

# Seventeen-Year Nationwide Trends in Antihypertensive Drug Use in Denmark



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**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 to 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 2 decades. © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;120:2193–2200)**

During the past 2 decades, several important trials on antihypertensive drugs have emerged, which have led to changes in treatment recommendations such as the JNC 8.<sup>1</sup> 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 relation with landmark studies.

## Methods

The study was conducted in Denmark from January 1, 1999 to December 31, 2015. Denmark has a population of approximately 5.7 million inhabitants, who all have free and unfettered access to tax-supported health care 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 gender from 1999 onward and hospital sector since 1997.<sup>2</sup> We retrieved data on use of antihypertensive drugs according to the Anatomical Therapeutic Chemical 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.<sup>2</sup> 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 gender from Statistics Denmark.<sup>3</sup> According to Danish law, no approval from an ethical committee was required for this study.

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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 Anatomical Therapeutic Chemical codes and drugs within these main classes of antihypertensive drugs are specified in [Supplementary Table S1](#).

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 gender, age groups (20 to 39 years, 40 to 64 years, 64 to 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 retrieved information on in-hospital use of antihypertensive drugs during 1999 to 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 Supplementary Material). The search returned 1,248 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 utilization 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  $\approx 20\%$  to  $\approx 35\%$  of the entire Danish population ([Table 1](#)). During 1999 to 2015, the number of Danish inhabitants remained relatively unchanged and the age and gender distribution did not change substantially ([Supplementary Table S2](#)).

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, whereas 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 ([Supplementary Table S3](#)). Although small regional differences were observed, the use of antihypertensive drugs in individual administrative regions of Denmark was consistent with the national trends ([Supplementary Table S4](#)).

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 0 from 2011 onward. 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 to 2001; thereafter 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 2 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, whereas 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 gender 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 ([Supplementary Figure S1](#)) 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 United States 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<sup>4-6</sup> and The Joint National Committee in The United States,<sup>1,7</sup> as well as major clinical trials. Below, we discuss the observed trends in the light of landmark studies.

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