

Editorial

Long-term Cardiovascular Risk After Acute Coronary Syndrome, An Ongoing Challenge



Riesgo cardiovascular a largo plazo tras un síndrome coronario agudo, todavía un reto

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In recent decades, spectacular advances have been made in secondary prevention of recurrent cardiovascular events in patients with previous acute coronary syndrome (ACS).¹ In patients with previous ACS, mortality and cardiovascular event rate have been substantially reduced, thanks to the discovery of the beneficial effects and the widespread use of antiplatelet therapy, beta-blockers, statins, and angiotensin-converting enzyme inhibitors, as well as the more targeted use of cardiac rehabilitation, aldosterone receptors blockers, and automatic implantable defibrillators, primarily in patients with significant left ventricular systolic dysfunction.^{2,3} Despite this, the prognosis of patients surviving ACS is far from favourable. It is now well known that some ACS patients with a low early mortality, such as those without ST-elevation on ECG, have a long-term mortality similar to those with ST-elevation ACS. This is due to the increased risk of recurrent coronary events, which increases the late mortality risk.⁴

Traditionally, the focus of post-infarct risk has been on the 12 months following the acute episode.⁵ This is mainly due to the rate of recurrent events being higher in the first months,⁴ and the recommended duration of dual antiplatelet therapy following ACS is 12 months.⁶ However, a late risk persists: cardiovascular events continue to occur, although at a lower rate, as do deaths due to cardiovascular cause, although again, less frequently than during the first 12 months. One article published in *Revista Española de Cardiología*⁷ presented an analysis of recurrent cardiovascular events—myocardial infarction, stroke, or cardiovascular death—in a cohort of 4858 patients treated in the *Complejo Hospitalario Universitario de Santiago de Compostela*. The article reported 329 events during the first year and 616 events over approximately 4 years of subsequent follow-up. This meant that risk decreased by half after the first year, compared with that observed in the first 12 months. However, it was not negligible (2.9 vs 7.3 events/100 person-years) in patients with no recurrent events during the first year. These data are useful because they can be used as an

estimation of contemporary risk for Spanish patients after an appropriately-treated ACS.

Reducing residual long-term cardiovascular risk has long been a concern, and considerable resources have been invested in clinical research on the subject. In recent years, we have witnessed a new era of favourable outcomes using different pharmacological strategies to enhance “standard” secondary prevention in patients with coronary disease. Among those, 2 bear mentioning: enhanced long-term antithrombotic therapy in addition to aspirin, and enhanced lipid-lowering therapy in addition to statins. Among the options for reducing late thrombosis recurrence, 3 options have been demonstrated to be equally effective at reducing coronary events. These are prolonged dual antiplatelet therapy beyond the first 12 months following ACS,⁸ use of dual antiplatelet therapy plus aspirin and ticagrelor in patients with an old infarct (between 1 and 3 years),⁹ or the addition of new anticoagulants, such as rivaroxaban, to dual antiplatelet therapy.¹⁰ However, the benefits of these 3 options in potentiating antithrombotic therapy are associated with a significant increase in the incidence of major bleeding. This risk is particularly significant with long-term anticoagulation,^{8–10} and the current economic cost is substantial. Another strategy that has been demonstrated to reduce the rate of coronary events, is the use of statins plus other lipid-lowering drugs, such as ezetimibe¹¹ or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, such as alirocumab,¹² to reduce cholesterol levels. However, the long-term safety of some of these drugs is not yet clear, and their cost, although currently unknown, is unlikely to be low.

These advances undoubtedly offer new opportunities to improve long-term secondary prevention. However, the cost is sufficiently high, from both a clinical perspective (potential serious side-effects) and an economic perspective, to make it unlikely that these drugs will be widely-indicated for reducing residual risk in the future. For this reason, identification of the highest-risk patients is particularly pertinent, that is, those who are most likely to benefit from very intense preventative therapy. Abu-Assi et al identified that the patients who generally experience more cardiovascular events are older patients, those with diabetes mellitus, previous ischaemic heart disease, history of heart failure, non-ST-elevation myocardial infarction, and significant multi-vessel coronary disease,⁷ but this is not new information. However,

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the factors indicating increased overall residual risk after the first year are somewhat different: notably smoking, vascular disease burden (peripheral arterial disease, previous stroke/transient ischaemic attack, or atrial fibrillation), renal impairment, and absence of initial coronary revascularisation. Investigation into simple instruments to allow identification of patients with high long-term risk of recurrent events is a clinical priority.¹³

Paradoxically, despite the sophisticated advances in identification and reduction of residual cardiovascular risk in patients with previous ACS, a significant number of patients remain in situations conducive to ongoing high vascular risk. These situations are due to basic reasons, such as doctors not making lifestyle recommendations, or patients not adhering to lifestyle changes—quitting smoking, healthy diet, and regular physical activity—or to effective pharmacological treatments for secondary prevention. This leads to a relatively high incidence of cardiovascular risk factors and poor control of these risk factors in this population.^{14,15} Therefore, research directed at optimising basic secondary prevention measures in at-risk patients remains essential. One example is the study of the role of a polypill to simplify secondary prevention treatment, in order to improve compliance,¹⁶ which could translate to long-term clinical benefits in high-risk patients. This hypothesis is currently being investigated in the international multicentre clinical trial Secondary prEvention of Cardiovascular disease in the Elderly (SECURE; ClinicalTrials.gov identifier: NCT02596126), coordinated by the *Centro Nacional de Investigaciones Cardiovasculares*¹⁷ (CNIC, National Center for Cardiovascular Research).

In conclusion, research should continue on the methods to improve long-term secondary prevention, because there is continued clinical need. However, should this research continue down the route of new treatments, ever stronger and more expensive, or is it possible that this clinical research model is approaching the threshold of acceptable complications and economic cost for the additional benefits it offers patients? The answer is not clear, but what is evident is that research will continue and will translate in one way or another into changes in patient care. In the coming years, the accurate identification of patients with high risk of recurrent events will continue to gain importance, so that efforts and spending can be concentrated on high-risk patients, thus improving risk-benefit and cost-effectiveness ratios in secondary prevention. Meanwhile, more “modest” research into methods for optimising basic secondary prevention with the safest, most effective, and cheapest known options appears to be more necessary than ever.

CONFLICTS OF INTEREST

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