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Editorial

Atherosclerosis & ischaemic heart disease: Here to stay or gone tomorrow

Atherosclerosis, with its clinical manifestations such as ischaemic heart disease (IHD), stroke and peripheral arterial disease, is a leading vascular disease worldwide[1]. The belief that atherosclerosis is a disease of the modern society is inaccurate. Studies in mummies dating as far back as 3300 BCE have evidenced the presence of atherosclerosis in all vascular beds and across various geographic regions, cultures and lifestyles of that time[1,2]. Although predisposing factors for atherosclerosis in ancient populations remain obscure, the use of domesticated animals (and consequently a fatty diet), air pollution (exposure to open fire and cooking in living quarters) and frequent infections leading to increased inflammatory burden have been postulated[1]. The whole-genome study of the Tyrolean Iceman, a 5300-yr-old glacier mummy from the Alps, revealed several single-nucleotide polymorphisms known to predispose to atherosclerosis in contemporary humans[2]. These observations may suggest that atherosclerosis is an inherent component of human ageing[2] with a strong gene-environmental interplay in which genes underlie vulnerability whereas the environmental factors determine whether the disease will become clinically manifest[3]. In the Ebers Papyrus dating back to 1555 BCE, the Egyptian doctors gave the following description of angina pectoris (or myocardial infarction): 'If thou examinist a man for illness in his cardia, and he has pains in his arms, in his breasts and on one side of his cardia…it is death threatening him'[4]. This probably represents the oldest documented description of clinical IHD.

Following Heberden's description of angina pectoris in 1772[5], a series of anatomic and pathological studies by Lobstein (who introduced the term arteriosclerosis), von Rokitansky and Virchow described the histological features of atherosclerosis and proposed several theories for its development. For instance, the Virchow's inflammatory theory of atherosclerosis stood the test of time and conceptually is similar to the current-day theories that consider atherosclerosis an inflammatory disease[6]. In 1879, Hektoen recognized coronary thrombosis secondary to sclerotic changes in the coronaries as the cause of myocardial infarction[7], whereas in 1912, Herrick[8] concluded that angina pectoris could be due to slow and gradual narrowing of the coronary arteries and he was credited as being the first to coin the term 'heart attack'. Following these studies which proved the link between coronary atherosclerosis and clinical IHD, it took almost half a century for epidemiologists to focus their attention on factors that predispose to the development of atherosclerosis. Up to the middle of 20th century, physicians paid little attention to eventual factors that predispose to the development of atherosclerosis. The remarkable history of disease and demise of Franklin D. Roosevelt, the President of the USA from 1933 to 1945, elegantly summarized by Mahmood *et al*[9] in their review on the historic perspective of Framingham Study showed how limited was the professional (medical) knowledge and societal awareness with respect to cardiovascular risk factors at that time. Just to mention one example, in the late fifties of the 20th century, a systolic blood pressure of up to 210 mmHg and a diastolic blood pressure of up to 110 mmHg were considered as normal[10].

It was not until the 1940s that Paul Dudley White – for many considered as the father of preventive cardiology - pioneered the concept of cardiovascular prevention. White was among the first to recognize the familial history of heart attack occurring in younger age, high-fat/cholesterol diet, arterial hypertension, tobacco use, diabetes mellitus and physical inactivity as risk factors for atherosclerosis and recommended action against all of these as measures to reduce the

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risk of this disease[11]. He stimulated interest and support for the classic Framingham Heart Study which was established by the National Heart Institute (later named the National, Heart, Lung and Blood Institute) in 1948 to study the epidemiology and risk factors for cardiovascular disease. The study's specific goal was to investigate how heart disease develops by studying the lifestyle of residents of Framingham (Massachusetts). The study set the tone for almost the next 70 yr of research in the field of cardiovascular epidemiology. Historic records showed that the first volunteer was recruited for the study 69 yr ago on 29th September 1948[9] - a date that coincides with the World Heart Day. In a landmark publication in 1961, the Framingham Study investigators identified arterial hypertension, elevated cholesterol and electrocardiographic evidence of left ventricular hypertrophy as risk factors for IHD[12]. These investigators coined for the first time the term 'risk factor'. As stated by Nabel and Braunwald[13], with identification of these factors and others that followed, the veil that masked the underlying mechanisms in angina and myocardial infarction was lifted, and the concept that coronary heart disease and its complications could be prevented was introduced.

The Framingham Study and the other studies that followed inspired numerous population-based strategies and professional guidelines, with specific targets aiming to adopt a healthy life. These prevention strategies took place mostly in high-income developed countries. Parallel with this epidemiological activism that gradually increased the awareness of society with respect to importance of disease prevention, numerous discoveries and developments occurred in the field of diagnosis and therapy of cardiovascular disease, particularly IHD. In the years following the 2nd World War, novel techniques and therapies such as coronary artery angiography, coronary artery bypass surgery, coronary care units, percutaneous coronary angioplasty, beta-blocking agents and powerful lipid-lowering agents (statins) were developed and used in clinical practice[14]. Continuous refinements in stent technology and development of highly effective antithrombotic therapy enabled percutaneous coronary intervention even in the most severe forms of IHD. The recent powerful lipid-lowering therapies, particularly proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and RNA interference, allow putting under control of even the most severe hyperlipidaemias[15]. Highly effective drugs have been developed to treat arterial hypertension and diabetes, the well-known risk factors for IHD. This progress revolutionized cardiovascular medicine so that IHD rarely represents a diagnostic or therapeutic dilemma in the current clinical practice.

The widespread modifications in lifestyle behaviour at the population level caused by population-based preventive strategies, treatment of cardiovascular risk factors by making cost-effective interventions accessible and affordable for individuals at high risk for developing IHD (or with disease) and better treatment of patients with IHD are responsible for several positive trends in the epidemiology of atherosclerosis and IHD, primarily in high-income developed countries. First, there have been dramatic declines in the IHD and stroke-related mortality in high-income countries since the middle of 20th century. Similar trends have also been reported in many low- and middle-income countries; however, no decline or opposite trends have been reported in several countries, particularly in sub-Saharan Africa, Eastern Europe and South-East Asia[16]. Second, there has been a decline in the incidence of myocardial infarction in European countries, England and the USA, with an annual reduction between 4 and 5 per cent in adults 35 to 74 yr of age[16]. Over the last two decades, there has been a change in the type of myocardial infarction as well. Most reports from Europe and the USA show steep declines in the incidence of ST-segment elevation myocardial infarction (STEMI) and less steep declines (or increases) in the incidence of non-STEMI over this time period. Opposite trends in the incidence of hospitalization for STEMI were reported in China[16]. Third, over the last three decades, parallel with the reduction in the incidence of IHD of new onset, there has been a decrease in the proportion of adults who smoked, and those with arterial hypertension and dyslipidaemia[17]. However, the strength of association between smoking, systolic blood pressure, dyslipidaemia and IHD did not change over time. This underscores the need for more preventive efforts targeting these cardiovascular risk factors. Although the prevalence of diabetes trended upward, the fraction of IHD attributable to diabetes decreased over time, due to attenuation of the association between diabetes and IHD[17]. Fourth, autopsy studies of soldiers who died in wars over the last 70 years have shown that the prevalence of atherosclerosis may have decreased. Thus, among soldiers who died in Korean (1950-1953), Vietnam (1955-1975) and Iraq (2003) wars, atherosclerosis was present in 77, 45 and 8.5 per cent

of the autopsies[18]. However, caution is warranted in interpreting these data due to various methods used to detect atherosclerosis in these three historical times.

Stimulated by the proof of cholesterol hypothesis of atherosclerosis, better definition of genetic risk factors, remarkable success of statins and other preventive measures, Brown and Goldstein[19] (the 1985 winners of Nobel prize in Physiology and Medicine for their discoveries concerning the regulation of cholesterol metabolism) anticipated that these achievements may end IHD as a major public health problem early in the 21st century. However, despite positive trends in the reduction of primary IHD in high-income developed countries, current epidemiological evidence suggests that IHD continues to be a major public health problem worldwide. Thus, with an estimated 17.3 million deaths, cardiovascular disease was the most common underlying cause of death in the world in 2013[20-22]. This accounts for 31.5 per cent of global deaths. With an estimated 8.2 million deaths, IHD was the leading cause of deaths due to cardiovascular disease. Further, an estimated 8.56 million cases of myocardial infarction and 10.3 new cases of strokes (67% of ischaemic origin) occurred in 2013 worldwide. Notably, 12 million deaths of cardiovascular origin occurred in low- and middle-income countries in 2013[20]. These data clearly show that epidemiological goals of ending the IHD as a major public health problem have not been fulfilled.

Reviews of epidemiological studies show that IHD is one of the most important causes of morbidity and mortality in India and thus a major public health problem. Studies have shown increasing IHD prevalence over the last 60 years, from 1 to 9-10 per cent in urban population and from >1 to 4-6 per cent in rural populations in the country[23]. All studies conducted in the last two decades indicate a 2- to 4-fold increase in the prevalence of IHD[24]. Between 2004 and 2015, the estimated number of patients with IHD increased from 29.8 to 61.5 million, whereas from 2000 to 2015, mortality attributable to IHD increased from 1.3 to >2.9 million[24]. The burgeoning of IHD in India can be explained by the alarming rise in the prevalence of cardiovascular risk factors such as obesity, abdominal obesity, arterial hypertension, dyslipidaemia and diabetes as well as highly prevalent unhealthy lifestyles such as smoking, physical inactivity, low fruit and vegetable consumption, alcohol abuse and the use of trans fat foods[25]. Even the most recent evidence from the urban and rural national capital region showed an overall worsening of the cardiovascular risk factors at population level[26]. Krishnan[27] and Sriharibabu[24] offered a clear view of epidemiology of IHD and preventive strategies being undertaken in the country. In a country with multiple problems standing high on the societal agenda, transforming the compelling evidence from these studies into large-scale efforts to first attenuate and later reverse trends toward the epidemic proportions of IHD and its risk factors or improve the therapy of patients with IHD remains difficult.

Due to the complexity of the problem, future changes in the epidemiology of IHD are difficult to predict. However, based on the current epidemiological parameters and trends, some predictions may be made. The positive trends towards reduction in the incidence of IHD, prevalence of some risk factors and embracement of a healthy lifestyle are projected to continue in most high-income countries. All-out war on cholesterol with the increased use of statins and modern lipid-lowering drugs (PCSK9 inhibitors and RNA interference strategies) with lowest possible cholesterol levels as targets of therapy will continue unless some serious adverse events with these drugs (or low cholesterol levels) are documented. Therapy against inflammatory components with an essential role in atherosclerosis will be used more frequently. There are strong indications that these strategies will delay or prevent atherosclerosis development or promote regression in case it was developed. Among novel strategies that aim to further improve IHD prevention, genetic factors are expected to take a more central stage. These will help in disentangling the complex interaction between risk factors and atherosclerosis. Genetic information is expected to improve risk stratification algorithms, provide information on the risk of atherosclerosis early in life (enabling primordial prevention in children and adolescents), predict drug efficacy or identify novel targets of therapy. Thus, future cardiologists will be more and more occupied with the interpretation of genomic tests in the setting of personalized prevention[28]. Parallel with these changes, a better treatment of IHD with the use of current and emerging new technologies or drugs will occur in developed countries. The ageing of the population and an increase in the prevalence of obesity, diabetes and chronic kidney disease (all of these increasing the risk of atherosclerosis) are expected to occur in the near future. To what extent these will put brakes on the favourable epidemiological developments remains to be seen. Although some developing countries may follow a trajectory directionally similar to that of

developed countries, many will follow a rise-and-fall pattern in the epidemiology of cardiovascular risk factors, IHD and related morbidity in the years to come. However, effective large-scale preventive strategies will be impeded by lack of resources and underdeveloped infrastructure in these countries. The healthcare systems in developing countries are faced with the huge task of treating an increasing number of patients with acute IHD (acute coronary syndromes). Since these numbers are trending upwards, this may exacerbate in the near future unless health infrastructure and facilities are improved.

As stated by Braunwald[28], a drastic reduction or even elimination of IHD could be the greatest victory that cardiology could aspire to. He also advocated the world cardiology community to set these goals for 2052 (150 years after Einthoven's string galvanometer and the birth of modern cardiology). We hope that these expectations will come true.

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