

Global perspectives on cardiometabolic risk and cardiovascular disease: from basic science to bedside

As guest editor of this special issue of the *Annals of Translational Medicine (ATM)*, I am pleased to present the work from invited authors who offer international perspectives on critically important topics related to cardiometabolic risk and cardiovascular disease (CVD). The World Health Organization (WHO) has estimated that CVD is the number one cause of mortality globally, with more people dying annually from CVD than from any other cause (1). With as many as 17.7 million people dying from CVD in 2015, CVD represents 31% of all deaths worldwide (1). Moreover, over three quarters CVD deaths occur in low and middle-income countries, highlighting that this problem is not unique to industrialized nations (1). Accordingly, this special issue of the *ATM* provides perspectives on CVD not only in the United States (US), but also worldwide. We present a global, comprehensive view of innovative research, reviews, editorials and perspectives from basic science at the bench level to clinic interventions and public health considerations. While this edition of *ATM* builds on much of the research and clinical care conducted at Tulane University School of Medicine in New Orleans, Louisiana, USA, it also highlights provocative insights from other authors from the USA, along with articles from basic science researchers, clinicians and public health specialists from Africa, Europe, Asia and South America.

The first paper is a comprehensive review of emerging concepts in genetics and genomics affecting the field of hypertension (2). In “*Hypertension genomics and cardiovascular prevention*”, Ng *et al.* propose that high blood pressure may be associated with a wide range of genetic factors, which may, in the future, impact pharmacological and lifestyle-based clinical interventions. One concept detailed is a genetic risk score (GRS), which may lead to improved recognition of high risk patients and has the potential of impacting the lives of numerous persons with hypertension and associated cardiovascular conditions. Nevertheless, the actual adoption of the GRS approach and the application of newer genomic data to clinical practice await further developments, such as a decrease in the technological cost of determining genetic variance. In the future, based on large genome-wide association studies and the wealth of associated data, hypertension genomics may emerge as an area with significant impact on our knowledge and care of people with hypertension.

A subsequent report in the field of hypertension is from the thought-provoking work of Brewster, titled “*Creatine kinase, energy reserve, and hypertension risk: from bench to bedside*” (3). Over several years, Brewster has extensively examined the relationship between the ATP-regenerating enzyme, creatine kinase (CK), and cardiovascular function. Her theoretical modelling suggests that energy expenditure may directly relate to blood pressure generation and that there may be effects of CK on the energy demands affecting hypertension. Her insightful data examine various races/ethnicities and show hypothesis-generating evidence that CK is a significant predictor of blood pressure and human resistance artery contractility. Furthermore, there may be a relationship between CK and other factors leading to increased blood pressure, including sodium retention. Brewster’s work involves both animal studies, human observation and delineates potential effects on blood pressure, especially in persons of African ancestry. Her theoretical model may explain, to some extent, the disparate levels of hypertension and associated diseases across the African diaspora.

Secondary hypertension (SH) remains a frequently underdiagnosed condition, mainly due to difficulties in its identification, which is affected by the cost and availability of advanced diagnostic procedures. Consequently, there are variations in the published incidences of SH, which is often associated with severe, resistant hypertension. A consortium of authors from South America led by Kotliar, as well as clinicians from Tulane University, present a novel and potentially cost-effective approach to the early diagnosis of patients with SH, in “*Improved identification of secondary hypertension: use of a systematic protocol*” (4). The team at Austral University Hospital, Buenos Aires, Argentina, created a comprehensive screening questionnaire that may help unmask the etiology of SH. Their Center of Hypertension, at the Institute of Cardiology (CHIC) protocol revealed a higher incidence of SH than reported in many prior peer-reviewed reports and may guide physicians and other providers to the early diagnosis of relevant conditions, such as pheochromocytoma and Cushing’s disease. Therefore, this CHIC protocol offers a new diagnostic paradigm that may contribute to the appropriate recognition and diagnosis of SH in a wider range of patients from moderate and severe hypertension.

Additionally, resistant hypertension (RHTN) is a potent CVD risk factor. In “*Advances in resistant hypertension*”, Calhoun,

from the University of Alabama at Birmingham, Alabama, USA, comments specifically on this important area of severe and poorly controlled hypertension (5). Increasingly, physicians and other clinicians have relied on evidence-based guidelines to assist with appropriate CVD diagnosis and treatment. The American College of Cardiology and American Heart Association, in conjunction with a large consortium of US professional organizations, published the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, perhaps the most extensive contemporary report offering guidance on treating hypertension, in all of its aspects (6). Calhoun outlines the historical evolution of the definition of RHTN and then clarifies the diagnosis as described in the recent 2017 guideline. Furthermore, he emphasizes the often under-recognized presence of pseudo-resistant hypertension, including poor blood pressure technique, clinical inertia and sub-optimal medication adherence. This provocative editorial also gives perspectives on best practices to control RHTN, including evidence of the superiority of mineralocorticoid receptor antagonists, specifically spironolactone.

Although many of the articles in this special edition are from Western or developed societies, it is critical to recognize the rise of CVD in low- and middle-income countries. Accordingly, 82% of all non-communicable diseases (NCDs) in 2015 were from low- and middle-income countries, of which 37% are caused by CVD, accounting for over three quarters of CVD deaths worldwide (1). The WHO suggests that the upcoming epidemic of CVD in non-industrialized countries may be prevented by addressing risk factors such as tobacco use, poor diet and obesity, lack of exercise and harmful use of alcohol (1). While CVD rates rise in both industrialized and non-industrialized nations alike, patients in lower income countries often do not have the benefit of integrated primary health care for early CVD detection and treatment, when compared to people in high-income countries (1). As a result, if public health officials and clinicians do not address the emerging burden of CVD globally, many people will die prematurely, often in their most productive years with the poorest people most affected.

Unfortunately, CVD has now become the leading cause of death in India and the global burden of cardiometabolic diseases is expected to increase, with individuals of lower socioeconomic backgrounds often having less than optimal therapy and consequently, poorer outcomes. Uday M. Jadhav describes an upcoming tsunami, not dissimilar to the disaster after the Indian Ocean earthquake in 2004 (7). In a country of 1.3 billion people, he describes a unique “atherogenic dyslipidemic profile” and a “South Asian phenotype”, with high propensity for metabolic syndrome. Jadhav notes in “*Cardio-metabolic disease in India—the upcoming tsunami*” that while there is a paucity of national data on CVD in India, there is increasing evidence to suggest a growing, widespread burden of CVD and cardiometabolic diseases. He unveils a provocative concept of “contaminated vegetarianism”, which may actually contribute to the obesity and metabolic syndrome epidemic by its inclusion of invisible fats that are often added during cooking, in the form of partially hydrogenated vegetable oils, butter and ghee (clarified butter). He also details what is unknown regarding any ethnic predisposition in South Asians and further suggests positive approaches that may assist with avoiding the upcoming tsunami, while addressing different social determinants of health and lifestyle.

Subsequently, Ji-Guang Wang describes the ambitious plans and progress for the improved diagnosis and control hypertension in China, the world’s most populous nation (8). He identifies comprehensive, progressive initiatives in China, which has a fast growing economy and ageing population, ripe for increasing levels of hypertension. Accordingly, he notes that the prevalence of hypertension in adults (18 years and older) has increased approximately by 50% from 2002 to this decade (8) and despite the improved management of hypertension, there remain major challenges. In addition, he highlights two unique initiatives: expanding the use of ambulatory blood pressure monitoring to guide diagnosis and treatment and the enhanced identification of primary aldosteronism and resistant hypertension. China, as noted in his article, “*Unique approaches to hypertension control in China*,” is utilizing modern technology to diagnose and improve control of the growing hypertension-related burden, including a web-based blood pressure measuring system, equipped with a validated automated electronic blood pressure monitor.

Similarly, for many decades, there has been a steadfast increase in the prevalence of hypertension and CVD in sub-Saharan Africa (sSA). This represents a shift in the public health paradigm, from the burden of communicable disease, such as tuberculosis and malaria to the growing impact of NCDs. This current state of heart disease is reviewed in the editorial, “*Hypertension and cardiovascular disease in the sub-Saharan African context*” by Seedat *et al.*, analyzing how different determinants of health, including economics, geography and obesity in sSA are factors to this increase in CVD (9). The authors give an historical overview of the state of NCDs, including a focus on obesity in South Africa, and its impact on hypertension in this population. Furthermore, a specific description of barriers to the successful implementation of CVD prevention and patient

education policies and strategies are also explored. In consideration of these factors, these authors propose that curtailing the rise of hypertension and CVD in sSA entails great challenges, but also the potential of significant successes. This editorial contains informative figures that illustrate factors leading to increased insulin resistance, affordability of prevention in low resource nations and methods to improve adherence to CVD medications.

Specifically in the USA and industrialized societies, heart failure (HF) is a leading cause of an extensive economic burden, associated with increasingly older populations. Efforts have been made in the Medicare program, which insures people in the US who are aged 65 years or older and persons with disabilities, to monitor and curtail the increasing monetary expenditures of caring for persons with HF, especially due to hospitalization and recurrent hospitalization. Nevertheless, projections have estimated that the prevalence of HF will increase 46% from 2012 to 2030, resulting in over 8 million Americans with HF, presenting a high economic burden (10). A unique approach to curtail the load of HF readmissions and its associated economic costs is presented by Zohrabian *et al.* in “*The economic case for US hospitals to revise their approach to heart failure readmission reduction*” (11). Zohrabian and colleagues detail the steep healthcare expenditures associated with HF and provide a novel approach to reduce HF costs, utilizing employer self-insurance. The authors suggest that a combination of wellness and chronic disease management programs, utilizing a self-insurance approach, may lead to both limiting unnecessary dollars spent for healthcare and improved health outcomes.

Moreover, in the US and other developed societies, modern diagnostic tools and advances therapeutic approaches, including devices, are widely available for the treatment of persons with acute cardiovascular conditions. Several papers in this special edition address unique aspects of advanced therapeutic interventions and surgery for persons with CVD, including coronary artery disease (CAD) and HF.

In major medical centers that have the ability to treat high-risk patients with hemophilia, the specific aspects of coronary interventions in this population are emerging and are not clearly defined. Therefore, in an attempt to provide clinicians with expert opinion on best practices, the article “*Current concepts in the management of stable ischemic heart disease and acute coronary syndrome in patients with hemophilia*”, by Jabbar *et al.* details unique aspects of this clinical situation (12). This review describes CAD, including stable ischemic heart disease (SIHD) and acute coronary syndrome (ACS) with hemophilia and the use of percutaneous coronary intervention (PCI). Therefore, Jabbar *et al.* note that, despite the potential benefits of PCI in these patients, the risk of hemorrhage presents a dilemma with hemophilia A and B. Furthermore, they recount an interesting clinical case that reveals the complex medical-decision making necessary for the appropriate management of SIHD and ACS in patients with hemophilia.

One of the most widely utilized therapeutic approaches to severe CAD is coronary artery bypass grafting (CABG). Prior to patients undergoing CABG, an accurate diagnostic assessment of the extent of the optimal CAD targets must be made, often approached only using anatomic visualization strategies. The article “*Physiologic assessment of moderate coronary lesions: a step towards complete revascularization in coronary artery bypass grafting*”, by Moscona *et al.* present a method utilizing the physiologic assessment of coronary lesions to effectively guide the complete revascularization in patients undergoing CABG (13). Through a retrospective review of medical records from patients at Tulane Medical Center, Moscona *et al.* via calculation of the fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) found that FFR/iFR-guided CABG was associated with higher rates of successful three-vessel anastomoses, venous grafting and graft distribution to the circumflex system. The authors offer the physiologic approach as an alternative, and perhaps superior method, for the diagnostic assessment of best CAD targets by cardiologists prior to CABG.

Finally, pulmonary arterial hypertension (PAH) is an often fatal condition, despite modern therapeutic options. Moreover, the right ventricle (RV) is the major determinant of prognosis in all types of PAH. In consideration that the left ventricular dysfunction and RV dysfunction are associated with neuro-hormonal activation, “*Neurohormonal modulation as therapeutic avenue for right ventricular dysfunction in pulmonary artery hypertension: till the dawn, waiting*”, by Roy Emanuel *et al.* (14) describes the pathophysiological background supporting the appropriate management of PAH related RV dysfunction. Unfortunately, patients with PAH and RV dysfunction often do not receive neuro-hormonal modulators, including beta adrenergic blockers (BB) and renin-angiotensin-aldosterone system (RAAS) inhibitors due to the fear of side effects. This provocative review, highlighting neuro-hormonal modulation, offers a potentially optimal therapeutic avenue for the management of RV dysfunction in PAH and proposes the need of further studies.

In conclusion, I would like to express my sincere gratitude to the *ATM* for providing all the authors this unique

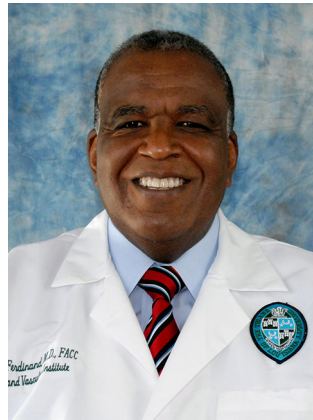
opportunity to address cardiometabolic risk and CVD with such depth and breadth, from an international perspective. We certainly hope that this special edition will be valuable to the readers of the journal and that it will stimulate fruitful thinking, useful discussions and dissemination of knowledge to the benefit of our patients and global populations.

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