REVIEW

The year in cardiology 2015: acute coronary syndromes

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Preamble

The year 2015 has been productive in studies on pathophysiology of ACS. In particular on the different mechanisms of disease and related outcomes. New information has been published on the early diagnosis of ACS and on prevention and treatment of microvascular obstruction. With regard to antithrombotic treatment, the year 2015 has brought important new data that will change practice.

New guidelines

Both the European Society of Cardiology (ESC)[1] and the American College of Cardiology/American College of Cardiology (ACC/AHA)[2] have published new guidelines on the management of acute coronary syndromes (ACS) in patients without persistent ST-segment elevation. In this review, we briefly highlight new recommendations only. With regard to early diagnosis of myocardial infarction (MI) ESC guidelines, for the first time, give a 1B recommendation for a rapid rule-out and rule-in protocol at 0 and 1 h if a high-sensitivity cardiac troponin test with a validated 0/1 h algorithm is available, with additional testing after 3−6 h if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS, while ACC/AHA recommend to measure troponin at presentation and 3−6 h after symptom onset. Both guidelines recommend an immediate invasive strategy within 2 hours of presentation in very high-risk patients, an early invasive strategy within 24 h in high-risk patients and an invasive strategy within 72 h in intermediate risk patients. Finally, ESC guidelines give 1A recommendation for the radial approach in experienced centres and provide a new flow chart for the management of antithrombotic drugs in patients with concomitant non-valvular atrial fibrillation (*Figure 1*). They also give for the first time 3B recommendation for not to preloading patients in whom coronary anatomy is not known with Prasugrel, because of the excess risk of bleeding in the absence of benefit on ischaemic events, as recently confirmed in the ACCOAST-PCI cohort (*Figure 2*).[3] Thus, as recently published, the benefit/risk of dual antiplatelet therapy (DAPT) pre-treatment appears to depend on the type of ACS, the time until angiography, and the onset of action of the drug.[4]

## Pathogenesis, early diagnosis, and risk stratification

It is well known that plaque fissure and plaque erosion are by far the most frequent pathological substrates of ACS. Studies published in the last year provide strong support to the notion that erosion and fissure are the expression of different mechanisms responsible for the transition from the stable to the unstable plaque. Indeed, Quillard et al.[5] found that toll-like receptor-2 (TLR2), neutrophils, and neutrophil extracellular traps (NETs) localized at sites of eroded human plaques. Notably, the number of luminal apoptotic endothelial cells correlated with neutrophil accumulation, amount of NETs, and TLR2 staining in eroded plaques, but not in 'vulnerable' atheromata. Accordingly, in vitro, TLR2 ligands (including hyaluronan, a matrix macromolecule abundant in eroded lesions) induced endothelial stress, characterized by reactive oxygen species production, endoplasmic reticulum stress, and apoptosis. These in vitro observations and analyses of human plaques indicate that TLR2 stimulation followed by neutrophil participation may render smooth muscle cell-rich plaques susceptible to superficial erosion and thrombotic complications by inducing endothelial stress, apoptosis, and favouring detachment of endothelial cells. In another study, Stakos et al.[6] found that the interaction of thrombin-activated platelets with neutrophils at the site of plaque rupture during acute MI results in local NETs formation and delivery of active tissue factor. The notion that NETs represent a mechanism by which neutrophils release thrombogenic signals during atherothrombosis may offer novel therapeutic targets.

Thus, while hyaluronan, TLR2, and neutrophils are the main players of plaque erosion, previous studies have shown that dysregulation of adaptive immunity plays a major role in plaque fissure. Recently, Kovalcsik et al.[7] have shown that the expansion of


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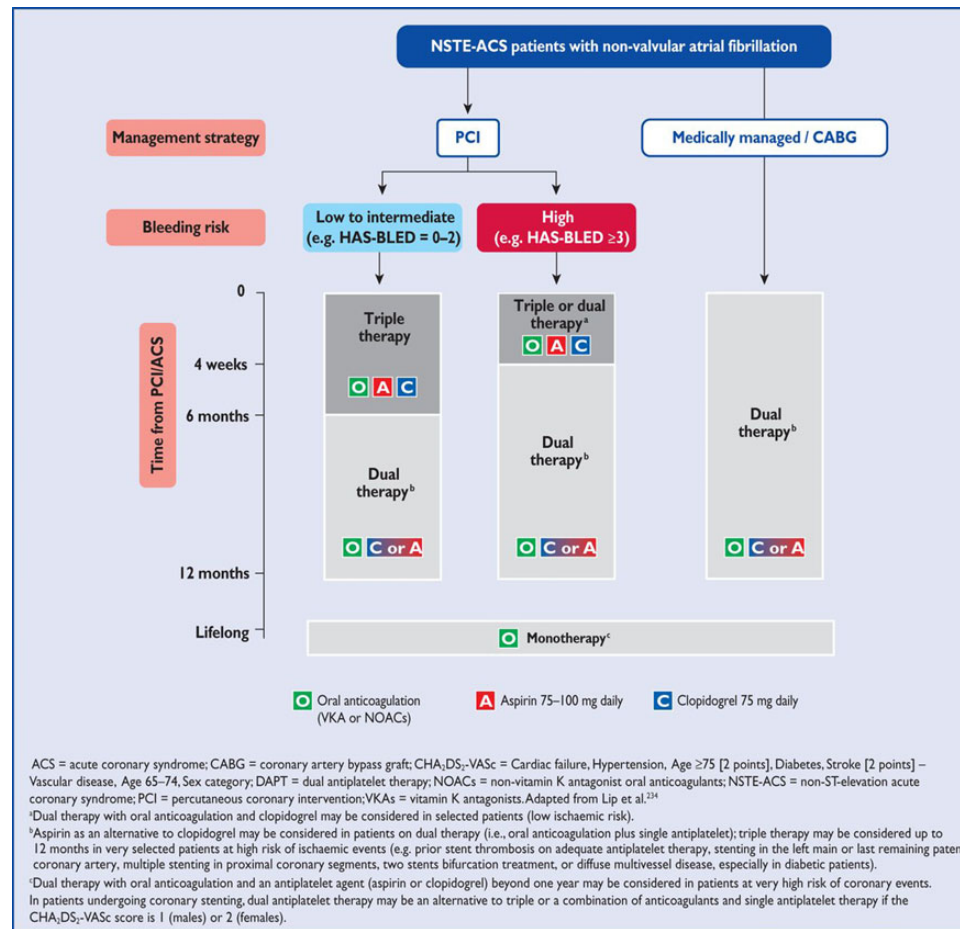
Figure 1 Antithrombotic strategies in patients with non-ST-elevation acute coronary syndromes and non-valvular atrial fibrillation proposed in the Guidelines of the European Society of Cardiology. Reprinted with kind permissions from Ref. 1.
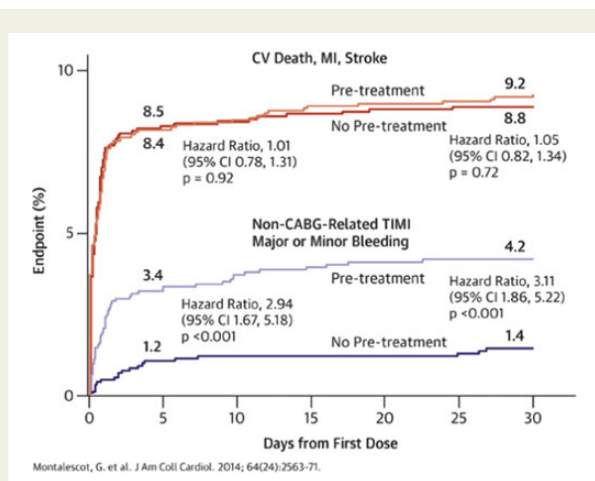
Figure 2 Effect of prasugrel pre-treatment in non-ST-elevation myocardial infarction undergoing percutaneous coronary intervention. Reprinted with kind permissions from Ref. 3.

CD28 null T cells, a subset effectors T cells expanded in ACS, is attributable to a dramatic reduction in proapoptotic molecules Bim, Bax, and Fas in CD28null T cells. They also found that the inhibition of proteasomal activity allows CD28null T cells to regain sensitivity to apoptosis, thus suggesting novel strategies for targeted elimination of these aggressive effector cells in ACS patients.

With regard to early diagnosis in a multicentre study, Reichlin et al.[8] enrolled 1320 patients presenting to the emergency department with suspected acute MI. The high-sensitivity cardiac troponin T 1-h algorithm, incorporating baseline values as well as absolute changes within the first hour, was validated against the final diagnosis. Acute MI was the final diagnosis in 17.3% of patients. With application of the high-sensitivity cardiac troponin T 1-h algorithm, 786 (59.5%) patients were classified as 'rule-out,' 216 (16.4%) were classified as 'rule-in' and 318 (24.1%) were classified to the 'observational zone.' The negative predictive value for acute MI in the rule-out zone was 99.9%. The positive predictive value for acute MI in the rule-in zone was 78.2%. Cumulative 30-day mortality was 0.0, 1.6, and 1.9% in patients classified in the rule-out, observational, and

rule-in groups, respectively. The authors concluded that this rapid strategy incorporating high-sensitivity cardiac troponin T baseline values and absolute changes within the first hour substantially accelerated the management of suspected MI by allowing safe rule-out as well as accurate rule-in of acute MI in three-quarters of the patients.

With regard to risk stratification, Schwartz et al.[9] examined the relationships of triglycerides to risk after ACS in 17,318 patients treated effectively with statins. The hazard ratio (HR) in the highest/lowest quintile (>175/<80 mg/dl) was 1.61 (95% confidence interval: 1.34–1.94). The relationship of triglycerides to risk was independent of low-density lipoprotein cholesterol. The authors concluded that among patients with ACS treated effectively with statins, fasting triglycerides predicted long- and short-term cardiovascular risk. The findings in this and in other recent studies provide strong evidence for the causal role of triglycerides in atherosclerotic vascular disease and suggest that triglyceride-rich lipoproteins may be an important additional target for therapy.[10]

In relation to new biomarkers Ng et al.[11] measured pro-substance P (ProSP), a stable surrogate marker for labile substance P, which has pro-inflammatory effects, increases platelet aggregation and clot strength, and reduces fibrinolysis measured, in 1148 MI patients. Multivariate Cox regression models showed ProSP level was a predictor of major adverse events (HR 1.30). ProSP levels with GRACE scores were independent predictors of 6-month death and/or reinfarction. ProSP-adjusted GRACE scores reclassified patients significantly mainly by down-classifying risk in those without events. The authors concluded that the ability of ProSP to predict recurrent MI in addition to mortality may confer clinical utility on the tachykinin system in risk stratification after MI.

Eitel et al.[12] investigated the role of cardiac magnetic resonance, performed within 10 days of the index event, in risk stratification in 738 patients with persistent ST-elevation myocardial infarction (STEMI). In a multivariate model that included clinical and other established prognostic parameters, microvascular obstruction was the only significant predictor in addition to the thrombolysis in myocardial infarction (TIMI) risk score of major cardiovascular events and provided an incremental prognostic value above clinical risk assessment and left ventricular ejection fraction. These findings highlight that microvascular obstruction after successful epicardial recanalization by a primary percutaneous coronary intervention (PCI) remains an unmet therapeutic target.

Finally, Niccoli et al.[13] found that plaque rupture and erosion, assessed by optical coherence tomography, were associated with different outcomes in patients with ACS thus confirming that plaque fissure and erosion not only have different mechanisms but they also have a different natural history and probably need different specific forms of treatment (*Figure 3*).

Percutaneous coronary intervention

Removal of the thrombus by manual thrombectomy before coronary stenting has the potential of reducing distal embolization and improving microvascular perfusion. Over the past 10 years, several randomized trials including the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS) study[14] suggested potential benefit of thrombectomy on all-cause mortality, target vessel revascularization, and MI rates. These findings have not been confirmed by the two largest trials, published this year. The Scandinavian Thrombus Aspiration
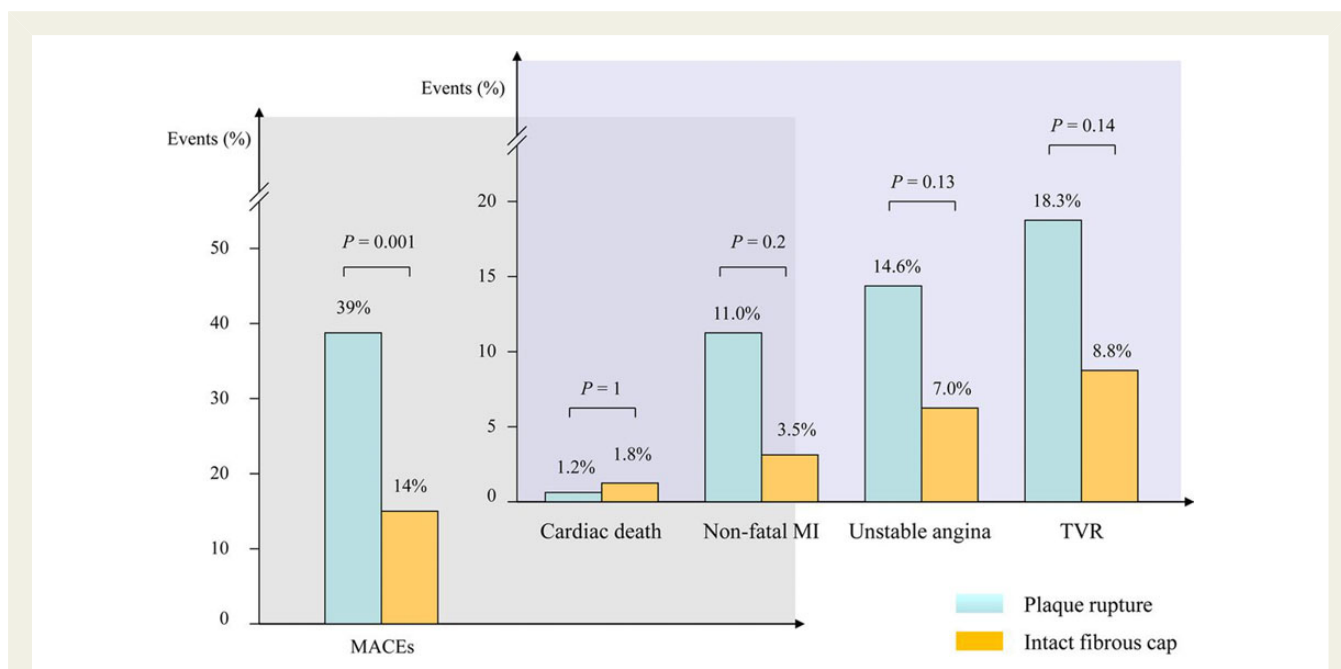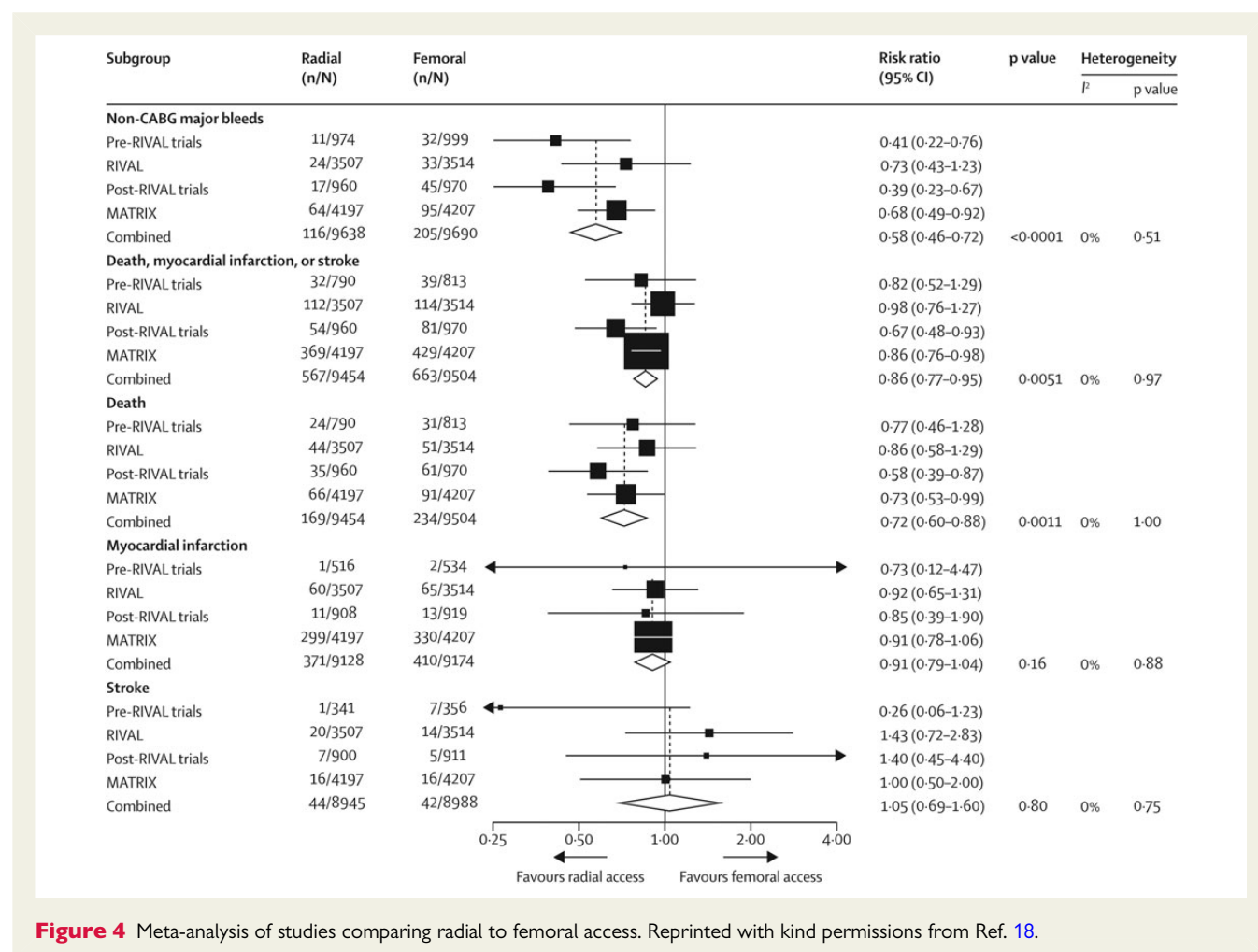
Figure 3 Major adverse cardiac event rates in patients with plaque rupture and in those with intact fibrous cap. The rate of cardiac death, non-fatal myocardial infarction, unstable angina, and target vessel revascularization in patients with plaque rupture and with intact fibrous cap. Reprinted with kind permissions from Ref. 13.

ST-Segment Elevation Myocardial Infarction (TASTE) trial randomized 7244 patients with STEMI to undergo primary PCI with thrombectomy or conventional primary PCI,[15] and the Trial of Routine Aspiration Thrombectomy with PCI vs. PCI Alone in Patients with STEMI (TOTAL) randomized 10,063 patients for a similar comparison.[16] Like in the TAPAS trial, there were improvements in ST-segment resolution and distal embolization with thrombectomy but these improvements in surrogate outcomes did not translate into clinical benefits. The investigators of both trials rightly concluded that thrombectomy failed to reduce the rate of death as well as the rates of various composite endpoints including or not heart failure, up to 1-year follow-up. These findings were consistent across numerous subgroups including patients with a high thrombus burden. In the TOTAL study, the pre-specified safety endpoint of stroke was significantly increased with thrombectomy. There was an increase primarily in ischaemic strokes but also in haemorrhagic strokes.[17] The greatest risk for stroke was within 48 h but there was a trend for an increased risk of stroke again with thrombectomy between 90 and 180 days which may be due to chance. However, the same paper presented a meta-analysis of 20 randomized trials confirming an excess risk of stroke associated with thrombectomy. Finally, thrombectomy in NSTEMI with a thrombus-containing lesion did not lead to a reduction in microvascular obstruction as assessed by cardiac magnetic resonance imaging performed within 4 days of MI in a smaller study of 440 patients, confirming further the global findings.

In ACS patients, bleeding complications are associated with worse short- and long-term clinical outcomes, and it is uncertain whether this relation is causal. In the MATRIX study, 8404 patients with an acute coronary syndrome, with or without ST-segment elevation who underwent invasive management, were randomized for a radial or a femoral access to perform coronary angiography and PCI.[18] The use of radial access improved the net clinical benefit (primary outcome). The effect was driven by a reduction of major bleeding (1.6 vs. 2.3%, RR 0.67, 95% CI 0.49−0.92; $P = 0.013$) and all-cause mortality (1.6 vs. 2.2%, RR 0.72, 95% CI 0.53−0.99; $P = 0.045$). The same authors provided an updated meta-analysis showing that radial access reduces major bleeding, major adverse cardiovascular events, and all-cause mortality, but not MI or stroke (Figure 4). These data strongly support radial access as the default strategy for patients with ACS undergoing invasive management.

In STEMI patients undergoing primary PCI, one-third of patients have significant stenoses in at least one other non-infarct-related coronary artery. Complete Versus Lesion Only Primary PCI trial (CvLPRIT, $n = 296$) showed that early treatment of significant non-culprit lesions during the index admission can improve clinical

Subgroup	Radial (n/N)	Femoral (n/N)		Risk ratio (95% CI)	p value	Heterogeneity I^2	p value
Non-CABG major bleeds							
Pre-RIVAL trials	11/974	32/999		0·41 (0·22–0·76)			
RIVAL	24/3507	33/3514		0·73 (0·43–1·23)			
Post-RIVAL trials	17/960	45/970		0·39 (0·23–0·67)			
MATRIX	64/4197	95/4207		0·68 (0·49–0·92)			
Combined	116/9638	205/9690		0·58 (0·46–0·72)	<0·0001	0%	0·51
Death, myocardial infarction, or stroke							
Pre-RIVAL trials	32/790	39/813		0·82 (0·52–1·29)			
RIVAL	112/3507	114/3514		0·98 (0·76–1·27)			
Post-RIVAL trials	54/960	81/970		0·67 (0·48–0·93)			
MATRIX	369/4197	429/4207		0·86 (0·76–0·98)			
Combined	567/9454	663/9504		0·86 (0·77–0·95)	0·0051	0%	0·97
Death							
Pre-RIVAL trials	24/790	31/813		0·77 (0·46–1·28)			
RIVAL	44/3507	51/3514		0·86 (0·58–1·29)			
Post-RIVAL trials	35/960	61/970		0·58 (0·39–0·87)			
MATRIX	66/4197	91/4207		0·73 (0·53–0·99)			
Combined	169/9454	234/9504		0·72 (0·60–0·88)	0·0011	0%	1·00
Myocardial infarction							
Pre-RIVAL trials	1/516	2/534		0·73 (0·12–4·47)			
RIVAL	60/3507	65/3514		0·92 (0·65–1·31)			
Post-RIVAL trials	11/908	13/919		0·85 (0·39–1·90)			
MATRIX	299/4197	330/4207		0·91 (0·78–1·06)			
Combined	371/9128	410/9174		0·91 (0·79–1·04)	0·16	0%	0·88
Stroke							
Pre-RIVAL trials	1/341	7/356		0·26 (0·06–1·23)			
RIVAL	20/3507	14/3514		1·43 (0·72–2·83)			
Post-RIVAL trials	7/900	5/911		1·40 (0·45–4·40)			
MATRIX	16/4197	16/4207		1·00 (0·50–2·00)			
Combined	44/8945	42/8988		1·05 (0·69–1·60)	0·80	0%	0·75

0·25   0·50   1·00   2·00   4·00

Favours radial access   Favours femoral access

Figure 4 Meta-analysis of studies comparing radial to femoral access. Reprinted with kind permissions from Ref. 18.

outcome compared with PCI of the culprit artery only.[19] The results of both CvLPRIT and Preventive Angioplasty in Myocardial Infarction (PRAMI)[20] together argue that there may well be an advantage to undertaking complete revascularization in STEMI patients. The evaluation of severity for these non-culprit lesions, and timing of treatment remain important questions. In the DANAMI 3-PRIMULTI study, 627 patients presenting with STEMI who had successful PCI of the infarct-related artery, were randomly allocated to either no further invasive treatment or complete FFR-guided revascularization before discharge.[21] Complete revascularization guided by FFR measurements reduced the risk of future events, an effect driven only by fewer repeat revascularizations. Nevertheless, these positive trials must be interpreted cautiously. Positivity was often driven by soft endpoints such as refractory angina and repeat revascularization. In addition, the control arm in all three trials was a culprit lesion only strategy without any pre-specified treatment strategy for the significant lesions present in non-culprit arteries. This may not fully reflect current practice in many institutions and the current recommendations. Thus, STEMI patients can safely have all their lesions treated during the index admission, although the selection of patients and the timing of the complementary PCI in non-culprit lesions need further evaluations.

Incomplete revascularization is common after PCI and is associated with adverse outcome. Adjunctive anti-ischaemic pharmacotherapy using ranolazine did not reduce the rate of ischaemia-driven revascularization or hospitalization without revascularization in patients with a history of chronic angina who had incomplete revascularization after PCI. Optimal anti-ischaemic therapy following incomplete revascularization remains to be defined.[22]

Reperfusion and remodelling

There is considerable uncertainty over the utility of supplemental oxygen in uncomplicated normoxic acute MI patients, with no clear recommendation for oxygen therapy in the STEMI guidelines. The randomized AVOID study ($n = 638$) did not demonstrate any benefit of routine oxygen therapy.[23] Instead, when oxygen was administered, there was evidence for increased myocardial injury, increase in myocardial infarct size on cardiac magnetic resonance with more recurrent MI (5.5 vs. 0.9%; $P = 0.006$) and more frequent arrhythmia (40.4 vs. 31.4%; $P = 0.05$).
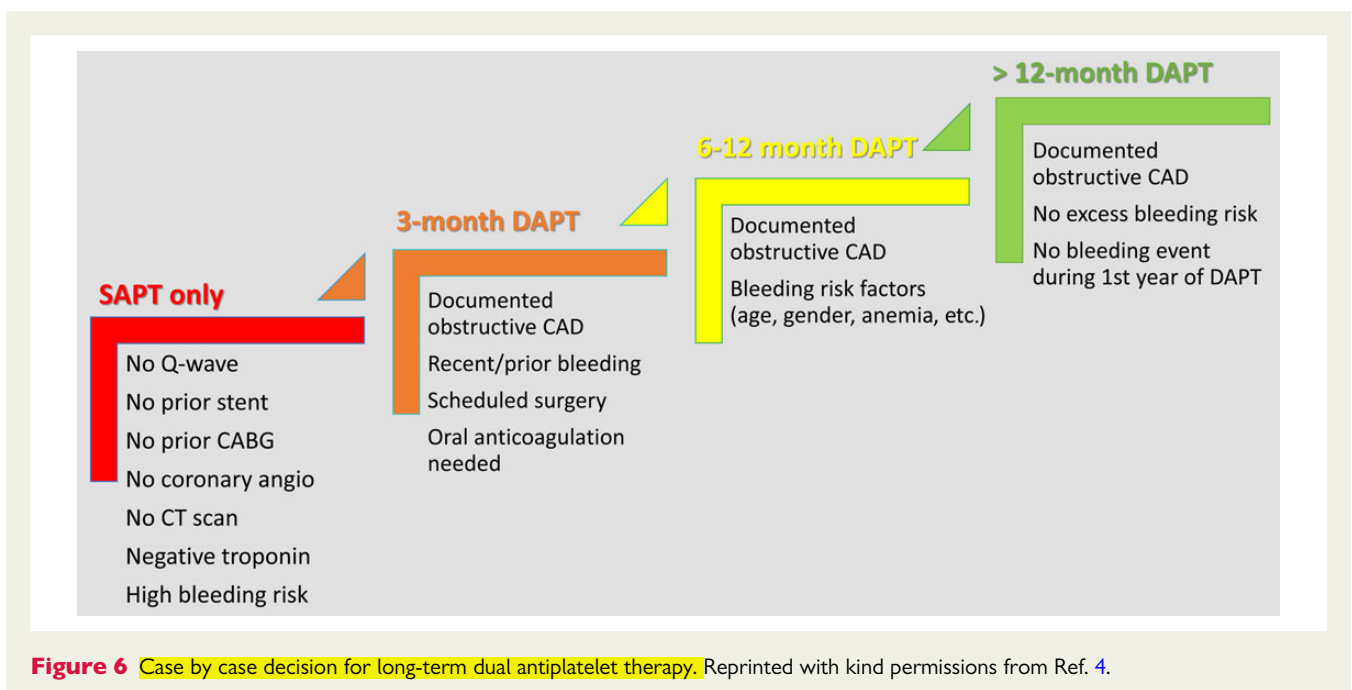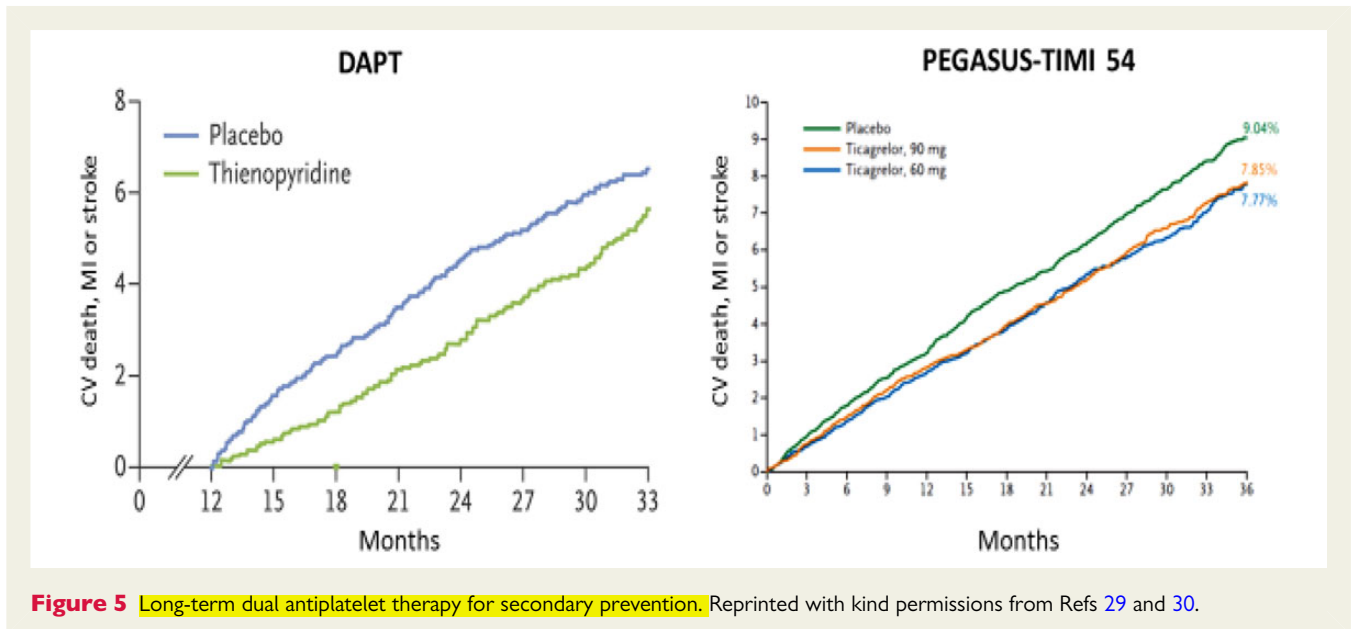
In STEMI patients with a fully occluded coronary artery [0–1 TIMI flow grade], repeated cycles of brief inflations of the angioplasty balloon were shown to reduce infarct size and improve the recovery of myocardial contractile function. In a recent randomized study, 90 STEMI patients with a 2–3 TIMI coronary flow grade at admission underwent direct stenting of the culprit lesion, followed (or not) by four cycles of inflation/deflation of the angioplasty balloon to trigger post-conditioning.[24] There was no effect on infarct size, suggesting that the timing of this mechanical intervention with respect to the onset of reperfusion is a key factor to prevent reperfusion injury. Remote ischaemic conditioning and post-conditioning have also been tested together in a small randomized open label study of 696 STEMI patients with borderline favourable results on cardiac magnetic resonance imaging and no difference on clinical outcomes.[25]

The mitochondrial permeability transition pore (mPTP) has been a pharmacologic target for preventing reperfusion injury. TRO40303 inhibits mPTP opening and has been shown to reduce infarct size in animal models of MI and was tested in a randomized double-blind clinical trial of 83 patients.[26] There was no effect of the drug on reperfusion injury, infarct size, or left ventricular function. Cyclosporine, a pharmacologic inhibitor of cyclophilin D (a major component of the mPTP), was also tested in primary PCI of ST-elevation MI.[27] The intravenous administration of cyclosporine just before PCI did not reduce the composite primary outcome of death from any cause, heart failure, or adverse left ventricular remodelling when compared with placebo. Although reperfusion injury is clinically important, the trials addressing this concept have failed so far to improve clinical outcome.

There is considerable release of aldosterone in acute MI, which is at its highest level shortly after the onset of MI. Aldosterone promotes a number of deleterious effects including sodium retention and potential arrhythmogenesis possibly due to potassium and magnesium depletion, as well as endothelial dysfunction, increased vascular tone, inhibition of neuronal re-uptake of catecholamines, cardiac myocyte necrosis, collagen deposition, and cardiac remodelling. In the randomized double-blind REMINDER study, 1012 patients with acute STEMI without a history of heart failure received either eplerenone, a mineralocorticoid receptor antagonist, or placebo within 24 h of symptom onset.[28] The primary endpoint of CV mortality, heart failure, sustained ventricular tachycardia or fibrillation, ejection fraction $\leq$40%, or elevated BNP/NT-proBNP was significantly reduced with eplerenone (adjusted HR 0.60; 95% CI 0.45–0.79; $P = 0.0003$). This reduction was mainly driven by lower BNP/NT-proBNP levels with eplerenone. The ALBATROSS study, recently presented at the ESC, also suggested potential benefit in the STEMI cohort of patients treated with spironolactone while the global results obtained in all types of ACS were negative. More data are warranted with mineralocorticoid receptor antagonists in MI.

Duration of antiplatelet therapy

The current 1-year recommendation for DAPT is a function of the duration of the pivotal trials for P2Y12 inhibitors in ACS. Prospective data from the DAPT[29] and Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54)[30] trials now confirm the benefit of prolonged DAPT to prevent MACE in patients with ACS (Figure 5). This benefit occurs at the cost of more bleeding complications, but no excess of intracranial or fatal bleeding. Prolonged DAPT is most logical when the diagnosis of obstructive coronary artery disease is manifest (i.e., documented spontaneous MI, typically with confirmed coronary disease on angiography) and when there are no bleeding contraindications.[4] This has been confirmed in a recent meta-analysis in which DAPT beyond 1 year among patients with prior MI decreased ischaemic events, including significant reductions in the individual endpoints of cardiovascular death, recurrent MI, and stroke. Dual antiplatelet therapy beyond 1 year increased also major bleeding, but not fatal bleeding or non-cardiovascular death.[31] A new analysis from the PEGASUS-TIMI 54 trial found the greatest reduction in ischaemic events with prolonged DAPT was observed

Figure 5 Long-term dual antiplatelet therapy for secondary prevention. Reprinted with kind permissions from Refs 29 and 30.

Figure 6 Case by case decision for long-term dual antiplatelet therapy. Reprinted with kind permissions from Ref. 4.

also in patients in whom P2Y12 inhibitor therapy had either not been discontinued or discontinued ≤30 while no benefit was observed in patients in whom P2Y12 inhibitor therapy had been discontinued >1 year prior to enrolment in the study.[32] Following coronary stenting, recent randomized studies, meta-analyses, and reviews emphasize the need for a case by case decision for the prolongation of DAPT beyond one year (*Figure 6*).[33–35]

Long-term outcomes

There is growing interest in MI and no obstructive coronary atherosclerosis (MINOCA). In a systematic review and meta-analysis,

Pasupathy et al.[36] report that the prevalence of MINOCA is 6% and that all-cause mortality at 12 months is rather high (4.7%), although lower than that observed among patients with MI and obstructive coronary artery disease (6.7%). They conclude that MINOCA should be considered as a working diagnosis with multiple potential causes that require evaluation so that directed therapies may improve its guarded prognosis. Interestingly, Grodzinsky et al.[37] found that patients with MINOCA experienced an angina burden after discharge at least as high as those with obstructive coronary artery disease, affecting 1 in 4 patients at 12 months. These findings confirm that more attention should be paid to patients exhibiting the intriguing syndrome of MINOCA.

In a national real world Swedish study in 108,315, MI patients Jerneberg et al.[38] found that the risk of major cardiovascular events at 1-year follow-up was 18.3%. Interestingly, for patients without a combined endpoint event during the first year, composite endpoint risk was 20.0% in the following 3 years. They conclude that the risk of cardiovascular events is considerably high beyond the first year post-MI, as frequently believed based on old studies, indicating a need for prolonged surveillance, particularly in patients with additional risk factors. Interestingly, a recent global registry of patients with Takotsubo cardiomyopathy shows that the outcome of these patients is worse than initially believed and similar to that of patients with ACS and obstructive coronary artery disease.[39]

With regard to long-term treatment, while waiting for the cardiovascular outcome trials conducted in ACS patients with monoclonal antibodies that inhibit proprotein convertase subtilisin−kexin type 9 (PCSK9), information was obtained with ezetimibe testing the LDL hypothesis on top of statins in ACS patients. The double-blind, randomized IMPROVE-IT trial evaluated 18 144 patients who received either the combination of simvastatin (40 mg) and ezetimibe (10 mg) or simvastatin (40 mg) monotherapy.[40] The primary end point of cardiovascular death, MI, unstable angina, coronary revascularization, or stroke was reduced after 7 years of follow-up (HR 0.936; 95% CI, 0.89−0.99; $P = 0.016$). The rate of CV death, MI, or stroke was also significantly reduced but mortality was not different between the two groups. The benefit was particularly marked in diabetic patients. Accordingly, the new ESC Guidelines give a 2a-B recommendation for the use of a non-statin agent in patients with LDL cholesterol $\geq$70 mg/dL ($\geq$1.8 mmol/L) despite a maximally tolerated statin dose.[1]

Perspectives

Major progress has been made in the understanding of ACS. In particular, it is now clear that plaque erosion and plaque fissure/rupture are expressions of different mechanisms of disease and portend different outcomes. Efforts are warranted to identify more specific forms of treatment for these two conditions. Further efforts are also needed in the early diagnosis of ACS when it remains undetermined after optimal troponin assessment. In the setting of STEMI, an unmet need is prevention and treatment of microvascular obstruction after successful primary PCI. With regard to antithrombotic treatment, it remains to establish which patients benefit from prolonged DAPT as well as the optimal treatment of patients needing triple therapy. Long-term mortality rates remain high underscoring the need for improving risk factor control. Finally, MINOCA is an intriguing and challenging clinical syndrome, which is probably under-recognized and under-treated.

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