Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research Paper

NT-proBNP in patients presenting with myocardial infarction and non-obstructive coronary arteries without left ventricular systolic dysfunction

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ARTICLE INFO

ABSTRACT

Background: Myocardial infarction and non-obstructive coronary arteries (MINOCA) affects 1 in 9 patients with acute coronary syndrome and has no evidence-based therapy. NT-proBNP is an established biomarker associated with prognosis in heart failure and ischemic heart disease, although there is a paucity of data in patients with MINOCA.

Methods: Prospective study of the diagnostic and clinical utility of measuring NT-proBNP in patients with MINOCA without left ventricular dysfunction or heart failure. Data collection was undertaken for patients with an initial diagnosis of MINOCA following urgent coronary angiography in the Golden Jubilee National Hospital (Clydebank, UK), a tertiary center. Demographics were collected in addition to left ventricular function by transthoracic echocardiography. NT-proBNP was measured from a clinically indicated blood sample obtained during routine venepuncture or within the catheter laboratory. Patient outcomes were collected prospectively by the clinical care team using digital follow-up.

Results: Fifty-five patients with an initial diagnosis of MINOCA and left ventricular ejection fraction >40 % were included. NT-proBNP was available in 87 % of patients with a median value of 312 pg/mL (interquartile range: 107, 725). Post-discharge, 40 % ($n = 24$) of patients were readmitted to the hospital, including 15 with chest pain. NT-proBNP ≥125 pg/mL was associated with rehospitalization ($P = 0.02$). Two patients died and bleeding complications with concomitant antiplatelet therapy occurred in eight patients.

Conclusion: NT-proBNP ≥ 125 pg/mL occurred in 72 % of patients presenting with MINOCA and an ejection fraction > 40% and was associated with rehospitalization.

1. Background

Myocardial infarction and non-obstructive coronary arteries (MINOCA) affects approximately 1 in 9 patients presenting with acute coronary syndrome (ACS) [1,2]. It is an initial diagnosis which includes heterogeneous vascular and myocardial disorders. Outcomes of patients with MINOCA are comparable with patients who have obstructive coronary disease in the 12 months following presentation (12-month mortality: 0.6 % vs. 2.3 %; $p = 0.68$), yet there is a lack of evidence to guide clinicians on therapeutic strategies post-myocardial infarction (MI) [3,4].

A provisional diagnosis of MINOCA may be made in a patient presenting with clinical, biochemical, electrocardiographic or imaging features of acute coronary syndrome in the absence of obstructive epicardial atherosclerotic disease or an alternative systemic cause of the presentation [1,5–7]. Treatment of MINOCA is empirical, and trial data are lacking. Biomarkers have potential to inform stratified therapy and clinical trials.

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NT-proBNP is an established biomarker for prognosis in heart failure and after myocardial infarction, although there is a paucity of data in patients with MINOCA [8–10]. We hypothesized that NT-proBNP is differentially elevated following MINOCA indicating potential to serve as an informative biomarker.

2. Methods

We performed a prospective observational cohort study of invasively managed patients with MINOCA in a tertiary care center in the West of Scotland between March and November 2021.

Patients underwent urgent clinically indicated coronary angiography and transthoracic echocardiography. Patients with a left ventricular ejection fraction of <40 % and/or clinical signs of heart failure were excluded.

Standard care blood samples were collected following insertion of the radial artery sheath or at the next routine venepuncture. The aliquots of blood were collected in 4 mL ethylenediaminetetraacetic acid (EDTA) tubes. The samples were analyzed biweekly in the hospital laboratory using the Roche Elecsys proBNP II assay, performed on a Cobas e601 analyser with calibration and quality control measures as per manufacturer specifications.

Clinical outcomes post-discharge were assessed using electronic health records (EHR). Anonymized patient data were analyzed using SPSS (version 28, IBM). Non-parametric testing of continuous data was performed with the Mann Whitney *U* test for independent samples and categorical variables were compared using Fisher's exact test. A Cox-regression survival analysis was performed to assess for a possible association between NT-proBNP concentration during the index admission and post-discharge adverse events including death or rehospitalisation, presented with a two-tailed significance level of <0.05, hazard ratio (HR) and 95 % confidence intervals (95 % CI). A cut-off threshold of 125 pg/mL was predefined.

Data collection and information governance were approved by the clinical governance department and hospital management for the purposes of a clinical service evaluation led by the attending standard care team using routinely collected blood samples. Routinely collected (usual care) data were gathered by members of the usual care medical team and ethics approval or explicit patient consent were not required.

3. Results

During the study period, fifty-nine patients had an initial diagnosis of MINOCA following urgent invasive angiography. A patient flow diagram of the analysis population is provided in Fig. 1. NT-proBNP results were obtained in 48 patients. The mean age was 63 (standard deviation [SD]: 13) years, the mean BMI was 28 (SD: 8) kg/m^2 and two thirds were female. Thirty-five patients (71.7 %) had an NT-proBNP > 125 pg/mL with a median value of 286 (interquartile range [IQR]: 100, 698) pg/mL. NSTEMI was the initial diagnosis in 48 (87 %) of 55 patients. Demographics and characteristics between patients with an NT-proBNP greater- or <125 pg/mL are presented in Table 1. A left ventricular ejection fraction >55 % and a history of hypertension were more common in patients with NT-proBNP < 125 pg/mL. Prescribed antiplatelet or anticoagulation therapy regimen following angiography is presented in Table 2. The most common antiplatelet regimen in this cohort was three months of dual antiplatelets followed by lifelong single antiplatelet thereafter (*n* = 29, 60.4 %).

The duration of follow-up was 267 days (IQR: 187, 333) and twenty-four (40 %) patients had an unplanned hospitalization during this time. Fifteen (63 %) of these patients were rehospitalized because of chest pain. Two deaths occurred, one due to a hemorrhagic stroke (NT-proBNP at baseline: 266 pg/mL) and the second was a sudden cardiac death in the community (NT-proBNP at baseline: 986 pg/mL). Combined major adverse cardiovascular events and chest pain readmissions occurred in seventeen (29 %) patients. Of these patients, fifteen (32 %) had NT-proBNP ≥125 pg/mL compared with one (8 %) patient with NT-proBNP < 125 pg/mL (*P* < 0.01, HR [95 % CI] = 18.0 [2.2, 146.4]), (missing NT-proBNP, *n* = 2). All-cause readmission to hospital was more commonly observed in patients with NT-proBNP ≥125 pg/mL (Fig. 2) during follow-up adjusting for left ventricular ejection fraction > 55 % (*P* < 0.01, HR [95 % CI] = 12.7 [2.8, 58.5]).

Bleeding events occurred in six (10 %) patients. These bleeding complications were defined using the BARC (Bleeding Academic
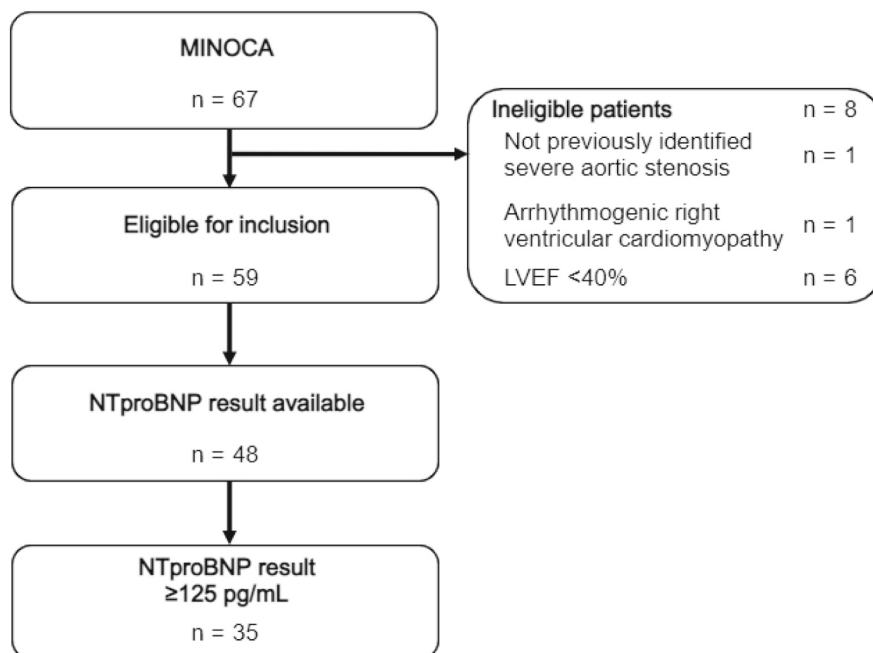

Fig. 1. CONSORT diagram of patient flow.

Table 1
Patient demographics and characteristics dichotomized by NT-proBNP value.

	All eligible patients	NT-proBNP <125 pg/mL	NT-proBNP ≥125 pg/mL	P value
	$n = 59$	$n = 13$	$n = 35$	
NTproBNP (pg/mL), median (IQR)	312 [107, 725]	61 [44, 73]	537 [265, 904]	<0.01
Age (years), mean (SD)	63 (12)	60 (10)	65 (13)	0.31
Female, n (%)	40 (67 %)	9 (69 %)	24 (68 %)	1.00
Caucasian, n (%)	56 (94 %)	13 (100 %)	33 (94 %)	1.00
Body mass index (kg/m^2), mean (SD)	28 (7)	31 (5)	26 (7)	0.06
History of smoking, n (%)	26 (54 %)	5 (38 %)	21 (60 %)	0.21
Diabetes mellitus, n (%)	4 (6 %)	1 (7 %)	1 (2 %)	0.69
Hypertension, n (%)	22 (37 %)	8 (61 %)	10 (28 %)	0.05
Chronic respiratory disease (not asthma), n (%)	9 (15 %)	0 (0 %)	9 (25 %)	0.09
NSTEMI, n (%)	52 (88 %)	11 (84 %)	30 (62 %)	0.92
LVEF ≥ 55 %, n (%)	37 (62 %)	92 (92 %)	20 (57 %)	0.04
LVEF 50–54 %, n (%)	14 (23 %)	1 (7 %)	7 (20 %)	0.42
LVEF 40–49 %, n (%)	8 (13 %)	0 (0 %)	8 (22 %)	0.09
Initial hs-TnI (ng/L), median (IQR)	198 [51, 590]	63 [44, 73]	323 [265, 904]	0.03
Peak hs-TnI (ng/L), median (IQR)	361 [63, 1911]	67 [45, 1901]	624 [170, 2070]	0.07
Creatinine Clearance[a] (mL/min), median (IQR)	93 [66, 113]	104 [80, 114]	84 [55, 115]	0.20
Hemoglobin (g/dL), median (IQR)	133 [125, 142]	138 [129, 153]	130 [125, 140]	0.17
Readmission to hospital, n (%)	24 (40 %)	2 (15 %)	18 (51 %)	0.05
Chest pain re-presentation, n (%)	15 (25 %)	1 (7 %)	12 (34 %)	0.06
Days until readmission, median (IQR)	56 [36, 99]	248 [244, 250]	56 [42, 87]	0.01

Numerical variables compared with Independent-Samples Mann-Whitney U test for independent samples; categorical variables tested with Fisher's exact test or Chi-square test; significance value of <0.05.

[a] Cockcroft Gault equation.

Table 2
Antiplatelet strategy following angiography dichotomized and frequency of bleeding during study follow-up period.

	Antiplatelet therapy following angiography	Bleeding complication		P value
		Yes	No	
	$n = 48$	$n = 5$	$n = 43$	
Direct oral anticoagulant, no antiplatelet agent, n (%)	3 (6.3 %)	0 (0 %)	3 (7 %)	0.387
Discontinue antiplatelets, n (%)	8 (16.7 %)	0 (0 %)	8 (18.6 %)	
One-month dual antiplatelet therapy, lifelong single antiplatelet thereafter, n (%)	1 (2.1 %)	0 (0 %)	1 (2.3 %)	
Lifelong single antiplatelet therapy, n (%)	5 (10.4 %)	1 (20 %)	4 (9.3 %)	
Six months dual antiplatelet therapy, lifelong single antiplatelet thereafter, n (%)	2 (4.2 %)	1 (20 %)	1 (2.3 %)	
Three months dual antiplatelet therapy, lifelong single antiplatelet thereafter, n (%)	29 (60.4 %)	3 (60 %)	26 (60.5 %)	

Categorical variables compared with Chi-square test; significance value of <0.05.

Research Consortium) bleeding criteria: two patients with BARC type 2, three patients with type 3A and one patient with a type 5 A bleeding [11].

4. Discussion

This single center prospective study of patients with MINOCA and left ventricular ejection fraction > 40 % without heart failure has found that NT-proBNP was increased (≥125 pg/mL) in 72 % of the patients and NT-proBNP during the index admission was associated with the likelihood of readmission to hospital and major adverse cardiovascular events.

Clinical guidelines categorise MINOCA into 4 sub-types and recommend systematic evaluation to establish a final diagnosis: 1) epicardial coronary artery disorders (e.g. atherosclerotic plaque rupture, ulceration, fissuring, erosion, or coronary dissection with non-obstructive or no coronary artery disease) (type 1 MI); 2) oxygen supply & demand mismatch (e.g. embolism) (type 2 MI); 3) coronary endothelial dysfunction (e.g. microvascular spasm) (type 2 MI); and 4) mimics of MI which should be considered separately as myocardial injury (e.g. myocarditis or Takotsubo syndrome) [5,6]. Empirical treatment with antiplatelets for presumed plaque events is commonplace, and without definitive imaging evidence of myocardial infarction may pose an unnecessary risk of bleeding. Existing studies have demonstrated that MINOCA patients have impaired survival rate compared with age and sex matched healthy individuals, emphasizing the importance of providing a final diagnosis [3,4,12].

A blood test for NT-proBNP is an established biomarker of early and long-term prognosis and as a biomarker of adverse left ventricular remodelling. Precedent for its use is well-demonstrated in large multi-center randomized control trials [13]. NT-proBNP is not routinely assessed in patients following primary PCI or in MINOCA. In addition to our data, in a study of 265 consecutive patients with MINOCA (102 with STEMI, 163 NSTEMI), NT-proBNP (pg/mL) mean concentrations measured within 24-h of admission were 1599 ± 3958 and 2960 ± 5459 in the STEMI and NSTEMI patients, respectively ($p = 0.030$) [14]. The mean LVEF was 54 % in each group ($p = 0.82$). Although the proportion of patients with increased NT-proBNP was not reported in this study, NT-proBNP has the potential to identify 'at-risk' patients with MINOCA.

The circulating half-life of NT-proBNP is approximately 120 min. However, most patients in our study had abnormally elevated levels (>125 pg/mL) despite this delay, suggesting persisted elevation in the convalescent phase (≥125 pg/mL group median time until sampling: four days [IQR: 3, 12]). Our results complement those of Xu et al. and the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapy (SWEDE-HEART) registry which indicates that NT-proBNP has potential use as a prognostic biomarker following MINOCA [14,15]. Anti-platelet therapy prescribed to MINOCA patients entails a risk of bleeding. Prior studies have reported that MINOCA patients have reduced event-free survival compared with age and sex matched controls [5].

In summary, in this cohort of patients with MINOCA, NTproBNP levels > 125 pg/mL demonstrated potential as a screening test for identifying patients at a higher risk of readmission. The importance of pursuing a final diagnosis following a coronary angiography was underlined, as emphasized by national and international guidelines. Such a step may enable personalised therapy prior to discharge and prevent unnecessary bleeding episodes, especially when antiplatelet therapies might not be indicated. Despite being the gold standard, cardiac magnetic resonance is under-utilised in managing MINOCA cases, pointing to an opportunity for improvement in patient care. Even though our patient cohort was limited, the high rates of readmission necessitate further research, underlining the need to enhance care protocols and identify therapeutic pathways for patients with MINOCA.
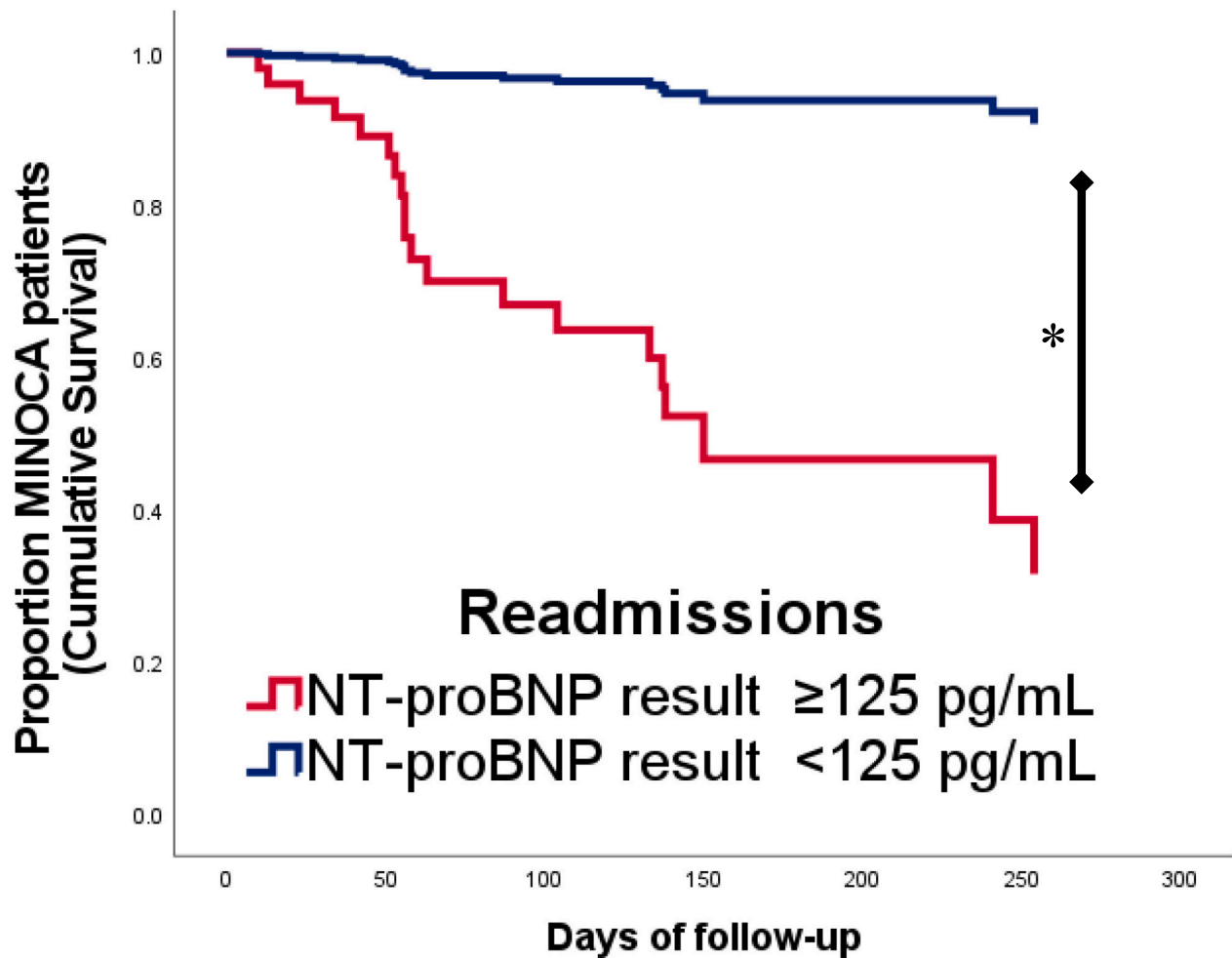
Fig. 2. Readmissions of MINOCA patients by normal or increased NTproBNP adjusted for hypertension and LVEF (%) – Cox-regression (P = 0.02).

5. Conclusion

NT-proBNP $\geq$ 125 pg/mL occurred in 72 % of patients with a working diagnosis of MINOCA and was associated with rehospitalization. Our study presents preliminary findings that warrant validation in future studies. NT-proBNP has potential utility for stratification of patients post-MINOCA for clinical and research purposes.

Declaration of competing interest

Professor Colin Berry is employed by the University of Glasgow which holds consultancy and research agreements for his work with companies that have commercial interests in the diagnosis and treatment of angina. The companies include Abbott Vascular, Astra Zeneca, Boehringer Ingelheim, GSK, HeartFlow, Menarini, Neovasc, Siemens Healthcare and Valo Health. The other authors do not have any potential conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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