

Fluid Matters in Choosing Antihypertensive Therapy: A Hypothesis That the Data Speak Volumes

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Assuming that blood pressure is lowered equivalently, diuretics are more effective than angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and α -adrenergic receptor blockers (α -blockers) at preventing heart failure, and they are more effective than ACEIs and α -blockers at preventing strokes. Compared with β -adrenergic receptor blockers (β -blockers) and ACEIs, CCBs are less effective at reducing myocardial infarcts and heart failure. There is currently no conceptual framework by which to organize data indicating that some antihypertensive medications are better than others at preventing cardiovascular diseases. The thesis of this article is that the fluid reduction or fluid retention attributable to antihypertensive medications, either alone or in combination, provides a basis for ranking these medications. Diuretics have a theoretical advantage compared with other antihypertensive medications because they reduce total body fluid more than other agents. Therefore, they are the preferred drugs for treating hypertension. The other antihypertensive agents that promote fluid reduction, ACEIs and angiotensin receptor blockers (ARBs), are next in preference, ranking a close second to diuretics. Because β -blockers have a neutral effect on total body fluid, they rank on a third tier of preference, after ACEIs and ARBs. CCBs and α -blockers are the least preferred medications for treating hypertension because they promote fluid retention. (J Am Board Fam Pract 2005;18:113–24.)

Provided that blood pressure is lowered comparably, diuretics have been demonstrated to be more effective than angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and α -adrenergic receptor blockers (α -blockers) at preventing heart failure, and diuretics have been found to be more effective than ACEIs and α -blockers at preventing strokes.^{1–5} Diuretics offer no advantage over ACEIs, CCBs, or α -blockers in preventing fatal coronary heart disease, preventing nonfatal myocardial infarcts, or lowering all-cause mortality, and diuretics offer no advantage over CCBs in preventing strokes.^{3,4} Compared with β -adrenergic receptor blockers (β -blockers) and ACEIs, CCBs are less effective at reducing myocardial infarcts and heart failure.^{1,2}

Although the preponderance of the evidence favors using diuretics as first line pharmacological therapy for the treatment of hypertension,⁶ the

research data do not uniformly support this conclusion. The Second Australian National Blood Pressure (ANBP2) study demonstrated that, particularly in men, there were fewer cardiovascular events and fewer deaths from any cause in the group treated with ACEIs than in the group treated with hydrochlorothiazide (HCTZ).⁷ The favorable results for the ACEI in ANBP2 may reflect, in part, the predominance of white persons in the study population. Several studies have documented that the nondihydropyridine CCBs diltiazem and verapamil are equivalent to, and in some instances better than, diuretics and β -blockers in preventing some cardiovascular diseases.^{8–10} The second Swedish Trial in Old Patients with Hypertension (STOP-Hypertension-2) trial found no difference in long-term cardiovascular outcomes between subjects taking diuretics and β -blockers and subjects taking ACEIs and CCBs.¹¹ The Captopril Prevention Project (CAPPP) compared captopril with diuretics and β -blockers and found that subjects treated with captopril were less likely to die from cardiovascular causes, but subjects in the captopril group were more likely to develop strokes.¹² One might argue that β -blockers potentially di-

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luted the benefit of the diuretics in the STOP-Hypertension-2 and CAPPP trials, but in the Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY) study, metoprolol was found to be superior to diuretics in terms of preventing sudden cardiovascular deaths.¹³

Of course, there are limitations in comparing the results of different antihypertensive trials. One limitation is that demographic differences such as age, gender, race, and ethnicity may confound the comparisons. Another limitation is that not all antihypertensive trials achieved equivalency in blood pressure reduction. For example, subjects in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study assigned to diuretic treatment had lower systolic blood pressures than subjects assigned to ACEI, CCB, or α -blocker treatment, and subjects in the CCB group had lower diastolic blood pressures than subjects in the diuretic group.^{3,4} Even though the ALLHAT investigators made appropriate adjustments for the differences in blood pressures, these differences cloud the interpretation of the results.¹⁴

This article proposes that, apart from blood pressure lowering itself, the fluid reduction or fluid retention property of each antihypertensive medication helps explain its relative merit in preventing cardiovascular diseases. The benefit of diuretics compared with other antihypertensive medications lies in the ability of diuretics to lessen total body fluid—total body fluid being the sum of the intravascular fluid, the intracellular fluid, the interstitial fluid, and fluid that is third-spaced (pleural effusions or ascites). That ACEIs are sometimes superior to diuretics in terms of cardiovascular outcomes lies in the fluid reduction properties of ACEIs. On the other hand, compared with diuretics, β -blockers, ACEIs, and clonidine, the relative inferiority of CCBs in reducing myocardial infarcts and heart failure¹ is the result of fluid retention. Finally, nondihydropyridine CCBs result in less fluid retention than do dihydropyridine CCBs. This may explain why some studies found no cardiovascular outcome differences when nondihydropyridine CCBs were compared with diuretics and β -blockers. This article will use the term “diuretic” to refer to thiazide medications such as HCTZ or chlorthalidone.

There is no method to directly and readily measure total body fluid. Weight gain or loss is used as

a surrogate marker for total body fluid increases or decreases. Based on the presence or absence of leg edema, it is possible to gauge whether the amount of interstitial fluid is increased or not. Based on the presence or absence of jugular venous distension, hepatojugular reflux, or an S3 or S4 cardiac murmur, it is possible to gauge whether the amount of intravascular fluid is increased or not, and based on the presence or absence of ascites or a pleural effusion, it is possible to gauge whether fluid is third-spaced or not. In general, if there is increased interstitial fluid, increased intravascular fluid, or increased third-spaced fluid, then there is increased total body fluid.

If total body fluid determines the relative merits of antihypertensive medications, it is unclear why, but intravascular volume is probably a factor. When there is excess interstitial fluid in the form of leg edema, increased cardiovascular pathology may result from repetitive, transient changes in the fluid volume of the intravascular compartment that results from fluid shifting to dependent parts of the body, via the blood vessels and lymphatics, depending on whether people are recumbent or upright.

Table 1 lists a number of different antihypertensive medications and the rates of edema that have been reported with each one. Only trials involving hypertensive subjects without diabetes are included.

Calcium Channel Blockers

Leg edema is a common dose-dependent side effect of the CCBs. Edema formation occurs even though CCBs increase renal sodium excretion (natriuresis).^{15,16} In the case of nifedipine, the edema occurs simultaneously with the natriuresis.¹⁷

CCBs increase renal blood flow by selectively dilating the renal afferent arterioles, thereby resulting in natriuresis and diuresis.¹⁸ The initial diuretic and natriuretic effects of most CCBs probably persist with long-term usage,^{19,20} but the natriuresis resulting from nifedipine may be transient.²¹

Edema occurs with CCBs because of vasodilation in the distal arterioles, thereby leading to increased intravascular capillary pressures and increased venous pressures, at least in the lower extremities,²² and eventually leakage of fluid into the extracellular space.

In placebo-controlled studies, the rate of edema was 11% in a group treated with nifedipine, 14% in

Table 1. Frequency of Edema in Controlled and Uncontrolled Trials of Different Antihypertensive Medications

Medication Reference	Total Daily Dose (mg)	Sample Size	Edema (%)
Dihydropyridine Calcium Channel Blockers			
Amlodipine			
Koenig, 1993 ³⁰	5–10	59	1.7
Frishman et al, 1995 ³¹	2.5	82	3.8
Kuschnir et al, 1996 ³²	5	77	16.9
Corea et al, 1996 ³³	5	84	3.6
Corea et al, 1996 ³³	10	28	14.3
Messerli et al, 2000 ²⁹	5	144	15
Messerli et al, 2000 ²⁹	10	144	32
Kloner et al, 2001 ³⁴	5–10	127	22.1
Felodipine			
Freeling et al, 1987 ³⁵	2.5–10	32	28.1
Dahlof and Hosie, 1990 ³⁶	10	53	18.9
Hammond and Cutler, 1993 ³⁷	5–10	71	29.6
Koenig, 1993 ³⁰	5–10	59	0.0
Fagan et al, 1994 ²⁶	5–10	137	12.4
Goldberg et al, 1995 ²⁴	Unspecified	43	14.0
Gradman et al, 1997 ³⁸	2.5–10	176	10.8
Schloze et al, 1999 ³⁹	5–10	84	7.1
Isradipine			
Hammond and Cutler, 1993 ³⁷	5–10	72	13.9
Eisner et al, 1991 ⁴⁰	2.5–10	78	7.7
Lacdapine			
UK Lacdapine, 1991 ⁴³	4	268	6.0
Nicardipine			
Gradman et al, 1992 ⁴¹	45	73	8.2
Gradman et al, 1992 ⁴¹	60	73	15.1
Nifedipine			
Daniels and Opie, 1986 ²³	40	35	11.4
Heagerty et al, 1988 ²⁵	20–40	210	12.4
Fagan et al, 1994 ²⁶	30–90	140	20.0
Steiner and Pauly, 1994 ²⁷	40	55	12.7
Brown et al, 2000 ²⁸	30–60	3,157	28.4
Messerli et al, 2001 ²⁹	30	130	5.4
Messerli et al, 2001 ²⁹	60	129	22.3
Nisoldipine			
Ruddy and Fodor, 1997 ⁴²	10–40	138	18.8
Nitrendipine			
Gennari et al, 1989 ⁴⁴	10	12	16.7
Morgan et al, 1990 ⁴⁵	20–40	38	5.3
Nondihydropyridine Calcium Channel Blockers			
Diltiazem			
Pool et al, 1986 ⁵⁸	120–360	45	8.9
Weir et al, 1987 ⁶⁰	240–360	39	2.6
Hedner et al, 1990 ⁵⁹	120–360	63	4.8
Ruddy et al, 1995 ⁶¹	180–360	54	5.6
Ruddy et al, 1995 ⁶¹	180–360	57	8.8
Nilsson et al, 1996 ⁶²	240–420	138	2–7
Cushman et al, 1998 ⁵⁷	120	150	2.7
Cushman et al, 1998 ⁵⁷	180	152	3.3
Verapamil			
Speders, 1989 ⁵¹	240–480	4,247	0.7
Gradman et al, 1992 ⁴²	240	72	4.2
Karlberg et al, 2000 ⁵²	240	96	13.5
White et al, 2001 ⁵⁰	180–540	580	2.8
α-Blockers			
Doxazosin			
Ott et al, 1987 ⁷²	1–16	63	12.7
Prazosin			
Melkid, 1984 ⁸⁰	2–4	79	10.1
Goldberg et al, 1988 ²⁴	2–20	193	22.3
Angiotensin-Converting Enzyme Inhibitors			
Benazapril			
Frishman et al, 1995 ³¹	10	85	1.2
Kushnir et al, 1996 ³²	20	77	1.3
Captopril			
Gennari et al, 1989 ⁴⁴	50	12	0.0
MacLean, 1994 ⁸⁸	50	29	0.0

Table 1. Continued

Medication Reference	Total Daily Dose (mg)	Sample Size	Edema (%)
Enalapril			
Eisner et al, 1991 ⁴⁰	5–40	82	0.0
Gradman et al, 1997 ³⁸	5–20	133	3.8
Cushman et al, 1998 ⁵⁷	5	144	3.5
Lisinopril			
Ruddy and Fodor, 1997 ⁴²	5–20	140	2.9
Ramipril			
Schloze et al, 1999 ³⁹	2.5–10	125	0.0
Trandolapril			
Steiner and Pauly, 1994 ²⁷	2	54	7.4
Karlberg et al, 2000 ⁵²	2	96	4.2
Captopril, Enalapril, or Lisinopril			
Goldberg et al, 1995 ²⁴	Unspecified	239	1.7
Enalapril or Lisinopril			
Hansson et al, 1999 ¹¹	10	2,205	8.7
Angiotensin Receptor Blockers			
Candesartan			
Kloner et al, 2001 ³⁴	16–32	123	8.9
Irbesartan			
Oparil et al, 2001 ¹⁰³	150	145	0.7
Losartan			
Goldberg et al, 1995 ²⁴	Unspecified	2,085	1.7
Oparil et al, 2001 ¹⁰³	50	146	0.0
Dahlof et al, 2002 ¹⁰⁵	50–100	4,605	11.7
Olmesartan			
Neutel, 2001 ¹⁰²	2.5–80	2,540	0.8
Oparil et al, 2001 ¹⁰³	20	145	0.7
Valsartan			
Corea et al, 1996 ³³	80	84	2.4
Oparil et al, 2001 ¹⁰³	80	142	2.1
Biswas et al, 2002 ¹⁰⁴	Unspecified	12,881	1.4
β-Blockers			
Atenolol			
Daniels and Opie, 1986 ²³	100	35	5.7
Ott et al, 1987 ⁷²	50–100	63	6.3
Weir et al, 1987 ⁶⁰	50–100	39	2.6
Heagerty et al, 1988 ²⁵	50–100	200	1.0
UK Lacidipine, 1991 ⁴³	50	265	3.8
Goldberg et al, 1995 ²⁴	Unspecified	68	1.5
Dahlof et al, 2002 ¹⁰⁵	50–100	4,588	13.9
Carvedilol			
Morgan et al, 1990 ⁴⁵	12.5–50	103	0.0
Dilavelol			
Materson et al, 1989 ¹¹²	200–1600	310	1.0
Metoprolol			
Freeling et al, 1987 ³⁵	100	32	0.0
Materson et al, 1989 ¹¹²	100–400	137	2.9
Hedner et al, 1990 ⁵⁹	50–200	63	4.8
Feliciano et al, 1990 ¹¹³	100–400	126	3.2
Dahlof and Hosie, 1990 ³⁶	100	52	0.0
Pindolol			
Morgan et al, 1990 ⁴⁵	Unspecified	39	0.0
Diuretics			
HCTZ			
Goldberg et al, 1995 ²⁴	Unspecified	27	1.8
HCTZ plus amiloride			
Brown et al, 2000 ²⁸	25–50/2.5–5	3,164	4.3

a group treated with felodipine, and 2% to 20% in the placebo groups.^{23,24} In non-placebo-controlled studies, the rates of edema with dihydropyridine CCBs ranged from 5% to 28% with nifedipine,^{25–29} 2% to 32% with amlodipine,^{29–34} 0% to 30% with felodipine,^{24,26,30,35–39} 8% to 14% with isradipine,^{37,40} 8% to 15% with nicardipine,⁴¹ 19%

with nisoldipine,⁴² 6% with lacidipine,⁴³ and 5% to 17% with nitrendipine.^{44,45} Two non-placebo-controlled studies, one using nifedipine and the other isradipine, did not report edema as an adverse event.^{46,47}

The nondihydropyridine CCBs verapamil and diltiazem also promote leg and ankle swelling.⁴⁸

Verapamil increases plasma volume,¹⁵ and it blunts postural cutaneous vasoconstriction in the lower extremities, as do amlodipine and nifedipine.⁴⁹ One placebo controlled study found that the prevalence of edema in patients with hypertension who were treated with verapamil was 3% compared with 5% in the placebo group.⁵⁰ Other non-placebo-controlled studies have found a 1% to 14% frequency of edema in subjects treated with verapamil.^{41,51,52} Several uncontrolled studies did not report edema as an adverse event of verapamil.^{53–56}

The frequency of edema in subjects treated with diltiazem is less variable than with verapamil. In placebo-controlled studies, the frequency of edema in the diltiazem group varied from 2% to 9%, compared with 0 to 3.3% in the placebo group.^{57–59} Non-placebo-controlled studies have found the frequency of edema with diltiazem to be 2% to 9%.^{60–62} Two non-placebo-controlled studies did not report edema as an adverse event of diltiazem.^{46,63}

α-Blockers

α-blockers promote fluid retention.^{64,65} Prazosin increases plasma volume, extracellular fluid volume, and weight.^{66–71} Doxazosin promotes weight gain in many, but not all, patients.^{71–74} Terazosin also causes weight gain,^{75–78} whereas withdrawing terazosin results in weight loss.⁷⁹

In a placebo-controlled study, edema was present in 22% of subjects treated with prazosin compared with 3% of the subjects in the placebo group.⁷⁰ In studies lacking a placebo group, edema occurred in 10% of subjects treated with prazosin⁸⁰ and in 13% of subjects using doxazosin.⁷²

Angiotensin-Converting Enzyme Inhibitors

ACEIs do not promote fluid retention.⁸¹ Captopril has natriuretic effects, reduces body weight, and lessens extracellular fluid volume.^{82–84} Enalapril has been shown to cause transient increases in interstitial fluid volume after 1 week of administration, but these increases are short-lived, and extracellular fluid volume returns to baseline after 6 weeks of therapy.⁸⁵ Other studies have demonstrated that changes in body weight, extracellular fluid, and plasma volume are minimal with ACEIs.^{86,87}

Most studies have reported a low prevalence of edema in subjects treated with an ACEI. The rates

of edema have varied from 0% with captopril,^{44,88} 0% to 4% with enalapril,^{38,40,57} 3% with lisinopril,⁴² 1% with benazapril,^{31,32} 0% with ramipril,³⁹ 4% to 7% with trandolapril,^{27,52} 2% in a study that used captopril, enalapril, or lisinopril,²⁴ and 9% in a study that used enalapril or lisinopril.¹¹ Only 4 of these studies were placebo-controlled, but in all 4, the frequency of edema in the ACEI group was comparable with or lower than the frequency of edema in the placebo group.^{24,31,32,57} Finally, a number of uncontrolled studies using ACEIs did not report edema as an adverse event.^{44,54,56,89–95}

Adding an ACEI to a dihydropyridine CCB lessens the edema caused by the CCB.^{27,31,32,38,39,92,96–98} The ability to dilate the venous capacitance vessels, thereby reducing elevated intracapillary and venous pressures brought about by the arteriole dilation of the CCB, is the likely mechanism by which ACEIs reduce the leg edema associated with CCBs.^{96,99} ACEIs also reduce edema caused by diabetic nephropathy.¹⁰⁰

Angiotensin Receptor Blockers

Like ACEIs, ARBs reduce edema. Valsartan promotes natriuresis and diuresis.¹⁰¹ In placebo controlled studies, losartan had a 1.7% edema rate compared with a 1.9% rate in the placebo group,²⁴ and olmesartan had a 0.8% edema rate compared with a 1.1% rate in the placebo group.¹⁰² Non-placebo-controlled studies using ARBs have reported variable rates of edema: 0.7% with olmesartan,¹⁰³ 1.4 to 2.4% with valsartan,^{33,103,104} 0.7% with irbesartan,¹⁰³ 9% with candesartan,³⁴ and 12% with losartan.¹⁰⁵ In the losartan trial, many of the subjects were also treated with HCTZ, thereby raising the question as to whether the edema rate would have been higher were it not for the use of the diuretic.¹⁰⁵ Two uncontrolled studies involving losartan and telmisartan did not report edema as an adverse event.^{56,106}

β-Blockers

Edema formation and fluid retention are not considered side effects of β-blockers.^{107–110} Two studies have reported either an absence of weight gain, or nonsignificant weight gain, in subjects treated with atenolol.^{73,84} In placebo controlled studies of atenolol, metoprolol CR, and pindolol, the edema rates for the β-blockers varied from 1.7% to 6%

compared with 1.9% to 20% in the placebo groups.^{23,24,59,111}

A number of non-placebo-controlled studies of β -blockers have reported variable rates of edema: 1% to 6% for atenolol^{25,43,60,72}; 0% to 5% for metoprolol^{35,36,59,112,113}; 0% for carvedilol⁴⁵; 0% for pindolol⁴⁵; and 1% for diltiazem.¹¹²

Two trials that lacked a placebo group documented lower extremity edema frequently in subjects treated with β -blockers. The LIFE trial found that 14% of subjects in the atenolol arm of the trial had edema,¹⁰⁵ and the STOP-Hypertension-2 study found an edema rate of 8.5% in the group treated with atenolol, metoprolol, pindolol, or HCTZ plus amiloride.¹¹ Because some of the subjects treated with β -blockers in both the LIFE trial and the STOP-Hypertension-2 study were also treated with a diuretic, the rate of edema associated with β -blockers might have been even higher were it not for the diuretic. Finally, numerous non-placebo-controlled studies of metoprolol, atenolol, propranolol, and pindolol did not report edema as an adverse event.*

Diuretics

Only 2 studies have reported the frequency of edema in subjects treated with thiazide diuretics. A placebo controlled study found the edema rate in subjects treated with HCTZ to be 1.8%, whereas the edema rate in the placebo group was 1.9%.²⁴ A non-placebo-controlled study found a 4.3% edema rate in the group treated with a 2-diuretic regimen consisting of HCTZ plus amiloride.²⁸ It is surprising that so many patients with hypertension who were treated with a diuretic had any edema whatsoever. One possible explanation is that many of these subjects may have had edema before enrolling in the study. HCTZ decreases the leg edema associated with CCBs, although not as effectively as ACEIs.⁹⁸

Limitations

There are limitations involved in comparing fluid retention properties between different trials of antihypertensive medications. The most important limitation is using weight change or leg edema as proxy markers for total body fluid. It is significant that many cardiovascular experts consider leg

edema caused by CCBs to be a local phenomenon that should not be considered fluid retention. In response to this argument, one can only provide a common sense answer: fluid is fluid. The leg edema resulting from CCBs looks and feels the same as the leg edema that results from heart failure. CCBs promote natriuresis and diuresis, but this does not eliminate the possibility of a simultaneous increase in total body fluid. Experts who claim that the leg edema associated with CCBs does not represent fluid retention focus on the role of the kidneys but ignore the gastrointestinal tract. They forget that intake of salt and water is not static. In response to the increased natriuresis and diuresis of CCBs, humans can compensate by increasing their ingestion and absorption of salt and water. As a result, the amount of intravascular fluid can remain constant with CCBs, or perhaps even increase because of vasodilation, whereas interstitial fluid in the form of leg edema increases. Therefore, total body fluid can increase simultaneously with increased renal excretion of salt and water.

A second limitation is that adverse events typically increase with higher dosages of medication. Although it may be fair to contrast the frequency and severity of leg edema between different antihypertensive medications by comparing starting doses and maximal doses, many antihypertensive trials use a range of doses of the same medication in the same study, thereby raising difficulties in comparing the frequency of adverse events between trials.

Another limitation is that adverse events may increase with prolonged medication usage. Some antihypertensive trials last for months and others last for years. As a result, it is reasonable to question whether the frequency and severity of adverse events identified in a trial of short duration are comparable with the frequency and severity of adverse events identified in a trial of long duration.

In addition, the majority of antihypertensive trials do not include a placebo group. For these studies, it is not clear whether the adverse events that occur are attributable to the medication or to other factors. Many antihypertensive trials use 2 medications, and each medication serves as a control for the other, but this is not the same as using a placebo control.

Many trials of antihypertensive medications allow the usage of multiple medications if blood pressure is inadequately controlled after adminis-

*Refs. 53, 89, 90, 93, 94, 106, 110, and 114–116.

tration of the initial medication. These additional medications have their own properties and side effects, thereby confounding any attempt to determine the adverse events attributable to the initial medication.

Finally, although many antihypertensive trials report the prevalence of adverse events, including edema, after the administration of the study medication, none mention the prevalence of these conditions before initiating therapy. The prevalence of idiopathic edema has not been documented in subjects with hypertension, but idiopathic edema and hypertension are both associated with obesity.¹¹⁷ Therefore, there may be a relationship between idiopathic edema and hypertension, and edema that is reported as an adverse event in antihypertensive trials may have been present before subjects enrolled in the study. It is a deficiency of the entire antihypertensive literature that investigators do not include information as to the edema rate of enrollees before the study. Future antihypertensive trials can correct this inadequacy by reporting the prevalence of edema as a baseline characteristic of participants.

Conclusion

In summary, the fluid reduction property of diuretics, ACEIs, and ARBs, the fluid neutral property of β -blockers, and the fluid retention property of CCBs and α -blockers provide a theoretical basis by which to rank the different classes of antihypertensive medications in a hierarchical manner. Diuretics are the preferred agents for treating hypertension, followed closely by ACEIs and ARBs. β -Blockers are next in terms of preference, and CCBs and α -blockers are the least preferred medications for treating hypertension.

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