ARBs in HEART FAILURE (HF) – Observations on CHARM Data

ARBs – CHARM-Overall study [1] (n=7601)

CHARM Overall – 1° Outcome {in HF patients already treated with conventional therapy e.g. ACEI, β-blocker, spironolactone, statin, ASA, etc}	Candesartan	Placebo	
All-cause mortality over 3.1 years	23.3%	24.9%	p=<0.055 unadjusted

- *For every **63** heart failure patients treated with candesartan for **3.1 years**, there was 1 less **death from any cause**.*

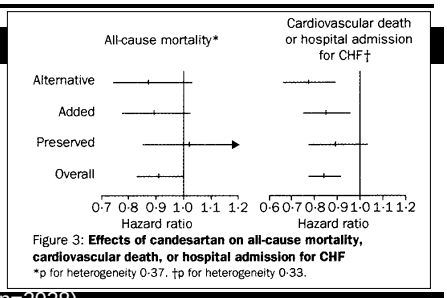

Figure 3: **Effects of candesartan on all-cause mortality, cardiovascular death, or hospital admission for CHF**
*p for heterogeneity 0·37. †p for heterogeneity 0·33.

ARBs in ACEI Intolerant patients – CHARM-Alternative study [2] (n=2028)

- **There is good evidence to support benefits of ARBs in HF patients intolerant to ACEIs** CHARM-Alternative; ValHeFT
- *For every **14** patients treated with candesartan for **2.75 years**, there was 1 less **CV death or CHF admission***

ARBs Added to ACEIs – CHARM Added [3] (n=2548)

- 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.

ARBs in Patients with Preserved LVF (>40%) – CHARM Preserved study [4] (n=3023)

- Key finding is that **none of the major outcomes in this study were statistically significant**!
- To put a positive spin on this sub-study, the "trend toward reduction CV death/CHF hospitalizations" is noted; however, there was no effect on all-cause hospitalizations or CV death and there was also a trend toward an increase in all-cause mortality in the candesartan group. (Which trend is most important?)
- Authors conclusion: "a moderate benefit, based on statistically borderline results".

Other Factors to Keep in Mind

- **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).

Adverse Events causing discontinuation	Candesartan	Placebo	
↑ SCr (e.g. doubling of SCr)	6.2%	3.0	p=<0.0001
↑ K+ (e.g. $K^+ > 6_{mmol/L}$)	2.2%	0.6%	p=<0.0001
Any adverse event / lab abnormality	21.0%	16.7%	p=<0.0001

FYI

Candesartan	Cost/Month
24mg po OD	$65
32mg po OD	$84

- **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 trials

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