What we really need to do to reduce cardiovascular events in hypertensive patients

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In this article:
- *Review of 13 comparative antihypertensive drug trials*
- *Where to begin when there are coexisting conditions*
- *Report takes aim at poor medication adherence*

Practice recommendations
- *In your efforts to reduce cardiovascular events in hypertensive patients, concentrate on getting patients to goal, rather than on which drugs to use to get them there (A).*
- *Beta-blockers – especially atenolol – should not be the drug of first choice when treating older patients with hypertension (A).*
- *Multiple drugs are required for adequate blood pressure control in most patients (A).*

Strength of recommendation (SOR)
A. Good quality patient-oriented evidence
B. Inconsistent or limited-quality patient-oriented evidence
Consensus, usual practice, opinion, disease-oriented evidence, case series

FORGET ABOUT A SILVER BULLET

Researchers have conducted numerous trials over the last decade to find an antihypertensive drug that best reduces cardiovascular events while reducing blood pressure. However, this objective review of 13 comparative antihypertensive drug trials over the past decade involving more than 168,000 patients reveals no great differences in the cardiovascular protective effects of diuretics, beta-blockers, calcium channel blockers, angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE) inhibitors.

In fact, this review indicates that there were no significant differences in the primary cardiovascular endpoints in more than 90% of the patients studied. Where a difference in secondary clinical outcome was demonstrated, fewer events consistently occurred in the regimen that reached the lower blood pressure level.

This assessment will likely fly in the face of the way that many would view this body of research. That's understandable. At first glance, it would appear that these 13 trials, with different methodology and endpoints, have produced conflicting conclusions with the confusion worsened by pharmaceutical companies seeking to interpret the results to best suit their marketing needs. (1-3)

It is not the quality of the data, however, that is in question; the controversy lies in the interpretation. Subjecting the studies to further statistical analysis would simply obscure the information.

By reviewing the data impartially and objectively as a whole, though, and interpreting individual studies in light of similar studies, it becomes evident that there is more consensus than conflict. The studies support the notion that we should concentrate on getting patients to goal, rather than focusing on which drugs we'll use to get them there.

METHODS

I performed a PubMed search of the last 10 years using the keywords *hypertension, comparative, drug trials*. I supplemented my search with references from the JNC 7, WHO, BHS/NICE, and European hypertension guidelines. For this review, I included only randomized controlled trials with clinical cardiovascular primary endpoints. The studies had to have enrolled at least 500 patients and followed them for at least 3 years. Thirteen trials satisfied these criteria. (4-17) All 13 are summarized in the *Table*,

but I will review 5 of the more recent trials here. They are:

- ASCOT-BPLA – Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm
- ALLHAT – Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
- ANBP2 – Second Australian National Blood Pressure Study
- LIFE – Losartan Intervention For Endpoint reduction
- VALUE – Valsartan Antihypertensive Long-term Use Evaluation.

Calcium channel blockers vs beta-blockers

ASCOT-BPLA studied 19,257 high-risk hypertensive patients on amlodipine (Norvasc), adding perindopril, or atenolol (Tenormin), adding bendroflumethiazide. (17) After 5.5 years, the primary end-point of nonfatal myocardial infarction (MI) and cardiovascular death was similar (relative risk [RR]=0.90; 95% confidence interval [CI], 0.79–1.02; *P*=.1052).

FAST TRACK

More than 60% of the patients in one trial required 2 or more drugs for good blood pressure control.

Total coronary endpoint, stroke, and mortality were all lower on amlodipine. Blood pressure was significantly lower on amlodipine compared with atenolol, with an average difference of 2.7/1.9 mm Hg over the trial duration (18).

At the end of the trial, patients on amlodipine also had a significantly higher HDL cholesterol, and lower body mass index, triglyceride, creatinine, and glucose levels. However, when researchers made a multivariate adjustment for all of these risk factors, cardiovascular event rate differences between the 2 groups disappeared, underscoring the importance of controlling for all risk factors in reducing clinical cardiovascular events (18,19).

A careful reading of ASCOT-BPLA, then, makes it clear that this study does not support the notion that newer antihypertensives (calcium channel blockers and ACE inhibitors) are superior to older ones (beta-blockers and diuretics) (20,21). This study actually demonstrates that while blood pressure reduction is vital, the differences between regimens are less important.

LARGEST HYPERTENSIVE TRIAL EVER STUDIED 4 DRUGS

ALLHAT, the largest hypertensive trial ever conducted, randomized 15,255 patients to chlorthalidone, 9061 to doxazosin (Cardura), 9048 to amlodipine, and 9054 to lisinopril (Prinivil/Zestril) (10,11). (The arm involving doxazosin was terminated after 3.2 years) (11,12).

Compared with the beta-blocker, more patients achieved target blood pressure control on chlorthalidone (63% vs 58%), and systolic blood pressure was about 2 mm Hg lower. Although the primary outcome of fatal coronary heart disease and nonfatal MI was equal in both groups (doxazosin=7.91%; chlorthalidone=7.76%; RR=1.03 [95% CI, 0.93–1.15]; *P*=.62), the doxazosin arm had more stroke, heart failure, and combined cardiovascular events.

Patients on amlodipine and lisinopril had a longer follow-up of 4.9 years. Systolic blood pressure was higher on amlodipine (0.8 mm Hg, *P*=.03) and lisinopril (2 mm Hg, *P*<.001) than on chlorthalidone. The primary endpoint (fatal coronary heart disease and nonfatal MI) was similar on the diuretic (11.5%), calcium channel blocker (11.3%; RR=0.98 [95% CI, 0.90–1.07]; *P*=.65), and ACE inhibitor (11.4%; RR=0.99 [95% CI, 0.91–1.08]; *P*=.81). Compared with the diuretic arm, the calcium channel blocker arm had a higher incidence of heart failure, while the ACE inhibitor arm had a higher incidence of heart failure, stroke, and combined cardiovascular disease. The results were similar whatever the initial glycemic state, renal function status, and racial makeup of the patients studied (23-26). More than 60% of patients in ALLHAT required 2 or more drugs for good blood pressure control (27).

"Diuretics first" for patients with or without diabetes?

In ALLHAT, although diabetes occurred more frequently and fasting glucose rose in patients on diuretics, these metabolic abnormalities did not result in more cardiovascular events. Even among patients with diabetes, heart failure was more common on doxazosin, amlodipine, and lisinopril compared with those on chlorthalidone (23,24).

Given that the ultimate aim of hypertensive therapy is to reduce clinical disease – not just to improve laboratory profiles – ALLHAT should put to rest any apprehension physicians have about diuretic use. These findings have even led to suggestions that diuretics be the first line antihypertensive agent, in both diabetic and nondiabetic patients (28-30).

ACE INHIBITOR VS DIURETIC

ANBP2 randomized hypertensive patients to initial treatment with an ACE inhibitor (n=3044) or a diuretic (n=3039) (12). With similar blood

YEAR	TRIAL	N	DRUGS COMPARED	PRIMARY ENDPOINT	RELATIVE RISK (95% CI)	P VALUE
1998	UKPDS (4)	758	Captopril vs atenolol	Clinical diabetic event	1.1 (0.86-1.41)	.43
				Diabetic death	1.27 (0.82-1.97)	.28
				Total mortality	1.14 (0.81-1.61)	.44
1999	CAPPP (5)	10,985	Captopril vs diuretic/beta-blocker	MI+stroke+CV death	1.05 (0.90-1.22)	.52
1999	STOP 2 (6)	6614	New vs conventional drugs	CV death	0.99 (0.84-1.16)	.89
		4418	ACE I vs conventional drugs	CV death	1.01 (0.84-1.22)	.89
		4409	CCB vs conventional drugs	CV death	0.97 (0.80-1.17)	.72
2000	INSIGHT (7)	6321	Nifedipine LA vs diuretic	CV death, MI, HF, stroke	1.1 (0.91-1.34)	.35
2000	NORDIL (8)	10,881	Diltiazem vs beta-blocker/diuretic	Stroke, MI, CV death	1.00 (0.87-1.15)	.97
2002	LIFE (9)	9193	Losartan vs atenolol	CV death, stroke, MI	0.87 (0.77-0.98)	.021
2002–3	ALLHAT (10,11)	24,303	Amlodipine vs chlorthalidone	Fatal CHD, nonfatal MI	0.98 (0.90-1.07)	.65
		24,309	Lisinopril vs chlorthalidone	Fatal CHD, nonfatal MI	0.99 (0.91-1.08)	.81
		24,314	Doxazosin vs chlorthalidone	Fatal CHD, nonfatal MI	1.03 (0.93-1.15)	.62
2003	ANBP2 (12)	6083	ACE I vs diuretic	CV event,* death	0.89 (0.79-1.00)	.05
2003	CONVINCE (13)	16,602	Verapamil vs atenolol/thiazide	Stroke, MI, CV death	1.02 (0.88-1.18)	.77
2003	INVEST (14)	22,576	Verapamil vs atenolol	Death, nonfatal MI, nonfatal stroke	0.98 (0.90-1.06)	.57
2004	VALUE (15)	15,245	Valsartan vs amlodipine	CV event†	1.04 (0.94-1.15)	.49
2004	JMIC-B (16)	1650	Nifedipine retard vs ACE I	Cardiac events‡	1.05 (0.81-1.37)	.86
2005	ASCOT (17)	19,257	Amlodipine (+ perindopril) vs atenolol (+ thiazide)	Nonfatal MI, fatal CHD	0.90 (0.79-1.02)	.1052

Table. More consensus than conflict among 13 comparative antihypertensive drug trials with cardiovascular primary endpoints

ACE I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.
***Defined as coronary events including MI, heart failure, acute occlusion of artery, dissecting or ruptured aortic aneurysm, and cerebrovascular events including stroke and transient ischemic attacks.**
† Defined as cardiac death, hospitalized heart failure, nonfatal MI, and emergency procedures to prevent MI.
‡ Defined as cardiac death or sudden death, MI, angina pectoris requiring hospitalization, heart failure requiring hospitalization, serious arrhythmia, and coronary interventions.

pressure reduction in both arms (26/12 mm Hg), treatment with the ACE inhibitor resulted in a lower incidence of the composite primary endpoint of cardiovascular events or total death that was of borderline significance (ACE inhibitor =22.8%; diuretic=24.2%; RR=0.89 [95% CI, 0.79–1.00]; *P*=.05).

FAST TRACK

There is evidence that beta-blockers are less useful in the older hypertensive patient.

Among women, there was no difference between the ACE inhibitor and diuretic groups. In the overall population, there was also no

difference individually of total mortality or incidence of first cardiovascular event or death.

Thus ANBP2 actually confirms the results from ALLHAT by showing that ACE inhibitors and diuretics are equivalent in reducing cardiovascular events in hypertension (31).

LOSARTAN *VS* ATENOLOL

In the LIFE study, 9193 hypertensive patients with left ventricular hypertrophy were randomized to either losartan (Cozaar) or atenolol. (9) Losartan treatment resulted in a marked reduction in stroke incidence, which produced a significant reduction in the composite primary end-point of death, MI, or stroke (11% vs 13%; RR=0.87 [95% CI, 0.77–0.98]; *P*=.021).

When only the 1195 patients with diabetes were assessed, there was a significant reduction not only in the primary endpoint but also in cardiovascular and total mortality (32). Surprisingly, the reduction of stroke incidence did not reach statistical significance in this diabetic population (RR=0.79 [95% CI, 0.55–1.14]; *P*=.204).

A word of caution, though: The results of LIFE should be taken together with data from other trials. No other study has demonstrated a special benefit from the renin-angiotensin antagonists in preventing stroke. In fact, ACE inhibitors were weaker than the comparator drugs in preventing stroke in both CAPPP *(Table)* and ALLHAT (5,10). Various reviews have suggested that among antihypertensive drugs, it is the diuretics and calcium channel blockers that may be more useful in stroke reduction (33,34).

CHALK THE BENEFIT UP TO THE DROP IN BLOOD PRESSURE

In the LIFE study, the treated mean systolic blood pressure was lower with losartan in the overall (1.1 mm Hg; *P*=.017) and diabetic (2 mm Hg; *P* value not stated) populations, and thus the clinical benefit could possibly have been from the better blood pressure reduction on losartan. Furthermore, there is evidence that beta-blockers are less useful in the older hypertensive patient, and are especially weak in preventing stroke incidence (35,36).

Rather than showing the superiority of the ARB, it is fair to say that LIFE actually confirms the importance of blood pressure reduction, and reveals the weaker cardiovascular protective effect of atenolol in older hypertensive patients.

VALSARTAN, AMLODIPINE IN HIGH-RISK PATIENTS

VALUE randomized 15,245 high-risk hypertensive patients to valsartan (Diovan) and amlodipine (15,37). Trial researchers sought to study the difference – for the same level of blood pressure reduction – between the 2 regimens in the incidence of cardiac events defined as sudden cardiac death, hospitalized heart failure, nonfatal MI, and emergency procedures to prevent MI. That said, the attained blood pressure was lower on the calcium channel blocker: 4.0/2.1 mm Hg at 1 month and 2.1/1.7 mm Hg at the end of study.

After 4.2 years, there was no significant difference in the primary endpoint of first cardiac event (10.6% valsartan/10.4% amlodipine; RR=1.04 [95% CI, 0.94–1.15]; *P*=.49). Diabetes was lower, but the rate of MI was higher on valsartan. After correction for the blood pressure difference, the composite of cardiac events, stroke, death, or MI was similar in the 2 groups.

VALUE patients reaching adequate blood pressure control by 6 months fared better, regardless of drug type used. Thus demonstrating that the benefit from good blood pressure control was more important than the subtle differences between antihypertensive drugs. The better metabolic profile in the angiotensin receptor blocker arm did not translate into a reduction in adverse clinical disease.

The VALUE trial suggests (as did ALLHAT) that drugs targeting the reninangiotensin system do not provide special cardiovascular protection (10,15).

WHERE TO BEGIN WHERE ARE COEXISTING CONDITIONS

Choosing an antihypertensive drug according to the clinical disease and target organ most at risk of damage is logical and in keeping with numerous guidelines (42-45). Thus, you'll want to treat hypertensive patients with these conditions as follows:

- **Angina pectoris.** Therapy should include a beta-blocker or calcium channel blocker, given their definite antianginal and possible anti-atherosclerotic effects (16,46,47).
- **Prior MI.** Start the patient on a beta-blocker (47).
- **Poor left ventricular function.** Start the patient on a diuretic, and then add an ACE inhibitor and beta-blocker, as needed (10,49,50).
- **Prior stroke (or a patient at special risk of stroke).** Begin therapy with a calcium channel blocker or a diuretic (33,34).

Diabetic proteinuria. An ARB or an ACE inhibitor is best suited to prevent and delay nephropathy (51-54).

CONSENSUS EMERGES FROM STUDIES SPANNING 10 YEARS

This objective review of the comparative hypertension drug trials shows that there are no great differences in the cardiovascular protective efficacy of the diuretics, beta-blockers, calcium channel blockers, ARBs, and ACE inhibitors.

There was no significant difference in the cardiovascular primary endpoint in 11 of the 13 trials reviewed, involving 91% of the randomized 168,593 patients *(Table)* (4-8,10,11,13-17). Of the remaining 2 trials, the difference in ANBP2 just reached a *P* value of .05, while the result in LIFE was driven by a lower stroke incidence on ARB treatment that is not noted in any of the other studies involving an ARB or ACE inhibitor (4-6,10,12-15).

FAST TRACK

Focus on how best to reach adequate blood pressure control by combining several antihypertensive drugs.

FOCUS ON CONTROLLING BLOOD PRESSURE WITH COMBINATION OF DRUGS

Given the very large number of patients studied in these well-conducted trials, if there were any especially useful, or detrimental, cardiovascular effect of a particular class of antihypertensive drug, it would have been obvious by now. Since most patients will require multiple drugs, the equivalent protective efficacy of different antihypertensive drugs is reassuring and suggests that physicians should not worry too much about which drug to start the patient on (28). Rather, the emphasis should be on how best to reach adequate blood pressure control by combining several antihypertensive drugs.

FAST TRACK

Treating patients to goal hinges on medication adherence. See related story on page 734.

SMALL BLOOD PRESSURE DIFFERENCES, BIG IMPACT

In LIFE (losartan vs atenolol), ALLHAT (doxazosin, amlodipine, lisinopril vs chlorthalidone), VALUE (amlodipine vs valsartan), and ASCOT (amlodipine vs atenolol), where a secondary cardiovascular endpoint was lower in one of the treatment arms, it was always the arm with the lower achieved blood pressure that had the better clinical outcome (9-11,15,17).

REPORT TAKES AIM AT AMERICA'S OTHER DRUG PROBLEMS: POOR ADHERENCE

MARYA OSTROWSKI, JFP Editor

With only 50% of patients typically taking their medications as prescribed and the cost of poor adherence reaching an estimated $177 billion annually in direct and indirect health care costs, one medication safety group is saying enough is enough.

The National Council on Patient Information and Education (NCPIE), a nonprofit coalition that includes health professional associations, government agencies, and pharmaceutical companies, issued a report this summer detailing a 10-step action plan for reducing the adverse health and economic consequences of poor medication adherence.

The plan, developed by a panel of experts that NCPIE convened, calls on the government and health care community to, among other things:

- *address the barriers to patient adherence for patients with low health literacy.*
- *develop a curriculum on medication adherence for use in medical schools.*
- *mount a unified national education campaign to make patient adherence a national health priority.*

"Medication adherence is America's new drug problem," said Carolyn M. Clancy, MD, director of the Agency for Healthcare Research and Quality. AHRQ has been working with NCPIE, the FDA, and the National Consumers League to develop a public education campaign on medication adherence, according to Clancy. The NCPIE report helps to bolster those ongoing efforts, she said.

On the heels of the report, NCPIE is planning on releasing videos that will teach seniors about properly taking their medications, according to Ray Bullman, NCPIE's executive vice president.

To learn more about NCPIE's initiatives, or for a copy of the report, Enhancing Prescription Medicine Adherence: A National Action Plan, point your browser to: www. talkabouttrx.org.

These achieved blood pressure differences although small, were significant. Small overall mean blood pressure differences could mask much larger blood pressure differences in the individual patient. Consider, for instance, the HOPE (Heart Outcomes Prevention Evaluation) trial, where a reported overall blood pressure

difference of only 3/1 mm Hg between the 2 treatment arms masked a difference of 10/4 mm Hg in 24-hour ambulatory blood pressure and a difference of 17/8 mm Hg in night-time blood pressure (39,40).

Thus, instead of trying to work out why antihypertensive drugs could exert apparently different cardiovascular protective efficacy in different trials, the simple and consistent message is that the lower the achieved blood pressure, the lower the adverse clinical cardiovascular outcome.

WHAT MAKES SENSE FOR YOUR PATIENT?

In selecting antihypertensive drugs, physicians should be guided by data supporting a particular drug in coexisting clinical conditions. (See "Where to begin when there are coexisting conditions") In the hypertensive patient who is free of clinical disease, a case can be made for a diuretic as the first-line drug, although calcium channel blockers, ARBs, and ACE inhibitors can also claim evidence to support their use. In the older patient, beta-blockers –especially atenolol – should not be the drug of first choice (35,36,41).

FAST TRACK

The lower the achieved blood pressure, the lower the adverse clinical cardiovascular outcome.

As this review of comparative hypertension drug trials shows, multiple drugs are required for adequate blood pressure control in most patients. Thus, physicians should not be too preoccupied about how to initiate treatment, but remember to add drugs until adequate control is achieved.

FAST TRACK

"Medication adherence is America's new drug problem." Carolyn M. Clancy, MD, AHRQ director

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Revista presei medicale

Elveţia: cancerul învins cu ajutorul luminii şi metalelor

Switzerland: cancer was depleated with the help of light and metals

ALIC MIRZA, 01.11.2007

Chimişti elveţieni de la Universitatea din Neuchatel, Ecole Polytechnique Federale din Lausanne (EPFL) şi de la Spitalul Universitar din acelaşi oraş au pus la punct o nouă armă împotriva cancerului. Ei au combinat un medicament care măreşte sensibilitatea celulelor canceroase faţă de lumină cu o serie de compuşi chimici ai ruteniului, un metal tranziţional în tabelul periodic al lui Mendeleev.

Substanţele au fost sintetizate la Institutul de Chimie al Universităţii din Neuchatel, a precizat conducerea acestuia într-un comunicat. Primele teste biologice desfăşurate la EPFL şi la Spitalul Universitar din Lausanne au dus la obţinerea unor „rezultate excelente" în lupta cu celulele tumorale din melanom.

Moleculele pe baza de metale, în special cele cu platină, sunt întrebuinţate pe scară largă în terapiile anticanceroase, dar prezintă un inconvenient major, şi anume efectele secundare. Ruteniul, care face parte din familia metalelor platinice, pare să fie soluţia salvatoare, afirmă cercetătorii, un potenţial confirmat de altfel în urma studiilor clinice.

Cât despre lumină, în general o rază laser distruge celulele canceroase sensibilizate cu un medicament faţă de acţiunea sa. Brevetat, noul plan de atac apărut în laboratoarele Universităţii din Neuchatel şi care combină lumina cu compuşii organo-metalici lasă să se întrevadă „speranţa că aceste ***produse*** *vor fi administrate pacienţilor într-un termen cât mai scurt", se mai afirmă în comunicat.*

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