Webcast

Identifying and Addressing Elevated Sodium Intake to Decrease Cardiovascular Risk: Expert Perspectives and Discussions

Part 1: Salt, Sleep, and Cardiovascular Risk

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Salt, Sleep, and Cardiovascular Risk

VIREND K. SOMERS, MD, PHD: Greetings and thank you for joining us for this webinar on identifying and addressing elevated sodium intake to decrease cardiovascular risk: expert perspectives and discussions. My name is Virend Somers. I'm a cardiologist at the Mayo Clinic. I will be joined by two outstanding colleagues, Dr. Deborah Clegg, who is the Vice President for Research and Professor of Internal Medicine at Texas Tech University in El Paso, Texas, and Dr. Gregg Pressman, who is the Director of Academics in Division of Cardiology at Einstein Medical Center in Philadelphia and Professor of Medicine at Thomas Jefferson University.

The agenda today is to talk on salt, sleep, and cardiovascular risk, and that will be done by me. This will be followed by hypertension and beyond: the impact of sodium across the cardiovascular disease spectrum, which will be covered by Dr. Gregg Pressman. Then Dr. Deborah Clegg will cover practical strategies to address the impact of increased sodium consumption on cardiovascular risk.

I'm going to start off on my topic, which is salt, sleep, and how these relate to increased cardiovascular risk. We'll cover four different areas. First we'll talk about salt and its relationship to blood pressure and then talk about salt intake in terms of diet and drugs. How much salt is in our diet and some of the drugs we take and what is the consequence of that? Then talk about sleep disorders and cardiovascular disease in general, setting the stage then to cover how narcolepsy is linked to cardiovascular disease and how high salt take intake in people with narcolepsy may in fact be a relatively unrecognized problem.

First, salt and blood pressure. What do we know? Well, increased salt intake is consistently associated with sustained increases in both plasma volume and blood volume. The increased salt intake may be accompanied by reduced ability in some people of the kidney to excrete sodium. So when the capacity of the kidney is to maintain sodium balance and extracellular fluid forming within the appropriate range is compromised, you get increases in blood pressure.

This increase in blood pressure is important to restore excretion of salt and water. This is called pressure natriuresis. This is one of the body's homeostatic mechanisms by which it deals with a high intake of salt. The salt increases the blood volume, the blood volume increases the blood pressure that increases the pressure natriuresis in the kidney, and that seeks to restore the homeostatic balance.

What about salt sensitivity? What does salt sensitivity mean? Now the problem with salt sensitivity is some people can effectively excrete high dietary salt intake without an increase in blood pressure and other people whom we term salt sensitive need a higher blood pressure to excrete the sodium effectively. This is a very heterogeneous characteristic with familiar component. People who tend to be salt sensitive or have a higher risk of salt sensitivity include women, African

Americans, postmenopausal women, and older people. In fact, 73% of black hypertensives are salt sensitive versus about half of white hypertensives.

So you see salt sensitivity is fairly common. It's linked to certain specific characteristics and we have hypertensive people. The fact that they're hypertensive automatically makes them likely to be salt sensitive. So if they fit any of the criteria of being African American or woman, postmenopausal or older age, that heightens the likelihood that they are less likely to be able to tolerate a salt load.

Salt-sensitive hypertension is defined as an increase in blood pressure associated with an increase in salt intake, and about half of humans with hypertension have salt sensitivity. As I mentioned, it varies based on sex, age, and race. Now if you look at a normotensive, about one in four normotensives are salt sensitive. This salt sensitivity even in the setting of normotensive--this is important. Salt sensitivity even in the setting of a normal blood pressure is associated with increased mortality because high salt intake doesn't just affect your blood pressure. It also can cause tissue injury. This is increasingly being recognized as a potential problem in people who are taking lots of salt.

End organ structure and function can be damaged by salt, and this may be the basis for higher mortality in normotensive people with salt sensitivity.

Lastly, a response to a high salt diet, as I mentioned before, your volume increases, cardiac output increases, and salt-resistant subjects respond with reciprocal decreases in systemic vascular resistance. So if you can handle salt, when your cardiac output goes up, your vascular resistance goes down to keep your blood pressure normal. But if you're salt sensitive, you have a paradoxical increase in that vascular resistance associated with an increase in blood pressure.

Let's talk about salt intake in terms of diet and drugs. Now this is going to be covered by my colleagues as well, but these are very important points, so we thought it would be appropriate to repeat some of this information. You'll hear it again from the other speakers.

Let's think about drugs. Let's think about a commonly-used drug, which is effervescent paracetamol. It's interesting, not just interesting, but also relatively unrecognized that effervescent paracetamol has about 1700 mg of sodium. In sodium oxybate, which is a drug used to treat narcolepsy, which I'll tell you more about shortly--it's a sleep disorder--sodium oxybate has 1640 mg of salt, about the same of sodium. The average U.S. salt intake is 3400 mg, but what's recommended is 2300 mg. The message here is that it's recommended we take in 2300 mg, but the average U.S. dietary intake is 3400 mg. If on top of that you're taking either sodium oxybate and/or effervescent paracetamol, you're taking in huge amounts of sodium above and beyond what the recommended value is, so keep those issues in mind.

What is the consequence of sodium loading? First, 2300 mg per day increase in sodium excretion is--by the way, when we talk about sodium excretion, that's the way we measure how much sodium we take in. So it's a good measure of how much salt you consume if we measure it in the urine and tell you how much salt was in the urine. That reasonably well predicts how much salt you ate.

If you have a 2300 mg a day increase in sodium excretion, you get a 3 to 6 mmHg increase in systolic blood pressure. Twenty-four-hour systolic blood pressure increases by 3.5 mmHg with three weeks of effervescent paracetamol, which I told you had about 1600 mg of sodium. If you salt load at these doses, you will blunt your nocturnal blood pressure decline. You can then transition to becoming a non-dipper because your blood pressure will fall less at night. Being a non-dipper carries its own set of cardiovascular risks above and beyond just having hypertension. Keep those considerations in mind.

More on sodium loading. Sodium-containing medications have been associated with a much higher increased risk of adverse cardiovascular events. If you're taking effervescent paracetamol and then you stop it, four weeks after stopping it your systolic blood pressure can be lower by 13 mmHg and diastolic by 2.5. Here are some epidemiologic projections saying that if you reduce your sodium intake by 1200 mg a day, which incidentally is less than how much sodium is in effervescent paracetamol and less than how much sodium is in sodium oxybate, if you lower your sodium intake by that much a day, you will reduce your heart attack risk by 12%, stroke risk by 8%, and all cause mortality by 4%.

We talked first about salt and blood pressure and I explained what salt does to Fs and how the hemodynamic response can differ in people who are salt sensitive versus salt resistant. Then we talk about dietary recommendations for salt intake and how certain drugs like effervescent paracetamol, like sodium oxybate, can have very substantial levels of sodium that can take you way above your recommended daily intake.

Now let's talk about something somewhat different, sleep disorders and heart disease. The reason we're going to talk about this is because we sometimes use high salt-containing drugs to treat sleep disorders and let's first understand what sleep disorders mean in terms of cardiovascular risk.

Well, here's some more of the obstructive sleep apnea. This is measurements of sympathetic activity shown by these spikes, breathing, and intra-arterial blood pressure when the subject was awake. This is a new diagnosis of obstructive sleep apnea, on no medications, and never been treated. He goes to sleep, he's in REMS sleep, and you see that blood pressure was 130/60 intra-arterially when he was awake. When he was asleep, it was much, much higher because these apneic events shown as OSA, they cause sympathetic vasoconstriction in response to fall in oxygen levels and the rise in carbon dioxide. That sympathetic vasoconstriction raises your blood pressure to levels of 240/130. This patient is going to be a reverse dipper. You see the blood pressure is 130/60 awake, but way higher during

sleep, particularly in REMS sleep. So blood pressure did not fall during sleep. It actually goes up, but you treat him with CPAP and here he's in REMS sleep and his blood pressure is not perfect, but it's much better.

The message here is that sleep apnea, which is very common, is linked to higher sympathetic activity and high blood pressure during sleep, and these high blood pressures and high sympathetic during sleep carry over into the daytime so that sleep apnea patients have a higher risk of daytime hypertension. People with sleep apnea tend to have a 30% to 40% to 50% increased risk of developing incident hypertension over a period of 4 to 10 years observation.

What are the cardiovascular implications of obstructive sleep apnea? Well, you've got this hypoxemia and reoxygenation. You've got autonomic dysfunction, namely sympathetic activation arousals, which also raised blood pressure and disrupted sleep, intrathoracic pressure changes, high CO2, and through these disease mechanisms to induce inflammation, endothelial dysfunction, increased coagulation, metabolic dysregulation, hemodynamic changes, left atrial enlargement, and sympathetic activation. You get these cardiovascular disease consequences like high blood pressure, atrial fibrillation, heart failure, coronary artery disease, stroke, pulmonary hypertension, diabetes, and heightened mortality.

It's important to know this because you can understand then that if you throw in high amounts of salt into this mix, you are going to exacerbate the risk of these cardiovascular disease conditions, particularly high blood pressure and high heart failure and stroke in terms of their overall risk of recurrence.

We know that if you don't sleep a long time, if you have a short sleep duration independent of sleep apnea--this is just not sleeping for a long period of night--if you sleep five hours or less a night, you're going to have a two-fold increased risk in future hypertension. So the chance of your being normotensive today, but you're habitually sleeping five hours or less a night, your risk of hypertension down the road is doubled.

Here's the Nurses Health Study showing the effects of a short sleep duration. You see sleep duration five, six, seven, eight. If you give eight hours of sleep duration a relative risk of 1 as reference point, you see that as your sleep duration decreases to 7 to 6 to 5, you get an almost two-fold increased risk of incident or new-onset coronary artery disease. So if you have no coronary artery disease today, but you sleep five hours a night habitually, over 10 years you have a two-fold increase in your risk of developing new-onset coronary artery disease. So that's important to know that if you have a sleep disorder like short sleep or obstructive sleep apnea, you have a higher risk of cardiovascular disease down the road.

Now let's talk about narcolepsy. Narcolepsy is a chronic neurologic sleep disorder. There are five predominant symptoms: excessive daytime sleepiness; cataplexy, which is the equivalent of a falling episode, the narcoleptic in getting to sleep, a

REMS sleep state, they fall to the ground; they have disrupted nighttime sleep, so sleep deprivation; sleep-related hallucinations; and sleep paralysis. The onset of symptoms typically occurs in childhood or adolescence.

This is the problem with narcolepsy. They have lots of comorbidities independent of everything else. If you just look at patients with narcolepsy, they have a much higher risk of hypertension in the yellow bars compared to non-narcoleptics in the gray bars of coronary atherosclerosis, congestive heart failure, and myocardial infarction. They also very importantly have a much greater risk of sleep apnea, so keep those things in mind.

Narcolepsy is associated with cardiometabolic abnormalities, arterial hypertension, we talked about ischemic heart disease, abnormal lipids, high risk of diabetes, and a high risk of atrial fibrillation.

This shows some of the literature in terms of their risk of obesity, hypertension, diabetes, dyslipidemia. The odds ratio, the increase in risk in comparison to what's expected here is two-fold higher risk of being obese, 30% increased risk of being hypertensive, almost two-fold increased risk of diabetes, and a 50% higher risk of having hyperlipidemia. So narcoleptics seem to be cardiovascularly and metabolically at greater risk. In fact, when you look at the BOND study, which was done a number of years ago looking at the cross-sectional risk of narcoleptics, they have a higher likelihood of stroke, heart attacks, revascularization, heart failure, and cardiac arrest.

If we think about narcolepsy and mortality, mortality rates are also high in patients with versus without narcolepsy based on a longitudinal claims database compared with the general population. People with narcolepsy had about 50% higher likelihood of death compared to those without narcolepsy.

Now this is the CV BOND study, which we recently completed. Here we looked at the incident likelihood of newly-diagnosed cardiovascular or renal conditions in people with narcolepsy versus matched non-narcolepsy controls. The key findings you see here are any stroke, heart failure, ischemic stroke, MACE, stroke atrial fibrillation or edema, and any CVD. All of these fall to the right of this line. We suggest that there's an increased risk in people with narcolepsy. This was the CV BOND study, following up on the BOND study, which showed a heighted cross-sectional risk. This is incident future risk and we note that the risk of cardiovascular events down the road is high in people with narcolepsy.

Bear in mind that sodium oxybate, which we talked about earlier has about 1600 mg of sodium. What happens if you give a narcoleptic sodium oxybate compared to a narcoleptic not receiving sodium oxybate? What happens to the hypertension risk? Well, these are data that were presented recently at the American College of Cardiology, preliminary findings addressing this question. We looked at incident or new-onset hypertension based on either a diagnosis or a diagnosis of giving somebody an antihypertensive drug.

Looking at both of these, particularly if you're combined a diagnosis of hypertension and initiation of antihypertensive therapy, we found a significantly higher risk of future hypertension over about six months of followup in people with narcolepsy. That's a fairly short follow-up period. This seems to be a reasonably significant stimulus to developing new hypertension in narcoleptics, giving them a high soft load via sodium oxybate.

I'm going to conclude by going over some of the things we talked about. We reviewed how salt can raise blood pressure and how your response to a salt load can help determine if you are salt sensitive or salt resistant. The salt sensitive people we need to worry about because they raise their blood pressure significantly. They're at a heightened risk for problems from salt intake. Bear in mind that diets contain a very high amount of salt in the U.S., much higher than what we're supposed to take, and when you add drugs like effervescent paracetamol and sodium oxybate or other sodium-containing drugs on top of that, you're going to get a much greater effect of salt consumption.

Sleep disorders, obstructive sleep apnea, short sleep, and narcolepsy are accompanied by a higher risk of cardiovascular disease. When we look at narcolepsy itself, narcolepsy is just independent of everything else linked to a very high likelihood of poor cardiovascular outcomes. It's also linked to high likelihood of sleep apnea. If you have a narcoleptic, he or she is much more likely to have obstructive sleep apnea, which puts them into this third panel here, the higher risk of CV disease and sleep disorders. If you start giving narcoleptics drugs that contain high amounts of salt like sodium oxybate, you are likely to increase their future risk of hypertension and more than likely other cardiovascular diseases.