

## **Population Dietary Salt Reduction and the Risk of Cardiovascular Disease – New Statement**

### **Statement from the British Hypertension Society**

#### **August 2016**

*In June 2011 the British Hypertension Society, after appraising the quality of publications questioning the appropriateness of population salt reduction, issued a statement supporting the implementation of national and global programmes of moderate reduction in salt intake. Today, the Society publishes a new statement in light of more recent publications.*

Raised blood pressure (BP) is the first cause of death and disability in adults worldwide, mainly due to cardiovascular disease (CVD). The risk of CVD increases progressively with increasing BP. However, the majority of CVD death and morbidity attributable to BP occur at level around or below 130/80 mmHg, because there are so many individuals in the population with this BP. Clinical guidelines would not treat the majority of these individuals with drugs. Furthermore, there is a graded relationship between BP and CVD down to at least 115/75 mmHg. Therefore a population-approach through non-pharmacological measures (diet and life-style) is the most feasible option, recommended by the World Health Organization<sup>1</sup> and adopted under a UN Resolution of the 66<sup>th</sup> World Health Assembly in 2013<sup>2</sup>.

High salt intake is associated with high blood pressure and a moderate reduction in salt consumption causes a significant reduction in blood pressure<sup>3</sup>. Furthermore, in well-conducted cohort studies<sup>4-5</sup> and in few intervention trials<sup>6</sup>, a lower salt consumption is associated with reduced cardiovascular events.

A recent publication in *The Lancet*<sup>7</sup> has reported that a low salt intake is associated with a high risk of CVD. The paper methodology suffers from flaws that have been repeatedly addressed in the medical literature in recent years and that are ignored<sup>8</sup>.

First, the use of morning urine fasting samples' sodium concentrations extrapolated to 24h urinary sodium excretion using the Kawasaki formula is an inappropriate method for estimating salt intake in individuals<sup>9-11</sup>. The authors' reference to their validation<sup>12</sup>, critiqued at the time of its publication<sup>13</sup>, neglects the presence of a significant bias when estimating individuals' sodium excretion as shown in the Bland-Altman plots, results superimposable to other validations<sup>9-11</sup>. They also do not mention that a similar validation in the Chinese cohort of the PURE study presents the results with less confidence<sup>14</sup>. The authors insist on the concept (uncritically repeated in the Editorial)<sup>15</sup> that the method could be useful to assess group means. However, they use data on individuals when assessing risk prediction in a cohort study design. This is misleading as it has been long established that several 24h urine collections are needed to approximate an individual's salt intake with a high degree of confidence (i.e. within 10%) and without bias<sup>16-18</sup>. In contrast, cohort studies that use the method of repeated 24h urine collections to assess salt intake, show beyond doubt a linear graded relationship between sodium excretion and cardiovascular outcomes with no increase at lower sodium intakes<sup>4-5</sup>.

Second, the present study is a republication of previous data from the ONTARGET and TRANSCEND Trials<sup>19</sup> and from the PURE Study<sup>20</sup> with the addition of EpiDREAM, screenees of the DREAM Trial. Not surprising, the results in this ‘larger’ sample are confirmatory of their previous results. There are several considerations to make: the authors split a continuously distributed biological variable in the population (blood pressure) in a biological meaningless dichotomy of ‘hypertension’ and ‘normotension’. By doing that, they reduce the statistical power of detecting relationships, particularly when studying trends. A similar mistake was made by Taylor et al.<sup>21</sup> leading to misleading conclusions, then corrected by a proper re-analysis of data<sup>6</sup>.

An important point is the consistent use of sick populations and patient groups to study the implications of a moderate reduction in salt consumption in the general population. The ONTARGET/TRANSCEND study selected 28,800 participants from high risk patients to undergo randomized clinical trials of anti-hypertensive treatments. Patients were old (66.5±7.2 yrs, and 2.4 years older in the low sodium group), 71% were men of white European background (but the low sodium group included 54% women), all with significant previous disease (48% with MIs, 21% CVAs, 70% hypertension and 37% diabetes), all highly medicated with beta-blockers (57%), diuretics (29%), calcium channel blockers (35%) and ~75% on blockers of the renin-angiotensin system. More interesting the proportion of patients on diuretics was higher in both the low (41%) and the high (43%) sodium groups (Table 1<sup>19</sup>). The reported higher cardiovascular mortality in the low sodium group was, in fact, only detected in the composite outcome of total CV death (Table 2<sup>19</sup>). This was exclusively accounted for by excess heart failure in this group, but not excess MI, stroke or non-CV death. Taken together, the results suggest that the overrepresentation in the low sodium group of patients at high risk of heart failure, more likely to take diuretics and at higher risk of death explains the high mortality detected in that group (reverse causality). Similar attention should be given to the PURE Study, an on-going epidemiological cohort study that has enrolled over 156,000 individuals in 17 countries. The sodium study only reported on 102,000 participants (65% of the original cohort) who were able to provide a urine sample. Compared to the overall original cohort, the sodium cohort had fewer participants from India (5 vs 18%) and more from China (42% v 30%), with unbalanced distribution across sodium groups (Table 1<sup>20</sup>). The low sodium group was 2.8 years older, had fewer men (29.6 v 58.1%), fewer participants from Asian ancestry (33.8 v 73.0%), more with history of cardiovascular disease (9.2 v 7.1%) and diabetes (10.6 v 8.4%), and a greater proportion of people on regular medications, suggesting the presence of self-selected sicker participants in the low sodium group. These unbalances are the likely result of self-selection bias and incorrect assessment of sodium intake. Studies with more stringent quality features have been able to avoid such biases and have obtained more reliable results<sup>5</sup>. Finally, the EpiDREAM cohort screened people at high-risk of type 2 diabetes, the majority of non-European ethnicity, over 70% obese women, with high proportion of treated individuals<sup>22</sup>. None of these studies’ results can be generalized to inform current public health strategies for a moderate reduction in sodium consumption in populations or to be considered of good quality to support a causal relationship between low sodium intake and increased cardiovascular mortality<sup>23</sup>.

*In conclusion, the evidence supporting global actions for a moderate reduction in salt consumption to prevent cardiovascular disease is strong and such studies should not overturn the concerted public health action to reduce salt intake globally.*

*Prepared by Prof FP Cappuccio, Vice-President, on behalf of the British Hypertension Society’s Guidelines and Information Service Working Party.*

## References

1. World Health Organization. Guideline: sodium intake for adults and children. Geneva: World Health Organization; 2012. p. 1–46
2. Sixty-sixth World Health Assembly follow-up to the political declaration of the high-level meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases. 25 May 2013. Available at: [http://www.ncdalliance.org/sites/default/files/rfiles/A66\\_WHA%20Final%20Resolution.pdf](http://www.ncdalliance.org/sites/default/files/rfiles/A66_WHA%20Final%20Resolution.pdf)
3. Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and meta-analyses. *Br Med J* 2013;346:f1326
4. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. *Circulation* 2014; 129: 981-9
5. Mills KT, Chen J, Yang W et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA* 2016; 315: 2200-10.
6. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet* 2011;378:380–2
7. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet* 2016; on-line May 20.
8. Cobb,LK, Anderson,CA, Elliott,P, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation* 2014; 129; 1173-86
9. Cogswell ME, Wang C-Y, Chen T-C, et al. Validity of predictive equations for 24-h urinary sodium excretion in adults aged 18-39 y. *Am J Clin Nutr* 2013; 98: 1502-13
10. Wang C-Y, Cogswell ME, Loria CM, et al. Urinary excretion of sodium, potassium, and chloride, but not iodine, varies by timing of collection in a 24-hour calibration study. *J Nutr* 2013; 143: 1276-82
11. Ji C, Venezia A, Miller MA, et al. Comparisons of spot vs 24-h urine samples for estimating population salt intake: validation study in two independent samples of adults in Britain and Italy. *Nutr Metab Cardiovasc Dis* 2014; 24: 140-7
12. Mente A, O'Donnell MJ, Dagenais G, et al. Validation and comparison of three formulae to estimate sodium and potassium excretion from a single-morning fasting urine compared to 24-h measures in 11 countries. *J Hypertens* 2014; 32: 1005-15
13. Campbell N. Validation and comparison of three formulae to estimate sodium and potassium excretion from a single-morning fasting urine compared to 24-h measures in 11 countries. *J Hypertens* 2014; 32: 2499-500
14. Peng Y, Li W, Wang Y, et al. Validation and assessment of three methods to estimate 24-h urinary sodium excretion from spot urine samples in Chinese adults. *PLoS ONE* 2016; 11(2): e0149655
15. O'Brien E. Salt – too much or too little? *Lancet* 2016; May 20; on-line
16. Liu K, Dyer AR, Cooper RS, et al. Can overnight urine replace 24-hour urine collection to assess salt intake? *Hypertension* 1979; 1: 529-36
17. Siani A, Iacoviello L, Giorgione N, et al. Comparison of variability of urinary sodium, potassium, and calcium in free-living men. *Hypertension* 1989; 13: 38-42
18. Lerchl k, Rakova N, Dahlmann A, et al. Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. *Hypertension* 2015; 66: 850-7
19. O'Donnell M, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA* 2011; 306: 2229-38
20. O'Donnell M, Mente A, Rangarajan S, et al. PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *New Engl J Med* 2014; 371: 612-23
21. Taylor RS, Ashton KE, Moxham T, et al. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane Review). *Am J Hypertens* 2011; 24: 843–53.
22. Anand SS, Dagenais GR, Mohan V, et al. Glucose levels are associated with cardiovascular disease and death in an international cohort of normal glycaemic and dysglycaemic men and women: the EpiDREAM cohort study. *Eur J Cardiovasc Prev Rehabil* 2012; 19: 755-64
23. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary sodium and cardiovascular disease risk – measurement matters. *New Engl J Med* 2016; June 2; on-line