Meta-Analyses of ARBs to Elucidate Link to Cancer, MI, and Dementia

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Domenic Sica, MD, Virginia Commonwealth University Health System, Richmond, Virginia, USA, gave an update on controversies surrounding angiotensin receptor blockers (ARBs). Eight different ARBs are currently available, all with variable pharmacological properties (Table 1). Before reviewing meta-analyses of ARBs, Dr. Sica reminded the audience that when considering a class effect, what applies to one drug may not necessarily pertain to all drugs in the class.

Table 1. Pharmacology of Angiotensin Receptor Blockers

Drug	Half-Life (h)	Bioavailability (%)	Volume of Distribution	% Renal/ Hepatic Clearance
Azilsartan 11	11	60	16 L	6/94
Candesartan	9	15	0.13 L/kg	60/40
Eprosartan	5	13	13 L	30/70
Irbesartan	11-15	60-80	53-93 L	1/99
Losartan	2	33	34 L	10/90
E-3174	6-9	—	12 L	50/50
Olmesartan	10-15	28	17 L	45/55
Telmisartan	24	42-58	500 L	1/99
Valsartan	6	~25	17 L	30/70

ARBs AND CANCER

A 2010 meta-analysis by Sipahi et al. [*Lancet Oncol*] indicated that ARB treatment was associated with an increased risk of cancer. When 4 randomized trials with a secondary endpoint of cancer were combined, the authors found that patients treated with ARBs had an increased likelihood of a new cancer diagnosis (RR, 1.11; 95% CI, 1.04 to 1.18; p=0.001). A subsequent meta-analysis of 15 long-term trials found a neutral effect of ARBs when compared with non-ARB controls (OR, 1.00; 95% CI, 0.95 to 1.04) [ARB Trialists Collaboration. *J Hypertens* 2011]. The United States Food and Drug Administration issued a statement in 2011 stating that there was no evidence of increased risk of cancer linked to ARB use [US FDA. Safety Announcement. http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm. Published June 2, 2011. Accessed June 21, 2013]. "It's not been laid to rest completely, but most analyses suggest there is little such relationship," summarized Dr. Sica.

ARBs AND MYOCARDIAL INFARCTION

A 2004 nonquantitative review of ARBs and risk of myocardial infarction (MI) implied that ARB use was associated with an increased risk of MI [Verma S, Strauss M. *BMJ*]. However, this idea was not supported in subsequent systematic review that included 19 trials (OR, 0.94 vs placebo; 95% CI, 0.75 to 1.16) [McDonald MA et al. *BMJ* 2005]. A 2011 meta-analysis of 37 randomized trials further supported the idea that ARBs are not associated with an increased risk of MI (OR, 1.01; 95% CI, 0.96 to 1.06) [Bangalore S et al. *BMJ*].

ARBs AND DEMENTIA

More studies are needed to determine the effect of ARB treatment on dementia, particularly Alzheimer disease (AD). There were no differences in Mini-Mental Status Examination (MMSE) scores overall in the Study on Cognition and Prognosis in the Elderly trial [SCOPE; [Skoog I et al. *Am J Hypertens* 2005]. However, in patients with a baseline MMSE score of 24 to 28, those taking candesartan had smaller declines in MMSE than controls (mean difference, 0.49; 95% CI, 0.02 to 0.97; p=0.04). A large study using the US Veterans Affairs administrative database of 819,491 patients (~98% male) suggested that ARB use was associated with a lower risk of AD compared with angiotensin-converting-enzyme inhibitors (HR, 0.81; 95% CI, 0.68 to 0.96; p=0.016) [Li NC et al. *BMJ* 2010]. Results from 3 smaller studies also indicated that older patients with hypertension taking ARBs may have better cognitive functioning [Tedesco MA et al. *Am J Hypertens* 1999; Fogari R et al. *J Hum Hypertens* 2006; Hajjar I et al. *Arch Int Med* 2012]

In conclusion, it is unlikely that ARBs increase the risk of cancer or of MI but it remains uncertain whether they can prevent dementia, particularly AD. Additional large scale studies would further clarify the effects of ARB treatment.