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Cardiovascular prevention: sometimes dreams can come true

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Cardiovascular disease (CVD) is a chronic condition driven by the complex interaction of different risk factors including genetics, lifestyle, environment, etc. which, differently from other pathologies, can be prevented. Treatment of CVD has been inconceivably successful but now it seems that it has reached a plateau suggesting that prevention is the way forward. However, the COVID-19 pandemic has spotted all the limits of the actual health system regarding territorial and, particularly, of preventive medicine. To this end, recently, the SCORE2 risk prediction algorithms, a contemporary model to estimate 10 years risk of CVD in Europe and the new guidelines on prevention have been released. The present review article describes a dream: how prevention of CVD should be addressed in the future. New concepts and paradigms like early genetically personalized and imaging driven risk factors, cardiac risk cartography, measurements of the exposome, estimation of costs of a delayed outcome vs. healthy lifespan, are all addressed. We highlight the importance of technologies and the concept of being engaged in a 'healthy' and not just 'sick' system as it is today. The concept of 'clearing house' with a 'care health team' instead of a 'heart team' is described. Finally, we articulate the four points necessary for the dream to come true.

Premise

Recently, the *European Heart Journal* has dedicated a focus issue on epidemiology and prevention, emphasizing the importance of risk scores in management of cardiovascular diseases (CVD).[1] In the same number, the new SCORE2 and SCORE2-OLDER (SCORE2 OP) were presented.[2] Both are an advanced risk prediction algorithm contemporary derived, calibrated, and validated. In the last 2 years, the America College of Cardiology (ACC)/American Heart Association (AHA) and the European guidelines on cardiovascular prevention have also been released.[3,4] This latter is a very comprehensive document based on the new risk scores, containing 54 new or revised recommendations related to risk factors and relative management, and testify how dynamic is, at present, the topic.

Nevertheless, the key question remains: are these scores and recommendations used? And, further, by whom? The population? The physicians? The cardiologists? Indeed, it is a difficult question. The reality is that prevention scores for CVD are not used as much as they should, to say the best. Busy general physicians in charge for the health of the population, probably do not have the time or do not consider the risk score a priority. Cardiologists do not deal with individuals, but with patients and do not consider population prevention part of their duty. At best, cardiologists are engaged 'one-off' in special occasions, such as a prevention day, week, or even monthly campaign. This is a pity because CVD could be prevented by reduction of risk factors, as clearly demonstrated by the Mendelian randomisation clinical trials.[5,6]

Newer, more planetary solutions with societal and political involvement are needed. This could be the right time to consider a 'global' preventative model as the COVID-19 pandemic and the climate changing emergencies have spotlighted how much health and safety of human kind can be threatened by human activities and how important is to prevent this from occurring.

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The editorial of L. Tokgozoglu and C. Torp-Pedersen[7] in the focus issue of the *European Heart Journal* and the article of Münzel *et al*.[8] are alluding to this. Here, we propose a conceptual view, not on prediction of CVD, but on prediction on how the CVD risks will be recognized and possibly targeted in the next 10 years.

From classical risk scores to polygenic and cumulative risks

The next generation of preventative measures cannot ignore the complex interplay among genetics, lifestyle, and environment. This means huge number of data continuously produced and, importantly, full of content. The recent advances in genomics will inevitably lead to the discovery of millions of variants with thousands of disease-associated genes. Such an enormous number of combinations will be difficult to be analysed by the human brain but, likely, not for technologies, such as artificial intelligence models, already able to connect deep longitudinal multimodal data. The same models will be applied to construct algorithms to make the best predictions of the genetic risk and not only. Genetic risk scores, including the relative contribution of each specific variant, have already been proposed and are linked to higher occurrence of CV events.[9–11] Mendelian randomization trials show that the degree of damage induced by classic risk factors, i.e. hypertension and high LDL-cholesterol, is dependent on the severity of the risk factors but also on the duration of the exposure to them throughout life.[5,6] This has led to the concept, at least for the two above mentioned, that not only the 'lower' but also the 'earlier' reduction the better. Technology, such as development of applicable sensors to monitor these parameters through life, linked with automatic drug delivery (*through drones*) will for sure help in the near future.[9]

Usually, these causal risk factors are detected later in life, thus it is unknown for how long they have been present.

Exposure to genetic risk is forever and this is a clear advantage. Despite this advantage, genetic risks also need to be integrated with other risks derived from a large number of individual-related variables and/or from the environment to which individuals are continuously exposed. Detection of the variables will also be facilitated by technologies through imaging, mobile-derived biometrics, metabolomics, etc. Such cumulative risks assessment will produce a 'personalised' risk prediction with increased accuracy. This, however, will not occur overnight. Polygenic risk factors depend on ethnic variants and are not internationally standardised. There are many several of them with still uncertain results but … works are in progress.

From imaging to cardiac risk cartography

Although not yet integrated even in the more advanced risk chart, imaging is already an important tool to detect by coronary calcium score the general atherosclerotic burden and the propensity to develop and/or the individual vulnerability detected by computed tomography and angiography. These techniques are excellent predictors of future CV events, are increasingly used and are guideline-recommended to determine risk assessments,[4,12–15] However, the future holds different images: those of the human cell atlas, an initiative to map every cell of the body.[16] Within this massive programme, a detailed cellular and molecular picture of the human heart has recently become available.[16] The first surprise is how many different cells constitute the heart, which is no longer considered just a muscle able to pump blood to the body but a complex organ, constituted by, in addition to myocytes, cardiac protective immune cells, fibroblasts, pericytes, myeloid and lymphoid cells, adipocytes, neuronal, endothelial, and smooth muscle cells, the last two representing the intricate network of the coronary circulation. The second surprise provided by the atlas is the possibility to establish how the cells communicate among themselves to allow the heart to work H24 over lifetime, delivering more than 2 billion of heartbeats. The third surprise is that by means of single-cell genomic analysis and machine learning programmes, it will be possible to understand which genes are switched on or off in every cell. Such a detailed imaging of the heart and of its circulation will provide, by comparison with the physiological appearance of each different cell of the heart, an early detailed picture of the changes occurring in every cell in response to environmental risk factors and to personal behaviour such as diet, smoking, physical exercise, etc. Such unprecedented scale of precision will reveal cellular alteration, occurring much before any damage will take place. This will project cardiology towards the era of 'extremely early personalised' prevention.

From classical risk factors to the 'exposome'

Exposome is a new concept that refers to exposure to several environmental risk factors, such as chemical and biological agents, pollutants, radiation but also transportation noise, light exposure, environment as well as and socio-economic conditions. Exposome reflects the need of re-thinking the actual (*too*) simplicist algorithms for calculation of CVD risk as human health is exposed to a flood of unimagined unhealthy influences every day, often originated by the man himself.

Two-third of the European population already lives in urban areas and this proportion is expected to increase rapidly. The same is true also for Asian, American, and Middle East inhabitants who are aiming to agglomerate in mega cities. By 2050, according to the 'World Population Prospects 2019', ∼68% of the world population (*7 billion people*) will live in cities (*compared to 55% of today*).

Although cities are made to produce wealth and well-being, provided through efficient social and health programmes, ironically, they are also sources of diseases, including CVD.[8] Urbanisation produces huge number of relatively newly recognised environmental stress such as traffic noise, nocturnal artificial light, pollution, soil and water contamination, psychosocial stress such as isolation, fear for crimes, work and economical strain, racial inequities, etc.

Cities, urbanisation, and industrialisation, highly depending on the existing inequality of social and sanitary services, also generate a large amount of emissions, contributing to global air pollution, a mixture of nano- and micro-sized particles, and gas responsible for the actual climate change.[17] This, in turn, will have an impact on social and environmental determinants of health. These include quality of food, drinking water, and air with increased risk for respiratory and CVD. Already air pollution is the most important environment risk factor and one of the most relevant cause of mortality worldwide.[18] Of note, 50% of death-induced by pollution is due to CVD.[8]

In addition to urbanisation, several other human sources contribute to air pollution, such as factories, power and disposable plants, industrial and commercial activities, shipping and air plants, etc. There are natural sources as well, including dust, and salt from volcanoes, forest, windblown soils and ocean salt from spray, etc. Just in Europe, it is estimated that air pollution is responsible for almost 700,000 premature deaths annually, if not more and about two-third of these are attributable to CVD, including hypertension, stroke, and ischaemic heart disease.[19] The expected further rise of temperature will also contribute to environmental threats including the spread to cooler areas of the world of warm-weather viruses and the spread of heat stress, storms, and extreme weather with drastic changes of the ecosystem. All these environmental risk factors to which unwillingly humans are already and will be exposed contribute to the exposome.

Measurements of exposome is difficult, it means connecting and grading the actual still poorly known environmental risk factors to create a complex interplay and network of influences that contribute to CVD and other diseases. This is unrealistic at present, but will be possible in the near future by the intensive use of technology, including remote sensors able to measure, through lifetime, all the external and internal influences connected to artificial intelligence and machine learning for the integration of all data. Omics technologies, in turn, will allow the causal attribution of each stressor. This will be an important innovation in terms of prevention as the possibility to deal with big data will allow to move the actual paradigm of 'one exposure-one disease-one outcome' towards a more realistic and comprehensive risk estimation. There is the need to think big and consider the totality of risk factors to which humans are exposed. The exposome may be the solution.

From life expectancy to healthy life span

Up to now, CV prevention has mainly focused on relatively young individuals (*aged 40-69 years*) and on hard endpoints such as hospitalisation, and mortality. The progresses in treatment of CVD and other diseases have produced good results as in the last 100 years life expectancy has constantly increased in several part of the world. Cardiology, in particular, has been highly successful as it has contributed for at least 7 years to the 10-year-increase of life expectancy which has recently occurred.[20] Of note, 2020 was the first year in the last decade that in US life expectancy has decreased, instead of increasing. It has decreased of one and a half year for the white population and of 3 years for the others, pointing out the relevance of social and economic influence on health. This is the consequence of COVID-19 pandemic which has adversely impacted on the care of all the other pathologies and, particularly so of CVD.[21] Beside the negative effects of the unexpected pandemic, the healthy lifespan of the population has not increased in parallel to the life expectancy. The period spent with illness and disability at the end of life, paradoxically, but not surprisingly, has increased as a response to the success of cardiology. The expected amount of healthy life can be anticipated using biomarkers integrated with omics technology. To some extent, this is already happening in cardiology, i.e. with estimation of frailty in aged patients before percutaneous or surgical interventions.[22] Frailty, however, measures the physical and intellectual state of patients but is not integrated with the many other internal or external influences. Once again, technology could be of great help here. This is an area worthwhile to explore as ageing is mouldable and the degree of late-life wellbeing can be improved if problems are spotted and prevented before occurring. Disability and sickness, at the end of life, should be another target of prevention, implementing a new concept: not just prevention of the outcome but also estimation of its cost.

How does the future of prevention look like?

Several changes will occur in the next few years on healthcare system which, undoubtedly, has been very successful up to now in terms of diagnosis and treatment but less so in terms of prevention. In reality, it is a sort of 'ill' or 'sick' rather than 'health' care system. The current COVID-19 pandemic has revealed all its limits, particularly regarding territorial and preventive medicine. As a consequence, national governments and Europe are demanding in strongest terms a change and are ready to invest on it. The main problem is that today the system is activated and reacts when somebody is not well. It is at this time that general practitioners or hospital specialists are consulted, the tests are performed, and, eventually, treatments are decided and delivered. This sequence is time consuming and it is not intended to respond and to deal with the huge increase of chronic diseases (*which represent more than 80% of the healthcare costs*) such as CVD and cancer or with pandemics like the one of COVID-19.

Today, there is a need to look at healthcare from the perspective of the healthy people and not of patients and doctors. The idea is to care for the maintenance of the individuals wellbeing as long as possible rather than just caring for individuals already ill. As such, prevention should be at the 'heart' of the future care system. This requires a drastic change in the delivery of prevention. It should not just be a list of what to do and not to do. Many individuals know what is good and what is bad for their health, but very few are ready to cut what is bad. This target needs a 'special approach'.

Individuals must become proactive towards their wellbeing and the system must care for them as much as it cares for sick patients. Technology will help. Soon, people will be able to monitor themselves and, in particular, their heart function (*in terms of rhythm and heart rate*, *blood pressure*, *glucose and cholesterol levels*, *weight*, *breathing*, *daily exercise*, *etc*.) can be tracked. The health records can then be stored in a 'remote server' with artificial intelligence able to follow them through the entire lifespan and to incorporate with all the other continuously incoming data. This server will also remotely be supervised by a 'care health team' instead of the actual 'heart team' that decides just on how and when to intervene. The 'care health team' actually will 'intervene' to avoid interventions! The genetic profile will also be streamed by the individuals to the server to be processed through algorithms together with the other risk factors, the exposome, and the imaging information. The 'server' and the 'care health team' should be intended as a sort of 'clearing house', accessible by the person and the 'care health team'. Those who are not perfect in terms of health risks can be directed, at a very early stage, to counselling, videos, etc. or engaged with specific social networks, with interrelation with peers until they are 'clear' from risks. The extra value of a 'clearing house' relies on the constant H24 contact and on the capability to intervene immediately. This will allow a life longer contact and not just a sporadic one at the time of completion of the risk chart. The other value relies on technology and on the involvement of the individuals who might also like to share their data, problems, sensations, and reserves which are important for population research, thus feeling an active part of the 'house'. In some countries, like the US, the UK, Sweden and Germany, a systematic digitalisation of individual health is ongoing with production of electronic health recording. If such goal is reached, it will be useful for cabling the health and the risk of the entire population.

A system like this will also be useful to deal with future pandemics which, unfortunately, will happen in response to climate changes and to the success of human kind.

Conclusions

In this brief article, we have underlined several negative effects on human health. This is the empty size of the glass. The full size is represented by the success of social intervention and medicine (*cardiology in particular*) to make people living longer by providing better treatments. It seems, however, that, at least for CVD, we have reached a 'plateau' of what treatment can do. The COVID-19 pandemic has spotted the necessity to build a better health system aiming to further improve health by preventing illnesses from occurring. Science shows that human progress has a price to pay in terms of biodiversity loss, climate changes, pollution, destruction of natural resources, etc. All of this generates a multiplicity of risk factors for human health. It is on this multiplicity of risk factors that prevention can drive the future. The idea of a central 'clear house' attended by a 'care health team' with experts (*not necessarily doctors*) looking simultaneously at integrated longitudinal risk factors of individuals with the aim of correcting them before people become patients may be considered a dream book. But dreams, sometimes, come true. After all, this dream needs only few points of common sense as:

(1) Significantly more money allocated to prevention. Currently, only 4% of public health funding goes to it.
(2) The funds need to be directed in a collective and coordinated effort towards population and planet progresses as these are correlated. Currently, they are directed to specific sick patients and do not consider the impact of progress on human life.
(3) The use of emerging technology needs to be universal with the sharing of the data as much as possible and as less as necessary. Universities, big pharma, and biotechnological companies need to join their efforts and share the most valuable experts for a global European public health project instead of concentrating in individual lucrative markets. Currently, everyone works independently and follows profitable strategies.
(4) The focus should be the maintenance of human wellbeing. Currently, it is the reduction of manifestation of patients' diseases.

Let us hope that our dream for a better prevention will come true. In the meantime, let us use the current CV risk chart as suggested and recommended.[1-4]

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Data availability

No new data were generated or analysed in support of this research.

Authors' contribution statements

Each author has substantially contributed to the preparation of this manuscript. R.F.: conception, design, and first draft; P.C., A.C., M.S., G.G.: critical reading, commenting, validation.

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