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Accuracy, user-friendliness and usefulness of the Cobas h232 Point-of-Care test for NT-proBNP in primary care: a pilot study

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ABSTRACT (Ned. vertaling)

Doelstellingen NT-proBNP (N-terminal pro-B-type Natriuretic Peptide) is een bewezen nuttige marker om hartfalen uit te sluiten in de huisartsensetting. Deze studie onderzocht de accuraatheid van de Cobas h232 point-of-care (POC) test in de huisartsensetting in vergelijking met een controlemeting in een ziekenhuislabo. Daarnaast werden de gebruiksvriendelijkheid en het nut van de POC-test onderzocht.

Methode Vijf huisartsenpraktijken werden gevraagd volwassen patiënten, verdacht van hartfalen te includeren en NT-proBNP te testen op de Cobas h232. De stalen werden vervolgens geanalyseerd in een ziekenhuislaboratorium met de Cobas e602, gebruikmakend van conventioneel transport en opslag. Overeenkomst tussen de metingen werd geanalyseerd met behulp van Bland-Altman plots en correlatie met de Passing-Bablok lineaire regressie analyse. Gebruiksvriendelijkheid en nut werden beoordeeld door middel van semigestructureerde vragenlijsten.

Resultaten Negentien huisartsen includeerden 94 patiënten. Lineaire regressie analyse tussen beide metingen toonde een helling van 1.05 (95% CI: 1.00-1.11) (R^2=0.97). Het gemiddelde verschil tussen beide metingen bedroeg 15.7% met 95% limits of agreement van -46.0% tot 77.4%. Gebruiksvriendelijkheid en nut kregen mediane scores van 4 of 5 op een 5-punts Likertschaal. Achttien van de 19 huisartsen bevestigden dat de test hun praktijkvoering beïnvloedde. Tijdens de studie is het vertrouwen bij de huisartsen om NT-proBNP te gebruiken significant gestegen van een gemiddelde score van 4.4 (95% CI: 3.2-5.6) tot 7.6 op 10 (95% CI: 7.1-8.2).

Conclusies De Cobas h232 NT-proBNP POC-test bleek een accurate, gebruiksvriendelijke en nuttige test in de huisartsensetting. Bijna alle deelnemende huisartsen waren ervan overtuigd dat deze POC-test voor NT-proBNP hun klinische besluitvorming zou kunnen verbeteren.

ABSTRACT

Aims NT-proBNP (N-terminal pro-B-type Natriuretic Peptide) has been shown to be useful to rule out heart failure in primary care. In this study we examined the accuracy of the Cobas h232 point-of-care (POC) instrument in primary care, compared with an in-hospital measurement. Furthermore, we investigated the user-friendliness and usefulness of the POC device.

Methods Five GP (general practitioner) surgeries were asked to include adult patients, suspected of heart failure, and to test NT-proBNP on the Cobas h232. The samples were subsequently analysed in a central hospital laboratory on the Cobas e602, using conventional transport and storage. Agreement of the paired measurements was analysed using Bland-Altman plots and correlation with Passing-Bablok linear regression analysis. User-friendliness and usefulness were assessed using semi-structured questionnaires.

Results Nineteen GPs included 94 patients. Linear regression analysis between both measurements showed a slope of 1.05 (95% CI: 1.00-1.11) (R^2=0.97). The mean difference between both measurements was 15.7% with 95% limits of agreement of -46.0% to 77.4%. User-friendliness and usefulness had median scores of 4 or 5 on a 5-point Likert scale. Eighteen out of 19 GPs confirmed that the device influenced their clinical practice. During the study, GPs' confidence to use NT-proBNP increased significantly from a mean score of 4.4 (95% CI: 3.2-5.6) to 7.6 out of 10 (95% CI: 7.1-8.2).

Conclusions The Cobas h232 NT-proBNP POC test showed to be an accurate, user-friendly and useful test in primary care. Nearly all participating GPs were convinced that the POC test for NT-proBNP could benefit clinical decision-making.

Introduction

The diagnosis of heart failure in young people is relatively straightforward. However, the diagnosis of heart failure in old age, especially slow-onset heart failure, is particularly difficult as the specificity of typical signs and symptoms of heart failure decreases drastically. (1, 2) The prevalence of heart failure in the general population is 1-2%, but increases progressively with age. (3) The Rotterdam study showed a prevalence of 1% in age group 55–64 years, 3% in age group 65–74 years, 7% in age group 75–84 years, and over 10% in those aged 85 and older. (4)

Echocardiography remains the reference standard to establish the diagnosis and aetiology of heart failure. But in the latest decades, research showed N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) to be an accurate and cost-effective marker in the diagnostic work-up of heart failure, even in older adults. (5-8) NT-proBNP is the inactive fragment of proBNP, which is synthesized in the ventricles in response to myocardial wall stress. (9) Different guidelines recommend the measurement of NT-proBNP in the hospital setting to identify patients eligible for echocardiography, as well as for ruling out heart failure in primary care. (10)

However, the implementation of NT-proBNP in primary care faces several limitations. The routine laboratory test takes time, health insurances do not always reimburse the cost and general practitioners (GPs) are often not familiar with the test. A point-of-care (POC) test offers great potential to implement NT-proBNP in primary care. This test provides a rapid result and the use could help educate GPs. However, to date there is limited data on user-friendliness and usefulness of a POC test for NT-proBNP in primary care.

Therefore we assessed the Cobas h232 (Hoffman-La Roche, Roche Diagnostics, Basel, Switzerland) in 5 GP surgeries in Belgium. The participating GPs were asked to complete a survey about the user-friendliness and usefulness of the device. The Cobas h232 results were compared with results from an in-hospital lab test to assess analytical accuracy.

Methods

Study population

Five GP surgeries, all located in the Northeastern part of Belgium were included in this pilot study. Four of these surgeries were group practices and one was a solo practice. In total 24 general practitioners and 5 medical practice assistants agreed to participate. The study started in August 2016 and lasted 5 months till January 2017. GPs were asked to recruit patients suspected of heart failure. There were no specific exclusion criteria. Consequently patients with comorbidities, such as chronic renal failure, COPD, atrial fibrillation and obesity were not excluded. All patients gave informed consent and the ethical review board of the University Hospitals/KU Leuven, Belgium approved the study (reference mp11149).

Analytical methods

The Cobas h232 is designed for POC testing of four different cardiac biomarkers, including Troponin T, NT-proBNP, CK-MB and myoglobin, and D-dimer. The measuring range for NT-proBNP is 60 to 9000 pg/mL. A test is performed on 150µL heparinized venous blood, using a Roche Cardiac proBNP test strip (Hoffman-La Roche, Roche Diagnostics, Basel, Switzerland) and takes 12 minutes. (11) Previously, the Cobas h232 showed a sensitivity of 82% and a specificity of 99% in the range <60pg/mL, a sensitivity of 97% and a specificity of 83% between 60pg/ml

and 3000pg/mL and a sensitivity of 82% and a specificity of 99% in the range >3000pg/mL. (12) Two age-dependent cut-offs, as recommended by the Belgian Health Care Knowledge Centre (KCE), were used. (13) The cut-off value of 125 pg/mL was used for patients < 75 years and 450 pg/mL for patients aged 75 years and older. The US Food and Drug Administration (FDA) also recommended these separate cut-offs for the proBNP Elecsys assay (Hoffman-La Roche, Roche Diagnostics, Basel, Switzerland). (14)

After the POC test, blood samples were stored at room temperature and analyzed within maximum 8 hours, using the proBNP II Elecsys Cobas e100 assay (Hoffman-La Roche, Roche Diagnostics, Basel, Switzerland) at the Laboratory of Clinical Biochemistry of Ziekenhuis Oost-Limburg (ZOL) in Genk, Belgium. This assay runs on the Cobas e602, a modular analytics instrument of the core unit Cobas 8000.

Legal framework Point-Of-Care Testing

In Belgium, evidence-based use of POC testing outside the hospital is subject to a proposition on legal regulations. Organizing training, quality management, working according to a protocol and registering the POC test results in the electronic patient record are fundamental elements mentioned in this proposal. This allows the physician who uses the POC test outside the hospital to expect reliable, accurate and reproducible results. This pilot study was designed in adherence with this proposal.

Educational training. Before the actual start of the study the GPs were invited for a first training. This training consisted of a theoretical background and an introduction on the use of the Cobas h232 device by the POC coordinator. A second training was organized, at the moment the Cobas h232 was installed in the primary care centers.

During this training, lead by the POC coordinator, every GP and practice assistant had to perform a dummy test and a quality control. Additional training was offered in case the users experienced problems or were insecure about the use.

Quality control management. A POC coordinator, employed in the Laboratory of Clinical Biochemistry of Ziekenhuis Oost-Limburg (ZOL) in Genk, Belgium, was appointed. The POC coordinator was responsible for the education of the users and the supervision of the timely execution of the quality controls. Quality control of the Cobas h232 device was performed on three levels. First, the device automatically executed an internal quality control when switched on. Second, an instrumental quality control (IQC) had to be executed every week by the users. Third, a liquid control, had to be executed by the users every week. The POC coordinator prepared the control samples in volumes of 150µL in Eppendorf tubes. The tubes were stored in the freezer and defrosted by the users when a liquid control was necessary.

Protocol. Heparin-filled tubes were used. The users identified themselves by scanning their personalized barcode, using the build-in scanner. The patient was identified by scanning the barcode on the eID (electronic identity card) of the patient. Alternatively, another barcode was scanned with a number that had to be linked to the patient afterwards by the POC coordinator. After identification a test strip was placed in the device. A sample of 150µL of blood was taken from the tube using a specifically marked pipette from Roche. The result displayed as <60pg/mL, >9000pg/mL, or a number in between. Meanwhile, the user informed the central laboratory and a taxi service was sent to collect the blood tube with the remaining blood. The transport was arranged in a time window of maximum 8 hours.

Connectivity. The connection between the different Cobas h232 devices and the IT middleware Cobas IT1000 in the central laboratory was established by a secured VPN connection. Cobas IT1000 transmitted the incoming results to the laboratory informatics system (LIS) where the national insurance number was linked to the patient information. Afterwards these data were sent to the hospital informatics system (HIS). The results of the POC test were integrated in the electronic patient record of the GP, using secured communication software.

Outcome measures

The user-friendliness and usefulness were assessed through a semi-structured questionnaire (see Appendix 1). Both the GPs and the medical practice assistants were asked to reply on questions about user-friendliness. Only GPs were questioned about usefulness. For all questions a 5-point Likert scale was used.

GPs completed a questionnaire before the study started and estimated their level of confidence in using NT-proBNP on a 10-point scale. This question was asked again in the final questionnaire.

Statistical analysis

Continuous data are presented as means and standard deviations and compared between groups with the Student's *t* test. Categorical data are presented as numbers and percentages and compared between groups using the Chi^2 test. The correlation between the Cobas h232 test results and the Cobas e602 results was analyzed and plotted using linear regression according to the Passing-Bablok regression method. The difference and agreement between the POC test and the reference test was analyzed according to the Bland–Altman method. User-friendliness and usefulness were examined by reporting the scores on the 5-point Likert scales.

The data analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA), Excel for Mac 2011 (Microsoft Corporation, Redmond, WA, USA) and XLStat version 19.02 (Addinsoft, Paris, France).

Results

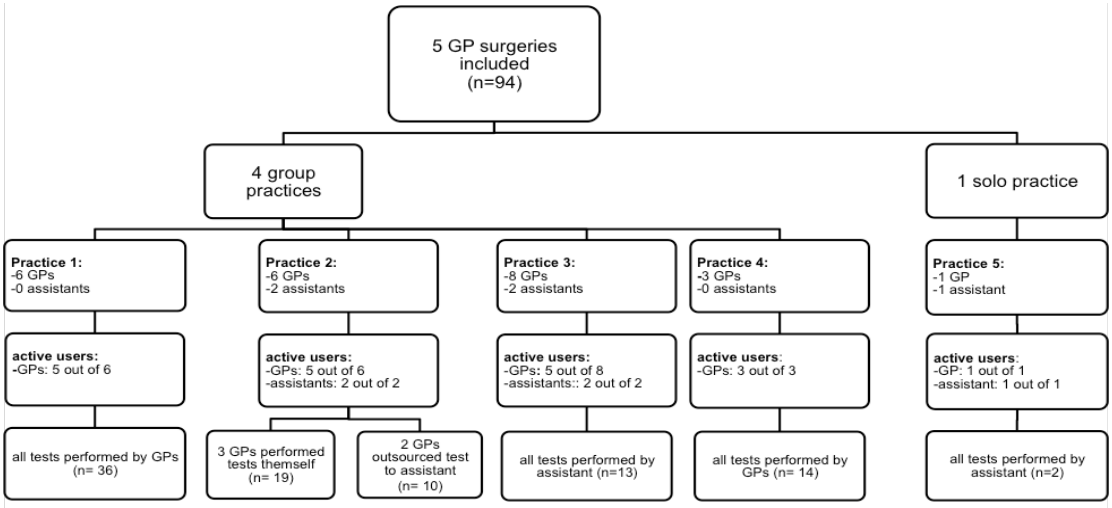
In total, 24 GPs and 5 practice assistants were invited to participate. Twenty GPs and all assistants attended the training and finally 19 GPs and 5 assistants participated in the study. Figure 1 shows the distribution of the users across the different practices. Characteristics of the users are described in Table 1.

Table 1. User characteristics (n = 29)

	GPs	Assistants
invited to participate, n	**24**	**5**
Trained to use Cobas h232, n (%)	***20 (83.3 %)***	***5 (100%)***
• **actively participated, n (%)**	19 (95.0%)	5 (100%)
○ used the device, n (%)	11 (57.9%)	5 (100%)
○ responded to the questionnaire	19 (100%)	4 (80%)
• **self-reported first contact with NT-proBNP, n**	**19**	**NA**
○ during basic training in medicine, n (%)	9 (47.3%)	
○ during an in service-training, n (%)	6 (31.6%)	
○ informed by a younger colleague, e.g. a trainee, n (%)	3 (15.8%)	
○ during this pilot study, n (%)	1 (5.3%)	
• **self-reported knowledge about diagnostic value of NT-proBNP, n**	**17**	**NA**
○ sufficient knowledge, n (%)	4 (23.5%)	
○ insufficient knowledge, n (%)	12 (70.6%)	
○ no knowledge, n (%)	1 (5.9%)	
• **used NT-proBNP before, n (%)**	12 (60.0%)	
• **primary indication for NT-proBNP, n**	**19**	**NA**
○ diagnostic uncertainty, n (%)	15 (78.9%)	
○ case-finding in patients with CV risk, n (%)	3 (15.8%)	
○ follow-up of heart failure, n (%)	1 (5.3%)	
○ prognosis of heart failure, n (%)	0 (0%)	
• **reported drawbacks to use NT-proBNP (multiple answers possible), n**	**19**	**NA**
○ cost for the patient	15 (78.9%)	
○ insufficient knowledge	7 (36.8%)	

GP, general practitioner; CV, cardiovascular; NA, not applicable.

Figure 1. Distribution of users across different practices



GP, general practitioner

In total, 94 patients were included with a mean age of 72.0±11.1 years (range: 40 - 91 years). The proportion of patients aged 75 and older was 50%. The characteristics of the patients are described in Table 2.

Table 2. Patient characteristics (n = 94)

Characteristics of patient population	Total population	Negative test *(n = 47)*	Positive test *(n = 47)*	*P*-value
Age mean ± SD	72.0 ± 11.1	70.0 ±12.9	74.1 ± 8.6	0.002°
Sex (woman), n (%)	53 (56.4%)	29 (61.7%)	24 (51%)	0.30*
SYMPTOMS				
Dyspnea, n (%)	72 (76.6%)	34 (72.3%)	38 (80.8%)	0.33*
Fatigue, n (%)	67 (71.3%)	32 (68.1%)	35 (74.5%)	0.49*
Edema, n (%)	40 (42.6%)	22 (46.8%)	18 (38.3%)	0.40*
MEDICATION				
Diuretics, n (%)	38 (40.4%)	14 (29.8%)	24 (51.1%)	0.036*
ACE-blockers, n (%)	35 (37.2%)	11 (23.4%)	24 (51.1%)	0.006*
Ca-blockers, n (%)	21 (22.3%)	14 (29.8%)	7 (14.9%)	0.08*
Beta-blocker, n (%)	36 (38.3%)	14 (29.8%)	22 (46.8%)	0.09*
REFERRALS §				
Cardiology + echocardiography, n (%)	28 (34.1%)	6 (14.6%)	22 (53.7%)	<0.001*
ED n (%)	4 (4.9%)	0 (0.0%)	4 (9.8%)	0.040*

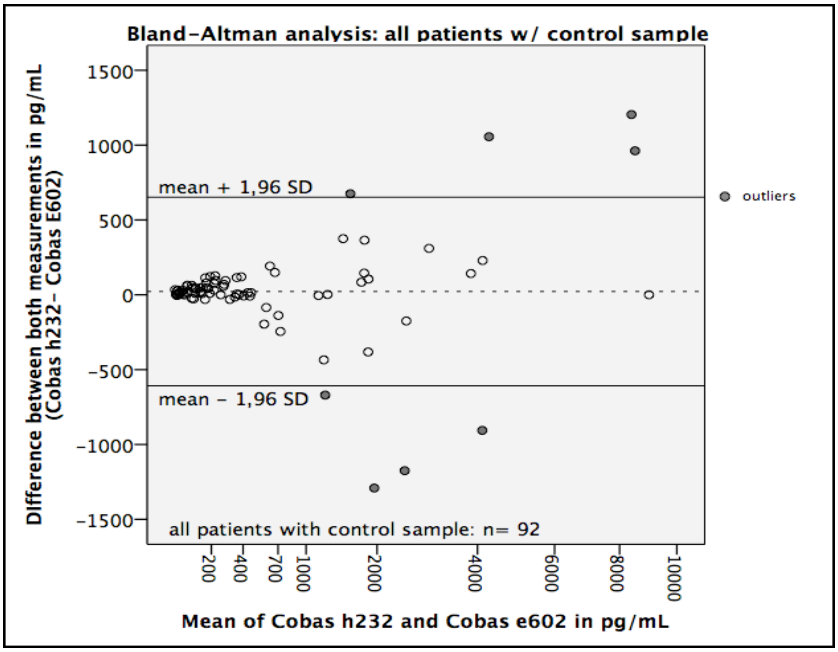
Negative or positive test stands for the result of the Cobas h232 POC test result, taking into account the age-dependent cut-off value. SD, standard deviation; ACE-blockers, angiotensin converting enzyme blockers; Ca-blockers, calcium channel blockers. ED, emergency department

§ 'referrals' was based on 82 registrations, 41 in both groups

*°Student's-t-test; *χ2 test*

Ninety-two out of 94 blood samples were reanalyzed on the Cobas e602. In two cases, the GP forgot to send the blood sample to the central laboratory. In Figure 2A, a Bland–Altman-plot shows the agreement in 92 patients between the NT-proBNP test results on the Cobas h232 and the Cobas e602.

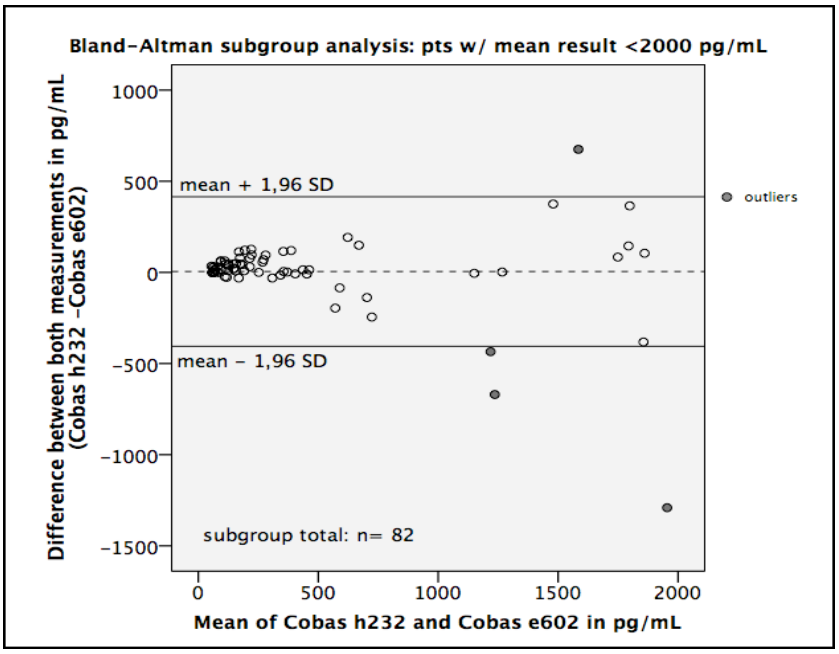
Figure 2A. Bland-Altman plot: comparison between the difference and the mean of both measurements



There was a mean difference of 22.1 pg/mL with 95% limits of agreement from −607.7 to 651.9 pg/mL. Relatively, the mean difference was 15.7% with 95% limits of agreement of -46.0% to 77.4%

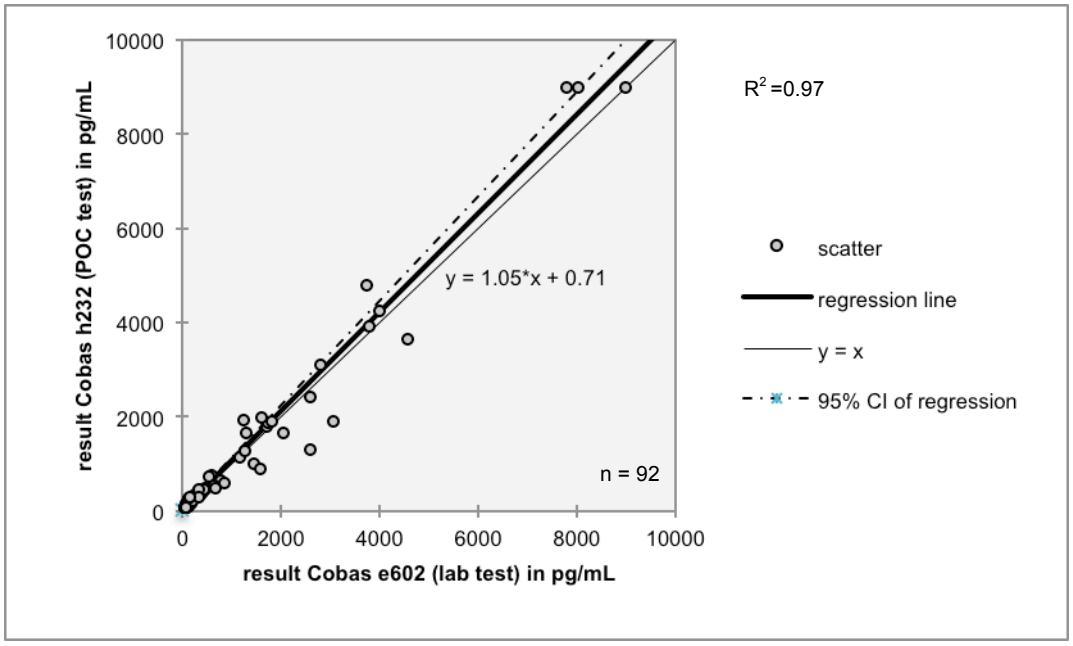
For measurements with a mean value less than 2000 pg/mL, little spread was observed, especially in the range close to the cut-off, which is shown in Figure 2B. A mean difference of 4.7 pg/mL with 95% limits of agreement from -405.5 to 414.9 pg/mL was found.

Figure 2B. Bland-Altman plot of subgroup with mean result <2000 pg/mL



Passing-Bablok linear regression analysis showed a slope of 1.05 (95% CI: 1.00 to 1.11) between both measurements (y=1.05x+0.71) with an R^2 of 0.97, as shown in Figure 3.

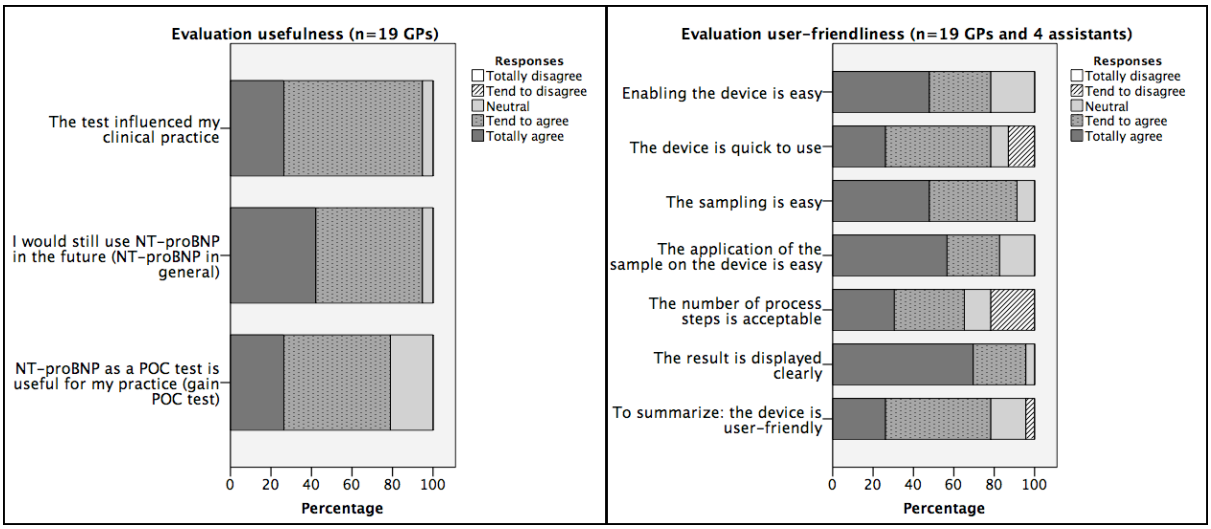
Figure 3. Passing-Bablok linear regression analysis comparing results on Cobas h232 and Cobas e602



The results of the questionnaire about usefulness showed median scores of 4 or 5 out of 5 for all items evaluated. Eighteen out of 19 responding GPs said that the device influenced their clinical practice. Also 18 out of 19 GPs would still use NT-proBNP in the future, of which 15 (78.9%) think it is useful as a POC test.

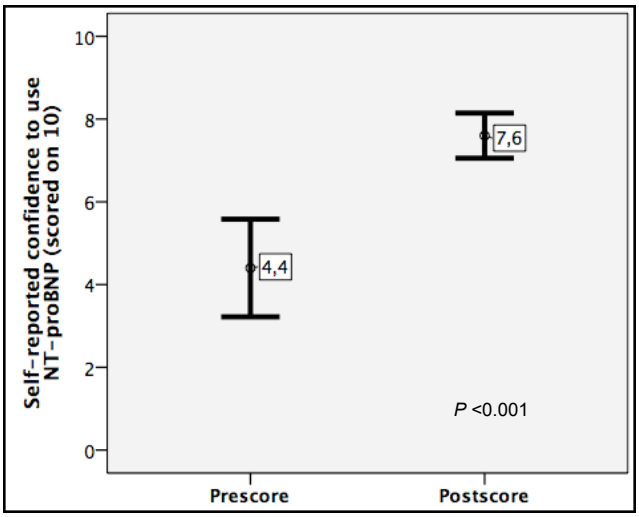
Almost all items about user-friendliness were evaluated as positive by at least 75% of the users, based on 23 responses, of which 4 responses of medical practice assistants. Only the number of process steps had a lower score, with only 65.2% of positive answers. The evaluation of the different questions is described in Figure 4.

Figure 4. Distribution of different responses on questionnaire about usefulness and user-friendliness



Before the study started, the GPs' confidence to use NT-proBNP had a mean score of 4.4 out of 10 (95% CI: 3.2-5.6), based on the responses of 15 GPs. Re-evaluation by these GPs after the study showed an estimated confidence of 7.6 (95% CI: 7.1-8.2) (*P* <0.001). The self-reported confidence to use NT-proBNP, before and after the study is described in Figure 5.

Figure 5. Self-reported confidence to use NT-proBNP before and after the study



Discussion

The Cobas h232 NT-proBNP POC test showed to be an accurate test in a primary care setting. Although, a slight overestimation by the Cobas h232 compared with the reference test needs further investigation. The users rated the device satisfactorily in terms of usefulness and user-friendliness. Almost all GPs confirmed to use NT-proBNP in the future and a large majority believed in the use of a POC test for NT-proBNP.

Accuracy

To our knowledge there is only one published study that evaluated the accuracy of the Cobas h232 NT-proBNP POC test in a primary care setting. Although comparable results were found, a discrepancy between primary care and hospital NT-proBNP results was shown (bias range: 14.3 to 23.7%). There was no significant bias when Cobas h232 was only used in a hospital setting (bias range: - 4.9 to 7.0%).(15) SKUP (Scandinavian evaluation of laboratory equipment for primary health care) found similar results, with the Cobas h232 results in primary care being

14% to 24% higher than the comparison method. (11) These results are in line with our findings as we found a 15.7% higher result of the Cobas h232 in comparison with the control test. In the SKUP report this bias was called unexpected because the Cobas h232 results from the hospital laboratory were in agreement with the comparison method. A possible explanation for the bias might be the delay between both analyses, although NT-proBNP is assumed to be stable during at least 8 hours. This bias might also be due to the difference between analysis of NT-proBNP on whole blood, in case of the Cobas h232 and on centrifuged blood, in case of the Cobas e602. Another explanation could be the correctness of the sampling, for instance the volume of blood applied on the test strip, but for this explanation equal bias is expected in both directions. Further research is needed to figure out the cause of this bias. However, an overestimation is safer than an underestimation for a test used in a primary care setting that focuses on ruling out heart failure. Together with less bias in the exclusion cut-off range, this device performed adequately.

User-friendliness and usefulness

Concerning user-friendliness and usefulness the Cobas h232 scored good to excellent. The score for user-friendliness is roughly comparable to the result in the SKUP report, which evaluated the device in 3 primary care surgeries. (11, 15) According to our results, progress can be made in the amount of procedural steps. Major comment of the GPs was the time-consuming aspect of the different steps and the execution of the different quality controls. Together with the reported increase in confidence in using NT-proBNP as a diagnostic test, the test was evaluated as user-friendly and useful to assist in cases with diagnostic uncertainty.

Use of NT-proBNP as a POC test

It can be questioned whether NT-proBNP should be available as a POC test. For comparison, there is much more evidence about the value of C-reactive protein as a POC test. (16-18) However, the majority of the GPs in our study considered the NT-proBNP POC test to be useful for their practice. This corresponds to an international study that questioned 2770 primary care doctors. NT-proBNP was desired as a POC test by 59% of the GPs.(19) A critical consideration is the immediacy of the result in case of slow-onset heart failure. For chronic illnesses Hardy et al. mentioned it might not be advantageous to know the result with the person sitting across from you. (20) Although, for example HbA1c POC testing described an improved patient-doctor relationship, improved levels of patient satisfaction and an increased sense of responsibility. (21, 22)

Maybe the future of NT-proBNP POC testing is situated in a panel of cardiovascular POC tests, which can be used for patients with dyspnea or chest pain. Tomonaga et al. emphasized the clinical value of 3-in-1 POC testing including cardiac Troponin T, NT-proBNP and D-dimer in diagnosing and risk stratification of patients with potentially cardiovascular symptoms in primary care. Furthermore, diagnoses were more accurate in the POCT group. (23)

Implementation in daily practice and future research

All GPs mentioned the cost as the major drawback in using NT-proBNP, although it is shown to be a cost-effective test. (7, 24, 25) The second drawback was the effect on the workflow and the time-consuming aspect. Most of the GPs believed that the best way to implement the POC test in their practice is to outsource the testing to an assistant as was done by different practices in our study. The same issue about

outsourcing has been described for CRP POC testing. (26) However, whether the GP or the assistant should perform the test remains a point of discussion. (20) Moreover, according to the American Association of Clinical Chemistry (AACC) a main issue of POC testing is non-laboratory personnel performing the test, as applies for both GP and assistant. Therefore, the AACC regulatory requirements of POC testing focus on two areas: training and competency of the personnel performing the test and verification of strict adherence to the test procedure. (27)

Besides the controversy about the test performer and his training, it should be emphasized that there are more regulatory requirements needed in a legal framework. It should also focus on setting up a quality management system, working according to a protocol and registering the POC test results in the electronic patient record. From a European perspective Larsson et al. emphasized that this framework is essential for the implementation of POC testing. (28)

Main issues on the research agenda are the impact of NT-proBNP POC testing on diagnosis and monitoring of heart failure in primary care and the continued implementation of a legal framework for POC testing on a much larger scale. Regarding connectivity, a reliable and possibly cloud-based IT-solution compatible with all different electronic health record programs, should be available. Concerning quality management, training and coordination, the role of central laboratories and their POC coordinators should be further investigated.

Strengths and limitations

The major strength of this study was the integration of all elements of a legal framework for POC testing in a realistic study protocol. The protocol was designed to

fully implement NT-proBNP POC testing in primary care. It included a realistic sampling and testing setting, a POC coordinator, training of the users, providing connectivity and conventional transport and storage. The relatively small numbers of participating GPs and tests performed could be seen as a limitation of the current study. Another limitation was possibly the lack of reminders for the GPs to use the device. This might also be one of the tasks of a future POC coordinator.

Conclusion

The Cobas h232 NT-proBNP POC test showed to be an accurate test in a primary care setting. An overestimation by the Cobas h232 needs further investigation. The device was deemed useful and user-friendly. Almost all GPs confirmed to use NT-proBNP in the future and a large majority saw benefit in the use of a POC test for NT-proBNP.

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REFERENCES

1. Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, et al. The diagnosis of heart failure in primary care: value of symptoms and signs. European journal of heart failure. 2004;6(6):795-800, 21-2.
2. Olofsson M, Edebro D, Boman K. Are elderly patients with suspected HF misdiagnosed? A primary health care center study. Cardiology. 2007;107(4):226-32.
3. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137-46.
4. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. European Heart Journal. 1999;20(6):447-55.
5. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, et al. 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. European journal of heart failure. 2005;7(4):537-41.
6. Fuat A, Murphy JJ, Hungin AP, Curry J, Mehrzad AA, Hetherington A, et al. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. The British journal of general practice : the journal of the Royal College of General Practitioners. 2006;56(526):327-33.
7. Goode KM, Clark AL, Cleland JG. Ruling out heart failure in primary-care: the cost-benefit of pre-screening using NT-proBNP and QRS width. International journal of cardiology. 2008;130(3):426-37.
8. Siebert U, Januzzi JL, Jr., Beinfeld MT, Cameron R, Gazelle GS. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. The American journal of cardiology. 2006;98(6):800-5.
9. Weber M, Hamm C. Role of B‐type natriuretic peptide (BNP) and NT‐proBNP in clinical routine. Heart. 2006;92(6):843-9.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failureThe 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. European Heart Journal. 2016;37(27):2129-200.
11. Jacobsen CE. Report from the evaluation SKUP/2013/97 of NT-proBNP on Cobas h 232. Norway: Scandinavian evaluation of laboratory equipment for primary health care (SKUP), 2013.
12. Alehagen U, Janzon M. A clinician's experience of using the Cardiac Reader NT-proBNP point-of-care assay in a clinical setting. European journal of heart failure. 2008;10(3):260-6.
13. Van Brabandt H, Van Den Steen D, Cleemput I. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. Federaal Kenniscentrum voor de Gezondheidszorg (KCE), 2005.
14. FDA approval K022516- Elecsys ProBNP.: FDA; 2002. Available from: https://http://www.accessdata.fda.gov/cdrh_docs/pdf2/k022516.pdf.

15. Gils C, Ramanathan R, Breindahl T, Brokner M, Christiansen AL, Eng O, et al. NT-proBNP on Cobas h 232 in point-of-care testing: Performance in the primary health care versus in the hospital laboratory. Scandinavian journal of clinical and laboratory investigation. 2015;75(7):602-9.
16. Point-of-care CRP testing in the diagnosis of pneumonia in adults. Drug and Therapeutics Bulletin. 2016;54(10):117.
17. NICE. Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults. Clinical guideline 191. 2014.
18. Verbakel JY, Lemiengre MB, De Burghgraeve T, De Sutter A, Aertgeerts B, Shinkins B, et al. Should all acutely ill children in primary care be tested with point-of-care CRP: a cluster randomised trial. BMC Medicine. 2016;14:131.
19. Howick J, Cals JWL, Jones C, Price CP, Plüddemann A, Heneghan C, et al. Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA. BMJ open. 2014;4(8).
20. Hardy V, Thompson M, Alto W, Keppel GA, Hornecker J, Linares A, et al. Exploring the barriers and facilitators to use of point of care tests in family medicine clinics in the United States. BMC family practice. 2016;17:149.
21. Shephard MD. Cultural and clinical effectiveness of the 'QAAMS' point-of-care testing model for diabetes management in Australian aboriginal medical services. The Clinical biochemist Reviews. 2006;27(3):161-70.
22. Shephard MD, Mazzachi BC, Shephard AK, McLaughlin KJ, Denner B, Barnes G. The impact of point of care testing on diabetes services along Victoria's Mallee Track: results of a community-based diabetes risk assessment and management program. Rural and remote health. 2005;5(3):371.
23. Tomonaga Y, Gutzwiller F, Lüscher TF, Riesen WF, Hug M, Diemand A, et al. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. BMC family practice. 2011;12:12-.
24. Hellinckx H. Cost-effectiveness and budget impact analysis of natriuretic peptide testing in the diagnosis of chronic heart failure: BeMedTech (former Unamec); 2012. Available from: http://www.bemedtech.be/wp-content/uploads/2012/10/Dossier-NT-pro-B-NP.pdf.
25. Collinson PO. The Cost Effectiveness of B-Type Natriuretic Peptide Measurement in the Primary Care Setting—A UK Perspective. Congestive Heart Failure. 2006;12(2):103-7.
26. Huddy JR, Ni MZ, Barlow J, Majeed A. Point-of-care C reactive protein for the diagnosis of lower respiratory tract infection in NHS primary care: a qualitative study of barriers and facilitators to adoption. 2016;6(3):e009959.
27. Camacho-Ryan O, R B. Monitoring Point-of-Care Testing Compliance.: American Association for Clinical Chemistry; 2016. Available from: https://http://www.aacc.org/publications/cln/articles/2016/february/monitoring-point-of-care-testing-compliance.
28. Larsson A, Greig-Pylypczuk R, Huisman A. The state of point-of-care testing: a european perspective. Upsala Journal of Medical Sciences. 2015;120(1):1-10.

APPENDICES

Appendix 1: Questionnaire (English translation)

Appendix 2: Protocol submitted to the Committee on Medical Ethics (original, dutch version)

Appendix 3: Approval of Committee on Medical Ethics

Appendix 1: Questionnaire (English translation)

Questionnaire NT-proBNP study

Section 1/17

Dear Colleague,
In the past months, you've had the opportunity to work with the Cobas h232, a point-of-care test for NT-proBNP, designed by Roche. Many thanks for your cooperation with the implementation of this POC test in your practice.

A second part of the study consists of the survey, which is presented to you now. By this survey, we want to investigate to what extent the test lived up to your expectations. Particularly, we are interested in the experienced user-friendliness and usefulness for your practice.

Actually, this survey assesses all elements of the legal framework of POC testing. This concerns the role of the point-of-care coordinator, organizing training for users of the test, attention to quality control, validation by means of a control test and connectivity between practice and laboratory. During this study, all of these factors were examined to see what works and what could be improved.

Thanks in advance for your cooperation
Dr. Chiel Hex

promotor Dr. Bert Vaes
co-promoter Dr. Jan Verbakel
Dr. Miek Smeets, Prof Dr. Frank Buntinx

* mandatory



Section 2/17: **Identification**
I would like to ask you to identify yourself in order to know whether you already answered the questionnaire. So I don't have to bother you with reminder emails.

I assure you that your data will be processed anonymously. Neither the researchers of the KU Leuven nor the employees of Roche or ZOL will be able to link the answers to your identity. They have only access to the results after encoding of the collected data.

Question 1: What is your name? *

_____

Section 3/17: **Participation kick-off / training**
During this study several training moments were organized.
In the run-up to the study, you got invited to participate in one of the kick-offevents in ZOL Genk or the Diagnosecentrum in Lommel. Afterwards we also came to your practice for a hands-on training. Can you indicate below what you think of this training?

Question 2: Was everything present during the trainings for you to use the device correctly? *
Mark,only one per row.

	Totally disagree	*Tend to disagree*	*Neutral*	*Tend to agree*	*Totally agree*	*Didn't attend a training*
The theoretical background of the test was clear so I could interpret the test result	□	□	□	□	□	□
The explanation of the practical use was sufficient to be able to use the device	□	□	□	□	□	□

Question 3: What could have been done better during the training?

_____

Section 4/17: **Active participation in the study?**
At the start of the study, we hoped that all GPs would participate actively in the study. It may of course be, that during the period of the study, you still not managed to carry out tests, for any reason whatsoever. For the evaluation of this questionnaire, it is useful to know whether you have done some tests.

Question 4: Did you perform at least one test (as an individual physician) or did your assistant/ nurse carry out at least one test? *
Mark only one per row.

□ Yes *Go to question 5.*
□ No *Go to question 6.*

Section 5/17: **NT-proBNP: sense of competence**
Prior to the study, we asked you to indicate how skilled you felt to interpret a NT-proBNP value. We now repeat the question to see if this has changed after the study.

Question 5: How skilled to judge the NT-proBNP value do you feel? *

	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	
Totally unskilled	□	□	□	□	□	□	□	□	□	□	***Totally skilled***

Go to question 9 (non-users: only do section 6 to 8, users continue at section 9)

Section 6/17: **Non-users**
We feel sorry that you could not or wanted to use the device.
We would love to aske some questions about this.

Question 6: What is the main reason why you are not using the test? *

□ The test procedure is too complicated *Go to question 8.*
□ The test procedure takes too much time *Go to question 8.*
□ I did not have interest in this NT-proBNP study *Go to question 8.*
□ I don't think of the availability of the test *Go to question 7.*
□ Otherwise *Go to question 8.*

Section 7/17 (non-users):
As the main reason for not using the test you answered that you do not think about it.
We would like to find out the specific reason for this.

Question 7: Why do you not think of the test? You may select more than one answer. *
Check all the relevant options.

- ☐ I don't think of/ have patients who are eligible for this test
- ☐ My practice is too busy
- ☐ It is not in my routine
- ☐ I don't see the value of the test
- ☐ Otherwise…

Section 8/17 (non-users): **Room for improvement? (Section non-users)**
We love to hear your ideas on possible improvements.

Question 8: What should be done for you to use this device? *

_____

Non-users: go to end of survey

Section 9/17 (users): **Active users**
We are happy to hear that you did use the test.

You will now get a few questions about how you evaluate the use of the device. It is important to know whether you used the device at least once yourself or only outsourced this to your practice nurse or assistant?

Question 9: Have you used the device at least once yourself or did you always let this been carried out by your assistant/ nurse?
Mark only one.

- ☐ At least once used the device itself
- ☐ Always carried out by nurse / assistant

Section 10/17 (users): **User-friendliness (usability)**
In this section, we are particularly interested in how user-friendly the device is for you.

Question 10: What do you think of the following aspects of user-friendliness? *
Mark only one per row.

	Totally disagree	*Tend to disagree*	*Neutral*	*Tend to agree*	*Totally agree*
Enabling the device is easy	☐	☐	☐	☐	☐
The device is quick to use	☐	☐	☐	☐	☐
The sampling is simple	☐	☐	☐	☐	☐
The application of the sample on the device is easy	☐	☐	☐	☐	☐
The number of process steps is acceptable	☐	☐	☐	☐	☐

The result is displayed clearly	□	□	□	□	□
To summarize: the device is user-friendly	□	□	□	□	□

Question 11: Below you can write down your comments regarding the procedure

_____

Section 11/17 (users): **Usefulness for practice**
In this section, we are particularly interested in how useful the device for you.

Question 12: What do you think of the following aspects of benefit to your practice? *
Mark only one per row.

	Totally disagree	*Tend to disagree*	*Neutral*	*Tend to agree*	*Totally agree*
This test influenced my clinical practice	□	□	□	□	□
I would still use NT-proBNP in the future? (NT-proBNP in general)	□	□	□	□	□
NT-proBNP as a POC test is useful for my practice (gain POC test)	□	□	□	□	□

Section 12/17 (users): **Quality control**
In this section, we are particularly interested in the application of different quality controls and punctuality of the sample collection.

Question 13: What is your opinion about the quality controls and sample collection? *
Mark only one per row.

	Totally disagree	*Tend to disagree*	*Neutral*	*Tend to agree*	*Totally agree*	*Didn't do QC*
Quality control was done at least once a week	□	□	□	□	□	□
Performing the liquid quality control (LQC) was easy	□	□	□	□	□	□
Performing the instrumental quality control (IQC) was easy	□	□	□	□	□	□
The lab was always notified in time to pick up a blood sample	□	□	□	□	□	□
The sample collection by the taxi service was always done in time	□	□	□	□	□	□

Section 13/17: **Role POC coordinator**
During the study, you could always contact our POC coodinator Cindy Verwichte, of the lab of ZOL Genk. We would like to gauge your experiences.

Question 14: What is your opinion about the role of the POC coordinator? *
Mark only one per row.

	Totally disagree	*Tend to disagree*	*Neutral*	*Tend to agree*	*Totally agree*
The POC coordinator was always reachable	□	□	□	□	□
The POC coordinator could answer your questions	□	□	□	□	□
The POC coordinator could offer a solution to you problems	□	□	□	□	□

Section 14/17: **Connectivity**
One of the important pillars of the legal framework of POC testing is the connectivity between the device in practice and the laboratory. The connection, in two directions is very important. In essence, we especially ask whether the result of the rapid test is sent to the laboratory and whether the result of the control sample enters your patient records. Again we would like to hear your experiences.

Question 15: What is your opinion about connectivity? *
Mark only one per row.

	Totally disagree	*Tend to disagree*	*Neutral*	*Tend to agree*	*Totally agree*
The connection was stable (the green light was always burning)	□	□	□	□	□
The results of the control sample was always sent to the patient record	□	□	□	□	□

Section 15/17: **Indication of the POC test**

Question 16: Can you rank the following indications in terms of importance?
Mark only one per column.

In terms of importance	*first indication*	*second indication*	*third indication*	*fourth indication*	*fifth indication*
Diagnostic uncertainty	□	□	□	□	□
Case-finding in patients with cardiovascular risk	□	□	□	□	□
Prognosis in known heart failure	□	□	□	□	□
Follow-up in treatment of heart failure	□	□	□	□	□
Another indication; you can specify this in a moment	□	□	□	□	□

Question 17: **What are other indications?**

_____

Section 16/17: **Some open questions to conclude**
In this section, we want to give you the chance to freely express your opinion about the device. We assess strengths and weaknesses. Of course we realize that answering open questions still requires some effort, but your opinion is very much appreciated.

Question 18: What do you think are the strengths of this device? *

_____

Question 19: What do you think are the shortcomings of this device? *

_____

Question 20: Which lab test would you use as a POC test in your practice?

_____

Section 17/17: **Thank you for your participation**

The team from the University of Leuven, ZOL Genk, Roche and I thank you for your cooperation. Do not forget to send.

Appendix 2: Protocol submitted to the Committee on Medical Ethics

Titel van de studie:

NT-proBNP Point-Of-Care Testing in de huisartsensetting: een pilootstudie

(reg nr. mp11149)

Student(en): Chiel Hex
Promotor: Bert Vaes (bert.vaes@med.kuleuven.be - u0087897 - Acad. Centr. voor Huisartsgeneeskunde)
Hoofdonderzoeker: Chiel Hex
Faculteit: Geneeskunde
Opleiding: Master in de huisartsgeneeskunde (Leuven e.a.)

Het onderzoek is: multicentrisch
De opdrachtgever is: academisch (universiteit,...)
Het onderzoek is: Het onderzoek is (gedeeltelijk) prospectief.
Het onderzoek is: Prospectief interventioneel onderzoek
Gebruikte methode: zonder geneesmiddelen

BIJKOMENDE GEGEVENS

Achtergrond:

NT-proBNP is een cardiaal neurohormoon dat gesecreteerd wordt door de hartventrikels als reactie op een volume- en/of druktoename in deze ventrikels. Uit meerdere studies blijkt dat de bepaling van plasma NT-pro BNP erg nuttig is als diagnostisch hulpmiddel bij congestief hartfalen. Het gebruik van deze labotest is tot op heden vooral in de ziekenhuissetting goed ingeburgerd. Zo wordt het voornamelijk op de spoedgevallendienst gebruikt bij de diagnostiek van acuut hartfalen. NT-proBNP heeft echter ook een prognostische waarde en wordt gebruikt voor het monitoren van de behandeling van hartfalen.

In de huisartsensetting wordt NT-proBNP nog niet zo vaak bepaald. In situaties met diagnostische onzekerheid zou een sneltest (point-of-care test), een nuttig hulpmiddel kunnen zijn. In dit onderzoek kijken we bovendien verder dan alleen de hyperacute gevallen. Ook bij patiënten met ‘slow-onset hartfalen’, die zich typisch bij de huisarts melden, zou de NT-proBNP POC-test voor een snellere diagnostiek en aanpak kunnen zorgen.

Vraagstelling:

Is de NT-proBNP sneltest (Cobas h232 POC) een gebruiksvriendelijk en nuttig hulpmiddel in de huisartsensetting? Wat is hierover de mening van de deelnemende artsen?

Methodologie:

Manier van recruteren:

Includeren van patiënten, waarbij de arts hartfalen vermoedt of niet kan uitsluiten, wanneer deze patiënten zich bij hem/haar aanbieden op raadpleging of tijdens huisbezoek.

Aantallen praktijken-artsen-proefpersonen:

-Aantal praktijken: 3 tot 5

-Aantal artsen: 15 to 20

-Aantal proefpersonen: 100 tot 150

Interventie

Aanbieden van NT-proBNP sneltest, in deze de Cobas H232 sneltest van Roche, bovenop de usual care.

Concrete aanpak:

Na verkrijgen van de toestemming zal de arts lege artis (‘volgens de regels van de kunst’) een bloedname verrichten waarbij een met heparine gevuld groen buisje wordt gebruikt. Hierna zal hij het toestel inschakelen en een NT-proBNP teststrip aanbrengen. Vervolgens zal hij met de bijgeleverde optrekspuit een hoeveelheid gehepariniseerd bloed uit het buisje optrekken. Daarna zal de arts dit bloedsample van 150 microliter aanbrengen op de teststrip. Het toestel begint hieropvolgend te analyseren. Hierbij dient vermeld te worden dat het toestel minstens om de 10 metingen gekalibreerd zal worden met een controletest. Na 12 minuten zal het toestel het resultaat weergeven als <60 pg/mL, >3000 pg/mL of een tussenliggende waarde.

Dit resultaat zal vergeleken worden met de bijgeleverde cut-off waarden van het toestel. Uit een eerdere studie in eerste lijn bleek een cut-off van 280 pg/mL de meest performante cut-offwaarde voor

dit toestel. Deze cut-off wordt als richtlijn meegegeven aan de deelnemende huisartsen, maar het staat hen vrij om deze cut-off als ondergeschikt te beschouwen aan hun pluis-niet pluisgevoel.
Na de testperiode zullen de artsen bevraagd worden door middel van een semi-gestructureerde vragenlijst ter evaluatie van de ervaren gebruiksvriendelijkheid en het nut van de sneltest voor hun praktijk.

Voordelen

- sneltest voor efficiëntere praktijkvoering
- gebruiksvriendelijk toestel, ter plaatse te bedienen door de huisarts. De huisarts moet dus niet wachten op de analyse door het labo.

Risico's:

-evt. bijwerkingen van een bloedname (ecchymose, "blauwe plek"); geen extra bijwerkingen i.v.m. usual care

Voorzieningen bij verwikkelingen:

-behandelend arts of wachtdoend arts is bereikbaar bij problemen

AANVULLINGEN OP EERDERE AANVRAAG:

-Tijdens de bloedafname zal een 2de bloedtube afgenomen worden; dus geen extra prik, maar wel een extra tube. Dit staal zal gebruikt worden om de bepaling van NT-proBNP ook uit te voeren in een centraal laboratorium (Ziekenhuis Oost-Limburg (ZOL) Genk) om het resultaat van de POC test te kunnen vergelijken met een gestandaardiseerde bepaling. Deze analyse betreft een kwaliteitscontrole van de POC-test, wat niet direct het onderwerp vormt van deze masterproef, maar wel belangrijk is om de kwaliteit te garanderen. De analyse- en transportkosten worden gedragen door Roche. Er zijn geen kosten voor de patiënt.
-Ook zouden deze bloedstalen verder bewaard worden door het labo voor eventuele latere controles betreffende deze studie rond NT-proBNP. In deze aanvraag wordt enkel de toestemming voor de bewaring gevraagd. Indien er later verder onderzoek zou gebeuren op deze bloedstalen, zal dit ter goedkeuring voorgelegd worden aan de Ethische Commissie.

Appendix 3: Approval Committee on Medical ethics

Van: Martine Goossens <martine.goossens@kuleuven.be>
Onderwerp: Betreft uw aanvraag Ethische begeleiding masterproeven met titel "NT-proBNP Point-Of-Care Testing in de huisartsensetting: een pilootstudie" (mp11149)
Datum: 10 mei 2016 13:35:29 CEST
Aan: Bert Vaes <bert.vaes@med.kuleuven.be>
Kopie: Chiel Hex <chiel.hex@student.kuleuven.be>
Antwoord aan: Martine Goossens <martine.goossens@kuleuven.be>

English version below

Geachte Heer/Mevrouw

De Opleidingspecifieke Ethische Begeleidingscommissie van de opleiding "Master in de huisartsgeneeskunde (Leuven e.a.)" heeft uw voorstel tot Masterproef "NT-proBNP Point-Of-Care Testing in de huisartsensetting: een pilootstudie" onderzocht en gunstig geadviseerd. Dit betekent dat de commissie van oordeel is dat de studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Dit gunstig advies van de commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor zelf verantwoordelijk. Indien u van plan bent uw masterproef te publiceren kan deze e-mail dienen als bewijs van goedkeuring.

Dear Mr/Ms

The Supervisory Committee on Medical ethics of the "Master in de huisartsgeneeskunde (Leuven e.a.)" programme has reviewed your master's thesis project proposal "NT-proBNP Point-Of-Care Testing in de huisartsensetting: een pilootstudie" and advises in its favour. This means that the committee has acknowledged that your project, as described in the protocol, is scientifically relevant and in line with prevailing ethical standards. This favourable advice does not entail the committee's responsibility for the planned project, however. You remain solely responsible. If you intend to publish your master's thesis, this e-mail may be used as proof of the committee's consent.

Met vriendelijke groeten

Opleidingsspecifieke begeleidingscommissie van de opleiding Master in de huisartsgeneeskunde (Leuven e.a.)