HYPERTENSION UPDATE

Is anyone leaving samples of thiazide diuretics?

February 2003

ALLHAT TRIAL OVERVIEW

In December, 2002 the long awaited ALLHAT trial was published.[1,2] This landmark randomized, double-blind, active-controlled trial was designed to determine if there were any clinical outcome differences in high-risk hypertensive patients treated with relatively newer antihypertensive agents (listed below) versus a low-dose diuretic. Classes/agents compared were as follows:

- calcium channel blocker (**CCB**) – amlodipine **NORVASC**
- ACE inhibitor (**ACEI**) – lisinopril **ZESTRIL / PRINIVIL**
- alpha (**α-**) **blocker** – doxazosin **CARDURA**
- low-dose thiazide type **diuretic** – chlorthalidone

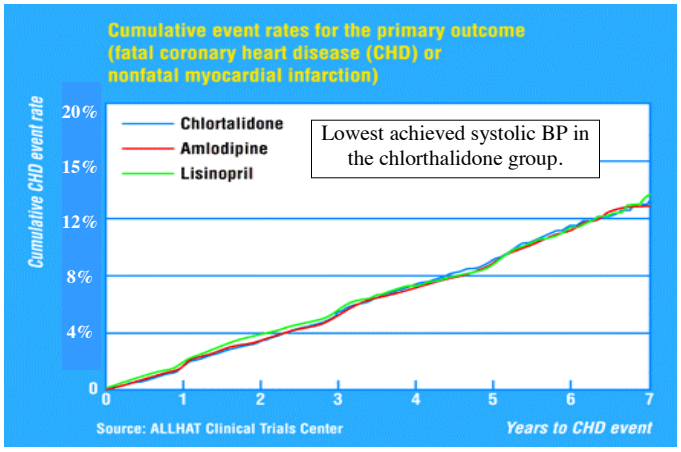
This trial, largest of its kind, studied **42,418** patients age ≥55 years (>93% between 55 & 79 yrs) with mild to moderate hypertension and at least one other CHD risk factor. Patients were randomized to one of the antihypertensive arms and received additional therapy with atenolol, clonidine, reserpine or hydralazine as necessary to achieve BP control.

The doxazosin arm was stopped early due to excess heart failure (HF) and stroke in doxazosin patients compared to the diuretic. Results were published in 2000.[3] The ACEI, CCB, versus diuretic arms of the trial followed patients for ~ 4-8 years. **This study found no differences in primary outcome (combined fatal CHD, non-fatal MI) between treatment groups. The authors concluded that thiazide type diuretics should be the preferred initial therapy in hypertension** (see Table 1).

Table 1: ALLHAT Results (Diuretic vs CCB, ACEI)

Outcomes 1°= primary outcome 2°= secondary outcome BP_{ave} at baseline = 146/84$_{mmHg}$ n=33,357	6 Year Event Rate per 100 Persons				
	Chlorthalidone 12.5-25mg od n=15,255	**Amlodipine 2.5-10mg od** n=9,048		**Lisinopril 10-40mg od** n=9,054	
1° fatal CHD & non-fatal MI	11.5	11.3	NS	11.4	NS
2°Stroke	5.6	5.4	NS	6.3	NNH=143
2°CHD-combined†	19.9	19.9	NS	20.8	NS
2°CVD-combined✞	30.9	32	NS	33.3	NNH=42
2°Death-All Cause	17.3	16.8	NS	17.2	NS
2°Renal Disease ES	1.8	2.1	NS	2.0	NS
HF clinical diagnosis	7.7	**10.2**	NNH=40	8.7	NNH=100
BP: average-5 yr	133.9/75.4$_{mmHg}$	134.7/74.6$_{mmHg}$		135.9/75.4$_{mmHg}$	

CHD= coronary heart disease **CVD**= cardiovascular disease **ES**= End Stage **HF**= heart failure **MI**= myocardial infarction **NS**= not significant vs chlorthalidone; **NNH**= number needed to harm (over 6 years for 1 extra event vs chlorthalidone)
† CHD death, nonfatal MI, coronary revascularization, hospitalized angina
✞ CVD death, nonfatal MI, **stroke**, coronary revascularization, hospitalized or treated angina, hospitalized or treated **HF**, and **peripheral arterial disease**.



What have we learned from ALLHAT?

- **Low-dose thiazide diuretics** are a cornerstone of antihypertensive therapy and preferred first-line agents due to **effectiveness**, **safety**, **tolerability** and **low cost**. Results consistent across age, gender & diabetes subgroups.
- Most patients will require **combination therapy** with more than one agent to achieve blood pressure control (**63%** of patients required **≥2 drugs** for control at 5 years; this is encouraging since the rate of blood pressure control in treated Canadian patients is about 13% [4]).
- **α-blockers** (e.g. doxazosin) are <u>not</u> first-line agents for hypertension based on unfavorable outcomes (↑HF). If used, consider additional antihypertensive agent.
- Concerns dispelled regarding CCBs (MI, cancer, bleeding)

ALLHAT: Important Limitations

- The <u>ACEI results</u> have limitations: 1) ACEI are known to be less effective in blacks & elderly; 2) Systolic BP was lower in diuretic versus ACEI group (2$_{mmHg}$ overall, 3$_{mmHg}$ in those age ≥65, 4$_{mmHg}$ in blacks) 3) **Atenolol**, clonidine and reserpine are not synergistic add-on agents.
- Increased HF in the CCB and especially ACEI arms was unexpected; however, edema would be more common in these groups and lead to a possible error in diagnosis. Efforts to validate the HF results, as was successfully done with the doxazosin arm [5,6], are in progress.
- The long-term impact of a slight increase in blood glucose seen with the diuretic is unknown and of some concern.
- β-blockers, angiotensin receptor blockers (ARBs) and antihypertensive combinations agents not studied.
- It is unknown whether results demonstrate "class effects".

How do the results of the lisinopril arm in ALLHAT compare to other ACEI trials?

- Limitations notwithstanding, the ALLHAT results will bring some reassessment of the role of ACEIs, specifically – have the unique benefits of ACEIs been overstated? [7]
- In ALLHAT, lisinopril was compared to an active treatment; in HOPE, ramipril was compared to placebo in both normotensive and hypertensive high-risk patients.
- The claim that ramipril (given at bedtime) provided benefit greater than expected with reduction in blood pressure alone is being questioned.[8] Sub-analysis of 1year results for 38 patients with peripheral arterial disease found that ambulatory BP was reduced by $17/8_{mmHg}$ (night time) and $8/2_{mmHg}$ (morning). Morning office BP readings were decreased by only $3/2_{mmHg}$ in the entire published results.
- In PROGRESS, perindopril alone did not reduce stroke but did when combined with the diuretic, indapamide.[9]

What about the metabolic effects of diuretics on potassium, glucose and lipids?

- In ALLHAT chlorthalidone had outcome benefits despite negative metabolic effects. This is consistent with other trials e.g. CAPPP, INSIGHT & SHEP (See Table 4) where thiazides outcomes were equal or better than ACEIs/CCBs.
- Metabolic effects are less with low-dose regimens.

Table 2 : ALLHAT metabolic result rate at 4 years

POTASIUM, mean change: ↓**0.3**$_{mmol/L}$ chlorthalidone$^{4.3⇨4.1}$ vs lisinopril$^{4.4⇨4.5}$
⇨hypokalemia (<3.5$_{mmol}$): 8.5% ^{chlorthalidone}, 1.9% ^{amlodipine}, 0.8% ^{lisinopril}

GLUCOSE, mean change: ↑ **0.23**$_{mmol/L}$ chlorthalidone vs lisinopril
⇨glucose ≥7$_{mmol/l}$: 32.7% ^{chlorthalidone}, 30.5% ^{amlodipine}, 28.7% ^{lisinopril}
⇨new onset diabetes: 11.6% ^{chlorthalidone}, 9.8% ^{amlodipine}, 8.1% ^{lisinopril}

Total Cholesterol, mean change: ↑ **0.044**$_{mmol/L}$ chlorthalidone vs lisinopril
⇨total chol. >6.2$_{mmol/l}$: 14.4% ^{chlorthalidone}, 13.4% ^{amlodipine}, 12.8% ^{lisinopril}

Can thiazides be used in diabetes?

- Low-dose thiazides are associated with positive outcomes in patients with diabetes as demonstrated in the SHEP and ALLHAT trials. ALLHAT included over **15,000** patients with diabetes. A detailed subanalysis of high-risk groups (e.g. diabetes, renal impaired) is planned.

How effective are non-pharmacological measures in treating hypertension?

- Lifestyle measures are effective and may equate to one antihypertensive in lowering BP. In the TONE study of elderly hypertensives on a single antihypertensive, salt restriction and weight loss (if obese) allowed more than 1/3 of patients to discontinue their medication.[10]
- **Lifestyle** measures may include:
  - ⇨**weight loss** for obese (≥4.5kg for BMI > 25)
  - ⇨**limit alcohol** consumption to ≤2 drinks/day
  - ⇨**moderate aerobic exercise** (>45min 4-5x/week)
  - ⇨**smoking cessation**
  - ⇨**diet**: e.g. **DASH**[11,12] diet: ↓fat; modest salt restriction

  (See also: **www.nhlbi.nih.gov/chd/lifestyles.htm**)
- **Assess for Drugs which ↑ BP**: adrenal steroids, appetite suppressants, caffeine, cocaine & other illicit drugs, cyclosporin, erythropoietin, licorice in chewing tobacco, nasal decongestants, NSAIDS/COXIBS, oral contraceptives, sympathomimetics, tacrolimus & venlafaxine.

Are ARBs considered equivalent to ACEIs?

- Evidence for beneficial outcomes (especially renal) with ARBs is growing but varying opinion on their optimal role.
- Unfortunately, several ARB outcome trials have avoided a head-to-head comparison with ACEIs or used β-blockers (e.g. LIFE) known to be less effective in elderly. See Table 4.
- ARBs are an alternative in patients who develop ACEI induced cough but are more expensive than most ACEIs.
- Losartan was not superior to captopril in patients with heart failure ELITE II; captopril reduced CV-death in post-MI patients more than losartan OPTIMAAL. However, both of these studies found that less patients discontinued losartan due to adverse effects.
- ACEI-ARB combinations show some promise for renal outcomes CALM, COOPERATE, however they are expensive.

Clinical Outcomes versus Surrogate Markers

Several trials support a growing emphasis on outcomes.
- doxazosin worse outcomes than chlorthalidone despite similar blood pressure control. ALLHAT-Doxazosin
- amlodipine more end-stage renal disease compared to ramipril despite similar blood pressure reduction. AASK

Table 3: Cost of Select Antihypertensive Agents

CLASS	NAME		DOSE	$/Month
Diuretic	CHLORTHALIDONE	ς	12.5-25mg OD	8
	HYDROCHLOROTHIAZIDE- HCT	ς	12.5-25mg OD	8
	HCT + TRIAMTERENE DYAZIDE	ς	½ -1 tab OD	8
	INDAPAMIDE LOZIDE		1.25-2.5mg OD	15
β-Blocker	METOPROLOL LOPRESOR, BETALOC		100mg SR OD	16
	ATENOLOL TENORMIN	ς	50-100mg OD	17-24
	ACEBUTOLOL MONITAN, SECTRAL	ς	200mg BID	22
	PROPRANOLOL INDERAL		160mg LA OD	38
ACEI	LISINOPRIL ZESTRIL, PRINIVIL		10-20mg OD	34-40
	ENALAPRIL VASOTEC		10-20mg OD	41-48
	RAMIPRIL ALTACE caps		5-10mg OD	34-41
	CAPTOPRIL CAPOTEN		25-50mg BID	25-40
ARBs	IRBESARTAN AVAPRO		150-300mg OD	
	LOSARTAN COZAAR		50-100mg OD	~45
	VALSARTAN DIOVAN caps		80-160mg OD	
CCBs	FELODIPINE RENEDIL, PLENDIL		5-10mg OD	31-42
	AMLODIPINE NORVASC		5-10mg OD	53-75
	NIFEDIPINE ADALAT, ADALAT PA & XL		30-60mg XL OD	40-59
	DILTIAZEM CARDIZEM & CD, TIAZAC ER		120-240mg CD	36-58
	VERAPAMIL ISOPTIN SR		180-240mg OD	33-38
Other	CLONIDINE CATAPRES	ς	0.1-0.2mg BID	20-30
	DOXAZOSIN CARDURA		4-8mg HS	26-46
	HYDRALAZINE APRESOLINE		25mg QID	31
	LABETALOL TRANDATE	ς	200mg BID	28
	METHYLDOPA ALDOMET		250mg BID	17
Diuretic Combination Products				
ACEI	LISINOPRIL+ HCT ZESTORETIC/PRINZIDE **10/12.5,20/12.5,20/25**		od	36-42
	ENALAPRIL + HCT VASERETIC 5/12.5, 10/25		od	36-41
	CILAZAPRIL + HCT INHIBACE PLUS 5/12.5	ς	od	35
	QUINAPRIL + HCT ACCURETIC 10/12.5, 20/12.5	ς	od	36
ARB	IRBESARTAN + HCT AVALIDE 150/12.5, 300/12.5		od	~45
	LOSARTAN + HCT HYZAAR 50/12.5, DS 100/25		od	
	CANDESARTAN + HCT ATACAND PLUS 16/12.5	ς	od	
	TELMISARTAN + HCT MICARDIS PLUS 80/12.5		od	
	VALSARTAN + HCT DIOVAN HCT 80/12.5, 160/12.5		od	
BB	ATENOLOL + CHLORTHALIDONE **TENORETIC** 50/25, 100/25	ς	od	$29-43

ς=scored tab indicated if ALL strengths scored **BB**=Beta-blocker
For detailed comprehensive listing of agents, see **www.rxfiles.ca**

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Table 4: Antihypertensives: Landmark & Recent Trials – Summary (for more detailed ☺ trial summary chart, see *Antihypertensives: Landmark and Recent Trials* at **www.rxfiles.ca**)

TRIAL	PRIMARY AGENTS	POPULATION STUDIED	CONTRIBUTION TO CURRENT KNOWLEDGE
AASK [13] 3-6.4yr, n=1,094	Ramipril **ALTACE** 2.5-10mg od, Metoprolol 50-200mg od, Amlodipine **NORVASC** 5-10mg od	**African Americans** with **hypertensive nephrosclerosis**	**Ramipril provided best renal protection**, followed by metoprolol (amlodipine arm **halted** early - safety concerns) Group with lower target BP goal no better than group with higher target (achieved goal: 128/78 vs **141/85**).
ALLHAT [1,3,14] 4.9yr n=42,418→33,357	Doxazosin **CARDURA** 2-8mg/day; study arm **stopped early**; Amlodipine **NORVASC** 2.5-10mg od, Lisinopril **ZESTRIL** 10-40mg od, Chlorthalidone 12.5-25mg od	**↑BP & 1 other risk factor** (prev MI, stroke, LVH, diabetes, smoke, ↓ HDL, hx CVD) ♀47%, black35%, hispanic16%, diabetes36%	**Chlorthalidone** (**thiazide**): **well tolerated, as effective & least expensive in lowering CV events.** Chlorthalidone had: much less HF than amlodipine; less stroke and HF than lisinopril; much less HF & stroke than doxazosin. Study design limits lisinopril interpretation: blacks respond less to ACEI; ACEI + β-blocker less synergistic than ACEI + diuretic.
CALM [15] 24 wk, n=199	Candesartan **ATACAND** 16mg od, Lisinopril **ZESTRIL** 20mg od, Combination	**Type 2 diabetes**, **↑BP & microalbuminuria**	Lisinopril especially & candesartan ↓ BP & microalbuminuria in Type 2 diabetes**. Combination of ACEI & ARB** may be more effective to ↓BP & albuminuria. {Recent **COOPERATE** [16]: trandolapril 3mg od + losartan 100mg od shows renal benefit}
CAPPP [17] 6.1yr, n=10,985	Captopril **CAPOTEN** 50-100mg po od/bid, Conventional tx (eg.atenolol/metoprolol 50-100mg od/HCT 25mg od)	**DBP>100** (BP 162/100 captopril, BP 160/98 conventional)	Captopril & conventional arms were equal in preventing CV morbidity & mortality; however less strokes in the conventional arm. In patients with diabetes, captopril had less cardiac & fatal events. This trial had baseline flaws.
ELITE II [18] 1.5yr, n=3,152	Losartan **COZAAR** 50mg od, Captopril **CAPOTEN** 50mg tid	**Heart Failure II-IV** EF <40% (Mean 31%), Mean 71yr	**Losartan 50mg od not superior to captopril in HF**, but less losartan discontinued due to side effects (9.7 vs 14.7%) (Previous smaller ELITE findings suggested losartan may be superior to captopril in reducing mortality in HF).
FACET [19] 2.5yr, n=380	Fosinopril **MONOPRIL** 20mg od, Amlodipine **NORVASC** 10mg hs	**↑BP & Type 2 diabetes**	Fosinopril significantly decreased major vascular events vs amlodipine, despite amlodipine decreasing BP by 4/2 mmHg more than fosinopril. Note: Trial was non blinded & 1/3 of patients were receiving both drugs.
HOPE [20, 21, 22] 4.5yr, n=9,297	Ramipril **ALTACE** 10mg po **hs**, {**Initial BP mean 139/79**} **Placebo**	**High CV risk** (CAD80%, PVD44%, diabetes38%, stroke/TIA11%), LVH 8% **≥55yrs & 1 other risk factor**	**Ramipril** significantly **reduces MI, stroke, CV death & all-cause death** vs **placebo** in **high-risk patients** (especially the 47% with hypertension [23]) not known to have a low ejection fraction or HF. Benefits greater in **diabetes**. BP reduction may be greater than the "modest" reported (due to HS dosing & differences in nighttime vs morning BP readings [24]).
HOT [25] 3.8yr, n=18,790	BP → **3 DBP target groups**: **≤90**, **≤85**, **≤80** mmHg (**Felodipine RENEDIL** 5→10mg od, +/-**ACE**, +/- **Beta-blocker**, +/-**diuretic**)	**↑BP** 170/105→to **3 DBP gps**: **≤ 90 gp =144/85, ≤ 85 gp=141/83, ≤80 gp=140/81**	**Most benefits** achieved at a BP of **~140/90**mmHg, small additional benefit obtained by further lowering BP. Lowest major CV events at 139/83mmHg; Lowest CV mortality at 139/87mmHg. **Patients with diabetes did better with DBP ≤80**, **supporting aggressive BP lowering in these patients**. {ASA75mg od: ↓ CV events, but ↑ non fatal major bleeds}.
IDNT [26] 2.6yr, n=1,715	Irbesartan **AVAPRO** 75→**300mg** od, Amlodipine **NORVASC** 2.5→ **10mg** od, **Placebo** {other agents}	**Type 2 diabetes** & **Nephropathy**, BP~159/87	**Irbesartan** is effective in **delaying** the **progression of nephropathy** due to type 2 diabetes (amlodipine no better than placebo despite a BP that was similar to irbesartan group). (Unfortunately, not compared to ACEI).
INSIGHT [27] ~3.5yr, n=6,321	Nifedipine **ADALAT** 30-60mg GITS od, HCT 25mg/amiloride 2.5mg (=½ **MODURET**) 1-2 tabs od	**↑BP & 1 other risk factor**	Nifedipine & co-amilozide equal in preventing CV death, stroke & all MI. Less fatal MI & heart failure in the diuretic arm. (Nifedipine: ↑peripheral edema stopped early in 8% pts; severe adverse events in mid-high dose co-amilozide [28 vs 25%]).
IRMA II [28] 2yr, n=590	Irbesartan **AVAPRO** 150mg od or 300mg od, **Placebo** {CCB 27%, diuretic 25%, β-blocker 19% , other 15%}	**↑BP, Type 2 diabetes, normal GFR & microalbuminuria**	**Irbesartan delays progression to nephropathy** in **Type 2 diabetes patients with microalbuminuria**. The effect was **dose related** with 300mg od having the greatest effect. (Unfortunately, not compared to ACEI).
LIFE [29, 30, 31] 4.8yr, n=9,193	Losartan **COZAAR** 50-100mg od +/-HCT 12.5-25mg od, Atenolol **TENORMIN** 50-100mg od +/-HCT 12.5-25mg od {HCT used in 44% of losartan & 38% of atenolol pts, but not directly compared to diuretics in the trial}	**↑ BP** 174/98 →144/81 losar; 145/81aten. & **left ventricular hypertrophy (LVH);** (diabetes 13%) (black 5.8%)	**Losartan** was more effective than atenolol in preventing **stroke** in hypertensive patients with **LVH** (**no** difference in **CV mortality** or **MI** or **stroke in blacks**). In **LVH patients with diabetes,** losartan **decreased CV death & total mortality**, but not MI or stroke (Atenolol group was at higher baseline risk. Fewer than 40% of all patients attained a SBP <140; Mean BP ~147/79). In **ISH** patients, losartan reduced stroke, CV & total mortality but not CV events.
NORDIL [32] 4.5yr, n=10,881	Diltiazem **CARDIZEM** 180-360mg od +/- ACEI, diuretic, α blocker, Diuretic +/- Beta-blocker +/- ACEI, α blocker	**DBP >100**	**Diltiazem** as effective as diuretic & β-blocker in reducing CV events (fatal/non-fatal stroke, MI & CV death). Diltiazem reduced fatal & non-fatal **stroke.** Treated **BP's were high** (diltiazem 155/89; diuretic/β-blocker 152/89).
OPTIMAAL [33] 2.7yr, n=5,477	Losartan **COZAAR** 12.5→50mg od, Captopril **CAPOTEN** 6.25x1→12.5→50mg tid	**High risk, post MI**, ~BP 123/71	**Captopril** ≤50mg TID **↓ CV death** more **than losartan** 50mg od in **post MI patients**. Medication discontinued due to adverse reactions: 7% for losartan vs 14% with captopril.
PROGRESS [34] 3.9yr, n=6,105	Perindopril **COVERSYL** 4mg od **+/-** indapamide **LOZIDE** 2.5mg od, **Placebo**	Previous **stroke/TIA** within 5yr, Normal BP 136/79 or hypertensive 159/94	**Perindopril + indapamide** ↓BP 12/5 & significantly **↓ rate of stroke** in normal & hypertensive patients with previous stroke/TIA. Perindopril **alone did not** ↓ stroke (↓BP only 5/3)**.** The **hypertensive group benefited most**.
QUIET [35] 2.3yr, n=1,750	Quinapril **ACCUPRIL** 10→20mg od, {BP 123/74} Placebo	**Post-angioplasty/atherectomy** with **preserved LV fx** EF 59%	**Quinapril** was well tolerated in patients after angioplasty with normal LV function, but **no effect** on the overall frequency of clinical outcomes or the angiographic progression of coronary atherosclerosis.
RENAAL [36] 3.4yr, n=1,513	Losartan **COZAAR** 50-100 71% mg od {+ other agents}, **Placebo** {diuretic 84%, CCB 81%, α-blocker 46%, β-blocker 37% , other 22%}	**Type 2 diabetes** with **Nephropathy,** BP~153/82	**Losartan** is more effective than placebo in **protecting** against the **progression of nephropathy** due to type 2 diabetes despite a BP that was similar in both groups. (Unfortunately, not compared to ACEI).
SHEP [37, 38,] 4.5yr, n=4,736	Chlorthalidone 12.5→25mg od **+/-**Atenolol 25-50mg od/ Reserpine 0.05-0.1mg/d; Vs **Placebo**	**ISH**,↑BP 170/77; **elderly** Mean 72yr, (diabetes 12%)	**Diuretic chlorthalidone ↓ stroke & CV events** in **elderly ISH** patients & had greater absolute **benefit in patients with diabetes**. **DBP<65**mm Hg was associated with an **↑ risk of stroke & CV disease (CVD)**. [39]
STOP-Hypertension 2[40] ~5yr, n=6,614	1.Conventional Metoprolol/Atenolol/ Pindolol; **+/-** HCT/amiloride 2.Felodipine/Isradipine 2.5mg od **+/-** β-blocker 3.Enalapril/Lisinopril 10mg od **+/-** HCT≤25mg od	**Elderly** Mean 76yr **↑BP** 194/98(→ ~159/81 in all 3 gps)	**Conventional & newer drugs** were **similar in CV mortality** & overall major events in this open trial of elderly hypertensives. 1/2 of all patients received more than one BP med. **Of the newer antihypertensives: ACE inhibitors had less MI & HF** than the calcium channel blockers.
SYST-EUR [41,42] 2yr, n=4,695	Nitrendipine (dihydropyridine) 10-20mg bid +/- enalapril 5-20mg hs & HCT 12.5-25mg od Vs **Placebo** (2/3 rec'd BP meds)	**ISH,** ↑BP 174/86; **elderly** Mean 70yr,(diabetes 10.5%)	In **elderly with ISH**, antihypertensive drug treatment **starting with nitrendipine** ↓ rate of CV complications, stroke & possibly dementia [43]. The **benefit was greater** in the **diabetes** arm. ↓ CV mortality & all CV events
UKPDS-38 [44] **UKPDS-39** [45] 8.4yr, n=1,148	**-38**: Tight vs Conventional BP control **-39**: Captopril 25-50mg BID vs Atenolol 50-100mg OD {Other: Furosemide, Nifedipine SR, Methyldopa, Prazosin}	**Type 2 diabetes**,**↑BP** ~160/94, Mean 56yr, **8.4yr study**	**Tight blood pressure** (**~BP 144/82**) control in patients with **type 2 diabetes** reduces diabetes related morbidity & mortality. Captopril and atenolol were similarly effective (BP reduction, preserve renal function & proteinuria & CV complications).
Val-HeFT [46, 47] 1.9yr, n=5,010	Valsartan **DIOVAN** 40→160mg bid, **Placebo**	**Heart Failure Class II-IV** EF < 40% (Mean 27%), Mean 63yr	Valsartan appears to benefit **ACE inhibitor-intolerant HF patients** (benefits predominantly seen in the 7% of patients **not** treated with an ACEI). {Concerns: **increased mortality** in subgroup already receiving **both** ACEI & β-blocker}.

ACEI=angiotensin converting enzyme inhibitor **ARB**=angiotensin receptor blocker **BP**=blood pressure **CAD**=coronary artery disease **CV**=cardiovascular **DBP**=diastolic blood pressure **Dx**=disease **EF**=ejection fraction **ESRD**=end stage renal disease **GFR**=glomerular filtration rate **HCT**=hydrochlorothiazide **HF**=heart failure **ISH**=isolated systolic hypertension **LVH**=left ventricular hypertrophy **MI**=myocardial infarction **pts**= patients **PVD**=peripheral vascular disease

Table 5: Selection Guide: Disease & Risk Factors (with consideration for ALLHAT findings as noted) [1, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57]

DISEASE or RISK FACTOR	1ST LINE INITIAL THERAPY	SECOND STEP THERAPY	NOTES & CAUTIONS
Uncomplicated Hypertension	**Thiazide** like diuretic (eg.HCT **or** chlorthalidone [12.5-25mg od]) β blocker (for age ≤60 years) ACE inhibitor Calcium channel blockers →LA-DHP	**COMBINATIONS** of 1st line drugs (If ACE intolerance→Angiotensin receptor blocker)	α blockers not recommended as initial therapy (If used may consider additional antihypertensive agent) **Monitor** for hypokalemia: seldom if using low dose thiazide (K^+ sparing diuretics rarely needed)
Isolated Systolic Hypertension (ISH)	**Thiazide** like diuretic (eg.HCT **or** chlorthalidone [12.5-25mg od]) Calcium channel blockers→LA-DHP	{ACEIs NOT usually recommended as ISH not related to a low renin state}	Hypokalemia→seldom if using low dose thiazide (K^+ sparing diuretics rarely needed)
Diabetes mellitus with nephropathy	**Type I** →ACE inhibitor Alternate→angiotensin receptor blocker **Type II** →angiotensin receptor blockers/ACE inhibitor Evidence from IDNT [irbesartan]/RENAAL [losartan]	Thiazide like diuretic (low dose→HCT 12.5-25mg od) β blocker (cardioselective-e.g. atenolol, metoprolol) Long acting calcium channel blockers (amlodipine had less kidney protection than ramipril or metoprolol [AASK])	If Scr >150 umol/l, use a loop diuretic rather than thiazide if volume control is needed. (If CrCl <30ml/min→thiazide diuretic less effective) May consider ACEI + ARB combination [CALM]
Diabetes mellitus without nephropathy	ACE inhibitor (Thiazides also an option given ALLHAT results)	Angiotensin receptor blockers **Thiazide** like diuretic (low dose→HCT 12.5-25mg od) β blocker (cardioselective-e.g. atenolol, metoprolol) Long acting calcium channel blockers	**Low dose thiazides** have evidence for CV outcome benefits in diabetes & minimal effect on glucose. **ALLHAT** included **>15,000** patients **with diabetes**, the largest antihypertensive trial ever in this population.
Diabetes mellitus without nephropathy & with systolic hypertension	Thiazide like diuretic (low dose) or ACE inhibitor Alternatively→ Calcium channel blockers →LA-DHP		
Angina, stable	β blocker +/- ACE inhibitors	Long acting calcium channel blockers	Vasospastic angina→long acting CCB (avoid β-blocker)
Prior MI	β blocker with or without ACE inhibitors	Combinations of additional agents	
Systolic Dysfunction	ACE inhibitor (thiazide or loop diuretics, β blocker & spironolactone as additive therapy)	Angiotensin receptor blockers Hydralazine + isosorbide dinitrate Amlodipine (helpful in diastolic dysfx; but↑HF[ALLHAT])	Avoid non-dihydropyridine calcium channel blockers (eg. diltiazem & verapamil)
Past Cerebrovascular Accident or TIA	**Strongly consider BP reduction after the acute phase** to ↓ recurrent cerebrovascular events		Antihypertensives may ↑ death in **acute** TIA/stroke,but ↓ long term risk. Evidence supports {chlorthalidone or amlodipine [ALLHAT]}, {perindopril + indapamide [PROGRESS]}, {losartan +/- HCT[LIFE]},{ramipril[HOPE]}&{diltiazem[NORDIL]}.
Renal disease	ACE inhibitor (diuretics as additive therapy)	Combinations of agents (including ACEI + ARB) (If ACE intolerance→Angiotensin receptor blocker)	Avoid ACE if bilateral renal artery stenosis
Left Ventricular Hypertrophy (LVH) **Dyslipidemia** **Peripheral Arterial Disease (PAD)**	Consider usual first line options (see comments column) In LVH patients→ losartan ↓ stroke vs atenolol (5%vs6.7%; NNT=59) [LIFE Lancet 2002]		LVH→Avoid hydralazine & minoxidil PAD→Avoid β blocker in pts with **severe** disease PAD → CCB useful option (eg. Raynaud's)

ACE=angiotensin converting enzyme **CCB**=calcium channel blocker **HCT**=hydrochlorothiazide **HF**=heart failure **TIA**=transient ischemic attack **LA-DHP**:Long-Acting Dihydropyridines: amlodipine, felodipine, nifedipine, nimodipine.

CONTRAINDICATIONS: **DIURETICS**: symptomatic gout, sulpha allergy, anuria. **β-BLOCKERS**: asthma/COPD, heart block/severe bradycardia, uncompensated HF, severe PAD.
ACEI / ARB: artery stenosis (solitary kidney or bilateral), history of angioedema, pregnancy-especially 2nd & 3rd trimester.
CCB: systolic BP <90, recent MI or pulmonary edema, sick sinus syndrome or 2nd/3rd degree AV block, systolic dysfunction/HF(especially diltiazem & verapamil).

TARGETS: **UNCOMPLICATED HTN⇨BP140/90** **RENAL Dysfunction/DIABETES [no proteinuria]⇨BP130/80** **RENAL Dysfunction/DIABETES [proteinuria >0.5-1g/d]⇨BP125/75**

MONITOR: urinalysis, CBC, lytes, BUN/Scr, ECG, fasting glucose & lipids. {Baseline: rule out secondary causes ie. Mineralocorticoid; assess end-organ damage & identify CV risk factors}

Table 6: Approach to Combination Therapy

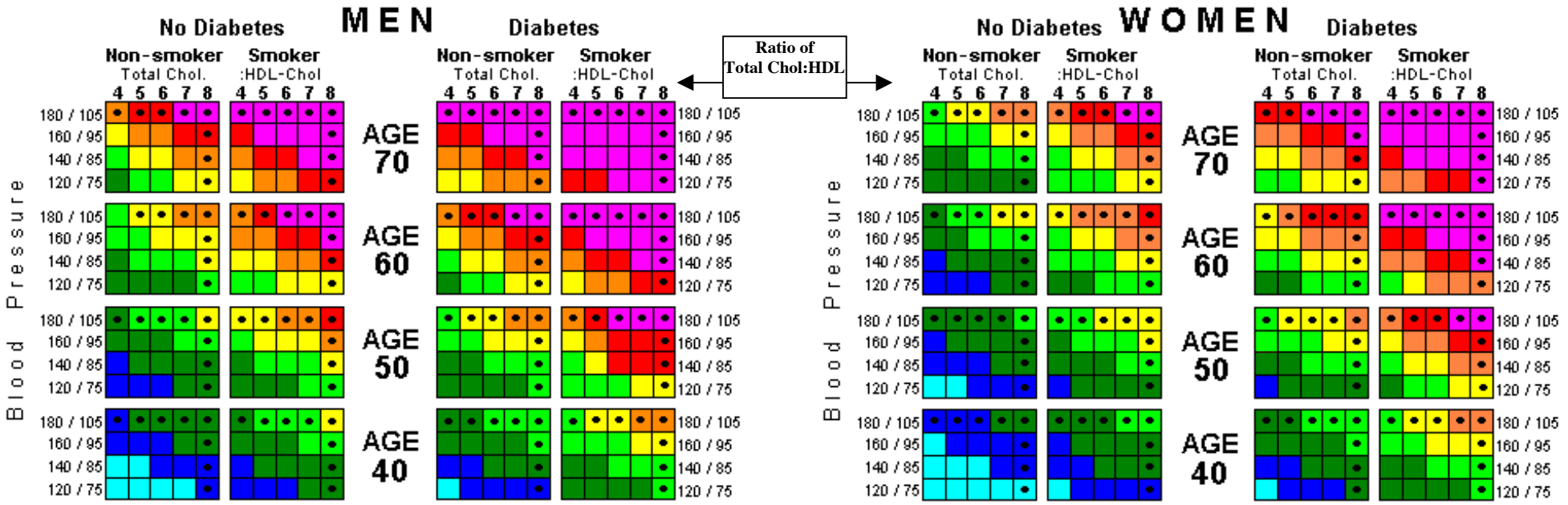
SYNERGISTIC COMBO'S: **THIAZIDES**→with ACEI, ARB & **β**-Blocker **β-BLOCKER**→with diuretic, CCB (+ACEI if post MI/HF)
ACEI or ARB→with diuretic & CCB **CCB**→ with ACEI & **β**-Blocker

The ABCD Approach			
	A= ACEI or ARB **B**= β-blocker	**C**= CCB **D**= diuretic [low-dose]	If initial drug is A or B, adding drug C or D provides a synergistic effect. If initial drug is C or D, adding drug A or B provides a synergistic effect; (C+diuretic, also option).

PROBLEMATIC COMBO'S:
- **hydralazine and diuretic** ⇨stimulate renin and sympathetic activity unless used together with β-blocker
- **verapamil or diltiazem** with a **β-blocker** ⇨negative effects on heart (e.g. ↓ heart rate and ↓ cardiac output)
- **β-blocker and clonidine** ⇨ concern about rebound hypertension if clonidine withdrawn abruptly
- **CCBS and α-blockers** ⇨ potential for excessive hypotension; increased risk of falls, etc.

LIFESTYLE changes for DIET (↓ Salt & Fat), EXERCISE, moderate alcohol use & stop SMOKING!
Also consider low dose ASA in high risk patients.

Table 7: CVD Risk Assessment Tables (Adapted From New Zealand Guideline Group with permission - http://www.nzgg.org.nz/library/gl_complete/bloodpressure/table1.cfm 58; also BMJ 59 & CMAJ 60)



Key to Risk Tables

RISK	Prognosis: 5 year CVD risk (non-fatal & fatal)	Benefit 1: CVD events prevented per 100 treated for 5 years *	Benefit 2: NNT for 5 years *
Very High	> 30%	> 10 per 100	< 10
	25-30%	9 per 100	11
	20-25%	7.5 per 100	13
High	15-20%	6 per 100	16
Moderate	10-15%	4 per 100	25
	5-10%	2.5 per 100	40
Mild	2.5-5%	1.25 per 100	80
	< 2.5%	< 0.8 per 100	> 120

Suggested starting point for discussion with patient about drug treatment.

- Cells with this marker indicate that in patients with very high levels of cholesterol (> about 8.5-9 mmol/L) or blood pressure (> about 170 / 100 mmHg), the risk equations may underestimate the true risk. **Therefore it is recommended that treatment be considered at lower absolute CVD risks than in other patients.**

* Assumes BP reduction of about 12 / 6 mmHg in patients with BP > 140-150 / 90, or cholesterol reduction of about 20% in patients with total cholesterol > 5.0-5.5 mmol/L, produces an approximate 30% reduction in CVD risk, whatever the pre-treatment absolute risk.

Also assess family history (↑ risk up to 50%), physical inactivity, obesity & LVH.

NZ-CVD-5yr Risk Tool: quick/easy way to estimate risk of CHD and stroke; the Framingham **10yr** risk assessment may also be used to estimate CHD risk. Antihypertensive benefit greater in those at highest risk!

Table 8: TARGETS Canadian

BLOOD PRESSURE [61]

Importance of accurate measurement e.g. 5 min resting

	Consider Treatment	Target
NO RISK FACTORS or target organ damage	≥160/100	<140/90
ISOLATED SYSTOLIC HTN (ISH)	SBP >160	SBP <140
MODERATE-HIGH RISK Patient	≥140/90	<140/90
♦If HOME BP Measurement	≥135/85	<135/85
DIABETES or RENAL Disease	≥130/80	<130/80
♦ If PROTEINURIA >0.5-1g/d	≥125/75	<125/75

LIPID [62]

Risk (often based on Framingham 10yr CAD risk)	LDL	T.Chol/HDL	TG
VERY HIGH *	<2.5	<4	<2
HIGH	<3	<5	<2
MODERATE	<4	<6	<2
LOW	<5	<7	<3

***Very High Risk** includes ALL patients with CAD / DIABETES & age 30+ / CVD / PAD.
VERY HIGH & HIGH Risk: Treat with medication & lifestyle changes concomitantly.
MODERATE & LOW Risk: May try lifestyle changes for 3-6 months before drug therapy.

BLOOD GLUCOSE [63]

	Optimal	Suboptimal	Inadequate
HbA_{1c} (%)	<7	7-8.4	>8.4
FPG (mmol/L)	4-7	7.1-10	>10
PPBG (mmol/L)	5-11	11.1-14	>14

Individualized Target Treatment Goals: give consideration to life expectancy, co-morbidity and risk of hypoglycemic side effects. **Monitor**: HbA_{1c} q3-6 months; calibrate meter yearly.

BP=blood pressure **CAD**=coronary artery disease **CVD**= cardiovascular disease **FPG**=fasting plasma glucose **HbA_{1c}**=glycosolated hemoglobin A_{1C} **HDL**=high density lipoprotein **LDL**=low density lipoprotein **PPBG**=postprandial (2hr) blood glucose **TG**=triglycerides

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