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Point-of-care testing of (N-terminal pro) B-type natriuretic peptide for heart disease patients in home care and ambulatory care settings

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ABSTRACT

Objectives: The role of point-of-care testing (POCT) out of hospital, especially in home care and ambulatory care settings, is an issue meriting further research. We reviewed studies reporting cardiovascular events as a result of the implementation of B-type natriuretic peptide or N-terminal pro B-type natriuretic peptide POCT (BNP/NT-proBNP POCT) for heart disease patients in the settings.

Design: Articles were searched via a PubMed engine until May 30, 2020.

Results: In total, six studies were selected. Three studies involving ambulatory care used the POCT to refer patients with suspected heart diseases to a specialist. The other three used the tests in home care to monitor patients with heart failure. In ambulatory care, the randomized controlled trials, in which referrals were made to a specialist, showed that the group using POCT had significantly fewer cardiovascular outcomes, such as hospitalizations and deaths, than the non-use group. In home care, adverse outcomes were predicted from changes in BNP levels.

Conclusions: In most studies, the use of BNP/NT-proBNP POCT in home care and ambulatory care settings demonstrated favorable results regarding the cardiovascular outcomes. The utility of POCT in the settings is suggested, while more investigations are required.

1. Introduction

The control of heart diseases, including heart failure (HF), remains a challenge [1,2]. Currently, approximately 26 million people worldwide live with HF, which is referred to be a global pandemic [1,2]. The development of methodology and policy about an early diagnosis and appropriate treatment for such heart diseases is a point to be considered [1]. An increased awareness of people including patients is also the point as heart diseases are preventative [1]. B-type natriuretic peptide (BNP) and N-terminal pro BNP (NT-proBNP) are thought to be the most relevant biomarkers for heart diseases, especially HF [3]. The concentration of BNP/NT-proBNP in blood can significantly change with a reflection to the change of cardiac functions [3]. The biomarkers are, thus, used for screening, diagnosis, and prognostic assessment of the condition, even though their cut-off levels are still debatable [3].

Abbreviations: POCT, point-of-care testing; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; RCT, randomized controlled trials; HF, heart failure; MACE, major adverse cardiac events; ADHF, acute clinical HF decompensation; HFpEF, HF with preserved ejection fraction; HFREF, HF with reduced ejection fraction; IRR, incidence rate ratio; OR, odds ratio; AUC, area under the curve; HR, hazard ratio; Sp, specificity; Sn, sensitivity.

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Point-of-care testing (POCT) is useable for rapid diagnosis and timely applied to care in out-of-hospital settings without any large-scaled equipment [4]. Considering the characteristics of POCT, BNP/NT-proBNP POCT is operational in home care or ambulatory care settings. While patients with HF are prevalently seen in the settings, a simply repeated monitoring of clinical signs is needed in patients with a chronic phase of HF and a quick judgement for referral and initial treatment is crucial in patients with acute or exacerbated phase of HF; therefore, BNP/NT-proBNP POCT would play an active role [4,5]. The diagnostic accuracy of BNP/NT-proBNP POCT on ambulatory care, such as primary, outpatient, or emergency care, has been studied [4]; however, that study did not focus on cardiovascular outcomes and did not include its use in home care setting. To what extent has the utility of BNP/NT-proBNP POCT been verified in home or ambulatory care? The purpose of the present study was to review the cardiovascular outcomes when BNP/NT-proBNP POCT is implemented in home care and ambulatory care settings.

2. Materials and methods

Articles were searched via a PubMed engine until May 30, 2020. A combination of BNP or NT-proBNP (“Natriuretic Peptide, Brain” [Mesh] OR “pro-brain natriuretic peptide (1–76)” [Supplementary Concept]), POCT (point-of-care OR rapid OR same time OR immediate OR bed-side OR monitoring OR screening OR Triage OR Heart Check OR iSTAT OR Cobas h232 OR Cardiac Reader OR RAMP), and home care or primary care (home OR primary care OR house call OR general practi* OR family medicine OR family physician) were used as keywords for the search.

The search identified 579 papers. Of these, papers not concerning humans (5 paper), papers not in English (31), abstracts or papers for which the text was not available (24), and non-original articles (96) were excluded. Next, the abstracts and the “materials and methods” sections of the selected papers were reviewed, and studies conducted in settings other than a home or ambulatory care (176), studies not concerning heart diseases such as HF (53), studies with unknown (undescribed) cardiovascular outcomes (123), studies that did not measure BNP/NT-proBNP with POCT (58) and studies with unknown (undescribed) measurement devices (7) were excluded. In total, six studies were ultimately eligible (Fig. 1).

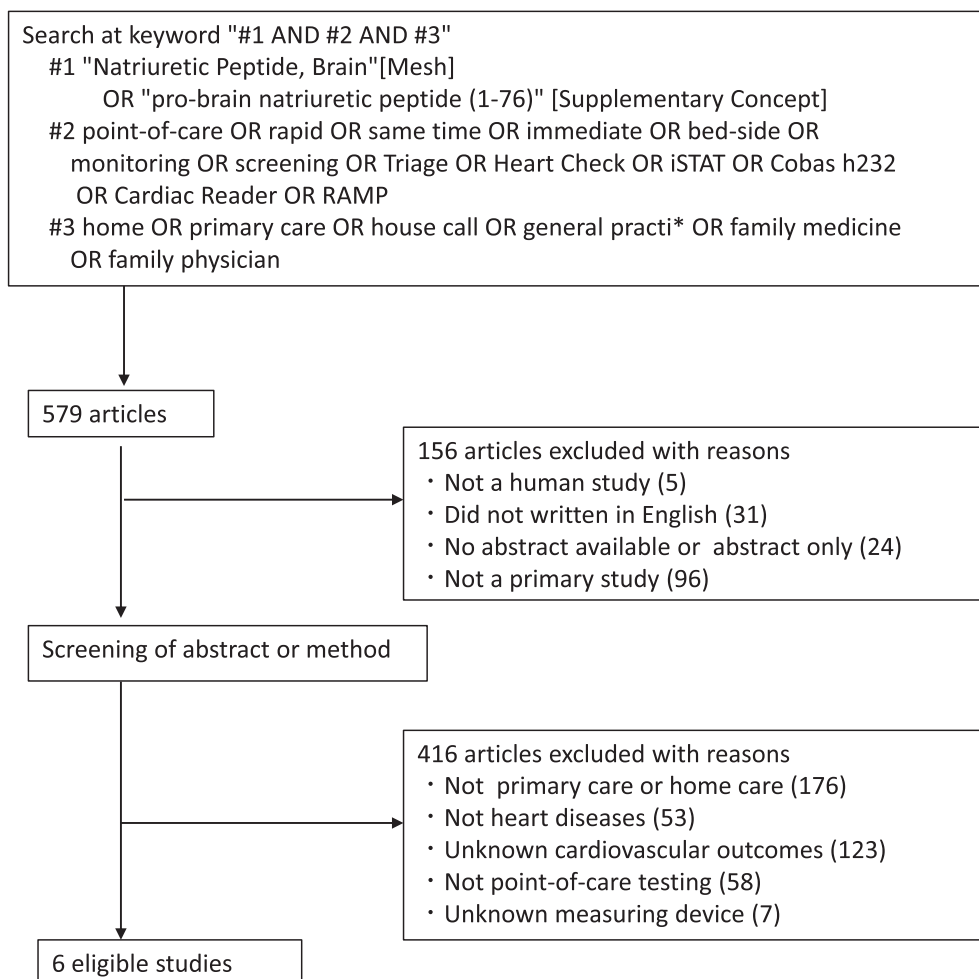


Fig. 1. Flowchart of the study selection process.

3. Results

3.1. Characteristics of the selected studies

Table 1 shows the studies of six papers selected. In three studies, BNP/NT-proBNP POCT was used for referral to a specialist [6–8]. In the remaining three studies, POCT was used to monitor the blood concentrations at home [9–11].

Regarding the study designs, there were three RCTs [6,7,11] (two of which were based on the Screening TO Prevent Heart Failure (STOP-HF) study [6,7]) and three cohort studies [8–10] (two of which were based on the Heart Failure Assessment with BNP in the Home Trial (HABIT) [9,10]). Clinical outcomes were cardiovascular events, hospitalizations, and deaths. Regarding the POCT devices, two types of BNP POCTs [6,7,9–11] and one type of NT-proBNP POCT [8] were used. The POCTs used were Triage® (Biosite) [6,7], Heart Check (Alere) [9–11], and COBAS h232 (Roche Diagnostics) [8].

3.2. Summarized findings of each study

The STOP-HF Study [6,7] was an RCT using BNP. Heart disease-prone patients in the intervention group screened by BNP underwent echocardiography and collaborative care by a specialist and primary care physician when BNP ≥ 50 pg/mL [6]. Emergent hospitalizations and deaths due to major adverse cardiac events (MACE: arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or HF) were significantly suppressed in the intervention group compared to the controls [6,7] (Table 1). In the intervention group, the medical costs increased, but were largely offset by savings from reduced hospitalization [7].

A study by Adlbrecht et al. [8] was a cohort study using NT-proBNP. Heart disease-prone patients with NT-proBNP > 125 pg/mL were referred to a specialist and underwent echocardiography. NT-proBNP showed an ability to detect the patients with a high risk for hospitalizations by cardiac reasons (Table 1).

The HABIT study [9,10] is a cohort study using BNP as a monitoring test at home. Patients with HF used finger-stick BNP self-testing (Heart Check) at home each day and sent the results along with their weights and symptoms to the database. A unit increase of BNP was

Table 1
Characteristics of the included studies in the review.

Authors, year (reference)	Design	Number (Men %)	Age	Cut-offs or predictors	Outcomes and results
Ambulatory care setting					
Ledwidge et al., 2013 [6].	RCT	1374 (44.3%)	64.8	BNP ≥ 50 pg/mL	Hospitalization: IRR 0.60 * OR 0.69 *
Ledwidge et al., 2015 [7].	RCT	1054 (47.1%)	65.8	BNP ≥ 50 pg/mL	Hospitalization: IRR 0.54 * Hospitalization and death: IRR 0.64 * AUC 0.815 *
Adlbrecht et al., 2012 [8].	Cohort study	1203 (48.3%)	65.3	NT-proBNP ≥ 125 pg/mL	Hospitalization: AUC 0.815 *
Home care setting					
Maisel et al., 2013 [9].	Cohort study	163 (87.1%)	63	Daily BNP or acute BNP rise (more than double)	ADHF: HR 1.84 * (daily BNP) HR 1.01 (acute BNP rise)
Maisel et al., 2016 [10].	Cohort study	160 (88.1%)	HFpEF: 66 HFrEF: 63	Daily fluctuations in BNP or acute BNP rise of >200 or >300 pg/mL	ADHF (HFpEF): HR 1.99 * (daily fluctuations) Sp 89.5%, Sn 40.0% (>200 pg/mL) * Sp 93.3%, Sn 33.3% (>300 pg/mL) * ADHF (HFrEF): HR 1.90 * (daily fluctuations) Sp 81.8%, Sn 22.2% (>200 pg/mL) Sp 87.5%, Sn 16.7% (>300 pg/mL)
McDonald et al., 2018 [11].	RCT and cohort study (by pooled data from RCT)	107 (80.4%)	65.0	RCT: daily BNP, Cohort study: daily fluctuations in BNP	RCT: hospitalization, ADHF, death: HR 1.16 Cohort study: ADHF: HR 2.22 *

RCT: randomized controlled trials, HF: heart failure, HFpEF: HF with preserved ejection fraction, HFpEF: HF with reduced ejection fraction, ADHF: acute clinical HF decompensation, IRR: incidence rate ratio, OR: odds ratio, AUC: area under the curve, HR: hazard ratio, Sp: specificity, Sn: sensitivity.
* Significance ($p < 0.05$).

positively correlated with acute clinical HF decompensation (ADHF), while acute BNP rises (two times greater or more in a three-day period) were not significant predictors of ADHF [9] (Table 1). The sub-analysis examined the differences between HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) [10]. Slowly varying changes in BNP (estimated by a moving average) equally predicted ADHF in both HFpEF and HFrEF (Table 1). A rapid increase in BNP (>200 pg/mL within three days) was associated with an increased risk of ADHF in HFpEF, not HFrEF (Table 1).

The HOME-HF study [11] was an RCT to monitor BNP in patients with HFrEF using Heart Check by themselves at home. No significant differences were found in the incidence and hazard ratio of HF-related death, hospitalization for ADHF, and ADHF treated with intravenous diuretics between the group in which all health care data including BNP and group in which BNP were blinded [11]. However, BNP variability was positively correlated with ADHF risk [11].

4. Discussion

The present review of BNP/NT-proBNP-POCT for heart disease patients in home care or ambulatory care settings revealed that most studies produced positive findings for cardiovascular outcomes. The implementation of BNP/NT-proBNP POCT could contribute to proper referrals of patients to specialists [6–8] and find the severity of heart diseases [8]. Furthermore, its monitoring at home could contribute to predicting the adverse events of HF [9–11]. This may partly be attributable to the strengths of POCT, such as easy usage by patients and/or primary care physicians (general or family physicians) and the provision of rapid results [4,9,11]. It seemed to promote the application of BNP/NT-proBNP POCT to home or ambulatory care.

Caution is necessary in drawing conclusions based on the findings for expanding the use of BNP/NT-proBNP POCT to home or ambulatory care. Unlike in-hospital care, cases of super-elderly patients and various types of HF are generally mixed in home or ambulatory care settings. It is known that the BNP/NT-proBNP concentration decreases in the case of severe obesity [12], older age [13], as well as renal dysfunction [14,15] and varies with sex [13]. The present review found no studies that considered such individual background factors. The utility of BNP/NT-proBNP POCT may, thus, differ between in-hospital and home or ambulatory care settings according to differences in the underlying conditions of patients. Namely, their threshold is a point to be discussed. The findings from the five studies on primary care (which were excluded from the present review because the clinical outcomes were undescribed [5, 16–19]) in a review article to assess the diagnostic accuracy of BNP/NT-proBNP POCT [4] might be useful to consider a reference level. Of the five studies, three studies [5,16,17] using NT-proBNP showed a sensitivity of 0.99 and specificity of 0.60 at a threshold of 125 pg/mL. The other two studies [18,19] using BNP showed the sensitivity ranging from 0.46 to 0.92 and specificity ranging from 0.38 to 0.82 with a threshold of 10–50 pg/mL. These thresholds were used in the studies on ambulatory care included in the present review [6–8], but the changes of BNP rather than the thresholds were used in the studies on home care in the present review [9–11]. Determining the validity of threshold and change of BNP/NT-proBNP POCT in the settings is future work.

A monitoring method has been discussed [11,20]. BNP-guided therapy is an approach using serial BNP tests to guide up-titration of medication [11,20]. In a review article of BNP-guided therapy by RCTs [20], a study, Swedish intervention study-Guidelines and NT-proBNP analysis in heart failure study, on primary care found no significant difference in the number of cardiovascular hospitalizations and deaths between the control group and BNP-guided therapy group (that study was excluded from the present review because NT-proBNP POCT was not used with POCT) [22]. The Canadian Agency for Drugs and Technologies in Health -CADTH- Rapid Response Report [23] stated that three of four systematic review articles [20,24–26] showed a reduction of HF-related hospitalizations by BNP-guided therapy, while the other outcomes (i.e., all-cause mortality) were not reduced. In cases of HFrEF and HFpEF, BNP-guided therapy was reported to only be beneficial for HFrEF [20,21,27]. Although a review article stated that BNP-guided therapy for elderly persons is ineffective [21], the other articles found it to be safe [21,28] and highly cost-effective [21,29]. Currently, treatment strategies for BNP-guided therapy (e.g., follow-up schedule, BNP/NT-proBNP target, and treatment algorithm) have not been standardized [20, 21] and no optimal BNP-monitoring strategy is identified [20,23]. Establishing BNP-guided therapy in home and ambulatory care would be also future work.

We acknowledged some limitations of the present review study. A small number of studies on this topic were available, while RCTs were included. Test devices and treatment strategies were not uniform between the studies. The patients with a high risk of heart diseases and HF were mainly studied. Thus, the findings should be generalized with care.

5. Conclusion

The findings from five of six studies included in the present review suggest that BNP/NT-proBNP POCT can be useful for improving the cardiovascular outcomes in home or ambulatory care settings. Since limited studies with several issues are available, further investigation is needed.

Declaration of competing interest

NS; EIKEN CHEMICAL Co., Ltd. There are no conflicts of interest to be disclosed for the other authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.plabm.2020.e00183>.

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Ethics approval and consent to participate

Not applicable.

Authors' contributions

NS searched the literature and wrote the manuscript. KK designed the study and supervised writing the manuscript. All authors approved the final submission.

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