Meta-Analysis: Impact of Drug Class on Adherence to Antihypertensives

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Abstract

Background—Observational studies suggest there are differences in adherence to antihypertensive medications in different classes. Our objective was to quantify the association between antihypertensive drug class and adherence in clinical settings.

Methods and Results—Studies were identified through a systematic search of English-language articles published from inception of computerized databases till February 1, 2009. Studies were included if they measured adherence to antihypertensives using medication refill data and contained sufficient data to calculate a measure of relative risk of adherence and its variance. An inverse-variance weighted random-effects model was used to pool results. Hazard ratios (HR) and odds ratios (OR) were pooled separately, and HRs were selected as the primary outcome. Seventeen studies met inclusion criteria. The pooled mean adherence by drug class ranged from 28% for beta-blockers to 65% for angiotensin II-receptor blockers (ARBs).There was better adherence to ARBs compared to angiotensin-converting enzyme inhibitors (ACEIs) (HR 1.33, 95%CI 1.13–1.57), calcium channel blockers (HR 1.57, 95% CI 1.38–1.79), diuretics (HR 1.95, 95%CI 1.73–2.20), and beta-blockers (HR 2.09, 95%CI 1.14–3.85). Conversely, there was lower adherence to diuretics compared to the other drug classes. The same pattern was present when pooling studies that used ORs. When accounting for publication bias, there were no longer significant differences in adherence between ARBs and ACEIs or between diuretics and beta-blockers.

Conclusion—In clinical settings, there are important differences in adherence to antihypertensives in separate classes with lowest adherence to diuretics and beta-blockers and highest to ARBs and ACEIs. Yet, adherence was suboptimal regardless of drug class.

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Keywords

hypertension; medication adherence; meta-analysis

Introduction

Hypertension is the most common chronic illness in developed countries and one of the most important risk factors for cardiovascular disease.[1] Numerous studies have shown that blood pressure lowering is associated with major reductions in coronary events, strokes, and mortality.[2, 3] While counseling about lifestyle factors plays a role, prescribing antihypertensive medications remains the cornerstone of the medical management of hypertension.[4]

Clinical practice guidelines, such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC7)[5], have been developed to assist clinicians with their selection of antihypertensive medications. These guidelines rely heavily on data from clinical trials to inform their preferences for antihypertensive medications. Yet, as a result of selection bias, run-in periods, and behavior reinforcement through close follow-up, adherence to medication in clinical trial settings may not be representative of adherence in "real world" settings.[6] For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the level of adherence to treatment at 1 year ranged from 83% to 88% depending on drug class.[7] In observational studies, adherence to antihypertensive medications is typically much lower.[8] Accordingly, clinical trials such as ALLHAT may underestimate the impact of differences in adherence to medications from separate drug classes in clinical settings.

The literature describing the association between antihypertensive drug class and adherence is characterized by a wide variety of patient populations, drug class comparisons, and definitions of adherence. This heterogeneity has made it difficult to draw conclusions about the clinical relevance of differences in adherence according to drug class. Quantifying the overall impact of drug class on adherence in observational settings would provide important evidence to guide the selection of blood pressure medications as well as to guide adherence monitoring. Accordingly, we performed a meta-analysis to determine the impact of antihypertensive drug class on adherence to blood pressure medications.

Methods

Data Sources and Searching

This study was performed as part of a larger systematic review of predictors of adherence to oral cardiovascular and diabetic medications. The research methodology was done in accordance with MOOSE guidelines.[9] With the assistance of a medical librarian (L.F.), potentially relevant articles were identified by searching publicly available computerized databases. The search included all articles and abstracts (including unpublished doctoral theses) referenced from database inception to February 1, 2009 in MEDLINE, Database of Abstracts of Reviews of Effects, National Health Service Economic and Evaluation Database, Health Technology Assessment Database, EMBASE, and PsycINFO. All relevant subject heading and free text terms for adherence or compliance and for both the generic class of drug [e.g., beta-blocker (BB), angiotensin-converting enzyme inhibitor (ACEI)] and the individual names of antihypertensive medications, generic and proprietary, were included (Appendix 1). Due to the large volume of literature on this topic, a set of methodological filters was applied to the search strategies of the larger databases

(MEDLINE, EMBASE and PsycINFO). Follow-up searches were performed by hand-searching bibliographies from selected articles.

Study Selection

Articles were eligible for inclusion if they were published in English and include community dwelling patients 18 years of age and older. Eligible study designs included observational cohorts in which adherence to antihypertensive medication was evaluated as an outcome. To reduce heterogeneity when pooling studies, studies were only eligible if they measured adherence using medication refill data. Articles also had to include data that compared adherence between at least two distinct antihypertensive drug classes, and had to report sufficient data to calculate a measure of relative risk of adherence and its variance.

A number of sociodemographic characteristics, medical and psychological conditions, and regimen complexity qualities have been shown to influence adherence.[10, 11] Accordingly, studies were excluded if they did not consider at least one potentially confounding characteristic in their analyses of the association between drug class and adherence. Studies in which adherence was measured by determining whether patients were *using* a medication at a single time-point were also excluded as this was not equivalent to studying adherence with a regimen over time. For the remaining studies, we assigned a quality rating using a checklist adapted from the recommendations of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR)(Appendix 2).[12, 13]

Two investigators (D.M., I.K.) independently reviewed all citations identified through the literature search using a predefined protocol. Articles that clearly did not meet inclusion criteria were excluded at the title and abstract level. The remaining articles were selected for full text review. When limited information was available from the abstract, full text was always obtained. Included articles underwent a quality assessment by two investigators (Z.S., I.K.). Disagreements regarding the selection and quality assessment of articles were resolved through discussion and full consensus was achieved at each stage of review.

Data Extraction

Two investigators (Z.S., I.K.) independently extracted data from selected studies using a standardized form. Information was collected regarding dates and sizes of the studies; types of patients enrolled; duration of follow-up; types of drug classes assessed; whether patients were concurrently taking antihypertensive medications from other drug classes; the proportion initiating ARBs; and whether the study had any pharmaceutical industry affiliation. Pharmaceutical affiliation was ascribed if the study received funding from a pharmaceutical company or if a study author was employed or served as a consultant for the industry. Adherence data pertaining to combination antihypertensive pills were not extracted.

Investigators also recorded the method used to define adherence; the mean adherence according to drug class; the measure of the relative risk of adherence between pairs of drug classes; and the types of covariates included in adjusted analyses. In accordance with ISPOR guidelines[14], we defined adherence as an umbrella term that encompasses two related categories of pill-taking behavior: compliance and persistence. Adherence was categorized as *compliance* if it measured the proportion of days covered (PDC) with medication, calculated as the sum of the days' supply for all prescriptions filled during the study time period divided by the total number of days in this time period. Individuals were then defined as compliant or non-compliant using a threshold of 80% for PDC. Adherence was categorized as *persistence* if it referred to either 1) a continuous measure of the number of days on a given antihypertensive from initiation of therapy to the end of the last supplied

prescription in the study period before a significant gap in coverage with the medication or 2) a dichotomous variable in which patients were categorized as persistent or non-persistent depending on whether they had any significant gaps in coverage during the study period. Persistence studies were sub-categorized according to whether they defined persistence as *medication persistence* (time to discontinuation of a given medication) or *therapy persistence* (time to discontinuation of all antihypertensive medication).[13] Dichotomous measures of adherence were used to calculate odds ratios (ORs) for adherence between two drug classes using logistic regression. Continuous measures of adherence were used to calculate hazard ratios (HRs) using Cox proportional hazards regression.

Data Synthesis and Analysis—Two pairs of studies[15–18] included overlapping data, and hence, two studies were excluded from quantitative analysis.[15, 17] The remaining studies were grouped for pooling according to comparisons of adherence between pairs of drug classes. Data were then subgrouped according to whether the measure of relative risk was an OR or HR. The pooled HR of adherence was selected as the primary outcome because 1) this was the most frequently used measure of adherence in the pooled studies and 2) the HR accounts for censoring and is thus the preferred measure of relative risk with prospective data. ARBs and diuretics were selected as the primary basis for comparison as they were the two drug classes with the most frequent pair-wise comparisons across studies. Individual estimates of log relative risks were pooled using random effects meta-analysis with inverse variance weighting in Stata, version 10 (College Station, TX). The i-squared statistic was used to estimate the percentage of variability across studies that is attributable to heterogeneity and was tested for deviation from zero. To test for sources of heterogeneity for our primary outcome, we performed sensitivity analyses that compared pooled HRs separately for articles in which adherence was defined as medication persistence and therapy persistence. Similarly, we performed sensitivity analyses by stratifying articles according to study size, study quality, country, and pharmaceutical affiliation. We used chi-square to test for significance in these analyses and log transformed HRs to approximate normality. To account for publication bias, we used the non-parametric "trim-and-fill" model.[19] We used this model when there were at least 3 studies available for pooling.

As a secondary means of comparing adherence between drug classes, we pooled the mean percent adherence by individual drug class across studies that measured adherence as persistence. We weighted our calculations according to person-months of exposure.

Results

Qualitative analysis (n=17)

The comprehensive search yielded 115 unique articles related to predictors of adherence to antihypertensive medications.(Figure 1) Seventeen articles met inclusion criteria.[15–18, 20–32](Table 1) Five studies were rated 'excellent' and satisfied all of the requirements on the quality checklist; twelve studies were rated 'good' and missed one or two items on the checklist. Included articles assessed adherence to antihypertensive medications between 1989 and 2004 for 935 920 patients. The studies measured adherence using medication refill data either from insurance claims or pharmacy refills in closed pharmacy systems in North American and Europe. Thirteen articles defined adherence as persistence (5 medication persistence; 8 therapy persistence) and four articles defined adherence as compliance. ARBs were the least likely drug class to be prescribed with rates from 2 – 23%.

Articles had large differences in their selection of covariates for adjusted analyses. Covariates included demographics (age, race, gender, income, ethnicity), burden of disease (comorbidities), complexity of medication regimen (number of medications, frequency of

dosing), health system barriers (insurance coverage, cost of care), health care utilization (numbers of hospitalizations and physician visits), and prescriber characteristics (type of physician).

Two articles provided data on overall compliance according to PDC.[28, 32] In the study by Zhang et al., 53% were compliant to antihypertensives (either an ACEI or ARB) and in the study by Siegel et al., 78% to 84% were compliant. The mean overall persistence with antihypertensives, available from 12 studies, ranged from 35% to 84%.

With respect to relative adherence, with one exception (Zhang et al.), there was better adherence (p<.05) to ARBs compared to other drug classes studied (ACEI, CCB, BB, diuretics), regardless of adherence definition.(Figure 2) Conversely, with two exceptions (van Wijk-BC., BB comparison; Erkens et al., CCB comparison), there was lower adherence to diuretics compared to other drug classes (p<.05).(Figure 3)

Quantitative analysis (n=15)

The pooled mean age of patients was 61.7 years, and 53.1% were female. The pooled mean person-months of adherence observation across studies was 12.3 months. Using HR as the primary measure of relative adherence, there was an increased risk of adherence to ARBs compared to ACEIs (HR 1.33, 95%CI 1.13–1.57), CCBs (HR 1.57 95% CI 1.38–1.79), BBs (HR 2.09 95% CI 1.14–3.85), and diuretics (HR 1.95 95%CI 1.73–2.20) (Figure 2). In contrast, there was a lower risk of adherence to diuretics compared to all the other drug classes (Figure 3). As a secondary analysis, four studies measured the relative risk of adherence using ORs. The pattern of relative adherence remained the same using OR as the measure of relative adherence with highest adherence to ARBs and lowest to diuretics and beta-blockers (Figure 2, Figure 3).

Data were available for pooled estimates of adherence for individual drug classes from 9 studies, though 2 studies only contained data for 4 of the 5 drug classes which introduced some between-study bias. The mean (95% CI) persistence to medication followed the expected pattern with highest mean persistence to ARBs 64.9% (64.3% – 65.6%; and ACEIs 57.6% (57.2% – 57.9%); intermediate persistence to CCBs 52.0% (51.6% – 52.5%); and lowest to BBs 28.4% (28.1% – 28.8%); and diuretics 51.0% (51.4% – 51.8%).

Overall, other than the comparison between ACEIs and ARBs, there was significant heterogeneity when pooling data (i-squared statistic 91.7% to 98.0%). This supported the use of the random effects model to estimate the relative risk of adherence between pairs of drug classes. Given this substantial heterogeneity, we performed subgroup analyses for our primary outcome to assess the impact of different definitions of adherence, study size, quality, location, inclusion criteria, and pharmaceutical affiliation on the estimates of the relative risk of adherence by drug class. All i-squared values were either reduced or increased by less than 1% in subgroup analyses.

Subgroup analyses supported the robustness of the overall conclusions. First, we tested the impact of defining adherence as medication persistence or as therapy persistence. The definition of adherence did not change the overall pattern, with higher adherence to ARBs compared to other drugs regardless of definition; however, the difference between ARBs and ACEIs did not remain significant when restricting studies to those measuring adherence as therapy persistence. Similarly, subgroup analyses involving study size, location, and quality made no qualitative difference to the pattern of adherence with higher adherence to ARBs compared to other drugs and lower adherence to diuretics compared to all other drugs, though differences between diuretics and beta-blockers were not always statistically significant. Thirteen studies restricted their inclusion of patients to those who were initiating

a first medication for hypertension and were not concurrently prescribed any other antihypertensives. There were no significant differences in the relationship between adherence and drug class when the meta-analysis was limited to these studies. Sufficient studies were available for testing the impact of pharmaceutical affiliation on relative adherence in two instances. The relative benefit of adherence to ARBs versus ACEIs was more pronounced (p =.006) in pharmaceutical-affiliated studies [pooled HR 1.41 (95% CI 1.17 – 1.70); 4 pooled studies] compared to non-pharmaceutical affiliated studies [HR1.09 (95%CI 1.06 – 1.11); 1 study]. There was no significant impact of pharmaceutical affiliation on the estimate of relative adherence between ARBs and diuretics.

Publication bias affected the estimate of relative adherence according to HR in two instances. There were no longer significant differences adherence between ARBs and ACEIs [HR 1.10 (95%CI 0.94 – 1.30)] or between BBs and diuretics [HR1.13 (95% CI 0.89–1.44)] after accounting for publication bias.

Discussion

We found that there was a significant relationship between adherence to antihypertensive medication and drug class. When compared to patients prescribed diuretics and BBs, the drug classes associated with the lowest adherence, patients prescribed ARBs were approximately twice as likely to have good adherence. Overall, ACEIs appeared to have the second best level of adherence, followed by CCBs, although insufficient data were available for definitive ranking of pair-wise comparisons and publication bias may have accounted for differences between ARBs and ACEIs.

There was a remarkable degree of consistency in the pattern of our results showing superior adherence to ARBs and ACEIs and inferior adherence to diuretics and beta-blockers. No single study dominated any of the pooled estimates and there was no substantial difference in the pattern regardless of the adherence definition, or the size, quality, and location of the study.

There are several possible reasons for these differences. Each of the drug classes is associated with distinct side-effects. Diuretics, for example, can cause urinary frequency, erectile dysfunction, fatigue, and muscle cramps.[33] They can also produce metabolic and electrolyte abnormalities that may lead physicians to discontinue them.

Another possible etiology for the differences in adherence by drug class may be variation in provider and patient beliefs about medications. Perceived benefit of treatment is a core component of several health behavior models[34] and has been associated with adherence in some studies of cardiovascular medications.[35] Prior studies have shown differences in physician perceptions of the effectiveness and tolerability of antihypertensive medication in separate classes.[36] Future studies might assess whether these differences mediate the relationship between adherence and drug class.

The higher rate of adherence to ARBs compared to diuretics suggests that drug cost plays a relatively minor role in antihypertensive adherence. It is possible that cost plays a more significant role in under-insured populations in which medication users are responsible for a significant portion of prescription costs; no articles were restricted to populations without prescription insurance or with low socioeconomic status.

There are several limitations to our conclusions. First, ARBs were prescribed at lower rates than are typical presently in developed countries. This may have biased the results comparing ARBs to other drug classes. There may have been factors related to selection of patients who are more adherent such that adherence to ARBs may be more related to patient

selection factors rather than the properties of the drug class itself. Until this is assessed, it is premature to recommend ARBs as first line medications for clinicians interested in minimizing adherence problems. Second, these findings may not be generalizable to patients who are already started on one or more antihypertensive medications. In practice, a growing number of patients are on multiple BP medications and some guidelines even recommend starting with combinations of drug classes for patients with BP markedly above goal. Nevertheless, in our five studies which considered this question, the pattern of adherence between drug classes was the same. Third, these analyses involved multiple statistical tests, and thus the nominal type I error rate of 5% must be interpreted with caution. Fourth, there was significant heterogeneity when pooling data. Still, the pattern of relative adherence remained the same in subgroup analyses. Another limitation is that we excluded articles that assessed adherence by drug class but did not report adjusted analyses of relative risks. A qualitative review of these articles was consistent with the pattern of adherence found in our meta-analysis. Finally, we did not have resources to review non-English language publications nor to contact authors for unpublished data. Of note, one study of Korean patients published after we completed our systematic search was also consistent with our findings showing highest adherence to ACEIs and ARBs and lowest to diuretics.[37]

Implications

Although rates of blood pressure control are improving in the US, more than half of hypertensive Americans continue to have their blood pressure above recommended levels[1] and poor adherence to antihypertensives remains an important cause of poor blood pressure control.[38, 39] Lack of adherence to antihypertensive treatment has been associated with complications including increased cardiovascular events and health care costs.[40, 41] Our findings remind us that it is important for clinicians to pay attention to adherence regardless of antihypertensive drug class as rates of adherence were suboptimal for all drug classes. Clinicians should pay special attention to adherence in patients who are prescribed diuretics and beta-blockers. Incorporating objective data from pharmacy refill claims or other sources may assist clinicians with assessing medication adherence and with optimizing their antihypertensive prescribing decisions.[42] Clinical trials that simulate real-world settings as much as possible should be pursued to assess whether differences in adherence by drug class are associated with differences in blood pressure control and related clinical outcomes.

Clinical Summary
More than half of US individuals with hypertension continue to have their blood pressure above recommended levels and poor adherence to antihypertensives remains an important cause of poor blood pressure control. Observational studies suggest that there may be important differences in adherence to antihypertensives in distinct drug classes. Yet, the literature describing the association between drug class and adherence is characterized by a wide variety of patient populations, drug class comparisons, and definitions of adherence. This heterogeneity has made it difficult to make firm conclusions about the clinical relevance of differences in adherence according to drug class. Accordingly, we performed a meta-analysis to determine the impact of antihypertensive drug class on adherence to blood pressure medications. We found that there was a significant relationship between adherence and antihypertensive drug class. When compared to patients prescribed diuretics and beta-blockers, the drug classes associated with the lowest adherence, patients prescribed angiotensin II receptor blockers were approximately twice as likely to have good adherence. Overall, angiotensin-converting enzyme inhibitors appeared to have the second best level of adherence, followed by calcium-channel blockers, although insufficient data was available for definitive rankings. Our findings demonstrate that it is important for clinicians to pay attention to adherence regardless of drug class as adherence was suboptimal for all drug

classes, and that clinicians should pay special attention to adherence in patients who are prescribed diuretics and beta-blockers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

None
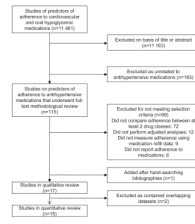
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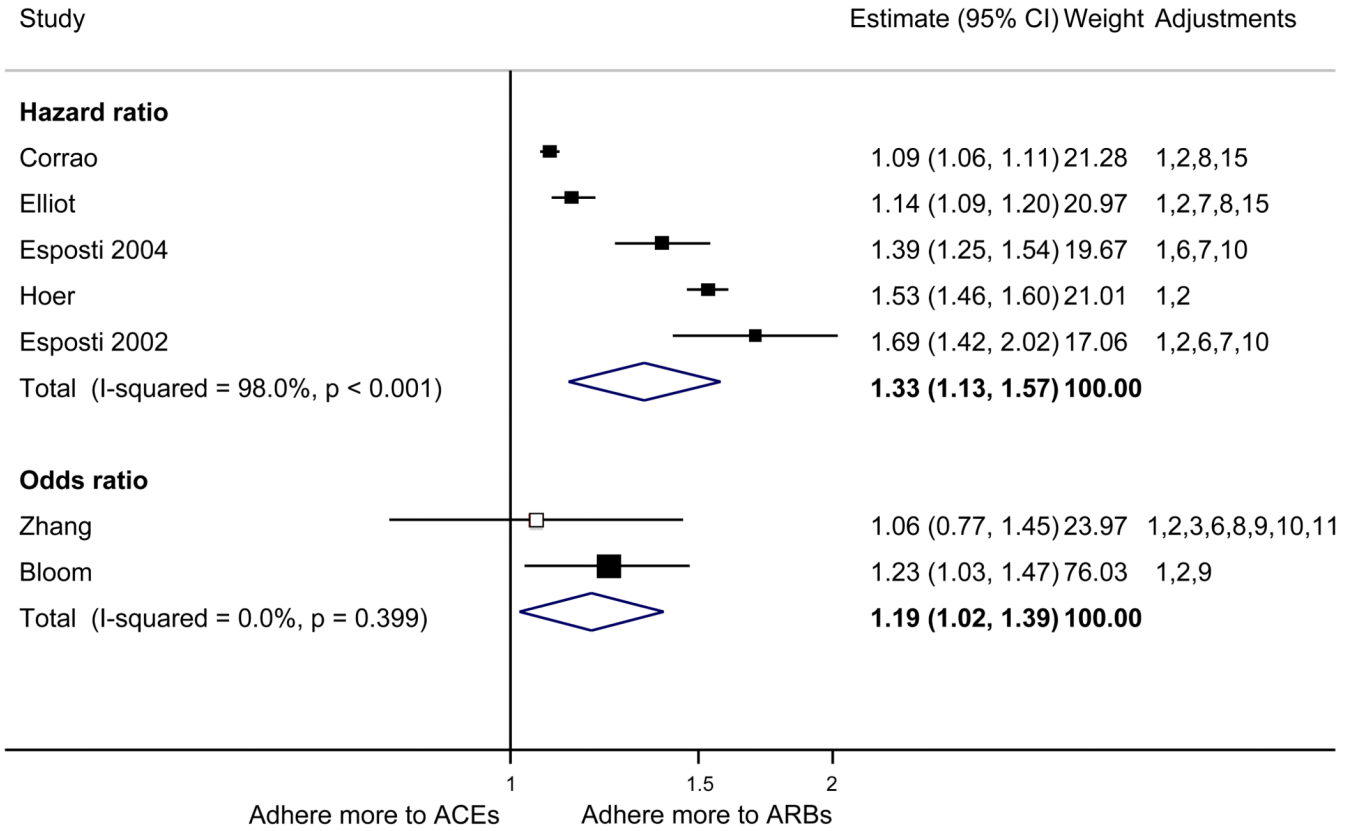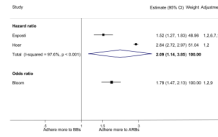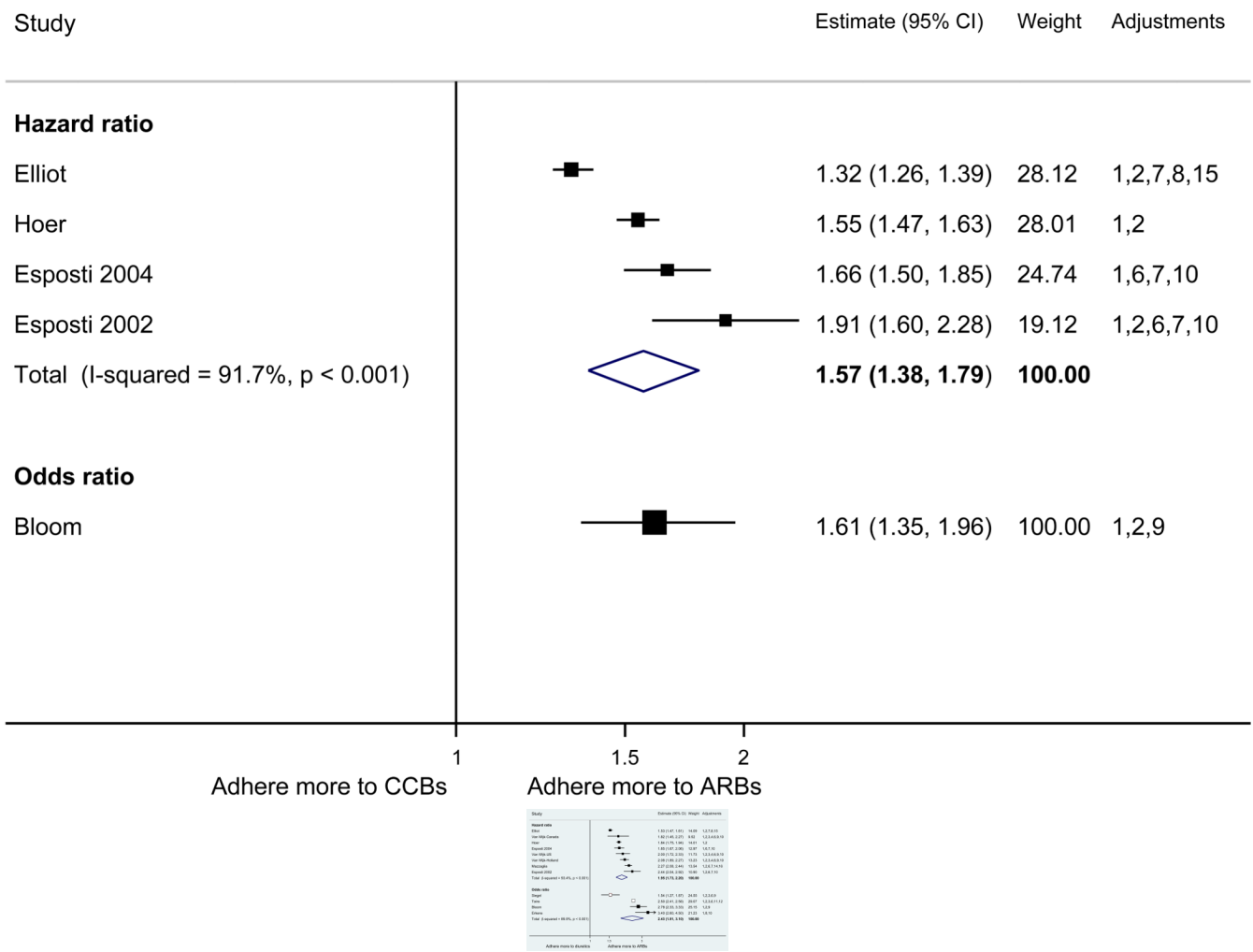
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Figure 1.
Literature search and selection

Study		Estimate (95% CI)	Weight	Adjustments
Hazard ratio				
Corrao		1.09 (1.06, 1.11)	21.28	1,2,8,15
Elliot		1.14 (1.09, 1.20)	20.97	1,2,7,8,15
Esposti 2004		1.39 (1.25, 1.54)	19.67	1,6,7,10
Hoer		1.53 (1.46, 1.60)	21.01	1,2
Esposti 2002		1.69 (1.42, 2.02)	17.06	1,2,6,7,10
Total (I-squared = 98.0%, p < 0.001)		**1.33 (1.13, 1.57)**	**100.00**	
Odds ratio				
Zhang		1.06 (0.77, 1.45)	23.97	1,2,3,6,8,9,10,11
Bloom		1.23 (1.03, 1.47)	76.03	1,2,9
Total (I-squared = 0.0%, p = 0.399)		**1.19 (1.02, 1.39)**	**100.00**	

1   1.5   2

Adhere more to ACEs   Adhere more to ARBs

Study		Estimate (95% CI)	Weight	Adjustments
Hazard ratio				
Elliot		1.32 (1.26, 1.39)	28.12	1,2,7,8,15
Hoer		1.55 (1.47, 1.63)	28.01	1,2
Esposti 2004		1.66 (1.50, 1.85)	24.74	1,6,7,10
Esposti 2002		1.91 (1.60, 2.28)	19.12	1,2,6,7,10
Total (I-squared = 91.7%, p < 0.001)		**1.57 (1.38, 1.79)**	**100.00**	
Odds ratio				
Bloom		1.61 (1.35, 1.96)	100.00	1,2,9

1   1.5   2
Adhere more to CCBs   Adhere more to ARBs
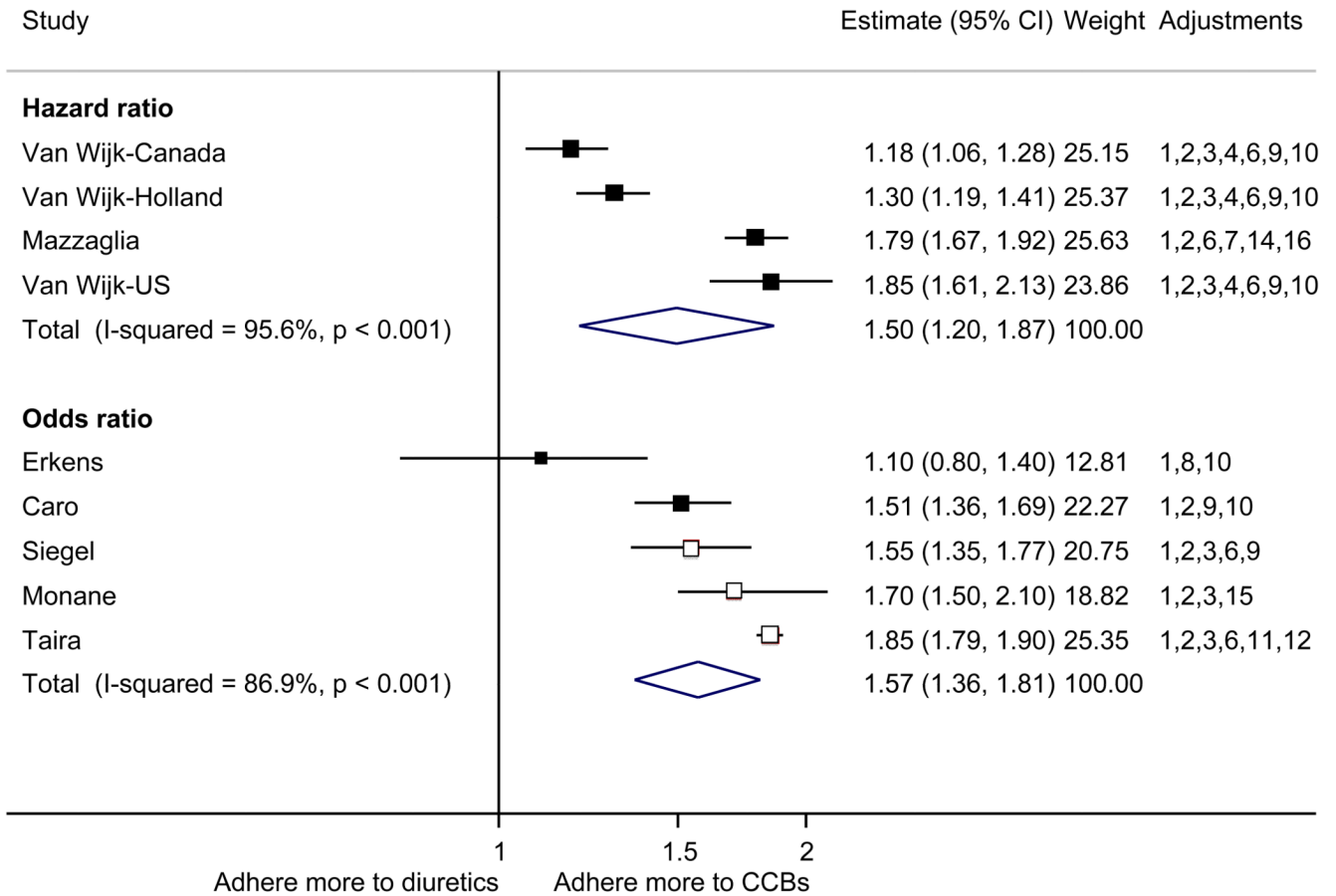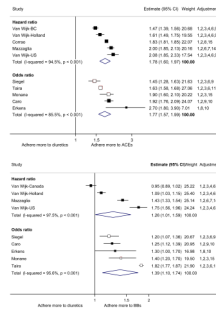
Figure 2.
Adherence to angiotensin receptor blockers compared to other antihypertensive drug classes: meta-analysis results. Hazard ratios and odds ratios with 95% confidence intervals on a logarithmic scale for individual or pooled study data for relative risk of adherence between pairs of classes of blood pressure medication. Black boxes refer to studies in which adherence is measured as persistence; red boxes refer to studies in which adherence is measured as compliance.

Adjustments: (1) age, (2) sex, (3) race/ethnicity, (4) income or receipt of social assistance, (5) residence, (6) comorbidity types, (7) comorbidity burden, (8) treatment with medication classes other than antihypertensives, (9) medication regimen characteristics (number of medications, frequency of dosing, number of pills per day), (10) health care utilization (prior hospitalizations, physician visits, use of other services), (11) out-of-pocket medication costs, (12) type of health insurance, (13) physician characteristics, (14) blood pressure at baseline, (15) year of first prescription, (16) family history of comorbidities

Abbreviations: ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium-channel blocker; CI, confidence interval

Figure 3.

Adherence to diuretics compared to other antihypertensive drug classes: meta-analysis results. Hazard ratios and odds ratios with 95% confidence intervals on a logarithmic scale for individual or pooled study data for each pair-wise comparison for relative risk of adherence between pairs of classes of blood pressure medication. Black boxes refer to studies in which adherence is measured as persistence; red boxes refer to studies in which adherence is measured as compliance.

Adjustments: (1) age, (2) sex, (3) race/ethnicity, (4) income or receipt of social assistance, (5) residence, (6) comorbidity types, (7) comorbidity burden, (8) treatment with medication classes other than antihypertensives, (9) medication regimen characteristics (number of medications, frequency of dosing, number of pills per day), (10) health care utilization (prior hospitalizations, physician visits, use of other services), (11) out-of-pocket medication costs,

(12) type of health insurance, (13) physician characteristics, (14) blood pressure at baseline, (15) year of first prescription, (16) family history of comorbidities

Abbreviations: ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium-channel blocker; CI, confidence interval

Table 1

Summary of Included Studies of Association of Antihypertensive Drug Class and Adherence

No	Reference	Country	Drug company affiliation	Years enrolled	Number of patients	Drug classes evaluated	Population	Percent initiating ARB	Period observed	Adherence definition	Type of adherence measure	Mean adherence rate	Covariates	Quality rating
1	Bloom[20]	United States	Yes	1995–1996	21 723	losartan, ACEI, CCB, BB, diuretic	Initiating a first medication for treatment of HTN	2.6%	12 months	Refilled first prescription on or within 3 months of the 1 year anniversary of first prescription	Medication Persistence*	64% ARB 58% ACE 50%CCB 43% BB 38% thiazide	1, 2, 9	Good
2	Caro et al.[21]	Canada	Yes	1989–1994	22 918	ACEI CCB, BB, diuretic	Initiating a first medication for treatment of HTN	None	12 months	Last prescription covered period until the end of observation period	Therapy Persistence†	89% ACEI 86%CCB 85% BB 80% diuretics 84% overall (at 6 mo)	1,2,9,10	Good
3	Esposti et al. 2002[22]	Italy	Yes	1997	16 783	losartan, ACEI, CCB, BB, diuretic	Initiating a first medication for treatment of HTN	1.9%	12 months	Days elapsed between first and last prescription	Therapy Persistence	58% ARB 40% ACEI 31% CCB 38% BB 30% diuretics 35% overall (>273 days elapsing between first and last prescription)	1,2,6,7,10	Good
4	Erkens et al.[23]	Netherlands	Yes	1997–2001	2 243	ARB, ACEI CCB, BB, diuretic	Initiating a first medication for treatment of HTN	19.9%	12 months	> 270 days elapsing between first and last prescription and additional prescription within 3 months after 1 year	Medication Persistence	62% ARB 60% ACE 35% CCB 35% BB 33% diuretics 44% overall	1,8,10	Good
5	Elliott et al.[24]	United States	Yes	2001–2002	60 685	valsartan lisinopril, amlodipine, HCTZ	Initiating a new medication for HTN; eligible if continuing prior HTN	15.3%	12 months	Days until lapse in therapy for ≥ 60 days	Medication Persistence	69%valsartan 65% lisinopril 60%amlodipine 56% HCTZ 62% overall No lapse in	1,2,7,8,15	Good

No	Reference	Country	Drug company affiliation	Years enrolled	Number of patients	Drug classes evaluated	Population	Percent initiating ARB	Period observed	Adherence definition	Type of adherence measure	Mean adherence rate	Covariates	Quality rating
							medication					therapy for ≥ 60 days		
6	Mazzaglia et al.[25]	Italy	Yes, minor	2000–2001	13 303	ARB, ACEI, CCB, BB, AB, diuretic	Initiating a first medication for treatment of HTN other than combination pills	10.4%	12 months	Days until lapse in therapy for ≥ 60 days	Therapy Persistence	61% ARB 63% ACEI 64% CCB 58% AB 50% BB 47% diuretic 58% overall (estimated from bar graph) No lapse in therapy for ≥ 60 days	1,2,6,7,14,16	Excellent
7	Monane et al.[26]	United States	No	1982–1988	8 643	ACEI, CCB, BB, diuretic, other (no ARBs)	Initiating a first medication for treatment of HTN; seniors (>65 years old) receiving Medicaid	None	12 months	PDC ≥ 80%	Compliance	20% overall	1,2,3,15	Excellent
8	Perrault et al.[27]	Canada	No	1998–2000	21 011	ARB, ACEI CCB, BB, diuretic, combined therapy	Initiating a first medication for treatment of HTN; adults 50–64 years old; no prior history of CVD or secondary HTN	13.0%	12 months	No lapse in therapy for ≥ 60 days	Therapy Persistence	73% ARB 71% ACEI 68% CCB 68% BB 61% diuretic 66% combo 67% overall	1,2,4,5,6,8,9,10	Excellent
9	Siegel et al.[28]	United States	No	2002–2003	40 492	ARB, ACEI, CCB, BB, AB, diuretic	Continuing or initiating a single medication for HTN; eligible if continuing	8.4%	18 months	PDC ≥ 80%	Compliance	84% ARB 81% ACEI 83% CCB 80% BB 79% AB 78% diuretic (includes patients on	1,2,3,6,9	Good

No	Reference	Country	Drug company affiliation	Years enrolled	Number of patients	Drug classes evaluated	Population	Percent initiating ARB	Period observed	Adherence definition	Type of adherence measure	Mean adherence rate	Covariates	Quality rating
							prior HTN medication; veterans only; at least 1 refill for drug class of interest during study period					multiple HTN medications)		
10	Taira et al. 2007[15]‡	United States	No	1999–2003	28 395	ARB, ACEI CCB, BB, diuretic	Initiating a first medication for treatment of HTN	Not Reported	3 years	PDC ≥ 80%	Compliance	Not reported	1,2,5,6,13	Good
11	Taira et al. 2006[16]	United States	Yes	1999–2004	114 232	All drug classes	Continuing or initiating medication treatment for HTN; eligible if continuing prior HTN medication	Not Reported	12 months	PDC ≥ 80%	Compliance	Not reported	1,2,3,6,11,12	Good
12	Van Wijk et al. 2005[17]*	Netherlands	No	1992–2002	2 325	ACEI, CCB, BB, AB, diuretic	Initiating a first medication for treatment of HTN; no other indications for HTN medication (eg; CVD, migraine); at least 1 refill for drug class of interest during study period	Not Reported	10 years	Refilled first prescription at least two times per year	Medication Persistence	61% overall (includes patients who discontinued and restarted during 10 year period)	1,2,12,13	Good

No	Reference	Country	Drug company affiliation	Years enrolled	Number of patients	Drug classes evaluated	Population	Percent initiating ARB	Period observed	Adherence definition	Type of adherence measure	Mean adherence rate	Covariates	Quality rating
13	Esposti et al. 2004[29]	Italy	Yes	2000	14 062	ARB, ACEI CCB, BB, diuretic	Initiating a first medication for treatment of HTN	6.9%	12 months	Days elapsed between first and last prescription	Therapy Persistence	55% ARB, 43% ACEI, 35% CCB, 43% BB, 33% diuretics 40% overall > 273 days elapsed between first and last prescription	1,6,7,10	Good
14	Corrao et al. [30]	Italy	No	1999–2002	445 356	All drug classes	Initiating a first medication for treatment of HTN; at least 1 refill for drug class of interest during study period	9%	12 months	Days until lapse in therapy for ≥ 60 days	Therapy Persistence	59% overall No lapse in therapy for ≥ 60 days	1,2,8,15	Excellent
15	Hoer et al. [31]	Germany	Yes	2000–2003	62 754	ARB, ACEI CCB, BB, diuretic	Initiating a first medication for treatment of HTN other than combination pills; no recent CVD related hospitalization; at least 1 refill for drug class of interest during study period	5.5%	12 months	Days until lapse in therapy for ≥ 60 days	Medication Persistence	53% ARBs 35% ACE 34% CCBs 14% BB 26% diuretics No lapse in therapy for ≥ 60 days	1,2	Good
16	Van Wijk et al. 2008[18]	United States, Canada, and Netherlands	No	1998–2004	9 664 United States 25 377 Canada 24 603	ARB, ACEI CCB, BB	Initiating a first medication for treatment of HTN;	9.9% US 1.6% Canada .7.1% Netherlands	12 months	No lapse in therapy for ≥180 days	Therapy Persistence	77% USA 77% Canada	1, 2,3,4,6, 9,10	Good

No	Reference	Country	Drug company affiliation	Years enrolled	Number of patients	Drug classes evaluated	Population	Percent initiating ARB	Period observed	Adherence definition	Type of adherence measure	Mean adherence rate	Covariates	Quality rating
					Nether-lands		seniors (>65 years old)					76% Netherlands		Excellent
17	Zhang et al.[32]	United States	No	2004	1 351	ARB, ACEI	Initiating ARB or ACEI; eligible if continuing prior HTN medication	22.8%	6 months	PDC ≥ 80%	Compliance	53% overall	1,2,3,6,8,9,10,11	

Covariates: (1) age, (2) sex, (3) race/ethnicity, (4) income or receipt of social assistance, (5) residence, (6) comorbidity types, (7) comorbidity burden, (8) treatment with medication classes other than antihypertensives, (9) medication regimen characteristics (number of medications, frequency of dosing, number of pills per day), (10) health care utilization (prior hospitalizations, physician visits, use of other services), (11) out-of-pocket medication costs, (12) type of health insurance, (13) physician characteristics, (14) blood pressure at baseline, (15) year of first prescription, (16) family history of comorbidities

Abbreviations: ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; BB, beta-blocker; AB, alpha blocker; HCTZ, hydrochlorothiazide; PDC, proportion of days covered; HTN, hypertension; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease

*
Medication persistence means that patients were considered persistent if they continued the initial prescribed drug class, but not if they switched or combined a medication from another drug class or if they discontinued all antihypertensive medication therapy

†
Therapy persistence means that patients were considered persistent if they remained on any hypertension medications from the time of treatment initiation which could include continuing the initially prescribed drug class, combining with another drug class, or switching to a different drug class without a lapse in treatment.

‡
Not included in pooled analysis due to overlapping data from other study