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INVITED EDITORIAL

Is it NICE to measure natriuretic peptides after a hospitalization for heart failure?

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This article refers to 'N-terminal pro-B-type natriuretic peptide post-discharge monitoring in the management of patients with heart failure and preserved ejection fraction – a randomized trial: The NICE study' by D.A. Pascual-Figal *et al.*, published in this issue on pages 776–784.

The role of natriuretic peptides (NPs) in the diagnosis of heart failure (HF) is well established, as shown by guidelines and consensus statements.[1,2] However, it is still unclear how to use these biomarkers to guide HF treatment. Indeed, recent randomized trials evaluating the usefulness of NPs for optimization of guideline-directed medical therapy (GDMT) have shown conflicting results.[3–6] In this context, studies aimed at assessing the role of NPs for the management of patients with HF are extremely welcome.

In this issue of the Journal, Pascual-Figal *et al.*[7] report the results of the multicentre, prospective, open-label, randomized NICE (NT-proBNP in the Management of Discharged Patients with Acutely Decompensated Heart Failure and Preserved Ejection Fraction) trial testing the benefit of serial post-discharge N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement after a hospitalization for HF in patients with HF with preserved ejection fraction (HFpEF). In this trial, patients hospitalized for acute HF caused by HFpEF were randomized in a 1:1 ratio at the time of discharge to a usual care arm and a NT-proBNP arm. In the latter, on top of usual care, the investigators had access to NT-proBNP concentrations at three pre-specified post-discharge clinical visits performed at 2, 4 and 12 weeks. Out of a planned sample size of 420 patients, a total of only 157 patients (37.4%) were enrolled in the study due to coronavirus disease 2019 (COVID-19) restrictions and anticipated futility at the first interim analysis. Although patients randomized to NT-proBNP-based care were treated with higher doses of diuretics and renin–angiotensin system inhibitors, the primary endpoint of HF rehospitalizations at 6 months was similar between the two groups (12.8% in the NT-proBNP arm vs. 11.4% in the control arm).[7] Worsening HF may include also events not followed by patients' hospitalization.[8] However, no differences were found also for other HF events, including urgent and outpatient visits. Rather unexpectedly, instead, a significantly lower risk of all-cause death at 6 months was observed in the NT-proBNP versus control arm (1 death, 1.3%, vs. 8 deaths, 10.1%; hazard ratio 0.12, 95% confidence interval 0.02–0.98). However, the low number of events in the context of a relatively small sample size, leaves the doubt that this secondary finding may be due to chance.[7] Quality of life and the 6-min walking test distance also had similar changes in both treatment arms with no significant difference.[7]

The authors should be congratulated for having performed this study even with the restrictions and challenges associated with the COVID-19 pandemic. The main limitations are acknowledged by the authors, including the relatively small sample size (with respect to the planned one), the unblinded design and the lack of use of sodium–glucose cotransporter 2 (SGLT2) inhibitors for HFpEF at the time of patients' enrolment (study period 2016–2019). Importantly, the NICE trial is clearly underpowered for the primary endpoint, especially considering that the authors calculated the planned sample size ($n = 420$) considering an expected rate of the primary endpoint of 30%, but an overall rate of 12.1% was then observed in the trial ($n = 157$).[7]

Analysing the findings of the NICE trial in the context of available evidence, one question arises: why do recent trials on NP monitoring in HF have conflicting results? Similarly to NICE, the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) and PRIMA II (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) studies were neutral with respect to the primary endpoint, whereas the STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial was positive.[3,5–7] Notably, there are some key differences between these trials in terms of study setting (acute vs. chronic HF), patients enrolled (HF with reduced ejection fraction [HFrEF], HFpEF, or both), sample size, primary endpoint and tested intervention (*Table 1*).[3,5–7] The latter seems particularly

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Table 1 Recent trials on natriuretic peptide monitoring in heart failure

Trial (year)	Setting	*N*	Intervention	Primary endpoint	Effect on the primary endpoint
STRONG-HF[3] (2022)	AHF post-discharge (any LVEF)	1078	Early GDMT optimization with close follow-up including NP monitoring	180-day all-cause death or HFH	Positive
GUIDE-IT[5] (2017)	CHF (HFrEF)	894	HF therapy optimization to achieve a NP target[a]	Time-to-first HFH or CV death	Neutral
PRIMA II[6] (2018)	AHF in-hospital (any LVEF)	405	HF therapy optimization to achieve a NP target[b]	180-day all-cause death or HFH	Neutral
NICE[7] (2024)	AHF post-discharge (HFpEF)	157	Close NP monitoring	HFH at 6 months	Neutral

AHF, acute heart failure; CHF chronic heart failure; CV, cardiovascular; GDMT, guideline-directed medical therapy; GUIDE-IT, Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure; HF, heart failure; HFH, heart failure hospitalization; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NICE, Management of Discharged Patients with Acutely Decompensated Heart Failure and Preserved Ejection Fraction; NP, natriuretic peptide; PRIMA II, Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?; STRONG-HF, Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies.
[a]Target NT-proBNP level <1000 pg/ml.
[b]NT-proBNP reduction >30% from admission to discharge.

important, since GUIDE-IT and PRIMA II tested a strategy of HF therapy optimization aimed to achieve a pre-specified NP target, whereas NP measurements were only an aspect of the study design of STRONG-HF, which was aimed to administer GDMT at target doses through frequent follow-up clinical visits and to use standard laboratory measurements including also NT-proBNP plasma concentrations.[3,5,6] Second, NICE did not use a protocol-based algorithm for optimizing medical therapy,[7] whereas STRONG-HF tested a strategy based on early GDMT up-titration and close follow-up with serial evaluation of multiple safety indicators and pre-specified changes in medications and their doses based on clinical symptoms and signs and changes in laboratory measurements, including NT-proBNP concentrations.[3,9] Last but not least, differences in GDMT optimization between the intervention and control arms were absent or modest in GUIDE-IT and PRIMA II,[5,6] whereas there was a huge difference in achieved GDMT doses between the high-intensity care and control arms in STRONG-HF.[3,10] Although treatment in the usual care arm of STRONG-HF resembled that of real-world registry-based data reporting undertreatment of patients with HF,[11–15] it is difficult that it may be reproduced in the context of a clinical trial performed in highly specialized tertiary care centres. These differences between trials in background medical therapy (control arms) and active GDMT optimization (intervention arms) may have contributed to the different outcomes.[3,5–7] In STRONG-HF, the high-intensity care strategy, including frequent follow-up visits, serial laboratory exams and NP plasma concentrations monitoring, was safe and effective in reducing mortality and HF rehospitalizations at 180 days among patients hospitalized for acute HF, irrespective of their left ventricular ejection fraction.[3,4,16]

Based on all these data, it seems reasonable to measure NP plasma concentrations during frequent follow-up after a hospitalization for acute HF both as a safety signal with diuretic up-titration and tapering of beta-blocker doses in cases of an increase in NP plasma concentrations, as done in STRONG-HF, and, *vice versa*, with a possible reduction in diuretic doses in case of a decrease in NP plasma concentrations having, however, GDMT optimization as primary target for treatment rather than changes in NP values alone. Optimization of medical therapy in HF needs a comprehensive monitoring based on clinical assessment (blood pressure, heart rate as well as clinical or subclinical signs of congestion and/or hypoperfusion), concomitant laboratory tests (renal and liver function, serum electrolytes), in addition to NP plasma concentrations. The NICE trial adds a piece to this complex puzzle and paves the way for future dedicated studies evaluating NP monitoring in HFpEF, that might be larger and test concomitant tailored optimization of therapy in these patients (including novel drugs and interventions).

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