The Impact of Cardiovascular Drugs on Diabetes: A review

Anna Grodzinsky, MD[1,2], **Suzanne V. Arnold, MD MHA**[1,2], **Dany Jacob, MD**[1,2], **Boris Draznin, MD**[3], and **Mikhail Kosiborod, MD**[1,2]

[1]Saint Luke's Mid America Heart Institute

[2]University of Missouri-Kansas City, Kansas City, MO

[3]University of Colorado Denver, School of Medicine

Abstract

Introduction—The prevalence of diabetes is steadily rising in the US, both in the general population and among those with cardiovascular disease (CVD). Understanding how to treat a patient with both conditions is becoming increasingly important. With multiple therapeutic options for CVD management, some medications will invariably impact glycemia in this group of patients. The concept of "DM-friendly" management of CVD is based on a treatment approach of selecting medications that do not impair glycemic control, provided equivalent cardioprotective effects. This article reviews the glycemic effects of various classes of medications commonly used to treat CVD.

Methods—Data sources were all PubMed and Google Scholar-referenced articles in English-language peer-reviewed journals from 1980 to the present. Studies selected could include observational studies or prospective clinical trials. Prospective clinical trials included in this review focused on investigating the association of the medication of interest with glycemic outcomes. Meta-analyses and systematic reviews were also included.

Results—The data on glycemic effects was lacking for many of the medication classes and individual medications examined. However, in our review, certain beta-blockers and renin angiotensin aldosterone system inhibitor (RAAS-i) agents, and select CCBs were consistently shown to have favorable glycometabolic profiles when compared with other commonly used cardiovascular therapies.

Conclusions—Several commonly prescribed medications for the treatment of cardiovascular disease, such as certain beta-blockers, RAAS agents, and ranolazine, are associated with favorable glycometabolic effects. As clinicians are more often faced with the challenge of treating patients with diabetes and concomitant cardiovascular disease, consideration of how common

cardiovascular medications may affect glycemia should be incorporated into the clinical decision making process.

Keywords

Diabetes; Cardiovascular disease

INTRODUCTION

The prevalence of diabetes mellitus (DM) is steadily rising in the developed world, with the Centers for Disease Control and Prevention estimating that 1 in 3 people in the US will carry a diagnosis of diabetes by 2050 should current trends continue.[1] Given the link between diabetes and the development of atherosclerosis, the prevalence of diabetes is even higher among patients with cardiovascular disease (CVD). In fact, the majority of patients with CVD have either diabetes or pre-diabetes.[2] As such, knowing how best to treat a patient with both conditions is becoming increasingly important for clinicians to understand.

The key goals of care in patients with diabetes and cardiovascular disease are to prolong life, prevent major adverse cardiac events, prevent microvascular diabetes complications, and improve quality of life. Improved glycemic control is one mechanism by which these outcomes can be positively impacted. Better glucose control is associated with a substantially reduced risk of microvascular complications,[3] a modestly reduced risk of major adverse cardiovascular events,[4] and improved quality of life.[5] Drug-disease interactions— where a medication to treat one condition impacts (either positively or negatively) a pre-existing condition—are common throughout medicine[6] and also play a role in the treatments for CVD. The concept of "DM-friendly" management of CVD implies choosing therapies with neutral or positive impact on glycemic control whenever possible without sacrificing optimal treatment of CVD. This paper reviews the glycemic effects of various classes of medications commonly used to treat CVD.

METHODS

A search of the literature was conducted on PubMed and Google Scholar databases. Articles in peer-reviewed journals of the English language since 1980 were included. Studies selected could include observational studies, prospective clinical trials, meta-analyses, and systematic reviews. Abstracts and unpublished studies were not included. Two investigators (A.G. and D.J.) performed the electronic searches and reviewed the results. Relevant articles were considered ones that focused on the association of the medication of interest with glycemic control. Variables used to assess glycemic control could include hemoglobin A1C, fasting plasma glucose, albuminuria, insulin sensitivity or resistance, incident diabetes, insulin secretion or plasma insulin levels.

RESULTS

Coronary Artery Disease

Antiplatelet agents—While there is some evidence of variable anti-ischemic effects with different P2Y12 inhibitors in patients with DM,[7] there are no known clinical studies

exploring the metabolic effects of these agents. As only minimal pre-clinical data are available, no conclusions can be made about the glycemic or metabolic effects of P2Y12 inhibitors. Similarly, there have been no studies of cilostazol, a PDE-3 inhibitor, on clinically meaningful glycemic outcomes. However, one study did show that cilostazol slows the progression of albuminuria in patients with DM.[8] Furthermore, in diabetic mice, it was shown to improve systemic insulin resistance by suppressing chronic inflammation in adipose tissue via modulation of both adipocyte and macrophage functions.[9]

Beta-blockers—Beta-blockers have many beneficial uses in patients with CVD: mortality reduction after an acute myocardial infarction, chronic angina,[12] systolic heart failure, atrial and ventricular arrhythmias, and hypertension.[10] Following an acute myocardial infarction, beta-blockers reduce mortality and recurrent nonfatal MI in all patients, regardless of diabetes status.[11] However, beta-blockers have been shown to have variable metabolic effects, which may be an important factor to consider when initiating treatment with these agents in patients with diabetes (and pre-diabetes). Conventional beta-blockers (e.g. metoprolol, atenolol) act by decreasing myocardial contractility. Reduced heart rate and cardiac output can lead to peripheral vasoconstriction, in turn leading to increased insulin resistance.[12,13] On the other hand, vasodilating beta-blockers (e.g. carvedilol, labetolol) have shown neutral or beneficial effects on metabolic parameters.[12,13] Bakris et al evaluated the metabolic effects of different beta-blockers in 1235 patients with type 2 diabetes mellitus and hypertension randomized to metoprolol or carvedilol and followed for 5 months.[12] Carvedilol improved insulin sensitivity, with a 9% reduction in the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR), and had a neutral effect on HbA1c. In contrast, patients randomized to metoprolol had no change in insulin sensitivity and a modest worsening in HbA1c (+0.15%; p<0.001).[12] Furthermore, following 5 months of maintenance dosing, fewer patients in the carvedilol group progressed to microalbuminuria as compared with those treated with metoprolol (OR 0.53, 95% CI 0.30-0.93).[12] This study was limited by a short duration of follow up and the use of surrogate markers rather than more concrete clinical outcomes such as cardiovascular events and mortality. However, it does suggest a potential for a clinically important metabolic difference between vasodilating and non-vasodilating beta-blockers. Similar results were seen in a small 24 week study, where patients treated with carvedilol had a mean absolute decrease in HbA1c of 0.1% as compared with a mean absolute increase of 0.3% in HbA1c levels in the atenolol group (p<0.001).[14] While most of the glycemic data on vasodilating beta-blockers has centered on carvedilol, small trials have examined the metabolic impact of nebivolol[18] and labetolol[15] and have found that they also have favorable effects on insulin sensitivity and lipid profile parameters. Importantly, carvedilol has similar (if not better) cardioprotective properties compared with non-vasodilating beta-blockers, both in coronary artery disease and heart failure[16–18]. However, despite these findings of a favorable glycometabolic profile of particular beta-blockers with at least equivalent cardioprotective effects, most patients with Type 2 diabetes are not prescribed DM-friendly beta-blockers following AMI, a practice that was associated with poorer glycemic control at follow-up.[19] In the same study, DM-friendly β-blocker prescription at discharge was associated with a trend toward a lower risk of worsened glucose control at 6 months after AMI (RR 0.80, 95% CI 0.60-1.08).[19]

Calcium channel blockers—Calcium channel blockers (CCB) are commonly used to treat angina, atrial arrhythmias, and hypertension. A number of studies have looked at the effect of CCB on glycemia in patients with and without diabetes.[20,21] Some small studies have shown a favorable glycemic profile with calcium channel blockers, and a recently published data from the REasons for Geographic and Racial Differences in Stroke (REGARDS), a US national cohort study of community-dwelling middle-aged and older adults, enrolled between 2003 and 2007 revealed that 1484 (29.6%) CCB users, of which 174 (3.4%) were verapamil users. Verapamil users had on average 10mg/dL lower serum glucose compared to CCB non-users with substantially greater differences among insulin users: 24mg/dL lower serum glucose among users of insulin in combination with oral agents and 37mg/dL lower among users of insulin alone.[81] In addition, cilnidpine has been to shown to have some favorable glycemic effects in small studies. Cilnidipine is a novel CCB (N-type and L-type) that is not yet available for clinical use China, Japan, and India, but not in the US, in the US and has been compared with amlodipine (L-type inhibitor) in patients without DM. However, there are no HbA1c data suggesting significant differences between dihydropyridine CCBs, and as such, the data to date are not convincing enough to impact our choice of calcium channel blocker use in patients with diabetes.

Ranolazine—Ranolazine is an antianginal medication that reduces myocardial ischemia through inhibition of the slowly inactivating component of the cardiac sodium current, which then reduces the intracellular sodium and calcium overload.[22,23] In addition to its antianginal effects, ranolazine may also improve fasting glucose and HbA1c. Post-hoc analyses from the Combination Assessment of Ranolazine in Stable Angina (CARISA) and MERLIN-TIMI 36 trials demonstrated statistically significant and clinically relevant reductions in HbA1c levels in patients treated with ranolazine vs. placebo.[24] CARISA patients who received ranolazine 750 mg or 1000 mg twice daily had a reduction in mean HbA1c of 0.50±0.13% and 0.73±0.13%, respectively, vs. 0.02±0.14 in the placebo arm.[24] Similarly, in a sub-group analysis of MERLIN-TIMI 36 trial, patients with diabetes treated with ranolazine had a reduction in A1C of 0.64% (7.5% to 6.9%) compared with a 0.22% (7.4% to 7.2%) decline in the diabetes patients treated with placebo. This effect was observed despite the use of 2 hypoglycemic agents in both arms at 4 months.[25] Another sub-group analysis of the MERLIN TIMI-36 showed that the glycemic effects of ranolazine was more pronounced at higher A1c levels, with a decrease in A1C of 1.2% in patients with baseline HbA1c levels 8% treated with ranolazine (versus 0.28% with placebo).[26] While the mechanism of action for the glycometabolic effect of ranolazine remains to be fully elucidated, recent preclinical studies suggest that it may be mediated by inhibition of sodium channel activity in pancreatic alpha cells and a resultant reduction in glucagon secretion.[27] Several prospective randomized clinical trials are presently ongoing to more clearly establish the glucose-lowering effect of ranolazine. In a study examining the effect on A1c of the addition of ranolazine to glimepiride in patients with type 2 diabetes, patients randomized to a 24-week regimen of ranolazine plus glimepiride (vs. placebo plus glimepiride) were found to have a numerically and statistically greater reduction in mean hemoglobin A1c (−0.47±0.971 vs. 0.03±0.949, p<0.001).[28] Similarly, a randomized trial evaluated the effect of ranolazine when given as monotherapy on glycemic control in subjects with type 2 diabetes. These patients were inadequately controlled with diet and exercise alone and were

treatment naive to antihyperglycemic therapy or had not received antihyperglycemic therapy in the 90 days (or thiazolidinediones for at least 24 weeks). In the ranolazine (vs. placebo) arm, mean A1c reduction was greater (−0.80±1.020 vs. −0.27±1.027, p<0.001).[28] A phase 3 study evaluating the glycemic outcomes associated with the use of ranolazine (vs. placebo) in patients with suboptimal glycemic control on metformin (500 mg daily in the ranolazine arm vs. 1000 mg daily in the placebo arm) recently reported a numerically, albeit not statistically, lower A1c at week 24 (7.72 vs. 7.86, p value=0.306).[29]

Nitrates—Commonly used as an antianginal medication, the effect of nitrates on glycemic control has been rarely studied but generally has been found to be metabolically neutral. There was a theoretical concern that the skeletal muscle contraction induced by nitric oxide would induce the translocation of GLUT-4 receptors that uptake peripheral glucose and worsen glycemic control. However, at least in small studies, this concern has not been clinically relevant. Piedrola et al found no effect of isosorbide mononitrate on insulin sensitivity in individuals with CAD over a six month period.[30] Henstridge et al similarly found that administration of isosorbide mononitrate did not significantly affect glucose levels or plasma insulin levels.[31]

Statins—Based on the 2013 Cholesterol Management ATP III guidelines, use of statin therapy is recommended for primary prevention of cardiovascular disease for patients with diabetes aged 40-75.[32] High-intensity statins are recommended for secondary prevention in all patients after myocardial infarction, including those with diabetes.[33] However, there has been recent concern about a potential association between statin therapy and an increased risk of incident type 2 diabetes.[34,35] A recent genetic meta-analysis of a heterogeneous trial population of patients with recent myocardial infarction, recent acute coronary syndrome, heart failure, hypertension, or no history of myocardial infarction (n=223463) suggested that use of high (vs. moderate) intensity statins was associated with a 12% higher odds of development of type 2 diabetes over a mean follow up 4.2 years.[36] Additionally, a recent analysis of a large population-based cohort showed that patients with higher adherence to statin therapy were more likely to develop diabetes than those with very low adherence.[37]

The mechanism by which statins may cause dysglycemia has not been firmly established, although a small study suggested that the diabetogenic effects of simvastatin and rosuvastatin are not driven by an adverse impact on insulin sensitivity but rather by a deterioration of insulin secretion.[38] In this study, both treatments were associated with a 0.8 to 0.9% absolute increase in hemoglobin A1c levels after 12 months (P<0.001 vs. baseline for both comparisons).At this time, the modest effect of statins on glycemic control is believed to be a class effect, supported by a systematic review showing that the genetic target for statins is also related to glycemic effects.[39] However, a very small study of 14 healthy male adults with metabolic syndrome showed that 6-month treatment with pitavastatin did not significantly change mean glucose- or insulin-related parameters.[40] While these results are encouraging, the true metabolic effects of pitavastatin will not be known until the release of the results of the J-PREDICT trial (Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance), which is evaluating

the incidence of new-onset diabetes in 1,240 patients with impaired glucose tolerance following 5-year treatment with pitavastatin.[82]

Together, these data suggest that although certain statins are likely associated with adverse glycemic effects, the effect appears to be modest. While the glycemic effects of statins are important, it must be noted that the modest risk of incident diabetes and worsened glycemic control is overshadowed by the cardiovascular protective effect of statins in patients at high-risk for coronary events.[41,42] Therefore, it is important not to withhold statins from patients with diabetes for this reason. The effect on glycemia is even less of a concern when statins are used for secondary prevention, where the statin benefit is much larger. However, in primary prevention, the increased risk of developing diabetes with statins may be a meaningful concern in patients with pre-diabetes and only a borderline indication for statin initiation.

Niacin, Fibrates and Fish Oil—There is a paucity of contemporary data examining the glycemic effects of both niacin and fibrates. A systematic review demonstrated that niacin, when used alone or in combination with statins, is associated with "modest, transient or reversible" increases in fasting glucose and elevation in hemoglobin A1c ($p<0.03$)[43] and a retrospective analysis (n=550) of the Duke Lipid Clinic database confirmed these findings.[44]

In the case of fibrates, two studies found that gemfibrozil use in patients with non-insulin dependent diabetes had no impact on glycemia.[45,46]

The data on the effect of fish oil on glycemia in patients with type 2 diabetes have also shown neutral effects. A systematic literature review concluded that while fish oil supplementation had expected effects on lipids, there was no significant effect on glucose control.[47]

Hypertension

The majority of antihypertensive medications have no data on glycemia, and therefore we will only be reviewing those medications for which there are any available data on glycemic effects.

Aliskerin—Aliskerin is a direct renin inhibitor indicated for treatment of hypertension. Improvement in insulin resistance has been show in mice models, but no clinical trials in humans have examined the effect of aliskerin on glycemia. While there are no human glycemic data, aliskerin has been shown to decrease microalbuminuria in patients with type 2 DM, both as monotherapy[48,49] and in combination with losartan. These findings suggest that aliskerin may have renoprotective properties in patients with hypertension, type 2 DM and nephropathy.[50] However, these results should be taken with caution given a subsequent large clinical trial that found no evidence to support the addition of aliskerin to an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) to prevent the composite end point of major adverse cardiac event, end stage renal disease, and other outcomes.[51] Furthermore, the trial was stopped prematurely due to safety concerns, with an excess of hyperkalemia and hypotension in the aliskerin arm.[51]

Hydralazine—Hydralazine is an antihypertensive medication that functions primarily as a peripheral vasodilator. Animal studies have suggested adverse effects of hydralazine on glycemia, which is believed to be a result of increased endogenous catecholamines.[52] To date, however, we are unaware of any human studies on the effects of hydralazine on glucose.

Centrally acting agents—An older preclinical study showed that clonidine caused a dose-related inhibition of glucose-stimulated insulin release by pancreatic beta cells, which would be expected to have a deleterious glycemic effect.[53] However, further research is needed in humans to better evaluate the glycemic effects of centrally acting agents.

Alpha 1 blockers—Selective alpha blockers, such as doxazosin and prazosin, have been shown in a number of studies to be associated with improved insulin sensitivity, although these studies did not include measures of glycemia (e.g., HbA1c) so as to better understand the magnitude of this effect on glycemic control.[54,55] While it is likely that alpha blockers have favorable glycemic effects, they should be cautiously used in patients with CVD, as there was an increased risk of incident congestive heart failure with doxazosin when compared with chlorthalidone in the ALLHAT trial.

Thiazides—There is substantial evidence that thiazide diuretics worsen glycemic controls, [56,57] which is believe to be due to a reduction in both insulin sensitivity and secretion.[58] In the ALLHAT trial, the chlorthalidone group had a greater increase in mean fasting glucose +8.5 mg/dL [0.47 mmol/L] vs +5.5 mg/dL [0.31 mmol/L] for amlodipine and +3.5 mg/dL [0.19 mmol/L] for lisinopril at 2 year follow up.[59] Furthermore, the incidence of new diabetes was 11.0% at 4 years, as compared with 9.3% for amlodipine and 7.8% for lisinopril.[60] Similarly, in the SHEP study, chlorthalidone (vs. placebo) was associated with an elevation in fasting blood glucose (0.51 mmol/L versus 0.31mmol/L; $p<0.01$) and an increase in the incidence of new onset diabetes (13% versus 8.7%; $p<0.001$) over 3 years of follow-up.[57] However, the clinical significance of these glycemic changes has been questioned. In ALLHAT, chlorthalidone was superior in preventing heart failure and stroke. [61] Similarly, in SHEP, new-onset diabetes was not associated with increased mortality over a follow-up period of 14 years.[57] In contrast, in a long-term cohort study of 795 hypertensive patients with a median follow up of 6 years, thiazide-associated incident diabetes was associated with a marked increased risk of cardiovascular events (RR 2.92, 95% CI 1.33-6.41).[62] Furthermore, this risk was comparable to the pre-existing diabetes group at the entry of the study (RR 3.57, 95% CI: 1.65-7.773), suggesting that thiazide-associated incident diabetes may be less benign than previously considered.[62]

Congestive Heart Failure

Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers—Prospective trials and observational data have reproducibly concluded that ACE inhibitors and angiotensin receptor blockers do not increase the risk of developing incident diabetes, although there are inconsistent data regarding whether these medications are metabolically neutral or protective.[63] When compared with placebo, both ACE inhibitors and ARBs have shown protective effects. Among patients without diabetes in the Health Outcomes

Prevention Evaluation (HOPE) trial, ramipril was associated with a marked reduction in the risk of developing incident diabetes over a mean of 5 years of follow-up (RR 0.66, 95% CI 0.51-0.85). Similarly, candesartan was associated with a decreased incidence of diabetes in the CHARM trial (RR 0.78, 95% CI 0.64-0.96);[64] however this risk reduction was no longer significant in the SCOPE trial, although the point estimate was quite similar (RR 0.81, 95% CI 0.62-1.06).[65]

When compared with thiazides and beta-blockers (both of which are known to adversely impact glucose control), ACE-inhibitors and ARBs also showed a reduced risk of incident diabetes. Lisinopril (as part of the ALLHAT study; RR 0.77, 95% CI 0.56-0.86),[61] captopril (as part of the CAPPP study; RR: 0.86; 0.74-0.99)[66] and losartan (as part of the LIFE study; RR 0.75, 95% CI 0.63-0.88)[67] have all showed comparatively better glycemic effects than thiazides or beta-blockers. However, in the STOP-2 hypertension trial, ACE inhibitors were found to carry equivalent risk of diabetes as compared with diuretics/beta-blockers (RR 0.96, 95% CI 0.72-1.27) or calcium channel blockers (RR 0.96, 95% CI 0.74-1.31) during a mean follow up of 5 years.[68] Regardless of whether ACE inhibitors and ARBs are neutral or improve glucose control, there is a wealth of evidence of improved renal outcomes of patients with diabetes treated with ACE inhibitors and angiotensin receptor blockers[69,70], and as such, they are strongly recommended for all patients with diabetes and hypertension or albuminuria, regardless of concurrent cardiovascular disease.

Mineralocorticoid receptor antagonists—The effect of mineralocorticoid receptor antagonists (MRA) on glucose appears to vary with the type of medication used. Although spironolactone has been shown in an observational study to improve insulin sensitivity parameters in patients with primary hyperaldosteronism,[71] in clinical trials, spironolactone has consistently been associated with a modest increase in hemoglobin A1C in patients with type 2 diabetes alone,[72] in diabetes complicated by nephropathy,[73] and in patients with uncontrolled hypertension.[74] In a study of patients with stable heart failure, spironolactone was shown to significantly increase hemoglobin A1C from 5.6% to 5.8% (P <0.0001) and plasma cortisol levels (11.3 μg/dl to 14.7 μg/dl, p=0.003) over a four-month treatment period.[75] However, the adverse effects of spironolactone on glucose do not appear to translate to eplerenone.[75] Post-hoc analysis of the EMPHASIS-HF trial indicated that eplerenone had no impact on the incidence of diabetes (HR 0.90, 95% CI 0.59-1.52) in patients with left ventricular dysfunction after myocardial infarction.[76]

While spironolactone has been shown to have adverse glycemic effects, animal studies have demonstrated its renoprotective properties, including prevention of renal fibrosis and reduction of proteinuria.[77] Furthermore, in clinical trials, spironolactone, but not losartan, was found to have incremental benefit on top of maximal ACE inhibition, in terms of renoprotection in diabetic nephropathy.[77] Other clinical trials have also suggested decreased albuminuria with the addition of spironolactone in patients with diabetic nephropathy.[78,79]

Loop Diuretics—Loop diuretics are associated with improved quality of life outcomes in patients with symptomatic heart failure.[80] In the DOSE trial, diuretics were shown to improve global visual assessment symptom visual analog scores (those that describe global assessment of disease) significantly from 45-50 to 65-70. While there are limited data on the

glycemic effects of loop diuretics, a single cross-sectional study of Swedish patients over the age of 80 found that elderly patients prescribed loop diuretics had higher rates of hyperglycemia as compared with patients not taking loop diuretics.[81] Given the cross-sectional, observational nature of this study, however, firm conclusions on the glycemic effects of loop diuretics cannot be made based on this single study.

CONCLUSIONS

Given the increased prevalence of diabetes and its strong association with CVD, it is becoming increasingly important for clinicians to understand how to treat each condition without adversely affected the other. Many of the available therapies for the treatment of CVD have been shown to impact glucose control. While this has only a modest effect on risk of major adverse cardiovascular events, glycemic control substantially impacts the patient's risk of microvascular complications and affects patient-reported quality of life. Importantly, however, the glycemic effects of the available treatments for CVD are variable, and as such, it is critical for the clinician to understand these effects, so that the medications selected to treat the CVD not only maximize cardiovascular outcomes but also minimize any adverse effects on the patient's comorbid diabetes.

Additionally, to complement efforts to balance favorable cardiovascular outcomes with optimization of glycemia, it is important to note that since 2008, the Food and Drug Administration has required clinical trial evidence attesting to the cardiovascular risk of new diabetes drugs.

In this article, we have reviewed the glycometabolic effects of multiple classes of cardiovascular drugs and have identified many areas where the clinician can potentially positively impact glycemic control while also optimally treating the CVD. For example, vasodilating beta-blockers, ranolazine, and RAAS antagonists are agents that have reproducibly been associated with favorable metabolic properties in patients with diabetes. In contrast, thiazide diuretics, non-vasodilating beta-blockers, and possibly hydralazine and clonidine may have adverse glycemic effects. Highlighting the differences in glycemic effects across different CVD medications is highly relevant, as research has shown that clinicians are rarely integrating these data in their CVD treatment decisions.[19] As the population of patients with diabetes and CVD continues to increase, a greater knowledge of these drug:disease interactions will be even more critical for clinicians. In the era of precision medicine, understanding the metabolic impact of cardiovascular medications may guide decision support tool development to better optimize a medical regimen that is symbiotic to both CVD and diabetes. More research is needed on the glycemic effects of commonly used medications for CVD for which uncertainty remains, so that these relationships can be further clarified. Finally, as novel CVD therapies are being considered for use, we encourage the trialists to also examine how these therapies will impact glycemic control.

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Table

Summary of glycemic effect of major classes of cardiovascular medications

Class of Medications	Specific Medication studied	Indication	Effect on Glycemia	Effect on Insulin Resistance / Sensitivity	Effect on A1C	Effect on incident diabetes	Plasma Glucose	Albuminuria	Level of Evidence
Phosphodiesterase inhibitor	Cilostazol	PAD	Unknown	→ insulin resistance				→	RCT; Animal studies
Beta-blockers	Atenolol	CAD; HTN	–		←				RCT
	Carvedilol	CAD; CHF	+	← insulin sensitivity	Neutral			→	RCT
	Metoprolol	CAD; CHF	–	No change	←				RCT
	Nebivolol	CAD; CHF	+	← insulin sensitivity					RCT
Calcium Channel Blockers	Amlodipine, clinidipine	CAD	Neutral	May → insulin sensitivity					RCT; Observational
Ranolazine	Ranolazine	CAD	++		→				Clinical trials (post hoc analysis)
Nitrates	Isosorbide Mononitrate	CAD	Unknown	No effect					Observational
Statin		CAD	–			←			Meta-analysis
Niacin		CAD	–		→				Observational
Fibrates		HLD	Unknown						
Fish Oil		CAD/HLD	Neutral		Neutral				Meta-analysis
Direct Renin Inhibitor	Aliskerin	HTN	Unknown						
Hydralazine		HTN	Unknown						
Centrally Acting Agents		HTN	Unknown						
Alpha 1 Blockers	Doxazosin	HTN	Unknown	Conflicting data		←			Clinical trials (post hoc analysis); Observational
Thiazides		HTN	–	→ insulin sensitivity		←	←		RCT; Observational

Class of Medications	Specific Medication studied	Indication	Effect on Glycemia	Effect on Insulin Resistance / Sensitivity	Effect on A1C	Effect on incident diabetes	Plasma Glucose	Albuminuria	Level of Evidence
Antiarrhythmic	Sotalol	Arrhythmia	–		←		←		RCT
ACE-I/ARB		CHF/HTN	++			→			RCT; Observational
	Captopril	CHF/HTN				→			RCT
	Lisinopril	CHF/HTN				→			RCT
	Ramipril	CHF/HTN				→			RCT
	Candesartan	CHF/HTN				→			RCT
	Losartan	CHF/HTN				→			RCT
Mineralocorticoid	Spironolactone	CHF			←			→	RCT; Observational
	Eplerenone	CHF			Neutral	Neutral			RCT
Loop Diuretics		CHF	Unknown				←		Observational
Digoxin		CHF	Unknown						

ACE-I = ACE Inhibitor; MRA = mineralocorticoid receptor antagonist; PAD = Peripheral Arterial Disease; CAD = Coronary Artery Disease; HTN = Hypertension; HLD = Hyperlipidemia; CHF = Congestive Heart Failure.