Future Developments in Chest Pain Diagnosis and Management

Anthony F.T. Brown, MB, ChB, FRCP, FRCSEd, FACEM, FCEMa,b,*
Louise Cullen, MBBS (Hons), FACEMa,b,c,
Martin Than, MBBS, FRCSEd(A&E), FACEM, FCEMd,e

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- Pulmonary embolism
- Aortic dissection
- Biomarkers

The clinician’s approach to a patient with chest pain should first focus on excluding the most potentially serious causes such as acute coronary syndrome (ACS), pulmonary embolism (PE), and acute aortic dissection (AAD), all of which can present without immediately obvious clinical, laboratory, radiological, or electrocardiography (ECG) findings. Once this initial phase of care is complete there is then no consensus on who, if anyone, should assess the patient next. This situation increases the risk of recurrent pain and repeat presentations.1

Alternate diagnoses at this stage include gastroesophageal reflux disease (GERD), musculoskeletal conditions including fibromyalgia, and psychological disorders. These conditions are often diagnosed by the primary care physician based on

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a School of Medicine, University of Queensland, Mayne Medical School, 288 Herston Road, Herston, Brisbane, Queensland 4006, Australia
b Department of Emergency Medicine, Royal Brisbane and Women’s Hospital, Butterfield Street, Herston, Brisbane, Queensland 4029, Australia
c School of Public Health, Queensland University of Technology, Victoria Park Road, Kelvin Grove, Brisbane, Queensland 4059, Australia
d Christchurch School of Medicine, University of Otago, Riccarton Avenue, Christchurch 8011, New Zealand
e Department of Emergency Medicine, Christchurch Hospital, Riccarton Avenue, Private Bag 4710, Christchurch 8011, New Zealand

* Corresponding author. Department of Emergency Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Butterfield Street, Herston, Brisbane, Queensland 4029, Australia.

E-mail address: af.brown@uq.edu.au

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response to a carefully chosen therapeutic trial, for instance a proton-pump inhibitor (PPI) for GERD, or following specialist referral.

Much of the focus of research on patients with chest pain is directed at technological advances in the diagnosis and management of ACS, PE, and AAD, despite there being no significant difference at 4 years as regards mortality, ongoing chest pain, and quality of life between patients presenting to the emergency department with noncardiac chest pain (NCCP) and those with cardiac chest pain. Moreover, NCCP patients significantly outnumber patients presenting with an underlying cardiac cause, particularly to the primary care physician.

This article examines future developments in the diagnosis and management of patients with suspected ACS, PE, AAD, gastrointestinal disease, and musculoskeletal chest pain.

FUTURE DEVELOPMENTS IN ACUTE CORONARY SYNDROME

The diagnosis of ACS is based on clinical judgment, serial 12-lead ECG analysis, and cardiac biomarkers and, if these are negative, some form of stress testing. Each of these modalities for the evaluation of a patient with potential ACS has difficulties. On the one hand any delay in the diagnosis or “rule in” of an acute myocardial infarction (AMI) precludes early pharmacologic or interventional treatment known to improve outcome by limiting infarct size. In contrast, chest pain units aimed at ensuring significant diagnoses are not missed to “rule out” patients with a low probability for ACS report a negative assessment in up to 98% of all patients tested. Despite this dichotomy in decision-making perspective, still as many as 2% to 5% of patients with ACS, that is, with either AMI or unstable angina pectoris (UAP), are missed and sent home from the Emergency Department (ED).

Future developments in the assessment and management of patients with ACS presenting to the ED with chest pain will include improved ECG analysis, novel biomarkers, newer imaging techniques, risk stratification tools, improved drugs, sonothrombolysis, and stem cell transplantation (Box 1).

Earlier Diagnosis

The key to improving the outcome in the diagnosis of ACS lies in the development of a coordinated approach to early detection, from the time the patient first accesses medical care. Thus, prehospital diagnosis of ST-elevation myocardial infarction (STEMI) with 12-lead ECG analysis can facilitate the primary goal of immediate opening of the infarct-related vessel, for instance by direct transfer of the patient to a hospital operating a catheter laboratory 24 hours a day.

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**Body Surface Mapping**

Standard 12-lead ECG analysis identifies STEMI and dictates the need for immediate reperfusion therapy for an optimal outcome. However, neither the ECG nor serum biomarkers have high early sensitivity to detect AMI in general, as they may remain negative immediately after the event. One option to improve the sensitivity in detecting AMI is ECG body surface mapping (BSM), which uses up to 80 ECG leads placed on the anterior and posterior chest to enable more complete visualization of cardiac electrical activity (Fig. 1).

The BSM output can be displayed in a 12-lead ECG format, in an 80-lead format, or on color contour or topographic maps. With recent advances in computer technology, BSM has become more user-friendly in aiding direct visualization of injury patterns, particularly in the right ventricle and posterior wall of the left ventricle associated with an inferior AMI.

BSM may also improve the diagnostic evaluation and treatment of patients with ST depression on a standard 12-lead ECG. In particular, BSM can differentiate a group of patients who in fact have ST elevation on BSM, who theoretically might therefore benefit from early reperfusion therapy. One BSM trial has also shown the ability to detect AMI prehospital. However, early detection of AMI with BSM comes at a cost of a lower specificity and higher false-positive results compared with the standard ECG.

**High-Frequency QRS Analysis**

Another approach to improve the detection of acute myocardial ischemia is ECG analysis of the high-frequency (HF) components of the QRS complex above 100 Hz. Those frequencies are usually not seen as notable morphologic alterations in the QRS complex on the standard 12-lead ECG machine, as these use noise-reducing filters to eliminate this HF range. However, the HF components can provide information about the severity of ischemia and myocardial infarction (MI). Although HF QRS analysis may offer additional noninvasive information in ACSs, it is currently hampered by marked interpatient variance, and a lack of large-scale clinical outcome trials in humans.

**Novel ACS Biomarkers**

**Overview**

Elevation of cardiac biomarkers is pivotal to the diagnosis of AMI. However, biomarkers that could detect ACS without myocardial necrosis may allow clinicians...
to recognize biologic events happening before necrosis occurs, thereby identifying earlier patients at higher risk of an adverse event\textsuperscript{26,27}; this could then lead to treatment targeted to limit or prevent an AMI. At present, these types of biomarker are not commercially available.

Although cardiac troponins provide important prognostic information, they do not accurately determine absolute risk for ACS.\textsuperscript{28} Several newer cardiac biomarkers have therefore been proposed for the diagnosis and risk stratification of patients with possible ACS. These markers include copeptin, myeloperoxidase (MPO), pregnancy-associated plasma protein A (PaPP-A), placental growth factor (PIGF), CD40 ligand, ischemia modified albumin (IMA), fatty acid binding protein (h-FABP), free fatty acids, growth differentiation factor 15 (GDF-15), serum choline, glycogen phosphorylase isoenzyme BB (GPBB), and high-sensitivity C-reactive protein (hsCRP) (Box 2).

Although many of these may provide additional short- and long-term prognostic information, at present none offer a clear diagnostic advantage over troponin alone. In addition, few are currently available in commercially approved kits.

**Copeptin**
Copeptin, the C-terminal part of the vasopressin prohormone, is secreted from the neurohypophysis and is activated in the endogenous stress response.\textsuperscript{29} The measurement of copeptin in addition to a biomarker with a different pathophysiological origin such as troponin can improve the diagnostic accuracy at presentation, and possibly eliminate the need for serial sampling. One study by Reichlin and colleagues\textsuperscript{29} found that combining copeptin and troponin T had a sensitivity of 98.8% and a specificity of 77.1% for diagnosing AMI.

**Myeloperoxidase**
MPO is released by neutrophils and macrophages, and so becomes elevated in coronary artery atherosclerotic lesions prone to rupture.\textsuperscript{26,30} MPO has shown promise in risk stratification of chest pain patients with persistently normal troponin levels, and may prove useful for the disposition of patients from the ED. Of note, MPO levels

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have been found to be elevated at baseline in patients subsequently shown to have AMI, even when symptom onset was less than 3 hours before blood analysis.\textsuperscript{30} However, MPO elevation is not specific to cardiac disease, as activation of neutrophils and macrophages occurs with many other disease processes.\textsuperscript{26}

**Pregnancy-associated plasma protein A**
PaPP-A is a marker of neovascularization that may also play a role in detecting atherosclerosis and plaque rupture.\textsuperscript{26,31} Although PaPP-A appears to have little correlation with other cardiac biomarker levels, it has shown promise at predicting the need for a revascularization procedure.\textsuperscript{31,32}

**Placental growth factor**
PlGF is a hormone that stimulates angiogenesis and macrophage recruitment,\textsuperscript{32} and may thus indicate inflammation predicting early AMI.\textsuperscript{26} However, studies to date used the higher cut-off values for the cardiac troponin reference standard that are now superseded, so new research comparing PlGF with the currently recommended levels for abnormal troponin is now necessary to reconfirm its efficacy.\textsuperscript{31}

**CD40 ligand**
CD40 ligand levels reflect both inflammation and platelet/plaque interactions,\textsuperscript{32} with encouraging results, particularly when combined with PlGF.\textsuperscript{26,31} More studies are needed before strong conclusions can be drawn.

**Ischemia modified albumin**
IMA molecules are produced when the metal terminus of the albumin molecule is damaged during ischemia.\textsuperscript{31,32} IMA should thus be useful for its strong negative predictive value for ischemia, even before necrosis. Current studies indicate good potential for IMA to rule out ACS when combined with troponin and ECG.\textsuperscript{32} However, it is currently difficult to assess the role of IMA due to the lack of standard reference criteria for nonnecrotic ischemia.\textsuperscript{31} IMA may also not be specific for cardiac ischemia.\textsuperscript{26}

**Fatty acid binding protein**
h-FABP is released rapidly post infarction,\textsuperscript{31} and may outperform myoglobin in the early detection of AMI. However, current studies indicate that h-FABP lacks specificity,\textsuperscript{31} and adds little diagnostic information to the newer ultrasensitive troponin assay results.\textsuperscript{33}

The real value of any new biomarker, including genetic and genomic markers, will be to better define ACS disease activity and to refine the risk stratification process, particularly by identifying ischemia without myocardial necrosis in ACS.

**Multimarker approach**
Combinations of biomarkers that complement each other in terms of their release curve improve the accuracy of the early detection of AMI, and so should reduce the delay to key interventions.\textsuperscript{34–38} In addition, multimarkers are able to rapidly rule out AMI with a high negative predictive value.\textsuperscript{35,37,39,40} The ability to safely and accurately exclude or \textquoteleft{}rule out\textquoteleft{} AMI improves the efficiency of a chest pain assessment unit and will allow earlier stress testing in the biomarker negative group, leading to a shorter hospital stay.

**Delta troponin and ultrasensitive troponins**
The use of delta troponin, the change in the troponin value over time, has improved the diagnostic accuracy for AMI.\textsuperscript{41–43} Newer ultrasensitive troponin assays may be able to
utilize very low levels of detection, and employ a “delta approach” that measures change between initial and incremental levels at zero and from 2 to 6 hours after the onset of symptoms, or from hospital arrival.44,45

Unfortunately, the list of conditions other than myocardial ischemia associated with an elevated troponin continues to increase. Characteristic changes in troponin levels associated with many non-ACS related diagnoses such as PE and sepsis are not well defined. Thus, exquisitely sensitive assays may well produce their own problems in interpretation, in the light of the already long list of medical conditions associated with a raised troponin level even at currently agreed cut-off levels.46 Particularly problematic will be if the newer ultrasensitive troponins are used indiscriminately, without careful consideration of need from the medical history and examination findings.

**Newer Imaging Modalities**

The choice of objective tests to identify ACS has expanded in recent times to include cardiac computed tomographic angiography (CCTA), plaque composition analysis, cardiac magnetic resonance imaging (CMRI), and positron emission tomography (PET) (Box 3).

**Cardiac computed tomographic angiography**

High-resolution CCTA offers noninvasive coronary angiography that may improve risk stratification, particularly in the intermediate-risk chest pain patient.47 CCTA allows evaluation of global and regional left ventricular function comparable with CMRI,48 and provides information about luminal narrowing and plaque composition. Several clinical and economic studies support the use of CCTA scanning to risk-stratify ED patients with ACS.49–55 However, although radiation dose is an issue, CCTA when negative allows the definitive rule-out of coronary artery disease in the low- and intermediate-risk group.51

**Plaque composition analysis**

Plaque composition analysis may also prove of particular use in predicting significant ACS,56 as these patients have more mixed and noncalcified plaques than patients with stable angina.57,58 Outcome data on plaque analysis by CCTA are limited, but it may provide additional prognostic information for patients with possible ACS.

Alternatives to CCTA aimed at the early diagnosis of a “vulnerable” plaque include intravascular ultrasound (IVUS), palpography and virtual histology, optical coherence

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**Box 3**

**Newer imaging modalities to identify ACS**

- Cardiac computed tomographic angiography (CCTA)
- “Vulnerable plaque” analysis:
  - CCTA
  - Intravascular ultrasound
  - Palpography and virtual histology
  - Optical coherence tomography
  - Near-infrared spectroscopy
- Cardiac magnetic resonance imaging
- Positron emission tomography
tomography (OCT), and near-infrared spectroscopy (see Box 3). However, there is at present little evidence that a local or regional therapeutic approach to asymptomatic “vulnerable” plaque reduces cardiac events compared with current optimal systemic therapy.

**Cardiac magnetic resonance imaging**

CMRI is already established in the assessment of congenital heart disease, the great vessels, pericardial disease, and chronic coronary artery disease. CMRI also allows the assessment of a wide spectrum of causes of chest pain. Although coronary anatomy imaging using coronary artery CMRI has been developed, few studies have assessed the clinical utility of CMRI for ACS in the ED setting.

CMRI may be a useful alternative investigative pathway in view of its lack of radiation exposure. In addition, stress-CMRI using adenosine or dobutamine may help to predict significant coronary artery disease, and may have a role in a select group of patients as an alternative noninvasive stress test.

**Positron emission tomography**

As not all coronary stenoses detected by CCTA are flow limiting, additional noninvasive testing should be considered before cardiac catheterization. PET hybrid computed tomography (CT) devices allow integration of the structure and function of the heart. Stress PET data may identify a hemodynamically significant stenosis, and when combined with the anatomic information from the CCTA helps guide revascularization decisions. Again, further research is needed to define its exact role in the management of ACS in the ED setting, although access will remain limited for some time yet.

**Risk Stratification Tools**

Risk stratification tools are essential in determining pretest probability (PTP), as no single clinical feature or investigation result alone is diagnostic for acute coronary syndrome. Accurate estimation of the PTP for ACS is fundamental to the appropriate use of resources. Several methods to determine pretest probability for ACS have been reported, including the physician’s own estimate, decision trees, logistic regression, attribute matching, and computer-based artificial neural networks.

Kline and colleagues determined that in a population with a pretest probability of ACS of less than or equal to 2%, the risk of testing will exceed its benefits. Unnecessary investigations in this group are then averted as the person is already at a very low risk of ACS.

**PREtest ConsultACS**

A computer-derived, quantitative pretest probability assessment derived from attribute matching has been developed for use in ACS, as well as in PE (see later discussion). PREtest ConsultACS matches an 8-component clinical profile from any individual patient considered at risk of ACS with a prior reference database of 14,800 patients to allow an estimate of PTP probability. Those with a PTP of 2% or less, or “test negative,” have a 45-day ACS outcome of just 0.3%. Prospective validation in other non-US populations is in progress.

However, many models still focus on ruling in the diagnosis of AMI to facilitate the early and appropriate use of cardiology services, rather than excluding ACS by clearly identifying a rule-out population suitable for early ED discharge. Thus the use of these tools is currently restricted by their heterogeneity and different end-point intention, which emphasizes the importance of adopting a standardized data definitions.
set for use in ACS research. These standardized data definitions will ensure use of a common language and framework to maximize value when extrapolating research findings between different studies.78

**Treatment Advances**

**Antiplatelet medication**

Early diagnosis allows the earlier initiation of treatment for STEMI and non-STEMI, and improved outcomes. Antiplatelet medication is central to the treatment of ACS, such that aspirin is now widely used in virtually all patients with undifferentiated chest pain. This indiscriminate use of aspirin, despite significant benefit for those with ACS-related diagnoses, currently lacks validation but is assumed to be safe.

Clopidogrel is another common antiplatelet medication used with aspirin, but it shows variability in platelet inhibition.79,80 Alternative dual antiplatelet treatment options include newer therapies such as prasugrel, which received Food and Drug Administration (FDA) approval in early 2009, and ticagrelor, both of which show improved platelet inhibition.81–83 Ticagrelor is an oral, reversible, direct-acting inhibitor of adenosine diphosphate receptor P2Y12 that has rapid, pronounced platelet inhibition. Ticagrelor has the advantage of a survival benefit without an overall increased rate of major bleeding when compared with clopidogrel.84

The use of other platelet inhibitors such as the glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors in the setting of STEMI has shown variable changes in coronary artery patency.85–87 While one small trial of prehospital treatment with a GP IIb/IIIa inhibitor has not shown clinical benefit,88 a larger study is underway investigating the benefit of early GP IIb/IIIa inhibition prior to percutaneous coronary intervention (PCI) in the setting of non-ST elevation acute coronary syndrome (NSTEACS).89

**Sonothrombolysis**

Another emerging approach toward improving vessel patency is sonothrombolysis, using low-frequency ultrasound for thrombus dissolution. This technique may become a valuable noninvasive route to improve vessel patency with thrombolytic therapy in the large majority of patients unable to access timely percutaneous interventions.90 Low-frequency ultrasound treatment increases tissue perfusion from coronary occlusion by thrombus dissolution.91

**Stem cell transplantation**

Finally, stem cell transplantation to improve the function of the injured myocardium is under investigation.92 Intracoronary injection of mononuclear bone marrow cells in patients with a recent MI appears to be safe.93 “Cellular cardiomyoplasty” trials administering intravenous allogenic human marrow stem cells (MSC) without immunosuppression to post-AMI patients are currently underway.92

**FUTURE DEVELOPMENTS IN PULMONARY EMBOLISM**

The decision whether to investigate a patient for a particular disease is a balance between the risks of harm from missing the diagnosis against the harm that might derive from the investigations themselves. Regarding PE, the threshold at which clinicians decide to commence investigating is dropping steadily,94 and current strategies in the assessment of a patient with a suspected PE certainly have the potential to cause harm. This problem arises due to the widespread indiscriminate use of D-dimer testing, from fear of missing the diagnosis, which leads to increased diagnostic imaging by CT pulmonary angiogram (CTPA) subsequent to the high false-positive rate of the D-dimer assays. This in turn increases cost, causes delay with ED
overcrowding, and exposes patients to the risks of unnecessary ionizing radiation and contrast nephropathy.

Similar to ACS, future developments in the assessment and management of patients presenting to the ED with chest pain suggestive of PE again include novel biomarkers, newer imaging techniques, risk stratification tools, and improved drugs. Additional strategies include percutaneous mechanical thrombectomy and reevaluation of the role of thrombolysis in submassive PE (Box 4).

**Novel Pulmonary Embolism Biomarkers**

Many novel biomarkers involved in inflammation, hemostasis, and vascular injury are under investigation to replace or supplement D-dimer testing in PE. Nordenholz and colleagues\(^95\) investigated 50 potential biomarkers for their predictive value in 304 ED patients evaluated for PE, and found that only D-dimer, C-reactive protein, and MPO demonstrated sufficient diagnostic accuracy to support their use clinically, with areas under the receiver-operating characteristic (ROC) curve of greater than 0.75.

**D-dimer testing using multiple rather than single cut-off levels**

D-dimer testing in clinical practice is currently based on a single cut-off level for a positive and a negative result created using ROC curve analysis. Although this dichotomous approach makes the test result easy to interpret, it is oversimplistic and fails to indicate how far above or below the cut-off the test result actually lies. Linkins and colleagues\(^96\) have suggested that the use of 3 probability-specific D-dimer cut-off points can exclude PE in a greater proportion of patients than using a single cut-off point, without sacrificing the negative predictive value.

**Ischemia-modified albumin**

While levels of ischemia-modified albumin are also being investigated for their diagnostic utility in ACS, a recent animal study has suggested that ischemia-modified albumin levels increase within 1 hour and up to the sixth hour post PE.\(^97\) However, it is unclear how IMA might, if at all, usefully discriminate between different underlying causes in a patient with undifferentiated chest pain.

**Growth arrest–specific gene 6**

Growth arrest–specific gene 6 (Gas6) is a protein that is elevated during pulmonary or systemic infection, but not with PE. As D-dimer levels increase in all these conditions, the addition of Gas6 testing may help reduce the false-positive rate for PE, thereby increasing the specificity of the D-dimer test.\(^98\)

**Myeloperoxidase**

MPO correlates with the presence of PE with an area under the ROC curve (AUC) of 0.78 compared with 0.93 for D-dimer, with a negative test helping rule out a PE.\(^95\)

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**Box 4**

**Future developments in patients with suspected PE**

- Novel biomarkers
- Newer imaging techniques
- Risk stratification tools
- Improved therapeutic agents
- Percutaneous mechanical thrombectomy
- Reevaluation of role of thrombolysis in submassive PE
MPO may also have additional diagnostic utility again used in conjunction with D-dimer, as a combination approach reduces the high false-positive rate from using D-dimer alone.\textsuperscript{99}

**Tissue plasminogen activator and plasminogen activator inhibitor type 1**

Once fibrin is formed in the thrombosis/fibrinolysis process, tissue plasminogen activator (tPA) activates plasminogen to plasmin to begin fibrin breakdown, with one of the subsequent breakdown products being D-dimer. This process is partly regulated by plasminogen activator inhibitor type 1 (PAI-1). Both tPA and PAI-1 are detectable in the circulation using an enzyme-linked immunosorbent assay once fibrinolytic system activation has occurred. Preliminary research has suggested very high sensitivity for tPA and PAI-1 in the detection of PE, but their clinical correlation is unclear.

**Imaging**

Various new imaging techniques are being investigated, including single photon emission computed tomography (SPECT) perfusion lung scan, magnetic resonance imaging angiography (MRA), and magnetic resonance venography of the veins of the thighs (MRV).

**Single photon emission computed tomography perfusion lung scan**

This nuclear medicine technique uses images in extra planes from a double- or triple-head camera, and has a better specificity than ventilation perfusion (VQ) planar scanning, with less scans reported as “indeterminate” or nondiagnostic.\textsuperscript{100,101} At present there are relatively few published data on its clinical use.

**Magnetic resonance imaging angiography**

Experience with MRA is much more limited than for VQ and CTPA scanning. Therefore, MRA is usually restricted to patients with contraindications to conventional imaging. Gadolinium-enhanced angiography (Gd-MRA) has demonstrated a specificity for PE in the high ninety percent range, with a sensitivity ranging from 85% to 100%, although there is concern about the incidence of nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD) in patients given gadolinium contrast. The FDA is monitoring the situation especially in patients with moderate (glomerular filtration rate <60 mL/min) to severe renal disease. Alternative contrast techniques using contrast specifically targeting thrombus, such as iron oxide microparticles, single chain antibodies, and T1 bright methemoglobin, are under investigation.

**PIOPED III**

A prospective multicenter investigation known as Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III), to determine the diagnostic accuracy of Gd-MRA of the pulmonary arteries in combination with magnetic resonance venography of the veins of the thighs (MRV) in patients with clinically suspected acute PE, is currently underway.

The aim is to recruit around 1200 patients with suspected acute PE over a period of 2 years using composite reference standards to diagnose venous thromboembolism (VTE) and exclude PE. All patients with PE and a matched group without PE will undergo Gd-MRA/MRV. This combination technique could eliminate the need for iodinated contrast material and ionizing radiation in the estimated 24% of patients with suspected PE, who have relative contraindications such as renal impairment, allergy, and pregnancy.\textsuperscript{102}
**ThromboView**

ThromboView (Agen Biomedical, Brisbane, Australia) consists of \(^{99m}\)Tc-labeled deimmunized anticrosslinked fibrin (anti–D-dimer) Fab’ fragments with a high affinity and a high specificity for D-dimer given intravenously. ThromboView is under investigation as a diagnostic tool for thromboembolic events such as PE detected by SPECT. ThromboView may be superior to conventional imaging by selectively disclosing acute thrombi, as it is able to distinguish between a fresh thrombus and other filling defects within the pulmonary arteries.\(^{103,104}\) A recent phase 2 study showed only comparable sensitivity and specificity to CTPA for PE. Phase 3 trials are in progress.

**Decision Analysis Risk Stratification**

Various new techniques are being used to provide an actual point-estimate of PTP of PE, over and above the physician’s usual unstructured Gestalt estimate, assisted by validated scoring systems such as the Canadian (Wells) or Geneva scores. These methods include a back-transformed logistic regression equation, and nonlinear models such as artificial intelligence or Bayesian Network analysis.\(^{105–107}\)

**Probability Software Database Tools**

PREtest ConsultPE (PREtest Consult Inc, Charlotte, NC) is a novel computerized method of pretest probability assessment derived from a process called attribute matching. The assessment requires the clinician to enter 10 predictor variables into a computer program (age, ± pleuritic chest pain, ± dyspnea, pulse oximetry reading, heart rate, ± prior VTE, ± recent surgery or trauma, ± estrogen use, ± hemoptysis, ± unilateral leg swelling).

Attribute matching works by a selection process whereby a computer algorithm compares the results of all 10 predictor variables obtained from the patient being evaluated to a library of 12,595 research patients previously evaluated for PE compiled from multiple hospitals. The algorithm returns only the “matched” patients who share the same profile of predictor variables as the patient under consideration. The algorithm then reports the proportion of patients with disease in this matched sample as a pretest probability, that is, the number of diseased patients divided by the total number of patients who fit the profile (Fig. 2).

The utility of PREtest ConsultPE includes 2 discrete steps. The clinician assesses the pretest probability of PE using a validated tool, and if the probability is low enough, no further testing is warranted. Other decision rules such as the “Charlotte Rule” were derived to allow the exclusion of a PE, but those exclusion criteria function in an “all or none” way without allowing integration into a continuum of testing available with PREtest ConsultPE.\(^{108,109}\)

The “test threshold” for PE has previously been estimated at 2%,\(^{95,104,105}\) which is the pretest probability that should be exceeded to justify the need for diagnostic testing. Prospectively, the summary 45-day outcome rate has been found to be 0.7% for the whole subgroup of patients with a PTP between zero and 2%. Although local standards may vary, the 1% threshold probably represents a reasonable international threshold to exclude PE.\(^{72,108,110,111}\) Therefore, if the patient’s pretest probability is zero to 2%, the risks inherent in further evaluation secondary to unwarranted treatment in the event of a false-positive test result outweigh the risks of the PE. Thus a patient with a quantitative PTP of 2% or less for PE does not need a D-dimer, or a CTPA, or any other pulmonary vascular imaging study, saving time, cost, and risk.

Moreover, those patients with a PTP of more than 2% may still be able to avoid exposure to unnecessary ionizing radiation by next adding biomarker testing to then
produce a posttest probability again below 1% (Fig. 3, shaded rectangle). Knowing that quantitative immunoturbidimetric or enzyme-linked colorimetric D-dimer assays demonstrate a LR(–) = 0.10 to 0.15 for the diagnosis of PE,112–114 a pretest probability of PE less than 7.5% followed by a negative D-dimer test result of less than 500 ng/mL then produces a posttest probability less than 1%. Once again, this rules out a PE without the need for any imaging.

Improvements in Therapeutic Agents

Several new therapeutic agents, including parenteral and oral anticoagulants, have been studied.

Parenteral anticoagulants
Idraparinux is derived from fondaparinux, and binds to antithrombin with such high affinity that its half-life is comparable to that of antithrombin itself. The advantage of idraparinux is that it may be given by subcutaneous injection once weekly, and does not require coagulation monitoring. However, it must be used with caution in patients with renal insufficiency as it is excreted via the kidneys, and is contraindicated in patients with a creatinine clearance of less than 30 mL/min. Protamine sulfate, used to counteract heparin, does not reverse the anticoagulant effects of idraparinux.

SSR 126517 shares the pharmacologic features of idraparinux, but with the advantage that its anticoagulant effect is reversed by giving intravenous avidin, a tetrameric glycoprotein.

Oral anticoagulants
Warfarin  Warfarin is currently the only orally available drug for long-term anticoagulation. Several problems make warfarin a difficult drug to use for physicians and patients alike; these include a narrow therapeutic margin, delayed onset of action, difficulty with reversal, many interactions with drugs and diet, a wide variation in anticoagulant effect, and the need for frequent laboratory monitoring. These problems may lead to recurrent thrombosis from undertreatment or to excessive bleeding with overtreatment. Bleeding complications with warfarin are among the most frequent adverse drug effects, with the risk of major bleeding between 1% and 5% per year. Therefore, there is an ongoing search for a replacement for warfarin for oral anticoagulation. Newer oral agents with fewer side effects than warfarin have undergone trials in VTE prevention, but treatment trials currently are limited and are usually restricted
to therapy for deep venous thrombosis (DVT). These agents include dabigatran etexilate, rivaroxaban, and apixaban.

**Dabigatran etexilate, rivaroxaban, and apixaban** Dabigatran etexilate is an oral small molecule prodrug that acts as a thrombin inhibitor, whose absorption is pH sensitive and is reduced by around 30% by PPIs. Effective doses of dabigatran etexilate are relatively high, and it is contraindicated in patients with renal failure because it is excreted via the kidneys. Rivaroxaban selectively inhibits factor Xa and is administered orally, with 80% bioavailability. Dabigatran etexilate must also be used cautiously in patients with renal insufficiency or in patients with severe liver disease, and is monitored by Factor Xa inhibition. Finally, apixaban is an orally administered selective inhibitor of factor Xa that can be monitored using a factor Xa inhibition assay or a diluted prothrombin time.

It is hoped that these agents will provide a better therapeutic window and easier monitoring, and may be simpler to reverse in an emergency, making them more convenient and safer to use than warfarin.

**Percutaneous mechanical thrombectomy**

Percutaneous mechanical thrombectomy (PMT) by mechanical fragmentation and thrombus aspiration is a novel approach that may benefit patients with massive PE
and right ventricular dysfunction. Patients who may particularly benefit would be those with major contraindications to thrombolysis, those at an increased bleeding risk, those who have failed thrombolysis, or when surgical thrombectomy is unavailable. Clot is fragmented via catheterization, and the fragments removed via an internal aspirator.\textsuperscript{115}

**Thrombolysis for pulmonary embolism**

Although meta-analysis has shown no benefit for thrombolysis in patients with PE without shock,\textsuperscript{116} these patients have significant morbidity at 6-month follow-up, with a 41% rate of cardiopulmonary problems, either right ventricular dysfunction on echo, heart failure (New York Heart Association score >I), or a 6-minute walk distance (6MWD) of less than 330 m.\textsuperscript{117}

The Pulmonary Embolism Thrombolysis (PEITHO) study being conducted in Europe is seeking to demonstrate whether thrombolysis with tenecteplase plus standard anticoagulation improves the outcome of patients presenting with high-risk submassive acute PE, when compared with standard anticoagulation alone. At present around one-third of the target of 1000 patients have been recruited.

**FUTURE DEVELOPMENTS IN ACUTE AORTIC DISSECTION**

AAD is one of the most common catastrophes of the aorta, classically affecting men 50 to 70 years old with hypertension, with sudden severe chest or back pain and a myriad of other possible symptoms and signs. AAD is time-critical and rapidly fatal if left untreated, particularly for ascending type A dissections.\textsuperscript{118}

Future developments in the assessment and management of patients with AAD presenting to the ED with chest pain will once again include novel biomarkers, plus newer imaging techniques such as contrast-enhanced ultrasound, endovascular treatment, and combined interventional and surgical treatment (Box 5).

**Novel Acute Aortic Dissection Biomarkers**

Serum smooth muscle myosin heavy chain, calponin, D-dimer, and serum-soluble elastin fragments are promising tests to help rule in or rule out the diagnosis of AAD.\textsuperscript{119,120}

**Serum smooth muscle myosin heavy chain**

Serum smooth muscle myosin heavy chain is specific for damage to the smooth muscle of the arterial wall, with diagnostic studies yielding a sensitivity of 90.9% and a specificity of 98% within 3 hours of symptom onset of suspected AAD, particularly with proximal lesions.\textsuperscript{121}

**Calponin**

Likewise, immunoassays against basic and acidic calponin, the troponin-like protein of smooth muscle, have shown potential to detect AAD in the first 6 to 24 hours.

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The moderate sensitivity and specificity suggest that technical improvements in the assay are still necessary before firm recommendations on its use can be made.122

**D-dimer**

D-dimer has been used for many years when negative to rule out thromboembolic diseases such as DVT and PE. A recent Austrian study supports the routine measurement of D-dimer to exclude AAD, with 100% negative predictive value for a cut-off level of 0.1 μg/mL.123 However, the optimal cut-off value for its clinical use is still disputed.124

**International Registry of Acute Aortic Dissection data on D-dimer**

Investigators from the International Registry of Acute Aortic Dissection (IRAD) have just published a substudy on biomarkers (IRAD-Bio) focusing on D-dimer119 in AAD. Although small, the study was one of the largest collections of proven AAD patients within a prospectively enrolled cohort of 87 positives out of 220 patients with suspected AAD. At the widely used D-dimer cut-off level of 500 ng/mL, a negative D-dimer had a sensitivity of 95.7% within 6 hours of the onset of symptoms. In addition, the investigators also noted that D-dimer was markedly elevated in AAD and suggested that using a D-dimer of 1600 ng/mL or more was useful as a “rule-in” cut-off to identify patients with a high probability of AAD. However, the diagnostic accuracy among patients with AAD is dependent on the type, extent, and the time from presentation.

**Serum-soluble elastin fragments**

Although the structural protein serum-soluble elastin fragments begins to leak from the aorta during the aging process, acute aortic injury causes serum levels to elevate sharply. Testing has shown early promise with a high predictive value, but as the test takes up to 3 hours to perform it is likely to be unacceptable given the urgency of the condition.

**Contrast-Enhanced Ultrasound**

Contrast-enhanced ultrasound (CEUS) involves introducing gas-filled microbubbles into the circulation to provide strong contrast on ultrasonography. These microbubbles can be modified to target certain tissue types, such as inflamed blood vessels, allowing CEUS to evaluate abdominal aortic dissection, particularly in patients with contraindications to CT contrast agents such as renal failure or severe allergy. CEUS may allow a more rapid and noninvasive diagnosis, especially in critical patients from intensive care units, because of its bedside availability. As the examination is dynamic, additional information about blood flow in the true and false lumen and about renal perfusion after dissection can be obtained. Thus CEUS may provide a good alternative to multislice CTA.125

**Endovascular Treatment**

Stanford type B aortic dissections confined to the descending, distal aorta have traditionally been managed medically, but this is changing with the advent of endovascular stenting with careful patient selection. Recent generations of stent grafts are able to avoid many of the earlier stent complications such as stroke, penetration of the aorta, graft collapse, leak, migration, or aneurysm extension, although evidence of longer term durability is unclear.124

One remaining concern is the radiation exposure of regular CT imaging of stents needed to ensure their integrity and placement, particularly in younger patients.126
**Combined Interventional and Surgical Treatment**

The combination of surgical aortic reconstruction with endovascular stent grafting has been shown to simplify type A aortic dissection management, reduce the circulatory arrest time, reduce the risk of surgical complications, and reduce the need for subsequent surgery on the descending aorta. Again, the long-term effectiveness has not been studied.127

**Triple Rule-Out Scan**

CTA is the imaging modality of choice in the investigation of both PE and AAD. Now that CCTA is becoming established, some have suggested using a modified scanner protocol aimed at simultaneously investigating for all 3 of PE, AAD, and coronary artery disease, known as the “triple rule-out scan.”

Previously, such scans were precluded as patients would have had to hold their breath for longer than 30 seconds to obtain adequate images from the lung apices to the diaphragm in older generation scanners. The advent of 64- and 128-slice CT scanners allows a faster scanning process and reduced movement artifact. Technical challenges still remain, in particular achieving consistent high levels of contrast intensity in all 3 vascular zones. Also, it is difficult to simultaneously image segmental pulmonary arteries and the distal coronary arteries supplied by the right and left ventricles, respectively.

A saline bolus to flush contrast out of the right side of the heart is used to obtain high and consistent visualization of the coronary arteries with minimal right heart enhancement in CCTA, whereas CTPA protocols are designed to achieve maximal enhancement of the pulmonary arteries and the right side of the heart. Therefore, triple rule-out scans require precise harmonization of contrast injection and imaging sequences.128

**Radiation dosage issues**

The exact radiation dose to the patient from a triple rule-out scan appears to be highly variable, depending on the scanner protocol used. For instance, the effective radiation dose can be reduced by more than 50% to $8.75 \pm 2.64$ mSv with ECG-based tube current modulation without loss of image quality.129 As traditional imaging studies for ACS and PE involve a chest radiation dosage as low as 5 mSv or less, this still represents a significant step up, so poor patient selection and indiscriminate use of the triple rule-out scan would have significant radiation exposure issues.

As scanner technology and contrast protocols improve, the challenge for clinical leaders will be how to focus triple rule-out scan use to avoid spiraling costs and excessive patient radiation exposure.

**FUTURE DEVELOPMENTS IN GASTROINTESTINAL DISEASE**

GERD is the most common cause of esophageal chest pain, although the majority (60%) of patients have no evidence of erosive esophagitis at conventional endoscopy. Such nonerosive reflux disease (NERD) by definition should still respond to acid suppression therapy such as a PPI, albeit with a lower response rate than in erosive GERD.130

**Novel Endoscopic Techniques**

Novel alternative upper gastrointestinal endoscopy techniques are available to demonstrate subtle submucosal abnormalities such as chromoendoscopy with Lugol iodine, confocal endomicroscopy, or narrow band imaging in conjunction with zoom
magnification. Their exact indication is unclear, as is the role of 24-hour pH and impedance monitoring in NERD.

In addition, finding an objective marker to differentiate NERD from functional heartburn might better guide empirical therapy, as the latter is a symptom complex unrelated to the reflux of gastric contents with no correlation of symptoms with acid reflux exposure.

Non-GERD–Related Esophageal Chest Pain

A large variety of therapies has been tried for non-GERD–related functional esophageal chest pain among patients with NCCP. Such treatment includes anticholinergics and muscle relaxants, botulinum toxin, psychotropic medications, cognitive-behavioral therapy, and surgery. Trials of novel visceral sensitivity modifying agents for presumed visceral hyperalgesia as a cause of NCCP, including theophylline, cilansetron (a 5-HT₃ antagonist), tegaserod (a partial 5-HT₄ agonist), octreotide, and fedotozine (a peripherally acting κ-opioid agonist), may demonstrate a cornerstone role, alone or in combination with a PPI.

FUTURE DEVELOPMENTS IN MUSCULOSKELETAL CHEST PAIN

A careful history and examination by palpation or pressure should suggest a musculoskeletal cause for NCCP, although this does not per se rule out a more serious cardiac cause, as they may coexist. Clinical predictors of musculoskeletal chest pain, including response to manual therapy, are currently under investigation for patients presenting with acute chest pain.

The role of radiological examination including MRI in musculoskeletal NCCP remains unproven, and newer imaging modalities are unlikely to ever be cost effective compared with focusing on understanding better the underlying mechanisms such as spinal referred pain.

SUMMARY

Future developments in the assessment and management of patients with ACS presenting to the ED with chest pain will include improved ECG analysis, novel biomarkers, newer imaging techniques, risk stratification tools, improved drugs, sonothrombolysis, and stem cell transplantation.

Similarly, developments in patients presenting to the ED with chest pain suggesting a PE will include novel biomarkers, newer imaging techniques, risk stratification tools, and safer drugs. Additional strategies may include PMT and reevaluation of the role of thrombolysis in submassive PE.

Developments for patients with suspected AAD presenting to the ED with chest pain will again include novel biomarkers, plus newer imaging techniques such as CEUS, endovascular treatment, and combined interventional and surgical treatment.

Developments in the treatment of gastrointestinal disease will include alternative endoscopic techniques, methods to differentiate non-GERD causes for pain, better recognition of functional heartburn, and validating new treatment modalities such as medication, cognitive-behavioral therapy, and surgery. Finally, developments in musculoskeletal chest pain will focus on a greater understanding of underlying mechanisms and the role, if any, of newer imaging techniques.

Most research on chest pain patients is thus focused on advances in the diagnosis and management of ACS, PE, and AAD, despite there being no significant difference at 4 years in mortality, ongoing chest pain, and quality of life between patients presenting to the ED with NCCP as opposed to cardiac chest pain. In addition, NCCP patients
significantly outnumber patients presenting with an underlying cardiac cause, particularly to the primary care physician.

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