

Roche CARDIAC point of care assays: *Diagnostic utility in clinical practice*

Rapid and accurate diagnosis is one of the main challenges in the emergency department (ED) and other critical care settings. Here, cardiac markers are a key component in triaging patients with suspected acute coronary syndrome (ACS), heart failure (HF) or pulmonary embolism (PE). Given the time-criticality of these conditions, results should be provided with a turnaround time of ideally 30 minutes or less and at most within 1 hour.¹ Point of care (PoC) testing is recommended in institutions that cannot consistently deliver results within 1 hour². It has also become a popular means of meeting increasing demands on physicians to see more patients in less time³. Both the intended use and the lack of standardization of cardiac markers necessitate – in accordance with guidelines – proof of clinical utility for PoC assays. Studies using the Roche CARDIAC T Quantitative (troponin T), proBNP (NT-proBNP) and D-Dimer assays show excellent concordance in clinical decision-making to laboratory-based testing. The investigations summarized in this review provide evidence that Roche's PoC technology reliably fulfills clinical needs^{4,5,6}, allows shorter turnaround times⁷, and helps improve patient management⁸. This clinical performance builds on the analytical agreement of Roche CARDIAC assays with their corresponding laboratory reference tests. This, in turn, enables continuity and harmonization of cardiac marker testing across PoC and the laboratory.

The need for clinical validation

Immunoassays for the determination of cardiac markers use specific antibodies directed to the corresponding antigens. However, different assays available on the market today use different antibodies. There is no primary reference material that could be used for standardization of all commercial methods. Thus, a lack of standardization means complexity in interpretation of results as differing methodologies for the same marker give different results.

Lack of standardization means that ultimately all cardiac marker assays – regardless of whether they are run on laboratory analyzers or PoC systems – need to be validated in studies proving the clinical utility not only of the parameter but also of the assay being used. Thus, the NACB and IFCC Standardization Committee states: "To avoid misinterpretation of results, one must consider the assay used, the available clinical evidence based on that individual assay, together with the clinical aim of an individual biomarker based study."⁹ The **cobas**[®] PoC assays for troponin T, NT-proBNP and D-dimer have been validated in clinical practice. Studies have demonstrated the excellent analytical and clinical concordance with the corresponding laboratory reference assays.

Troponin

Compelling evidence for the diagnostic and prognostic value of cardiac troponin has prompted a redefinition of the diagnosis of acute myocardial infarction (AMI) in the guidelines of the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC). Today, an elevated cardiac troponin is a cornerstone for ruling in AMI. The Universal Definition of Myocardial Infarction states: "Detection of a rise and/or fall of the measurements is essential to the diagnosis of AMI".¹⁰ This includes minimal myocardial injuries without ST-segment elevation. However, while cardiac troponin elevation is typically related to myocardial damage, it should not be relied on exclusively for the diagnosis of AMI (see highlighted text page 2). Low or marginal elevations of troponin concentrations in serum can be caused by a number of non-coronary cardiac and noncardiac diseases. For emergency physicians, therefore, not only a single value but serial measurements of cardiac troponin, characteristic changes in the electrocardiogram (ECG) and the clinical presentation complete the picture in the assessment of suspected ACS and diagnosis of AMI.^{11,12,13,14}



The time-saving and accelerated clinical decision-making enabled by Point of Care (PoC) testing would not benefit patient management and resource utilization if PoC assay results were not reliable and comparable to laboratory assays measured on much more sophisticated analyzers. Hence, a prospective multicenter trial by Derhaschnig et al., including 794 patients with suspected ACS, proved the high clinical utility of the Roche CARDIAC T Quantitative test during routine use in the coronary care unit.⁴ The study revealed that the PoC assay has a clinical performance comparable to the laboratory test method (Elecsys Troponin T), achieving close to the same diagnostic sensitivity, diagnostic specificity and area under the curve (Table 1, Figure 1^{4,15}). In clinical terms, thus, the PoC assay would allow clinicians to obtain the same safety in patient diagnosis and clinical decision-making.

Kellett et al. confirmed, furthermore, the diagnostic efficiency of the Roche CARDIAC T and M (myoglobin) assays in suspected ACS patients with non-diagnostic ECG. The study revealed that the bedside tests identified nearly all AMI patients with non-diagnostic ECG within 4 hours of presentation. The detection of these patients in the ED with the Roche PoC tests was as sensitive as in patients with a diagnostic ECG.¹⁶ An analysis by Storrow et al. ties in with these results demonstrating identical sensitivities to running the tests on the reference method in the central lab.¹⁷ The relevance of the Roche CARDIAC T troponin test for risk stratification was revealed by Guo et al. The authors demonstrated that in patients with chest pain, the assay is an independent, powerful and valuable tool for risk stratification that has a high sensitivity, specificity and negative predictive value for diagnosing AMI. Patients with positive troponin T results had higher rates of all-cause death, cardiac death, and for developing AMI and acute heart failure.¹⁸

Diagnostic value	Time after onset of symptoms					
	0-4 hours		4-8 hours		8-12 hours	
	Roche CARDIAC T Quantitative	Elecsys Troponin T	Roche CARDIAC T Quantitative	Elecsys Troponin T	Roche CARDIAC T Quantitative	Elecsys Troponin T
Diagnostic sensitivity, % (95% CI)	65 (59-70)	58 (52-63)	87 (84-90)	82 (78-85)	93 (91-96)	90 (87-93)
Diagnostic specificity, % (95% CI)	93 (90-96)	98 (97-100)	93 (90-96)	98 (96-99)	90 (86-93)	98 (97-100)
Positive predictive value, % (95% CI)	93 (89-96)	98 (96-100)	95 (92-97)	98 (97-99)	93 (91-96)	99 (98-100)
Negative predictive value, % (95% CI)	66 (61-71)	60 (55-66)	84 (81-88)	79 (75-83)	90 (86-93)	86 (82-90)

Table 1: Diagnostic 2 × 2 comparison of Roche CARDIAC T Quantitative (troponin T) and of Elecsys Troponin T for diagnosis of acute myocardial infarction in 794 individuals calculated with a clinical cut-off of 0.05 ng/mL, table modified from Derhaschnig, U.⁴, CI = confidence interval

The troponin 99th percentile: past, present and future

Despite extensive efforts, standardization of cardiac troponin I (cTnI) assays has proven elusive. Due to the variable structure of the molecule and different antibodies in use, different cTnI assays still demonstrate 20-40 fold variability.¹⁹ As a way to address this, the 99th percentile of a reference population was proposed as an analytical criterion to define the troponin cut-off²⁰, at a time when commercial assays did not adequately measure these low levels²¹. Thus, various decision limits for troponin tests remain in use, including cut-offs corresponding to the WHO's clinical AMI definition and limits defined by an assays' coefficient of variation.²² As the next generation of troponin assays come on the market, clinical experience with the 99th percentile as a cut-off for the diagnosis of AMI is still

limited. For example, a lower cut-off will detect greater numbers of patients with elevations that are not due to an acute ischemic event.²³ This is echoed by Hugo Katus, the discoverer of troponin testing: "The use of highly sensitive assays will open a fascinating perspective for investigating the distressed heart but may also cause confusion regarding AMI definition and its impact in clinical medicine."²⁴ One implication, already reflected in the guidelines, is a greater emphasis on changes in troponin levels – the so-called "typical rise or fall".¹⁰ Going forward, a more precise definition of these changes and the full implications of lower cut-offs for AMI diagnosis have to be elucidated via clinical studies.

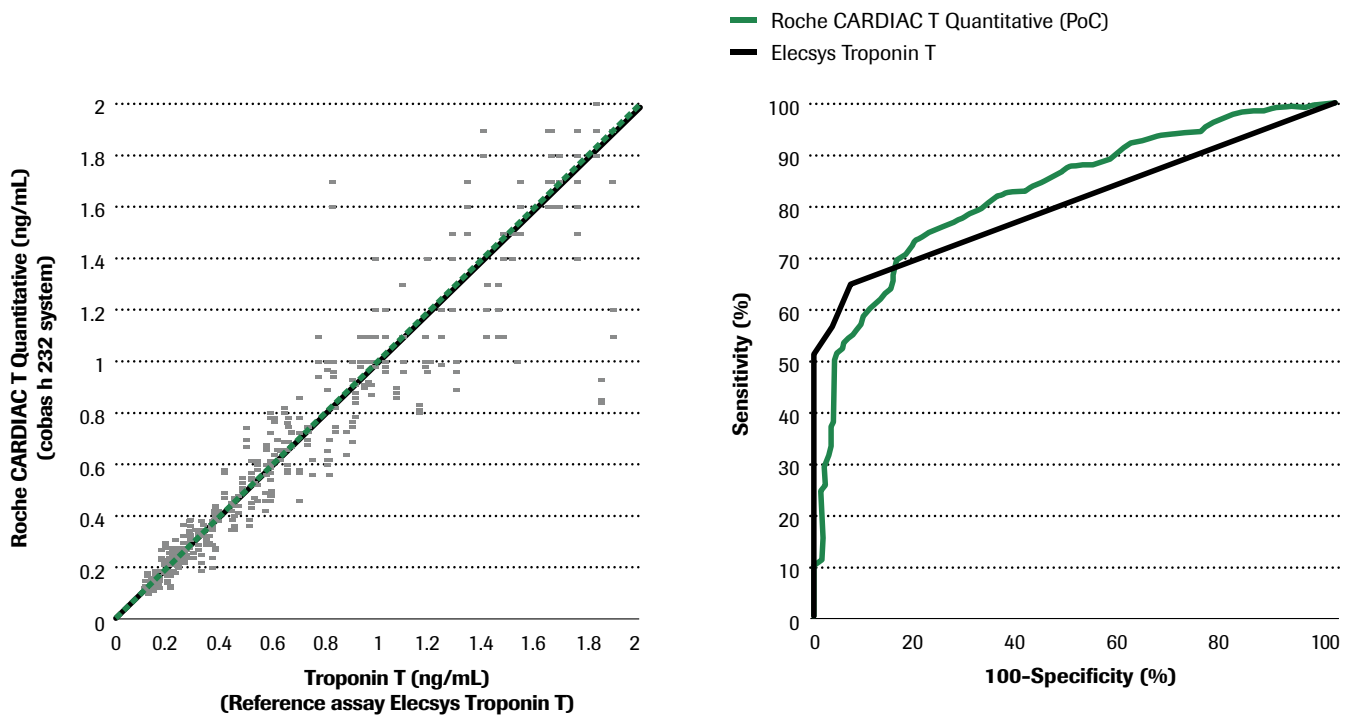


Figure 1: In method comparison, Roche CARDIAC T Quantitative shows good comparability to the reference Elecsys Troponin T assay (left). In clinical use with blood samples taken between 0 to 4 hours after onset of acute myocardial infarction symptoms, both assays match closely in diagnostic performance as shown in receiver-operator characteristics (ROC) curves (right).^{4,15} Area under the curves: Roche CARDIAC T Quantitative (PoC) = 0.80 (95% CI = 0.78-0.83), Elecsys Troponin T (lab) = 0.85 (95% CI = 0.82-0.88). PoC = point of care. Method comparison data using heparinized venous whole blood for Roche CARDIAC T Quantitative and serum sample on Elecsys.

Given the time-critical nature of suspected ACS, the NACB guidelines endorse PoC testing as a way for cardiac markers to be available within the shortest possible time.¹ In a multicenter study, involving 4,609 samples in five different hospitals, Gaze et al. showed that the Roche CARDIAC T Quantitative assay used in emergency departments or coronary care units improved the turnaround time by more than one hour compared to central laboratory measurements.⁷ In Storrow's study, PoC testing for myoglobin and troponin T decreased the time to baseline ED results by approximately 30 minutes compared to the local laboratory. The authors conclude: "Routine use of PoC cardiac marker testing in the ED may improve time to treatment and time to disposition and may potentially improve patient outcomes."¹⁷ In fact, a management protocol has been validated by Collinson et al. in a trial with 263 patients. PoC testing enabled a rapid discharge protocol for managing low-risk patients admitted with suspected ACS. Time to diagnosis and length of stay for these patients was significantly reduced as a result.⁸

NT-proBNP

A patient with acute heart failure (AHF) requires immediate diagnostic evaluation and care – errors or delays in diagnosis are associated with higher mortality, longer time to discharge and higher treatment costs.²⁵ Natriuretic peptides are meanwhile indispensable tools for the diagnosis of patients suspected of having AHF, in the monitoring of patients with compensated left-ventricular dysfunction, and in the risk stratification of patients with ACS.^{26,27} Numerous studies have demonstrated the clinical value of NT-proBNP testing, particularly in safely ruling out AHF in the ED and improving the diagnostic accuracy of AHF in primary care.^{28,29,30} It is also a strong predictor of in-hospital and long-term mortality of heart failure patients.^{31,32} Consequently, the 2008 ESC heart failure guidelines recommend NT-proBNP testing for diagnosing and staging AHF, as well as for making hospitalization/discharge decisions and identifying patients at risk for clinical events.³³

The Roche CARDIAC proBNP test was the first PoC assay for the quantitative determination of NT-proBNP. A number of studies in the clinical environment have demonstrated good analytical

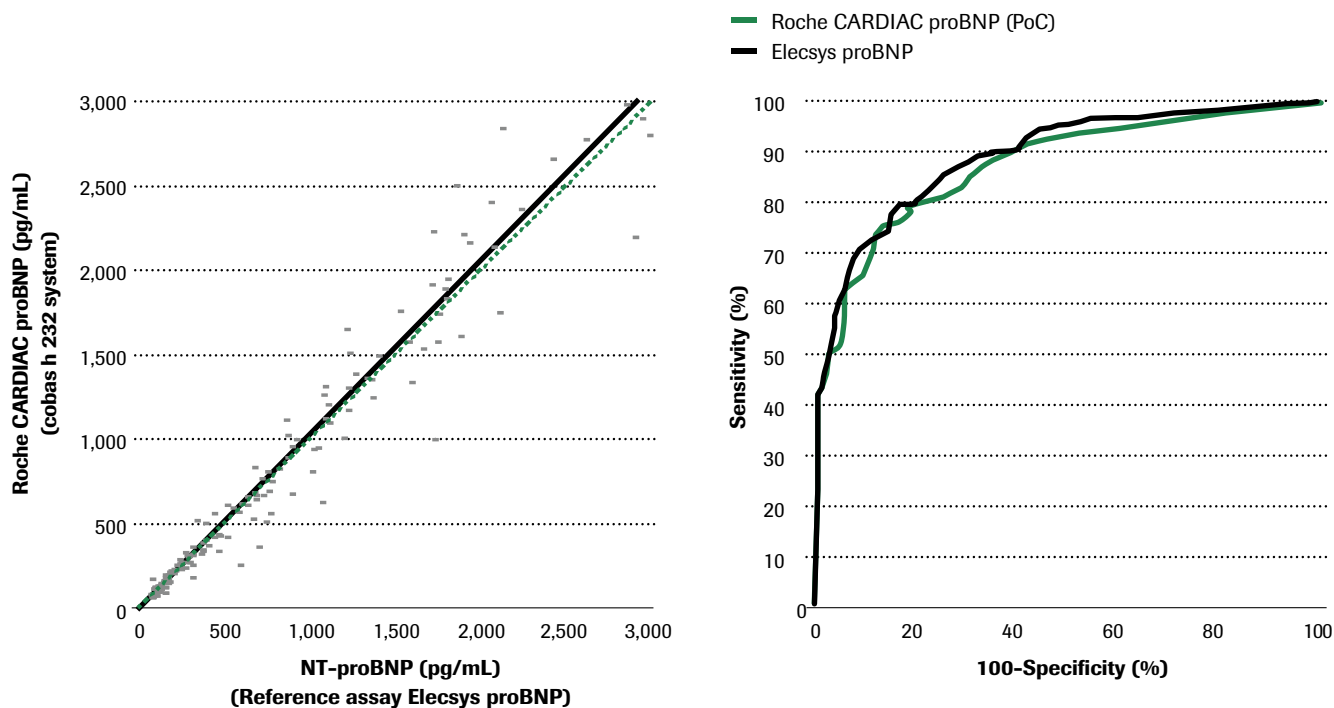


Figure 2: In method comparison, Roche CARDIAC proBNP shows an excellent agreement with the reference Elecsys proBNP assay (left). In clinical use for diagnosis of individuals suspected of having heart failure, both assays match in diagnostic performance as shown in receiver-operator characteristics (ROC) curves (right).^{5,15} Area under the curves: Roche CARDIAC proBNP (PoC) = 0.88 (95% CI = 0.85-0.92), Elecsys proBNP (lab) = 0.89 (95% CI = 0.86-0.92). PoC = point of care, CI = confidence interval. Method comparison data using heparinized venous blood for Roche CARDIAC proBNP and heparinized venous plasma sample on Elecsys.

performance characteristics and excellent clinical agreement with the established laboratory method (Elecsys proBNP).^{5,34,35,36}

The CARPRO study proved clinical equivalence between the Roche CARDIAC proBNP PoC test and Elecsys proBNP, the laboratory reference, for the diagnosis of individuals suspected of having heart failure. This multicenter trial involved 217 patients with chronic heart failure NYHA stage I to IV and a reference population consisting of 189 individuals with hypertension, diabetes, COPD, or asthma, or healthy individuals. The PoC test measured on the **cobas h 232** system showed excellent agreement with the laboratory method and identical diagnostic performance as exemplified by the area under the ROC curve (Figure 2). In addition, method comparison revealed no differences between the two generations of the **cobas**[®] PoC systems used in this study – the Cardiac reader and the **cobas h 232** systems (Table 2).⁵

Alehagen et al. evaluated blood samples of 440 patients with ACS and worsening heart failure in a routine clinical setting. Their study demonstrated a good level of correlation ($r = 0.96$, 95% CI 0.94-0.97) between the PoC and the laboratory NT-proBNP

assays and a diagnostic concordance of 93%. The sensitivity of the Roche CARDIAC proBNP assay was 97% and the specificity 83%. Cardiologists felt that the information given by the PoC system was a valuable addition to their routine practice, covering the diagnostically relevant range of 60 to 3,000 pg/mL. Patients with NT-proBNP concentrations of 3,000 pg/mL and over did not present a diagnostic challenge.³⁵ The study is notable also because it emphasized the high clinical usability of the Roche CARDIAC proBNP PoC test in the hands of non-laboratory staff. Nurses rated the handling of the PoC device easy to learn. Analyses were performed competently and without compromising the quality or validity of the data. In addition, the PoC method proved to be cost-effective. The total cost for all 440 laboratory analyses was EUR 13,442 versus EUR 9,093 for 440 Roche CARDIAC proBNP PoC assays, including costs for quality control testing. The authors conclude: “The Cardiac reader proBNP test may be used in a clinical setting with excellent results. The usefulness of the PoC method is high.”³⁵

Due to its reliability and clinical value, the Roche CARDIAC proBNP PoC assay has been used in studies that explored additional uses for NT-proBNP in other settings where the availability of prompt

Diagnostic value	Point of care testing		Laboratory
	Roche CARDIAC proBNP on cobas h 232	Roche CARDIAC proBNP on Cardiac reader	Elecsys proBNP
Diagnostic sensitivity, % (95% CI)	89 (84-93)	87 (82-91)	89 (84-93)
Diagnostic specificity, % (95% CI)	65 (58-72)	66 (59-72)	67 (60-73)
Positive predictive value, % (95% CI)	74 (68-79)	74 (68-79)	75 (69-80)
Negative predictive value, % (95% CI)	84 (78-89)	82 (76-88)	85 (78-90)

Table 2: Diagnostic 2 x 2 comparison of Roche CARDIAC proBNP and Elecsys proBNP for diagnosis of left ventricular systolic dysfunction in all individuals calculated with an age independent diagnostic cut-off of 125 pg/mL⁵, CI = confidence interval

lab results poses a challenge. A recently published prospective observational study in 631 diabetic patients in primary care demonstrated a strong and independent correlation between NT-proBNP and short-term prognosis of cardiovascular events. The study showed the high negative predictive value of NT-proBNP to identify individuals not having an intermediate risk for cardiovascular events. It further validated the use of the PoC assay in an ambulatory care setting.³⁷ Here, the on-the-spot availability of NT-proBNP test results enables an immediate assessment during the patient's visit and thus can help avoid repeat consultations and potentially unnecessary referrals. Goode et al. also demonstrated the cost-effectiveness of NT-proBNP in primary care.³⁰

D-dimer

Deep vein thrombosis (DVT) and pulmonary embolism (PE) have signs and symptoms that are neither sensitive nor specific³⁸, so clinicians may overlook them or suspect DVT or PE where none is present. Early and precise rule-out of DVT avoids exposing patients without thrombosis to the risks of anticoagulant therapy.³⁹ The ESC 2008 guidelines recommend that "a negative D-dimer result in a highly sensitive assay safely excludes PE in patients with a low or moderate clinical probability" and reduces the need for imaging and, hence, irradiation. D-dimer measurement combined with clinical probability assessment is the logical first step in patients admitted to the ED.⁴⁰ The development of quantitative, rapid and highly sensitive PoC D-dimer assays enables use in emergency settings, with results available in minutes rather than hours.⁴¹

Several studies have proven that the Roche CARDIAC D-Dimer PoC test is highly accurate in the exclusion of DVT in symptomatic outpatients.^{6,41} In the multicenter CARDIM study 637 patients with clinically suspected DVT were tested with the Roche CARDIAC D-Dimer assay and in parallel with Tina-quant D-Dimer and VIDAS D-Dimer (bioMérieux). The

Roche CARDIAC D-Dimer assay showed a diagnostic sensitivity of 97% and a specificity of 61% for the diagnosis of DVT in this study. This indicates a diagnostic power for the exclusion of DVT corresponding to that of the two standard and guideline endorsed laboratory methods. All three assays show virtually identical ROC curves (Figure 3). The authors summarize that the Roche CARDIAC D-Dimer PoC assay is a reliable tool to exclude DVT in symptomatic outpatients.⁶

Legnani et al. also showed that the Roche CARDIAC D-Dimer test is highly accurate and produces results corresponding to those obtained with a highly sensitive laboratory assay (VIDAS D-dimer). The trial included 87 consecutive out-patients with suspected DVT and showed a diagnostic sensitivity for DVT of up to 100%. Legnani et al. concluded: "The Roche CARDIAC D-Dimer test is quantitative with objective measurement reading, suited for emergency situations and individual tests. It can be directly performed by inexperienced staff in the emergency room without any further laboratory equipment and using whole blood. For these reasons it seems to have a great clinical potential." The more so, because other qualitative PoC assays are based on visual reading and therefore provide variable results due to a high level of inter-observer variability.⁴¹

A large management study in primary care just finished in the Netherlands (AMUSE study) was conducted with the participation of more than 300 general practitioners and over 1,000 patients with suspected DVT. Signs and symptoms were measured using a new clinical decision rule (CDR) developed for primary care use. Initial results show that Roche CARDIAC D-Dimer testing combined with the primary care CDR safely rules out DVT in low-risk patients. Comparing five different PoC assays, the Roche CARDIAC D-Dimer test was the best performing assay in this population and study setup, with the highest sensitivity and the lowest number of missed cases.⁴²

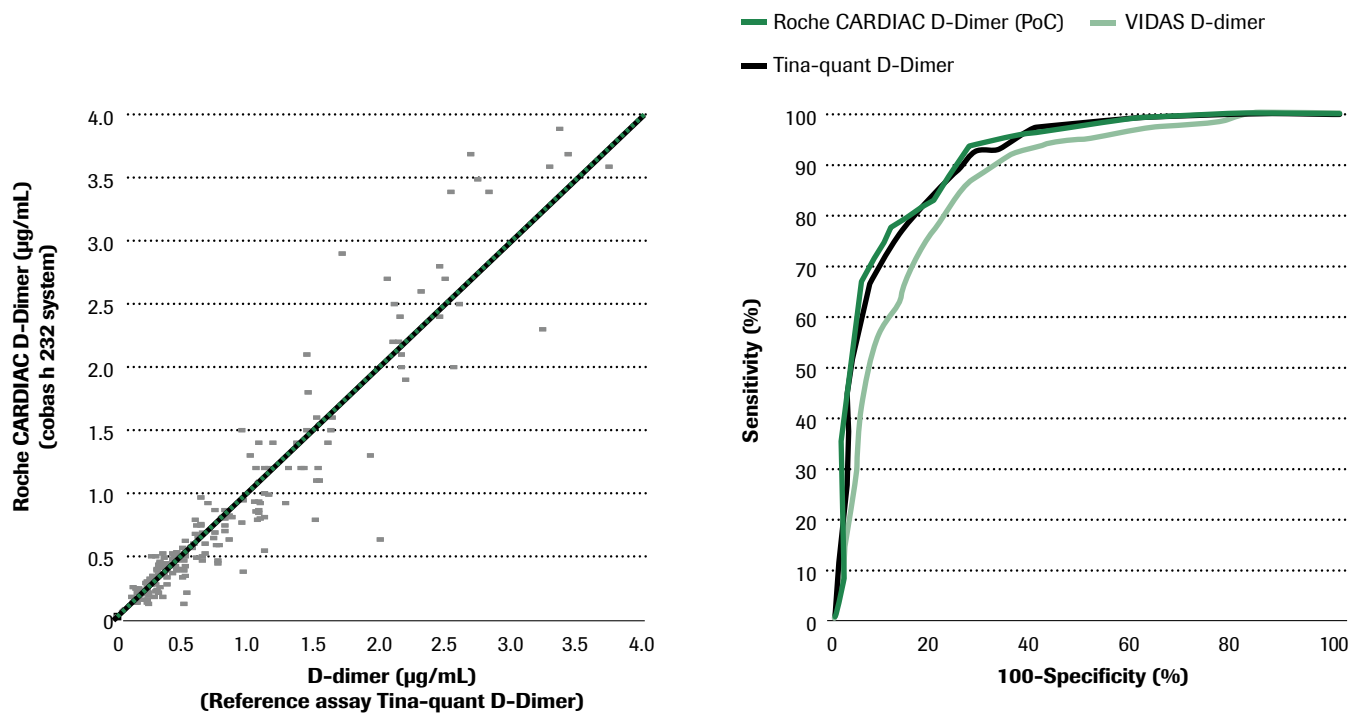


Figure 3: In method comparison, Roche CARDIAC D-Dimer shows a very good agreement with the reference Elecsys D-Dimer assay (left). In clinical use for diagnosis of individuals suspected of having deep vein thrombosis, both assays match in diagnostic performance as shown in receiver-operator characteristics (ROC) curves (right).^{6,15} Area under the curves: Roche CARDIAC D-Dimer (PoC) = 0.88 (95% CI = 0.85-0.91), Tina-quant D-Dimer (lab) = 0.91 (95% CI = 0.88-0.93), Vidas D-dimer (lab) = 0.90 (95% CI = 0.86-0.92). PoC = point of care, CI = confidence interval. Method comparison data using heparinized venous blood for Roche CARDIAC D-Dimer and citrated venous plasma sample for the Tina-Quant D-Dimer assay.

Discussion

“The growing diversity of cardiac marker assays used worldwide emphasizes the need for both analytical and clinical validation of all commercial assays prior to the clinical acceptance of these biomarkers” states the NACB and IFCC Committee for Standardization of Markers of Cardiac Damage.⁹ The Roche CARDIAC PoC assays for troponin T, NT-proBNP and D-dimer have been validated in clinical practice and shown to have diagnostic utility comparable to lab testing. Studies in different settings and populations in different parts of the world show excellent concordance in clinical value to the respective Roche laboratory reference.^{4,5,6}

This proof of clinical concordance meets expert guidelines that address the lack of assay standardization.⁹ It is the basis for safely applying **cobas**[®] PoC assays by Roche in clinical routine – either when low test volumes make PoC the preferred alternative (e.g. in primary care or smaller hospitals) or in critical care settings where a rapid turnaround offers significant workflow and patient management benefits.^{8,43} In fact, due to the clinical performance of the Roche CARDIAC T Quantitative troponin T assay, Vizcaino et al.

showed it to provide good correlation to a troponin I assay used in the central laboratory.³⁶

The clinical performance shown in studies is the result of standardizing and calibrating these PoC tests to the respective Roche laboratory reference methods.^{44,45} This manifests itself in the analytical agreement seen in method comparison studies.^{34,46,47} In short, harmonization has been consistent between Roche PoC and laboratory assays. This ensures quality and reliability of cardiac marker results. Furthermore, it allows interchangeable use in serial and follow-up testing across a healthcare institution or network. With NT-proBNP each assay has to prove acceptable analytical and clinical agreement with the reference method as a precondition for licensed use of the antibodies.⁴⁸ Christenson states in a recent review of current NACB guidelines: “All results of cardiac biomarker testing in an institution should be in harmony to allow accurate serial monitoring and facilitate interpretation.”⁴⁹

Continuity of care of this kind is a key healthcare goal, as emphasized by the Joint Commission and the College of American

Pathologists (CAP) in their hospital and laboratory accreditations. It helps to improve quality in multiple ways. Training is simplified, test results are consistent and test interferences and result differences are minimized. Computerized PoC devices with electronic data capture that are capable of storing and transmitting results automatically to laboratory and hospital information systems support this continuity.³

Clinicians in cardiology, emergency medicine and critical care must rely upon diagnostic results that are part of their medical decision processes. Cardiac marker testing devices need to pro-

vide results that are precise and accurate enough to meet these needs and are clinically comparable. As required by guidelines, Roche CARDIAC PoC assays have been shown in clinical studies to fulfill these requirements. In critical settings where time is short, the availability of results within minutes may enable crucial treatment decisions that make a difference in terms of patient survival and outcome. Given their suitability to bedside use, **cobas**[®] PoC assays thus also enable users to follow guidelines requiring a short test turnaround time. Finally, in line with recent recommendations, Roche's standardization efforts ensure continuity in follow-up testing in the central laboratory.

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