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N-terminal prohormone brain natriuretic peptide: a biomarker for detecting cardiovascular risks in patients with rheumatoid arthritis or osteoarthritis?

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Rheumatoid arthritis (RA) is associated with an increased risk for cardiovascular (CV) events including cardiac insufficiency, acute myocardial infarction and stroke.¹ It is assumed that the release of proinflammatory cytokines and acute-phase proteins furthers the progression of atherosclerosis.^{2–3} This process seems to be further accelerated and aggravated by the administration of cyclooxygenase (Cox) inhibitors (coxibs and non-steroidal anti-inflammatory drugs (NSAIDs)). Therefore, without defining how this could be done, the Food and Drug Administration and European Agency for the Evaluation of Medicinal Products have recommended CV-risk stratification and individualised risk assessment in patients with RA before using coxibs or NSAIDs.

The B type natriuretic peptide (BNP) is a hormone synthesised by cardiomyocytes in response to increased wall tension. The plasma level of its stable, inactive breakdown product, N-terminal prohormone BNP (NT-proBNP), has been identified as a universal predictor of CV risks⁴ even in patients with clinically inapparent impaired CV function. Patients with RA are known to be burdened with an increased incidence of CV impairment.¹ There is preliminary evidence that the serum levels of NT-proBNP in these patients reflect this burden.⁵

Recently, we observed that the use of NSAIDs and coxibs goes along with CV-unwanted drug effects in patients with osteoarthritis (OA) with elevated NT-proBNP values. We analysed the NT-proBNP values in patients with RA (n = 240) and OA (n = 69) and compared the results with those of healthy, age and gender-matched blood donors (n = 2264). We found that patients with RA showed significantly higher NT-proBNP values than matched controls. Moreover, we found a fraction of patients with RA who showed increased NT-proBNP levels without clinical signs of CV dysfunction. We postulate that this fraction comprises a group at risk for CV side effects due to Cox-inhibition.

Patients were recruited from the Department of Rheumatology, Charité University Hospital, Berlin, Germany. The diagnosis of rheumatic diseases was classified according to the American College of Rheumatology criteria. Serum samples were collected after diagnosis and stored deep frozen. Clinical data were documented. We analysed the samples collected from patients at the initial contact.⁶

Besides the few characteristics shown in table 1, the patient cohorts displayed typical distributions of age, sex, autoantibody formation, drug use, and so on. Despite the relatively young

age, patients with RA presented with many CV diseases (table 1).

As in controls, the NT-proBNP levels in patients with RA increased with age and were higher in women than men and altogether higher than in matched controls. But, in contrast with controls (p ≤ 0.01), 39% (table 1) of the patients with RA had NT-proBNP values above the limit of 125 pg/ml. Many of these patients with RA (n = 93) were known to have CV impairments. The diagnosis of (treated) hypertension dominated in the group with low NT-proBNP levels (77%), and the prevalence of coronary artery disease increased from 5% to 30%, with increased NT-proBNP levels. However, almost half of the patients with increased NT-proBNP levels had no apparent signs of impaired CV function (table 1). NT-proBNP values >450 pg/ml are regarded as a serious risk indicator. In our patients with RA, this high limit was exceeded in five women and one man, aged ≥75 years. More importantly, 11 women and 4 men were at lower ages (49–74 years). In other words, 8.8% of the patients with RA presented with high NT-proBNP values, indicating an acute risk of a serious CV event. Of these 21 patients only 10 had symptoms or diagnoses indicating CV dysfunction.

Many of our patients with OA exceeded the limit of 125 pg/ml (49.3%; table 1). However, these patients were >10 years older on average than our patients with RA. Correspondingly, the difference in the NT-proBNP values between patients with OA and controls did not reach significance (table 1). Most of those exceeding the limit of 125 pg/ml had diagnosed CV impairment, often hypertension, but also increased incidence of coronary artery disease (33%). Still several (29%) were without clinical signs of CV impairment. Six patients with OA showed values >450 pg/ml NT-proBNP (8.7%)—one of them without known CV disease. Again, these patients with high NT-proBNP values without CV symptoms might be a specific risk population.

Treatment with Cox inhibitors is frequent in joint disorders and was high in all patient groups (table 1). In this retrospective analysis, most sera were collected before the withdrawal of rofecoxib and valdecoxib, and before special awareness was focused on the use of Cox inhibitors. Thus, the

Abbreviations: Cox, cyclooxygenase; CV, cardiovascular; NSAID, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal prohormone natriuretic peptide; RA, rheumatoid arthritis

Table 1 Patient characteristics and cardiovascular diseases related to N-terminal prohormone brain natriuretic peptide values

	RA	OA
Patients number of females	240 (184)	69 (47)
Mean (SD) age	55.7 (14)	68.3 (8.7)
CV diseases/symptoms*	84 (35%)	46 (67%)
Cox inhibitors†	213 (88%)	30 (43%)
NT-proBNP; 95% confidentiality range	98.6; 9.3 to 1044.2 (53.9; 8.0 to 365.4)‡	103.0; 10.9 to 971.1 (87.3; 13.7 to 555.3)‡
p Values (compared with controls)	<0.01	NS
NT-proBNP ≤ 125 pg/ml	147 (61%)§	35 (51%)§
Fraction without CV disease*	0.73	0.37
NT-proBNP 125–450 pg/ml	72 (30%)§	28 (40%)§
Fraction without CV disease*	0.51	0.41
NT-proBNP > 450 pg/ml	21 (9%)§	6 (9%)§
Fraction without CV disease*	0.52	0.16

Cox, cyclooxygenase; CV, cardiovascular; CV, CV disease; NT-proBNP, N-terminal prohormone brain natriuretic peptide; OA, osteoarthritis; RA, rheumatoid arthritis.

*Symptoms included: hypertension, coronary heart disease, myocardial infarction, chronic heart failure, arrhythmia, stroke and others.

†Most patients used different selective and non-selective inhibitors of cyclooxygenases, including celecoxib, diclofenac, ibuprofen, rofecoxib and others. In addition, glucocorticoids were prescribed when needed.

‡Healthy blood donors, matched for age and sex.

§n (%) of patients showing no (≤ 125 pg/ml), mildly (> 125 pg/ml) or severely elevated (> 450 pg/ml) NT-proBNP values.

prescription of coxibs and NSAIDs was high in general and many patients received glucocorticoids in addition. This would not be compatible with current recommendations. The increase of NT-proBNP > 125 pg/ml in many patients with no diagnosis of CV disease so far (30% in disease RA and 43% in patients with OA) could indicate that screening for CV risk in patients with RA and OA has to be performed more carefully, possibly by employing NT-proBNP as a marker, as suggested by others.⁵

In summary, this study on patients with RA and OA suggests that increased NT-proBNP levels across all age groups and gender could help to single out cardiologically asymptomatic individuals, possibly at risk for CV events. Thus, this marker could be a valuable tool for risk assessment before the initiation of coxib or NSAID treatment, and for early identification of patients with rheumatic diseases requiring preventive CV treatment. On the other hand, many patients with RA and

OA show low NT-proBNP values. They may enjoy pain relief from Cox inhibitors without risky CV side effects. This, however, will have to be proven in further studies.

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