18HLT10 CardioMet

Providing the measurement infrastructure to allow quantitative diagnostic methods for biomarkers of coronary heart diseases

A Joint Research Project within the European Metrology Research Programme EMPIR.

EMPIR EURAMET
The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

EMPIR Project CardioMet - Overview

- **11.3 million new cases of cardiac diseases and 1.8 million deaths/year in the EU with estimated costs of € 210 billion/year**
- **Large between-methods variability due to a lack of traceability chains required by IVD Regulation 2017/746**
- **Measurement of cardiac biomarkers is challenging due to the low concentrations, structural heterogeneity & complex biological matrix**

WP1: Biomarkers for long term CVD risk assessment

- Define metrology needs and performance specifications for conventional biomarkers
- Standardization of ApoA-I, B, C-I, C-II, C-III, E & apo(a) through the development of an IDMS RMP & CRMs
- Document the clinical utility of apolipoprotein profiling advanced lipoprotein testing

WP2: Biomarkers for acute myocardial infarction

- Development of a candidate reference method for cTnI
- Application to patient samples & EQA materials
- Development of a biosensor for quasi-continuous monitoring of cardiac biomarkers

WP3: Biomarkers for acute and chronic heart failure

- Reference a measurement procedure for NT-proBNP
- Application of reference measurement procedure for NT-proBNP to EQAS
- Understanding issues for 1-32 BNP measurements in clinics

EMPIR Project CardioMet - Consortium

BAM

UME

Leiden University
Medical Center

UPPSALA
UNIVERSITET

UK NEQAS

WP1: Biomarkers for patient stratification and long-term CVD risk assessment

Objective: provide the metrological support needed for clinicians to accurately predict CVD risk and properly stratify patients to select the best therapy

- ✓ Task 1.1 : document the state of the art in terms of CVD risk assessment and patient stratification based on conventional biomarkers with the goal of defining metrology needs and performance specifications for accurately estimating long-term CVD risk.
- ✓ Task 1.2 : standardization of a panel of apolipoproteins (apo) A-I, B, C-I, C-II , C-III, E and apo (a) through the development of an IDMS reference method and matrix CRMs
- ✓ Task 1.3 : document the clinical utility of alipoprotein profiling vs currently used lipid markers and determine performance specification of advanced lipoprotein testing methods for accurate CVD risk assessment and patient stratification.

Why reliable lipid / lipoprotein testing is important

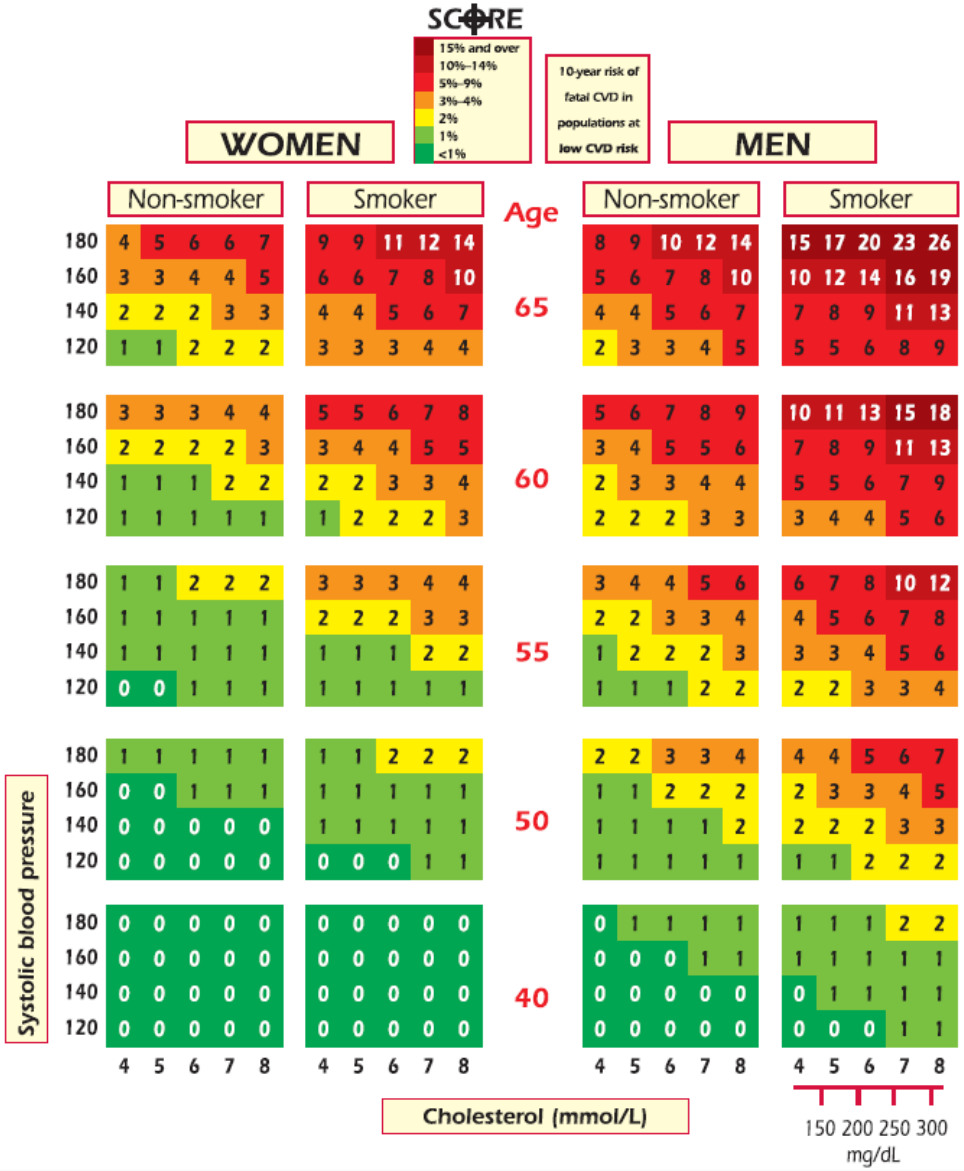


Table 6 Risk factor goals and target levels for important cardiovascular risk factors

Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20–25 kg/m^2. Waist circumference <94 cm (men) or <80 cm (women).
Blood pressure	<140/90 mmHg[a]
Lipids[b] LDL[c] is the primary target	**Very high-risk: <1.8 mmol/L (<70 mg/dL),** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)[d] **High-risk: <2.6mmol/L (<100 mg/dL),** or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) **Low to moderate risk: <3.0 mmol/L (<115 mg/dL).**
HDL-C	No target but >1.0 mmol/L (>40mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.
Triglycerides	No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c <7%. (<53 mmol/mol)

Task 1.1: Defining metrology needs for estimating long-term CVD risk with current biomarkers

Objective : document the state of the art regarding CVD risk prediction on the basis of diagnostic tests currently used in day to day clinical practice and determine what is the measurement uncertainty needed for routine methods to accurately stratify patients based on concentration of conventional biomarkers (e.g. LDL-C, non-HDL-C, TG, …).

European Heart Journal (2009) **30**, 2165–2173
doi:10.1093/eurheartj/ehp299

CardioPuls

SWEDEHEART: Sweden's new online cardiac registry, the first of its kind

Covering all hospitals in Sweden, SWEDEHEART is unique because it allows long-term follow-up and immediate feedback, says Ulf Stenestrand, MD, PhD, Associate Professor of cardiology and Senior consultant interventional cardiologist, Department of Cardiology, University Hospital, Linköping, Sweden, and President of SWEDEHEART.

- ✓ Using the Swedish cardiac registry, establish the relationship between the concentration of conventional biomarkers (e.g. LDL-C, non-HDL-C, ApoB…) and CVD events with the objective to estimate the rate of residual CVD risk during high intensity secondary preventive treatment

Task 1.1: conventional biomarkers

Clinical Chemistry 56:6
977–986 (2010)

Lipids, Lipoproteins, and Cardiovascular Risk Factors

Seven Direct Methods for Measuring HDL and LDL Cholesterol Compared with Ultracentrifugation Reference Measurement Procedures

W. Greg Miller,[1*] Gary L. Myers,[2] Ikunosuke Sakurabayashi,[3] Lorin M. Bachmann,[1] Samuel P. Caudill,[2] Andrzej Dziekonski,[1] Selvin Edwards,[2] Mary M. Kimberly,[2] William J. Korzun,[1] Elizabeth T. Leary,[4] Katsuyuki Nakajima,[5] Masakazu Nakamura,[6] Göran Nilsson,[7] Robert D. Shamburek,[8] George W. Vetrovec,[1] G. Russell Warnick,[9] and Alan T. Remaley[8]

- ✓ Organize an EQA scheme to document accuracy and between-methods agreement of assays relying on conventional biomarkers with a focus on direct LDL-C assays in presence of elevated concentrations of triglycerides
- ✓ Propose recommendations for analytical performance criteria for assays relying on conventional biomarkers currently used to estimate long-term CVD risk.

Lipids Analytical Performance Criteria Work Group

- **Nader Rifai, PhD** *(Boston Children's Hospital)*
- **Mariko Harada-Shiba, MD, PhD** *(National Cerebral and Cardiovascular Center)*
- **Vincent Delatour, PhD** *(Laboratoire National de Métrologie et d'Essais)*
- **Jacques Genest, MD, FRCP©, FAHA** *(McGill University Health Centre - Division of Cardiology)*
- **Greg Miller Jr, PhD** *(Virginia Commonwealth University)*
- **Anette Varbo, MD, PhD** *(Region Hovedstaden - Copenhagen University Hospital)*
- **Børge Nordestgaard, MD, DMSc** *(University of Copehagen)*
- **John Chapman, PhD** *(Pierre and Marie Curie - Sorbonne Université)*

Centers for Disease Control and Prevention

- **Hubert Vesper, PhD**, *Director – CDC's Clinical Standardization Programs*
- **Uliana Danilenko, PhD**
- **Nasim Khoshnam, BS, MS**
- **Fidelia Pokuah, BS, MPH**

Lipids Analytical Performance Criteria Work Group

Background

- Accurate blood lipid measurements are critical for correct patient classification and monitoring the success of treatments
- Accuracy and precision requirements for blood lipid tests were defined by the NCEP over 20 years ago
- Findings about the accuracy and reliability of tests results from patients with certain conditions and new target goals for blood lipids outlined in new clinical practice guidelines warrant the review and revision of current performance criteria

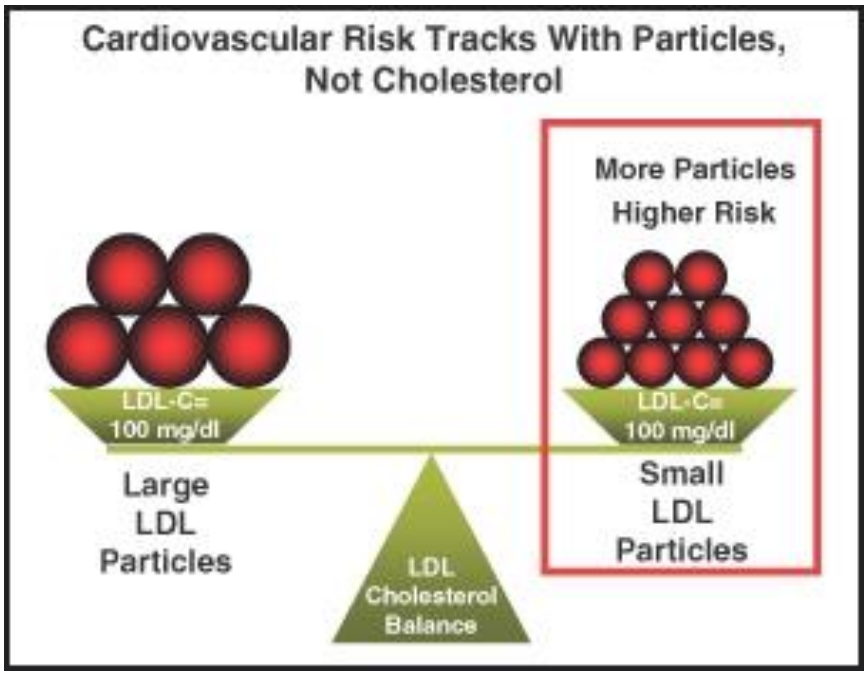
Objective

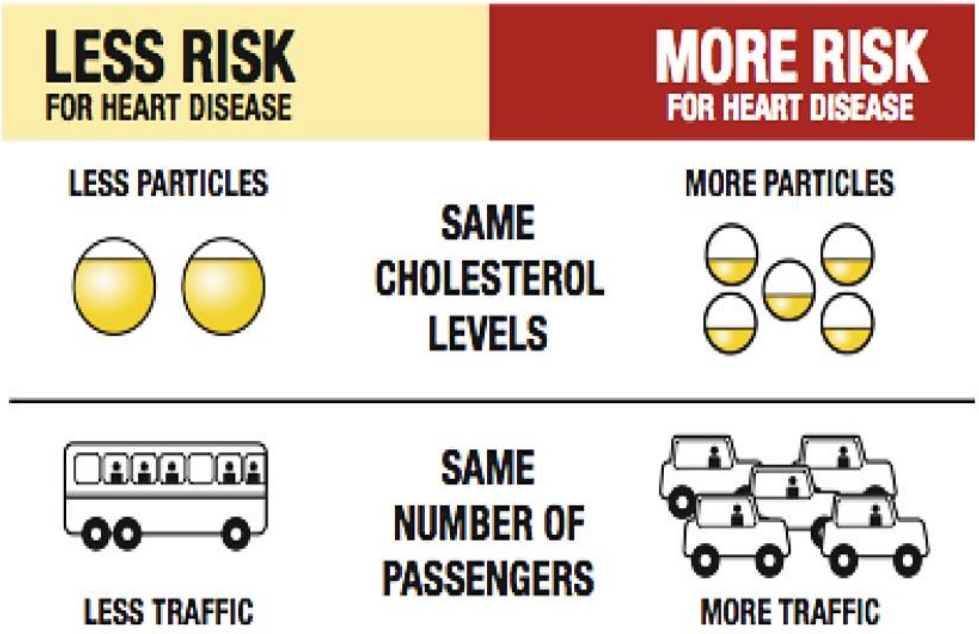
- Review current analytical performance criteria in light of analytical performance of blood lipid testing
- Develop recommendations for new analytical performance goals where needed
- Publish recommendations in peer reviewed journal

Scope

- The working group will focus on currently used performance criteria for total cholesterol, total glycerides, HDL-cholesterol, LDL-cholesterol and will investigate the possibility to establish performance goals for other CVD markers such as non-HDL-cholesterol and apoB.

Beyond LDL-C in CVD risk assessment





Beyond LDL-C in CVD risk assessment

Clinical Chemistry 55:3
407–419 (2009)

Special Report

Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

John H. Contois,[1*†] Joseph P. McConnell,[2] Amar A. Sethi,[3] Gyorgy Csako,[3] Sridevi Devaraj,[4] Daniel M. Hoefner,[5] and G. Russell Warnick[6]

"In light of the mounting evidence, the members of this working group of the Lipoproteins and Vascular Diseases Division of the AACC believe that **apoB and alternate measures of LDL particle concentration should be recognized and included in guidelines, rather than continuing to focus solely on LDL-C.**"

Clinical Chemistry 59:5
752–770 (2013)

Special Report

Association of Apolipoprotein B and Nuclear Magnetic Resonance Spectroscopy–Derived LDL Particle Number with Outcomes in 25 Clinical Studies: Assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on Best Practices

Thomas G. Cole,[1*] John H. Contois,[2] Gyorgy Csako,[3] Joseph P. McConnell,[4] Alan T. Remaley,[3] Sridevi Devaraj,[5] Daniel M. Hoefner,[4] Tonya Mallory,[4] Amar A. Sethi,[6] and G. Russell Warnick[4]

CONCLUSIONS: In most studies, both apo B and LDL-P were comparable in association with clinical outcomes. The biomarkers were nearly equivalent in their ability to assess risk for CVD and both have consistently been shown to be stronger risk factors than LDL-C. We support the adoption of apo B and/or LDL-P as indicators of atherogenic particle numbers into CVD risk screening and treatment guidelines. Currently, in the opinion of this Working Group on Best Practices, apo B appears to be the preferable biomarker for guideline adoption because of its availability, scalability, standardization, and relatively low cost.

Beyond LDL-C in CVD risk assessment

Clinical Chemistry 64:7
1006–1033 (2018)

EUROPEAN FEDERATION OF CLINICAL CHEMISTRY
AND LABORATORY MEDICINE

Special Report

Quantifying Atherogenic Lipoproteins: Current and Future Challenges in the Era of Personalized Medicine and Very Low Concentrations of LDL Cholesterol. A Consensus Statement from EAS and EFLM

Michel R. Langlois,[1*] M. John Chapman,[2] Christa Cobbaert,[3] Samia Mora,[4] Alan T. Remaley,[5] Emilio Ros,[6] Gerald F. Watts,[7] Jan Borén,[8] Hannsjörg Baum,[9] Eric Bruckert,[10] Alberico Catapano,[11] Olivier S. Descamps,[12] Arnold von Eckardstein,[13] Pia R. Kamstrup,[14] Genovefa Kolovou,[15] Florian Kronenberg,[16] Anne Langsted,[14] Kari Pulkki,[17] Nader Rifai,[18] Grazyna Sypniewska,[19] Olov Wiklund,[8] and Børge G. Nordestgaard,[14] for the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative

Despite the overwhelming evidence that LDLC-targeted strategies effectively reduce CVD, there is substantial between-subject variability in the response to lipid-lowering therapies and the reduction of CVD risk *(7)*. Furthermore, accumulating evidence indicates that a focus solely on the assessment and management of LDLC is not an optimal strategy for all patients

Clearly, additional biomarkers beyond LDLC are needed to identify and treat more persons at high CVD risk

Consensus-based recommendation. Non-HDLC and apoB tests are more accurate than dLDLC and cLDLC, especially for measurements in samples that are hypertriglyceridemic, nonfasting, or at low LDLC concentrations.

Beyond LDL-C in CVD risk assessment

Clinical Chemistry 59:5
723–725 (2013)

Editorials

NMR ES-DMA

Immuno-nephelometry
Immuno-turbidimetry
LC/MS/MS

VAP

NMR
ES-DMA
VLP

Beyond LDL Cholesterol in Assessing Cardiovascular Risk: apo B or LDL-P?

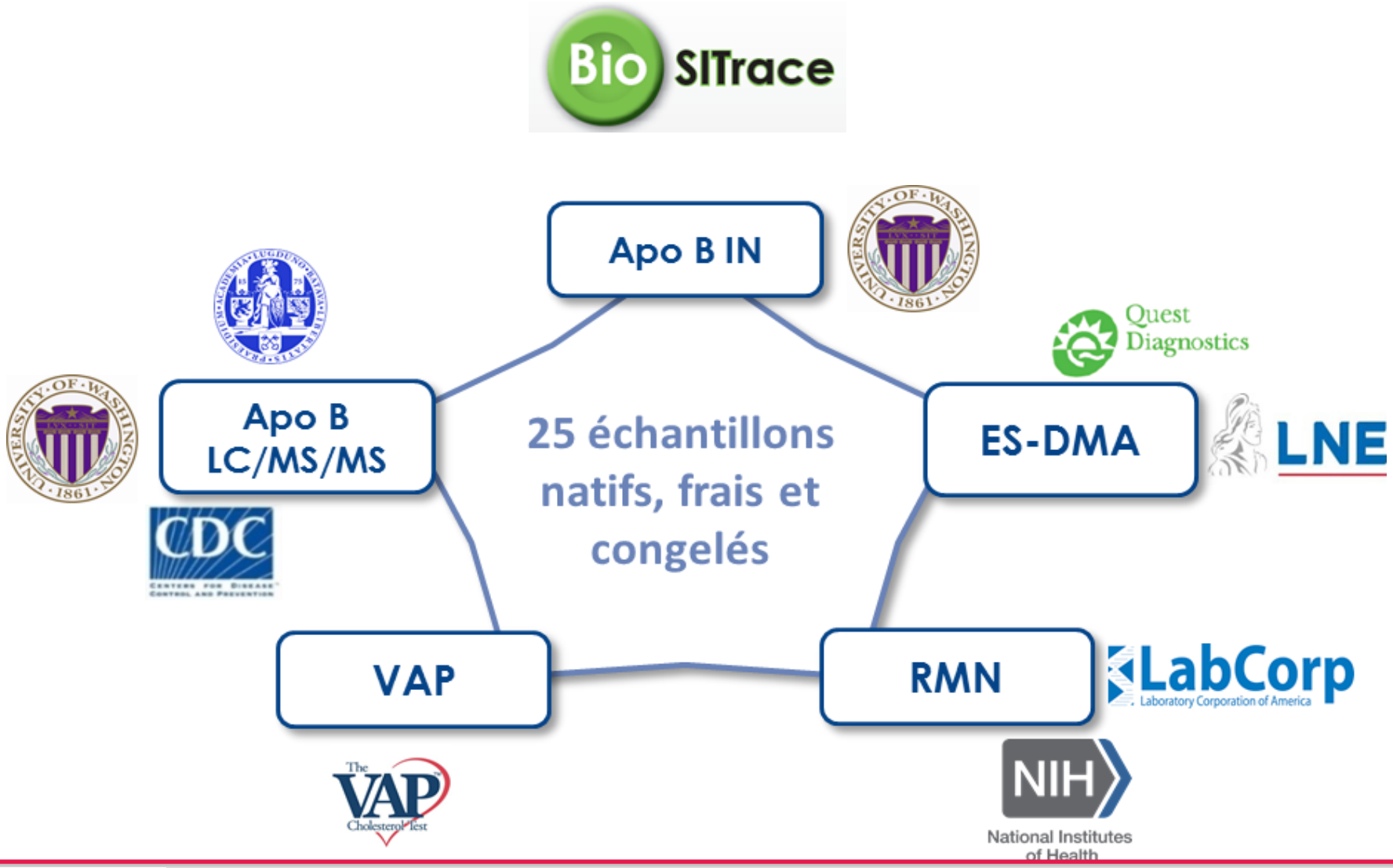
Stephen R. Master[1,3*] and Daniel J. Rader[2,3*]

Plasma concentrations of LDL cholesterol (LDL-C)[4] are positively associated with increased risk of atherosclerotic cardiovascular disease. There is a variety of robust evidence indicating that this association is causal in nature. First, rare and common genetic variants that specifically influence LDL-C concentrations are also strongly associated with cardiovascular risk (*1*). Second, interventions that reduce LDL-C, especially but not exclusively statin therapy, reproducibly reduce cardiovascular events (*2*). In fact, the data with statins are so strong that they are often used in patients whose LDL-C concentrations are not particularly increased, a setting in which statins have still been shown to reduce cardiovascular risk. Thus there is substantial interest in lipoprotein-related biomarkers that provide information about future cardiovascular risk above and beyond LDL-C itself.

Several methods have emerged that allow a more direct quantification of the number of LDL particles. Because an LDL particle contains a single molecule of apo B, it is possible to directly estimate the number of particles through a simple measurement of apo B concentration (particularly when expressed in molar units). apo B is typically measured by immunonephelometry or immunoturbidimetry, and reagents are available from a wide variety of manufacturers. Standardization of these measurements has been facilitated by the availability of WHO-IFCC reference materials (SP3–07, SP3–08) (*4, 5*). apo B analytical measurements have shown good reproducibility across laboratories (6%–8% CV in 2012 College of American Pathologists survey), although a number of preanalytical biological confounders, including diurnal and seasonal effects, have been described (*6*).

How do the different ALT methods compare with each other?

Comparability of non-HDL-P measurements by IN, LC-MS/MS, NMR, ES-DMA and VAP



Comparability of non-HDL-P measurments by IN, LC-MS/MS, NMR, ES-DMA and VAP

Clinical Chemistry 64:10
1485–1495 (2018)

Lipids, Lipoproteins, and Cardiovascular Risk Factors

Comparability of Lipoprotein Particle Number Concentrations Across ES-DMA, NMR, LC-MS/MS, Immunonephelometry, and VAP: In Search of a Candidate Reference Measurement Procedure for apoB and non-HDL-P Standardization

Vincent Delatour,[1*†] Noemie Clouet-Foraison,[1†] François Gaie-Levrel,[1] Santica M. Marcovina,[2] Andrew N. Hoofnagle,[3] Zsuzsanna Kuklenyik,[4] Michael P. Caulfield,[5] James D. Otvos,[6] Ronald M. Krauss,[7] Krishnaji R. Kulkarni,[8] John H. Contois,[9] Alan T. Remaley,[10] Hubert W. Vesper,[4] Christa M. Cobbaert,[11] and Philippe Gillery[12]

- ✓ **The different candidate reference methods for non-HDL-P do not yet provide equivalent results**
- ✓ **LC/MS/MS is the most suitable candidate RMP to standardize ApoB as it would provide results traceability to the SI**
- ✓ **Primary calibrators are needed to calibrate the IDMS RMP**

Apolipoproteins by Mass Spectrometry (WG-APO MS)

Membership

Name	Position	Country	Term	Time in Office
C. Cobbaert	Chair	NL	1st	2017 01 - 2019 12
U. Ceglarek	Member	DE		
V. Delatour	Member	FR		
J. Dittrich	Member	DE		
C. Hirtz	Member	FR		
A. Hoofnagle	Member	US		
Z. Kuklenyik	Member	US		
L.R. Ruhaak	Member	NL		
H.W. Vesper	Member	US		
H. Althaus	IVD Representative/Siemens	DE		
U. Prinzing	IVD Representative/Roche	DE		
G.M. Kostner	Consultant	AT		
H. Schimmel	Consultant	BE		
I. Zegers	Consultant	BE		

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Terms of Reference

- To achieve standardization of a panel of clinically relevant serum apolipoproteins (apo) A-I, B, C-I, C-II , C-III, E and apo (a) (including qualitative phenotyping where needed). Standardization is done in such a way that measurement results are traceable to SI as outlined in ISO 17511. Other traceability chains will be used in cases where traceability to SI cannot be achieved.
- To evaluate clinical performance and clinical utility of serum apolipoprotein panel(s) for CVD risk stratification and treatment, in comparison to or together with contemporary blood lipids.

Task 1.2 : Apolipoprotein profiling by LC/MS/MS

Objective : set up an MS-based reference measurement system for standardization of a panel of clinically relevant apolipoproteins

- ✓ Production and characterization of primary calibrators
- ✓ Development of an IDMS-based reference measurement procedure for the multiplexed analysis of apoA-I, B, C-I, C-II, C-III, E and Apo(a)
- ✓ Production and characterization of commutable CRMs and EQA materials
- ✓ Evaluation of the clinical performance and clinical utility of apolipoprotein profiling for CVD risk stratification and treatment

Task 1.3 : Towards advanced lipoprotein testing?

Objectives :

- ✓ **Document the clinical utility of advanced lipoprotein testing methods for accurate CVD risk assessment and patient stratification;**
- ✓ **Propose performance specification and suitable routes for standardization**

- ➢ identify theoretical subgroups of patients with acute coronary syndrome and specific lipid disorders for which apolipoprotein profiling and other advanced lipoprotein testing methods are expected to have the highest value added for CVD risk assessment and patient stratification compared with conventional makers
- ➢ Establish a patients cohort and measure samples by apolipoprotein profiling and other available advanced lipoprotein testing methods with the objective to :
  - document the clinical utility of advanced lipoprotein testing to unravel residual CVD risk that cannot be diagnosed with conventional markers,
  - establish standardized reference ranges for apolipoproteins

Circulation

American Heart Association.

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Are advanced lipoprotein testing and subfractionation clinically useful?

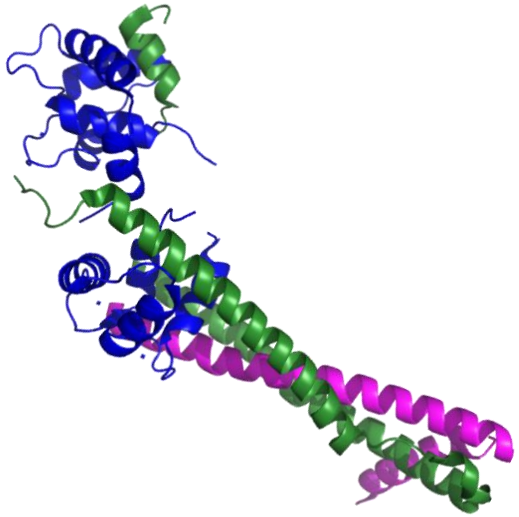
Advanced Lipoprotein Testing and Subfractionation Are Not (Yet) Ready for Routine Clinical Use

Samia Mora, MD, MHS

Mora et al. Circulation 2009;119:2396-2404

Cardiac troponin (cTn): Complex of three regulatory proteins

- Troponin T
  - → Specific marker
  - → 35 924 Da
  - → Binds to Tropomyosin
- Troponin I
  - → Specific marker
  - → 24 008 Da
  - → Binds to Actin
- Troponin C
  - → Cardiac and slow skeletal same
  - → 18 403 Da
  - → Ca binding part



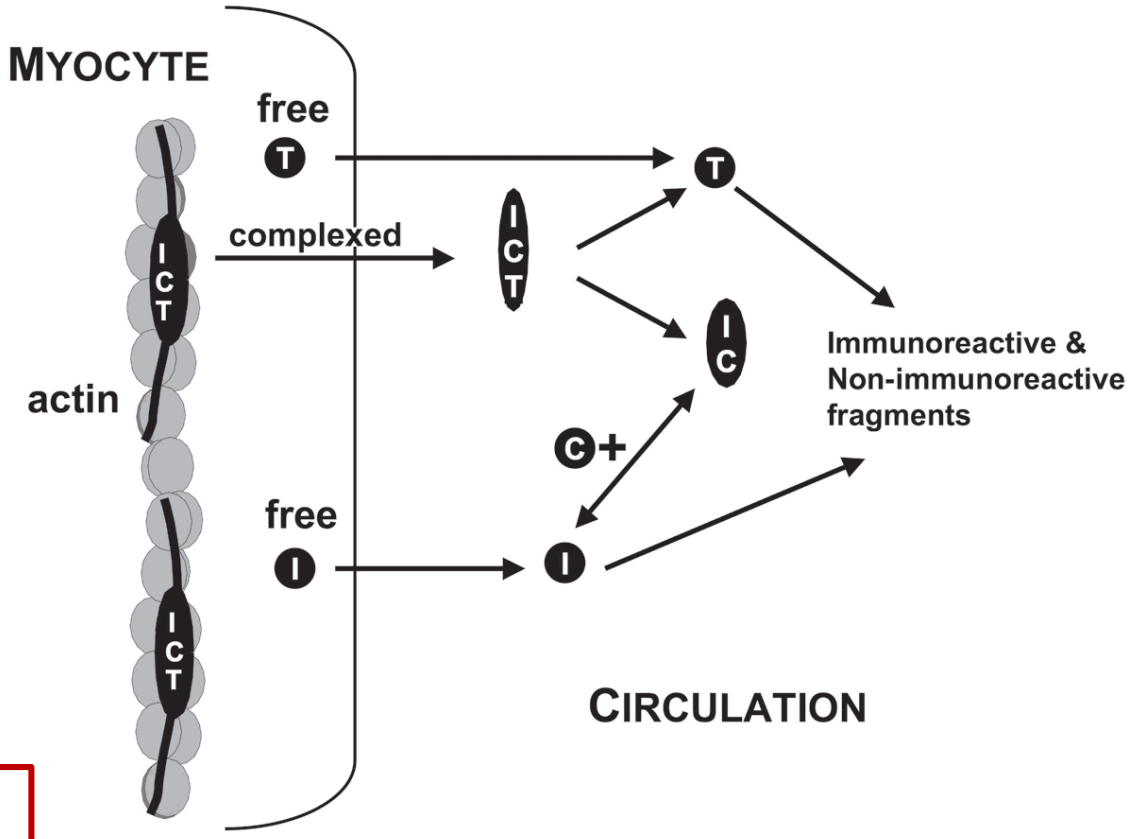
https://en.wikipedia.org/wiki/Troponin#/media/File:Troponin_Ribbon_Diagram.png

⇒ Diagnosis of acute coronary syndrome in combination with electrocardiograms

WP2: Troponin Degradation in Blood

After release into the blood:

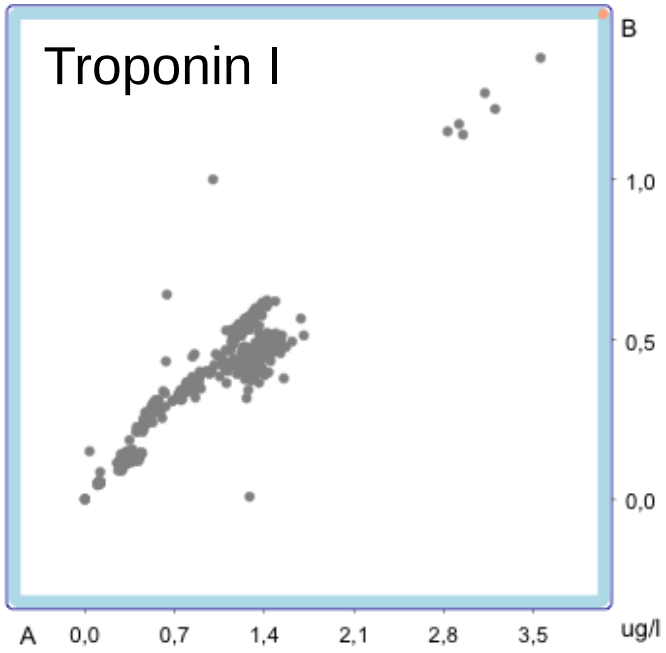
- Trimer ICT
- Dimer IC
- Monomers I, C, T
- Fragments
- Phosphorylation
- Acetylation
- Glycosylation



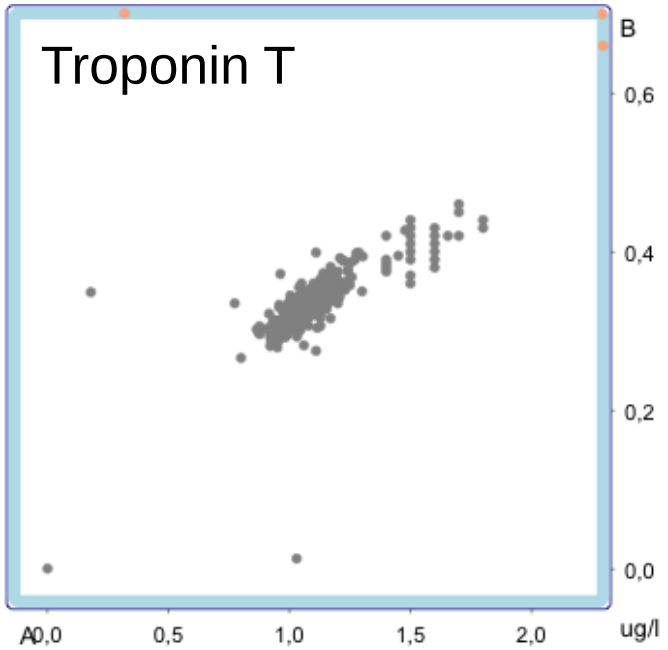
For diagnosis, the increase of cTn over 3 h is important

Wu A. Analytical Issues for Clinical Use of Cardiac Troponin. Cardiovascular Biomarkers: Pathophysiology and Disease Management, Morrow DA (ED.), 2006.

Proficiency test for cardiac markers CM 4/19 organised by RfB



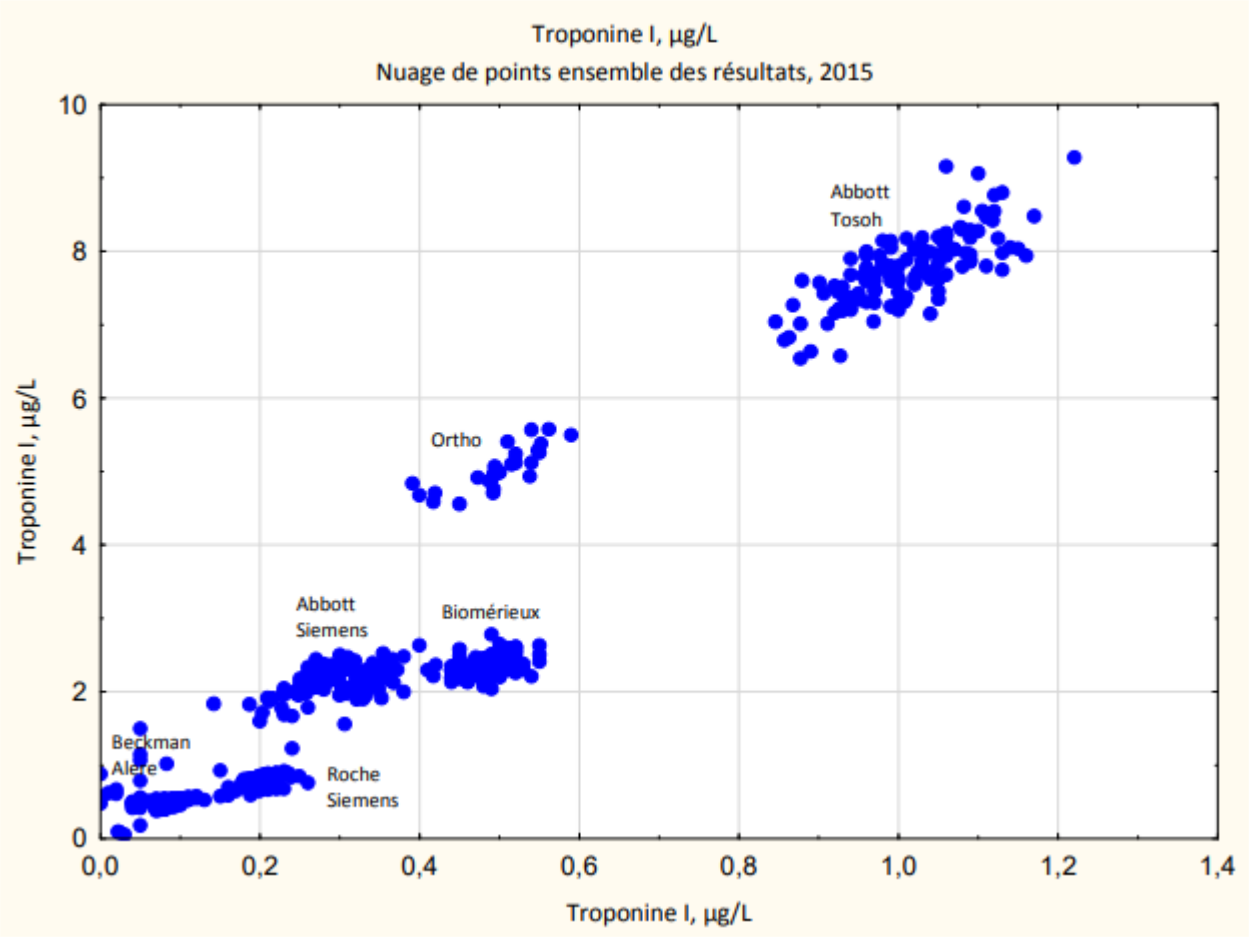
sample	A/µg/L	B/µg/L
mean	0.915	0.36
CV	57.201	55.458
participants	472	



sample	A/µg/L	B/µg/L
mean	1.099	0.334
CV	14.104	10.327
participants	590	

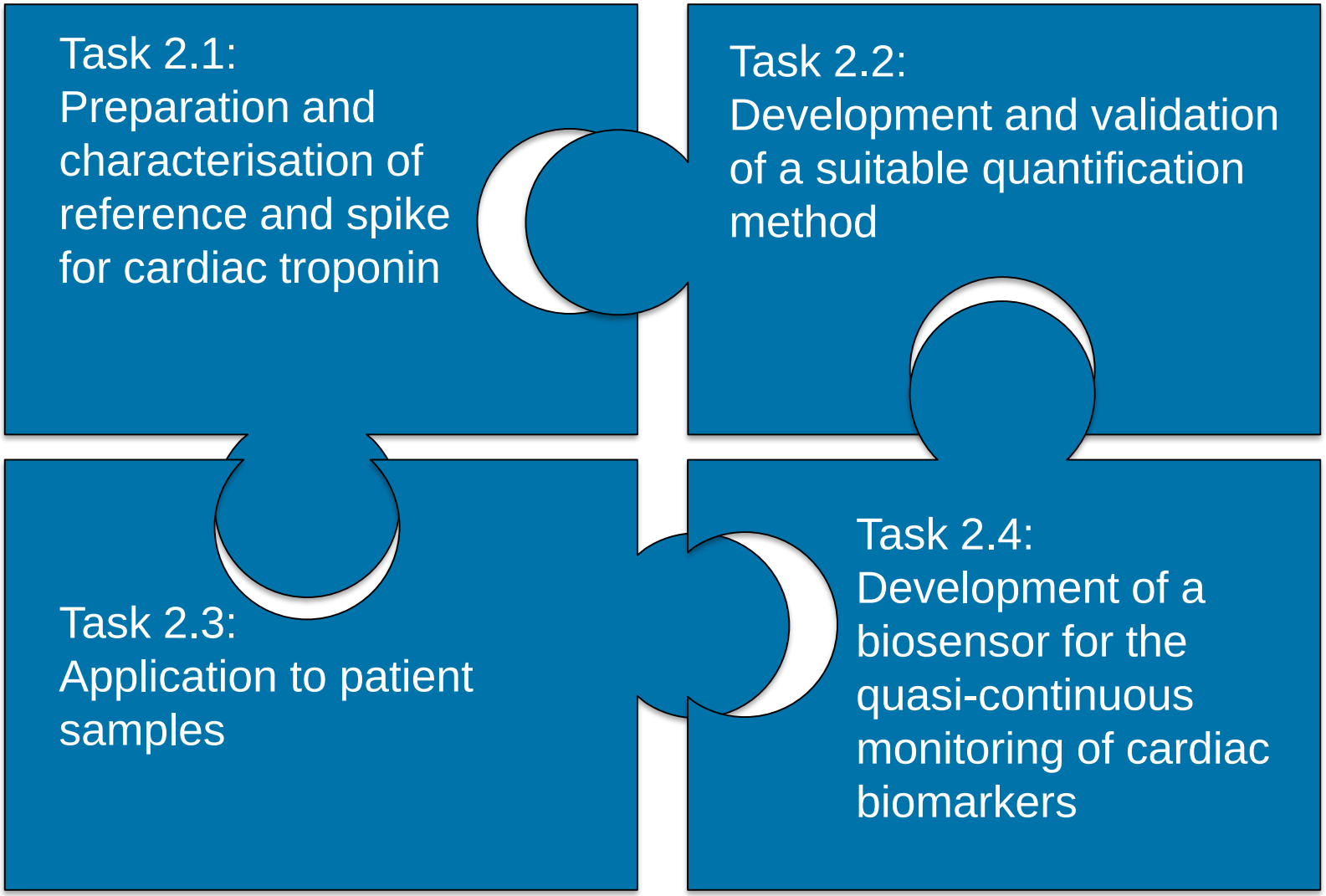
Results from the French mandatory EQA scheme in 2015

figure 1 : Troponine I (µg/L) – Nuage de points ensemble des résultats, 2015



Between-lab CV : 79%!

WP2: planned activities



WP2: connection with IFCC WG-cTnI

Standardisation of Troponin I (WG-TNI)

Membership

Name	Position	Country	Term	Time in Office
R. Christenson	Chair	US	1st	2017 07 - 2019 12
D. Armbruster	Member	US		
J. Barth	Member	UK		
A. Katrukha	Member	FI		
J. Noble	Member	UK		
M. Panteghini	Member	IT		
A. Saenger	Member	US		
H. Schimmel	Member	BE		
L. Wang	Member	US		

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

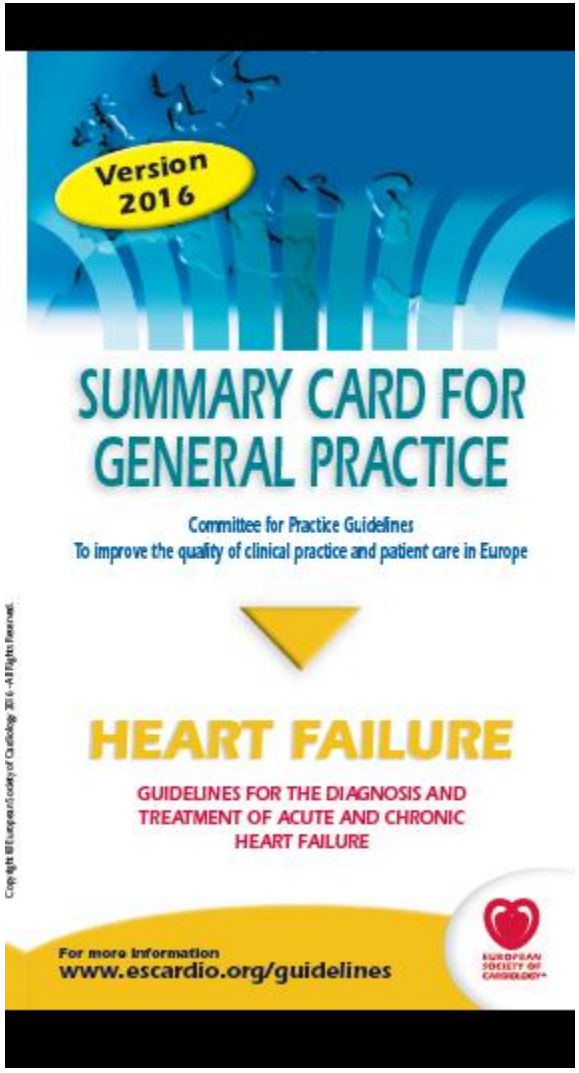
Terms of Reference

- Development of a candidate secondary reference measurement procedure and candidate secondary reference material for cardiac troponin I (cTnI)
- Testing for cTnI standardization and clinical validation by comparison with validated commercial assays in a round robin study

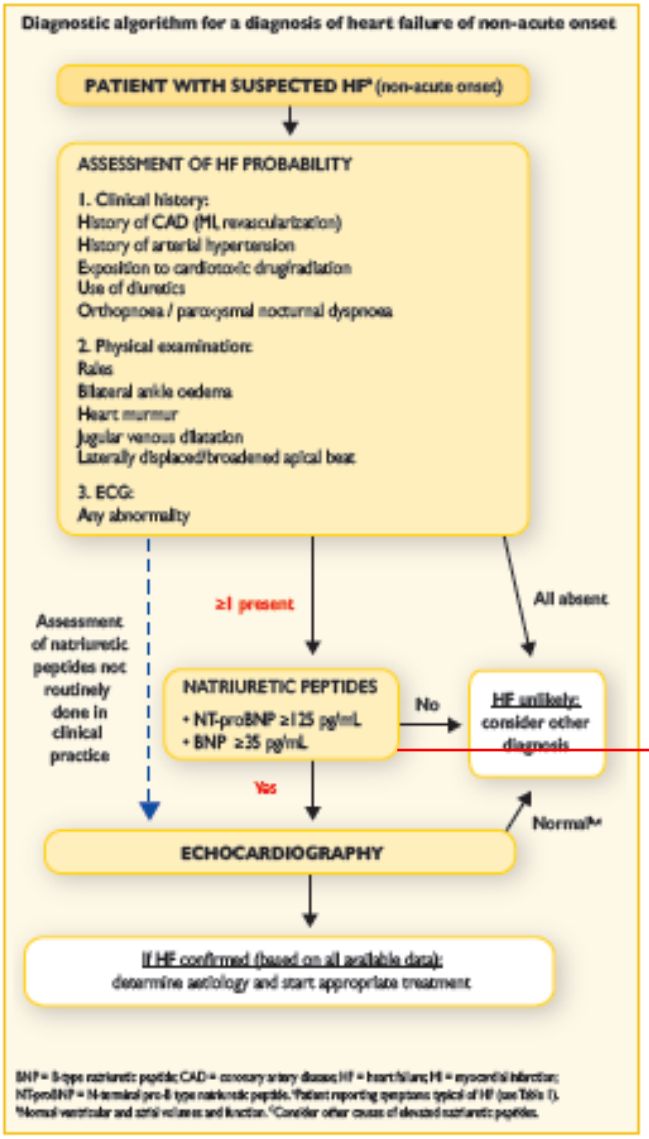
Current Projects

- Preparation of a secondary reference material for cTnI consisting of three cTnIpositive serum pools (Phase 2)
- Validation of cTnI standardization through a round robin after a value transfer using the secondary reference material as common calibrator (Phase 3)

- NIST produced certified reference material SRM 2921 (pure cardiac troponin complex)
- NIST developed an ID-LC-MS/MS method for cTnI: *Analytical and Bioanalytical Chemistry (2018) 410:2805–2813*



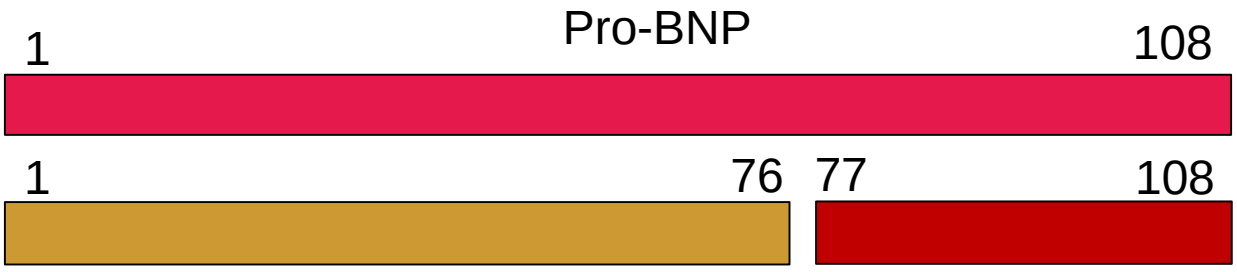
https://www.escardio.org/static_file/Escardio/Guidelines/Publications/HF/d8025_Summary_Card-HF-6%20for%20web.pdf



NT-proBNP ≥125pg/mL

BNP ≥35pg/mL

Brain Natriuretic Peptides



NT-proBNP

76 amino acid glycosylated protein

Not active

Stability 60-120min

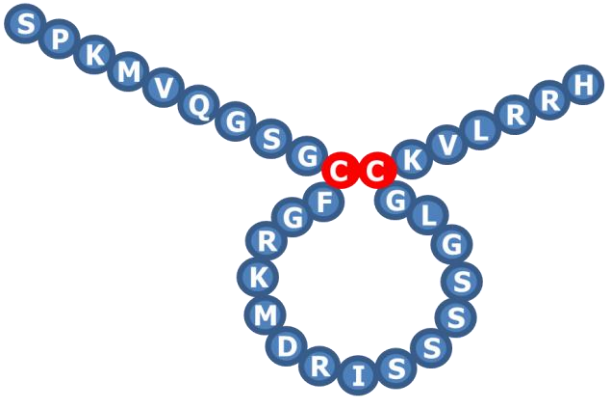
BNP

32 amino acid peptide

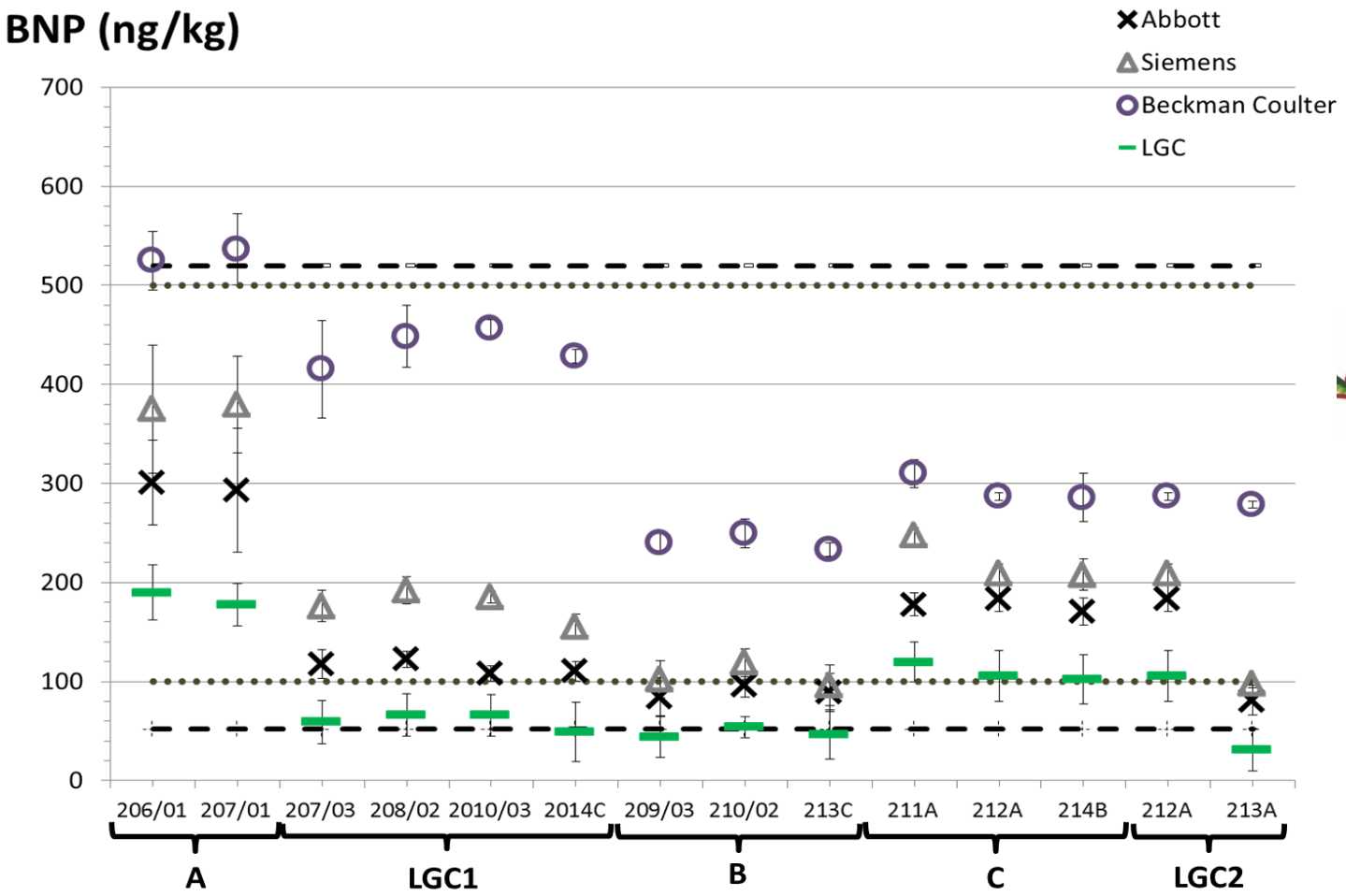
Active form

Stability 20min

Bio-therapeutic



WP3 : Need for BNP standardization!



UK NEQAS
Cardiac Markers

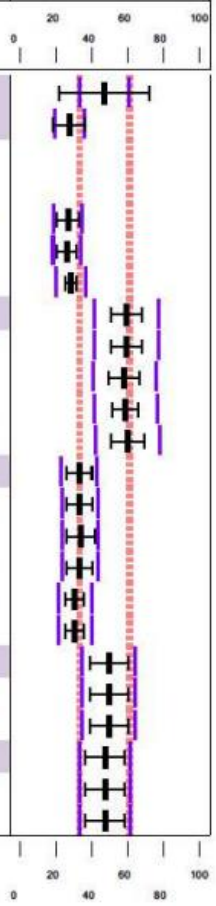
Poor agreement between the different available immunoassays!

WP3 : Need for BNP standardization!

Results from the French mandatory EQA scheme in 2014

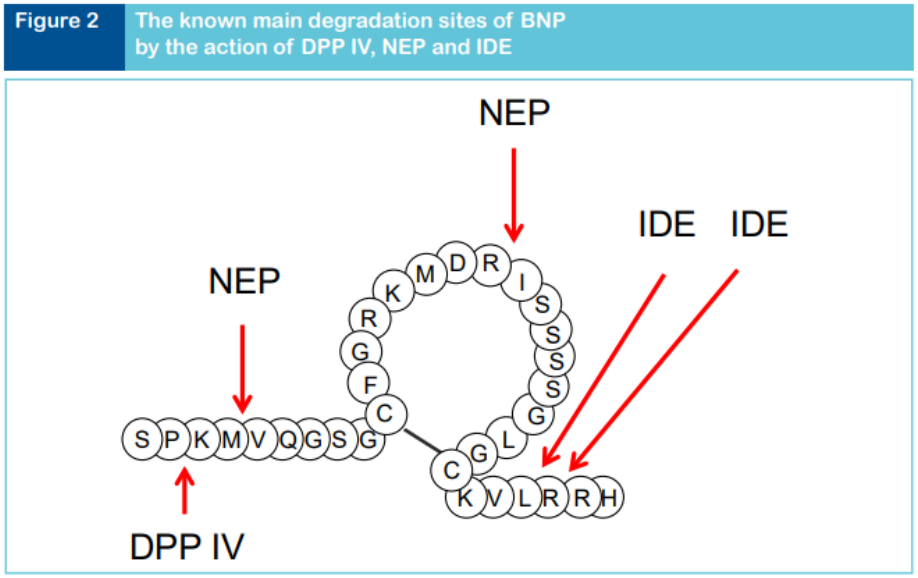
tableau II : BNP (ng/L) – résultats, échantillon C6

BNP (ng/L)			C6		
Techniques ou appareils	Effectif	%	Moyenne (ng/L)	CV (%)	Moyenne +/- 2ET
TOUTES TECHNIQUES	517		46,9	27,3	
EIA, fluorimétrie	32	6,2	27,6	16,2	
ABBOTT, AxSYM BNP, 8G82	4	0,8	–	–	
– ABBOTT AxSYM/AxSYM +	4		–	–	
TOSOH Bioscience, AIA séries | ST AIA Pack BNP	28	5,4	26,6	11,8	
– TOSOH Bioscience AIA-2000	16		25,9	10,7	
– TOSOH Bioscience AIA-360	7		28,2	5,5	
EIA, luminométrie	127	24,6	59,3	7,5	
BECKMAN COULTER, Triage BNP w/Access, Dx & LXi systems	127	24,6	59,3	7,5	
– BECKMAN COULTER Access/Access 2	41		58,1	7,3	
– BECKMAN COULTER UniCel DxC 600/600i	7		58,9	6,1	
– BECKMAN COULTER UniCel DxI 600/800	79		60,1	7,5	
IA, chimiluminescence (CLIA)	120	23,2	32,9	11,1	
SIEMENS, ADVIA Centaur BNP	106	20,5	33,3	10,8	
– SIEMENS ADVIA Centaur CP	8		33,6	12,0	
– SIEMENS ADVIA Centaur/Centaur XP	98		33,2	10,8	
SIEMENS, Dimension Vista | LOCI BNP	14	2,7	30,5	8,4	
– SIEMENS Dimension Vista	14		30,5	8,4	
IA, chimiluminescence (CMIA)	170	32,9	49,5	10,8	
ABBOTT, ARCHITECT 'i' systems | BNP, 8K28	170	32,9	49,5	10,8	
– ABBOTT ARCHITECT i1000SR/i2000SR	170		49,5	10,8	
IMMUNOCHROMATOGRAPHIE	68	13,2	47,4	11,7	
BIOSITE (ALERE), Triage BNP w/Triage Meter	68	13,2	47,4	11,7	
– BIOSITE (ALERE) Triage Meter systems	68		47,4	11,7	



Between-lab CV : 27%!

1-32 BNP degradation patterns



iJIFCC 2016

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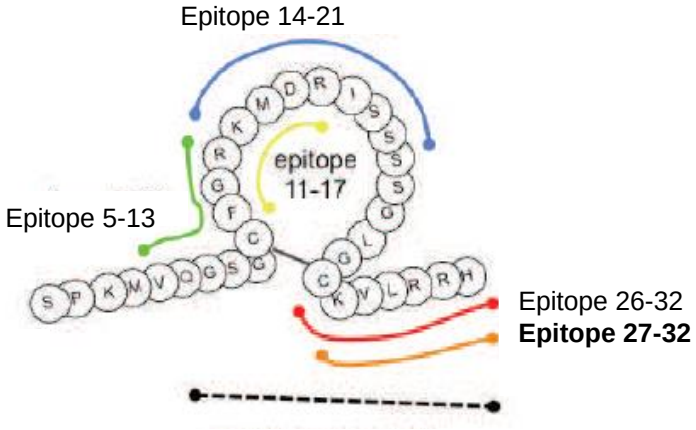
Plasma BNP and NT-proBNP Assays by Automated Immunoanalyzers: Analytical and Clinical Study

BNP(1-32) SPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH

BNP(3-32) KMVQGSGCFGRKMDRISSSSGLGCKVLRRH
BNP(4-32) MVQGSGCFGRKMDRISSSSGLGCKVLRRH
BNP(5-32) VQGSGCFGRKMDRISSSSGLGCKVLRRH
BNP(5-31) VQGSGCFGRKMDRISSSSGLGCKVLRR
BNP(5-27) VQGSGCFGRKMDRISSSSGLGCK
BNP(5-26) VQGSGCFGRKMDRISSSSGLGC

WP3 : Challenges in BNP measurement

Assay	Antibody	Standard materials
Alere Triage BNP	capture / detection	Recombinant BNP
Beckman Coulter	capture / detection	Recombinant BNP
Abbott	capture / detection	Synthetic BNP
Siemens (Bayer)	capture / detection	Synthetic BNP
Siemens (Dade Behring**)**	capture / detection	Synthetic BNP
ET Healthcare	capture	proBNP glycosylated



The different available immunoassays

do not target the same epitope

and rely on different types of calibrators

DE GRUYTER

Clin Chem Lab Med 2017; 55(9): 1397–1406

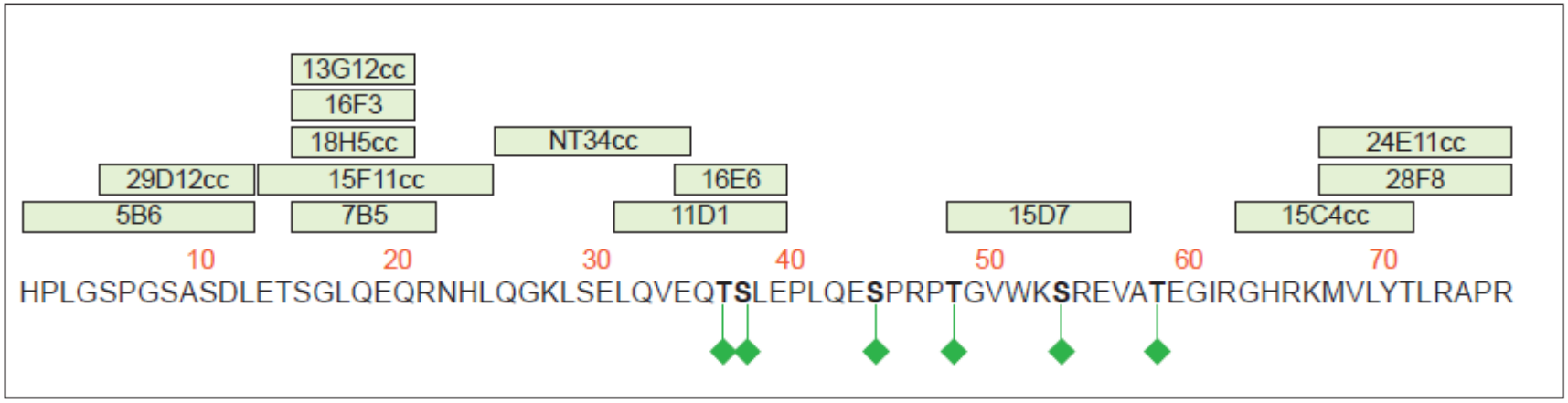
Open Access

Attila F. Torma, Kate Groves, Sabine Biesenbruch, Chris Mussell, Alan Reid, Steve Ellison, Rainer Cramer and Milena Quaglia*

A candidate liquid chromatography mass spectrometry reference method for the quantification of the cardiac marker 1-32 B-type natriuretic peptide

- ✓ SI traceable primary calibrator fully characterized
- ✓ Stabilisation protocol for BNP in plasma
- ✓ Candidate RMP for quantification of BNP in plasma
- ✓ Reference method target values assigned to 40 EQA materials
- ✓ Correlation between IDMS and immunoassays established
- ✓ Method available for monitoring metabolites
- ✓ Interlaboratory comparisons LGC / NIST

NT-proBNP immunoassay detection



https://shop.hytest.fi/spree/products/2930/Human_proBNP__BNP_and_NT-proBNP_TechNotes.pdf?1560756922

Objective : enhance BNP measurements and improve patient outcomes through provision of reference measurement procedures & standardization of EQAS :

- ✓ development of a candidate reference measurement procedure for NT-proBNP
- ✓ application to EQA schemes and clinical samples
- ✓ Definition of procedures for the calculation of measurement uncertainty within EQAS
- ✓ Definition of commutability requirements for EQA materials for NT-proBNP
- ✓ Monitor BNP circulating forms to understand issues for 1-32 BNP measurement

Stakeholders & Partners

Medical associations, national & international organizations

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

International Consortium for Harmonization of Clinical Laboratory Results

DGKL Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e.V.

SFBC

AACC

EFLM EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

JCTLM

NIH

Health Authorities

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

NHS Greater Glasgow and Clyde

EQA Providers

UK NEQAS Cardiac Markers

EQUALIS

RfB Referenzinstitut für Bioanalytik

Manufacturers

Quest Diagnostics

promise ADVANCED PROTEOMICS

VAP DIAGNOSTICS LAB

LabCorp Laboratory Corporation of America

SOLOMONPARK

SUN DIAGNOSTICS

Hospitals

HÔPITAUX UNIVERSITAIRES PITIÉ SALPÊTRIÈRE CHARLES FOIX

C·H·O·R·I Children's Hospital Oakland Research Institute

UCSF Benioff Children's Hospitals

NWRL

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Thank you for your attention!

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