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# New prevention scenarios: polygenic risk

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Although coronary heart disease is a highly preventable disease, it is still the leading cause of morbidity and mortality in developed countries. This is also due to the fact that the risk models used in clinical practice have proved ineffective in identifying people at risk: up to 30% of cases of myocardial infarction do not have traditional risk factors used in risk estimation models. Although the genetic component of myocardial infarction has been known for many years, with an inheritance rate of between 40% and 60%, it is not yet used as a risk factor in primary prevention models such as the Heart Card or the European SCORE. Recent advances in genomics and the use of clinical big data have allowed the development of genetic risk scores called Polygenic Risk Score (PRS), capable of identifying populations with average LDL-C levels, but with the same risk of heart attack of carriers of hypercholesterolaemia. The clinical usefulness of the PRS lies precisely in identifying high-risk individuals who are invisible to traditional models. The clinical applications of PRS for coronary artery disease are discussed in this report.

## Need to improve risk models

Coronary heart diseases are part of what are called complex or multi-factorial diseases, in which numerous aetiologies converge, not all of which are easily recognizable. Numerous advances have been made in the last 50 years in primary prevention, identifying more and more risk factors involved in the development of atherosclerotic plaques and their subsequent destabilization and consequent rupture. For example, just considering that cholesterol was not differentiated into LDL-C and HDL in the past decades but was used as a single biomarker.[1]

Prospective studies based on hundreds of thousands up to millions of individuals have made it possible to develop risk models based on the combination of multiple risk factors. This made it possible to identify thresholds of risk levels in the next 5 or 10 years from the moment in which the parameters are collected in an individual, in order to have indications on when or not to start a drug therapy aimed at reducing risk. Several countries have developed models based on more or less large populations, with local characteristics, in some cases also considering the ancestral origin of individuals.[2] The best known predictive risk models are the European SCORE, the Italian Heart Card and the Framingham, later replaced by pooled cohort equations in the USA. The clinical utility of these models has been widely demonstrated, despite their predictive abilities, measured with a discrimination index called AUC, are not excellent, not exceeding the 0.8 threshold. Furthermore, some parameters have a disproportionately high weight: age, for example, plays an excessive role in the assessment of risk, so much so that it has led to the establishment of age limits for the application of these models, in order to prevent that the risk estimation is too influenced by this parameter.[3] The need to improve traditional models is also evident when estimating the incidence of heart attack cases that escape the risk assessment. In fact, up to 30% of cases of myocardial infarction do not have the risk factors used in classical prediction models.[4] To aggravate this situation, it is the finding that patients with ST-elevation myocardial infarction (STEMI) that did not present risk factors had higher mortality in the 30 days following the event.[5] The limit of the risk models used in clinical practice in the prevention of coronary heart disease is therefore clear.

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## The genetic component of myocardial infarction

Myocardial infarction is a multifactorial disease with a large hereditary component, estimated through large-scale studies at ~40–60%.[6] The genetic component of heart attacks has been shown to be of two types: monogenic and polygenic. Genes such as APOB, LDLR, and PCSK9 are known, which, in the presence of pathogenetic mutations, are responsible for alterations in the metabolism of LDL cholesterol, causing familial hypercholesterolaemia. These mutations can be identified thanks to sequencing with next-generation sequencing (NGS) technology and bioinformatics analyses, whose pathogenicity is then confirmed by the geneticist. Identifying carriers of pathogenic mutations in the genes causing familial hypercholesterolaemia is crucial, as these patients have about three times the risk of developing heart attacks than non-carriers. Carriers are however rare, with a prevalence of about 0.5% and are often identified in routine checks due to the abnormal level of LDL they exhibit.[7]

There is also another way of genetically inheriting the condition of familial hypercholesterolaemia, the polygenic one, in which there are no mutations (i.e. errors in the genetic code that cause an alteration of the encoded protein), but an increase in alleles of common variations called polymorphisms. Polymorphisms are variations that do not cause an alteration of the gene, each with a small effect on the risk: when these variations are added together, they confer a significant increase in the genetic risk of developing the phenotype. In a recent study published in *JAMA Cardiology*, a prevalence of polygenic hypercholesterolaemia of about 5% was highlighted, demonstrating how polymorphisms are able to identify a larger population than mutations.[8]

Another very important genetic component of the myocardial infarct is that which, despite the absence of high-LDL cholesterol levels, confers a three times higher risk of heart attack,[9] allowing the identification of patients invisible to traditional risk models. This component is called the polygenic score for coronary heart disease and its main mechanism of action is to interact with LDL cholesterol, multiplying its risk. This means that people with LDL levels that are not considered to be of concern in themselves (e.g. 130–160 mg/dL) actually have the same risk as those with hypercholesterolaemia (LDL > 190 mg/dL), a condition that we could call 'invisible hypercholesterolaemia'.[10] This phenomenon is worrisome because millions of people have LDL cholesterol levels between 130 and 160 mg/dL. In the presence of a high polygenic score, these subjects develop atherosclerotic plaques with the same intensity and risk as those with hypercholesterolaemia, but in a more subtle way, because it is invisible to traditional risk models. In fact, the polygenic score is not correlated with any other risk factors, such as hypertension or other lipids, so that those with a high polygenic score cannot be identified in any way except through genetic analysis.[11]

## The Polygenic Risk Score

As explained above, we can say that myocardial infarction is characterized by different genetic components. Large-scale studies carried out in recent years have allowed the development of polygenic scores based on polymorphisms. Polygenic scores called, in the English Language, Polygenic Risk Score (PRS) can also be composed of millions of genetic variations located in coding and inter-genic regions of the genome, thus being also involved in gene transcription. Polygenic Risk Scores are formed by a weighted sum of the polymorphisms associated with the development of the disease. The development of new PRS for coronary heart disease has accelerated dramatically in the last 3 years, thanks to the use of prospective genomic datasets to carry out large-scale clinical validations such as the UKBiobank. This biobank was developed thanks to a British government project that involved more than 500 000 people, followed for 10 years and with both genetic and clinical data available to researchers through electronic health records.[12] The availability of clinical and genetic data from a very large number of people has allowed the development of integrated models, which have shown how LDL cholesterol confers different risks depending on the PRS. A result of great clinical value is to have shown how people with LDL between 130 and 160 mg/dL and with high PRS have the same risk as those with hypercholesterolaemia (LDL > 190 mg/dL) and average PRS.[10]

The genetic analysis that allows to calculate the PRS can be carried out using a simple salivary swab, while the subsequent bioinformatics analyses allow to generate a report that can be used in clinical practice, identifying, for example, the real risk conferred by LDL cholesterol according on the PRS.

## Clinical applications

The PRS is very useful when inserted within an estimate of the absolute risk, as it makes it possible, through the estimation of the genetic component of myocardial infarction, to reclassify individuals from medium risk to high risk. In this way, it is possible to identify people who otherwise would not be addressed in primary prevention. The PRS is of great use in cases of intermediate risk, when the decision whether or not to initiate drug therapy is uncertain.[11] The PRS allows to add an additional risk factor as a risk-enhancing factor. Risk enhancing factors are all those risk factors that increase the risk by at least two times, such as family history or high levels of triglycerides. Advances in imaging have also made it possible to identify new individuals with risk enhancing factors, for example through Echo Doppler analyses of the carotids or calcium score of the coronary arteries. In the case of intermediate risk, the PRS can therefore be used as a risk enhancing factor, since it is capable of identifying 20% of the population with a risk of more than 200%, thus falling within the definition of risk-enhancing factor.[11] We know that traditional risk factors translate into clinical phenomena with advancing age, when atherosclerotic plaques are already forming. The PRS allows for the extension of prevention to younger age groups: individuals with high PRS should not have LDL levels above 130 mg/dL,[10] thus identifying needs and understanding the characteristics of similar groups of people, with the ultimate goal of achieving maximum intervention precision at the individual level (precision prevention). The PRS can

also be used where there are no clear manifestations of other traditional risk factors. Doing the test in these patients allows to understand the causes of the disease and to start a cascade screening among family members, to allow to identify other members with elevated PRS who need more attention in monitoring LDL levels and a more rigorous application primary prevention strategies. First-degree family members of people with high PRS are in fact 40% likely to have high PRS as well.[13]

## Conclusions

The PRS has proved to be a valid new risk assessment method to add to the arsenal used in clinical practice. This allows the doctor to identify high-risk people more effectively and earlier and initiate them into an adequate primary prevention path. In this way, it will be possible to decrease the number of cases of myocardial infarctions that cannot be prevented due to the limitations of the models currently used in clinical practice. This approach aimed at a better medicine able to understand more and more precisely the needs of the individual will allow further successes in reducing the number of cases of myocardial infarction in the population.

**Conflict of interest:** none declared.

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