



Cardiovascular disease in the youngest: is it time for precision prevention?

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The current paradigm for the primary prevention of cardiovascular diseases in the US and in Europe is based upon absolute risk assessment to guide treatment decision (1,2). Over the years, a number of models were developed to tailor risk estimation to specific populations (see Table 2 in reference 2 for an overview), to limit systematic measurement error due to poor model calibration (3). All the different models share a common promise, i.e., that one single measurement of a limited number of “core” risk factors, including age, blood pressure, blood lipids, smoking and diabetes, is able to estimate the individual’s probability of experiencing a cardiovascular event over the following 10 years with a discrimination ability between 70% and 85% (4). However, this satisfactory “average performance” has been seriously questioned whenever risk models have been applied to specific population subgroups, such as those defined by ethnicity (5), socio-economic status (6) or young age (7). In this latter study (7), Singh and colleagues investigated risk estimation and eligibility to statin treatment in the context of a retrospective registry of individuals experiencing a first-time myocardial infarction (MI) before the age of 50, between 2000 and 2016. The 10-year risk of cardiovascular event was estimated from the Pooled Cohort Equation (PCE) (1) based on data on risk factors prior to the event, as ascertained through record linkage with electronic medical records. To define statin eligibility, the authors considered both the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for treatment of blood cholesterol, and the 2016 US Preventive Services Task Force (USPSTF)

recommendations for statin use in primary prevention. The study included 1,475 type 1 MI patients, of which 57% were ST-segment elevation MIs. The median age at onset was 45 years, but almost 1 out of 5 was below the age of 40; and 80% were men. The overwhelming majority of patients (83%) reported one or more major MI risk factors; however, the median 10-year predicted risk was 4.8%, meaning that only 49% and 29% of patients would have met the ACC/AHA and USPSTF criteria for statin eligibility, respectively. These fractions were even lower among young women.

The authors acknowledged a number of limitations that may warrant cautious when generalizing their findings to other settings. Study hospitals are located in high socio-economic status communities, and 72% of included MI patients were white. The retrospective collection of risk factors is prone to missing-not-at-random data, since individuals at higher risk are also more likely to have a cholesterol measurement before the event. Fatal out-of-hospital cases are likely to be excluded by design in the YOUNG-MI registry (8). Finally, it was not possible to estimate the prevalence of risk factors in the overall young population by design, due to the lack of a control group. Despite these limitations, this study uncovers a field of missed opportunities for prevention. In fact, according to latest estimates by the World Health Organization, about 80% of premature ischemic heart disease and stroke is preventable (9), especially so when primordial and primary prevention begin early in life (10). Given the relevant economic, social and personal implications of an MI in young age, the authors’ final statement on “the need for

better risk assessment tools among young adults” seems highly shareable. A couple of specific actions may serve to pursue this aim.

First, several authors reported that 10-year risk scores are likely to underestimate risk in younger individuals and women, irrespective of the presence of risk factors (4,11). This was confirmed in the YOUNG-MI registry data, as reported above. In other words, in young individuals age is the single most powerful predictor of event probability over a short time period such as 10 years. The latest US and European guidelines (1,2) have ultimately introduced the assessment of long-term risk of disease as a supplementary tool to improve risk communication and increment risk awareness among individuals who have a low probability of event in the short-term period despite the presence of one or more risk factors. One study in the Italian population demonstrated that the joint use of short-term and long-term risk models has the potential to improve the risk stratification and treatment allocation based on short-term risk alone (12). In particular, the joint use might save un-necessary treatment initiation as well as reduce the proportion of future cardiovascular events that are “missed” by current prevention strategies, especially in women. This clinical utility analysis deserves replication in other populations and calls for future research on the cost-effectiveness assessment of alternative intervention profiles in the primary prevention of cardiovascular disease.

Second, standard risk scores generally developed on the entire range of adulthood age (40 to 64 for the SCORE model, or even to 79 as for the PCE) are probably neglecting information that is of paramount importance in events occurring at young ages. To improve the risk estimation in the youngest, it would be conceivable to use the genetic or family profile. Recent studies of Mendelian genetics have highlighted the role of the duration of exposure to hypercholesterolemia on cardiovascular risk, suggesting that early detection and treatment of familial hypercholesterolemia may lead to a significant reduction in cardiovascular events (13). In a large cohort of more than 20,000 initially-healthy individuals, a genetic risk score was found to improve discrimination and reclassification of cardiovascular disease (CVD) event when added to a standard risk model, especially so among young study subjects (14). Familiarity for MI especially at an early age is not included in the most utilized risk assessments. It is usually related to the genetic profile but we also know that

for a long period of life they are shared with environmental factors, including social position, diet and physical activity (15). Furthermore, the assessment of subclinical atherosclerotic damage may be useful in identifying young patients with a higher cardiovascular risk. In the CARDIA (Coronary Artery Risk Development in Young Adults) study we found confirmation of this hypothesis. The sharing of healthy lifestyle factors, including normal body mass index, moderate alcohol intake, healthy diet, recommended levels of physical activity and no tobacco use in young adults (18–30 years) was independently associated with a lower risk of subclinical atherosclerosis after 20 years (16). Finally, the inflammatory component could improve the prediction of coronary risk especially in those patients who do not share traditional risk factors (17), potentially contributing to a more accurate risk stratification also in the youngest.

Third, the prevalence of dyslipidemia, smoking, hypertension, or diabetes was elevated in the YOUNG-MI registry, with 83% of patients reporting at least one of these risk factors. The INTERHEART study estimated a larger population attributable risk for traditional risk factors in younger men (93.0%) and women (96.5%) than among their older counterparts, strongly suggesting that when a traditional risk factor is present in a person less than 50 years old, its detrimental effect on coronary risk is greater (18). The indication for statin therapy in the young, based upon a standard risk threshold valid for the “average population”, is often not mandatory given the low cardiovascular risk profile. However, statin therapy in lower-risk individuals has a favorable benefit-risk ratio: randomized controlled trials indicate approximately 20% benefit in 5 years for 1 mmol/L low-density lipoprotein (LDL) cholesterol lowering (19). Adverse events (myopathy, diabetes, hemorrhagic stroke) remain limited in extent when compared with the benefits.

In conclusion, the YOUNG-MI registry casts a light upon a number of missed opportunities by the current paradigm of cardiovascular disease prevention in the youngest. Time has probably come to switch from the “one size fit all” approach—which characterizes both risk estimation models and treatment thresholds—towards a more personalized, “precision” prevention strategy, which is able to provide “the right intervention at the right population at the right time” (20). The increasing availability of large epidemiological studies, health care databases, biobanks and other “big data” sources can really

fuel the paradigm shift in the near future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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