Planning secondary prevention: Room for improvement

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Word count (max 3000 including references and excluding abstract): text (2445) + references (785) = total (3230).

Abstract

The prognosis of patients after acute coronary syndromes is still suboptimal, mainly due to the risk of recurrence of adverse coronary events, which are greatest during the first year but persist over one's lifetime. Meaningful progresses in preventing recurrence of adverse events have been achieved. However there remains much room for improvement by embracing innovative therapies and investing in multidisciplinary approaches.

Pharmacological interventions focused on optimising antithrombotic and lipid-lowering therapies are both pillars of secondary prevention with recent ground-breaking advances. Moreover, new approaches in diabetic patients with cardiovascular disease and new targets on anti-inflammatory treatment may significantly improve prevention strategy outcomes in the future. However, pharmacological treatments are expensive and can have significant side effects. Developing better tools to identify high-risk patients and promote more personalised strategies for each patient should be an absolute priority. Furthermore, adherence to medication is still low and represents a real challenge; several strategies to improve low adherence to treatment are currently under discussion.

Non-pharmacological interventions are also essential. Improving communication with patients and advance surveillance for those secondary risk factors that may negatively impact prognosis is crucial. Encouraging multidisciplinary teams that work effectively to optimize all aspects of secondary prevention, including a cardiac rehabilitation programme is the optimal approach.

Current secondary prevention strategies and suggestions for improvement areas are discussed in this manuscript. But the question remains: Will research in

secondary prevention continue focusing on stronger and more expensive drugs or is it time that we embrace a more patient centred clinical and research model?

Abstract word count: 251

Keywords: cardiovascular disease, acute coronary syndrome, secondary prevention, antithrombotic therapy, lipid-lowering, cardiac rehabilitation.

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During the last decades there has been significant progress in the prevention of recurrent cardiovascular events after acute coronary syndromes (ACS)(1). Although current secondary prevention therapies have achieved a substantial success in reducing the risk of cardiovascular events and mortality after ACS(2), the prognosis of patients who survive ACS is still far from benign, mainly due to the risk of major adverse coronary events, which increase late mortality(3).

The rate of recurrent events is greatest during the first 6-12 months after the acute event(3), during which it is recommended to have a more aggressive pharmacological approach (4, 5). However, the risk of recurrence of ACS and cardiovascular mortality persist long after the first year. Recent studies have shown that after this time the risk is reduced by more than half but still remains substantial(6).

Reducing long-term residual cardiovascular risk and improving quality of life is a primary goal in the clinical practice and research. This manuscript aim to review prevention strategies that may help to improve current results, including pharmacological and non-pharmacological interventions.

1. Pharmacological strategies

1.1 Strengthening secondary prevention

Antithrombotic therapy. Standard antithrombotic treatment during the first twelve months following an ACS is dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor)(5). Recent studies suggest that a more individualized treatment should be proposed for each patient. On the one hand, in patients with high bleeding risk the $P2Y_{12}$ inhibitor administration could be shortened to 3–6 months(5). On the

other hand, new evidence has shown different and more effective options to reduce late thrombosis recurrence by potentiating the antithrombotic therapy.

The DAPT study compared the benefits of a prolonged dual antiplatelet therapy, with aspirin and a thienopyridine drug (clopidogrel or prasugrel), beyond the first 12 months (up to 30 months) after a coronary stent procedure in which a drug-eluting stent was placed. After randomization, continuing with two antiplatelet drugs compared to aspirin alone, was more effective in reducing the risks of stent thrombosis (hazard ratio (HR), 0.29) and major adverse cardiovascular and cerebrovascular events (HR, 0.71) but was associated with an increased risk of moderate or severe bleeding (2.5% vs. 1.6%)(7).

A positive result was also found in the PEGASUS-TIMI 54 study. Differences between three groups (aspirin plus ticagrelor 90 mg twice/day, aspirin plus ticagrelor 60 mg twice/day and aspirin plus placebo) were analysed. All patients had experienced a myocardial infarction 1 to 3 years early and were followed for a median of 33 months. The reduction in the primary end point (cardiovascular death, myocardial infarction or stroke) showed a HR of 0.85 for ticagrelor's 90mg group vs. placebo and a HR of 0.84 for ticagrelor's 60mg group vs. placebo. Rates of TIMI major bleeding were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%)(8).

One other study showed the benefit of the addition of rivaroxaban to dual antiplatelet therapy. This study randomized patients with recent ACS to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. It was noticed that against placebo (10,7% reduction), rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction or stroke in 9.1% for rivaroxaban 2.5

mg and 8.8% for rivaroxaban 5 mg, but increased the risk of major bleeding and intracranial haemorrhage (without a significant increase in fatal bleeding)(9).

These studies have proven that a more aggressive antithrombotic treatment is effective at reducing coronary events with the additional cost of a significant increase in the incidence of major bleeding (especially in patients with long term anticoagulation). The answer to the question of whether this reduction in thrombotic risk is worth the cost of increasing bleeding risk is still to be solved. It is clear that a better classification of patients regarding their thrombotic risk for recurrence and their bleeding risk is needed, in order to provide each patient the most appropriate treatment according to their requirements.

Lipid control. Lipid-lowering drugs are considered as the second pillar of secondary prevention. It is well established that patients with proven coronary artery disease (CAD) are considered at very high cardiovascular risk, and therefore the LDL-Cholesterol (LDL-C) goal in these patients must be under 70 mg/dl (or a reduction of at least 50% if the baseline is between 70 – 135 mg/dl). Intensive lipid-lowering strategies, focused in reducing LDL-C, decrease the recurrence of cardiovascular events; hence, this must be an absolute priority within the proposed targets. Statin therapy is fully established and has demonstrated entirely its benefits(5). However, in a non-negligible proportion of patients treatment with statins alone is not possible or is insufficient to achieve adequate cholesterol control. In these cases using ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (in monotherapy or in combination), is recommended.

The ODYSSEY investigators analysed the reduction in LDL-C levels that alirocumab provided when added to statin therapy at the maximum tolerated

dose. Against placebo, alirocumab showed a 62% reduction in LDL-C baseline levels, an effect that remained consistent over 78 weeks. More importantly, in a post hoc analysis alirocumab reduced the rate of major adverse cardiovascular events (HR, 0.52)(10). With a similar study design, the OSLER investigators concluded that evolocumab is effective in reducing LDL-C levels (by 61% from the baseline), and in exploratory analysis it also reduced the incidence of cardiovascular events (HR, 0.47)(11).

In the light of these results PCSK9 inhibitors, although expensive, look promising. However, stronger evidence is needed to clarify their long-term safety and cost-effectiveness, especially their effectiveness in reducing cardiovascular risk. For the first quarter of 2017, it is expected that the FOURIER trial determine whether the addition of evolocumab to statin therapy reduces cardiovascular morbidity and mortality(12).

Special issues in diabetic patients with CAD. Diabetic patients with cardiovascular disease will be able to benefit from considerable changes in the next years. Currently, after an ACS clinical practice guidelines advice a multifactorial approach in patients with diabetes mellitus (DM), but no specific recommendations are available for glucose-lowering drugs(5). However, this can change substantially after the conclusions elucidated in the EMPA-REG and LEADER trials.

The EMPA-REG studied the cardiovascular morbidity and mortality in patients with type 2 diabetes and established cardiovascular disease who were treated with empaglifozin, a sodium-glucose co-transporter-2 (SGLT-2) inhibitor. Against placebo, results in the empaglifozin group showed a significant reduction in

number of deaths from cardiovascular causes (38% of relative risk reduction) and hospitalization for heart failure (35% of relative risk reduction)(13). Consequently, experts suggest that in diabetic patients with cardiovascular disease SGLT-2 inhibitors should be considered early in the course of DM(5). In any case there is a demand for more studies that establish whether the results obtained with empaglifozin extrapolate or not to other SGLT-2 inhibitors and that help to understand their mechanisms of benefit.

The LEADER trial has a similar approach with liraglutide, a glucagon-like peptide 1 (GLP-1) agonists. This study compared liraglutide versus placebo in patients with type 2 diabetes and high cardiovascular risk and revealed lower rates of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke (HR of 0.87)(14). Nevertheless, more research on the benefits and cost-effectiveness of GLP-1 agonists are needed.

Prevention of inflammation or anti-inflammatory treatment. There is a strong relationship between inflammatory markers and the risk of future cardiovascular events. Inflammation occurs in the vasculature as a response to injury caused by different cardiovascular risk factors and is a possible mechanism of atherosclerosis. It is suspected that a state of systemic inflammation (secondary to acute infections or unbalanced inflammatory diseases) plays a role in the rupture and thrombosis of vulnerable plaque and can precede an ACS(15). Consequently, several strategies to stop an inflammatory condition that can trigger or perpetuate cardiovascular disease are being tested and may be considered as new therapies for secondary prevention.

Based on the observation of the association between acute respiratory infections (for example during the peak influenza virus circulation) and ACS, some studies propose annual influenza vaccination in patients with established CVD(5). More evidence is needed to make a firm recommendation on this issue.

Future utilities in preventive cardiology of monoclonal antibodies, aside from PCSK9 inhibitors, may appear in coming years. Canakinumab is a specific monoclonal antibody that inhibits interleukin-1β (IL-1β) and can potentially hinder inflammatory pathways. It is approved for treatment of several rheumatic diseases and there is an on-going trial assessing whether inhibition of IL-1β with canakinumab could reduce recurrence of cardiovascular events in patients with ACS and persisting inflammation(16). However, this area of knowledge remains unexplored and first results are still pending.

1.2 Advancing in treatment efficiency

Just as important as advancing the research of better drugs focused on reducing residual risk after an ACS, is to enable patients to benefit from these treatments. It is known that adherence to medication in individuals with CVD is low (17). This is one of the major problems in secondary prevention (5). Improving adherence to treatment is a persistent challenge and more efforts are needed to identify the reasons of poor adherence to medication. Generally these are asserted to be multifactorial. Some examples are cost-related problems, non-detected or non-treated depression and patient's poor understanding of their disease and the importance of treatment(18). Simplifying the treatment regime to the lowest acceptable level is strongly recommended.

There are also pharmacological measures aimed at improving adherence to treatment. The best example is the study of the role of a polypill to simplify secondary prevention treatment in order to improve compliance, which could convert 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).

2. Improving patient selection

Advances in pharmacological treatment are promising, yet all these treatments are expensive and can have significant side effects. We need to emphasis the necessity to develop better tools that allow us to identify in an accurate way the highest-risk patients, which are most likely to benefit from a very intensive preventive approach, improving risk-benefits and cost-effectiveness ratios. It is known that factors indicating increased overall residual risk after the first year differ slightly from risk factors of recurrence during the first twelve months. There are in greater hazard of long-term recurrence those patients that after an ACS keep smoking, have major vascular disease burden, renal impairment or those who do not receive initial coronary revascularization(19).

Moreover there is a need to clarify the power of different genetic markers in differentiating high-risk patients. However, the generalized used of DNA-based test for cardiovascular risk assessment is currently not recommended due to the lack of agreement regarding which genetic markers should be included or calculated(5). Therefore future studies should assess clinical benefit and cost-effectiveness of the inclusion of genetic data in the risk assessments or scores.

3. Non-pharmacological strategies

Despite sophisticated advances in new drugs aimed at reducing residual cardiovascular risk in patients with previous ACS, a significant number of patients live in highly toxic environments that benefit the presence of high vascular risk. These situations, that may negatively influence the prognosis of cardiovascular disease, are mainly due to basic reasons usually underestimated and omitted in daily clinical practice. For example, patients with lack of social support, low socio-economic status, excessive stress at work, undetected depression or anxiety are in greater risk to continue smoking, making unhealthy food choices, less physical activity and having low adherence to medication. These place them in greater risk of recurrence of vascular events (20, 21). Consequently, more efforts are needed to reinforce non-pharmacological strategies.

Investing more time and developing better skills to communicate patients their diagnosis and prognosis, may improve their understanding of the chronic nature of their condition and the vital importance of lifestyle modification to reduce future adverse events and improve quality of life. Basically, it is essential to encourage the creation of multidisciplinary teams that work together to optimize all aspects of secondary prevention.

It is strongly recommended to establish cognitive-behavioural strategies to facilitate lifestyle modifications in patients with difficulties (5). The longer and more general the intervention program is the better results are obtained(22). It is important to start with an appropriate prevention strategy before hospital discharge, as prevention treatment tends to decrease after hospitalization(17, 23).

The appropriate framework for the organization and coordination of the multidisciplinary team should be a cardiac rehabilitation (CR) programme, which are efficacious in reducing mortality, morbidity and improving quality of life. However there is still a lack of definitive evidence to determine which is the best CR schedule. Referral and participation in CR must be advocated by the acute care team and begin during hospitalization as greater benefits have been achieved in the adherence and prognosis when this occurs.

Planning CR should enable sufficient time to give advice and accomplish health education for patients, and the opportunity should be taken to evaluate social support screen patients for psychosocial risk factors that may worsen their prognosis. New alternatives in CR models that achieve better cost-effective profiles and that ensure the participation of all patients during the programme and their continuity once it is finished should be explored.

In addition to all interventions focused in the individual level, we cannot forget of all the possibilities for improvement that exist at the population level.

Small changes in the risk of disease across a whole population lead to greater reductions in disease burden than larger changes on an individual level(5). For this reason it is crucial that health professionals, through individual actions and professional associations, advocate to promote a healthy lifestyle throughout the population.

Conclusions

Secondary prevention of cardiovascular disease should be implemented and carried out everywhere and at any time: from the pharmacological treatment in each individual to the policies at national level. A range of diverse approaches has

proven to be a clinical necessity. Therefore health care professionals have the responsibility to continue with research on developing future preventions strategies that lead to the definition of better tactics in long-term prevention. It is not clear the direction this investigation will take in the future. Will it continue searching stronger and more expensive drugs or is it possible that this clinical research model is approaching the threshold of acceptable complications and economic cost for the additional benefits it provides to patients? Probably a key for success will be to learn how to identify which patients have very high risk of recurrent events after an ACS so that greater efforts can concentrate on them. Notwithstanding the potential for innovation in personalised medicine, there is still a huge room for improvement in secondary prevention at a personal and societal level and efforts should concentrate on the several strategies here discussed.

Acknowledgemnts

CNIC is supported by the Spanish Ministry of Economy and Competitiveness (MINECO) and the Pro-CNIC Foundation, and is a Severo Ochoa Center of Excellence (MINECO award SEV-2015-0505).

Disclosures

- ACB has no conflicts.
- DF has no conflicts.
- AP has no conflicts.
- GM has no conflicts.

- RMA has received consulting fees from Astra-Zeneca.
- HB receives research funding from the Instituto de Salud Carlos III (PIE16/00021), Astra-Zeneca, BMS, Janssen and Novartis; is Scientific Coordinator of the SECURE trial, and has received consulting fees from Abbott, Astra-Zeneca, Bayer, BMS-Pfizer, Novartis; and speaking fees or support for attending scientific meetings from Astra-Zeneca, Bayer, BMS-Pfizer, Ferrer, Novartis, Servier and MEDSCAPE-the heart.og.

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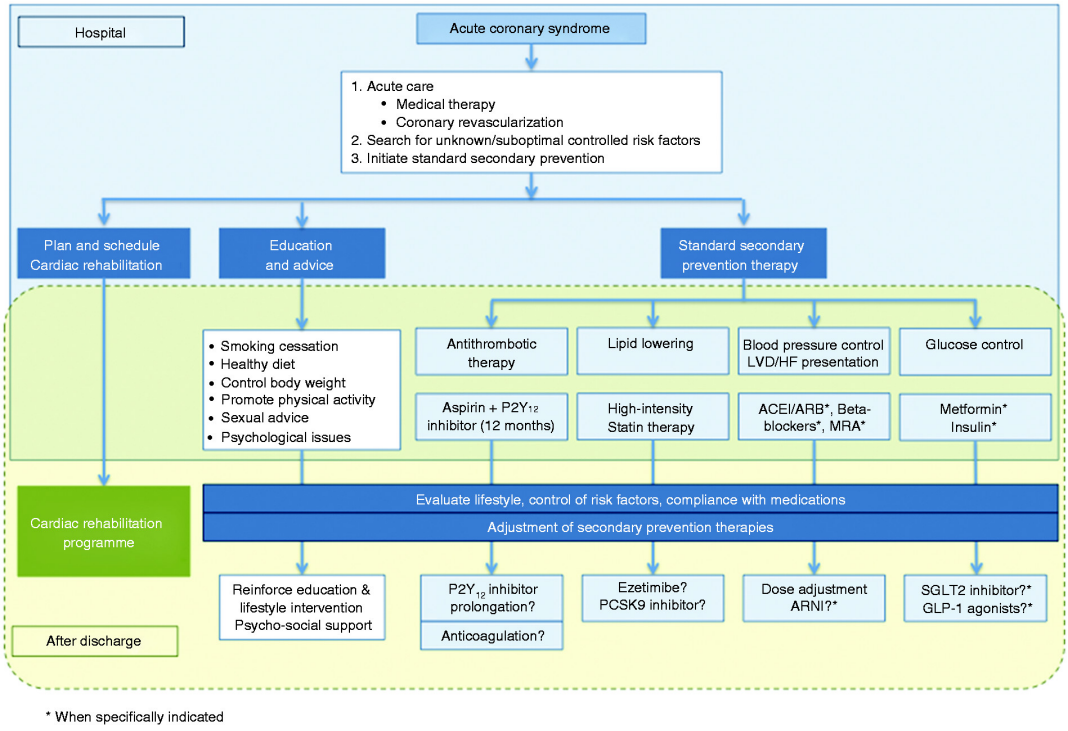

Figure 1. Summary of secondary prevention interventions after acute coronary syndromes. LVD: left ventricle dysfunction; HF: heart failure; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ARNI: angiotensin receptor neprilysin inhibitor.

Trial	Design	Main findings
DAPT study[22]	After placing DES randomized to: – Aspirin + clopidogrel or prasugrel – Aspirin + placebo Follow-up: 12–30 months	Continuation with thienopyridine treatment beyond 12 months reduced: – Risk of stent thrombosis (HR 0.29, 95% CI 0.59–0.85) – Major adverse CV and cerebrovascular events (HR 0.71, 95% CI 0.17–0.48) – Increased risk of moderate or severe bleeding (2.5% vs. 1.6%, $p = 0.001$)
PEGASUS-TIMI 54[23]	Double-blind 1:1:1 After a MI 1–3 years previously, randomised to aspirin plus: – Ticagrelor 90 mg b.i.d. – Ticagrelor 60 mg b.i.d. – Placebo Median follow-up: 33 months	Active treatment: – Reduced CV death, MI or stroke: ○ Ticagrelor 90 mg (HR 0.85, 95% CI 0.75–0.96) ○ Ticagrelor 60 mg (HR 0.84, 95% CI 0.74–0.95) – Increased risk of TIMI major bleeding ○ Ticagrelor 90 mg (2.60%, $p < 0.001$) ○ Ticagrelor 60 mg (2.30%, $p < 0.001$) ○ Placebo (1.06%)
ATLAS ACS 2-TIMI 51[24]	Double-blind After an ACS, randomised to: – Rivaroxaban 2.5 mg b.i.d. – Rivaroxaban 5 mg b.i.d. – Placebo Follow-up: mean of 13 months, up to 31 months	Active treatment (2.5 mg and 5 mg): – Reduced death from CV, MI or stroke (HR 0.84, 95% CI 0.74–0.96) – Increased risk of major bleeding and intracranial haemorrhage (2.1% vs. 0.6%, $p < 0.001$), without a significant increase in fatal bleeding

Table 1. Studies suggesting a benefit of more aggressive antithrombotic treatments for secondary prevention after acute coronary syndromes.

Trial	Design	Main findings
IMPROVE-IT[25]	Double-blind After an ACS, randomized to: – Simvastatin 40 mg + ezetimibe 10 mg – Simvastatin 40 mg + placebo Median follow-up: 6 years	Active treatment: – Further reduced LDL-C level by 16.7 mg/dl ($p < 0.001$) – Reduced CV death, nonfatal MI, unstable angina, coronary revascularisation or nonfatal stroke (HR 0.93; 95% CI 0.89–0.99)
FOURIER[26]	Double-blind With atherosclerotic CV disease, LDL-C above 70 mg/dL with statin therapy, randomised to: – Evolocumab 140 mg every 2 weeks or 420 mg monthly – Placebo Median follow-up: 2.2 years	Active treatment: – Further reduced LDL-C level by 59% ($p < 0.001$) – Reduced CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation (HR 0.85, 95% CI 0.79–0.92) – No difference in adverse effects (including new-onset diabetes or neurocognitive events)

Table 2. Studies suggesting a benefit of more aggressive lipid-lowering therapy beyond statins after acute coronary syndromes.

Routine clinical assessment

- Clinical history: cardiovascular symptoms, adherence to medication
- Screening for unknown/suboptimal cardiovascular risk factor and comorbidities:
  - Blood pressure monitoring
  - Lipid control and medication optimization
  - Diabetes mellitus screening and medication adjustment
- Electrocardiogram and cardiac imaging

Exercise training and physical activity counselling and supervision

- Guided by exercise testing and occurring in hospital during initial phases

Promote lifestyle changes and cognitive–behavioural strategies that help to incorporate changes into daily routine

- Advice and health education on the chronic nature of coronary artery disease
- Diet and nutritional counselling
- Weight control management
- Smoking cessation

Psychosocial management

- Social support when experiencing social isolation or of low socioeconomic status
- Stress and anxiety
- Depression
- Sexual dysfunction

Box 1. Cardiac rehabilitation components and targets.