What's the scoop on ACEI & ARB combinations causing harm?
(Picked up by the media: CBC, CTV, Globe & Mail, etc. Jan 16, 2009)

We have had a few questions today (Jan 19, 2009) on the media concerns raised regarding ACEI & ARB combinations leading to increased harm. A warning was released from the Heart and Stroke Foundation of Canada.[1] This information appears to be based on the recent 2009 hypertension guideline recommendations (CHEP).[2] The concerns largely come from results of the ONTARGET trial published in 2008. Previous trials also offer some information on possible harm versus benefit. In this Q&A, we are briefly summarizing some of the related information. The ONTARGET trial summary was included in our Hypertension Trials chart from Oct 08, which was included in our 7th Edition Drug Comparison Charts book. Guideline comments and related information from our book is included below.

Quick note:

- ACEI+ARB combinations often offer no additional outcome benefit, but increased adverse effects when used solely for hypertension. (Limited benefits noted in select patients with nephropathy or heart failure.)
- If choosing either an ACEI or an ARB, in someone who tolerates both: consider extensive outcome evidence (especially cardiovascular) and lower cost with ACEI. ARBs generally equivalent at high dose. Target ACEI doses for HF & Post-MI generally towards the higher end of the dosage range if tolerated.

ACE + ARB Combination Therapy Issues

1) What's new in the 2009 Canadian Hypertension Guidelines (ACEI+ARB)
http://hypertension.ca/chep/wp-content/uploads/2009/01/2009-short-clinical-summary-final-1.pdf

In 2008 there were several new clinical trials of interest to clinicians. The ONTARGET trial found that an ACE inhibitor or an angiotensin receptor blocker had similar cardiovascular outcomes when prescribed to people with cardiovascular disease or type II diabetes[3,4]. The ONTARGET trial also found that while the combination of an ACE inhibitor with an angiotensin receptor blocker had some extra blood pressure lowering it had ***more side effects*** *such as* ***hyperkalemia***, ***hypotension*** *and* ***renal impairment*** *and did not improve patient outcomes compared to the ACE inhibitor alone. In people with stage 3 chronic kidney disease (GFR > 30 ml/min) the combination of an ACE inhibitor with an ARB reduced urine protein levels but did not reduce cardiovascular outcomes and did* ***increase adverse renal outcomes*** *including the need for acute dialysis compared to the ACE inhibitor alone[4].*

The only data to support improved patient outcomes from the combination of an ACE inhibitor with an angiotensin receptor blocker is in people with heart failure where the combination reduces recurrent hospitalization. There are ongoing trials of combination of an ACE inhibitor with an angiotensin receptor blocker in people with chronic kidney disease and diabetes. Hence ***the use of combination of ACE inhibitor and ARB therapy should only be considered in selected*** *and closely monitored people with* ***advanced heart failure or proteinuric nephropathy*** *(table 1). For people already on the combination and stable, clinicians need to consider that prescribing just one of the two classes reduces cardiovascular events to the same extent and that other therapeutic regimes have the potential to reduce cardiovascular events and blood pressure to a greater degree.*

2) RxFiles statement on ACE + ARB Combinations:

- **ACEI+ARB**: no better CV benefit & ↑SE ↓BP, ↑K+, & worse renal outcomes in hypertension trial: Ontarget; small benefit in proteinuria Calm,Cooperate & persistent HF Charm; but ↑SE & no greater efficacy MI trial; VALIANT.

◆ONTARGET Summary (from RxFiles 7th Ed. http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-HTN-trial-summary.pdf)

Ontarget [3,] 56 months, n=25,620	**Ramipril** 5mg od x 2wk → 10mg od **vs Telmisartan** 80mg od **vs Combo of each**	↑**BP 142/82; high risk** with vascular disease or (diabetes with end organ damage), but **without** heart failure; BMI ~28 **Age ~ 66yr, (diabetes ~38%)**	Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema NNT=500, 0.1 vs 0.3% & cough NNT=33 , 1.1 vs 4.2%, but more hypotension NNH=112, 2.6 vs 1.7% symptoms. The combination of the two drugs was associated with more adverse events leading to discontinuation NNH=24 vs ramipril (hypotension NNH=33, diarrhea, syncope, renal dysfunction NNH=31, 13.5 vs 10.2%, & ↑ potassium NNH=45) without an ↑ in benefit. Ramipril lowered BP less than comparators, but had equal clinical benefit. A substudy suggests ↑ CV death in diabetics with SBP<130. (However, telmisartan fared no better than placebo on the primary outcome, in the TRANSCEND trial n=5926 56months in patients at high risk of CV disease unable to tolerate ACEIs)

BP=Blood pressure **HF**=heart failure **K**=potassium **SE**=side effect

1) Heart & Stroke Foundation Warning: http://www.heartandstroke.sk.ca/site/apps/nlnet/content2.aspx?c=inKMILNlEmG&b=3658009&ct=6634669&src=home

Blood-pressure drug alert issued- Heart and Stroke Foundation warns about dangers of combining two medications The Globe and Mail Jan 17,2009. Stressed that severe complications were rare, but said there is no justification for putting patients at risk when there is no additional benefit.

2) Canadian Hypertension Education Program (CHEP) 2009 Guidelines: http://hypertension.ca/chep/wp-content/uploads/2009/01/2009-short-clinical-summary-final-1.pdf

Additional References

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3) [i] Yusuf S, Teo KK, Pogue J, et al for the ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008: 358:1547-1559. The angiotensin-converting enzyme inhibitor (ACEI) ramipril and the angiotensin receptor blocker (ARB) telmisartan are equally effective for secondary cardiovascular prevention. The combination of both drugs is no more effective and causes more adverse effects at greater cost. ACEIs should remain the drug of choice for secondary prevention in high risk cardiovascular patients unless the drug is not tolerated because of angioedema or cough, in which case ARBs provide an effective alternative. (LOE = 1b).

4) Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, et al.; ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008 Aug 16;372(9638):547-53. In people at high vascular risk, telmisartan's effects on major renal outcomes are similar to ramipril. Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes.

The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008 Aug 29.

Mogensen CE, Neldam S, Tikkanen I, Oren S, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000;321:1440-4.

Nakao N, Yoshimura A, Morita H et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 2003;361:117-24.

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 heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003 Nov 13;349(20):1893-906. Epub 2003 Nov 10. (McMurray J, et al. The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol. 2006 Feb 21;47(4):726-33. Epub 2006 Jan 26.)

CHARM Trial Summary 2003: ARBS in HF http://www.rxfiles.ca/rxfiles/uploads/documents/CHARM-Comments.pdf

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ARBs in HF: Excerpt from RxFiles CHARM Comments Dec 2003

ARBs Added to ACEIs – CHARM Added [3] (n=2,548)

- Consider in context that CHARM results are conflicting with other studies (ValHeFT, VALIANT)
- CHARM supports possible cardiovascular benefit of ACEI + ARB combination; however adverse events also ↑'d
- *For every **25** patients treated with candesartan+ACEI for **3.4 years**, there was 1 less **CV death or CHF admission***
- **ACEI doses were often lower than usual recommended heart failure target dose** (**HFTD**) from outcome trials:

enalapril 16.8mg/day	(HFTD ~ **20**-40mg/day [V-HeFT II, SOLVD])
lisinopril 17.7mg/day	(HFTD ~ **35**mg/day better than 5mg/day [**ATLAS** trial])
captopril 82.2mg/day	(HFTD ~ **150**mg/day [SAVE, OPTIMAAL])
ramipril 6.8mg/day	(HFTD ~ **10**mg/day [AIRE])

Several outcome trials showing ACEI benefits in HF have used higher target doses. Whether it is better to pursue the higher ACEI target doses or moderate ACEI doses in combination with an ARB is yet unanswered.

- **Adverse event rates** were always significantly higher in the overall candesartan group (this is especially relevant in the subgroup(s) where benefits were questionable or marginal).

↑ doubling of SCr	6.2% vs 3%	p=<0.0001
↑ hyperkalemia	2.2% vs 0.6%	p=<0.0001
↑ any AE or lab abnormality	21% vs 16.7%	p=<0.0001

- **Target dose** of candesartan was high (**32mg/day**); mean dose achieved at 6 months (24mg/day)
  Note: Losartan 50mg OD was not superior [ELITE II] & less effective [OPTIMAAL] to captopril 50mg TID in heart failure patients and post-MI patients respectively (subtherapeutic dose?)
- **VALIANT** [5] (n=14,808): 1) valsartan 160mg BID as effective as captopril 50mg TID in post-MI patients; 2) combination of valsartan [80mg BID] + captopril [50mg TID] resulted in an increase in adverse events without improving survival.
  {Captopril caused more cough, rash & taste disturbance; Valsartan caused more hypotension & renal dysfunction. The combination regimen resulted in more frequent discontinuation vs captopril alone as follows: hypotension 1.9% vs 0.8%, renal cause 1.3% vs 0.8%, any adverse event 9% vs 7.7%.}

- Adding ARBs to HF patients on β-blockers was not harmful in CHARM trial, a concern raised in previous trials.
- Combining ACE + ARB helped patients reduce proteinuria in the CALM & COOPERATE trial

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