Perusal of risk stratification of acute myocardial infarction for half a century

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This editorial refers to ‘Growth differentiation factor-15 as a prognostic marker in patients with acute myocardial infarction’¹, by S.Q. Khan et al., on page 1057

Acute coronary syndrome and acute myocardial infarction (AMI) in particular, is a dangerous presentation of coronary artery disease (CAD). Myocardial infarction is the main cause of death in Western countries, with an in-hospital mortality of 6–13%. Overall mortality including death outside hospital has been estimated at 30–40%. After recovering from infarction, surviving patients remain vulnerable to cardiovascular events such as heart failure, recurrence of angina, reinfarction, arrhythmia, and sudden cardiac death. Treatment of AMI has advanced tremendously over the past 50 years, including establishment of coronary care units with defibrillation devices and haemodynamic monitoring, pharmacotherapies such as β-blockers and angiotensin-converting enzyme inhibitors, various thrombolytic and adjunctive therapies, and percutaneous coronary interventional procedures (PCI).¹

Many of these have proven to be beneficial in aborting AMI and reducing short- and long-term mortality and cardiovascular events.¹ Obviously a good AMI risk stratification may facilitate assessment of prognosis, not only for improved appreciation of risk and communication of this to patients, but also for identifying patient subsets who warrant a different treatment approach, as well as for decision making for allocation of treatment resources.

Tools for such stratification have evolved over the past five decades, targeted at evaluation of myocardial damage, resulting haemodynamic stress and electrical instability, and residual ischaemia. Prognostic factors have been documented, including the extent of left ventricular dysfunction, residual ischaemia and vulnerable plaque, severity and extent of CAD, electrical instability, and prevalence of atherosclerotic risk factors (Table 1).² Systematic prognostic stratification for AMI in the pre-thrombolytic era was pioneered by Peel and Norris in the 1960s, relying on multivariate discriminative analysis of bedside clinical features including age, shock, congestive heart failure, conduction or rhythm disorders, oliguria, respiratory rate, concentration of cardiac enzymes, and level of consciousness.³,⁴ Many such indices are imprecise, empirical, and open to criticism. The indices which emerged in the following two decades focused on analysis of haemodynamic data, objective bedside indicators of heart failure or jeopardized myocardium, and direct infarct size assessment using the blood cardiac enzyme release pool, echocardiography, and radioisotopic scintigraphy.⁵ Different clinical subsets with different in-hospital mortalities were identified. In the thrombolytic and PCI era, a gradual reduction in hospital mortality was observed, but the long-term outcome remains problematic. The TIMI risk score is a representative of such risk indices developed for ST-segment elevation AMI using multivariable methods and counting information in the history (age, diabetes mellitus, hypertension, or angina), examination findings (systolic blood pressures, heart rate, Killip class, and body weight), and data at presentation (ECG patterns, time to treatment).⁶ This risk score showed stable prognostic performance in 30-day mortality across multiple time points (1–365 days). Another user-friendly risk score is the GRACE score, which considers age, heart rate, systolic blood pressure, renal dysfunction, Killip class, cardiac arrest, elevated cardiac enzymes (including troponin), and ST-segment deviation, and relates to 30-day (3.1–11.2%) or 1-year mortality (4.2–27.2%) in patients with non-ST-segment elevation AMI.⁷

Advances in biotechnology in the past decade have demonstrated several novel prognostic biomarkers related to cardiovascular outcome, independent of bedside clinical factors. These include cardiac troponin, high sensitivity C-reactive protein (hsCRP), brain natriuretic peptide (BNP), and N-terminal pro β-type natriuretic peptide (NT-ProBNP), which are related to underlying left ventricular dysfunction or the inflammatory process.⁸–¹⁰ Growth differentiation factor-15 (GDF-15) is the newest addition. It is a member of the transforming growth factor-β cytokine superfamily, upregulated and secreted by cardiomyocytes during ischaemia and reperfusion, and has been shown to have anti-apoptotic action. It may relate to infarct size...
and resulting left ventricular dysfunction and multiple stress pathways, but has been hypothesized to reflect a unique pathophysiological axis not represented by available markers of necrosis, inflammation, or haemodynamic stress. GDF-15 has a strong association with death at 1 year that is consistent across a variety of relevant subgroups, independent of most major clinical prognostic indicators.\textsuperscript{11,12} The adjusted risk of death is greater for each standard deviation increase in GDF-15 than for NT-ProBNP; both provide complementary prognostic information independent of other clinical or biochemical risk factors. A retrospective stratification using GDF-15 in the FRISC-II trial confirmed its benefit in identifying patients for invasive procedures in non-ST-elevation acute coronary syndrome.\textsuperscript{13} The study of Khan et al.\textsuperscript{14} reports similar prognostic information on GDF-15 for death and heart failure up to a mean follow-up period of 505 days, on an unselected real-world AMI cohort outside a randomized trial, and provides an external validation of this novel cardiovascular biomarker. Although no decline of GDF-15 concentration in serial sampling of GDF-15 post-AMI up to 72 h was reported in a previous study, blood sampling in the recovering phase of AMI (3–5 days) in Khan’s project will miss the early deaths during the first 72 h. Further studies are needed for a better understanding of its role in the pathobiology of acute coronary syndrome and full characterization of pre-analytical perturbations in sample handling. Most importantly, while the immunoradiometric method for GDF-15 assay ought to be further smoothed out for faster reporting in a shorter time, its independent benefit in guiding treatment decisions (and other novel biomarkers alike) should be confirmed by prospective randomized clinical trials.\textsuperscript{15}

After perusal for half century, the time has come for a more accurate risk stratification post-AMI using bedside clinical parameters and some prognostic biomarkers. The key issue of whether these biomarkers will help clinicians to manage patients should be addressed, and hopefully answers will be forthcoming in the very near future.

Conflict of interest: none declared.

References

Table 1 Prognostic features after myocardial infarction

<table>
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<tr>
<th>Left ventricular dysfunction</th>
<th>Residual myocardial ischaemia/</th>
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A/V, atrioventricular; BNP, brain natriuretic peptide; CPK, creatine phosphokinase; CAD, coronary artery disease; Echo, echocardiography; GDF-15, growth differentiation factor-15; hsCRP, high sensitivity C-reactive protein; LV, left ventricular; NT ProBNP, N-terminal pro natriuretic peptide; VT, ventricular tachycardia.


CARDIOVASCULAR FLASHLIGHT

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Transient right bundle branch block in a young patient

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A 32-year-old man with a history of hypertension and no prior coronary heart disease was referred to our hospital with suspected acute coronary syndrome. He suffered from chest pain during his work. Except an upper respiratory tract infection, his personal history was unremarkable. The initial electrocardiogram (ECG) demonstrated ST-elevation in lead V2. The first Troponin T was negative but increased to 0.45 μg/L (normal <0.01 μg/L) during the next 6 h. The second ECG (Panel A) showed complete right bundle branch block (RBBB). Therefore, coronary angiography was performed, which excluded coronary artery disease and documented preserved left ventricular ejection function (LVEF). For further evaluation, the patient underwent cardiac magnetic resonance (CMR) imaging the next day, which revealed a mid-myocardial delayed enhancement in the basal septal, anteroseptal, and inferolateral walls (Panel B). In addition, there was a septal wall motion abnormality and a slightly reduced LVEF (45%). Thus, these findings were consistent with (peri-)myocarditis. Therapy with a non-steroidal antiphlogistic drug and ACE-inhibitor was started. Seven days after admission, the RBBB had resolved (Panel C) and concomitant follow-up CMR documented significant decrease of delayed enhancement in the septum (Panel D) and normalized LVEF. This case demonstrates the good correlation of dynamic ECG changes and transient myocardial involvement as here with myocarditis lesions in the region of the electrical conduction system in the septum.

Panel A. Initial ECG showing complete right bundle branch block.
Panel B. Cardiac magnetic resonance imaging demonstrating mid-myocardial delayed enhancement in the basal septal, anteroseptal, and inferolateral walls.
Panel C. ECG 7 days after admission with resolved right bundle branch block.
Panel D. Follow-up cardiac magnetic resonance with decreased delayed enhancement of the septal wall.

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