

PHARMACOVIGILANCE CENTER (PVC) SAFETY COMMUNICATION

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Combined Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) Use in the Military Health System (MHS).

Audience: Pharmacy, Patient Safety, Family Practice, General Practice and Internal Medicine, Advanced Practice Nursing, Nurse Practitioners, Physician Assistants: Please share with providers and pharmacists at your MTFs and regions.

Hypertension is the leading cause of Cerebral Vascular Disease (CVD) and premature death worldwide. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommendation for stage one patients without complications was to treat with thiazide-type diuretics and consider ACEIs, ARBs, Calcium Channel Blockers (CCBs), beta-blockers or combinations if needed¹. ACEI/ARB combination therapy was a consideration for use in patients with diabetic nephropathy, or proteinuria.

ACEIs and ARBs target the renin-angiotensin-aldosterone system which regulates blood volume, arterial pressure, and cardiac and vascular function. Both agents inhibit the hypertensive effects of angiotensin (AT)-II, which acts to increase systemic vascular resistance and arterial pressure. AT-II also increases blood pressure by stimulating the adrenal cortex to release aldosterone, which in turn causes sodium and water reabsorption and potassium excretion, and by promoting the secretion of antidiuretic hormone which leads to fluid retention. ACEIs block the conversion of AT-I to AT-II and increase the levels of bradykinin, which can reduce blood pressure through its own vasodilatory effects. Many tissues contain

enzymatic pathways capable of converting AT-I to AT-II and are not affected by ACEIs; therefore ACEIs do not block AT-II production completely. ARBs inhibit AT-II from activating the angiotensin specific receptor, AT1.

In theory, the use of ACEIs and ARBs in combination should optimize the blockade of the RAAS system. However, current research suggests that while ARB in combination with ACEI may modestly affect blood pressure it does not reduce total mortality, and in some cases may be deleterious. **There has been a major recommendation change between JNC 7 and JNC 8. JNC 8 new recommendations** state that physicians should continue to adjust medication regimen to maintain BP control by combining drugs in the four classes (diuretics, CCBs, ACEI, and ARB), but the panel expressly **does not recommend simultaneous use of an ACEI and an ARB in the same patient**²

The PVC evaluated the prescribing practices for ACEI/ARB combination therapy in the military health data and report selected demographic characteristics of patients who filled concomitant prescriptions for ACEIs and ARBs. Prescription records were from the Pharmacy Data Transaction Service (PDTS). Only ACEI and ARB prescriptions dispensed from October 1, 2012 to September 30, 2013 were included in this analysis. Patients were considered to have ACEI/ARB combination therapy if they had two sequential prescriptions of ACEIs in a drug era and two sequential prescriptions of ARBs in a drug era with no more than a 15 day gap period between the two prescriptions. The ACEI and ARB prescriptions were considered as taken concomitantly if there was an overlap of 60 days or more between the ACEI and ARB drug eras.

From October 1, 2012 to September 30, 2013, there were 15,014 co-prescribed ACEI/ARB combination drugs dispensed within the MHS (Table 1). The vast majority of the drugs were repeatedly filled and taken together for over a year

(15%). Female patients were dispensed 48.30% of the prescriptions and 1.9% of the prescriptions were dispensed to patients under the age of 45. Patients in the Army, the largest Service, were given ACEI/ARB prescriptions most often followed by the Air Force.

Table 1. Counts & percentages of overlapping ACE-I/ARB prescriptions for 60+ days by patient characteristics FY2013		
	N	%
Total	15,014	(100%)
Age Groups		
0 - 4	0	(0.0%)
5 - 14	5	(0.0%)
15 - 17	5	(0.0%)
18 - 24	13	(0.1%)
25 - 34	48	(0.3%)
35 - 44	226	(1.5%)
45 - 64	3,932	(26.2%)
65+	10,785	(71.8%)
Male	7,762	(51.7%)
Female	7,252	(48.3%)
Active Duty (AD)/Guard		
Family Member of AD/Guard	207	(1.4%)
Retiree	116	(0.8%)
Family Member Retiree/Other	7,565	(50.4%)
7,126	(47.5%)	
Service		
Army	5,466	(36.4%)
Navy	3,453	(23.0%)
Air Force	5,073	(33.8%)
Marine Corps	757	(5.0%)
Other	265	(1.8%)

*percentages do not add to 100% in each category due to rounding

Recommendation to Healthcare Providers:

The goal of treatment is still to adjust patient's medications until target blood pressures are maintained in order to reduce CVD complications. However, **primary care providers are urged not to co-prescribe ACEIs and ARBs in the same patient.** The combination of ACEIs *and* ARBs may provide some benefit to those with special considerations, such as those with proteinuria;

such patients should be **referred to specialist** for evaluation of the need for co-prescribing of an ACEI *and* ARB. If a patient is co-prescribed an ACEI *and* ARB **by a specialist**, providers are urged to follow the patient closely; making sure kidney functions are regularly monitored. Primary Care providers who previously started their patients on ACEIs *and* ARBs for blood pressure control are asked to consider switching one of these classes of drugs to another approved class of hypertensive drugs.

Healthcare providers are encouraged to document and report adverse events related to the use of these medications in the medical chart, to the DoD's Patients Safety Reporting System, and to FDA's MedWatch Safety Information and Adverse Event Reporting Program:

<http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>

Send requests for additional information regarding this safety communication or the analysis conducted by the PVC to COL Trinka Coster (trinka.s.coster.mil@mail.mil).

HOW ARE WE DOING?

OPPORTUNITY FOR IMPROVEMENT:

A large number of patients in the MHS are dispensed ACEIs and ARBs simultaneously and are on combination treatment for long term (>1 year). Guidelines have recently changed to recommend that ACEI and ARB combinations not be used together in the same patient.

There is an opportunity for improvement by changing ACEI/ARB combination therapy regimens to blood pressure medications combined with either an ACEI or an ARB, to reflect the current JNC 8 recommendations, unless the patient is under the care of a specialist.

1. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) Express. National Heart, Lung, and Blood Institute. Bethesda, Md. 2003. *JAMA*. 2003;289:2560–71.
2. Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 8) Express. National Heart, Lung, and Blood Institute. Bethesda, Md. 2003. *JAMA*. 2013;289:2560–71.

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