Preface

Mechanisms-based therapeutic strategies in type 2 diabetes

Prevalence of diabetes mellitus (DM) is increasing rapidly, and individuals with DM are at high risk for cardiovascular (CV) disorders that affect the heart, brain and peripheral vessels. The International Diabetes Federation currently estimates that 382 million people are affected by type 2 DM (T2D), with a global age-adjusted prevalence of 10%. If these trends continue, 592 million people, or one adult in 10, will have diabetes by 2035 (1). This equates to approximately three new cases every 10 seconds or almost 10 million per year. Most importantly, a substantial proportion of affected people are unaware of their condition and do not receive treatment. Epidemiological studies have shown a strong association between T2D and the risk of CV events (2). Indeed, T2D increases the risk of micro- and macrovascular complications and it is associated with an approximate two-fold greater risk of mortality as compared with the general population (3). Metabolic alterations occurring in DM subjects, namely insulin resistance, reduced insulin secretion or their combination are responsible for endothelial dysfunction, increased platelet reactivity, inflammation and myocardial damage—all factors triggering and accelerating atherosclerotic vascular disease, coronary thrombosis and heart failure (HF). On this ground, understanding the pathophysiology of DM-related CV complications may be invaluable to elaborate novel mechanism-based therapeutic strategies to combat CVD burden associated with DM.

The range of articles featured in this focused issue—"mechanism-based therapeutic strategies in type 2 diabetes"—provides key insights on emerging aspects related to the pathogenesis of cardiac and vascular disease as well as CV risk factors in patients with T2D. Collectively, evidence discussed here support a wide translational vision linking disease mechanism to therapeutic approaches. The opening editorial by the guest editors—Drs. Paneni and Costantino—strengthens the importance of translational research in diabetes. The authors focus here on the emerging role of "omics" technologies in the analysis and interpretation of diabetes-related biological signals and their putative link with CV phenotypes.

The article by Dr. Cosentino, from the Cardiology Unit of Karolinska Institute, offers a timely overview of recent mechanisms underpinning vascular damage in patients with T2D. The editorial particularly focuses on the emerging phenomenon known as "metabolic memory", which may help to link long-lasting effects of hyperglycemia to atherosclerotic vascular disease and macrovascular complications. Epigenetic mechanisms are strongly involved in this process and drive the progression of vascular damage despite the achievement of optimal glycemic control.

A comprehensive and critical description of most recent advances in the pathophysiology and treatment of arterial hypertension in T2D is reported in the review article by Dr. Volpe and associates, from the Cardiology Department, University of Rome "Sapienza". Here, the authors describe the common mechanisms, the potential sites of therapeutic interactions and the currently recommended blood pressure targets to be achieved under pharmacological treatment in hypertension and diabetes. The document will prove invaluable to Cardiologists, Internists and Diabetologists.

Drs. Avogaro and Fadini from the Department of Medicine—University of Padua—present a very interesting article on the most recent advances underlying diabetes-related vascular calcification, an early feature triggering the atherosclerotic process. Specifically, the article describes in detail the molecular events preceding vascular calcification, namely inflammation, transdifferentiation of vascular cells and homing of circulating pro-calcific cells. These aspects deserve attention since osteogenic precursors are being considered as potential biomarkers to stratify atherosclerotic and mortality risk in the diabetic population.

Another important aspect to be considered when it comes to vascular damage is represented by vascular repair mechanisms. In this regard, Kuschnerus and colleagues from the Department of Cardiology, Charité—Universitätsmedizin Berlin, thoughtfully describe the mechanisms underpinning impaired function of vascular cells (i.e., endothelial cells, macrophages, adipocytes) and their role in T2D-related CV complications. The authors also provide key insights on novel therapeutic approaches employed to counteract these adverse processes such as lifestyle modifications, cell therapy, modulation of microRNAs as well as anti-diabetic drugs, namely incretin-based approaches.

Beside vascular complications, HF is a frequent condition occurring in patients with DM (4). Although DM is strongly associated with coronary artery disease (CAD), many cases of left ventricular dysfunction occur in subjects with non-obstructive CAD. In DM subjects, several factors including hyperglycemia (glucotoxicity), free fatty acids oxidation

(lipotoxicity), and inflammation contribute to define the phenotype known as diabetic cardiomyopathy, characterized by cardiac fibrosis, left ventricular hypertrophy, diastolic dysfunction and increased filling pressures (5). Understanding the molecular cues implicated in the progression of diabetic cardiomyopathy is a very important task to reduce HF-related burden in this setting. The article by Dr. Lebeche from the Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, offers a timely and very interesting translational perspective on emerging mechanisms responsible for a cardiac phenotype in diabetes, including maladaptive insulin signaling and other metabolic alterations. The article has a specific focus on the role of resistin—a novel cysteine-rich hormone secreted by rodent fat cells—as a determinant of impaired glucose metabolism and insulin action in the diabetic heart. The roles of resistin in human CVD as well as resistin-targeted therapies are also discussed. Along the same line, a comprehensive review by Dr. Sciarretta and Sadoshima from Cardiovascular Research Institute of Rutgers New Jersey Medical School, addresses the role of autophagy, an intracellular system for protein degradation, in the pathogenesis of diabetes and obesity-related cardiac dysfunction. The article carefully describes the mechanisms whereby metabolic disturbances impair the autophagic process, and how autophagy reactivation may contribute to rescue diabetic cardiomyopathy phenotype. Restoration of autophagy represents a future potential therapeutic intervention to reduce cardiac abnormalities in patients with obesity, metabolic syndrome and T2D.

Alteration of cardiac structure and function is inevitably associated with an array of detrimental consequences, including arrhythmias. Atrial fibrillation (AF) remains the most frequent sustained cardiac arrhythmia worldwide and its incidence increases with ageing, CV risk factors and comorbidities (6). Experimental and clinical evidences suggest that DM and AF are strongly interconnected. The review by Dr. De Sensi and Dr. Breithardt, from the Cardiology Unit, Misericordia Hospital, Grosseto and Department of Cardiovascular Medicine, University Hospital, Münster, addresses in detail new molecular pathways implicated in the etiology of AF and their relevance for mechanism-based therapeutic strategies in this setting. Advances in in risk stratification, drug therapy (i.e., new anticoagulants) and catheter ablation are also described.

Taken together, the articles included in this focused issue offer a timely update on new mechanisms and putative therapeutic strategies to prevent CVD in patients with DM. These novel insights will contribute to raise knowledge among CV scientists as well as clinicians operating in the field of diabetes and CVD.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 6th edition. Brussels, Belgium: International Diabetes Federation. Available online: https://www.idf.org/diabetesatlas
2. Beckman JA, Paneni F, Cosentino F, et al. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J 2013;34:2444-52.
3. Haffner SM, Lehto S, Rönnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
4. Dei Cas A, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail 2015;3:136-45.
5. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007;115:3213-23.
6. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840-4.

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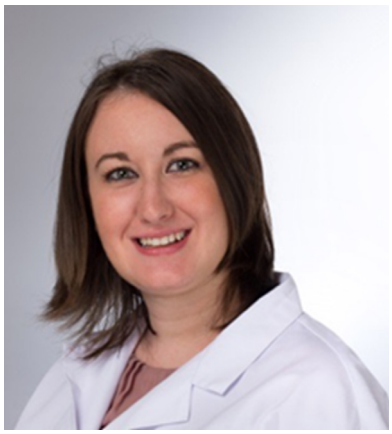

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