

The relentless crumbling of the renin-angiotensin system (RAS)-blockade halo

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In 1999 a thorough review article in the *New England Journal of Medicine* stated that “*Patients with diabetes mellitus may represent a special sub-group for whom calcium antagonist therapy increases the risks of cardiovascular complications* (1).” This dictum was met with unanimous approval by the medical community since at that time it was clear beyond any doubt that diabetes was the sole domain of angiotensin converting enzyme (ACE) inhibitors. In fact, in what they called a “consensus approach,” a rather distinguished group of nephrologists and endocrinologists concluded that “*in patients with diabetes... the preferred initial therapy is an ACE-inhibitor, with the dose titrated upward to the moderate or high dose range, as tolerated* (2).” So powerful was the marketing machine of Big Pharma at that time that rather solid evidence of benefits of calcium channel blockers (CCB) in diabetes (3), showing that CCB based therapy reduced cardiovascular morbidity and mortality about twice as much in diabetic than in non-diabetic hypertensive patients (Table 1) was completely ignored. The statement of Mancina *et al.* (4) pertaining to the diabetic subpopulation of the INSIGHT study “*that nifedipine could be considered as first-line therapy for hypertensive diabetics,*” was met with disbelief in the US and considered an aberration.

Not that the data for benefits with ACE-inhibitors in diabetics were shaky; clearly numerous prospective RCTs showed ACE inhibitor therapy to be beneficial in the diabetic subpopulation (5,6). Although these benefits were initially observed mainly in patients with type 1 diabetes, subsequently MICRO-HOPE trial (7) extended these benefits to type 2 diabetes subgroup. Angiotensin receptor blockers (ARB) soon proved to be equally effective in the diabetic population which triggered a lively discussion

whether or not even normotensive patients with diabetes should prophylactically receive renin-angiotensin system (RAS) blocker for cardioprotection and nephroprotection. Little surprise that with HOPE trial, the ACE-inhibitor bandwagon spilled over to non-diabetic hypertensive patients as well. Not to initiate antihypertensive therapy with either an ACE-inhibitor or an ARB was almost considered malpractice in the early 21st century. This, despite the fact that whenever other drug classes such as CCBs or even thiazide diuretics such as chlorthalidone were pegged against RAS-blockers in hypertensive or coronary artery disease patients, study after study documented equal or even superior outcome of the comparator drug class (8-10). However, since many more companies manufactured RAS blockers than CCBs there was an overwhelming predominance of trials with ACE-inhibitors and ARBs. The arrogance of the RAS-blockade evangelists at that time is perhaps best documented by the basic hypothesis of the VALUE trial (9) which stated “*that for the same level of blood-pressure (BP) control, valsartan-based treatment would be superior to amlodipine-based treatment in reduction of cardiac morbidity and mortality*” and “*valsartan was expected to reduce cardiac morbidity beyond its BP-lowering effect.*” Amlodipine was chosen as comparator because it effectively lowers BP but has not been proven to have specific cardioprotective properties.

It was not to be. Quite to the contrary, although there was a small BP difference in favor of amlodipine, the putative cardioprotective properties of RAS-blockade fell miserably short in that both myocardial infarction and angina were significantly more common in the valsartan than in the amlodipine arm. Some of the relative inefficacy of RAS-blockade in ALLHAT and possibly VALUE trials

Table 1 Adjusted relative hazards associated with active calcium channel blockers (CCB) based treatment as compared with placebo in diabetic and non-diabetic patients from SYST-EUR trial (3)

| Endpoint | Diabetic patients | Non-diabetic patients | P value |
|--------------------------------------|-------------------|-----------------------|---------|
| Overall mortality | 0.45 | 0.94 | 0.04 |
| Mortality from cardiovascular causes | 0.24 | 0.87 | 0.02 |
| Cardiovascular events | 0.31 | 0.74 | 0.01 |
| Stroke | 0.27 | 0.62 | 0.13 |
| Cardiac events | 0.37 | 0.79 | 0.12 |

may well have been due to excessive BP variability that recently has been documented with this class of drugs (11). In contrast, long acting drugs such as chlorthalidone or amlodipine provide smoother 24-hour BP control and less BP variability.

We recently performed a systematic review and meta-analysis of randomized trials in over 25,000 patients asking the question whether diabetes mellitus remained a compelling indication for use of renin angiotensin system blockers (12). It turned out that RAS blockers are not superior to other antihypertensive drug classes such as thiazides, CCB, and β blockers at reducing the risk of hard cardiovascular and renal endpoints. There was also no difference in the hard renal outcome of end stage renal disease. Our findings support the recommendations of the guidelines of the European Society of Cardiology/European Society of Hypertension and eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure that there is convincing evidence to use any antihypertensive agents including RAS-blockers in patients with diabetes (13,14).

The recent paper of Barzilay *et al.* (15) further explores the question of whether RAS blockade deserves to have preferred status over other anti-hypertensive medications for the treatment of people with diabetes. After thoroughly going through studies in aggregate, the authors note that contrary to many current guidelines and “accepted medical dogma” patients with diabetes mellitus and hypertension, renal disease, or cardiovascular disease should be treated with an ACE-inhibitor or an ARB is not supported by evidence. To the contrary, they conclude similar to the panel members appointed to the Eighth Joint National Commission on the Treatment of Hypertension that of antihypertensive medications that lower BP effectively should be the preferred approach to treatment and do not advocate for preferential use of any class of antihypertensive medication.

We thoroughly agree.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Response to: Barzilay JI, Whelton PK, Davis BR. Does renin angiotensin system blockade deserve preferred status over other anti-hypertensive medications for the treatment of people with diabetes? *Ann Transl Med* 2016;4:202.

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