



Point-of-care B-type natriuretic peptide and portable echocardiography for assessment of patients with suspected heart failure in primary care: rationale and design of the three-part Handheld-BNP program and results of the training study

Caroline Morbach¹ · Thomas Buck^{2,3} · Christian Rost^{4,5} · Sebastian Peter^{4,6} · Stephan Günther^{4,7} · Stefan Störk¹ · Christiane Prettin⁸ · Raimund Erbel² · Georg Ertl¹ · Christiane E. Angermann¹ · On Behalf of the Handheld-BNP Research Network

Received: 17 August 2017 / Accepted: 7 November 2017 / Published online: 15 November 2017
© Springer-Verlag GmbH Germany, part of Springer Nature 2017

Abstract

Background Patients with suspected heart failure (HF) often present first to general practitioners (GPs). Timely and accurate HF diagnosis and reliable prognostic information have remained unmet goals in primary care, where patient evaluation often relies on clinical assessment only. The Handheld-BNP program investigates whether additional use of portable echocardiography (ECHO) and point-of-care determination of B-type natriuretic peptide (BNP) improves the accuracy of HF diagnosis and aids risk prediction in primary care.

Methods and results A research network was established between 2 academic centers, 2 × 6 cardiologists, and 2 × 24 GPs inexperienced with ECHO and BNP. The Training Study investigates the feasibility of implementing GP use and interpretation of ECHO and BNP. After training, competence is assessed using multiple-choice testing (pass mark: > 80% correct diagnoses). In the cluster-randomized four-arm Screening Study, each GP passes in random order through four study arms: clinical assessment (CA), CA + BNP, CA + ECHO, and CA + ECHO + BNP. Cardiologists' diagnoses serve as reference. Primary endpoint is the rate of correct GP diagnoses per study arm. In the Prognostic Follow-Up Study, patients are followed up centrally for 72 months. Forty-four GPs were successfully trained. With 225 ± 34 (75 ± 3) and 233 ± 28 (81 ± 7) min, respectively, total ECHO (BNP) training times were similar between centers I and II. Furthermore, training results did not differ between centers.

Conclusions Standardized training of limited duration enabled GPs to use ECHO and BNP for HF diagnosis. The Handheld-BNP program will provide robust evaluation of the diagnostic effectiveness and prognostic value of these tools in primary care.

Trial Registration <http://www.controlled-trials.com> (ISRCTN23325295).

Keywords Portable echocardiography · B-type natriuretic peptide · Heart failure · Diagnosis · Prognosis · Primary care

Introduction

In developed countries, the prevalence of heart failure (HF) is approximately 1–2% of the adult population, increasing to

≥ 10% in individuals > 70 years of age [1–3]. The life-time risk of HF at age 55 is 33% for men and 28% for women [3]. HF significantly increases mortality risk and is associated with poor quality of life and high treatment costs, mainly due to frequent hospital admissions [4, 5]. Thus, there is an urgent need for effective diagnostic and treatment strategies in HF.

Patients with signs and symptoms potentially indicative of HF usually present first to their general practitioner (GP) [6–8], but accurate diagnosis of HF has proven challenging in primary care, because HF signs and symptoms are

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00392-017-1181-3>) contains supplementary material, which is available to authorized users.

✉ Christiane E. Angermann
Angermann_c@ukw.de

Extended author information available on the last page of the article

non-specific, particularly in the elderly and in the presence of comorbidities [7, 9, 10]. Previous studies have reported that GPs show low diagnostic accuracy and high proportions of incorrect diagnoses in patients with suspected HF [11–13]. In particular, over-diagnosis of HF has been well documented, and only 25–50% of patients with a clinically based GP diagnosis have the presence of HF confirmed on specialist evaluation [11, 12, 14]. Therefore, if no further assessment was made, up to 50% of patients diagnosed with HF by their GP could receive inappropriate therapy. Available data suggest that, in reality, a large proportion of such patients are not referred for cardiologist assessment [8, 15].

Definite diagnosis of HF requires cardiac imaging allowing for thorough morphological and functional cardiac assessment [16]. The investigation most commonly used to confirm or exclude HF is echocardiography. There are several factors that impact on the application of echocardiography for HF diagnosis, including cost, availability, and capacity, particularly in primary care.

Diagnostic uncertainty and misdiagnosis are unresolved problems that constitute a major obstacle to optimal patient care in the community. Given that prognosis in HF patients is related to disease stage, and evidence-based therapies have been shown to ameliorate HF symptoms, slow disease progression, and improve clinical outcomes in patients with overt HF [1, 17–20], there is need for a diagnostic algorithm to improve the speed and accuracy of HF diagnosis by GPs.

Growing evidence suggests the potential utility of natriuretic peptides (NPs) as diagnostic cardiac biomarkers. For many years, European Society of Cardiology (ESC) guidelines have recommended measurement of NP concentrations as an initial diagnostic test in suspected HF when echocardiography is not immediately available, especially in the non-acute setting [16, 21, 22]. Elevated NP concentrations help to establish a working diagnosis, with patients having normal levels unlikely to have HF [16]. NPs have proven useful in the differential assessment of patients with dyspnoea in the emergency department [23–25] and improved the diagnosis in patients referred to a rapid access hospital clinic, in whom HF was suspected on clinical grounds [14]. In addition, various studies have suggested that NP measurements might also enhance HF diagnosis in primary care, albeit probably not as a diagnostic tool in its own right [26–33]. In a large Dutch trial, NP determination was the most powerful supplementary diagnostic test when added to standardized diagnostic work up in primary care patients with suspected HF [34].

The availability of point-of care systems for biomarker testing (POCT) makes on-site NP measurement from capillary blood feasible and easy, eliminating the need to transport blood samples for biomarker assessment elsewhere. Satisfactory correlations have been shown between POCT results and values measured by central laboratory testing

[35–39]. A recent systematic evaluation of immunoassay POCT confirmed excellent practicality and satisfactory analytical performance for B-type NP and other biomarkers in various clinical settings, suggesting that POCT of NPs might potentially enhance real-time management of patients with suspected HF at a moderate cost, although longer term outcome data from such investigations are not yet available [40]. In a survey of Dutch family practitioners, B-type NP was one of the most desired POCT, but was not yet in widespread routine use [41].

One reason for current underuse of NP testing in GP practices might be uncertainty about the best cut-off levels to apply, especially in patients with sub-acute symptoms [42]. Results of NP studies performed in the community are often inconsistent with studies in clinical or emergency settings. Moreover, NP concentrations are modulated not only by age and sex, but also by various common comorbidities and risk factors [43–45]. Observational findings in primary care patients demonstrated poor correlation of B-type NP with echocardiographic parameters of LV dysfunction [46], and the positive predictive value for cut-off values recommended by the current guidelines in the non-acute setting is low, thus limiting their value as an HF screening tool. Of note, the English National Institute for Health and Care Excellence (NICE) currently recommends much higher NP thresholds to trigger referral to echocardiography and specialist assessment in patients with suspected HF [47]. As recently demonstrated by meta-analysis, using separate cut-off values for “ruling in” and “ruling out” HF while creating a “grey zone” in between also does not improve the proportion of patients with correct HF diagnoses [11].

Advances in technology have also led to the development of miniaturized, portable echocardiographic devices, providing the potential to extend the use of echocardiography to the bedside and to healthcare professionals other than cardiologists. Comparative assessment showed good correlation between diagnostic results obtained with these handheld devices compared with standard echocardiography and confirmed their safety [48, 49]. Although the lack of spectral Doppler and lower resolution of many miniaturized echocardiography devices limit assessment of left ventricular (LV) filling characteristics and of valvular disease, satisfactory to excellent capabilities in detecting LV systolic dysfunction, LV hypertrophy, significant mitral incompetence and other cardiac abnormalities have been demonstrated in various clinical settings and patient populations [48, 50–53]. Since the introduction of portable echocardiography machines into clinical practice, evidence is growing that their availability may increase the diagnostic accuracy of cardiovascular assessment and lead to modification of clinical diagnosis and subsequent patient management [54, 55].

The benefits achievable with portable echocardiography seem to apply to fully qualified cardiologists and internists,

as well as junior doctors, medical students, and GPs [48, 53, 56–58]. However, questions such as the kind of training required to operate the devices and interpret the results, and the ultimate diagnostic yield achievable by portable echocardiography in various clinical situations are still the subject of ongoing research. Both the American Society and the European Association of Echocardiography agree that examinations with handheld ultrasound devices cannot substitute for standard echocardiography and recommend that non-cardiologists should undergo dedicated, individualized training in performance and appropriate interpretation. Furthermore, quality control to ensure appropriate use and accurate diagnosis based on examination results is advised [59, 60].

In the past, training programs in portable echocardiography have ranged from 2-h bedside tutorials to several hours or even days of didactic and practical training, with variable outcomes [48]. More recently, studies in which internists or GPs employed handheld devices in patients with suspected HF yielded encouraging diagnostic and prognostic results [53, 56, 57, 61], but larger scale prospective trials using a randomized controlled design are lacking.

The three-part Handheld-BNP program was designed to investigate the diagnostic and prognostic effectiveness of portable echocardiography (ECHO) and POCT B-type NP measurement (BNP), alone and in combination (ECHO + BNP), when added to clinical assessment compared with clinical assessment alone in diagnostically naïve patients attending GP practices with signs and symptoms potentially indicative of HF. The aim of the Screening Study is to clarify whether and to what extent the use of these tools in addition to clinical assessment improves the diagnostic capabilities of GPs compared with the reference diagnosis of cardiologists. The Prognostic Follow-Up Study investigates whether GPs' and cardiologists' diagnosis, and ECHO and BNP results provide clinically relevant prognostic information over a 6-year observation period. In the preceding Training Study, a structured, quality-controlled training program was developed and applied to enable GPs to perform and interpret ECHO and BNP and utilize the test results in HF diagnosis. In this manuscript, we describe the rationale and design of the Handheld-BNP program and report the training contents, time requirements and results for 44 GPs participating in the training program in two different regions of Germany.

Methods

Study design and setting

The Handheld-BNP program was developed within the Competence Network Heart Failure [62] in collaboration

with the Clinical Trial Center Leipzig, Germany, as an investigator-initiated prospective, controlled, cluster-randomized four-arm multicenter trial. The study is coordinated at the University Hospitals Würzburg and Essen, Germany, funded by the Federal Ministry for Education and Research (BMBF), and performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol was pre-registered at <http://www.controlled-trials.com> (ISRCTN23325295) and approved by all responsible Ethics Committees.

Organization and site selection

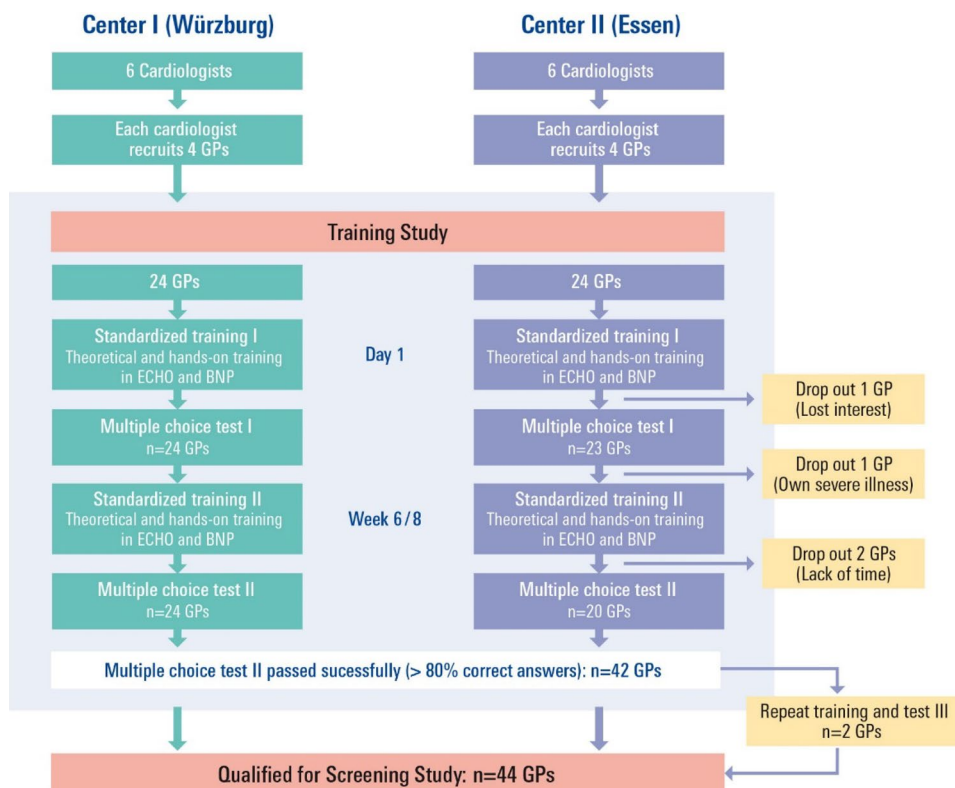
Physicians at the two University Hospitals (center I: Würzburg, Bavaria; center II: Duisburg-Essen, North Rhine Westphalia) initiated the Handheld-BNP program by each choosing six local cardiologist practices as cooperating sites. Each partner cardiologist was asked to identify four referring general practices (Fig. 1). GPs with the previous experience in ECHO or BNP were not eligible. One cardiologist practice and four referring GPs were defined as a study cluster. Cardiologists and GPs committed to comply with the Handheld-BNP program protocol by signing a formal contract, which also regulated reimbursement for patient contribution and reference assessment. GPs also consented to undergo structured ECHO and BNP training. Information on serious adverse events (including death and hospital admissions) is sought from all participating physicians and patients by telephone. In addition, standardized questionnaires are sent to GPs and patients by regular mail. Further information is collected by other means (e.g., death certificates and hospital letters).

Equipment

Portable echocardiography ECHO is performed using a portable battery-operated OptiGo[®] ultrasound device (Philips Medizinsysteme Ultraschall, Hamburg, Germany) equipped with a 2.5 MHz phased-array transducer and a compact flash card for image storage. Scan options include B-mode and color Doppler imaging. The OptiGo[®] device has no spectral Doppler capabilities.

Point-of-care determination of B-type NP Plasma B-type NP levels are determined using a rapid fluorescence immunoassay (Triage[®] BNP Test) implemented on a portable Triage[®] MeterPlus device (Biosite Diagnostics, La Jolla, CA, USA). This point-of-care device delivers results within 15 min on a paper printout. Stability characteristics, precision, and analytical sensitivity of the Triage[®] BNP Test have been previously described [63].

Fig. 1 Selection of participating physicians and flow of the training study. *BNP* B-type natriuretic peptide measurement using Triage[®]MeterPlus (Biosite Diagnostics, La Jolla, CA, USA), *ECHO* handheld echocardiography using OptiGo[®] (Philips Medizinsysteme Ultraschall, Hamburg, Germany), *GP* general practitioner



Training

To ensure comparable basic knowledge about the clinical diagnosis of HF, the Framingham and National Health and Nutrition Examination Survey (NHANES) criteria for HF [13, 64, 65] were discussed during the training, and associated literature was distributed.

The ECHO training program was developed by investigators at the University Hospital Essen according to the recommendations of the American Society of Echocardiography [60], and delivered at both study centers in a standardized fashion by experts. The training consisted of hands-on sessions, case studies, and didactic handouts (see online supplement for more details). During hands-on sessions, GPs were trained to follow a simplified imaging protocol of the LV parasternal long- and short-axis views and the apical four-chamber view, and instructed to recognize LV enlargement and decreased systolic function as possible indicators of HF with reduced systolic function (HFrEF), and LA enlargement and increased LV wall thickness as possible indicators of HF with preserved ejection function (HFpEF).

Each GP performed at least two B-type NP measurements using the Triage[®]MeterPlus to allow familiarization with practical aspects of the procedure. In the absence of B-type NP cut-off values validated specifically in patients presenting with suspected HF in primary care, and because GPs tend to over-, rather than under-diagnose HF [11, 14,

66, 67], the Handheld-BNP program uses B-type NP cut-off values validated previously in patients presenting with dyspnea to hospital emergency rooms [23–25]. Details of the validation of these cut-off values are provided in the online supplement. With the goal of predicting, rather than just ruling out, HF, GPs were advised that HF was unlikely to be the cause of a patients' signs and symptoms if the B-type NP level was < 100 pg/mL, whereas a B-type NP level > 400 pg/mL indicated that HF was the most probable diagnosis. To overcome the uncertainty of the 'grey zone' in between both values, GPs were asked to carefully consider all available clinical information and use ECHO for further clarification if available to them at that time before their final diagnostic decision. Handout materials with information on BNP levels in health and disease and on potential confounders as age, sex, body weight, atrial fibrillation, renal dysfunction, or infections [43–45] were distributed.

All GPs participated in at least two training sessions, 4–6 weeks apart (Fig. 1). After each session, training success was evaluated with a case-based multiple-choice test (pass mark: > 80% correct diagnoses). If the pass mark was not achieved, repeat training and further testing were scheduled. Training times until each GP felt confident to perform and interpret ECHO and BNP and passed the test were measured.

Randomization

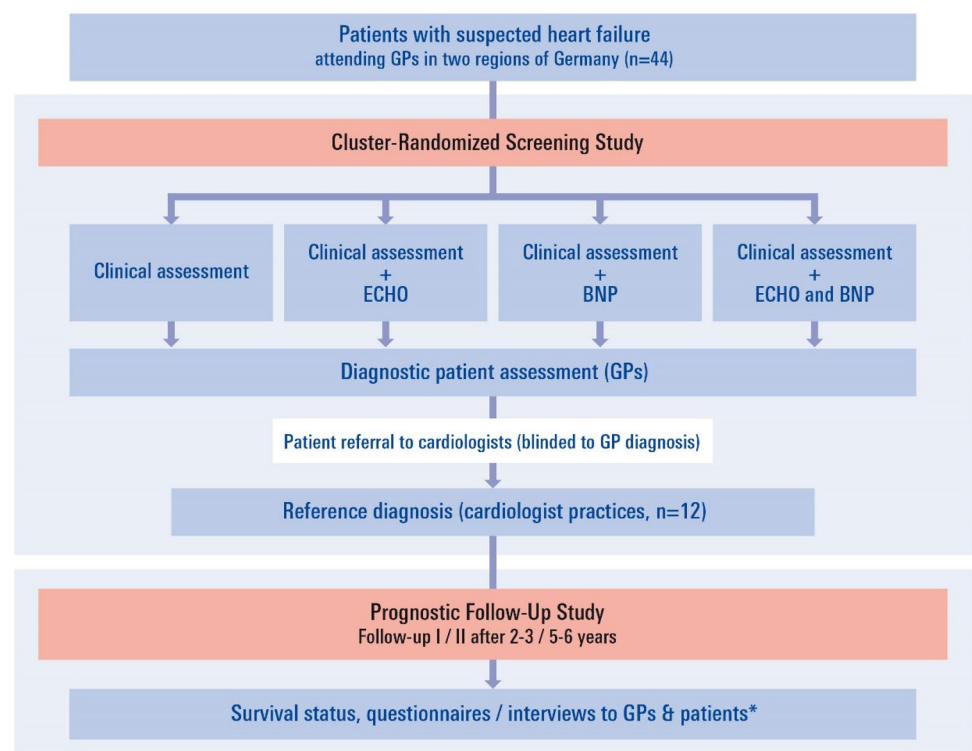
Each cardiologist practice has two portable OptiGo® ultrasound devices and two Triage®MeterPlus devices available, which are supplied to the four referring GPs of the study cluster according to an allocation scheme generated by the Clinical Trial Center Leipzig. This randomizes GPs in a 1:1:1:1 ratio to one of four possible orders in which they use each of the four diagnostic approaches: clinical assessment only, with ECHO, with BNP or with ECHO + BNP (Fig. 2, see Table e1, online supplement, for possible sequences, in which GPs might use the different diagnostic modalities). Each diagnostic modality is made available for at least 5 months with the goal of recruiting and diagnosing at least five patients per period. The patients themselves are not randomized, but enter one of the four study arms depending on the diagnostic modality available to their GP at the time of their presentation.

Study hypotheses and endpoints

In the Training Study, we hypothesized that standardized practical and theoretical training of limited duration provided by experts would enable GPs to make diagnostic use of BNP and ECHO in patients with suspected HF based on clinical findings. The endpoint was expert training time required by GPs to achieve a > 80% test score.

In the Screening Study, we hypothesize that the use of either point-of-care BNP testing or ECHO improves the diagnostic accuracy of GPs compared with diagnosis by cardiologists obtained within 2 weeks of study enrolment, and that the best diagnostic results will be achieved when GPs have both BNP and ECHO available. The primary endpoint is the rate of correct GP diagnoses per study arm. Concordance (diagnostic success) or discordance (diagnostic failure) between the GPs' and cardiologists' diagnosis are determined for each patient to estimate the sensitivity, specificity, and positive and negative predictive values of each of the four diagnostic modalities. Secondary endpoints include the proportions of patients diagnosed by cardiologists with HF with reduced ejection fraction (HFrEF) versus HF with preserved ejection fraction (HFpEF) versus those in whom HF is excluded (overall, and in the two regions where the study is performed). Furthermore, alternative diagnoses in patients, in whom HF is excluded, risk and comorbidity profiles, medications according to the cardiologists' records, ECG findings, and mood and quality of life as assessed with standardized validated questionnaires will be evaluated in the study population. Average time required to perform each of the four diagnostic modalities and concordance of BNP values with the cardiologists' diagnosis of HFrEF or HFpEF will also be recorded. In addition, we plan to use epidemiological data and NP values obtained at baseline to determine the most appropriate NP values for HF diagnosis

Fig. 2 Flow diagram for the screening and follow-up studies. *BNP* B-type natriuretic peptide measurement using Triage®MeterPlus (Biosite Diagnostics, La Jolla, CA, USA), *ECHO* handheld echocardiography using OptiGo® (Philips Medizinsysteme Ultraschall, Hamburg, Germany), *GP* general practitioner



in the Handheld-BNP program population also considering patient age and sex.

In the Prognostic Follow-Up Study, we hypothesize that the GPs' and cardiologists' diagnosis, ECHO results, and NP measurements provide clinically relevant prognostic information, irrespective of their diagnostic capacity. The primary endpoint is all-cause mortality. Secondary endpoints include all-cause hospitalization, possible outcome differences between the two study regions, the prognostic significance of the GPs' and cardiologists' diagnosis (HF or not), and the comparative prognostic value of ECHO and BNP measurements.

Patient eligibility

Patient eligibility is determined by GPs based on clinical history and physical examination. Male and female patients aged ≥ 18 years presenting with signs and symptoms potentially indicative of HF (e.g., dyspnea, edema, fatigue, and decreased physical capacity) are eligible, if able and willing to provide written informed consent. Patients with obvious alternative diagnoses (e.g., acute infections) or not providing informed consent are excluded. GPs were asked to consecutively approach all suitable patients.

Enrolment visit

To make their diagnostic decision, GPs use all clinical information and the study tool(s) available to them at that time. They complete a short GP case report form (CRF), in which demographics and vital parameters, body weight, heart rhythm, New York Heart Association (NYHA) functional class, ECHO and BNP results are documented as applicable, together with their diagnosis (HF or not). The time required by GPs to apply each diagnostic modality needs to be recorded, and blood is drawn and processed for central long-term storage (at $-80\text{ }^{\circ}\text{C}$) and later analysis. Recruitment form, IC sheet, the GP-CRF and serum, plasma, and cell samples are transferred to center I on the same day. After a quality check, GP-CRFs are transferred to the Clinical Trial Center Leipzig database.

Reference diagnosis

A cardiologist appointment within 2 weeks is allocated before patients leave their GP. Cardiologists are not informed of the GP diagnosis, and ECHO and BNP results. They perform all necessary procedures to reach a conclusive diagnosis, including clinical evaluation, 12-lead ECG, laboratory assessments, and standard echocardiography and Doppler [16, 21, 22]. At the cardiologist visit, patients are also invited to complete the 36-item Short Form health survey (SF-36) [68] and the nine-item patient health questionnaire

(PHQ) [69]. If HF is diagnosed, cardiologists are asked to document the type of HF and the most probable etiology. If HF is excluded, the most likely cause of patients' symptoms must be chosen from the following: anemia, chronic obstructive pulmonary disease, other pulmonary disease, chronic venous insufficiency, coronary artery disease, malignancy, obesity, psychosomatic disorder, renal failure, or others. GPs are notified of the final cardiologist diagnosis and receive treatment recommendations to ensure timely and appropriate medical care.

Long-term follow-up

Patients and GPs are contacted for follow-up after 2–3 and 5–6 years. Both groups receive structured questionnaires by ordinary mail, with a pre-paid envelope for return. Alternatively, center I team members contact patients or GPs by telephone to administer the same questionnaires. Patients are asked to report their current symptoms and physical capabilities, to complete the two-item PHQ [70], and to list visits to GPs and cardiologists and hospital stays since enrolment or since the previous follow-up. GPs are asked to report patients' current NYHA class, body weight and blood pressure, medications, cardio- and cerebrovascular events or interventions, new diagnoses, and number and date of visits to GPs and cardiologists and hospital stays since the last contact. A subgroup of 200 patients recruited by GPs in Bavaria will undergo the second follow-up in person at the center I outpatient clinics. For deceased patients, GPs complete a death-CRF to document date, place and mode of death, as well as the likely cause (cardiac versus non-cardiac, or unknown).

Statistical analysis

Variables are given as mean (standard deviation), median (quartiles), and n (percent), as appropriate. Comparisons are made using Student's t test, Mann–Whitney U test, Kruskal–Wallis test, and χ^2 -testing, as applicable.

In the Training Study, concordance of the GPs' test results with the true test case diagnoses was assessed using kappa statistics. In the cluster-randomized Screening Study, the primary endpoint per patient is the indicator for concordant (= 1) or discordant (= 0) diagnoses of GPs and cardiologists using each diagnostic modality. Each GP's results within the four study arms will be compared by statistical methods for dependent variables. To account for basic differences between individual GPs we plan to calculate a 'GP-score' describing each individual GP's performance across the four diagnostic options yielding a single value which will be used for the primary analysis (see online supplement for more details).

Receiver-operating characteristic (ROC) curves and areas under the curve (AUC) will be calculated to determine the sensitivity, specificity, and optimal cut-off points for the ability of ECHO and BNP to facilitate HF diagnosis in the subgroups of patients undergoing one or both of these tests. Cox regression analysis using multivariable regression models will be employed to examine the independent prognostic value of abnormal ECHO and BNP. In the Prospective Follow-Up Study, survival curves according to HF diagnosis (yes or no), ECHO results, and BNP levels are constructed using the Kaplan–Meier method. Comparisons are made using the log-rank test. Data will be analyzed with SPSS or R statistical software. p values < 0.05 are considered statistically significant. All significance tests are two-sided.

Sample size considerations

Participating GPs estimated that one to three diagnostically naïve patients with suspected HF would present to their practices each month. Given a response rate of 40–50%, recruitment of one patient per month and practice seemed realistic. If all 48 GPs were trained successfully and completed recruitment as anticipated, a maximum of 248 patients would enter each study arm. Experience to date shows that only 41 GPs started recruitment, decreasing the expected maximum patient number achievable. Assuming an arbitrary concordance rate of 80% between GPs and cardiologists with clinical assessment only, a 10% increase in diagnostic accuracy with either ECHO or BNP, and a 16% increase with ECHO + BNP, study power would be $> 99\%$. If GPs' diagnostic accuracy based on clinical assessment only would be lower and the increase in diagnostic accuracy with the use of ECHO and/or BNP higher, the power would

increase. If concordance rates between GPs using BNP, ECHO, and ECHO + BNP versus cardiologists were lower by 2 or 4%, then study power would be 95 or 79%, respectively. If only 30 or 20 GPs were to include five patients with each modality, the resulting power would be 93 or 79%, respectively. In view of the number of unknown factors, we have planned redundant recruitment in the Handheld-BNP program, which, if successful, will also allow for sufficient patient numbers in each of the four study arms to perform the secondary analyses.

Results

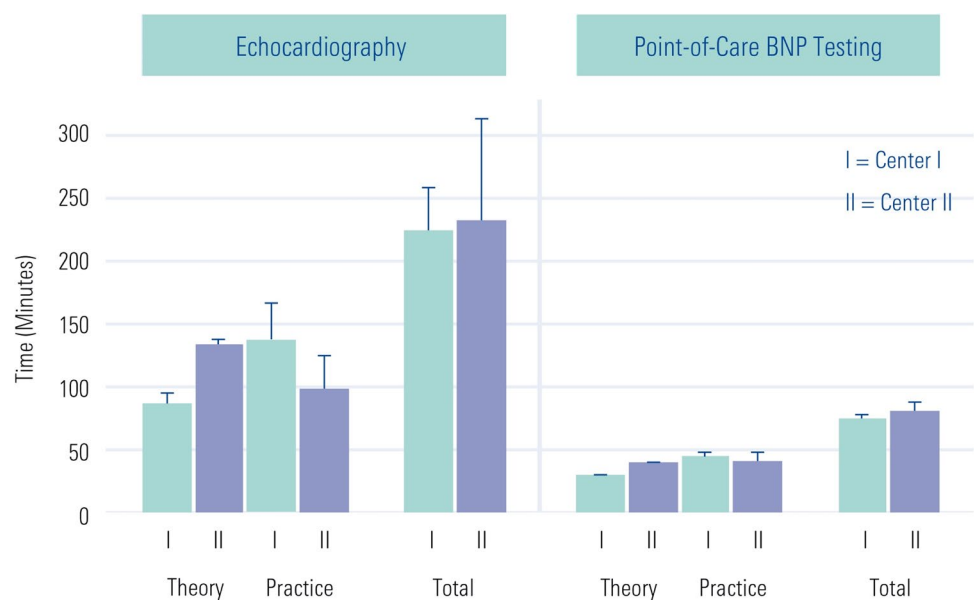
Recruitment and characteristics of general practitioners

All 12 partner cardiologist practices were successful in recruiting four GPs each. Therefore, 48 GPs entered the Training Study. During training, four GPs terminated participation for various reasons (Fig. 1). After two training sessions, 42 GPs had passed the multiple-choice test successfully and thus qualified for the Screening Study, while two GPs had to undergo a third training session and testing before they passed. Mean age of the 44 GPs was 50.4 ± 7.7 years, 91% were males, and mean practice duration was 21.9 ± 8.1 years, with no difference between study centers.

Training results

Mean training times for GPs at the two study centers were comparable (Fig. 3). ECHO training times were 225 ± 34

Fig. 3 Time required to achieve sufficient training of general practitioners. I Center I (Würzburg), II Center II (Duisburg-Essen), BNP B-type natriuretic peptide measurement using Triage[®]MeterPlus (Biosite Diagnostics, La Jolla, CA, USA), echocardiography handheld echocardiography using OptiGo[®] (Philips Medizinsysteme Ultraschall, Hamburg, Germany)



and 233 ± 28 min at centers I and II, respectively ($p = \text{n.s.}$). Corresponding time requirements for BNP training were also similar at both centers (75 ± 3 and 81 ± 7 min, $p = 0.004$).

Training success rates are shown in Fig. 4. After the first ECHO training, GPs interpreted 80 and 87% of ECHO test cases correctly at center I and center II, respectively [κ values \pm standard errors of the estimate (SE) were 0.54 ± 0.06 and 0.71 ± 0.05 , respectively]. After the last training session, diagnostic accuracy was higher, at 88 and 92% (0.72 ± 0.05 and 0.81 ± 0.04), respectively. BNP-based case interpretations had a diagnostic accuracy of 92% (0.83 ± 0.02) at center I and 93% (0.84 ± 0.02) at center II.

Discussion

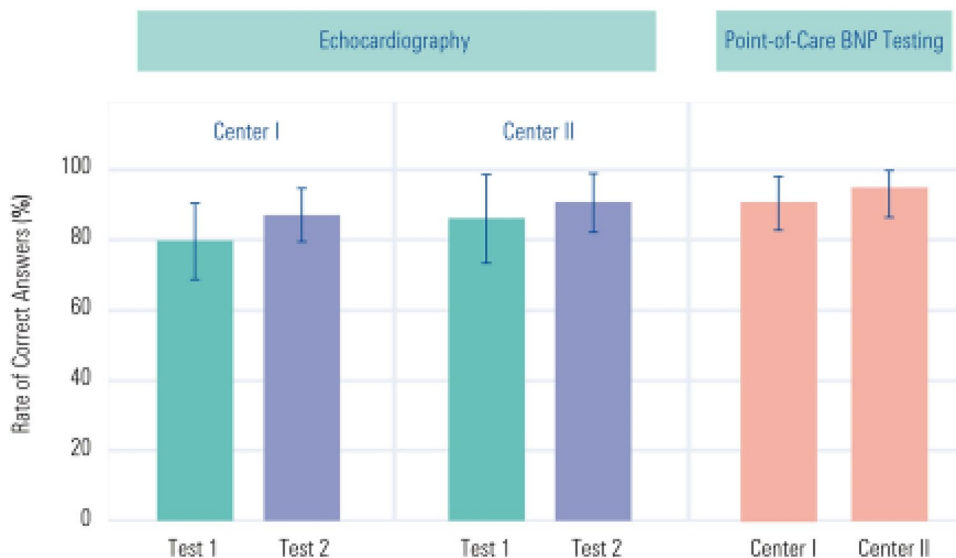
The three-part Handheld-BNP program is an investigator-initiated, prospective, controlled multicenter trial examining whether the use of portable echocardiography and/or point-of-care B-type NP measurements improves the diagnostic and prognostic capabilities of GPs in patients with suspected HF. Using a rigorous, four-arm cluster-randomized design, the comparative performance of four different point-of-care diagnostic algorithms can be evaluated for each participating GP. In addition, long-term follow-up will provide robust data on the prognostic relevance of a HF diagnosis in this patient population, and about the predictive value of echocardiographic findings and B-type NP levels obtained at first presentation. Cross-region comparisons of patient characteristics, and diagnostic and prognostic results will allow the detection of possible differences between a predominantly rural area (Würzburg, Bavaria) and a largely metropolitan area (Duisburg-Essen, North Rhine Westphalia) and thus enable assessment of the generalizability of the study results.

In the Training Study, all GPs underwent the same structured, standardized training program. Training contents were tailored specifically to the needs of non-cardiologists without the previous experience with either technique. The use of quality-controlled training ensured comparable knowledge and skills across all GPs participating in the Screening Study. Training times and success rates indicated the feasibility and effectiveness of the educational modules and suggest that widespread implementation could be possible. Mean training times of ≈ 4 h for ECHO and ≈ 1.5 h for BNP seemed acceptable to trainees and trainers, with only four GPs terminating training early. Thus, the Training Study demonstrated that standardized structured training of limited duration enables GPs to use ECHO and BNP for clinical decision-making in patients with suspected HF.

Limitations

Despite its rigorous design, the Handheld-BNP program has some potential limitations. The first applies to validation of HF diagnosis by GPs. Reference standard misclassification constitutes a problem inherent in most diagnostic accuracy studies that may introduce bias [71, 72]. Criteria for the diagnosis of HF have varied considerably across different clinical trials. In the Handheld-BNP program, we request that diagnosis be based on criteria proposed by the European Society of Cardiology [16, 21, 22], and cardiologists are free to perform all tests considered necessary to achieve a conclusive diagnosis. Nevertheless, attributing causation remains a problem in clinical practice and misdiagnosis might sometimes be difficult to avoid in some patients in the absence of invasive diagnostic facilities, even for cardiologists (for example, in elderly patients with multiple coexisting diseases and risk factors, especially if LV systolic

Fig. 4 Scores achieved by general practitioners on qualification quizzes. I Center I (Würzburg), II Center II (Duisburg-Essen), BNP B-type natriuretic peptide measurement using Triage[®]MeterPlus (Biosite Diagnostics, La Jolla, CA, USA), echocardiography handheld echocardiography using OptiGo[®] (Philips Medizinsysteme Ultraschall, Hamburg, Germany)



function is preserved). On the other hand, using the cardiologists' diagnosis as the reference seems appropriate, because it reflects the usual diagnostic pathway in Germany, where referral to a cardiologist for further evaluation would be the next step if HF is suspected.

Another limitation relates to the ultrasound device used in the Handheld-BNP program. Scan options of the OptiGo® system include B-mode and color Doppler imaging, but no spectral Doppler. We chose this simple tool to allow GPs to rapidly assess cardiac anatomy and systolic function. We were aware that while the findings of LV enlargement and decreased LV systolic function on ECHO, in conjunction with patient clinical assessment and history, would facilitate definite diagnosis of HFrEF, identifying or ruling out HFpEF would be less clear cut, since a validated gold standard for HFpEF diagnosis is missing [16]. If suspected on clinical grounds, a diagnosis of HFpEF needs to be supported by objective measures of cardiac structural and functional alterations, and an elevated NP level [14, 16]. We trained GPs to recognize increased LA size and LV wall thickness in the presence of normal LV systolic function as possible indicators of HFpEF, but advanced Doppler technologies capable of revealing corresponding functional myocardial alterations were unavailable to them. We felt, however, that GP-performed ECHO should not fully substitute for standard echocardiography performed by a trained cardiologist. Thus, we first aimed to explore the added value of simplified ECHO for GPs regarding HF diagnosis, in general. By adding the fourth study arm in the Handheld-BNP program, in which GPs have both ECHO results and B-type NP levels available, we sought to clarify whether combining both tools might help to enhance the diagnosis of HFpEF as well.

Patient selection bias might prove another limitation. This would occur if GPs enrolled subjects with an established history of HF or selected only those they believe to have a high probability of HF. To minimize this bias, only diagnostically naïve patients were eligible and GPs were asked to consecutively approach all eligible patients for study participation.

Bias could also be introduced by uncertainty about the best B-type NP cut-off value in patients with sub-acute symptoms in a community setting. On one hand, only a minority of patients diagnosed with HF in primary care have that diagnosis confirmed by a cardiologist [11, 14, 66, 67], and the positive predictive value of the low cut-off values recommended in the current guidelines for ruling out HF is also low [27, 29, 73, 74]. Conversely, randomized prospective trials evaluating higher BNP cut-off values in primary care, which were largely imputed from studies involving patients with dyspnea in the emergency room, are scarce in the literature [12, 26], and the 'grey zone' between cut-off values of 100 and 400 pg/mL, which have been recommended for 'ruling in' and 'ruling out' HF with reasonable certainty [74], may limit the practical usefulness of B-type

NP as a diagnostic tool. Aiming for prediction of HF, rather than just ruling this out, we decided to advise GPs that HF was unlikely if the B-type NP level was < 100 pg/mL and probable when the B-type NP level was > 400 pg/mL, accepting that the study results would be influenced by this training strategy with some cases of HF being missed. However, these BNP cut-off levels also correspond to those included in the current NICE recommendations for referral of patients with suspected non-acute HF for echocardiographic examination and specialist assessment within 6 weeks of presentation [47].

There might also be a positive GP selection bias, because GPs willing to participate in a training program and undergo systematic quality-control may be particularly interested and motivated, meaning that their diagnostic capabilities might not be representative of all GPs.

Finally, few data are available on the concordance rates between German GPs and cardiologists, and concordance rates from other healthcare systems may not necessarily be applicable in this country [75]. Our estimated concordance rates are, therefore, arbitrary. However, the planned sample size should yield sufficient power even if recruitment goals are not met by every GP.

Conclusions

This is the first prospective, randomized controlled trial investigating the effectiveness of ECHO, BNP or their combination for improving HF diagnosis in a community setting in Germany, and will be the largest diagnostic and long-term prognostic study in primary care worldwide. The findings will inform decisions about more widespread use of these tools in general practice, potentially facilitating more timely HF diagnosis and appropriate management strategies tailored to individual patient risk and needs.

Acknowledgements The authors thank all general practitioners and cardiologists contributing to the Handheld-BNP program. General practitioners receive honoraria for patient enrolment and follow-up (€200 per randomized patient for enrolment visit, completion of case report form and delivery of biomaterials, and €20 per completed of follow-up case report form). Cardiologists receive honoraria for expert patient assessment (€200 per patient for baseline heart failure diagnosis and completion of case report form). The authors also thank patients willing to participate in the Handheld-BNP program. Patients are not compensated for study participation. The authors wish to especially thank Prof. Dr. Goetz Gelbrich (Institute for Clinical Epidemiology and Biometry, University of Würzburg) for statistical advice, Monika Hanke for supervision and quality control of data collection, and Robert Wenzl for expert graphical design of the figures. The authors also thank the clinical research teams at both study centers, and the study and data managers at the Clinical Trial Center Leipzig and at the Comprehensive Heart Failure Center, Würzburg. English language editing support was provided by Nicola Ryan, BSc, independent medical writer, supported by the University of Würzburg. The Handheld-BNP program is funded in the frame of the Competence Network Heart

Failure by the Federal Ministry of Education and Research (BMBF), Germany (BMBF, Grants 01GI0205 and 01GI1202A). Equipment and test kits for BNP point-of-care testing are provided by Biosite Diagnostics GmbH, Gießerallee 31, 47877 Willich (now Alere Technologies GmbH, Löbstedter Str. 103–105 07749 Jena). Ultrasound equipment is provided by Philips Medizinsysteme Ultraschall, Röntgenstr. 24, 22335 Hamburg.

Compliance with ethical standards

Conflict of interest Dr. Störk reported receiving grants from the Federal Ministry for Education and Research, Boehringer, and Santhera; grants and personal fees from Servier, Pfizer, Novartis, Roche Diagnostics, and Thermo Fisher/Brahms; and personal fees from AstraZeneca, Genzyme, Medtronic, and Bayer. Dr. Ertl reported receiving grants from the German Ministry of Education and Research; and grants and personal fees Novartis and Boehringer Ingelheim. Dr. Angermann reported receiving funding for the Handheld-BNP program in the frame of the Competence Network Heart Failure by the Federal Ministry of Education and Research (Grants 01GI0205 and 01GI1202A) and nonfinancial support of the Handheld-BNP program from Biosite Diagnostics (now Alere Technologies), Germany, and Philips Medizinsysteme Ultraschall, Germany. Outside the current project, Dr. Angermann reported grants, personal fees, nonfinancial support, and other from ResMed; grants, personal fees, and other from Novartis; grants and nonfinancial support from Thermo Fisher; grants and personal fees from Boehringer and Vifor; nonfinancial support from the University Hospital Würzburg and the Comprehensive Heart Failure Center Würzburg; and grant support from the German Ministry for Education and Research. All other authors state that they have no conflicts of interest to declare.

References

- Kannel WB (2000) Incidence and epidemiology of heart failure. *Heart Fail Rev* 5:167–173
- Mosterd A, Hoes AW (2007) Clinical epidemiology of heart failure. *Heart* 93:1137–1146
- Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH (2004) Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 25:1614–1619
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics C, Stroke Statistics S (2017) Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 135:e146–e603
- Hobbs FD, Kenkre JE, Roalfe AK, Davis RC, Hare R, Davies MK (2002) Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. *Eur Heart J* 23:1867–1876
- Hobbs FD, Korewicki J, Cleland JG, Eastaugh J, Freemantle N, Investigators I (2005) The diagnosis of heart failure in European primary care: the IMPROVEMENT programme survey of perception and practice. *Eur J Heart Fail* 7:768–779
- Fuat A, Hungin AP, Murphy JJ (2003) Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. *BMJ* 326:196
- Stork S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S (2017) Treatment of chronic heart failure in Germany: a retrospective database study. *Clin Res Cardiol* 106:923–932
- Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE, Hoes AW (2012) High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 55:2154–2162
- Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lambers JW, Hoes AW (2005) Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 26:1887–1894
- Remes J, Miettinen H, Reunanen A, Pyorala K (1991) Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 12:315–321
- Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, Gordon G, Bagg W, Oxenham H, Yandle T, Richards M, Sharpe N (2003) Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol* 42:1793–1800
- McKee PA, Castelli WP, McNamara PM, Kannel WB (1971) The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 285:1441–1446
- Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC (1997) Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 350:1349–1353
- Clarke KW, Gray D, Hampton JR (1994) Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 71:584–587
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 37:2129–2200
- Wierchowicki M, Poprawski K, Nowicka A, Kandziora M, Piatkowska A (2005) Knowledge of primary care physicians, cardiologists from cardiology clinics, internal and cardiology department physicians about chronic heart failure diagnosis and treatment. *Pol Merkuriusz Lekarski* 18:210–215
- Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325:293–302
- Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN (1992) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 327:685–691
- Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC et al (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 327:669–677
- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez

- MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Guidelines ESCcFP (2012) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 33:1787–1847
22. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Guidelines ESCcFP (2008) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 29:2388–2442
 23. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, Breathing Not Properly Multinational Study I (2002) Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 347:161–167
 24. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP (2004) Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 350:647–654
 25. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS (2002) B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from breathing not properly (BNP) Multinational Study. *Circulation* 106:416–422
 26. Burri E, Hochholzer K, Arenja N, Martin-Braschler H, Kaestner L, Gekeler H, Hatzisaak T, Buttiker M, Fraulin A, Potocki M, Breidhardt T, Reichlin T, Socrates T, Twerenbold R, Mueller C (2012) B-type natriuretic peptide in the evaluation and management of dyspnoea in primary care. *J Intern Med* 272:504–513
 27. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, Hardman SM, Dargie HJ, Cowie MR (2005) The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 7:537–541
 28. Mogelvang R, Goetze JP, Schnohr P, Lange P, Sogaard P, Rehfeld JF, Jensen JS (2007) Discriminating between cardiac and pulmonary dysfunction in the general population with dyspnea by plasma pro-B-type natriuretic peptide. *J Am Coll Cardiol* 50:1694–1701
 29. Fuat A, Murphy JJ, Hungin AP, Curry J, Mehrzad AA, Hetherington A, Johnston JL, Smellie WS, Duffy V, Cawley P (2006) The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *Br J Gen Pract* 56:327–333
 30. Collinson PO (2006) The cost effectiveness of B-Type natriuretic peptide measurement in the primary care setting—a UK perspective. *Congest Heart Fail* 12:103–107
 31. Sim V, Hampton D, Phillips C, Lo SN, Vasishtha S, Davies J, Penney M (2003) The use of brain natriuretic peptide as a screening test for left ventricular systolic dysfunction—cost-effectiveness in relation to open access echocardiography. *Fam Pract* 20:570–574
 32. Barrios V, Llisterri JL, Escobar C, Alfaro P, Colado F, Ridocci F, Matali A (2011) Clinical applicability of B-type natriuretic peptide in patients with suspected heart failure in primary care in Spain: the PANAMA study. *Expert Rev Cardiovasc Ther* 9:579–585
 33. Taylor CJ, Roalfe AK, Iles R, Hobbs FR, investigators R, Barton P, Deeks J, McCahon D, Cowie MR, Sutton G, Davis RC, Mant J, McDonagh T, Tait L (2017) Primary care REFerral for Echocardiogram (REFER) in heart failure: a diagnostic accuracy study. *Br J Gen Pract* 67:e94–e102
 34. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW (2011) The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation* 124:2865–2873
 35. Lang NN, Wong CM, Dalzell JR, Jansz S, Leslie SJ, Gardner RS (2014) The ease of use and reproducibility of the alert heart check system: a comparison of patient and healthcare professional measurement of BNP. *Biomark Med* 8:791–796
 36. Monfort A, Da Silva K, Vodovar N, Gayat E, Cohen-Solal A, Manivet P (2015) Clinical evaluation of the heart check system, a new quantitative measurement of fresh capillary BNP. *Biomark Med* 9:1323–1330
 37. Olausson J, Peterson C, Bergstrom M, Larsson A (2015) Evaluation of the meritas(R) BNP test for point-of-care testing. *Clin Lab* 61:727–730
 38. Di Somma S, Zampini G, Vetrone F, Soto-Ruiz KM, Magrini L, Cardelli P, Ronco C, Maisel A, Peacock FW (2014) Opinion paper on utility of point-of-care biomarkers in the emergency department pathways decision making. *Clin Chem Lab Med* 52:1401–1407
 39. Iwaz JA, Maisel AS (2016) Recent advances in point-of-care testing for natriuretic peptides: potential impact on heart failure diagnosis and management. *Expert Rev Mol Diagn* 16:641–650
 40. Pecoraro V, Banfi G, Germagnoli L, Trenti T (2017) A systematic evaluation of immunoassay point-of care-testing to define impact on patients outcomes. *Ann Clin Biochem* 54:420–431
 41. Cals JW, Schols AM, van Weert HC, Stevens F, Zeijen CG, Holtman G, Lucassen WA, Berger MY (2014) Point-of-care testing in family practices: present use and need for tests in the future. *Ned Tijdschr Geneesk* 158:A8210
 42. Tait L, Roalfe AK, Mant J, Cowie MR, Deeks JJ, Iles R, Barton PM, Taylor CJ, Derit M, Hobbs FD (2012) The REFER (REFerral for Echocardiogram) protocol: a prospective validation of a clinical decision rule, NT-proBNP, or their combination, in the diagnosis of heart failure in primary care. Rationale and design. *BMC Cardiovasc Disord* 12:97
 43. Madamanchi C, Alhosaini H, Sumida A, Runge MS (2014) Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. *Int J Cardiol* 176:611–617
 44. Maisel A, Mueller C, Adams K Jr, Anker SD, Aspromonte N, Cleland JG, Cohen-Solal A, Dahlstrom U, DeMaria A, Di Somma S, Filippatos GS, Fonarow GC, Jourdain P, Komajda M, Liu PP, McDonagh T, McDonald K, Mebazaa A, Nieminen MS, Peacock WF, Tubaro M, Valle R, Vanderhyden M, Yancy CW, Zannad F, Braunwald E (2008) State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail* 10:824–839
 45. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R, Luchner A, McDonagh T, Mair J, Nieminen M, Francis G (2003) Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 24:1710–1718
 46. Smith H, Pickering RM, Struthers A, Simpson I, Mant D (2000) Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. *BMJ* 320:906–908
 47. Excellence NIoHaC Chronic heart failure in adults: management. CG108. <https://www.nice.org.uk/guidance/cg108/>

- [chapter/1-Guidance-diagnosing-heart-failure](#). Accessed 29 Sept 2017
48. Seraphim A, Paschou SA, Grapsa J, Nihoyannopoulos P (2016) Pocket-sized echocardiography devices: one stop shop service? *J Cardiovasc Ultrasound* 24:1–6
 49. Prinz C, Voigt JU (2011) Diagnostic accuracy of a hand-held ultrasound scanner in routine patients referred for echocardiography. *J Am Soc Echocardiogr* 24:111–116
 50. Stoica R, Heller EN, Bella JN (2011) Point-of-care screening for left ventricular hypertrophy and concentric geometry using hand-held cardiac ultrasound in hypertensive patients. *Am J Cardiovasc Dis* 1:119–125
 51. Fukuda S, Shimada K, Kawasaki T, Fujimoto H, Maeda K, Inanami H, Yoshida K, Jissho S, Taguchi H, Yoshiyama M, Yoshikawa J (2009) Pocket-sized transthoracic echocardiography device for the measurement of cardiac chamber size and function. *Circ J* 73:1092–1096
 52. Kono Y, Fukuda S, Shimada K, Oe H, Maeda K, Kawasaki T, Fujimoto H, Otsuka K, Kubo T, Jissho S, Taguchi H, Yoshiyama M, Ito H, Yoshikawa J (2011) Pocket-sized echo for evaluation of mitral and tricuspid regurgitation. *JACC Cardiovasc Imaging* 4:921
 53. Bornemann P, Johnson J, Tiglaos M, Moghul A, Swain S, Bornemann G, Lustik M (2015) Assessment of primary care physicians' use of a pocket ultrasound device to measure left ventricular mass in patients with hypertension. *J Am Board Fam Med* 28:706–712
 54. Spencer KT, Anderson AS, Bhargava A, Bales AC, Sorrentino M, Furlong K, Lang RM (2001) Physician-performed point-of-care echocardiography using a laptop platform compared with physical examination in the cardiovascular patient. *J Am Coll Cardiol* 37:2013–2018
 55. Fedson S, Neithardt G, Thomas P, Lickerman A, Radzienda M, DeCara JM, Lang RM, Spencer KT (2003) Unsuspected clinically important findings detected with a small portable ultrasound device in patients admitted to a general medicine service. *J Am Soc Echocardiogr* 16:901–905
 56. Lipczynska M, Szymanski P, Klisiewicz A, Hoffman P (2011) Hand-carried echocardiography in heart failure and heart failure risk population: a community based prospective study. *J Am Soc Echocardiogr* 24:125–131
 57. Evangelista A, Galuppo V, Mendez J, Evangelista L, Arpal L, Rubio C, Vergara M, Liceran M, Lopez F, Sales C, Miralles V, Galinsoga A, Perez J, Arteaga M, Salvador B, Lopez C, Garcia-Dorado D (2016) Hand-held cardiac ultrasound screening performed by family doctors with remote expert support interpretation. *Heart* 102:376–382
 58. Filipiak-Strzecka D, John B, Kasprzak JD, Michalski B, Lipiec P (2013) Pocket-size echocardiograph—a valuable tool for nonexperts or just a portable device for echocardiographers? *Adv Med Sci* 58:67–72
 59. Sicari R, Galderisi M, Voigt JU, Habib G, Zamorano JL, Lancellotti P, Badano LP (2011) The use of pocket-size imaging devices: a position statement of the European Association of Echocardiography. *Eur J Echocardiogr* 12:85–87
 60. Seward JB, Douglas PS, Erbel R, Kerber RE, Kronzon I, Rakowski H, Sahn LD, Sisk EJ, Tajik AJ, Wann S (2002) Hand-carried cardiac ultrasound (HCU) device: recommendations regarding new technology. A report from the Echocardiography Task Force on New Technology of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 15:369–373
 61. Yates J, Royse CF, Royse C, Royse AG, Canty DJ (2016) Focused cardiac ultrasound is feasible in the general practice setting and alters diagnosis and management of cardiac disease. *Echo Res Pract* 3:63–69
 62. Mehrhof F, Löffler M, Gelbrich G, Özcelik C, Posch M, Hense HW, Keil U, Scheffold T, Schunkert H, Angermann C, Ertl G, Jahns R, Pieske B, Wachter R, Edelmann F, Wollert KC, Maisch B, Pankuweit S, Erbel R, Neumann T, Herzog W, Katus H, Müller-Tasch T, Zugck C, Dungen HD, Regitz-Zagrosek V, Lehmkuhl E, Stork S, Siebert U, Wasem J, Neumann A, Gohler A, Anker SD, Kohler F, Mockel M, Osterziel KJ, Dietz R, Rauchhaus M, Competence Network Heart F (2010) A network against failing hearts—introducing the German “Competence Network Heart Failure”. *Int J Cardiol* 145:135–138
 63. Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, Clopton P, Maisel A (2001) A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 37:386–391
 64. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D (1999) Profile for estimating risk of heart failure. *Arch Intern Med* 159:1197–1204
 65. Schocken DD, Arrieta MI, Leaverton PE, Ross EA (1992) Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 20:301–306
 66. Wheelton NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD (1993) Echocardiography in chronic heart failure in the community. *Q J Med* 86:17–23
 67. Hlatky MA, Fleg JL, Hinton PC, Lakatta EG, Marcus FI, Smith TW, Strauss HC (1986) Physician practice in the management of congestive heart failure. *J Am Coll Cardiol* 8:966–970
 68. Ware JE (1996) The SF-36 health survey. In: Spilker B (ed) *Quality of life and pharmacoeconomics in clinical trials*. Raven, Philadelphia, pp 337–346
 69. Lowe B, Grafe K, Zipfel S, Witte S, Loerch B, Herzog W (2004) Diagnosing ICD-10 depressive episodes: superior criterion validity of the Patient Health Questionnaire. *Psychother Psychosom* 73:386–390
 70. Kroenke K, Spitzer RL, Williams JB (2003) The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 41:1284–1292
 71. Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J (2004) Sources of variation and bias in studies of diagnostic accuracy: a systematic review. *Ann Intern Med* 140:189–202
 72. Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PM (2006) Evidence of bias and variation in diagnostic accuracy studies. *CMAJ* 174:469–476
 73. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJ, Mant J, Nice Guideline Development Group for Acute Heart Failure (2015) The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ* 350:h910
 74. Kelder JC, Cramer MJ, Verweij WM, Grobbee DE, Hoes AW (2011) Clinical utility of three B-type natriuretic peptide assays for the initial diagnostic assessment of new slow-onset heart failure. *J Card Fail* 17:729–734
 75. Papanicolaos I, Jha AK (2017) Challenges in international comparison of health care systems. *JAMA* 318:515–516

Affiliations

Caroline Morbach¹ · Thomas Buck^{2,3} · Christian Rost^{4,5} · Sebastian Peter^{4,6} · Stephan Günther^{4,7} · Stefan Störk¹ · Christiane Prettin⁸ · Raimund Erbel² · Georg Ertl¹ · Christiane E. Angermann¹ · On Behalf of the Handheld-BNP Research Network

¹ Comprehensive Heart Failure Center, University and Department of Medicine I, Cardiology, University Hospital Würzburg, Am Schwarzenberg 15, 97078 Würzburg, Germany

² Department of Angiology and Cardiology, University Hospital Essen, Essen, Germany

³ Department of Cardiology, Heart Center Westfalen, Klinikum Westfalen, Dortmund, Germany

⁴ Department of Medicine I, University Hospital Würzburg, Würzburg, Germany

⁵ Cardiological Practice, Ludwigstr. 29, 97070 Würzburg, Germany

⁶ Kitzinger Land Hospital, Kitzingen, Germany

⁷ Barmherzige Brüder Hospital, Regensburg, Germany

⁸ Clinical Trial Center Leipzig, University of Leipzig, Leipzig, Germany