expert roundtable »

Do Thiazide Diuretics Cause Diabetes? If So, Is It of Clinical Significance?

Moderated by **Barry Carter, PharmD**[1]
Discussants: **Jan Basile, MD**[2]; **William Cushman, MD**[3]; and **Domenic Sica, MD**[4]

The following Expert Roundtable Discussion was held on July 2, 2010. Dr. Barry Carter from the University of Iowa moderated the topic "Do Thiazide Diuretics Cause Diabetes? If So, Is It of Clinical Significance?" with Drs. Jan Basile from the Medical University of South Carolina and the Ralph H. Johnson VA Medical Center, William Cushman from the University of Tennessee College of Medicine and the Memphis VA Medical Center, and Domenic Sica from the Virginia Commonwealth University participating.

The discussion focused primarily on: (1) the potential for new onset diabetes following initiation of thiazide diuretics, (2) the relationship of other drugs used in the treatment of hypertension, (3) review of clinical trial data, (4) review clinical practice guidelines, (5) the risks associated with thiazide diuretics, including hypokalemia, (6) dosing strategies to mitigate risks in this class of drugs, (7) thiazide treatment in combination with other therapeutic options, (8) strategies for reducing the need for additional antihypertensive agents, (9) promoting lifestyle modifications that can overcome adverse metabolic effects of the thiazide diuretics. (*Med Roundtable Cardiovasc Ed.* 2010;1(3):152–159)

TRIALS DISCUSSED:
ACCORD, ALLHAT, DREAM, DPP, NAVIGATOR, NHANES, SHEP, VALUE

COMPOUNDS DISCUSSED:
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From the University of Iowa, Iowa City, IA[1]; the Medical University of South Carolina and the Ralph H. Johnson VA Medical Center, Charleston, SC[2]; University of Tennessee College of Medicine the Veterans Affairs Medical Center, Memphis, TN[3]; and the Virginia Commonwealth University, Richmond, VA[4]
Address for correspondence: Barry Carter, PharmD, Professor, College of Pharmacy and Professor and Associate Head for Research, Department of Family Medicine, University of Iowa, S 527 PHAR, College of Pharmacy Iowa City, IA 52242-1112
E-mail: barry-carter@uiowa.edu
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DR. CARTER: The most recent National Health and Nutrition Examination Survey (NHANES) data suggests that blood pressure control in 2007 and 2008 was achieved in 50% of individuals with hypertension. The Healthy People 2010 goals included a target of 50% for blood pressure control, so it appears that we have achieved that target. It's become clear that to achieve high control rates in populations many patients will require two to four antihypertensive medications. It is also clear that one of the most effective components of such regimens is a thiazide-type diuretic. While beta blockers may not be appropriate first line therapy today, they are still important agents for patients with ischemic heart disease, heart failure or those who have suffered a myocardial infarction.

However, over the past 30 years, questions have arisen about the metabolic effects of these drugs, and specifically their ability to increase blood glucose. This Roundtable Discussion will focus on the potential for new onset diabetes, following initiation of thiazide diuretics. We will also focus on the relationship of other drugs in new onset diabetes in order to place potential therapies in the proper perspective.

While various studies have suggested there might be an increased risk of new onset diabetes with thiazides, large outcome studies have also found that these drugs are some of the most effective agents to reduce morbidity and mortality. JNC 7 recommended that therapy should generally be initiated with a thiazide, based on these clinical trials. However, the potential for new onset diabetes has created one of the key controversies in hypertension.

I am Barry Carter and I am a Professor in the College of Pharmacy and a Professor and Associate Head for Research in the Department of Family Medicine, College of Medicine at the University of Iowa, and I will be moderating this discussion. I am joined by Dr. Jan Basile, a Professor of Medicine at the Seinsheimer Cardiovascular Health Program in the Division of General Internal Medicine at Medical University of South Caro-

lina, and at the Ralph H. Johnson VA Medical Center, Charleston, S.C.; Dr. William Cushman, Professor of Preventive Medicine, Medicine and Physiology at the University of Tennessee College of Medicine, and Chief Preventive Medicine at the Veterans Affairs Medical Center in Memphis, TN; and Dr. Domenic Sica, a Professor of Medicine and Pharmacology and Chairman of Clinical Pharmacology and Hypertension in the Division of the Nephrology and Eminent Scholar at Virginia Commonwealth University in Richmond.

I would like to begin with a discussion of the findings from observational studies and clinical trials that suggest an increased risk of new onset diabetes with thiazides. Bill, can you provide an overview of some of the key clinical trial data regarding this?

DR. CUSHMAN: Sure, I'll talk in general terms. Many clinical trials have shown some differences in glucose levels or new onset diabetes. Short-term trials frequently showed that glucose levels are, maybe, 5 or 6 mg/dL higher on full doses of thiazide-type diuretics, compared with placebo. And, in addition, the use of beta blockers often has been associated with some increases in glucose to about the same degree, although, occasionally much higher levels are noted.

Conversely, blockers of the renin-angiotensin system (RAS), specifically angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have been associated with some decreases in glucose levels over time. All of these differences are fairly small. Some studies did not show any differences—either increases in glucose with thiazides or even beta blockers or decreases with RAS blockers. But, putting all of the data together would suggest that there are some differences.

Now, there had been several prospective studies specifically testing the incidence of diabetes particularly with an ACE-inhibitor or an ARB. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial tested whether ramipril would reduce the incidence of diabetes, since the data from the Heart Outcomes Prevention Evaluation (HOPE) trial suggested that glucose was reduced with ramipril. There was no significant decrease in the incidence of diabetes by the primary outcome that they used in the DREAM trial. There was, however, a trend in that direction and there were some benefits seen in two hour postprandial glucose levels.

A more recent study, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), tested valsartan and nateglinide for diabetes prevention, a trial similar to the DREAM study; however, NAVIGATOR also assessed the effects of these drugs on cardiovascular outcomes. Both the DREAM and the NAVIGATOR trials were in patients with impaired glucose tolerance. The NAVIGATOR trial did show a significant reduction in diabetes incidence. It was a larger trial and achieved a slightly greater risk reduction. Qualitatively, these results were not really that much different than DREAM, even though the effect in DREAM was not significant. NAVIGATOR did not show a difference in cardiovascular outcomes even with this reduction in the incidence of diabetes.

> ***"Most of the time we're talking about an absolute difference in diabetes incidence within these trials of a couple percent."***
>
> *~ Bill Cushman, MD*

To put this into some context, most of the time we're talking about an absolute difference of just a few percent in diabetes incidence within these trials. Even the NAVIGATOR trial reported only small percent absolute difference in the incidence of diabetes. The glucose level differences are usually about of 5-10 mg/dl at the most. Those levels are fairly trivial when you look at the relationship between glucose levels and cardiovascular risk.

For example, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, we were looking at differences in glucose that were about ten times the differences that we see with antihypertensive drugs—as much as 50-60 mg/dL differences in glucose in order to try to detect a difference in cardiovascular outcomes. However, in ACCORD, even with this large a difference in glucose, we did not see a significant difference in cardiovascular outcomes within the trial. The important point is that glucose difference with antihypertensive drugs, relatively speaking, are quite small.

DR. CARTER: Bill referred to some of the newer data but, Jan and Dom, can you talk about the data from 2005 from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)? Here they looked at patients divided into whether they had impaired fasting glucose, normal glycemia, or overt diabetes. And those outcomes were as good, or better, with thiazide-based therapy as with ACE-inhibitor- or calcium channel blocker-based treatment, correct?

DR. BASILE: Yes; let me first back up on Bill's comment. I think that he highlighted many of the important points. I think in post-hoc and subgroup analysis, a couple of large studies have found that agents that block the RAAS system, specifically ACE-inhibitors and ARBs, decreased the incidence of new onset diabetes. In a large meta-analysis, with ACE-inhibitors, it was about a 27% reduction and with ARBs it was about 23%.

Yet, in prospective studies such as the DREAM study, as Bill has discussed, when there's less chance of confounding from either cross over, drop out, etc. (all the problems that you have with retrospective post-hoc analysis), a significant reduction in preventing diabetes using the ACE inhibitor ramipril in a dose up to 15 mg of ramipril was not found. Furthermore, in NAVIGATOR, one of the primary endpoints was the prevention of diabetes comparing the addition of valsartan, 160 mg a day, with placebo and led to a significant but only 14% reduction in new onset diabetes.

So, I think most clinicians are aware that, when adding an agent like an ACE inhibitor or an ARB, you're less likely to develop new onset diabetes. But as Bill said, in most of these studies, the absolute differences were only about 1% and 3% between ACE-inhibitors, ARBs and thiazide diuretics.

In ALLHAT, a double-blind, prospective outcomes trial, new onset diabetes occurred in 11.6% of patients receiving the thiazide-type diuretic chlorthalidone, 9.8% in those receiving the calcium channel blocker amlodipine and 8.1% in those receiving the ACE-inhibitor, lisinopril. So, as Bill has mentioned, these percentages were 1% to 3% less than with a thiazide diuretic. And, even in those patients that became diabetic during the trial or were diabetic on entry, the composite primary outcome was the same regardless of randomization to either of the three different classes of agents used in ALLHAT.

So, that's ALLHAT. Dom or Bill may want to talk about SHEP or some of the other trials where similar outcomes have been observed, but it's been interesting to see how all of this information has evolved and how the hypertension community has interpreted it. It leaves clinicians a little unclear exactly where an ACE inhibitor and an ARB should be used instead of agents like thiazide diuretics in patients who are prone to diabetes or have frank diabetes.

DR. CARTER: Dom, before I ask you about mechanisms, do you have anything else to add to this?

DR. SICA: A couple of things. It is a widely touted fact that ACE-inhibitor and ARB use provides protection from cardiovascular events as well as having non-diabetogenic effects. I really think that's a secondary consideration in the use of these drugs. I don't think that the gain from saying, "I'm going to start an ACE-inhibitor because it has this cardiovascular protective feature," should ever supercede the issue of how well blood pressure is reduced with these drugs. Though all too often, the clinician thinks that this is a favorable feature and the patients would benefit from it; however, if blood pressure is not lowered in the course of therapy then any non-blood pressure feature is of limited significance. So, I think there's a lot of confusion on the clinician front on this issue. So, I guess if I choose a word for the new onset diabetes issue, the word would be "overplayed."

> ***"…a couple of large studies have found that agents that block the RAAS system … decreased the incidence of new onset diabetes."***
>
> *~ Barry Carter, PharmD*

The second point is that the array of data that's out there is fairly confusing. It's presumed that there is a class effect for this phenomenon. But, we don't actually know that to be a fact and we don't know whether doses of specific ACE-inhibitors or ARBs may compare to equal doses of another ACE-inhibitor or ARB. So, the dose ranging consideration here remains unclear and I think, even as Jan said, from the DREAM trial, they used 15 mg of ramipril and it didn't really look like there was much benefit on the diabetogenic front. So, I think as all three of us have stated, this is a fairly puzzling area. It's overplayed and maybe much less clinically relevant in the big scheme of things.

DR. CARTER: Dom, you mentioned the class affect, referring to ACE inhibitors and the ARBs. But it also appears that there's probably not a class affect with the beta blockers in regard to their ability to induce new onset diabetes, and that perhaps vasodilating beta blockers may not do that as much, or as significantly, as the non-vasodilating beta blockers, is that true?

DR. SICA: Yes, I would agree. I think there are some data with carvedilol that would suggest it's more diabetes friendly in a soft kind of way than would be the case for a drug like metoprolol, to which it has been compared at high doses. I think the data with nebivolol as relates to new-onset diabetes are less clear than the data is with carvedilol. But even there, the carvedilol data are a fairly nominal finding that doesn't carry with it, I think, a whole lot of weight in the big scheme of things.

DR. CUSHMAN: If I could just add something, and that is to reiterate and expand a little bit on what Jan and Dom have said. In ALLHAT, none of the comparative drugs were superior to the diuretic chlorthalidone in preventing cardiovascular events, as Jan said. Yet, the diuretic was actually better at preventing some events regardless of whether it was somebody with pre-diabetes, diabetes, or normal glucose levels. In particular, heart failure incidence was very consistently lower with chlorthalidone. Generally, the relative differences between drugs were the same, regardless of what glycemia group the participants were in,

even though diabetics had a higher risk of events.

Now, what was also examined in ALLHAT was whether the small differences in glucose translated to differences in cardiovascular outcomes. There really were no adverse effects on cardiovascular outcomes to speak of. As a matter of fact, any diabetes that did develop seemed to be more benign if it was in the context of being on chlorthalidone, the diuretic. The long term effects of these glucose differences in follow up after randomized therapy in ALLHAT are also being looked at; they have been presented but have not been published yet.

DR. CARTER: Thank you, Bill. Dom, could you provide us with an overview of the theories on the possible mechanisms for the new onset diabetes, particularly with the thiazides and then perhaps also discuss ACEs and ARBs?

DR. SICA: Sure. It is an area that's debated but even now with several years of debate in our back pocket, we still don't have a good answer. I think the pathways are multiple with diuretics. First of all, the presumption that it's a class effect with diuretics probably relates to the thiazide diuretics and not to loop diuretics and/or potassium-sparing diuretics. There appears to be a dose dependency. The higher the dose the greater the overall potential, although the slope that describes the relationship between low and high doses probably does vary amongst the different thiazide-type diuretics. These drugs have been sparingly studied head-to-head in a similar patient population to look at what the differences might be. So, that's a little bit in the way of background.

The thiazide-type diuretics have a range of adaptive responses that occur with their use, which to a degree are dependent upon the level of volume change. So, whenever we're contemplating diabetogenic effect it's a matter of what are the changes and the level of activation of the sympathetic nervous system, which for these drugs as stated is highly dependent upon the volume state. So, people have proposed that there may be the issue of sympathetic activation, which may confer risk for blood sugars going up. I probably would prefer to use the term blood sugars going up than creating frank diabetes, which is much less common than a couple of milligram percent rise in blood sugar.

There are electrolyte changes, which seem to occur with these drugs. Probably the most pertinent of which are changes in magnesium and potassium. Magnesium has been loosely linked with changes in blood sugar. As such, low magnesium values have been suggested to have a relationship to increases in blood glucose values; however, this is not a consistent finding or one with a well worked-out mechanistic basis. Most of the play seems to relate to changes in serum potassium with the presumption that serum potassium marks specific degrees of total body deficit of potassium. Unfortunately it does not do a good job of defining the total body deficit of potassium in a patient who is hypokalemic. So the theories that have been developed have generally been related to serum potassium with background thinking that the level of potassium depletion could be quite variable. And, there is expected imprecision when using serum potassium values for defining diabetes risk.

> ***"It's overplayed and maybe much less clinically relevant in the big scheme of things, that is, the K for preventing new-onset diabetes."***
>
> *~ Domenic Sica, MD*

The serum value change has a wide-ranging influence as to insulin release and insulin action, which, when summed, can increase blood sugar values. Other electrolytes have been less relevant. There is also emerging data suggesting that the degree to which abdominal obesity is present predicts new-onset diabetes. Visceral fat may influence metabolism and promote insulin resistance via the liver through the portal circulation, and, in a recent study, treatment with hydrochlorothiazide for three months was associated with liver fat accumulation and fat redistribution from the subcutaneous to the visceral space in patients with abdominal obesity. Of note, this fat redistribution was associated with worsening insulin resistance and a low-grade inflammatory state.

If you add it all up it becomes bewildering. I think each patient may have a somewhat different mechanism. So I believe the mechanisms are probably heterogeneous and likely patient specific. There may be over-arching themes that apply, but each person likely has an inherent sensitivity to the diabetogenic effects of thiazide-type diuretics. Since changes in blood sugar are part of a continuum and we never know where on the continuum an individual patient is who may have mild glucose intolerance and/or the metabolic syndrome, you don't know what's going to trigger a rise or whether the rise is proportional to the drug and dose. So, I think it's a moving target.

I believe if "hypokalemia" is an issue, then it'll be quite difficult to show that with current technology in a convincing way. Since potassium changes are so variable in individual patients and as I said poorly reflective of total body deficits. That is a brief summary of several of the mechanisms that have been proposed.

DR. CARTER: Great, thanks, Dom. Jan, from your perspective, is there a specific patient whom you would think of that might be particularly prone to this in spite of what their serum glucose might happen to be at baseline?

DR. BASILE: Yes. I enjoyed Dom's take on all of this. But when I see patients, the major thing that I take from the literature and the area that I think clinicians should pay particular attention to is potassium, and perhaps magnesium balance. Although, most clinicians do not pay that much attention to magnesium, and it may be a major driver here, but certainly they do pay attention to potassium. It's widely available on basic metabolic panels. Thiazides have long been known to be associated with hypokalemia, and dating back over 50 years now, this association of hypokalemia with glucose intolerance has been known.

So, whatever the exact mechanism, I think it's been well documented in the literature, observationally, that with associated hypokalemia, glucose values are more likely to go up and new onset diabetes is more likely to occur. Even in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, which compared an amlodipine-based treatment arm to a valsartan-based treatment arm, both of which could have a thiazide diuretic added, the valsartan-based regimen was associated with a 3.3% reduction in new onset diabetes. Of note, those individuals were less likely to have hypokalemia. So, I think hypokalemia is something that I pay a lot of attention to as a clinician whenever I use thiazide diuretic therapy. In order to prevent new-onset diabetes, potassium should be kept close to normal, or slightly above normal, if possible.

We haven't talked about the different thiazide-type diuretics. There is a lot of controversy concerning the different thiazide-type diuretics as outcomes have been best with chlorthalidone used both in the Systolic Hypertension in the Elderly Program (SHEP) trial, and in the ALLHAT trial. In both of these trials it was chlorthalidone and not hydrochlorothiazide that was used. Recent analysis has shown that equipotent BP-lowering doses of chlorthalidone, 25 mg, when compared to hydrochlorthiazide, 50 mg, lead to similar rates of hypokalemia. That said, one needs to pay attention to potassium regardless of the specific thiazide diuretic chosen.

In practice, many clinicians will use an ACE or an ARB with a thiazide diuretic. It appears that the RAAS blocking partner ameliorates the hypokalemia that may occur from the thiazide diuretic, leading to an improvement in insulin sensitivity, and insulin release, as Dom has nicely pointed out. The prevention of hypokalemia, I think, is paramount when using a thiazide diuretic.

> ***"The prevention of hypokalemia, I think, is paramount when using a thiazide diuretic."***
>
> *~ Jan Basile, MD*

Finally, before I ask my colleagues their thoughts on this, I want to mention that in a retrospective analysis of the SHEP trial, in 7% of patients who were hypokalemic, outcomes were no better than those on placebo. So, I think it really resonates with me that I want to keep potassium at 4.0 mEq/L or more when I'm using a thiazide diuretic in all patients with hypertension.

DR. SICA: Well, that's really the point that I was going to bring up: So would that mean you're willing, if someone's at 3.9, to treat them, to get them above 4? Conventionally, we diagnose hypokalemia as 3.5 or below. And, part of the dilemma here is in interpreting the serum values; we have a strict stratification line in most of the trials and we don't think of this comparatively; if, for instance, the serum potassium drop with a diuretic is from 4.5 and you go to 4.1—asking this rhetorically, Jan—would you treat that? Because a 0.4 mEq/L decrease must be a significant change. Therefore you should treat them to bring them to their ideal baseline, which we don't do.

So, trying to figure out if there's a line of division—at 3.5 and below that you treat—may be scratching the surface. I don't think we have a good point of reference. We may have hypokalemia, but we most certainly, and I think Barry would agree with this, do not have a goal potassium to seek out in order to remedy the situation. So if you go to 3.3 with a diuretic, there's little to no evidence anywhere to say that going to 4 or 4.2 or 4.5 is necessary to eliminate the changes. So we have poor guidelines about where to go.

DR. BASILE: You're right, there is no good evidence how to handle that situation. Perhaps it is the change in potassium as well as the absolute level that affects insulin's effects on glucose.

DR. CARTER: I take your point, Dom, I think it's a good one. I like to see my patients with a potassium of 4.0 mEq/L or more when they're on a thiazide. It's just a general rule of how I approach utilization of thiazide-type diuretics, but you are correct, there is no strong evidence or guidelines to support this approach.

DR. SICA: I think a lot of people do that. It's just that when you start to look at all the variations, there's a circadian rhythm for potassium. There are all sorts of measurement considerations, so you almost want to say, "Have I seen a decrease of 0.5 mEq/L?" Jan, I approach it this way, if I see a 0.5 mEq/L change in the potassium then there is probably a significant loss, whatever my

starting value. Then I consider what I do with the approach to treating this, either using an aldosterone receptor antagonist, or an ACE inhibitor, or ARB if additional blood pressure lowering is necessary. If blood pressure is at goal then potassium supplementation would be the logical treatment option. So, I think, my approach is probably similar to yours with maybe just a little bit of a twist to it. I don't know what Bill's approach is; Bill?

DR. CUSHMAN: Actually, I was involved in the SHEP analyses of potassium. Part of the problem with a lot of this is that it is a retrospective analysis and people who develop hypokalemia may be sicker for other reasons. What we don't have and really need are prospective studies testing potassium correction in the presence of a diuretic to look at the effect on glucose. I think there are proposals to do studies looking at that but it's not entirely clear.

I do like a little bit higher potassium based on not only the SHEP data but at least the theory that at least one mechanism exacerbating elevations in glucose is hypokalemia. So, it gives me an excuse to add a RAAS blocker, or a K-sparing agent. The K-sparing agents can also preserve magnesium, which we're not often measuring. But I don't necessarily automatically add it if the potassium is 3.7 or 3.8. I do aim to try to get K above 3.5.

Now, when we look at the trials like ALLHAT and SHEP that used chlorthalidone, both had a relatively lower incidence of hypokalemia than people thought—around 10% to 12% if you use 3.5 as the artificial cut point for hypokalemia. And, in those trials potassium chloride replacement was given to try to get or keep potassium above 3.5. In those circumstances thiazide diuretic use was associated with very good cardiovascular outcomes.

Now, whether giving supplemental KCl, which I don't often do, is the right thing to do in that setting, I don't know. And my guess is that that would be less effective than using a potassium-sparing agent, which I will usually add if the patient is tending to be hypokalemic and their blood pressure is not controlled. So, I think part of what I'm saying is that we do need more prospective studies to see whether we can make a significant difference in even these small differences in glucose by either correcting or preserving potassium or using RAAS blockers.

DR. CARTER: Bill, in your comment concerning potassium and chloride supplementation, I had a question with regards to that because there clearly are data that demonstrate that it's somewhat more difficult to get potassium back up with KCl in comparison to some of the potassium sparing diuretic agents. That may relate to adherence, in part, but it may be pharmacologic as well. Are there agents that you think are particularly better at not only improving the potassium but also magnesium?

DR. CUSHMAN: Yes, well first of all, of course, giving KCL doesn't do a thing if there's also a magnesium deficiency. But it appears that you need usually 40, 60, 80 millimoles of potassium in order to correct thiazide induced hypokalemia if somebody truly does have significant hypokalemia. That's a lot more potassium than most doctors prescribe. So, it clearly is a lot simpler and a lot more effective and perhaps even cheaper to give a K-sparing agent either in a combination product or as an add-on. And, again, all the K-sparing agents preserve magnesium.

DR. SICA: Yes, they all do, Bill—amiloride, triamterene, eplerenone, and spironolactone.

DR. CUSHMAN: Okay. I would like to add a few additional points on strategies to minimize glucose elevations and perhaps new onset diabetes following thiazides. First, if a patient is maintaining a high salt intake while taking thiazides, this will also promote hypokalemia as well as reduced antihypertensive efficacy. We should be continuing to promote low salt diets which should help minimize hypokalemia.

The other point I would like to raise is that lifestyle modifications such as weight loss, moderate physical exercise and salt reduction can overcome most or all of the adverse metabolic effects of the thiazide diuretics. Of course, these strategies also contribute to blood pressure reduction and can reduce the need for future additions of other antihypertensive agents. Therefore, we should continue to vigorously promote lifestyle modifications, especially in patients with the metabolic syndrome or those who are overweight without other risk factors.

DR. CARTER: Bill, these are excellent points and often overlooked once drugs have been initiated. Would others like to comment?

DR. BASILE: To Bill's point about weight loss and exercise, if I have a patient with pre-diabetes (HbA1c of greater than 5.7% but less than 6.5%) who has well controlled BP on a thiazide with normal serum potassium, I would continue to promote weight loss and exercise, as Bill has stated. In such a patient, however, I would be more likely to add metformin to prevent new-onset diabetes and before adding a RAAS blocker since BP was already well controlled. I would be interested in my colleagues' take on this.

DR. CUSHMAN: I would certainly agree with promoting lifestyle changes, but I am not using metformin yet to prevent diabetes, since I don't believe we have sufficient long-term outcome data in the prediabetic population to do this routinely. The Diabetes Prevention Program (DPP) was not large or long enough to prove safety in this population.

DR. CARTER: And, Dom, Bill, or Jan, what about the specific use of something

like spironolactone due to the fact that many of these patients who seem to be at risk have central adiposity and as Dom said that increased sympathetic activity leads to increases in aldosterone. Is there a particular role for spironolactone in this population that's at risk for new onset diabetes?

DR. BASILE: Part of my dilemma with maintaining potassium with potassium replacement resides in the fact that, as Bill and Dom have mentioned, there really is no correction of body deficit with exogenous potassium, whether it's potassium chloride, acetate, citrate, or bicarbonate, whatever the potassium salt that's given. Therefore, I would prefer to use a K-sparing diuretic because then we preserve both potassium and magnesium and hopefully replace total body stores. I would hope that by approaching it in this manner, I would have the best chance of preventing and managing diabetes in these patients.

Concerning spironolactone, we have limited information on how it affects new-onset diabetes, although clearly it preserves potassium.

The patients I'm seeing today are often referred with difficult-to-control hypertension or resistant hypertension and are often on both a RAAS blocking agent and a thiazide diuretic. I'm therefore seeing less hypokalemia than I've encountered in the past, unless the patient has a secondary issue that may be associated with potassium loss. The fact that we are using RAAS blocking agents early and often, as well as using more mineralocorticoid receptor blocking agents such as spironolactone and eplerenone, decreases the likelihood that hypokalemia will be encountered.

DR. SICA: I agree. I see it less frequently. Somehow, though, I think it's got a lot to do with the diuretics that are used. In that, most of the hard to treat hypertensives come in hard to treat on low dose hydrochlorothiazide. So, I think everyone is pleased with hydrochlorothiazide because you get less hypokalemia with it, but it's mainly because it's under-dosed and it's a fairly short acting diuretic. But I think we're wedded either to monotherapy or fixed-dose products to HCTZ as our preferred diuretic. It gives us a warm and fuzzy feeling because it doesn't do much harm.

DR. CARTER: Good point, Dom, thanks. Your point about underdosing is important here. The evidence with HCTZ is with doses of 25-50 mg or higher and the evidence also shows that chlorthalidone is twice as potent as HCTZ. The evidence-based dosing for chlorthalidone is 12.5 to 25 mg per day. In these equipotent doses, my colleagues and I have found no difference between these drugs on hypokalemia. Does anybody else have any other comments?

DR. CUSHMAN: Yes, I'd like to make one more comment, and it's really in follow-up to what we we've just been talking about. In both SHEP and ALLHAT, as I mentioned, hypokalemia, if you define it arbitrarily as less than 3.5, wasn't very common. And that was despite the fact that in neither of those trials could you use a RAAS blocker in combination with the diuretic. So, I do think that even, and I agree with Dom, that a lot of the higher incidence of hypokalemia that we saw back, maybe in the in 1970's and 80's, was perhaps from using much higher doses of diuretics than we feel we'd even need today. But, if we use appropriate doses of chlorthalidone (12.5-25 mg) or of hydrochlorothiazide (25-50 mg), we are going to see some hypokalemia, but I do think that we're going to ameliorate that more with the frequent use of RAS blockers and then K-sparing drugs.

DR. SICA: Although, Bill, I would say that it's very hard to come up with a good reference in the literature to show that ACE-inhibitors and ARBs attenuate the hypokalemia in a convincing way. There are very limited data to suggest you change total body stores of potassium with either of those drugs. So, I think it's a conventional belief but I don't know necessarily that the drugs are that great, although we use them. It may be worth 0.1 mEq/L, at most 0.2 mEq/L, but really no more than that, and again it's probably dose-dependant. It is also true that aldosterone goes up with the ACE-inhibitor, or an ARB limits the utility of these drug classes. In the chronic kidney disease patient given an ACE inhibitor or an angiotensin-receptor blocker serum potassium rises can be more substantial than 0.1-0.2 mEq/L and cannot be used as an example of what happens to serum potassium values in a patient with diuretic-related hypokalemia.

DR. CUSHMAN: Yes, good point. There is one other issue that occasionally occurs. There are reports from the 1950's and 1960's of extreme elevations in glucose (>400 mg/dL), sometimes with ketoacidosis, that were associated with the addition of diuretics. Of course, in those days, doses of 200-400 mg per day of HCTZ or 100-200 mg of chlorthalidone were common. We rarely see such cases but we just had a hospital admission for a patient with new onset diabetes (glucose >700 mg/dL). He happened to be taking several drugs that can raise blood glucose including a thiazide. I normally would hold the diuretic for a month or two until it is clear what we need to use to control the glucose on an outpatient basis. I then add the thiazide back to the regimen since outcomes and BP control are best with a thiazide. In these cases, whether extreme elevations in glucose, or simply a minor increase that tips someone over the threshold for new onset diabetes, if blood glucose is well controlled with effective hypoglycemic drugs, there is little evidence that the thiazides will worsen glucose control.

DR. CARTER: Well, if I could summarize what we've heard, it appears that diuretics are associated with about a 1% to 3% absolute increased risk of new onset diabetes or about a mean increase in glucose of approximately 3 to 5 mg/dL. It doesn't appear that those small changes in blood glucose, in any way negatively influence the cardiovascular benefits that are achieved with proper diuretic doses. However, there may be an association between hypokalemia and new onset diabetes, although as we've heard the mechanism is still unknown, a bit confusing, and clearly, very complex. But if hypokalemia does occur, it does seem to be prudent to try to keep potassium at a high normal range, and it's been suggested to keep it at 4 mEq/L, probably by using a potassium sparing diuretic to improve the potassium, or perhaps the use of diuretic-ACE-inhibitor combinations, which older studies have shown can minimize the effect on hypokalemia, blood sugar and uric acid. It is also critically important to promote lifestyle modifications including sodium restriction, moderate physical exercise and weight loss. These strategies will not only minimize hypokalemia and new onset diabetes, they will also improve blood pressure control. Finally, it is difficult to assess what to do when new onset diabetes does occur. When diuretics are held, we often don't observe much improvement in glucose control. Proper control of blood sugar with diet, exercise and hypoglycemic agents will almost always allow the addition of the thiazide back into the regimen in order to achieve good blood pressure control.

I'd like to thank our panel for a great discussion for a very important topic in hypertension. Thank you.

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