

N-Terminal Pro-B-Type Natriuretic Peptide, Vascular Disease Risk, and Cholesterol Reduction Among 20,536 Patients in the MRC/BHF Heart Protection Study

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Objectives	We sought to assess the ability of N-terminal pro-B-type natriuretic peptide (N-BNP) to predict vascular events in high-risk people and to test whether statins benefit people with high levels of N-BNP.
Background	The predictive value of N-BNP for occlusive vascular events and the effects of statins in people with high N-BNP levels are uncertain.
Methods	A total of 20,536 people were assigned randomly to simvastatin 40 mg daily or placebo for an average of 5 years. Five baseline N-BNP groups were defined (<386; 386 to 1,171; 1,172 to 2,617; 2,618 to 5,758; and $\geq 5,759$ pg/ml).
Results	Baseline N-BNP was strongly predictive of future vascular events independently of other characteristics. Compared with participants with N-BNP <386 pg/ml, those with levels $\geq 5,759$ pg/ml had adjusted relative risks for major vascular events (MVEs) (i.e., major coronary events [MCE] [nonfatal myocardial infarction or coronary death], stroke, or revascularization) of 2.26, for MCE of 3.09, for stroke of 1.80, and for heart failure (hospitalization or death) of 9.23 (all $p < 0.0001$). Overall, simvastatin allocation reduced the relative risk of MVE by 24% (95% confidence interval 19 to 28). There was a trend toward smaller (but still significant) proportional reductions in MVE among participants with greater baseline N-BNP levels, but the absolute benefits of simvastatin allocation were similar at all N-BNP levels. Simvastatin allocation was also associated with a 14% (95% confidence interval 0 to 25) proportional reduction in heart failure. No excess risk of other vascular and nonvascular outcomes was observed with simvastatin allocation among participants with greater baseline values of N-BNP.
Conclusions	In this study, N-BNP levels were strongly predictive not only of heart failure but also of MVEs. In people with high N-BNP levels consistent with heart failure, statin allocation significantly reduced vascular risk, with no evidence of hazard. (Heart Protection Study; http://www.controlledtrials.com/ISRCTN48489393/48489393) (J Am Coll Cardiol 2007;49:311-9) © 2007 by the American College of Cardiology Foundation

Brain-type natriuretic peptide (BNP), a hormone secreted in the ventricular myocardium during periods of increased ventricular stretch and wall-tension, plays an important role in the regulation of blood pressure, blood volume, and sodium balance (1). Upon secretion, the BNP precursor is split into the biologically active peptide and the more stable amino terminal prohormone fragment (N-BNP or NT-proBNP). For several years, it has been known that N-terminal pro-B-type

natriuretic peptide (N-BNP) levels provide sensitive (and reasonably specific) tests for the diagnosis of heart failure and left ventricular dysfunction (2-5) and provide good indicators of disease severity and prognosis in patients with heart failure (6). In addition, because N-BNP is released after cardiac ischemia, it also may provide a useful biomarker for the detection and prediction of vascular morbidity and mortality (7); a recent systematic review found N-BNP to be a strong indicator of future cardiac events in patients both with and without symptomatic heart failure (8).

There is overwhelming evidence that lowering low-density lipoprotein (LDL) cholesterol by using statins reduces vascular risk in a wide range of people (9). However, it has been suggested that these benefits may not extend to patients with or at high risk of developing heart failure (10,11), chiefly because low plasma lipid levels have been associated with poorer prognosis among heart failure patients in observational studies (12,13). Consequently, hy-

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Abbreviations and Acronyms

BNP	= brain-type natriuretic peptide
CI	= confidence interval
LDL	= low-density lipoprotein
LVEF	= left ventricular ejection fraction
MCE	= major coronary event
MI	= myocardial infarction
MVE	= major vascular event
N-BNP	= N-terminal pro-B-type natriuretic peptide

potheses have been generated concerning the possible importance in heart failure patients of coenzyme Q₁₀ levels (which are reduced by statins), as well as the possible beneficial effects that lipoproteins may have through binding and detoxifying endotoxins (11,14). Two large randomized placebo-controlled trials of rosuvastatin in patients with heart failure, the CORONA (Controlled rosuvastatin multinational study in heart failure) study (15) and the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico acuto) heart failure

study (16), are now underway to help resolve these uncertainties.

In this report, blood samples taken before entry into the randomized placebo-controlled Heart Protection Study (17) of statin therapy in 20,536 patients were used to assess: 1) the relationships between N-BNP and the incidence of subsequent major vascular events and heart failure; 2) whether the effects of statin treatment on vascular risk differ according to N-BNP level; and 3) the effect of lowering LDL cholesterol with a statin on the incidence of heart failure.

Methods

Details of the objectives, design, and methods of the Medical Research Council/British Heart Foundation Heart Protection Study have been reported previously (17,18), and are summarized in this section.

Recruitment and eligibility criteria. Between 1994 and 1997, 20,536 men and women ages 40 to 80 years at high risk of vascular disease were recruited from 69 United Kingdom hospitals, assigned randomly to receive 40 mg of simvastatin daily or matching placebo (and, separately, using a 2-by-2 factorial design, to receive antioxidant vitamins or matching placebo capsules) (19), and followed for an average of 5 years. Ethics and regulatory approval was obtained from relevant authorities. To be eligible, patients had to have either a previous diagnosis of coronary disease, occlusive disease of noncoronary arteries, or diabetes (type I or II) or, for men ages 65 years or older, to have been treated for hypertension. Subjects with heart failure were eligible provided that they were not breathless at rest, but heart failure diagnoses were not recorded at baseline.

Screening, run-in phase, and randomization. At the initial screening visit, nurses completed a brief questionnaire about the patient's past medical history and other relevant factors; measured the person's height, weight, and blood pressure; and took a nonfasting blood sample. Potentially

eligible patients were given information about the study and asked for their written agreement to participate. Consenting participants entered a "run-in" phase, consisting of 4 weeks of placebo followed by 4 to 6 weeks of 40 mg of simvastatin daily. Compliant individuals who did not have a major problem during the run-in and who were not withdrawn by their family doctor were assigned randomly into the study and had their current medication recorded.

Measurement of blood lipids and N-BNP. Screening blood samples were cooled and sent by overnight courier to the coordinating central laboratory for immediate separation and assay and for long-term storage. Lipid fractions (including LDL measured directly) were analyzed as previously reported (18). The assay of N-BNP in stored plasma samples was based on the noncompetitive N-BNP assay described by Karl et al. (20). After an average of 4.6 years, nonfasting blood was collected from all participants attending final follow-up. A random sample of 1,174 of these participants (approximately 5%) was selected, and baseline and final follow-up N-BNP levels were remeasured. Within- and between-assay coefficients of variation were <5% for measurements of blood lipids and N-BNP.

Follow-up of vascular events. Participants were to be seen in the study clinics at regular periods throughout follow-up (with nonattending patients followed by telephone or, alternatively, through their family doctor). At each follow-up, information was recorded about any suspected myocardial infarction (MI), stroke, vascular procedure, or other serious adverse experience (including hospitalization for any reason). Further details were sought from family doctors about all reports (including admissions to hospital for heart failure or breathlessness) that might relate to major vascular events, cancers or deaths, and from United Kingdom national registries about certified causes of death. Outcomes (including heart failure) were coded by the coordinating center clinical staff in a blinded fashion (17). The primary prespecified end point for subgroup analyses was "major vascular events" (MVE), which was defined as major coronary events (MCE) (i.e., coronary death and nonfatal MI), any stroke (fatal or nonfatal), or coronary or noncoronary revascularization. Heart failure was defined as hospitalization for heart failure and death from heart failure (including deaths for which the underlying cause was coronary). During the study, 20,469 participants (99.7%) had complete follow-up for both mortality and morbidity.

Statistical analysis. Five baseline N-BNP groups were defined such that similar numbers of MVEs occurred in each group, which ensured similar sized confidence intervals around risk estimates for this end point. These 5 groups had baseline N-BNP measurements of <386; 386 to 1,171; 1,172 to 2,617; 2,618 to 5,758; and ≥5,759 pg/ml. The few patients with missing N-BNP at baseline (n = 137; 0.7%) were allocated to the middle group (findings were not materially altered by their exclusion). Relative hazards of MVE, MCE, stroke, and heart failure for each N-BNP group compared with the lowest group were estimated using

Cox proportional hazards regression and presented as “floating absolute risks” (21), which allow an appropriate variance to be ascribed to each group (including the reference group). Analyses were performed before and after adjustment for baseline age, gender, prior diseases, drug use, randomization to simvastatin, apolipoprotein A₁, apolipoprotein B, systolic blood pressure, cigarette smoking status, body mass index, and estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula (22). Chi-square tests for linear trend in the relative risk with increasing log N-BNP level were performed.

Analyses of the effect of randomization to simvastatin on risk of first MVE, MCE, and stroke were performed both overall and separately within each N-BNP group using log-rank analyses. Chi-square tests for linear trend in the effect of simvastatin with increasing log N-BNP level were performed. Log-rank analyses were used to estimate the effect of randomization to simvastatin on the overall risk of heart failure but not separately in each N-BNP group (as a result of the relatively small number of such events). This analysis was repeated after censoring of patients who, in the absence of heart failure, had a nonfatal MI (to examine the possibility that any apparent effect on heart failure may be secondary to effects on MI). In the 1,174 participants with repeat N-BNP samples, comparisons of the average change in log N-BNP between the simvastatin and placebo groups were performed using the Student's *t* test. All statistical tests were 2-sided and performed on an intention-to-treat basis.

Results

N-BNP and cardiovascular risk factors at baseline. Baseline N-BNP levels were substantially skewed (skewness coefficient of 2.7), with a median of 1,091 pg/ml and an interquartile range of 330 to 3,028 pg/ml. The baseline characteristics of study participants in the five N-BNP-defined groups are shown in Table 1. Patients with greater N-BNP levels at baseline were older, more likely to have existing coronary disease, and more likely to be taking cardioprotective drugs than subjects with lower baseline N-BNP levels. Patients with greater baseline N-BNP levels also had slightly lower mean blood pressure, which was independent of reported blood pressure-lowering drug use. In contrast, proportions of men, mean blood lipid levels, and cigarette smoking rates varied little by N-BNP level, whereas subjects with high N-BNP levels were slightly leaner than those with low N-BNP. Mean glomerular filtration rate also decreased steadily with increasing baseline N-BNP level. Perhaps as a consequence of the inclusion criteria for the trial (virtually all subjects had either prior vascular disease or diabetes), diabetes in this population was more commonly observed among subjects with lower N-BNP levels.

N-BNP and the incidence of MVE, MCE, stroke, and heart failure. The 5-year floating absolute risks of MVE, MCE, stroke, and heart failure by baseline N-BNP group are shown in Table 2, both before and after adjustment for

other baseline risk factors (also see Fig. 1). The risks of MVE, MCE, stroke and, particularly, heart failure increased progressively with increasing N-BNP. Compared with individuals with N-BNP levels <386 pg/ml, the unadjusted relative risk for subjects with baseline N-BNP levels ≥5,759 pg/ml was 2.78 for MVE, 4.70 for MCE, 2.47 for stroke, and 16.0 for heart failure (all *p* < 0.0001). Taking into account the differences in baseline characteristics had a marked effect on these estimates, with the relative risks being reduced to 2.26 for MVE, 3.09 for MCE, 1.80 for stroke, and 9.23 for heart failure (but all were still *p* < 0.0001). Among individuals with N-BNP <386 pg/ml, further subdivision (<40; ≥40, <100; and ≥100, <386 pg/ml) did not demonstrate substantial differences in annual event rates: 3.3%, 3.4%, and 3.5% for MVE; 1.1%, 1.2%, and 1.3% for MCE; 0.7%, 0.9%, and 0.8% for stroke; and 0.1%, 0.1%, and 0.2% for heart failure, respectively.

Simvastatin allocation and risk of MVE, MCE, and stroke by N-BNP level. The randomization of large numbers of people in the study produced good balance in baseline characteristics between the treatment groups both overall (17) and separately in each baseline N-BNP group (including for the use of concomitant medications). Compared with allocation to placebo, allocation to simvastatin reduced LDL cholesterol by an average of 1 mmol/l during the 5-year treatment period. The effect of simvastatin allocation on the incidence of MVE, MCE, and stroke by baseline N-BNP level is shown in Figure 2. Overall, as previously reported (17), the relative risk of MVE was reduced by 24% (95% confidence interval [CI] 19 to 28). There was a significant trend (*p* = 0.03) toward smaller, although still highly statistically significant, proportional reductions in MVE risk with simvastatin among participants who had greater baseline N-BNP levels (despite similar absolute LDL cholesterol reductions in each N-BNP group: data not shown). However, because people with greater baseline N-BNP levels had a greater absolute risk of MVE, the absolute benefits of simvastatin were similar at all levels of N-BNP (Fig. 3). Overall, allocation to simvastatin reduced the relative risk of MCE by 27% (95% CI 21 to 33) and the relative risk of stroke by 25% (95% CI 15 to 34). The trend in the proportional reduction in MVE risk by N-BNP level reflected a highly significant trend for MCE (*p* < 0.0001), with no clear trend for stroke (*p* = 0.23). The proportional reductions in vascular death (overall risk reduction 17%; 95% CI 9 to 25) and nonvascular death (overall risk reduction 5%; 95% CI –7 to 15) were not significantly different across the different N-BNP groups (Fig. 4). In particular, there was no suggestion of any adverse effect of statin therapy among patients with greater N-BNP levels.

Simvastatin allocation, heart failure, and follow-up N-BNP. Randomization to simvastatin was associated with a marginally significant 14% (95% CI 0 to 25) proportional reduction in the risk of hospitalization or death due to heart failure (348 [3.4%] simvastatin vs. 402 [3.9%] placebo; *p* = 0.05) during the scheduled treatment period. This estimate was unaffected when patients who had a

Table 1 Baseline Characteristics by Baseline N-BNP Level

	N-BNP Level (pg/ml)				
	<386	386-1,171	1,172-2,617	2,618-5,758	≥5,759
Subjects, n	5,658	4,862	4,209	3,371	2,436
Mean (SD) N-BNP, pg/ml	141 (122)	732 (224)	1,802 (417)	3,907 (890)	10,349 (4,295)
Mean (SD) age at randomization, yrs	59.0 (8.5)	63.2 (8.1)	65.6 (7.3)	67.5 (6.7)	69.2 (6.1)
Men, %	75.9	74.1	74.4	75.3	77.2
Mean (SD) blood lipids*					
Apolipoprotein A ₁ , g/l	1.21 (0.22)	1.21 (0.21)	1.20 (0.21)	1.19 (0.21)	1.18 (0.21)
Apolipoprotein B, g/l	1.15 (0.24)	1.14 (0.23)	1.14 (0.23)	1.14 (0.24)	1.13 (0.24)
High-density lipoprotein cholesterol, mmol/l	1.05 (0.33)	1.07 (0.31)	1.05 (0.31)	1.05 (0.32)	1.06 (0.32)
Low-density lipoprotein cholesterol, mmol/l	3.40 (0.87)	3.38 (0.82)	3.36 (0.82)	3.37 (0.83)	3.35 (0.84)
Mean (SD) blood pressure, mm Hg*					
Systolic	145.5 (24.3)	144.3 (23.0)	144.0 (23.1)	144.2 (23.4)	142.4 (23.7)
Diastolic	82.9 (12.8)	81.4 (12.1)	80.6 (12.2)	80.5 (12.3)	80.4 (12.5)
Mean (SD) estimated glomerular filtration rate, ml/min*	77.63 (15.73)	74.92 (14.91)	72.78 (14.96)	70.80 (15.14)	65.58 (15.31)
Cigarette smoking status, %*					
Current smokers	14.8	15.4	13.3	12.7	13.5
Ex-smokers	59.9	60.2	61.6	61.4	59.8
Body mass index, kg/m ² *					
Mean (SD)	28.0 (4.6)	27.5 (4.3)	27.5 (4.4)	27.4 (4.4)	27.1 (4.5)
Obese (≥30), %	27.5	23.9	23.3	22.8	20.1
Overweight (≥25), %	76.0	71.9	72.3	70.1	66.0
Prior coronary heart disease, %*					
Myocardial infarction	22.2	35.1	45.5	54.6	60.9
Other CHD without MI	23.1	26.0	25.0	22.4	19.6
None	53.9	37.7	28.2	21.8	18.3
Other prior disease, %*					
Cerebrovascular disease	16.9	14.9	15.0	15.1	19.1
Peripheral vascular disease	34.4	32.2	32.2	32.4	33.3
Other coronary disease	39.3	52.7	60.3	65.7	66.8
Diabetes	40.5	29.4	24.9	21.5	21.0
Drug use, %*					
ACE inhibitors	15.6	15.1	17.9	20.2	33.6
Beta-blockers	10.6	20.5	30.1	37.0	33.9
Diuretics	17.2	20.1	22.2	26.4	43.0
Any treatment for hypertension	35.4	37.3	43.3	45.5	49.1
Aspirin	52.2	62.6	68.7	69.4	67.7
Lipid-lowering drug	0.4	0.3	0.2	0.2	0.4

Categories are defined such that an approximately equal number of subsequent major vascular events occurs in each group. *Adjusted for age and gender.

ACE = angiotensin-converting enzyme; CHD = coronary heart disease; MI = myocardial infarction; N-BNP = N-terminal pro-B-type natriuretic peptide.

nonfatal MI before any heart failure event being observed were censored at the time of their MI. Levels of N-BNP were remeasured in blood collected after an average of 4.6 years from a random sample of 1,174 participants. On average, follow-up N-BNP levels were 1.49 (95% CI 1.42 to 1.57) times higher than baseline levels. However, this relative increase in N-BNP level during the study differed significantly ($p < 0.001$) according to treatment allocation: 1.37 (95% CI 1.28 to 1.47) for patients allocated to simvastatin versus 1.64 (95% CI 1.52 to 1.76) for patients allocated to placebo. Exclusion of 341 patients who had a major vascular event, other vascular event, or admission to hospital for heart failure or angina in the period between the baseline and follow-up N-BNP samples did not explain this difference: after such exclusions, the mean proportional increases in N-BNP levels were 1.28 (95% CI 1.19 to 1.38)

with simvastatin and 1.46 (95% CI 1.36 to 1.58) with placebo ($p = 0.01$). (Randomization to receive vitamins in the Heart Protection Study was associated with a 20% [95% CI 4 to 38] increase in hospitalization or death due to heart failure [408 (4.0%) vitamins vs. 342 (3.4%) placebo; $p = 0.01$]. Among those with repeat N-BNP measurements, the mean proportional increases in N-BNP level during the study were 1.57 [95% CI 1.46 to 1.68] with vitamins and 1.42 [95% CI 1.32 to 1.52] with placebo [$p = 0.04$]).

Discussion

N-BNP is a strong indicator of future vascular event risk. This study of more than 20,000 people at high risk of vascular disease, including patients with mild-to-moderate heart failure, provides reliable evidence that N-BNP is

Table 2 Risk of Major Vascular Events, Stroke, Major Coronary Events, and Heart Failure Hospitalization or Death, by Baseline N-BNP Level

	N-BNP Level (pg/ml)					p Value*
	<386	386–1,171	1,172–2,617	2,618–5,758	≥5,759	
Subjects, n	5,658	4,862	4,209	3,371	2,436	
Major vascular event						
Number of events (%)	919 (16.2%)	913 (18.8%)	952 (22.6%)	916 (27.2%)	918 (37.7%)	
Unadjusted HR (95% CI)	1.00 (0.94–1.07)	1.17 (1.10–1.25)	1.45 (1.36–1.54)	1.81 (1.70–1.93)	2.78 (2.60–2.96)	<0.0001
Fully adjusted HR (95% CI)†	1.00 (0.93–1.08)	1.13 (1.06–1.21)	1.32 (1.24–1.41)	1.59 (1.49–1.70)	2.26 (2.10–2.43)	<0.0001
Major coronary event						
Number of events (%)	345 (6.1%)	356 (7.3%)	394 (9.4%)	422 (12.5%)	593 (24.3%)	
Unadjusted HR (95% CI)	1.00 (0.90–1.11)	1.20 (1.08–1.34)	1.56 (1.41–1.72)	2.15 (1.95–2.36)	4.70 (4.33–5.09)	<0.0001
Fully adjusted HR (95% CI)†	1.00 (0.89–1.13)	1.10 (0.99–1.22)	1.30 (1.18–1.44)	1.63 (1.48–1.80)	3.09 (2.81–3.39)	<0.0001
Stroke						
Number of events (%)	215 (3.8%)	183 (3.8%)	224 (5.3%)	212 (6.3%)	195 (8.0%)	
Unadjusted HR (95% CI)	1.00 (0.87–1.14)	1.00 (0.86–1.15)	1.43 (1.26–1.63)	1.75 (1.53–2.00)	2.47 (2.14–2.84)	<0.0001
Fully adjusted HR (95% CI)†	1.00 (0.86–1.17)	0.89 (0.77–1.03)	1.21 (1.06–1.38)	1.42 (1.24–1.63)	1.80 (1.54–2.10)	<0.0001
Heart failure						
Number of events (%)	58 (1.0%)	83 (1.7%)	125 (3.0%)	168 (5.0%)	325 (13.3%)	
Unadjusted HR (95% CI)	1.00 (0.77–1.29)	1.67 (1.35–2.07)	2.96 (2.48–3.53)	5.16 (4.43–6.00)	16.02 (14.36–17.86)	<0.0001
Fully adjusted HR (95% CI)†	1.00 (0.76–1.32)	1.49 (1.20–1.87)	2.47 (2.07–2.94)	3.86 (3.32–4.47)	9.23 (8.10–10.52)	<0.0001

*Test of linear trend between log(N-BNP) concentration and risk; †adjusted for age, gender, prior vascular disease (myocardial infarction, cerebrovascular disease, other coronary disease, peripheral vascular disease, diabetes, and all 2-, 3-, 4- and 5-way interactions between these disease categories), baseline drug use, randomization to simvastatin, apolipoprotein A₁, apolipoprotein B, systolic blood pressure, cigarette smoking status, body mass index, and estimated glomerular filtration rate.

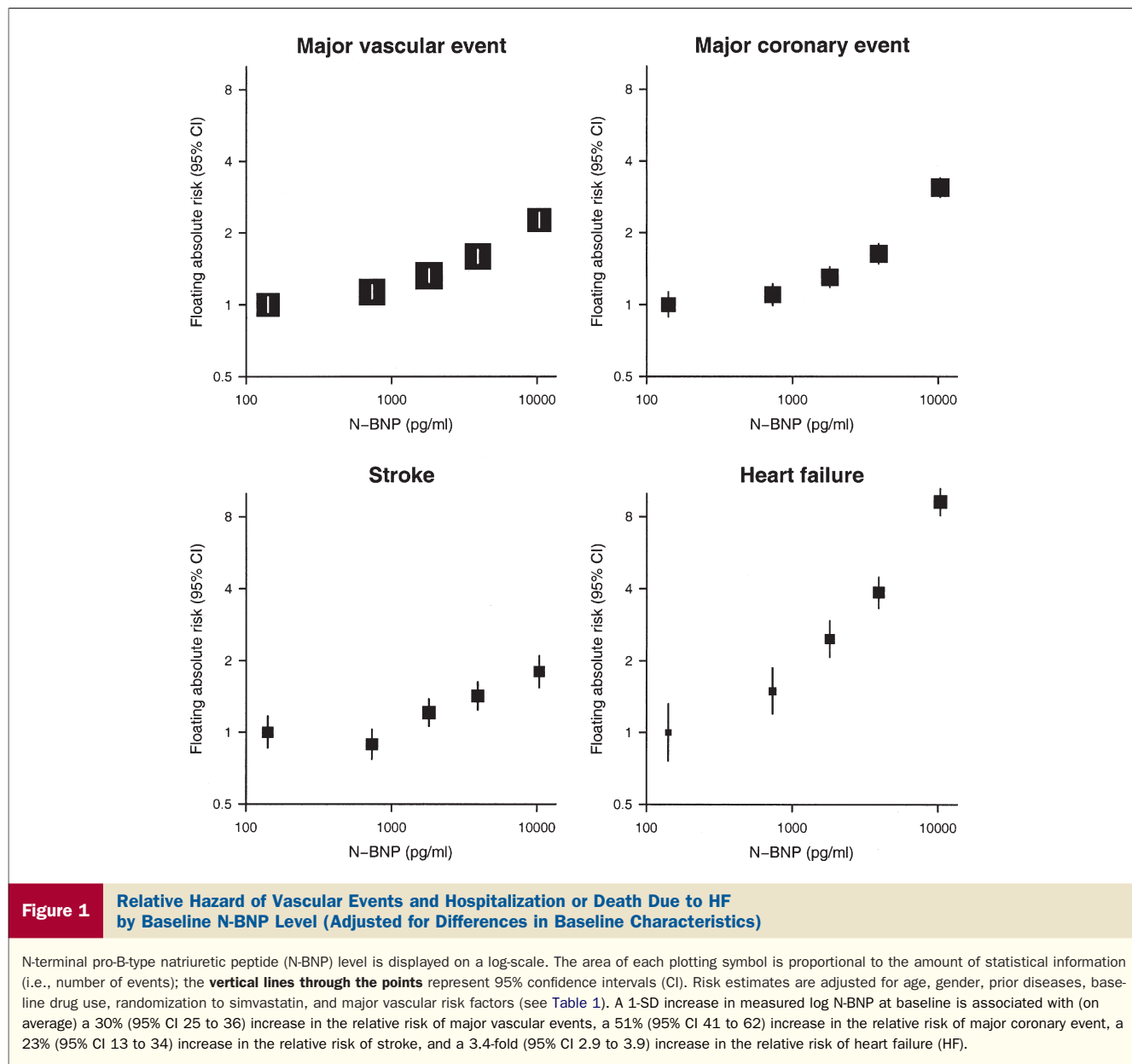
CI = confidence interval; HR = hazard ratio; N-BNP = N-terminal pro-B-type natriuretic peptide.

strongly and positively related not only to subsequent hospitalization or death due to heart failure but also to major occlusive vascular events in such patients. When compared with individuals who had baseline measurements of N-BNP level <386 pg/ml (28% of the study population but, by design, 20% of MVE events), individuals with baseline N-BNP measurements ≥5,759 pg/ml (12% of the population but 20% of MVE events) had more than twice the risk of MVE and more than 3 times the risk of MCE, even after accounting for differences in other baseline characteristics (Table 2).

Previous studies of the prognostic strength of N-BNP for occlusive vascular events typically have been based on patients with acute coronary syndromes (23–25). In one study of 6,809 patients with non-ST-segment elevation acute coronary syndrome, the risk of MI over the following 30 days increased with increasing quartile of N-BNP, from 2.7% in the lowest quartile to 7.5% in the highest quartile (25). Similar observations also have been made in non-hospitalized individuals (26–28). For example, in the Framingham Heart Study, a 1-SD increase in log BNP was associated with a 28% increase in the risk of a first cardiovascular event (which is consistent with the respective estimate in the Heart Protection Study; see footnote to Fig. 1) and a 53% increase in the risk of stroke or transient ischemic attack (26). A recent population-based study in Denmark found that the 5-year incidence of major cardiovascular events increased by 92% for each SD increase in log N-BNP, whereas ischemic stroke risk increased by 76% (27). However, these values should be interpreted with caution because the relationships do not seem to be straight

lines (i.e., the relative risk associated with a given difference in baseline log N-BNP is not the same at all levels of log N-BNP) (see Fig. 1). Moreover, the strength of the relationship between long-term “usual” log N-BNP levels and risk is likely to be underestimated by analyses based on single “baseline” N-BNP measurements because of regression dilution bias (29). A recent review of 24 studies that used BNP or N-BNP to estimate relative risks for death, cardiac death, sudden death, or cardiovascular events concluded that N-BNP was a strong prognostic indicator of these outcomes in populations both with and without heart failure (8). Our findings support this conclusion, providing clear evidence that N-BNP is a powerful marker of vascular events in a wide range of people at high vascular event risk. **Lowering LDL cholesterol reduces vascular risk irrespective of N-BNP level.** The present results show that lowering LDL cholesterol by 1 mmol/l with a statin reduces the risk of vascular events at all levels of baseline N-BNP studied, including among individuals with high levels consistent with a diagnosis of heart failure. Although the proportional reduction in MVE risk appeared to be smaller for patients with the highest baseline N-BNP levels (Fig. 2), the absolute numbers of MVEs avoided per 1,000 patients treated was similar across baseline N-BNP categories because of the higher absolute risks among people with higher N-BNP levels (Fig. 3).

The hypothesis that cholesterol reduction could cause harm in patients with heart failure was initially stimulated by observational studies that found low blood cholesterol levels to be associated with increased mortality in such individuals (12,13). Possible explanations for this phenom-



enon were developed, including the suggestion that, in the presence of heart failure, lipoproteins may provide protection through the binding and detoxifying of endotoxins (14). This hypothesis has helped perpetuate a belief that patients with or at high risk of developing heart failure (even those with pre-existing coronary disease) should not be treated with statins until the results from clinical trials of patients with heart failure are known (10,11). However, previous cholesterol-lowering trials have failed to provide any evidence in favor of this position: indeed, if anything, they have suggested the opposite. Secondary analysis of a trial in MI survivors with average cholesterol levels found that pravastatin was equally effective among those who presented with left ventricular ejection fraction (LVEF) between 25% and 40% as in those with LVEF >40% (although patients with severe heart failure [LVEF <25%]

were not eligible for that study) (30). In another study, patients with congestive heart failure experienced similar proportional benefits from treatment with atorvastatin as patients without heart failure (31). The present large study has shown that lowering LDL cholesterol with simvastatin reduces the risk of MVE among patients with elevated N-BNP levels that are consistent with heart failure. In addition, the proportional effects of simvastatin allocation on the risk of vascular and nonvascular death were similar irrespective of N-BNP level, with no evidence that lowering LDL cholesterol in patients with higher N-BNP levels produced any adverse effects.

Cholesterol reduction and risk of heart failure. In the Heart Protection Study, reducing LDL cholesterol with simvastatin by an average of 1 mmol/l for 5 years was associated with a marginally significant 14% (95% CI 0 to

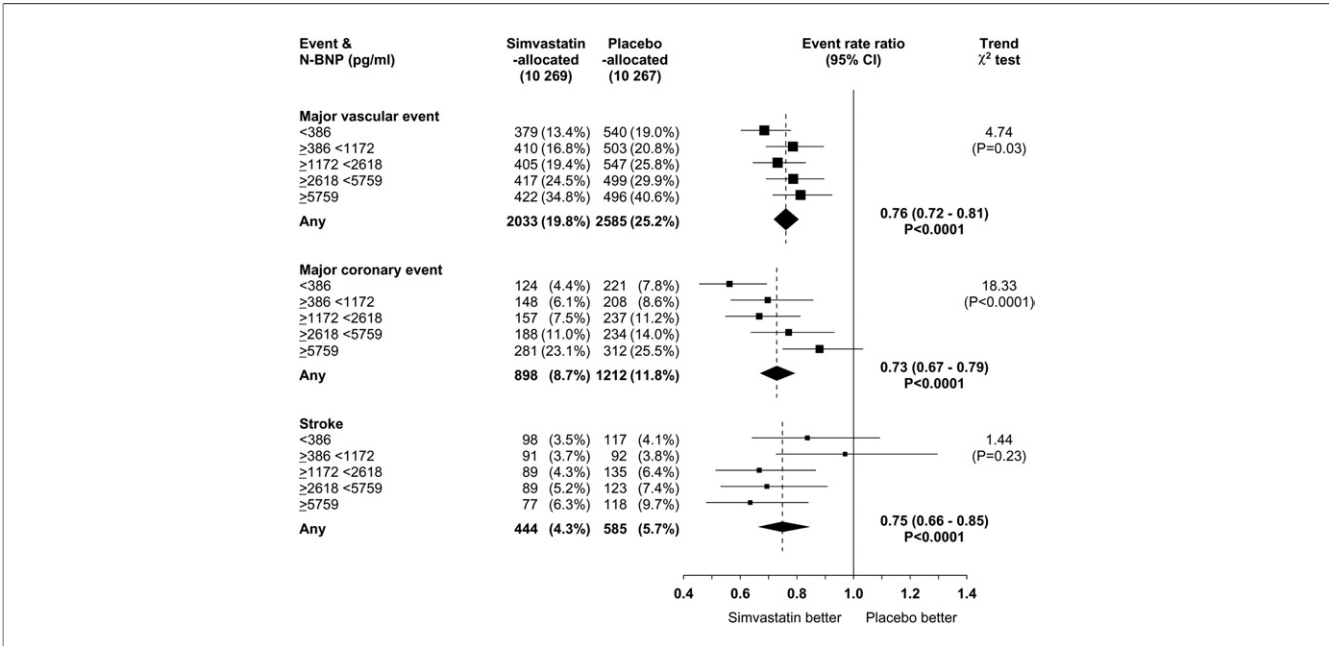


Figure 2 Effects of Simvastatin on Vascular Events in Participants Subdivided by Baseline N-BNP Level

CI = confidence interval; N-BNP = N-terminal pro-B-type natriuretic peptide.

25) proportional reduction in the risk of hospitalization or death due to heart failure. Although this reduction remains statistically consistent with there being little or no reduction in risk, it does not provide support for concerns that lowering LDL cholesterol might materially increase the risk

of heart failure. Moreover, the mean increase in N-BNP levels during the study was lower among those allocated to simvastatin than among those allocated placebo. It is possible that these findings reflect a reduced incidence of vascular events (which may not have been fully taken into account in our analyses), rather than direct effects of statin therapy on heart function. In a previous randomized trial of hypercholesterolemic patients with coronary heart disease but without evidence of congestive heart failure, simvastatin produced a significant 20% proportionally lower risk of developing heart failure during the following 5 years (32), whereas in another secondary prevention trial atorvastatin produced a significant 50% reduction in the development of new heart failure (31). Other large statin trials generally have failed to show significant effects of cholesterol reduction on heart failure risk, but the confidence intervals have been wide because of low event rates or early termination after the emergence of clear benefit on the primary end point of occlusive vascular events (33).

Study limitations. Because the presence of heart failure was not recorded at baseline in HPS, it was not possible to estimate directly the effect of simvastatin in patients with and without heart failure at randomization. Instead, N-BNP was used as a surrogate measure for baseline evidence of heart failure because it is well established that it provides a highly sensitive indicator of existing heart failure (2), as well as a powerful indicator for future risk of heart failure (as is also suggested in the present study). No adjustment was made for multiple comparisons, and the apparent trend toward smaller relative reductions in major coronary events with simvastatin among patients with

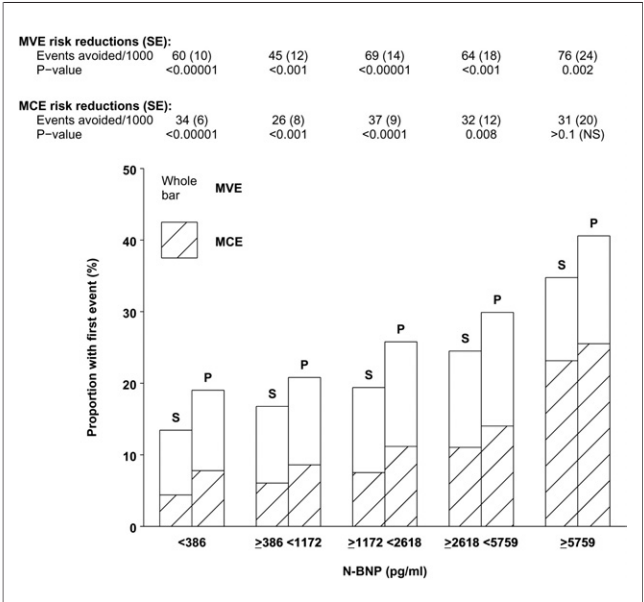


Figure 3 Absolute Benefits of Simvastatin Allocation on First MVE and First MCE, by Baseline N-BNP Level

Absolute benefits of simvastatin allocation on first major vascular event (MVE) and first major coronary event (MCE) in participants subdivided by baseline N-terminal pro-B-type natriuretic peptide (N-BNP) level. P = placebo; S = simvastatin.

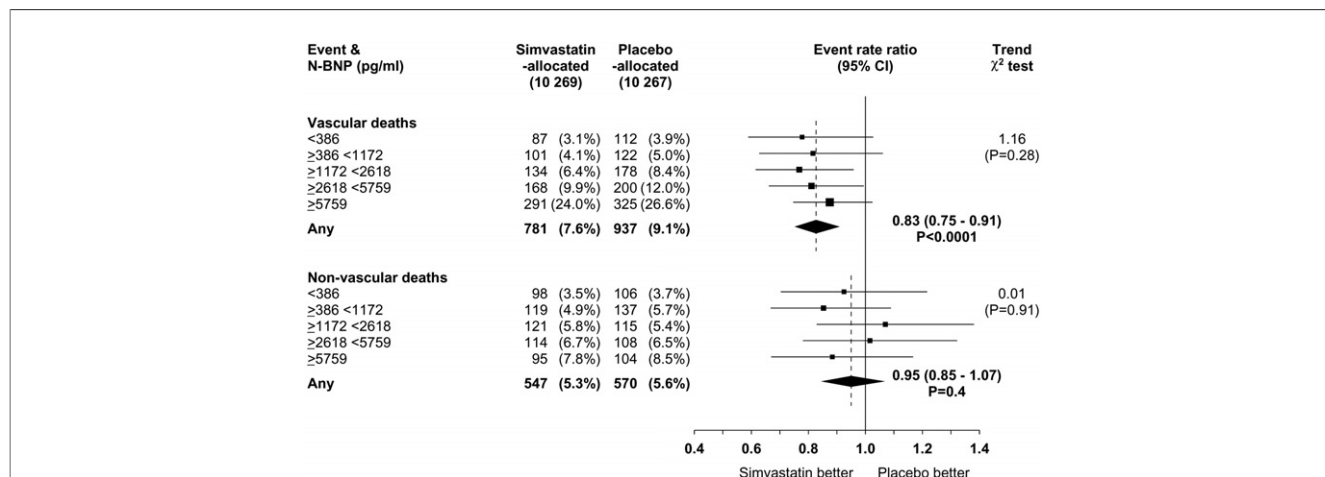


Figure 4 Effects of Simvastatin on Vascular and Nonvascular Mortality in Participants Subdivided by Baseline N-BNP Level

CI = confidence interval; N-BNP = N-terminal pro-B-type natriuretic peptide.

higher baseline N-BNP levels may have been inflated by the play of chance. Another potential limitation was that hospitalization or death due to heart failure was not prespecified as an end point. However, further information was sought systematically about all reports of possible heart failure to ensure that prespecified outcomes (such as MI) were not missed. Hence, reports of hospitalization or death due to heart failure were confirmed centrally in most cases based on blind review of medical records. Finally, it is possible that because this study comprises people selected to participate in a randomized controlled trial, the observational relationships between baseline N-BNP and risk may not necessarily be generalizable to other populations. Nevertheless, they should be widely generalizable to the types of high-risk patients studied.

Conclusions. In people at high risk of vascular disease, N-BNP is strongly related to the subsequent incidence of MVE, major coronary event, and stroke, as well as being highly predictive of the risk of hospitalization or death due to heart failure. Reducing LDL cholesterol by 1 mmol/l with statin therapy produced highly significant reductions in the risk of MVEs, even in people with greater N-BNP levels consistent with a diagnosis of heart failure, without evidence of hazard. Because the use of 40 mg of simvastatin typically reduces LDL cholesterol by 1.5 mmol/l, full compliance may result in even greater benefits among these high-risk patients.

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▶ APPENDIX

For a list of acknowledgments and the Heart Protection Study Collaborative Group Writing Committee, please see the online version of this article.