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Global Spotlights

Modulation and personalization of therapy after acute coronary syndromes: the road to precision

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> To every complex problem, there is an answer that is clear, simple and wrong.
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> H.L Mencken

The mortality and morbidity associated with acute coronary syndromes (ACSs) have declined markedly over the past 50 years, mainly due to the introduction of the intensive care units, early reperfusion strategies, antithrombotic drugs, and lipid-lowering therapies.[1] However, ACS still represents a major cause of mortality and morbidity worldwide.[1] Furthermore, ACS-related mortality has remained relatively stable over the past decade, underlining the need for novel strategies to further improve prognosis in these patients.[1] Precision medicine, a medical model that proposes individualized customization of healthcare, as opposed to a 'one-drug-fits-all' approach, may represent a breakthrough for the implementation of treatments in ACS.[2] Indeed, precision medicine is increasingly being adopted in several medical fields, such as oncology and hematology, but its use in cardiovascular (CV) medicine has not been as straightforward.[2] Possible reasons behind this delay may lie in the fact that CV diseases have a high prevalence in the general population, and they appear, at least superficially, quite homogeneous. Furthermore, the need for an evidence-based approach generated by large randomized controlled trials has probably also played a role in hindering the development of individualized approaches for ACS.[2]

Recent improvements in the understanding of the underlying pathophysiological mechanisms of atherosclerosis and ACS, combined with the availability of new, phenotype-specific pharmacological treatments, call for the urgent implementation of a tailored approach in ACS patients, based on practical, upfront common strategies aiming at personalized, patient-oriented treatments.[3] Three key steps may be identified in this practical algorithm for implementing precision medicine when administering medical therapy after ACS: (i) precise diagnosis; (ii) personalization of therapy; and (iii) modulation of therapy (*Figure 1*). Pathological, pathophysiological and *in vivo* studies using advanced imaging techniques, such as optical coherence tomography or magnetic resonance imaging, have helped to overcome the conventional notion that heart attacks develop from coronary artery stenosis.[3,4] Indeed, ACS associated with plaque rupture or erosion, so-called type-1 myocardial infarction (MI), accounts for up to 60%–80% of total ACS. It is now well-recognized that MI can occur without apparent epicardial coronary artery thrombus or stenosis, a condition known as MI with non-obstructed coronary arteries, which requires different diagnostic and therapeutic approaches.[4]

The identification of specific phenotypes (precise diagnosis, *Figure 1*) that may benefit from specific therapeutic approaches in ACS is the first step towards precision medicine in these patients.[4] Although substantial progress has been achieved in this regard, conflicting data about the efficacy and safety of anti-inflammatory therapies for secondary prevention after ACS, such as canakinumab, methotrexate, or colchicine, underline the need for the use of biomarkers and other tools for enhanced selection of specific ACS phenotypes more susceptible likely to yield benefit from these treatments. Furthermore, phenotype-specific therapy should be tailored to the individual patient's characteristics (personalization of therapy, *Figure 1*), taking into account procedural, clinical, and genetic characteristics that may deeply influence the response to pharmacological treatments.[2] An emblematic example of this is antiplatelet agents: indeed, response to antiplatelets varies widely across individuals according to the bleeding and ischemic risks, and according to genotype, which may affect response to specific antiplatelet agents, such as the presence of cytochrome 2C19 loss-of-function alleles in clopidogrel-treated patients.[5]

Finally, the selected therapy needs to be modulated over time and constantly adapted to dynamic changes in the patient, to ensure that the risk/benefit ratio provided by each treatment always remains favorable (modulation of therapy, *Figure 1*). Regarding antithrombotic

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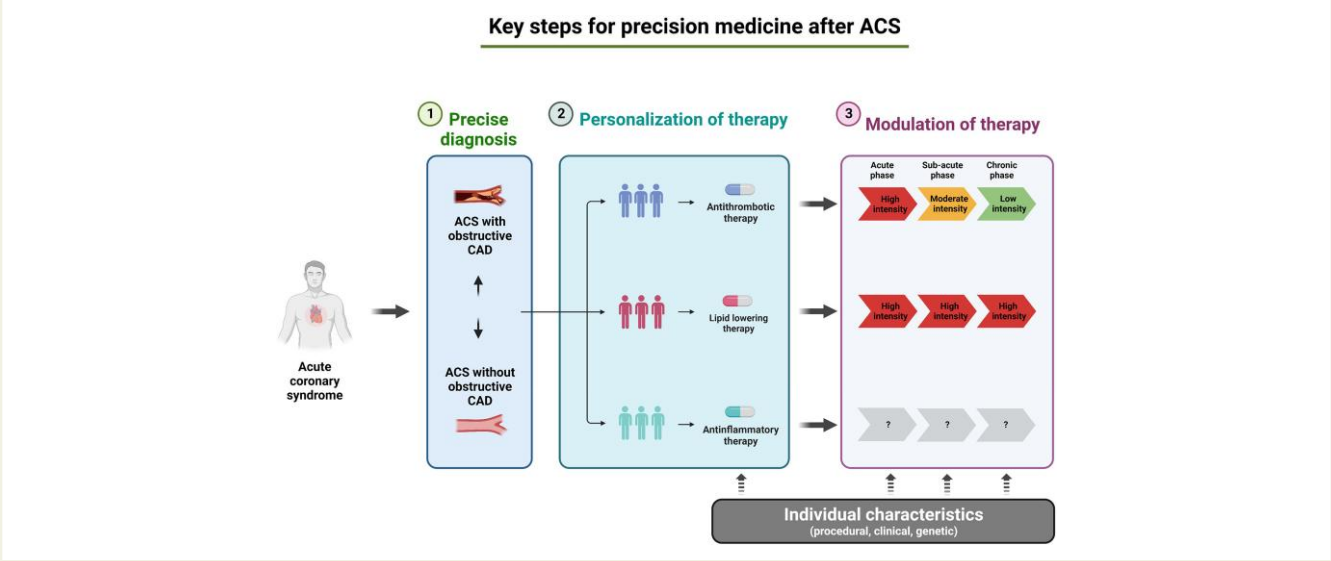

Figure 1 Key steps for precision medicine after ACS. Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease

therapy, the availability of less thrombogenic stent platforms and the awareness that thrombotic risk is highest in the first 1–3 months after ACS have raised the important question of whether the intensity and duration of antiplatelet therapy should be systematically de-escalated after an initial course of standard dual antiplatelet therapy (DAPT) with potent $P2Y_{12}$ inhibitors (i.e. prasugrel and ticagrelor).[6] Indeed, antiplatelets are inevitably associated with increased bleeding, whose prognostic impact may outweigh the benefits to be derived from a reduction in ischemic events, especially once the highest thrombotic risk phase typical of the early months has passed.[7] Promising de-escalation strategies included guided (using platelet function or genetic testing tools) or unguided de-escalation of $P2Y_{12}$ receptor intensity inhibition (i.e. switching from prasugrel or ticagrelor to clopidogrel), DAPT shortening, and aspirin-free strategies after a short course of standard DAPT.[8] While recent data on antithrombotic and lipid-lowering treatments support an early and intensive treatment strategy, the current trend for antiplatelet agents is 'de-escalation' for most patients after the acute phase. Conversely, lipid lowering treatments should remain at high intensity and should even be rapidly reinforced by the addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for very high risk patients whose low-density-lipoprotein (LDL) cholesterol remains >70 mg/dL under a fixed combination of high-intensity statins and ezetimibe. Indeed, achieving a profound decrease in LDL cholesterol during the first few days after the index event, using a combination of high-intensity statins and ezetimibe for most patients, with the very early (<30 days) addition of a PCSK9 inhibitor for those with an LDL-C level remaining above 70 mg/dL, has been associated with a reduction in ischemic events, without any trade-off in terms of safety.[9,10] This intensive initial strategy should be maintained for the long term, as the stepwise approach is associated with an excess of recurrent ischemic events, whereas an intensive strategy upfront is associated with a decrease in ischemic events, without safety concerns, even at very low LDL levels (<30 mg/dL).[9,10] The different temporal trends in the safety and efficacy of antiplatelet and lipid-lowering therapies are evidence that personalization but also modulation of therapy are two sides of the same coin on the road to precision medicine in patients with ACS. Both personalization and modulation of treatment should take account of each individual patient's risk, with a view to optimization of the risk/benefit ratio of therapies (*Figure 1*).

In conclusion, optimal control of risk factors and patient compliance with guidelines-recommended treatments are key to reducing adverse events after ACS, regardless the specific phenotype identified, and the therapies implemented.

Authors' contributions

P.S. and M.G. wrote the first draft and all four authors contributed to the development of this manuscript.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Code availability

Not applicable.

Ethical approval

Ethical Approval was not required.

Data availability

No data were generated or analyzed for this manuscript.

Conflict of interest

P.S. declares that he has received speaker fees from Astra Zeneca, Axis TV, BMS, Les laboratoires Servier, Novartis, Novonordisk, Sanofi, and Vifor, outside the present work. G.B.Z. declares that he has consulted for Amarin, Balmed, Cardionovum, Crannmedical, Endocore Lab, Eukon, Innovheart, Guidotti, Meditrial, Microport, Opsens Medical, Replycare, Teleflex, Terumo, and Translumina, outside the present work. M.B. declares that he has received speaker fees or honoraria from Amgen, Herbapol, Kogen, KRKA, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, sanofi-aventis, Teva, and Zentiva; consultant to Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Novartis, Novo-Nordisk, Polfarmex, and sanofi-aventis; grants from Amgen, Mylan/Viatris, Sanofi, and Valeant; and CMO at Nomi Biotech Corporation Ltd, outside the present work; M.G. declares that he has received consulting fees or honoraria from Terumo, outside the present work.

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