Welcome to issue 18 of Acute Coronary Syndrome Research Review.

Researchers from Scotland report in the *Lancet* that a high-sensitivity cardiac troponin I assay has an optimal level for predicting which patients with suspected acute coronary syndrome can be discharged safely, without needing to undergo serial troponin testing. The paper concludes that this approach could have major benefits for both patients and healthcare providers.

Four papers from the October issue of *Circulation Cardiovascular Interventions* discuss different aspects of the management of patients who are successfully resuscitated following an out-of-hospital cardiac arrest. The findings add to the debate around immediate coronary angiography and percutaneous coronary intervention in these patients.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Professor John French

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**Bivalirudin or unfractionated heparin in acute coronary syndromes**

**Authors:** Valgimigli M et al.

**Summary:** The MATRIX trial recruited 7213 patients with an acute coronary syndrome (ACS) for whom percutaneous coronary intervention (PCI) was anticipated and randomised them to receive either bivalirudin or unfractionated heparin. Patients in the bivalirudin group were subsequently randomly assigned to receive or not to receive a post-PCI bivalirudin infusion of ≥4 hours. The primary outcome for the comparison of a post-PCI bivalirudin infusion with no post-PCI infusion was the occurrence of net adverse clinical events (NACE), defined as the composite of death, myocardial infarction (MI), stroke, major bleeding, urgent target-vessel revascularisation (TVR) and stent thrombosis (ST). At 30 days, no significant differences were seen between bivalirudin and heparin for the rates of major adverse cardiovascular events (MACE; a composite of death, MI, or stroke) (10.3% and 10.9%, respectively; relative risk [RR] 0.94; 95% CI, 0.81 to 1.09; p=0.44) and NACE (11.2% and 12.4%, respectively; RR 0.89; 95% CI, 0.78 to 1.03; p=0.12). Post-PCI bivalirudin infusion, as compared with no infusion, did not significantly decrease the rate of urgent TVR, definite ST, or NACE (11.0% and 11.9%, respectively; RR 0.91; 95% CI, 0.74 to 1.11; p=0.34).

**Comment:** The MATRIX trial had 3 study questions, firstly the best access route (radial or femoral), whether bivalirudin was better than heparin with a 20% higher use rate of GP2B3A inhibitors in the heparin arm, and whether among patients assigned to bivalirudin, post-PCI cessation or a longer infusion gave best results. This presentation concerns the 7200 patients assigned to either bivalirudin or heparin. As with the HORIZONS trial, the rate of cardiac death among ACS patients (55% STEMI) was lower than that in the heparin group. This was associated with a lower rate of bleeding, although there was no difference in the reinfarction rates and no statistical difference in the stent thrombosis rates overall. Interestingly, the reduced bleeding rate associated with randomisation to bivalirudin was not dependent on the arterial access route. Whether the results change the perception that bivalirudin does not have advantages in ACS patients is unclear.


**Abstract**
High-sensitivity troponin T predicts infarct scar characteristics and adverse left ventricular function by cardiac magnetic resonance imaging early after reperfused acute myocardial infarction

Authors: Nyugen TL et al.*

Summary: These researchers sought to determine the sampling period for high-sensitivity troponin T (hs-TnT) that would best predict cardiac magnetic resonance imaging (CMRI)-measured infarct scar characteristics and left ventricular (LV) function. The study enrolled 201 patients with first presentation with ST-segment elevation myocardial infarction (STEMI) and subjected them to serial measurements of hs-TnT levels (at admission, peak, 24 hours, 48 hours, and 72 hours) after STEMI. At a median of 4 days post-STEMI, CMRI evaluated indexed LV volumes, LV ejection fraction (LVEF) and infarct scar characteristics (scar size, scar heterogeneity, myocardial salvage index, and microvascular obstruction). Peak and serial hs-TnT levels were positively correlated with early indexed LV volumes and infarct scar characteristics, and negatively correlated with myocardial salvage index and LVEF. In univariate analyses, both 48- and 72-hour hs-TnT levels similarly predicted “large” total infarct scar size (odds ratios [ORs] 3.08 and 3.53, both p<0.001), myocardial salvage index (ORs 1.68 and 2.30, both p<0.001), and LVEF <40% (ORs 2.16 and 2.17, both p<0.001). In multivariate analyses, 48- and 72-hour hs-TnT levels predicted large infarct scar size (ORs 2.05 and 2.31, both p<0.001), poor myocardial salvage (OR 1.39 [p=0.031] and OR 1.55 [p=0.009]) and LVEF <40% (OR 1.47 [p=0.018] and OR 1.43 [p=0.026]). hs-TnT levels also had a similar capacity to predict post-STEMI microvascular obstruction.

Comment: This study showed that hs-TnT is associated with larger infarcts on cardiac magnetic resonance imaging and that hs-TnT levels measured 48–72 hours post-STEMI are closely associated with infarct size. While larger studies will be needed to determine whether this parameter is as robust a prognostic marker compared to other parameters including microvascular obstruction (MVO) derived from cardiac MRIs, due to the low cost of this test it should be performed, when available. Whether similar findings may be achieved with high-sensitivity troponin I assays needs to be determined.

* John French is a co-author of this study.


Six-year prognostic value of microvascular obstruction after reperfused ST-elevation myocardial infarction as assessed by contrast-enhanced cardiovascular magnetic resonance

Authors: Regenfus M et al.

Summary: This German group of researchers assessed the long-term prognostic impact of cardiac magnetic resonance (CMR) parameters, especially microvascular obstruction (MVO), after reperfused STEMI. The study involved 249 patients who underwent CMR after reperfused first STEMI, for measurements of LVEF, infarct size (IS), and the amount of MVO. At a median 6.0 years of follow-up, MACE occurred more often in the 61 patients with MVO compared with the 12 patients who did not have MVO (p<0.0001). In multivariate analysis, the extent of MVO remained the strongest predictor (p<0.001) for occurrence of MACE and provided incremental prognostic information besides clinical variables and LVEF (p=0.028, c-index increase from 0.723 to 0.817).

Comment: This study determined the late prognostic significance of MVO, a finding first reported by Wu et al. in 1998. While MVO and TIMI risk score were the independent predictors of late mortality, it isn’t clear whether key previously described post-STEMI prognostic factors including ECG and angiographic characteristics, ST recovery and myocardial perfusion grade known as ‘blush’ and angiographic frame counts, were included in the multivariate analyses. The traditional biomarker creatine kinase, not troponin(s), was included. What key markers of late outcomes remain durable in the current era, compared to earlier decades, need clarification.

Reference: Am J Cardiol. 2015;116(7):1022-7
Stoke in the TOTAL trial: a randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction

Authors: Jolly SS et al.

Summary: The TOTAL trial (n=10,732) was an international, multicentre, randomised trial of routine manual thrombectomy vs. percutaneous coronary intervention alone in STEMI patients. There was no difference in the primary efficacy outcome (reduction in thrombus burden) but thrombectomy was associated with a significant increase in stroke. This reanalysis of TOTAL data sought to understand these findings. Stroke within 30 days, the primary safety outcome, was increased in the thrombectomy group (0.7% vs 0.3%; hazard ratio [HR] 2.06; 95% CI, 1.13 to 3.75). The between-group difference in stroke was apparent within 48 h (0.3% vs 0.1%; HR 3.00; 95% CI, 1.09 to 8.25). There was an increase in strokes within 180 days with minor or no disability (Rankin 0–2) (0.4% vs 0.3%; HR 1.38; 95% CI, 0.68 to 2.82) and in strokes with major disability or fatal (Rankin 3–6) (0.7% vs 0.3%; 2.69; 1.42 to 5.08). Most of the absolute difference was due to an increase in ischaemic strokes within 180 days (0.7% vs 0.4%; HR 1.71; 95% CI, 1.03 to 3.00), but there was also an increase in haemorrhagic strokes (0.2% vs 0.04%; p=0.001). A meta-analysis of randomised trials (n=21,173) showed an increase in risk of stroke (OR 1.59; 95% CI, 1.11 to 2.27) but a trend towards lower mortality (0.87; 0.76 to 1.00).

Comment: The practice of coronary aspiration thrombectomy during primary PCI has been controversial in STEMI management over the last decade, with initial enthusiasm based on the unexpected improvement in mortality in the underpowered TAPAS trial, which subsequent major studies (TASTE and TOTAL) have failed to confirm. The current guidelines of ACC/AHA/SCAI have now given this practice a level 3 recommendation; that is, thrombus aspiration is not recommended. This is based on a meta-analysis of trials, the major one being from TOTAL showing in fact a higher stroke rate among patients undergoing aspiration thrombectomy. Thus, in some cases undergoing primary PCI for STEMI, there may be particular reasons such as a very high thrombus burden, for example on optical coherence tomography (OCT), where thrombectomy may be performed on a minority of individual patients, but in the absence of further evidence this cannot be recommended.

Reference: Eur Heart J. 2015;36(35):2364-72

High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study

Authors: Shah AS et al.

Summary: In this study, 6304 patients with suspected ACS admitted to 4 hospitals in Scotland underwent measurement of plasma troponin levels at presentation using a high-sensitivity cardiac troponin I assay as well as the standard-of-care troponin assay. The optimal level of the high-sensitivity assay was assessed in two independent validation cohorts: 1126 patients who presented with suspected ACS to the Royal Infirmary of Edinburgh and 308 patients who presented to the Henderson County Medical Center, Minneapolis. 792 (16%) patients in the derivation cohort had index MI. At 30 days, 32 (1%) patients re-presented with MI and 75 (2%) died from cardiac causes. In patients without MI at presentation, low troponin levels gave excellent negative predictive value for the composite endpoint (index type 1 MI, or type 1 MI or cardiac death at 30 days). Troponin levels of <5 µg/L were found in 2311 (61%) of 3799 patients below the 99th centile at presentation, giving a negative predictive value of 99.6%. The negative predictive value decreased with higher troponin levels and was <99.5% with levels of ≥5 µg/L. The negative predictive value was consistent across groups stratified by age, sex, risk factors, and previous cardiovascular disease. The two validation cohorts showed that troponin levels <5 µg/L identified patients with type 1 MI with an overall negative predictive value of 99.4%. At 1 year, these patients had a lower risk of MI and cardiac death compared with those with a troponin level of ≥5 µg/L (0.6% vs 3.3%; adjusted HR 0.41; 95% CI, 0.21 to 0.80; p<0.0001).

Comment: This study involved over 6000 patients in Scotland, of whom 16% ended up having an MI and 2% cardiac death. This study found that the level of troponin I measured by the high-sensitivity Abbott assay of less than 5 µg/L had a high negative predictive value for MI or cardiac death over the following year. While it is proposed that these patients may be discharged from hospital based on troponin, it would be desirable that this approach be subjected to a randomised trial with current standard of care, which has been updated in the latest ESC NSTEAC guidelines for serial troponins at either 1 or 3 hours if these are performed by high-sensitivity assays together with serial ECGs. Such a study will require more than the 6000 patients included in this study, which had an absolute event rate of 75 patients.

Predicting the presence of an acute coronary lesion among patients resuscitated from cardiac arrest

Authors: Waldo SW et al.

Summary: These US investigators describe the development and validation of a risk prediction model for the presence of an acute coronary lesion among patients with a cardiac arrest. Records from an ongoing institutional registry for the period 2009 to 2014 identified 247 patients who underwent coronary angiography after resuscitation from a cardiac arrest. Backwards stepwise selection of candidate covariates was used to create a logistic regression model for the presence of an angiographic culprit lesion and internally validated with bootstrapping. A clinical point score was generated and its prognostic abilities compared with contemporary measures. 130 (52%) patients had an acute lesion in a coronary artery. A 4-factor model that included angina, congestive heart failure symptoms, shockable arrest rhythm (ventricular fibrillation/ventricular tachycardia) and ST-elevations showed excellent discrimination (optimism corrected C-Statistic, 0.88) and calibration (p=0.540) for an acute coronary lesion. Compared with electrocardiographic findings alone, a point score based on this model more accurately predicted the presence of an acute lesion among patients resuscitated from a cardiac arrest (integrated discrimination improvement, 0.10; 95% CI, 0.04 to 0.19; p<0.001).

Comment: See next page.

Reference: Circ Cardiovasc Interv. 2015;8(10):e002198
Abstract

Early coronary angiography and survival after out-of-hospital cardiac arrest

Authors: Vyas A et al.

Summary: These researchers used data from the Cardiac Arrest Registry to Enhance Survival (CARES) to identify 4029 adult patients admitted to 374 hospitals after successful resuscitation from OHCA because of ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), or unknown shockable rhythm. Early coronary angiography (occurring within 1 calendar day of cardiac arrest) was performed in 1953 (48.5%) patients, of whom 1253 (64.2%) received coronary revascularisation. Patients who underwent early coronary angiography were younger (59.9 vs 62.0 years); more likely to be men (78.1% vs 64.3%), have a witnessed arrest (84.6% vs 77.4%), and have STEMI (32.7% vs 7.9%); and less likely to have known cardiovascular disease (22.8% vs 35.0%), diabetes mellitus (11.0% vs 17.0%), and renal disease (1.8% vs 5.8%; p<0.001 for all comparisons). Analysis of 1312 propensity score-matched pairs revealed that early coronary angiography was associated with higher odds of survival to discharge (OR 1.52; 95% CI, 1.28 to 1.80; p<0.0001) and favourable neurological outcome (1.47; 1.25 to 1.71; p<0.0001). After further adjustment for coronary revascularisation, both odds ratios were significantly attenuated in the models, suggesting that revascularisation was a key mediator of the survival benefit.

Comment: See next page.

Reference: Circ Cardiovasc Interv. 2015;8(10):e002321
Abstract

Post-resuscitation ECG for selection of patients for immediate coronary angiography in out-of-hospital cardiac arrest

Authors: Stær-Jensen H et al.

Summary: Coronary angiographic findings were reviewed from 210 resuscitated patients (mean age 62 years) admitted after out-of-hospital cardiac arrest (OHCA) without a clear noncardiac cause. Irrespective of their first post-resuscitation ECG, the patients were referred to immediate coronary angiography (ICA). The aim of this investigation was to determine whether this ECG is useful for selecting patients with no need of ICA. Post-resuscitation ECGs were assessed in a blinded fashion and patients were allocated to 1 of 3 groups: (1) ST-elevation or presumably new left bundle branch block (LBBB), (2) other ECG signs indicating MI, and (3) no ECG signs indicating MI. All coronary angiograms were re-evaluated blinded for post-resuscitation ECGs. Six-month survival with good neurological outcome was 54%. Reduced Thrombolysis in Myocardial Infarction (TIMI) flow (0–2) was identified in 55%, 34% and 18% of patients and a ≥90% coronary stenosis was found in 25%, 21% and 19% of patients in groups 1, 2 and 3, respectively. An acute coronary occlusion was found in 11% of patients in group 3. ST-elevation/LBBB identified patients with reduced TIMI (0–2) flow with 70% sensitivity and 62% specificity. Among patients with initial nonshockable rhythms (24%), 32% had significantly reduced TIMI flow.

Comment: See next page.

Abstract
Immediate percutaneous coronary intervention is associated with improved short- and long-term survival after out-of-hospital cardiac arrest

Authors: Geri G et al.

Summary: This study involved 1722 non-trauma OHCA patients (median age 60 years) admitted to a Parisian hospital after return of spontaneous circulation: 628 (35.6%) without coronary angiography, 615 (35.7%) with coronary angiography without PCI, and 479 (27.8%) with both. Among these groups, day 30 survival rates were 21%, 35% and 43%, respectively; 10-year survival rates were 11.9%, 29% and 38%, respectively (p<0.01 for each). Immediate PCI was associated with a lower 30-day (OR 0.71; 95% CI, 0.54 to 0.92; p=0.02) and long-term mortality rate (HR 0.44; 95% CI, 0.27 to 0.71; p<0.01) than no PCI. In propensity score–matching analysis that examined the influence of PCI on short- and long-term survival, PCI remained associated with a lower risk of long-term mortality (adjusted HR 0.29; 95% CI, 0.14 to 0.61; p<0.01).

Comment: The management of patients who have restoration of circulation following an out-of-hospital cardiac arrest (OHCA) is problematic, as neurological status specifically hypoxic brain injury or the extent thereof, rather than an occluded coronary artery, determines long-term outcome. However, the likelihood of neurological recovery cannot easily be assessed in a reliable manner in these emergency circumstances. Thus, whether every patient with OHCA, assuming they were appropriate for initial resuscitation, should undergo emergency angiography is debated with somewhat different views on either side of the Atlantic. Making appropriate judgements regarding emergency angiography are complicated by confounding in interpretations of the post-resuscitation ECGs. In the October issue of Circulation Cardiovascular Interventions, there are 4 papers addressing different aspects of this problem. Waldo and colleagues presented data from 247 patients that allowed them to develop a 4-factor model that had a powerful C-statistic (0.88) at predicting an acute lesion: the factors are angina, congestive heart failure symptoms, shockable rhythm (VF/VT) and ST elevation. However, this model needs validation in another larger data set. The paper of Starr-Jensen et al. tried to assess whether the initial ECG after resuscitation following OHCA was informative. Assessment of the ECGs was blinded and 3 groups were defined: ST elevation or presumed new LBBB, other ischaemic changes without ST elevation, and no ECG changes. Angiograms were also assessed blinded to outcomes, and reduced TIMI flow was found in 55% in the first group, and only 18% in the last. Vyas et al report data from the large cardiac arrest registry (CARES) and propensity-matched patients on ECG findings, though these were often absent. The fourth paper of Geri et al. looked at 14 years’ experience of out-of-hospital arrests in Paris. They included those who either didn’t undergo angiography, underwent angiography and PCI and also those who underwent angiography without PCIs. Those who underwent PCI had better outcomes and half of those patients had ST elevation on the ECG. Appropriately powered trials have commenced ‘in this space’ and they will hopefully provide evidence to guide practice.


Abstract

Research Reviews are prepared with an independent commentary from relevant specialists.

POST-MI PATIENTS REMAIN AT HIGH AND PERSISTENT RISK1-4

up to 20% RISK of a recurrent CV event in the first year1,2

~20% RISK of a recurrent CV event in the subsequent 3 years*1

After a successful intervention, what more can we do to protect them from their underlying disease?

*The APOLLO HELICON analysis was a retrospective cohort study that included 108,315 patients from a national Swedish registry with a primary diagnosis of acute MI between July 2006 and June 2011. The primary endpoint was risk for non-fatal MI, non-fatal stroke, or cardiovascular death. The cumulative 1 year incidence of the primary endpoint was 18.3%. In patients who were event free at 1 year, the cumulative incidence of the primary endpoint was 28% after the following 3 years.1 On the basis of pooled data (Framingham Heart Study, Atherosclerosis Risk in Communities Study, and National Heart, Lung, and Blood Institute), the American Heart Association reported that 19% of men and 26% of women aged ≥45 years will die within 1 year after a first MI.1
