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Diabetes and Cardiovascular Disease: Emerging Therapeutic Approaches

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Abstract

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in persons with types 1 or 2 diabetes (T1D, T2D). Although beneficial roles for strict control of hyperglycemia have been suggested, such a strategy is not without liabilities. Specifically, the risk of hypoglycemia and its consequences remain an omnipresent threat with such approaches. The advent of the Cardiovascular Outcomes Trials (CVOTs) for new anti-diabetes treatments has uncovered unexpected benefits of cardiovascular protection in some of the new classes of agents, such as the glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and the sodium glucose cotransporter-2 (SGLT-2) inhibitors. Further, state-of-the-art approaches, such as antibodies to proprotein convertase subtilisin-kexin type 9 (PCKSK9); RNA therapeutics; agents targeting distinct components of the immune/inflammatory response; and novel small molecules that block the actions of receptor for advanced glycation endproducts (RAGE) signaling, also hold potential as new therapies for diabetes and CVD. Finally, interventions such as weight loss, such as through bariatric surgery, may hold promise for benefit in diabetes and CVD. In this Brief Review, some of the novel approaches and emerging targets for the treatment of diabetes and CVD are discussed. Ultimately, identification of the optimal timing and combinations of such interventions, especially in the context of personalized approaches, together with emerging disease-modifying agents, holds great promise to reduce the burden that diabetes poses to the cardiovascular system.

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in types 1 and 2 diabetes (T1D, T2D)[1–3]. Beyond the inherent increase in mortality in diabetic subjects, when diabetes is combined with manifestations of CVD, such as myocardial infarction or stroke, the mortality rate is nearly doubled, leading to an estimated reduction in life expectancy of approximately 12 years[4]. Notably, a recent study reporting on the Swedish National Diabetes Register included 271,174 patients with T2D and matched them with 1,355,870 control subjects; subjects were studied for median follow-up of 5.7 years. Five specific risk factors for CVD were included in the model, elevated level of glycated hemoglobin, elevated level of low density lipoprotein cholesterol level, albuminuria, smoking status and elevated blood pressure levels. The authors found that for the T2D

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subjects who had these five risk factor variables within the target range, there was no significant excess risk of death, myocardial infarction or stroke when compared to the control population. The authors did report, however, that in the T2D subjects, the risk for hospitalization for heart failure was higher than that observed in the control subjects. Importantly, elevation of the glycated hemoglobin outside the target range was the strongest predictor of stroke and acute myocardial infarction[5]. Yet, although strict control of hyperglycemia may afford some benefit in reduction of major macrovascular events in T1D and T2D patients, the increased risk of hypoglycemia and its associated consequences render such a therapeutic approach not necessarily applicable to all subjects[6–8]. Hence, there is an urgent need to identify new therapies for diabetes and its CVD consequences in order to enhance quality and duration of life in the ever-growing number of subjects affected by these disorders. This Brief Review highlights some of the recent therapeutic advances for diabetes and CVD and considers emerging pre-clinical approaches at various stages in the development pipeline.

Thiazolidinediones (TZDs), the advent of cardiovascular outcome trials (CVOT) and the effects of new diabetes medications on major adverse cardiovascular events (MACE)

The discovery that rosiglitazone was associated with a significant risk for myocardial infarction and possible increase risk of CVD death led the Food and Drug Administration (FDA) to issue a missive requiring that manufacturers of new diabetes drugs conduct “non-inferiority” trials to demonstrate that the emerging therapies would not result in increased CVD risk[9]. Recently, such CVOTs have led to the discovery of unexpected benefits of some of the newer classes of glucose-lowering agents on CVD.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) and Dipeptidyl peptidase-4 (DPP-4) Inhibitors: Targeting The GLP-1 Axis—GLP-1, a potent incretin hormone, is produced in the L-cells of the distal ileum and colon. It exerts distinct functions, depending on the specific site in the body. For example, in the periphery, GLP-1 functions to inhibit gastric acid secretion and inhibit glucagon secretion. Other actions are considered to be central, in the nervous system, in which GLP-1 induces satiety. At the level of the pancreas, GLP-1 enhances insulin secretion[10]. The receptor agonists, therefore, mimic the effect of endogenous GLP-1. Although not all members of the GLP-1 RA family of agents exerted benefit in MACE, a major trial known as LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) reported on findings in 9,340 T2D patients who were at high CVD risk. Subjects received either liraglutide or a placebo for a median follow-up period of 3.8 years. Significant cardiovascular benefits were observed in the liraglutide vs. placebo-treated subjects, as the rate of first occurrence of death from CV causes, nonfatal myocardial infarction or nonfatal stroke was lower in T2D patients treated with liraglutide vs. placebo[11].

In other studies, testing a distinct GLP-1 RA, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), once weekly semaglutide was administered vs. placebo in T2D subjects with known high CVD risk. In that study, the rate of CVD death, nonfatal myocardial infarction or stroke was significantly lowered by semaglutide[12]. A recent report, however, indicated that semaglutide

carries a safety warning, as its use was associated with mild to moderate gastrointestinal side effects and retinopathy vs. placebo treatment[13]. In the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) study, once weekly treatment of T2D patients with or without previous CVD resulted in no significant difference in the incidence of any component of MACE between the two subject groups[14]. In the FREEDOM-CVO trial, subdermal implantation of exenatide is being tested for one year in patients with T2D; efficacy results regarding CVD and MACE are still pending[15].

Other studies have focused on the testing of dipeptidyl peptidase-4 (DPP-4) inhibitors in T2D; DPP-4 inhibits GLP-1 degradation; therefore, agents that inhibit DPP-4 increase the availability of GLP-1. In a number of studies to date, SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI)) (saxagliptin vs. placebo); EXAMINE (The Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in patients with type 2 diabetes mellitus and acute coronary syndrome) (EXAMINE) (alogliptin vs. placebo); TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) (sitagliptin vs. placebo) and Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) (linagliptin vs. placebo), no significant benefits of the DPP-4 inhibitor vs. placebo were observed with respect to any component of MACE. It remains uncertain whether this class of agents contributes to increased hospitalization for heart failure; further work will be required to settle that point[16–19]

Taken together, unlike the studies testing DPP-4 inhibitors, trials testing GLP-1-RAs revealed unexpected cardiovascular benefits. The reasons for the disparate effects of these two agents with distinct mechanisms of action, yet both targeting the GFP-1 RA pathway, on CVD, however, are not clear. Drucker and Nauck recently noted that although there do not appear to be substantial differences in the effects of either class of agents on the ability to lower HbA1c, there are notable distinctions. Whereas weight loss commonly accompanies use of the GLP-1 RAs, treatment with the DPP-4 inhibitors is associated with reduced gain of weight[20]. If and how body weight may be a surrogate for possible broader cardiometabolic benefits of the GLP-1 RAs has not been reported. Furthermore, if and how concerns regarding gastrointestinal side effects and retinopathy related to the GLP-1 RAs and if and how the possibility of increased hospitalizations for heart failure associated with the use of the DPP-4 inhibitors may affect their long-term usage remains to be determined.

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors—The SGLT-2 inhibitors, which decrease plasma glucose levels by prevention of renal glucose resorption, thereby causing glucosuria, also represent a new class of agents directly targeting hyperglycemia for which CVD benefits have been observed. In the first such study to report findings, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME), empagliflozin was tested in subjects with T2D and established CVD and reported a decreased risk of MACE, as follows[21]. Although there were no significant between-group differences in the rates of myocardial infarction or stroke in the empagliflozin vs. placebo-treated subjects, empagliflozin was associated with significantly

lower rates of death from cardiovascular causes, hospitalization for heart failure and death from any cause.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) reported that treatment with canagliflozin vs. placebo significantly reduced the risk of CV death, non-fatal myocardial infarction or stroke compared to placebo in T2D subjects; there was no significant reduction in all-cause mortality[22]. In the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial, T2D patients were treated with dapagliflozin vs. vehicle. In patients who had or were at risk for atherosclerotic heart disease, treatment with dapagliflozin exerted no significant effect on MACE when compared with placebo; however, this treatment resulted in a lower rate of CVD death or hospitalization from heart failure vs. the placebo treatment[23]. In an additional trial, ertugliflozin is under study for CVD outcomes in patients with T2D[24]. The first three studies noted above have established the beneficial effects of SGLT-2 inhibitors in CVD but also showed that there were a number of notable adverse effects that require further consideration, including increased risk of genital mycotic infections, increased fracture risk, diabetic ketoacidosis and in patients with known peripheral arterial disease (PAD), an increased risk of amputation (canagliflozin) was observed. If and to what degree these possible complications affect long-term prospects for this class of agents remains to be determined.

Furthermore, at this time, it is not clear why certain of the SGLT-2 inhibitors, but not all, afford benefit for CVD outcomes. It is possible that there are yet-to-be-identified distinct effects of these various agents' specific chemical structures on metabolism and CVD risk factors. It has been reported that among the various agents in this class, there are differences in selectivity for SGLT-1 vs. SGLT-2; along with differences in potency and pharmacokinetics[25]. If and how such factors may ultimately impact benefits in CVD, or not, will require further research to address such possibilities.

Finally, given the possible complications from the newer classes of anti-hyperglycemia agents discussed above, it will be important to outline specific indications and contra-indications for each of these newer agents that show cardiovascular benefit. In this context, Cosentino and colleagues recently published a report from the Cardiovascular Round Table (CRT) of the European Society of Cardiology (ESC) to consider potential guidelines for the implementation of these new agents that have shown CVD benefit[26].

Novel Approaches to Lipid-Lowering in Diabetes: Targeting Proprotein Convertase subtilisin-kexin type 9 (PCSK9)

PCSK9 functions to promote the degradation of the low-density lipoprotein receptor (LDL-R), thereby reducing the clearance of LDL from the circulation. The development of novel antibodies that target PCSK9 has led to their testing in statin-treated subjects, including those with diabetes. In Efficacy and Safety of Alirocumab Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients with hypercholesterolemia (ODYSSEY COMBO-II) trial testing alirocumab vs. placebo, of the patients on maximally-tolerated statins and treated with alirocumab, 31% had diabetes. By 24 weeks of alirocumab therapy, in the diabetic subjects, LDL-C was reduced by 49.1% and in the non-diabetic subjects, LDL-C

was reduced by 51.2%, that is, essentially comparable[27]. In the published reports on alirocumab in ODYSSEY OUTCOMES[28], efficacy or not, in diabetic patients was not explicitly discussed, although it was noted that adverse events including “diabetes worsening or diabetic complication among patients with diabetes at baseline”, or “new-onset diabetes among patients without diabetes at baseline” did not differ between subjects treated with alirocumab vs. placebo[28]. However, in the case of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, evolocumab was tested in patients with and without diabetes who were on statins and had known atherosclerotic disease; the study showed that this treatment reduced CVD risk in both diabetic and non-diabetic subjects and, importantly, did not increase the risk of development of T2D[29].

Collectively, these findings suggest that the PCSK9 inhibition appears safe in diabetic subjects and that patients with diabetes may benefit from this treatment. Certainly, however, more trials testing benefits of this class of agents will continue to provide the key data regarding the utility / safety of targeting this axis in diabetes.

Targeting the Immune/Inflammatory Response in Diabetes

Evidence suggests that diabetes is accompanied by a pro-inflammatory state, as there is upregulation of seminal factors that regulate and/or biomark inflammatory responses, such as high sensitivity C-reactive protein (hsCRP), toll-like receptors (TLRs), oxidative stress and Nuclear Factor-kB (NF-kB), and advanced glycation endproducts (AGEs) and their chief cell-surface receptor, RAGE (receptor for AGEs)[30–35]. Levels of hsCRP have been shown to predict CVD events in patients with diabetes[36] and levels of hsCRP are associated with plasma soluble RAGE levels[37], thus highlighting the interconnected nature of inflammatory sources and foci in both T1D and T2D. Burke and colleagues studied hearts from diabetic and non-diabetic subjects who died suddenly from CVD. They found that the atherosclerotic lesions from T2D vs. control subjects displayed higher levels of RAGE and one of its S100/calgranulin ligands (S100A12); larger necrotic cores; greater total and distal plaque load; and higher intimal staining for macrophages, T lymphocytes and HLA-DR expression compared to the non-diabetic subjects[38]. On account of these and other findings, therapeutic approaches have targeted the immune/inflammatory response for CVD outcomes and in such studies, diabetic subjects were included. Examples of such studies include the following, detailed below.

Targeting Interleukin-1 Beta—The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), was a randomized double blind placebo study in which canakinumab vs. placebo was administered to subjects who had had recent vascular events and an hsCRP > 2.0 mg/L; the total number of subjects in the study was 10,061. Of these, 4,057 had T2D; 4,960 had “pre-diabetes” and the remainder had normal glucose levels. The patients were followed for a median period of 3.7 years. Overall, the trial was positive in considering all subjects; a significant reduction in death, non-fatal myocardial infarction or stroke was observed. In the subset analysis, the patients with diabetes benefitted as well and similarly to the subjects without diabetes[39, 40]. Interestingly, it was also found that canakinumab did not reduce the incidence of new-onset diabetes over the study duration,

even in the face of significant reductions in levels of hsCRP and IL-6. In the first six to nine months of treatment, however, the patients treated with canakinumab did experience a reduction in HbA1c, the effects were not sustained over the duration[40]. Indeed, in an earlier Phase IIb study in which canakinumab was administered to 556 T2D patients at high vascular risk, the treatment resulted in reduced levels of hsCRP and IL-6, without major effect on atherogenic lipids[41], thereby suggesting that the increased vascular risk in diabetes is not solely on account of lipid abnormalities, but, more broadly, due to unique effects on activation of inflammatory pathways specific to glucose and its direct and/or indirect consequences.

Of note, however, the treatment with canakinumab was associated with a higher incidence of fatal infection vs. placebo, although there were no significant differences in all-cause mortality[40]. If and how this finding affects usage in patients with diabetes remains to be seen.

Methotrexate—In a study targeting the immune/inflammatory response, the Cardiovascular Inflammation Reduction Trial (CIRT), low-dose methotrexate was administered to 4,786 patients with either T2D or metabolic syndrome who had previous myocardial infarction or who had evidence of multi-vessel coronary artery disease[42]. The trial's primary endpoints were death from CVD or nonfatal myocardial infarction or stroke. The trial was stopped after a median of 2.3 years; it was found that the treatment with methotrexate did not lower levels of IL-1 beta, IL-6 or hsCRP when compared to placebo and that the primary outcome was not met.

Colchicine—A number of studies have addressed the effects of colchicine in CVD and immune/inflammatory responses. Nidorf and colleagues tested colchicine in 532 subjects with established coronary artery disease followed for a median of 3 years. The primary outcome (acute coronary syndrome, out of hospital cardiac arrest or noncardiometabolic ischemic stroke) was significantly reduced in the colchicine vs. placebo-treated subjects. Both diabetic and non-diabetic subjects were included in the trial; however, the authors did not specifically state if the benefits were equivalent in both groups[43]. In another study in which the effect of colchicine treatment on transcoronary gradients of levels of IL-1beta, IL-18 and IL-6 was probed, treatment with colchicine resulted in significant reductions in these levels. The authors noted that as there were significantly more diabetic patients in the acute coronary syndrome group treated with colchicine vs. the acute coronary syndrome group not treated with colchicine, they performed a sensitivity analysis with adjustment for diabetes and oral hypoglycemic agents. They reported that this adjustment yielded similar significant differences in cytokine levels between groups[44]. In addition, Deftereos and colleagues treated subjects (N=151) with acute ST-segment elevation myocardial infarction with colchicine vs. placebo (< 12 hours from the onset of pain) and found that subjects receiving colchicine demonstrated significant reductions in infarct size, as measured by area under the curve (AUC) for Creatine Kinase-MB fraction and MRI-determined infarct size. Both diabetic and non-diabetic subjects were included; however, the authors did not report treatment effects by diabetes status[45].

In an imaging study, treatment of 80 subjects with recent acute coronary syndrome with colchicine plus optimal medical therapy vs. optimal medical therapy alone for approximately one year resulted in significant reductions in low attenuation plaque volume and hsCRP[46]. At this time, a number of new trials testing the effects of colchicine on CVD are under way.

Icosapent Ethyl—Icosapent ethyl is a stable eicosapentaenoic acid (EPA) that was recently tested in 8,179 subjects for prevention of cardiovascular events. In the Reduction of Cardiovascular Events Trial (REDUCE-IT), patients with hypertriglyceridemia despite the use of statins were followed for a median of 4.9 years and received either icosapent ethyl twice daily vs. placebo. The primary endpoint in the study was a composite of cardiovascular death, nonfatal myocardial infarction or stroke, coronary revascularization, or unstable angina. Compared to the placebo-treated group, the group receiving icosapent ethyl demonstrated significantly reduced primary endpoint[47]. It was noted in the study that the benefits of icosapent ethyl were observed in both diabetic and non-diabetic subjects. Side effects included higher hospitalization for atrial fibrillation or flutter in the icosapent ethyl group vs. the placebo with a trend toward more serious bleeding events in the former group as well. The authors of that work speculated that the mechanism of action of this agent might, in part, be explained through changes in inflammation, since the hsCRP levels were significantly reduced by this agent[47].

In summary, the recent series of trials targeting the immune/inflammatory response have shown varied effects on CVD in general and, specifically, in patients with T2D and metabolic syndrome. These considerations underscore the premise that diabetes-associated inflammation may bear unique features, such that not all anti-immune/inflammatory response-targeted strategies will be effective. On the other hand, these studies may suggest that a key biomarker for utility, particularly in the diabetic / metabolic syndrome sub-group may be effectiveness on lowering hsCRP and other inflammatory markers.

Weight Loss – Medical & Surgical Approaches in Obesity and Diabetes

Obesity is an important risk factor for many disorders; among these are insulin resistance and T2D and, independently, CVD[48–50]. The broad benefits of healthy eating, for example, were suggested by a recently reported study called FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) in which cognition was improved in an elderly Finnish population practicing healthy eating, compared to a dietary counseling-only control[51]. In the context of metabolism, randomized clinical trials demonstrated that life style interventions to reduce body mass and to increase physical activity exerted a number of metabolic benefits, and, in persons with T2D, improved glycemic control[52–54]. Whether these results also imbued benefit in terms of reduced CVD was not clear. However, the Action for Health in Diabetes (Look AHEAD) Study, an intensive life style intervention study, demonstrated a number of benefits to health, however, the primary outcome was not met, as there were no significant reductions in CVD morbidity and mortality[54–57].

In a follow-up subset analysis of Look AHEAD, the goal was to determine if the incidence of CVD varied on account of changes in weight or in fitness. The primary outcome of the study and the subset analysis was death from CV causes, non-fatal myocardial infarction or

stroke or hospital admission for angina. The secondary outcomes included coronary artery bypass grafting, carotid endarterectomy, percutaneous coronary intervention, hospitalization for congestive heart failure, peripheral vascular disease, or total mortality[58]. The authors included as the reference group individuals who had received standard disease education and support intervention. In the aggregate, the interpretation of the data obtained by this analysis suggested that there was an association between the magnitude of the weight loss and the incidence of CVD in subjects with T2D[58].

It was thus logical to determine if there were benefits of bariatric surgery on macrovascular disease outcomes in T2D. A retrospective observational matched cohort study of 20,235 T2D subjects with severe obesity compared cardiovascular outcomes in patients undergoing, or not, bariatric surgery[59]. In that study, 5,301 subjects had undergone bariatric surgery and 14,934 were considered the control subjects, without surgery. At the five years follow-up, the patients who had undergone bariatric surgery had a significantly lower risk of macrovascular events vs. the control group (2.1% vs. 4.3%; hazard ratio (HR)=0.60)[59]. It is important to note that bariatric surgery, compared to medical weight loss approaches, also may affect gut hormones and other factors that might exert distinct effects on risk factors related to CVD. Randomized controlled clinical trials will be required to address these key questions.

RNA Therapeutics

Emerging evidence links microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) to the pathogenesis of diabetes and its complications[60–62]. In the area of CVD and diabetes, experimental evidence has shown the utility of antagonizing these pathways in pre-clinical models. Impaired regression of diabetic atherosclerosis was overcome, in part, by administration of anti-miRNA33 oligonucleotides. Compared to control oligonucleotides, administration of oligonucleotides targeting miRNA33 resulted in decreased atherosclerotic plaque macrophage content and inflammation in diabetic Reversa mice after lipid lowering, which was traced to upregulation of the key cholesterol transporter, *Abca1*[63]. In non-diabetic mice, targeting the lncRNA Chast (cardiac hypertrophy associated transcript) using GapmerR (single-stranded antisense oligonucleotides (ASOs) for silencing LncRNAs and mRNAs)-mediated silencing prevented and attenuated pathological cardiac remodeling in mice undergoing transverse aortic constriction (TAC)[64]. In non-diabetic mice, Malat1 (metastasis-associated lung adenocarcinoma transcript1) was shown to play important protective roles in ischemic stroke, as mice devoid of Malat1 displayed increased expression of pro-apoptotic and pro-inflammatory factors after ischemic stroke[65]. Further, Malat1 regulates angiogenesis after hind-limb ischemia via regulation of VEGFR2[66]. In other studies, GapmeR-mediated silencing of the lncRNA maternally expressed gene 3 (Meg3) prevented the induction of MMP2 with diminished cardiac fibrosis and improved diastolic performance after TAC in mice[67].

Therapies targeting RNA and DNA are emerging as opportunities for novel strategies against a variety of disorders[68, 69]. ASOs, Small interfering RNAs (siRNAs), miRNAs and aptamers are a few examples of such strategies. Examples of FDA-approved RNA therapeutics include fomiversen (ASO indicated for cytomegalovirus retinitis); pegaptanib targeting VEGF165,

which was approved for use in age-related macular degeneration; eteplirsen, which restores the translational reading frame in the dystrophin gene, thereby serving as a therapy for Duchenne muscular dystrophy; and nusinersen, an ASO which is indicated for spinal muscular atrophy[69].

Collectively, these examples of pre-clinical studies and FDA-approved therapies hold promise for novel targets for cardiovascular medicine and diabetes, particularly on account of the ability to target specific mutations in key genes related to cardiovascular homeostasis or injury. However, as diabetes is a chronic and long-term disease, the safety and tolerability of therapies targeting RNAs and DNAs will be critical to establish.

Novel Small Molecule Approaches and Diabetic Vascular Complications

A key consequence of the hyperglycemia associated with T1D and T2D is the generation of AGEs. AGEs result from nonenzymatic post-translational modification of proteins and lipids due to high glucose conditions; however, inflammatory and pro-oxidative mechanisms also result in the generation of AGEs. For example, a chief AGE found in vivo, carboxymethyl lysine (CML)-AGE may be produced by high glucose and via activation of the myeloperoxidase system, in a process that requires NADPH oxidases[70, 71]. AGEs may also be formed by hypoxia and ischemia/reperfusion, thereby highlighting further links to diabetes, in which tissue hypoxia and increased myocardial infarcts and strokes characterize the disease[72]. CML-AGE and other AGEs are detected in the plasma of diabetic patients[73] and in atherosclerotic plaques[74]. Recent work has shown that CML-AGE is enriched in the adipose tissues of subjects with obesity, even in the absence of diabetes[75]. Further, in a mouse model of high fat feeding, feeding mice a diet of 60% kcal/fat resulted in increased accumulation of AGEs even before the animals were insulin resistant or diabetic[76]. Together, these two studies in human and animal models of obesity suggest that AGEs may increase even in the absence of hyperglycemia.

The discovery of RAGE as a chief signaling receptor for AGEs led to the finding that, beyond AGEs, RAGE was a multi-ligand receptor. In addition to AGEs, the immunoglobulin superfamily molecule RAGE also bound pro-inflammatory ligands such as S100/calgranulins, high mobility group box 1 (HMGB1) and lysophosphatidic acid (LPA)[77–79]. RAGE and its ligands are highly expressed in human diabetic atherosclerosis[42, 80, 81]. To test the role of RAGE in diabetic atherosclerosis and vascular diseases, numerous strategies have been employed in pre-clinical animal models, such as soluble RAGE (extracellular ligand-binding domains of RAGE that bind up RAGE ligands and block their activation of the cell surface receptor); anti-RAGE antibodies; and mice (or their bone marrow) devoid of *Ager* (the gene encoding RAGE)[82–88]. The discovery that the cytoplasmic RAGE domain bound the formin, DIAPH1, and that this interaction was important for RAGE signaling in vascular cells and monocytes/macrophages identified a novel platform for therapeutic intervention in disorders in which RAGE ligands accumulate and contribute to pathobiology, such as diabetic complications, obesity and CVD[89–93]. In contrast to the heterogeneous and multiple binding sites for RAGE ligands on the extracellular RAGE domains[94–96], the binding site of DIAPH1 on the RAGE tail is suitable for small molecule binding. Solution NMR spectroscopy was used to identify interaction surfaces between the cytoplasmic domain of

RAGE and DIAPH1 FH1 due to the exquisite sensitivity of chemical shifts to the chemical environment and showed residues 3–6 of the RAGE tail interact with FH1 and the K_D is <10 μM. Mapping the observed chemical shift changes onto the molecular surface of the cytoplasmic domain of RAGE identified that interaction surface between the cytoplasmic domain of RAGE and DIAPH1 FH1 consists of a small positively charged patch formed by Q3, R4, R5, and Q6 with a total area less than 200 $Å^2$ [97]. Recent work using super-resolution stochastic optical reconstruction microscopy (STORM) and single particle tracking (SPT) supported the strong connection between RAGE and DIAPH1, both spatially and with respect to their effects on the dynamics of the actin cytoskeleton[98].

These findings prompted the screening of the ChemBridge CT488 library compounds at a single concentration, 10 μM, to test if such molecules would block the interaction of the cytoplasmic domain of RAGE with antibody-captured DIAPH1 from cultured cells. Thirteen compounds which specifically bound to the cytoplasmic domain of RAGE, not DIAPH1, were identified with nM dissociation constants. In vascular cells, they blocked RAGE ligand-induced inflammation and migration, suppressed ischemic injury in the diabetic isolated perfused heart and blocked upregulation of inflammatory mRNA transcripts in liver and kidney after infusion of RAGE ligand CML-AGE into wild-type mice[99].

Taken together, these pre-clinical data support that the interaction of the cytoplasmic domain of RAGE with the formin, DIAPH1, may represent a novel platform for drug development for diabetes and its cardiovascular and other complications. Work is underway to advance the potency, safety, novelty and druggability of a primary and a “back-up” scaffold, all deduced from molecules identified through the initial screen from the ChemBridge library. Note that the RAGE/DIAPH1 axis is presented as one example of a signal transduction axis adversely affected by high levels of glucose and the generation of AGEs. Certainly, other targets in this area might include, but are not limited to, blocking AGE production itself and facilitating AGE clearance, all as efforts to quell AGE-associated augmentation of immune/inflammatory and pro-oxidative responses.

Perspectives – Looking Forward in Diabetes

Figure 1A summarizes the key endogenous and exogenous metabolic disturbances vis-à-vis glucose metabolism and their molecular consequences that contribute to increased CVD in diabetes. The advent of the CVOTs results and some of the surprising benefits on MACE uncovered in these trials underscores that the direct and/or indirect effects of higher than normal levels of glucose significantly perturb metabolic homeostasis, thereby exacerbating factors that increase CVD risk. Superimposed on these endogenous sources of aberrant glucose metabolism, exogenous factors, such as those in the diet and in the environment, may amplify AGEs exposure, thereby contributing to upregulation of pro-atherogenic processes. Although hosts of studies have uncovered adverse effects of glucose on extra- and intracellular properties, their long-term negative effects, such as on glycation (discussed above) and on epigenetic factors and “metabolic memory” [100, 101] also have been postulated to play key roles in CVD in diabetes. Further, the effects of diabetes on perturbation of lipid/lipoprotein metabolism, in addition to their unique and independent effects, also intersects with these glucose-driven mechanisms, as glycation of lipids and lipoproteins may change

the function of these species and, further, through receptor/RAGE-dependent mechanism, may mediate and exacerbate cellular perturbation[102, 103]. Consequently, glucose-dependent immediate and long-term effects activate signaling pathways and alter gene expression programs that mediate vascular cell dysfunction. Coupled with immune cell perturbation, these factors may combine to increase vascular perturbation and, thereby, increase risk for CVD in these metabolic disorders.

How, then, may emerging strategies be utilized to combat these risk-associated factors and, thereby, reduce the risks of CVD in diabetes and metabolic dysfunction? Figure 1B illustrates examples of the evolving agents and approaches for diabetes and CVD. Strategies to target the adverse effects of endogenous and exogenous glucose metabolism; to reduce pro-atherogenic low density lipoprotein levels in maximally-statin-treated subjects; to modulate RNA biology with novel therapeutics against miRNAs, lncRNAs or to silence mRNAs; to directly attack vascular inflammation and its consequences with agents against cytokines such as IL-1 beta; and novel, pre-clinical development targets such as RAGE/DIAPH1 (to block the adverse signaling of AGEs) all hold promise, perhaps in combination, to assuage the assault on the vascular and immune systems imparted by high levels of glucose and their direct/indirect consequences. Although not discussed in this review, efforts targeting epigenetic mechanisms, such as DNA methylation and histone methylation and acetylation are already in development, especially in cancer[104–106]. Given the emerging roles for epigenetics in the maladaptive “memories” imbued by high levels of glucose, it may be logical to test such agents in diabetes, as well.

Finally, it is very important to consider sex differences in CVD and associated mortality in diabetes. Yamagishi recently summarized results of multiple clinical studies that affirmed in a meta-analysis of 820,0000 people that the HR for death from CVD in diabetic persons was 2.32 compared to non-diabetic people, even after statistical measures to adjust for age, sex, smoking status and the BMI[107, 108]. That study, and others, reported that the excess relative risk for CVD of death was larger in women than in men with diabetes. Recognition of the importance of sex-based differences in CVD is already being strongly urged for the design of preclinical studies, as, recently, there is increased emphasis on the inclusion of male and female animals and their primary cells in pre-clinical studies for CVD-type pathologies[109]. Collectively, the dissection and consideration of sex-based differences in diabetic CVD in therapeutic approaches hold great promise for uncovering fundamental new insights into the pathogenesis of CVD as well as the development of new classes of personalized therapeutic strategies.

In conclusion, recent advances have paved the way for therapies that afford benefit to the cardiovascular system both by direct reduction of hyperglycemia and by mitigation of its long-term consequences. Given the vast epidemics of obesity and T2D[110], such efforts to suppress CVD risk are essential to maintain long-term health and quality of life worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AGE	advanced glycation endproduct
ASO	Antisense oligonucleotide
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcomes Study
CANVAS	The Canagliflozin Cardiovascular Assessment Study
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus
Chast	Cardiac hypertrophy associated transcript
CIRT	Cardiovascular Inflammation Reduction Trial
CML-AGE	Carboxymethyl lysine advanced glycation endproduct
CRT	Cardiovascular Round Table
CVD	Cardiovascular disease
CVOTs	Cardiovascular outcome trials
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
DPP-4	Dipeptidyl peptidase-4
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
EXAMINE	The Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in patients with type 2 diabetes mellitus and acute coronary syndrome
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
FDA	Food and Drug Administration
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
GLP-1 RAs	Glucagon-like peptide receptor agonists
HMGB1	High mobility group box 1
HR	Hazard Ratio
HS-CRP	High Sensitivity C-reactive protein
IL-1 beta	Interleukin-1 Beta
LDL-R	Low density lipoprotein receptor
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
Lnc RNA	Long noncoding RNA
Look AHEAD	Action for Health in Diabetes
LPA	Lysophosphatidic acid
MACE	Major adverse cardiac events
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
MiRNA	Micro RNA
NF-kB	Nuclear Factor-Kappa B
ODYSSEY COMBO II	Efficacy and Safety of Alirocumab Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia
PAD	Peripheral Arterial Disease
PCSK9	Proprotein convertase subtilisin-kexin type 9
RAGE	Receptor for advanced glycation endproducts
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial
SAVOR-TIMI	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI))
SGLT-2	Sodium glucose cotransporter-2
SI RNA	Small interfering RNAs
SPT	Single particle tracking

STORM	Super-resolution stochastic optical reconstruction microscopy
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAC	Transverse aortic constriction
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TLRs	Toll like receptors
TZD	Thiazolidinedione

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Highlights

- Cardiovascular disease remains a leading cause of morbidity and mortality in persons with types 1 or 2 diabetes.
- The requirement for Cardiovascular Outcomes Trials (CVOTs) for new anti-diabetes treatments has uncovered unexpected cardioprotective benefits in some of the new classes of agents, such as the glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and the sodium glucose cotransporter-2 (SGLT-2) inhibitors.
- Recent studies testing antibodies to proprotein convertase subtilisin-kexin type 9 (PCKSK9) have shown cardiovascular benefit in subjects both without and with diabetes, thereby providing a new complementary therapy in diabetes and dyslipidemia.
- Recent approaches to target inflammation have shown benefit in subjects with diabetes, such as antagonists of Interleukin-1 Beta. Other agents such as colchicine also show promise for cardiovascular protection in diabetes.
- Novel and emerging targets for therapeutic intervention in diabetic cardiovascular disease, such as RNA therapeutics and targeting the Receptor for Advanced Glycation Endproducts (RAGE) axis also hold promise to reduce the burden that diabetes poses to the cardiovascular system

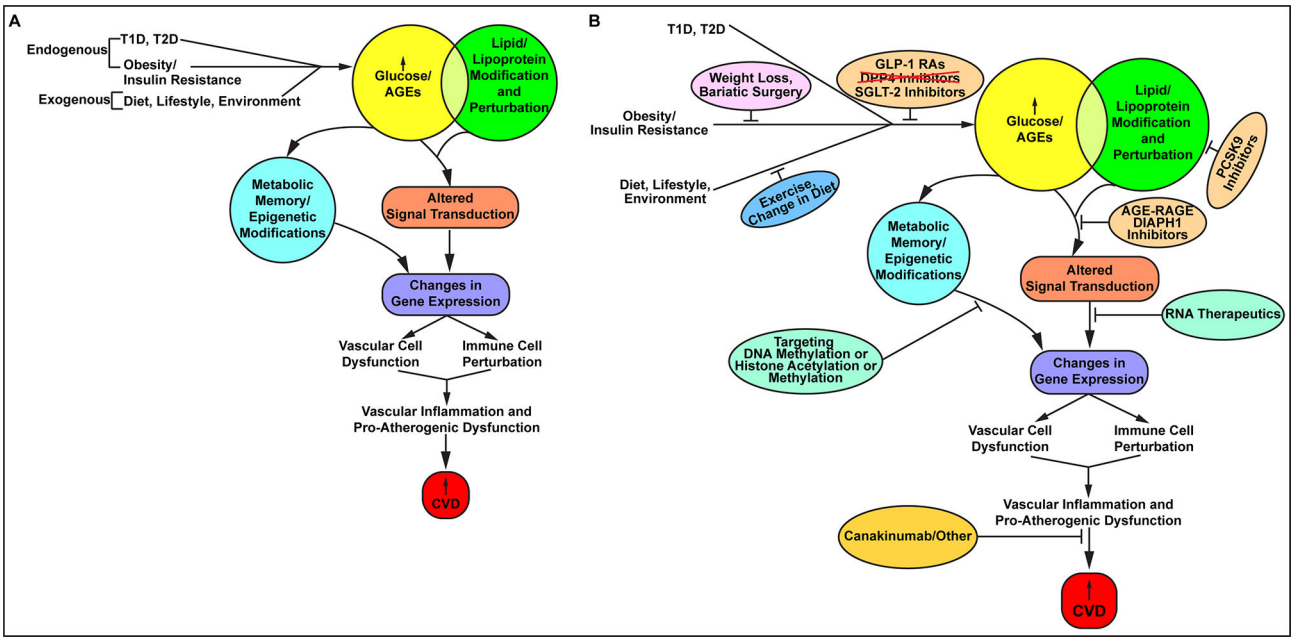

Figure 1. Pathobiological mechanisms and therapeutic targets for diabetes and CVD.

(A). Examples of proposed mechanisms of diabetes and CVD. Both endogenous and exogenous forces may converge to increase glucose levels, one consequence of which is the formation nonenzymatically glycated proteins or lipids, called AGEs, or advanced glycation endproducts – factors that have been linked mechanistically to the pathogenesis of CVD. Independently, lipid abnormalities in obesity and diabetes pose independent risk for CVD. Further, these two pathways may converge, as glycation of lipids and lipoproteins has been shown in multiple basic science experiments to regulate factors that aggravate CVD risk. Once ignited, the actions of glucose, AGEs and lipids modulate signaling pathways and factors that regulate gene expression, including microRNAs and lncRNAs. The consequences of these changes in gene expression may be vast, affecting the functions of both vascular cells and immune cells. Indeed, increased “vascular inflammation” occurs in diabetes and leads to the upregulation of factors that augment CVD risk. In addition, long-term epidemiologic studies have underscored that in both T1D and T2D, the effects of hyperglycemia may be long-lived, leading to epigenetic changes that may affect gene expression patterns and CVD risk for many years. Finally, fundamental changes in body mass and reductions in physical activity may portend increased obesity, insulin resistance, and if left unchecked, T2D. **(B) Emerging therapeutic strategies in diabetes and metabolic dysfunction to combat CVD.** Recent results from CVOTs demonstrated unexpected cardiovascular benefit from the use of newer classes of agents targeting hyperglycemia, namely, the GLP-1 RAs and the SGLT-2 inhibitors. However, the DPP4 inhibitors have not been shown to exert the same degree of benefits in CVD, but may be associated with higher rates of heart failure. Further, some of the members of these classes of agents have been associated with some risks, such as increased mycotic infections, increased retinopathy and risk of amputations, for unclear reasons. For maximally treated with statins subjects or in subjects with statin intolerance, studies have begun to show that the new series of antibodies targeting PCSK9 may exert equivalent benefit in CVD in non-

diabetic and diabetic subjects. Recent discoveries on the roles of miRNAs and lncRNAs in diabetic complications in preclinical models may lead to broader testing and use of ASOs and GapmeRs for diabetes and CVD. The recent success of canakinumab, as illustrated in the CANTOS trial, solidified for the first time in a large clinical trial the benefits of targeting inflammation for CVD. In the CANTOS trial, it was shown that diabetic subjects and non-diabetic subjects benefitted from this approach. It is to be noted that there was an increased risk of serious infection in the canakinumab-treated group vs. the placebo. If and how this may affect overall utility for diabetic subjects remains to be determined. In the field of cancer, novel approaches to targeting DNA methylation and histone methylation and acetylation are gaining traction; given the evidence of “metabolic memory” in diabetic complications, such approaches may well soon be tested in diabetes and CVD. Lifestyle interventions, although tantalizing, have long proved to be difficult to achieve and sustain. Recent work has suggested that bariatric surgery may exert possible CVD benefits on account of weight loss, but, as well, to other to-be-elucidated factors (such as changes in gut hormones, as an example). Finally, novel approaches to disease modification, such as antagonism of the RAGE/DIAPH1 signaling pathway, have shown benefit in preclinical models of inflammation and diabetes. Work is ongoing to test these concepts. Note that this review was meant to illustrate but some of recently emerging targets for diabetes and CVD. Given the scope of the epidemics of obesity and diabetes, such efforts are both timely and, potentially, life-saving.