

Exercise-based cardiac rehabilitation: different angles to grasp its beauty

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Received 25 May 2021; editorial decision 26 May 2021; accepted 28 May 2021; online publish-ahead-of-print 21 June 2021

Given the ever-improving quality of invasive and pharmacological therapy for coronary artery disease, one might wonder if the role of an older treatment modality, cardiac rehabilitation (CR), persists. To combat any doubts, many have recently sought out to answer this question. All have chosen a different methodology and all have arrived at different, albeit mainly positive, conclusions.

A recent Cochrane review chose to include only randomized controlled trials (RCTs) into their analyses.¹ Specifically, RCTs were chosen in which exercise-based interventions were compared to no exercise. As a main result, the study found that exercise-based CR reduced the risk of cardiovascular mortality but not total mortality. The CROS study² and its successor the CROS-II study³ looked at CR from a different perspective. With the aim in mind to reflect current clinical reality as closely as possible, strict criteria were set to only include recent studies about multi-component CR. Also, and interestingly, retrospective and prospective controlled cohort studies are included in the analysis. The authors chose to do so to expand the study population, but also to better reflect real-life clinical reality, as RCTs tend to select for highly motivated people eager to participate in clinical trials. Both studies show effectiveness of CR in selected populations (acute coronary syndrome and coronary artery bypass grafting) by reducing total mortality. Twice however it is underscored that large heterogeneity persists in CR delivery throughout Europe and that international standards for CR delivery, but also for scientific evaluation are highly needed.

The study from Ekblom *et al.*⁴ shines yet another light on the problem. This study nicely demonstrates how a thoroughly kept large registry can offer very interesting and applicable results for clinical practice. In a large study population of over 20 000 patients, it was shown that exercise-based CR was associated with reduced total mortality, and for the first time this was shown independently in both men and women. The methodology using the nationwide cohort from the SWEDEHEART registry offers real-world data that is highly

applicable to clinical practice. As the authors mention, limitations of the registry-based study are that cause–effect relationship cannot be confirmed, detailed data about dose and duration of each modality in CR is not known and cause-specific mortality data is lacking.

All these studies shine a different light on CR and, while using different methodologies, none of these methods should be considered superior to one another. In their perspective paper, Murad *et al.*⁵ argue that the classical depiction of the evidence pyramid, in which RCTs, systematic reviews, and meta-analyses are at the top, falls short as a classification of levels of evidence and as a surrogate for risk of bias. Depending on the research question other, non-randomized study designs can be considered equal or superior to RCTs as long as the methodologies are designed to maximally reduce the risk of bias. The variety in methods and results of the aforementioned studies only illustrates the difficulty in studying CR.

But why is it so hard to study CR? First, while guidelines exist, specific implementation of CR strongly differs throughout Europe. The heterogeneity in CR delivery was indeed nicely demonstrated and specifically addressed by the CROS study authors.^{2,3} Clear standards, structured CR programmes, referral processes, and measures of performance are often lacking, which highlights the need for minimum standards and quality indicators in preventive programmes.⁶

Second, CR is considered standard of care and it has thus been argued that setting up RCTs in which a rehabilitation programme is withheld from a control group is unethical.⁷ In the most recent RCT this was accounted for by randomizing matched pairs of patients from different hospitals that either were known with a very high or very low referral rate for CR.⁸ Also, patients and healthcare providers cannot be blind to the arm allocation in CR RCTs.⁹ In countries where CR uptake is high, true randomization and thus conduction of RCTs will in the future be difficult.

Third, and most importantly, CR is not one standardized molecule that is administered to patients in equal doses. CR is a multifactorial

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intervention in a multiple risk factor population. Personalization of therapy is inherent to the intervention and is strongly recommended.⁶ While some have tried to study the comparative effectiveness of the CR core components,^{9,10} large heterogeneity within the target population as well as in treatment modalities makes it hard to undoubtedly proof the benefit of each individual component. That is why we must admit that while convincing evidence shows the benefit of CR, we still don't know what the ideal number of CR sessions is for each patient group, we don't know how long the 'learning effect' lasts after cessation of CR, we don't really know why there are gender differences in outcomes (could different dosage play a role?) and we don't know how to ideally tailor a programme to individual patients . . . just yet.

After many RCTs, the Cochrane review and meta-analysis, the two CROS trials and many other studies, this study by Ekblom et al. using the SWEDEHEART registry again adds to the growing evidence base and is yet another step in the direction of real-world evidence of the benefit of CR. But up to now, all fail to dig into the details of each different modality.

A new modality for CR delivery that is currently being studied is telerehabilitation.^{11,12} This digital-age equivalent to centre-based CR is proposed, among other things, as a solution for low rehabilitation uptake, as a method to provide low-cost long-term CR and as a means in the pursuit of personalizing CR and cardiovascular care in general.

Moreover, depending on the form of delivery, telerehabilitation might offer the additional advantage of enabling detailed analysis of treatment modalities. Recent¹³ and ongoing studies often use smartphone applications or other online formats to enable CR. Large datasets will thus become available on patient characteristics, patient comorbidities, and on what type of patients do exactly how much of each of the CR modalities. New data analysis techniques such as big data analysis and artificial intelligence might be an ideal partner to such large datasets that might offer us new, detailed insights into the respective benefits of each modality of CR. Once we can better define what is beneficial for each patient, we are once again a step further in personalizing care for our patients.

For now, we are not there yet. Every new study and especially every new research methodology takes us a step forward in this fascinating question. It will take many angles to grasp the real beauty of

CR, but these recent studies boldly demonstrate that we are well on our way.

Conflict of interest: none declared.

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