International Journal of Cardiology 296 (2019) 30–31

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Event recurrence after myocardial infarction: Prediction is very difficult, especially about the future

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ARTICLE INFO

Article history:
Received 29 July 2019
Received in revised form
7 August 2019
Accepted 14 August 2019
Available online 17 August 2019

An almost epidemic number of people are actually suffering from ischemic heart disease (IHD), making this condition the leading cause of death worldwide [1]. According to the projection of the World Health Organization, by 2030, over 10 million deaths (13.4% of global deaths) would be attributable to IHD.

Over years, continuous implementation of timely and effective treatments substantially improved the survival rate of patients following myocardial infarction (MI), leading to a growing number of patients with established IHD, vulnerable to subsequent cardiovascular events [2,3]. These patients have been traditionally considered a rather homogenous group for risk of future events, and then treated with similar secondary prevention strategies. However, this supposed homogeneity is a false mirage, as a profound risk heterogeneity across this "mixed-up" group exists. As proof, among 18,436 patients with cardiovascular disease, Kaasenbrood et al. [2], have recently shown a large variation in estimated 10-year risk of recurrent cardiovascular events, that was <10% in approximately half patients while remained >20–30% in one-third.

Therefore, treating all post-MI patients with the same (one-size-fits-all) strategy is no longer appropriate. A more tailored approach to individualize secondary prevention interventions is urgently needed to identify patients at higher risk, potentially deriving the most benefit from more intense treatments. However, how to identify post-MI patients who are more likely to experience recurrent events remains a challenge [2].

Albeit traditional risk factors have demonstrated negative prognostic impact in secondary prevention, their performance in predicting future events remains suboptimal [2]. With this regards, the case of LDL-C is a striking example. In the secondary prevention setting, where the vast majority of individuals have dysfunctional lipoproteins, LDL-C has proven to keep its negative prognostic value, but to be a poor (clinically-inconclusive) predictor of recurrent events [4].

In this issue of IJC, Ohm et al. [5] investigated the value of achieved lipid levels after MI for predicting the risk of recurrent cardiovascular events. They investigated a cohort of 25,643 first-ever MI survivors in Sweden (2005–2013). The main questions addressed are the following: (a) which is the predictive capacity of different lipid fractions for recurrent cardiovascular events after first MI, and (b) does their individual assessment have any additional value over clinical risk estimation?

The study population was grouped into quintiles based on total cholesterol, LDL-C, HDL-C, and triglycerides levels at first follow-up visit (4–14 weeks post-MI).

The timeframe for lipids assessment was appropriate, as after 4 weeks maximal (LDL-lowering) effect of statins is expected. However, the individual response to statins can vary over time, with 10% of patients showing an initial unsatisfactory response, and another 10% experiencing a progressive loss of response over time [6]. Moreover, adherence to statins can substantially change during follow-up. One-shot lipids measurement, performed very early after MI, only represent a snapshot of lipids status in such long-term study (mean 4.1 years), and patients crossover among quintiles cannot be excluded. Although changes in statin intensity at follow-up were considered in the analysis, this adjustment might not be sufficient. Another issue is the use of Friedewald formula that, although practical, entails many limitations compared with direct LDL-C measurements.

To assess the association between each of the lipid fractions and recurrent events, the authors used two Cox proportional-hazards models (the first unadjusted, and the second adjusted for age, gender, and year of follow-up visit). Using the lowest quintile as reference, no significant association with outcomes was observed across LDL-C quintiles apart from moderate increase in risk in the highest quintile.

Furthermore, the authors assessed whether the addition of any of the lipid fractions would increase the predictive power of a clinical risk model from TRA2°P-TIMI 50 trial. In this study, the performance

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.07.001.
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https://doi.org/10.1016/j.ijcard.2019.08.032

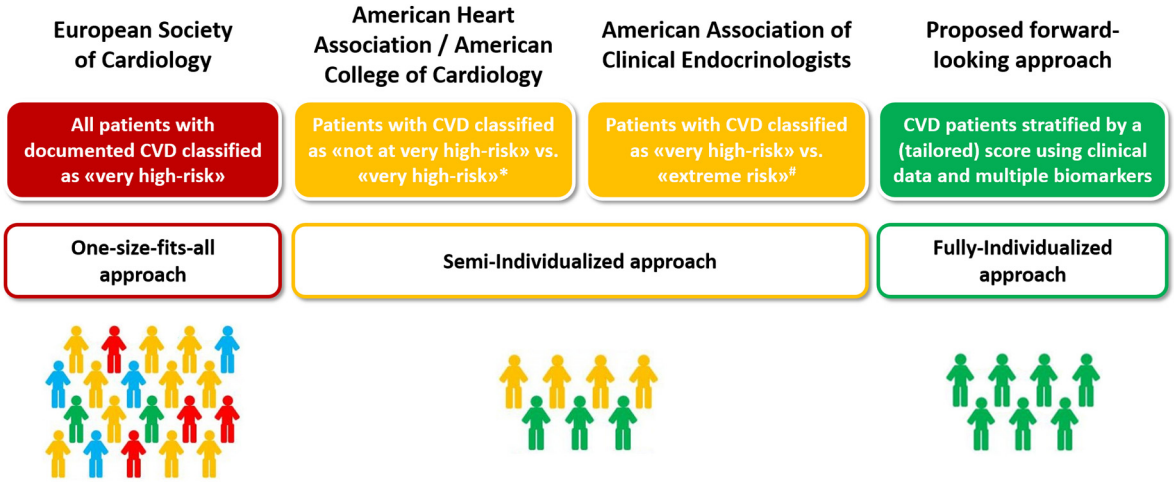

Fig. 1. Contemporary versus individualized approach in secondary prevention. CVD: cardiovascular disease. *Very high-risk patients: multiple major cardiovascular events and/or concomitant multiple high-risk conditions. #Extreme risk patients: progressive or premature CVD, or concomitant diabetes, chronic kidney disease, or heterozygous familial hypercholesterolemia.

of TRA2°P-TIMI 50 model was poor, testifying the actual difficulty in predicting recurrent events after first-MI. Of interest, the addition of any of the lipid fractions to the model was able to improve only modestly its predictivity, with a C-statistics that always remained lower than 0.6 (not much better than flipping a coin).

Some considerations are needed to avoid misleading interpretations. These results are not questioning "the lower, the better" paradigm, as this was not possible with a so-designed study. LDL-C is directly implicated in the development and recurrence of cardiovascular disease [6], and the benefit of LDL-C lowering has been showed to be continuous, safe, and more evident in patients with recent MI [6].

This study showed that nor LDL-C neither other lipid fractions were of value for identifying patients at higher risk for recurrent events after first-MI. These results are not surprising, as similar findings have been previously reported by Puri et al. [4] analyzing 985 patients with coronary atherosclerosis receiving potent statins. At 24 months follow-up, LDL-C did not predict major adverse cardiovascular events. Conversely, C-reactive protein associated significantly with cardiovascular events, supporting the role of persistent systemic inflammation in residual cardiovascular risk [4,7].

The authors indirectly questioned current European "target-oriented" approach for LDL-C. European Guidelines [1], following a (too) practical approach, classify all patients with documented cardiovascular disease as "very high-risk", and suggest for them a single LDL-C target of 70 mg/dl. Differently, American Guidelines [8,9] further stratify secondary prevention patients into a higher and a lower risk subset based on additional clinical data, then suggesting different strategies/targets. This "semi-individualized" approach appears opening a door for a "fully-individualized" in future, tailored on patient's characteristics (Fig. 1).

The value of the present analysis is to point out that, despite its relevance, LDL-C cannot be considered as the only biomarker potentially informative in secondary prevention, and a comprehensive cardiovascular assessment is mandatory [1,8,9]. Recently, advanced lipidomic and nucleic acid profiling analyses have identified new promising risk biomarkers, as ceramides, phosphatidylcholines [10], and circulating microRNAs [11], that could refine cardiovascular risk algorithms, allowing a more individualized patients management.

For the time being, Niels Bohr's maxim "Prediction is very difficult, especially about the future" perfectly reflects our knowledge on events recurrence after MI. Our future aim is to challenge this contemporary (and actually failing) paradigm, moving from the status of "very difficult" to "moderately difficult" and, hopefully, "not that difficult, and mostly feasible" as soon as possible.

Declaration of competing interest

None.

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