Letter to the Editor

More Fuel to the Debate on the “Epidemics of Primary Aldosteronism”

To the Editor:

To re-emphasize his views on primary aldosteronism (PA), Kaplan stated that the Primary Aldosteronism Prevalence in Italy Study1 “has...problems that question the reported prevalence of PA of 11.2%”; however, in exemplifying them, he collected several inaccurate statements.2

He contended that referral of patients with more severe resistant hypertension might have led to overestimating the PA prevalence, but no patient had resistant hypertension and only a minority had grade 3 hypertension; moreover, exclusion of the 2 centers with the highest prevalence did not markedly lower the prevalence rate of PA.1

Second, Kaplan2 questioned the aldosterone/renin ratio (ARR) performance and criticized that only 1 ARR was performed, evidently ignoring that the ARR was done at screening in all of the patients1 and once again after, on average, 4 weeks in the 317 patients who had the saline infusion test.3 Although performed under different conditions, the 2 ARRs showed a strong significant (P<0.0001) correlation; moreover, Bland-Altman plot, Passing-Bablok regression, and concordance correlation coefficient excluded any significant between-test variability. Importantly, no aldosterone-producing adenoma (APA) patient pinpointed with the first ARR was missed with the second, and vice versa. Thus, the claimed poor reproducibility of the ARR is not supported by the data. Moreover, although performing an ARR is no more expensive than a lipid profile, its result can have a greater impact on lifetime cardiovascular risk of those hypertensive subjects who have a long-term curable APA.

Third, despite quoting a head-to-head comparison of the captopril and the saline infusion test,4 surprisingly, Kaplan contended that “there are inadequate comparative data to be certain that the captopril suppression test may be as good as tests of sodium the saline suppression test.”2 Instead, this highly statistically powered study conclusively showed that the 2 tests performed similarly for excluding an APA if the patients are on an adequate sodium intake.4

Fourth, stating that “a [computed tomography] or MRI was used to make the definitive diagnosis in most patients”2 again reveals an inaccurate reading of the Primary Aldosteronism Prevalence in Italy Study: 43 of the 126 with PA had adrenal venous sampling at 5 (not 4 as reported) centers, but the preoperative diagnosis entailed mineralocorticoid scintigraphy whenever adrenal venous sampling was unavailable. Furthermore, by use of rigorous criteria, which entailed demonstration of adenoma at pathology and correction of the hyperaldosteronism, hypokalemia, and arterial hypertension at follow-up postadrenalectomy,1 an APA was diagnosed in 4.8% of the 1125 consecutive hypertensive patients. Thus, rather than affirming “despite the size of the study population, we are left with uncertainty as to the true prevalence of PA,”2 it is fair to conclude that the prevalence of surgically curable PA in hypertensive subjects is high and no uncertainties remain on prevalence of APA.1,3,4 and uncertainties pertain only to idiopathic hyperaldosteronism, because it cannot reliably be differentiated from low-renin hypertension due to the lack of accepted criteria for diagnosing this PA subtype.

Finally, Kaplan’s conclusion that missing a case of PA is not a “big deal” inasmuch as “a little of spironolactone or eplerenone is likely as easy (and less expensive) than any other antihyper-

Appendix. Mean List of Participating Centers and PAPY Study Investigators

<table>
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<th>Center</th>
<th>Investigators</th>
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<tr>
<td>Padova, Italy, DMCS Internal Medicine 4</td>
<td>Gian Paolo Rossi, Andrea Semplizini, Chiara Ganzaroli, Achille Cesare Pessina</td>
</tr>
<tr>
<td>Padova, Italy, Endocrinology</td>
<td>Franco Mantero, Decio Armanini, Giuseppe Opecher, Mee-Yung Mattarello</td>
</tr>
<tr>
<td>Ancona, Italy, Endocrinology</td>
<td>Gilberta Giaconetti, Vanessa Ronconi, Marco Boscaro</td>
</tr>
<tr>
<td>Reggio Emilia, Italy, Azienda Ospedaliera ASMN di Reggio Emilia Internal Medicine</td>
<td>Ermanno Rossi</td>
</tr>
<tr>
<td>Pisa, Italy, Internal Medicine</td>
<td>Giampaolo Bernini, Angelica Moretti</td>
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<tr>
<td>L’Aquila, Italy, Department of Internal Medicine and Public Health</td>
<td>Claudio Ferri, Giovambattista Desideri</td>
</tr>
<tr>
<td>Palermo, Italy, Internal Medicine</td>
<td>Giuseppe Andronico, Giovanni Corasola</td>
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<td>Brescia, Italy, Internal Medicine</td>
<td>Damiano Rizzoni, Enzo Porteri, Enrico Agabiti-Rosei</td>
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<td>Legnano, Italy, Internal Medicine</td>
<td>Gaetana Palumbo, Carlo Costantini, Maria Teresa Lavazza</td>
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<td>Roma, Italy, Internal Medicine</td>
<td>Claudio Letizia, Chiara Caliumi</td>
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<td>Trieste, Italy, Internal Medicine</td>
<td>Bruno Fabris</td>
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<tr>
<td>Firenze, Italy, Endocrinology</td>
<td>Massimo Mannelli, Gabriele Parenti</td>
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<tr>
<td>Torino, Italy, Endocrinology</td>
<td>Mauro Maccario, Ezo Ghigo</td>
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<tr>
<td>Reggio Calabria, Italy, Nephrology</td>
<td>Francesca Mallamaci, Graziella Caridi, Carmine Zoccali</td>
</tr>
<tr>
<td>Bari, Italy, Internal Medicine</td>
<td>Anna Belfiore</td>
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tensive medication" ignores the facts that the “unpleasant” adverse effects of spironolactone can make it unacceptable, particularly in men, and the better tolerated eplerenone is unavailable in many countries. Moreover, in APA patients, the superiority, or even the equivalence, of these agents over adrenalectomy is unproven. Instead, data suggest that the latter can be more efficacious than spironolactone in regressing LV hypertrophy and aortic stiffening.

Opinion leaders’ statements can have a tremendous impact on current practice and therefore should rely on evidences and not on inaccurate reports of the literature. It is therefore worrying to note that the level of evidence that supports Kaplan’s views on this issue can at best be classified as II B level C by the American Heart Association criteria.

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Disclosures
None.

More Fuel to the Debate on the "Epidemics of Primary Aldosteronism"
Gian Paolo Rossi, Achille C. Pessina and Franco Mantero
for the Primary Aldosteronism Prevalence in Italy Study Investigators (see Appendix)

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