PharmaNote®

Volume 27, Issue 5 February 2012

ARE ALL ANGIOTENSIN RECEPTOR BLOCKERS CREATED EQUAL IN THE MANAGEMENT OF HEART FAILURE?

Jason Powell, Pharm.D. Candidate

Heart Failure (HF) is estimated to affect 5.8 million people in the United States. In 2006, 1 out of every 8.6 death certificates in the United States mentioned HF, accounting for over 250,000 deaths. The frequency of HF in patients older than 65 years is 10 per 1000 and is influenced by factors such as obesity, hypertension, diabetes, and an increased incidence of myocardial infarction (MI).[1] This translates into a conservative estimated cost of $39.2 billion in direct and indirect costs.[1]

Cost utilization data from the EPHUSUS study demonstrated that even patients managed properly require a large amount of resources.[1] There were 3,434,000 ambulatory care visits due to HF in 2007.[1] Patients are being discharged on an angiotensin converting enzyme inhibitors (ACEi) or an angiotensin receptor blockers (ARB) 92-95% of the time when they have left ventricular systolic dysfunction after an acute coronary syndrome.[1] The Medicaid-Fee-For-Service program analyzed the percent of ACEi and ARB claims from 1991 to 2008, which looked at claims for any disease state. In 1991, ACEi made up 100% of the total ACEi or ARB claims and by 2008, ARBs became 35.3% of the total claims.[2] ARBs are becoming more commonly prescribed and this number will most likely grow as they become generic. This article will briefly review the classification of HF according to current guidelines, the role of ARBs in HF, review the recommended dosing for ARBs, and discuss the major ARB HF trials.

HF Guidelines and Classification

Guidelines used for the treatment of HF are established by both the American College of Cardiology/American Heart Association (ACC/AHA)[3] and the European Society of Cardiology (ESC).[4] According to the most recent ACC/AHA guidelines, treatment of HF is dependent on the progression of the disease. Multiple therapies including ACEi/ARBs, beta blockers (β-blocker), statins, aldosterone antagonists, diuretics and digoxin are used.[3] The ACC/AHA guidelines classify HF into 4 stages; A, B, C, and D. HF can further be broken down into the New York Heart Association classification (**Table 1**).[3]

The ACC/AHA guidelines recommend the use of ACEi in all stages of HF unless the individual is intolerant to an ACEi.[3] Two contraindications

Inside This Issue:

Table 1 | HF Overview[3]

Stage or Class	Description	Characteristics of stage
Stage A	Individuals that have risk factors for developing HF	Age, hypertension, previous MI, diabetes, obesity, and dyslipidemia
Stage B	Cardiac remodeling	Left ventricular hypertrophy, valvular disease or a reduced LVEF of 45% or lower
Stage C	Experiencing symptoms of HF	Symptoms include: shortness of breath, decreased exercise tolerance, lower extremity edema, and difficulty breathing
NYHA I	No limitations to ordinary physical activity	
NYHA II	Slight limitation to their normal daily activities	
NYHA III	Physical activity becomes greatly limited	
NYHA IV	Symptoms even at rest with some medication options still available	
Stage D	Symptoms with all medication options exhausted	

*Chart is adapted from the ACC/AHA guidelines[3]
HF: heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

for the use of an ACEi include a history of a life-threatening adverse reaction (angioedema or anuric renal failure) due to an ACEi or pregnancy.[3] Another consideration for potentially avoiding an ACEi is the development of a dry cough theorized to be caused by the inhibition of bradykinin breakdown by angiontensin converting enzyme (ACE), which occurs with ACEi usage. This would not be expected with the use of an ARB as ARBs do not affect ACE. Valsartan and candesartan are the only ARBs currently approved in the US for use in HF (**Table 2**).[5,6]

ARBs in HF

The *Meta-Analysis of Renin-Angiotensin-Aldosterone Blockade for HF in Presence of Preserved Left Ventricular Function* combined the major trials I-Preserve and CHARM-Preserved, along with lesser known trials pep-CHF and Hong Kong Diastolic, all of which had a minimum duration of one year with at least one year of follow-up. Endpoints of the trials varied and included: death or hospitalization for any cardiovascular cause; cardiovascular death or hospitalization for HF; death of hospitalization for HF; and symptoms and quality of life.[9] These trials were combined to investigate whether the use of an ACEi or ARB in patients with preserved left ventricular ejection fraction (LVEF) would decrease the number of re-hospitalizations; 8,152 participants with preserved LVEF were included in the analysis. The difference in re-hospitalization rate in the ARB/ACEi group was statistically significantly different when compared to those without an ACEi/ARB (RR= 0.90; 95% Confidence Interval (CI) 0.81-0.99; p=0.032).[9] However, both the CHARM-preserve and I-Preserve studies, when looked at individually, showed that there was no benefit with the use of ARBs in HF in patients with preserved LVEF (> 40% and ≥ 45%, respectively) in

Table 2 | Initial and target dosing for ARBs in HF [5-8]

ARB	Initial Dose	Target Dose
Candesartan (Atacand®)*	4mg to 8mg daily	32mg daily (CHARM)
Irbesartan (Avapro®)	75mg to 150mg daily	300mg daily
Losartan (Cozaar®)^	25mg to 50mg daily	150mg Daily (HEAAL)
Valsartan (Diovan®)*	20mg to 40mg twice daily	160mg twice daily (Val-Heft)

*=FDA approved for HF[5,6]; ^=FDA approved for hypertension with Left ventricular hypertrophy[8] d
ARB: angiotensin receptor blocker; FDA: Food and Drug Administration; HF: heart failure; mg: milligram

terms of hospitalizations and all-cause mortality.[10,11]

TELMISARTAN IN HF

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) compared telmisartan (Micardis®) and ramipril (Altace®) in patients with vascular disease or high-risk diabetes. The primary outcome was the composite of death from cardiovascular causes, MI, stroke, and hospitalizations from HF.[12] Notably, patients hospitalized for HF with coronary, peripheral, or cerebrovascular disease, or diabetes with end-organ damage were considered to have had an outcome event. The study included 25,620 patients with both groups having similar baseline characteristics and cardiovascular therapies. Ramipril and telmisartan were titrated to target doses of 10 mg and 80 mg, respectively. For the primary outcome, telmisartan was found to be non-inferior to ramipril (RR=1.01; 95% CI 0.94-1.09; p=0.0038 for non-inferiority). Telmisartan 80 mg was also non-inferior to ramipril 10 mg in preventing deaths from cardiovascular events alone (RR=0.99; 95% CI 0.91–1.07; p= 0.001 for non-inferiority) or hospitalizations for HF (RR=0.95; 95% CI 0.82–1.10; p= 0.83). The telmisartan group had a lower incidence of cough (1.1% vs. 4.2%, P<0.001) and angioedema (0.1% vs. 0.3%, P = 0.01), but a higher rate of hypotensive symptoms (2.6% vs. 1.7%, P<0.001) compared to ramipril.[12] This trial suggests that ARBs, more specifically telmisartan, may have an important role in managing HF. This study was sponsored by Boehringer Ingelheim Pharmaceuticals Inc, the manufacturer of telmisartan.

VALSARTAN IN HF

The Valsartan Heart Failure Trial (Val-Heft) and Valsartan in Acute Myocardial Infarction Trial (VALIANT) examined the use of valsartan (Diovan®) in HF.[13,14] In Val-Heft (n=5010), eligible patients were classified as having NYHA Class II, III, or IV symptoms and had a LVEF of < 40%. This trial was designed to study the addition of valsartan to optimized therapy for HF, including those on a β-blocker and ACEi (93% of participants), to those on optimized therapy without the addition of valsartan.[13] The target dose of valsartan was 160 mg twice daily, although this dose was only achieved in 84% of the participants. The primary outcome was a composite of hospitalizations for HF, death from any cause, cardiac arrest, and intravenous inotropic or vasodilator therapy for at least four hours. Overall, the addition of valsartan to already optimized HF therapy reduced the risk of the primary endpoint (RR=0.87; 95% CI 0.77–0.97; p= 0.009) (**Table 3**) but did not improve all-cause mortality (RR=1.02; 95% CI 0.88–1.18; p= 0.80) (**Table 4**). Further analysis found that the risk of hospitalization for HF was reduced by 27.5% with valsartan add-on therapy (P<0.001) (**Table 5**). In patients that were not on an ACEi at baseline (n=366), there was a signifi-

Table 3 | Results of ARBs on combined cardiovascular mortality and hospitalizations in Heart Failure

ARB	Trial	Result	Interpretation
Candesartan	CHARM-overall[18]	HR=0.84; 95% CI 0.77-0.91 p<0.0001	Candesartan lowers risk when used in HF
	CHARM-Added[19]	HR= 0.85 p=0.011	Candesartan lowers risk when added to ACEi
	CHARM-Alternative[20]	HR=0.77; p=0.0004	Candesartan lowers risk in ACEi intolerant patients
	CHARM-Preserve[10]	HR 0.89; p=.118	No benefit seen when LVEF > 40%
Irbesartan	N/A	N/A	N/A
Losartan	OPTIMAAL[22]	RR=1.19; 95% CI 0.99–1.43 p=0.072^ RR=1.03; 95% CI 0.89–1.18 p=0.722®	Non-inferior to captopril Non-inferior to captopril
Valsartan	Val-Heft[13]	RR=0.87; 95% CI 0.77–0.97 p=0.009*	Lowered risk when added ACEi

*Not found to be non-inferior based of pre-determined upper confidence interval maximum of 1.10; ^ only CV death.
ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CI: confidence interval; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; N/A: not applicable; RR: relative risk

cantly lower risk of the combined end point in the valsartan group (RR= 0.56; 95% CI 0.39-0.81; p<0.001), but the overall risk of death (RR= 0.67; 95% CI 0.42-1.06; p=0.017) was not statistically significantly different.[15] The authors concluded that valsartan prevented hospitalizations in those intolerant to ACEi, but it does not seem to offer any benefit in terms of all-cause mortality, which makes it less ideal compared to an ACEi.[13]

VALIANT evaluated patients with HF that had had an MI within the previous 0.5-10 days.[14] The 14,808 participants had similar baseline characteristics and were randomized to receive valsartan 160 mg, captopril 50 mg (Capoten®), or combined therapy with both valsartan and captopril. The primary outcome of this trial was death from any cause during follow-up. Valsartan, alone and in combination with captopril, was compared to captopril alone. Valsartan was found to be similar to captopril for total mortality (HR=1.00; 95% CI 0.90-1.11; p=0.98) (**Table 4**). However, the valsartan plus captopril group trended toward increased mortality compared to captopril alone (HR=0.98; 95% CI 0.89 to 1.09; p=0.73), but was still found to be non-inferior. The authors concluded that valsartan is equally effective as captopril in preventing death in patients with HF and recent MI, and that the combination of an ACEi and ARB may lead to increased adverse drug events (ADE) with no additional benefit in mortality.[14]

Lee, et. al. conducted a small scale open-label randomized trial in South Korea with 455 participants comparing valsartan 160 mg twice daily (BID) to enalapril (Vasotec®) 10 mg BID, and their effect on N-terminal pro-brain natriuretic peptide (NT-proBNP) over 12 months.[16] Notable differences in baseline characteristics were observed, such as the valsartan group having a higher percent of men (p=0.0014), having a higher percent of patients with diabetes (p=0.005), and lower percent with hyperlipidemia (p=0.049). However, NT-proBNP levels were not significantly different between groups (no p value reported) at baseline. Both valsartan and enalapril demonstrated a significant decrease in NT-proBNP levels from baseline (p<0.05).[16]

Studies using valsartan such as Val-heft[13] and VALIENT[14], have all used a target dose of 160 mg BID. In a 10-week study, Anand, et al. compared once-daily versus twice-daily dosing of valsartan in 115 patients with chronic stable HF, reaching an average total daily dosing reaching 256 mg and 245 mg, respectively.[17] Patients were in NYHA

Table 4 | Results of ARBs on All-cause mortality in Heart Failure

ARB	Trial	Result	Interpretation
Candesartan	CHARM-overall1[18]	HR= 0.91; 95% CI 0.83–1.00 p=0·055	No difference with or without candesartan if on optimal therapy
	CHARM-Added[19]	HR 0.84; p=0.02^	Lower risk of CV death when added with ACEi
	CHARM-Alternative[20]	HR 0.85; p=0.072	No difference between ACEi or candesartan
	CHARM-Preserve[10]	HR=0.99; p=0.918	Candesartan lowered risk of death in preserved HF
Irbesartan	I-PRESERVE[11]	HR=1.00; 95% CI 0.88-1.14; p=0.98	Irbesartan was no better than placebo
Losartan	ELITE II[21]	HR= 1.13; 95% CI 0.95-1.35; p=0.16	Non-inferior to captopril
	OPTIMAAL[22]	RR=1.13; 95% CI 0.99–1.28; p=0.069	Potentially non-inferior*
Valsartan	Val-Heft[13]	RR=1.02; 95% CI 0.88–1.18; p= 0.80	No added benefit with valsartan to optimal therapy
	VALIANT[14]	RR=1.00; 95% CI 0.90-1.11; p=0.98	Non-inferior to captopril post MI

*Not found to be non-inferior based of pre-determined upper confidence interval maximum of 1.10
^ only CV death
ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CI: confidence interval; CV: cardiovascular; HF: heart failure; HR: hazard ratio; MI: myocardial infarction; RR: relative risk

class II or III, had a LVEF < 40%, and were on an ACEi and a β-blocker at baseline. The authors found no differences between groups in tolerability or ADE, but did not investigate any clinical outcomes such as all cause mortality or hospitalizations. This article concluded that it may be possible to dose valsartan once daily in HF, but better trials are needed.[17]

CANDESARTAN IN HF

The effects of Candesartan on Mortality and Morbidity in patients with chronic Heart Failure (CHARM) series (n=7,601) was comprised of the CHARM-added,[19] CHARM-Alternative,[20]and CHARM-Preserved[10] studies which evaluated candesartan (Atacand®) at a target dose of 32 mg daily in HF patients. CHARM-Overall, which included all three subsets, found no difference in all cause death, its primary outcome, between candesartan and placebo (HR= 0.91; 95% CI (0.83–1.00); p=0·055) with a trend towards a benefit in the candesartan group.[18] There was a statistical difference in the risk of cardiovascular death and risk of first hospital admission for HF favoring candesartan over placebo (20% vs. 24%, respectively; HR 0.84; 95% CI 0.77-0.91; p<0.0001) (**Table 3**).[18] Based on CHARM-OVERALL, candesartan appears to prevent hospitalizations in patients with HF and may reduce all-cause mortality.

The CHARM-added study evaluated patients with a LVEF ≤ 40% currently on an ACEi, which was continued throughout the trial.[19] Candesartan 32 mg was either added onto therapy, which included an ACEi, or it was left off. The primary outcome was cardiovascular (CV) mortality or hospitalization for HF. When combined with an ACEi, candesartan reduced the rate of CV mortality and hospitalizations for HF (HR= 0.85; p=0.011) (**Table 3**) when compared to those not given candesartan and receiving only an ACEi. Unlike the other two studies, CHARM-Alternative[20] and CHARM-preserve[10], CV mortality was also lower in the candesartan group (HR 0.84; p=0.02) (**Table 4**).[19] Adding candesartan to patients on optimal therapy with a beta-blocker and an ACEi who remain symptomatic can reduce CV mortality and hospitalizations.[19]

Charm-Alternative evaluated the addition of candesartan to patients with a LVEF ≤ 40% who were ACEi intolerant. [20] Results showed that CV mortality and hospitalizations for HF, the two components of the primary outcome, were lower in the candesartan group (HR=0.77; p=0.0004) (**Table 3**), but all-cause death was not reduced (HR 0.85; p=0.072) (**Table 4**) when added to a patient not on an ACEi. When looked at separately, the CV mortality was not different between the candesartan group and placebo (HR 0.85; p=0.072).[20] Since the use of an ACEi is the only difference between the CHARM-Added and CHARM-Alternative trials, this finding emphasizes that an ACEi is the medication of choice in these patients due to its benefit in reducing CV mortality and all-cause death.[19,20]

CHARM-Preserved evaluated patients with LVEF > 40% with or without the use of an ACEi.[10] Patients received candesartan 32 mg or placebo, which was added to baseline therapy that included all treatment options except ARBs. After a median follow-up of 36.6 months, the primary out-

Table 5 | Prevention of Hospitalizations by ARBs in Heart Failure

ARB	Trial	Result	Interpretation
Candesartan	N/A	N/A	N/A
Irbesartan	I-PRESERVE[11]	HR= 0.95; 95% CI 0.85-1.08; p=0.44	Irbesartan did not prevent hospitalizations vs. placebo
Losartan	ELITE II[21]	HR=0.92; 95% CI 0.78-1.08; p=0.32*	Non-inferior to captopril
	OPTIMAAL[22]	HR=1.04; 95% CI 0.94-1.16; p=0.45	Non-inferior to captopril
Valsartan	Val-Heft[13]	27.5% reduction (P<0.001)	Lower when added to optimal therapy

*hospitalizations only for HF;
*combined outcome of all-cause mortality and hospitalizations for HF; ^ sudden cardiac death/resuscitated cardiac arrest; ® fatal/non-fatal MI.
ARB: angiotensin receptor blocker; CI: confidence interval; HR: hazard ratio; N/A: not applicable

come, CV mortality or hospitalization, was not different between groups (HR 0.89; p=0.118) (**Table 3**), or all-cause mortality (HR=0.99; p=0.918) (**Table 4**).[10] In patients with preserved LVEF, the use of an ARB appears to offer no benefit to patients with or without an ACEi.

Losartan in HF

The ELITE II trial was a superiority trial that evaluated 3,152 participants who were at least 60 years of age, had NYHA class II–IV symptoms, and a LVEF ≤ 40%, and randomized them to receive either losartan (Cozaar®) 50 mg daily or captopril 50 mg three times daily (TID).[21] This study found no significant difference between groups in the primary end point of all-cause mortality (HR= 1.13; 95% CI 0.95-1.35; p=0.16) (**Table 4**). Also, no significant differences were found for sudden death or resuscitated cardiac arrest (HR=1.25; 95% CI 0.98-1.50; p=0.08), hospitalizations for any reason (HR=1.04; 95% CI 0.94-1.16; p=0.45), or hospitalizations due to HF (HR=0.92; 95% CI 0.78-1.08; p=0.32) (**Table 5**). The ADE rate was higher in the captopril group compared to the losartan group (p<0.001).[21] This trial demonstrated the potential role of losartan in HF due to its non-inferiority finding on all-cause mortality compared to captopril.

The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) trial examined 5477 patients who were ≥ 50 years old with acute MI and evidence of HF or an LVEF < 35%.[22] Approximately 80%of patients (n=4417) met the criteria to be classified as having HF using AHA/ACC guidelines[2] and more specifically an LVEF < 35%. Patients were randomized to receive losartan 50 mg daily or captopril 50 mg TID. In terms of the primary outcome, all-cause mortality, there was no difference observed between groups (RR=1.13; 95% CI 0.99–1.28; p=0.069) (**Table 4**). However, the upper one-sided limit of 1.28 in the CI was higher than the predetermined acceptance rate of 1.10 to be considered non-inferior. The results also found no significant difference between groups in sudden cardiac death or resuscitated cardiac arrest (RR=1.19; 95% CI 0.99–1.43; p=0.072) (**Table 3**) and fatal/non-fatal MI (RR=1.03 (0.89–1.18); p=0.722) (**Table 3**). The authors concluded that losartan was not non-inferior to captopril in the reduction of all-cause mortality, but if further studied this medication might show benefit, specifically with CV mortality.[22]

The Heart Failure endpoint evaluation of the AII-antagonist losartan (HEAAL) Trial studied 3846 patients with HF (NYHA class II–IV) and a LVEF ≤ 40% who were intolerant to an ACEi.[23] Patients were randomized to receive losartan 25 mg daily titrated over three weeks to a target dose of 150 mg or 50 mg daily, as tolerated. In the 150 mg group, the average dose after titration was 129 mg compared to 46 mg in the group randomized to 50 mg a day. The primary end points for this trial were death or admissions for HF. Losartan 150 mg reduced the rate of the primary outcome compared to losartan 50 mg (HR=0.90; 95% CI 0.82-0.99; p=0.027). The study also found that patients in the 150 mg group had fewer cardiovascular deaths and admissions for HF then those in the 50 mg group (HR=0·88; 95% CI 0.79–0.97; p=0.011). There was no difference in all cause death or all-cause hospital admission between groups (HR=0.95; 95% CI 0.88–1.03; p=0.24). Importantly, the ADE rate was not significantly different between the two groups (p=0.44). Compared to OPTIMALL[22] and ELITE II[21], the HEAAL trial demonstrated that titrating losartan up to 150 mg can be more beneficial than 50 mg QD.[23]

Irbesartan in HF

The Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-Preserve)[11] trial evaluated the use of irbesartan (Avapro®) in patients with a LVEF ≥ 45% (preserved ejection fraction), experienced a HF hospitalization in the previous 6 months, and who had a NYHA class II, III, or IV diagnosis. This study included 4,128 participants that were randomized to receive irbesartan at a target dose 300 mg daily, or placebo. Participants started on 75 mg of irbesartan the titrated up to target dose over 2-4 weeks as tolerated; the mean dose reached was 227 mg. The study found no significant difference in the primary outcomes of all-cause death (HR=1.00;

95% CI 0.88-1.14; p=0.98) (**Table 4**) or hospitalizations for a cardiovascular cause and (HR= 0.95; 95% CI 0.85-1.08; p=0.44) (**Table 5**).[11] When the outcomes were combined there continued to be no difference between groups (HR= 0.95; 95% CI (0.86-1.05); p=0.35). The I-Preserve trial's findings are consistent with the CHARM-Preserved trial,[10] suggesting that there appears to be no benefit using an ARB in preserved HF.

Differences between ARBs in HF

It does not appear that all ARBs are equal when it comes to the treatment of HF, evidenced by the differences in outcomes from published trials. Candesartan and valsartan are good alte natives to an ACEi based on the CHARM-Alternative[20] and Val-Heft/VALIANT trials when an ACEi cannot be tolerated.[13,14] Results from the OPTIMAAL,[22] ELITE,[21] and HEAAL[23] studies suggest that losartan may have a role in the therapy of HF, but at this time it has not been approved for the treatment of HF by the FDA. Candasartan and losartan are the only ARBs shown to be non-inferior to an ACEi in both all-cause mortality and risk for HF hospitalizations.[21,24,14] Valsartan has been shown to lower hospitalizations for HF, but it was not as beneficial as an ACEi in reducing all-cause mortality.[13,14] It is proposed that because ACEi reduce the breakdown of bradykinin, unlike ARBs, increased bradykinin levels could have a positive effect on ventricular remodeling,[11] which may explain why ACEis have more compelling data in the reduction of mortality in patients with HF. The ACC/AHA continues to recommend the use of an ACEi over an ARB, but when an ARB is needed, only those with data in HF, such as candesartan and valsartan, should be used.[3]

References

1. Roger VL, Go AS, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011 Feb 1;123(4):e18-e209.
2. Bian B, Kelton CM, Guo JJ, Wigle PR. ACE Inhibitor and ARB utilization and expenditures in the Medicaid fee-for-service program from 1991 to 2008. J Manag Care Pharm. 2010 Nov-Dec;16 (9):671-9.
3. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2005 Sep 20;46(6):e1-82.
4. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008 Oct;10(10):933-89.
5. DIOVAN (valsartan) tablet [Package Insert]. Novartis Pharmaceuticals Corporation; Revised 2011, Bethesda, MD.
6. ATACAND (candesartan cilexetil) tablet [Package Insert]. AstraZeneca LP; Revised 2011, Bethesda, MD.
7. AVAPRO (irbesartan) tablet [Package Insert]. Bristol-Myers Squibb Company; revised 2011, Bethesda, MD.
8. COZAAR (losartan potassium) tablet [Package Insert].Cardinal Health; Revised 2011, Bethesda, MD.
9. Meune C, Wahbi K, Duboc D, Weber S. Meta-analysis of Renin-Angiotensin-aldosterone blockade for heart failure in presence of preserved left ventricular function. J Cardiovasc Pharmacol Ther. 2011 Sep-Dec;16(3-4):368-75.
10. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003 Sep 6;362(9386):777-81.
11. Massie BM, Carson PE, McMurray et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008 Dec 4;359(23):2456-67.
12. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008 Apr 10;358(15):1547-59.
13. Cohn JN, Tognoni G; Valsartan HF Trial Investigators (Val-Heft). *A randomized trial of the angiotensin-receptor blocker valsartan in chronic HF*. N Engl J Med. 2001 Dec 6;345(23):1667-75.
14. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan in Acute Myocardial Infarction Trial Investigators (VALIANT). Valsartan, captopril, or both in myocardial infarction complicated by HF, left ventricular dysfunction, or both. N Engl J Med. 2003 Nov 13;349 (20):1893-906.
15. J.N. Cohn. Val-HeFT: changing the heart failure horizon. Eur. Heart J. Suppl. 2003 5: C25-C28.
16. Lee YS, Kim KS, Lee JB, Ryu JK, et al. Effect of valsartan on N-terminal pro-brain natriuretic Peptide in patient with stable chronic HF: comparison with enalapril. Korean Circ J. 2011 Feb;41(2):61-7.
17. Anand IS, Deswal A, Kereiakes DJ, et al. Comparison of once-daily versus twice-daily dosing of valsartan in patients with chronic stable HF. Vasc Health Risk Manag. 2010 Aug 9;6:449-55
18. Pfeffer MA, Swedberg K, Granger CB, CHARM Investigators and Committees, et al. Effects of candesartan on mortality and morbidity in patients with chronic HF: the CHARM-Overall programme. Lancet. 2003 Sep 6;362(9386):759-66.
19. McMurray JJ, Ostergren J, Swedberg K, CHARM Investigators and Committees, et al. Effects of candesartan in patients with chronic HF and reduced left-ventricular systolic function taking angiotensin- converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003; 362: 767–771.
20. Granger CB, McMurray JJ, Yusuf S, CHARM Investigators and Committees et al. Effects of candesartan in patients with chronic HF and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003; 362: 772–776.
21. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic HF: randomised trial--the Losartan HF Survival Study ELITE II. Lancet. 2000 May 6;355(9215):1582-7.
22. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group.Lancet. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myo-

cardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet.2002 Sep 7;360(9335):752-60.
23. Konstam MA, Neaton JD, Dickstein K, HEAAL Investigators et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with HF (HEAAL study): a randomised, double-blind trial. Lancet. 2009 Nov 28;374(9704):1840-8.
24. Konstam MA, Poole-Wilson PA, Dickstein K, et al. Design of the HF endpoint evaluation of AII-antagonist losartan (HEAAL) study in patients intolerant to ACE-inhibitor . Eur J Heart Fail. 2008 Sep;10 (9):899-906.

Clinical Trial Update

Title [1]– Effect of Aspirin on Vascular and Nonvascular Outcomes: Meta-analysis of Randomized Controlled Trials: The benefits of aspirin (ASA) for secondary prevention of cardiovascular (CV) events such as myocardial infarction (MI) and CV disease (CVD) is well documented. However, in patients without established CVD, it is uncertain whether the potential benefits of ASA therapy outweigh the potential risks, most notably the risk for bleeding.

Seshasi et al. performed a meta-analysis to investigate the benefits of ASA therapy in patients without established CVD. To be included in the meta-analysis, eligible studies had to be randomized placebo controlled trials, enroll at least 1000 participants without a history of coronary heard disease (CHD) or stroke, have at least one year of follow-up, have CVD events as the main outcomes (i.e. CHD, stroke, heart failure, cerebrovascular disease, and peripheral arterial disease), and provide information on bleeding events. Secondary prevention trials, trials that were mixed primary and secondary prevention trials, or trials that compared ASA to another antiplatelet agent were excluded. Nine trials met eligibility criteria which included 102,621 participants and approximately 700,000 person-years at-risk for analysis.

The primary outcomes were total CHD mortality and total cancer mortality; only the CHD results will be discussed here. The authors noted a heterogeneous definition for major bleeding used in the included studies and categorized their primary safety outcome as "clinically nontrivial bleeding." which included fatal bleeding from any site, cerebrovascular or retinal bleeding, bleeding from hollow viscus, bleeding requiring hospitalization and/or transfusion, or study-defined major bleeding.

The effects of aspirin were calculated using unadjusted odds ratios (ORs) for each study, which were then combined using random-effects meta-analysis; the I^2 statistic was used to quantify heterogeneity between studies. Number needed to treat (NNT) and number needed to harm (NNH) were calculated and represented the number of persons that would need to be treated with ASA for 6 years to avoid or experience an outcome event, respectively.

A total of 2169 CHD events were observed during approximately 700,000 years of person-years at-risk; 1540 events were classified as a non-fatal MI while 592 were classified as fatal CHD events. ASA was associated with a 10% reduction in total CVD events, driven by a 20% reduction in risk for non-fatal MI. CV death however was not significantly reduced compared to placebo (OR 0.99); the NNT was 120 for CVD events. In total, 40,712 bleeding events were observed (OR 1.70), of which 10,049 were categorized as clinically nontrivial bleeding events (OR 1.31) (Table). The NNH was 73 for nontrivial bleeding.

Notably, effects of ASA on non-fatal MI or total CVD events was not dose related, nor was any difference in effect observed between sexes.

The authors concluded that the reduction in CVD events with ASA was outweighed by the increased risk for bleeding, and therefore ASA therapy in people without prior CVD is not warranted and treatment should be considered on a patient-by-patient basis.

Event rate per 1000 person-years of follow-up

Event	ASA	Placebo
Nonfatal MI	4.1	5.1
Total CVD Events	12.8	14.1
CVD Mortality	3.9	4.0
All-cause mortality	11.0	11.7
Total Bleeding	36.0	21.2
Nontrivial Bleeding	9.7	7.4

ASA: aspirin; CVD: cardiovascular disease

1. Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of Aspirin on Vascular and Nonvascular Outcomes: Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2012 Jan 9. [Epub ahead of print].

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research
University of Florida