In this issue:

Welcome to issue 19 of Acute Coronary Syndrome Research Review.

A paper from the Flinders Medical Centre has implications for organisation of cardiac care in Australia. The study authors undertook an evaluation of a disease-specific streaming model of care compared to an acuity-based design in cardiac care delivery. The findings suggest that a “condition-based” redesign that streams cardiac patients by presenting diagnosis into teams designed to treat that condition may improve capacity and productivity.

A comparison between early coronary CT angiography (CCTA) and standard ‘optimal’ care including high-sensitivity troponin testing among patients with suspected ACS presenting to the emergency department concludes that CCTA is not superior for detecting significant coronary artery disease. Moreover, discharge rates from the emergency department and length of stay were similar between early CCTA and standard optimal care.

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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Limitation of infarct size and no-reflow by intracoronary adenosine depends critically on dose and duration

Authors: Yetgin T et al.

Summary: These researchers used a porcine model of AMI to examine the effects of intracoronary adenosine on infarct size and no-reflow, using clinical bolus and experimental high-dose infusion regimens. Swine (mean 54 kg) were subjected to a 45-min mid-left anterior descending artery occlusion followed by 2 h of reperfusion. At reperfusion, animals in protocol A received an intracoronary bolus of 3 mg adenosine injected over 1 min (n=5) or saline (n=10). Animals in protocol B received an intracoronary infusion of 50 μg/kg/min adenosine (n=15) or saline (n=21), starting 5 min prior to reperfusion and continuing throughout the 2-h reperfusion period. In protocol A, area-at-risk, infarct size, and no-reflow were similar between groups. In protocol B, risk zones were similar, but adenosine was associated with significant reductions in infarct size from a mean of 59% of the area-at-risk in control swine to 46% (p=0.02), and no-reflow from a mean 49% of the infarct area to 26% (p=0.03).

Comment: Intracoronary adenosine, as well as its clinical use for measurement of fractional flow reserve, has been used widely to treat both no-reflow and slow-flow post-PCI. The conceptually appealing use of adenosine infusions to try to prevent no-reflow and to increase myocardial salvage has been proposed for some years but evidence in the clinical arena to support its use has been largely lacking. This study from the Thorax-centre in Rotterdam provides some explanations, as this study used more prolonged infusions of intracoronary adenosine than have generally been used clinically, both prior to and following mechanical vessel opening, suggesting mechanisms of benefit.


Abstract

Abbreviations used in this issue:

ACS = acute coronary syndrome; AMI = acute myocardial infarction;
CABG = coronary artery bypass graft surgery;
CCTA = coronary computed tomography angiography;
CS-AMI = acute myocardial infarction managed by cardiogenic shock;
ED = emergency department; HR = hazard ratio; LV = left ventricular;
MI = myocardial infarction;
NSTEACS = non-ST-segment elevation acute coronary syndromes;
NSTEMI = non-ST-segment elevation myocardial infarction;
PCI = percutaneous coronary intervention;
STEMI = ST-segment elevation myocardial infarction.

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The association of previous revascularisation with in-hospital outcomes in acute myocardial infarction patients: Results from the National Cardiovascular Data Registry

**Authors:** Gruberg L et al.

**Summary:** This US study compared door-to-balloon time delays >90 min and in-hospital major adverse cardiovascular or cerebrovascular events (MACCE) amongst 15,628 STEMI patients with a history of coronary artery bypass graft surgery (CABG), previous PCI, or no previous revascularisation undergoing primary PCI. Patients with previous CABG were significantly older and more likely to have multiple comorbidities (p<0.0001). Previous CABG was associated with a lower likelihood of a door-to-balloon time ≤90 min compared with patients with no previous revascularisation. However, door-to-balloon times did not differ significantly between patients with previous PCI and those without previous revascularisation. The unadjusted MACCE risk was significantly higher in patients with a history of CABG compared with patients without previous revascularisation (OR 1.68; 95% CI, 1.23 to 2.31), but multivariable logistic regression analyses revealed no significant differences in MACCE risk between the 2 groups. Moreover, risk-adjusted in-hospital outcomes were similar for patients with a previous PCI and those without previous revascularisation.

**Comment:** It has long been reported since the early years of use of fibrinolytic therapy that patients with prior CABG presenting with STEMI have historically been at higher risk. The NCDR database allows interrogation of risk-associated differences because of the large cohort size. The unadjusted risk of these prior procedures was approximately double those with no prior revascularisation, but after adjustment for baseline risk, the mortality was similar. Interestingly, this occurred even though there was a longer delay to primary PCI, compared to patients without CABG.


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**Is there an ideal level of platelet P2Y\(_{12}\) receptor inhibition in patients undergoing percutaneous coronary intervention? “Window” analysis from the ADAPT-DES study (Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stents)**

**Authors:** Kirtane AJ et al.

**Summary:** The ADAPT-DES study performed routine platelet function testing (VerifyNow) following clopidogrel loading in 8582 patients undergoing drug-eluting stent implantation. These data were analysed to determine whether there is an ideal level of platelet reactivity, optimising safety and efficacy. Patients were stratified into quintiles of P2Y\(_{12}\) reaction units (PRU). The PRU medians of the 5 quintiles were 57, 130, 187, 244 and 317 (most to least inhibited). A monotonic association existed between successively higher PRU quintiles and stent thrombosis, whereas for clinically relevant bleeding, the greatest risk occurred in the lowest PRU quintile, with similar risks across the 4 higher quintiles. These relationships remained significant in fully adjusted multivariable analyses (adjusted HR for clinically relevant bleeding in Q5 vs Q1: 2.32; 95% CI, 1.17 to 4.59; p=0.02; adjusted HR for stent thrombosis in Q5 vs Q1: 0.61; 95% CI, 0.47 to 0.77; p<0.001). No significant independent associations were observed between the level of PRU and mortality.

**Comment:** Though it is conceptually attractive attempting to measure platelet function, using the VerifyNow point of care assay has been largely disappointing in terms of risk prediction. Perhaps this is because studies thus far have been predominantly in patients with stable coronary heart disease, whereas the ADAPT-DES study recruited patients who were approximately half ACS patients. Interestingly, this study showed an association between increased platelet-resistant units (PRU) and stent thrombosis. Also, amongst the lowest quintile of PRUs, there was an association with bleeding. These data may suggest that there could be a “sweet spot” where the PRU was in the range 95–215 (second and third quintiles). In fact, the third quintile, while showing a slightly reduced bleeding risk, did have a demonstrable increase in stent thrombosis suggesting that perhaps the lower part of this range (95–159 PRU) is optimal. This data relates only to clopidogrel, which in Australia is used less frequently, with the widespread use of ticagrelor post ACS.


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**Improving Outcomes**

*In patients with ACS, BRILINTA reduces the risk of CV death, MI or stroke vs clopidogrel at 12 months (primary composite endpoint: ARR 1.9%, RRR 16%; p<0.001).¹²

**STREAMLINED AUTHORITY CODE 5746**

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

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**Trends in short- and long-term outcomes for Takotsubo cardiomyopathy among Medicare fee-for-service beneficiaries, 2007 to 2012**

**Authors:** Murugiah K et al.

**Summary:** These US researchers assessed nationwide trends in hospitalisations and outcomes among Medicare fee-for-service beneficiaries with principal and secondary diagnoses of Takotsubo cardiomyopathy from 2007 to 2012. Hospitalisation rates for principal or secondary diagnosis of Takotsubo cardiomyopathy increased from 5.7 per 100,000 person-years in 2007 to 17.4 in 2012 (p for trend < 0.001). Patients were predominantly women and of white race. For principal Takotsubo cardiomyopathy, in-hospital, 30-day and 1-year mortality was 1.3%, 2.5% and 6.9%, respectively; the 30-day readmission rate was 11.6%. For secondary Takotsubo cardiomyopathy, in-hospital, 30-day and 1-year mortality was 3%, 4.7% and 11.4%, respectively, and the 30-day readmission rate was 15.8%. Over time, mortality and readmission rates remained unchanged in both cohorts. Patients aged ≥85 years had higher in-hospital, 30-day and 1-year mortality and 30-day readmission rates. Among patients with principal Takotsubo cardiomyopathy, male and nonwhite patients had higher 1-year mortality than their counterparts, whereas in those with secondary Takotsubo cardiomyopathy, mortality was worse at all 3 time points. In both cohorts, nonwhite patients had higher 30-day readmission rates.

**Comment:** The issue of long-term outcomes for Takotsubo cardiomyopathy has not received much attention and, as LV function improves, data regarding management has been sparse. Overall survival is good, with 94% living for one year. It is of note that older patients, males and nonwhite subjects (an American publication) tended to do worse. While these findings are encouraging in terms of mortality, there are management issues that need clarification. In particular, in those who have normalised LV function several months after the acute event, is it safe to withdraw any of their vasodilator therapies? This should be the subject of future research.

**Reference:** JACC Heart Fail. 2016;4(3):197-205

**Abstract**

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**Authors:** Levine GN et al.

**Summary:** This updated guideline provides health care professionals with a resource for the management of multivessel disease and the use of aspiration thrombectomy in the setting of STEMI.

**Comment:** The American primary PCI guidelines have focused on two changes. Firstly, regarding STEMI patients with multivessel disease, the recommendation has changed from class III to class IIb, regarding the indication for multivessel PCI versus culprit vessel-only in the setting of primary PCI. Secondly, based on the updated studies, the prior recommendation of a class IIa recommendation for aspiration thrombectomy has now changed to class IIIB level of evidence, that is no benefit; further trials are unlikely. Multivessel interventions in primary PCI are being addressed in the ongoing COMPLETE trial, but as the conservative arm, which requires severe symptoms for non-culprit artery intervention, is more conservative than usual Australian practice, there is no substantive evidence to guide whether routine multivessel PCI in STEMI needs to be at presentation or can be undertaken in an early staged procedure.

**Reference:** J Am Coll Cardiol. 2016;67(10):1235-50

**Abstract**

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**Condition-specific streaming versus an acuity-based model of cardiovascular care: A historically-controlled quality improvement study evaluating the association with early clinical events**

**Authors:** Chew DP et al.

**Summary:** These Australian researchers explored the clinical and health service implications of a “condition-based” redesign in cardiac care delivery, rather than acuity-based, within a tertiary hospital cardiology unit. 2018 patients were admitted after implementation of the streaming model and 1830 patients were admitted prior. Subsequent to the implementation, there were reductions in the use of angiography (pre: 35.4% vs post: 31.2%, p=0.007) and echocardiography (pre: 59.4% vs post: 55.6%, p=0.007). Length of stay was shortened in the entire cohort (pre: 2.7 days vs post: 2.3 days, p=0.0003). By 30 days, the propensity-adjusted HR for major adverse cardiac events and death or any cardiovascular admission was 0.76 (95% CI, 0.59 to 0.97; p=0.026).

**Comment:** This interesting paper from Flinders Medical Centre reports that the outcomes of patients admitted with ACS were in part dependent on the sub-speciality interest of the attending cardiologist. Those admitted under an interventional cardiologist did better than those who were admitted under those with other sub-speciality interests. Perhaps this is not surprising but it does have implications for organisation of cardiac care in Australia. By implication, whether every cardiology patient should be directly admitted under the appropriate cardiology sub-specialist, and thus how on-call and other services are organised, has significant implications even for large tertiary cardiology departments like that at Flinders Medical Centre.

**Reference:** Heart Lung Circ. 2016;25(1):19-28

**Abstract**

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**Independent commentary by Professor John French.** Director of Coronary Care and Cardiovascular Research at Liverpool Hospital, Sydney, and conjoint Professor at the University of New South Wales. After basic physician training he undertook a PhD at the University of Adelaide, further cardiology training at Greenlane Hospital, Auckland, New Zealand, and a Wellcome Trust Postdoctoral Fellowship at University College London, UK. Prior to his current position Professor French was appointed to Greenlane Hospital and the University of Auckland from 1992-2003. Professor French has been an investigator and co-investigator in numerous randomised controlled trials, and was on the steering committees of the SHOCK, OAT, HERO-2 and CRISP-AMI trials. Professor French has served on the clinical endpoints committees of several major trials. Professor French’s current major research interests include the acute coronary syndromes especially ST elevation MI, and cardiac biomarkers, especially high-sensitivity troponins.
Changes in mortality on weekend versus weekday admissions for Acute Coronary Syndrome in the United States over the past decade
Authors: Khoshchehreh M et al.
Summary: These researchers used data from the US Nationwide Inpatient Survey (2001–2011) to examine in-hospital mortality and utilisation of invasive cardiac procedures following ACS admissions on the weekend versus weekdays. Among the 13,988,772 identified ACS admissions, adjusted mortality was higher for weekend admissions for non-ST-elevation ACS (OR 1.15; 95% CI, 1.14 to 1.16) and only somewhat higher for STEMI (OR 1.03; 95% CI, 1.01 to 1.04). Moreover, patients admitted in the weekend were significantly less likely to receive coronary revascularisation intervention/therapy on their first day of admission (OR 0.97; 95% CI, 0.96 to 0.98 for STEMI and OR 0.75; 95% CI, 0.75 to 0.75 for NSTEMACS). For ACS patients admitted during the weekend who underwent procedural interventions, in-hospital mortality and complications were higher as compared to patients undergoing the same procedures on weekdays.

Comment: While prior data has shown differences in ACS admission rates and outcomes depending on the season and the time of day, this commentator is not aware of differences between weekdays and weekends. This dataset of ~14m ACS admissions reported adjusted mortality was higher (HR 1.15) for weekend, compared to weekday admissions, which appears to be due to lower rates of coronary revascularisation intervention/therapy for NSTEMACS during the first hospital day. Among STEMI patients there was statistically higher mortality (HR 1.03) and slightly fewer same day procedures. One suspects there may be less early interventions on weekends performed on NSTEMACS patients in Australia than on similar patients in the US, and these data suggest that weekend interventional services should be enhanced.

Reference: Int J Cardiol. 2016;210:164-72
Abstract

Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study
Authors: Dedic A et al.
Summary: These researchers sought to determine whether a diagnostic strategy supplemented by early coronary computed tomography angiography (CCTA) improves clinical effectiveness compared with standard optimal care encompassing high-sensitivity troponin assays (hs-troponins) for patients presenting to the emergency department (ED) with symptoms suggestive of an ACS. Among the 500 enrolled patients (mean age 54 years), 236 (47%) were women. The primary endpoint was the number of patients identified with significant coronary artery disease requiring revascularisation within 30 days. There was no between-group difference in the primary endpoint (22 [9%] patients underwent coronary revascularisation within 30 days in the CCTA group vs 17 [7%] in the standard optimal care group; p=0.40). Discharge rates were similar (65% after CCTA vs 59% after standard optimal care; p=0.16), as were length of stay durations (6.3 h in both groups; p=0.80). The CCTA group had lower direct medical costs ($357 vs $511; p<0.01) and less outpatient testing after the index ED visit (10 [4%] vs 26 [10%]; p<0.01). There was no between-group difference in incidence of undetected ACS.

Comment: A randomised comparison between early CCTA and standard ‘optimal’ care with high-sensitivity (HS) troponins in patients presenting to an emergency department with a suspected ACS should be of interest. In both arms, median stay was 6.3 h and there were no differences in late event rates. Unfortunately, in spite of reading the on-line supplementary material, this commentator could not determine how many patients had current standard of care HS troponin testing at 0 and 3 hours, as conventional assay intervals at 0 and 6 hours were also listed on the website. Nor was it clear whether the HS troponin upper reference limit, the level of 10% co-efficient of variation (recommended), or some higher level (quoted) was used for clinical decision-making. However, a trial as the title alludes to, comparing CCTA with an accelerated clinical pathway, with HS troponin testing at 0 and 1 hours, would be valuable.

Abstract

Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): a open-label randomised controlled trial
Authors: Tegn N et al.
Summary: This Norwegian study enrolled patients aged ≥80 years with NSTEMI or unstable angina and assigned them to an invasive strategy that included early coronary angiography with immediate assessment for PCI, CABG, and optimum medical treatment (n=228). During a median follow-up of 1.53 years, the primary composite endpoint of MI, need for urgent revascularisation, stroke, or death, occurred in 40.6% of patients in the invasive group and 61.4% of those in the conservative group (HR 0.53; 95% CI, 0.41 to 0.69; p=0.0001). Hazard ratios for the separate components of the primary composite endpoint were 0.52 (95% CI, 0.35 to 0.76; p=0.0010) for MI, 0.19 (0.07 to 0.52; p=0.0010) for the need for urgent revascularisation, 0.60 (0.25 to 1.46; p=0.2650) for stroke, and 0.89 (0.62 to 1.28; p=0.5340) for death from any cause. Four (1.7%) major and 23 (10.0%) minor bleeding complications were recorded in the invasive group, while the conservative group had 4 (1.8%) major and 16 (7.0%) minor bleeding complications.

Comment: The elderly are frequently admitted to hospital with NSTEMACS, but as contemporary trials to inform care guidelines are scarce, whether these patients would benefit from a routine early invasive strategy or conservative treatment is unclear. This relatively small trial from Norway shows benefits of an early invasive approach in ≥80 years over ~1.5 years of follow-up, due to reduced non-fatal outcomes, without a major bleeding hazard. Whether this non-fatal event reduction would translate to reduced mortality in a larger trial is speculative, though reduced morbidity, as found in this report, in the elderly is a very worthwhile treatment goal.

Abstract
Temporal trends and outcomes of patients undergoing percutaneous coronary interventions for cardiogenic shock in the setting of acute myocardial infarction: a report from the CathPCI Registry

Authors: Wayangankar SA et al.

Summary: This US investigation analysed data from the Cath-PCI Registry for temporal trends in demographics, clinical characteristics, management strategies, and in-hospital outcomes in 56,497 patients with AMI complicated by cardiogenic shock (CS-AMI) who underwent PCI during the period January 2005 through December 2013. Compared with cases performed during the period 2005–2006, CS-AMI patients receiving PCI from 2011–2013 were more likely to have diabetes, hypertension, dyslipidaemia, previous PCI, or dialysis, but were less likely to have chronic lung disease, peripheral vascular disease, or heart failure within 2 weeks (p<0.01). Between 2005 and 2006 to 2011 and 2013, intra-aortic balloon pump use decreased (from 49.5% to 44.9%; p<0.01), drug-eluting stent use declined (65% to 46%; p<0.01), and the use of bivalirudin increased (from 12.6% to 45.6%). Adjusted in-hospital mortality increased from 27.6% in 2005–2006 to 30.6% in 2011–2013 (adjusted OR 1.09; 95% CI, 1.005 to .173; p=0.04) for patients who were managed with an early invasive strategy (<24 h from symptoms).

Comment: This large cohort study reports apparently higher mortality for cardiogenic shock (CS) in recent years compared to 2005–6. Associated with this change were less use of drug-eluting stents, intra-aortic balloon pumps (IABP), less multivessel PCI and markedly more bivalirudin. However, both all-comer mortality rates are higher than the ~40% mortality reported from other all-comer registries and contemporary clinical trials, possibly suggesting some case selection bias. Only 7.2% had other mechanical circulatory support and although bleeding rates went down a higher rate of radial access may lead to better outcomes. Irrespective of the exact figure, because of the very high mortality in CS, trials addressing contemporary drug strategies, and non-IABP mechanical support, are urgently needed.