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CLINICAL RESEARCH

STOP-HF Trial

Higher Endogenous BNP and Cardiovascular Protection in Subjects at Risk for Heart Failure

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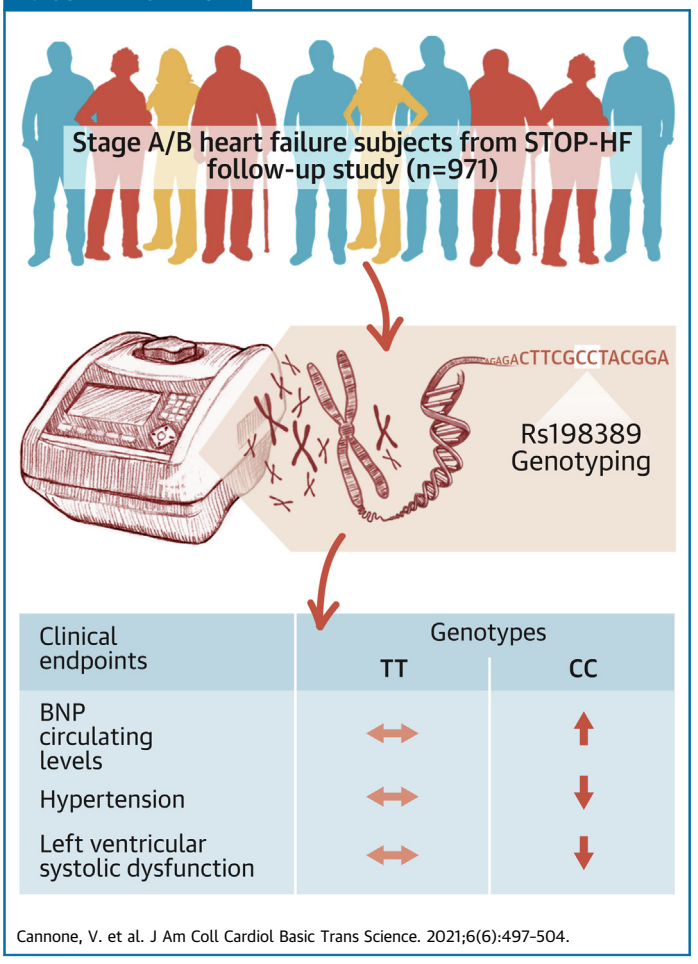
VISUAL ABSTRACT



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HIGHLIGHTS

- **Among subjects at risk for heart failure (Stage A and B), the minor C allele of the B-type natriuretic peptide (BNP) genetic variant rs198389 is associated with higher circulating levels of BNP.**
- **Rs198389 C allele is also associated with lower risk of hypertension, new onset of left ventricular systolic dysfunction, and major adverse cardiovascular events.**
- **These data support the role of BNP genetic testing and BNP-based therapy for the prevention of heart failure.**

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

HF = heart failure

LVSD = left ventricular systolic dysfunction

pGC-A = particulate guanylyl cyclase A receptor

RAAS = renin-angiotensin-aldosterone system

SNP = single nucleotide polymorphism

SUMMARY

B-type natriuretic peptide (BNP) possesses blood-pressure–lowering, antifibrotic, and aldosterone-suppressing properties. In Stage A and B heart failure, the carriers of the minor C allele of the BNP genetic variant rs198389 have higher circulating levels of BNP and are at decreased risk of hypertension, new-onset left ventricular systolic dysfunction, and hospitalization for major adverse cardiovascular events. Future studies are warranted to investigate the role of BNP genetic testing and BNP-based therapy in the prevention of heart failure. (J Am Coll Cardiol Basic Trans Science 2021;6:497–504)

The landmark St Vincent's Screening to Prevent Heart Failure (STOP-HF) study investigated the efficacy of B-type natriuretic peptide (BNP)-based screening in combination with collaborative care between primary care physicians and cardiovascular specialists in the prevention of new-onset heart failure (HF) and left ventricular dysfunction (1). The cohort included subjects with risk factors for the development of HF (Stage A HF) and subjects with structural heart abnormalities but without signs or symptoms of HF (Stage B HF). Importantly, this trial demonstrated that a clinical approach focused on a BNP-based screening and cooperative care reduced the risk to develop left ventricular dysfunction and HF.

Besides being the gold standard biomarker for HF, the cardiac hormone BNP, which is secreted by the heart, possesses "protective" cardiovascular properties (2). Through its molecular target, the particulate guanylyl cyclase A receptor (GC-A), BNP mediates vasodilation, natriuresis, suppression of aldosterone, inhibition of cardiac hypertrophy, and fibrosis. Indeed, increase in endogenous BNP associated with the minor C allele of the single nucleotide polymorphism (SNP) rs198389 was associated with reduced blood pressure, odds of hypertension, and cardiovascular mortality in a study of black and white subjects from general communities in the United States (3). A recent genome-wide association study of the FINRISK population did not identify rs198389 as being associated with incident HF (4), yet the study did not assess myocardial structure or function through any myocardial-imaging modality. Therefore, it remains unclear whether such lifelong elevations of endogenous BNP related to rs198389 might still be associated with a more favorable cardiovascular outcome in subjects at risk of HF and whether those lacking the protective genotype might be at increased cardiovascular risk.

In the current study, we investigated the STOP-HF follow-up program by genotyping this cohort for rs198389 and analyzed BNP circulating levels along with the clinical characteristics related to rs198389 genotypes. We also performed a follow-up analysis that aimed to assess the risk of left ventricular dysfunction and, importantly, employed echocardiography to assess myocardial structure and function. We hypothesized that, in Stage A and B HF subjects, the rs198389 minor C allele is associated with higher circulating levels of BNP. Consistent with BNP biological properties, the carriers of the C allele would have lower blood pressure, risk of hypertension, and left ventricular dysfunction. In contrast, the homozygotes for the major allele would be at increased cardiovascular risk. Such findings would further support the development of natriuretic peptide/GC-A targeted therapy in the prevention of cardiovascular disease while also advancing the concept of BNP genetic screening in the assessment of risk of HF.

METHODS

For an expanded Methods section, please see the Supplemental Appendix for this paper.

RESULTS

GENOTYPE FREQUENCIES AND CIRCULATING BNP PLASMA LEVELS. We genotyped 971 subjects with Stage A and B HF from the cohort of the STOP-HF follow-up study. **Table 1** describes the clinical characteristics of the study population. The frequencies of

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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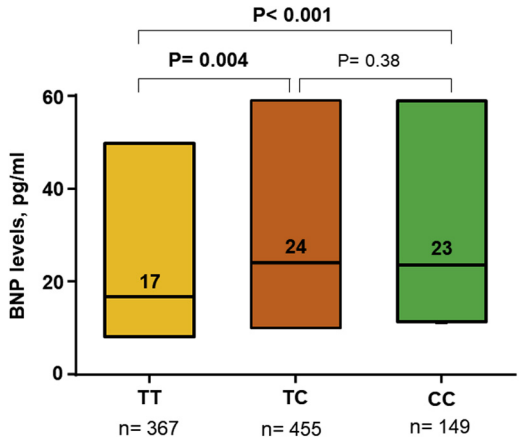
TABLE 1 Characteristics of the Study Population According to rs198389 Genotypes

	All (N = 971)	TT (n = 367)	TC (n = 455)	CC (n = 149)	*P* Value TT vs CC*
Age, yrs	65.6 ± 10.1	65.8 ± 10.3	65.6 ± 10.0	65.2 ± 9.8	0.86
Male	519 (53.5)	189 (51.5)	240 (52.7)	90 (60.4)	0.063
Intervention	486 (50.1)	189 (51.5)	223 (49.0)	74 (49.7)	0.50
Cardiometabolic phenotype					
BMI, kg/m^2	28 (25-32)	28 (26-31)	28 (25-31)	28, (26-32)	0.32
Obesity	360 (37.1)	146 (39.8)	159 (34.9)	55 (36.9)	0.85
Heart rate beats/mini	70.9 ± 12.4	70.4 ± 13.3	71.1 ± 12.1	71.5 ± 11.2	0.27
SBP mm Hg	137.6 ± 20.4	139.0 ± 21.3	137.1 ± 20.3	135.9 ± 18.5	0.25
DBP mm Hg	81.0 (11.8)	81.0 (13)	81.3 (11)	80.0 (11.3)	0.53
BNP, pg/ml	22 (9.1-56)	17.5 (7.8-50.4)	24.4 (9.8-58)	23.2 (11.3-58.5)	<0.001†‡
Total cholesterol, mmol/l	4.5 ± 1.0	4.4 ± 1.0	4.5 ± 0.9	4.4 ± 1.1	0.92
LDL, mmol/l	2.3 (1.8-2.9)	2.3 (1.8-2.9)	2.3 (1.8-2.9)	2.2 (1.7-2.8)	0.61
HDL, mmol/l	1.2 (0.9-1.5)	1.2 (0.9-1.5)	1.2 (1.0-1.5)	1.2 (0.9-1.5)	0.47
Triglycerides, mmol/l	1.5 (1.1-2.2)	1.5 (1.2-2.2)	1.5 (1-2.2)	1.6 (1.1-2.1)	0.74
Glucose, mmol/l	6.3 (5.3-8.5)	6.4 (5.4-8.5)	6.1 (5.2-8.5)	6.5 (5.4-8.9)	0.61
Creatinine, μmol/l	85.5 ± 22.6	85.8 ± 24.6	85.9 ± 21.0	83.5 ± 21.7	0.29
Cardiovascular disease history					
Hypertension	709 (73.0)	285 (77.7)	324 (71.2)	100 (67.1)	0.014
Diabetes mellitus	483 (49.7)	183 (49.9)	224 (49.2)	76 (51.0)	0.98
Dyslipidemia	749 (77.1)	283 (77.1)	351 (77.1)	115 (77.2)	0.73
Vascular disease	171 (17.6)	64 (17.4)	78 (17.1)	29 (19.5)	0.68
Angina/IHD	82 (8.4)	28 (7.6)	40 (8.8)	14 (9.4)	0.63
Myocardial infarction	101 (10.4)	37 (10.1)	45 (9.9)	19 (12.8)	0.47
Peripheral vascular disease	25 (2.6)	11 (3.0)	10 (2.2)	4 (2.7)	>0.99
Arrhythmia/atrial fibrillation	124 (12.8)	43 (11.7)	67 (14.7)	14 (9.4)	0.46
Stroke	30 (3.1)	10 (2.7)	13 (2.9)	7 (4.7)	0.25
TIA	31 (3.2)	17 (4.6)	10 (2.2)	4 (2.7)	0.30
Valvular heart disease	14 (1.4)	2 (0.5)	10 (2.2)	2 (1.3)	0.37
Doppler echocardiography					
Ejection fraction, %	66 (61-71.6)	66 (61-71)	66 (61-71)	67 (61-73)	0.11
LVSD (EF <50%)	37 (3.8)	12 (3.3)	18 (4.0)	4 (2.7)	0.95
LAVI, ml/m^2	24.9 (21.1-30.6)	24.9 (21.2-30.8)	25 (20.7-30.2)	24.4 (21.5-30.3)	0.60
Elevated LAVI (>34 ml/m^2)	159 (16.4)	61 (16.6)	76 (16.7)	22 (14.8)	0.70
LVMI, g/m^2	95.8 ± 24.2	97.5 ± 24.4	94.2 ± 23.7	96.5 ± 24.7	0.59
Left ventricular hypertrophy	138 (14.2)	56 (15.2)	59 (13)	23 (15.4)	0.93
E/E'	8.2 (6.5-10.4)	8.4 (6.7-10.4)	8.1 (6.4-0.3)	8.0 (6.3-10.3)	0.27
Medications					
ACE inhibitor	294 (30.3)	134 (36.5)	119 (26.2)	41 (27.5)	0.15
Angiotensin receptor blocker	226 (23.3)	84 (22.9)	115 (25.3)	27 (18.1)	0.70
Aldosterone antagonist	8 (0.8)	2 (0.5)	4 (0.88)	2 (1.3)	0.29
Any RAAS modifying therapy	505 (52.0)	214 (58.3)	223 (49.0)	68 (45.6)	0.10
Alpha-blocker	73 (7.5)	33 (9.0)	34 (7.5)	6 (4.0)	0.059
Beta-blocker	315 (32.4)	122 (33.2)	139 (30.5)	54 (36.2)	0.36
Calcium-channel blocker	250 (25.7)	97 (26.4)	116 (25.5)	37 (24.8)	0.97
Diuretic	266 (27.4)	114 (31.1)	119 (26.2)	33 (22.1)	0.17
Oral antidiabetic	383 (39.4)	142 (38.7)	182 (40.0)	59 (39.6)	0.59
Insulin	58 (6.0)	23 (6.3)	24 (5.3)	11 (7.4)	0.87
Statin	663 (68.3)	260 (70.8)	299 (65.7)	104 (69.8)	0.98
Aspirin	579 (59.6)	221 (60.2)	266 (58.5)	92 (61.7)	0.53
Antiplatelet (non-aspirin)	597 (61.5)	228 (62.1)	276 (60.7)	93 (62.4)	0.73
Warfarin	35 (3.6)	16 (4.4)	11 (2.4)	8 (5.4)	0.44
Novel oral anticoagulant	16 (1.6)	6 (1.6)	7 (1.5)	3 (2.0)	0.79

Values are mean ±SD, n (%), or median (25th-75th percentile). *The *P* values shown represent an adjusted model including pre-specified covariates age, sex, diabetes, vascular disease (angina, ischemic heart disease, myocardial infarction, peripheral vascular disease), hypertension, obesity, and arm intervention. †$P < 0.05$ in a multivariable model including pre-specified covariates and RAAS-modifying therapy. ‡$P < 0.05$ in a multivariable model including pre-specified covariates and number of antihypertensive agents.

ACE = angiotensin converting enzyme; BMI = body mass index; BNP = B-type natriuretic peptide; bpm = beats per minute; DBP = diastolic blood pressure; E/e' = ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; EF = ejection fraction; HDL = high-density lipoprotein; IHD = ischemic heart disease; LA = left atrium; LAVI = left atrial volume index; LDL = low-density lipoprotein cholesterol; LVMI = left ventricular mass index; LVSD = left ventricular systolic dysfunction; RAAS = renin angiotensin aldosterone system; SBP = systolic blood pressure; TIA, transient ischemic attack.

FIGURE 1 rs198389 Genotypes and BNP Plasma Levels



B-type natriuretic peptide (BNP) plasma levels are presented according to rs198389 genotypes (TT, TC, CC). Multivariable analysis adjusted for age, gender, diabetes, hypertension, obesity, vascular disease, allocation to intervention, or control arm.

the rs198389 genotypes were TT: 38% (n = 367), TC: 47% (n = 455), and CC: 15% (n = 149).

In the pre-specified multivariable analysis, both the TC and CC genotypes had significantly higher median circulating levels of BNP compared with the homozygotes for the major allele (TC: 24.4, 25th and 75th percentile [Q1-Q3]: 9.8-58 pg/ml vs TT: 17.5, Q1-Q3: 7.8-50.4 pg/ml; $P = 0.004$; CC: 23.2, Q1-Q3: 11.3-58.5 pg/ml; vs TT, $P < 0.001$) (Figure 1). The TC and CC genotypes did not differ in terms of circulating levels of BNP ($P = 0.38$).

CARDIOMETABOLIC PHENOTYPE AND THERAPY. Prevalence of hypertension was significantly lower in the CC genotype compared with the homozygotes for the major allele (CC: 67.1% vs TT: 77.7%, odds ratio [OR]: 0.59; 95% confidence interval [CI]: 0.39-0.89; $P = 0.014$) (Figure 2). Among the heterozygotes, there was an intermediate prevalence of hypertension, closer to that of the CC group (TC: 71.2% vs TT, OR: 0.72; 95% CI: 0.52-1.01; $P = 0.057$). Prevalence of diabetes was not different between the genotypes (CC: 51.0% vs TT: 49.9%, OR: 1.0; 95% CI: 0.67-1.48; $P = 0.98$]. Importantly, the clinical phenotype was similar between the heterozygotes and homozygotes for the minor allele.

Univariate analysis showed greater use of renin-angiotensin-aldosterone system (RAAS)- modifying therapy ($P = 0.009$) and higher average number of antihypertensive medications (1.6 ± 1.2 vs 1.3 ± 1.0, $P = 0.024$) in the TT genotype. However, as shown in the Table, these were not significantly different in multivariable adjusted analyses. We also performed 2 additional multivariable adjusted analyses including RAAS-modifying therapy and a number of antihypertensive agents as covariates in addition to the covariates listed here. Importantly, both models confirmed higher circulating levels of BNP (both $P < 0.001$) in the CC genotype. In the entire cohort, genotypes did not differ in terms of blood pressure, body mass index, and creatinine levels.

LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AND HEART FAILURE IN THE FOLLOW-UP ANALYSIS. We analyzed our cohort for new onset of left ventricular systolic dysfunction (LVSD), defined as ejection fraction <50% and more than 5% decrease. In the median 4.95 (Q1-Q3: 3.26-6.61) years of follow-up, the incidence of LVSD was significantly lower among the homozygotes for the minor C allele compared with the homozygotes for the major T allele (CC: 1 [0.67%] vs TT: 16 [4.5%], adjusted OR: 0.10, 95% CI [0.01-0.82]: $P = 0.032$) (Figure 3). This difference remained significant when the model was adjusted for the number of antihypertensives ($P = 0.049$) but not for RAAS-modifying therapy ($P = 0.054$). Conversely, no difference was found between the TC (n = 10 [2.2%]) and the other genotypes. In regard to new-onset hospitalization for symptomatic HF, the low number of events (4 in the TT genotype and no events in the TC or CC genotypes) did not allow us to evaluate the risk associated with rs198389 genotypes. Mortality and new onset of left ventricular diastolic dysfunction or hypertrophy were not different among genotypes.

ANALYSIS OF TC+ CC GENOTYPES COMBINED AND MAJOR ADVERSE CARDIOVASCULAR EVENTS. We also analyzed our cohort by comparing TT genotype versus the TC+CC genotypes combined to increase our statistical power. Importantly, the analysis revealed that the prevalence of major adverse cardiovascular events (hospitalization for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis and embolus, or HF) was significantly lower among the carriers of the C allele (TC+CC: 24 [4%] vs TT: 26 [7.1%], $P = 0.040$) (Figure 4) and, consequently, higher in the TT genotype. The combined analysis further confirmed that in the TC+CC genotypes, prevalence of hypertension was significantly lower ($P = 0.018$), BNP levels were significantly higher ($P < 0.001$), there was no association between genotype and diabetes ($P = 0.92$), and new onset of LVSD was less prevalent ($P = 0.017$) compared with the TT

genotype. Interestingly, among the carriers of the C allele, the use of angiotensin-converting enzyme inhibitors was significantly lower in the TT genotype (TC+CC: 26.5% vs TT: 36.5%; $P < 0.01$). The differences between TC+CC versus TT in terms of major adverse cardiovascular events and new-onset LVSD remained significant when the multivariable model was further adjusted for RAAS-modifying therapy and number of antihypertensives ($P = 0.040$ and 0.049, respectively).

ANALYSIS OF STAGE A AND B HF SUBGROUPS. When we divided our entire cohort into those with confirmed Stage A (n = 630) and B (n = 305) subgroups, the difference in terms of median BNP was confirmed in the Stage A cohort (CC: 20.9; Q1-Q3, 9.4-38.3 pg/ml; vs TT: 13.6; Q1-Q3: 5.4-28.2 pg/ml; $P < 0.001$). However, there were no differences between the genotypes in terms of baseline prevalence of hypertension (CC: n = 62 of 95 [65.3%] vs TT 171 of 232 [73.7%] when adjusted for covariates [OR: 0.66; Q1-Q3; 0.39-1.14; $P = 0.14$]). In the Stage B cohort, median BNP of all genotypes was higher than stage A and remained different between homozygous genotypes (CC: 59; Q1-Q3: 17.7-113.5 pg/ml vs TT: 39.5; Q1-Q3: 16.9-70 pg/ml; $P = 0.030$). In contrast with the Stage A Subgroup, the differences between genotypes in baseline hypertension reached statistical significance in the adjusted model (CC: n = 33 of 46 [71.7%] vs TT: n = 106 of 124 (85.5%); $P = 0.030$). There was no difference between genotypes observed for baseline prevalence of diabetes in either Stage A or Stage B subgroups.

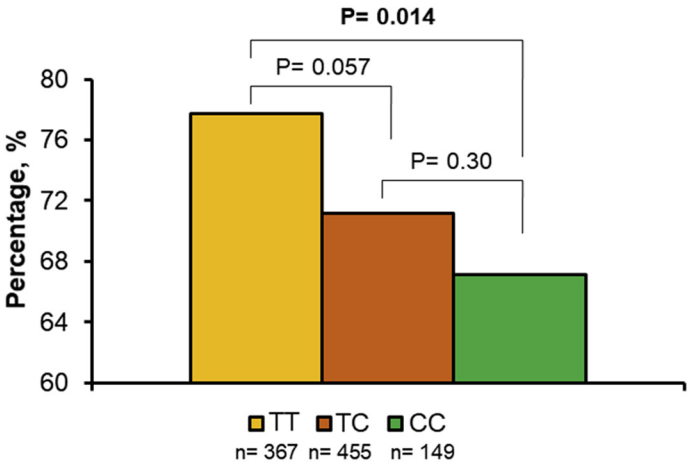
In the follow-up analysis of Stage B HF subgroup alone, new-onset LVSD tended to be lower in the CC genotype versus TT genotype (CC: 1 [2.4%] vs TT: 13 [10.7%]; $P = 0.070$).

BNP LEVELS OVER TIME. Considering that the carriers of the minor C allele have higher circulating levels of BNP, we compared the change in BNP levels over the follow-up period. The CC genotype and TT genotype increased by similar amount (CC: 4.66 ± 0.71 pg/ml, TT: 4.58 ± 0.47 pg/ml, $P = 0.97$) per annum, maintaining their significantly different set point over time (Supplemental Figure 1).

DISCUSSION

We report, for the first time, that in a well-phenotyped cohort of subjects at risk for HF (Stage A and B HF), from the STOP-HF study, the minor C allele of the BNP genetic variant rs198389 was associated with higher circulating levels of BNP, lower risk of hypertension, and—importantly—new-onset LVSD. Further, in a 5-year follow-up study, carriers of the C allele also had a lower risk of major adverse cardiovascular events. In contrast, in those subjects who lacked the protective BNP genetic variant, circulating BNP levels were lower, whereas risk of new-onset LVSD and major adverse cardiovascular events was higher.

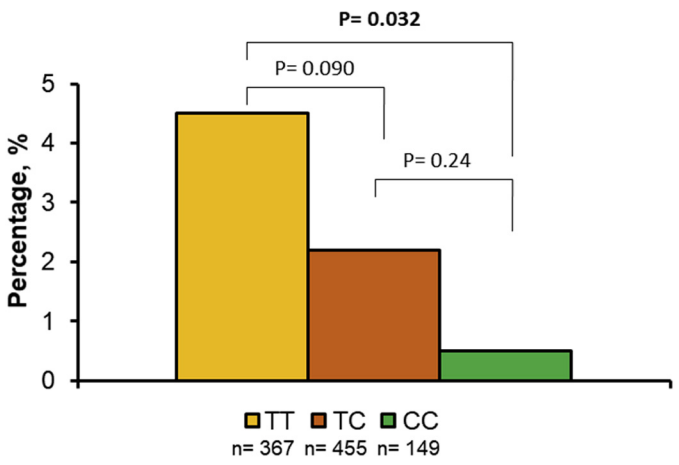
FIGURE 2 rs198389 Genotypes and Hypertension



In our cohort of subjects with Stage A and B heart failure, prevalence of hypertension is shown according to rs198389 genotypes (TT, TC, CC). Multivariable analysis adjusted for age, gender, diabetes, hypertension, obesity, vascular disease, allocation to intervention, or control arm.

BNP is a cardiac hormone secreted by the heart as a compensatory response to myocardial stretch in the presence of volume overload (2). BNP biological properties aim to decrease circulatory congestion by inducing vasodilation, diuresis, and natriuresis. Importantly, BNP also inhibits aldosterone, cardiac hypertrophy, and fibrosis. Biological properties and stimuli for production of BNP make this cardiac hormone a well-established and reliable biomarker in the diagnosis and assessment of HF (5). In the STOP-HF Trial, Ledwidge et al. also demonstrated that BNP-based screening, along with collaborative care, decreases the risk of new-onset left ventricular dysfunction and HF in subjects at risk of HF (Stage A and B HF) (1). Previous studies have shown the association between the minor C allele of the BNP genetic variant rs198389 and higher circulating levels of BNP in subjects with cardiovascular disease and in general communities including white and black individuals (3,6-14). In vitro studies showed that the rs198389 minor allele is also associated with higher activity in the promoter region of the BNP gene, providing a potential mechanism for the increased plasma levels observed in different cohorts (6). In general communities, the carriers of the rs198389 C

FIGURE 3 Rs198389 Genotypes and New-Onset Left Ventricular Systolic Dysfunction



Percentage of new-onset left ventricular systolic dysfunction in a median follow-up of 4.95 years (Q1-Q3: 3.26 years-6.61 years) according to rs198389 genotypes. Multivariable analysis adjusted for age, gender, diabetes, hypertension, obesity, vascular disease, allocation to intervention, or control arm.

allele have lower blood pressure values and lower risk of hypertension, all-cause death, and cardiovascular mortality (3,13). In subjects with coronary artery disease, the C allele is associated with lower E/E' and reduced risk of postoperative ventricular dysfunction following coronary artery bypass grafting, whereas in Americans with European ancestries, the rs198389 is inversely related with left ventricular mass (8,13-15). In contrast, studies of the Nppa-Nppb locus in the European Prospective Investigation into Cancer (EPIC)-Norfolk study and genome- wide association analysis of the FINRISK cohort did not find an independent association between rs198389 and incident HF (4,16). However, neither of these 2 studies had access to Doppler-echocardiography data.

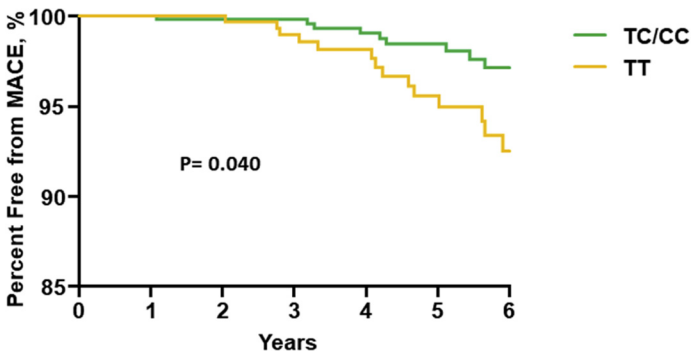
The STOP-HF trial provided an opportunity to extend previous studies on rs198389 into the area of HF, with a special emphasis on subjects at risk for HF who were rigorously recruited into the parent and follow-up study. Using this well-characterized population, we performed genotyping for rs198389. Specifically, for the first time, we investigated the clinical characteristics associated with rs198389 genotypes in subjects with Stage A and B HF. The clinical relevance of our study relies on the opportunity of analyzing the cardiovascular phenotype and risk of subjects who are exposed to higher circulating levels of BNP throughout their lifetimes, based upon rs198389 genotype. Importantly, the phenotype that we observed in our cohort is consistent with the biological properties of this cardiac hormone. In line with BNP blood-pressure-lowering effect, which involves vasodilatory and natriuretic properties, prevalence of hypertension was significantly lower among the carriers of the minor C allele, who have higher circulating levels of BNP compared with the homozygotes for the major allele. Importantly, among the carriers of rs198389 minor allele, the risk of developing new-onset LVSD in a 5-year follow-up was significantly lower compared with TT genotype. As BNP inhibits myocyte hypertrophy and activation of cardiac fibroblasts, together with suppression of the RAAS (2), higher plasma levels of BNP associated with rs198389 C allele may antagonize deleterious remodeling of the cardiac structure over time. In support of this hypothesis, among the carriers of the minor allele, the use of angiotensin-converting enzyme inhibitors was less prevalent, possibly as a consequence of the BNP protective effect. These findings in humans with Stage A and B HF are consistent with our previous report that chronic elevation of BNP in hypertensive rats produced by BNP gene therapy improved myocardial structure and function (17). Notably, the carriers of the C allele were also at lower risk of major adverse cardiovascular events, suggesting that the higher circulating levels of BNP in this group might exert a favorable pleiotropic effect on cardiovascular clinical outcomes in the long term. Conversely, subjects lacking the protective rs198389 C allele associated with higher BNP levels were identified as subjects at increased cardiovascular risk. Further studies should also address the relevance of genetic testing in subjects with Stage A and B HF. An early-risk assessment might lead to appropriate therapies, which would reduce risk of progression of HF and major adverse cardiovascular events.

SUBGROUP ANALYSIS. When we divided our cohort according to Stage A and Stage B HF, in both subgroups the homozygotes for the minor C allele have higher plasma levels of BNP. Of note, in the subgroup of subjects with Stage B HF, the associations between the minor C allele and lower prevalence of hypertension was replicated, whereas the homozygotes for the minor allele tended to develop LVSD less frequently than major allele homozygotes in the 5-year follow-up. The analysis of the Stage A subcohort did not show any relationship between rs198389 genotypes and clinical characteristics. The discrepancy between the 2 stages of HF could be related to the higher prevalence of hypertension and LVSD in the Stage B subgroup, which allowed differences between alleles to reach statistical significance in this subcohort.

RS198389 AND BNP LEVELS OVER TIME. To investigate whether the SNP rs198389 might be associated with a specific pattern of change in BNP levels over time, we analyzed hormone plasma levels in rs198389 homozygotes in the follow-up analysis. Importantly, the modification in circulating levels of BNP was similar between the CC and TT genotypes, with both genotypes increasing by the same amount over the years. This finding suggests that the C minor allele might confer a different and higher set point to production of BNP, and it would be in line with the higher promoter activity associated with the C allele (6). Similar to our findings, a previous study conducted by Arora et al. (18) reported that another SNP, rs5068, which is associated with higher circulating levels of atrial natriuretic peptide, influences the set point of this natriuretic peptide without altering the ratio of increase in response to a physiological stress test like saline infusion.

POTENTIAL DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS. The current study does not aim to address the question of the entire genetic background influencing phenotype variations of BNP levels, which is likely the result of many genetic variants acting jointly. In our study, we rather used the opportunity offered by a SNP like rs198389, which is associated with higher BNP levels, to investigate the clinical phenotype and risk associated with chronic exposure to higher levels of this protective cardiac hormone in subjects at risk of HF. Our study supports further work to explore the use of precision medicine approaches based on genotype in the implementation of the STOP-HF program. The study also has therapeutic implications, especially for the prevention of HF. Here, we found that lifelong elevation of BNP not only reduces the risk of hypertension and major adverse cardiovascular events but also—importantly—reduces the progression of LVSD. At least 3 potential therapeutic approaches could be considered building on the protective properties of BNP and its molecular target pGC-A. First, the use of neprilysin inhibition should be considered, which inhibits the degradation of native natriuretic peptides, thus increasing their circulating levels. Although this is under investigation (NCT04687111), recent studies suggest that the use of the neprilysin inhibitor sacubitril with valsartan principally increases plasma atrial natriuretic peptide, with little effect on BNP (19). Secondly, the use of chronically administered low dose BNP could be used in Stage A and B HF. This approach is supported by the work of McKie et al. (20) showing that long-term subcutaneous administration of BNP had a beneficial action on cardiorenal function in subjects with Stage B HF and systolic dysfunction. A third and highly innovative approach, which remains unexplored to date in HF, is the use of novel small-molecule-positive allosteric modulators that serve to enhance receptors sensitivity to circulating endogenous peptides or hormones (21). Such an approach could convert a human who lacks the protective rs198389 minor allele into one who is more responsive to lower circulating levels of BNP.

FIGURE 4 rs198389 Genotypes and Percent Free of Major Adverse Cardiovascular Events



Percent of subjects free of major adverse cardiovascular events in a follow-up of median 4.95 years (Q1-Q3: 3.26 years-6.61 years) according to rs198389 genotypes. Major adverse cardiovascular events defined as hospitalization for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis and embolus, or heart failure. The Gehan-Breslow-Wilcoxon test was used to test for genotype differences in the survival curves because it does not require an assumption of proportional hazards over time.

STUDY LIMITATIONS. Our sample size might have not been large enough to evaluate the association between rs198389 genotypes and new-onset HF or the clinical phenotype in the Stage A HF subgroup. Further studies in larger cohorts with longer follow-up are needed to investigate these relationships. As our study cohort consists of subjects enrolled in the STOP-HF follow-up study, almost half of the subjects were part of the STOP-HF trial, which included a control group receiving usual care and an intervention arm that received collaborative care between primary care physician and cardiovascular specialist based on BNP plasma levels. To account for this confounding factor, which might have affected our results, we included allocation to intervention or control arm as one of the pre-specified covariates in our adjusted model of analysis. Future observational studies in larger cohorts of subjects at risk of HF are warranted to confirm the associations that we reported between the minor allele of rs198389 and lower cardiovascular risk.

CONCLUSIONS

Among subjects at risk for HF (Stage A and B HF) the minor C allele of the BNP genetic variant rs198389 is associated with higher circulating levels of BNP and favorable clinical phenotype and outcome, characterized by lower risk of hypertension, new-onset LVSD, and major adverse cardiovascular events. Our results support the concept that chronic exposure to slightly higher circulating levels of BNP could exert a protective cardiovascular effect in subjects at risk of HF. In contrast, our study identifies subjects lacking the protective rs198389 genotype as being at higher risk of new-onset LVSD and major adverse cardiovascular events. Importantly, our findings lay the foundation for future clinical studies aimed to test the role of natriuretic peptides in genetic testing and therapy for the prevention of left ventricular dysfunction.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In Stage A and B heart failure, the carriers of the minor C allele of the B-type natriuretic peptide (BNP) genetic variant rs198389 have higher circulating levels of BNP and are at decreased risk of hypertension and new-onset left ventricular systolic dysfunction.

TRANSLATIONAL OUTLOOK: Future studies are warranted to investigate the use of BNP-based therapy in the prevention of heart failure and the response according to rs198389 genotype.

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KEY WORDS B-type natriuretic peptide, heart failure, single nucleotide polymorphism, STOP-HF Trial, rs198389

APPENDIX For the Methods section and a supplemental figure, please see the online version of this paper.