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Real World Evidence Supports Optimally Dosed Thiazide-Type Diuretics As Preferred In Treatment Regimens of Older Hypertensives

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To the Editor

Makam et al¹ explored the clinical relevance of metabolic adverse events associated with thiazide diuretic antihypertensive therapy in high-risk older patients. We commend them for attempting to “validate results of clinical trials in real world settings.” Unfortunately, the 2,120 veterans studied were considerably more selective than the hundreds of thousands of participants (including the Department of Veteran Affairs [VA] patients) randomized in relevant clinical trials conducted since the 1950s. They used national VA administrative data to study veterans 65 years selected from a sample of 19,878 who met their inclusion/exclusion criteria from an available population of 35,865 with documented hypertension - but untreated for 9 months or longer. Insufficient information was provided, including initial and achieved blood pressure (BP) levels, to explain why the 1,060 “cases” were started on thiazide diuretics and why the 18,186 “controls” remained untreated. The total number of veterans with hypertension—likely 1–2 million, was not provided and the exceptional 77% BP control rates to < 140/90 mmHg (<http://www.va.gov/QUALITYOFCARE/initiatives/compare/high-blood-pressure-control.asp>) were not mentioned. Those prescribed thiazide-

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type diuretics appeared similar to the matched 1,060 controls for the baseline variables reported (~12 % had known malignancy). However, propensity matching in an observational study design cannot control for unknown factors to the same degree as randomization in placebo-controlled clinical trials and does not provide the benefit of blinding to minimize ascertainment bias.

In contrast to Makam et al¹'s focus on intermediate outcomes, selective hospitalizations, and emergency department visits, prospective randomized clinical trials have systematically collected clinical outcomes in a masked manner to assure complete and bias free reporting of endpoints. In the Hypertension in the Very Elderly Trial (HYVET)², diuretic treatment (versus placebo) resulted in 64%, 21%, and 30% reductions, respectively, in risks of heart failure (HF) ($p<0.001$), all-cause mortality ($p=0.02$), and stroke ($p=0.06$), and fewer serious adverse events ($p=0.001$) – prompting early termination of the trial due to apparent benefit of diuretic treatment. In the Systolic Hypertension in the Elderly Program (SHEP)³, diuretic treatment (vs. placebo) yielded 36%, 27%, and 49% reductions, respectively, in risks of stroke ($p=0.0003$), non-fatal myocardial infarction or coronary heart disease death ($p=0.015$), and HF ($p<0.0001$)⁴.

Based on the Second Australian National Blood Pressure Study (ANBP2)⁵ and a network meta-analysis⁶, Makam et al concluded that other antihypertensive classes are as effective as thiazides in reducing cardiovascular events in older adults. However, ANBP2 did not raise safety concerns regarding diuretics and the network meta-analysis authors concluded that “Low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality. Clinical practice and treatment guidelines should reflect this evidence, and future trials should use low-dose diuretics as the standard for clinically useful comparisons.”

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)⁷, the thiazide-like diuretic chlorthalidone was compared with drugs from 3 classes of antihypertensive agents with a better metabolic profile (the angiotensin-converting-enzyme inhibitor lisinopril, calcium-channel blocker amlodipine, and alpha-receptor blocker doxazosin) for prevention of all-cause mortality and cardiovascular and renal outcomes. Participants were high-risk hypertensive patients 55 years ($N=42,418$), recruited from 623 mostly primary practice clinics across the United States, Canada, Puerto Rico, and US Virgin Islands. Participants included 15,084 Blacks, 8,072 Hispanics, 7,067 enrolled from 70 VA clinics, and 19,841 women. The only general medical exclusion was a known illness that might lead to a non-cardiovascular disease (CVD) death during the trial. Discontinuation rates of assigned medications, including symptomatic adverse effects, were highest in the lisinopril arm. (Table) Makam et al cite the association between hypokalemia and mortality in ALLHAT⁸ without mentioning the statistically significant disparity (interaction $p<0.01$) in hazard ratios across treatment arms, which strongly suggested the increased mortality in the chlorthalidone arm was due to underlying conditions, such as malignancies, associated with both loss of potassium and high mortality rather than a specific effect of the diuretic. Also, they failed to mention the association of hyperkalemia with CVD and that age-related declines in renal function make older patients susceptible to development of hyperkalemia, especially when treated with non-thiazide antihypertensives.

Neaton and Kuller⁹ noted that ALLHAT was the only hypertension treatment trial with adequate power to detect moderate but important differences in several major clinical outcomes. Chlorthalidone (12.5–25 mg/day) was unsurpassed in preventing CVD and renal outcomes. It was superior to doxazosin (2–8 mg/day), lisinopril (10–40 mg/day) and amlodipine (2.5–10 mg/day) in preventing new-onset HF. It was also superior to doxazosin and lisinopril in preventing stroke (for lisinopril, in Blacks only)^{4,10}.

Laboratory abnormalities associated with diuretic treatment of hypertension are relatively uncommon, usually easy to manage and typically of no serious consequence. The cost in lives lost, disability and medical care provision resulting from stroke and HF make use of properly dosed diuretics (chlorthalidone 12.5–25 mg/day or equivalent doses of other thiazide-type diuretics) preferred in treatment regimens of most hypertensive patients.

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Treatment arm	ALLHAT Randomized Treatment Arms Adverse Events and Clinical Events				Makam et al. Observational cases and matched controls Adverse Events Only	
	Chlorthalidone N=15255	Amlodipine N=9048	Lisinopril N=9054		THZ ¹ -non-Users N=1060	THZ ¹ -Users N=1060
	Heart Failure, Stroke, Combined CVD, and ESRD outcomes ² (average follow-up 4.9 years)				Adverse Events (follow-up 9 months)	
Heart Failure	7.7% (N=870)	10.2% (N=706) RR=1.38 p<0.001 ⁴	8.7% (N=612) RR=1.19 p<0.001 ⁴		N/A	N/A
Stroke	5.6% (N=675)	5.4% (N=377) RR=0.93 p=0.28 ⁴	6.3% (N=457) RR=1.15 p=0.02 ^{4,5}		N/A	N/A
Combined CVD	30.9% (N=3941)	32.0% (N=2514) RR=1.04 p=0.12 ⁴	33.3% (N=2514) RR=1.10 p<0.01 ^{4,5}		N/A	N/A
ESRD	1.8% (193)	2.1% (N=129) RR=1.12 p=0.33 ⁴	2.0% (126) RR=1.11 p=0.38 ⁴		N/A	N/A
>25% decrease in eGFR	N/A	N/A	N/A		3.2% (N=29)	5.5% (N=50) RR=1.76 P=0.015
ED ² visit or hospitalization for adverse event	See below	See below	See below		2.0% (N=21)	3.8% (N=40)
Discontinuation of assigned treatment at 1 and 5 years ³						
Year 1	12.9% (1790/13,853)	12.4% 1023/8215	17.6% (1436/8157)		6.0% (64/1060)	14.3% (152/1060)
Year 5	19.3% (1249/6496)	19.6% (769/3920)	27.4% (1032/3768)		N/A	N/A
Reported (by clinic) medical reasons for not taking assigned treatment at 5 years						
N/A						
Symptomatic Adverse Effects	4.3% (282/6496)	4.6% (180/3920)	7% (264/3768)			
Elevated BP	1.3% (84/6496)	1.0% (38/3920)	3.5% (131/3768)			
Low BP	1.4% (91/6496)	1.3% (51/3920)	2.0% (76/3768)			
Other adverse effects (e.g., abnormal laboratory values)	1.1% (71/6496)	0.4% (17/3920)	0.9% (34/3768)			
Morbid event	1.1% (73/6496)	1.5% (45/3920)	1.3% (49/3768)			

ALLHAT Randomized Treatment Arms Adverse Events and Clinical Events				Makam et al. Observational cases and matched controls Adverse Events Only	
Treatment arm	Chlorthalidone N=15255	Amlodipine N=9048	Lisinopril N=9054	THZ ¹ -non-Users N=1060	THZ ¹ -Users N=1060
Potassium (K) and sodium (Na) perturbations					
		At Year 1		At 9 months	
Laboratory finding					
K ⁺ < 3.5 mEq/L	12.9% (1185/9159)	2.1% (113/5371)	1.0% (53/5201)	1.4% 15/1060	4.5% 47/1060
K ⁺ < 3.2 mEq/L	3.5% (277/9159)	0.3% (17/5371)	0.2% (8/5201)	N/A	N/A
K ⁺ > 5.4 mEq/L	1.2% (110/9159)	1.9% (102/5371)	3.6% (187/5201)	N/A	N/A
Na ⁺ < 135 mEq/L	N/A	N/A	N/A	2% 21/1060	6.5% 68/1060
Primary Safety Outcomes					
Hospitalization for GI bleeding ²	8.8% (N=817)	8.0% (N=449) p=0.15 ⁴	9.6% (N=526) p=0.07 ⁴		
Angioedema	0.05% (N=8)	0.03% (N=3)	0.42% (N=38) p<0.001 ⁴		

¹ THZ indicates thiazide

² 6-year rates in % (total number of events); mean follow-up 4.9 years, CVD indicates cardiovascular disease, ESRD end-stage renal disease, GI gastrointestinal bleeding, ED emergency department; combined CVD is defined in ref. 7

³ Discontinued randomized blinded drug and not on open label from the same drug class

⁴ Compared with chlorthalidone; RR indicates Relative Risk;

⁵ significant outcome by race interaction for lisinopril vs. chlorthalidone comparison for stroke (RR; 95% CI = 1.40; 1.17–1.68 in Blacks and 1.00; 0.85–1.17 in non-Blacks, interaction p=0.01) and for combined CVD (RR; 95% CI=1.19; 1.09–1.30 for Blacks and 1.06; 1.00–1.13 for non-Blacks, interaction p=0.04)