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Acute coronary syndromes: the tipping point of coronary artery disease

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Heart attacks are the tipping point, from the nuisance of exercise-induce angina to a potentially lethal outcome. In spite of enormous progress made since Eisenhower's famous heart attack on 25 September 1955,[1,2] acute coronary syndromes remain the major cause of mortality in Western countries, as again documented in the most recent ESC Atlas published earlier this year.[3] As pointed out by Filippo Crea, Ronnie Binder, and myself in the 2017 '**Year in cardiology: acute coronary syndromes**',[4] the SWEDEHEART registry[5] showed that overall mortality related to this condition declined impressively, but patients presenting in cardiogenic shock or after cardiopulmonary resuscitation still have an unacceptable fatality rate. The most recent ESC guidelines in the management of ST-segment elevation myocardial infarction[6] are summarized and include—among others—an upgrade on the recommendation of radial access,[7,8] of drug-eluting over bare metal stents, complete revascularization, enoxaparin, and early discharge, while thrombus aspiration and bivalirudin utilization have been downgraded, particularly as with radial access there seems to be no benefit over heparin.[9] Unfortunately, neither balloon pumps[10] nor complete revascularization attempts have improved outcomes in shock[11] so far, which will certainly modify future recommendations in this population.

The management of unstable patients with acute coronary syndrome (ACS) is further addressed in a clinical research manuscript entitled '**Impact of treatment delay on mortality in ST-segment elevation myocardial infarction patients presenting with haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial**', by Thomas Meyer and colleagues from the University of Göttingen in Germany.[12] Specifically, they investigated the impact of contact-to-balloon time on mortality in 12 675 patients with ST-segment elevation myocardial infarction or STEMI, with and without haemodynamic instability. For patients treated within 60–180 min from first medical contact, the relationship between contact-to-balloon times and mortality was near linear. In cardiogenic shock patients with no out-of-hospital cardiac arrest, every 10-min treatment delay resulted in 3.31 additional deaths per 100 patients, 2.09 in out-of-hospital cardiac arrest patients with shock, 1.34 in those without shock, and 0.34 in haemodynamically stable patients (*Figure 1*). Thus, in patients with cardiogenic shock, special efforts to shorten contact-to-balloon time should be applied in particular to high-risk STEMI patients. The implications of these results are further discussed in an **Editorial** by William C. Wijns from the National University of Ireland-Galway in Ireland.[13]

The underlying cause of an ACS is clot formation in the coronary circulation.[14] The size and biological properties of the forming clot will determine whether the patient will present with a STEMI, NSTEMI, or unstable angina. This has been addressed in the PLATO substudy '**Fibrin clot properties independently predict adverse clinical outcome following acute coronary syndrome**' by Robert F. Storey and colleagues from the University of Sheffield in the UK in 4354 patients.[15] After adjusting for cardiovascular risk factors, each 50% increase in lysis time was associated with cardiovascular death or myocardial infarction, with hazard ratios of 1.17 and 1.36, respectively. Similarly, each 50% increase in maximum turbidity was associated with a 1.24-fold increased risk of cardiovascular death. After adjustment for other prognostic biomarkers, the association with cardiovascular death remained significant for lysis time, but not for maximum turbidity. Thus, fibrin clots that are resistant to lysis independently predict adverse outcome in ACS. Novel therapies targeting fibrin clot properties might be a new avenue for improving prognosis in such patients, a conclusion that is further discussed in an **Editorial** by Felicita Andreotti from the Catholic University Medical School in Rome, Italy.[16]

Inflammation is an important trigger of ACS.[17,18] The higher activity of effector T-cells suggests that adaptive immunity might play a role in coronary instability. The shedding of the functional CD31 domain 1–5 leads to uncontrolled lymphocyte activation. In experimental models, matrix metalloproteinase-9 (MMP-9) has been implicated in endothelial CD31 cleavage. Interestingly, higher serum levels of MMP-9 have been observed in acute coronary syndrome. In their basic science article entitled '**Matrix metalloproteinase-9 might**

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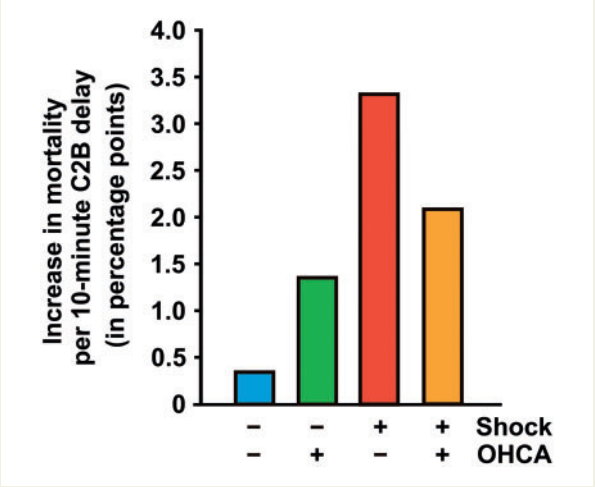
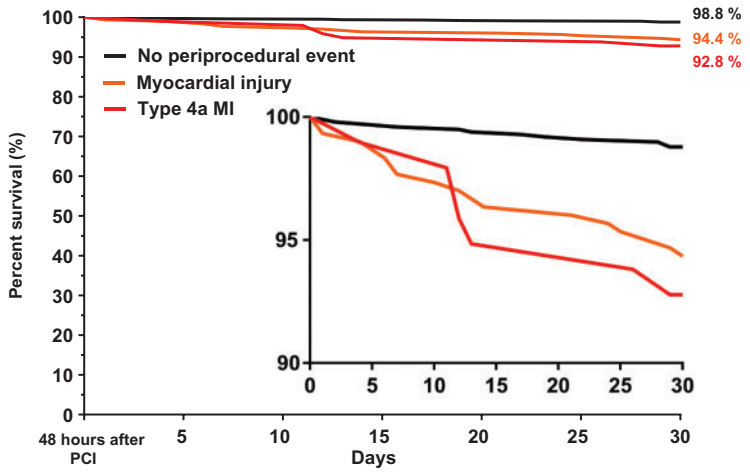


Figure 1 Increase in mortality risk (in percentage points) in PCI-treated patients with a contact-to-balloon time between 60 and 180 min resulting from a 10-min delay as shown for the four groups of study participants with and without out-of-hospital cardiac arrest and cardiogenic shock, respectively. The standard error for each bar is <0.02 (from Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, Fleischmann C, Werner GS, Olbrich HG, Ott R, Mudra H, Seidl K, Schulze PC, Weiss C, Haimerl J, Friede T, Meyer T. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. See pages 1065–1074).

affect adaptive immunity in non-ST segment elevation acute coronary syndromes by increasing CD31 cleavage on CD4$^+$ T-cells', Giovanna Liuzzo and colleagues from the Catholic University in Rome, Italy investigated the mechanisms underlying CD31 dysregulation in 30 patients.[19] The ratio between the domains was significantly lower in ACS than in stable angina or in controls. After stimulation with anti-CD3/CD28, the 1–5/6 domain ratio was significantly lower and MMP-9 was higher in ACS than in stable angina. CD31 domain 1–5 expression in activated CD4$^+$ T-cells from ACS patients increased after treatment with a specific MMP-9 inhibitor. Thus, enhanced MMP-9 release appears to play a key role in determining the cleavage and shedding of the functional CD31 domain 1–5 in CD4$^+$ T-cells of ACS patients and might represent a therapeutic target to modulate T-cell dysregulation in ACS. This conclusion is comprehensively discussed in an **Editorial** by Peter Libby from the Brigham and Women's Hospital in Boston, Massachusetts (USA).[20]

Acute coronary syndromes not only occur spontaneously but may be a consequence of elective interventions or surgery, i.e. Type 4 and 5 infarctions.[21] In a second paper entitled '**Periprocedural myocardial infarction and injury in elective coronary stenting**', Johanne Silvain and colleagues from the Université Paris 6 Sorbonne in Paris, France assessed the incidence, risk factors, and prognosis of periprocedural myocardial infarction and myocardial injury in patients undergoing elective percutaneous coronary intervention (PCI).[22] Of the 1390 undergoing elective PCI, the primary endpoint of myocardial infarction, stent thrombosis, and myocardial injury occurred in 29% of patients. Independent risk factors for the primary endpoint were left main PCI, total stent length of >30 mm, multiple stenting,



No. at risk			
No periprocedural event	989	984	977
Myocardial Injury	301	292	286
Type 4a MI	97	92	90

Figure 2 Survival without cardiovascular events at 30 days (from Zeitouni M, Silvain J, Guedeney P, Kerneis M, Yan Y, Overtchouk P, Barthelemy O, Hauguel-Moreau M, Choussat R, Helft G, Le Feuvre C, Collet J-P, Montalescot G; for the ACTION Study Group. Periprocedural myocardial infarction and injury in elective coronary stenting. See pages 1100–1109).

chronic kidney disease, and age above 75 years. At 30 days, patients with periprocedural myocardial infarction and myocardial injury had a 3.8-fold higher rate of cardiovascular events, mainly driven by ischaemic events (*Figure 2*). At 1 year, the risk of ischaemic events remained 1.7-fold higher. These findings are put into context in an **Editorial** by Kristian Thygesen from the Aarhus University Hospital in Denmark.[23]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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