Trends in baseline characteristics of hypertensive patients on Angiotensin-converting enzyme inhibitors compared to other antihypertensive medications

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Abstract

Background and objective: Observational studies are considered more appropriate in the assessment of comparative effectiveness in the general population. We aimed to explore the trends in differences in baseline characteristics in terms of age, sex, blood pressure, body mass index, smoking and diabetes between users of Angiotensin-converting enzyme inhibitors and other antihypertensive drug classes in observational studies since the launch of Angiotensin-converting enzyme inhibitors.

Methods: We reviewed observational studies that compared Angiotensin-converting enzyme inhibitors with mono-therapies of calcium channel blockers, beta-blockers and diuretics in primary care treatment of hypertensive patients. Electronic search of studies in Medline and Embase were performed up until to June 2014. Randomized control trials, non-antihypertensive, non-comparative or combined antihypertensive drug classes observational studies and studies with participants <100 patients were excluded.

Results: A total of 28 studies were included in the review. There was a declining trend in the mean difference in baseline systolic and diastolic blood pressure over time but no clear pattern was observed for the difference in proportion of male sex, diabetes and smoking or the difference in mean age and body mass index .

Conclusion: Findings from this study suggest a downward trend in the differences in mean systolic and diastolic blood pressure of angiotensin-converting enzyme inhibitors users compared to diuretics and beta-blockers users and no clear pattern in other baseline variables.

Key words: Angiotensin-converting enzyme inhibitors, diuretics, beta blockers, calcium channel blockers, baseline characteristics, age, sex, blood pressure, observational studies

Background

Randomized controlled trial (RCT) is the gold standard for evaluating treatment efficacy[1] while observational studies are considered more appropriate in the assessment of comparative effectiveness in the general population.[2;3] RCTs have proven that antihypertensive therapies are effective in lowering the blood pressure and reducing the risk of cardiovascular disease compared to placebo.[4] However studies suggested conflicting results in the effect on the cardio/stroke protection properties among the major anti-hypertensive drug classes: diuretics, beta blockers, calcium channel blockers and ACE-inhibitors.[5-8] In addition, most RCTs are conducted under controlled setting and different population from what can be encountered in daily clinical practice.[9] Observational studies, on the other hand, represent the real world and capture the channeling of new drugs to severely ill patients at drug launch and are essential in the assessment of the long-term beneficial effects of therapies.[2]

However, observational studies are subjected to a number of biases and confounding due to the lack of randomized treatment assignment.[1] The speculations of the lack of comparability of treatment groups tend to be more pronounced around the time the drug is launched into the market.[3] Often, failure of patients to respond to the existing therapy or the presence of an adverse event with existing therapy results in channeling to the new medication.[10] This leads to confounding and possibly non-positivity between the groups under study.[11] In view of this, we hypothesized that any obvious differences in baseline characteristics of patients receiving new treatment versus the comparator (i.e., standard of care) would diminish over time. In this review, we aimed to investigate the differences in baseline characteristic of ACE-Inhibitors and other anti-hypertensive drug classes in observational studies since drug launch overtime.

Objective

The primary objective of this review was to explore the trends in differences in baseline characteristics (age, sex, smoking and blood pressure) between users of ACE-inhibitors and other comparator drugs in observational studies since the launch of ACE-inhibitors.

Methods

Inclusion and exclusion criteria

Types of studies

Any observational study (retrospective or prospective cohort studies) that compared ACE-inhibitor with mono-therapies of calcium channel blockers, beta-blockers and Diuretics in primary care treatment of hypertensive patients were eligible to be included for this review. Exclusion criteria were review studies, randomized control trials, observational studies that were non-antihypertensive, non-comparative, combined antihypertensive drug classes and studies with no presentation of baseline characteristic by drug classes. Also studies with <100 patients were excluded.

Types of patients

Studies containing patients with essential hypertension, initiating antihypertensive therapy, above 18 years of age with clinically diagnosed hypertension defined as a systolic and diastolic blood pressure of >140mmHg/ 90mmHg and at least three month of treatment with the intervention were included in the review.

Types of Interventions

Studies had to include mono-therapies of the four major classes of anti-hypertensive: Angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers and diuretic.

Types of Outcomes

All possible outcomes in studies from controlled blood pressure < 140mmHg/90mmHg to antihypertensive adherence, cardiovascular morbidity (non-fatal and fatal stroke, myocardial

infarction, angina, coronary heart disease, congestive heart failure), cardiac mortality and all-cause mortality were considered.

Search methods for identification of studies

Eligible studies were sought through electronic search of Medline and Embase up until June 2014.The search strategy was developed with the help of experts and was tailored using full text, MESH terms, title and abstracts to identify observational studies evaluating four antihypertensive drug classes with at least ACE-Inhibitors drug class in primary care of hypertensive patients. No other means were used to limit or restrict search terms.

The detailed description of the search strategy of the Medline database is presented in Appendix 1. First titles and abstracts were screened to identify potentially relevant studies. Then further comprehensive review of full publications as performed to identify eligible studies. The references of included articles were carefully scrutinized to identify additional studies missed by the electronic search.

Data collection

A formal data extraction form was designed by adapting critical appraisal skills programme (CASP)[12] for this review to obtain important information about participants, data source, antihypertensive drug classes, baseline characteristics, method of analysis and control of confounders from reports of eligible studies. Data extraction was performed on eligible articles and controversial articles were discussed with a second reviewer. Data was collected on the following study characteristics: the type of study; the number of participants; the time the study was conducted; the duration of follow-up time; patient's baseline characteristic such as age, gender, ethnicity, blood pressure, body mass index (BMI), smoking and diabetes mellitus. For the descriptive purpose of the pattern in the differences of baseline characteristics over time, the first year of the study's enrollment period was defined as the

index date of antihypertensive drug exposure for its population. To address concerns on misclassification of index dates of exposure, studies with relatively long duration and no clearly defined year of enrollment period were excluded from the subgroup analysis.

Results

Study inclusion

A total of 28 studies were included in this review from the 547 hits obtained from Medline and Embase electronic. Of these, 501 were excluded by examining the titles and abstracts because they failed to meet the inclusion and exclusion criteria. The full content of 44 selected articles were further scrutinized, of which another 10 studies were excluded due to baseline tables being presented as combined anti-hypertensive drug groups.[13-19;19-21] An additional 6 case control studies were excluded.[22-27] For details of articles retrieved, selected and finally included in this review see flow chart Figure 1.

67.9% and 32.1% of the studies were retrospective and prospective, respectively. 75% of studies used large electronic health databases. Studies were conducted in the USA, Canada, Netherlands, Italy, France, Greece, China and Hong Kong from 1989 to 2011 and spanned over 30 years. The duration of studies varied from 1 year to 19 years and the median study duration was 6 years. (Figure 2).

All but one study recruited patients with essential hypertension[28] and studies had population ranging from 205 to 360167 patients. Information on baseline age was reported by 96.4% of studies, of which 71.4% reported an average age between 54.5 to 72.2 years. Of these, 32.1%, 25% and 14.3% of studies fell into the average age group categories of <63 years, 63 to 70 years and greater than 70 years respectively. Most of the studies reported on sex and the population of males were less than 50% except for one study that included only male participants. For an overview of variable information reported in review see Table 1. An overall summary of included studies and excluded studies are presented in the Table 2 and 3 respectively.

The 4 classes of anti-hypertensive drugs of interest were present in all but two studies.[29;30] Other anti-hypertensive drug classes such as angiotensin receptor blockers, alpha-blocker, vasodialator and no treatment were assessed as comparators in 18 studies. All studies assessed mono-therapy of antihypertensive while some studies also evaluated combination antihypertensive therapy. Most of the patients were defined as new users on one of the six classes of antihypertensive drugs with a few studies accounting for the patients that switched drugs but the dosage of drugs used were not explicitly stated in most of the studies. Detailed information on individual study's characteristics in Appendix 2.

Outcomes were assessed after a follow-up time of between 3 months to 7 years. The outcome of interest of various studies were lowering of blood pressure, adherence to anti-hypertensive therapy, risk of fracture, diabetes, cardiovascular diseases and death and all-cause mortality. Various analytical methods such as student's t test, chi square test, logistic regression, linear mixed model and Cox proportional hazard were used while matching, stratification, adjustments in multivariate models and propensity score were performed in most studies to adjust for confounding.

Some of the baseline characteristics explored in this review were age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), stages of hypertension, coronary heart disease, heart failure, diabetes, stroke, two or more co-morbidities and chronic disease scores. Not all studies reported on these baseline characteristics, but in studies that did, there was no clear pattern in the difference in proportion of male sex and diabetes. While the difference in mean age, BMI and proportion of smoking showed no declining or increasing trends. Although the mean difference in baseline SBP and DBP suggested a possible declining pattern over time. See Figure 3-9.

Figure 3 shows the trends in the mean difference in baseline SBP between ACE-Inhibitors versus diuretics in comparison to the mean differences IN SBP between ACE-Inhibitors versus beta-blockers. The mean difference in baseline SBP between ACE-Inhibitor versus diuretics was about 7mmHg and it was observed to gradually decline over a decade after which it leveled off in the last half decade. A similar pattern and slightly lesser difference was observed in the mean difference in baseline SBP of ACE-Inhibitors versus beta-blocker. Slight changes were observed over a decade except that the last half decade, when the scenario changed, the average systolic blood pressure of beta-blocker was observed to be greater than those on ACE-Inhibitor. With further exploration of the trends of the mean difference in DBP of ACE-Inhibitor versus diuretics and ACE-Inhibitor versus beta-blocker s, it seems the mean difference in DBP of ACE-Inhibitor versus diuretics declined from 3mmHg to 2mmHg over a decade while that of ACE-Inhibitors versus beta-blockers declined from 1.8 to 0.8. At the end of the study, there were 3 studies present with different values in DBP that made it difficult to make a valid conclusion about the direction of the pattern. (Figure 4).

Discussion

Using observational studies, this review explored the trends in differences in baseline characteristics (age, sex, smoking, BMI and blood pressure) between users of ACE-inhibitors and older antihypertensive drugs classes since the launch of ACE-inhibitors.

We found a declining pattern in the mean difference of baseline systolic blood pressure of patients on ACE-Inhibitors versus diuretic and beta-blocker over the first decade of drug launch. This became relatively stable and showed no further increasing or decreasing trends in the last half decade. Also there appeared to be an obvious difference in mean differences in baseline diastolic blood pressure between drug class comparison group: ACE-Inhibitor versus diuretics group and the ACE-Inhibitor versus beta-blocker. A declining pattern observed over time, although not very convincing. For the other baseline characteristics, the differences in proportion of sex, smokers, diabetes patients and the mean differences of age and body mass index showed no clear pattern over time.

The findings of this study were in-line with our hypothesis that patients with poorer prognosis are often channeled to a newer drug at the time of its launch but the observed differences in baseline characteristics slowly diminish over time until drug class groups become comparable. Although a clear pattern was not observed in other variables as we expected, the presence of difference in the mean baseline systolic and diastolic blood pressure between ACE-Inhibitors and other comparators and a declining pattern over time supports the hypothesis. The patterns were similar and ACE-Inhibitor users had a much higher average systolic and diastolic blood pressure compared to diuretic and beta-blockers, which diminished over time. More so, the declining pattern in the baseline systolic and diastolic blood pressure mean differences seemed more obvious especially when the studies of Gelber et al[31] and Trompet et al[32] were examined more closely and considered as outliers. They

recruited mainly elderly population of 71 to 93 years and 85 to 90 years respectively, who had higher average systolic and diastolic blood pressure than other studies and as a result, the deviation observed in the trend.

A major strength of this review was the inclusion of studies with a large study population and a long duration of year examined. It was difficult to assess the difference in baseline characteristic among few studies that had relatively longer enrollment period.[33;34] Thus, they were excluded from the sub-analysis, resulting in loss of information. Other limitations were the low number of studies and the wide variation in the inclusion and exclusion criteria of the studies, these may have been responsible for the no clear pattern seen in the other baseline variables.

Conclusion

The findings of this review suggest a downward trend in the difference in mean systolic blood pressure of angiotensin-converting enzyme inhibitors users compared to diuretics and beta-blockers users. Although a declining pattern was also observed for diastolic blood pressure mean difference, this was not really convincing and inclusion of more studies after 2002 are needed to make a valid conclusion. The assessment of differences in the other baseline variables showed no clear pattern.

Table 1: Study summary

Study characteristics	No. of studies (n=28)	Total (%)
Observational study		
Retrospective	19	67.9
Prospective	9	32.1
	28	100
Data source		
Electronic database	21	75
Primary data	7	25
	28	100
Study enrollment duration		
1-3 years	12	42.9
4-7 years	8	28.6
8-11 years	5	17.9
>11 years	3	10.7
	28	100
Drug class		
< 4 drugs	2	7.1
≥4 drugs	26	92.9
	28	100
Baseline characteristics		
Age	27	96.4
Sex	21	75
Baseline SBP	9	32.1
Baseline DBP	9	32.1
BMI	6	21.4
Smoking	6	21.4
Diabetes	13	39.3
Overall Mean baseline Age	20	71.4
< 63 years	9	32.1
63-70 years	7	25%
>70 years	4	14.3
Analysis		
Student's t test & Chi's square	3	10.7
linear regression	8	28.6
Cox proportional hazards	17	60.7
	28	100
Method of Adjustment		
Propensity score	5	17.9
Others	23	82.1
	28	100

Table 2: Summary of Included study characteristics

Study ID	Country	Study duration	No. of patients	No. of comparators	Outcome	Analysis	Baseline variables	Method of adjustment
Ishiguro et al (2008)[33]	Japan	1981 -1999	22307	4	Change in SBP from the baseline after 2 months (±2 weeks)	Multiple regression analysis	Age, Gender, SBP, DBP, Stages of hypertension,	Semi-parametric regression model
Petrella et al (2011)[35]	Canada	2000 - 2010	10120	5	BP control (<140/90 mm Hg) after 3, 6, and 9 months of treatment	Student's t test	Age, Gender, SBP, DBP, Weight	
Solomon et al (2011)[36]	USA		379061	6	Four typical osteoporotic fractures well defined in health care utilization data: hip, distal forearm, humerus, and pelvis	Cox proportional hazards regression	Age, Gender, Race, SBP, DBP, Chronic disease scores	
Leader et al (1997)[37]	USA	1987 - 1994	1406	9	Risk of Acute Myocardial Infarction	Cox Proportional Hazard	Age (Catergorized), Gender,Race, Stage of hypertension	

Padwal et al (2004)[29]	Canada	1995 - 2000	76176	3	Time to diagnosis of diabetes	Cox Proportional Hazard	Age, SES Income quintile: 1 (poorest) to 5 (richest), Mean length of follow-up, Dyslipidemia
Mazzaglia et al (2005)[38]	Italy	2000 - 2001	13303	6	Discontinuation of first-line treatment	Cox Proportional Hazard	Age, Gender, SBP, DBP, Stage of hypertension, Coronary heart disease, Heart failure, Diabetes, Stroke, Two or more comorbidities, Chronic disease score
Blackburn et al (2007)[39]	Canada	1994 - 2003	19249	4	First occurrence of any of the following events: death from any cause; all cause stroke or transient ischaemic attack; myocardial infarction or unstable angina	Cox Proportional Hazard	Age, Gender, Mean length of follow-up, Diabetes, Chronic disease score

Esposti et al (2002)[40]	Italy	1997 - 1999	7312	5	3 years stay-on-therapy pattern for antihypertensive drug classes	Cox Proportional Hazard	Age, Gender, SBP, Two or more comorbidities,	
Bourgault et al (2005)[41]	Canada	1997 - 2000	21326	5	Treatment discontinuation and initiation of a new course of therapy after discontinuation	Cox Proportional Hazard	Age, Gender, Mean length of follow-up	
Karpanou et al (2006)[34]	Greece	1986 - 2004	11148	6	Pulse pressure reduction after 6-month therapy	Cox Proportional Hazard	Age, Gender, SBP, DBP, Obese, Smokers, Diabetes,	
Caro et al (1999)[42]	Canada	1989 - 1994	22918	4	Antihypertensive therapy compliance	Logistic regression analysis	Age, Gender, Mean length of follow-up	
Wong et al (2010)[43]	China	1990 - 2002	2531	4	Cumulative incidence of add-on therapy at around 1 year after their first-ever prescription	Chi-square tests	Age, Gender	Stratified
Esposti et al (2004)[44]	Italy	2000 - 2001	14062	5	Persistence With Treatment & annual Average Cost by Class of Drug Prescribed at Enrollment and Persistence Pattern	Cox Proportional Hazard	Age, Gender, Coronary heart disease, Diabetes, Two or more co-morbidities	

Weiss et al (2006)[45]		2001 -2005	5373	4	The continuation of the initial drug or its replacement during the 6 months after beginning therapy.	Chi-square test	Age, Gender, Heart failure, Diabetes	
Patel et al (2007)[46]	USA	2001 - 2003	242882	5	1-year persistence and compliance rates & time to therapy discontinuation of anti-hypertension mono-therapy	Cox Proportional Hazard	Age, Gender, Coronary heart disease, Diabetes	Propensity score
Wassertheil-Smoller et al (2004)[47]	USA		11294	4	Incidence of coronary heart disease, stroke, and CVD mortality	Cox Proportional Hazard	Age, Race, SBP, DBP, Body mass index, Smoking, Diabetes	Propensity score
GRESS et al (2000)[48]	USA	Ongoing	3804	6	Risk of type 2 Diabetes Mellitus	Cox Proportional Hazard	Age, Gender,Race, SBP, DBP, Body mass index, Coronary heart disease, Stroke	
Klungel et al (1998)[28]	Netherlands	1987–1992 1993–1995	1355	4	Sex differences	Polytomous logistic regression	Age, Gender, Body mass index, Smoking, , Diabetes, Stroke	

AU et al (2004)[49]	USA	1996 -1999	1966	6	Risk of all-cause mortality	Cox Proportional Hazard	Age, Smoking, ACS, Heart failure, Diabetes, Chronic disease score	Stratified
Tardif et al (2004)[30]	USA	1995 - 2002	12608	2	Total and cardiovascular mortality new diagnoses of angina, MI, stroke, CHD, complicated hypertension, and renal disease	Cox Proportional Hazard	Age, Gender, Mean length of follow-up, Dyslipidemia, Coronary heart disease, Heart failure, Diabetes, Stroke,	Propensity score adjustment
Trompet et al (2008)[32]	Netherlands		204	4	Change in cognitive functioning over time	linear mixed models	Gender, SBP, DBP	
Wong et al (2008)[50]	Hong Kong	2004 - 2007	93286	6	Cumulative incidence of drug discontinuation within 180 days	binary logistic regression analysis	Age, Gender, Two or more comorbidities	
Gelber et al (2013)[31]	Hawaii	1991 -1993	2197	7	Risk of cognitive impairment	Cox Proportional Hazard	Age, Gender, SBP, DBP, Body mass index, Smoking, Diabetes, CVD	
Greving et al (2005)[51]	Netherlands	1996 - 1999	3102	6	ARBs as initial and second-line treatment	Cox Proportional Hazard	Age (categorized), Gender	Stratified

Levi-Marpillat et al (2014)[52]	France	2005 - 2011	2780	5	Short-term BP variability	Logistic regression models	Age, Gender, Body mass index, Smoking, Dyslipidemia, Coronary heart disease, Diabetes, Stroke, CVD	Propensity scores
Evans et al (2013)[53]	Canada	1994 - 2002	36214	6	Achieving optimal adherence (≥80%) at 1 year	Multivariable Logistic regression models	Age, Gender	
Roy et al (2013)[54]	Canada	1999 - 2007	185476	6	Risk reduction of ESRD	Cox Proportional Hazard	Age, Gender, Dyslipidemia, Heart failure, Diabetes, Stroke, Chronic disease score	
Smith et al (1997)[55]	USA	1989 - 1993	5201	7	Change in serum Creatinine over 3-years	Multivariate linear regression	Age, Gender, SBP, DBP, Body mass index, Smoking, CVD	

Table 3:	Summary of excluded studies
Study	Reason for exclusion
Verma et al (2007)[56]	Comparision was only ACE-I versus ARB and no baseline characteristics of cohort was presented before matching
Papadakis et al (2005)[13]	Antihypertensive class grouped together and was not considered on the basis of drug class
Herrin et al (2013)[14]	Baseline Characteristics of the COPD Patients WITH Hypertension by antihypertensive medication combination
Maxwell et al (1999)[15]	Demographic and health characteristics presented by CCB and other antihypertensive drug class combined
Veronesi et al (2007)[16]	RCT
Feringa et al (2006)[17]	Evaluated a broad range of cardiac medication (including statins, nitrates, coumarins, and digoxin) and baseline table was not by medication
Johnson et al (2005)[18]	Evaluation was antihypertensive drug class by number of antihypertensive drugs
Hasford et al (2002)[19]	Compared ARB to other antihypertensive drug classes combined
Alderman et al (2010)[21]	Compared two groups of combined antihypertensive drug class and presented baseline table as combined
Chen et al (2004)[20]	Baseline characteristic table not presented by drug class
Bourgault et al	Case control study with no baseline characteristic by drug class

(2001)[22]	
gonza´lez-pe´rez et al (2003)[23]	Case control study with no baseline characteristic by drug class
van wijk et al (2006)[24]	Case control study with no baseline characteristic by drug class
Van Wijk et al (2004)[25]	Case control study with no baseline characteristic by drug class
Mukamal et al (2010)[26]	Case control study with no baseline characteristic by drug class
Azoulay et al (2012)[27]	Case control study with no baseline characteristic by drug class

Figure 1: FLOW CHART OF SEARCH STRATEGY

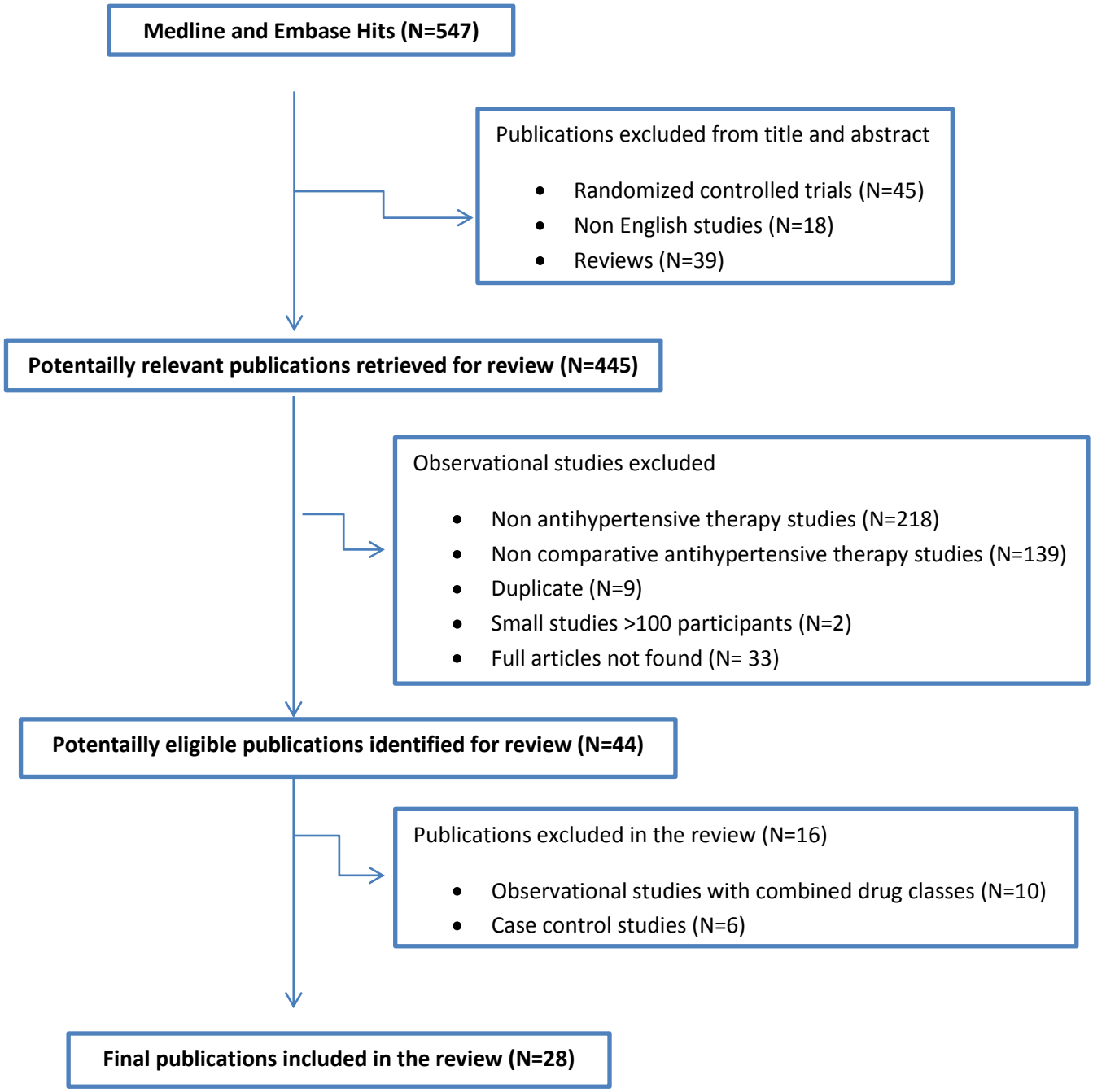


Figure 2: Duration of included studies

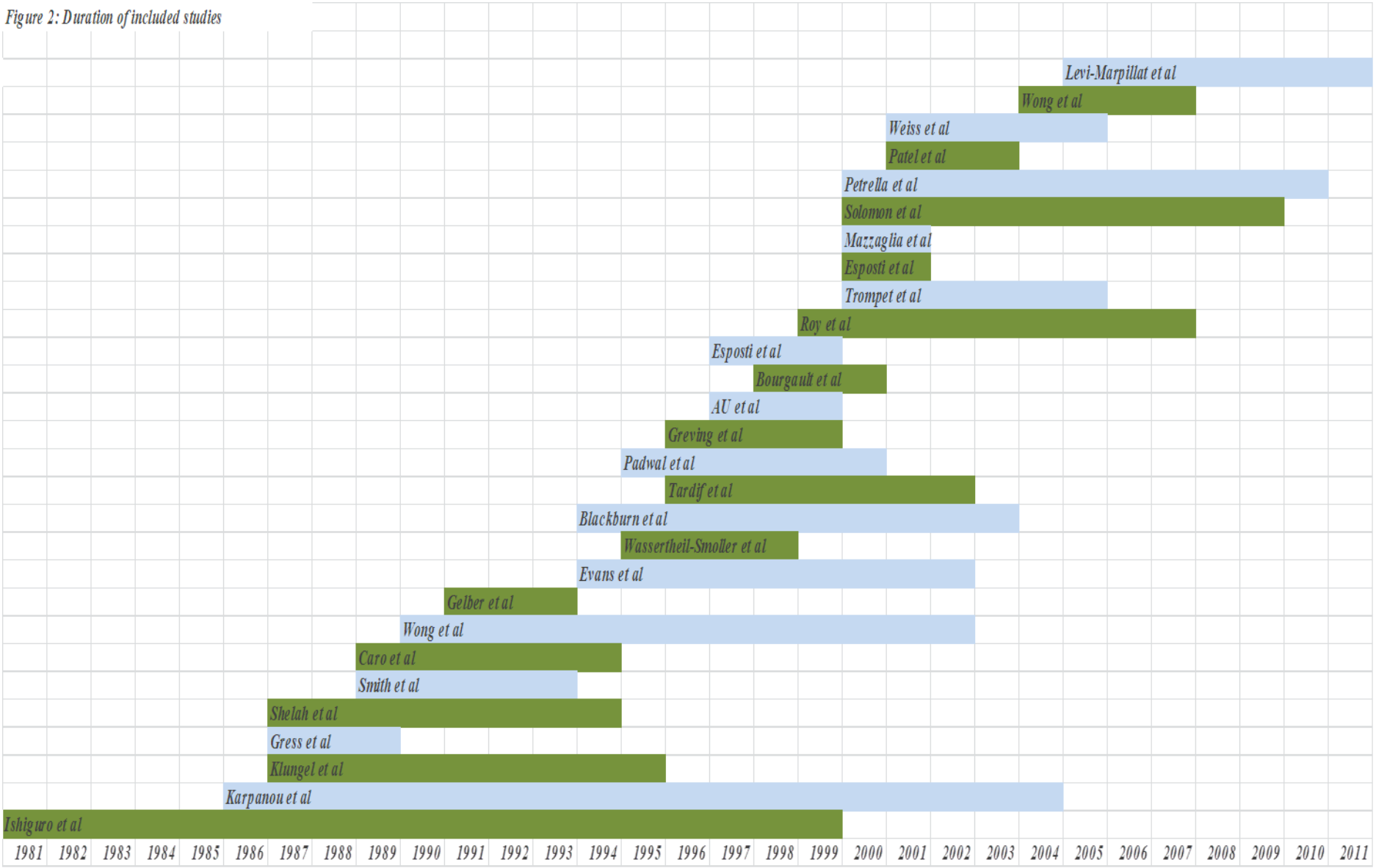


Figure 3:Trends in sbp mean difference between ACE-I vs ß-Blocker and ACE-I vs Diuretic

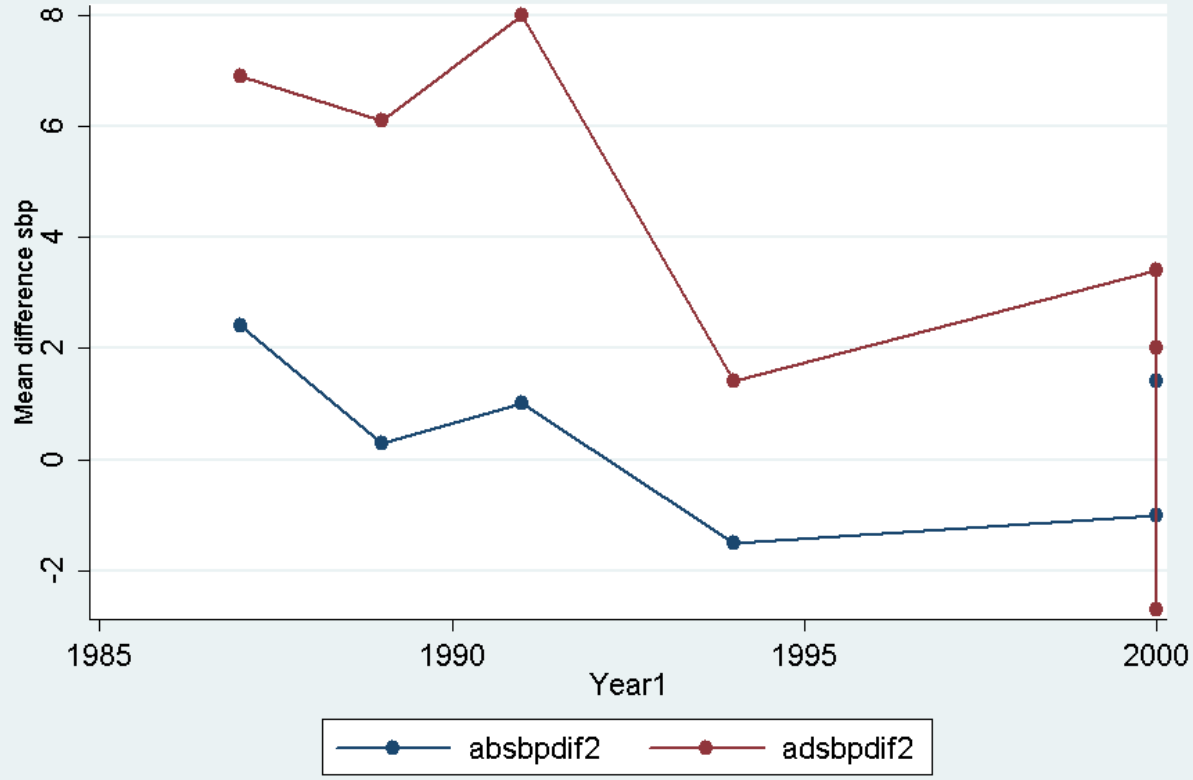


Figure 4:Trends in dbp mean difference between ACE-I vs ß-Blocker and ACE-I vs Diuretic

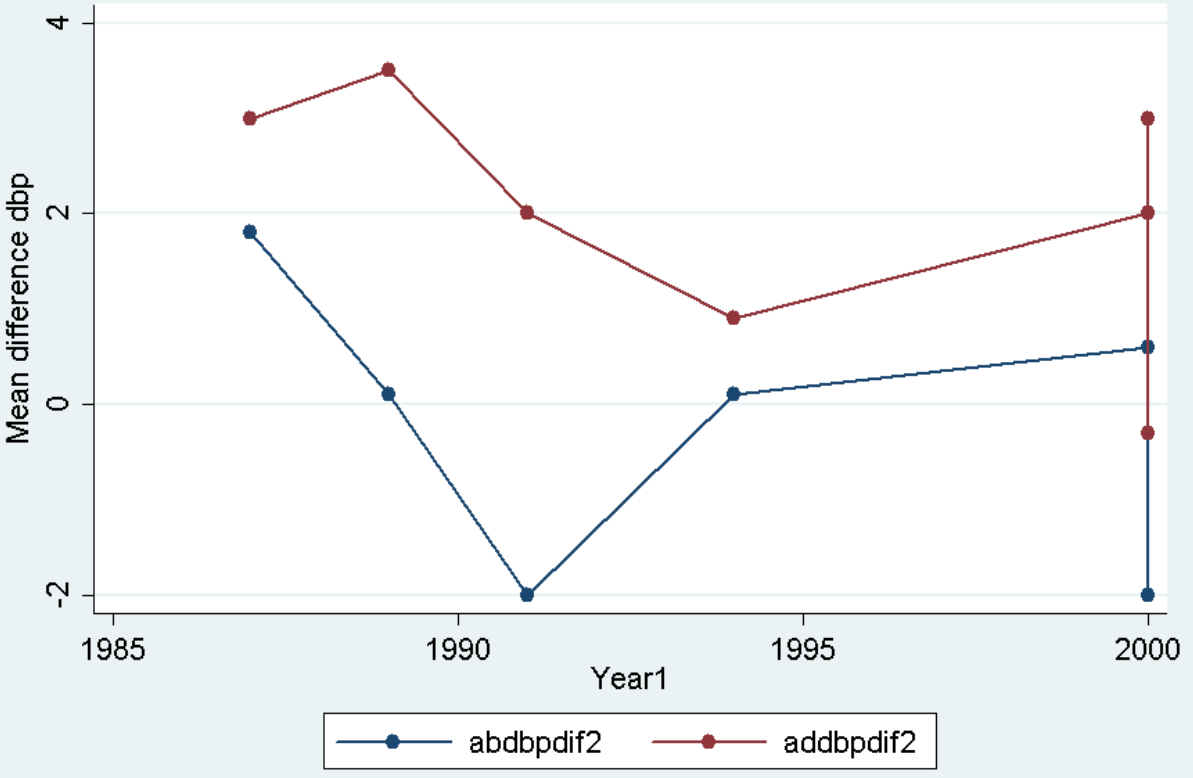


Figure 5:Trends in sex proportion difference between ACE-I vs ß-Blocker and ACE-I vs Diuretic

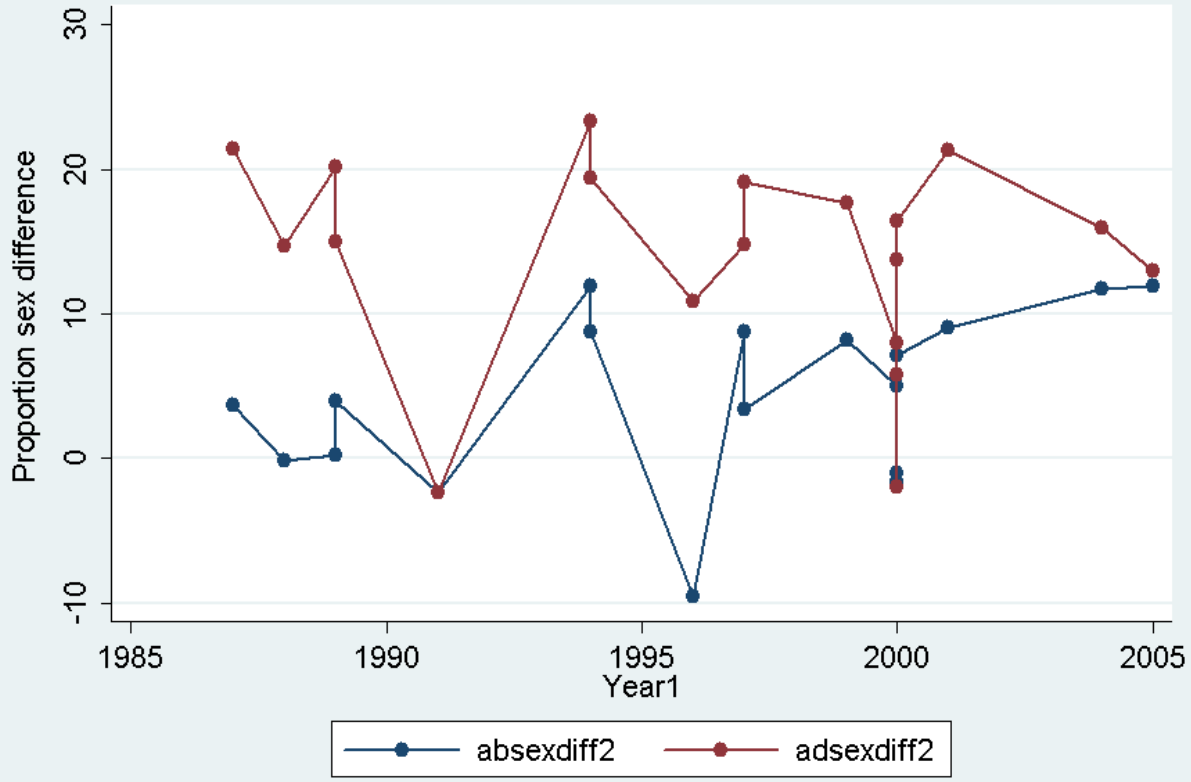


Figure 6:Trends in diabetes proportion difference between ACE-I vs ß-Blocker and ACE-I vs Diuretic

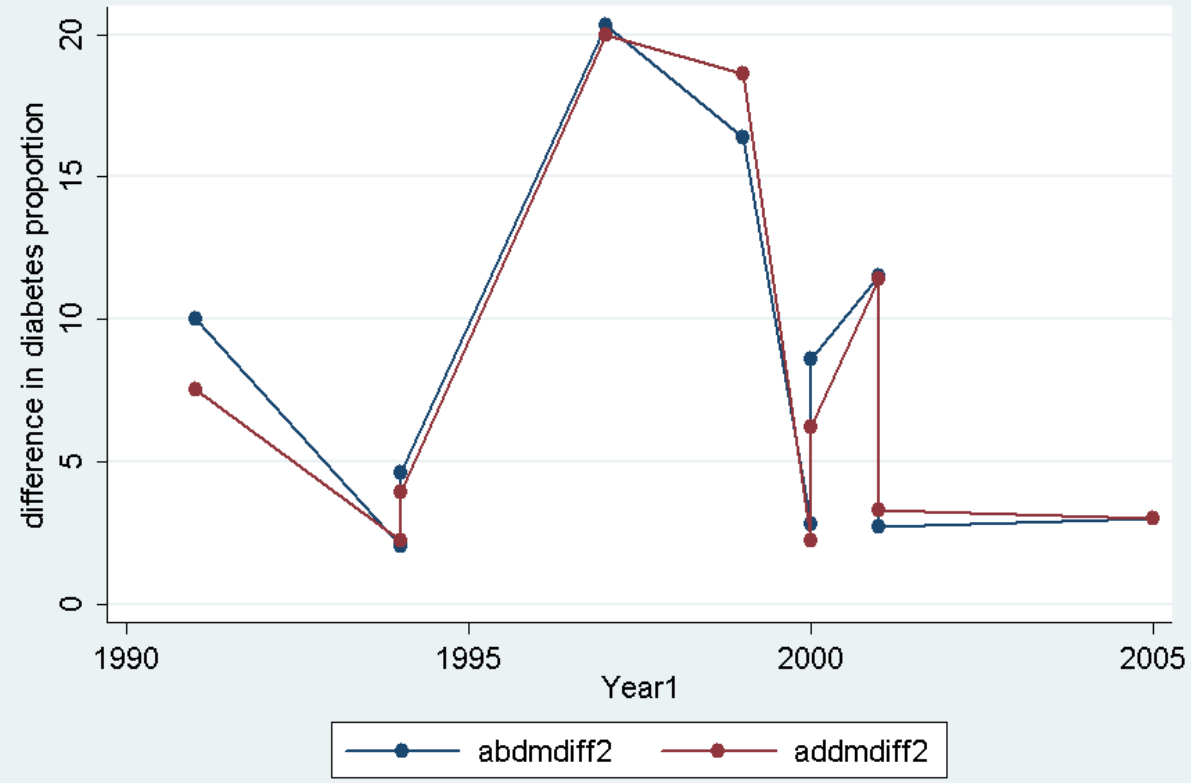


Figure 7:Trends in smoking proportion difference between ACE-I vs ß-Blocker and ACE-I vs Diuretic

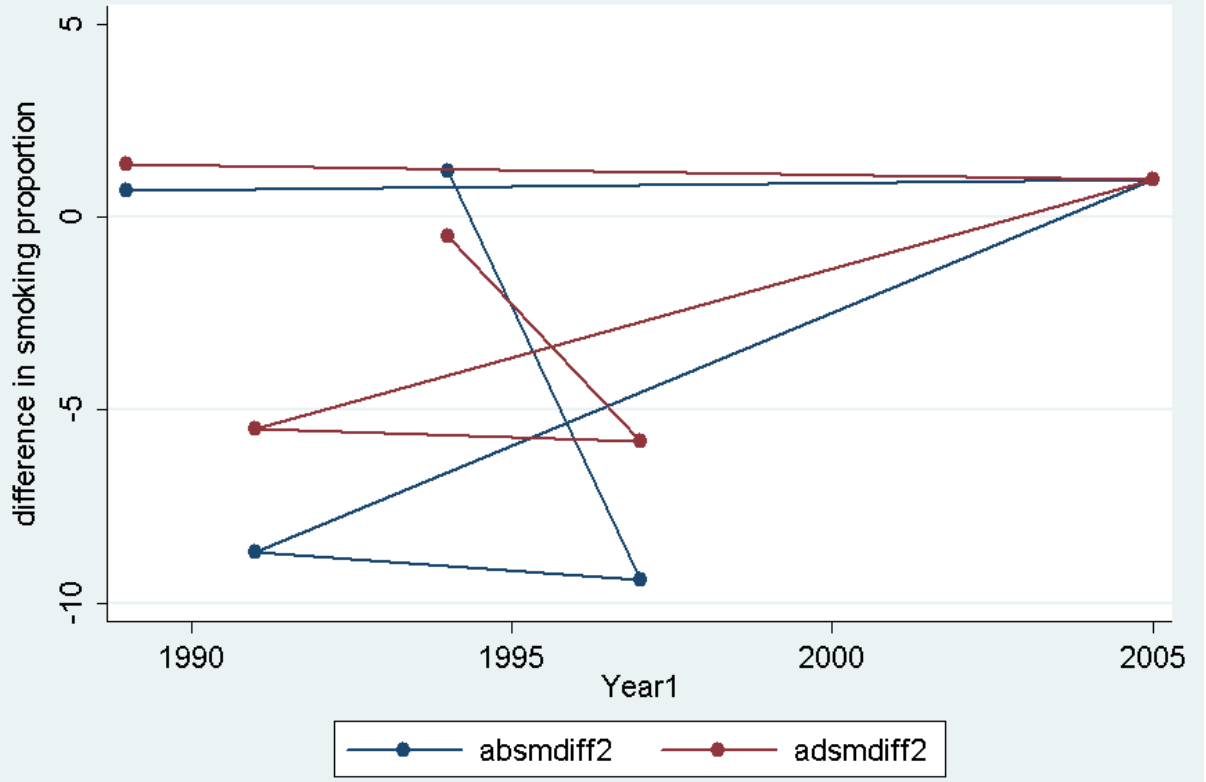


Figure 8:Trends in BMI mean difference between ACE-I vs ß-Blocker and ACE-I vs Diuretic

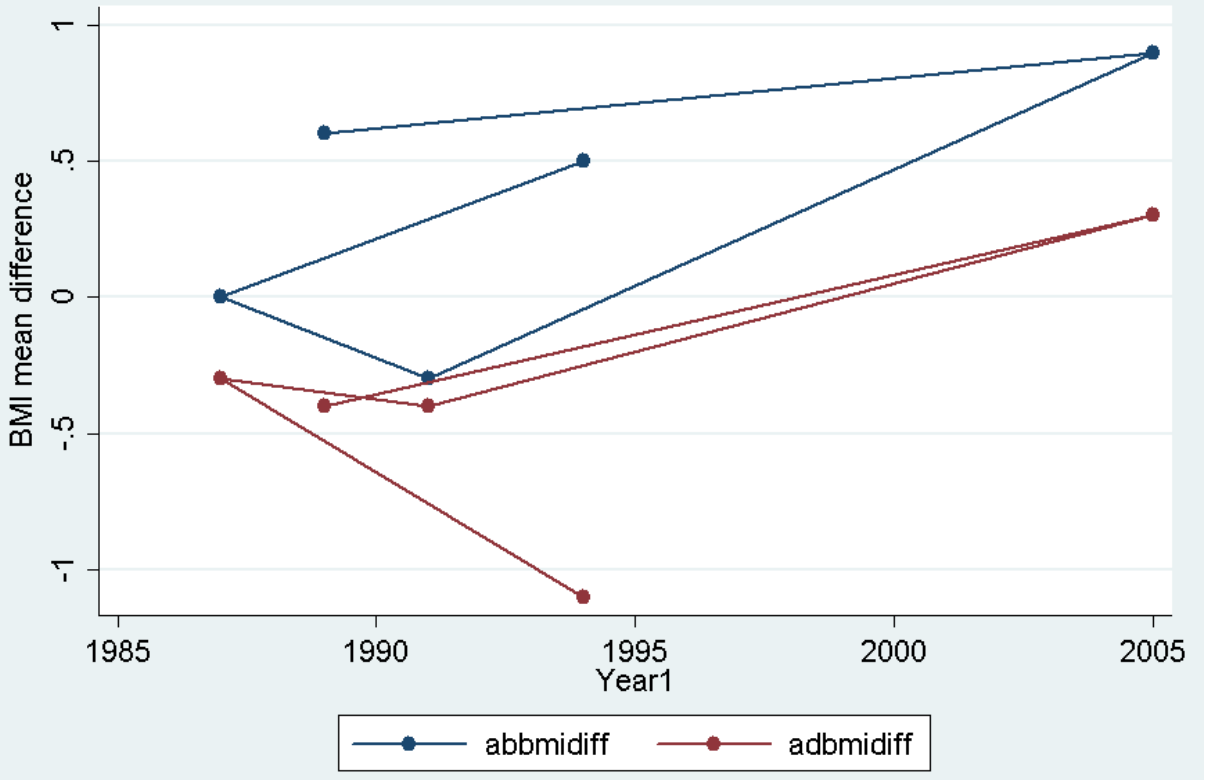
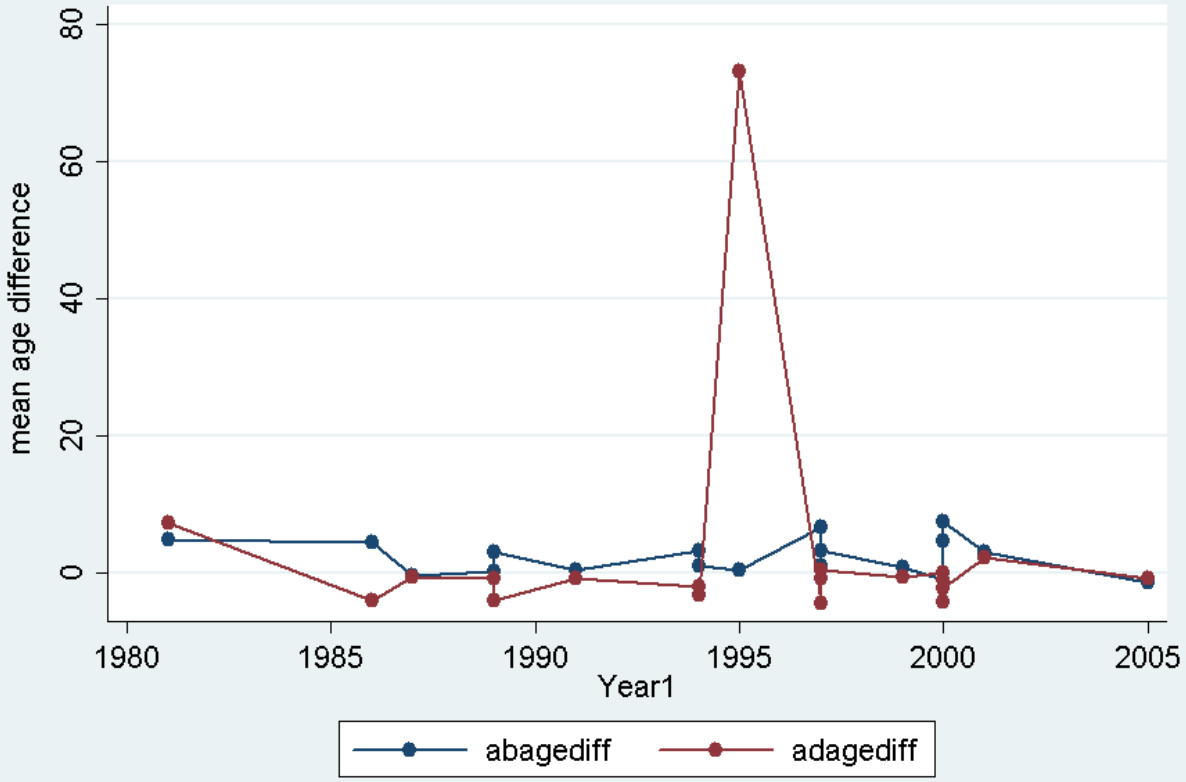
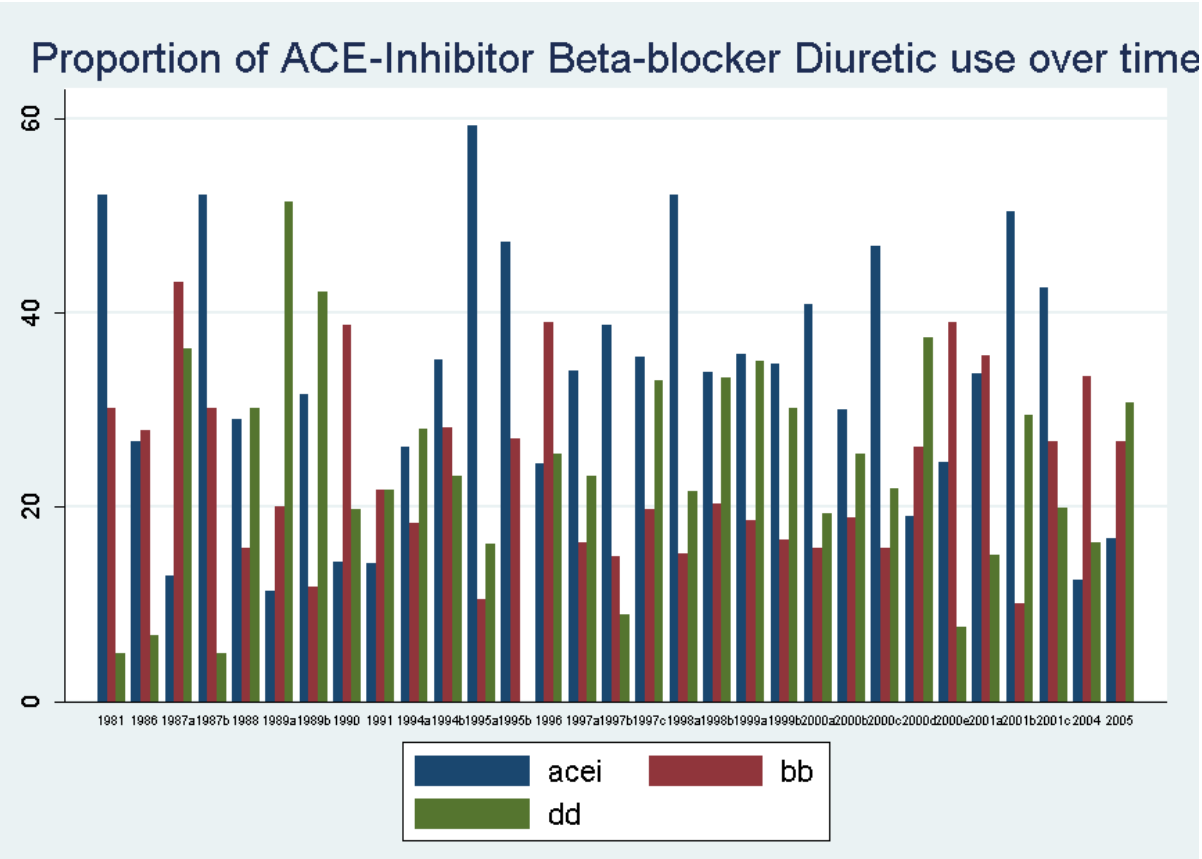


Figure 9:Trends in mean age difference between ACE-I vs ß-Blocker and ACE-I vs Diuretic





Appendix 1.	Search strategy for Pubmed
#1	(""Hypertension""[Mesh]) OR (hypertension[Title/Abstract]) OR (hypertensive[Title/Abstract])
#2	(("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR (Angiotensin-Converting Enzyme Inhibitors[Title/Abstract]) OR (Angiotensin-Converting Enzyme[Title/Abstract])
#3	(("Diuretics"[Mesh]) OR (DIURETICS[Title/Abstract]) OR (Diuretic[Title/Abstract]))
#4	(("Adrenergic beta-Antagonists"[Mesh]) OR (Adrenergic beta-Antagonists[Title/Abstract]) OR (Adrenergic beta-Antagonist[Title/Abstract]) OR (beta-blocker[Title/Abstract]) OR (beta-blockers[Title/Abstract]))
#5	(("Calcium Channel Blockers"[Mesh]) OR (CALCIUM CHANNEL BLOCKERS[Title/Abstract]) OR (CALCIUM CHANNEL BLOCKER[Title/Abstract])))
#6	(("Cohort Studies"[Mesh]) OR (Cohort Studies[Title/Abstract]))
#7	#1 AND #2 AND #3 AND #4 AND #5 AND #6

CHARACTERISTICS OF STUDIES

Characteristics of included studies

Study 1	**Ishiguro et al (2008)[33]**
Methods	Type: Retrospective Observational study
	Study conducted: 1981 - 1999
	Location: Japan
	Data source:
	No. of subjects included: 1204
	Enrollment year/ Index date: 1981 - 1999
Participants	Inclusion criteria: Essential hypertension with no exposure to antihypertensive drug before the onset of AHT in database
Interventions	No. of comparators: 4
	No. of ACE-Inhibitors users: 628
	No. of CCBs users: 152
	No. of B-Blockers blockers: 364
	No. of Diuretics users: 60
	Other : NSAIDs
Exposure	Measurement of exposure: Drug database
	Drug status: New drug user
	Switched drug: Not clear
	Average duration of follow-up: 3 years and 6 years
	Dosage: Not stated
Confounding	Baseline variables: Age, Gender, SBP, DBP, Stage of hypertension
	Analysis: Multiple regression analysis
	Confounders: Adjusted for confounders
	Methods of adjustment: Matching, Semi-parametric regression model(PS)
Outcomes	The change in SBP from the baseline after 2 months (±2 weeks)

Study 2	**Petrella et al (2011)[35]**
Methods	Type: Retrospective Observational study
	Study conducted: 2000 -2010
	Location: Canada
	Data source: Secondary data
	No. of subjects included: 10120
	Enrollment year/ Index date: 2000 - 2005
Participants	Inclusion criteria: >18 year with diagnosis of hypertension or initial of AHT at index date of 2005, non-diabetic patients
Interventions	No. of comparators: 5
	No. of ACE-Inhibitors users: 3110
	No. of CCBs users: 1020
	No. of B-Blockers blockers: 1050
	No. of Diuretics users: 1450
	No. of ARBs users: 3490
	Other : (Mono & Combination Therapy)
Exposure	Measurement of exposure: SWO database
	Drug status: New drug user
	Switched drug: Not stated
	Average duration of follow-up: 9 months
	Dosage: Not stated
Confounding	Baseline variables: Age, Gender, SBP, DBP, Weight
	Analysis: Student's t test
	Confounders: Not well accounted for
	Methods of adjustment: Not stated
Outcomes	BP control (<140/90 mm Hg) after 3, 6, and 9 months of treatment

Study 3	**Solomon et al (2011)[36]**
Methods	Type: Prospective Observational study Study conducted: Not stated Location: USA Data source: Secondary data No. of subjects included: 360167 Enrollment year/ Index date: Not stated
Participants	Inclusion criteria: > 65 year with diagnosis of hypertension, no filled prescription for AHT in prior 30 days
Interventions	No. of comparators: 6 No. of ACE-Inhibitors users: 67806 No. of CCBs users: 79445 No. of B-Blockers blockers: 107457 No. of Diuretics users: 21064 No. of ARB users: 24635 No. of Loop diuretics users: 59760 Other : (Mono-therapy)
Exposure	Measurement of exposure: Medicare beneficiaries data Drug status: New drug user Switched drug: No Average duration of follow-up: 12 months(stratified:1 - 90, 91 -180, 181 - 365 days) Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Race, SBP, DBP, Chronic disease score Analysis: Cox proportional hazards regression Confounders: Adjusted for confounders Methods of adjustment: 2 Models with potential confounder
Outcomes	Four typical osteoporotic fractures well defined in health care utilization data: hip, distal forearm, humerus, and pelvis

Study 4	**Leader et al (1997)[37]**
Methods	Type: Retrospective Observational study Study conducted: 1987 -1994 Location: USA Data source: Secondary data No. of subjects included: 1,406 Enrollment year/ Index date: 1988 - 1991
Participants	Inclusion criteria: 18 and 59 years Medicaid recipients, newly diagnosed uncomplicated essential hypertensive in calendar year 1988 or 1991, no previous diagnosis of coronary heart disease
Interventions	No. of comparators: 9 (Mono and combined therapy) ACE-Inhibitors: 283 CCBs: 244 B-Blockers: 154 Diuretics: 294 Vasodilator: 35 Other combinations: 396
Exposure	Measurement of exposure: Pennsylvania's Medicaid Management Information Drug status: New drug user Switched drug: Not stated Average duration of follow-up: 2.6 years Dosage: Not stated
Confounding	Baseline variables: Age (Categorized), Gender, Race, Stage of hypertension Analysis: Cox Proportional Hazard Confounders: age, sex and race Methods of adjustment: Fully adjusted model
Outcomes	Risk of Acute Myocardial Infarction

Study 5	Padwal et al (2004)[29]
Methods	Type: Retrospective Observational study Study conducted: 1995 - 2000 Location: Canada Data source: Secondary data No. of subjects included: 76,176 Enrollment year/ Index date: 1995 - 2000
Participants	Inclusion criteria: ≥ 66 years , no diabetes at baseline with newly prescribed monotherapy with ACE-Inhibitors, CCBs, or BB
Interventions	No. of comparators: 3 (Monotherapy) ACE-Inhibitors: 35993 CCBs: 19598 B-Blockers: 20585
Exposure	Measurement of exposure: 5 databases: Registered Persons Database, Ontario Drug Benefit Database (ODB), Canadian Institute for Health Information Hospital Discharge Abstract Database (CIHI-DAD), Ontario Health Insurance Plan (OHIP) database & Ontario Diabetes Database (ODD) Drug status: New drug user Switched drug: Not stated Average duration of follow-up: 12 months Dosage: Not stated
Confounding	Baseline variables: Age, SES Income quintile: 1 (poorest) to 5 (richest), Mean length of follow-up, Dyslipidemia Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Time to diagnosis of diabetes

Study 6	Mazzaglia et al (2005)[38]
Methods	Type: Retrospective Observational study Study conducted: 2000 -2001 Location: Italy Data source: Secondary data No. of subjects included: 13303 Enrollment year/ Index date: 2000 -2001
Participants	Inclusion criteria: Aged 35 years , newly diagnosed hypertensive patients, registered with one of the participating GPs for at least 1 year before entry into the study, receiving at least one antihypertensive medication
Interventions	No. of comparators: 6 Mono & Combination Therapy ACE-Inhibitors: 4602 CCBs: 2700 B-Blockers: 1780 Diuretics: 2177 ARBs: 1382 α-Blockers: 662
Exposure	Measurement of exposure: The Health Search Database Drug status: New drug user Switched drug: Yes Average duration of follow-up: 12 months Dosage: Not stated
Confounding	Baseline variables: Age, Gender, SBP, DBP, Stage of hypertension, Coronary heart disease, Heart failure, Diabetes, Stroke, Two or more comorbidities, Chronic disease score Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Discontinuation of first-line treatment

Study 7	Blackburn et al (2007)[39]
Methods	Type: Retrospective Observational study Study conducted: 1994 -2003 Location: Canada Data source: Secondary data No. of subjects included: 19249 Enrollment year/ Index date: 1994 -2003
Participants	Inclusion criteria: > 40 years on the date of the initial prescription and were excluded if another antihypertensive medication class was filled within 3 months after the first-ever prescription
Interventions	No. of comparators: 4 (Monotherapy) ACE-Inhibitors: 10189 CCBs: 2173 B-Blockers: 2246 Diuretics: 4641
Exposure	Measurement of exposure: Linked Administrative Database (Saskatchewan) Drug status: New drug user Switched drug: Yes/ No Average duration of follow-up: 2.3 years (SD 2.0) Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Mean length of follow-up, Diabetes, Chronic disease score Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	First occurrence of any of the following events: death from any cause; all cause stroke or transient ischemic attack; myocardial infarction or unstable angina

Study 8	Esposti et al (2002)[40]
Methods	Type: Retrospective Observational study Study conducted: 1997 - 1999 Location: Italy Data source: Secondary data No. of subjects included: 7312 Enrollment year/ Index date: 1997 - 1997
Participants	Inclusion criteria: > 20 years of age, prescribed antihypertensive for the first time in the period between 1 January 1997 and 31 December 1997
Interventions	No. of comparators: 5 (Monotherapy) ACE-Inhibitors: 2418 CCBs: 1882 B-Blockers: 1166 Diuretics: 1648 ARB: 198
Exposure	Measurement of exposure: Ravenna Local Health Unit drugs database Drug status: New drug user Switched drug: No Average duration of follow-up: 3 years Dosage: Not stated
Confounding	Baseline variables: Age, Gender, SBP, Two or more comorbidities Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	3 years stay-on-therapy pattern for antihypertensive drug classes

Study 9	Bourgault et al (2005)[41]
Methods	Type: Retrospective Observational study Study conducted: 1994 -2000 Location: Canada Data source: Secondary data No. of subjects included: 21326 Enrollment year/ Index date: 1997 -1999
Participants	Inclusion criteria: Aged 18–80 years, diagnosis of hypertension between January 1, 1994 and September 30, 1999newly dispensed AHT between January 1, 1997 and September 30, 1999
Interventions	No. of comparators: 5 (Monotherapy) ACE-Inhibitors: 7104 CCBs: 2400 B-Blockers: 3989 Diuretics: 6831 ARB: 1002
Exposure	Measurement of exposure: Saskatchewan health-care databases Drug status: New drug user Switched drug: Yes Average duration of follow-up: 39-month Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Mean length of follow-up Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Treatment discontinuation and initiation of a new course of therapy after discontinuation

Study 10	Karpanou et al (2006)[34]
Methods	Type: Retrospective Observational study
	Study conducted: 1986-2004
	Location: Greece
	Data source: Secondary data
	No. of subjects included: 11148
	Enrollment year/ Index date: 1986-2004
Participants	Inclusion criteria: Untreated uncomplicated essential hypertension
Interventions	No. of comparators: 6 (Mono & Combination Therapy)
	ACE-Inhibitors: 2328
	CCBs: 3370
	B-Blockers: 2427
	Diuretics: 592
	ARB: 1961
	α-Blockers: 470
Exposure	Measurement of exposure: Database
	Drug status: New drug user
	Switched drug: Not stated
	Average duration of follow-up: 6 months
	Dosage: Not stated
Confounding	Baseline variables: Age, Gender, SBP, DBP, Obese, Smokers, Diabetes
	Analysis: Cox Proportional Hazard
	Confounders: Adjusted for confounders
	Methods of adjustment:
Outcomes	Pulse pressure reduction after 6-month therapy

Study 11	Caro et al (1999)[42]
Methods	Type: Retrospective Observational study
	Study conducted: 1989 -1994
	Location: Canada
	Data source: Secondary data
	No. of subjects included: 22918
	Enrollment year/ Index date: 1989 -1994
Participants	Inclusion criteria: Newly diagnosed hypertension, not receiving antihypertensive drug in the previous 10 months, received initial single antihypertensive treatment from 1 of 4 drug classes
Interventions	No. of comparators: 4 (Monotherapy)
	ACE-Inhibitors: 7241
	CCBs: 3305
	B-Blockers: 2713
	Diuretics: 9659
Exposure	Measurement of exposure: Saskatchewan health-care databases
	Drug status: New drug user
	Switched drug: Not stated
	Average duration of follow-up: 6 months to 5 years
	Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Mean length of follow-up
	Analysis: logistic regression analysis
	Confounders: Adjusted for confounders
	Methods of adjustment:
Outcomes	Antihypertensive therapy compliance

Study 12	Wong et al (2010)[43]
Methods	Type: Retrospective Observational study Study conducted: 1990 - 2002 Location: China Data source: Secondary data No. of subjects included: 2511 Enrollment year/ Index date: 1990 - 2002
Participants	Inclusion criteria: Participants with uncomplicated hypertension on one class of antihypertensive
Interventions	No. of comparators: 4 (Mono & Combination Therapy) ACE-Inhibitors: 361 CCBs: 681 B-Blockers: 974 Diuretics: 495
Exposure	Measurement of exposure: Hong Kong Hospital Authority database Drug status: New drug user Switched drug: No Average duration of follow-up: 48 weeks Dosage: Not stated
Confounding	Baseline variables: Age, Gender Analysis: chi-square tests Confounders: Age & sex Methods of adjustment: Stratified
Outcomes	Cumulative incidence of add-on therapy at around 1 year after their first-ever prescription

Study 13	Esposti et al (2004)[44]
Methods	Type: Retrospective Observational study Study conducted: 2000 -2001 Location: Italy Data source: Secondary data No. of subjects included: 14062 Enrollment year/ Index date: 2000 -2001
Participants	Inclusion criteria: All new users of antihypertensive drugs, ≥20 years of age, receiving a first prescription
Interventions	No. of comparators: 5 (Monotherapy) ACE-Inhibitors: 3938 CCBs: 3341 B-Blockers: 2471 Diuretics: 3344 ARBs: 968
Exposure	Measurement of exposure: Ravenna Local Health Unit drugs database Drug status: New drug user Switched drug: Yes Average duration of follow-up: 12 months Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Coronary heart disease, Diabetes, Two or more comorbidities Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Persistence With Treatment & annual Average Cost by Class of Drug Prescribed at Enrollment and Persistence Pattern

Study 14	Weiss et al (2006)[45]
Methods	Type: Retrospective Observational study Study conducted: 2001 -2005 Location: Maine Data source: Secondary data No. of subjects included: 5373 Enrollment year/ Index date: 2001 -2005
Participants	Inclusion criteria: Newly diagnosed hypertensive patient on monotherapy
Interventions	No. of comparators: 4 (Monotherapy) ACE-Inhibitors: 2014 CCBs: 510 B-Blockers: 1263 Diuretics: 941
Exposure	Measurement of exposure: Maine Medicaid database Drug status: New drug user Switched drug: Yes Average duration of follow-up: 6 months Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Heart failure, Diabetes Analysis: chi-square test Confounders: Methods of adjustment: Confounders not adjusted for
Outcomes	The continuation of the initial drug or its replacement during the 6 months after beginning therapy.

Study 15	Patel et al (2007)[46]
Methods	Type: Retrospective Observational study Study conducted: 2001 -2003 Location: USA Data source: Secondary data No. of subjects included: 242882 Enrollment year/ Index date: 2001 -2003
Participants	Inclusion criteria: ≥ 18 years, filled at least 1 prescription for a target medication during the 3-year study identification period
Interventions	No. of comparators: 5 (Monotherapy) ACE-Inhibitors: 78616 CCBs: 36246 B-Blockers: 82841 Diuretics: 34934 ARBs: 10245
Exposure	Measurement of exposure: MedImpact's database Drug status: New drug user Switched drug: Not stated Average duration of follow-up: 12 months Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Coronary heart disease, Diabetes Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment: Propensity score adjustment
Outcomes	1-year persistence and compliance rates & time to therapy discontinuation of anti-hypertension mono-therapy

Study 16	Wassertheil-Smoller et al (2004)[47]
Methods	Type: Prospective Observational study Study conducted: 1994 -2004 Location: USA Data source: Secondary data No. of subjects included: 11294 Enrollment year/ Index date: 1994-1998
Participants	Inclusion criteria: Postmenopausal women aged 50 to 79 years at baseline
Interventions	No. of comparators: 4 (Monotherapy) ACE-Inhibitors: 2952 CCBs: 3096 B-Blockers: 2077 Diuretics: 3169
Exposure	Measurement of exposure: Drug status: New drug user Switched drug: Not stated Average duration of follow-up: 5.9 years Dosage: Not stated
Confounding	Baseline variables: Age, Race, SBP, DBP, Body mass index, Smoking, Diabetes Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment: Propensity score
Outcomes	Incidence of coronary heart disease, stroke, and CVD mortality

Study 17	GRESS et al (2000)[48]
Methods	Type: Prospective Observational study Study conducted: 1987 - 1995 Location: USA Data source: Secondary data No. of subjects included: 3804 Enrollment year/ Index date: 1987 - 1989
Participants	Inclusion criteria: 45 to 64 hypertensive patients, non-diabetic
Interventions	No. of comparators: 6 (Mono & combined therapy) ACE-Inhibitors: 162 CCBs: 96 B-Blockers: 543 Diuretics: 458 Others: 1071 No antihypertensive therapy: 1474
Exposure	Measurement of exposure: The Atherosclerosis Risk in Communities (ARIC) study Drug status: New drug user Switched drug: Yes/ No Average duration of follow-up: 3 years and 6 years Dosage: Not stated
Confounding	Baseline variables: Age, Gender,Race, SBP, DBP, Body mass index, Coronary heart disease, Stroke Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Risk of type 2 Diabetes Mellitus

Study 18	Klungel et al (1998)[28]
Methods	Type: Prospective Observational study Study conducted: 1987 - 1995 Location: Netherlands Data source: Primary data No. of subjects included: 1204 Enrollment year/ Index date: 1987 - 1995
Participants	Inclusion criteria: 20–59 men and women
Interventions	No. of comparators: 4 (Monotherapy) ACE-Inhibitors CCBs B-Blockers Diuretics
Exposure	Measurement of exposure: The Monitoring Project on Cardiovascular Risk Factors (Monitoring Risk Factors and Health in The Netherlands) Drug status: New drug user Switched drug: Yes/ No Average duration of follow-up: Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Body mass index, Smoking, , Diabetes, Stroke Analysis: Polytomous logistic regression Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Sex differences

Study 19	AU et al (2004)[49]
Methods	Type: Retrospective Observational study Study conducted: 1996 -2001 Location: USA Data source: Secondary data No. of subjects included: 1966 Enrollment year/ Index date: 1997 -1999
Participants	Inclusion criteria: COPD patients with hypertension
Interventions	No. of comparators: 6 ACE-Inhibitors: 664 CCBs: 642 B-Blockers: 257 Diuretics: 153 α-Blockers: 190 Other Mono-therapy: 60
Exposure	Measurement of exposure: Ambulatory Care Quality Improvement Project (ACQUIP) Drug status: New drug user Switched drug: Yes/ No Average duration of follow-up: 2 years Dosage: Not stated
Confounding	Baseline variables: Age, Smoking, ACS, Heart failure, Diabetes, Chronic disease score Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment: Stratified
Outcomes	Risk of all-cause mortality

Study 20	Tardif et al (2004)[30]
Methods	Type: Prospective Observational study Study conducted: 1995 - 2002 Location: USA Data source: Secondary data No. of subjects included: 13167 Enrollment year/ Index date: 1995 - 1999
Participants	Inclusion criteria: >18 years with hypertension
Interventions	No. of comparators: 2 Monotherapy ACE-Inhibitors: 12608 CCBs: 559
Exposure	Measurement of exposure: Diverse administrative database Drug status: New drug user Switched drug: Not stated Average duration of follow-up: 4.4 years Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Mean length of follow-up, Dyslipidemia, Coronary heart disease, Heart failure, Diabetes, Stroke Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment: Propensity score adjustment
Outcomes	Total and cardiovascular mortality new diagnoses of angina, MI, stroke, CHD, complicated hypertension, and renal disease

Study 21	Trompet et al (2008)[32]
Methods	Type: Prospective Observational study
	Study conducted: 2000 - 2005
	Location: Netherlands
	Data source: Secondary data
	No. of subjects included: 310
	Enrollment year/ Index date: 2000 - 2005
Participants	Inclusion criteria: 85 years with hypertension
Interventions	No. of comparators: 4 Mono-therapy
	ACE-Inhibitors: 59
	CCBs: 54
	B-Blockers: 81
	Diuretics: 116
Exposure	Measurement of exposure: A population-based cohort
	Drug status: New drug user
	Switched drug: Not stated
	Average duration of follow-up: annually
	Dosage: Not stated
Confounding	Baseline variables: Gender, SBP, DBP
	Analysis: linear mixed models
	Confounders: Adjusted for confounders
	Methods of adjustment:
Outcomes	Change in cognitive functioning over time

Study 22	Wong et al (2008)[50]
Methods	Type: Retrospective Observational study Study conducted: 2004 - 2007 Location: Hong Kong Data source: Secondary data No. of subjects included: 93286 Enrollment year/ Index date: 2004 - 2007
Participants	Inclusion criteria: >18 years with hypertension, attended a primary care clinic at least once and received a antihypertensive medication
Interventions	No. of comparators: 6 Mono & combined therapy ACE-Inhibitors: 7153 CCBs: 21636 B-Blockers: 19177 Diuretics: 9398 Other : 35922
Exposure	Measurement of exposure: Hong Kong Hospital Authority database Drug status: : Not stated Switched drug: : Not stated Average duration of follow-up: 180 days Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Two or more comorbidities Analysis: binary logistic regression analysis Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Cumulative incidence of drug discontinuation within 180 days

Study 23	Gelber et al (2013)[31]
Methods	Type: Prospective Observational study Study conducted: 1991 - 2010 Location: Hawaii Data source: Secondary data No. of subjects included: 2197 Enrollment year/ Index date: 1991 - 1993
Participants	Inclusion criteria: Japanese ancestry men born 1900–1919 with hypertension and without dementia
Interventions	No. of comparators: 7 (Mono & combined therapy) ACE-Inhibitors: 100 CCBs: 299 B-Blockers: 153 Diuretics: 153 Other : 586 No therapy: 906
Exposure	Measurement of exposure: TheHonolulu-Asia Aging Study Drug status: New drug user Switched drug: Not stated Average duration of follow-up: 5.8 years Dosage: Not stated
Confounding	Baseline variables: Age, Gender, SBP, DBP, Body mass index, Smoking, Diabetes, CVD Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment:
Outcomes	Risk of cognitive impairment

Study 24	Greving et al (2005)[51]
Methods	Type: Retrospective Observational study Study conducted: 1996 - 1999 Location: Netherlands Data source: Secondary data No. of subjects included: 3101 Enrollment year/ Index date: 1996 - 1999
Participants	Inclusion criteria: Hypertensive patient, newly treated with antihypertensive drugs
Interventions	No. of comparators: 6 (Mono & combined therapy) ACE-Inhibitors: 623 CCBs: 281 B-Blockers: 994 Diuretics: 647 ARB: 234 Other multiple therapy: 322
Exposure	Measurement of exposure: Integrated Primary Care Information (IPCI) database Drug status: New drug user Switched drug: Yes Average duration of follow-up: 1 year Dosage: Not stated
Confounding	Baseline variables: Age (categorized), Gender Analysis: Cox Proportional Hazard Confounders: Adjusted for confounders Methods of adjustment: Stratified
Outcomes	ARBs as initial and second-line treatment

Study 25	Levi-Marpillat et al (2014)[52]
Methods	Type: Prospective Observational study Study conducted: 2005 - 2011 Location: France Data source: Secondary data No. of subjects included: 6177 Enrollment year/ Index date: 2005 - 2011
Participants	Inclusion criteria: Essential hypertension with no exposure to antihypertensive drug before the onset of AHT in database
Interventions	No. of comparators: 5 (Monotherapy) ACE-Inhibitors: 813 CCBs: 1247 B-Blockers: 1292 Diuretics: 1486 ARBs: 1339
Exposure	Measurement of exposure: Drug status: New drug user Switched drug: Yes/ No Average duration of follow-up: Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Body mass index, Smoking, Dyslipidemia, Coronary heart disease, Diabetes, Stroke, CVD Analysis: Logistic regression models Confounders: Adjusted for confounders Methods of adjustment: Propensity scores
Outcomes	Short-term BP variability

Study 26	Evans et al (2013)[53]
Methods	Type: Retrospective Observational study
	Study conducted: 1994 - 2002
	Location: Canada
	Data source: Secondary data
	No. of subjects included: 36214
	Enrollment year/ Index date: 1994 - 2002
Participants	Inclusion criteria: ≥40 years of age, new antihypertensive medication
Interventions	No. of comparators: 6 (Mono & combined therapy)
	ACE-Inhibitors: 8623
	CCBs: 3281
	B-Blockers: 6907
	Diuretics: 5690
	ARBs: 1600
	Other Multiple therapy: 10113
Exposure	Measurement of exposure: Saskatchewan administrative databases
	Drug status: New drug user
	Switched drug: Not stated
	Average duration of follow-up: 1 year
	Dosage: Not stated
Confounding	Baseline variables: Age, Gender
	Analysis: multivariable logistic regression models
	Confounders: Adjusted for confounders
	Methods of adjustment:
Outcomes	Achieving optimal adherence (≥80%) at 1 year

Study 27	Roy et al (2013)[54]
Methods	Type: Retrospective Observational study
	Study conducted: 1999 - 2007
	Location: Canada
	Data source: Secondary data
	No. of subjects included: 185476
	Enrollment year/ Index date: 1999 - 2007
Participants	Inclusion criteria: 45 to 85 newly diagnosed and treated for hypertension
Interventions	No. of comparators: 6 (Mono & combined therapy)
	ACE-Inhibitors: 41933
	CCBs: 22231
	B-Blockers: 20070
	Diuretics: 36421
	ARBs: 32489
	Other : 32332
Exposure	Measurement of exposure: the Re´gie de l'assurance maladie du Que´bec (RAMQ)
	Drug status: New drug user
	Switched drug: Not stated
	Average duration of follow-up: 5.1 years
	Dosage: Not stated
Confounding	Baseline variables: Age, Gender, Dyslipidemia, Heart failure, Diabetes, Stroke, Chronic disease score
	Analysis: Cox Proportional Hazard
	Confounders: Adjusted for confounders
	Methods of adjustment:
Outcomes	Risk reduction of ESRD

Study 28	Smith et al (1997)[55]
Methods	Type: Prospective Observational study
	Study conducted: 1989 - 1993
	Location: USA
	Data source: Secondary data
	No. of subjects included: 1296
	Enrollment year/ Index date: 1989 -1990
Participants	Inclusion criteria: adults aged 65 years or older
Interventions	No. of comparators: 7 (Mono & combined therapy)
	ACE-Inhibitors: 72
	CCBs: 109
	B-Blockers: 127
	Diuretics: 327
	Loop Thiazide: 102
	Other Multiple therapies: 559
Exposure	Measurement of exposure: The Cardiovascular Health Study
	Drug status: New drug user
	Switched drug: Yes/ No
	Average duration of follow-up: 3 years
	Dosage: Not stated
Confounding	Baseline variables: Age, Gender, SBP, DBP, Body mass index, Smoking, CVD
	Analysis: Multivariate linear regression
	Confounders:
	Methods of adjustment:
Outcomes	Change in serum Creatinine over 3-years

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