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**CURRENT OPINION**
*Clinical update*

# The year in cardiology 2017: acute coronary syndromes

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## Preamble

Acute coronary syndromes (ACS) remain the major cause of mortality in Western countries in spite of the enormous progress made over the last decades. Indeed, a recent analysis of the SWEDEHEART registry showed that mortality related to this condition has declined significantly over the last three decades.[1] Unfortunately, patients presenting in cardiogenic shock or after cardiopulmonary resuscitation still have an unacceptably high mortality. The most recent *European Society of Cardiology* (ESC) guidelines for the management of ST-segment elevation myocardial infarction (STEMI) addressed this issue.[2] The new aspects of the current guideline are summarized in *Figure 1* and include—among others—an upgrade on the recommendation of radial access, of drug-eluting over bare metal stents, complete revascularization, enoxaparin and early discharge, while thrombus aspiration and bivalirudin utilization were downgraded. The main studies considered in this review are summarized in *Table 1*.

## Mechanisms

### Plaque erosion vs. plaque fissure

There is growing interest in plaque erosion because, in the statin era, its prevalence as pathologic substrate of plaque instability is increasing. Franck *et al.*[3] have set up the first experimental model of plaque erosion and found that the key players of erosion were neutrophils recruitment, hyaluronan accumulation and Toll-like receptor 2 signalling activation resulting in endothelial cell apoptosis and thrombus formation. Accordingly, neutrophil loss-of-function and Toll-like receptor 2 deficiency reduced endothelial cell injury and local thrombosis. These findings confirm that the pathobiology of plaque erosion is different of that of plaque fissure.[3] In another study, Scalone *et al.*[4] found that not all plaque fissures are born equal. Indeed, among patients with ACS they identified two subsets of patients according to the presence or absence of macrophage infiltration of the culprit plaque assessed by optical coherence tomography. These two subsets of patients exhibited different clinical and biomarker profiles.[4]

In a recent review article, Crea and Libby[5] proposed a pathogenetic classification of ACS and advocate this more mechanistic approach to the categorization of ACS to provide a framework for future tailoring, triage, and therapy for patients in a more personalized and precise manner (*Figure 2*). In addition, Lüscher and Templin[6] have recently proposed to add Takotsubo syndrome (TTS) as an additional microcirculatory form of ACS requiring special care.

### Epigenetic modulation of immune signalling in acute coronary syndromes

Based on analyses involving two independent Chinese populations of ACS cases and matched controls, Li *et al.*[7] found novel and reproducible associations between ACS and methylation profiles in peripheral blood cells. Further analyses on cell subtype-specific methylation data suggested that the identified associations were mainly attributed to methylation alterations within certain immune cell subtypes, especially $CD8^+$ T cells, $CD4^+$ T cells, and B cells. The replicated loci suggested a role in ACS-relevant functions including chemotaxis, thrombosis, and apoptosis; functions of top ACS-associated methylation loci in purified T and B cells also revealed vital pathways relevant to atherogenic signalling and adaptive immune response, suggesting that inflammatory signalling and other immune functions in ACS might be regulated at an epigenetic level. This is the largest and the most detailed epigenome-wide analysis of ACS to date.[7]

### Remodelling after acute myocardial infarction

T cells are required for proper healing after myocardial infarction (MI). The mechanism of their beneficial action, however, is unknown. In this experimental study, Borg *et al.*[8] demonstrated that T cells invading the injured heart undergo substantial purinergic metabolic reprogramming. They up-regulate their enzymatic machinery for the accelerated hydrolysis of adenosine triphosphate to produce in a final step, via CD73, adenosine which by activation of A2b purinergic

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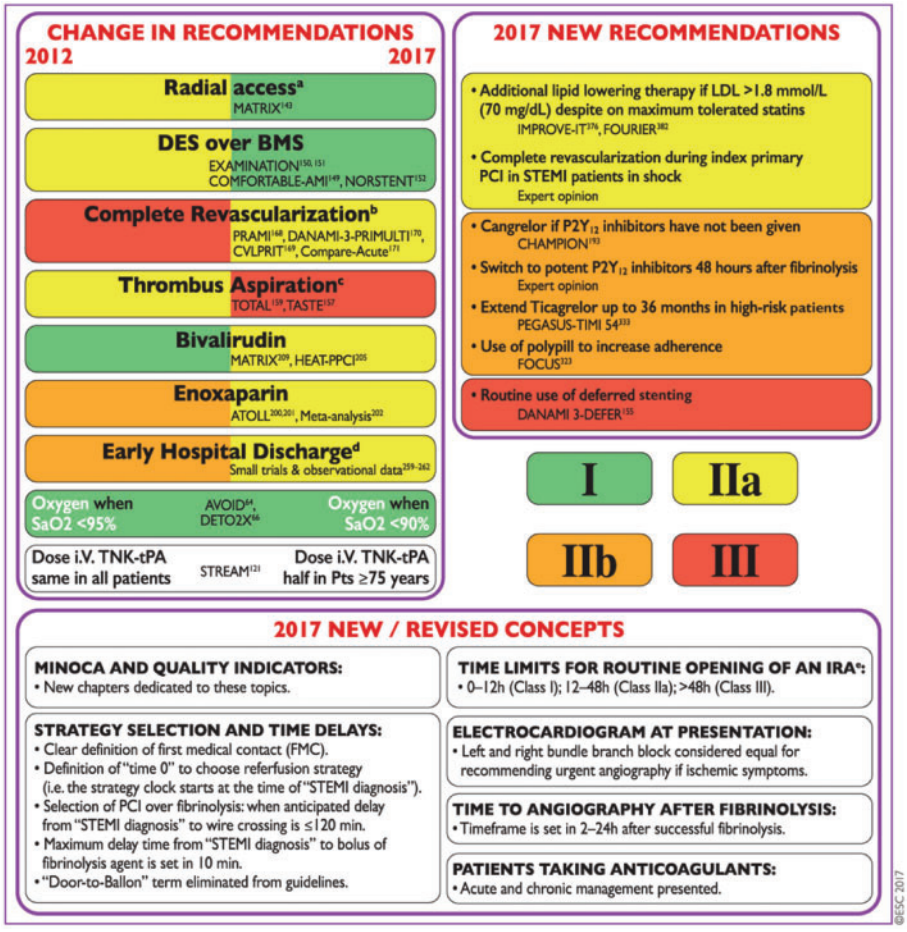


**Figure 1** New aspects of the 2017 ST-segment elevation myocardial infarction Guidelines (from Ibanez *et al.*[2]).

receptors expressed on T cells inhibits in a feedback loop manner the formation of important proinflammatory and profibrotic cytokines. Thus, resolution of inflammation after MI importantly involves changes in extracellular purine metabolism on T cells and provides a compelling example of the importance of adenosine in adaptive immunity preventing adverse ventricular remodelling after MI. Interestingly, as adenosine $A_{2b}$ receptors are likely to be activated only in an environment lacking oxygen, this feature could provide specificity in the therapy of the ischaemic myocardium.

# Early diagnosis

## Troponins

The ESC 2015 guidelines on the management of ACS included a 0-/1-h algorithm incorporating serial hs-cTn testing in patients with suspected ACS admitted to the emergency department without evidence of ischaemia on electrocardiography to rule out low risk patients in a short time period.[9] This algorithm opened a wide debate regarding its efficacy and safety.[10] Two large multicentre studies seem to confirm the effectiveness and safety of the algorithm proposed by ESC. In one study in 2222 patients, Pickering *et al.*[11] found that the 0-/1-hour algorithm using hs-cTnT allowed to safely rule out about 50% of patients who had a prevalence of MI less than 0.5. Similar results were obtained using hs-cTnI.[11] In the other study in 2828 patients, Boeddinghaus *et al.*[12] found very similar results using hs-cTnI. Furthermore during 2-year follow-up mortality in ruled out patients was about 2% only. Both studies highlight that the ESC guidelines 0-/1-h algorithm should only be implemented associated to a robust clinical risk assessment.

## Clinical scores

Patients with TTS typically present with clinical features similar to those of ACS caused by thrombotic occlusion of large epicardial coronary arteries. Thus, early cardiac catheterization is necessary to make a correct diagnosis and remains the reference standard diagnostic test for TTS as for most patients with ACS. Nevertheless, non-invasive clinical parameters would be desirable to identify patients, who present with the clinical picture of ACS but instead suffer from TTS. Ghadri *et al.*[13] developed the InterTak score based on seven simple descriptors which can be obtained bedside (*Figure 3*). Receiver operating characteristic curves demonstrated that the InterTak score was able to distinguish TTS from ACS with an area under the curve (AUC) of 0.971 in the derivation cohort and of 0.901 in the validation

**Table 1 Summary of the main studies**

| Topic | Main messages | References |
|---|---|---|
| Introduction | • The nationwide SWEDEHEART registry analysis shows prolonged survival and lower risk of recurrent ischaemic events in STEMI patients during the last 20 years | Szummer *et al.*[1] |
| | • ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation (2017) | Ibanez *et al.*[2] |
| Mechanisms | • Flow disturbance, neutrophil recruitment, and TLR2 signalling activation are mechanisms involved in the pathogenesis of superficial intimal erosion | Franck *et al.*[3] |
| | • A retrospective study performed by OCT shows that atherosclerotic plaque ruptures can be caused by predominant inflammatory or non-inflammatory mechanisms | Scalone *et al.*[4] |
| | • A new pathophysiological classification of ACS might improve clinical management and treatment strategies | Crea and Libby[5] |
| | • TTS should be considered a microvascular form of ACS | Lüscher and Templin[6] |
| | • Immune signalling and cellular functions involved in pathogenesis of ACS might be regulated at an epigenetic level | Li *et al.*[7] |
| | • T cells invading the injured heart undergo purinergic metabolic reprogramming influencing adverse ventricular remodelling after MI | Borg *et al.*[8] |
| Early diagnosis | • Debate on hs-cTn-based algorithms in Emergency Department | Crea *et al.*[10] |
| | • 0-/1-h algorithm to rule-out AMI, in conjunction with all available clinical information, seems to be effective and safe | Pickering *et al.*[11], Boeddinghaus *et al.*[12] |
| | • InterTAK Diagnostic Score is able to distinguish TTS from ACS with high sensitivity and specificity | Ghadri *et al.*[13] |
| Risk stratification | • Plasma levels of gut-microbiota-dependent trimethylamine N-oxide predict both short- and long-term risks of MACE in stable subjects | Li *et al.*[14] |
| | • miR-26b-5p, miR-660-5p, and miR-320a increase risk prediction of MACE when added to the GRACE score in patients presenting with STEMI | Jakob *et al.*[15] |
| | • Blood telomere length is an independent predictor of mortality during the first year post-AMI whereas vascular telomere length is a tissue-specific biomarker of vascular oxidative stress | Margaritis *et al.*[16] |
| | • PRECISE-DAPT score predicts out-of-hospital bleeding in patients treated with DAPT identifying patients in whom the benefits of prolonged DAPT outweigh the risks | Costa *et al.*[17] |
| Treatment | • In NSTEMI an early invasive strategy has no benefit, over a selective invasive strategy, in reducing the 10-year composite and individual outcomes of death or MI | Hoedemaker *et al.*[18] |
| | • In NSTEMI, a routine invasive strategy reduces long-term risk of death or non-fatal MI | Wallentin *et al.*[19] |
| | • In high-risk NSTEMI, an invasive strategy performed within the first 12 hours is associated with a lower risk of death and MI as compared with a strategy performed at 24–48 h | Deharo *et al.*[21] |
| | • In AMI with multivessel CAD and cardiogenic shock, PCI of the culprit lesion only, with the option of staged revascularization of non-culprit lesions, lowers the risk of a composite of death or severe renal failure requiring renal-replacement therapy when compared with immediate multivessel PCI | Thiele *et al.*[22] |
| | • In STEMI patients with multivessel coronary artery disease undergoing primary PCI a complete revascularization at the index procedure or, in particular using a staged approach, is associated with lower mortality and repeat revascularization rates | Iqbal *et al.*[23], Elgendy *et al.*[24] |
| | • In STEMI FFR-guided complete revascularization is associated to a better outcome when compared with culprit lesion only PCI | Smits *et al.*[25] |
| | • ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS (2017) | Valgimigli *et al.*[26] |
| | • Meta-analysis showing that optimal DAPT duration to reduce ischaemic risk after DES differs according to clinical presentation (stable ischaemic heart disease vs. ACS), while prolonged DAPT increases bleeding risk in both conditions | Palmerini *et al.*[27] |
| | • In patients treated with antiplatelet therapy after ACS, both MI and bleeding significantly impact mortality. The risk of mortality was equivalent between BARC 3b bleeding and MI, and was higher following BARC 3c bleeding | Valgimigli *et al.*[28] |
| | • Meta-analysis showing that in patients with DES, bleeding is an independent predictor of mortality occurring within 1 year and that prolonged DAPT reduces ischaemic risk, but it is associated with greater bleeding-related mortality | Palmerini *et al.*[29] |

*Continued*

**Table I** *Continued*

| Topic | Main messages | References |
|---|---|---|
| | • After STEMI bleeding risk significantly exceeds ischaemic risk within the first month, subsequently the ischaemic risk exceeds the bleeding risk supporting the use of intensified platelet inhibition during the first year after STEMI | Giustino *et al.*[30] |
| | • Prognostic models, developed using population-based linked electronic health records, provide personalized estimates of risks of major cardiovascular and bleeding events 1 year after AMI, helping tailored DAPT decisions | Pasea *et al.*[31] |
| | • In PCI-treated ACS patients early guided de-escalation of P2Y 12 inhibition to clopidogrel is non-inferior to standard treatment with prasugrel at 1 year after PCI in relation to net clinical benefit | Sibbing *et al.*[32] |
| | • In PCI-treated ACS patients early de-escalation of P2Y 12 inhibition to clopidogrel reduces bleeding complications without increasing the risk of ischaemic events | Cuisset *et al.*[33] |
| | • In ACS low-dose Rivaroxaban versus aspirin 100 mg daily, in addition to clopidogrel or ticagrelor, has similar risk of clinically significant bleeding | Ohman *et al.*[36] |
| | • Supplemental oxygen therapy in patients with suspected or proven ACS and an oxygen saturation ≥ 90% does not reduce 1-year all-cause mortality | Hofmann *et al.*[37] |
| ACS in women | • A collaborative sex-specific meta-analysis of randomized trials shows that there are not significant differences in efficacy and safety of prasugrel, ticagrelor, and intravenous cangrelor between men and women | Lau *et al.*[38] |
| | • A nationwide study shows an increase of STEMI annual incidence in France from 2004 to 2014 among women <65 years | Gabet *et al.*[39] |
| | • In young patients with AMI, female gender is independently and significantly associated with worse outcomes | Sabbag *et al.*[40] |

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; DES, drug eluting stent; FFR, fractional flow reserve; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TTS, Takotsubo syndrome.

cohort, suggesting that this score might be of clinical utility during daily clinical practice.

# Risk stratification

## Biomarkers

Three different studies have identified new interesting biomarkers for risk stratification of patients admitted with ACS. Li *et al.*[14] found that gut-microbiota-dependent trimethylamine N-oxide (TMAO) levels were an independent predictor of major cardiovascular events (MACEs) in two independent cohorts of 530 and 1683 patients, respectively (*Figure 4*). The importance of these findings is underlined by the modifiable nature of TMAO, both with diet, and with potential therapeutics under development, offering new perspectives for treatment strategies.[14]

In another study in 1002 patients with STEMI, Jakob *et al.*[15] found that the addition of 3 miRNAs levels (26b-5, 660-5, and 320a) to the *Global Registry of Acute Coronary Events* (GRACE) score increased AUC for the prediction of MACEs with a net reclassification improvement of 0.20. MiR-26b-5p has been suggested to prevent adverse cardiomyocyte hypertrophy, whereas miR-320a promotes cardiomyocyte death and apoptosis, and miR-660-5p has been related to active platelet production. Therefore, these three miRNAs may reflect pathophysiological mechanisms relevant for clinical outcome.[15]

In a smaller study in 290 patients with AMI telomere length in peripheral blood cells independently predicted total and cardiovascular mortality. They also demonstrated that telomere length was a tissue-specific biomarker of oxidative stress *in vivo*. They concluded that telomere length is an easily measurable biomarker that could predict mortality post-AMI, potentially reflecting redox-mediated activation of circulating inflammatory cells.[16]

Taken together these three innovative studies have identified novel biomarkers for risk stratification which may also become potential therapeutic targets.

## Clinical scores

In the era of dual antiplatelet therapy (DAPT) prediction of bleeding risk might help identifying patients who may benefit of prolonged treatment. Costa *et al.*[17] pooled 14 963 patients treated with DAPT after coronary stenting—largely consisting of aspirin and clopidogrel and without indication to oral anticoagulation—at a single-patient level from eight multicentre randomised clinical trials with independent adjudication of events.[17] They developed a score (PRECISE-DAPT) based on five simple descriptors (age, creatinine clearance, haemoglobin, white blood cell count, and previous spontaneous bleeding), which was found to predict risk with a c-index for out-of-hospital thrombolysis in myocardial infarction (TIMI) major or minor bleeding of 0.73 [95% confidence interval (CI) 0.61–0.85] in the derivation cohort, which was confirmed in two validation cohorts.

The retrospective utilization of the score in patients with ACS enrolled in trials of short vs. long DAPT duration confirmed that the latter significantly increased bleeding in patients at high risk (score ≥25), but not in those with lower risk profiles, and exerted a significant ischaemic benefit only in this latter group.

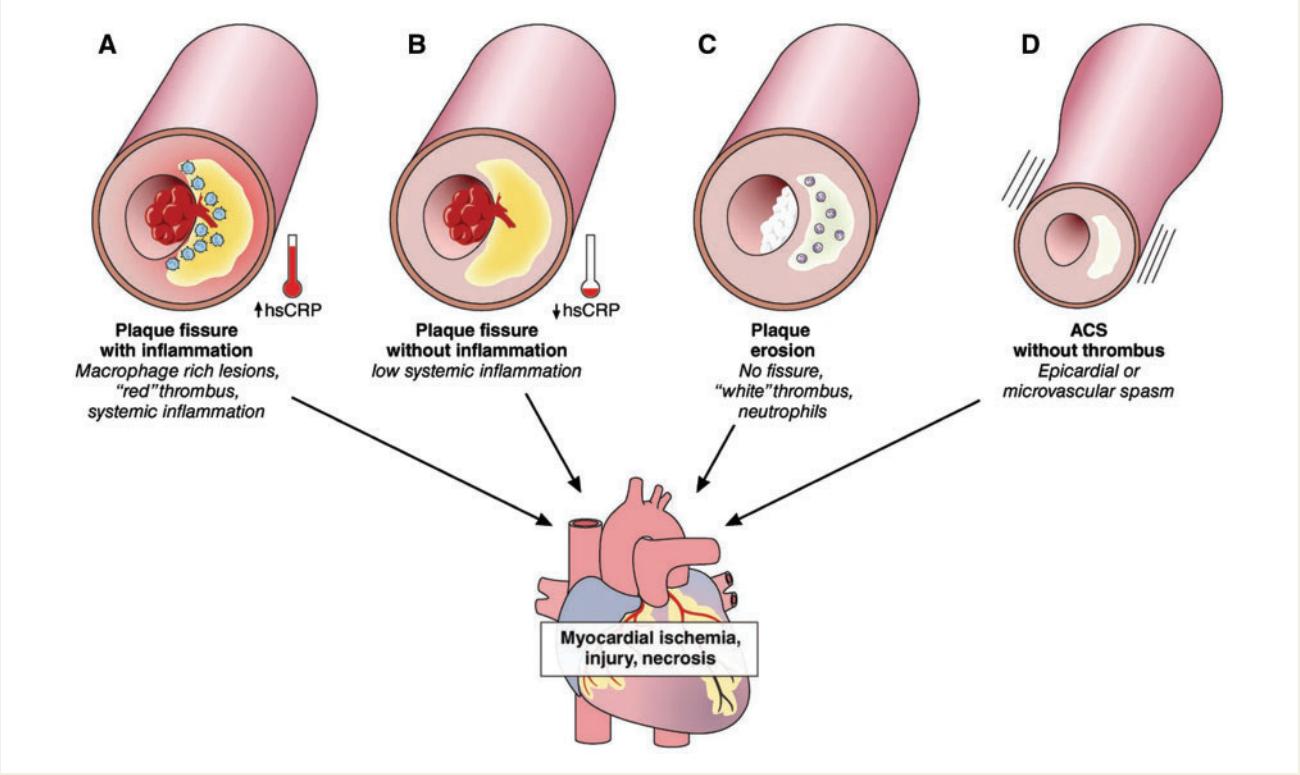


**Figure 2** Four diverse mechanisms cause acute coronary syndromes. (*A*) Plaque rupture, also referred to as fissure, traditionally considered the dominant substrate for acute coronary syndrome, usually associates with both local inflammation, as depicted by the blue monocytes, and systemic inflammation, as indicated by the gauge showing an increase in blood C-reactive protein (measured with a high-sensitivity assay). (*B*) In some cases, plaque rupture complicates atheromata that do not harbour large collections of intimal macrophages, as identified by optical coherence tomography criteria, and do not associate with elevations in circulating C-reactive protein. Plaque rupture usually provokes the formation of fibrin-rich red thrombi. (*C*) Plaque erosion appears to account for a growing portion of acute coronary syndrome, often provoking non-ST-segment elevation myocardial infarction. The thrombi overlying patches of intimal erosion generally exhibit characteristics of white platelet-rich structures. (*D*) Vasospasm can also cause acute coronary syndrome, long recognized as a phenomenon in the epicardial arteries but also affecting coronary microcirculation (from Crea and Libby[5]). ACS, acute coronary syndrome; hsCRP, high-sensitivity C-reactive protein.

| Criteria | Points | Prediction of TTS | OR (95% CI) | P-value |
|---|---|---|---|---|
| Female sex | 25 | | 68 (29.0 - 163.7) | P<0.001 |
| Emotional trigger | 24 | | 65 (20.3 - 205.8) | P<0.001 |
| Physical trigger | 13 | | 8.7 (4.6 - 17.3) | P<0.001 |
| Absence of ST-segment depression* | 12 | | 7.2 (3.1 - 16.8) | P<0.001 |
| Psychiatric disorders | 11 | | 7.0 (3.1 - 15.5) | P<0.001 |
| Neurologic disorders | 9 | | 4.9 (2.2 - 11.3) | P<0.001 |
| QTc prolongation | 6 | | 2.8 (1.3 - 5.7) | P=0.006 |
| | 100 | 0.1 1 10 100 | | |

**Figure 3** Clinical predictors for the diagnosis of Takotsubo syndrome. Multiple logistic regression analysis. Odds ratios of the parameters female gender, emotional trigger, physical trigger, absence of ST-segment depression, psychiatric disorders, neurologic disorders, and QTc prolongation, which were chosen to build the InterTAK Diagnostic Score. Error bars demonstrate the 95% confidence interval. *Except in lead aVR (from Ghadri *et al.*[13]). TTS, Takotsubo syndrome; OR; odds ratio; CI, confidence interval.

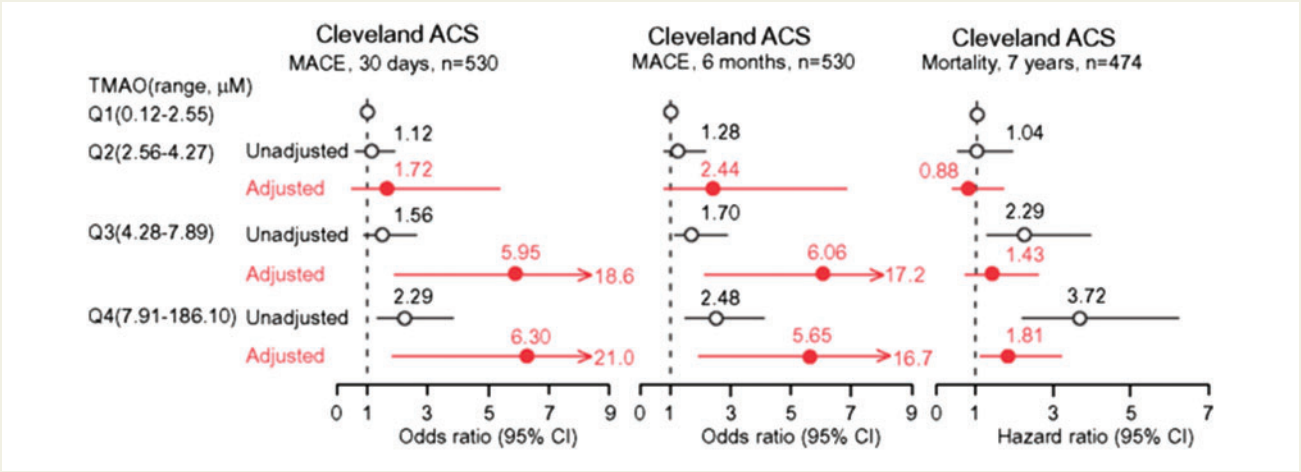


**Figure 4** Forest plots indicating the risks of incident major adverse cardiac events at 30 days and 6 months and all-cause mortality by 7 years according to the quartiles of trimethylamine N-oxide levels, multivariable logistic regression model for odds ratio or multivariable Cox model for hazard ratio included adjustments for age, gender, HDL, LDL, smoking, presence or absence of a history of diabetes mellitus, hypertension, hyperlipidaemia, revascularization, or coronary artery disease, C-reactive protein level, estimated glomerular filtration rate, initial troponin T level, and diagnosis of either STEMI, NSTEMI or unstable angina. The 5–95% confidence interval is indicated by line length (from Li *et al.*[14]). CI: confidence interval; MACE, major adverse cardiac event; TMAO: trimethylamine N-oxide; Q, quertile.

Thus, PRECISE-DAPT might help identifying patients who might benefit of long DAPT duration with clopidogrel, while these findings cannot be extrapolated to treatment with prasugrel and ticagrelor.

# Treatment

## Invasive vs. non-invasive strategy

During long-term follow-up of the ICTUS trial,[18] in which 1200 non-ST-segment elevation MI (NSTEMI) patients with an elevated cardiac troponin T were randomized to an early invasive vs. ischaemia driven strategy, no difference was found in the composite endpoint of all cause mortality or MI after 10 years [33.8% vs. 29.0%, hazard ratio (HR) 1.12; 95% CI 0.97–1.46; $P = 0.11$]. These findings are in contrast to the results of the long-term outcomes of the FRISC-II[19] and RITA-3[20] studies, where a benefit of an early invasive strategy was shown. Although long-term follow-up studies shed light on persisting impacts, we have to bear in mind, that they may represent out-dated and managements including old drugs and balloon angioplasty without stenting. The reasons of these discrepancies remain unclear although the bulk of evidence suggests that an invasive strategy is the preferable strategy.

## Timing of revascularization

Immediate restoration of blood flow to ischaemic myocardium reduces morbidity and mortality in ACS patients presenting with STEMI. However, in ACS patients with NSTEMI optimal timing of coronary angiography and percutaneous coronary intervention (PCI) can be further risk stratified.

In a *post-hoc* analysis of the TAO trial,[21] 4701 NSTEMI patients with a GRACE score of >140 were categorized into three groups according to timing of coronary angiography from admission (<12, ≥12–<24, and ≥24 h). The primary endpoint was the composite of all-cause death and myocardial infarction within 180 days. The analysis showed that performing coronary artery angiography in high risk NSTEMI patients less than 12 hours after presentation was associated with a lower risk of death and MI (HR 0.76; 95% CI 0.61–0.94; $P = 0.01$) compared with the procedure performed at 12–24 h.

## Culprit vessel vs. multivessel revascularization

The majority of ACS patients in cardiogenic shock present with multivessel disease. Current guidelines recommend complete revascularization of the culprit as well as non-culprit arteries in cardiogenic shock.[2] In the CULPRIT-SHOCK trial[22] 706 ACS patients in cardiogenic shock with multivessel disease were randomly assigned to PCI of the culprit lesion only, with the option of staged revascularization of non-culprit lesions, or immediate multivessel PCI. The primary endpoint, a composite of death or renal failure leading to renal-replacement therapy within 30 days after randomization, occurred more often in the immediate multivessel PCI group than in the culprit lesion only PCI group [relative risk (RR), 0.83; 95% CI 0.71–0.96; $P = 0.01$] (*Figure 5*). This difference was mainly driven by lower all-cause mortality in the culprit lesion only PCI group (RR 0.84; 95% CI 0.72–0.98; $P = 0.03$). The results of this trial challenge current European and North American guidelines, which favour multivessel PCI in cardiogenic shock. As there was no significant difference in renal replacement therapy, which would have been expected due to higher contrast medium exposure in the full revascularization group, and the survival curves separate only after the first week, a biological plausible hypothesis for higher survival in the culprit lesion only group needs elaboration. While in STEMI patients without cardiogenic shock complete revascularization, in particular using a staged approach, has been confirmed to be beneficial in a recent observational study[23] and in a recent meta-analysis,[24] the pendulum in patients with cardiogenic shock swung in the opposite direction.

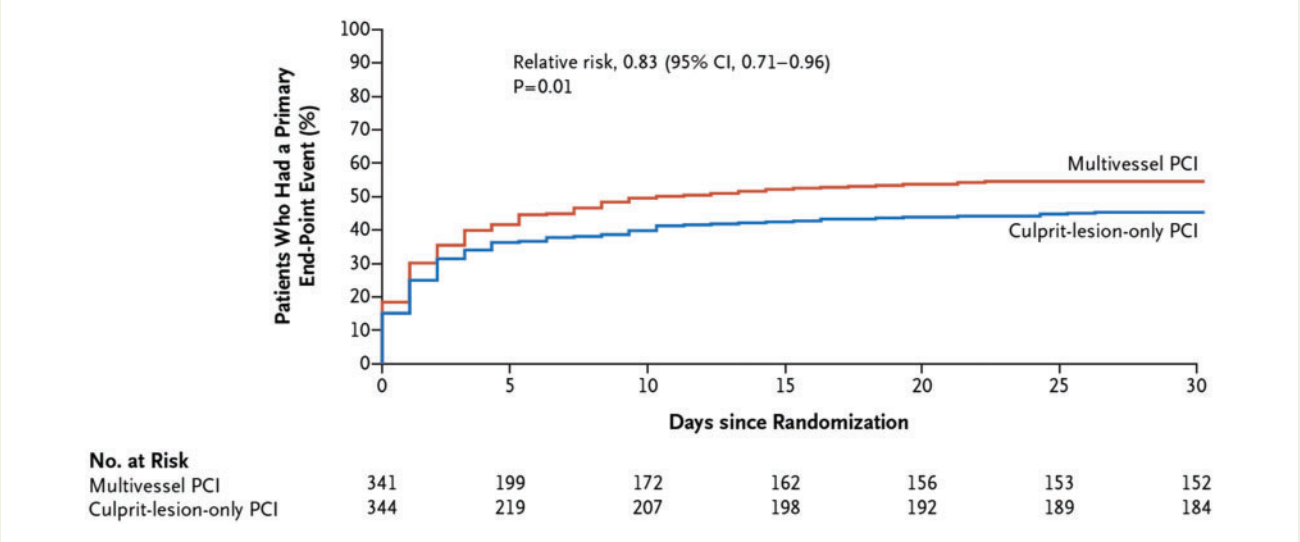


**Figure 5** The Kaplan–Meier time-to-event curves for the primary Endpoint of a composite of death from any cause or severe renal failure leading to renal-replacement therapy. In acute coronary syndromes patients presenting with cardiogenic shock culprit-lesion-only percutaneous coronary intervention was associated with a lower occurrence of the primary endpoint at 30 days compared to multivessel percutaneous coronary intervention (from Thiele *et al.*[22]). CI, confidence interval; PCI, percutaneous coronary intervention.

## Fractional flow reserve

Another trial in STEMI patients with multivessel disease investigated fractional flow reserve (FFR) guided complete revascularization vs. culprit lesion only PCI.[25] The primary endpoint was a composite of death from any cause, nonfatal myocardial infarction, revascularization, and cerebrovascular events at 12 months. The primary outcome occurred in 23 patients in the complete-revascularization group and in 121 patients in the infarct-artery-only group, a finding that translated to 8 and 21 events per 100 patients, respectively (HR 0.35; 95% CI 0.22–0.55; $P < 0.001$). However, this composite endpoint was mainly driven by a difference in revascularization (6.1% vs. 17.5%; HR 0.32; 95% CI 0.20–0.54). The results suggest that FFR is feasible in acute STEMI patients and reduces later revascularization procedures, however, the value obtained during the acute procedure could be influenced by vascular changes occurring in STEMI patients.

## Duration of dual antiplatelet treatment

The cornerstone of post-PCI antithrombotic medication is DAPT,[26] which not only reduces the risk of stent thrombosis, but also subsequent spontaneous MI. Trials consistently show that DAPT increases also the risk of bleeding with longer duration being associated with higher bleeding rates. Personalized medicine tailoring DAPT duration based on procedural and patient factors takes into account individual differences in ischaemic and bleeding risk. Guidance on post-PCI management with focus on specific subgroups including patients requiring oral anticoagulation is given by a focused ESC update on DAPT in coronary artery disease.[26] In the DAPT-STEMI trial 870 STEMI patients were randomly assigned to 6 vs. 12 month DAPT after undergoing PCI with a Zotarolimus eluting stent and an event free 6 months period (presented by Dr Elvin Kedhi at the Transcatheter Cardiovascular Therapeutics meeting, Denver, CO, USA, 1 November 2017). The primary outcome, all-cause mortality, MI, revascularization, stroke, and TIMI major bleeding at 18 months for 6-month vs. 12-month DAPT, was 4.8% vs. 6.6% ($P$-value for non-inferiority = 0.004, $P$-value for superiority = 0.26). The results suggest that among STEMI patients who remained event free at 6 month following PCI with a Zotarolimus eluting stent, cessation of DAPT at 6-months vs. continuing for an additional 6 months is non-inferior for clinical outcomes at 18 months.

Similar results were found in a meta-analysis of trials comparing 3-month vs. 6-month vs. 12 month DAPT after PCI.[27] This meta-analysis evaluated ischaemic as well as bleeding events in ACS patients stratified by duration of DAPT. Prolonged DAPT increased bleeding rate regardless of clinical presentation while the ischaemic risk after 3-month DAPT was higher compared to 6-month or 12-month DAPT. In keeping with the DAPT-STEMI trial, there was no significant difference in ischaemic endpoints in ACS patients taking 6 months vs. 12 months of DAPT.

The right balance between ischaemic and bleeding events by tailoring DAPT duration may impact clinical outcomes after ACS. In an analysis of the TRACER trial,[28] which was a prospective, randomized, double-blind trial of vorapaxar vs. placebo in patients hospitalized for NSTEMI, the long-term impact of MI and bleeding was investigated in 12 944 NSTEMI patients. Bleeding was graded according to Bleeding Academic Research Consortium (BARC) criteria. Myocardial infarction was associated with a five-fold increase in mortality and BARC type 2 and 3, but not type 1, bleeding also had a significant impact on mortality. Myocardial infarction was associated with a greater risk of mortality compared to BARC 2 (RR 3.5; 95% CI 2.08–4.77; $P < 0.001$) and BARC 3a bleeding (RR 2.23; 95% CI 1.36–3.64; $P < 0.001$), but the risk was similar to BARC 3 b bleeding (RR 1.37; 95% CI 0.81–2.30; $P = 0.242$) (*Figure 6*). Another meta-analysis investigated the associations among bleeding, mortality, and DAPT duration after drug-

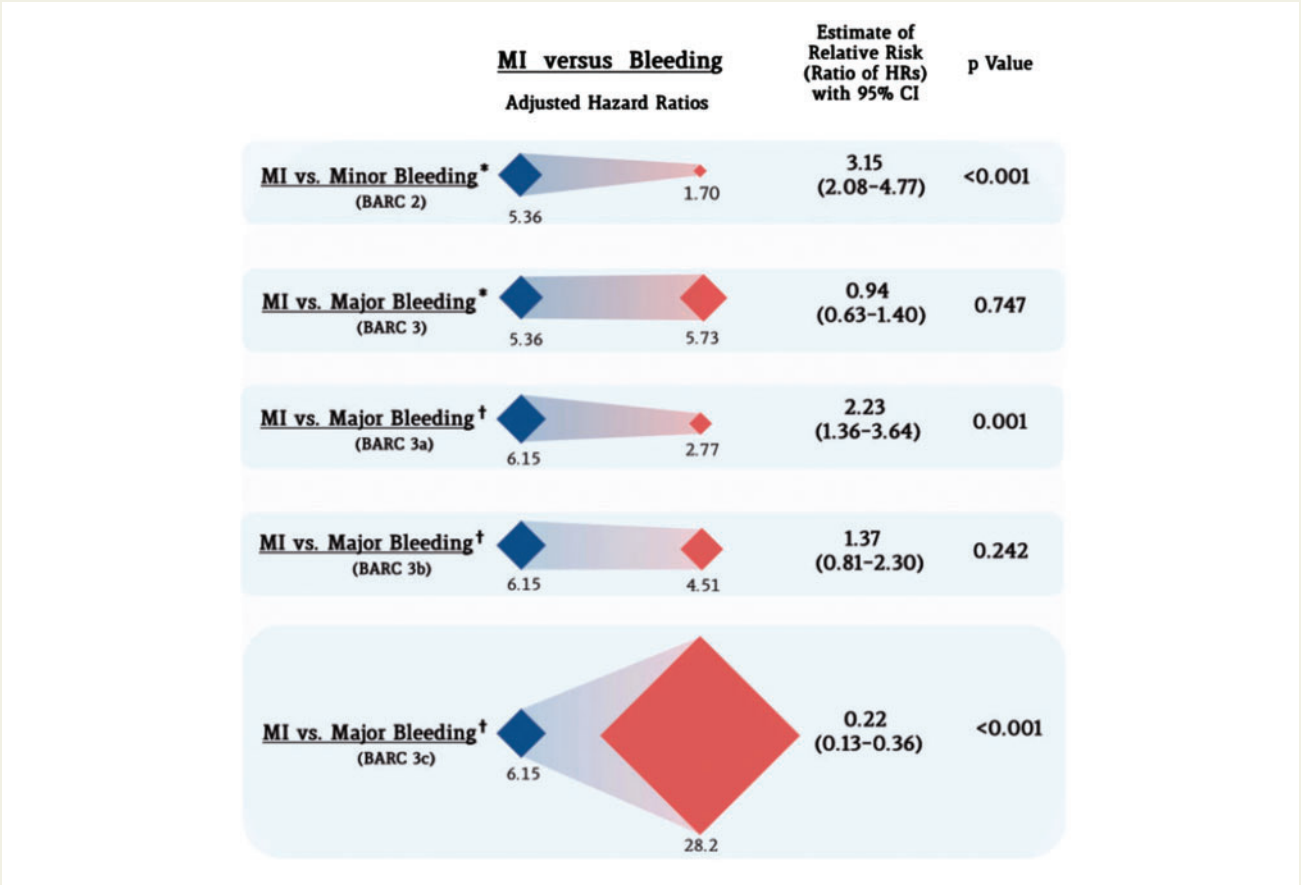


**Figure 6** Differential impact of myocardial infarction vs. bleeding on mortality. Blue rhombuses represent the magnitude (adjusted hazard ratio) of the impact on mortality of late myocardial infarction. Red rhombuses represent that of bleeding of different severity. On the right part of the figure, the estimate of the relative risk (ratio of the hazard ratios) for each category is presented. *The estimates of the impact of events on mortality is derived from Model 1, including Bleeding Academic Research Consortium 3 bleeding as a single category. †The estimates of the impact of events on mortality is derived from Model 2, including Bleeding Academic Research Consortium 3 bleeding subcategories separately. MI, myocardial infarction; CI, confidence interval; HR, hazard ratio; BARC, Bleeding Academic Research Consortium (from Valgimigli *et al.*[28]).

eluting stent implantation with individual patient data obtained from six randomized controlled trials.[29] A time-adjusted multivariate analysis showed that bleeding was an independent predictor of mortality occurring within 1 year of the bleeding episode (HR 6.93; 95% CI 4.53–10.60; $P < 0.0001$). Shorter DAPT was associated with lower rates of all-cause death compared with longer DAPT (HR 0.85; 95% CI 0.73–1.00; $P = 0.05$), which was driven by lower rates of bleeding-related deaths with shorter DAPT compared with prolonged DAPT (HR 0.65; 95% CI 0.43–0.99; $P = 0.04$).

The time course of ischaemic and bleeding events after ACS was investigated in 3602 STEMI patients from the HORIZONS-AMI trials.[30] Most ischaemic and bleeding events occurred in the early post-ACS phase and then markedly decreased. While the rates of bleeding exceeded those of ischaemia within the first month, the daily risk of ischaemia significantly exceeded the daily risk of bleeding beyond 30 days. These findings support the use of intensified platelet inhibition during the first year after STEMI.

In a prognostic model for cardiovascular events and bleeding in 12 694 MI survivors using population-based electronic health records there was a net clinical benefit of prolonged DAPT in 63–99% patients depending on how benefits and harms were weighted.[31]

These studies and analyses provide safety data on DAPT shortening below 12 months in selected ACS patients, point to the impact of bleeding on mortality and suggest individualizing the approach to post-PCI medical management.

## De-escalation of antiplatelet treatment

As the newer P2Y12 inhibitors ticagrelor and prasugrel are more potent than clopidogrel, they reduce ischaemic events, but may increase bleeding events. Most of the benefit after ACS in terms of reduction of ischaemic events of ticagrelor or prasugrel compared to clopidogrel is observed within the first weeks. A strategy of early de-escalation of antiplatelet treatment based on platelet function testing (PFT) was tested in the TROPICAL-ACS trial[32]; 2610 patients were randomly assigned to standard DAPT with aspirin and prasugrel or a platelet function test-guided step-down regimen (1 week prasugrel followed by 1 week clopidogrel and platelet function test-guided maintenance therapy with clopidogrel or prasugrel from day 14 after

hospital discharge). The primary endpoint was the net clinical benefit, a combination of cardiovascular death, myocardial infarction, stroke or bleeding BARC grade 2 or higher up to one year after randomization. The primary endpoint occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group (HR 0·81; 95% CI 0.62–1.06, *P*-value for non-inferiority = 0.0004, *P*-value for superiority = 0.12). Thus, early de-escalation of antiplatelet treatment as an alternative DAPT approach in patients with ACS managed with PCI did not improve the net clinical benefit. Furthermore, the practicability of switching DAPT regimens, then performing PFT testing and switching back in case of high on-treatment platelet function is questionable.

A similar approach—although not platelet function test-guided—was investigated in the TOPIC trial.[33] In this study 646 patients, who were event free one month after ACS, were assigned to switch to aspirin and clopidogrel (switched DAPT) or to continuation of their drug regimen (unchanged DAPT with aspirin and ticagrelor or prasugrel). The primary endpoint, a composite of cardiovascular death, urgent revascularization, stroke and BARC ≥2 bleeding at 1 year post-ACS, occurred more often in the unchanged DAPT group (26.3%) vs. the switched DAPT group (13.4%) (HR 0.48; 95% CI 0.34–0.68, $P < 0.01$). While there was no difference in ischaemic endpoints, a significant reduction of bleeding events was observed in the switched DAPT group. This single centre trial suggests, that a DAPT step-down strategy, by switching to the lower potent clopidogrel one month after an ACS, may prevent bleeding complications. Given the significant reduction of ischaemic events by ticagrelor or prasugrel in comparison to clopidogrel observed in the large, randomized, double-blind PLATO[34] and TRITON-TIMI 38[35] trials, the lack of difference in the open-label TOPIC trial was unexpected. While de-escalation DAPT therapy seems safe considering reduced bleeding events, the efficacy regarding ischaemic events remains to be proven.

## Oral anticoagulants

In the GEMINI-ACS-1 trial[36] 3037 ACS patients were randomly assigned to receive on top of a P2Y12 inhibitor either aspirin or low dose rivaroxaban, an oral factor Xa inhibitor. The primary endpoint was TIMI clinically significant bleeding not related to coronary artery bypass grafting up to day 390. Significant bleeding was similar with rivaroxaban vs. aspirin therapy (total 154 patients (5%); 80 participants (5%) of 1519 vs. 74 participants (5%) of 1518; HR 1.09; 95% CI 0.80–1.50; $P = 0.5840$). Although there was no signal of an increased risk of stent thrombosis after cessation of aspirin therapy, the trial was not powered to assess differences in ischaemic endpoints. The strategy of replacing aspirin by a factor Xa inhibitor as post-ACS treatment on top of a P2Y12 inhibitor needs further evidence by a cardiovascular outcomes trial investigating the net clinical benefit of this promising antithrombotic regimen.

## Supplemental oxygen therapy

Supplemental oxygen therapy in patients with suspected or proven ACS was considered routine for decades although the benefit in patients without baseline hypoxemia was unproven. In the DETO2X–SWEDEHEART trial 6629 patients with suspected MI and an oxygen saturation of 90% or higher were randomly assigned to receive either supplemental oxygen (6 L per minute for 6–12 h, delivered through an open face mask) or ambient air.[37] The primary Endpoint of death from any cause within 1 year after randomization occurred in 5.0% of patients (166 of 3311) assigned to oxygen and in 5.1% of patients (168 of 3318) assigned to ambient air (HR 0.97; 95% CI 0.79–1.21; $P = 0.80$). There was also no significant difference in rehospitalisation within one year or peak troponin levels between groups. Thus, the trial did not show any signal of harm of supplemental oxygen in suspected MI, although there was no benefit either for patients with oxygen saturation of 90% or higher.

# Acute coronary syndromes in women

## Antiplatelet treatment

Sex-specific differences have been described in response to antiplatelet therapies. In a collaborative sex-specific meta-analysis of phase III or IV randomized trials of potent P2Y12 inhibitors, including prasugrel, ticagrelor, and intravenous cangrelor, Lau *et al.*[38] analysed seven trials that enrolled a total of 24 494 women and 63 346 men. They found that the efficacy and safety of the potent P2Y12 inhibitors were comparable between men and women.

Thus, sex should not influence patient selection for the administration of potent P2Y12 inhibitors.

## Prevalence and outome in young patients

Gabet *et al.*[39] analysed trends in annual incidence of hospitalized ACS in France from 2004 to 2014. Despite an overall decrease in age-standardized admissions for ACS in both women and men, they observed a global increase of 6.3% from 2004 to 2014 among women aged <65 years. The increase was particularly marked for women <65 years hospitalized for STEMI, especially among the 45–54 years and 55–64 years age groups with respective mean annual percent changes of 3.6% and 2.0% per year, respectively. Similar unfavourable trends were observed for NSTEMI in both women and men.[39] Another study among 3949 patients admitted with ACS at age < 55 years. Sabbag *et al.*[40] found that after adjustment for GRACE score, diabetes and enrolment year, women had a lower likelihood to undergo coronary angiography during hospitalization. Importantly, female gender was independently associated with higher risk of in-hospital mortality, 30-day major adverse cardiac and cerebral events, and 5-year mortality.

Taken together these studies suggest that both prevention and treatment of ACS in young women need to be improved.

# Conclusions

In the past year, substantial progress has been made in our understanding of the pathophysiology of ACS in particular with regard to mechanisms of plaque instability and to cardiac remodelling after MI. New scores and biomarkers have been identified which help clinicians to risk stratify ACS patients; a better risk stratification, in turn, might improve tailoring of treatment intensity. Furthermore, the identification of new biomarkers might help to better personalize treatment strategies based on new therapeutic targets. New studies on timing of invasive procedures and treatment strategies for patients with multivessel disease and for those presenting in cardiogenic

shock have shown how to further improve the outcome of ACS in these patient subsets. The demonstration that during long-term follow-up the impact on mortality of major bleeding is similar to that of recurrent MI has stimulated several new studies investigating how to personalize post-PCI antithrombotic treatment. Finally, several studies have shed new light on sex-related issues focusing in particular on young women with ACS.

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## References


1. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, James S, Kellerth T, Lindahl B, Ravn-Fischer A, Rydberg E, Yndigegn T, Jernberg T. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J* 2017;**38**:3056–3065.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
3. Franck G, Mawson T, Sausen G, Salinas M, Masson GS, Cole A, Beltrami-Moreira M, Chatzizisis Y, Quillard T, Tesmenitsky Y, Shvartz E, Sukhova GK, Swirski FK, Nahrendorf M, Aikawa E, Croce KJ, Libby P. Flow perturbation mediates neutrophil recruitment and potentiates endothelial injury via TLR2 in mice: implications for superficial erosion. *Circ Res* 2017;**121**:31–42.
4. Scalone G, Niccoli G, Refaat H, Vergallo R, Porto I, Leone AM, Burzotta F, D'Amario D, Liuzzo G, Fracassi F, Trani C, Crea F. Not all plaque ruptures are born equal: an optical coherence tomography study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1271–1277.
5. Crea F, Libby P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. *Circulation* 2017;**136**:1155–1166.
6. Luscher TF, Templin C. Is takotsubo syndrome a microvascular acute coronary syndrome? Towards of a new definition. *Eur Heart J* 2016;**37**:2816–2820.
7. Li J, Zhu X, Yu K, Jiang H, Zhang Y, Deng S, Cheng L, Liu X, Zhong J, Zhang X, He M, Chen W, Yuan J, Gao M, Bai Y, Han X, Liu B, Luo X, Mei W, He X, Sun S, Zhang L, Zeng H, Sun H, Liu C, Guo Y, Zhang B, Zhang Z, Huang J, Pan A, Yuan Y, Angileri F, Ming B, Zheng F, Zeng Q, Mao X, Peng Y, Mao Y, He P, Wang QK, Qi L, Hu FB, Liang L, Wu T. Genome-wide analysis of DNA methylation and acute coronary syndrome. *Circ Res* 2017;**120**:1754–1767.
8. Borg N, Alter C, Gorldt N, Jacoby C, Ding Z, Steckel B, Quast C, Bonner F, Friebe D, Temme S, Flogel U, Schrader J. CD73 on T cells orchestrates cardiac wound healing after myocardial infarction by purinergic metabolic reprogramming. *Circulation* 2017;**136**:297–313.
9. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J; Management of Acute Coronary Syndromes in Patients Presenting without Persistent STSEotESoC. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
10. Crea F, Jaffe AS, Collinson PO, Hamm CW, Lindahl B, Mills NL, Thygesen K, Mueller C, Patrono C, Roffi M; Force EN-AGT. Should the 1h algorithm for rule in and rule out of acute myocardial infarction be used universally? *Eur Heart J* 2016;**37**:3316–3323.
11. Pickering JW, Greenslade JH, Cullen L, Flaws D, Parsonage W, Aldous S, George P, Worster A, Kavsak PA, Than MP. Assessment of the European Society of Cardiology 0-hour/1-hour algorithm to rule-out and rule-in acute myocardial infarction. *Circulation* 2016;**134**:1532–1541.
12. Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Badertscher P, Cupa J, Burge T, Machler P, Corbiere S, Grimm K, Gimenez MR, Puelacher C, Shrestha S, Flores Widmer D, Fuhrmann J, Hillinger P, Sabti Z, Honegger U, Schaerli N, Kozhuharov N, Rentsch K, Miro O, Lopez B, Martin-Sanchez FJ, Rodriguez-Adrada E, Morawiec B, Kawecki D, Ganovska E, Parenica J, Lohrmann J, Kloos W, Buser A, Geigy N, Keller DI, Osswald S, Reichlin T, Mueller C. Direct comparison of 4 very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I. *Circulation* 2017;**135**:1597–1611.
13. Ghadri JR, Cammann VL, Jurisic S, Seifert B, Napp LC, Diekmann J, Bataiosu DR, D'Ascenzo F, Ding KJ, Sarcon A, Kazemian E, Birri T, Ruschitzka F, Luscher TF, Templin C; Inter TAKc-i. A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry. *Eur J Heart Fail* 2017;**19**:1036–1042.
14. Li XS, Obeid S, Klingenberg R, Gencer B, Mach F, Raber L, Windecker S, Rodondi N, Nanchen D, Muller O, Miranda MX, Matter CM, Wu Y, Li L, Wang Z, Alamri HS, Gogonea V, Chung YM, Tang WH, Hazen SL, Luscher TF. Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. *Eur Heart J* 2017;**38**:814–824.
15. Jakob P, Kacprowski T, Briand-Schumacher S, Heg D, Klingenberg R, Stahli BE, Jaguszewski M, Rodondi N, Nanchen D, Raber L, Vogt P, Mach F, Windecker S, Volker U, Matter CM, Luscher TF, Landmesser U. Profiling and validation of circulating microRNAs for cardiovascular events in patients presenting with ST-segment elevation myocardial infarction. *Eur Heart J* 2017;**38**:511–515.
16. Margaritis M, Sanna F, Lazaros G, Akoumianakis I, Patel S, Antonopoulos AS, Duke C, Herdman L, Psarros C, Oikonomou EK, Shirodaria C, Petrou M, Sayeed R, Krasopoulos G, Lee R, Tousoulis D, Channon KM, Antoniades C. Predictive value of telomere length on outcome following acute myocardial infarction: evidence for contrasting effects of vascular vs. blood oxidative stress. *Eur Heart J* 2017;**38**:3094–3104.
17. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; Investigators P-DS. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;**389**:1025–1034.
18. Hoedemaker NPG, Damman P, Woudstra P, Hirsch A, Windhausen F, Tijssen JGP, de Winter RJ; ICTUS Investigators. Early invasive versus selective strategy for non-ST-segment elevation acute coronary syndrome. The ICTUS trial. *J Am Coll Cardiol* 2017;**69**:1883–1893.
19. Wallentin L, Lindhagen L, Ärnström E, Husted S, Janzon M, Johnsen SP, Kontny F, Kempf T, Levin LÅ, Lindahl B, Stridsberg M, Ståhle E, Venge P, Wollert KC, Swahn E, Lagerqvist B; FRISC-II study group. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. *Lancet* 2016;**388**:1903–1911.
20. Fox KA, Poole-Wilson P, Clayton TC, Henderson RA, Shaw TR, Wheatley DJ, Knight R, Pocock SJ. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;**366**:914–920.
21. Deharo P, Ducrocq G, Bode C, Cohen M, Cuisset T, Mehta SR, Pollack C Jr, Wiviott SD, Elbez Y, Sabatine MS, Steg PG. Timing of angiography and outcomes in high-risk patients with non-ST-segment-elevation myocardial infarction managed invasively: insights from the TAO trial (Treatment of Acute Coronary Syndrome With Otamixaban). *Circulation* 2017;**136**:1895–1907.
22. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S, Zeymer U; Investigators C-S. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1710261.
23. Iqbal MB, Nadra IJ, Ding L, Fung A, Aymong E, Chan AW, Hodge S, Della Siega A, Robinson SD; British Columbia Cardiac Registry Investigators. Culprit vessel versus multivessel versus in-hospital staged intervention for patients with ST-segment elevation myocardial infarction and multivessel disease: stratified analyses in high-risk patient groups and anatomic subsets of nonculprit disease. *JACC Cardiovasc Interv* 2017;**10**:11–23.
24. Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;**10**:315–324.
25. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angeras O, Richardt G, Omerovic E; Compare-Acute I. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;**376**:1234–1244.
26. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG,

Windecker S, Zamorano JL, Levine GN; Group ESCSD; Guidelines ESCCfP; Societies ESCNC. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–254.

27. Palmerini T, Della Riva D, Benedetto U, Bacchi Reggiani L, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Sangiorgi D, Biondi-Zoccai G, Genereux P, Angelini GD, Pufulete M, White J, Bhatt DL, Stone GW. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J* 2017;**38**:1034–1043.
28. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, Van de Werf F, Harrington RA, Mahaffey KW, Tricoci P. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;**38**:804–810.
29. Palmerini T, Bacchi Reggiani L, Della Riva D, Romanello M, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Ahn JM, Park SJ, Schupke S, Kastrati A, Montalescot G, Steg PG, Diallo A, Vicaut E, Helft G, Biondi-Zoccai G, Xu B, Han Y, Genereux P, Bhatt DL, Stone GW. Bleeding-related deaths in relation to the duration of dual-antiplatelet therapy after coronary stenting. *J Am Coll Cardiol* 2017;**69**:2011–2022.
30. Giustino G, Mehran R, Dangas GD, Kirtane AJ, Redfors B, Genereux P, Brener SJ, Prats J, Pocock SJ, Deliargyris EN, Stone GW. Characterization of the average daily ischemic and bleeding risk after primary PCI for STEMI. *J Am Coll Cardiol* 2017;**70**:1846–1857.
31. Pasea L, Chung SC, Pujades-Rodriguez M, Moayyeri A, Denaxas S, Fox KAA, Wallentin L, Pocock SJ, Timmis A, Banerjee A, Patel R, Hemingway H. Personalising the decision for prolonged dual antiplatelet therapy: development, validation and potential impact of prognostic models for cardiovascular events and bleeding in myocardial infarction survivors. *Eur Heart J* 2017;**38**:1048–1055.
32. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Dézsi CA, Holdt L, Felix SB, Parma R, Klopotowski M, Schwinger RHG, Rieber J, Huber K, Neumann F-J, Koltowski L, Mehilli J, Huczek Z, Massberg S; Investigators T-A. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017;**390**:1747–1757.
33. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, Verdier V, Morange PE, Alessi MC, Bonnet JL. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 2017;**38**:3070–3078.
34. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
35. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; Investigators T-T. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.
36. Ohman EM, Roe MT, Steg PG, James SK, Povsic TJ, White J, Rockhold F, Plotnikov A, Mundl H, Strony J, Sun X, Husted S, Tendera M, Montalescot G, Bahit MC, Ardissino D, Bueno H, Claeys MJ, Nicolau JC, Cornel JH, Goto S, Kiss RG, Guray U, Park DW, Bode C, Welsh RC, Gibson CM. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet* 2017;**389**:1799–1808.
37. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, Arefalk G, Frick M, Alfredsson J, Nilsson L, Ravn-Fischer A, Omerovic E, Kellerth T, Sparv D, Ekelund U, Linder R, Ekstrom M, Lauermann J, Haaga U, Pernow J, Ostlund O, Herlitz J, Svensson L; Investigators DXS. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med* 2017;**377**:1240–1249.
38. Lau ES, Braunwald E, Murphy SA, Wiviott SD, Bonaca MP, Husted S, James SK, Wallentin L, Clemmensen P, Roe MT, Ohman EM, Harrington RA, Mega JL, Bhatt DL, Sabatine MS, O'Donoghue ML. Potent P2Y12 inhibitors in men versus women: a collaborative meta-analysis of randomized trials. *J Am Coll Cardiol* 2017;**69**:1549–1559.
39. Gabet A, Danchin N, Juilliere Y, Olie V. Acute coronary syndrome in women: rising hospitalizations in middle-aged French women, 2004-14. *Eur Heart J* 2017;**38**:1060–1065.
40. Sabbag A, Matetzky S, Porter A, Iakobishvili Z, Moriel M, Zwas D, Fefer P, Asher E, Beigel R, Gottlieb S, Goldenberg I, Segev A. Sex differences in the management and 5-year outcome of young patients (<55 years) with acute coronary syndromes. *Am J Med* 2017;**130**:1324.e15–1324.e22.