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Do laboratories follow heart failure recommendations and guidelines and did we improve? The CARdiac MARker Guideline Uptake in Europe (CARMAGUE)

Abstract

Background: Natriuretic peptides (NP) are well-established markers of heart failure (HF). During the past 5 years, analytical and clinical recommendations for measurement of these biomarkers have been published in guidelines. The aim of this follow-up survey was to investigate how well these guidelines for measurement of NP have been implemented in laboratory practice in Europe.

Methods: Member societies of the European Federation of Clinical Chemistry and Laboratory Medicine were invited in 2009 to participate in a web-based audit questionnaire. The questionnaire requested information on type of tests performed, decision limits for HF, turn-around time and frequency of testing.

Results: There was a moderate increase (12%) of laboratories measuring NP compared to the initial survey in 2006. The most frequently used HF decision limits for B-type NP (BNP) and N-terminal BNP (NT-proBNP) were, respectively, 100 ng/L and 125 ng/L, derived from the package inserts in 55%. Fifty laboratories used a second decision limit. Age or gender dependent decision limits were applied in 10% (8.5% in 2006). The vast majority of laboratories (80%) did not have any criteria regarding frequency of testing, compared to 33% in 2006.

Conclusions: The implementation of NP measurement for HF management was a slow process between 2006 and 2009 at a time when guidelines had just been established. The decision limits were derived from package insert information and literature. There was great uncertainty concerning frequency of testing which may reflect the debate about the biological variability which was not published for most of the assays in 2009.

Keywords: B-type natriuretic peptide; follow-up; guideline implementation; heart failure; natriuretic peptides; N-terminal B-type natriuretic peptide (NT-proBNP).

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Introduction

The well-established heart failure (HF) markers B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) should, by now be widely integrated in the diagnosis, prognosis and disease monitoring of patients with acute and chronic HF. Guidelines addressing the analytical issues of these biomarkers were published 5 years ago by the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice group [1] and 1 year later, guidelines concerning diagnosis and treatment of acute and chronic HF were produced by the European Society of Cardiology (ESC) [2]. Further, the BASEL study showed that a rapid BNP determination in patients with acute dyspnoea reduced the initial hospital admission rate, the use of intensive care and initial time to discharge [3]. In addition, there was demonstrable cost effectiveness with reduced total treatment costs at 360

days (\$10,144 in the BNP group vs. \$12,748 in the control group). Recently, it was shown that NT-proBNP guided HF care reduced expenditures for all-cause re-hospitalisation by 55% per year survived and resulted in €8784 compared to usual care only [4]. Similar findings have been confirmed by other workers [5].

The original CARdiac MARker Guideline Uptake in Europe (CARMAGUE) study, an audit of the implementation of cardiac markers guidelines in European countries in 2006 revealed, that only 56% of the laboratories measured BNP or NT-proBNP [6]. The aim of the second survey was to compare the implementation of cardiac markers into clinical practice following publication of the universal definition of myocardial infarction and guidelines concerning natriuretic peptide measurement in acute and chronic HF. In addition, we wished to determine if there has been any change in behaviour since the previous survey was performed. The results covering markers of acute coronary syndrome markers have already been summarised [7]. The data on the HF markers BNP and NT-proBNP are presented here.

Materials and methods

The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group Cardiac Markers conducted an online survey to assess the patterns of use of cardiac biomarkers and the interaction between clinicians and laboratory physicians in the use of cardiac biomarkers for diagnosis and management of ischaemic heart disease. The aim of the survey was to document the present situation in the use and implementation of cardiac biomarkers of HF and acute coronary syndromes (ACS) in European countries. The design of the electronic questionnaire was tested in a pilot study published previously [6, 8].

The questionnaire 'Use and implementation of cardiac markers in acute coronary syndrome and heart failure' was generated by a specialist (JS) with experience in developing surveys. The questionnaire was implemented as a standard web-form hosted on a website at Helsinki University Central Hospital. The link to this form was emailed, with the help of the International Federation of Clinical Chemistry and Laboratory Medicine main office, to the National Representatives and Presidents of EFLM National Societies on 8 May, 2009. The recipients were asked to forward the letter to laboratories in each country. The mailing lists of national external quality scheme providers and known audit groups were used, in addition, as well as personal contacts. The study did not aim to achieve 100% coverage of all the laboratories in each country, but the intention was to obtain a representative sample of laboratories so as to use the lessons learned to perform a more definitive assessment subsequently. The survey is available on the website <http://www.carmague.fi/2/>.

The questionnaire comprised a total of 210 questions on different aspects of the use of cardiac markers. The questions covered areas such as clinical protocol development, menu of tests performed, preferred marker, turn-around-time (TAT), sample characteristics, reference limits and decision limits for diagnosis and management of ACS and HF.

The collected data were stored with a Perl script into a flat-file database and downloaded to a personal computer for further processing. The results were analysed using Microsoft Excel 2003 and custom software developed by one of the authors (JS). The custom software used was a dynamic link library created with Borland Delphi to add custom functionality to Excel. Excel macros written in Excel's own macro programming language, Visual Basic for Applications, were used as an interface between the custom dynamic link library and Excel. The data analysis was a descriptive tabulation of the numbers of different responses and combinations of responses for each question. Some of the data was pre-processed before counting the numbers of different responses to take into account variations in spelling in free form text fields, e.g., different variations in the name of a country were standardised before the final analysis. The methodology used for the questionnaire was checked by manually doing the processing steps from the raw data to the descriptive summary statistics for many raw data rows (individual answers) and many columns (individual variables) and other cross-checks. No errors were found.

Results

Participating laboratories

The second survey covered more countries and laboratories compared to the first survey in 2006 (8 different countries and responses from 220 laboratories vs. 303 laboratories in 28 countries). The responders were from a full range of laboratories and characteristics were quite comparable between the surveys (Table 1). Not all respondents provided answers to all questions, hence some sections of the survey had <303 total responses.

As in 2006 the majority of laboratories provided a service which covered 24-h patient admission (2006: 95% and 2009: 98% of laboratories). There were slightly more laboratories of hospitals that had a separate chest pain unit for <24 h stay (2006: 37% and 2009: 42% of laboratories) and an emergency unit for more than 12 h stay (2006: 84% and 2009: 88% of laboratories). There were less

	2006	2009
Number of countries	8	28
Number of participating hospitals	220	303
University hospitals, %	26.7	34.0
Central hospitals, %	29.0	25.3
District hospitals, %	39.6	36.0
Primary care hospitals, %	4.6	4.7
Hospitals with 24-h admission, %	97.8	97.6
Hospitals with separate chest pain unit, %	41.9	38.1
Hospitals with separate coronary care unit, %	88	83.3
Hospitals with emergency unit, %	87.9	84.8

Table 1 Characteristics in the two surveys.

hospitals with a coronary care unit than in 2006 (2006: 87% vs. 2009: 83% of laboratories). The laboratory service was available 24 h a day in 95% of respondents (94% in 2006) for ACS markers, but a 24 h service for HF markers was available in only 83%.

Heart failure markers BNP and NT-proBNP

Of the 303 participants, 206 measured either BNP (n=78; 38%) or NT-proBNP (n=128; 62%), the same proportion of BNP to NT-proBNP measurement seen in 2006 (2006 BNP vs. NT-proBNP: 37.5% vs. 62.5%). There was a moderate increase of laboratories measuring natriuretic peptides between 2006 and 2009 (56% in 2006 vs. 68% in 2009). The most frequently used BNP assays were Abbott, Biosite and Siemens (Advia Centaur BNP), and for NT-proBNP, Roche. Stat measurement was available in approximately half of the laboratories who offered natriuretic peptides (51% of BNP users and 45% of NT-proBNP), slightly less than in 2006 (BNP/NT-proBNP in 2006: 58%). The turn-around time (TAT) from receiving the sample in the laboratory to validated test result was ≤60 min in 59 (92%) BNP users (64 BNP respondents available) and in 82 (94%) NT-proBNP users (87 NT-proBNP respondents available) for emergency requests, 10% more than in 2006 (84 of 103 laboratories).

One decision limit for natriuretic peptide measurement was typically reported for HF diagnosis. For BNP the most frequently used decision limit was 100 ng/L (49 laboratories; 61% of BNP users), 15 laboratories used a second decision limit (e.g., mostly 400 ng/L or 500 ng/L). For NT-proBNP 35 laboratories used 125 ng/L as decision limit, 16 laboratories used 300 ng/L and 32 used a second decision limit (varying between 300 and 1800 ng/L). Age or gender dependent decision limits were used by 14% for the BNP and 25% for the NT-proBNP assay respective compared to 8.5% in 2006. About 55% of the laboratories utilised the decision limits provided by the manufacturers' assay package insert (Table 2). BNP was mainly measured in EDTA-plasma (86%), but also in heparin plasma (11%) and serum (3%; Figure 1A). NT-proBNP was measured either in heparin plasma or in serum or in both. A few laboratories used EDTA-plasma or other specimen combinations (Figure 1B).

In striking contrast to the 2006 survey, where 67% of laboratories had protocols for the frequency of BNP/NT-proBNP testing and the number of samples to be collected, around 80% of laboratories did not have sampling protocols in the present survey. Out of the 20% with established sampling protocols 15 laboratories described

	BNP/NT-proBNP, %	BNP, %	NT-proBNP, %
	2006	2009	2009
Package insert	59	56	55
Peer-reviewed literature	24	11	10
Age- and gender-related reference limits	8.5	10	10
Locally derived decision/ reference limits	8.5	8	9
Published literature	n.a.	14	16

Table 2 Methods of choice of BNP/NT-proBNP decision limits chosen by laboratories participating in the 2006 CARMAGUE survey and the follow-up survey in 2009. n.a., not applicable.

diverse protocols, e.g., only a single sample at admission, measurement every 1–2 days, or measurement only twice during hospital stay, etc. It is remarkable that approximately 15% of the BNP or NT-proBNP assays did not have any external quality assurance, although this improved by about 6% compared to 2006.

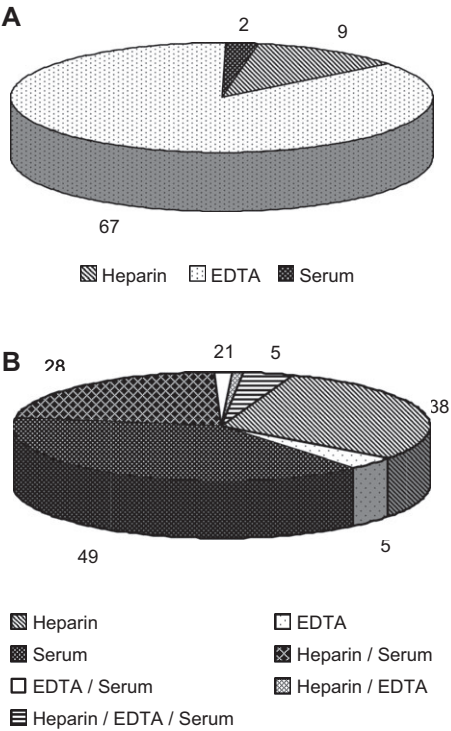


Figure 1 Specimen used for BNP (A) and NT-proBNP (B) measurement. Absolute numbers are indicated.

Discussion

This second CARMAGUE survey produced results across a wider range of European countries. The surveys in 2006 and 2009 revealed that the implementation of HF markers into clinical practice was a slow process with an increase of laboratories who measured BNP/NT-proBNP of only about 12%. In 2009 there were still one-third of laboratories who did not offer HF markers, although new HF guidelines were published in 2007/2008 [1, 2]. The favoured cut-off value for BNP assays was 100 ng/L. Only a few used a second cut-off value of 400 ng/L. Both values were proposed by the ESC HF guidelines for ruling out and ruling in HF, respectively [2]. The BNP concentration of 100 ng/L is the concentration at which many assays are harmonised with each other and values below and above do not necessarily agree between the different BNP assays. However, the cut-off value of 100 ng/L taken by the ESC HF guidelines 2008 seems to be derived from the Breathing Not Properly (BNP) study [9], which investigated patients with acute HF in the emergency department rather than chronic HF patients. Therefore, the BNP and NT-proBNP thresholds recommended by the ESC HF guidelines 2008 are confusing, whereas the NACB guidelines 2007 clearly cited the cut-off values for acute HF. Thresholds for chronic HF were in debate at that time and natriuretic peptide measurement was considered only as a part of the diagnostic evaluation for acute presentations with shortness of breath [2]. Recently, the ESC working group on acute cardiac care recommended an algorithm of BNP and NT-proBNP cut-off values in acute HF patients [10]. Rule-out values should therefore be 100 ng/L for BNP or 300 ng/L for NT-proBNP, and rule-in values should be 500 ng/L for BNP and age-related rule-in values for NT-proBNP (450, 900, and 1800 ng/L for ages <50, 50–75, and >75 years). Higher or lower cut-off values have to be considered in case of renal failure or obesity, respectively [10]. The favoured NT-proBNP cut-off value of 125 ng/L was recommended from the package insert, and the 300 ng/L cut-off value was recommended by the NACB guidelines [1] for ruling out acute HF. In case of NT-proBNP testing a second cut-off was frequently used, and partially reflected the NACB 2007 [1] and ESC 2008 guidelines [2]. Age- and gender-related BNP or NT-proBNP cut-off values were applied in less than one quarter of laboratories although several studies showed an age and gender dependency in chronic HF patients [11–14]. However, we found that the percentage of laboratories using such age and gender dependent concentrations was markedly higher than in our first survey.

In a national proficiency testing study conducted 2 years before this survey was done the differences in

analytical performance of BNP and NT-proBNP assays were evaluated [15]. As previously, it was shown that there was a marked systemic difference of absolute concentrations between the commercially available BNP assays and that absolute NP concentrations should be interpreted with care in follow-up studies of patients if different assays are used. The most commonly used BNP assays were Biosite, Siemens Advia Centaur, Beckman and Abbott, which is comparable with the BNP methods of this survey. In the national study slightly more BNP (53%) than NT-proBNP (47%) assays were used whereas in our present study NT-proBNP assays were more commonly applied (62%). This difference may be explained by national diversity in the use of assays contrasting our survey results which reflect the diversity of assays used in 28 countries.

Generally, BNP should be measured in EDTA-plasma to prevent its degradation (stability at room temperature is for up to 4 h). NT-proBNP is stable at room temperature for at least 2 days, and the preferred specimens are serum or heparin-plasma [10]. In EDTA-plasma a negative bias of approximately 10% compared with serum was observed [16]. However, for the BNP Access-Beckman Coulter assay, using the same antibodies as the Triage BNP test, contradictory results have been published. Dupuy et al. found heparin-plasma to be an equivalent specimen type to EDTA-plasma for BNP measurement [17], whereas Daves et al. showed that EDTA-plasma significantly underestimated the BNP values compared to heparin-plasma when analysed within 20 min from blood collection [18]. Santos et al. investigated the stability of BNP in heparin- and EDTA-plasma in more detail during several hours of storage at room temperature [19]. They found that the stability of BNP was less in heparin-plasma than in EDTA-plasma with lower values obtained for heparin-plasma, even if the measurements were performed immediately after blood collection [19]. For the Abbott or Siemens Advia Centaur BNP assay, EDTA-plasma is the only suitable sample type [20, 21]. The recent ESC recommendations clearly state that for BNP measurement EDTA-plasma is required [10]. Nevertheless, six Abbott BNP, one Biosite and one Siemens Advia Centaur users reported using heparin-plasma for measurement.

Only one-fifth of laboratories had protocols for the frequency of testing, which may reflect the uncertainty of laboratorians or clinicians as to when to repeat BNP/NT-proBNP measurement. The concerning question ('Do you have any criteria regarding frequency of BNP/NT-proBNP testing and number of samples to be collected? If yes, please specify.') allowed free text to specify the particular protocol. However, the limited number of text answers did not allow any conclusions whether these biomarkers were

used for screening for access to echocardiograms or for the management of acute or chronic HF patients. It seemed that measurement was done on clinicians request without any oral or written agreement for standard measurement in HF patients between laboratories and clinicians. The biological variability for BNP was not published for most of the assays in 2009. The recent ESC recommendations 2011 concluded that frequent blood sampling is not required and only changes >30% are clinically relevant [10]. In our 2006 survey around 20% of laboratories did not have any EQA [6]. It is astonishing that still 15% of the laboratories participating in the questionnaire did not have an EQA for BNP or NT-proBNP, despite the fact that these HF markers have been widely integrated into EQA programs.

Limitations

A limitation of this study is that not all laboratories of the countries involved in this survey responded. There might have been different results if all hospitals had replied, however, it was not the aim of this survey to reach a 100% response rate which is hard to yield in such surveys. The percentages of the type of hospitals (see Table 1) were very similar between the previous and the current survey so that we strongly believe that our results reflect the present situation of use of HF markers in laboratories very well. A further limitation is that the questionnaire was not developed together with manufacturers.

However, one of the co-authors is a professional specialist in generating questionnaires and more importantly, we wanted to have an independent and not manufacturer driven questionnaire.

Conclusions

In the current survey we demonstrated that HF markers BNP and NT-proBNP were implemented slowly into clinical routine practice between 2006 and 2009, despite the incorporation of these markers into the guidelines and the documented cost-effectiveness. Rule-out values in acute HF patients as well as age and gender dependent reference values are well-defined and should be applied. It is of great concern, that there are still laboratories not participating in any external quality assurance concerning BNP/NT-proBNP.

Conflict of interest statement

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