

Review Article

Meta-Analysis of the Hemodynamic Properties of Antihypertensive Medications

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Background. While all antihypertensive medications lower blood pressure, hemodynamic properties of various classes of antihypertensive medications may differ. **Objective.** To perform a meta-analysis to compare the hemodynamic properties of different classes of antihypertensive medications. **Methods.** Studies involving the treatment of hypertension using the effect of ACEIs, β -blockers, CCBs and thiazide diuretics on plasma volume (PV), cardiac output (CO) or stroke volume (SV) were searched using online databases prior to May 2011. Studies had to be written in the English language, studying human subjects with a single pharmacological agent (monotherapy), and with a minimum duration of 4 weeks. **Results.** Seventy-five (75) studies that enrolled a total of 1522 subjects were included. All four antihypertensive classes lowered blood pressure. β -blockers decreased heart rate; the other classes had no effect upon heart rate. ACEIs increased PV; the other classes had no effect upon PV. β -blockers and thiazide diuretics decreased CO while ACEIs and CCBs had no effect upon CO. β -blockers and CCBs increased SV, thiazide diuretics decreased SV, and ACEIs did not change SV. **Conclusion.** In the treatment of uncomplicated hypertension, the various classes of antihypertensive medications differ from each other in terms of their non-blood pressure lowering hemodynamic properties.

1. Introduction

While all antihypertensive medications lower blood pressure, the non-blood-pressure-lowering hemodynamic properties of the various classes of antihypertensive medications may differ. Numerous studies documenting the effects of different antihypertensive medications upon heart rate (HR), plasma volume (PV), cardiac output (CO), and stroke volume (SV) have been published, but the sample sizes of most of these studies have been small, typically less than 20 subjects each. Differences in hemodynamic properties that distinguish one class of antihypertensive medication from another might not be evident in studies with such small samples. Furthermore, if there are differences in hemodynamic properties among the different classes of antihypertensive drugs, such differences

might help clinicians customize the selection of drugs for individual patients.

We performed this meta-analysis in order to clarify and compare the hemodynamic properties of four different classes of antihypertensive medications: angiotensin converting enzyme inhibitors (ACEIs), β -adrenergic receptor antagonists (β -blockers), calcium channel blockers (CCBs), and thiazide diuretics.

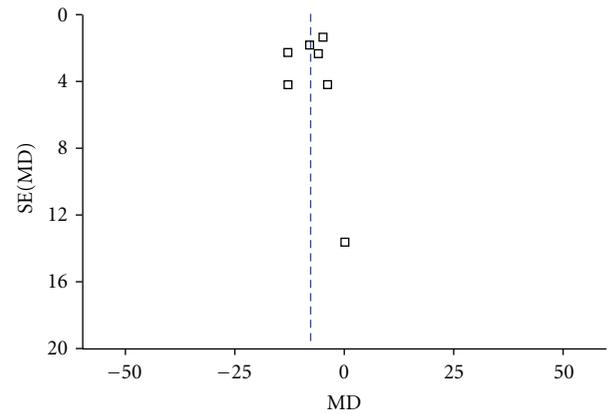
2. Methods

2.1. Search Strategy and Selection Criteria. Investigators (I. H. Iftikhar, R. P. Blankfield, N. Hassan) searched Pubmed for

trials that evaluated the hemodynamic properties of the following classes of antihypertensive drugs: ACEIs, β -blockers, CCBs and thiazide diuretics. We chose these medications because there is more hemodynamic data regarding these agents than other classes of antihypertensive drugs. Boolean operators (AND, OR) were used to combine the Medical Subject Heading (MeSH) text terms for the antihypertensive classes and the hemodynamic variables. In order to ensure that all relevant articles were identified, additional searches for individual antihypertensive medications in each class were performed, and each individual medication was paired with one of the several hemodynamic variables in sequential fashion. Specifically, each drug was paired with the term "hypertension" along with either "plasma volume," "cardiac output," "stroke volume," or "hemodynamics," and a search was made for each of these pairings. In this manner, searches were made for all common drug names in each class (Table 1). Studies published prior to May 2011 were eligible for inclusion. Reference lists of all identified articles were searched for additional articles that did not appear in the database searches. No attempt to identify unpublished studies was undertaken, and no attempt was made to contact authors.

Once potentially relevant articles were identified by the initial search, two investigators (I. H. Iftikhar, R. P. Blankfield) independently evaluated studies for inclusion. Inclusion criteria were: (1) the published article had to be written in the English language, (2) the study had to include only human subjects with uncomplicated hypertension, (3) the study drug had to be administered only through the oral route, (4) a single pharmacological agent (monotherapy) was used to treat the hypertension, and (5) the duration of the study had to be a minimum period of 4 weeks. Studies were included if they contained data regarding PV, CO, and/or SV. Studies that provided data on cardiac index or stroke index were included if there was enough information to calculate CO or SV. Studies in which subjects used different antihypertensive medications at different times, but not simultaneously, were included. All case reports, case series, and review articles were excluded. Studies that included subjects with diabetes mellitus, heart failure, or coronary artery disease were excluded. If multiple publications of the same trial were identified, only the most recent publication was chosen for inclusion. Studies that did not include standard deviation data were excluded. Disagreements were resolved through discussion among reviewers.

2.2. Data Extraction. For studies that met the inclusion criteria, extracted data included the first author's name, year of publication, number of subjects, pre- and posttreatment mean arterial pressure with standard deviations, pre- and posttreatment mean HR with standard deviations, pre- and posttreatment mean PV with standard deviations, pre- and posttreatment mean CO with standard deviations, and pre- and posttreatment mean SV with standard deviations. For studies that reported mean systolic and mean diastolic blood pressures but not mean arterial pressures, mean arterial pressures were calculated. Data was extracted from articles that reported mean cardiac index (CI) or mean stroke index



SE indicates standard error of mean
MD indicates mean difference

FIGURE 1: Funnel plot of stroke volume changes for thiazide diuretics.

(SI) only if mean CO and/or mean SV could be calculated based upon mean body surface area data or mean height and weight data. This method of calculating CO or SV provides an approximation to the individual data [1]. We chose to use CO and SV rather than CI and SI because there was considerably more data available for CO and SV than there was for CI and SI. All included studies were peer reviewed and were assumed to represent valid information regarding drug effect.

2.3. Quantitative Data Synthesis. The absolute effectiveness of each drug regimen was quantified by estimating the mean difference of outcomes before and after intervention. Effectiveness was pooled across studies using the DerSimonian and Laird random effects meta-analyses models.

Heterogeneity was assessed with I^2 index and the tau-squared test. To assess the risk of publication bias, funnel plots of standard error and difference in means were constructed. A funnel plot of the SV data for thiazide diuretics (Figure 1) is representative of the funnel plot data. NCSS software version 2007 was used to analyze the data.

3. Results

3.1. Trial Flow. A total of 227 potentially relevant articles were identified, of which 152 were excluded, primarily due to insufficient outcome data. Figure 2 summarizes the results of the selection and exclusion process. Seventy-five (75) articles that enrolled a total number of 1522 subjects treated with ACEIs, β -blockers, CCBs and thiazide diuretics were included [2–76].

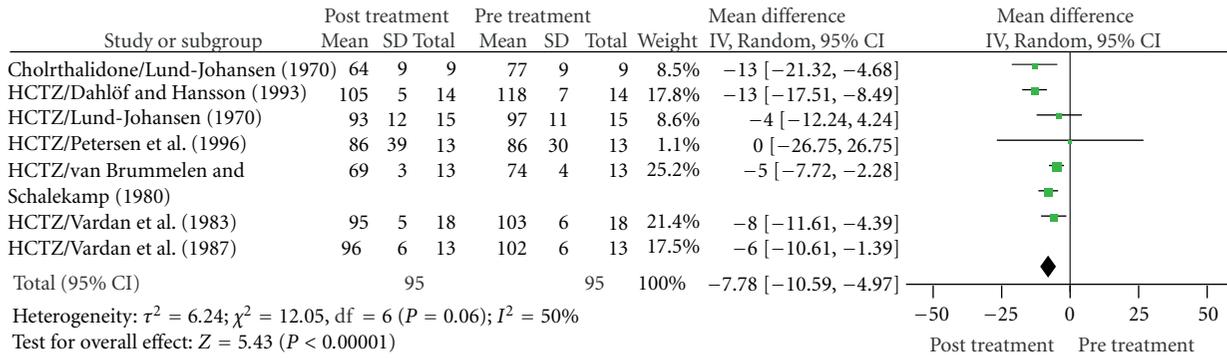
For studies that measured PV, 125 Iodine-labeled albumin was used. For studies that measured CO, the methodologies varied. Twenty-six studies used a dye dilution technique, 8 used Doppler ultrasound, 7 used the Fick technique, 5 used impedance cardiography, 1 used the indirect Fick technique, 1 used thermodilution, and 1 used technetium labeled albumin. For studies that measured SV, the methodologies also

TABLE 1: Summary of the drug names searched in online databases.

	β -blockers		ACEIs	CCBs	Diuretics
acebutolol	carvedilol	metipranolol	captopril	amlodipine	chlorothiazide
alprenolol	celiprolol	metoprolol	benazapril	bepidil	chlorthalidone
amosulalol	cyanopindolol	nadolol	enalapril	diltiazem	hydrochlorthiazide
arotinolol	dihydroalprenolol	nebivolol	fosinopril	felodipine	indapamide
atenolol	epanolol	oxprenolol	lisinopril	isradipine	
befunolol	esmolol	penbutolol	perindopril	nicardipine	
betaxolol	exaprolol	pindolol	quinapril	nifedipine	
bevantolol	flestolol	practolol	ramipril	nimodipine	
bisoprolol	icatibant	prizidilol		nisoldipine	
bopindolol	indenolol	propranolol		nitrendipine	
bucindilol	iodpcyanaopindolol	sotalol		verapamil	
bufuralol	labetalol	talinolol			
bupranolol	landiolol	tertatolol			
butoxamine	levobunolol	tilisilol			
carazolol	medroxalol	timolol			
carteolol	mepindolol	tobanum			



FIGURE 2: Summary of selection and exclusion process for meta-analysis articles.



SD indicates standard deviation

MD indicates mean difference

FIGURE 3: Forest plot of change in stroke volume for thiazide diuretics.

varied. Ten used echocardiography, and 9 used multiple gated acquisition scans. Many of the studies that measured CO calculated SV. Likewise, many of the studies that measured SV calculated CO.

Table 2 summarizes the total number of studies and the total number of subjects for each hemodynamic variable according to class of antihypertensive medication. A few studies included data on more than one medication. Other studies reported more than one trial of a single medication, or else reported subgroups of a single medication trial that were best analyzed as separate trials.

3.2. Study Characteristics. The studies included in the meta-analysis enrolled men and women with uncomplicated hypertension. The majority of the subjects were men. Most of the studies did not mention the ethnicity or race of the subjects. When race or ethnicity was identified, the majority of the subjects were Caucasian. Subjects ranged from 18–87 years old, but most were between 30–60 years of age. Most of the studies did not mention exclusion criteria, but some of the studies specified exclusion criteria that included coronary artery disease, heart failure, chronic obstructive lung disease, renal disease, and diabetes mellitus.

3.3. Heterogeneity Analysis. The tests for heterogeneity were significant in the majority of analyses, indicating that a nonrandom model would be inadequate for the present study. Therefore, random effect estimates were used throughout the meta-analysis to protect against possible undetected heterogeneities.

I^2 index was used to account for variability in effect size estimates across the studies. The Tau-squared test was used to account for variance between the studies. The I^2 index for the data on SV for the different antihypertensive classes is 70% for the SV data on CCBs, 94% for the SV data on ACEIs, 33% for the data on β -blockers, and 50% for the SV data on thiazides. The SV data suggests low-to-moderate heterogeneity for the CCBs and ACEIs, and medium heterogeneity for the β -blockers and thiazides [77].

3.4. Quantitative Data Synthesis. Table 3 summarizes the changes in hemodynamic variables from baseline according to class of antihypertensive drug. A forest plot of the thiazide diuretic SV data (Figure 3) is representative of the data analysis used to construct Table 3.

ACEIs, CCBs, β -blockers, and thiazide diuretics all lowered MAP (-16 [CI -24 to -9], -15 [CI -18 to -13], -14 [CI -16 to -13], -12 [CI -17 to -7] mmHg, resp., $P < 0.001$ for each).

β -blockers lowered HR (-12 [CI -14 to -10] beats/minute, $P < 0.001$). ACEIs, CCBs, and thiazide diuretics had no significant effect upon HR.

ACEIs raised PV (44 [CI 0.3 to 88] mL, $P < 0.05$). β -blockers, CCBs, and thiazide diuretics had no significant effect upon PV.

β -blockers and thiazide diuretics decreased CO (-0.65 [CI -0.86 to -0.43] lit/min, $P < 0.001$, and -0.63 [CI -0.75 to -0.51] lit/min, $P < 0.01$, resp.). ACEIs and CCBs had no significant effect upon CO.

CCBs and β -blockers increased SV (4 [CI 1 to 7] mL, $P < 0.01$, and 4 [CI 3 to 6] mL, $P < 0.001$, resp.). Thiazide diuretics reduced SV (-8 [CI -11 to -5] mL, $P < 0.01$). ACEIs had no significant effect upon SV.

In a subgroup analysis, dihydropyridine CCBs and nondihydropyridine CCBs both increased SV (5 [CI 1 to 9] mL, $P = 0.02$, versus 5 [CI 1 to 9] mL, $P = 0.02$, resp.).

4. Discussion

While all antihypertensive drugs lower BP, the various classes of antihypertensive medications differ in their effects upon other hemodynamic variables. β -blockers reduce HR but none of the other classes of antihypertensive drugs do so. β -blockers and thiazide diuretics reduce cardiac output while ACEIs and CCBs have no effect upon CO. CCBs and β -blockers increase SV, thiazide diuretics decrease SV, and ACEIs have no effect upon SV. Our findings regarding ACEIs and PV, and our findings regarding thiazide diuretics and SV may be noteworthy.

TABLE 2: Summary of the number of studies and subjects included in meta-analysis according to antihypertensive medication class and hemodynamic category.

	MAP		Heart rate		Plasma volume		Cardiac output		Stroke volume	
	<i>n</i> *	<i>N</i> **	<i>n</i> *	<i>N</i> **	<i>n</i> *	<i>N</i> **	<i>n</i> *	<i>N</i> **	<i>n</i> *	<i>N</i> **
ACEIs	18	277	16	231	6	78	14	212	14	198
β -blockers	29	591	25	591	8	150	25	581	16	411
CCBs	16	312	13	256	7	127	11	198	11	194
Thiazides	11	124	8	103	7	102	7	87	7	95

n* = total number of studies.*N* = total number of subjects.

TABLE 3: Mean changes in hemodynamic variables with confidence intervals.

	Change in MAP with CI (mmHg)	Change in HR with CI	Change in PV with CI (mL)	Change in CO with CI (lit/min)	Change in SV with CI (mL/stroke)
ACEIs	-16 (-24 to -9) [#]	0.8 (-0.4 to 2)	44 (0.3 to 88)*	0.10 (-0.22 to 0.44)	2 (-3 to 7)
β -blockers	-14 (-16 to -13) [#]	-12 (-14 to -10) [#]	57 (-23 to 140)	-0.65 (-0.86 to -0.43) [#]	4 (3 to 6) [#]
CCBs	-15 (-18 to -13) [#]	0.4 (-2 to 3)	59 (-16 to 130)	0.14 (-0.10 to 0.33)	4 (1 to 7)**
Thiazides	-12 (-17 to -7) [#]	0 (-2 to 2)	-110 (-290 to 57)	-0.63 (-0.75 to -0.51)**	-8 (-11 to -5)**

P* < 0.05.*P* < 0.01.[#]*P* < 0.001.

ACEIs increase PV but none of the other classes of antihypertensive drugs change PV. The effect of ACEIs upon PV is surprising because ACEIs are not recognized as causing fluid retention [78]. To the extent that an increase in plasma volume results in an increase in intra-arterial volume, one would expect an increase in plasma volume to be accompanied by an increase in CO, assuming that there is a corresponding increase in intra-arterial volume [79–81]. Since our study found that ACEIs are not associated with an increase in CO despite an increase in PV, perhaps the vasodilatation that accompanies angiotensin converting enzyme inhibition involves the venous circulation rather than the arterial circulation [78].

If all antihypertensive drug classes reduce the risk of adverse cardiovascular events comparably, as a recent meta-analysis determined [82], then distinguishing hemodynamic differences between the different categories of antihypertensive medications has little clinical significance. On the other hand, since a network meta-analysis found that low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality [83], then factors apart from BP reduction may be clinically relevant. Because all categories of antihypertensive medications lower BP equivalently [84], differences in other hemodynamic properties may be significant. In particular, our finding that diuretics lower SV, whereas other antihypertensive medications do not, may be noteworthy because reductions in SV would be expected to reduce the likelihood of turbulent blood flow, thereby slowing the progression of atherosclerotic cardiovascular disease [85].

There are several limitations of this meta-analysis. Most of the studies included in the meta-analysis enrolled less than 20 subjects. When subjects are stratified by hemodynamic variable and drug class, the number of subjects in many of the categories is modest: many of the categories include less than 200 subjects, and several categories include less than 100 subjects. Another limitation is that most of the studies included in the meta-analysis compared an antihypertensive drug to placebo or no treatment, but few studies compared one antihypertensive medication with another. Accordingly, the data allow one to make qualitative comparisons of the hemodynamic properties of the different classes of antihypertensive medications. As a result, one can say that one class of medication decreases CO while another class does not. However, the data do not allow quantitative comparisons of the magnitude of the effect between the different classes of antihypertensive medications. Consequently, the results do not allow one to say that one class of medication lowers BP more than another, nor do the results allow one to say that one class of medication raises SV more than another. It is a limitation of this study that the variability in the CO and SV measures due to a wide variation in methodologies used could not be taken into account in the model.

The lack of uniform drug dosage within all four categories of antihypertensive medications limits identifying precisely the hemodynamic effect of the different medications. Variability in dosage may be especially relevant to thiazide diuretics because the dose of these drugs in many of the trials was higher than the doses that are typically used in contemporary medical practice [86]. Accordingly, the

magnitude of the hemodynamic effects of thiazide diuretics as they are currently prescribed are unlikely to be the same as the magnitude of the hemodynamic effects of thiazide diuretics at the doses used in the studies included in this meta-analysis. Even though the magnitude of any hemodynamic effect would be expected to be dose dependent, the qualitative direction of that effect would not be expected to be dose dependent.

An additional limitation is that we excluded studies that enrolled subjects with diabetes, heart failure, and coronary artery disease. Therefore, our results may not be generalizable to hypertensive patients with these comorbidities. It is possible that we missed some studies by limiting the study to English language publications. However, there were only a dozen non-English language studies that were identified by the initial search strategy, only two of which contained data that appeared as if it might be relevant to the meta-analysis, and we could not be certain that we could accurately extract the relevant data. It is also a limitation that our results reflect a publication bias since we did not attempt to locate unpublished data. Finally, it is a limitation that we could not incorporate the many studies that reported cardiac index and stroke volume index data, but which did not report cardiac output or stroke volume data.

In summary, in the treatment of uncomplicated hypertension, the various classes of antihypertensive medications differ from each other in terms of their non-blood-pressure-lowering hemodynamic properties.

Conflict of Interests

The authors report no potential conflict of interests with any companies/organizations whose products or services may be discussed in this paper.

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