Evaluation of NT-proBNP and High Sensitivity C-Reactive Protein for Predicting Cardiovascular Risk in Patients with Arthritis Taking Longterm Nonsteroidal Antiinflammatory Drugs

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ABSTRACT. *Objective.* Patients with arthritis frequently are at increased risk for future cardiovascular (CV) events. We investigated the performance of the cardiac biomarkers N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity C-reactive protein (hsCRP) for predicting CV events in patients with arthritis taking chronic nonsteroidal antiinflammatory drugs (NSAID).
Methods. We evaluated 2-year CV outcomes in a prospective, nested biomarker study among patients (N = 6273) with rheumatoid arthritis and osteoarthritis treated with NSAID in the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) trial. Patients were stratified by quartiles of baseline NT-proBNP and established cutpoints of NT-proBNP and hsCRP.
Results. NT-proBNP demonstrated a strong graded relationship with CV outcomes, including CV death (p for trend < 0.0001), myocardial infarction (MI) (p for trend = 0.02), heart failure (HF) (p for trend < 0.0001), and a composite of thrombotic events (CV death, MI, stroke) or HF (p for trend < 0.0001). Baseline levels of hsCRP were not associated with CV events (CV death/MI/stroke/HF; p for trend = 0.65). NT-proBNP remained strongly predictive of CV events after adjustment for age, sex, diabetes, hypertension, hyperlipidemia, smoking, type of arthritis, body mass index, creatinine clearance, history of CV disease, and hsCRP (CV death/MI/stroke/HF: Q4 vs Q1 hazard ratio 3.53, 95% CI 1.89–6.58). Patients with a NT-proBNP level below 100 pg/ml had a 0.94% rate of thrombotic events or heart failure at 2 years.
Conclusion. NT-proBNP is a simple and robust noninvasive indicator of CV risk in patients with arthritis. Risk stratification based on NT-proBNP may facilitate identification of patients with arthritis who are at low CV risk during chronic NSAID treatment. (J Rheumatol First Release April 1 2011; doi:10.3899/jrheum.100880)

Key Indexing Terms:
ARTHRITIS   NONSTEROIDAL ANTIINFLAMMATORY DRUGS
CARDIOVASCULAR RISK   N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE
                        HIGH SENSITIVITY C-REACTIVE PROTEIN

A focus of treatment for patients with arthritis is controlling the disabling pain and inflammation that are hallmarks of the disease process. For this reason, chronic administration of nonsteroidal antiinflammatory drugs (NSAID) is a common therapy for patients with arthritis. Because gastrointestinal complications and bleeding are common complications, cyclooxygenase (COX-2) selective inhibitors were developed to decrease gastrointestinal risks[1,2,3]. There is accumulating evidence, however, that selective and most nonselective cyclooxygenase inhibitors are associated with increased cardiovascular (CV) risk[4,5,6,7]. The suppression of prostacyclin and prostaglandin E_2 is the most thoroughly

developed and most likely potential explanation[7]. Rheumatologic guidelines, therefore, recommend that the potential thrombotic risk of any NSAID be considered when prescribing these medications[8,9]. To accomplish this task it is imperative to be able to stratify the CV risk of patients for whom longterm treatment with NSAID is being considered. A simple noninvasive strategy using biomarkers may have the potential to facilitate risk assessment and assist physicians in determining the balance of potential benefits and risks when prescribing chronic NSAID.

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted by ventricular myocytes during periods of increased ventricular stretch and wall tension[10,11,12]. The BNP prohormone is split into the biologically active peptide and the more stable N-terminal fragment (NT-proBNP)[13,14]. Measurement of circulating levels of BNP or NT-proBNP is useful in the diagnosis and prognostic assessement of patients with heart failure or left ventricular dysfunction and for stratification of risk in patients with unstable and stable ischemic heart disease[15,16,17]. The increased synthesis of NT-proBNP in heart failure is thought to be primarily a consequence of increased wall stress. This mechanism also may contribute to elevation of natriuretic peptides in ischemia, as the first consequence of diminished oxygen delivery is impaired myocardial relaxation and consequent decrease in ventricular compliance. In exercise testing for ischemia, natriuretic peptides rise rapidly and transiently and the magnitude of increase is proportional to the size of the ischemic territory. In addition, experimental evidence suggests that other insults associated with ischemia, such as hypoxia-induced upregulation of gene expression, may play a role[18,19,20]. Evidence suggests that NT-proBNP also identifies subjects without clinically manifest cardiac disease who are at increased risk for CV morbidity and mortality[21]. Conversely, patients with and without established CV disease who have low blood concentrations of natriuretic peptides are at very low risk of CV death. Data from several small studies have suggested that natriuretic peptides may be useful for CV risk stratification in patients with arthritis[22,23,24,25].

High sensitivity C-reactive protein (hsCRP) is a well studied inflammatory biomarker that is an established predictor of CV risk in apparently healthy individuals and in patients with established cardiac disease[16]. Studies in patients with arthritis have demonstrated an association between hsCRP and the presence of atherosclerosis, but the ability of hsCRP to predict CV outcomes in this population is unclear[26,27,28].

To determine if NT-proBNP or hsCRP is effective for risk stratification and could be used to identify patients with arthritis who are at low CV risk during chronic NSAID treatment, we established a prospective, nested biomarker study within the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) trial to evaluate the rela-tionship of these biomarkers with CV outcomes among patients with rheumatoid arthritis (RA) and osteoarthritis (OA) treated with NSAID[29].

MATERIALS AND METHODS

Patient population. The results of the MEDAL trial have been published[30]. The trial randomized 23,504 subjects to etoricoxib (60 mg or 90 mg daily) or diclofenac (150 mg daily) between September 2002 and May 2006. This analysis includes subjects enrolled in the prospective, nested biomarker study. Patients with OA or RA aged 50 years or older were eligible for enrollment if they had a clinical diagnosis of OA or RA of the knee, hip, hand, or spine or a clinical diagnosis of RA that required chronic treatment with an NSAID. Patients with a history of myocardial infarction (MI), coronary artery bypass graft surgery, or percutaneous coronary intervention within 6 months before enrollment were excluded. Additional key exclusion criteria included morbid obesity, significantly impaired renal function, and concomitant dual antiplatelet therapy[30]. The first approximately 6800 consecutive patients at eligible centers were included in the biomarker study (3388 randomized to etoricoxib and 3383 randomized to diclofenac).

Endpoints. Clinical outcomes for this analysis were the prespecified endpoints of CV death, MI (fatal and nonfatal), heart failure (HF), and the composite Anti-Platelet Trialists' Collaboration endpoint (APTC) consisting of MI, stroke and vascular death[31]. Each of these endpoints was adjudicated by an independent clinical endpoints committee.

Biomarker testing. A sample of blood was obtained at the time of enrollment. Plasma samples were stored at –20°C or colder at the enrolling site until shipment to the central laboratory, where they were stored at –70°C or colder. Samples were batched and sent to the TIMI Clinical Trials Biomarkers Laboratory (Boston, MA), where they were maintained at –80°C until thawed and analyzed by personnel blinded to treatment allocation and clinical outcomes. NT-proBNP and hsCRP concentrations were measured on the Cobas 6000 modular analyzer using the proBNP II immunoassay (lower detection limit 5 pg/ml and coefficients of variation 3.1% at 46 pg/ml and 2.7% at 125 pg/ml) and the Tina-quant CRP (Latex) high sensitive immunoturbidimetric assay (lower detection limit 0.03 mg/l and coefficients of variation 5.7% at 0.55 mg/l and 2.5% at 12.36 mg/l); all from Roche Diagnostics (Indianapolis, IN, USA).

Statistical analysis. Plasma concentrations of NT-proBNP and hsCRP are reported as median values with interquartile ranges. Both biomarkers were modeled as continuous and categorical variables. NT-proBNP was analyzed by quartiles and an *a priori* cutpoint of 100 pg/ml[25], and hsCRP was divided into established cutpoints of 0–1, 1–3, and > 3 mg/l[32]. Sensitivity analyses using quartiles of hsCRP did not alter our results. ANOVA and chi-square tests for trend were used to compare baseline characteristics across biomarker levels. Kruskal-Wallis tests were used to assess correlation of NT-proBNP and hsCRP values with other continuous variables. Wilcoxon rank-sum tests were used to compare biomarker levels between patients with and those without specific clinical outcomes.

Because in this biomarker subcohort, by chance, the treatment effect of etoricoxib compared to diclofenac was heterogeneous with the overall trial result (hazard ratio 1.65 in this data set vs 0.95 in the overall study), all of the analyses in this substudy are limited to the relationship between NT-proBNP and hsCRP and outcomes in the entire population (both NSAID groups combined), with randomized treatment allocation included as a stratification variable. Event rates are reported as Kaplan-Meier failure estimates at 2 years. Cochran-Armitage trend tests were used to compare outcomes by biomarker levels unless there were no events in a group, in which case a log-rank trend test was performed. A Cox proportional hazards model was used to evaluate the relationship between NT-proBNP and hsCRP and outcomes adjusted for age, sex, diabetes mellitus, hypertension, hyperlipidemia, current smoking, type of arthritis, body mass index (BMI), creatinine clearance, and history of CV disease. We also evaluated bio-

marker discrimination and reclassification using the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI)[33]. In addition, we performed an exploratory analysis to determine the optimal cutpoint for NT-proBNP in predicting outcomes using the IDI and NRI. Two-tailed p values < 0.05 were considered significant. All analyses were performed with SAS 9.1 (SAS Institute, Cary, NC, USA) and R 2.9.2.

RESULTS

Biomarker concentrations and baseline characteristics. There were 6273 evaluable baseline NT-proBNP samples and 6345 baseline hsCRP samples. The baseline characteristics of those included in this substudy were similar to those in the entire trial (Appendix 1).

The median concentration (25th and 75th percentile) of NT-proBNP was 78 pg/ml (40 to 148 pg/ml). Table 1A shows patient characteristics at enrollment by quartile of baseline NT-proBNP. Higher levels of NT-proBNP were significantly associated with older age, female sex, lower BMI, RA, prior hypertension, not being a current smoker, prior heart failure, prior atherosclerosis, and lower creatinine clearance.

As expected, the levels of hsCRP differed significantly between RA and OA populations. Among patients with RA, the median concentration of hsCRP was 5.8 mg/l (2.4 to 13.8 mg/l). In patients with OA, the median concentration of hsCRP was 2.7 mg/l (1.1 to 5.6 mg/l). Higher concentrations of hsCRP were associated with younger age, female sex,

Table 1A. Baseline characteristics by NT-proBNP quartile. Data are presented as mean ± SD for continuous variables and percentage for dichotomous variables.

| Characteristic | Quartile of NT-proBNP (pg/ml) | | | | p for Trend |
	< 40.1 (n = 1569)	40.1–77.8 (n = 1568)	77.9–148.0 (n = 1568)	> 148.0 (n = 1568)	
Age, yrs	60 ± 7	62 ± 8	64 ± 8	68 ± 9	< 0.0001
Male	35.9	24.3	21.1	19.0	< 0.0001
Body mass index, kg/m^2	31 ± 6	31 ± 6	30 ± 6	29 ± 6	< 0.0001
RA (vs OA)	19.3	22.8	22.5	26.9	< 0.0001
Risk factors					
Hypertension	42.9	44.4	47.0	61.3	< 0.0001
Hyperlipidemia	39.1	35.5	34.8	36.6	0.13
Diabetes	13.1	12.1	11.0	11.5	0.11
Current smoker	10.6	11.2	10.3	7.8	0.005
Cardiovascular history					
Prior heart failure	0.13	0.51	0.57	1.91	< 0.0001
Prior atherosclerosis	9.0	10.1	15.2	22.8	< 0.0001
Presenting characteristics					
Systolic blood pressure, mm Hg	128 ± 14	129 ± 14	129 ± 14	133 ± 15	< 0.0001
Creatinine clearance, ml/min	75 ± 16	73 ± 16	72 ± 16	68 ± 17	< 0.0001

OA: osteoarthritis; RA: rheumatoid arthritis.

Table 1B. Baseline characteristics by high sensitivity C-reactive protein (hsCRP) levels. Data are presented as mean ± SD for continuous variables and percentage for dichotomous variables.

| Characteristic | hsCRP (mg/l) | | | p for Trend |
	≤ 1 (n = 1240)	1–3 (n = 1834)	> 3 (n = 3271)	
Age, yrs	64 ± 9	64 ± 9	63 ± 8	< 0.0001
Male	32.9	27.3	21.5	< 0.0001
Body mass index, kg/m^2	28 ± 5	29 ± 5	32 ± 7	< 0.0001
RA (vs OA)	12.8	15.9	30.6	< 0.0001
Risk factors				
Hypertension	42.6	46.9	52.3	< 0.0001
Hyperlipidemia	42.3	39.5	32.5	< 0.0001
Diabetes	10.5	11.5	12.9	0.02
Current smoker	7.3	9.4	11.5	< 0.0001
Cardiovascular history				
Prior heart failure	0.48	0.60	0.98	0.056
Prior atherosclerosis	15.2	14.1	13.7	0.19
Presenting characteristics				
Systolic blood pressure, mm Hg	127 ± 14	129 ± 15	131 ± 14	< 0.0001
Creatinine clearance, ml/min	72 ± 15	71 ± 16	73 ± 17	0.059

OA: osteoarthritis; RA: rheumatoid arthritis.

higher BMI, RA, prior hypertension, current smoking, and diabetes mellitus (Table 1B).

NT-proBNP and cardiovascular outcomes. Baseline levels of NT-proBNP were significantly higher in patients who experienced CV events compared to those who did not (Table 2). The median concentration of NT-proBNP in patients without CV events was below 78 pg/ml. In quartile analysis, NT-proBNP (Figure 1) showed a graded relationship with the 2-year risk of CV death (p for trend < 0.0001), MI (p for trend = 0.02), HF (p for trend < 0.0001), and the composite CV death/MI/stroke/HF (p for trend < 0.0001). Notably, those patients with an NT-proBNP level below the median had rates of thrombotic events or heart failure less than 1%. Analyses using a previously described cutpoint of > 100 pg/ml also demonstrated consistent ability to predict risk of CV death (0.79% vs 0.20%; p < 0.0001), MI (1.08% vs 0.45%; p = 0.0003), HF (1.07% vs 0.00%; p < 0.0001), and the composite CV death/MI/stroke/HF (4.03% vs 0.94%; p < 0.0001).

Elevated levels of NT-proBNP (greater than median) identified a significantly higher risk of cardiovascular events in both patients with (N = 915, 5.3% vs 0%; p = 0.008) and those without (N = 5357, 3.1% vs 1.0 %; p < 0.0001) a history of CV disease. After adjustment for age, sex, diabetes, hypertension, hyperlipidemia, smoking, type of arthritis, BMI, creatinine clearance, history of CV disease, and hsCRP, NT-proBNP remained highly predictive of CV death (p for trend = 0.004), MI (p for trend = 0.02), and the composite CV death/MI/stroke/HF (p for trend < 0.0001) (Figure 2). An NT-proBNP in the highest quartile was associated with more than 5-fold risk of CV death, 2-fold risk of MI, and 3-fold risk of thrombotic events or heart failure. When NT-proBNP was added to the clinical model above, there was a significant improvement in discrimination (IDI: p < 0.0001) and reclassification (NRI: p < 0.0001). An exploratory analysis to identify the optimal cutpoint for NT-proBNP to maximize both discrimination (IDI) and classification (NRI) yielded similar results, 102.4 and 103.4 pg/ml, respectively.

hsCRP and cardiovascular outcomes. Baseline levels of hsCRP were significantly higher in patients who had CV death and HF compared to those who did not, but were not statistically significantly different in patients who had an MI or the composite of CV death/MI/stroke/HF (Table 3). Examination of RA and OA patients separately did not reveal any meaningful change in the results. There were no

Table 2. Clinical outcomes and baseline NT-proBNP concentrations, presented as median (25th to 75th percentiles).

| | 2-Year Outcomes | | |
Baseline NT-proBNP, pg/ml	Had Outcome	Did Not Have Outcome	p
Cardiovascular death	166.5 (98.3–360.0)	77.4 (39.9–147.0)	< 0.0001
Myocardial infarction	118.0 (55.9–207.8)	77.5 (39.9–147.3)	0.0029
Heart failure	229.5 (127.8–429.5)	77.5 (39.9–147.1)	< 0.0001
CV death/MI/stroke/HF	142.4 (83.09–267.9)	76.7 (39.7–145.5)	< 0.0001

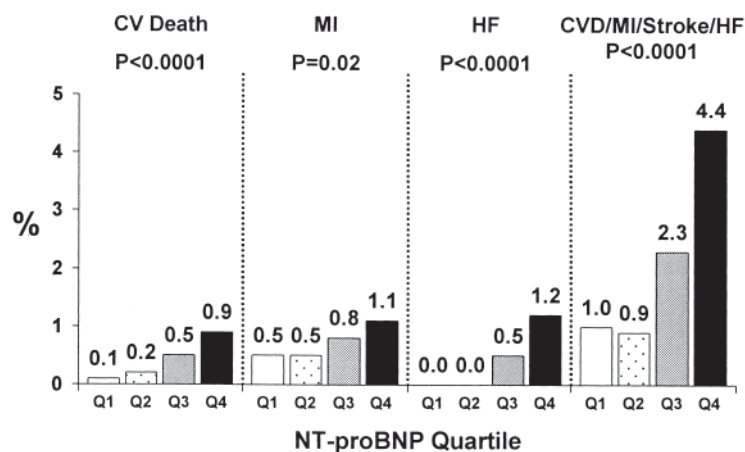CV: cardiovascular; HF: heart failure; MI: myocardial infarction.

Figure 1. Two-year outcomes by quartile of NT-proBNP. Association between baseline NT-proBNP levels and cardiovascular (CV) death (CVD), myocardial infarction (MI), and stroke and heart failure (HF). P values are for trends across NT-proBNP quartiles (Q1 to Q4).
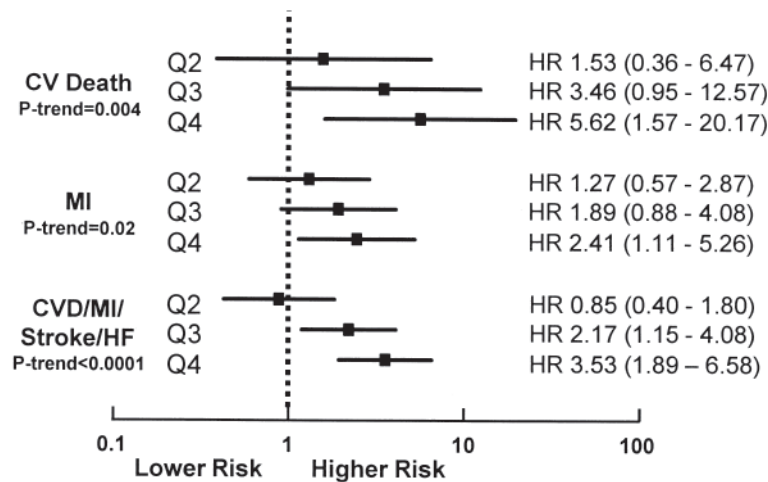
Adjusted Hazard Ratio

CV Death
P-trend=0.004
Q2 — HR 1.53 (0.36 - 6.47)
Q3 — HR 3.46 (0.95 - 12.57)
Q4 — HR 5.62 (1.57 - 20.17)

MI
P-trend=0.02
Q2 — HR 1.27 (0.57 - 2.87)
Q3 — HR 1.89 (0.88 - 4.08)
Q4 — HR 2.41 (1.11 - 5.26)

CVD/MI/ Stroke/HF
P-trend<0.0001
Q2 — HR 0.85 (0.40 - 1.80)
Q3 — HR 2.17 (1.15 - 4.08)
Q4 — HR 3.53 (1.89 – 6.58)

0.1 — 1 — 10 — 100
Lower Risk   Higher Risk

Figure 2. Multivariable-adjusted analysis of the association between baseline NT-proBNP level and 2-year risk of cardiovascular (CV) death (CVD), myocardial infarction (MI), and stroke and heart failure (HF). Point estimates of relative risk (95% confidence intervals) are shown. Regression model includes age, sex, diabetes mellitus, hypertension, hyperlipidemia, current smoking, type of arthritis, BMI, creatinine clearance, hsCRP, and history of CV disease.

Table 3. Clinical outcomes and baseline high sensitivity C-reactive protein (hsCRP) concentrations, presented as median (25th to 75th percentiles).

| | 2-Year Outcomes | | |
Baseline hsCRP, mg/l	Had Outcome	Did Not Have Outcome	p
All subjects			
Cardiovascular death	3.79 (2.27–9.47)	3.11 (1.26–6.92)	0.018
Myocardial infarction	3.63 (1.36–8.76)	3.11 (1.26–6.93)	0.34
Heart failure	5.52 (3.79–11.11)	3.12 (1.26–6.94)	0.015
CV death/MI/stroke/HF	3.63 (1.54–10.81)	3.10 (1.26–6.91)	0.07
Subjects with rheumatoid arthritis			
Cardiovascular death	7.22 (3.43–21.09)	5.75 (2.36–13.78)	0.33
Myocardial infarction	7.92 (5.54–12.51)	5.73 (2.36–13.79)	0.22
Heart failure	6.63 (5.06–16.63)	5.77 (2.37–13.79)	0.54
CV death/MI/stroke/HF	7.83 (3.44–13.64)	5.73 (2.35–13.79)	0.11
Subjects with osteoarthritis			
Cardiovascular death	2.61 (1.80–8.02)	2.73 (1.12–5.53)	0.15
Myocardial infarction	2.43 (1.14–5.10)	2.74 (1.12–5.57)	0.87
Heart failure	4.85 (3.79–11.11)	2.73 (1.12–5.54)	0.01
CV death/MI/stroke/HF	2.58 (0.99–6.80)	2.74 (1.12–5.53)	0.50

CV: cardiovascular; HF: heart failure; MI: myocardial infarction.

significant relationships observed between hsCRP, using established cutpoints, and CV death (p for trend = 0.14), MI (p for trend = 0.68), HF (p for trend = 0.11), or the composite CV death/MI/stroke/HF (p for trend = 0.65) (Figure 3). Discrimination (IDI: p = 0.74) and reclassification (NRI: p = 0.07) were not improved with the addition of hsCRP to the clinical model.

NT-proBNP risk algorithm. In an exploratory analysis, we tested a simple risk algorithm to help discriminate high and low risk subjects with respect to future CV events while taking chronic NSAID therapy. Because NT-proBNP levels increase with age, we divided patients into 2 groups: NT-proBNP > age and NT-proBNP ≤ age. Patients with baseline NT-proBNP levels > age had a substantially higher 2-year risk of CV death (0.66% vs 0.14%; p = 0.001), MI (0.96% vs 0.56%; p = 0.03), and the composite of CV death/MI/stroke/HF (3.15% vs 1.07%; p < 0.0001) compared to subjects with an NT-proBNP level ≤ age (Table 4).

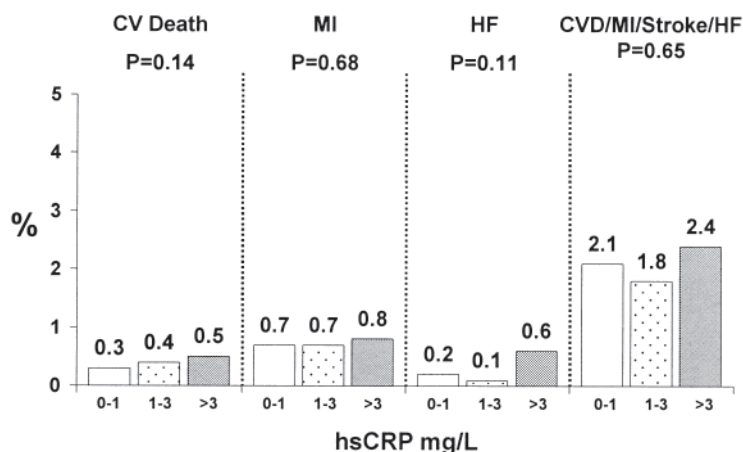*Ruff, et al: NT-proBNP and CV risk in arthritis*

Figure 3. Two-year outcomes by hsCRP. Association between baseline hsCRP levels and cardiovascular (CV) death (CVD), myocardial infarction (MI), and stroke and heart failure (HF). P values are for trends across hsCRP groups.

Table 4. Clinical outcomes stratified by NT-proBNP > age and NT-proBNP ≤ age. Event rates are expressed as Kaplan-Meier failure estimates at 2 years. Cox proportional hazard models adjusted for treatment allocation were used to calculate hazard ratios.

	2-Year Outcomes			
	NT-proBNP > Age	NT-proBNP ≤ Age	Hazard Ratio	p
Cardiovascular death, %	0.66	0.14	4.17	0.001
Myocardial infarction, %	0.96	0.56	1.79	0.03
CV death/MI/stroke/HF, %	3.15	1.07	3.03	< 0.0001

CV: cardiovascular; HF: heart failure; MI: myocardial infarction.

DISCUSSION

In our prospective study of > 6000 patients, we found that a single elevated NT-proBNP level in patients with arthritis taking NSAID is associated with increased risk of cardiovascular death, thrombotic events, and heart failure. The ability of NT-proBNP to identify patients at higher risk of adverse CV outcomes is independent of traditional risk factors. Conversely, patients with low NT-proBNP levels had a very low risk of ischemic events and no hospitalization for HF. As such, NTproBNP could be helpful in selecting patients who are reasonable candidates for chronic NSAID treatment.

Clinical implications. Patients with arthritis, both RA and OA, have increased CV mortality compared to the general population[34,35]. However, the management of patients with arthritis focuses on controlling the disabling pain and inflammation that are the principal manifestations of the disease. Chronic NSAID administration is effective first-line therapy in controlling the symptoms of arthritis, but there is accumulating evidence that traditional and COX-2 selective inhibitors are associated with increased CV risk[4,36]. Common risk scores that incorporate traditional CV risk factors such as the Framingham or Systematic Coronary Risk Evaluation (SCORE) have not been validated in this population[37,38]. A method of risk stratification is needed to identify which patients with arthritis can be safely treated with chronic NSAID therapy.

These analyses suggest that NT-proBNP may be useful as a simple, noninvasive method of screening patients with arthritis before starting or continuing chronic NSAID therapy. A pilot study suggested a cutpoint of < 100 pg/ml to identify patients with arthritis at low risk for CV events[25]. In our study, patients with an NT-proBNP level < 100 pg/ml had < 1% cumulative risk of CV death, MI, stroke, or heart failure at 2 years, with exploratory analyses supporting this as an optimal cutpoint. Patients above that value have over a 3-fold increase in risk. Consistent with a previous proposal[39], the clinical utility of a cutpoint of 100 pg/ml, or the simple algorithm NT-proBNP ≤ age, may provide a practical threshold to identify arthritis patients who can be treated with NSAID with a very low overall rate of CV events.

Although hsCRP is predictive of a broad range of CV risk in other populations, in our study higher levels of hsCRP were associated with CV death and heart failure, but did not predict risk of thrombotic events. A possible explanation is that hsCRP in this population was predominantly a marker of the general inflammation associated with arthritis disease severi-

ty and did not adequately discriminate the more subtle elevations attributed to the presence and risk of atherosclerosis.

Limitations. Limitations of the study merit consideration. The subjects in the planned biomarker substudy may be different from those in the entire MEDAL study, which may influence the generalizability of the findings, although the robust size of the biomarker cohort mitigates the risk that important differences are present. Finally, we compared baseline characteristics of subjects in the MEDAL trial only to those in the biomarker substudy, and found them to be similar (Table 1). Another limitation is that because there is no placebo comparison in the MEDAL study, the CV risk of NSAID compared with no treatment cannot be ascertained. Moreover, because of the heterogeneity of the randomized treatment comparison in this subgroup compared with the primary result, we are limited to evaluating the observed risk in patients treated with NSAID. Also, these results may not be representative of the CV risk of other traditional or COX-2 selective NSAID not studied in this trial. Additionally, these analyses are based on a single NT-proBNP level obtained at baseline. NT-proBNP levels are dynamic and change over time and thus serial measurements might have improved prognostic performance in our study population. Serial measurements of natriuretic peptides have been shown to provide enhanced risk-predictive ability in patients with acute coronary syndrome, heart failure, and in the elderly[40,41,42]. Nevertheless, studies in community settings have demonstrated improvement in the prediction of CV events over clinical models with measurement of a biomarker at a single timepoint[43,44]. Much of this improvement is conferred by accurate classification of subjects with low biomarker levels as low risk, despite the presence of traditional CV risk factors. Additionally, a measurement of a single NT-proBNP level in stable outpatients with arthritis may be more representative of true risk compared to a single determination in acute cardiac disease, where there is greater dynamic variation in biomarker concentration.

In patients with arthritis taking NSAID, NT-proBNP concentration predicts cardiovascular mortality and morbidity independent of traditional risk factors. Measurement of a single baseline NT-proBNP level is a simple, noninvasive method that may, if < 100 pg/ml, help identify patients with arthritis in whom there is low cardiovascular risk during chronic NSAID treatment. Although our results are consistent with prior investigations, additional studies evaluating this application with the proposed cutpoints will be valuable.

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APPENDIX 1.

Baseline characteristics of subjects in the MEDAL study. Data are presented as mean ± SD for continuous variables and percentage for dichotomous variables.

Characteristic	Overall Study	Biomarker Cohort
Age, yrs	63 ± 9	63 ± 9
Male	26.0	25.8
Body mass index, kg/m^2	30 ± 6	30 ± 6
RA (vs OA)	24.3	22.8
Risk factors		
Hypertension	49.1	48.9
Hyperlipidemia	30.9	36.5
Diabetes	11.1	12.2
Current smoker	11.7	10.3
Cardiovascular history		
Prior heart failure	1.5	0.7
Prior atherosclerosis	12.9	14.0
Presenting characteristics		
Systolic blood pressure, mm Hg	131 ± 15	130 ± 15
Creatinine clearance, ml/min	73 ± 17	72 ± 16

OA: osteoarthritis; RA: rheumatoid arthritis.

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