

Primary Aldosteronism and Cardiovascular Events: It is time to take guideline recommendations seriously

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It is nowadays widely accepted that primary aldosteronism is the most frequent cause of endocrine hypertension. Prevalence rates among patients with hypertension are 6% in the primary care setting and 11% in tertiary care referral centers (1). The 2016 Endocrine Society Practice Guidelines (2) recommend screening of hypertensive subjects with increased pre-test probability which accounts to roughly 50% of all hypertensives. Nevertheless, these recommendations stand isolated and are not fully reflected by current hypertension guidelines in the US or Europe. More importantly, current health care data suggest that little has changed in terms of screening: according to a 2015 survey only 1% of hypertensives are screened in Italy and 2% in Germany by general practitioners (3). It is in this context in the current issue of the journal, that Ohno et al. publish their data from the recently founded Japan Primary Aldosteronism Study (4).

Using the large data set of 2582 patients with primary aldosteronism the authors analysed clinical and biochemical factors associated with prevalent cardiovascular disease. The patients were treated in 15 university hospitals and 14 city hospitals between 2006 and 2016. The data were entered into a nation-wide registry and analysed retrospectively after rigid chart review. Primary aldosteronism was diagnosed following strict diagnostic criteria including confirmatory testing and ACTH stimulated adrenal vein sampling. Successful cannulation of both adrenal veins was mandatory for inclusion, using stringent criteria: a selectivity index >5 (corresponding to the ratio of the cortisol concentration in the adrenal vein to that in the inferior vena cava) defined technical success of the procedure, whereas a lateralization index of >4 (aldosterone to cortisol ratio of the dominant adrenal side divided by the non-dominant side) indicated unilateral aldosteronism. Data of the patient cohort were compared with two hypertensive control cohorts: a smaller cohort from the Kyoto

Medical Center comprising 236 patients using sex, age and systolic blood pressure as matching variables, and 1263 similarly matched hypertensive subjects of the population-based Nagahama Study. Because of the large number of patients and the careful matching the Ohno study has an unprecedented power. It is its first (“the best”) finding that Japanese patients with primary aldosteronism have an adverse cardiovascular risk profiles, such as higher BMI, more prominent proteinuria and a higher diabetes rate. This leads to the second finding: patients with primary aldosteronism have strikingly higher rates of cardiovascular disease: The prevalence of cardiovascular disease was 11% versus 3.4% in the matched hypertensive group. This striking difference results from a 3 to 5 times higher stroke rate in primary aldosteronism: 7.2% versus 2.5% in the Kyoto Medical Center controls, 8.4% versus 1.6% in the population based hypertensive control subjects. Especially the high rate of cerebral hemorrhage (2.7%) and subarachnoid hemorrhage (0.5%) are bothersome, consequences of long-term uncontrolled hypertension. The third relevant point made by this study is related to potential risk factors predisposing to cardiovascular disease: In multivariate analysis, a low serum potassium ≤ 3.5 mEq/l was associated with an 1.8 fold risk of adverse outcome, as was unilateral aldosteronism (odds ratio 1.9) and a baseline plasma aldosterone level of ≥ 125 pg/ml (odds ratio 1.9). These data are very consistent: more florid cases of primary aldosteronism, i.e. aldosterone producing adenoma, a strong biochemical phenotype and accordingly low serum potassium levels, lead to more cardiovascular comorbidities. This should make it simple for the clinician: clear-cut cases of primary aldosteronism carry the highest risk to develop cardiovascular comorbidities and should be picked up as early as possible.

Why, then, is primary aldosteronism still underdiagnosed? Barriers to appropriate

screening of high risk populations are manifold. There is no clear lead symptom (despite hypokalemia as a late symptom). In the recently published *Prevalence and Clinical Manifestations of Primary Aldosteronism Primary Care Practice* trial in Torino (5) only 29% of patients were hypokalemic. Secondly, biochemical screening for primary aldosteronism is cumbersome and requires pre-analytical considerations. This includes adaptation of hypertensive medication to minimize its influence on the aldosterone to renin, adjustment of salt consumption, and correction of hypokalemia, if present. Thirdly, subtype determination of primary aldosteronism for identification of aldosterone producing adenoma requires a tertiary referral center offering adrenal vein sampling. Clearly this remains a major bottle neck in diagnostic work-up since few centers are available, and even in so-called expert centers technical success rate may be discouragingly low (6).

Recent data suggest that unilateral adrenalectomy in patients age 50 or younger, who have aldosterone producing adenoma, is associated with excellent hypertension cure rates (7). Also, it is undisputed that case finding and treatment of primary aldosteronism is cost effective (8). Moreover, personalized treatment of primary aldosteronism by adrenalectomy or mineralocorticoid receptor antagonist reduces left ventricular mass hypertrophy and microalbuminuria to levels of optimally treated control hypertensives over a time span of >10 years.

In summary, the conclusions taken from the Ohno study are simple: patients with primary aldosteronism are at high risk for cardiovascular and cerebrovascular events. Patients should be identified early on focusing on high risk populations as defined by current guidelines (2), vigorously diagnosed and treated. This strategy will reduce the burden of disease and save lives.

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NONE

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