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Editorial

Secondary Prevention: The Ongoing Challenge

Prevención secundaria: el reto permanente

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Experts recommend the use of cardiac rehabilitation among patients with coronary disease.[1] As hospital stays for acute coronary syndromes decrease, cardiac rehabilitation is assuming an increasingly important role in secondary prevention. There is a large amount of data indicating that cardiac rehabilitation improves several important intermediate end points, including exertional ischemic symptoms, depression and hostility scores, sense of wellness, understanding of the disease, and compliance with risk factor modification. With regard to survival, earlier randomized trials assessing the efficacy of cardiac rehabilitation after myocardial infarction have been limited by small sample size. When the results of individual trials were pooled, cardiac rehabilitation was associated with survival gains of 20%–30%.[2,3] However, as these trials were conducted in the 1980s, it is uncertain that these data can be generalized to contemporary practice.

The study by Brotons et al., published in this issue of *Revista Española de Cardiologia*[4] contributes to address this gap in knowledge by evaluating the efficacy of secondary prevention between 2004 and 2005. The authors report on 1224 patients with cardiovascular disease (coronary disease, cerebrovascular disease or peripheral arterial disease) from 42 practices in Spain, similarly distributed between control and intervention, the latter consisting of education and structured intervention based on the patient's risk factor profile. There was no benefit of the intervention on the primary endpoint (all-cause mortality and hospital readmissions) and marginal effects of questionable clinical significance on intermediate endpoints (risk factor profile), except for depression, which exhibited a notable difference between the two arms favoring intervention. These results underscore the importance of publishing "negative trials", despite the prevalent study publication bias whereby statistically significant outcomes are more likely to be reported than non-significant outcomes.[5] Indeed, the study generates several important questions.

WHY ARE THE RESULTS ESSENTIALLY NEGATIVE WHEN PRIOR STUDIES INDICATE AN IMPORTANT EFFECT OF SECONDARY PREVENTION?

To answer this question, several key aspects of the methodology must be discussed. The study applied a cluster randomized design[6] to 42 general practices. With this design, groups or clusters rather than individual patients are randomized. This approach is particularly suited to the evaluation of behavioral interventions or processes of care with the goal of maximizing "real life" clinical practice relevance. This renewed interest in cluster randomized trials is consistent with the burgeoning interest in comparative effectiveness research.[7] Comparative effectiveness research is defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care".[8] The purpose of comparative effectiveness research is to enable stake holders to improve health care for individuals and populations.[7] A key element of this definition is the focus on "real life" data that can be directly applied to clinical practice. This objective of "real life relevance" requires a departure from conventional approaches to the design of studies.[9]

The novel research paradigms required to conduct comparative effectiveness research entail unique challenges as illustrated by the present study by Brotons et al.[4] Cluster randomized trials must account for clustering in the sample size calculations[6] as was done in the Brotons et al. study.[4] In addition, to ensure internal validity, the allocation status must be masked to those who identifying or recruit individuals into the trial.[6] This may be difficult to achieve, as, in cluster randomized trials, there are two levels of participation: the cluster and the individual. It is difficult to conceal the allocation of the cluster to persons who recruit the individuals within that cluster. It is also not possible to blind the persons delivering the intervention to the nature of the intervention and likewise, it is also difficult to blind patients to the fact that they are receiving intervention. This lack of blinding can compromise the internal validity of the trial. All such concerns impact the interpretation of the Brotons data. Rather than a criticism of the present study, these concerns must be envisioned as illustrative of the type of challenge that all interventions of that nature can encounter.

Another key aspect of that study is that the intervention incorporates some elements that can be now considered as part of clinical practice, except perhaps for the evaluation and treatment of depression. Thus, the mere fact of randomizing clusters can serve as a "wake up call" for all practices, regardless of allocation, leading to modification of clinical practice habits in the control groups thereby contaminating the control group by the intervention. To this end, the improvement in hypolipemic agents and statins was of the same magnitude

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before and after the intervention among the intervention and the control groups, illustrating this point. This in turn can help explain why the only component that was positively impacted by the intervention was the management of depression, which remains currently the subject of some controversy within the cardiology community and is thus not universally adopted.[10]

WHAT ARE THE CLINICAL AND RESEARCH IMPLICATIONS OF THIS STUDY?

The authors concluded that a comprehensive program of secondary prevention of cardiovascular diseases in general practice did not reduce mortality or hospital readmissions, but improved healthy lifestyle and reduced depression. As these intermediate endpoints are known themselves to improve outcomes, one can hypothesize that these beneficial effects will lead to favorable downstream outcomes. This hypothesis is supported by the paper by Witt et al.,[11] which indicated substantial survival benefits of participation in cardiac rehabilitation in a geographically defined, non-selected cohort of patients with myocardial infarction. It is noteworthy that the survival benefit associated with participation in rehabilitation was greater in more recent years, perhaps pointing to the gradually broadened scope of cardiac rehabilitation and its increasing importance of ambulatory management of cardiovascular disease.[1]

The study pertains to individuals somewhat younger than that in recent cohorts of persons with cardiovascular disease.[12,13] Importantly, it included only men, while approximately half of the patients with coronary disease are women. Thus, the applicability of the results to all patients with cardiovascular disease is uncertain. Another consideration is that optimizing healthy habits and reducing depression has benefits that extend beyond the cardiovascular subsystem and is likely to also favorably impact other outcomes such as quality of life and/or health care utilization. Finally, all patients in the study by Brotons et al.[4] had cardiovascular disease but with diverse clinical manifestations (including coronary disease, cerebrovascular disease or peripheral arterial disease). The intervention was similar, regardless of the type of manifestation of cardiovascular disease. While this streamlined approach is understandable in the context of a research study, the need to customize approaches to rehabilitation and exercise was recently emphasized in several publications;[14] including recommendations of the European Association of Cardiovascular Prevention and Rehabilitation.[15]

What can we conclude from this study in light of previous publications on cardiac rehabilitation? Cardiac rehabilitation improves functional status and promotes the adoption of a healthy lifestyle. Efforts to increase awareness of the benefits of cardiac rehabilitation programs, as well as innovative strategies to improve its implementation are warranted. Further studies of program design are needed to optimize its use and impact among all patients.

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CONFLICTS OF INTEREST

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