

Antihypertensive medications and risk of diabetes mellitus

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Purpose of review

Over the past decade post-hoc analyses of clinical trials and observational studies have tended to show that participants treated with thiazide diuretics are at greater risk for newly diagnosed diabetes mellitus than those treated with other medication classes. We review the results of several recent studies on the impact of thiazide-related hyperglycemia and diabetes mellitus on cardiovascular disease outcomes. We also examine the impact of the glucose-sparing effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on preventing cardiovascular disease.

Recent findings

No consistent or conclusive evidence has been found that hyperglycemia or diabetes mellitus in association with thiazide diuretic use is associated with increased cardiovascular disease outcomes. This benign outcome may be a consequence of the fact that only a segment of such diuretic-associated cases is induced by the usual etiologic mechanisms that are associated with classic 'diabetes mellitus'. Likewise, no evidence has been found that the glucose-lowering effect of angiotensin-converting enzyme inhibitors is associated with decreased cardiovascular disease risk.

Summary

We conclude that thiazide diuretics are safe to use, even in hypertensive individuals at risk for incident glucose disorders. The use of angiotensin-converting enzyme inhibitors for protection against glucose disorders and subsequent cardiovascular disease remains to be determined.

Keywords

angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, elevated glucose, hypertension, thiazide diuretic

Abbreviations

ACE	angiotensin-converting enzyme
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARB	angiotensin receptor blocker
CVD	cardiovascular disease
HR	hazard ratio
CI	confidence interval

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Introduction

It is well established that the use of thiazide diuretics for the treatment of hypertension can elevate blood glucose levels. More recently, post-hoc analyses of large clinical trials performed since 1999 have shown that the risk of diabetes mellitus is also higher in patients treated with diuretics (with or without β -blocker use) compared with placebo or angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (reviewed in [1–9]). One group of investigators [8] concluded that if 'newer' antihypertensive medications (calcium channel blockers and ACE inhibitors) were used in place of 'older' medications (thiazide diuretics and β -blockers) the absolute difference in new-onset diabetes mellitus would be 5.6 ± 2.3 cases per 1000 patients per year.

Given the deleterious effects of newly diagnosed diabetes mellitus on cardiovascular disease (CVD), concern has been raised regarding the appropriateness of thiazide diuretics for the treatment of hypertension, especially in people prone to developing diabetes mellitus (e.g. obese people, those with metabolic syndrome, and those with mildly elevated glucose levels not in the diabetic range). Is the proven effect of blood pressure lowering with thiazide diuretics on reducing CVD risk attenuated by their dysglycemic effect? Conversely, it is not known whether the lower diabetes mellitus incidence associated with ACE inhibitor use represents a true CVD preventive effect.

The purpose of the present report is to review and critique

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several recent studies that have examined the prognostic impact of thiazide-associated hyperglycemia and incident diabetes mellitus on CVD outcomes. We also review the glucose-protective effects of ACE inhibitor or ARB use on CVD outcomes.

Recent clinical studies examining cardiovascular disease outcomes with regard to thiazide-induced hyperglycemia

In a prospective population-based study reported by Dunder *et al.* in 2003 [10], a cohort of 1860 men, age 50 years at initial examination, was followed for a mean of 17.4 years. Among participants who developed a myocardial infarction after age 60 years ($n = 253$), there was a significantly greater increase in glucose levels between ages 50 and 60 than among those who did not have a myocardial infarction. In multivariate Cox proportional hazard models, the increase in blood glucose was an independent risk factor for myocardial infarction in participants receiving anti-hypertensive medications at age 60 years. Most of the anti-hypertensive therapy consisted of thiazide diuretics and β -blockers. No effect of a rise in glucose levels on risk of myocardial infarction was noted in participants not on anti-hypertensive medications. Based on these data, the authors concluded that thiazide-induced hyperglycemia had a deleterious effect on coronary heart disease risk. This study [11] has been criticized, however, for failing to adjust for the effects of hypertension *per se* on rising glucose levels.

A second detailed study of the effects of thiazide diuretic-associated hyperglycemia on CVD was reported by Verdecchia *et al.* [12,13]. In a cohort of 795 initially untreated hypertensive adults, followed for a median of 6 years (range 1–16 years), new onset diabetes mellitus occurred in 5.8% of participants. Antihypertensive therapy included a diuretic in around 53% of participants who developed new diabetes mellitus compared with around 30% in those in whom diabetes mellitus did not develop. After adjustment for confounders, the authors found the relative risk for a CVD event was 2.92 [95% confidence interval (CI) 1.33–6.41] times higher in those with new onset diabetes mellitus compared with those who did not develop the condition. Analysis did not find an independent association of diuretic use with subsequent coronary heart disease events (a point to which we shall return below). The results of this study are open to several criticisms. Most notably, analyses were based on only a small number ($n = 463$) of CVD events. The definition of CVD events included 10 instances of transient ischemic attacks, which are not considered to be hard endpoints. Lastly, many participants were treated with a wide array of medications, making it difficult to parse out the individual effect of diuretic therapy on glucose levels and CVD outcomes.

In contrast to the authors' interpretation of the above two studies, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [14**] did not demonstrate a deleterious effect of thiazide-associated hyperglycemia on CVD outcomes. ALLHAT was a multi-center randomized clinical trial designed to determine whether the occurrence of fatal coronary heart disease or nonfatal myocardial infarction is lower for high-risk hypertensive patients treated initially with a calcium channel blocker (CCB) or an ACE inhibitor compared with a diuretic. In that study, the 4 and 6-year cumulative incidence of new onset diabetes mellitus (defined as a fasting glucose level >125 mg/dl) among participants without diabetes at baseline was 11.0 and 13.8% in those assigned to chlorthalidone, 9.3 and 12.0% in those assigned to amlodipine, and 7.8 and 11.0% in those assigned to lisinopril. These rates allow a calculation that provides an important perspective on thiazide-associated diabetes: if the CCB is assumed to be metabolically neutral, then (based on the 4-year rates) 85% (9.3/11.0) of diabetes associated with a diuretic is not induced by the diuretic, at least in an older, mostly overweight, ethnically diverse population.

Similarly to other studies, ALLHAT found that the risk of coronary heart disease increased significantly in the presence of new-onset diabetes [hazard ratio (HR) 1.64, 95% CI 1.15–2.33; see Table 1]. Yet, among participants on chlorthalidone, the relative risk estimate for coronary heart disease in those who developed newly diagnosed diabetes mellitus during the first 2 years of follow up (HR 1.46, 95% CI 0.88–2.42) was lower than that of the other two treatment arms (amlodipine, HR 1.71, 95% CI 0.87–3.34; lisinopril, HR 2.23, 95% CI 1.07–4.62). Although an interaction term between incident diabetes mellitus and treatment with amlodipine or lisinopril versus chlorthalidone treatment on coronary heart disease risk was statistically nonsignificant, suggesting that the effect of incident diabetes mellitus on coronary heart disease was similar in all three treatment groups, the low statistical power of such tests is well known when samples have not been sized to address interactions. These results are similar to those of Verdecchia *et al.* [12,13] (see above) who also found that incident diabetes mellitus was associated with increased risk of CVD but did not find an association of diuretic use with incident CVD.

This apparent conundrum – of increased diabetes mellitus in association with thiazide diuretic use and yet no association of thiazide use with coronary heart disease, despite a higher incidence of diabetes mellitus with thiazide use – deserves an explanation. First, it is possible that elevated glucose levels are a surrogate marker for other processes associated with a medication's effect. For example, in the Cardiac Arrhythmia Suppression Trial (CAST) [15], antiarrhythmia medications successfully suppressed premature

Table 1. Cox regression models examining the effect of incident diabetes during the first 2 years of follow up on subsequent cardiovascular disease (CVD) and renal endpoints in those with normoglycemia (fasting glucose <100) or impaired fasting glucose (100–125 mg/dl) at baseline

Event	n	No. events	Diabetes incidence yes/no HR (95% CI, P)	P for trt–diabinc interaction
Coronary heart disease				
Total	6216	339	1.64 (1.15–2.33, 0.006)	0.21
Chlorthalidone	2899	162	1.46 (0.88–2.42, 0.14)	
Amlodipine	1674	91	1.71 (0.87–3.34, 0.12)	
Lisinopril	1643	86	2.23 (1.07–4.62, 0.03)	
Total mortality				
Total	6357	508	1.31 (0.95–1.81, 0.10)	0.19
Chlorthalidone	2961	241	1.05 (0.66–1.67, 0.83)	
Amlodipine	1717	138	1.92 (1.07–3.44, 0.03)	
Lisinopril	1679	129	1.31 (0.64–2.70, 0.46)	
Stroke				
Total	6300	149	1.61 (0.92–2.84, 0.10)	0.24
Chlorthalidone	2934	66	1.83 (0.85–3.95, 0.12)	
Amlodipine	1702	42	2.63 (0.97–7.09, 0.06)	
Lisinopril	1664	41	0.48 (0.06–3.60, 0.47)	
Cerebro and cardiovascular disease				
Total	5751	854	1.04 (0.80–1.35, 0.77)	0.36
Chlorthalidone	2703	400	0.96 (0.66–1.37, 0.80)	
Amlodipine	1556	229	1.14 (0.69–1.90, 0.61)	
Lisinopril	1492	225	1.31 (0.76–2.26, 0.33)	
Heart failure				
Total	6279	201	1.37 (0.84–2.24, 0.21)	0.36
Chlorthalidone	2937	88	0.96 (0.46–2.00, 0.91)	
Amlodipine	1691	71	1.29 (0.53–3.10, 0.58)	
Lisinopril	1651	42	3.66 (1.30–10.32, 0.01)	
End-stage renal disease				
Total	6351	29	2.86 (0.97–8.39, 0.06)	0.49
Chlorthalidone	2960	16	3.05 (0.82–11.33, 0.10)	
Amlodipine	1714	4	— ^a	
Lisinopril	1677	9	3.80 (0.39–36.83, 0.25)	

HR for incident diabetes at 2 years (yes/no) (controlling for treatment group, 2-year blood pressure, age, race, gender, smoking, baseline fasting glucose, baseline BMI, 2-year serum potassium, and atenolol and statin use at 2 years).

^aModel did not converge due to small number of events.

ventricular beats. Despite this, mortality was increased in patients treated with antiarrhythmia medications compared with those receiving no treatment of arrhythmia. In other words, a major health endpoint did not necessarily reflect other effects of the medications. Second, older studies have shown that glucose levels often decrease if diuretic therapy is discontinued for whatever reason [16]. This is unlike ‘classic’ diabetes mellitus which is persistent. This finding suggests that the elevation in glucose levels induced by diuretic use is by mechanisms other than through insulin resistance – the underlying mechanism for ‘classic’ diabetes mellitus. (A primary candidate mechanism is decreased insulin secretion due to potassium depletion, discussed below.) As illustrated in the preceding paragraph, only a small proportion of diabetes arising while taking a diuretic is actually induced by the diuretic. Closer evaluation of Table 1 shows that incident diabetes mellitus in participants treated with lisinopril was associated with a significantly elevated risk of coronary heart disease. Also those

treated with amlodipine who developed diabetes mellitus had higher total mortality and stroke. Given that these medications are ‘glucose protective’ or ‘glucose neutral’, the development of diabetes mellitus in association with their use suggests the presence of a high degree of insulin resistance. It is in these subgroups, and not in those developing elevated glucose levels on a thiazide diuretic, in whom incident diabetes mellitus had its deleterious effects. Finally, analysis of ALLHAT showed that even though the incidence of diabetes mellitus at year 4 of follow up was higher in participants on chlorthalidone, the absolute difference in fasting glucose levels between them and those treated with amlodipine and lisinopril was small, at 1.5 and 4.0 mg/dl, respectively. Such small differences should not impact relative CVD risk.

The ALLHAT results are open to several criticisms. Chief among them is the relatively short duration of follow up. The average follow up was 2.9 years after diabetes mellitus

was detected at the second year of follow up. The effects of diabetes mellitus on the cardiovascular system occur over many years. Then, too, there was up to 20% dropout from assigned medication. While these concerns are legitimate, the findings from the Systolic Hypertension in the Elderly Program (SHEP) Follow up Study [17], reported in 2005, are similar to those of ALLHAT. SHEP was a study of thiazide-diuretic therapy versus placebo for the treatment of isolated systolic hypertension in adults aged 65 years and over. Unlike the studies of Dunder, Verdecchia, and ALLHAT, the SHEP study was not 'contaminated' by the use of multiple antihypertension medications. For the most part, only a β -blocker or reserpine was added to the diuretic in the active arm of the study if the blood pressure goal was not achieved. The duration of follow up, including the active trial period, was on average more than 14 years. During follow up, incident diabetes mellitus related to diuretic use (during the 5 years of the trial) was not associated with increased CVD risk (HR 1.04, 95% CI 0.75–1.46) compared with increased CVD risk associated with incident diabetes mellitus that occurred on placebo therapy (HR 1.56, 95% CI 1.11–2.18). Moreover, just as in ALLHAT [18], SHEP participants with prevalent diabetes mellitus at baseline who were treated with a diuretic had significantly lower CVD mortality than those who were treated with placebo (HR 0.69, 95% CI 0.68–0.95). The authors of this study concluded, like the ALLHAT investigators, that diuretic-induced hyperglycemia had no adverse impact on CVD. The long duration of follow up and the relative lack of contamination of diuretic use with other antihypertension medications make these conclusions robust.

The mechanism by which diuretic use leads to hyperglycemia is thought to be through hypokalemia (i.e. $K < 3.5$ meq/l), which reduces insulin secretion. Strategies to maintain potassium levels may therefore prevent hyperglycemia. In a review of 39 active-controlled trials and 20 placebo-controlled trials by Zillich *et al.* [19**] there was a linear trend relating a decrease in potassium with an increase in glucose level (for a 1 meq/l decrease in potassium there was an increase in glucose of about 10 mg/dl). The correlation between these levels was significant ($R^2=0.37$, $P < 0.01$). Trials in which potassium supplementation was used and in which potassium levels were maintained within the normal range yielded more modest glucose changes. An editorial commentary [20**] that accompanied Zillich *et al.* reviewed the well controlled small sequential trials that unequivocally established the ability of induced hypokalemia to raise blood glucose, and potassium repletion to reverse the glucose changes. To date, no randomized clinical trial has been done to test these findings.

Impact of the glucose protective effect of

angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on cardiovascular disease risk

The above studies indicate that thiazide-associated diabetes mellitus does not result in a significantly increased risk of CVD endpoints, probably because of the admixture of thiazide-induced cases. The recently described glucose-protective effects of ACE inhibitors reported in many trials raises the possibility that these agents may decrease CVD risk through this mechanism. To address this possibility, Gillespie *et al.* [21] performed a literature review of randomized controlled trials of ACE inhibitors or ARBs versus placebo or traditional therapy in which the endpoint of new onset diabetes mellitus was examined. Eleven trials were identified. The odds ratio of new onset diabetes mellitus was 0.78 (95% CI 0.73–0.83) and was consistent across trials for the treatment of hypertension, coronary heart disease, or heart failure. Further analysis showed, however, that neither ACE inhibitors nor ARBs reduced the odds of overall mortality or of cardiovascular or cerebrovascular events among all studies combined or in the hypertension trials in particular. Most odds ratios were close to unity. Based on these results the authors concluded that hypertension control determined the development of CVD endpoints more than the lack of development of new diabetes mellitus. Only in individuals with preexisting coronary heart disease was ACE inhibitor or ARB use associated with reduced mortality or fewer CVD endpoints. The authors of that analysis did not feel that the reduced incidence of diabetes mellitus alone could explain these findings given the short period of time in which they were detected (since the effects of diabetes mellitus take a long time to occur).

The results of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study [22] are in accord with this assessment. The use of rosiglitazone (a medication that improves glucose sensitivity) was associated with a 60% decrease in diabetes or death in people with impaired glucose tolerance or impaired fasting glucose. By contrast, the use of ramipril failed to make an impact on the primary endpoints of death or diabetes, though it did lower post-challenge 2 h glucose levels [23**]. Compared with placebo, ramipril lowered fasting glucose levels by less than 1 mg/ml – an effect that would not be expected to impact CVD outcomes.

Finally, a recent study [24**] related to the subject of anti-hypertensivemedications and risk of diabetes deserves mention. It is commonly believed that the treatment of renal disease, especially in the context of diabetes, should be based on ACE inhibitor or ARB therapy. The evidence for this rests largely on data pointing to lower degrees of proteinuria on such therapy. A nested case-control study [25] of a cohort of patients with diabetes from Canada treated with

antihypertensive medications in 1982–1986 and followed through 1997 (many of whom would have had metabolic syndrome and are at risk for incident diabetes) showed that the risk for the development of renal failure after the first 3 years of follow up was 2.5 times higher in those treated with an ACE inhibitor than in those treated with a diuretic. Somewhat similar conclusions were reached in the ALLHAT study. It follows that there is no strong evidence that ACE inhibitors or ARBs should be preferred to thiazides or other medications in the treatment of hypertension for renal protection, except in the presence of moderately heavy proteinuria. Recent studies [26,27] suggest that the developments of proteinuria and renal failure are separate processes with different genetic and clinical risk factors.

Conclusion

In this review we have presented data to suggest that thiazide-related diabetes mellitus is not associated with increased CVD risk and that the glucose protective effects of ACE inhibitors and ARBs do not decrease CVD risk. Given these findings it is safe to conclude that thiazide diuretics can and should be part of a therapeutic approach for the treatment of hypertension, even in people at risk for hyperglycemia. Attention to maintaining potassium balance may mitigate some of the glucose-elevating effects of thiazide diuretics. It is important to recognize, however, that the treatment of hypertension nowadays often requires the use of multiple medications. The mild dysglycemic effects of thiazide diuretics may be balanced by the mild glucose-protective effects of other medications such as ACE inhibitors.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 388).

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