Clinica Chimica Acta

Update on current practice in laboratory medicine in respect of natriuretic peptide testing for heart failure diagnosis and management in Europe. The CARdiac MArker Guideline Uptake in Europe (CARMAGUE) study.

--Manuscript Draft--

Manuscript Number:	CCACTA-D-20-01914
Article Type:	VSI: Cardiovascular Markers
Keywords:	guideline implementation; heart failure; B-type natriuretic peptide; N-terminal B-type natriuretic peptide; biomarkers, follow-up; laboratory practice
Corresponding Author:	Angelika Hammerer-Lercher, MD Institute for Laboratory Medicine Aarau, SWITZERLAND
First Author:	Angelika Hammerer-Lercher, MD
Order of Authors:	Angelika Hammerer-Lercher, MD
	Damien Gruson
	Sanja Stankovic
	Paul Collinson
	Janne Suvisaari
	Kari Pulkki
	Christopher J. Duff
	Hannsjörg Baum
	Ana Stavljenic-Rukavina
	Kristin M. Aakre
	Michel R. Langlois
	Paivi Laitinen
Abstract:	Background The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) initiated the CArdiac MARker Guidelines Uptake in Europe (CAMARGUE) Study to survey if current biomarker testing for heart failure (HF) in Europe is in accordance with up-dated guidelines. Methods A web-based questionnaire was distributed to clinical laboratories via European biochemical societies in 2019. Questions covered the type of natriuretic peptide (NP) assays performed, decision limits for HF, and opinion concerning requirement of different thresholds in patients with renal failure or obesity. Results There were 347 participating laboratories mostly from European countries with 266 offering NP testing. NP testing was increased from 67% to 77% between 2013 and 2019. NT-proBNP remained the preferred biomarker. Recommended decision limits were implemented for BNP (85%) and better focused for NT-proBNP (40%) than in the previous survey. The survey revealed that laboratorians are willing to support the translation of adjusted cut-off values for age, gender and for patients with conditions like renal insufficiency. Conclusion

	Guidelines stimulate clinical laboratories to offer NP testing with high value for the diagnosis and management of HF, and to present adjusted medical decision limits. Future guidelines should encourage the use of personalized cut-offs for some confounding factors.
Suggested Reviewers:	Pieter Vermeersch pieter.vermeersch@uzleuven.be
	Wytze Oosterhuis w.oosterhuis@zuyderland.nl
	Mauro Panteghini Mauro.Panteghini@unimi.it

Update on current practice in laboratory medicine in respect of natriuretic peptide testing for heart failure diagnosis and management in Europe. *The CARdiac MArker Guideline Uptake in Europe (CARMAGUE) study.*

Running Title: Heart failure guidelines in clinical practice

Angelika Hammerer-Lercher[1], Damien Gruson[2], Sanja Stankovic[3], Paul Collinson[4], Janne Suvisaari[5], Kari Pulkki[5,], Christopher J. Duff[6, 7], Hannsjörg Baum[8], Ana Stavljenic-Rukavina[9], Kristin M. Aakre[10,11], Michel R. Langlois[12], Paivi Laitinen[5*] for the EFLM Task Group Cardiac Markers.

[1]Institute for Laboratory Medicine, County Hospital Aarau AG, Aarau, Switzerland

[2]Department of Clinical Biochemistry, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium.

[3]Center for Medical Biochemistry, Clinical Center of Serbia, Belgrade, Serbia

[4]Departments of Cardiology, St George's University Hospitals NHS Foundation Trust and St. George's University of London, UK

[5]Clinical Chemistry, HUS Diagnostic Center, Helsinki University and Helsinki University Hospital, Helsinki, Finland

[6]Department of Clinical Biochemistry, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

[7]School of Primary, Community and Social Care, Keele University, Stoke-on-Trent, UK.

[8]Regionale Kliniken Holding RKH GmbH, Germany

[9]DIU Libertas International University, Zagreb, Croatia

[10]Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

[11]Department of Clinical Science, University of Bergen, Bergen, Norway

[12]Department of Laboratory Medicine, AZ St-Jan Hospital Bruges, and Ghent University, Ghent, Belgium

Submission/Author checklist

We used the authors checklist to ensure that the following items are present if not stated otherwise:

One author has been designated as the corresponding author with contact details:

• E-mail address

• Full postal address

All necessary files have been uploaded:

Manuscript:

• Include keywords

• All figures (include relevant captions)

• All tables (including titles, description, footnotes)

• Ensure all figure and table citations in the text match the files provided

• Indicate clearly if color should be used for any figures in print

Graphical Abstracts / Highlights files (where applicable): not applicable

Supplemental files (where applicable): not applicable

Further considerations

• Manuscript has been 'spell checked' and 'grammar checked'

• All references mentioned in the Reference List are cited in the text, and vice versa

• Permission has been obtained for use of copyrighted material from other sources (including the Internet): not applicable

• A competing interests statement is provided, even if the authors have no competing interests to declare

• Journal policies detailed in this guide have been reviewed

• Referee suggestions and contact details provided, based on journal requirements

Update on current practice in laboratory medicine in respect of natriuretic peptide testing for heart failure diagnosis and management in Europe. *The CARdiac MArker Guideline Uptake in Europe (CARMAGUE) study.*

Running Title: Heart failure guidelines in clinical practice

Angelika Hammerer-Lercher[1], Damien Gruson[2], Sanja Stankovic[3], Paul Collinson[4], Janne Suvisaari[5], Kari Pulkki[5,], Christopher J. Duff[6, 7], Hannsjörg Baum[8], Ana Stavljenic-Rukavina[9], Kristin M. Aakre[10,11], Michel R. Langlois[12], Paivi Laitinen[5] for the EFLM Task Group Cardiac Markers.

[1]Institute for Laboratory Medicine, County Hospital Aarau AG, Aarau, Switzerland

[2]Department of Clinical Biochemistry, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium.

[3]Center for Medical Biochemistry, Clinical Center of Serbia, Belgrade, Serbia

[4]Departments of Cardiology, St George's University Hospitals NHS Foundation Trust and St. George's University of London, UK

[5]Clinical Chemistry, HUS Diagnostic Center, Helsinki University and Helsinki University Hospital, Helsinki, Finland

[6]Department of Clinical Biochemistry, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

[7]School of Primary, Community and Social Care, Keele University, Stoke-on-Trent, UK.

[8]Regionale Kliniken Holding RKH GmbH, Germany

[9]DIU Libertas International University, Zagreb, Croatia

[10]Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

[11]Department of Clinical Science, University of Bergen, Bergen, Norway

[12]Department of Laboratory Medicine, AZ St-Jan Hospital Bruges, and Ghent University, Ghent, Belgium

Abstract

Background: The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) initiated the CArdiac MARker Guidelines Uptake in Europe (CAMARGUE) Study to survey if current biomarker testing for heart failure (HF) in Europe is in accordance with up-dated guidelines.

Methods: A web-based questionnaire was distributed to clinical laboratories via European biochemical societies in 2019. Questions covered the type of natriuretic peptide (NP) assays performed, decision limits for HF, and opinion concerning requirement of different thresholds in patients with renal failure or obesity.

Results: There were 347 participating laboratories mostly from European countries with 266 offering NP testing. NP testing was increased from 67% to 77% between 2013 and 2019. NT-proBNP remained the preferred biomarker. Recommended decision limits were implemented for BNP (85%) and better focused for NT-proBNP (40%) than in the previous survey. The survey revealed that laboratorians are willing to support the translation of adjusted cut-off values for age, gender and for patients with conditions like renal insufficiency.

Conclusion: Guidelines stimulate clinical laboratories to offer NP testing with high value for the diagnosis and management of HF, and to present adjusted medical decision limits. Future guidelines should encourage the use of personalized cut-offs for some confounding factors.

Update on current practice in laboratory medicine in respect of natriuretic peptide testing for heart failure diagnosis and management in Europe. *The CARdiac MArker Guideline Uptake in Europe (CARMAGUE) study.*

Running Title: Heart failure guidelines in clinical practice

Angelika Hammerer-Lercher[1], Damien Gruson[2], Sanja Stankovic[3], Paul Collinson[4], Janne Suvisaari[5], Kari Pulkki[5,], Christopher J. Duff[6, 7], Hannsjörg Baum[8], Ana Stavljenic-Rukavina[9], Kristin M. Aakre[10,11], Michel R. Langlois[12], Paivi Laitinen[5] for the EFLM Task Group Cardiac Markers.

[1]Institute for Laboratory Medicine, County Hospital Aarau AG, Aarau, Switzerland

[2]Department of Clinical Biochemistry, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium.

[3]Center for Medical Biochemistry, Clinical Center of Serbia, Belgrade, Serbia

[4]Departments of Cardiology, St George's University Hospitals NHS Foundation Trust and St. George's University of London, UK

[5]Clinical Chemistry, HUS Diagnostic Center, Helsinki University and Helsinki University Hospital, Helsinki, Finland

[6]Department of Clinical Biochemistry, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

[7]School of Primary, Community and Social Care, Keele University, Stoke-on-Trent, UK.

[8]Regionale Kliniken Holding RKH GmbH, Germany

[9]DIU Libertas International University, Zagreb, Croatia

[10]Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

[11]Department of Clinical Science, University of Bergen, Bergen, Norway

[12]Department of Laboratory Medicine, AZ St-Jan Hospital Bruges, and Ghent University, Ghent, Belgium

Highlights

- NP testing by laboratories substantially increased (10%) between 2013 and 2019
- NT-proBNP remained the preferred biomarker
- Decision limits from guidelines were more often used than in the previous survey
- Laboratorians are willing to support the implementation of adjusted cut-off values
- 73% of participating laboratories have already been accredited/certified

Update on current practice in laboratory medicine in respect of natriuretic peptide testing for heart failure diagnosis and management in Europe. *The CARdiac MArker Guideline Uptake in Europe (CARMAGUE) study.*

Running Title: Heart failure guidelines in clinical practice

Angelika Hammerer-Lercher[1], Damien Gruson[2], Sanja Stankovic[3], Paul Collinson[4], Janne Suvisaari[5], Kari Pulkki[5,], Christopher J. Duff[6, 7], Hannsjörg Baum[8], Ana Stavljenic-Rukavina[9], Kristin M. Aakre[10,11], Michel R. Langlois[12], Paivi Laitinen[5] for the EFLM Task Group Cardiac Markers.

[1]Institute for Laboratory Medicine, County Hospital Aarau AG, Aarau, Switzerland

[2]Department of Clinical Biochemistry, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium.

[3]Center for Medical Biochemistry, Clinical Center of Serbia, Belgrade, Serbia

[4]Departments of Cardiology, St George's University Hospitals NHS Foundation Trust and St. George's University of London, UK

[5]Clinical Chemistry, HUS Diagnostic Center, Helsinki University and Helsinki University Hospital, Helsinki, Finland

[6]Department of Clinical Biochemistry, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

[7]School of Primary, Community and Social Care, Keele University, Stoke-on-Trent, UK.

[8]Regionale Kliniken Holding RKH GmbH, Germany

[9]DIU Libertas International University, Zagreb, Croatia

[10]Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

[11]Department of Clinical Science, University of Bergen, Bergen, Norway

[12]Department of Laboratory Medicine, AZ St-Jan Hospital Bruges, and Ghent University, Ghent, Belgium

***Corresponfing Author:**
Päivi Laitinen
Ylikemisti, FT, dosentti, TtM/Chief clinical chemist/ PhD, Adjunct Professor, EuSpLM

HUS Diagnostiikkakeskus, HUSLAB, Kliininen kemia/
HUS Diagnostic Center, HUSLAB, Clinical chemistry
PL 720/PO Box 720
HUSLAB-talo
Topeliuksenkatu 32
FI-00029 HUS
paivi.h.laitinen@hus.fi
Tel:+358 50 427 9208

Words: 3138
Figures: 4
Tables: 2

Key words:

guideline implementation; heart failure; B-type natriuretic peptide; N-terminal B-type natriuretic peptide; biomarkers, follow-up; laboratory practice

Abbreviations:

HF, heart failure; ESC, European Society of Cardiology; AHA, American Heart Association; NP, natriuretic peptide; BNP, B-type natriuretic peptide; MR-proANP, mid-regional pro Atrial Natriuretic Peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; CARMAGUE, CAardiac MArker uptake of GUidelines in Europe; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; FDA, Food and Drug Administration; EU, European Union; n.a., not applicable; POCT, point of care testing; ACC or ACCF, American College of Cardiology Foundation; COR, class of recommendation; LOE, level of evidence; NICE, the National Institute for Health and Care Excellence; HFA, Heart Failure Association; y; years.

Abstract

Background: The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) initiated the CArdiac MARker Guidelines Uptake in Europe (CAMARGUE) Study to survey if current biomarker testing for heart failure (HF) in Europe is in accordance with updated guidelines.

Methods: A web-based questionnaire was distributed to clinical laboratories via European biochemical societies in 2019. Questions covered the type of natriuretic peptide (NP) assays performed, decision limits for HF, and opinion concerning requirement of different thresholds in patients with renal failure or obesity.

Results: There were 347 participating laboratories mostly from European countries with 266 offering NP testing. NP testing was increased from 67% to 77% between 2013 and 2019. NT-proBNP remained the preferred biomarker. Recommended decision limits were implemented for BNP (85%) and better focused for NT-proBNP (40%) than in the previous survey. The survey revealed that laboratorians are willing to support the translation of adjusted cut-off values for age, gender and for patients with conditions like renal insufficiency.

Conclusion: Guidelines stimulate clinical laboratories to offer NP testing with high value for the diagnosis and management of HF, and to present adjusted medical decision limits. Future guidelines should encourage the use of personalized cut-offs for some confounding factors.

1. Introduction

The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) plays an important role in the continuing education of specialists in laboratory medicine and for the promotion and dissemination of best practices in clinical laboratories, contributing to evidence-based medical decision and patient safety [1].

Biomarkers, and more specifically testing for natriuretic peptides (NP), are important components of the diagnosis and management of heart failure (HF). Testing for Natriuretic peptides (NP), more precisely for B-type natriuretic peptide (BNP), N-terminal pro B-type natriuretic peptide (NT-proBNP) and mid-regional pro A-type Natriuretic Peptide (MR-proANP), has been incorporated into multiple European and International guidelines because of its high value for the clinical setting of heart failure (HF). NP are also becoming important companion assays and endpoints to assess the efficiency of new treatments for HF [2,3].

The EFLM initiated the CAMARGUE (CArdiac MARker Guideline Uptake in Europe) study that aims to monitor the implementation of guidelines encompassing the use of biomarker tests for acute coronary syndrome and heart failure (HF) [4-8]. A CAMARGUE follow-up study was undertaken in 2019 to monitor the use of biomarker testing in HF, acute coronary syndrome and dyslipidaemia and the level of implementation of related guidelines.

The present article present the results of the 2019 edition of the CAMARGUE survey concerning the HF part.

2. Materials and Methods

A web-based questionnaire was developed by the EFLM TG-CM. The questions focused on recent recommendations of the ESC (European Society of Cardiology), at the time of the survey [9]. The questionnaire comprises of 27 multiple-choice and free text questions regarding heart failure testing, and covered the following topics: analytical methods and manufacturer used, reported measurement units, decision threshold for acute and chronic HF, opinion concerning different thresholds in obesity or renal failure and quality assurance.

The survey was sent to EFLM National Societies from 40 member countries in spring 2019 and was accessible between April and August 2019 via web-link. Details of the survey and its performance were published previously [4-6]. A total of 347 European and a minority of laboratories outside Europe responded with more than 10 answers and were included for evaluation. As some respondents did not answer all the questions, some sections of the survey had missing data. Therefore, percentage calculations always refer to the responses that supplied data for the individual question.

3. Results

3.1. Participating laboratories

In this fourth CARMAGUE survey, 347 participants answered more than ten questions, of which a total of 266 laboratories from 33 countries responded to the HF questions (Table 1). These laboratories were mostly from Europe (256 laboratories) and a few from other countries (4 from USA, 2 from Canada, 1 New Zealand, 1 Argentina, 1 Lebanon, 1 Israel). As in the previous questionnaires the majority of laboratories (93%) provided a 24-hour service (95% in 2006, 83% in 2009, 93% in 2013).

3.2. Natriuretic Peptides

NP measurement was provided by 76% (n=266 out of 347) of the responding laboratories, which is slightly more than in the previous surveys (67% in 2013, 68% in 2009). The common stated concentration unit was ng/L or pg/mL (95%). NT-proBNP was still the most widely used NP assay (79% of laboratories offering an NP; 68% in 2013 survey), and BNP was used in 21% (Figure 1A). Twenty (7.5%) laboratories measured more than one NP and mostly combined NT-proBNP from Roche with a BNP assay (Figure 1B). There were also 7 laboratories performing POCT assays (5 Quidel or Alere Triage, 1 Radiometer AQT90 Flex, 1 not determined). MR-proANP was not commonly used (n=4) and only in laboratories, that also measured NT-proBNP.

3.3. Decision limits for acute HF

We asked, whether a single cut-off value (not reference values) was applied to rule-out acute HF. This was agreed in 61% and denied in 39% of respondents answering this yes or no question (n=180). Similar to the previous surveys, there was a variety of answers for stating the specific cut-off. For NT-proBNP, 40% (n=44/110) used the ESC 2016 guideline conform rule-out cut-off of 300 ng/L, 28% stated the 125 ng/L value (n=31/110) and 14% used age or

gender dependent values (n=15/110; Figure 2 and 3A). The most commonly utilized decision limit for BNP was the ESC 2016 guideline recommended rule-out cut-off of 100 ng/L (85%; n=23/27; Figure 3B).

A further question was, whether a single cut-off value was used to rule-in acute HF, which was the case in 25% of 161 participants answering this yes or no question. When asking for specific cut-offs, several different ones were stated for NT-proBNP with values ranging from 115 ng/L up to 2000 ng/L. There were 39% (n=86) participants of 223 NT-proBNP users, who applied age-dependent cut-off values to rule-in acute HF. However, 52% (n=45/86) of these respondents only answered this question only with "yes" with no further information concerning values. Nevertheless, most frequently (29%; n=25/86) the ESC recommended cut-off levels of >450 ng/L for patients <50 years, >900 ng/L for patients 50-75 years old and >1800 ng/L for >75 years old patients were stated. In 6% of laboratories (n=5/86) the two age dependent cut-off values from the FDA-cleared package insert were used: 125 ng/L for <75 years old and 450 ng/L for >75 years old patients. Of all BNP users, 28% provided more detailed answers concerning the single rule-in cut-off values for acute HF (n=17/61 of BNP users). The most common cut-off of 100 ng/L was utilized in 71% (n=12/17), followed by 400 ng/L in 12% (n=2/17) and 500 ng/L in 12% (n=2/17).

3.4. Decision limits for chronic HF

Respondents were asked, whether they reported cut-off values (not reference value) to rule-out chronic heart failure. Nearly half of 192 respondents answering this yes or no question (47%) reported in the affirmative. As extracted from a more specific separate question, the NT-proBNP cut-off of 125 ng/L derived from the ESC guidelines was stated in about one third (32%; n=23/72), and one fifth (21%; n=15/72) applied 400 ng/L as cut-off value. Several participants reported using 125 ng/L for <75 years old and 450 ng/L for >75 years old patients

(12%; n=9/72). Further, various other thresholds were stated from different respondents. Concerning BNP only two participants responding to this question (n=2/16 of BNP users) applied the ESC guideline cut-off value of 35 ng/L. More than half of respondents (63%; n=10/16) used 100 ng/L as a cut-off value for ruling-out chronic HF.

3.5. Opinions of participants

We were interested in the opinion of laboratorians concerning the application of different cut-off values in widely discussed topics, but not explicitly stated in the guidelines so far. One question addressed the need to provide age-dependent and a further one, gender-dependent cut-off values in the guidelines. The majority of respondents would appreciate this, 90% (n=152/169) supported age and 80% (n=114/142) gender specific cut-offs. Also more than half the respondents (63%; n=82/131) saw a requirement for different cut-off values (not reference value) for patients with renal insufficiency suspected of having acute or chronic heart failure, with most supporting the implementation of higher cut-off values (90%; n=74/82) and only a minority supporting lower ones (10%; n=8/82). In contrast, less than half of respondents (40%; n=43/107) saw a benefit in different cut-off values (not reference value) for obese patients suspected having acute or chronic heart failure. In this case 72% (n=31/43) indicated lower cut-off values, but 30% (n=12/43) higher ones. Since the new HF medication Sacubitril/Valsartan (synonyms: angiotensin-receptor-neprilysin-inhibitor/ARNI) has become available on the marked, we wanted to corroborate whether the clinicians in the hospitals already used it as treatment for HF patients. There were 85 participants responding to this question resulting in 93% positive answers (yes: n=79/85; no: n=6/85).

3.6. Quality assurance

Seventy three percent of laboratories were accredited or certified. Internal and external quality assurance was performed by 99% and 92%, respectively, of respondents. Three further

questions address the utilization of protocols. In 41% (n=96/237) a rule-out protocol for natriuretic peptide was applied, whereas in 45% (n=107/237) not, and 14% were not sure about that (n=34/237). The protocol derived from different sources, but the most common one was from the ESC guidelines (Figure 4).

4. Discussion

The value of testing for natriuretic peptides for the diagnosis and management of HF is recognized and translated into European and International guidelines. Furthermore, measurement of natriuretic peptides became an important endpoint in clinical trials related to HF. It is therefore important to assess the implementation of guidelines by clinical laboratories into practice and best practices associated to biomarker testing in HF.

We performed this follow-up CARMAGUE survey in 2019, because the previous one (2013), highlighted that there was a large uncertainty concerning which cut-off values should be applied to rule in or to rule out patients with acute or chronic HF. At this time, two different ESC algorithms were available, published separately in 2012 (Table 2), perhaps contributing to this dilemma. The 2016 ESC guidelines were clear and unequivocal for ruling out decision limits in acute HF patients and also incorporated a further NP, MR-proANP. The main findings of this updated survey are: first, laboratories offering NP testing increased substantially from 67% in 2013 to 77% in 2019. Second, NT-proBNP remained the preferred marker (79%), MR-proANP was rarely used. Third, the recommended medical decision limits for acute HF were very well implemented for BNP (85%) and better focused for NT-proBNP (40%) than in the previous survey. Fourth, the majority of laboratorians would appreciate specific age-dependent (90%) and gender-dependent (80%) cut-off values for HF as well as different cut-off values (not reference value) for patients with renal insufficiency (63%) suspected having acute or chronic HF. Such a requirement for obese patients was not so well supported in the answers, only 40% saw a benefit. Finally, accreditation of laboratories depends on national regulations

and is not a prerequisite in many European countries, nevertheless, 73% of respondent laboratories had been accredited/certified. Further, there is an appreciated upwards trend of performing EQA for NP assays, with nearly all of participating laboratories having such a scheme (92% in 2019 vs. 84% in 2013) .

This survey revealed encouraging data, showing that more than half of respondents applied a single cut-off value to rule out acute HF (61%). The new ESC guidelines, published two years before the survey was rolled out, were thus very well taken up by laboratorians and increasingly implemented in practice. This can be illustrated by a 10fold increase in the use of the 300 ng/L cut-off for NT-proBNP (40% in 2019 vs. 4% in 2013) and a nearly doubling in the use of 100 ng/L cut-off for BNP (85% in 2019 vs. 48% in 2013). However, there were still nearly one third of participants who reported a 125 ng/L cut-off for NT-proBNP, which is recommended for ruling out chronic HF or derived from the package insert as the medical threshold for patients <75 years. At this point, it should be emphasized that the guideline derived cut-off values are well established and have achieved a class I recommendation for diagnosis and prognosis for several years (Table 2).

Although the recent guidelines were clear in respect of single decision thresholds for ruling out acute or chronic HF, specific higher thresholds for ruling in HF were not clearly addressed. The purpose of the relatively low rule out cut-off values was to reach a high negative predictive value to safely exclude patients from having HF. For ruling in acute HF higher cut-off values may be more practicable in order to save costs that would arise for HF workup in case of mildly elevated levels. The ICON-RELOADED (International Collaborative of NT-proBNP Study) study verified the formerly reported age-dependent decision limits for NT-proBNP to rule in acute HF (450/900/1800 ng/L for <50/50-75/75y) [19], which were moreover, integrated into the ESC/HFA position paper and practice guidance published 2019 (Table 2) [18], just when the present survey was rolled out. In that position paper also higher cut-offs were recommended for BNP. The present survey revealed that indeed a third (29%) of respondents, who applied

age-dependent NT-proBNP thresholds to rule in acute HF, used them (450/900/1800 ng/L for <50/50-75/75y). However, the recent ESC position paper was probably coincidental with the common laboratory practice of using these well-known NT-proBNP thresholds that were corroborated by the ICON-RELOADED study in 2018 and stated before in the ESC recommendations 2012 (Table 2). We thus recognized an upwards trend of age-dependent rule in thresholds in this setting compared to the 2013 survey (29% in 2019 vs. 17% in 2013).

The ESC position paper states similar cut-offs for ruling out chronic HF as the ESC guidelines 2016 (BNP <35 ng/L; NT-proBNP <125 ng/L), but, lists slightly higher ones for ruling in chronic HF. Only the NICE national clinical guidelines recommend higher cut-off values for ruling out chronic HF (BNP <100 ng/L; NT-proBNP <400 ng/L; Table 2), which were found to be optimal in UK primary care. In this case, the intention was to avoid unnecessary investigations contributing to patient anxiety and potentially overwhelming cardiology services due to too low cut-offs. Notably, since 2019 NICE favours NT-proBNP over BNP measurement. As far as could be extracted from the present questionnaire, one third of the respondents answering the question concerning thresholds to rule out chronic HF used the ESC guideline recommended NT-proBNP threshold of 125 ng/L (32%), which is four times more often than in the 2013 survey. The NICE threshold was applied in 21% (NT-proBNP 400 ng/L) of laboratories and still, the age-dependent threshold of the package insert, already stated for acute HF, was used in 12%. For BNP the former NICE threshold was the preferred one in 63% of participants answering this question, the ESC guideline recommended cut-off was only used in two laboratories. This may be partly explained by a relatively low number of answers to this question (n=16 out of 61 BNP users), but could also be due to the use of the package insert upper reference limit, which is also 100 ng/L for most BNP assays. Generally, this follow-up survey revealed that although there were still various threshold used in laboratory or clinical practice, an encouraging shift to guideline recommended thresholds in the acute and chronic HF setting were recognized.

As renal failure or obesity have been found to influence NP levels, an adaption of the decision thresholds of NP was suggested [20-25]. In HF patients with renal failure NP are increased compared to those without. There is a significant correlation between glomerular filtration rate and both NP, NT-proBNP and BNP [20, 22]. The very recent practical guidance of the Heart Failure Association of the ESC therefore, recommends increasing the BNP threshold from 100 ng/L to 200 ng/L to rule out acute HF [18]. However, a higher threshold may not necessarily be required, if age-dependent cut-offs were used to rule in acute HF [18, 26]. Indeed, most of the participants of this survey (90%) would appreciate age-dependent cut-off values and more than half (52%) stated to use them in case of NT-proBNP. Thus, it can be expected, that the recommended thresholds from the ESC practice guidance will rapidly be applied by laboratories. Consequently, the impact of renal failure on the threshold values for NT-proBNP, but not BNP, may be negligible, because the recommended values seem to be high enough to rule in acute HF. Indeed, 63% of respondents effectively saw a benefit of adapted thresholds in the presence of renal failure. In contrast, only 40% of respondents deemed it worth having different cut-off values in obese patients. That both higher and lower cut offs were suggested indicate that laboratorians may be less familiar with the studies indicating that NP concentrations will decrease with increasing body mass index [23, 24]. According to the recent ESC practice guidance the thresholds should be reduced by 50% in obese patients to be sensitive enough for ruling out HF.

There is an ongoing discussion whether NP are useful biomarkers for HF monitoring, and in particular whether BNP can be measured to monitor HF improvement if patients are treated with the new dual drug sacubitril-valsartan [27]. This drug is approved for systolic HF with reduced ejection fraction and has obviously gained great acceptance; 93% of respondents (n=79/85) used this treatment. The uncertainty derived from moderate increased BNP concentrations (Siemens assay) in the first weeks after treatment in the PARADIGM-HF trial

while NT-proBNP declined [28, 29]. However, by the end of the trial both, BNP and NT-proBNP concentrations had declined. Therefore, in the long term both NP may show the beneficial effects of treatment. Nevertheless, it is still not clear, whether the effects were influenced by the elimination of patients who withdraw or died or whether it is due to effects on the molecular basis of the peptides circulating as various fragments and for NT-proBNP/proBNP in differently glycosylated states [30, 31]. Of note, the dynamics of BNP measured with different assays were very heterogeneous after sacubitril-valsartan treatment [32], which should be further investigated in larger studies. It has to be emphasized, that the treatment effect of neprilysin inhibition targets more effectively other peptides than BNP such as atrial natriuretic peptide or adrenomedullin. The increasing BNP values may be challenging in the first weeks after treatment, but clinicians should be aware, that these increases are rather modest and in case of suspicion of acute decompensation of HF, there are more pronounced increases of BNP accompanied by clinical symptoms. A biomarker should always be interpreted in context with the clinical findings.

Lastly, our survey highlighted that, even if accreditation of laboratories depends on national regulations and is not a prerequisite in many European countries, 73% of laboratories were accredited or certified and that internal and external quality assurance was performed by 99% and 92%, respectively, of respondents. This demonstrates that NP testing are performed in environments with a continuous monitoring of the quality and training of the stakeholders, contributing to the reliability and accuracy of the results as well as patient safety.

5. Limitations

A limitation of this study is that not all laboratories of the countries involved in this survey responded. Results might have been different if all clinical laboratories had participated. However, a 100% response rate is hard to yield in such surveys. The proportion of different laboratory types (university vs. local) were very similar to those obtained with previous

CAMARGUE and other EFLM questionnaires so that we strongly believe that our results may reflect the present situation of natriuretic peptide testing in European laboratories.

6. Conclusion

Testing for natriuretic peptides is of high clinical impact for the diagnosis and management and HF. European and international guidelines stimulate clinical laboratories to offer natriuretic peptide testing as well as to adopt the recommendations for best practices and use of adjusted medical decision limits. Specialists in laboratory medicine are now expecting that guidelines provide and encourage the use of more personalized cut-offs for some conditions like renal insufficiency and confounding factors such as age and gender.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Funding

This research received fundings from Abbott and Roche.

Declaration of Competing Interest

The authors have no other competing interests or conflicts of interest to declare concerning this survey.

References:

[1] https://www.eflm.eu/site/page/a/1000/ (Accessed Sep. 2020)

[2] Januzzi JL Jr, Camacho A, Piña IL, Rocha R, Williamson KM, Maisel AS,et al. Reverse Cardiac Remodeling and Outcome After Initiation of Sacubitril/Valsartan. Circ Heart Fail 2020;13:e006946.

[3] Ambrosy AP, Braunwald E, Morrow DA, DeVore AD, McCague K, Meng X, et al. Angiotensin Receptor-Neprilysin Inhibition Based on History of Heart Failure and Use of Renin-Angiotensin System Antagonists. J Am Coll Cardiol 2020;76:1034-48.

[4] Pulkki K, Suvisaari J, Collinson P, Ravkilde J, Stavljenic-Rukavina A, Hammerer-Lercher A, et al. A pilot survey of the use and implementation of cardiac markers in acute coronary syndrome and heart failure across Europe. The CARdiac MArker Guideline Uptake in Europe (CARMAGUE) study. Clin Chem Lab Med 2009;47:227-34.

[5] Collinson PO, van Dieijen-Visser MP, Pulkki K, Hammerer-Lercher A, Suvisaari J, Ravkilde J, et al. Evidence-based laboratory medicine: how well do laboratories follow recommendations and guidelines? The Cardiac Marker Guideline Uptake in Europe (CARMAGUE) study. Clin Chem 2012;58:305-6.

[6] Hammerer-Lercher A, Collinson P, van Dieijen-Visser MP, Pulkki K, Suvisaari J, Ravkilde J, et al. Do laboratories follow heart failure recommendations and guidelines and did we improve? The CARdiac MArker Guideline Uptake in Europe (CARMAGUE). Clin Chem Lab Med 2013;51:1301-6.

[7] Collinson P, Hammerer-Lercher A, Suvisaari J, Apple FS, Christenson RH, Pulkki K, et al. How well do laboratories adhere to recommended clinical guidelines for the management of myocardial infarction-the CARdiac MArker Guidelines Uptake in Europe study (CARMAGUE). Clin Chem 2016;62:1264-71

[8] Hammerer-Lercher A, Collinson P, Suvisaari J, Christenson RH, Pulkki K, van Dieijen-Visser MP, et al. Are Heart Failure Management Recommendations and Guidelines Followed

in Laboratory Medicine in Europe and North America? The Cardiac Marker Guideline Uptake in Europe (CARMAGUE) Study. JALM 2016;1:483-93

[9] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 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. J Heart Fail. 2016;18:891-975.

[10] Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, et al. Recommendations for the use of natriuretic peptides in acute cardiac care: A position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Eur Heart J 2012;33:2001-6.

[11] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. 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 J Heart Fail 2012;14:803-69.

[12] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. 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. 2008;29:2388-442.

[13] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in

Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1-e90.

[14] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.

[15] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM,et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail 2017;23:628-51.

[16] Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update (Internet). National Clinical Guideline Centre (UK). London: Royal College of Physicians (UK); 2010 Aug. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0046956/ (Accessed Sep. 2020)

[17] Taylor CJ, Moore J, O'Flynn N. Diagnosis and management of chronic heart failure: NICE guideline update 2018. Br J Gen Pract 2019;69:265-6.

[18] Mueller C, McDonald K, de Boer RA, Maisel, A., Cleland J, Kozhuharov N., et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715-731.

[19] Januzzi JL, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, et al. N-terminal pro-B-type natriuretic peptide in the Emergency Department: the ICON-RELOADED Study. J Am Coll Cardiol 2018;**71**:1191–1200.

[20] van Kimmenade RR, Januzzi JL Jr, Bakker JA, Houben AJ, Rennenberg R, Kroon AA, et al. Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. J Am Coll Cardiol 2009;53:884-90.

[21] Ibrahim N, Januzzi JL. The potential role of natriuretic peptides and other biomarkers in heart failure diagnosis, prognosis and management. Expert Rev Cardiovasc Ther 2015;13:1017-30.

[22] Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. J Am Coll Cardiol 2006;47:91-97.

[23] Richards M, Nicholls MG, Espiner EA, Lainchbury J G, Troughton RW, Elliott J, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. J Am Coll Cardiol. 2006;47:52-60.

[24] Bayes-Genis A, Lloyd-Jones DM, Van Kimmenade RRJ, Lainchbury JG, Richards AM, Ordonez-Llanos J, Santalo M, Pinto YM, Januzzi JL. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med 2007;**167**:400–407.

[25] Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, Frohlich ED. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;**43**:1590–1595.

[26] McCullough PA, Sandberg KR. B-type natriuretic peptide and renal disease. Heart Fail Rev. 2003;8:355-358.

[27] Apple FS, Daniels LB, Januzzi J, Omland T, Ordonez-Llanos J, Jaffe A. Role of BNP vs NT-proBNP Testing in the Age of New Drug Therapies: Sacubitril-Valsartan. Clin Chem 2019;65:1076-1083.

[28] Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 2015;131:54-61.

[29] Myhre PL, Vaduganathan M, Claggett B, Packer M, Desai AS, Rouleau JL, et al. B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. J Am Coll Cardiol. 2019;73:1264-1272.

[30] Halfinger B, Hammerer-Lercher A, Amplatz B, Sarg B, Kremser L, Lindner HH. Unraveling the Molecular Complexity of O-Glycosylated Endogenous (N-Terminal) pro-B-Type Natriuretic Peptide Forms in Blood Plasma of Patients with Severe Heart Failure. Clin Chem 2017;63:359-368.

[31] Amplatz B, Sarg B, Faserl K, Hammerer-Lercher A, Mair J, Lindner HH. Exposing the High Heterogeneity of Circulating Pro B-Type Natriuretic Peptide Fragments in Healthy Individuals and Heart Failure Patients, Clin Chem 2020;66:1200-9.

[32] Ibrahim NE, McCarthy CP, Shrestha S, Gaggin HK, Mukai R, et al. Effect of Neprilysin Inhibition on Various Natriuretic Peptide Assays. J Am Coll Cardiol 2019;73:1273-84.

Table 1: Summary data of the past four questionnaires.

	NP in EU 2006	**NP in EU 2009**	**NP in 2013**		**NP in EU 2019**
			EU	**North America**	
Total participants (n)*	220	303	442	91	347
Countries	8	39	36	n.a.	33
Universities/Teaching/Tertiary Care (%)	55	58	50	64	61
NP participants (%)	56	68	67	58	77
NP participants (n)	123	206	294	53	266
Data including only NP participants:					
24 h laboratory service (%)	95	83	93	96	93
Age or gender related decision limits (%)**	8.5	21	NT-proBNP: 45 BNP: 5	NT-proBNP: 47 BNP: 10	NT-proBNP: 25 BNP: 0
Accreditation/certification (%)	n.a.	n.a.	69	96	73
EQA (%)	79	85	84	96	92

* Total number of responses with usable data. ** values for the 2013 EU/North American and the 2019 surveys are summarized percentages of acute and chronic heart failure stated separately for BNP and NT-proBNP, respectively.

NP, natriuretic peptide; NT, N-terminal; EU, European Union; n.a., not applicable; EQA, external quality assurance.

Table 2: HF cut-off values according to guidelines and recommendations that were published at the time of this survey. The classification into acute or chronic HF was taken from the statements in these publications.

Guideline/Recommendation	BNP	NT-proBNP	COR, LOE	Reference
Acute and chronic HF				
ESC guidelines 2008	Rule-out: <100 ng/L Grey zone: 100-400 ng/L Rule-in: >400 ng/L	Rule-out: <400 ng/L Grey zone: 100-2000 ng/L Rule-in: >2000 ng/L	n.a.	[12]
ACC/AHA guidelines 2009	Not stated	Not stated	IIa, A	[13]
ACCF/AHA guidelines 2013	Not stated	Not stated	I, A	[14]
ACC/AHA/HFSA guideline 2017, focused update	Not stated	Not stated	I	[15]
Chronic HF				
NICE national clinical guideline 2010 (UK)	Rule-out <100 ng/L 100-400 ng/L* >400 ng/L#	Rule-out: <400 ng/L 400-2000 ng/L* >2000 ng/L#	n.a.	[16]
ESC guidelines 2012	Rule-out <35 ng/L	Rule-out <125 ng/L	IIa, C	[11]
ESC guidelines 2016	Rule-out <35 ng/L	Rule-out <125 ng/L	(essential initial investigation)	[9]
NICE national clinical guideline update 2018 (UK)	NT-proBNP is favored	Rule-out: <400 ng/L 400-2000 ng/L* >2000 ng/L#	n.a.	[17]
ESC/HFA position paper/ practice guidance 2019	For age <50 years Rule-out: <35 ng/L Grey zone: 35-150 ng/L	For age <50 years Rule-out: <125 ng/L Grey zone: 125-600 ng/L	n.a.	[18]

	Rule-in: >150 ng/L	Rule-in: >600 ng/L		
Acute HF				
ESC recommendations 2012	Rule-out: <100 ng/L Grey zone: 100-500 ng/L Rule-in: >500 ng/L	Rule-out: 300 ng/L Rule in <50y: 450 ng/L 50-75y: 900 ng/L >75y: 1800 ng/L	n.a.	[10]
ESC guidelines 2012	Rule-out <100 ng/L	Rule-out <300 ng/L	IIa, C	[11]
ESC guidelines 2016	Rule-out <100 ng/L	Rule-out <300 ng/L	I, A	[9]
ESC/HFA position paper/ practice guidance 2019	For age <50 years Rule-out: <100 ng/L Grey zone: 100-400 ng/L Rule-in: >400 ng/L	Rule-out <50y: 300 ng/L Rule in <50y: 450 ng/L 50-75y: 900 ng/L >75y: 1800 ng/L	n.a.	[18]
FDA cleared package inserts (summarized for the different assays)	100 ng/L	<75y: 125 ng/L >75y: 450 ng/L	n.a.	

*Patients with these medium values should be referred to a transthoracic Doppler 2D echocardiography and specialist assessment within 6 weeks.

#Patients with these high NP levels have a poor prognosis and should be referred to a transthoracic Doppler 2D echocardiography and specialist assessment within 2 weeks.

COR, class of recommendation; LOE, level of evidence; ESC, European Society of Cardiology; ACC or ACCF, American College of Cardiology Foundation; AHA, American Heart Association; NICE, the National Institute for Health and Care Excellence; HFA, Heart Failure Association; y; years; FDA, Food and Drug Administration.

Figure legends:

Figure 1: Methods used for BNP and NT-proBNP measurement.

A: NT-proBNP was still the most widely used NP method with a clear preference for the Roche assay (58%). B: Twenty (7.5%) laboratories measured more than one NP and mostly combined NT-proBNP from with a BNP assay from the same or a different company.

Figure 2: Flow chart for decision limits.

There were 266 participants, who answered HF questions. Because some laboratories used more than one assay for BNP or NT-proBNP measurement, these participants were also able to answer questions concerning cut-offs for both, BNP and NT-proBNP. Thus, there were a maximum of 223 answers for NT-proBNP and a maximum of 61 answers for BNP possible. Since not all participants answered all questions, the number of responses is lower.

*, ESC recommendation 2012; #, ESC/HFA 2019 position paper; §, FDA threshold stated in the package insert not differentiating between acute and chronic HF.

Figure 3: Decision limits for rule-out acute HF

A: The decision limits for NT-proBNP were less diverse than in the previous survey with the most frequent decision limit of 300 ng/L, which is stated in the ESC guidelines. B: For BNP there was a clear preference for the 100 ng/L decision limit, which is guideline conform. Diagonal lines in columns, decision limits as stated either in the ESC guidelines published 2016.

Figure 4: Source of rule-out protocol for natriuretic peptide

The protocol derived from different sources with the most common one from the ESC guidelines.

Figure 1 A,B

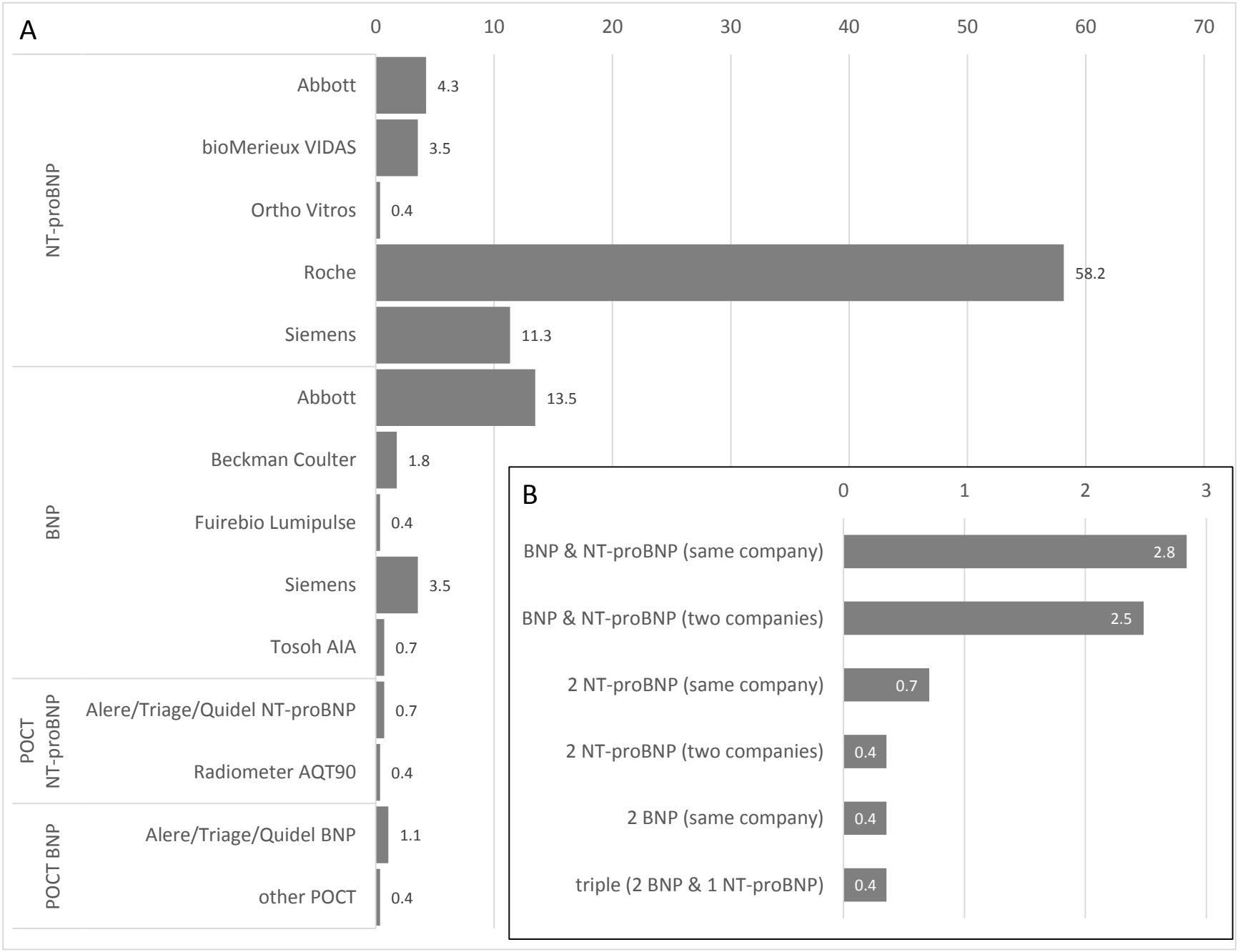

A
0
10
20
30
40
50
60
70
NT-proBNP
Abbott
4.3
bioMerieux VIDAS
3.5
Ortho Vitros
0.4
Roche
58.2
Siemens
11.3
BNP
Abbott
13.5
Beckman Coulter
1.8
Fuirebio Lumipulse
0.4
Siemens
3.5
Tosoh AIA
0.7
POCT NT-proBNP
Alere/Triage/Quidel NT-proBNP
0.7
Radiometer AQT90
0.4
POCT BNP
Alere/Triage/Quidel BNP
1.1
other POCT
0.4
B
0
1
2
3
BNP & NT-proBNP (same company)
2.8
BNP & NT-proBNP (two companies)
2.5
2 NT-proBNP (same company)
0.7
2 NT-proBNP (two companies)
0.4
2 BNP (same company)
0.4
triple (2 BNP & 1 NT-proBNP)
0.4

Figure 2

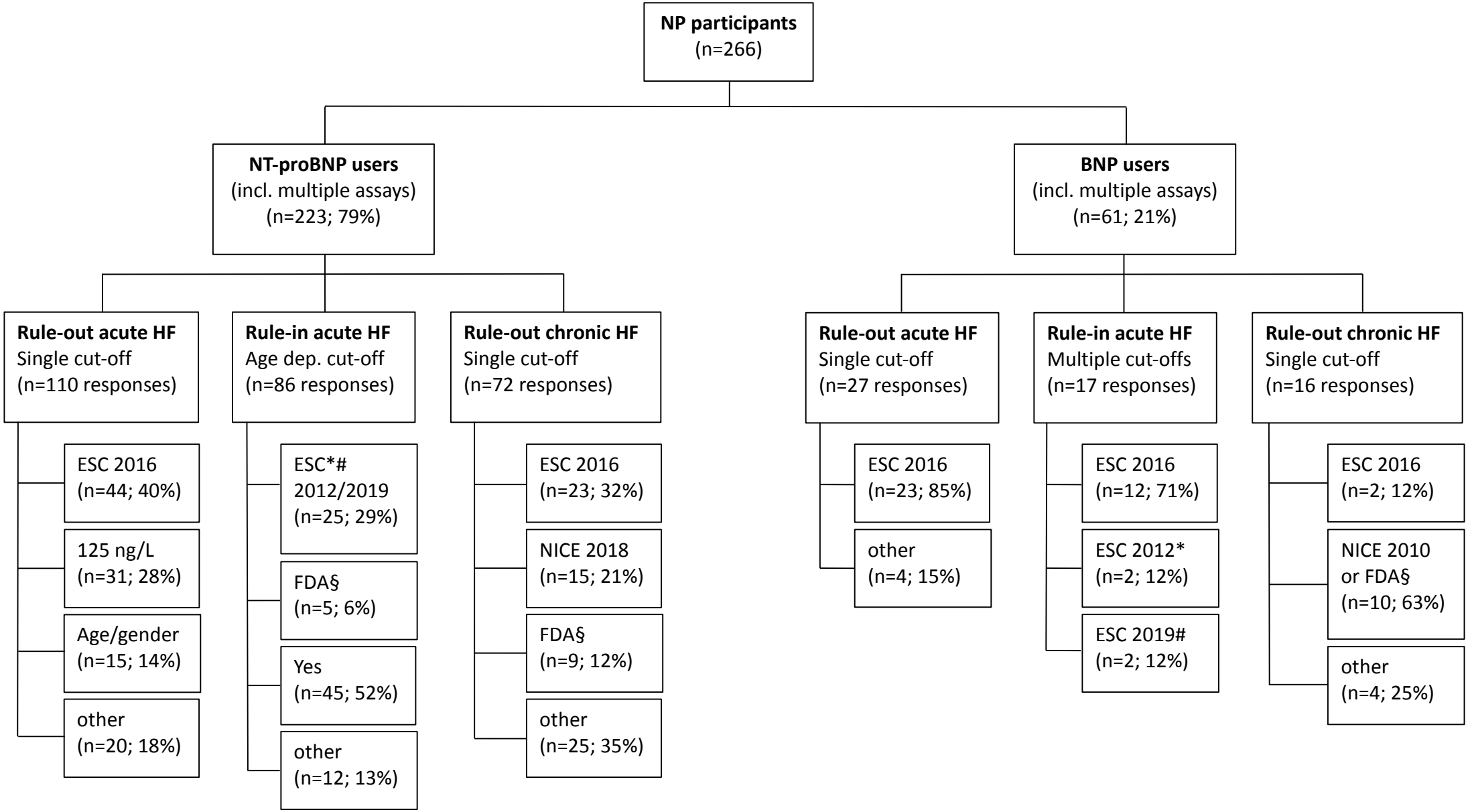

NP participants
(n=266)
NT-proBNP users
(incl. multiple assays)
(n=223; 79%)
BNP users
(incl. multiple assays)
(n=61; 21%)
Rule-out acute HF
Single cut-off
(n=110 responses)
Rule-in acute HF
Age dep. cut-off
(n=86 responses)
Rule-out chronic HF
Single cut-off
(n=72 responses)
Rule-out acute HF
Single cut-off
(n=27 responses)
Rule-in acute HF
Multiple cut-offs
(n=17 responses)
Rule-out chronic HF
Single cut-off
(n=16 responses)
ESC 2016
(n=44; 40%)
125 ng/L
(n=31; 28%)
Age/gender
(n=15; 14%)
other
(n=20; 18%)
ESC*#
2012/2019
(n=25; 29%)
FDA§
(n=5; 6%)
Yes
(n=45; 52%)
other
(n=12; 13%)
ESC 2016
(n=23; 32%)
NICE 2018
(n=15; 21%)
FDA§
(n=9; 12%)
other
(n=25; 35%)
ESC 2016
(n=23; 85%)
other
(n=4; 15%)
ESC 2016
(n=12; 71%)
ESC 2012*
(n=2; 12%)
ESC 2019#
(n=2; 12%)
ESC 2016
(n=2; 12%)
NICE 2010
or FDA§
(n=10; 63%)
other
(n=4; 25%)

Figure 3 A

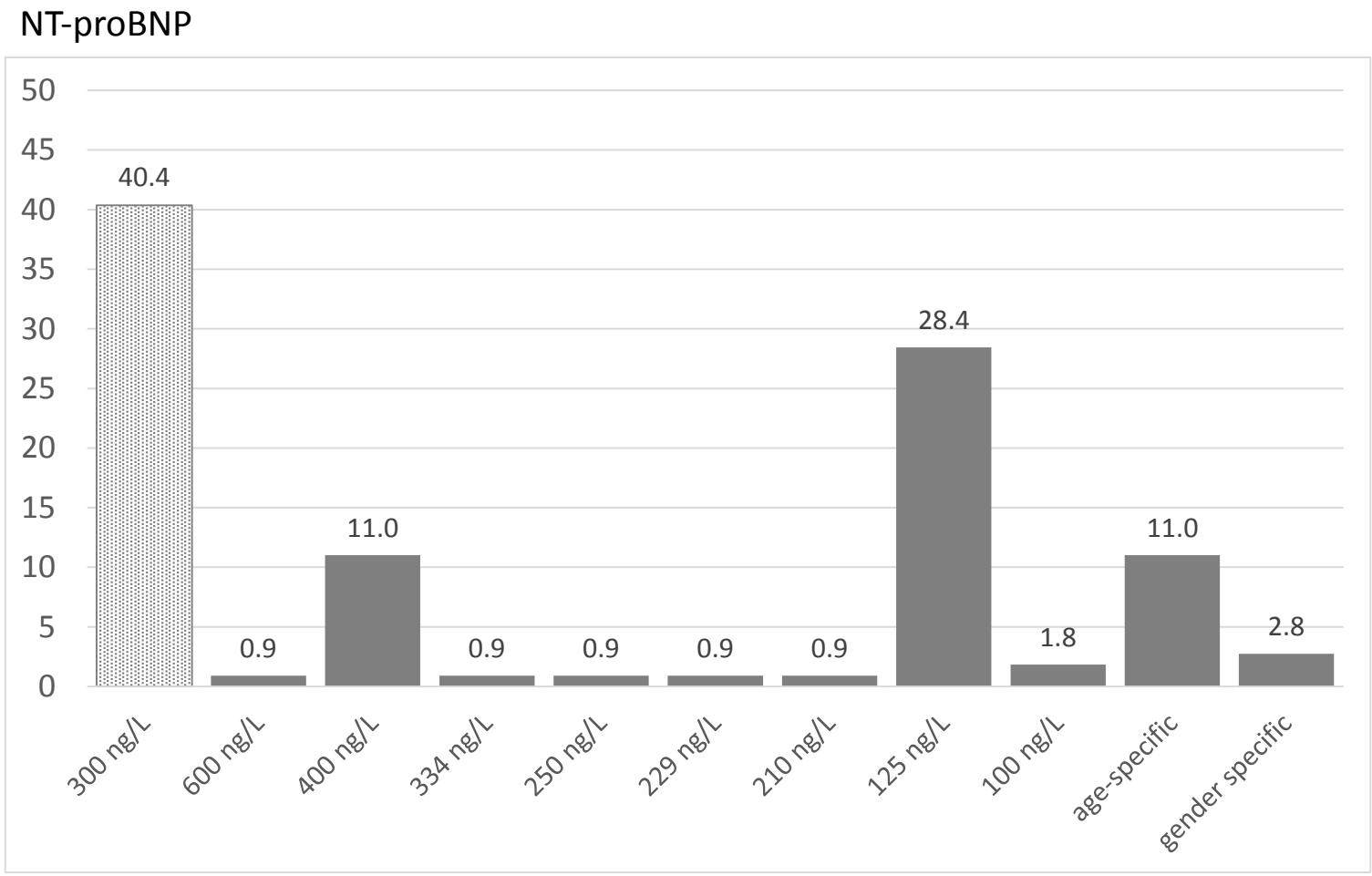

NT-proBNP
50
45
40
35
30
25
20
15
10
5
0
40.4
0.9
11.0
0.9
0.9
0.9
0.9
28.4
1.8
11.0
2.8
300 ng/L
600 ng/L
400 ng/L
334 ng/L
250 ng/L
229 ng/L
210 ng/L
125 ng/L
100 ng/L
age-specific
gender specific

Figure 3 B

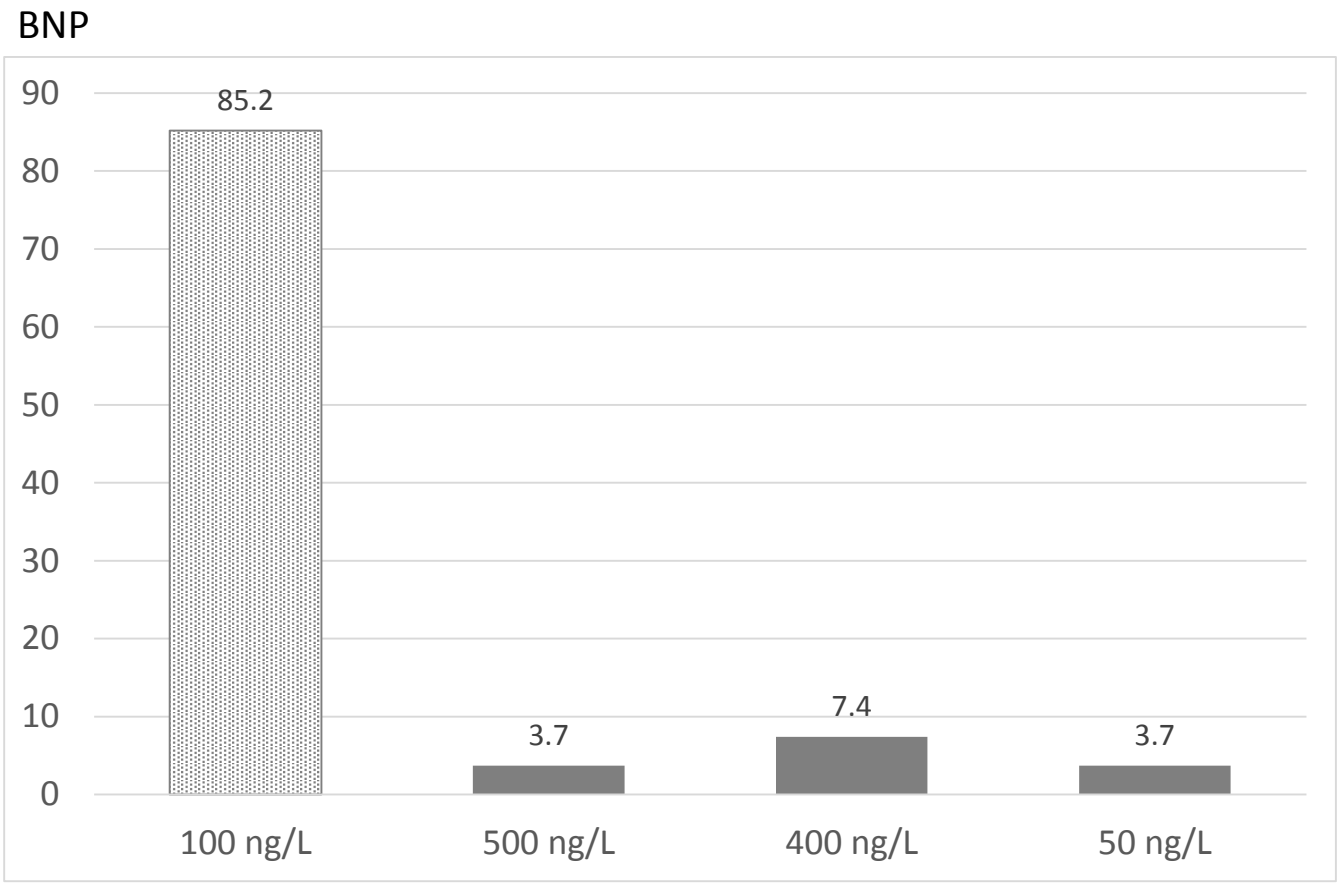
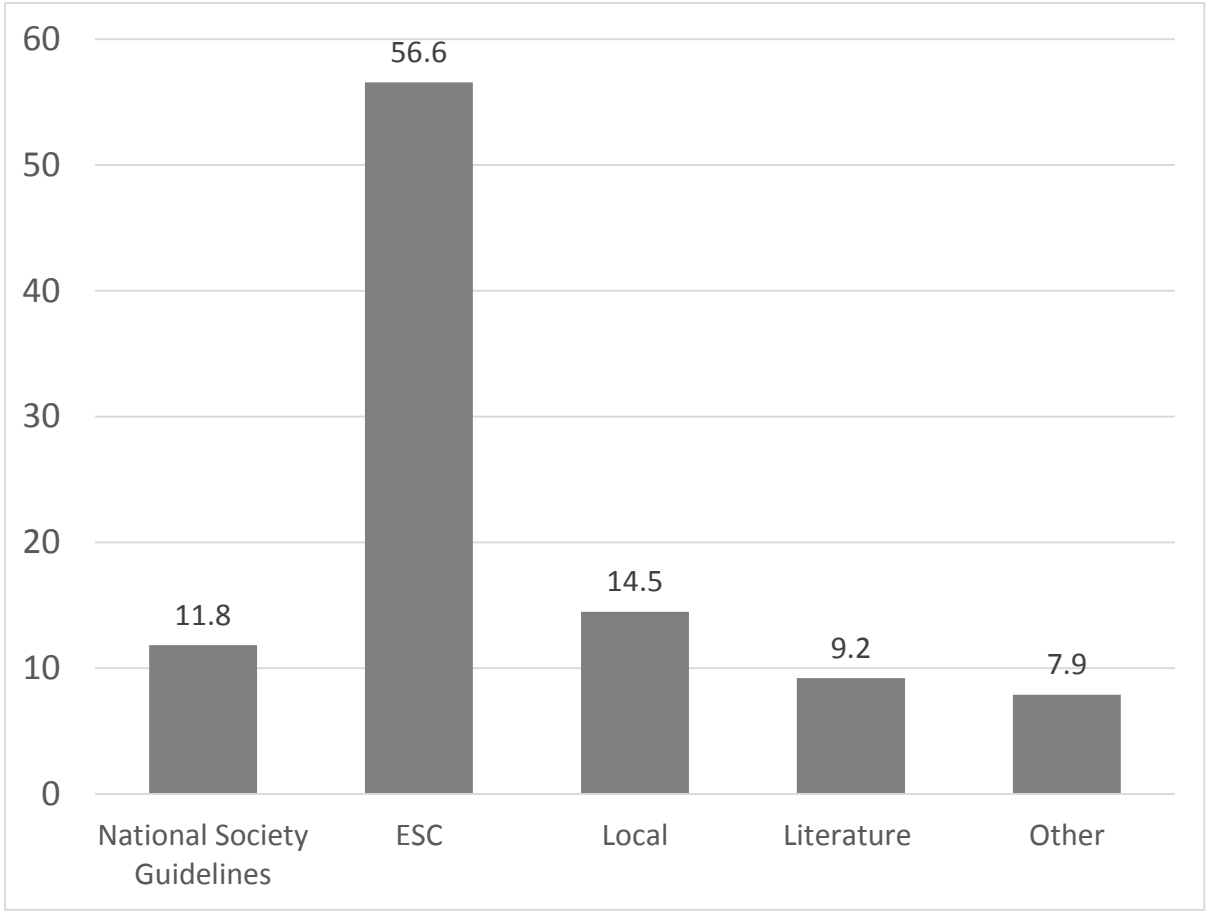

BNP
90
80
70
60
50
40
30
20
10
0
85.2
3.7
7.4
3.7
100 ng/L
500 ng/L
400 ng/L
50 ng/L

Figure 4


60
50
40
30
20
10
0
56.6
11.8
14.5
9.2
7.9
National Society Guidelines
ESC
Local
Literature
Other