ACCOMPLISH [1,2]: ACEI + Amlodipine vs ACEI + Hydrochlorothiazide in High Risk Hypertensives

- Trial: n=11,506; 36months (mean follow-up); an international multi-center, Novartis funded RCT to evaluate two combination antihypertensive approaches on CV outcomes in high CV risk patients (mostly white overweight Americans with CHD &/or DM but not HF). Trial halted early after mean of 3 yrs.
- Treatment studied: **benazepril** LOTENSIN 20→40mg Mean ~36mg **+ amlodipine** NORVASC 5→10mg daily Mean ~7.7mg (n=5744) Lotrel in USA **vs**
  benazepril 20→40mg Mean ~36mg **+ hydrochlorothiazide** (HCT) 12.5→25mg daily Mean ~19mg (n=5762) Lotensin HCT in USA
  {Following max doses of studied drugs, add on therapy could include β-blockers, α-blockers, clonidine, spironolactone & loop diuretics. Lack of info on 3rd drug limits interpretation.}
- Population: ♂~60% or ♀, any ethnicity white 84%; American 71%. Age mean: 68. Target BP: <140/90 mmHg or <130/80 mmHg if diabetes/renal disease
- Inclusion criteria: **A)** age ≥60 with hypertension (HTN): SBP≥160mmHg or currently on antihypertensive therapy and evidence of cardiovascular or renal disease or target end organ damage and 1 of the following: previous MI, stroke/TIA, previous hospitalization for unstable angina, coronary revascularization, peripheral arterial occlusive disease, diabetes (DM), left ventricular hypertrophy, or renal events (SCr>133umol/L ♀, 150umol/l ♂, or macroalbuminuria) OR **B)** age 55-59 if evidence of ≥2 or more CV diseases or target organ damage
  {Demographics: prior MI 23% & stroke/TIA 13%, previous hospitalization for unstable angina 11% & coronary revascularization 36%, smoking 11%, CrCl <60 ml/min 18%, renal disease 6%, DM 60%, LVH 13%, Dyslipidemia 75%, A. fib 7%. BP change: (amlodipine arm BP~145/80→131.6/73.3 mmHg; HCT arm BP~145/80→132.5/74.4 mmHg); amlodipine ↓ BP 0.9/1.1 mmHg more than HCT; [97% on previous BP meds & 75% on ≥2 antihypertensives, but only 37% controlled BP <140/90].
  Baseline drugs: on ASA ~65%, lipid agents ~68%, β-blockers ~48%. Cholesterol Total (mean 4.8 mmol/L), HDL (mean 1.3 mmol/L); BMI=31 kg/m2; Wt=89kg; glucose 7 mmol/L; Scr 88 umol/L}
- Exclusion criteria: angina prior 3months, HF or left ventricular EF <40%, MI/ACS/coronary revascularization in prior 1month, stroke/ischemic event prior 3month, severe/refractory HTN, or other illnesses, physical impairments or mental condition that may interfere with study

Table 1: ACCOMPLISH results:

Endpoints Recruitment Oct03-May05; Trial halted after a mean follow-up of 3 years	ACEI + Amlodipine % n=5744	ACEI + HCT % n=5762	ARR %	RRR %	NNT/ 3yrs	p value
1° CV death, non fatal MI & stroke, hospitalization for angina, resuscitation after sudden cardiac arrest & coronary revasc.	9.6 (552 events)	11.8 (679 events)	**2.2**	**18.4**	**46** 95% CI: 30-96	<0.001
2° CV death, non fatal MI & stroke (HOPE 1° Endpoint)	5.0 (288 events)	6.3 (364 events)	**1.3**	**21**	**77** 95% CI: 47-218	0.002
2° coronary revascularization	5.8	6.7	**0.9**	**14**	**113**	0.04
2° fatal & non-fatal MI	2.2	2.8	**0.6**	**21**	**171**	0.04
2° fatal & non-fatal stroke	1.9	2.3	0.4	17	NS	0.17
2° hospitalizations for heart failure	1.7	1.7	-	-	NS	0.77
2° CVD mortality	1.9	2.3	0.4	17	NS	0.08
2° mortality-all cause	4.1	4.5	0.4	9	NS	0.24
Discontinuation due to adverse events	13.4	14.3	0.9	6.3	NS	0.6

Both arms: cough (ACEI) in ~20%, hyperkalemia in 0.6% ; Amlodipine arm: ↑edema 31.2% vs 13.4%; HCT arm : ↑dizziness 20.7 vs 25.4%, hypotension 2.5 vs 3.6% & hypokalemia 0.1 vs 0.3%.

1°=primary outcome 2°=secondary outcome ABPM=ambulatory BP monitoring ARR=absolute risk reduction BP=blood pressure CV=cardiovascular EF=ejection fraction HCT=Hydrochlorothiazide HF=heart failure HTN=hypertension LVH=left ventricular hypertrophy MI=myocardial infarction NNT=number needed to treat to benefit 1 patient NS=not significant RRR=relative risk reduction

Of Note:

- Adverse Events: amlodipine arm worse for edema; HCT arm worse for dizziness & hypokalemia. {Angioedema 0.9% in amlodipine arm}
- BP control - achievement of target BP: ACEI + amlodipine arm 75%; ACEI + HCT arm 72%. (Initial BP control only in ~37%, both arms)
- Hospitalization for HF same for 'ACEI + amlodipine' & 'ACEI + HCT'; high dose of ACEI +/- furosemide may account for these results.

CUT TO THE CHASE: WHERE DOES THIS TRIAL LEAVE THIAZIDE DIURETICS?

- This trial suggests that an ACEI+amlodipine combination may be preferred to an ACEI+HCT combination in ACCOMPLISH type patients.
  - Magnitude of benefit: ⇨1° endpoint (including the softer endpoints): 1 person benefited for every 46 patients treated over 3 years.
    ⇨For typical major CV endpoints: 1 less non-fatal MI/stroke or CV death for every 77 patients treated over 3 yrs
- HOWEVER, there are some important qualifiers given the ACCOMPLISH trial design:
  - HF patients were excluded, and HF outcomes were worse with amlodipine compared to the thiazide & ACEI in ALLHAT[3]
  - The ACEI+amlodipine arm had greater BP reduction leading to question of whether BP control or specific drugs had greater role in outcome.
    {Amlodipine: benefit similar to thiazide or ACEI in ALLHAT; better than thiazide + β-blocker in ASCOT-BPLA[4]; not beneficial for renal outcomes AASK & IDNT (5, 6),}
  - Best thiazides evidence currently lies with chlorthalidone & indapamide (ALLHAT, Elderly>60yr HYVET, ISH SHEP, Stroke/TIA PROGRESS)[7,8,9];
    ⇨Potential differences between HCT and chlorthalidone: [10,11,12]
    - There is evidence that chlorthalidone doses of 12.5-25mg are ~2x more potent/effective than that HCT doses of 12.5-25mg
    - The duration of effect with HCT is shorter than that for chlorthalidone. Although reported BP differences are small, timing of the HCT administration & BP measurement may be factors. An ambulatory BP monitoring (ABPM) substudy is awaited to see if actual BP differences were greater than reported.
- Cost considerations: Thiazides have cost-effective role for both initial & add-on therapy: benazepril 40mg + HCT 25mg daily $600/yr
  Annual Cost: HCT 25mg/day: $48 vs Amlodipine 10mg/day: $900 benazepril 40mg + amlodipine 10mg daily $1450/yr
- Practically, physicians may sometimes use an ACEI/low-dose thiazide combination in addition to a CCB (amlodipine) rather than automatically maximizing dosages of just two agents. The trial does not offer any insight on this common management alternative.

Take Home: An ACEI (benazepril) + amlodipine is a reasonable combination option in some patients with HTN & additional risk factors. In ACCOMPLISH type patients it appeared to be better than an ACEI + HCT combination; magnitude of benefit on major CV outcomes non-fatal MI/stroke, CV death was an absolute risk reduction of 1.3% (NNT=77 / 3 years). There was no difference in CV or all-cause mortality. This result should be interpreted in context of design limitations and previous trial evidence where thiazides have done well. Difference in BP reduction may partly explain the result, and actual differences may have been greater due to timing of HCT and BP measurement (further ABPM analysis awaited). Choice of antihypertensive should be based on compelling indications (comorbidities e.g. HF, post-MI, asthma, diabetes, nephropathy), contraindications & patient factors (race, side effects, cost). Combination antihypertensive regimens can dramatically achieve BP targets & offer benefit in a high percentage of patients.

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Essential Evidence Plus: "This study of patients with coronary disease or coronary disease equivalents, the combination of benazepril and amlodipine provided a small benefit in terms of the composite cardiovascular outcome. However, it did not reduce all-cause mortality or cardiovascular mortality. These findings should not prompt a change in our usual management of hypertension, since this was a very-high-risk group of older patients. We should not change our practice to adopt this much more expensive alternative for high-risk patients unless another study confirms these " findings, which run somewhat counter to those of ALLHAT. (LOE = 1b) "

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