

India's March to Halt the Emerging Cardiovascular Epidemic

Meenakshi Sharma, Chandrasekharan C. Kartha, Bratati Mukhopadhyay, Ramesh K. Goyal, Suresh K. Gupta, Nirmal K. Ganguly, Naranjan S. Dhalla

Ayurvedic physicians of ancient India (2500 and 500 BC) recognized the heart as a controlling center connected to the entire body through channels (siras and dhamanis), which supplied nutrients to various tissues and provided passage for waste products. They claimed that any obstruction in these channels led to sickness in the body and performed treatment on the basis of personal knowledge of various herbal formulations, which continue to be used by current practitioners of the traditional Indian systems of medicine. Practice of modern cardiology and treatment of heart disease with allopathic drugs became a reality in India soon after the world war II, and research on the pathogenic and therapeutic aspects of cardiovascular diseases (CVD) was also initiated during the same period. We present the current status of cardiovascular research in India with emphasis on emerging information on risk factors for CVD and Indian efforts for arresting growing incidence of CVD, providing affordable care, and discovering new remedies.

Epidemiological Transition in CVDs

Epidemiological studies on CVD in India have been reviewed recently.¹ During the last decade, CVDs have emerged as the leading cause of morbidity and mortality in India and are responsible for healthcare burden to the tune of \$237 billion during 2005 to 2015.² Hospital-based studies from 1946 to 1962 reported an incidence rate of coronary heart disease ranging from 6% to 23% in cardiac patients of low-income groups and as high as 35% in high- and middle-income groups. A dramatic epidemiological transition has been witnessed during the last 2 decades. This transition is coupled with increased life expectancy from 58.3 to 65.2 years, lifestyle changes, rapid unplanned expansion of cities, and rural migration. CVDs presently account for two thirds of the mortalities because of noncommunicable diseases with 52% of deaths occurring <70 years of age and the mortality rates being higher in urban areas (>35%) and lower in rural areas (<10%).^{1,3} Cross-sectional studies from different parts of the country indicate that the

prevalence of coronary heart disease has gone up from 1.7% in rural and 2% in urban areas, respectively, in 1960 to 1970 to 7.4% in rural and 14% in urban areas by 2013. Hypertension is also a leading cause of morbidity (30% in the adult population). Prevalence of diabetes mellitus is 17% in urban and 9% in rural India. Mortality from heart failure is 18.6%. A recent population-based urban stroke registry at Ludhiana found age-standardized stroke incidence rate of 130 per 100 000 population.⁴ It has to be noted that large-scale longitudinal studies to estimate the burden of heart diseases have not been conducted in India.

Risk Factors for CVDs in Indian Population

Major nonmodifiable risk factors for CVDs in the Indian population are advancing age, family history, sex, and ethnicity. Major modifiable risk factors include hypertension, dyslipidemia, diabetes mellitus, obesity, and lifestyle risk factors, such as smoking, inadequate physical activity, and less use of fresh vegetables and fruits (zero to 1 serving of fruit in a week).⁵ There are 275 million tobacco consumers in India in the age group ≥ 15 years; 164 million use smokeless forms of tobacco.⁶ Although conventional risk factors are important, novel risk factors are considered to increase the risk of CVD in Indians. These factors include high lipoprotein (a), plasminogen activator inhibitor-1, fibrinogen, and low tissue plasminogen activator.⁵

The added cardiovascular risk in people of South Asian origin cannot be explained by conventional risk factors alone. Several candidate gene studies have reported that Indians have a genetic predisposition to atherothrombotic risk.⁵ A genetic basis for an increased coronary heart disease risk among South Asians is supported by the finding that South Asians tend to have higher lipoprotein (a) levels than other ethnic groups.⁷ Asian Indian phenotype refers to certain unique clinical and biochemical abnormalities in Indians, which include increased insulin resistance, greater abdominal adiposity, that is, higher waist circumference, despite lower body mass index, lower

From the Indian Council of Medical Research, New Delhi, India (M.S.); Rajiv Gandhi Center for Biotechnology, Trivandrum, India (C.C.K.); Policy Center for Biomedical Research, Faridabad, India (B.M.); Delhi Pharmaceutical Sciences and Research University, India (R.K.G., S.K.G.); Jawaharlal Nehru University, New Delhi, India (N.K.G.); and Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Center, Winnipeg, Canada (N.S.D.).

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Correspondence to Naranjan S. Dhalla, PhD, Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Center, Winnipeg, Canada R2H 2A6. E-mail nsdhalla@sbr.ca

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adiponectin, and higher high-sensitivity C-reactive protein levels.⁸ It seems likely that South Asians' enhanced susceptibility to CVD results from both genetic and environmental influences.⁹ There is evidence that a traditional vegetarian diet consumed by populations as found in Pune in India could lead to a genetic mutation in the gene *FADS*, which codes for a fatty acid desaturase catalyzing the rate limiting steps in the biosynthesis of long-chain poly unsaturated fatty acids that may increase inflammatory potential and individual's risk for heart disease.¹⁰

Translational Research

Major Indian centers for translational cardiovascular research and their focus are given in Online Table I.

Current Indian pursuits that have translational potential are (1) discoidin domain receptors and cardiac fibrosis, (2) cyclophilin A and vascular disease in diabetes mellitus, (3) interleukin-1 receptor-associated kinase in atherosclerosis, (4) catenestatin in hypertension, (5) genetic and evolutionary perspectives of dilated cardiomyopathy, (6) targeting cytochrome b5 reductase 3 to modulate hypertension, (7) identifying strategies to control acute coronary syndrome, (8) unravelling the role of sleep apnea in coronary artery disease, (9) exome-sequencing guided diagnostics for cardiomyopathy, and (10) community-level interventional studies.

Development of Valve and Vaccine for Rheumatic Heart Disease

Rheumatic heart disease (RHD) continues to be a major cardiovascular problem in India.¹¹ More than 2 million patients are estimated to experience RHD. The RE-LY (randomized evaluation of long term anticoagulant therapy) investigators observed that RHD contributes to 33% of the atrial fibrillation burden in India. RHD is also the leading cause of structural heart-valve damage in the country. Because a large majority of patients with RHD in India are unable to afford expensive imported artificial valves, an indigenous TTK Chitra valve was developed at Sree Chitra Tirunal Institute for Medical Sciences and Technology at Trivandrum. This valve has >90 000 implantations to date. Efforts are also being made to develop a vaccine against group A *Streptococcus*—the causative agent for rheumatic fever. The wide heterogeneity of group A *Streptococcus* isolates from throat swabs of children with rheumatic fever poses challenges for development of an ideal vaccine.

Development of Fibrinolytics and Coronary Stents

Given the limited access, thanks to high cost of imported streptokinase, investigators at the Institute of Microbial Technology at Chandigarh developed an indigenous natural streptokinase in 2001 and a recombinant streptokinase in 2009, and recently, a third generation of clot-specific streptokinase by fusing the core of streptokinase with fibrin-binding domain 4 and 5 of human fibronectin. This clot buster has been given permission for phase II clinical trial. The requirement for coronary stents has increased considerably in India. Sahajanand Medical Technology at Surat has developed minimally invasive coronary stent systems.¹² Their sirolimus and everolimus drug-loaded stents have a blend of biodegradable

polymers and a hydrophilic top layer. Institute of Chemical Technology at Mumbai developed inffinium—a drug-eluting stent, which received CE (Conformité Européenne) mark for biodegradable polymeric drug-coating technology.

Stem Cell Research in India

Indian efforts in research on cardiac regeneration include investigations using induced pluripotent stem cells, attempts to enhance the yield of cardiac stem cells for implantation, genetically modify progenitor cells for improving their function, and assessing efficacy of stem cell transplantation through clinical trials.^{13–15}

Translational Research on Herbal Medicines

India has a rich heritage of ancient knowledge on herbal drugs.^{16,17} An early major contribution to cardiovascular sciences in modern India is the discovery by Rustom J. Vakil on the use of reserpin—an alkaloid from the extract of roots of *Rauwolfia serpentina*—in treating patients with hypertension. Recently, several herbal medicines have been shown to possess antiplatelet, hypolipidemic, anti-inflammatory, hypoglycemic, and hypotensive actions. Gugulipid—a cholesterol-lowering agent developed from the plant *Commiphora mukul* by scientists at Central Drug Research Institute at Lucknow has an activity comparable with clofibrate. Allyl methyl sulfide and allyl methyl sulfoxide, 2 ingredients of garlic, have been shown to increase the expression of Na⁺/K⁺-ATPase protein, decrease intracellular calcium levels, and attenuate cardiac hypertrophy.¹⁸ Herbs namely *Withania somnifera*, *Curcuma longa*, and *Ocimum sanctum* and their combinations have been found beneficial in reducing myocardial injury.

Government of India has established a separate ministry Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy to encourage research and promotion of Indian traditional systems of medicine. Ayurvedic Biology Program of Science and Engineering Research Board of Department of Science and Technology is an independent new program which supports basic and translational research on Ayurvedic concepts and Ayurvedic medicines for use in clinical practice. Ayurnutrigenomics is an emerging field of research for understanding pathogenesis and evolving strategies for management of CVD.¹⁹

Funding for Cardiovascular Research

In 2007, Government of India created the Department of Health Research under the Ministry of Health and Family Welfare with a mandate to promote basic, applied, and clinical research through development of infrastructure, manpower, and skills in cutting-edge areas. The problem of noncommunicable diseases was addressed in the National Health Policy in 2017¹⁹, and the Government announced an increase in public health expenditure to 2.5% of the gross domestic product. The major objective of this policy was to shift focus from sick care to wellness and target reduction of morbidity and mortality because of CVDs by 25%.

Indian Council of Medical Research under Department of Health Research coordinates Department of Science and Technology, Science and Engineering Research Board, Department of Biotechnology, and Council of Scientific and

Industrial Research for funding various research projects. Funds disbursed by these agencies for cardiovascular research are not available in the public domain. Currently, there is no separate and specific budgetary provision for funding cardiovascular research. The budget of Indian Council of Medical Research for funding research in all domains in the current year (2017–2018) is an equivalent of \$232 million, which is significantly less in comparison with 32 billion dollars a year—the budget of National Institute of Health in the United States. Funding for projects is based on recommendations of program advisory committees of the funding agencies, which call for proposals from investigators, review them, and make recommendations for funding. Universities and institutions also support investigator centric projects. A few Indian scientists have been successful in obtaining funding from international agencies, such as The Wellcome Trust, Melinda Gates Foundation, National Institutes of Health, United States, and through bilateral programs between India and countries, such as Australia, Canada, France, Germany, United Kingdom, and the United States.

Publications

An analysis of total number of publications from India listed in PubMed during 1985 to 2015 revealed that the number of publications related to cardiovascular research are increasing, although considerably less compared with publications related to cancer research (Figure [A]).

Ten thousand four hundred articles related to cardiovascular sciences were published during the last 10 years. A subject-wise classification of these publications is given in Figure (B). More than 50% of the publications are related to hypertension, coronary artery disease, atherosclerosis, and myocardial infarction. Notably, only a small proportion of these articles are published in journals with an impact factor ≥ 5 (Figure [C]).

Way Forward

The future course is to unravel the causes for greater risk for CVD in Indians, identifying population groups at increased risk and the risk factors, which are to be targeted, and discovering cost-effective ways of treating established disease.

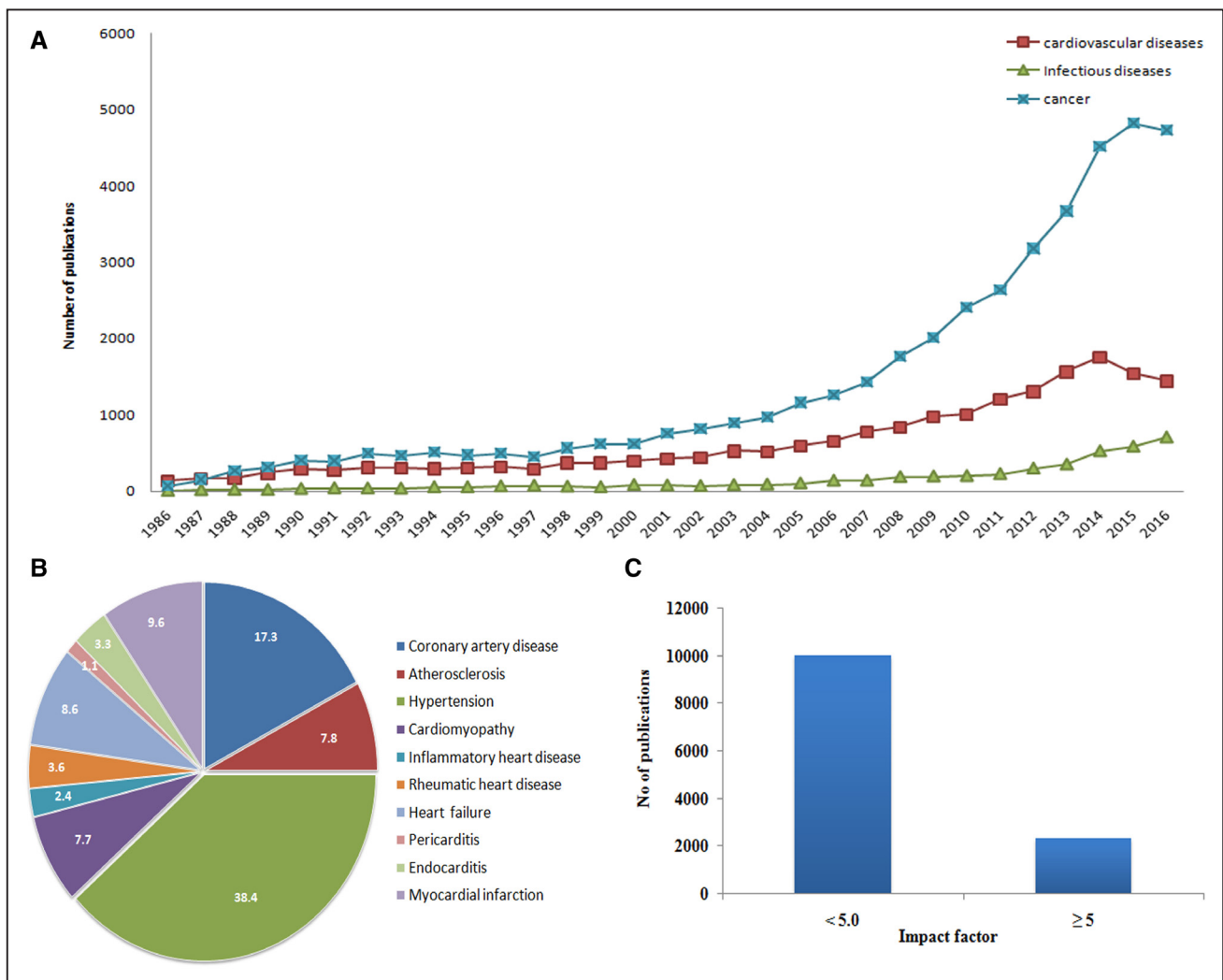


Figure 3. A, Trend of total number of scientific publications in the fields of cardiovascular research, cancer research, and infectious diseases research from India during the last 30 y. B, Subject-wise classification of cardiovascular research publications from India during the last 10 y. Total number of cardiovascular research publications during the period was 10400. C, Classification of cardiovascular research publications from India during last 10 y based on impact factor of journals, categorized as those with impact factor >5 and ≥ 5 . The information given here was retrieved from PubMed.

Sadly, cardiovascular research is pursued only by a small proportion of >4000 practicing cardiologists in India. The number of basic scientists pursuing cardiovascular research is around 200.

The complete absence of orientation toward research and limited community perspective in formative years of medical education, paucity of clinical cardiologists dedicated to doing quality research, limited avenues for cross talk between basic scientists and clinicians, and declining standards of academic centers have been indicated as impediments to high-quality cardiovascular research in India.²⁰ The way forward is through specific policies, to restructure medical education, enhance capacity for translational research, improve interinstitutional collaboration, and facilitate multi-institutional studies.

To meet the challenge of near total dependence on imported materials/devices needed for treating CVDs, academia and industry have to partner and stimulate innovation for development of diagnostic and therapeutic devices, keeping in mind the Indian realities (eg, shortage of power and power cuts in rural areas which necessitate instruments, which can be run on battery power and point-of-care diagnostic devices that can be used at primary healthcare settings). To meet the above demands, it is also vital to find ways of augmenting financial resources for cardiovascular research.

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Disclosures

None.

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Supplementary Table. Indian institutions with their focus on cardiovascular research

Institution	Focus
All India Institute of Medical Sciences, New Delhi	Cardiovascular physiology and pharmacology, stem cell research for cardiac regeneration, clinical research, medical device development
Central Drug Research Institute, Lucknow	Cardiovascular drug discovery
Delhi University for Pharmaceutical Sciences and Research, Delhi	Cardiovascular drug discovery
Indian Institute of Technology, Chennai	Cardiovascular genetics, basic cardiovascular research, atherosclerosis, hypertension
Indian Institute of Technology, Mumbai	Medical device development
Institute of Genomics and Integrative Biology, New Delhi	Cardiovascular genetics, hypertension, vascular disease
Institute for Stem Cell Biology and Regenerative Medicine (InStem), Bangaluru	Genetic cardiomyopathies, basic research, stem cell research
Jawaharlal Institute for Postgraduate Medical Education & Research, Puducherry	Cardiovascular pharmacogenomics
Madurai Kamaraj University, Madurai	Cardiovascular basic research
Public Health Foundation of India, Centre for Chronic Conditions and Injuries, New Delhi	Cardiovascular epidemiology, prevention, health education, policy development, advocacy programs
Postgraduate Institute of Medical Education and Research, Chandigarh	Basic and clinical cardiovascular research, rheumatic heart disease, cardiomyopathies, hypertension, cardiovascular genetics
Rajiv Gandhi Centre for Biotechnology, Trivandrum	Cardiovascular disease biology, basic and translational research for biomarkers, identification of novel drug targets
Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum	Clinical and basic research, medical device development, public health research
St.John's Medical College, Bengaluru	Cardiovascular epidemiology and prevention
Thrombosis Research Institute, Bengaluru	Atherosclerosis vaccine
Translational Health Sciences & Technology Institute, Faridabad	Discovery of formulations of plant based drugs for cardiovascular diseases, Development of affordable and cost effective medical devices and stem cell research and tissue engineering for cardiac regeneration.