfizer, Alere, A. Menarini, Novartis, Servier, and Abbott. No other disclosures were reported.

**Funding/Support:** The STOP-HF study was funded by the Heartbeat Trust, an independent charity focused on heart failure prevention; the Health Services Executive and the Health Research Board of the Irish Government; and the European Commission Framework Programme 7 Health Project 261409 Metabolic Road to Diastolic Heart Failure (MEDIA) project. The Heartbeat Trust has received unrestricted educational and research grants from Pfizer, A. Menarini, Alere, Roche, Takeda, Abbott, Covidien, and Servier.

**Role of the Sponsors:** None of the funders had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

**Additional Contributions:** We thank the St Vincent's Primary Care Physician Collaborative Group for their input and support for the STOP-HF study.

**REFERENCES**

1. Heidenreich PA, Trogon JG, Khavjou OA, et al; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiopulmonary;

Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123(8):933-944.

2. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-869.

3. Fox KM; European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362(9386):782-788.

4. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyörälä K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Card Fail*. 1997;3(4):249-254.

5. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U; EUROASPIRE Study Group. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil*. 2009;16(2):121-137.

6. Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM. Cardiovascular health behavior and health factor changes (1988-2008) and projections to 2020: results from the National Health and Nutrition Examination Surveys. *Circulation*. 2012;125(21):2595-2602.

7. Onodera M, Nakamura M, Tanaka F, et al. Plasma B-type natriuretic peptide is useful for cardiovascular risk assessment in community-based diabetes subjects: comparison with albuminuria. *Int Heart J*. 2012;53(3):176-181.

8. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med*. 2004;350(7):655-663.

9. Tarnow L, Gall MA, Hansen P, Hovind H, Parving H. Plasma N-terminal pro-B-type natriuretic peptide and mortality in type 2 diabetes. *Diabetologia*. 2006;49(10):2256-2262.

10. McGrady M, Reid CM, Shiel L, et al. N-terminal B-type natriuretic peptide and the association with left ventricular diastolic function in a population at high risk of incident heart failure: results of the Screening Evaluation of the Evolution of New-Heart Failure Study (SCREEN-HF). *Eur J Heart Fail*. 2013;15(5):573-580.

11. Wachtell K, Bella JN, Rokkedal J, et al. Change in diastolic left ventricular filling after 1 year of antihypertensive treatment: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. *Circulation*. 2002;105(9):1071-1076.

12. Rathi S, Deedwania PC. The epidemiology and pathophysiology of heart failure. *Med Clin North Am*. 2012;96(5):881-890.

13. Bangalore S, Wild D, Parkar S, Kukin M, Messerli FH.  $\beta$ -Blockers for primary prevention of heart failure in patients with hypertension: insights from a meta-analysis. *J Am Coll Cardiol*. 2008;52(13):1062-1072.

14. Mitka M. Results of CURE trial for acute coronary syndrome. *JAMA*. 2001;285(14):1828-1829.

15. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2011;(1):CD004816.

16. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet*. 2005;365(9453):82-93.

17. Hobbs FD, Erhardt L. Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in 5 European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. *Fam Pract*. 2002;19(6):596-604.

18. Yarnall KS, Pollak KI, Østbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? *Am J Public Health*. 2003;93(4):635-641.

19. Østbye T, Yarnall KS, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care? *Ann Fam Med*. 2005;3(3):209-214.

20. Sabatine MS, Morrow DA, de Lemos JA, et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. *J Am Coll Cardiol*. 2004;44(10):1988-1995.

21. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J*. 1998;135(5 Pt 1):825-832.

22. Yoshimura M, Yasue H, Okumura K, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. *Circulation*. 1993;87(2):464-469.

23. Phelan D, Watson C, Martos R, et al. Modest elevation in BNP in asymptomatic hypertensive patients reflects sub-clinical cardiac remodeling, inflammation and extracellular matrix changes. *PLoS One*. 2012;7(11):e49259. doi:10.1371/journal.pone.0049259.

24. Karuppiah S, Graham F, Ledwidge M, et al. Elevated BNP with normal systolic function in asymptomatic individuals at risk for heart failure: a marker of diastolic dysfunction and clinical risk. *Ir J Med Sci*. 2006;175(4):5-13.

25. Alfie J, Aparicio LS, Waisman GD. Current strategies to achieve further cardiac and renal protection through enhanced renin-angiotensin-aldosterone system inhibition. *Rev Recent Clin Trials*. 2011;6(2):134-146.

26. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J*. 1991;12(3):315-321.