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VIEWPOINT
Hypertension

Settling the controversy of salt substitutes and stroke: sodium reduction or potassium increase?

Franz H. Messerli [1]*, Martin O'Donnell[2], Andrew Mente [3], and Salim Yusuf[3]

[1]Department of Cardiology, Inselspital Universitatsspital Bern, 3010, Freiburgstrasse, Bern, Switzerland; [2]Department of Geriatric Medicine, Galway University Hospital, Galway, Ireland; and [3]Population Health Research Institute, McMaster University, Hamilton, ON, Canada

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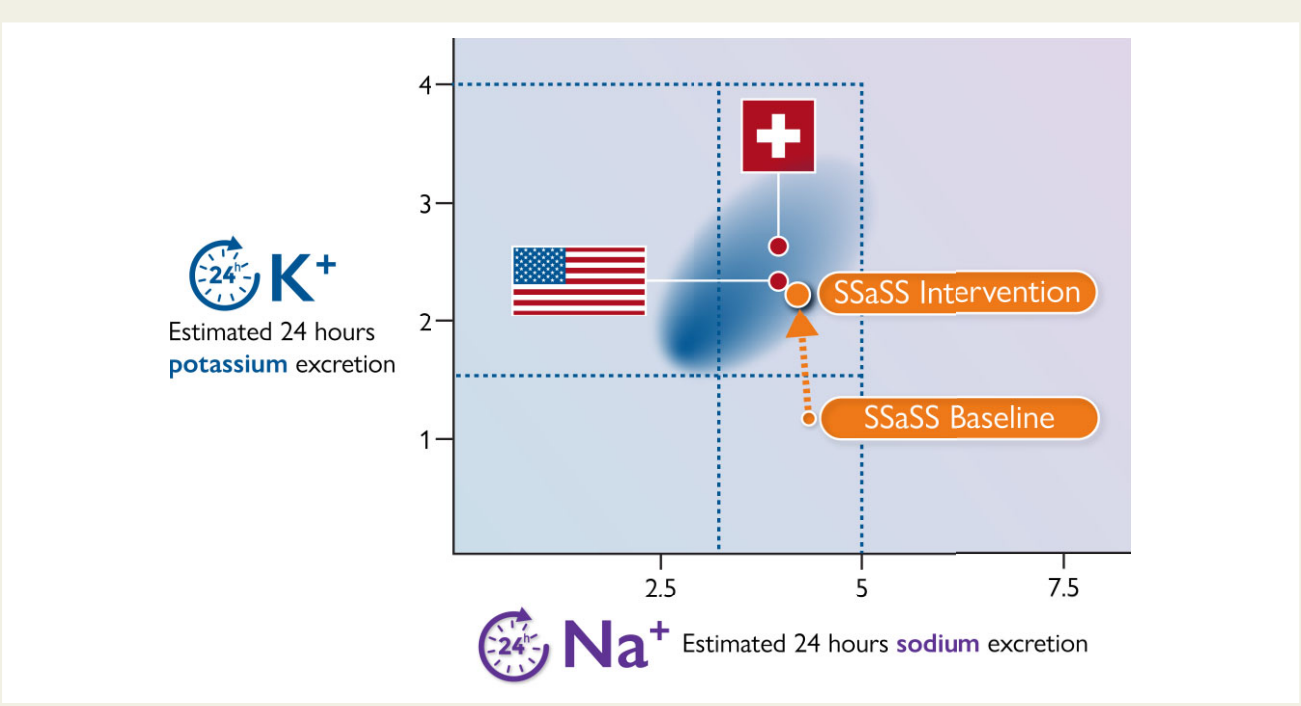

Graphical Abstract Urinary sodium and potassium excretion in the SSaSS trial before and after the intervention with the salt substitute compared with NHANES and Swiss data are projected on heat map for the composite of cardiovascular events by O'Donnell *et al.*[3]

Ever since the provocative study of Ambard and Beaujart[1] more than a century ago, the link between dietary salt intake and blood pressure (BP) has been controversial. Numerous studies have shown that a high salt diet is associated with higher BP, and at levels above 5 g/day, also with increased cardiovascular disease risk. In the PURE study overall mean systolic BP was higher by 2.11 mmHg per 1 g increase in sodium intake.[2] The BP increase was larger in older individuals (2.97 mmHg per 1 g) and in those with

* Corresponding author. Email: franzmesserli@gmx.com; messerli.f@gmail.com

hypertension (2.49 mmHg per 1 g) whereas there was little effect in those without hypertension or those <55 years. There is consensus that salt intake should be reduced in populations consuming a high salt intake, especially among older patients with hypertension. For many physicians who treat cardiovascular disease, salt has become a bête noir and for decades patients have been advised to limit their salt intake. However, it remains unclear whether salt intake should be reduced in people consuming levels of salt that are common in Western countries, especially in those without hypertension. The European Society of Cardiology, the American Heart Association (AHA), the World Health Organization (WHO), and other institutions have issued guidelines as to reducing habitual salt intake not only for patients with hypertension but also for healthy normotensive subjects, below 2 g of sodium (which corresponds to 5 g of salt). The evidence supporting a target of 2 g/day of sodium is derived from small short-term clinical trials, of which the 30-day dietary approaches to stop hypertension–sodium feeding trial was particularly influential.[3] However, as O'Donnell *et al.* indicated, these guidelines were developed without effective interventions to achieve sustained low sodium intake in free-living individuals, without a feasible method to estimate sodium intake reliably and without high-quality evidence that, compared with a moderate intake, a low sodium intake would reduce cardiovascular events.[4]

Of note, BP is merely a surrogate endpoint that might reflect parallel changes in clinically relevant outcomes such as heart attacks, strokes, or deaths. A fall in BP especially if small, may not reliably predict a reduction in clinical events, as counter-regulating mechanisms may affect the outcome. There is consensus that the controversy as to the risk-benefit analysis of reducing sodium to levels below 2 g/day can only be resolved by a prospective randomized trial.

SSaSS. In this context, the large open-label, cluster-randomized SSaSS[5] trial involving 20 995 persons from 600 villages in rural China is most noteworthy. In this trial, participants were randomized to receive a salt substitute (which contained 75% sodium chloride and 25% potassium chloride) or regular salt. The study reported that among persons who had a history of stroke or were >60 years of age and had high BP, the rates of stroke, major cardiovascular events, and death were lower with the salt substitute than with regular salt (sodium chloride) (see *Graphical Abstract*).

The authors stated, 'Our data also provide reassurance about the efficacy and safety of sodium-intake reduction for the prevention of cardiovascular events and death'. This statement implies that the authors considered the reduction in sodium intake associated with the switch to the salt substitute as key to the reductions in stroke, major cardiovascular events, and death. Similarly, after the presentation of the SSaSS trial at the Meeting of the European Society of Cardiology, the discussant Bryan Williams concluded: 'Those who doubted the benefits of a salt restriction for cardiovascular disease prevention were wrong, the debate stops here…' [6] Other commentaries like 'Will the positive Findings from the SSaSS trial on Salt Substitution silence the Salt Skeptics?'[7] and 'Cutting out even a little Salt can have Big Health Benefits'[8] further emphasized that cardiovascular benefits of this trial were thought to be caused mainly by a reduction in salt intake.

We analysed the effect of the salt substitution in the SSaSS trial on 24-h Na^+ and K^+ excretion and compared the values to the average level of intakes in the USA as reported in the National Health and Nutrition Examination Survey (NHANES) data[9] (Table 1).

At baseline, the study population was characterized by high Na^+ intake of 4.3 g/day and very low K^+ intake of 1.4 g/day compared with a mean intake of 3.608 and 2.155 g/day, respectively, in the USA based on the NHANES data.[9] The intervention reduced Na^+ intake by a modest 8.1% from baseline of 4.3–3.95 g/day, a level still higher than the average intake in the USA (based on NHANES[9]) and in Switzerland[10] about twice the intake recommended by WHO and European Society of Cardiology and almost 3 times the AHA recommendations. Most recently, on 14 October 2021, the FDA issued guidance to support an average sodium intake reduction to 3.0 g/day.

Of note, in the SSaSS trial, the concentration of sodium in the salt substitute was one third lower than in regular salt, but the reduction in sodium intake in the intervention group was only 8%. This indicates that participants increased sodium consumption from other sources, possibly to compensate for the lower sodium content of the substitute.

In contrast, the intervention increased K^+ excretion substantially by 57% to 2.2 g/day, levels approximating the mean intake of 2.16 g/day in the USA. As seen in Graphical Abstract, the intervention with the salt substitute in the SSaSS trial shifted dietary electrolyte intake from a low K^+/high Na^+ Chinese diet towards the one of the average American (3.61 g/day). However, this level of sodium intake represents the very crux of the salt controversy, time and again it has been labelled as being excessive by the above guidelines.

Based on meta-analysis of trials, the observed 8% reduction in sodium intake would be expected to reduce BP by about 1 mmHg, while the increase in potassium would be expected to reduce BP

Table 1 Effect of salt substitution in the SSaSS trial on 24-h Na^+ and K^+ excretion for comparison average level of Na^+ and K^+ excretion in the US[9] and Switzerland[10] are presented

	Sodium	Potassium
USA (NHANES)	3.16 g/day	2.16 g/day[9]
Switzerland	3.63 g/day	2.57 g/day[10]
24-h urinary excretion at baseline	4.3 g (187 mmol)	1.4 g (36 mmol)
Effect of intervention (salt substitute)	−0.35 g (15.21 mmol)	+0.8 g (20.64 mmol)
Change from baseline %	8.1%	57.3%

by about 3 mmHg in a population with low potassium intake such in the SSaSS where the intake was 1.4 g/day, a level that is much lower than the average intake in the USA[11] (Table 1). A potassium deficient diet can cause excessive sodium reabsorption by upregulating the tubular NCC (Na/Cl co-transporter) with subsequent fluid-volume expansion and hypertension.[12] Hence the low potassium diet-induced sodium reabsorption through NCC may be the key driver in the pathogenesis of salt-sensitive hypertension.

Therefore, it is highly likely that most, if not all benefits observed in SSaSS were due to the increase in potassium with the salt substitute. Importantly, the dietary Na^+/K^+ ratio decreased from 3.1 to 1.8 with the salt substitute intervention. According to the recent data of Ma *et al.*,[13] a decrease in the Na^+/K^+ ratio, from above the 75th percentile to below the 25th percentile as observed in SSaSS can be estimated to reduce the cardiovascular risk by as much as 30%. Remarkably similar to SSaSS, in a previous randomized trial, although smaller and of lower methodological rigour, the use of a salt substitute reduced cardiovascular mortality. Then as well there was only a small (10%) reduction in sodium intake and a large (>70%) increase in potassium intake.[14]

Hence the above claims that SSaSS provides evidence for the benefits of a low sodium intake are difficult to justify. SSaSS does not shed light on the ongoing controversy whether current guidelines for low sodium intake are appropriate and it certainly does not support recommendations to reduce sodium intake to 2 g/day or less.

In summary, the SSaSS trial demonstrates that moving from a 'low potassium, high sodium' diet toward an average potassium/but persistently high sodium intake (an intake numerically still higher than the average consumption in Switzerland[10] and in the USA[9]), prevents stroke, cardiovascular events, and death. These data, therefore, provide reassurance about the efficacy and safety of *increasing* potassium intake but do not help to answer the foremost question of the salt controversy whether reducing sodium intake to the low levels advised by guidelines is safe or beneficial.

Conflict of interest: none declared.

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