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B-Type Natriuretic Peptide Assessment in Patients Undergoing Revascularization for Left Main Coronary Artery Disease

Analysis From the EXCEL Trial

Editorial, see p 479

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BACKGROUND: Elevated B-type natriuretic peptide (BNP) is reflective of impaired cardiac function and is associated with worse prognosis among patients with coronary artery disease (CAD). We sought to assess the association between baseline BNP, adverse outcomes, and the relative efficacy of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in patients with left main CAD.

METHODS: The EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) randomized patients with left main CAD and low or intermediate SYNTAX scores (Synergy Between PCI With TAXUS and Cardiac Surgery) to PCI with everolimus-eluting stents versus CABG. The primary end point was the composite of all-cause death, myocardial infarction, or stroke. We used multivariable Cox proportional hazards regression to assess the associations between normal versus elevated BNP (≥100 pg/mL), randomized treatment, and the 3-year risk of adverse events.

RESULTS: BNP at baseline was elevated in 410 of 1037 (39.5%) patients enrolled in EXCEL. Patients with elevated BNP levels were older and more frequently had additional cardiovascular risk factors and lower left ventricular ejection fraction than those with normal BNP, but had similar SYNTAX scores. Patients with elevated BNP had significantly higher 3-year rates of the primary end point (18.6% versus 11.7%; adjusted hazard ratio [HR], 1.62; 95% confidence interval [CI], 1.16–2.28; P=0.005) and higher mortality (11.5% versus 3.9%; adjusted HR, 2.49; 95% CI, 1.48–4.19; P=0.0006), both from cardiovascular and noncardiovascular causes. In contrast, there were no significant differences in the risks of myocardial infarction, stroke, ischemia-driven revascularization, stent thrombosis, graft occlusion, or major bleeding. A significant interaction ($P_{interaction}$=0.03) was present between elevated versus normal BNP and treatment with PCI versus CABG for the adjusted risk of the primary composite end point at 3 years among patients with elevated BNP (adjusted HR for PCI versus CABG, 1.54; 95% CI, 0.96–2.47) versus normal BNP (adjusted HR, 0.74; 95% CI, 0.46–1.20). This interaction was stronger when log(BNP) was modeled as a continuous variable ($P_{interaction}$=0.002).

CONCLUSIONS: In the EXCEL trial, elevated baseline BNP levels in patients with left main CAD undergoing revascularization were independently associated with long-term mortality but not nonfatal adverse ischemic or bleeding events. The relative long-term outcomes after PCI versus CABG for revascularization of left main CAD may be conditioned by the baseline BNP level.

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Clinical Perspective

What Is New?

- In patients with left main coronary artery disease undergoing revascularization in the EXCEL trial, elevated baseline B-type natriuretic peptide (BNP) was associated with a higher risk of 3-year all-cause, cardiovascular, and noncardiovascular mortality, but not of nonlethal ischemic events.
- The association between BNP and mortality persisted after adjustment for risk factors, including history of congestive heart failure, left ventricular ejection fraction, and SYNTAX score (Synergy Between PCI With TAXUS and Cardiac Surgery).
- Event-free survival after coronary artery bypass grafting was relatively independent of baseline BNP, whereas the 3-year composite rate of death, myocardial infarction, or stroke after percutaneous coronary intervention rose with increasing BNP level.

What Are the Clinical Implications?

- For patients with left main coronary artery disease undergoing revascularization, measuring baseline BNP levels can add prognostic information beyond traditional cardiovascular risk factors, including left ventricular ejection fraction and the SYNTAX score.
- The relative long-term outcomes after percutaneous coronary intervention versus coronary artery bypass grafting for revascularization of left main coronary artery disease may be conditioned by the baseline BNP level, with higher BNP levels favoring coronary artery bypass grafting and lower BNP levels favoring percutaneous coronary intervention.

B-type natriuretic peptide (BNP) is secreted in response to increased atrial and ventricular pressure and volume loads,[1,2] but may also be elevated in response to myocardial hypoxia.[3,4] Elevated BNP has been independently associated with a worse prognosis in patients with ischemic heart disease,[5–9] and with mortality after noncardiac[10,11] as well as cardiac surgery.[12] However, the prognostic implications of BNP after treatment of left main (LM) coronary artery disease (CAD) have not been studied, and whether having elevated versus normal baseline BNP is associated with the relative outcomes after LMCAD revascularization by percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) is unknown.[13]

The EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) demonstrated that in patients with LMCAD and low or intermediate SYNTAX scores (Synergy Between PCI With TAXUS and Cardiac Surgery), PCI with everolimus-eluting stents was noninferior to CABG with respect to the rate of the composite end point of death, stroke, or myocardial infarction (MI) at 3 years.[14]

We sought to assess the association between baseline BNP and adverse outcomes after LMCAD treatment, and whether the relative efficacy of PCI versus CABG differs for patients with elevated versus normal BNP.

METHODS

Study Design and Study Population

The study design, protocol, and primary results of the EXCEL trial have been previously described in detail.[14,15] In brief, EXCEL was a prospective, international, unblinded, multicenter, randomized trial that compared coronary stenting versus CABG in patients with LMCAD. Key inclusion criteria were visually estimated diameter stenosis of the LM coronary artery ≥70%, or >50% to <70% if determined by means of noninvasive or invasive testing to be hemodynamically significant; a site-assessed SYNTAX score ≤32[16]; and a consensus among the members of the heart team regarding eligibility for revascularization with either PCI or CABG. Eligible patients were randomized 1:1 to undergo either PCI with cobalt–chromium fluoropolymer-based everolimus-eluting XIENCE stents (Abbott Vascular, Santa Clara, CA) or CABG. The trial conformed to the Declaration of Helsinki and was approved by the investigational review board or ethics committee at each participating center. All patients signed informed consent before randomization. The data, analytic methods, and study materials are proprietary to the sponsor and will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Definitions

The primary end point of the EXCEL trial was the rate of a composite of death from any cause, stroke, or MI at 3 years. The definitions of MI as well as other end points have been previously reported.[14] An independent clinical events committee reviewed and adjudicated all adverse events. A baseline BNP level was recommended to be drawn in all patients. BNP ≥100 pg/mL was defined as elevated based on previous studies demonstrating that a cutoff of 100 pg/mL predicted mortality and cardiovascular adverse events among patients with heart failure[17] and stable CAD.[18] The same definition of elevated BNP was used in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist).[19,20]

Statistical Analysis

Comparisons of baseline and procedural characteristics, medical history, and clinical events were conducted by χ^2 test or Fisher exact test for categorical variables, Student *t* test or Pearson correlation for continuous variables, and log-rank test for time-to-event variables. Adjusted comparisons were conducted using multivariable Cox proportional hazards regression. The association between BNP and adverse outcomes was adjusted for the following covariables: randomized treatment, age, sex, body mass index, diabetes mellitus, smoking, previous MI, clinical presentation (acute coronary syndrome versus stable CAD), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score. We tested for statistical interactions between BNP and randomized treatment by including

interaction terms between BNP and treatment in the adjusted models. We examined outcomes in patients with elevated versus normal baseline BNP levels, as well as in analyses in which BNP was modeled as a continuous variable (using the logarithmic scale). Additional multivariable models were fit that also adjusted for left ventricular ejection fraction (LVEF) and a history of congestive heart failure (CHF), in addition to the covariable set listed above (fully adjusted models). To further account for these 2 factors, 2 sensitivity models were fit: one stratified multivariable model using the same covariable set listed above with different strata for patients with normal LVEF (defined as LVEF >50%) and the absence of CHF versus patients with either reduced LVEF or CHF, and another multivariable model that was restricted to patients with normal LVEF and absence of CHF. A final sensitivity analysis using multivariable shared frailty Cox proportional hazards models accounted for the possible clustering of patients within treating hospitals. The relationship between BNP and the risk of adverse outcomes was further explored by entering log-transformed BNP as a nonlinear term (penalized spline with 2 degrees of freedom) in Cox proportional hazards regression models separately for PCI and CABG patients.[21,22] Firth's bias reduction method was applied to all statistical models pertaining to individual end points to mitigate the risk of model overfitting.[23,24] All tests were 2-sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population and Patient Characteristics

A total of 1905 patients with LMCAD from 126 centers in 17 countries were randomized in the EXCEL trial; baseline BNP data were available in 1037 patients (54.4%), constituting the present study cohort. Baseline characteristics for patients with and without data on BNP are presented in Table I in the online-only Data Supplement. The distribution of BNP among the cohort is presented in Figure I in the online-only Data Supplement, demonstrating a nonnormal right-skewed pattern with a median (interquartile range) of 70.0 (23.7–198.0) pg/mL, ranging from 0.2 to 6178.0 pg/mL. BNP was elevated (≥100 pg/mL) in 410 of 1037 (39.5%) patients. Baseline characteristics of patients with elevated versus normal BNP are presented in Table 1. Elevated BNP was associated with older age, a higher prevalence of cardiovascular risk factors, and lower LVEF. Patients with elevated BNP were more likely than patients with normal BNP to present with MI, but angiographic characteristics were not significantly different among patients with elevated and normal BNP, including the SYNTAX score (Table 2). BNP considered as a continuous variable (log[BNP]) was not correlated with diameter stenosis (correlation coefficient, 0.03; 95% confidence interval [CI], –0.03 to 0.09; $P=0.37$), lesion length (correlation coefficient, –0.02; 95% CI, –0.08 to 0.05; $P=0.62$), or baseline SYNTAX score (correlation coefficient, 0.00; 95% CI, –0.06 to 0.06; $P=0.73$). During the course of the study, patients with elevated BNP were more likely than patients with normal BNP to be treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonists, nitrates, oral anticoagulants, and antiarrhythmic drugs but not antiplatelet drugs, beta blockers, or statins (Table II in the online-only Data Supplement).

Table 1. Baseline Characteristics in Patients With Normal and Elevated Baseline BNP

	Normal BNP <100 pg/mL N=627	Elevated BNP ≥100 pg/mL N=410	*P* Value
Geographic region			
Europe	439/627 (70.0)	309/410 (75.4)	0.06
North America	133/627 (21.2)	92/410 (22.4)	0.64
Asia	12/627 (1.9)	3/410 (0.7)	0.002
South America	31/627 (4.9)	6/410 (1.5)	0.003
Age, y	64.7±9.4	67.2±9.4	<0.0001
Female	137/627 (21.9)	114/410 (27.8)	0.03
Body mass index, kg/m^2	28.3±4.7	28.3±4.6	0.99
Hypertension	445/627 (71.0)	323/410 (78.8)	0.005
Hyperlipidemia	445/626 (71.1)	297/410 (72.4)	0.64
Diabetes mellitus	172/627 (27.4)	116/410 (28.3)	0.76
Insulin-treated	34/627 (5.4)	33/410 (8.0)	0.09
Hemoglobin A1c, %	6.2±1.3	6.1±1.0	0.81
Current cigarette smoker	130/625 (20.8)	93/408 (22.8)	0.45
Previous PCI	89/627 (14.2)	58/408 (14.2)	0.99
Chronic obstructive pulmonary disease	32/626 (5.1)	39/409 (9.5)	0.006
Congestive heart failure	31/625 (5.0)	37/408 (9.1)	0.009
Peripheral vascular disease	43/624 (6.9)	49/408 (12.0)	0.005
Chronic kidney disease*	84/618 (13.6)	89/402 (22.1)	0.0004
Dialysis	1/627 (0.2)	1/410 (0.2)	0.99
Left ventricular ejection fraction, %	58.4±8.3	55.5±10.3	<0.0001
≤40%	19/574 (3.3)	37/401 (9.2)	<0.0001
Presenting clinical syndrome			
Recent MI†	66/626 (10.5)	76/409 (18.6)	0.0002
ST-segment–elevation MI	5/623 (0.8)	9/407 (2.2)	0.06
Non–ST-segment–elevation MI	58/623 (9.3)	64/407 (15.7)	0.002
Unstable angina	169/626 (27.0)	104/409 (25.4)	0.58
Stable angina	355/626 (56.7)	206/409 (50.4)	0.05
Other‡	36/627 (5.74)	23/410 (5.61)	0.93

Values are n/N (%) or mean±SD. BNP indicates B-type natriuretic peptide; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

*Creatinine clearance <60 mL/min as calculated by the Cockcroft-Gault formula.

†Occurred within 7 days.

‡Silent ischemia, dyspnea, cardiomyopathy, or other.

Table 2. Angiographic and Procedural Characteristics in Patients With Normal and Elevated Baseline BNP

	Normal BNP <100 pg/mL N=627	Elevated BNP ≥100 pg/mL N=410	*P* Value
Number of non-LM diseased vessels			
0	109/620 (17.6)	65/403 (16.1)	0.55
1	208/620 (33.5)	131/403 (32.5)	0.73
2	200/620 (32.3)	127/403 (31.5)	0.80
3	103/620 (16.6)	80/403 (19.9)	0.19
LM diameter stenosis, %	64.8±12.4	65.2±12.0	0.71
LM lesion location			
Ostial lesion	230/604 (38.1)	142/394 (36.0)	0.51
Midshaft	261/604 (43.2)	160/394 (40.6)	0.42
Distal lesion	475/604 (78.6)	309/394 (78.4)	0.94
Bifurcation lesion	268/475 (56.4)	181/309 (58.6)	0.55
SYNTAX score (baseline)*	26.4±9.3	27.1±8.7	0.16
0 to 22	223/607 (36.7)	117/391 (29.9)	0.03
23 to 32	241/607 (39.7)	178/391 (45.5)	0.07
>32	143/607 (23.6)	96/391 (24.6)	0.72
Residual SYNTAX score	6.1±6.6	6.8±6.3	0.14
PCI procedural characteristics			
Staged procedure(s) planned	21/329 (6.4)	19/218 (8.7)	0.30
Distal LM bifurcation PCI	187/306 (61.1)	116/198 (58.6)	0.57
Provisional 1-stent strategy	130/187 (69.5)	75/116 (64.7)	0.38
Planned 2-stent strategy	57/187 (30.5)	41/116 (35.3)	0.38
Number of stents in LM	1.5±0.7	1.5±0.8	0.97
Number of treated non-LM vessels	0.7±0.8	0.7±0.8	0.55
CABG procedural characteristics			
Off-pump CABG	106/307 (34.5)	90/202 (44.6)	0.02
Number of conduits	2.5±0.7	2.4±0.7	0.04
Number of arterial conduits	1.5±0.6	1.3±0.5	0.0006
Procedure duration, min	249.3±66.9	226.7±74.0	<0.0001
Cross clamp duration, min	57.1±29.1	53.4±22.8	0.50

Values are n/N (%) or mean±SD. BNP indicates B-type natriuretic peptide; CABG, coronary artery bypass grafting; LM, left main coronary artery; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

*Core laboratory assessed SYNTAX score.

Clinical Outcomes

The relative 3-year risk of adverse events after CABG versus PCI was consistent in patients with versus without data on BNP (Table III in the online-only Data Supplement). The unadjusted and adjusted 3-year risk of the primary end point of death, stroke, or MI was significantly higher for patients with elevated versus normal BNP (Table 3, Figure 1). This was driven primarily by a higher risk of death (11.5% versus 3.9%; adjusted hazard ratio [HR], 2.49 [1.48–4.19; *P*=0.0006]), whereas the 3-year unadjusted and adjusted risks of MI, stroke, repeat revascularization, stent thrombosis or graft occlusion, and major bleeding were not significantly different between the two groups (Table 3, Figure II in the online-only Data Supplement). The risks of both cardiovascular and noncardiovascular death were greater in patients with elevated compared with normal BNP levels. The association between BNP and adverse outcomes was similar when BNP was modeled as a continuous variable, with steadily increasing mortality with greater BNP levels (adjusted HR, 1.31 per each 10-fold increase in BNP; 95% CI, 1.13–1.53; *P*=0.0004; Figure III in the online-only Data Supplement, Table IV in the online-only Data Supplement). When LVEF and a history of CHF were added to the covariable set, elevated BNP (whether considered as a continuous or categorical variable) remained significantly associated with a higher risk of the primary end point, all-cause death, and noncardiovascular death, but not cardiovascular death (Table 3, Table IV in the online-only Data Supplement).

With BNP considered as a categorical variable, a significant interaction was present between elevated versus normal BNP and treatment with PCI versus CABG for the adjusted risk of the primary composite end point at 3 years (adjusted HR for PCI versus CABG, 1.54; 95% CI, 0.96–2.47 among patients with elevated BNP versus adjusted HR, 0.74; 95% CI, 0.46–1.20 among patients with normal BNP; $P_{interaction}$=0.03; Table 4). This interaction remained significant when LVEF and history of CHF were added to the covariable set ($P_{interaction}$=0.04; Table 5). Similarly, there was a statistically significant interaction between baseline BNP and treatment for the risk of the primary end point when BNP was modeled as a continuous variable ($P_{interaction}$=0.002; Figure 2, Table IV in the online-only Data Supplement, Figure IV in the online-only Data Supplement), which persisted after addition of LVEF and CHF to the covariable set ($P_{interaction}$=0.002; Table 6). The observed interaction between baseline BNP and treatment with PCI versus CABG with regard to the 3-year risk of the primary end point also persisted when the statistical model was stratified by whether patients had normal LVEF without CHF, as well as when the analysis population was restricted to patients with normal LVEF without CHF (Table 6). Last, the interaction between BNP and treatment modality persisted after accounting for possible clustering of patients within specific hospitals, irrespective of whether BNP was modeled as a categorical or continuous variable (Table 6). The results pertaining to nonfatal end points were consistent in analyses in which Fine-Gray subdistribution hazards regression was used to adjust for death as a competing risk.

Table 3. Unadjusted and Adjusted 3-Year Risk of Adverse Clinical Outcomes Associated With Elevated Versus Normal B-Type Natriuretic Peptide

3-Year Outcomes	Unadjusted Hazard Ratio (95% Confidence Interval)	$P_{unadjusted}$	Adjusted Hazard Ratio* (95% Confidence Interval)	$P_{adjusted}$*	Fully Adjusted Hazard Ratio† (95% Confidence Interval)	$P_{adjusted}$†
Primary end point‡	1.63 (1.18–2.24)	0.003	1.62 (1.16–2.28)	0.005	1.61 (1.13–2.28)	0.008
All-cause death	3.09 (1.89–5.07)	<0.0001	2.49 (1.48–4.19)	0.0006	2.19 (1.29–3.73)	0.004
Cardiovascular death	3.05 (1.47–6.33)	0.003	2.36 (1.11–5.01)	0.03	2.06 (0.95–4.44)	0.07
Noncardiovascular death	3.12 (1.60–6.10)	0.0009	2.61 (1.27–5.35)	0.009	2.33 (1.12–4.86)	0.02
Myocardial infarction	1.10 (0.70–1.71)	0.69	1.21 (0.76–1.92)	0.43	1.27 (0.79–2.03)	0.33
Stroke	1.34 (0.60–3.00)	0.47	1.16 (0.50–2.72)	0.73	1.11 (0.45–2.75)	0.82
Ischemia-driven revascularization	0.95 (0.62–1.47)	0.82	0.94 (0.60–1.46)	0.77	1.02 (0.65–1.62)	0.92
Stent thrombosis/graft occlusion	0.60 (0.27–1.35)	0.21	0.54 (0.24–1.24)	0.15	0.56 (0.24–1.33)	0.19
BARC 3–5 bleeding	1.45 (0.88–2.39)	0.14	1.32 (0.79–2.21)	0.29	1.35 (0.79–2.32)	0.27

BARC indicates Bleeding Academic Research Consortium.

*Adjusted for the following covariables: randomized treatment, age, sex, body mass index, diabetes mellitus, smoking, previous myocardial infarction, clinical presentation (acute coronary syndrome vs. stable coronary artery disease), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score.

†Adjusted for the covariable set used in * plus congestive heart failure and left ventricular ejection fraction.

‡The composite of all-cause death, myocardial infarction, or stroke.

DISCUSSION

The major findings from the present analyses from the EXCEL trial are that among patients with LMCAD and low or intermediate SYNTAX scores undergoing revascularization, (1) elevated baseline BNP levels were associated with a higher 3-year risk of the primary composite end point of death, MI or stroke, driven by greater mortality from both cardiovascular and noncardiovascular causes, but not of nonfatal adverse ischemic or bleeding events; and (2) a significant interaction was present between baseline BNP level and revascularization by PCI versus CABG for the 3-year primary composite end point such that event-free survival was relatively higher in patients with lower BNP levels after PCI, whereas the relative risk of the primary composite end point was relatively lower in patients with higher baseline BNP levels after CABG.

Patients in EXCEL who had elevated BNP levels at baseline had a considerably higher adjusted risk of dying after treatment for LMCAD than those with normal BNP. This is consistent with previous reports from other patient cohorts with ischemic heart disease.[5–9] The observed association between BNP and excess mortality may in part be related to impaired cardiac function among patients with elevated BNP, as in the present study patients with an elevated BNP had a lower LVEF and higher prevalence of congestive heart failure than those with lower BNP levels. However, in EXCEL, as well as in several other studies, the relationship between BNP and LVEF was modest[6,8]; most patients had a LVEF within the normal range and were free from overt heart failure (even those in whom BNP was elevated), and the association between elevated BNP and higher mortality persisted after adjustment for LVEF and a history of CHF. Furthermore, previous studies have reported modest relationships between BNP and other indices of cardiac function, and the association between BNP and excess mortality has persisted after adjustment for both systolic and diastolic dysfunction.[6] Thus, BNP appears to be a useful prognostic biomarker for mortality in patients with CAD with and without heart failure.

Recent studies have demonstrated that BNP is secreted from hypoxic myocardium, even in the absence of left ventricular dysfunction.[3,4] BNP may thus be a marker of myocardial ischemia,[25] with reduced event-free survival.[26–28] A role has also been suggested for

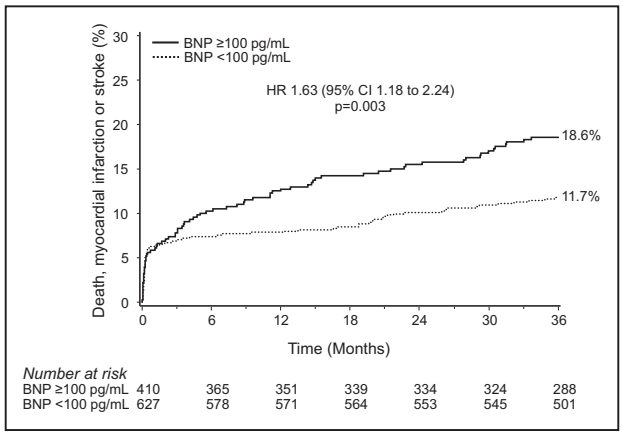

Figure 1. Kaplan–Meier failure rates for the occurrence of the 3-year primary end point in patients with elevated versus normal B-type natriuretic peptide.

The primary end point was the composite of all-cause death, myocardial infarction, and stroke at 3-year follow-up. BNP indicates B-type natriuretic peptide; CI, confidence interval; and HR, hazard ratio.

Table 4. Crude 3-Year Kaplan–Meier Event Rates and Adjusted Hazard Ratios of Adverse Clinical Outcomes for Patients Treated With PCI Versus CABG According to B-Type Natriuretic Peptide

	Normal BNP (<100 pg/mL)			Elevated BNP (≥100 pg/mL)			
	PCI	CABG	Adj. Hazard Ratio (95% Confidence Interval)	PCI	CABG	Adj. Hazard Ratio (95% Confidence Interval)	$P_{interaction}$
Primary end point*	10.3% (32)	13.1% (41)	0.74 (0.46–1.20)	21.1% (42)	16.1% (33)	1.54 (0.96–2.47)	0.03
Death	4.5% (14)	3.2% (10)	1.19 (0.52–2.70)	12.6% (25)	10.3% (21)	1.38 (0.75–2.55)	0.77
Myocardial infarction	6.5% (20)	8.6% (27)	0.81 (0.44–1.48)	8.1% (16)	8.4% (17)	1.08 (0.55–2.15)	0.53
Stroke	1.0% (3)	3.2% (11)	0.34 (0.10–1.20)	4.2% (10)	1.6% (5)	3.60 (0.10–1.20)	0.02
Ischemia-driven revascularization	11.2% (34)	6.8% (21)	1.63 (0.94–2.85)	10.5% (20)	6.7% (13)	1.75 (0.86–3.54)	0.88
Target vessel	9.2% (28)	6.8% (21)	1.33 (0.75–2.38)	9.4% (18)	6.3% (12)	1.69 (0.81–3.55)	0.62
Target lesion	7.2% (22)	6.5% (20)	1.15 (0.62–2.14)	8.4% (16)	5.7% (11)	1.58 (0.73–3.45)	0.53
Stent thrombosis or graft occlusion	1.0% (3)	5.8% (18)	0.17 (0.05–0.57)	0% (0)	4.1% (8)	—	—

Adjusted for the following covariables: randomized treatment, age, sex, body mass index, diabetes mellitus, smoking, previous myocardial infarction, clinical presentation (acute coronary syndrome vs. stable coronary artery disease), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score. Adj. indicates adjusted; CABG, coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

*The composite of all-cause death, myocardial infarction, or stroke.

natriuretic peptides in the regulation of metabolic pathways related to lipolysis and glucose homeostasis, which are both important in the pathophysiology of ischemic heart disease and atherosclerosis.[29] Consistent with these reports, an elevated baseline natriuretic peptide level has been associated with a higher risk of late adverse ischemic events (not just mortality) in some studies of patients with CAD treated conservatively.[5,6] In the present large-scale study, however, no significant associations were present between baseline BNP levels and nonfatal ischemic events, including MI, stroke, stent thrombosis, symptomatic graft occlusion, and repeat revascularization. This discordance from previous studies may be explained by the performance of effective revascularization in EXCEL, thereby reducing the ischemic burden. Unfortunately, serial BNP levels postprocedure were not assessed, which precludes determining whether BNP levels declined after LMCAD revascularization (and with high compliance with guideline-directed medi-

Table 5. Interaction Sensitivity Analyses: Hazard Ratios for Elevated BNP Versus Normal BNP for Patients Undergoing CABG and PCI

	Hazard Ratio (95% Confidence Interval) PCI Versus CABG		
Primary End Point*	Elevated BNP	Normal BNP	$P_{interaction}$
Fully adjusted model	1.54 (0.96–2.48)	0.76 (0.47–1.25)	0.04
Sensitivity Model I	1.54 (0.96–2.47)	0.74 (0.46–1.19)	0.03
Sensitivity Model II†	1.52 (0.84–2.76)	0.72 (0.41–1.24)	0.07
Sensitivity Model III	1.52 (0.94–2.45)	0.75 (0.46–1.23)	0.04

Fully adjusted model: Multivariable Cox proportional hazards regression adjusted for the covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous myocardial infarction (MI), clinical presentation (acute coronary syndrome vs. stable coronary artery disease [CAD]), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score, congestive heart failure (CHF), left ventricular ejection fraction (LVEF). Sensitivity Model I: Stratified multivariable Cox proportional hazards regression adjusted for the following covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous MI, clinical presentation (acute coronary syndrome vs. stable CAD), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score, and stratified according to the absence of CHF with normal LVEF (defined as LVEF>50%) vs. either the presence of CHF or a reduced LVEF.

Sensitivity Model II: Multivariable Cox proportional hazards regression adjusted for the covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous MI, clinical presentation (acute coronary syndrome vs. stable CAD), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score, and with the study population restricted to patients without CHF and with a normal ejection fraction (N=697 [67% of the study cohort]).

Sensitivity Model III: Multivariable Shared Frailty Cox proportional hazards regression adjusted for the covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous MI, clinical presentation (acute coronary syndrome vs. stable CAD), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, baseline SYNTAX score, CHF, LVEF and geographic region (North America vs. Europe vs. Other), and with site of enrollment included in the model as a random effect. BNP indicates B-type natriuretic peptide; CABG, coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

*Composite of all-cause death, MI, or stroke.

†Because of a smaller number of events, the Firth correction was used.

Table 6. Interaction Sensitivity Analyses: Hazard Ratios per 10-Fold Increase in BNP for Patients Undergoing CABG and PCI

Primary End Point*	Hazard Ratio (95% Confidence Interval) Per 10-Fold Increase in BNP		
	PCI	CABG	$P_{interaction}$
Fully adjusted model	1.32 (1.14–1.53)	0.95 (0.82–1.10)	0.002
Sensitivity Model I	1.33 (1.16–1.54)	0.97 (0.85–1.11)	0.001
Sensitivity Model II†	1.26 (1.05–1.52)	0.97 (0.81–1.16)	0.04
Sensitivity Model III	1.33 (1.14–1.54)	0.96 (0.83–1.11)	0.002

Fully adjusted model: Multivariable Cox proportional hazards regression adjusted for the covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous myocardial infarction (MI), clinical presentation (acute coronary syndrome vs. stable coronary artery disease [CAD]), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score, congestive heart failure (CHF), left ventricular ejection fraction (LVEF). Sensitivity Model I: Stratified multivariable Cox proportional hazards regression adjusted for the following covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous MI, clinical presentation (acute coronary syndrome vs. stable CAD), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score, and stratified according to the absence of CHF with normal LVEF (defined as LVEF>50%) vs. either the presence of CHF or a reduced LVEF.

Sensitivity Model II: Multivariable Cox proportional hazards regression adjusted for the covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous MI, clinical presentation (acute coronary syndrome vs. stable CAD), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, and baseline SYNTAX score, and with the study population restricted to patients without CHF and with a normal ejection fraction (N=697 [67% of the study cohort]).

Sensitivity Model III: Multivariable Shared Frailty Cox proportional hazards regression adjusted for the covariate set: age, sex, body mass index, diabetes mellitus, smoking, previous MI, clinical presentation (acute coronary syndrome vs. stable CAD), chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, baseline SYNTAX score, CHF, LVEF and geographic region (North America vs. Europe vs. Other), and with site of enrollment included in the model as a random effect. BNP indicates B-type natriuretic peptide; CABG, coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

*Composite of all-cause death, MI, or stroke.

†Because of a smaller number of events, the Firth correction was used.

cal therapy as practiced in EXCEL).[14] In this regard, persistently elevated BNP levels may portend a worse prognosis than elevated BNP levels that subsequently decline or normalize.[30,31]

An interaction was present between baseline BNP level and revascularization type for the primary 3-year composite end point of death, MI, or stroke. Specifically, as seen in Figure 2, after adjustment for differences in important covariables, event-free survival after CABG was relatively independent of baseline BNP level, whereas the 3-year composite rate of death, MI, or stroke after PCI rose steadily with increasing baseline BNP level. As a result, 3-year event-free survival was relatively higher after PCI in patients with lower BNP levels, whereas the risk of the primary composite end point was relatively lower after CABG in patients with higher baseline BNP levels. These data are consistent with the association noted between reduced cardiac function and worse outcomes after PCI compared with CABG in the SYNTAX trial.[32] The mecha-

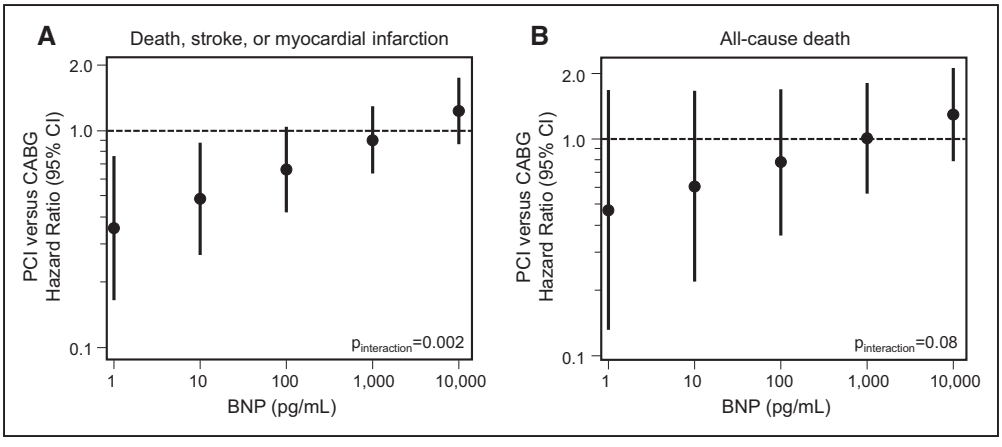

Figure 2. Adjusted association between B-type natriuretic peptide (BNP) and the 3-year risk of adverse clinical outcomes according to revascularization assignment.

Multivariable Cox proportional hazards regression. Shown is the adjusted hazard ratio associated with percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG) for patients according to baseline BNP levels, modeled as a log-linear continuous variable, as regards **(A)** the risk of the 3-year primary composite end point, and **(B)** all-cause death. The *P* value refers to the interaction between treatment assignment and the linear term for log(BNP). CI indicates confidence interval.

nisms underlying this observation are uncertain. In the SYNTAX trial, complete revascularization was achieved more frequently after CABG compared with PCI (an analysis that is pending from EXCEL),[16] which may be particularly important in patients with elevated BNP levels attributable to impaired cardiac function[33] and extensive ischemia.[34] However, the interaction between BNP and revascularization method with regard to the risk of the primary composite end point persisted after adjustment for LVEF, CHF, and the SYNTAX score. Whether elevated BNP levels reflect aspects of ischemia or cardiac function that are not routinely assessed (eg, diastolic dysfunction) and that are more effectively treated with CABG than PCI remains to be established.

Study Strengths and Limitations

As the largest randomized trial to date of patients with LMCAD undergoing revascularization, EXCEL provides useful insights into the association between baseline BNP and the risk of adverse outcomes after contemporary LMCAD treatment. However, several limitations should be considered. First, the present analysis was post hoc, and the findings should thus be considered exploratory. Second, assessment of BNP levels was not mandated, and modest differences in baseline characteristics were present between patients in whom BNP measures were and were not assessed. Local laboratories were used for BNP measurement, which may also have added some imprecision. Although the case report form asked specifically for BNP and sites were trained to collect this biomarker, we cannot rule out that some sites assessed N-terminal pro-BNP; however, the results were consistent in models that adjusted for site as a random effect. Third, with a sample size of 1037 patients, our study may not have sufficient statistical power to detect subtle associations between BNP and adverse clinical outcomes. However, to our knowledge, the present study represents the largest prospective cohort of patients with baseline BNP data who underwent LM revascularization. Fourth, despite multivariable analysis, unmeasured confounders may not have been identified. Fifth, although the interaction between baseline BNP level and revascularization type on the 3-year occurrence of the primary outcome measure was strong, subgroup testing was not adjusted for multiplicity, and this observation should be considered hypothesis generating. Additional studies are needed to clarify whether patients with LMCAD and high BNP levels should preferentially undergo CABG, and conversely whether low BNP levels connote a particular benefit from LMCAD revascularization by PCI. Sixth, follow-up is complete only through 3 years, and longer-term surveillance is necessary to determine whether further differences between PCI and CABG emerge over time, in all patients and as a function of baseline BNP level. Finally, our findings only apply to the patients enrolled in the present study, namely those with LMCAD and low or intermediate SYNTAX scores with clinical and anatomic equipoise for percutaneous or surgical revascularization. Relatively few patients had markedly reduced left ventricular function, and although ≈25% of randomized subjects had high SYNTAX scores by angiographic core laboratory analysis, further studies are required to determine whether BNP may play an even greater prognostic role in such patients.

CONCLUSIONS

In the EXCEL trial, patients with LMCAD and elevated BNP levels undergoing revascularization had higher 3-year rates of the primary composite outcome measure of death, MI, or stroke, driven by greater cardiovascular and noncardiovascular mortality, compared with those with a normal BNP. The relative long-term outcomes after PCI versus CABG for revascularization of LMCAD may be conditioned by the baseline BNP level, with higher BNP levels favoring CABG and lower BNP levels favoring PCI.

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