Antiplatelet treatment of acute coronary syndromes: novel clinical and translational perspectives

Filippo Crea1,2

1Department of Cardiovascular Medicine, Fondazione Poli clinico Universitario A. Gemelli IRCCS, Rome, Italy; and
2Department of Cardiovascular and Pulmonary Sciences, Catholic University of the Sacred Heart, Rome, Italy

With thanks to Amelia Meier-Batschelet, Johanna Huggler, and Martin Meyer for help with compilation of this article.

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This Focus Issue on Acute Cardiovascular Care contains the Special Article entitled ‘Data standards for acute coronary syndrome and percutaneous coronary intervention: the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart)’ by Gorav Batra from Uppsala University in Sweden, and colleagues. Standardized data definitions are essential for monitoring and benchmarking the quality of care and patient outcomes in observational studies and randomized controlled trials. There are no contemporary pan-European data standards for acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI).1 The European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart) project of the European Society of Cardiology (ESC) aimed to develop such data standards for ACS and PCI. Following a systematic review of the literature on ACS and PCI data standards and evaluation of contemporary ACS and PCI registries, we undertook a modified Delphi process involving clinical and registry experts from 11 European countries, as well as representatives from relevant ESC Associations, including the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and Acute CardioVascular Care (ACVC). This resulted in final sets of 68 and 84 ‘mandatory’ variables and several catalogues of optional variables for ACS and PCI, respectively. Data definitions were provided for these variables, which have been programmed as the basis for continuous registration of individual patient data in the online EuroHeart IT platform. By means of a structured process and the interaction with major stakeholders, internationally harmonized data standards for ACS and PCI have been developed. In the context of the EuroHeart project, this will facilitate country-level quality of care improvement, international observational research, registry-based randomized trials, and post-marketing surveillance of devices and pharmacotherapies.

Cardiac biomarkers have a strong value for diagnosis and monitoring of major cardiac diseases with the examples of high-sensitivity cardiac troponin I and high-sensitivity cardiac troponin T for ACS and B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) for heart failure.2–4 In a Viewpoint article entitled ‘Interferences with cardiac biomarker assays: understanding the clinical impact’, Arnaud Nevraumont from the Cliniques universitaires Saint-Luc and Université catholique de Louvain in Brussels, Belgium, and colleagues5 note that their main weakness remains the susceptibility to analytical interferences. Indeed, each of these tests can be impaired by interferences leading to incorrect results with potentially life-threatening consequences. The optimization of assays as well as the continuous education and communication between clinical laboratories and physicians remain key factors to limit the real threat of analytical interferences.

The Global Registry of Acute Coronary Events (GRACE) score was developed to evaluate risk in patients with ACS with or without ST-segment elevation.6 In a Clinical Research article entitled ‘Ethnicity-dependent performance of the Global Registry of Acute Coronary Events risk score for prediction of non-ST-segment elevation myocardial infarction in-hospital mortality: nationwide cohort study’, Saadiq Moledina from Keele University in Stoke-on-Trent, UK, and colleagues indicate that little is known about its performance at predicting in-hospital mortality for ethnic minority patients.7 The authors identified 326 160 admissions with non-ST-segment elevation myocardial infarction (NSTEMI) in the Myocardial Infarction National Audit Project (MINAP), 2010–17, including White (n = 299 184) and ethnic minorities (excluding White minorities) (n = 26 976). They calculated the GRACE score for in-hospital mortality and assessed ethnic
group baseline characteristics by low, intermediate, and high risk. The performance of the GRACE risk score was estimated by discrimination (area under the receiver operating characteristic curve [AUC]) and calibration (calibration plots). Ethnic minorities presented younger and had increased prevalence of cardiometabolic risk factors in all GRACE risk groups. The GRACE risk score for White (AUC 0.87) and ethnic minority (AUC 0.87) patients had good discrimination. However, whilst the GRACE risk model was well calibrated in White patients (expected to observed [E : O] in-hospital death rate ratio 0.99; slope 1.00), it overestimated risk in ethnic minority patients (E : O ratio 1.29; slope: 0.94) (Figure 1).

Moledina et al. conclude that the GRACE risk score provides good discrimination overall for in-hospital mortality, but it is not well calibrated and overestimates risk for ethnic minorities with NSTEMI. The contribution is accompanied by an Editorial by François Schiele and Nicolas Meneveau from the University Hospital of Besançon in France.8 The authors of this provocative editorial highlight that we may just have to accept that a risk score for predicting mortality in ACS, however well validated, calibrated, or accurate it may be, is no longer necessary for the management of NSTEMI in the context of today’s antithrombotic and interventional strategies.

Double antiplatelet therapy plays a key role in the treatment of ACS.9 Post-ACS P2Y12 inhibitor non-adherence is common and associated with greater risk of major adverse cardiovascular events (MACEs). Non-adherence can follow different trajectories from an inability to initiate, implement, or continue therapy for the intended duration. In a Clinical Research article entitled ‘P2Y12 inhibitor adherence trajectories in patients with acute coronary syndrome undergoing percutaneous coronary intervention: prognostic implications’, Ricky D. Turgeon from the University of British Columbia in Vancouver, BC, Canada, and colleagues aimed to evaluate P2Y12 inhibitor adherence trajectories among ACS patients treated with PCI, their frequency, and association with MACE.10 The authors conducted a cohort study of adults discharged alive after PCI for ACS (2012–16) using the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry linked with administrative data. The primary outcome was P2Y12 inhibitor adherence trajectory in the year after PCI assessed using group-based trajectory modelling. They used logistic regression and Cox proportional-hazards regression to assess associations of trajectories with risk factors and MACEs. A total of 12 844 patients were included (mean age 62 years, 24% female) and five trajectories were identified: early consistent non-adherence (11.0%), rapid decline (7.7%), delayed initiation (6.0%), gradual decline (20.5%), and persistent adherence (54.8%). Compared with persistent adherence, rapid decline (hazard ratio [HR] 1.23)) and delayed initiation (HR 1.41) were associated with higher MACE in the overall cohort, whereas early consistent non-adherence was associated with higher MACE only in the subgroup receiving a drug-eluting stent (DES) (HR 2.44) (Figure 2).

Turgeon and colleagues conclude that after PCI for ACS, patients follow one of five distinct P2Y12 inhibitor adherence trajectories. Rapid decline and delayed initiation are associated with a higher risk of MACE, whereas early consistent non-adherence is only associated with higher MACE risk in patients receiving DES. This manuscript is accompanied by an Editorial by Yaling Han and Yang Li from the General Hospital of Northern Theater Command in Shenyang, China.11 The authors conclude that the data published in the article will be helpful to evaluate the trajectories of adherence to P2Y12 inhibitors among patients with ACS treated with PCI and the association with MACE, but the lack of detailed information on

![Figure 1](https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehy486)
Patients, the individualized time of P2Y12 inhibitor discontinuation, the causal relationship between bleeding and non-adherence, as well as types of P2Y12 inhibitors and DES, still call for additional large-scale registries specifically examining these points. Performing similar studies in different geographic areas may also be useful to evaluate the impact of socioeconomic factors on P2Y12 inhibitor adherence trajectories. Despite these unknowns, the present study represents a valuable contribution to the identification of five distinct trajectories of P2Y12 inhibitor adherence, risk factors for P2Y12 inhibitor non-adherence trajectories, and the association of P2Y12 inhibitor trajectory with MACE and major bleeding.

Platelet activation plays a key role in the pathogenesis of ACS. Adverse cardiovascular events have day/night patterns with peaks in the morning, potentially related to endogenous circadian clock control of platelet activation. Circadian nuclear receptor Rev-erbα is an essential and negative component of the circadian clock. In a Translational Research article entitled ‘Circadian nuclear receptor Rev-erbα is expressed by platelets and potentiates platelet activation and thrombus formation’, Jianfeng Shi from Shanghai Jiao Tong University in China, and colleagues point out that to date, the expression profile and biological function of Rev-erbα in platelets have never been reported. Here, the authors report the presence and functions of circadian nuclear receptor Rev-erbα in human and mouse platelets. Both human and mouse platelet Rev-erbα showed a circadian rhythm that positively correlated with platelet aggregation. Global Rev-erbα knockout and platelet-specific Rev-erbα knockout mice exhibited impaired haemostasis as assessed by prolonged tail-bleeding times. Rev-erbα deletion also reduced ferric chloride-induced carotid arterial occlusive thrombosis, prevented collagen/epinephrine-induced pulmonary thromboembolism, and protected against microvascular micro-thrombi obstruction and infarct expansion in an acute myocardial infarction model. In vitro thrombus formation assessed by CD41-labelled platelet fluorescence intensity was significantly reduced in Rev-erbα knockout mouse blood. Platelets from Rev-erbα knockout mice exhibited impaired agonist-induced aggregation responses, integrin αIIbβ3 activation, and α-granule release. Consistently, pharmacological inhibition of Rev-erbα by specific antagonists decreased platelet activation markers in both mouse and human platelets. Mechanistically, mass spectrometry and co-immunoprecipitation analyses revealed that Rev-erbα potentiated platelet activation via oligophrenin-1-mediated RhoA/ERM (ezrin/radixin/moesin) pathway.

The authors conclude that they provide the first evidence that circadian protein Rev-erbα is functionally expressed in platelets and potentiates platelet activation and thrombus formation. Rev-erbα may serve as a novel therapeutic target for managing thrombosis-based cardiovascular disease. This contribution is accompanied by an Editorial by Simon Tual-Chalot and Konstantinos Stellos from Newcastle University in Newcastle upon Tyne, UK.
note that the discovery of clock elements in platelets lays the foundation for a novel chrono-pharmacological-based antiplatelet therapy to inhibit or ameliorate acute thrombotic events. Future studies are needed to ascertain the relevance of the circadian platelet clock and its target genes and explain the time-dependent onset of ACS. Tual-Chalot and Stellos believe that from now on future drug development should also consider the drug target’s circadian rhythmicity and metabolism throughout the 24-hour day.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled ‘An attempt to better show some results such as the comparison of mortality and major adverse cardiovascular events between the abnormal and normal coronary flow reserve cohorts’, Houyong Zhu from the Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University in China, and colleagues comment on the recent publication ‘Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis’ by Mihir Kelshiker from Imperial College London, UK, and colleagues.16,17 Kelshiker et al. respond in a separate comment.18

Dr. Crea reports speaker fees from Amgen, Astra Zeneca, Servier, BMS, other from GlyCardial Diagnostics, outside the submitted work.

The editors hope that readers of this issue of the European Heart Journal will find it of interest.

References

16. Zhu H, Chen T, Huang J. An attempt to better show some results such as the comparison of mortality and major adverse cardiovascular events between the abnormal and normal coronary flow reserve cohorts. Eur Heart J 2022;43:2338–2339.