Management of Difficult or Resistant Hypertension in General Practice

(Role of the Hypertension Clinic?)
“Thiazide diuretics have a flat dose-response curve so there is no point in pushing up the dose in patients who don’t have a satisfactory response to low doses…”

Right or wrong?
WRONG!

… at least at the doses commonly used in New Zealand

Hydrochlorothiazide 12.5mg (as in *Inhibace Plus* and *Accuretic*) and bendrofluazide 2.5mg are (often) ineffective doses, but doctors are sometimes unwilling to increase them.

The most effective thiazide(-like) antihypertensive drug is chlorthalidone which is dosed at 12.5 or 25mg daily.

12.5mg chlorthalidone is approximately equipotent with 25mg hydrochlorothiazide or 5mg bendrofluazide (and this 25mg similar potency to 50mg HCTZ and 10mg BFZ).

(Chlorthalidone has other advantages over the other drugs though including a much longer $\frac{1}{2}$ life).
Practical Approach to combination therapy (over 55-60 years)

(allow minimum of 2 weeks between dose adjustments)

Thiazide ½ dose (eg chlorthalidone 12.5mg)

↓

Not at target

add ACE-inhibitor ½ dose (eg cilazapril 2.5mg)

↓

Not at target

Up thiazide to full dose (chlorthalidone 25mg)

↓

Not at target

Up ACE-inhibitor to full dose (cilazapril 5mg)

↓

Not at target

Add CCB ½ dose (eg amlodipine 5mg)

↓

Not at target

Up CCB to full dose (eg amlodipine 10mg)
Practical Approach to combination therapy (under 55-60 years)

(allow minimum of 2 weeks between dose adjustments)

ACE-inhibitor ½ dose (eg cilazapril 2.5mg)
\[ \downarrow \]
Not at target
Up ACE-inhibitor to full dose (cilazapril 5mg)
\[ \downarrow \]
Not at target
Thiazide ½ dose (eg chlorthalidone 12.5mg)
\[ \downarrow \]
Not at target
Add CCB ½ dose (eg amlodipine 5mg)
\[ \downarrow \]
Not at target
Up thiazide to full dose (chlorthalidone 25mg)
\[ \downarrow \]
Not at target
Up CCB to full dose (eg amlodipine 10mg)
If initial BP > 160 +/- 100
Start first 2 drugs simultaneously
Definition of Resistant Hypertension

BP **Not at Target** (<140/90 or 130/80 in DM, CKD or TOD)

despite

**Full Doses** of

a **Minimum** of **3**

**Complementary** Drugs

one of which is a **Diuretic**
**JNC 7 Guidelines (2003)**

**Classification of Blood Pressure**

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>or</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>or</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>or</td>
</tr>
<tr>
<td>Stage 2</td>
<td>&gt; 160</td>
<td>or</td>
</tr>
</tbody>
</table>
Compelling indications for individual drug classes

- Compelling Indication
  - Heart failure
- Post myocardial infarction
- High CVD Risk
- Diabetes
- CKD
- Recurrent Stroke Prevention

- Initial therapy options
  - Thiaz/BB/ACEI/ARB/Aldo Ant
  - BB/ACEI/Aldo Ant
  - Thiaz/BB/ACEI/ARB/CCB
  - Thiaz/BB/ACEI/ARB/CCB
  - ACEI/ARB
  - Thiazide/ACEI
JNC-7 Blood Pressure Treatment
Treat to BP < 140/90 or < 130/80 in pts with diabetes or CKD
Start with lifestyle modifications

Without Compelling Indications
Stage 1
Thiazide for most

Stage 2
Thiazide + ACE-I ARB, BB, or CCB

With Compelling Indications
Drug(s) for compelling indications

↓
Not at goal BP
Optimise dosages or add additional drugs until goal BP achieved

Most people will require at least 2 drugs
High blood pressure affects about 26% of adult population
26% of (say) 3.8 million = 988 000

Up to 1/3 of these are undiagnosed or untreated (329 000)

Of the 2/3 who are treated, up to 1/3 are not at target BP (219 600)

Thus – nearly 550 000 untreated or undertreated
• Continuum of increasing CV risk from SBP 115mmHg
• CV mortality doubles for every 10/5 increase in BP > 120/70mmHg
• High BP causes
  - 35% of all cardiovascular deaths
  - 50% of all stroke deaths
  - 25% of all CAD deaths
  - 50% of all congestive heart failure
  - 25% of all premature deaths
  - commonest cause of CKD overall and commonest cause of ESRD in older individuals
Causes of Resistant Hypertension

• Suboptimal drug therapy
• White coat hypertension (20%)
• Coexisting conditions – esp. obesity/metabolic syndrome/OSA
• Antagonising substances (usually sodium)
• Non-compliance
• Coexisting medications – eg NSAID’s, OCA
• Unrecognised secondary causes of hypertension
Important Secondary (identifiable) Causes of Hypertension

- Sleep apnoea
- Drug induced/ related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Cushing’s Syndrome or steroid therapy
- Phaeochromocytoma
- Coarctation of the aorta
- Thyroid/ parathyroid disease
Causes of Resistant Hypertension

• Suboptimal drug therapy
• White coat hypertension (20%)
• Coexisting conditions – esp. obesity/metabolic syndrome/OSA
• Antagonising substances (usually sodium)
• Non-compliance
• Coexisting medications – eg NSAID’s, OCA
• Unrecognised secondary causes of hypertension
• 80-85% of the hypertensive population is overweight or obese

• A substantial minority of these individuals meet the criteria for “Metabolic Syndrome”

• Abdominal obesity carries the greatest risk

• Many obese hypertensives have coexisting OSA
### Ethnic Specific Values for Waist Circumference

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Waist circumference (as measure of central obesity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europids</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥94 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥80 cm</td>
</tr>
<tr>
<td><strong>South Asians</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥90 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥80 cm</td>
</tr>
<tr>
<td><strong>Chinese</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥90 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥80 cm</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥85 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥90 cm</td>
</tr>
<tr>
<td><strong>Ethnic South and Central Americans</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use South Asian recommendations until more specific data are available</td>
</tr>
<tr>
<td><strong>Sub-Saharan Africans</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use European data until more specific data are available</td>
</tr>
<tr>
<td><strong>Eastern Mediterranean and middle east (Arab) populations</strong></td>
<td>Use European data until more specific data are available</td>
</tr>
</tbody>
</table>
# Metabolic Syndrome Definitions

## WHO
- FPG > 6.1 or 2hr GTT > 11.1

**Plus at least 2 of:**
- Abdo obesity (W/H ratio > 0.9, BMI > 30, or waist girth > 94cm)
- TG > 1.7 or HDL < 0.9
- BP > 140/90 or on antihypertensives

## 2001 NCEP
- 3 out of 5 of:
  - Waist circ > 102cm (men) 88cm (women)
  - TG > 1.7
  - HDL < 1
  - BP > 130/85
  - FPG > 6.1

## IDF
- Increased waist circumference

**Plus at least 2 of:**
- TG > 1.7
- HDL < 1.03 (men) or 1.25 (women)
- BP > 130/85
- FPG > 5.6
Obese pt

- OSA
- Inflammation/oxidative stress
- Na/volume retention
- SNS activation
- Endothelial dysfunction
- Insulin + leptin resistance
- Renal dysfunction
- Other drugs causing hypertension
OSA

- Hypertension
- Atherogenic factors
- Insulin resistance
- Atrial fibrillation

Obesity
Causes of Resistant Hypertension

• **Suboptimal drug therapy**
  - White coat hypertension (20%)
  - Coexisting conditions – esp. obesity/metabolic syndrome/OSA
  - Antagonising substances (usually sodium)
  - Non-compliance
  - Coexisting medications – eg NSAID’s, OCA
  - Unrecognised secondary causes of hypertension
Commonest Cause of Resistant Hypertension

- Incorrect antihypertensive treatment

  - Commonest deficiency is Diuretic/s

    - No diuretic/ Not enough diuretic/ wrong Diuretic
For individuals aged > 55-60 years thiazide diuretic remains 1st choice antihypertensive for most

Exception is White patients < 55-60 years in whom an ACE-Inhibitor should be the first choice

Older individuals and blacks tend to have low renin volume-dependent hypertension and respond better to diuretics and CCB’s. Younger whites tend to have renin-driven hypertension and respond better to agents that interrupt the RAAS
Similarly

Long-term control of BP in patients on an ACE-inhibitor or ARB is highly dependent of the dose of diuretic

Drugs which block the RAAS or SNS convert the patient into a salt-sensitive individual who will respond in a dose-dependent fashion to a diuretic

“All” regimens containing > 2 drugs should “always” include a diuretic (and a diuretic is often the 2nd drug, even in individuals < 55 years)
Complementary Drugs

**R**
(RAAS +/- SNS blockade)
- Beta blockers
- ACE inhibitors
- ARB’s
- Clonidine
- Methyldopa

**V**
(Natriuretic +/- direct vasodilatation)
- Diuretics
  - Thiazide, loop, AA,K-sparing
- CCB’s
- Alpha blockers
- Minoxidil
**Some “Wrong” Combinations**

Beta blocker + ACE-inhibitor

Beta blocker + ARB

ACE inhibitor + ARB

**Some “Right” Combinations**

Thiazide + ACE inhibitor

Calcium channel blocker + ACE inhibitor

Beta blocker + alpha blocker
Drug Doses are as Important as Choice of Drug Combinations in Achieving BP Targets

Diuretics and ACE-Inhibitors are often underdosed

Cilazapril < 2.5mg daily, Quinapril and Enalapril < 20mg daily – often useless

Low dose thiazides – bendrofluazide 2.5mg, hydrochlorothiazide 12.5mg often ineffective – don’t be scared increasing doses, or (preferably in my view) swapping to chlorthalidone
Possible Problems with Diuretics

**Thiazides**

- Commonest problems are underdosing + failure to combine with a RAAS blocker
- Less effective at low GFR / GFR < 40 swap to chlorthalidone/ GFR < 30 swap to frusemide (BD dosing)
- Sometimes cause hyponatraemia in the elderly – replace with spironolactone or frusemide

**Loop diuretics**

- Frusemide too short acting to be a useful antihypertensive in general, but useful in CKD, either on it’s own or in combination with a thiazide

**Aldosterone Antagonists**

- Spironolactone both long-acting and potent – good alternative to thiazides when required. Main drawback is anti-androgenic side-effects in men (10%). Eplerenone free of anti-androgenic side-effects by not currently obtainable in NZ

**Potassium Sparing** (Amiloride + Triamterene)

- Fairly weak diuretics and only available in NZ in combination with thiazides
Are Beta Blockers Appropriate as Initial Therapy in Hypertension?

Beta blockers are effective anti-anginals and are clearly indicated post-MI where there is strong clinical trial evidence for their use in preventing reinfarction. Also improve outcomes in heart failure. Unclear however whether in the absence of these indications (in hypertension) they offer much cardioprotective effect. Cardioprotection was suggested by some early studies, but this has not been borne out in later studies, some even suggesting worse outcomes on beta blockers (including ASCOT, LIFE, and HOPE)

Recent Meta-analysis (Lancet 2005;366:895)

13 RCT’s, 106 000 pts - adverse outcomes associated with atenolol, but not other beta blockers. All beta blockers are associated with increased risk of stroke, but non-atenolol beta blockers (alone or in combination with diuretics) are not associated with increased risk of MI or all-cause death.
Current Place of Beta Blockers in Hypertension

- Presence of compelling indication/s (IHD, post MI, AF, heart failure)

- In absence of compelling indication add in as 3\textsuperscript{rd} or 4\textsuperscript{th} agent (after diuretic, ACE/ARB +/- CCB)

- (Possibly) as first-line agent in whites < 55 years if ACE-I/ARB-intolerant (or if resting tachycardia)
Survey of 31 Auckland (Procare) GP’s attending CME sessions on 7+8 August 2008

Do you have any patients in your practice with uncontrolled hypertension?  Yes 31 No 0

Do you have any difficulty accessing appropriate advice from specialist services for patients with difficult hypertension, or where you suspect an underlying secondary cause of hypertension?  Yes 29 No 1 No answer 1

Would you refer patients to a “quick turnaround” hypertension clinic? Yes 31 No 0

If so, how many patients would you refer annually?
1 1 2-5 21 >5 9
Aims of the clinic

- Achieve target BP in most patients
- Follow patients until BP at target on 2 consecutive visits
- Sort out and manage secondary (treatable) causes of hypertension
- Address general cardiovascular risk including lifestyle issues
Dr grades GP referral

Nurse arranges pre-investigations including ABPM if required/ on day of clinic pt arrives 30 mins before Dr appointment has several resting BP’s measured according to JNC-7 guideline

1 hour clinic review with Dr/ further investigations initiated +/-treatment changes made/ General CV risk including lifestyle issues reviewed

Fortnightly nurse-clinic visits to titrate medication increases according to parameters set by Dr until BP at target/ Further education on general CV risk and lifestyle issues + referrals to smoking cessation dietitian etc where appropriate

Final clinic review with Dr and discharge back to GP
Establishment of a Difficult Hypertension Clinic in Whangarei, New Zealand: the first 18 months
Walter van der Merwe

Abstract
A Difficult Hypertension Clinic was established at Whangarei Hospital (Whangarei, Northland, New Zealand) in March 2006 in response to a perceived need amongst general practitioners. The experience with the first 150 patients is reviewed. Mean BP at referral was 162/89 mmHg, and mean number of antihypertensive drugs was 2.49. Mean BP at discharge from the Difficult Hypertension Clinic was 138/78 mmHg and mean number of antihypertensive drugs 3.16.

The commonest cause of hypertension resistance was underprescription of diuretics. Secondary or contributory causes of hypertension were identified in 28 (19%) of patients, and white coat hypertension in three (2%). The Difficult Hypertension Clinic established in our hospital is an effective model for achieving clinical targets and care recommended in evidence-based guidelines.
150 new patients seen over 1\textsuperscript{st} 18 months

\downarrow

Mean age 58 years, mean referral BP 162/89 in patients taking a mean of 2.48 antihypertensive drugs

\downarrow

Discharge BP mean 138/78 and mean discharge meds 3.16 Average 2.7 Dr clinic visits and 2 nurse clinic (titration) visits

\downarrow

Commonest cause of hypertension resistance – underprescription of diuretics
Paired t-test P value < 0.00005
Treatment of Hypertension in Patients 80 years of Age or Older (HYVET Study)

In this study, patients 80 years of age or older with sustained systolic hypertension were randomly assigned to receive either the diuretic indapamide, with or without the angiotensin-converting-enzyme inhibitor perindopril, or matching placebos, for a target blood pressure of 150/80 mm Hg.
### Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Active Treatment (N=1933)</th>
<th>Placebo (N=1912)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — y[^1^]</td>
<td>83.6±3.2</td>
<td>83.5±3.1</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>1174 (60.7)</td>
<td>1152 (60.3)</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>While sitting</td>
<td>173.0±8.4/90.8±8.5</td>
<td>173.0±8.6/90.8±8.5</td>
</tr>
<tr>
<td>While standing</td>
<td>168.0±11.0/88.7±9.3</td>
<td>167.9±11.1/88.6±9.3</td>
</tr>
<tr>
<td>Orthostatic hypotension — no. (%)†</td>
<td>152 (7.9)</td>
<td>169 (8.8)</td>
</tr>
<tr>
<td>Isolated systolic hypertension — no. (%)</td>
<td>623 (32.3)</td>
<td>623 (32.6)</td>
</tr>
<tr>
<td>Heart rate — beats/min</td>
<td>74.3±9.1</td>
<td>74.3±9.3</td>
</tr>
</tbody>
</table>

### Cardiovascular history

| Cardiovascular disease — no. (%)        | 223 (11.5)                | 229 (12.0)       |
| Hypertension — no. (%)                  | 1737 (89.9)               | 1718 (89.9)      |
| Antihypertensive treatment — no. (%)    | 1241 (64.2)               | 1245 (65.1)      |
| Stroke — no. (%)                        | 130 (6.7)                 | 131 (6.9)        |
| Myocardial infarction — no. (%)         | 59 (3.1)                  | 63 (3.2)         |
| Heart failure — no. (%)                 | 56 (2.9)                  | 55 (2.9)         |

### Cardiovascular risk factors

| Current smoker — no. (%)                | 123 (6.4)                 | 127 (6.6)        |
| Diabetes — no. (%) ‡                   | 132 (6.8)                 | 131 (6.9)        |
| Total cholesterol — mmol/liter         | 5.3±1.1                   | 5.3±1.1          |
| High-density lipoprotein cholesterol — mmol/liter | 1.35±0.38                | 1.35±0.37        |
| Serum creatinine — µmol/liter          | 88.6±20.5                 | 89.2±20.5        |
| Uric acid — µmol/liter                 | 280.4±79.3                | 279.0±81.3       |
| Body mass index                        | 24.7±5.8                  | 24.7±5.5         |

[^1^]: Plus-minus values are means ±SD. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586; to convert values for uric acid to milligrams per deciliter, divide by 59.48; and to convert values for serum creatinine to milligrams per deciliter, divide by 88.4.

[^†]: Orthostatic hypotension is defined as a drop in systolic blood pressure of more than 10 mm Hg or a reduction in diastolic blood pressure of more than 10 mm Hg while standing.

[^‡]: Diabetes is defined as reported diabetes, the receipt of antidiabetes treatment, or a random blood glucose measurement of more than 11.1 mmol per liter (200 mg per deciliter).

[^§]: The body mass index is the weight in kilograms divided by the square of the height in meters.
1933 patients on active treatment and 1912 placebo

Mean age 83.6 years (both groups)

Mean seated BP 173/90 (both groups)

Mean BP reduction in treatment group 15/6.1

Followed for mean 4 years
Mean Blood Pressure, Measured while Patients Were Seated, in the Intention-to-Treat Population, According to Study Group


<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo group</th>
<th>Active-treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1912</td>
<td>1933</td>
</tr>
<tr>
<td>1</td>
<td>1468</td>
<td>1540</td>
</tr>
<tr>
<td>2</td>
<td>701</td>
<td>754</td>
</tr>
<tr>
<td>3</td>
<td>330</td>
<td>373</td>
</tr>
<tr>
<td>4</td>
<td>191</td>
<td>207</td>
</tr>
<tr>
<td>5</td>
<td>116</td>
<td>118</td>
</tr>
</tbody>
</table>

No. at Risk

- Placebo group
- Active-treatment group
Table 2. Main Fatal and Nonfatal End Points in the Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Rate per 1000 Patient-Yr (No. of Events)</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal</td>
<td>12.4 (51)</td>
<td>17.7 (69)</td>
<td>0.70 (0.49–1.01)</td>
</tr>
<tr>
<td>Death from stroke</td>
<td>6.5 (27)</td>
<td>10.7 (42)</td>
<td>0.61 (0.38–0.99)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>47.2 (196)</td>
<td>59.6 (235)</td>
<td>0.79 (0.65–0.95)</td>
</tr>
<tr>
<td>From noncardiovascular or unknown causes</td>
<td>23.4 (97)</td>
<td>28.9 (114)</td>
<td>0.81 (0.62–1.06)</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>23.9 (99)</td>
<td>30.7 (121)</td>
<td>0.77 (0.60–1.01)</td>
</tr>
<tr>
<td>From cardiac cause*</td>
<td>6.0 (25)</td>
<td>8.4 (33)</td>
<td>0.71 (0.42–1.19)</td>
</tr>
<tr>
<td>From heart failure</td>
<td>1.5 (6)</td>
<td>3.0 (12)</td>
<td>0.48 (0.18–1.28)</td>
</tr>
<tr>
<td>Fatal or nonfatal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any myocardial infarction</td>
<td>2.2 (9)</td>
<td>3.1 (12)</td>
<td>0.72 (0.30–1.70)</td>
</tr>
<tr>
<td>Any heart failure</td>
<td>5.3 (22)</td>
<td>14.8 (57)</td>
<td>0.36 (0.22–0.58)</td>
</tr>
<tr>
<td>Any cardiovascular event†</td>
<td>33.7 (138)</td>
<td>50.6 (193)</td>
<td>0.66 (0.53–0.82)</td>
</tr>
</tbody>
</table>

* Death from cardiac causes was defined as fatal myocardial infarction, fatal heart failure, and sudden death.
† Any cardiovascular event was defined as death from cardiovascular causes or stroke, myocardial infarction, or heart failure.
Treatment Group had:

- 30% reduction in rate of fatal or non-fatal stroke
- 39% reduction in rate of death from stroke
- 21% reduction in rate of death from any cause
- 23% reduction in rate of death from cardiovascular causes
- 64% reduction in rate of heart failure
ACCOMPLISH Trial (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension)

Summarising 100’s of outcome studies the consensus remains that degree of BP lowering is more important than how it is achieved.

Choice of initial agent determined by age and race of pt as well as compelling indications and contraindications.

Most patients will require > 1 drug to achieve target BP and JNC 7 suggests that Stage 2 hypertension be treated with combination therapy from the start.

Currently commonest combination is (highly effective) RAAS blocker (ACE-I or ARB) + thiazide with long-acting CCB usually 3rd drug. Because of concern about possible metabolic (+ ? proinflammatory – Valmarc study) side effects of thiazides, particularly diabetes, there is interest in whether RAAS blocker/CCB would be an effective first-line combination.
• The optimal combination drug therapy for treatment of hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic

• This double-blind trial, in which high-risk patients with hypertension were randomly assigned to treatment with benazepril plus either amlodipine or hydrochlorothiazide, showed that benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular events in this population
Effects of Treatment on Systolic and Diastolic Blood Pressure over Time

Kaplan-Meier Curves for Time to First Primary Composite End Point


No. at Risk
Benazepril plus amlodipine  
5512 5317 5141 4959 4739 2826 1447
Benazepril plus hydrochlorothiazide  
5483 5274 5082 4892 4655 2749 1390
### Hazard Ratios for the Primary Outcome and the Individual Components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death from cardiovascular causes and cardiovascular events</td>
<td>0.80 (0.72–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Component</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>0.80 (0.62–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or nonfatal)</td>
<td>0.78 (0.62–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke (fatal or nonfatal)</td>
<td>0.84 (0.65–1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.75 (0.50–1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>0.86 (0.74–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>1.75 (0.73–4.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

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**Benazepril plus Amlodipine Better**

**Benazepril plus Hydrochlorothiazide Better**

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Table 2. Hazard Ratios for Primary, Secondary, and Other Prespecified End Points, and Results of the Subgroup Analysis.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Benazepril–Amlodipine Group (N=5744)</th>
<th>Benazepril–Hydrochlorothiazide Group (N=5762)</th>
<th>Hazard Ratio (95% CI) &amp; P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
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</tr>
<tr>
<td>Composite of cardiovascular events and death from cardiovascular causes — no. (%)</td>
<td>552 (9.6)</td>
<td>679 (11.8)</td>
<td>0.80 (0.72–0.89) &lt;0.001</td>
</tr>
<tr>
<td>Individual component — no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>107 (1.9)</td>
<td>134 (2.3)</td>
<td>0.80 (0.62–1.03) 0.08</td>
</tr>
<tr>
<td>Fatal and nonfatal myocardial infarction</td>
<td>125 (2.2)</td>
<td>159 (2.8)</td>
<td>0.78 (0.62–0.99) 0.04</td>
</tr>
<tr>
<td>Fatal and nonfatal stroke</td>
<td>112 (1.9)</td>
<td>133 (2.3)</td>
<td>0.84 (0.65–1.08) 0.17</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>44 (0.8)</td>
<td>59 (1.0)</td>
<td>0.75 (0.50–1.10) 0.14</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>334 (5.8)</td>
<td>386 (6.7)</td>
<td>0.86 (0.74–1.00) 0.04</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>14 (0.2)</td>
<td>8 (0.1)</td>
<td>1.73 (0.73–4.17) 0.20</td>
</tr>
<tr>
<td>Subgroup — no. with primary end point/total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>365/3448 (10.6)</td>
<td>461/3515 (13.1)</td>
<td>0.80 (0.69–0.91) 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>187/2296 (8.1)</td>
<td>218/2466 (9.7)</td>
<td>0.83 (0.68–1.01) 0.06</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>386/3813 (10.1)</td>
<td>474/3827 (12.4)</td>
<td>0.81 (0.71–0.92) 0.002</td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>260/2363 (11.0)</td>
<td>323/2240 (13.8)</td>
<td>0.79 (0.67–0.93) 0.004</td>
</tr>
<tr>
<td>Presence of diabetes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>307/3478 (8.8)</td>
<td>383/3468 (11.0)</td>
<td>0.79 (0.68–0.92) 0.003</td>
</tr>
<tr>
<td>No</td>
<td>245/2266 (10.8)</td>
<td>296/2294 (12.9)</td>
<td>0.82 (0.69–0.99) 0.02</td>
</tr>
<tr>
<td>Secondary and other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of cardiovascular events — no. (%)</td>
<td>494 (8.6)</td>
<td>592 (10.3)</td>
<td>0.83 (0.71–0.93) 0.002</td>
</tr>
<tr>
<td>Composite of death from cardiovascular events, nonfatal myocardial infarction, and nonfatal stroke — no. (%)</td>
<td>288 (5.0)</td>
<td>364 (6.3)</td>
<td>0.79 (0.67–0.92) 0.002</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>236 (4.1)</td>
<td>262 (4.5)</td>
<td>0.99 (0.76–1.30) 0.24</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure — no. (%)</td>
<td>100 (1.7)</td>
<td>96 (1.7)</td>
<td>1.04 (0.79–1.38) 0.77</td>
</tr>
<tr>
<td>Primary end point plus hospitalization for congestive heart failure — no. (%)</td>
<td>617 (10.7)</td>
<td>738 (12.9)</td>
<td>0.83 (0.74–0.92) 0.0005</td>
</tr>
</tbody>
</table>

* Hazard ratios are for the benazepril–amlodipine group.
† The P values are derived from a log-rank test.
### Table 3. Results of Prespecified Safety Analysis.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Serious</td>
<td>Drug-Related Serious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1189 (20.7)</td>
<td>1461 (25.4)</td>
<td>18 (0.3)</td>
<td>31 (0.5)</td>
<td>2 (&lt;0.1)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1792 (31.2)</td>
<td>772 (13.4)</td>
<td>10 (0.2)</td>
<td>8 (0.1)</td>
<td>4 (0.1)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Dry cough</td>
<td>1177 (20.5)</td>
<td>1220 (21.2)</td>
<td>7 (0.1)</td>
<td>7 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>53 (0.9)</td>
<td>34 (0.6)</td>
<td>7 (0.1)</td>
<td>13 (0.2)</td>
<td>2 (&lt;0.1)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>34 (0.6)</td>
<td>33 (0.6)</td>
<td>10 (0.2)</td>
<td>11 (0.2)</td>
<td>6 (0.1)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (0.1)</td>
<td>17 (0.3)</td>
<td>2 (&lt;0.1)</td>
<td>12 (0.2)</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>142 (2.5)</td>
<td>208 (3.6)</td>
<td>22 (0.4)</td>
<td>30 (0.5)</td>
<td>6 (0.1)</td>
<td>9 (0.2)</td>
</tr>
</tbody>
</table>

* Safety data were ascertained on the basis of reports by participants or investigators, discovered on physical examination or report by the central laboratory.
• The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.
ACCOMPLISH was a large (11,400) outcome study of high risk hypertensives > 55 yrs and SBP > 160. Many obese and 60% diabetic. Pts randomised to Benazepril/HCTZ or Benazepril/Amlodipine combinations. Excellent BP control with 76% having BP at target at 18 months and few dropouts for side effects. 50% obese 60% diabetes mellitus

Pts randomised from 2003. Trial stopped early in October 2007 by data safety and monitoring committee following interim analysis of 60% of expected information from the trial.

ACEI/CCB – 81.7% BP < 140/90 ACE/HCTZ 78.5%/ Mean SBP difference 0.7

Over a mean f/u of 39 months, cardiovascular morbidity/mortality was reduced by 20% with the ACEI/CCB compared with the ACEI/HCTZ
Check out my website

www.hypertensionclinic.co.nz