Prevention of Acute Vascular Events: Precision, Personal, and Conventional Medicine

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Cardiovascular diseases (CVDs) are the number one cause of death globally, taking an estimated 18 million lives each year. Four out of 5 CVD deaths are due to heart attacks and strokes and one third of these deaths occur prematurely in people under 70 years of age. In a ‘Hot Line Session’ at the European Society of Cardiology Congress-2019, PURE study results on the causes of death due to CVD were announced. Professor Salim Yusuf, senior author of the study and Principal Investigator of PURE clinical trials, said: “The high rates of cardiovascular disease and related mortality in low-income countries are likely related to gaps in access to, or availability of, healthcare”.

INTEHEART study of potentially modifiable risk factors associated with myocardial infarction in 52 countries showed that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychological factors, consumption of fruits, vegetables and alcohol, and regular physical activity account for most of the risk for myocardial infarction worldwide in both sexes and at all ages in all regions. The authors concluded that, “This finding suggests that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction [1]. Khera and associates from the Harvard University, working on risk factor management for CVDs, concluded, “Across studies involving 55,685 participants, genetic and lifestyle factors were independently associated to coronary artery disease. Even among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease, than was an unfavorable lifestyle [2]. The World Health Organization (WHO) estimates, that over 75% of premature CVD is preventable and risk factor amelioration can help reduce the growing CVD burden. Furthermore, primary prevention of CVD is of particular interest, as developing countries experience a greater burden of these metabolic diseases and can be prevented by careful modifiable risk reduction.

The rate of CVD worldwide is predicted by experts to increase rapidly as the prevalence or risk factors for CVD rises in previously low-risk countries. Currently 80% CVD mortality occurs in developing nations. Because of this observation, there is a growing interest in developing a cost effective, ‘one-size fits all’-approach, to the development of a ‘Poly Pill’ for the primary prevention of CVD-related acute events. A small pilot trial of a polypill for primary prevention, in a few hundred healthy older people in Iran, has been completed according to the US-run www.clinicaltrials.gov. The polypill used in this study contained aspirin 81 mg, 12.5 mg enalapril, 2.5 mg atorvastatin. The 2000 participants in the study, “Use of Multidrug Pill in Reducing Cardiovascular Events (UMPIRE)” participants were at higher risk of CVD events than those who took part in the Indian Polycap Study (TIPS), a phase 2 study, which examined the effects of a polypill in essentially healthy people with one risk factor for CVD. In this study, the subjects took Polycap, manufactured by the Indian company Cadila, which had 12.5 mg Atenolol, Ramipril 5 mg, Simvastatin 20 mg and Aspirin 100 mg. A new trial examining adherence to a polypill consisting of aspirin, a statin, and two hypertensive agents has begun in the UK, Ireland, and Netherlands, with participants in India also expected to join the study at a later date. In March of 2019, the American College of Cardiology (ACC) and the American Heart Association (AHA) released new guidelines that suggest most adults without a history of heart disease should not take low-dose daily aspirin to prevent first
heart attack. Based on ASPREE, ARRIVE, and ASCEND trials, the ACC/AHA guidelines concluded that the risk of side effects from aspirin, particularly bleeding, outweighed the potential benefit [5].

Huffman and associates in a recent issue of JAMA (2019) published their viewpoint on “The Implementation Strategies for Cardiovascular Polypills” and concluded that, “Almost 20 years after the concept of cardiovascular disease polypills was first proposed, substantial evidence has accumulated regarding the effects of polypill-based strategies for global atherosclerotic vascular disease (ASVD) prevention and control. The focus of polypill research and action now should shift from small- to moderate- sized studies to concerted, sustained, and large-scale efforts, by multiple global and local stakeholders [3]. In the same issue of JAMA, Joyner and Paneth express their viewpoint on “Cardiovascular Disease Prevention at Crossroads: Precision Medicine or Polypill [2]”. The authors advocating the precision medicine approach to the prevention of CVDs, conclude, “A clinical trial of precision medicine vs the polypill will also have the benefit of addressing fundamental issues about the merits of complexity vs simplicity in a delivery performance activity like clinical medicine [4]”. The authors state that, “Just like polypill is a form of primary prevention, the precision medicine is a form of secondary prevention, adding genomic information to the array of tools, available to health professional to decide who, when, and how, to treat with the goal of preventing CVD.

President Barack Obama launched a unique program during his State of the Union address in January 2015 [6]. “Tonight, I am launching a new Precision Medicine Initiative, to bring us closer to curing diseases like cancer and diabetes- and to give all of us access to the personalized information to keep ourselves and our families healthier”. Francis Collins, the author of the article explains that, “The initiative has a near-term focus on cancers and a longer- term aim to generate knowledge applicable to the whole range of health and disease”. This is a classic example of the “Top Down” approach, to find a solution with no real hypothesis behind one of the largest publicly funded research project. As suggested by the Authors of the JAMA article, it would have been probably wiser to have planned a well thought out hypothesis -driven initiative, to find molecular and genetic mechanisms responsible for the development of metabolic diseases such as hypertension, obesity, type-2 diabetes and vascular diseases [4]. A recent article by a consortium of experts, reports in the New England Journal of Medicine, that development of a splice modulating antisense oligonucleotide to a particular patient with seizures, offers a possible template for the rapid development of patient-customized treatments [8]. Innovative personalized medicine has potential to save lives worldwide, if they are only affordable.

Metabolic risk factors include, oxidative stress, inflammation, excess weight, obesity, type-2 diabetes, endothelial dysfunction, hardening of the arteries, altered blood glucose, insulin resistance, increased blood lipids, and presence of subclinical atherosclerosis. Composite gene scores that contribute the increased metabolic risks need to be included in fine tuning aggregate risk score stratification. Limitations of this approach especially for the developing countries, which bear the most burdened of increased incidence and prevalence of metabolic diseases is the phenomenal cost of risk stratification and drug regimens needed for such personalized precision medicine approach. Most cardiovascular disease deaths occur in low-and middle-income countries. National insurance programs in these countries have historically excluded coverage of CVD therapies, because the cost-effectiveness providing such coverage has been unclear. Coverage of all 3 major types of CVD treatment, -primary prevention, secondary prevention, and tertiary treatment, would be expected to have high impact and reasonable cost-effectiveness in low- and middle-income countries [9].

At the time of this writing, Precision Medicine as suggested by Joyner and Paneth is beyond the reach of majority of countries. As suggested by the above-mentioned authors, prestigious research institutes like the National Health Institutes of Health, USA, can initiate experimental studies, to develop well thought-out clinical trials, to explore challenges and opportunities in Precision Medicine approach, to find mechanisms that predispose individuals to metabolic studies such as hypertension, obesity, diabetes and vascular diseases, which have reached epidemic proportions worldwide. According to a seminal article on the topic of precision medicine, the authors conclude, “Despite a clear path forward, mainstream application of precision medicine, there continues to be debate about whether a precision medicine approach will have a global impact on CVD prevention and treatment, or will serve a small group of patients [10]”. When it comes to personalized medicine, even in an advanced country like the USA, just a few cardiologists are incorporating personalized medicine.
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into clinical treatment [11]. We have not been able to convince the importance of using ambulatory blood pressure devices and ambulatory glucose monitoring devices in clinical settings, as these applications are not covered by most of the health insurance plans. The vast majority of the evidence on the benefits and potential harm of interventions to reduce CVD risk comes from high-income countries. The limited observational epidemiological data from low- and middle-income countries, recently extended by the INTEHEART case-control study, in 52 countries across the world support the view, - that cardiovascular risk factors are equally predictive of CVD events in a wide range of low-, middle- and high-income countries [1]. Thus, it seems reasonable to assume that the evidence related to lowering risk factors for CVD by using conventional approaches is also applicable to people in different settings.

Bibliography