Accepted Manuscript

Title: Seventeen-Year Nationwide Trends in Antihypertensive Drug Use in Denmark

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PII: S0002-9149(17)31463-7
DOI: http://dx.doi.org/doi: 10.1016/j.amjcard.2017.08.042
Reference: AJC 22901

To appear in: *The American Journal of Cardiology*

Received date: 31-5-2017
Accepted date: 30-8-2017

Please cite this article as: Jens Sundbøll, Kasper Adelborg, Kathryn E. Mansfield, Laurie A. Tomlinson, Morten Schmidt, Seventeen-Year Nationwide Trends in Antihypertensive Drug Use in Denmark, *The American Journal of Cardiology* (2017), http://dx.doi.org/doi: 10.1016/j.amjcard.2017.08.042.

Seventeen-Year Nationwide Trends in Antihypertensive Drug Use in Denmark

Running title: Trends in antihypertensive drugs use

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Conflicts of interest: None.

Abstract

Recent trends in use of antihypertensive drugs are unknown. From Danish nationwide prescription data, we obtained information on primary care use of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, diuretics, aldosterone receptor antagonists and calcium channel blockers. During 1999–2015, the use of antihypertensive drugs per 1,000 inhabitants/day increased from 184 to 379 defined daily doses (DDD), corresponding to a rise in the prevalence proportion of users from ≈20% to ≈35%. From 1999 to 2015, a notable increase was observed for angiotensin converting enzyme inhibitors (from 29 to 105 DDD per 1,000 inhabitants/day ≈260%) and angiotensin II receptor blockers (from 13 to 73 DDD per 1,000 inhabitants/day ≈520%). For diuretics the use remained stable, with a slight decrease (from 89 to 81 DDD per 1,000 inhabitants/day ≈-10%). The use of aldosterone receptor antagonists increased until 2007 and remained unchanged at around 3.5 DDD per 1,000 inhabitants/day thereafter (average change ≈65%). The use of beta blockers doubled during the study period (from 17 to 34 DDD per 1,000 inhabitants/day ≈100%), entirely driven by increasing use of metoprolol. Similar trends were observed for calcium channel blockers (from 34 to 82 DDD per 1,000 inhabitants/day ≈140%), where amlodipine drove the overall increase. In conclusion, antihypertensive drug use has increased remarkably during the past two decades.

Key words: Antihypertensive drugs, trends, epidemiology

Introduction

During the past two decades, several important trials on antihypertensive drugs have emerged, which has led to changes in treatment recommendations such as the JNC 8.[1] Barriers to implementation of international guidelines can arise at different levels such as national, regional, institutional, and individual provider level. The implementation of guideline recommendations in clinical practice is unclear and nationwide trends in use of antihypertensive drugs can provide important insight into how rapidly results from clinical trials and guidelines are adopted in clinical practice. The objective of this study was to examine 17-year trends in use of antihypertensive drugs in Denmark and provide a discussion of their temporal relationship with landmark studies.

Methods

The study was conducted in Denmark from 1 January 1999 to 31 December 2015. Denmark has a population of approximately 5.7 million inhabitants, who all have free and unfettered access to tax-supported healthcare at general practitioners and hospitals. Partial reimbursement for prescribed medications, including antihypertensive drugs, is also covered by taxes. Antihypertensive drug sales in Danish community pharmacies comprise purchases of prescription drugs, including prescriptions to in- and outpatients at discharge from hospitals.

MEDical STATistics (Medstat) is a publicly accessible database providing data on drug use in the Danish primary sector since 1996, divided by age and sex from 1999 onwards and hospital sector since 1997.[2] We retrieved data on use of antihypertensive drugs according to the Anatomical Therapeutic Chemical (ATC) classification system from Medstat. Data registered in Medstat include drug sale in defined daily doses

(DDD). The DDD is a WHO-defined measure of drug consumption representing the assumed average maintenance dose required by an adult when the drug is used for its main indication. Reporting data as DDD allows for comparison of trends in drug utilization independent of varying prices and pack sizes. Changes in WHO-defined DDD for each drug are incorporated into Medstat updates each year allowing for comparison of drug use over time.[2] As the actual denominator used in the calculations of the prevalence of users is not provided directly in Medstat, we obtained information on the size of the Danish population during 1999 to 2015 according to age groups and sex from Statistics Denmark.[3] According to Danish law, no approval from an ethical committee was required for this study.

We identified use of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, aldosterone receptor antagonists (ARAs), beta blockers, and calcium channel blockers (CCBs). Specific ATC codes and drugs within these main classes of antihypertensive drugs are specified in Supplemental Table 1.

We compiled data from dispensed prescriptions of antihypertensive drugs in DDD per 1,000 inhabitants/day from Danish community pharmacies and the number of antihypertensive drug users per 1,000 inhabitants. We stratified drug use by sex, age groups (20-39 years, 40-64 years, 64-80 years, and >80 years), age groups separately for men and women, and administrative regions (Capital Region of Denmark, North Denmark Region, Central Denmark region, Region Zealand, and Region of Southern Denmark, available since 2007). Additionally, we retrived information on in-hospital use of antihypertensive drugs during 1999–2015.

To identify clinical trials that may have influenced the trends in use of antihypertensive drugs, we performed a systematic search in MEDLINE (Pubmed) in

collaboration with a qualified research librarian. The search included terms for specific antihypertensive drug classes, indications for their use, and was restricted to clinical trials within the study period (full search string available in the Supplemental Material). The search returned 1248 hits from which JS identified 22 landmark trials by screening abstracts supplemented by a review of references of included studies (Figure 1). In addition to trials on hypertensive populations, we included heart failure trials as all the studied antihypertensive drugs (apart from CCBs) are used in heart failure treatment and hence influence the utilisation trends.

Results

From 1999 to 2015, the overall use of antihypertensive drugs per 1,000 inhabitants increased from 184 DDD to 379 DDD (Table 1 and Figure 1). In addition, the prevalence of antihypertensive drug users increased from ≈20% to ≈35% of the entire Danish population (Table 1). During 1999–2015, the number of Danish inhabitants remained relatively unchanged and the age- and sex distribution did not change substantially (Supplemental Table 2).

During the study period, the use of ACE inhibitors increased more than 3-fold and the use of ARBs more than 5-fold (Table 1). Diuretics decreased only slightly, while the use of beta blockers doubled and the use of CCBs more than doubled. In-hospital use of antihypertensive drugs constituted a negligible fraction of the total use (3 DDD per 1,000 inhabitants/day in 2015), and the use decreased during the 17-year study period (Supplemental Table 3). Although small regional differences were observed, the use of antihypertensive drugs in individual administrative regions of Denmark was consistent with the national trends (Supplemental Table 4).

ACE inhibitors were the most frequently used antihypertensive drug (Table 1). For ramipril, enalapril, and combination drugs (ACE inhibitors and diuretics), the use increased markedly over time until 2010 when they declined slightly (Figure 2). The use of other ACE inhibitors was low throughout the study period. More men than women used ACE inhibitors and the use was most frequent in age categories above 65 years (Figure 3).

The overall use of ARBs increased slightly until 2009, after which only the use of losartan increased dramatically (Figure 2). Use of combination pills with ARBs and diuretics increased more steadily throughout the study period. The remaining ARBs increased similarly until 2009 but then dropped abruptly to remain close to zero from 2011 onwards. Slightly more women than men used ARBs and the use was most frequent in age categories above 65 years (Figure 3).

The use of diuretics peaked around 2007, succeeded by a moderate decrease through 2015 (Figure 2). The most frequently used diuretics were furosemide and combination pills with thiazides and potassium. The use of thiazides without potassium was low and ceased completely after 2010. The use of bumetanide was consistently low. More women than men used diuretics and the use increased proportionally with advancing age category (Figure 3).

The use of spironolactone increased abruptly from 1999–2001, whereafter the use was consistent (around 3.5 DDD per 1,000 inhabitants/day). Similarly, the use of eplerenone increased after its 2004 introduction and became stable two years thereafter at around 0.1 DDD per 1,000 inhabitants/day. More women than men used ARAs and the use increased proportionally with increasing age (Figure 3).

The use of metoprolol increased substantially over the study period (from 6.7 DDD per 1,000 inhabitants/day in 1999 to 22.7 in 2015). The use of the remaining beta blockers was below 5 DDD per 1,000 inhabitants/day and decreasing for atenolol and sotalol, while carvedilol increased slightly. Overall use was the same for men and women and most frequently used in those above 65 years of age (Figure 3).

Throughout the study period the use of amlodipine increased consistently from 18 DDD per 1,000 inhabitants/day in 1999 to reach 72 in 2015. The use of the remaining CCBs (felodipin, nifedipin, verapamil, and diltiazem) was low and decreased slightly during the study period. Use of CCBs showed an equal sex distribution in 1999, but over time, the use increased relatively more for men than for women (Figure 3). The use of CCBs was most frequent in those above 65 years of age (Figure 3).

For all classes of antihypertensive drugs, the age-stratified analyses among men and women separately (Supplemental Figure 1) were in accordance with the overall age-stratified analysis (Figure 3).

Discussion

During the past 17 years, the use of antihypertensive drugs in Denmark has more than doubled. In particular, ramipril and enalapril were the most commonly used ACE inhibitors, and losartan, amlodipin and metoprolol by far the most used ARB, CCB, and beta blocker, respectively. A recent trend study from the US agreed overall with our findings, but no study has examined the profound changes we observed after 2010.

The overall trends are likely driven by recommendations in international clinical guidelines from European Societies of Cardiology and Hypertension[4-6] and The Joint

National Committee in The United States,[1,7] as well as major clinical trials. Below, we discuss the observed trends in the light of landmark studies.

The use of ACE inhibitors increased dramatically during the study period, driven by enalapril, ramipril, and combinations of ACE inhibitors and diuretics. The increase was likely fuled by the HOPE trial[8] in 2000 showing that ramipril reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who were not known to have a low ejection fraction or heart failure. The EUROPA trial in 2003 further supported treatment with an ACE inhibitor in patients with stable coronary heart disease without apparent heart failure.[9] The slight decrease observed for most ACE inhibitors after 2010 may be associated with the losartan patent expiration in 2009 causing a shift to ARBs for patients with side effects to ACE inhibitors (*e.g.*, cough).

During 1999–2010, the use of ARBs increased continuously and similarly for all ARBs. This steady increase may have been supported by the ValHeFT trial[10] (2001) and the LIFE trial (2002),[11] favoring use of valsartan and losartan, respectively. This was followed by results from the CHARM trials in 2003 demonstrating beneficial effect of candesartan on various outcomes and in various patient groups.[12-14] The CHARM-preserved trial,[15] however, failed to demonstrate any significant reduction in cardiovascular death and heart failure hospitalization in patients with preserved (>40%) left ventricular ejection fraction. The most striking change in use of ARBs occurred after 2009 where the use of losartan surged while the use of candesartan and other ARBs correspondingly plummeted, presumably prompted by expiration of the losartan patent in 2009. Contributing to this surge in losartan use, the HEAAL study (2009) demonstrated that high-dose losartan (150 mg/day) in patients with heart failure reduced all-cause mortality and hospitalization for heart failure more effectively, as compared to

low-dose losartan (50 mg/day).[16] Likewise, the ONTARGET trial confirmed ARBs as an equally effective alternative to ACE inhibitors and with a better safety profile.[17]

The use of diuretics decreased only slightly during the study period. The use of furosemide and thiazides in combination with potassium was most used. The high use of thiazides is likely supported by the ALLHAT trial published in 2002,[18] recommending thiazide-type diuretics as first-line drug for essential hypertension. The slight decrease in thiazide use in the last part of the study period could have been influenced by the ACCOMPLISH trial from 2008.[19] The trial concluded that ACE inhibition in combination with amlodipine was superior in reducing adverse cardiovascular events compared with ACE inhibitors and thiazides. However, also in 2008, the HYVET trial[20] provided evidence that antihypertensive treatment with the thiazide indapamide reduces all-cause mortality in older patients.

The indication for ARA use is primarily congestive heart failure and hyperaldosteronism and to a much lesser extent hypertension. The RALES study[21] (1999) was the first of a series of trials to examine the effect of ARAs on mortality in patients with congestive heart failure and demonstrated a 30% reduction in all-cause mortality with spironolactone in a randomization of heart failure patients. The RALES trial prompted the subsequent EPHESUS trial[22] (2003), which also supported eplerenone use for heart failure following myocardial infarction. The later EMPHASIS-HF trial[23] (2011) also supported the use of eplerenone in the treatment of moderate heart failure with mild symptoms.

Apart from metoprolol, beta blockers saw only minor changes in use throughout the study period. For metoprolol, the use increased continuously since 1999. Metoprolol is used for a broad range of cardiovascular diseases and the increasing use likely mirrors

an increase in the prevalence of these diseases during the study period.[24] Moreover, in 1999, the MERIT-HF trial[25] (metoprolol) and CIBIS-II trial[26] (bisoprolol) both demonstrated a 34% relative risk reduction in all-cause mortality in the treatment arm for heart failure patients with reduced ejection fraction. Carvedilol for heart failure was investigated in the COPERNICUS trial[27] (2002) that randomized patients with severe heart failure to carvedilol or placebo and demonstrated a reduced risk of death or heart failure hospitalization by 31% compared with placebo. The MERIT-HF[25] and COPERNICUS[27] trials were followed by the COMET trial[28] (2003) favouring the use of carvedilol over metoprolol (40% vs. 34% relative risk reduction for mortality).

The accelerated use of amlodipine after 2004 coincides with the publication of the VALUE trial in 2004.[29] This trial demonstrated that in hypertensive patients, stroke and myocardial infarction incidence was lower in the amlodipine group than in the valsartan group. In 2005 the ASCOT-BPLA trial also identified amlodipine as most effective in preventing major cardiovascular events.[30] The ACCOMPLISH trial (2008) further favored CCBs over thiazides in patients at high risk of cardiovascular complications.[19]

The nationwide coverage eliminated selection bias and the Medstat database is complete and data prospectively recorded.[2]

In conclusion, use of antihypertensive drugs more than doubled during the past two decades, driven by increased use of ramipril, enalapril, losartan, metoprolol, and amlodipine.

Acknowledgements

Funding: Funding was provided through the Department of Clinical Epidemiology,

Aarhus University Hospital, Aarhus, Denmark. The funding source had no role in study design; in the collection, analysis, and interpretation of data; in writing the report; and in the decision to submit the article for publication.

Author contributions: J.S., K.A., and M.S. conceived the idea and designed the study. J.S. ascertained the statistic results. All authors interpreted the data and reviewed the literature. J.S. drafted the first manuscript. All authors critically reviewed the manuscript and approved the final version for submission. M.S. have the overall responsibility for the accuracy of the data and the manuscript.

Ethics approval: As this study did not involve patient contact or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

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Figure legends

Figure. 1. Timeline in use of antihypertensive drugs in Denmark and publication year of landmark studies, 1999−2015.

Abbreviations: ACCOMPLISH: Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients study; ALLHAT: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic study; ASCOT-BPLA: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial; CHARM-Added: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial; CHARM-Alternative: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: CHARM-Alternative trial; CHARM Low LVEF: Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials; CHARM-preserved: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial; CIBIS-II: The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial; COMET: Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial; COPERNICUS: Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure; ESH/ESC guideline: European Society of Hypertension guideline on hypertension; EMPHASIS-HF: Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms study; EPHESUS: Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction study; EUROPA: Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study); HEAAL: Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial; HOPE: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients study; HYVET: Treatment of Hypertension in Patients 80 Years of Age or Older study; JNC: Joint National Committee guideline on hypertension; LIFE: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study; MERIT-HF: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol

CR/XL Randomised Intervention Trial in Congestive Heart Failure; ONTARGET: Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events; RALES: The effect of spironolactone on morbidity and mortality in patients with severe heart failure study; ValHeFT: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure; VALUE: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine study.

Figure. 2. Use of angiotensin converting enzyme inhibitors (A), angiotensin II receptor blockers (B), diuretics (C), aldosterone receptor blockers (D), beta blockers (E), and calcium channel blockers (F) in defined daily doses per 1,000 inhabitants/day in the primary health care sector, 1999–2015.[a]

[a]Note the different scales on the y-axis. Other ACEIs include captopril, lisinopril, perindopril, quinapril, benazepril, fosinopril, trandolapril, moexipril, zofenopril, and ACEI/calcium channel blocker combinations. Other ARBs include valsartan, eprosartan, irbesartan, telmisartan, olmesartan, and ARB/calcium channel blocker combinations. Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

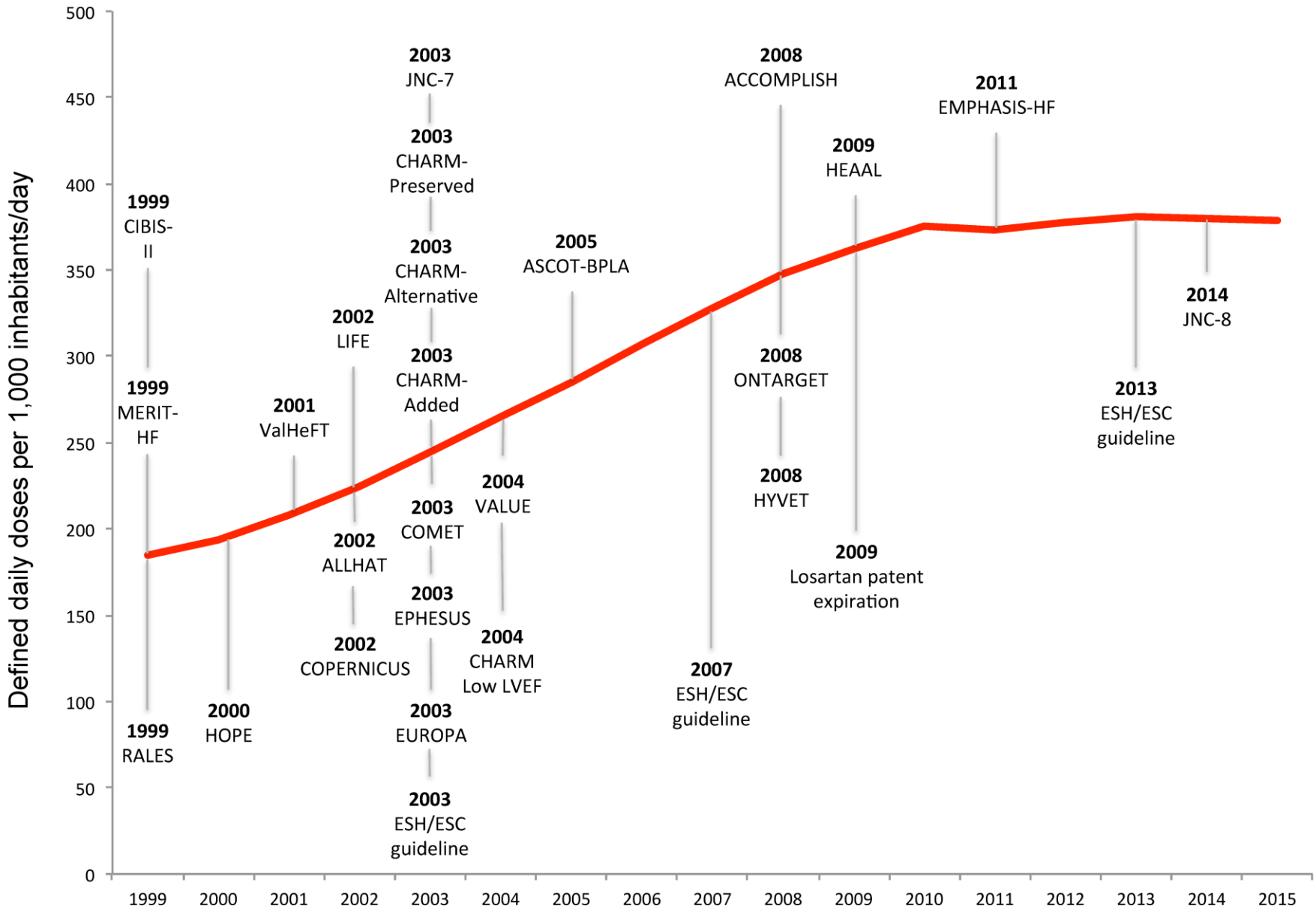
Fig. 3. Age- and sex-stratified primary care use of antihypertensive drugs in defined daily doses per 1,000 inhabitants/day, 1999–2015.[a]

[a]Note the different scales on the y-axis. Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; ARA, aldosterone receptor antagonists; CCB, calcium channel blockers.

Table I. Antihypertensive drug use in the primary health care sector during 1999–2015 in Denmark.

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Overall																	
DDD[a]	184	194	208	225	244	266	285	307	328	348	362	375	373	378	381	380	379
Users[b]	195	206	221	237	255	274	293	309	325	337	355	359	361	361	360	355	352
ACE inhibitors																	
DDD[a]	29	32	36	42	48	55	62	71	78	88	101	109	110	111	110	107	105
Users[b]	27	29	32	35	40	46	52	58	63	68	82	82	79	77	75	72	70
ARBs																	
DDD[a]	12	14	17	22	27	31	34	39	44	49	47	49	53	59	64	67	72
Users[b]	15	17	20	25	29	32	35	39	43	47	46	47	52	55	59	62	65
Diuretics																	
DDD[a]	89	89	91	92	94	98	100	101	101	101	99	98	93	89	88	85	81
Users[b]	76	78	81	82	86	90	93	94	94	93	92	92	88	85	82	78	75
ARAs																	
DDD[a]	2.3	2.8	3.2	3.3	3.4	3.4	3.5	3.6	3.8	3.8	3.6	3.6	3.7	3.7	3.7	3.8	3.8
Users[b]	4.71	6.31	7.17	7.63	7.79	7.93	8.34	8.51	8.56	8.56	8.52	8.49	8.61	8.77	9.1	9.25	9.5
Beta blockers																	
DDD[a]	17	18	20	23	25	28	30	31	32	33	33	33	33	34	34	34	34
Users[b]	36	40	44	48	52	56	59	61	63	64	64	65	66	67	67	67	67
CCBs																	
DDD[a]	34	36	38	40	41	44	48	54	60	64	70	75	78	80	82	82	82
Users[b]	36	37	38	39	40	42	45	49	53	57	62	65	67	68	68	67	67

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor blockers; ARA, aldosterone receptor blockers; CCBs, calcium channel blockers.
[a]Defined daily doses per 1,000 inhabitants/day
[b]Number of users per 1,000 inhabitants



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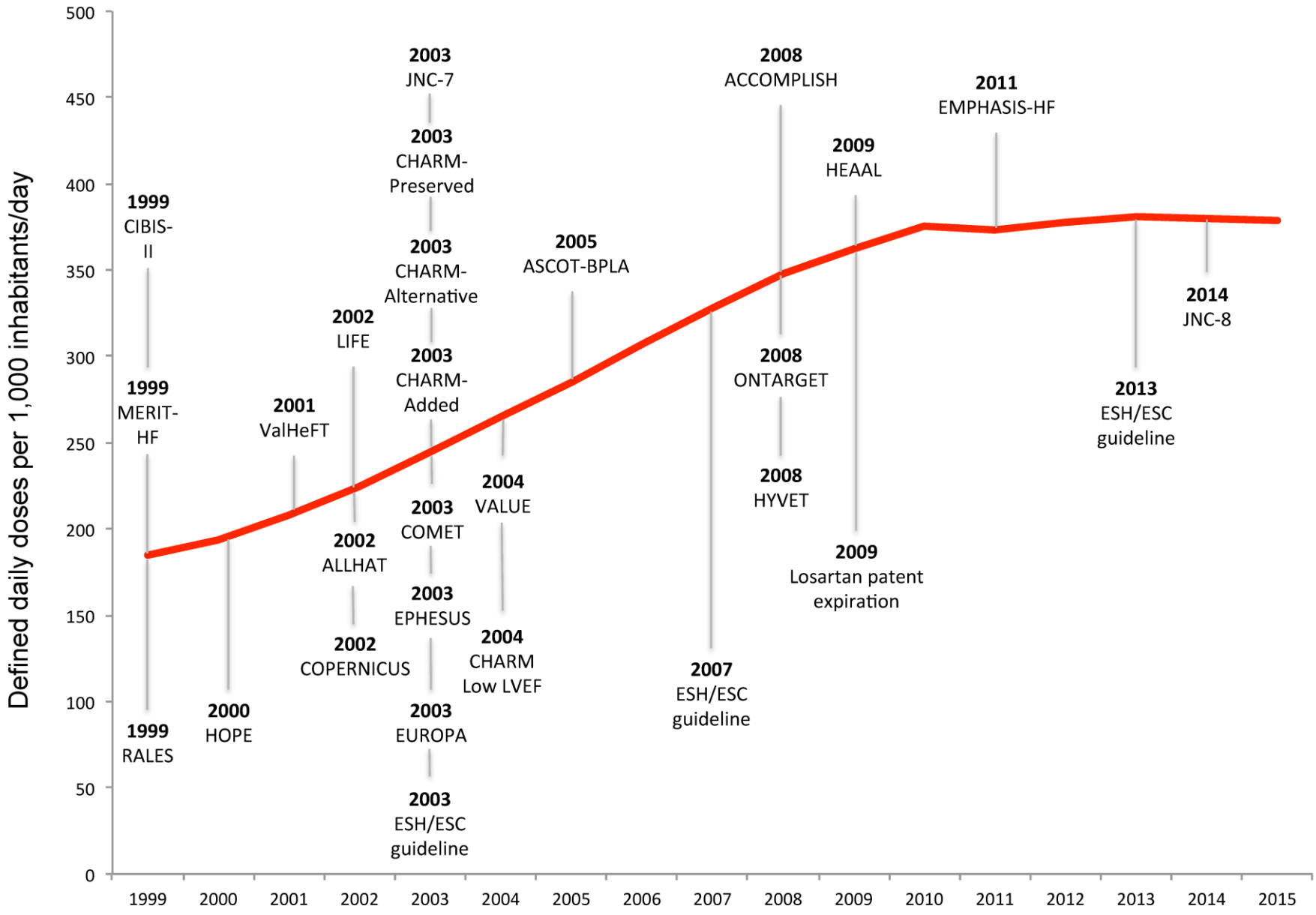

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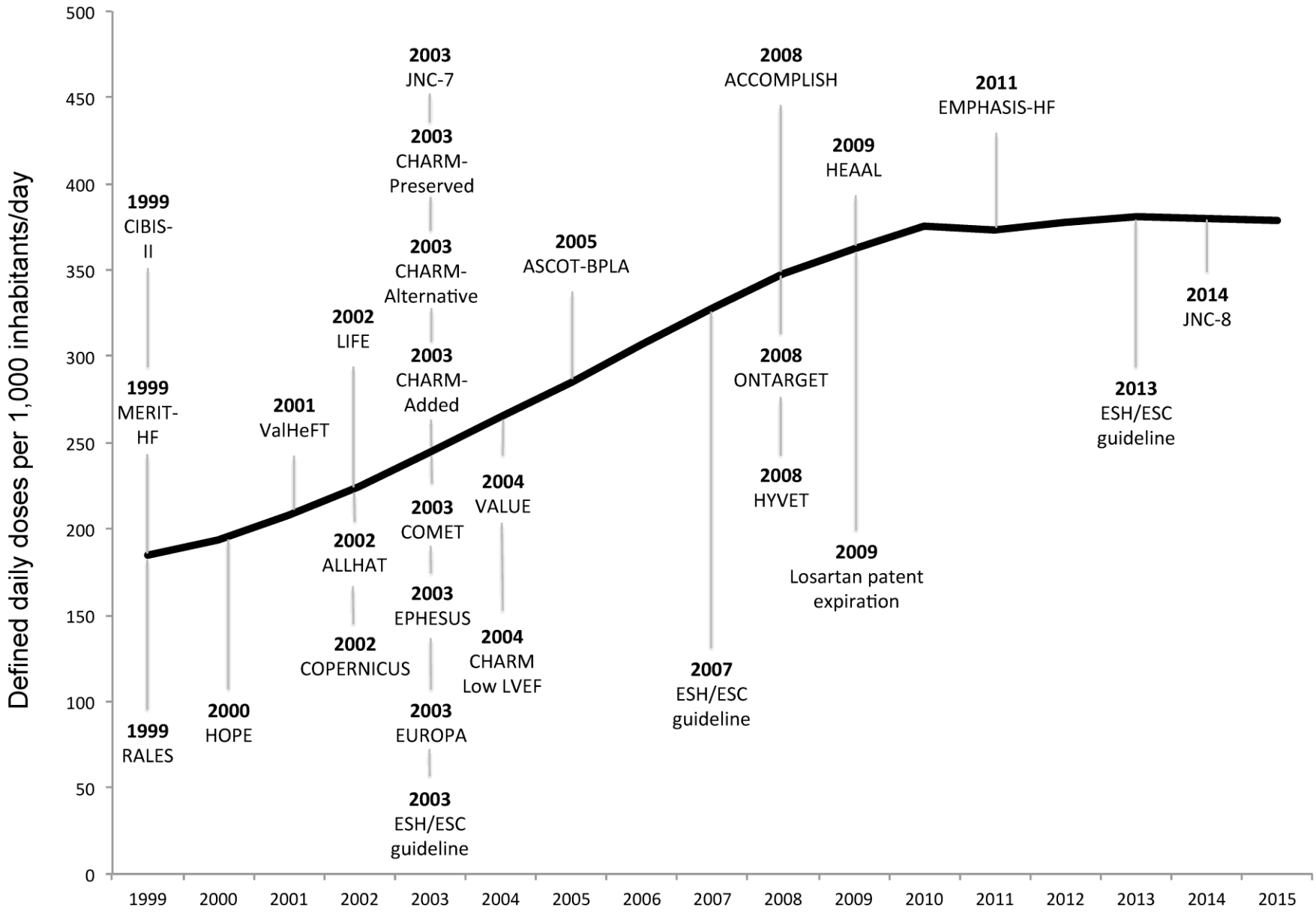

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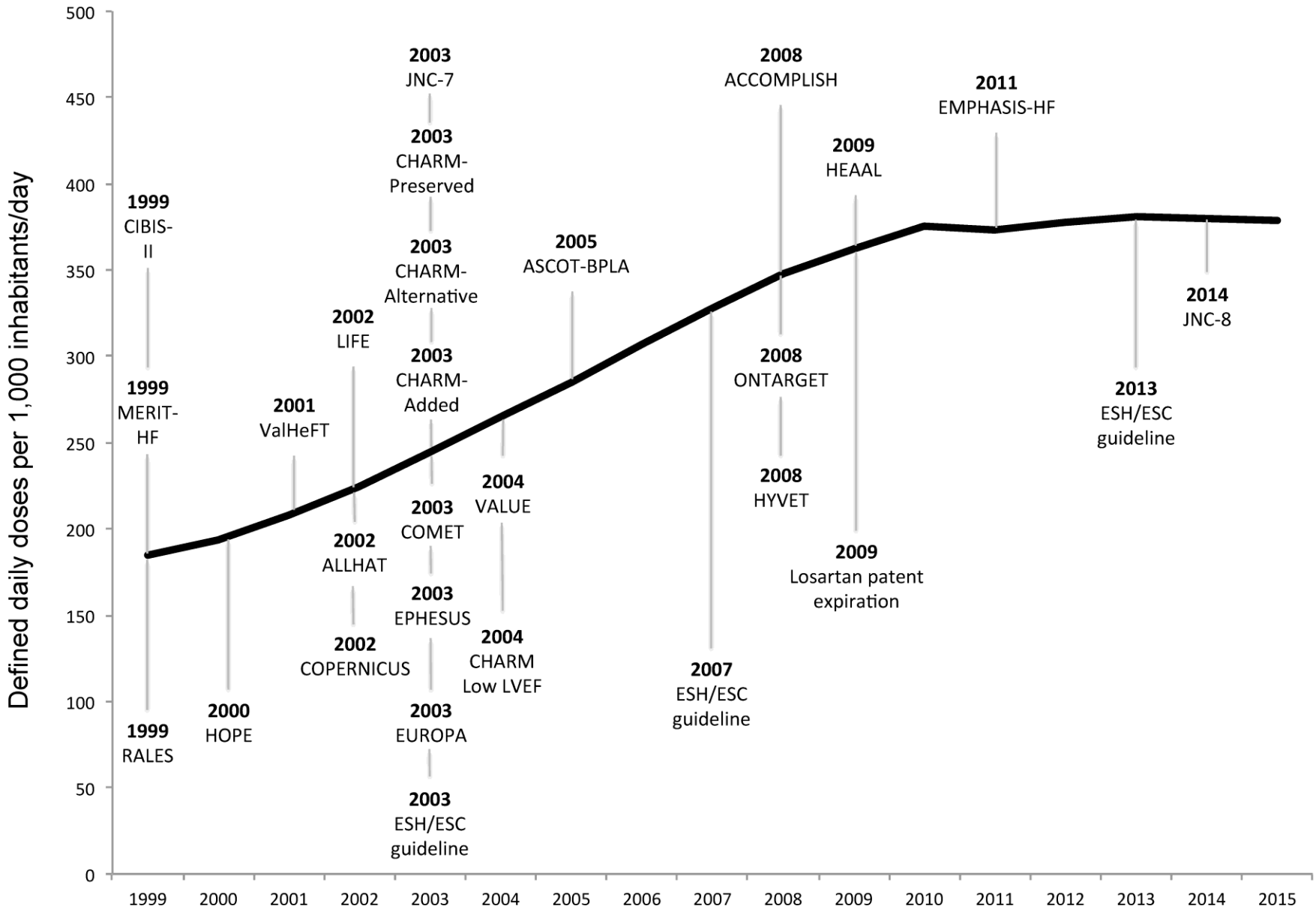

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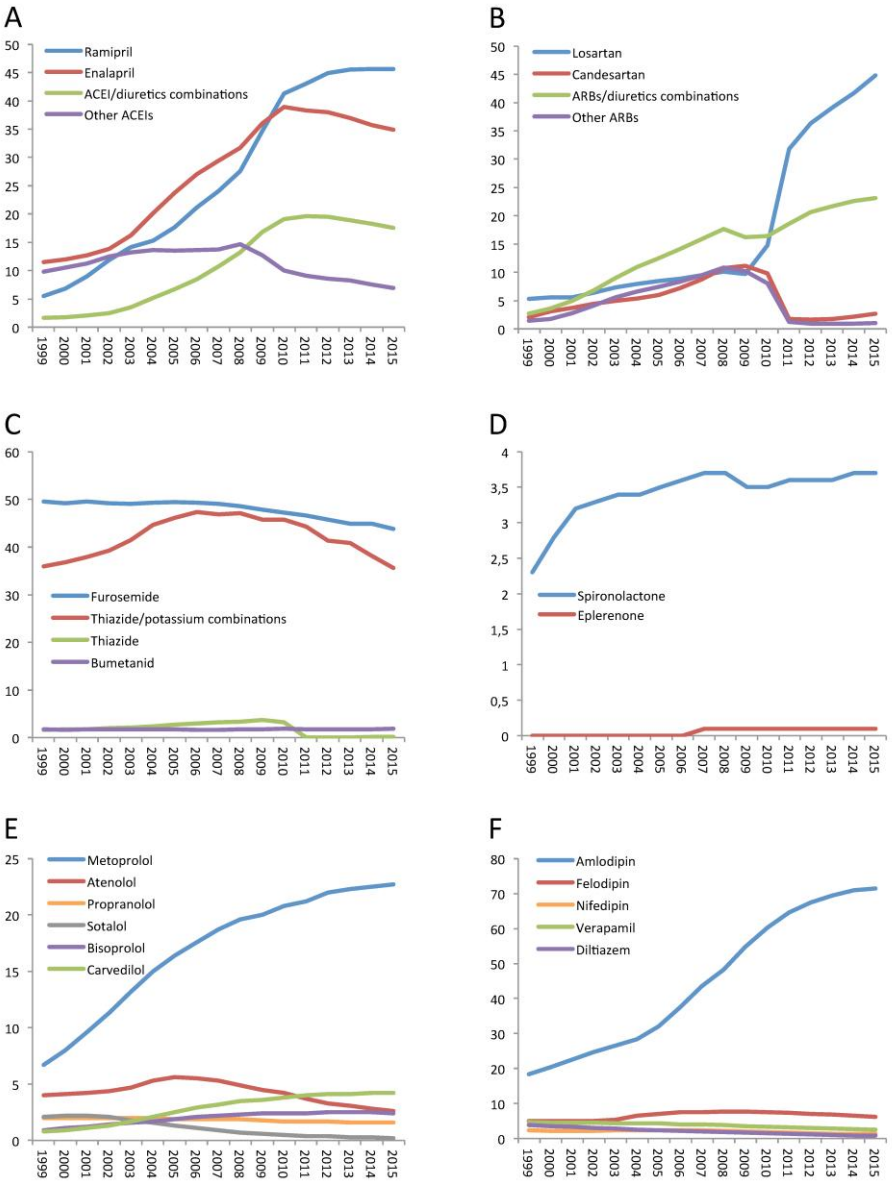

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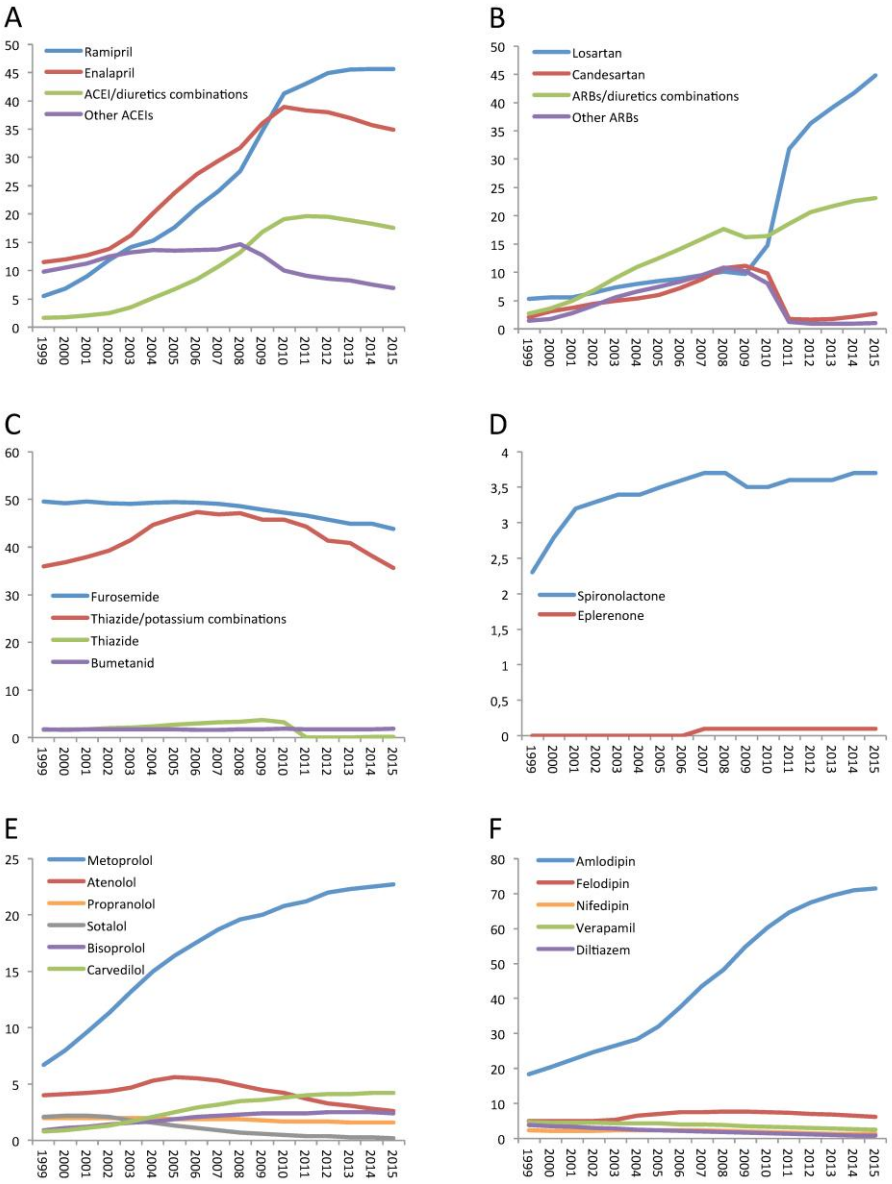

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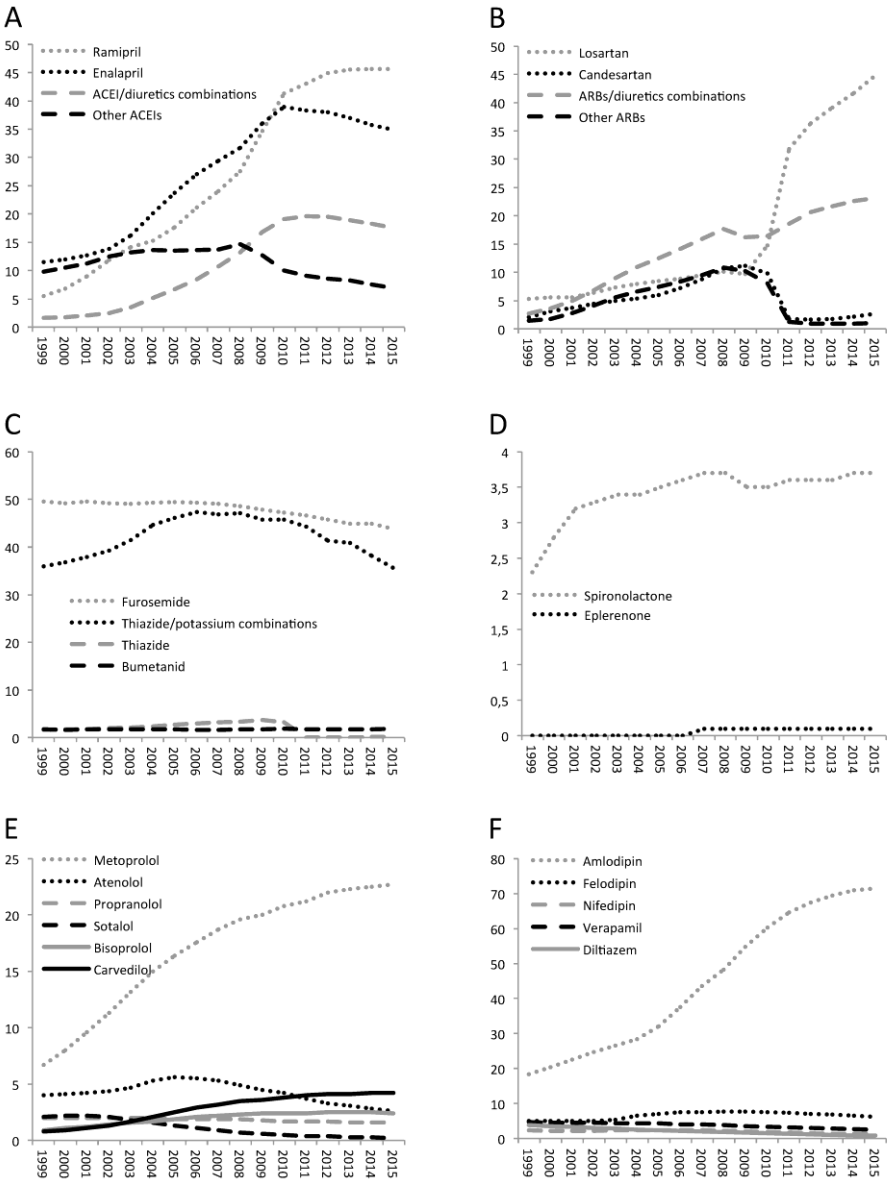

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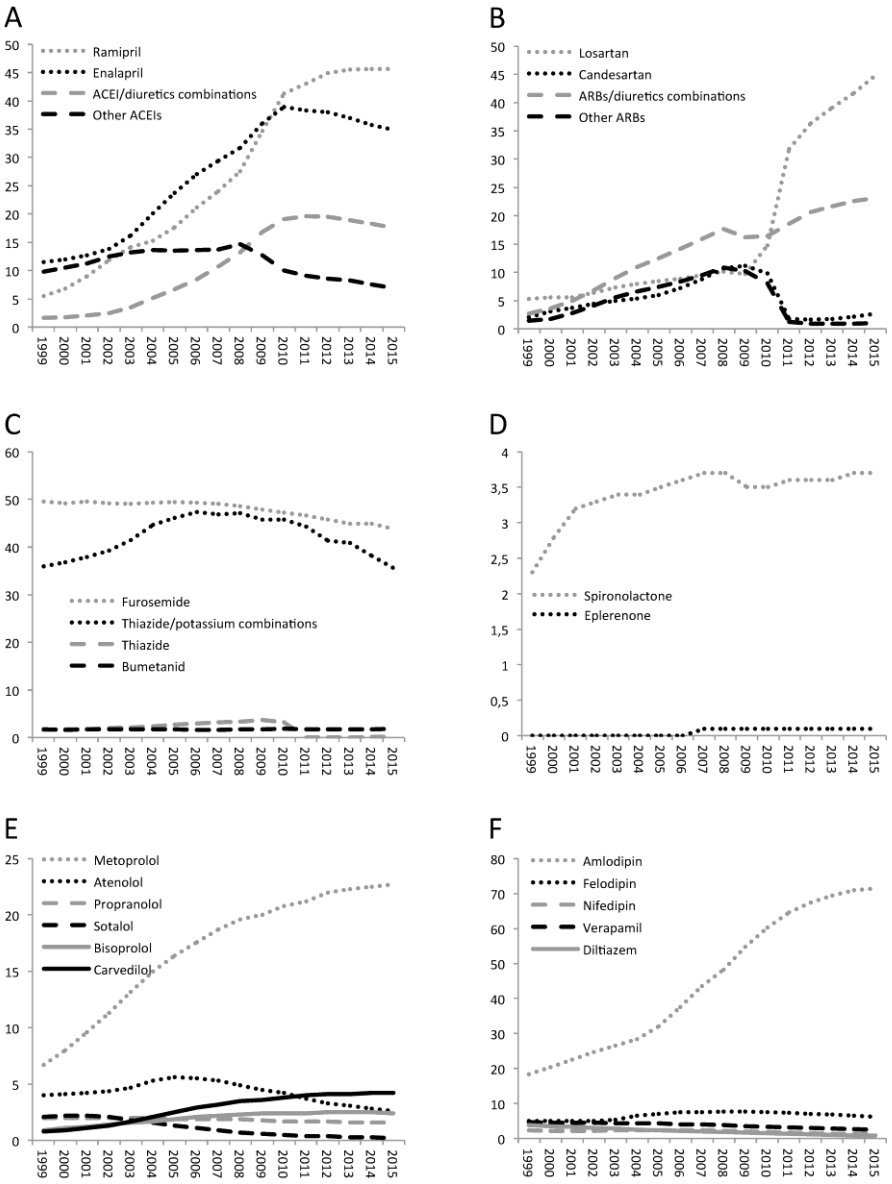

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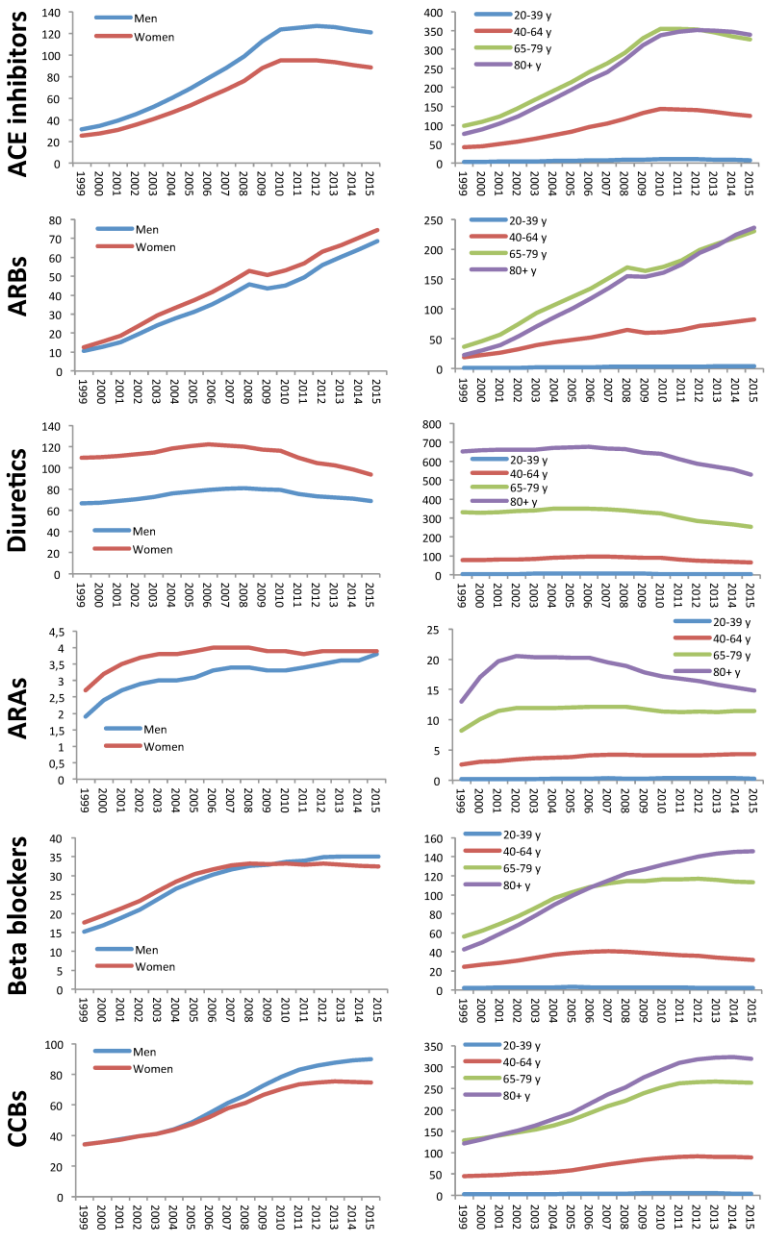

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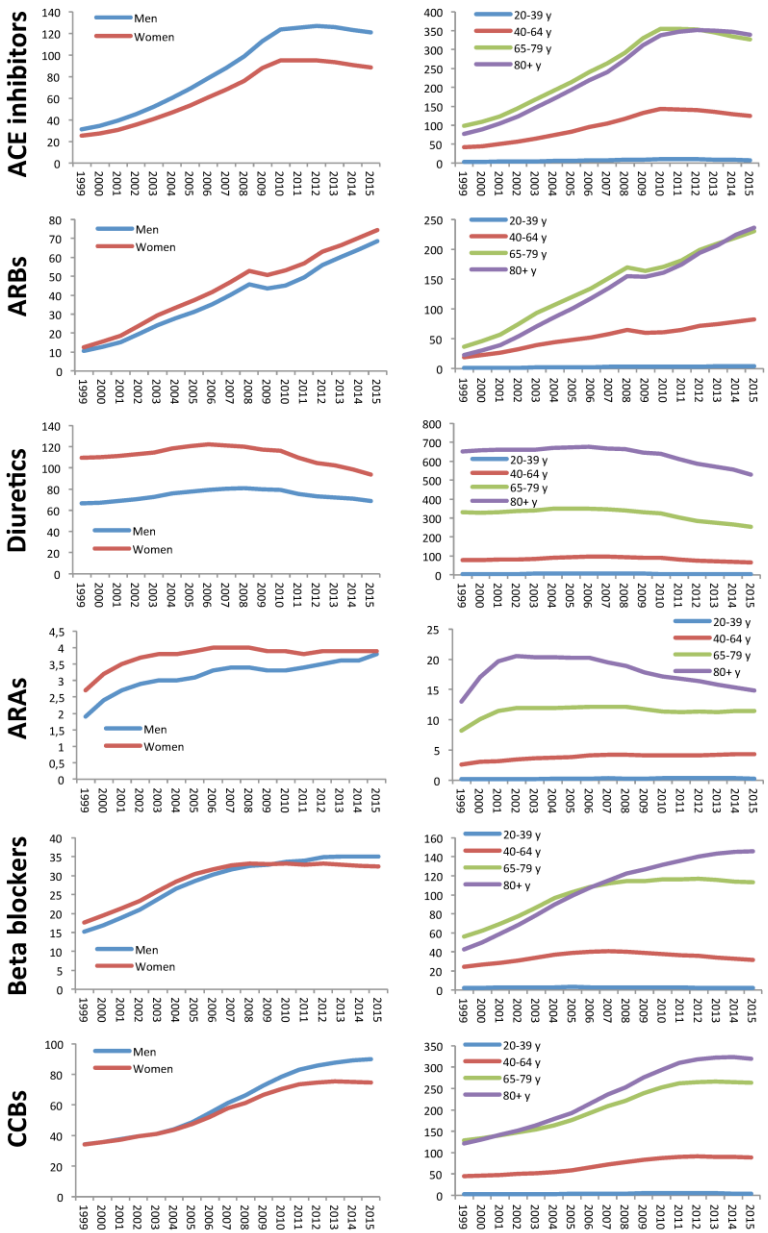

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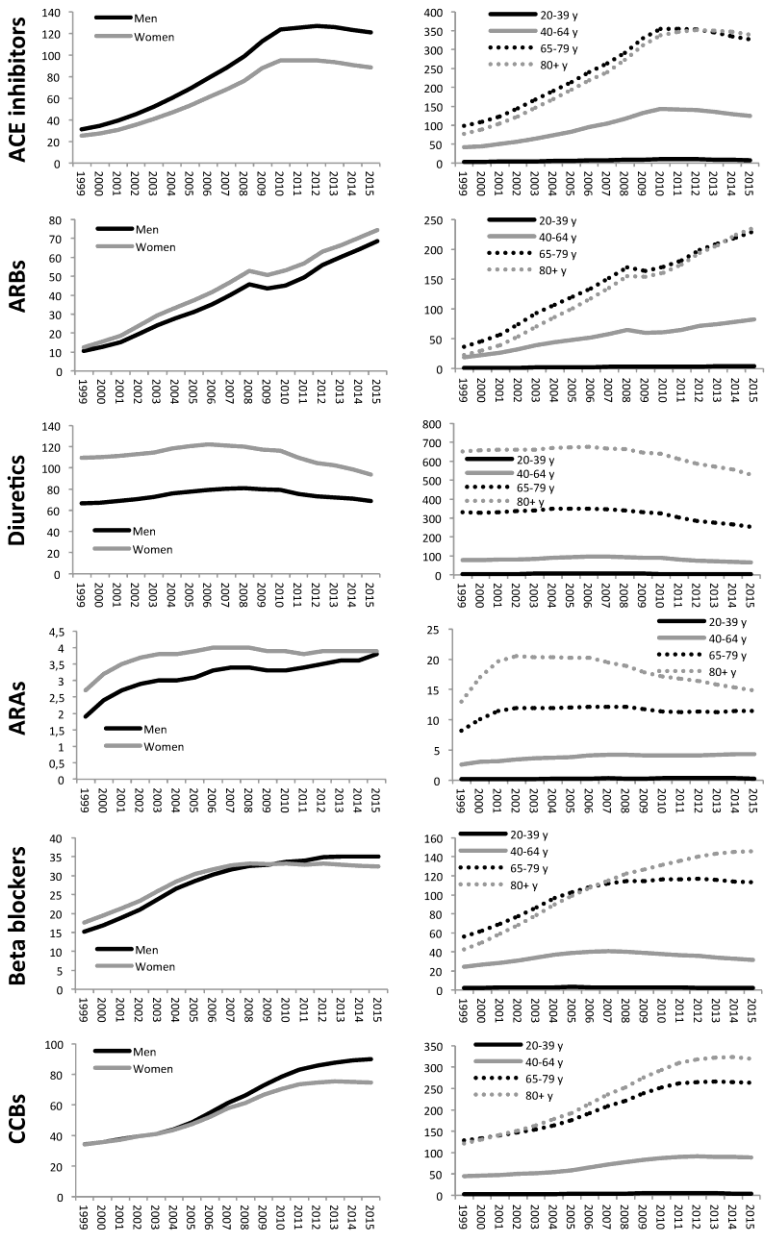

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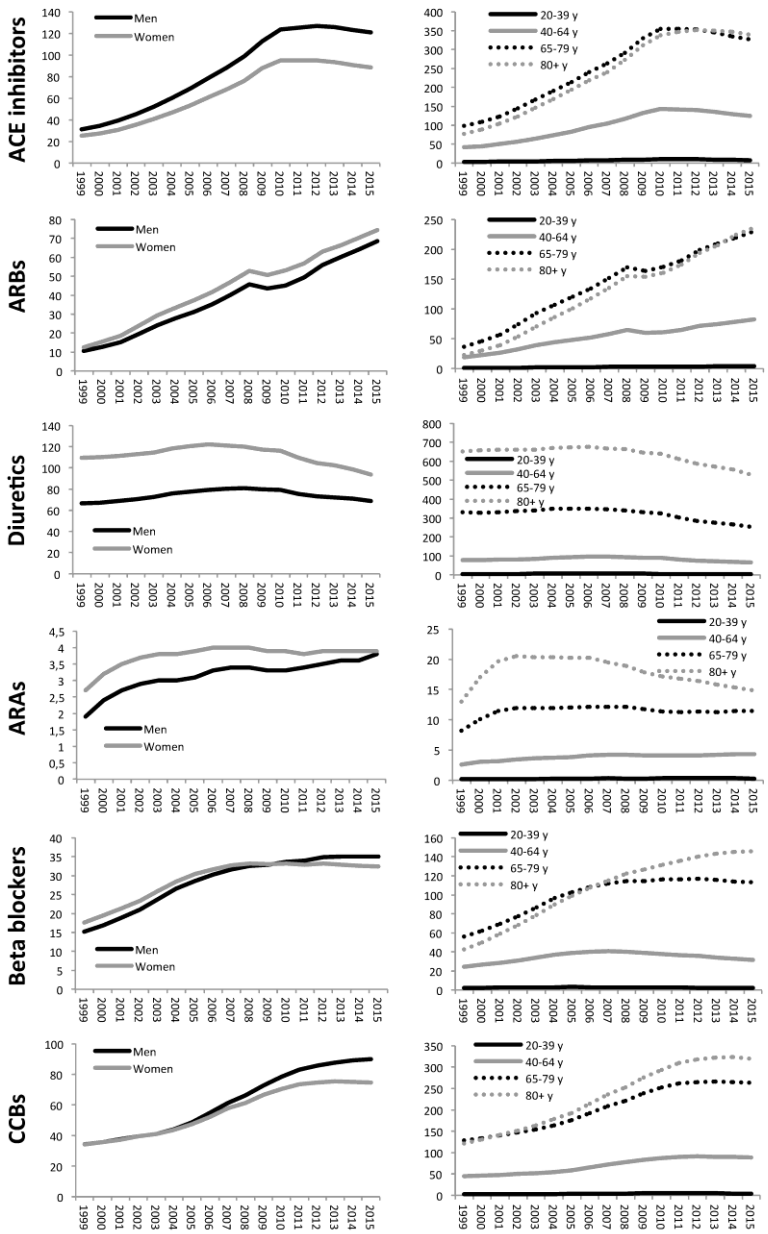

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