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The year in cardiology 2018: acute coronary syndromes

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Introduction

The management of acute coronary syndromes (ACS) is a true success story. Indeed, in 1955 when the then President of the United States *Dwight D. Eisenhower* had an infarction, the President's personal physician, *Dr. Howard Snyder*, interpreted his symptoms as a gastrointestinal illness (1). It took 10 hours to transfer him to a local hospital where an electrocardiograph had to be brought in from another hospital – a situation that today would be malpractice (2). The ECG showed an anterolateral acute myocardial infarction with ST-segment elevations or a STEMI as we would call it today based on the recent definition of myocardial infarction (3). Based on the Fourth Universal Definition of Myocardial Infarction Eisenhower experienced a clear cut type 1 infarction *(Table 1).* Today, we distinguish not only 5 types of infarction, but also myocardial injury, defined by an elevated cardiac troponin (cTn) value, which is also is associated with an adverse prognosis. To differentiate myocardial injury from myocardial infarction, criteria in addition to abnormal biomarkers are required such as ECG changes and evidence of ischemia.

In the 50ies not many diagnostic tools or even any effective treatment was available (4). Not only was an ECG not commonly available, cardiac enzymes were still to be introduced and unavailable at that time. The management of acute myocardial infarction was mainly "tender loving care", i.e. nitroglycerin and morphine for pain relief. Defibrillation had still to be introduced by *Paul M. Zoll* a year later (5). Aspirin was labelled as remedy for fever and pain and considered contraindicated for heart patients (6) until *Sir John Vane* discovered that it inhibits platelet aggregation (7), Betablockers had still to be developed by *Sir James Black*, Nobel Prize Laureate in 1988 (8) Finally, *Akiro Endo's* seminal discovery of statins only occurred in the 70ties and shown to reduce mortality as late as 1992. Lastly, it took another couple years until inhibitors of the P_2Y_{12} receptor became common: practice (11, 12). The most important step, proved to be rapid and effective reperfusion and revascularization. Although streptokinase and later tissue plasminogen activators were somewhat successful, it required a bold colleague such as *Andreas R. Grüntzig* to develop percutaneous coronary intervention (13, 14). Later, stents (and especially drug eluting stents) improved the results of primary percutaneous coronary angioplasty and made it the first line therapy in patients with acute coronary syndromes ACS (15, 16). As a result of all these impressive developments, mortality of acute myocardial infarction declined stepwise, but eventually dramatically over the past decade (17) *(Figure 1)*. Again this year further steps have been taken to improve the management of patients with ACS as outlined in this review.

The studies included in this review deal initially with

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TABLE 1. The fourth universal definition of myocardial infarction (from ref. 3)

• Type 1 myocardial infarction: Emphasis on the causal relationship of plaque disruption with coronary atherothrombosis.
• Type 2 myocardial infarction: Settings with oxygen demand and supply imbalance unrelated to acute coronary atherothrombosis.
• Type 2 myocardial infarction: Relevance of presence or absence of coronary artery disease to prognosis and therapy.
• Differentiation of myocardial injury from type 2 myocardial infarction.
• Type 3 myocardial infarction: Clarify why type 3 myocardial infarction is a useful category to differentiate from sudden cardiac death.
• Types 4–5 myocardial infarction: Emphasis on distinction between procedure-related myocardial injury and procedure-related myocardial infarction.
• Cardiac troponin: analytical issues for cardiac troponins.
• Emphasis on the benefits of high-sensitivity cardiac troponin assays.
• Considerations relevant to the use of rapid rule-out and rule-in protocols for myocardial injury and myocardial infarction.
• Issues related to specific diagnostic change ('delta') criteria for the use of cardiac troponins to detect or exclude acute myocardial injury.
• Consideration of new non-rate-related right bundle branch block with specific repolarization patterns.
• ST-segment elevation in lead aVR with specific repolarization patterns, as a STEMI equivalent.
• ECG detection of myocardial ischemia in patients with an implantable cardiac defibrillator or a pacemaker.
• Enhanced role of imaging including cardiac magnetic resonance imaging for the diagnosis of myocardial infarction.

pathophysiologic mechanisms, early diagnosis, risk stratification and outcomes in specific subpopulations, the mid portion reports new data on pharmacotherapy while the last part provides latest data on interventional treatment of acute coronary syndromes.

Mechanisms

Alterations of innate and adaptive immunity

In patients with ACS, the higher activity of effector T-cells suggests that mechanisms involving adaptive immunity dysregulation might play a role in coronary instability. The shedding of the functional CD31 domain 1–5 leads to uncontrolled lymphocyte activation. Flego et al found that enhanced MMP-9 release plays a key role in determining the cleavage and shedding of the functional CD31 domain 1–5 in CD4+ T-cells of ACS patients (18). They propose the following sequence of events in ACS and systemic evidence of inflammation: MMP-9, released by innate immunity cells and by T-cells, causes the cleavage of CD31 domain 1–5; the increased expression of MMP-9 might affect TCR-dependent T-cell activation and induce T-cell hyper-reactivity, through the alteration of cellular pathways linked to CD31 cleavage. They also propose that molecules such as MMP-9 and CD31 could represent desirable molecular targets for specific anti-inflammatory treatments and might be used as clinical biomarkers of prognosis in patients with ACS.

Plaque erosion on the rise

At least one third of ACS is caused by plaque erosion and with its recognition the prevalence is probably increasing (19). *Dai et al* assessed the culprit plaque in 822 patients present ST elevation myocardial infarction by optical coherence tomography (OCT) and found

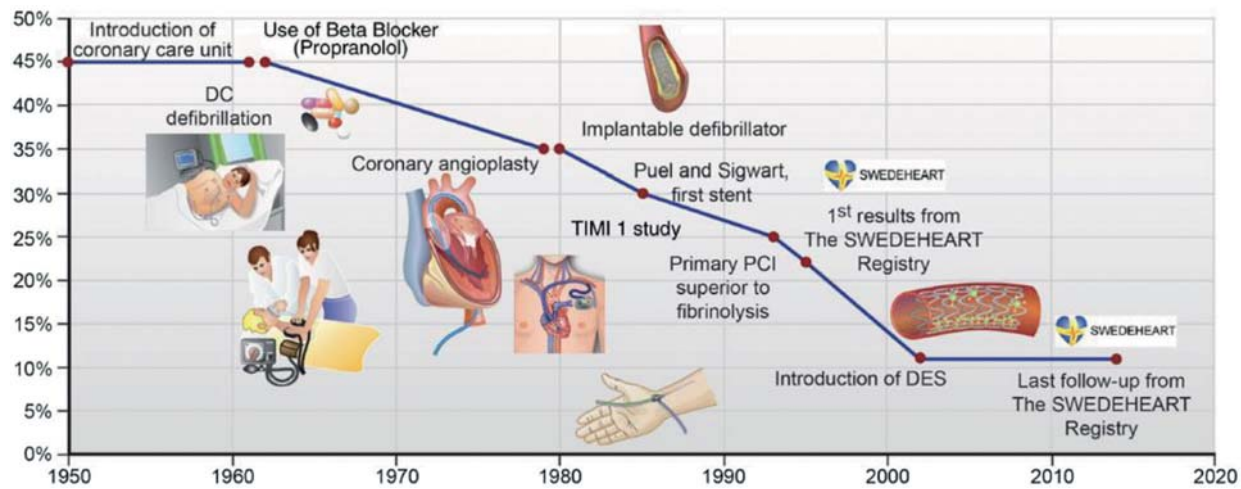

FIGURE 1. Change in mortality of acute myocardial infarction over time (from ref. 17).

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that plaque erosion was a predictable clinical entity distinct from plaque rupture in STEMI patients. Indeed, at the multivariable analysis, age <50 years, current smoking, absence of other coronary risk factors, lack of multi-vessel disease, reduced lesion severity, larger vessel size, and nearby bifurcation were significantly associated with plaque erosion (20). Substantial differences between plaque erosion and plaque fissure were also found by *Sugyiama et al* who performed 3-vessel OCT in 51 patients with ACS and observed that compared with those with culprit plaque rupture, patients with plaque erosion had a smaller number of nonculprit plaques and the lower levels of panvascular instability, affirming that distinct pathophysiologic mechanisms operate in plaque erosion and plaque rupture (21).

Finally, in a mechanistic study, *Pedicino et al* evaluated the gene/protein expression of HYAL2 (enzyme degrading hyaluronan to its pro-inflammatory 20 kDa isoform) and of the hyaluronan-receptor CD44 (22). Gene and protein expression of HYAL2 and CD44v6 were higher in patients with plaque erosion as compared to those with plaque rupture. HYAL2 might represent a potential new biomarker in ACS. This clinical study shows that plaque erosion is characterized by a profound alteration of hyaluronic metabolism and that, after further validation, HYAL2 might represent a potentially useful biomarker for the non-invasive identification of this mechanism of coronary instability.

New insight into post-MI remodeling

In an elegant experimental study *Reboll et al* identified Emc10 as a previously unknown angiogenic growth factor that is produced by bone marrow–derived monocytes and macrophages as part of an endogenous adaptive response that can be enhanced therapeutically to repair the heart after MI (23). In another study *Miyazaki et al.* investigated whether osteocrin (OSTN) potentially functioning as a natriuretic peptide clearance receptor-blocking agent can be used as a new therapeutic peptide for treating congestive heart failure after MI. In a mouse model they found that infusion of OSTN (24) resulted in an increased plasma atrial natriuretic peptide and in an improvement of congestive heart failure after MI as indicated by the reduced weight of hearts and lungs and by the reduced fibrosis. Similar results were confirmed in a transgenic model overexpressing OSTN. Finally, Frankenreiter et al in a preclinical study found that lack of BK mitochondrial channels renders the heart more susceptible to ischemia/reperfusion injury while BK channels seem to permit the protective effects triggered by PDE5 inhibitors as well as by preconditioning. Thus, this study establishes mitochondrial cardiomyocyte BK channels as a promising target for limiting acute cardiac damage as well as adverse long-term events that occur after MI (25).

Early diagnosis

Troponin

The timing of Tn assessment in suspected AMI admitted to the emergency department remains controversial (26). *Badertscher et al* compared the negative predictive value (NPV) for the presence of AMI (equivalent of diagnostic safety), and the proportion of patients triaged toward rule-out (equivalent of diagnostic accuracy) in a large multi-centre study enrolling patients presenting with suspected AMI to the emergency department (27). Among 2547 patients eligible for analysis with hs-cTnT, AMI was the final adjudicated diagnosis in 387 patients (15%). The 0/1 h algorithm provided safety similar to that of the 0/3 h algorithm (NPV, 99.8% [95% CI: 99.4–99.9] versus 9 9.7% [95% CI: 99.2–99.9]; P 0.645) but allowed the rule-out of significantly more patients compared with the 0/3 h algorithm (60% versus 44%; P<0.001). Among 2197 patients eligible for analysis with hs-cTnI, AMI was the final diagnosis in 327 patients (15%). The 0/1 h algorithm provided higher safety compared with the 0/3 h algorithm (NPV, 99.6% [95% CI: 99.1–99.9%] versus 97.8% [95% CI: 96.7–98.5]; P<0.01) and allowed the rule-out of a similar portion of patients compared with the 0/3 halgorithm (52% versus 51%; P=0.507). The authors concluded in line with the ESC guidelines that the 0/1 h algorithm is superior to the 0/3 h algorithm using hs-cTnT as well as hs-cTnI because it more favorably combines safety with efficacy.

In a prospective multicenter diagnostic study enrolling 3,254 unselected patients presenting with suspected AMI to the emergency department, *Twerenbold et al* assessed the diagnostic performance of the ESC 0/1 h-algorithm using hs-cTnT and hs-cTnI in patients with renal dysfunction defined as an estimated glomerular filtration rate below 60 mL/min/1.73 m (28). The prevalence of AMI was substantially higher in patients with than in those without renal dysfunction (31% versus 13%, P<0.001). Importantly, using hs-cTnT, the percentage of patients eligible for rule-out was much lower among patients with than among those without renal dysfunction (18% versus 68%, P<0.001). Similar findings were observed with hs-cTnI. The authors conclude that many of the challenges in patients with renal dysfunction admitted to emergency department with suspected AMI are related to the high prevalence of commonly yet undiagnosed cardiac comorbidities including hypertensive heart disease and diabetic cardiomyopathy associated with chronic cardiomyocyte injury and therefore increases in hs-cTn plasma concentrations and an increased prevalence of ECG abnormalities. These challenges need to be addressed in future studies.

Cardiac Myosin-Binding Protein

In 1954 unselected patients presenting to the emergency department with symptoms suggestive of AMI, Kaier et al measured concentrations of Cardiac Myosin-Binding Protein C (cMyC) and hs-cTn at presen-

tation. In 17% of the patients, the final diagnosis was AMI (29). The final diagnosis of AMI was independently adjudicated using all available clinical and biochemical information without knowledge of cMyC. Discriminatory power for AMI, as quantified by the area under the receiver operating characteristic curve was comparable for cMyC, hs-cTnT (0.927) and hs-cTnI (0.922) and superior to cTnI measured by a contemporary sensitivity assay (0.909). In early presenters (chest pain <3 h), the improvement in rule-in/rule-out classification with cMyC was larger compared with hs-cTnT and hs-cTnI (both P<0.001). The authors conclude that cMyC at presentation provides discriminatory power comparable to hs-cTnT and hs-cTnI in the diagnosis of AMI, and may perform favorably in patients presenting early after symptom onset. A limitation of this study is lack of comparison of cMyC performance vs the 0/1hour algorithm by hs-cTn proposed in this setting by the European Society of Cardiology.

Risk stratification

Biomarkers

Klingenberg et al found that in coronary thrombi of ACS patients, cysteine-rich angiogenic inducer 61 (Cyr61 or CCN1) gene transcripts were highly up-regulated compared with peripheral mononuclear cells. Furthermore, in a murine ischaemia–reperfusion model, myocardial Cyr61 expression was markedly increased compared with the controls (30). Cyr61 levels were determined in human serum using an enzyme-linked immunosorbent assay in 2168 ACS patients referred for coronary angiography. Cyr61 improved risk stratification for all-cause mortality when added to the reference GRACE risk score at 30 days (C-statistic 0.88 to 0.89, P= 0.001) and 1 year (C-statistic 0.77 to 0.80, P<0.001) and was comparable to hs-cTn (30 days: 0.88 to 0.89, P< 0.001; 1 year: 0.77 to 0.79, P<0.001). Similar results were obtained for the composite endpoint of all-cause mortality or myocardial infarction.

Several other biomarkers (including clot lysis time, macrophage migration inhibitory factor, Circulating progenitor cells and imterleukin-8) have been found to predict cardiovascular outcome after ACS in studies published during the last year (31–34). It remains to establish their incremental utility in the clinical arena in addition to validated risk predictors and which of these biomarkers might become therapeutic target.

Cardiac magnetic resonance

De Waha et al performed a pooled analysis using individual patient data from 7 randomized primary PCI trials and 1688 patients in which microvascular obstruction was assessed within 7 days after reperfusion by CMR using late gadolinium enhancement imaging (35). Microvascular obstruction: was present in 960 (56.9%) of patients, and median microvascular obstruction (percent left ventricular myocardial mass) was 0.47% (IQR 0.00–2.54). A graded response was present between the extent of MVO (per 1.0% absolute increase) and subsequent mortality [Cox adjusted hazard ratio (HR: 1.14, 95%) confidence interval (CI: 1.09–1.19), P<0.0001] and hospitalization for HF (Cox adjusted HR: 1.08, 95% CI: 1.05–1.12, P<0.0001). Microvascular obstruction remained significantly associated with all-cause mortality even after further adjustment for infarct size (Cox adjusted HR: 1.09, 95% CI: 1.01–1.17, P=0.03). This patient-level metanalysis confirms that microvascular obstruction is frequent after apparently successful primary PCI and portends a worse outcome. Its prevention and treatment remain an unmet need.

Provocative tests in myocardial infarction with no obstructive atherosclerosis

Montone et al prospectively evaluated 80 consecutive patients with a diagnosis of myocardial infarction with no obstructive coronary atherosclerosis (MINOCA), excluding patients with aetiologies other than suspected coronary vasomotor abnormalities and performed an invasive provocative test using acetylcholine or ergonovine immediately after coronary angiography (36). Provocative test was positive in 46.2% of the patients without any complication. Among patients with a positive test, epicardial spasm was detected in 64.9% patients and microvascular spasm in 35.1% patients. After a median follow-up of 36 months, patients with a positive test had a significantly higher occurrence of death from any cause [32.4% vs. 4.7%], cardiac death [18.9% vs. 0.0%], and readmission for ACS [27.0% vs. 7.0%] as well as a worse angina status as assessed by Seattle Angina Questionnaire [Seattle score: 88 vs. 100] when compared with patients with a negative test. The authors conclude that in patients presenting with MINOCA and suspected coronary vasomotor abnormalities, a positive provocative test for spasm is safe and identifies a high-risk subset of patients. These findings support the recommendation given in the European Guidelines on ST segment elevation myocardial infarction (37) which recommend an accurate diagnostic work up in patients with MINOCA in order to establish its cause and an appropriate aetiological treatment.

Acute coronary syndromes in women

Radial vs femoral access

Gargiulo et al sought to investigate the comparative efficacy and safety outcomes across sex of radial versus femoral access in ACS patients participating in the MATRIXA-Access (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial. Among 8,404 patients, 26.6% were women and 73.4% were men (38). Men had a lower risk of access site bleeding (male vs. female rate ratio [RR]: 0.64; p=0.0016), severe bleeding (RR:

0.17; P=0.0012), and transfusion (RR: 0.56; P=0.0089). When comparing radial versus femoral, there was no significant interaction for MACCE and NACE stratified by sex (p_{int}=0.15 and 0.18, respectively), although for both coprimary endpoints the benefit with transradial access was relatively greater in women (RR: 0.73; P=0.019; and RR: 0.73; P=0.012, respectively). Similarly, there was no significant interaction between male and female patients for the individual endpoints of all-cause death (p_{int}=0.79), myocardial infarction (p_{int}=0.25), stroke (p_{int}=0.18), and Bleeding Academic Research Consortium type 3 or 5 (p_{int}=0.45).

Sex differences in high-intensity statin use

Peters et al studied 16,898 U.S. adults <65 years of age with commercial health insurance of which 26% were women and 71,358 U.S. adults >66 years of age with government health insurance of which 49% were women. They had filled statin prescriptions within 30 days after hospital discharge for MI (39). The adjusted risk ratio for filling a high-intensity statin comparing women with men was 0.91 (95% CI: 0.90 to 0.92). Women were less likely than men to fill high-intensity statins within all subgroups analysed, and the disparity was largest in the youngest and oldest adults and for those without prevalent comorbid conditions. Thus, despite recent efforts to reduce gender differences in guideline-recommended therapy, women continue to be less likely than men to fill a prescription for high-intensity statins following hospitalization for MI. The underlying reasons for this disparity require further study.

Long term-outcome

Takotsubo syndrome

Ghadri et al compared long-term mortality of patients with Takotsubo syndrome (TTS) from the International Takotsubo Registry to an age- and sex-matched cohort of patients with ACS. In addition, short- and long-term outcomes were compared between different groups according to triggering conditions (40). Overall, 1,613 TTS patients had a comparable long-term mortality risk with ACS patients. TTS patients triggered by physical stress showed higher mortality rates than ACS patients during long-term follow up, whereas TTS triggered by emotional stress had better outcomes their ACS comparators.

TABLE 2. Proposal for a new classification of Tako-Tsubo syndrome based on triggers (based on ref. 40)

Class I	TTS related to emotional stress
Class II	TTS related to physical stress including diseases
Class IIa	TTS secondary to physical activities, medical conditions, or procedures
Class IIb	TTS secondary to neurologic disorders
Class III	TTS without an identifiable triggering factor

As a consequence, the authors propose a new classification based on triggers, which can serve as a clinical tool to predict short- and long-term outcomes of TTS *(Table 2).*

Medical treatment

Antithrombotic therapy

Anti-platelet drugs

After an ACS dual anti-platelet therapy for 12 months is the default anti-thrombotic regimen irrespective of treatment modality. Whether a shorted period of 6 months DAPT may be non-inferior to 12 or more months was investigated in the SMART-DATE trial (41). A total of 2712 ACS patients undergoing PCI were randomly assigned to 6 months DAPT or 12 months (or longer). The primary endpoint was a composite of all-cause death, myocardial infarction, or stroke at 18 months. While the non-inferiority margin was met (cumulative event rate 4.7% versus 4.2%; absolute risk difference 0.5%; upper limit of one-sided 95% CI: 1.8%; P non-inferiority=0.03 with a predefined non-inferiority margin of 2·0%), myocardial infarction occurred more frequently in the 6-month DAPT group (24 [1.8%] patients versus ten [0.8%]; 2·41 [1.15–5.05]; P=0.02). Furthermore, there were numerically more stent thrombosis in the 6-month DAPT group (15 (1.1%) patients in the 6-months DAPT group versus 10 (0.7%) patients in the 12-month or longer DAPT group; P=0.32). Therefore, the safety of a shortened DAPT duration after ACS cannot be proclaimed.

The two potent P_2Y_{12} inhibitors ticagrelor and prasugrel were compared in ACS patients in the PRAGUE-18 trial (42). A total of 1,230 ACS patients were randomized to either treatment option on the background of continued aspirin use. The combined endpoint was cardiovascular death, myocardial infarction, or stroke at 1 year. No significant differences were observed for the primary endpoint (6.6% of prasugrel patients versus 5.7% of ticagrelor patients; HR: 1.167; 95% confidence interval: 0.742 to 1.835; P=0.503), cardiovascular death (3.3% vs. 3.0%; P=0.769), myocardial infarction (3.0% vs. 2.5%; P=0.611), stroke (1.1% vs. 0.7%; P=0.423), all-cause death (4.7% vs. 4.2%; P=0.654), definite stent thrombosis (1.1% vs. 1.5%; P=0.535), and all bleeding (10.9% vs. 11.1%; P=0.999). Thus, it appears that both potent P_2Y_{12} inhibitors are similar in their effectivity.

De-escalation from a potent of P_2Y_{12} inhibitor to clopidogrel is an alternative treatment strategy in ACS patients especially in cost sensitive environments. In the TROPICAL ACS trial (43) patients were randomly assigned to either standard treatment with prasugrel for 12 months (control group) or to a guided de-escalation regimen (1 week prasugrel followed by 1 week clopidogrel and platelet function testing guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge; guided de-escalation group). When the impact of age, as a continuous variable,

TABLE 3. Triple versus dual antithrombotic therapy after myocardial infarction in patients with atrial fibrillation undergoing PCI (data from ref. 46, DAPT was used as reference treatment)

	Triple therapy	ASA+warfarin	Clopidogrel+warfarin
Cardiovascular outcome adjust. HR			
0–90 days	0.86 (0.70–1.07)	0.82 (0.54–1.26)	0.90 (0.68–1.19)
91–365 days	0.78 (0.58–1.05)	0.62 (0.48–0.79)	0.68 (0.49–0.95)
Major bleeds adjust. HR			
0–90 days	2.16 (1.48–3.13)	1.30 (0.60–2.85)	1.28 (0.71–2.32)
91–365 days	1.61 (0.98–2.66)	1.01 (0.63–1.62)	1.08 (0.57–2.04)

was analysed on the primary endpoint (cardiovascular death, myocardial infarction, stroke, or bleeding ≥ grade 2 according to Bleeding Academic Research Consortium criteria) after guided de-escalation vs. control treatment, an increasing relative risk reduction was observed by decreasing age (p=0.02), due to significant reductions in bleeding. In elderly patients (age >70, n = 370), the absolute risk of events was higher without significant differences between guided de-escalation vs. control group (15.5% vs. 13.6%; HR 1.17, 95% CI: 0.69–2.01; P=0.56). Guided de-escalation for P_2Y_{12} inhibitors depend on patient's age with younger patients deriving a significant net clinical benefit.

The GLOBAL LEADERS trial (44) included 15991 all-comer PCI patients (ACS including STEMI or stable CAD) and compared short dual antiplatelet regimen (DAPT) with aspirin (ASA) plus ticagrelor given only during the first month and followed by ticagrelor 90 mg bid monotherapy versus guideline-recommended therapy (1-year DAPT, followed by ASA monotherapy). The primary end-point of all-cause mortality or new Q-wave MI at 2 years displayed a statistical trend: 3.8% ticagrelor monotherapy vs. 4.4% one year DAPT (RR: 0.87, 95% CI: 0.75–1.01, P=0.073). All-cause mortality at 2 years was not different: 2.81% ticagrelor monotherapy vs. 3.17% one year DAPT (P=0.182). Interestingly, the results were almost exactly the same among ACS and among stable CAD patients.

Oral anticoagulants

Oral anticoagulation (OAC) is indicated in patients with atrial fibrillation at increased risk for stroke. After an ACS a combination of OAC with antiplatelet therapy is warranted in atrial fibrillation patients. Four randomized trials have compared anti thrombotic regimens including the combination of DAPT with OAC or a single antiplatelet with OAC in this scenario. In a meta-analysis (45) the safety and efficacy of dual versus triple

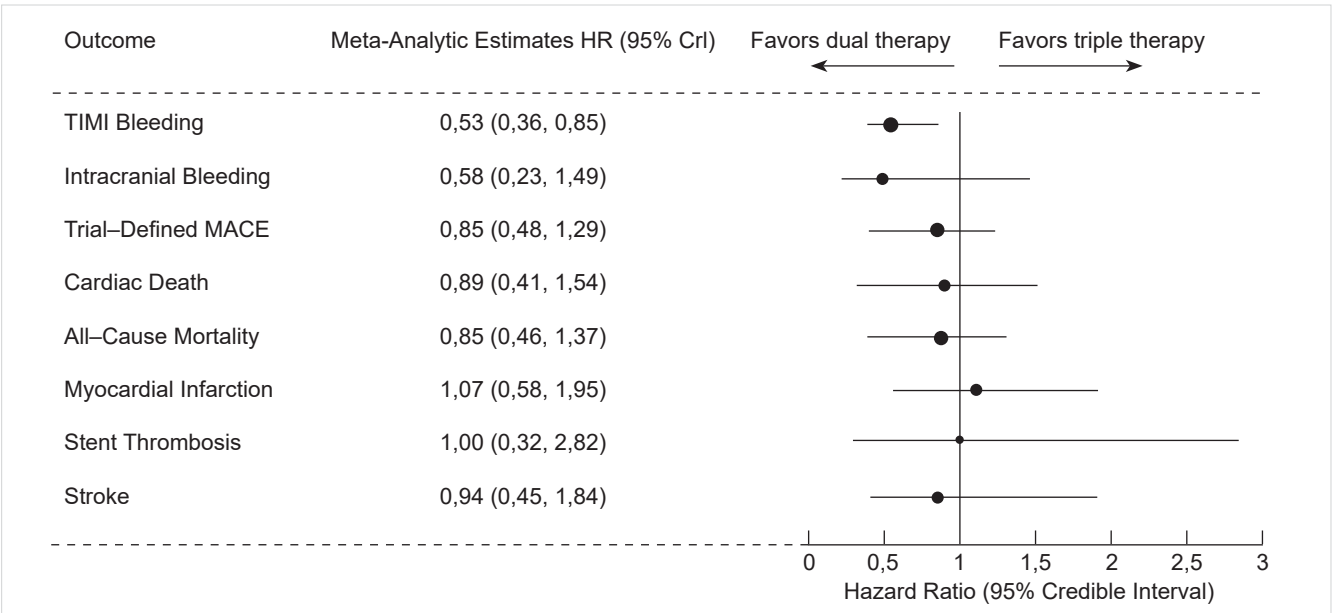

FIGURE 2. Summary of bleeding risks and ischemic risks with dual versus triple antithrombotic therapy (from ref. 45) All the four trials have demonstrated a reduction in bleeding with dual therapy (DAT) compared with triple therapy (TAT), but DAT may not only reduce bleeding events but is comparable to TAT for the reduction of MACE

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antithrombotic therapy was studied *(Figure 2)*. Compared with the triple therapy arm, TIMI major or minor bleeding showed a reduction by 47% in the dual therapy arm [4.3% versus 9.0%; hazard ratio (HR) 0.53, 95% credible interval (CrI) 0.36–0.85, I2 = 42.9%]. There was no difference in the trial-defined major adverse cardiac events (MACE) (10.4% vs. 10.0%, HR 0.85, 95% CrI 0.48–1.29, I2 = 58.4%), or in individual outcomes of all-cause mortality, cardiac death, myocardial infarction, stent thrombosis, or stroke between the two arms. These findings support the concept that dual therapy (one anticoagulant+one antiplatelet drug) may be a better option than triple therapy (one anticoagulant + two antiplatelet drugs) in many patients with atrial fibrillation following PCI.

The important yet not definitely resolved question whether triple or dual antithrombotic therapy after myocardial infarction should be used in patients with atrial fibrillation undergoing PCI was further investigated in a study based on the Swedish registries (46). The study included: n= 7116 patients with atrial fibrillation (AF) undergoing PCI during acute myocardial infarction (AMI). Landmark analysis was done for the first 3 months (0–90 days) and for 91–365 days. At discharge, 16.2% received triple therapy (aspirin, clopidogrel, and warfarin), 1.9% aspirin plus warfarin, 7.3% clopidogrel plus warfarin, and 60.8% dual antiplatelets *(Table 3)*.

Besides atrial fibrillation, the detection of a left ventricular (LV) thrombus warrants initiation of oral anticoagulation in ACS patients because of an increased risk of systemic embolism (SE). Such an event occurred in 16.3% of patients with LV thrombus and 2.9% of patients without LV thrombus in a study by Maniwa (47). A multivariate analysis showed that LV thrombus was an independent predictor for systemic embolism in ACS patients. Among 84 patients treated with vitamin K antagonists, 34 patients within the therapeutic range ≥50% of time were compared to 50 within TTR <50% of time. Only one embolic event (2.9%) developed in those within the therapeutic range ≥50% of time, while 9 embolic events (19%) developed in the <50% group (P = 0.036). While patients with LV thrombus seem to benefit from OAC, the optimal duration of OAC for this indication is still uncertain and would need interpretation in the context of the neutral COMMANDER trial (with rivaroxaban) (48) and possibly further trials.

The addition of OAC with Rivaroxaban 2.5 mg orally twice daily to DAPT with aspirin and clopidogrel was investigated in the ATLAS ACS-2 TIMI 51 trial. In a post-hoc analysis (49) fatal and irreversible efficacy events including non-bleeding cardiovascular death, myocardial infarction, and ischemic stroke were compared to fatal or irreversible safety events, including fatal and intracranial bleeding. The addition of low dose Rivaroxaban to DAPT was associated with 115 (95% confidence interval [CI:]: 18 to 212) fewer fatal or irreversible ischemic events (663 for placebo versus 548 for therapy) and 10 (95% CI: −11 to 32) additional fatal or irreversible seriously harmful events (33 versus 23 for placebo) per 10 000 patient-years of exposure. The authors conclude that there was a net reduction in fatal or irreversible events for ACS patients when low dose Rivaroxaban is added to DAPT.

Periprocedural anticoagulation

The latest ESC guidelines on revascularization (50) have downgraded the recommendation for Bivalirudin as anticoagulant during primary PCI. In the VALIDATE-SWEDEHEART trial (51) with 6006 ACS patients (3005 with STEMI and 3001 with NSTEMI) randomized to bivalirudin or heparin during primary PCI at 180 days, a primary end-point event occurred in 12.3% of the patients (369 of 3004) in the bivalirudin group and in 12.8% (383 of 3002) in the heparin group (hazard ratio, 0.96; 95% confidence interval [CI:], 0.83 to 1.10; P=0.54). Definite stent thrombosis was observed in 0.4% patients with bivalirudin and 0.7% patients with heparin, (hazard ratio, 0.54; 95% CI: 0.27 to 1.10; P=0.09).

In the MATRIX trial (52) 7,213 patients were randomly assigned to receive either bivalirudin or heparin with or without GPIs at discretion of the operator. Thus also here the rates of MACE (a composite of death, myocardial infarction, or stroke) is not significantly lower in ACS patients receiving bivalirudin than in those receiving heparin, irrespective of GPI use.

Lipid lowering agents

ODYSSEY OUTCOMES trial enrolled 18,924 patients after an acute coronary syndrome with low-density lipoprotein (LDL) cholesterol level of at least 1.8 mmol per liter in spite of statins at the maximal tolerated dose. Patients were randomized to alirocumab or placebo. The median duration of follow-up was 2.8 years. A primary end-point event occurred in 903 (9.5%) patients in the alirocumab group and in 1052 (11.1%) patients in the placebo group (HR: 0.85; 95% CI: 0.78 to 0.93; P<0.001). Mortality was lower after alirocumab (3.5% (334 pts) vs. 4.1% (392 pts), HR: 0.85; 95% CI: 0.73 to 0.98). There was no difference in safety measures (53). The US authors reviewed the new data for the 2018 guidelines on the management of blood cholesterol (54). The use of ezetimibe/simvastatin versus simvastatin in IMPROVE-IT trial reduced the primary outcome by 1.8% over 7 years (HR: 0.90; 95% CI: 0.84–0.96, 7-year number needed to treat: 56). The PSCK9 inhibitor evolocumab in the FOURIER study decreased the primary outcome by 1.5% over 2.2 years (HR: 0.80; 95% CI: 0.73–0.88; 2.2=year number needed to treat: 67). The ODYSSEY OUTCOMES trial is described above. For ezetimibe and the PSCK9 inhibitors, rates of musculoskeletal, neurocognitive, gastrointestinal, or other adverse event risks did not differ between the treatment and control groups.

Oxygen therapy

Whether supplemental oxygen in patients with STEMI impacts on procedure-related and clinical outcomes was studied in a pre-specified sub-group analysis of the DETO2X-AMI trial (55). 1361 STEMI patients were assigned to receive oxygen, and 1446 assigned to ambient air. The pre-specified primary composite endpoint of all-cause death, rehospitalization with MI, cardiogenic shock, or stent thrombosis at 1 year occurred in 6.3% (86 of 1361) of patients allocated to oxygen compared to 7.5% (108 of 1446) allocated to ambient air [hazard ratio (HR) 0.85, 95% confidence interval (95% CI): 0.64–1.13; P=0.27]. In accordance with current guidelines the routine use of supplemental oxygen in normoxemic patients with STEMI undergoing primary PCI was not beneficial.

Interventional therapy

During the last year, a lot of very interesting new data on PCI in acute coronary syndromes were published. Below are selected studies about peri-/post-procedural medication, about revascularization strategy in STEMI and non-STEMI, bioresorbable scaffolds, thrombus aspiration, fractional flow reserve and spontaneous coronary dissection.

Peri-procedural pharmacological treatment

The SECURE PCI study (56) investigated atorvastatin pre-treatment before PCI for ACS. Periprocedural loading dose of atorvastatin did not decrease 30-day major adverse cardiovascular events (MACE) in patients with ACS and planned invasive management in the SECURE PCI trial. This: trial was conducted at 53 sites in Brazil among 4191 patients with ACS and planned PCI. Patients were randomized to receive 2 loading doses of 80mg of: atorvastatin (n=2087) or matching placebo (n=2104) before and 24 hours after a planned PCI. All patients received 40 mg of atorvastatin for 30 days starting 24 hours after the second dose of study medication. Only 64.7% patients underwent PCI 8% underwent coronary artery bypass graft surgery, and 27.3% had medical management alone. At 30 days, 6.2% patients in the atorvastatin group and 7.1% in the placebo group had a MACE (absolute difference, 0.85% [95% CI: −0.70% to 2.41%]; hazard ratio, 0.88; 95% CI: 0.69–1.11; P=.27). These findings do not support the routine use of loading doses of atorvastatin among unselected patients with ACS and intended invasive management.

Multivessel PCI in hemodynamically stable STEMI

A metaanalysis of 11 randomized trials comparing complete revascularization with culprit-only revascularization in patients with ST-segment elevation MI without cardiogenic shock included 3561 patients (57). Compared with a culprit-only strategy, complete revascularization significantly reduced risk for death or MI (relative risk [RR]: 0.76; 95% confidence interval [CI]: 0.58 to 0.99; P=0.04). Meta-regression showed that performing complete revascularization at the time of primary PCI was associated with better outcomes (P=0.016). The 6 trials performing complete revascularization during primary PCI (immediate revascularization) were associated with a significant reduction in risk for both total mortality (RR: 0.62; 95% CI: 0.39 to 0.97; P=0.03) and MI (RR: 0.40; 95% CI: 0.25 to 0.66; P<0.001), whereas the 5 trials performing only staged revascularization did not show any significant benefit in either total mortality (RR: 1.02; 95% CI: 0.65 to 1.62; p=0.87) or MI (RR: 1.04; 95% CI: 0.48 to 1.68; P=0.86). The limitation however was, that some of these trials allowed staged revascularization to be performed with a delay, during second hospital stay. Thus, data are still inconclusive whether complete revascularization in hemodynamically stable STEMI should be performed as a single procedure (i.e. during primary angioplasty) or as two procedures during the single (initial) hospital stay.
Chronic total occlusion (CTO) in a noninfarct-related artery (non-IRA) in patients with ST-segment–elevation myocardial infarction (STEMI) is linked to increased mortality. It remains unclear whether staged revascularization of a non-IRA CTO in patients with ST-segment–elevation myocardial infarction translates to improved outcomes. This meta-analysis (6 studies, 1253 patients) compared outcomes between patients presenting with STEMI with concurrent CTO who underwent PCI of noninfarct-related artery CTO versus those who did not (58). There was a significant difference in major adverse cardiovascular events (OR, 0.54; 95% CI: 0.32–0.91), cardiovascular mortality (OR, 0.43; 95% CI: 0.20–0.95), and heart failure readmissions (OR, 0.57; 95% CI: 0.36–0.89), favoring patients in the CTO PCI group. No significant differences were observed between the 2 groups for all-cause mortality (OR, 0.47; 95% CI: 0.22–1.00), myocardial infarction (OR, 0.78; 95% CI: 0.41–1.46), repeat revascularization (OR, 1.13; 95% CI: 0.56–2.27), and stroke (OR, 0.51; 95% CI: 0.20–1.33).

Multivessel PCI in STEMI with cardiogenic shock

The CULPRIT-SHOCK trial compared culprit PCI versus multivessel PCI in patients with AMI and cardiogenic shock. This trial randomized 706 patients to culprit lesion only PCI (with possible staged revascularization) versus immediate multivessel PCI performed during the acute index procedure. The outcomes at 30 days (presented in 2017) demonstrated lower all-cause mortality of 43.3% after culprit-only PCI compared to 51.5% after acute multivessel PCI (P=0.03). One-year all-cause mortality was also lower after culprit only PCI

but the p value failed to reach significance (50% vs. 57%, P=0.07). Landmark analysis confirmed that the mortality benefit from culprit-only PCI is confined to the initial 30 days (59).

The analysis of 659 STEMI patients with multivessel coronary artery disease presenting with cardiogenic shock and undergoing primary PCI in Korea (the KAMIR-NIH registry) (60) retrospectively compared 260 patients with multivessel PCI and 399 with IRA-only PCI. The risk of all-cause death was significantly lower in the multivessel PCI group than in the IRA-only PCI group (21.3% vs. 31.7%; hazard ratio: 0.59; 95% confidence interval: 0.43 to 0.82; P=0.001). Multivessel PCI was independently associated with reduced risk of 1-year all-cause death and patient-oriented composite outcome. The authors conclude that multivessel PCI for complete revascularization may be a reasonable strategy to improve outcomes in patients with STEMI and cardiogenic shock. However, these are just registry result and contrast the higher level of evidence from the randomized CULPRIT-SHOCK trial discussed above.

Thus, currently there is sufficient evidence to recommend the best possible strategy for STEMI with multivessel disease: (a) Only the culprit artery (IRA) should be treated in the acute phase during the index procedure – unless a critical, flow limiting lesion is present in another artery AND (b) patient should be discharged home with complete revascularization whenever possible (i.e. pre-discharge staged PCI is recommended). Unfortunately, health care reimbursement systems in many countries stimulate a less optimal strategy – staged PCI during second hospital stay usually offers better reimbursement.

Stents and PCI techniques

The European Absorb Consortium presented outcomes of 10.312 patients treated with everolimus-eluting BRS during routine clinical practice. Overall 12-months mortality was 1.2%, cardiac death 0.6%, any MI 2.7% and definite or probable scaffold thrombosis 1.6% (34 cases acute – 63 subacute – 60 late). Landmark analysis with a prespecified landmark set at 30 days showed a scaffold thrombosis rate at 30 days of 0.94% which decreased between 1 and 12 months to 0.58%. No predilatation, bifurcation lesion and DAPT interruption carried the highest risk for scaffold thrombosis. The study demonstrated favorable clinical outcome data for BVS, with target lesion failure comparable to data of second-generation DES. Clinical outcome after treatment with everolimus-eluting bioresorbable scaffold might be improved by specific implantation protocols.

One single center descriptive registry (62) of 657 patients, who received 925 coronary bioresorbable scaffolds, described different mechanisms underlying early and late bioresorbable scaffold (BRS) thrombosis (ScTs). Twenty-eight ScTs were recorded: 14 early (2.2%), 5 late (0.9%), and 9 very late (1.7%). Incomplete BRS deployment was a predictor of the early scaffold thrombosis, while late thrombosis was associated with large vessel size and BRS undersizing.

Routine thrombus aspiration is now class III indication during PCI in STEMI. This is largely based on the TOTAL (and TASTE) (63) trials. In a follow-up paper (64), the authors demonstrated the risks of over-interpreting the interim data and prematurely stopping a trial. Should such approach be used in the TOTAL trial, the key finding of increased stroke risk related to thrombus aspiration during primary PCI would never have been detected.

The FUTURE trial (65) analyzed, whether in multivessel disease patients FFR helps to guide decision making for PCI or CABG or medical treatment only and thereby improves clinical prognosis compared to traditional management. All-comer patients with stable or stabilized angina and multivessel disease including LAD were randomized at the time of angiography to either FFR-guided or angio-guided decision making. Recruitment was stopped at 938 patients after DSMB recommendation due to an increased all-cause mortality in the FRR-guided arm (3.7% vs. 1.5%, HR: 2.39, 95% CI: 1.05–5.43, P=0.038). Medical treatment alone was recommended for 17% patients in the FFR-guided arm versus 9% in the angio-guided arm. There was no difference in the primary end-point (all-cause mortality + myocardial Infarction + repeat revascularization + stroke) at one year.

Some authors have questioned whether primary PCI performed during the off-hours can achieve the same results as that performed during the working hours. *Reinstadler et al* (66). found no significant differences in myocardial damage following primary PCI whether undertaken during or after routine working hours. These data suggest efficacy and safety for primary PCI in STEMI patients independent of the time of revascularization in contemporary health care systems.

Invasive strategy in non-STEMI

A randomized, investigator-initiated, parallel-group trial (67) evaluated the long-term effects of immediate invasive intervention in 323 patients with NSTEMI assigned to either immediate (median time to intervention 1.4 hours) or delayed (61.0 hours) invasive strategy. After 3 years follow-up, immediate invasive intervention was associated with a lower rate of death or new MI, compared with a delayed invasive strategy (12.3% (20/162 pts) vs. 22.5% (36/161 pts), hazard ratio 0.50, 95% confidence interval 0.29 to 0.87, P = 0.014). The observed benefit of immediate intervention was mainly driven by an increased early reinfarction risk in delayed strategy. Three-year mortality was 9.3% in the immediate invasive strategy, and 10.0% in the delayed strategy (P = 0.83).

The VERDICT trial (68) displayed only a non-significant trend towards better clinical outcomes with very early (median 4.7 hours) coronary angiography compared to angiography performed after a median time of 61.6 hours from randomization. However, this trend became significant in a subgroup of patients with GRACE risk score >140.

Left main PCI

The DELTA-2 registry (69) enrolled 3986 consecutive patients with unprotected left main coronary artery stenosis treated by PCI with second-generation drug-eluting stents. The results were compared with those from the historical DELTA 1 CABG cohort using propensity score stratification. At a median of 501 days of follow-up, the occurrence of the primary endpoint of death, MI, or stroke was lower in the PCI DELTA 2 group compared with the historical DELTA 1 CABG cohort (10.3% vs. 11.6%; adjusted hazard ratio: 0.73; 95% confidence interval: 0.55 to 0.98; p Ľ 0.03). Of note, an advantage of PCI was observed with respect to stroke (0.8% vs. 2.0%; adjusted hazard ratio: 0.37; 95% confidence interval: 0.16 to 0.86; p Ľ 0.02), while an advantage of CABG was observed with respect to target vessel revascularization (14.2% vs. 2.9%; adjusted hazard ratio: 3.32; 95% confidence interval: 2.12 to 5.18; P<0.0001).

Spontaneous coronary dissection

The multicenter Canadian Spontaneous Coronary Artery Dissection (SCAD) Cohort Study (70) included 750 patients presenting with non-atherosclerotic ACS and documented SCAD on coronary angiography confirmed by core laboratory analysis. The most typical patient was a young (or middle aged) woman. Stress (emotional or physical) was the most frequent precipitating factor, while fibromuscular dysplasia was the most frequent predisposing condition. TIMI flow 3 was preserved in 64% patients on the initial angiogram. Thus, 86% of the patients were treated conservatively and only one patient (0.1%) died.

What's Next

What is the next frontier? The biggest unmet need is effective management of patients presenting with cardiogenic shock or after being resuscitated because of sudden cardiac death. Indeed, mortality had not changed over the last decade and is still in the range of 40% – 60% at one year (71), while those presenting in stable conditions enjoy a survival rate of up to 98% in-hospital and 90% at one year. What should be done to reduce mortality in this patient population? The first minutes after cardiac arrest are the most crucial ones. Everybody should master cardio-pulmonary resuscitation in order to prevent irreversible neurological damage – and here we have to fill an educational gap within the population at large. Then, the door-to-balloon-time should be shortened further by fast tracks in the hospitals. Third, percutaneous pumps and assist devices are novel tools to overcome the acute hemodynamic problems, unload the LV, avoid multiorgan damage and potentially allow for recovery of pump function. However, the intraaortic balloon pump proved ineffective and the Impella and extracoperal membrane oxygenation remains to be tested properly. Forth, novel anti-inflammatory strategies (72), as recently documented in the CANTOS Trial (73) might help to reduce infarct size and facilitate hemodynamic recovery. And finally, there is still hope that stem cell therapies might assist in regenerating the heart muscle after an infarction in the future, once we will find the right way to reactivate regenerative pathways as is possible in fish and amphibia (74–77).

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