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Emerging strategies for diabetes and cardiovascular disorders: Introduction and foreword

Prakash Deedwania

University of California, San Francisco, 2315 East Kashian Lane, Fresno, CA 93701, United States of America

Diabetes mellitus (DM) and cardiovascular (CV) disorders/diseases (CVD) are major public health problems. Both are chronic conditions that are increasing in the US and rest of the world. Both of these disorders are amongst the top 10 leading causes of death and disability in the world. In the United States, DM affects approximately 25 million people and many more have pre-diabetes. Globally, the International Diabetes Federation estimates that nearly 400 million persons are afflicted with DM and these numbers are rapidly increasing so that by 2045 more than 500 million will have DM. These numbers should not be surprising given the high prevalence (70–75% of US adults) of overweight and obesity in the population. The Center for Disease Control has forecasted that 1 out of 3 children born in last decade will be at risk of developing DM by 2025. With these alarming numbers, it seems appropriate to consider that DM has become a major pandemic of the 21st century.

DM increases the risk of CVD by 2–4-fold and its presence in those with CVD is one of the most powerful predictors of adverse clinical outcome. Certainly, CVD are the major consequences of DM and most people with DM will die of CVD complications. People with DM have 2 out of 3 chance of developing CVD over the course of their lifetime. The CVD complications in DM occur at an earlier age, and more often in women than men. The increased risk of CVD in DM is not only related to glycemic perturbations; rather, it is largely accounted for by the associated hypertension, atherogenic dyslipidemia, increased oxidative stress and inflammatory reactions, as well as the prothrombotic milieu frequently present in the diabetic patients. Many of these same risk factors are also responsible for increased risk of renal disorders and dysfunction frequently seen in patients with DM.

It is important to recognize that with significant advances in therapeutic modalities for management of CVD during the last several decades, there had been a remarkable decline in the CVD mortality. However, the overall incidence rates for CVD have not decreased which is largely attributed to the increase in the cases of DM in the population during this period. Thus, it is clear that the future efforts directed towards containing the ongoing epidemic of CVD will also need to focus on preventive measures aimed at reducing the burden of DM in the population.

It is well recognized that as many as two- thirds of patients with CVD with either acute coronary syndrome or stable ischemic heart disease have either previously diagnosed DM or will be subsequently diagnosed with it. It is, therefore, essential for the clinical cardiologist to be familiar with the latest therapeutic strategies and advances for the management of these patients. Although, in the past the available drugs for glycemic control in DM had been largely neutral or even had some harmful effects, the newer agents, like Sodium-glucose Cotransporter-2 inhibitors (SGLT2i) and Glucagon like Peptide 1 (GLP1) agonists have recently been shown to be not only effective and safe for glycemic control, but also have cardio-protective effects. These developments as well as better understanding and expansion of our knowledge regarding the prevalence, associated risk factors, pathophysiology of underlying processes involved, and development of various therapeutic strategies have been the primary stimulus for us to put together this special issue of the Progress in Cardiovascular Diseases titled “An Overview of Emerging Strategies for Diabetes and Cardiovascular Disorders “. I have invited the leading experts in their respective fields to share their knowledge by providing critical appraisal of the recent advances in the respective area(s) as these relate to the clinical management of DM and CVD.

We are very fortunate that Professor Eugene Braunwald has provided his valuable insights in the opening chapter titled “Diabetes, Heart Failure, and Renal Dysfunction: The Vicious Circles”. In this chapter, he emphasizes various interactions between DM, heart failure (HF), and renal dysfunction and proposes that interruption of these vicious circles with the newer cardio-protective drugs such as SGLT2i represent important therapeutic goals for the clinicians to reduce the burden of CVD in DM. His succinct and clear description of the underlying chain of events and the pathophysiologic processes involved provides considerable insights to the reader for better understanding the links between these disorders and provides helpful guidance for the selection of appropriate therapeutic choices to break the vicious cycles with the goal of reducing the disease burden. The next chapter by Henry Greenberg emphasizes the obvious” Preventing Preventable Chronic Disease: An Essential Goal”. This chapter details the evolution of cardiac risk factors, preventive strategies, and interactions between economic developments and societal structure as these relate to chronic disorders like DM and CVD. The impact of these chronic conditions on the health care costs and the need for appropriate policy development is also proposed. Continuing this discussion the next chapter by Nelson et al. describes the epidemiology of DM and the relative risk of atherosclerotic CVD (ASCVD) and HF in DM with a focus on the competing risks. These authors emphasize that ASCVD and HF represent the single largest cause of morbidity and mortality in patients with DM. As described

E-mail address: pdeedwania@fresno.ucsf.edu.

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in this chapter it is important to understand that although a common consequence of DM, HF is often a neglected "forgotten" complication and its early recognition with implementation of comprehensive risk reduction strategies utilizing the newer cardio-protective drugs like SGLT2i (that have been shown to be particularly effective) should improve the outcome in these patients. The following chapter by Murtaza et al. provides an updated review of the various stages of diabetic cardiomyopathy and discusses the underlying pathophysiologic processes and structural changes involved. They also describe the utility of various diagnostic measures including cardiac biomarkers and imaging modalities. Finally, they describe the epidemiology, role of various risk factors, and novel therapeutic strategies for patients with diabetic cardiomyopathy.

The subsequent chapters are dedicated to the discussion of various therapeutic strategies to reduce the burden of CVD in DM. In these chapters, special emphasis has been put on discussing the role of lifestyle changes and the utilization of evolving therapeutic strategies, including special focus on the newer anti-diabetic drugs and their role as cardioprotective agents. The chapter by Carbone et al. describes the link between obesity, caloric imbalance, physical inactivity, and diabetes with special emphasis on the underlying mechanisms responsible including the role of insulin resistance and systemic inflammation and structural changes in various adipose tissues in the body. They then provide detailed and convincing evidence for the pivotal role of therapeutic lifestyle changes, including dietary interventions, increased physical activity, exercise training, and cardio-respiratory fitness in reducing obesity and the associated risk of DM and CVD. The chapter by Gupta et al. focuses on the evolving role of pharmacotherapeutic approaches for diabetic dyslipidemia to reduce the risk of CVD in DM. In this chapter, we discuss the pathobiology of atherogenic dyslipidemia in DM and then describe the results from various statin trials on reductions in Major Adverse Cardiac Events (MACE) with statin therapy in diabetic patients. In order to fully comprehend these findings it is important to emphasize that the seminal findings of the landmark UKPDS study had previously established the pivotal role of low-density lipoprotein cholesterol (LDL-C), more than glucose and blood pressure, in predicting the risk of macrovascular events (myocardial infarction/MI and stroke) in DM. A number of the statin trials have further substantiated the critical role of LDL-C by demonstrating significant decreases in MACE in the DM cohorts with intensive LDL-C lowering therapy. The STENO-2 trial confirmed these prior observations by showing that more than 70% of the dramatic reduction in CVD mortality demonstrated in that trial with comprehensive risk factor modification was attributed to the use of statin therapy. In the chapter on diabetic dyslipidemia we also describe the therapeutic role of non-statin drugs including fibrates, ezetimibe, proprotein convertase subtilisin/kexin-9 inhibitors, and the emerging (currently not available) drugs like inclisiran, bempedoic acid, and anti-inflammatory agent canakinuamab in patients with DM.

Perhaps the most dramatic development in the changing spectrum of therapeutic strategies for reducing the burden of CVD in DM has been the introduction of newer anti-diabetic drugs, like SGLT2i and GLP1 agonists, both of which have shown promising results in reducing the risk of MACE and CVD in the recently completed CVD outcome trials (CVOTs). The pharmacology of these drugs as well as the design and results of the CVOTs are described and discussed in details in the chapters by Acharya and Deedwania as well as Garg et al. The chapter by Acharya and Deedwania provides detailed description of the evolution of the large CVOTs because of the mandate by Federal Drug Administration for approval of all new anti-diabetic drugs following the adverse CVD outcomes observed with rosiglitazone. The resulting large CVOTs have enrolled more than 200,000 patients with DM with either CVD or at increased risk of developing CVD. These CVOTS have examined effects of DPP4 inhibitors, SGLT2 inhibitors, and GLP1 agonists. As described in detail in the tables and text in our chapter the results of these CVOTS demonstrated that DPP-4 inhibitors were mostly neutral (except for small increase in risk of HF in the SAVOR trial). In contrast, all of the trials with SGLT2 inhibitors showed significant benefit in reducing MACE, especially HF related events. These findings have generated considerable interest in the recognition of HF (the forgotten one) in DM. Because of the dramatic and consistent findings in all 3 trials with SGLT2i various guideline committees now recommend SGLT2i as second line anti-diabetic drugs (after metformin) for treatment of DM patients who are at risk of developing HF. A number of prospective studies have also been launched to confirm and evaluate mechanistic insights responsible for the beneficial effects of SGLT2i in HF. The chapter by Garg et al. provides further insights regarding potential mechanism (s) responsible for the beneficial effects of SGLT2i and GLP1 agonists in patients with DM and CVD. Although, most of these mechanisms remain to be established, these include osmotic diuresis and natriuresis (and their impact on ventricular loading conditions), effects on cardiac metabolism and energetics, as well as effects on myocardial and renal sodium/hydrogen exchanger. Some of these effects also result in favorable alterations in cardiac structure and function. They also provide some plausible mechanistic insights regarding the beneficial effects of GLP1 agonists. It is important to note that the treatment with GLP1agonists is primarily associated with reductions in atherosclerotic MACE outcomes and it has no impact on HF related outcomes. These beneficial effects of GLP1 agonists might be attributed to positive effects on traditional CVD risk factors as demonstrated by BP reductions, decrease in body weight, as well as favorable effects on lipids and glycemic parameters. In experimental studies, treatment with GLP1 agonists had been shown to improve endothelial function, reduce vascular smooth muscle cell proliferation, and reduce cerebral and MI size in the experimental animal models. Whether any of these effects contribute to the improved outcome observed in CVOTs remain to be established. However, based on the positive results of the CVOTs with GLP1 agonists, most major guidelines now recommend GLP1 agonist drugs as second line agents after metformin for patients with DM who are at high risk for atherosclerotic MACE (e.g.: MI or stroke).

The chapter by Godoy et al. describes and discusses the virtues and limitations of myocardial revascularization by coronary artery bypass grafting (CABG) versus coronary angioplasty for patients with DM and CAD. They discuss the results of several large randomized trials comparing two treatment strategies and conclude that based on the findings of these studies it is safe to conclude that for DM patients with stable coronary artery disease, myocardial revascularization with CABG is preferred. Although, this issue can be argued extensively, because of the availability of improved stents and better technique for angioplasty, this will need to be settled by evaluations in a properly designed randomized controlled trials.

Finally, the chapter by O'Keefe et al. titled "The Elephant in the Room: Why Cardiologists Should Stop Ignoring DM" provides an interesting perspective on the whole issue of the need for cardiologists to be more attuned to the emerging treatment strategies for patients with DM and CVD. As discussed in most other chapters in this issue of the journal, it is likely that patients with DM will see the cardiologist as often as they see their primary care physician and likely more often than their endocrinologist. Furthermore, with the well demonstrated CV benefits of the newer agents like SGLT2i and GLP1 agonists, cardiologists are well suited to prescribe these medications to their patients with proper understanding of the benefits and risks associated with these drugs in their patients with CVD. Despite these obvious reasons for the involvement of cardiologists, the available evidence shows that cardiologists are not prescribing these newer agents to their patients with CVD. O'Keefe et al. also discuss possible reasons for the under prescription of the newer cardio-protective drugs and provides good insights regarding the safety and efficacy of these agents concluding with a call to action for increased utilization of these agents.

In summary, DM continues to be a major public health challenge and a powerful risk factor for various forms of CVD. Despite prior emphasis on the microvascular manifestations of DM (such as blindness, kidney

failure, etc.), it is now well established that most patients with DM die of CVD and related MACE. Additionally, many patients presenting with different forms of CVD either have previous diagnosis of DM or will be subsequently diagnosed to have DM. The Presence of DM in patients with CVD is also a powerful predictor of adverse outcomes. We now know that the comprehensive management of all major risk factors is essential and beneficial in reducing the risk of CVD complications in DM and improve CVD outcomes. In the past the traditional hypoglycemic agents used for the management of DM patients was not shown to improve CVD outcomes. However, the newer drugs such as SGLT2i and GLP1 agonists have demonstrated cardio-protective effects in addition to improved glycemic control in patients with DM and CVD as well as those without CVD but at subsequent higher risk of developing CVD. Most National and International guidelines now recommend the use of these newer agents with cardio-protective efficacy as second line agents for DM and CVD. However, their use in the clinic in such patients has been slow and it is our hope that the evidence presented in various chapters in this special issue dedicated to emerging concepts and therapeutic strategies for patients with DM and CVD will stimulate the readers to use these newer approaches and treatments in their patients with the goal of reducing the risk of future CVD events and improve outcomes.