Welcome to the thirteenth issue of Acute Coronary Syndrome Research Review.

We begin this issue with a review of type 2 myocardial infarction (T2MI), also known as supply/demand MI, a commonly encountered clinical challenge that is surrounded by diagnostic uncertainty. The paper reviews the definition of T2MI, the controversies surrounding its universal adoption in clinical practice, and future directions for research. The reviewers call upon the clinical cardiology community to give T2MI more attention.

Findings on the association between fish consumption and acute coronary syndrome have been inconsistent. Now, a large meta-analysis (involving over 400,000 participants) reports an inverse association between fish consumption and the risk of acute coronary syndromes (ACS). It seems that fish consumption is beneficial in the primary prevention of ACS and that higher consumption is associated with higher protection.

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,

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Supply/demand type 2 myocardial infarction: should we be paying more attention?

Authors: Sandoval Y et al.

Summary: Type 2 myocardial infarction (T2MI), also known as supply/demand MI, is a commonly encountered clinical challenge. It is anticipated that it will be detected more frequently following the approval of high-sensitivity cardiac troponin assays for clinical use in the USA. This paper reviews the definition, epidemiology, aetiology, pathophysiology, prognosis, management, the controversies surrounding the acceptance of T2MI in clinical practice, and future directions for research that may help to improve its diagnosis.

Comment: For busy clinicians, the presentation of patients with elevated blood troponin levels but without an apparent acutely unstable coronary plaque is common. In the Third Universal Definition of MI this has been called T2MI, and is sometimes known as ‘troponinitis’. In this review paper, the lack of clarity of diagnostic criteria is outlined and the authors suggest that any future universal MI definitions should attempt to more closely define T2MI. The vast majority of patients with T2MI present with a non-ST-elevation myocardial infarction (NSTEMI) rather than STEMI. Thus, there is an urgent need for randomised trials to characterise optimal pharmacological and investigational/interventional management of such patients.

Reference: J Am Coll Cardiol. 2014;63(20):2079-87

As with other anti-platelet agents, BRILINTA prolongs bleeding time and should be used with caution in ACS patients who may be at risk of increased bleeding. Premature discontinuation could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient’s underlying disease.1

Abbreviations used in this review:

ACCS – acute coronary syndromes; CAD – coronary artery disease; MI – myocardial infarction; NSTEACS – non-ST-segment-elevation acute coronary syndrome; NSTEMI – non-ST-elevation myocardial infarction; pPCI – primary percutaneous coronary intervention; STEMI – ST-elevation myocardial infarction; T2MI – Type 2 myocardial infarction

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PBS Information: Authority Required (STREAMLINED). Treatment of acute coronary syndrome (myocardial infarction or unstable angina) in combination with aspirin.

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Prognosis of patients with non-ST-segment-elevation myocardial infarction and non-obstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial

Authors: Planer D et al.

Summary: This trial investigated the impact of nonobstructive coronary artery disease (CAD) in patients presenting with non-ST-segment-elevation acute coronary syndromes (NSTEACS) and abnormally elevated troponin I or troponin T levels according to laboratory upper limits of normal. Of 2442 patients with elevated troponin, 2246 (91.9%) had obstructive lesions (quantitative coronary angiography diameter stenosis >50%) and 197 patients (8.1%) had nonobstructive CAD on coronary angiography. A propensity score adjustment yielded 117 patients with nonobstructive CAD matched with 331 patients with obstructive CAD, with similar baseline characteristics between the matched groups. In the entire cohort, angiographic findings revealed a significantly greater diameter stenosis in patients with obstructive CAD versus those with nonobstructive CAD (maximum 87.4 vs 22.6; p<0.0001). These differences remained highly significant in the matched cohort. Among the propensity score-matched patients, overall 1-year mortality was significantly higher in patients with nonobstructive CAD (8.2% vs 1.8%; hazard ratio [HR] 3.44; 95% CI, 1.05 to 11.28; p=0.04), driven by greater noncardiac mortality. Conversely, rates of recurrent MI and unplanned revascularisation were significantly higher in patients with obstructive CAD.

Comment: This report from the ACUITY trial is the largest report of characterisation of patients with NSTEMI and no obstructive angiographic coronary disease (no stenosis >50%) from a core laboratory. The important finding of an increased death rate due to non-cardiac causes alludes to the clinical heterogeneity in these patients. As they tended to be younger, some may have had inherited thrombophilias, others emboli from plaque erosions and many type 2 MI. As the authors indicate, these angiographic findings should lead to further investigation for other potential causes, including noncardiac diagnoses.

http://circinterventions.ahajournals.org/content/7/3/285.long

Characteristics of plaque disruption by intravascular ultrasound in women presenting with myocardial infarction without obstructive coronary artery disease

Authors: Iqbal SN et al.

Summary: Plaque morphology findings are discussed for 42 women with MI and <50% angiographic stenosis who underwent intravascular ultrasound investigation (n=114 vessels). Sixteen patients had plaque disruption (PD; 14 ruptures and 5 ulcerations <50% angiographic stenosis who underwent intravascular ultrasound investigation). Percent plaque burden was lower in disrupted plaques than in the largest plaque in the same vessel (31.9% vs 49.8%, p=0.005) and were rarely located at the site of largest plaque (1/19). Disrupted plaques were typically fibrous and were not more eccentric or remodelled than the largest plaque in the same vessel.

Comment: With a phenomenon of MI without significant, more accurately “non-flow limiting” coronary artery disease, it has been known for over a decade that among women and younger people the rates of inherited thrombophilia are higher in patients who have non-flow-limiting disease. Not unexpectedly, however, intravascular ultrasound has shown that indeed there is plaque in these patients. The likely mechanism is that asymptomatic plaque rupture and healing, which has become an increasingly recognised phenomenon, probably does not occur in these patients but there is propagation of the thrombus to complete or near complete occlusions. Certainly, measuring inherited thrombophilia genes should be considered in such patients, especially if there is a past history of venous thromboembolism.

http://www.ahajournals.org/article/20122-87031400082-9/abstract

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Five-year survival in patients with ST-segment–elevation myocardial infarction according to modalities of reperfusion therapy: the French Registry on Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) 2005 cohort

Authors: Danchin N et al.

Summary: These investigators assessed 5-year mortality in patients with STEMI from the FAST-MI 2005 cohort according to use and type of reperfusion therapy of those who presented with a first event ≤12 hours from onset. 447 (30%) received fibrinolysis (66% pre-hospital; 97% with subsequent angiography), 84% with subsequent percutaneous coronary intervention (PCI), 583 (39%) had primary PCI (pPCI), and 462 (31%) received no reperfusion. Crude mortality rates were 88% for the fibrinolytic-based strategy, 83% for pPCI, and 59% for no reperfusion. Adjusted HRs for 5-year death were 0.73 (95% CI, 0.50 to 1.06) for fibrinolysis versus pPCI, 0.57 (95% CI, 0.36 to 0.88) for pre-hospital fibrinolysis versus pPCI, and 0.93 (95% CI, 0.34 to 0.31) for fibrinolysis versus pPCI beyond 90 minutes of call in patients having called <180 minutes from onset. However, propensity score–matched analyses revealed no significant differences in survival rates between fibrinolysis and pPCI, both in the whole population (88% lysis, 85% pPCI) and in the population seen early (87% fibrinolysis, 85% pPCI beyond 90 minutes from call).

Comment: This 5-year mortality follow-up report from the FAST-MI registry of 2005 reports a lower mortality for patients receiving pre-hospital fibrinolysis for STEMI than those treated by primary PCI. While those receiving pre-hospital "lysis" were lower risk, as patients with complicated comorbidities are likely to be transferred to hospital for repertusion, adjusted analyses did not show a mortality benefit except in one subgroup. Those patients presenting at <3h who were estimated to have at least 60 min transfer delays to the cardiac catheterisation laboratory, the so-called STREAM (trial)-like patients did have a 5-year mortality benefit when receiving pre-hospital "lysis." The challenge in the Australian health system is to achieve this pharmaco-invasive strategy "success"; routine times to angiography for rescue PCI and angiography for those who achieve pharmacological reperfusion need improvement.

http://tinyurl.com/pzg3quu

Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a prespecified analysis from the EUROMAX trial

Authors: Zeymer U et al.

Summary: Outcomes are described for 2198 STEMI patients in the EUROMAX trial who were randomised during transport for pPCI to bivalirudin (0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion; n=1089) or heparins (unfractionated heparin or low-molecular-weight heparin) only with GPI use restricted to bailout (n=460). At 30 days, the primary outcome of death or non-coronary artery bypass grafting (CABG)-related major bleeding was significantly lower with bivalirudin (5.1%) than with heparins plus routine GPI (7.6%; p=0.0425) or bailout plus GPI bolus (9.8%; p=0.0056). Multivariate analysis confirmed a lower likelihood of the primary outcome with bivalirudin (adjusted odds ratio [OR] 0.53; 95% CI, 0.33 to 0.87) and major bleeding (adjusted OR 0.44; 95% CI, 0.24 to 0.82) compared with heparins alone with bailout GPI rates. Rates of stent thrombosis were higher with bivalirudin compared with heparins plus routine or bailout GPI (1.6% vs 0.6% vs 0.4%; p=0.09 for each comparison).

Comment: The thought-provoking HEAT trial, as yet unpublished, has led to a further evaluation of the use of bivalirudin in STEMI among Australian Interventional Cardiologists. The further analysis of data with bailout use of GP IIb/IIIa in the EUROMAX trial is thus apposite. The finding that in the group in whom bailout GPI IIb/IIIa use occurred in the heparin arm (25% use) compared to 12% in the bivalirudin arm, but still a higher rate of bleeding, may be considered an argument against bailout thromboysis of the need for bivalirudin in patients undergoing the radial approach to PCI STEMI. The issue of early stent thrombosis in the first 4h post-PCI still remains with bivalirudin. Whether heparin or Cangrelor or prolonged infusion of GPI inhibitors used with a call to emergency 911 that should be undertaken remains unclear and will require future studies.

http://eurheartj.oxfordjournals.org/content/35/15/979.abstract

Trends in door-to-balloon time and outcomes following primary percutaneous coronary intervention for STEMI: Australian perspective

Authors: Brennan AL et al.

Summary: Data from the Melbourne Interventional Group registry were analysed in this assessment of annual temporal trends in door-to-balloon time (DTBT) between 2006 and 2010. The study researchers examined whether a reduction in DTBT was associated with improved clinical outcomes among 1926 STEMI patients undergoing pPCI. While baseline demographics, clinical and procedural characteristics remained similar in the STEMI cohort across the 5 years, increases were observed in out-of-hospital cardiac arrest (from 3.6% in 2006 to 9.4% in 2010; p<0.0001) and cardiogenic shock (from 7.7% to 9.6%; p=0.07). Median DTBT was reduced from 95 min in 2006 to 75 min in 2010 (p=0.01). The proportion of patients achieving a DTBT of <90 min increased from 45% in 2006 to 67% in 2010 (p=0.01). Lower mortality and major adverse cardiac event rates were observed with DTBT <90 min (all p<0.1). In multivariable analysis, a DTBT <90 min was associated with improved clinical outcomes at 12 months (OR 0.48; 95% CI, 0.33 to 0.73; p<0.01).

Comment: This Melbourne Interventional Group report on patients undergoing primary PCI for STEMI within 12 hours of symptom onset. There was progressive reduction in door-to-balloon time between 2006 and 2010. There was no difference in mortality across this period of time, nor were there changes in major cardiac events. However, in those with door-to-balloon times <90 minutes, major adverse cardiac event rates were lower. The study, even with ~2000 patients, is underpowered to determine mortality with changes in door-to-balloon times.


German nationwide data on current trends and management of acute myocardial infarction: discrepancies between trials and real-life

Authors: Feisinger E et al.

Summary: These researchers analysed data on in-patient hospitalisations of acute MI (onset of symptoms <28 days) in Germany from the years 2005, 2007, and 2009. The analyses accounted for mortality, in-hospital mortality, treatments, and costs. A total of 16,1, 16,6, and 17.2 million hospitalisations showed the proportion of coded acute MI to remain relatively constant (1276, 1272 and 1181 per 100,000 hospitalisations in 2005, 2007 and 2009, respectively). There was a decrease over time in the proportion of STEMI (from 631 to 546 and then 454 per 100,000 hospitalisations) and a corresponding increase in NSTEMI (645, 726 and 727 per 100,000 hospitalisations). Increases were recorded for the proportion of older patients >75 years (+4.6%) and comorbidities such as hypertension (+5.8%), diabetes (+17.7%), left ventricular failure (+19.8%), peripheral artery disease (+13.3%) and chronic kidney disease (+165.4%). In-hospital mortality remained relatively stable during the study period in acute MI cases overall (11.1%, 10.7%, 10.8%) but changed slightly in STEMI (11.2%, 10.9%, 12.2%) and NSTEMI (11.0%, 9.9%, 9.9%). Causing about 1.2% of hospitalisations, acute MI accounted for 2.5% (1.2 billion €) of in-hospital health expenditures.

Comment: This is an interesting large nationwide trend in MI care and outcomes. While the Swede-heart registry have reported these data from Sweden since the late 1990s, this German report covers the years 2005, 2007 and 2009. It has shown that the mortality from MI, either STEMI or non-STEMI was 10–12%, approximately double that reported from major clinical trials. The overall rates of angiography are also lower. Interestingly, the PCI STEMI death rate has increased, perhaps reflecting maybe wider coverage and more invasive and interventional procedures in higher-risk patients. Large registries often provide complementary information to clinical trials and it is important that Australia joins the developed world that is doing this.

http://eurheartj.oxfordjournals.org/content/35/15/079.abstract

Performance of risk stratification for acute coronary syndrome with two-hour sensitive troponin assay results

Authors: Cullen L et al.

Summary: This study sought to determine the utility of troponin assays in accurate risk stratification of patients with possible acute coronary syndromes (ACS) at 2h post-presentation. The analyses included 685 patients presenting to the emergency department (ED) with symptoms of ACS. Troponin was measured at 0, 2 and 6h post-presentation. Fifty–one patients (7.4%) had 30-day acute MI or cardiac death; 76 (11.1%) had secondary outcomes (all–cause death, ACS and revascularisation procedures). Diagnostic accuracy did not differ significantly between early and late biomarker strategies when used with the current risk stratification processes. Incorporation of a significant delta failed to improve the stratification at 2h post-presentation.

Comment: The issue of accelerated chest pain pathways with early troponin assays has a lot of appeal in the Emergency Department. This local study from the Royal Brisbane Hospital reports use of 2-hour sensitive troponin assays with the Alinity TnT assay was used, which has a detection limit of 0.01ng/L. The 99th centile is 0.04 ng/L, although the 10% centile is 0.06 ng/L. This 2-hour algorithm worked satisfactorily to identify the 7.4% of patients who have MI or cardiac death. This event rate frequency is typical for similar cohorts. It would be helpful that these data are replicated in large systemswide linkage studies to facilitate system-wide assessment of safety and efficacy of such an accelerated chest pain pathway.

Reference: Heart Lung Circ. 2014;23(6):428-34
Fish consumption and acute coronary syndrome: a meta-analysis

Authors: Leung YSS et al.

Summary: This group of Canadian researchers conducted a dose-response meta-analysis of data from 11 prospective cohort and 8 case-control studies (408,305 participants) that evaluated the association between fish consumption and ACS among general populations without cardiovascular disease history. Among prospective cohort studies, the highest category of fish consumption, i.e. ≥4 times per week, was associated with the greatest risk reduction in ACS (relative risk [RR] 0.79; 95% CI, 0.70 to 0.89). In dose-response analysis, each additional 100 g serving of fish per week was associated with a 5% reduced risk (RR per serving 0.95; 95% CI, 0.92 to 0.97). According to analyses by subgroup and meta-regression, there was no apparent difference in risk reduction by sex or age groups. There was no statistical heterogeneity among prospective cohort (p=0.73) or case-control (p=0.29) studies.

Comment: The strength (or lack of) associations between the amount of fish consumption (and fish oils) and primary and secondary prevention of ACS have been variably reported. This may be because the amount of fish consumed and doses of fish oils administered have varied quite significantly between studies. This meta-analysis of 11 prospective cohort and 8 case-control studies reports an inverse relationship between the amount of fish consumed and the risk of an ACS. For every 100g of extra fish consumed per week the risk reduced 5%. In terms of secondary prevention recent trials have had low doses of fish oils, and these data support the performance of future trials evaluating high doses of fish oils.

http://www.amjmed.com/article/S0002-9343(14)00355-6/abstract

Effects of timing, location and definition of reinfarction on mortality in patients with totally occluded infarct related arteries late after myocardial infarction

Authors: Adlbrecht C et al.

Summary: At >24 h (calendar days 3–28) after MI, the Occluded Artery Trial (OAT) randomised 2201 stable post-MI patients with totally occluded infarct-related arteries (IRA) to either undergo PCI with optimal medical therapy (PCI group), or optimal medical therapy alone (MED group). PCI had no impact on the composite of death, re-infarction, or class IV heart failure over an extended follow-up of up to 9 years. This paper reports the impact of early and late re-infarction and definition of MI on subsequent mortality. Re-infarction was adjudicated using an adaptation of the 2007 universal definition of MI and the OAT definition (≥2 of the following: symptoms, EKG and biomarkers). In Cox regression analyses adjusted for baseline characteristics the 169 (PCI: n=95; MED: n=74) patients who developed re-infarction by the universal definition had a 4.15-fold (95% CI, 3.03 to 5.69; p<0.001) increased risk of death compared to patients without re-infarction. This risk was similar between treatment groups and when MI was defined by the stricter OAT criteria. Re-infarctions occurring within 6 months of randomisation had similar impact on mortality as re-infarctions occurring later, and the impact of re-infarction due to the same IRA and a different epicardial vessel was similar.

Comment: Re-infarction has an attributable risk for late mortality, which provides justification for its inclusion in large randomised clinical trials. As with other studies in which the re-infarction is early in the open artery trial (OAT), the occurrence of re-infarction was associated with a two- to three-fold mortality increment; there were also increased class 3–4 heart failure admissions. This increased risk was irrespective of whether the event occurred in the culprit or non-culprit artery and the timing. These data support continuing inclusion of MI as a component of the primary endpoint in clinical trials.

http://www.internationaljournalofcardiology.com/article/S0167-5273(14)00585-3/abstract

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CV = cardiovascular; RRR = relative risk reduction; ARR = absolute risk reduction; ACS = acute coronary syndrome.