Biochemical markers play a pivotal role in the diagnosis and management of patients with acute coronary syndrome (ACS), as witnessed by the incorporation of cardiac troponins into new international guidelines for patients with ACS and in the re-definition of myocardial infarction. Despite the success of cardiac troponins, there is still a need for the development of early markers that can reliably rule out ACS from the emergency room at presentation and also detect myocardial ischaemia in the absence of irreversible myocyte injury. Under investigation are two classes of indicators: markers of early injury/ischaemia and markers of inflammation and coronary plaque instability and disruption. Finally, with the characterisation of the cardiac natriuretic peptides, laboratory medicine is also assuming a role in the assessment of cardiac function.

Introduction
The significance of the contribution of laboratory medicine to clinical cardiology has grown in importance over the years. Until 20 years ago, the clinical laboratory only placed at the cardiologist's disposal a few assays for the retrospective detection of cardiac tissue necrosis, such as enzymatic methods for creatin kinase (CK) and lactate dehydrogenase catalytic activities. However, in the later part of the 20th century, highly sensitive and specific assays for the detection of myocardial damage, such as cardiac troponins, as well as assays for reliable markers of myocardial function, such as cardiac natriuretic peptides, have become available, assigning to the laboratory a pivotal role in the diagnosis and follow-up of patient with cardiac disease. This is witnessed by the recent incorporation of these markers into new international guidelines and in the re-definition of myocardial infarction (MI). The aim of this paper is to review the current contribution of the determination of biochemical markers to clinical cardiology and to discuss some important developments in this field.

The detection of myocardial necrosis
The World Health Organisation (WHO) has traditionally defined MI as requiring the presence of at least two of three diagnostic criteria, namely, an appropriate clinical presentation, typical changes in the electrocardiogram (ECG) and raised "cardiac" enzymes, essentially total CK or its MB iso-enzyme (CK-MB) activities. In September 2000, the joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) committee published its consensus recommendations for a new definition of MI. In particular, the ESC/ACC definition of acute MI requires the rise and fall of the biochemical marker of myocardial necrosis together with other criteria, comprising ischaemic symptoms, the development of pathologic Q waves, ischaemic ECG changes or a coronary artery intervention. Thus, according to the WHO definition, an acute MI could be diagnosed without biochemical evidence of myocardial necrosis, while the ESC/ACC' criteria stipulate that the biomarkers be elevated and, subsequently, be shown to fall in the appropriate clinical context. Quite simultaneously with the ESC/ACC re-definition of MI, other expert committees published companion documents, where in patients with no ST-segment elevation at ECG, but with ischaemic symptoms, a positive cardiac troponin result identifies patients who have non-ST-segment elevation myocardial infarction (NSTEMI) and who could benefit from aggressive medical therapy.
The new consensus documents have therefore based the new definition of MI on biochemical grounds, a choice that was guided by the advent of new markers of myocardial necrosis, such as cardiac troponins.\(^7\) The superior troponin's clinical value comes from its higher sensitivity to smaller myocardial injury and its virtually total specificity for cardiac damage.\(^8\) Despite the ability to detect quantitatively smaller degrees of myocardial necrosis, cardiac troponins need 4-10h after symptom onset to appear in serum, at about the same time as CK-MB elevations become detectable, and peak at 12-48h, remaining then abnormal for several days.\(^10\) This prolonged release pattern indeed makes it difficult to diagnose a re-infarction by the use of serial troponin measurements, suggesting a continuing role for CK-MB for this purpose.\(^1\) There is, however, a relationship between the severity of the infarct and the duration of the elevated serum troponins. The release periods of troponin in patients with NSTEMI are significantly less than those with ST-elevation at ECG, and troponin elevations in traditionally defined unstable angina patients, representing microscopic infarct, might last only several hours at a time.

In applying the results of cardiac troponin testing to the defining of MI, one should keep in mind that these markers actually reflect myocardial necrosis but do not indicate its mechanism. Thus, an elevated value in the absence of clinical evidence of ischaemia should prompt a search for other causes of cardiac damage. Many non-ischaemic pathophysiological conditions can cause myocardial necrosis and therefore elevations in cardiac troponin concentrations.\(^11-17\) The occurrence of myocardial damage in clinical contexts other than MI frequently obliges physicians to determine whether such damage occurs in the clinical setting of acute myocardial ischaemia, thus leading to the diagnosis of MI, or not. Strictly speaking, even in the "troponin era", the diagnosis of MI remains clinical. Measurement of cardiac troponin provides a valuable diagnostic test for MI only when used together with other clinical information. In particular, to satisfy the diagnostic criteria for MI, troponin elevations should be accompanied by objective instrumental evidence that myocardial ischaemia is the likely cause of myocardial damage. This should particularly be the case when only one marker measurement is available and its characteristic release kinetics cannot be demonstrated, or when marker changes remain stable over time, or are not consistent with the onset of symptoms.\(^18\) Ideally, three measurements of cardiac troponin are suggested, with a sampling frequency of hospital admission, 6 and 12 h later, to demonstrate changing values. This biochemical strategy can readily show if the temporal variations in the troponin concentrations in serum are consistent with the onset of symptoms and may very often obviate the need for subsequent extensive confirmation testing. An important issue in the practical use of cardiac troponins is the appropriate definition of decision limits. From a clinical perspective, there is evidence that any amount of detectable cardiac troponin release is associated with an increased risk of new adverse cardiac events. Currently available data demonstrate no threshold below which elevations of troponin are harmless and without negative implications for prognosis.\(^19\) In agreement with the outcome studies, the consensus documents define myocardial necrosis as an increase of cardiac troponin values which exceeds the upper reference limit of the healthy population, set at the 99th percentile of the value distribution to limit the number of false-positive designations of myocardial injury.\(^20\) On the basis of current available data, however, it would seem reasonable to expect analytical methods to give an undetectable value or a very low troponin value as "normal". None of the commercially available troponin assays has shown acceptable analytical imprecision at these low concentration values to obtain accurate discrimination between "minor" myocardial injury and analytical noise.\(^22\) In the context of clinical practice, a pre-determined higher cardiac troponin concentration that meets the requested goal for desirable imprecision, i.e., a total co-efficient of variation (CV) ≤10%,
should therefore be used as the cut-off point for MI until the assays are improved.\textsuperscript{23} The use of the actual 10% CV troponin concentration, instead of the lower 99th percentile reference limit, as decision cut-off could slightly decrease the clinical sensitivity of the biochemical criterion used for the MI diagnosis, but should permit physicians to avoid the occasional spurious increase in serum troponin concentrations resulting from analytical noise.

It is well demonstrated that the use of the new, more sensitive diagnostic criteria for MI leads to an average increase in the number of infarcts from 20% to 30% in patients admitted with suspected acute coronary syndrome (ACS).\textsuperscript{24} However, the percentage of patients re-categorised from angina to MI is also critically dependent on the performance of the troponin assay used. Although higher precision at lower troponin concentrations does not automatically equate with higher clinical sensitivity, the use of a high-sensitivity troponin assay would allow identification of a substantial and additional proportion of patients with MI compared with a less sensitive troponin assay.\textsuperscript{25}

Decision limits other than the 99th percentile and 10% CV values have been clinically defined for some of the cardiac troponin methods and used for risk stratification of patients with ACS.\textsuperscript{19} Although the data from these clinical trials are compelling, the use of cardiac troponin for MI diagnosis is different from its use for risk stratification. Differences in the prevalence of ACS in different populations have to be considered and if the purpose of measuring cardiac troponin is only to risk-stratify patients with ACS for adverse events, consideration should be given to lowering the troponin cut-off below the 10% CV value. However, these low troponin cut-off are not likely to be appropriate for the diagnosis of MI in a cohort of patients with chest pain and a lower prevalence of disease where false-positive results, produced by a cardiac troponin assay as a result of analytical imprecision, could have a much larger negative impact.

In addition to differences in the imprecision of the commercially available troponin assays, another possible source of disagreement between methods is the lack of standardisation of assays measuring cardiac troponin I (cTnI). More than 15 companies presently market assays for cTnI measurements by employing different standard materials and antibodies with different epitope specificities. Consequently, different results from different cTnI systems and assay generations may be obtained and this problem may cloud the interpretations of reported data, creating a substantial problem for the clinical and laboratory communities.\textsuperscript{26} Theoretically, standardisation and traceability of cTnI measurements require a complete reference measurement system, including a purified troponin complex as the primary reference material, a matrixed (serum-based) secondary reference material and a reference procedure that can be used to assign a cTnI value to the secondary reference material and to evaluate the analytical performance of the field methods. Once obtained, the most important benefit of standardisation is the availability of common reference and decision limits for different commercial assays. However, until adequate cTnI standardisation is possible, reference limits and clinical thresholds need to be determined separately for each assay and platform.\textsuperscript{27}

Due to the existence of an international patent, only cardiac troponin T (cTnT) assays from a single diagnostic manufacturer are commercially available, so that result standardisation for this marker is not a problem. On the other hand, a difficult clinical problem with cTnT is the significance of elevated concentrations commonly found in patients with renal failure but no clinical signs of recent myocardial damage.\textsuperscript{28} Data from outcome studies have suggested that cTnT elevations are associated with added cardiovascular risk in uraemic patients although a persistent uncertainty remains concerning the connection between elevated serum cTnT and reduced renal function.\textsuperscript{28}

**Early detection of myocardial damage**

Some practical aspects for optimising the
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sampling protocols and for combining, case by case, troponin measurements with other biomarkers in the clinical routine setting still need to be clarified. In general, it is important that hospitals tailor their diagnostic strategies for the investigation of patients with suspected ACS to local circumstances and to the way that the test results will be used. One appealing approach relies on the use of a combination of two markers to enable the detection of MI in patients who seek care early and late after symptom onset. These should be a rapidly rising marker and a marker that takes longer to rise but is more specific, such as cardiac troponin. This two-marker strategy is predicated on the assumption that early diagnosis will change care by providing the ability to discharge patients earlier, thus improving flow within the emergency department setting, and by facilitating identification of patients that may be candidates for aggressive interventions and, more generally, facilitating the triage of patients who are admitted to various parts of the hospital. Myoglobin is the marker that currently most effectively fits the role as an early marker. Its concentrations in blood appear quickly, reaching the maximum between 6 and 12 h after the onset of symptoms. It then falls to normal over the next 24 h, rapidly cleared from the serum by the kidneys. Myoglobin has, however, low specificity for cardiac necrosis, so that the use of this marker requires associate cardiac troponin measurements to confirm myocardial injury and eliminate myoglobin false-positives. Some studies have also shown a potential prognostic value for myoglobin in ACS patients. It is however difficult to determine how these could apply to clinical practice. With regard to the sampling protocol for detection of acute MI using the strategy employing early and late markers, specimen collections at the time of hospital admission and 4,8 and 12 h later has been recommended. Shorter protocols have also been proposed to rapidly exclude MI in the emergency department. Despite the undoubted success of myoglobin for detecting early myocardial necrosis in suspected patients 4-6 h after hospital admission, there is still a need for the development of earlier markers that can reliably rule out myocardial damage from the emergency room at patient presentation and, hopefully, detect myocardial ischaemia both with and without the presence of irreversible myocyte injury. Fortunately, both industry and academia are relentlessly producing an intense research effort to find new serum biomarkers that are released very early during myocardial ischaemic injury. Under investigation are two main classes of indicators: markers of early injury/ischaemia and markers of inflammation and coronary plaque instability and disruption.

Markers of cardiac ischaemia

Recent publications have explored the rationale for diagnosing myocardial ischaemia in advance, or in the absence, of the occurrence of irreversible damage. As the explicit goal is to maintain micro-circulatory flow to prevent even minor infarctions, only a marker that precedes necrosis and permits the prevention of its consequences can meet clinical needs. A marker of cardiac ischaemia could also be valuable in distinguishing acute MI from non-ischaemic causes of myocardial necrosis that lead to increases in cardiac troponins. The observed increase in free fatty acids unbound to albumin (FFAu) in the blood with acute myocardial ischaemia has recently been evaluated for the early identification of cardiac injury. Two groups of investigators have preliminarily studied the sensitivity of this marker at patient presentation to the emergency room and have shown that FFAu elevations occur well before other, more traditional, markers of cardiac necrosis. In particular, the sensitivity of FFAu at admission was >90% in both studies. The discovery that albumin, in the serum of patients with myocardial ischaemia, exhibited lower metal-binding capacity for cobalt than the albumin in serum of normal subjects was originally made by Bar-Or et al. Based on these observations, an assay was recently developed in which the cobalt not sequestered at the N-terminus of albumin is detected using a colorimetric indicator. In sera of normal subjects, more cobalt is sequestered by albumin leaving less cobalt to react with the indicator. Conversely, in sera from patients...
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with ischaemia, less cobalt is bound by the ischaemia-modified albumin (IMA), leaving more free cobalt to react with indicator. Significant changes in albumin cobalt binding have been documented to occur minutes after transient ischaemia induced by balloon angioplasty and to return toward baseline within 12 h. However, increases in IMA could also be observed during ischaemia related to the injury of organs other than myocardium. In addition, a deletion defect of the N-terminus of albumin has recently been documented in a non-ischaemic individual that was responsible for reduced cobalt binding and, consequently, for false-positive test results. Thus, the specificity of the measurement of IMA for myocardial ischaemia warrants additional investigation.

Markers of inflammation and plaque instability

Substantial evidence supports a pathogenic role for both local and systemic inflammation in ACS. In consideration of the important role that inflammatory processes play in determining plaque stability, recent work has focused on whether plasma markers of inflammation may help improve risk stratification and identify patient groups who might benefit from particular treatment strategies. Of these markers, C-reactive protein (CRP) has been the most widely studied and much has been written and discussed regarding its relationship to inflammation, coronary artery pathology and coronary disease outcome. The landmark study by Liuzzo et al showed that patients presenting with unstable angina and elevated plasma concentrations of CRP had a higher rate of death, MI and need for revascularisation compared with patients without elevated concentrations. In more recent trials, other investigators have confirmed the increased risk in ACS associated with higher CRP concentrations.

In each of the above studies, the predictive value of CRP was independent of, and additive to, cardiac troponin. More importantly, CRP was found to have prognostic value even among patients with negative cardiac troponin and no evidence of myocyte necrosis. Methodological issues have however been highlighted and the independence between CRP and troponin release questioned. Furthermore, the optimal cut-off for defining high CRP concentrations among patients with ACS remains to be determined. Finally, there is no evidence that CRP is helpful for identifying ACS patients who will benefit from a particular treatment.

CRP is not the only inflammatory marker of coronary events that has been studied. Other biochemical parameters reflecting inflammatory response such as the classical white blood cell (WBC) count, or other more complicated and expensive markers of platelet, monocyte/macrophage and polymorphonuclear neutrophil activation, have been proposed. Increases in WBC have been associated with adverse clinical outcomes and a higher mortality rate in the setting of ACS. With its simplicity and widespread availability; it could represent a very attractive marker for risk stratification in ACS. However, further research should be performed to determine if WBC could be used for targeting specific therapies.

CD40 ligand is a trimeric, transmembrane protein present in platelets and, together with its receptor CD40, is an important contributor to the inflammatory processes that lead to coronary thrombosis. After platelet stimulation, CD40 is rapidly translocated to their surface and then cleaved, generating a soluble fragment [soluble CD40 ligand (sCD40L)] having prothrombotic activity. Recent papers provided important information about the clinical relevance of sCD40L in ACS patients. Elevation of sCD40L indicated an increased risk of cardiac events during six months of follow-up. Furthermore, in patients who were negative for myocardial necrosis, as assessed by cardiac troponin, sCD40L seemed to identify a further subgroup at increased cardiac risk, suggesting that measurement of sCD40L may have additive benefits if combined with the current biochemical standard for MI. Since these studies were primarily designed to assess various therapeutic strategies in selected groups of ACS patients and not to study the clinical value of sCD40L, their results should,
however, be confirmed in specific studies performed on unselected populations. As sCD40L is known to be elevated in individuals with a broad spectrum of inflammatory conditions, a question on marker specificity also arises.

Myelo-peroxidase (MPO) is a mediator enzyme secreted by a variety of inflammatory cells, including activated neutrophils and monocytes/macrophages, such as those found in atherosclerotic plaque. It possesses pro-inflammatory properties and may contribute directly to tissue injury. Two recent experiments evaluated MPO as a predictor of cardiac risk in populations with different prevalences of ACS. In both studies, a single measurement of plasma MPO at hospital admission predicted the risk of major adverse cardiac events in the ensuing 30-day and six-month periods. Even in the absence of myocardial necrosis, i.e., consistently negative cardiac troponin, baseline measurements of MPO significantly enhanced the identification of patients at risk. Also, MPO predicted adverse outcome independently of sCD40L; in ACS patients with undetectable troponin concentrations and sCD40L concentrations below the established diagnostic threshold value, high MPO concentrations remained predictive for increased cardiac risk. This may imply that neutrophil activation represents an adjunct pathophysiological event in ACS that is distinctly different from platelet activation.

Monocyte chemoattractant protein-1 (MCP-1) is a chemokine responsible for the recruitment of monocytes to sites of inflammation that appears to play a critical role in the promotion of plaque instability. In case-control studies, plasma MCP-1 concentrations were associated with restenosis after coronary angioplasty. However, in a prospective study on a large cohort of ACS patients, the distribution of MCP-1 values in the healthy subjects and the study population overlapped considerably. These seem moreover to be a general problem for all the markers of inflammation mentioned here, indicating that they are probably not useful for diagnosing unstable ACS in individual cases.

A growing understanding of the importance of atherosclerotic plaque rupture in the pathogenesis of coronary events has led to the identification of an expanding array of markers for plaque instability. Experimental studies have demonstrated that phospholipase D enzyme activation and consequent release of choline in blood are related to the major processes of coronary plaque destabilisation. Based on these processes, increased blood concentrations of choline have to be anticipated after plaque disruption and myocardial ischaemia in patients with ACS. In a recent study, choline detected troponin-negative patients with high-risk unstable angina with a sensitivity and specificity of 86%. Additional studies are however needed to fully investigate the clinical significance of this marker.

Pregnancy-associated plasma protein A (PAPP-A) is known as a high molecular weight (200 kDa) glycoprotein synthesised by the syncytiotrophoblast and is typically measured during pregnancy for down syndrome screening. It was reported to be an insulin-like growth factor (IGF)-dependent IGF binding protein-4 specific metalloproteinase, thus being a potentially pro-atherosclerotic molecule. Bayes-Genis et al. showed the presence of PAPP-A in unstable plaques from patients who died suddenly of cardiac causes and described increased PAPP-A concentrations in the serum of patients with both unstable angina and acute MI. PAPP-A measurement appeared to be valuable for detecting unstable ACS even in patients without elevations of biomarkers of necrosis, such as cardiac troponins, thus potentially identifying high-risk patients whose unstable clinical situation might otherwise remain undiagnosed. Preliminary results provide evidence that circulating PAPP-A during ACS is different from PAPP-A isolated from pregnancy sera physiologically, PAPP-A circulates in a hetero-tetrameric complex consisting of two PAPP-A subunits covalently bound with two subunits of the pro-form of eosinophil major basic protein (pro-MBP), its endogenous inhibitor. PAPP-A found in unstable plaques...
is conversely present as a homodimer, thus making it difficult to measure PAPP-A by immunoassays which are designed to detect intact molecules. Also, the kinetics of PAPP-A release and the corresponding optimal sampling protocols in ACS remain to be determined.

Cardiac natriuretic peptides
The last part of this review is devoted to consider the role and the importance that biomarkers are assuming in the clinical assessment of cardiac function. This is an area where biochemical tests have traditionally not played any role. With the recent clinical characterisation of cardiac natriuretic peptides, these promises to be an emerging field of Laboratory Medicine. Natriuretic hormones are a family of related peptides with similar peptide chains as well as degradation pathways. Cardiac natriuretic peptides include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), while other natriuretic peptides, such as C-type natriuretic peptide and urodilatin, are not produced and secreted by cardiac tissue but by other tissues. ANP and BNP derive from precursors, the pre-pro-hormones, which contain a signal peptide sequence at the N-terminal end. The pro-hormones are further split into inactive N-terminal fragments and the biologically active peptide hormones.

Whereas ANP is secreted mainly from atrial cardiomyocytes, BNP is preferentially produced and secreted in the left ventricle, although this may be a simplification, as the right side of the human heart also synthesises and secretes BNP in response to disease. The precise mechanisms controlling production and secretion of cardiac natriuretic peptides are still unclear, although ventricular stretch and wall tension are likely to be important. In general, the plasma concentrations of these peptides are increased in diseases characterised by an expanded fluid volume, such as renal failure, primary aldosteronism and congestive heart failure (CHF), or by stimulation of peptide production caused by ventricular hypertrophy or strain, thyroid disease, excessive circulating glucocorticoid or hypoxia. In agreement with a recent commentary, it is therefore surprising that researchers focused for so long on the single issue of whether cardiac natriuretic peptides identified left ventricular (LV) systolic dysfunction or not and did not recognise that these peptides should be used in a more general way in order to detect all cardiac abnormalities, including LV hypertrophy, LV diastolic dysfunction, atrial fibrillation and significant cardiac valve disease. It is now clear that measurement of cardiac natriuretic peptides in plasma does not unequivocally diagnose the specific underlying cause of a myocardial dysfunction but rather verify the need for further cardiac examination. High concentrations of these markers call for further investigations: echocardiography is therefore required to identify the underlying cardiac pathology, revealing the systolic and diastolic ventricular function and thus determining the appropriate treatment. This was instrumental for the ESC to incorporate cardiac natriuretic peptides in the first step for the evaluation of symptomatic patients suspected of having CHF.

Although the reliable role of cardiac natriuretic peptides in the identification and management of patients with symptomatic and asymptomatic ventricular dysfunction remains to be fully clarified, the clinical usefulness of cardiac natriuretic peptides (especially BNP and Nt-proBNP) in the evaluation of patients with suspected heart failure, in prognostic stratification of patients with CHF, in detecting LV systolic or diastolic dysfunction and in the differential diagnosis of dyspnoea has been confirmed even more recently. BNP and Nt-pro-BNP have also emerged as prognostic indicators of long-term mortality early after an acute coronary event. This association was observed across the spectrum of ACS, including patients with ST-elevation MI (STEMI), NSTEMI and unstable angina, those with and without elevated cardiac troponins, and those with and without clinical evidence of heart failure. However, more work remains to be carried out to determine the optimal decision limits for clinical interpretation, as well as the specific therapeutic strategies of persistent cardiac dysfunction.
natriuretic peptide elevation in these patients. Quite recently, plasma natriuretic peptide concentrations were also related to risk of cardiovascular events and death in apparently asymptomatic persons. Important issues related to the clinical use of cardiac natriuretic peptides are still open. A working list could include: the need of standardisation of cardiac natriuretic peptide immunoassays and of better definition of their analytical performance, with regard to the antibody specificity, calibrator characterisation and influence of pre-analytical factors; more complete understanding of cardiac secretion, molecular heterogeneity and metabolism of cardiac natriuretic peptides and knowledge of their biological variation; and, from the clinical point of view, possible differences between BNP and Nt-proBNP, definition of optimal decision limits and use in combination with other biochemical markers, clinical findings, or haemodynamic parameters. Additional studies are also needed to analyse the clinical relevance of cardiac natriuretic peptides in the patient follow-up, as well as their cost-effectiveness in different clinical settings.

Conclusion
Over the last 50 years, the contribution of Laboratory Medicine to the management of cardiac diseases has become increasingly sophisticated. In the 1950s, Karmen et al. first reported that enzyme release from necrotic cardiac myocytes could be detected in the serum and could aid in the diagnosis of MI. The ensuing years witnessed progressive improvement in the cardiac-tissue specificity of biochemical markers and a corresponding enhancement in the clinical sensitivity and specificity of their use. For the foreseeable future, proteomic research for novel biomarker discovery is likely to give further significant contributions. There is now accumulating evidence that a multi-marker strategy, employing a patho-biologically diverse set of biomarkers, is likely to help significantly in the assessment of patients with cardiac disease. In particular, markers of plaque destabilisation and/or markers of myocardial ischaemia could be added to the existing markers of cardiac necrosis and function in this paradigm if shown to contribute additional independent information.

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