Editorial Commentary

Medical Versus Surgical Treatment of Primary Aldosteronism

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A growing body of literature associates primary aldosteronism (PA) with increased risk of cardiovascular complications, including cardiovascular attributable death, left ventricular hypertrophy, stroke, proteinuria, and atrial fibrillation. This increased cardiovascular risk is in no doubt related in large part to aldosterone-induced increases in blood pressure (BP), which are often resistant and severe. Additional mechanisms that are seemingly independent of increases in BP that likely contribute to the development and progression of cardiovascular disease in PA patients include aldosterone-induced inflammation, fibrosis, cellular hypertrophy, and oxidative stress.[1] Further, in line with classical physiological effects, aldosterone and high dietary sodium exposure promotes intravascular fluid retention with associated increases in intracardiac heart volumes, including the left atrium, which would be anticipated to contribute to increased risk of incident atrial fibrillation.[2]

Demonstration of the increased risk of PA in relation to cardiovascular outcomes, including atrial fibrillation, has been largely based on retrospective or cross-sectional analyses. For example, in one of the earliest reports, Milliez et al[3] retrospectively compared the history of specific cardiovascular events in 124 patients with confirmed PA and 465 control patients with primary hypertension. In spite of seemingly similar levels of BP control, the PA patients were significantly more likely to have had a history of stroke and myocardial infarction and were >12 times as likely to have been previously diagnosed with an episode of atrial fibrillation. Reincke et al[4] conducted a longitudinal assessment of patients included in a German registry of PA who had been treated with adrenalectomy and a mineralocorticoid receptor antagonist (MRA). Although the 10-year all-cause mortality was similar to PA patients to that of matched hypertensive controls, the PA patients were significantly more likely to have died from cardiovascular complications than the control patients without PA. Combined, these 2 studies are important in documenting the increased cardiovascular risk associated with having PA, and unfortunately, the persistence of that risk with treatment that included adrenalectomy and use of MRAs.

Wu et al[5] conducted a longitudinal analysis of patients with PA included in the Taiwan National Health Insurance database. The analysis is impressive in having reported outcomes in 3362 PA patients during an average follow-up of 5.75 years. Consistent with earlier findings, PA patients overall were more likely to have had a major cardiovascular event during the follow period than control patients with primary hypertension. What makes the study especially informative, however, is that the investigators were able to compare outcomes in large numbers of PA patients treated with adrenalectomy versus use of MRAs alone. In that regard, adrenalectomy was associated with greater reductions in all-cause mortality compared with treatment with MRAs alone, suggesting the potential superiority of surgical treatment of PA compared with medical therapy with a MRA alone.

In the current edition of *Hypertension*, Rossi et al[6] add importantly to the above studies in having prospectively determined the relative clinical benefit of treating PA with adrenalectomy versus pharmacological therapy. Using the strength of the PAPY cohort (Primary Aldosteronism Prevalence in Hypertension)[7], the investigators were able to prospectively determine long-term outcomes in patients with rigorously confirmed PA who had been treated with adrenalectomy or medical therapy based on demonstration of lateralization of aldosterone secretion.

The analysis is based on complete follow-up data from 1001 patients of the original PAPY cohort. Of the study participants, 107 were diagnosed with PA, and of those, 41 had demonstration of lateralization of aldosterone secretion and underwent adrenalectomy. The remaining 66 PA patients failed to lateralize and were treated medically. The 894 patients confirmed not to have PA served as hypertensive controls. The patients undergoing adrenalectomy were biochemically confirmed to have been cured of PA. Importantly, BP control was good in each of the 3 groups during the course of the study, with a random sampling of 10% of the patients indicating similar levels of achieved systolic and diastolic BP.

After a median follow-up of 11.8 years, there was no statistical difference in the primary end point, that is, all-cause mortality, between PA patients and the hypertensive controls, although the PA patients manifested a trend for worse survival that was attributable to the PA patients who were being treated medically. Major cardiovascular event rates were overall low and largely the same in both the PA

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patients and hypertensive controls. However, the medically treated PA patients did have a higher rate of incident atrial fibrillation compared with both the PA patients treated surgically and the hypertensive controls. By multivariate analysis, the medically treated PA patients had an 82% increased risk of developing atrial fibrillation during the almost 12-year follow-up period.

Given the strength of the study design, the findings of Rossi et al provide compelling data that surgical treatment of PA with adrenalectomy is superior to medical treatment at least in terms reducing risk of incident atrial fibrillation. The findings indicate that surgical and medical treatments are not equivalent in spite of similar BP reductions. It seems intuitive that the most likely explanation for the discrepancy between the 2 treatment modalities was that use of MRAs, at least at the doses now commonly used, does not fully prevent excess MR activation in the setting of true PA. Coupled with the findings from Wu et al suggesting that the superiority of adrenalectomy compared with use of MRAs alone translate into overall survival benefit, the current findings suggest that clinicians having diagnosed PA should be more aggressive about testing for a culprit aldosterone-producing adenoma and preferentially recommending adrenalectomy when technically feasible.

Relatedly, a recent study by Hundemer et al[8] provides insight into the use of MRAs for treating PA. Although a retrospective analysis, the study is impressive in having assessed 10-year incidence of major cardiovascular events in 602 patients with confirmed PA who had been treated medically with a MRA. A matched cohort of 41 853 patients with primary hypertension served as the control group. All patients were without known prior cardiovascular disease at baseline. Patients with PA had an almost 2-fold higher incidence of combined cardiovascular events compared with patients with primary hypertension and a significantly higher risk of all-cause mortality. Not surprising, the PA patients also had a higher risk of developing atrial fibrillation. These differences in death and cardiovascular events rates occurred in spite of similar BP levels in the PA patients and the hypertensive control patients.

In what should probably be considered preliminary because of the small number of patients included in the analyses, the authors reported additional findings with potentially important clinical implications.[8] In the first case, they found that PA patients treated with an MRA whose plasma renin activity (PRA) had unsuppressed with treatment (ie, increased ≥1 μg/L per hour) did not have a significant difference in cardiovascular events or death compared with patients with primary hypertension. In contrast, PA patients whose PRA remained suppressed had an almost 3 times higher rate of incident cardiovascular events and a significantly higher likelihood of dying. Again, these differences occurred in spite of similar levels of BP between patients with suppressed and unsuppressed PRA. The PA patients whose PRA increased with treatment had been started on a higher initial dose of spironolactone or eplerenone compared with the PA patients whose PRA remained suppressed (spironolactone 50 versus 43 mg and eplerenone 65 versus 53 mg, respectively). The observed effect needs confirmation, but the implications of the findings are potentially far-reaching in suggesting that clinicians when treating PA medically should be titrating MRA doses not just according to the BP and serum potassium results but until the PRA is no longer suppressed. To what extent this is possible on an individual basis needs elucidation.

In the second case, the authors reported that PA patients treated with adrenalectomy had a significantly lower incidence of major cardiovascular events than both the MRA-treated PA patients and the hypertensive control patients. Such a benefit would exceed that reported by Rossi et al in suggesting that surgical treatment of PA is not only superior to medical treatment but also reduces risk even below that of treated primary hypertension. Although provocative, the findings are at a minimum in line with the now repeated demonstration that adrenalectomy better reduces long-term cardiovascular risk than MRAs for treatment of PA.

The above findings provide both guidance and direction on how best to manage PA. In terms of clinical guidance, retrospective and now prospective studies provide compelling evidence that surgical treatment of PA is more effective than medical therapy, such that the former should be considered the preferred treatment on demonstration of lateralization of aldosterone excess. In terms of direction, recent retrospective findings suggest that medical therapy of PA might be best guided not just by BP control but by evidence of biochemical efficacy as indicated by the change in renin activity. Given its potential clinical significance, confirming change in renin activity as an index of therapeutic efficacy when treating PA, whether with MRAs or perhaps other classes of agents, including MR-modulating peptides or novel inhibitors of aldosterone synthase, should be a priority of clinical researchers.

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