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# Twenty-year time trends in use of evidence-based heart failure drug therapy in Denmark

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## Abstract

European guidelines for heart failure (HF) have continuously incorporated new evidence since the first publication in 1995. We aimed to explore time trends in utilisation of pharmacological treatment for HF and dispensing of recommended dosages among patients with a first-time diagnosis of HF. We performed a historical cohort study of patients with a first-time HF diagnosis from 1997 to 2015, identified in the Danish National Patient Registry. Dispensed pharmacological treatment included angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor blockers (MRAs), digoxin and diuretics. Furthermore, we estimated the proportion of patients receiving the recommended target dosages 1 year after the diagnosis. The utilisation increased and correlated with publication of landmark studies, and among patients diagnosed in 2015, approximately two of three received ACEI/ARB and beta-blocker, respectively. Less than half of the patients redeeming prescriptions for ACEIs, ARBs, beta-blockers or MRAs received the recommended target dosages. The utilisation of pharmacological therapy for HF appears to be correlated with the publications of landmark Phase III clinical trials. However, a high proportion of patients do not receive the recommended target dosages. Despite improvements over time, a substantial gap appears to remain between guideline recommendations and pharmacological therapy in routine care.

# Introduction

The aims of treating patients with heart failure (HF) are to improve clinical status, functional capacity and quality of life, to prevent hospital admission and reduce mortality.[1] Clinical trials from the last decades have demonstrated life-prolonging effects of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonist (MRA) and beta-blockers, all of which have at least since 2001 been recommended to all HF patients with reduced ejection fraction (EF).[2] In 2014, the angiotensin receptor neprilysin inhibitor (ARNI) was shown superior to ACEI in reducing the risks of death and hospitalisation for HF,[3] and accordingly, ARNI was in 2016 added as a treatment option in the current guidelines from the European Society of Cardiology (ESC).[1]

Several factors may influence the utilisation of pharmacological treatment for HF, such as disease burden, patient compliance with treatment, disease awareness and clinical guidelines. The European guidelines for treatment of HF are updated regularly,[1, 2, 4-8] and temporal trends in real-world utilisation may reflect how well health services adopt and implement the recommendations in daily clinical practice. However, only few studies have examined trends in utilisation of treatment for HF, mainly from the USA and in selected populations. [9-12] Recently, a Danish study examined the trends in nationwide utilisation of antihypertensive drugs, which overlap with HF medication, but the study population was not restricted to individuals diagnosed with HF.[13] Accordingly, a nationwide study on utilisation of HF treatment among HF patients has to our knowledge not been performed so far and contemporary data are needed to inform health care systems.

The objective of the study was to provide an overall picture of utilisation of HF-related pharmacological treatment and publications of landmark studies and European guidelines for HF over time.

# Materials and Methods

***Data sources***

Data were obtained from three nationwide registries: 1) The Danish National Patient Registry was established in 1977 and contains prospectively registered information on all inpatients, and after 1995 also all outpatients.[14] Diagnoses were coded in accordance with the International Classification of Diseases 8$^{th}$ Revision (ICD-8) before 1994 and the 10$^{th}$ revision (ICD-10) from

1994 and onwards. Supplementary Table 1 gives all the applied ICD codes. 2) The Danish National Prescription Registry contains individual-level data on all dispensed prescriptions since 1994 and was used to retrieve all information on pharmacological treatments.[15] Medications were coded in accordance with Anatomical Therapeutic Chemical (ATC) Classification System. All applied ATC codes are given in Supplementary Table 2. 3) The Civil Registration System contains individual-level information on sex, date of birth, vital information and migration.[16] All Danish citizens are assigned a unique 10-digit Civil Registration number, which enabled unambiguous linkage between the registers.

***Design and study population***

We performed a historical cohort study of all in- and outpatients with a first-time hospital diagnosis of HF from 1997 up to and including 2015. Baseline was the first discharge date of HF for the inpatients and the first date of the HF diagnosis for the outpatients. All patients were followed for redemption of prescriptions for pharmacological treatment of HF. We excluded patients <30 years of age, patients with invalid Civil Registration number or inconsistent vital status, and/or patients dying on the day of the diagnosis.

***Comorbidity***

At baseline, we identified diseases associated with HF, including history of coronary artery disease, myocardial infarction, hypertension, valvular heart disease, atrial fibrillation, cardiomyopathy, diabetes mellitus, hyperthyroidism, anaemia and chronic kidney disease. All comorbidities were retrieved as inpatient or outpatient contacts (Supplementary Table 1).

***Utilisation of pharmacological treatment for HF***

We performed three analyses of utilisation, in which the pharmacological treatment was evaluated in main classes (diuretics, ACEIs, ARBs, beta-blockers, MRAs, ivabradine, digoxin and ARNI) and drug-specifically. Firstly, we examined the proportion of patients who initiated pharmacological treatment for HF within the initial 3 months after baseline (Supplementary Figure 1A). Secondly, to allow for possible drug substitution in the months after baseline, we examined the proportion of patients who dispensed treatment 9-12 months after baseline among patients alive 9 months after baseline (Supplementary Figure 1A). Thirdly, we examined the proportion of patients who dispensed 0, 1, 2-3 or >3 drugs from the main medication classes within the initial 3

months and 9-12 months after baseline. Furthermore, we examined the proportion of patients who dispensed 0, 1, 2 or 3 classes of ACEI/ARB/ARNI (counted as one group), beta-blocker and/or MRA.

***Recommended target dosages***

We estimated the proportion of patients who received the recommended target dosages among patients who had HF for 1 year and received HF-related pharmacological treatment. One year after, the diagnosis was chosen to allow for possible drug substitution and/or up-titration of treatment. As the clinical guidelines from the ESC have regularly changed the recommendations, we pragmatically used the recommended target dosages given in the ESC 2016 guideline as reference values (Supplementary Table 3).[1] Patients were excluded in the respective analyses if they redeemed less than two drug-specific prescriptions within 180 days prior to day 365 for the analysed drug. By identifying a patient's two last redeemed prescriptions, we estimated the mean daily dosage as the number of pills dispensed at the first redemption divided by number of days between the two redemptions, multiplied by the strength of the pills (Supplementary Figure 1B). We could not include combination drugs because information on the related tablet strength was inaccessible (Supplementary Table 3).

***Calendar effects of landmark studies***

As landmark studies have influenced the European guidelines for HF through time,[1, 2, 4-6, 8] we outlined the timeline in utilisation of pharmacological treatment for HF and its correlation with the publication of landmark studies and ESC guidelines. Supplementary Tables 5-12 provide a complete summary of all HF-related landmark studies and references.

***Subgroup analyses***

As information on EF was not available in the National Danish Patient Registry, we performed additional analyses in two HF subpopulations, in which we expected the proportion of HF with reduced EF to be high. The first population was restricted to patients with implanted pacemakers, including implantable cardioverter defibrillator and cardiac resynchronization therapy, which are reserved for HF patients with reduced EF. In the second population, we excluded patients above the age of 70 years, women, patients with hypertension and atrial fibrillation, and patients without

myocardial infarction, in accordance with the characteristics of HF patients with preserved EF.[1] In both subpopulations, we estimated the cumulative incidences of dispensing 0-3 and 9-12 months after the diagnosis of HF and pacemaker registration, respectively, and the number of dispensed drug classes.

### *Statistics*

All continuous data were presented as mean (standard deviation) and categorical data as number (percentage). To examine utilisation, we applied a time-to-event approach using time from baseline as time scale and used the Aalen-Johansen estimator to compute cumulative incidence of dispensing adjusted for the competing risk of death. Cumulative incidences were computed 3 months after baseline and 12 months after baseline, last-mentioned among patients alive 9 months after the diagnosis. We estimated the proportion of patients receiving the recommended dosage as described earlier and used the Clopper-Pearson method to compute 95% confidence intervals. Because age and sex composition of the population may have changed during the study period, we age- and sex-standardised all reported cumulative incidences and treatment proportions to the 2015 cohort profile. All analyses were performed by incidence year of HF.

All analyses were performed in Stata version 15 (StataCorp. College Station, Texas, USA).

### *Ethics*

The Danish Data protection Agency approved the study (reference 2015-57-0001). Registry-based studies do not require approval from an ethics committee in Denmark according to Danish law. Statistics Denmark delivered all data.

## Results

### *Baseline characteristics*

From 1997 to 2015, 225,403 patients were diagnosed with HF at Danish hospitals. The annual incidence ranged between 10,610 and 14,115 patients. Baseline characteristics stratified by year of diagnosis are given in Figure 1 and Supplementary Table 13. The proportion of women increased from 51% in 1997 to 58% in 2015. There was a slight decrease in mean age at the diagnosis of HF during the study period. The burden of comorbidity increased over time, particularly with respect to hypertension and atrial fibrillation.

***Temporal trends in utilisation of pharmacological treatment for HF***

In the study period, the utilisation of ACEIs, ARBs, beta-blockers and MRAs increased, whereas utilisation of digoxin and diuretics decreased (Figure 2). The most frequently dispensed drugs were ramipril, losartan, metoprolol and spironolactone (Supplementary Figures 2-3 and Supplementary Tables 14-15). No patients redeemed prescriptions for hydralazine and isosorbide dinitrate within 3 months after diagnosis in our study period, except 0.1% in 1998, 1999 and 2000, respectively (not shown in Figure 2). The patients redeemed prescriptions for ivabradine from 2008 to 2015, ranging from 0.1% in 2008 to 0.6% in 2014 within 3 months (not shown in Figure 2). In our study period, no patients redeemed prescriptions for ARNI within 3 months after the diagnosis of HF. One year after the diagnosis, only patients diagnosed in 2015 redeemed prescriptions for ARNI (0.1%) (not shown in Figure 2).

Within the initial 3 months, the cumulative incidence of patients receiving more than 3 drug classes increased among patients diagnosed with HF from 1997 to 2015 and the cumulative incidence of patients receiving 0 or 1 drug class slightly decreased (Figure 3A). Among patients who were alive 9 months after the HF diagnosis, the cumulative incidence of patients receiving more than 3 classes increased. Figure 3B shows the treatment intensity restricted to the following drug classes: ACEI/ARB/ARNI, beta-blockers, and/or MRA. The proportion of patients who redeemed no drug classes decreased, whereas the proportions of redeemed prescriptions from 2 or 3 classes increased in our study period. All percentages are given in Supplementary Table 16.

***Temporal trends in fulfilment of recommended target dosages***

In general, less than 50% of the patients received the recommended target dosages for ACEI, ARBs, beta-blockers or MRAs, respectively (Figure 4 and Supplementary Table 17). Data for ivabradine are given in Supplementary Table 17. Data on the proportion of patients alive 1 year after the diagnosis of HF stratified by incidence year are given in Table 1. The data show a continually decreasing trend in 1-year mortality, from 32% among patients diagnosed with HF in 1997 to 23% among patients diagnosed in 2015.

***Utilisation patterns and landmark studies of HF***

The utilisation of HF medication 3 months after the diagnosis of HF correlated with the time of publications of landmark studies and ESC guidelines (Figure 5). The utilisation of beta-blockers

increased concurrently with the publications of landmark studies in the late 1990s and early 2000s, and ESC guidelines from 1997, 2001, 2005 and 2008. Patients redeeming prescriptions for ACEIs and ARBs increased during the study period, with the most pronounced increase of ARBs. The landmark trials of ACEIs were published before our study period began. Supplementary Figure 4 shows the cumulative incidence of utilisation 9-12 months after the diagnosis of HF.

**Subgroup analyses**

Population sizes by year are given in Supplementary Table 18. The utilisation of ACEIs, ARBs, beta-blockers and MRAs increased and use of digoxin and diuretics decreased (Supplementary Figures 5-6). The use of ACEI was high in the second population, with a cumulative incidence of approximately 80% after 3 months.

Generally, we noted that the proportion of patients receiving medication from more drug classes increased and the proportion of patients receiving medication from no or 1 group decreased (Supplementary Figures 7-8).

# Discussion

***Principal findings***

In this nationwide cohort study of patients with incident HF from 1997 to 2015, we demonstrated developments in the utilisation of pharmacological treatment for HF from the late 1990s up to contemporary clinical practice. Among patients diagnosed with HF in 2015, approximately two out of three patients received ACEI/ARB and beta-blocker, respectively, within 3 months after the diagnosis of HF. The publications of landmark Phase III clinical trials of HF and ESC guidelines appeared to have influenced on the utilisation pattern although yearlong delays were observed. As our supplementary analyses supported the results from the primary analyses, the primary analyses most likely reflected compliance with the guidelines for HF with reduced EF. The quality of pharmacological treatment has improved over time but it still seems to differ substantially from the evidence-based recommendations in many patients.

***Trends in utilisation and landmark studies and guidelines***

In the treatment of chronic HF, an ACEI or an ARB combined with a beta-blocker are cornerstones and recommended to all patients with reduced EF.[1] We found that the utilisation of

these mentioned medications increased from 1997 to 2016. Previous studies have also reported similar improvements but in older time spans,[9-12] with the newest study including data from 2005.[12] In addition to lack of contemporary data, the previous studies may have been limited to mainly US settings and/or by potential selection problems. On the contrary, time trend data from Sweden suggest no pharmacological improvements from 2003-2012; however, the study included only HF patients with New York Heart Association (NYHA) class II–IV and EF <30%.[17]

In our study, the most marked increase was pertained to beta-blockers, which is in accordance with publication of related landmark studies beginning with the U.S Carvedilol Heart Failure Study in 1996 and incorporation of beta-blocker recommendations in the 1997 ESC guideline.[7, 18] However, the treatment coverage did not reach 50% until about 10 years later, which indicates a relatively long delay period from evidence to practice. A similar delay has been reported for thrombolysis in acute myocardial infarction[19] and highlights the importance of improving the implementation of scientific evidence into clinical practice more efficiently. The increase in utilisation of ACEIs was less distinct compared to ARBs. Notably, the landmark studies on ACEIs (Figure 5) were published in 1987 and the early 1990s, whereas studies on ARBs were published about 10 years later. Furthermore, recommendations of ARBs use were given in the 2001 ESC guideline.[2] One year after the diagnosis of HF, the total utilisation of ACEI and ARB reached a maximum of only about 60%. Our subgroup analysis among HF patients with a high probability of reduced EF suggested that the proportion might be above 80%. The utilisation of MRAs was attributed to spironolactone and we noted a substantial increase in utilisation from 1998, which may be explained by recommendations in the ESC 1997 guideline.[7] This guideline included recommendations on adding spironolactone to an ACEI and a loop diuretic, based on evidence from 1996.[20] Approximately 25% redeemed a prescription for a MRA among patients diagnosed with HF in 2015. This proportion appeared low compared to the Swedish study and the Danish Heart Failure Registry, in which the proportions were above 40%.[17, 21] Our proportion may be lower because our cohort included all patients with a diagnosis of HF and therefore not restricted to symptomatic patients with EF ≤35% who would be the primary candidates for MRA.

We noted minor declines in utilisation 1 year after the diagnosis (Figure 2), which may represent discontinuation of treatment among patients whose cardiac function recovers. For instance, approximately one third of patients with idiopathic dilated cardiomyopathy show improvements in symptoms and EF on optimal medical therapy.[22] The recent TRED-HF trial has

underlined permanent continuation of medical therapy for HF with reduced EF independent of cardiac recovery.[23] However, our data reflect care patterns before the publication of the TRED-HF trial.

We examined the intensity of treatment in terms of number of prescribed drug classes. The proportion of patients treated with more than 3 drug classes has increased since 1997. Our analysis restricted to the main drug classes did also support an increment in the use of more classes in our study period (Figure 3B).

We noted that the crude 1-year mortality decreased approximately by 10% on the absolute scale. Improvements in prognosis over years among Danish HF patients have been reported previously.[24] However, changes in other factors apart from pharmacological treatment may have influenced the prognosis, including changes in the risk profile of the patients and improved non-pharmacological treatment.[25]

***Dosage***

Our study indicates a small increase in the proportion of patients receiving the recommended target dosages. However, less than half of the patients who redeemed prescriptions for ACEIs, ARBs, beta-blockers or MRAs received the recommended target. HF patients receiving suboptimal dosages has previously been described but the reasons are unknown.[26] Suboptimal use of HF treatment still seems to be a challenge in modern clinical practice. However, even though the guideline recommended target dosage is often considered the optimal therapy, evidence suggests that the dosage itself may not be the principal marker of effectiveness. For instance, reduction in heart rate seems to be associated with survival and not the tolerated dosage for beta-blockers.[27, 28]

***Implications***

Our findings augment a sustained need to merge the gap between scientific evidence and clinical practice. Initiatives to improve physicians' adherence to guideline recommendations may be needed. A systematic review found that implementation of reminders in electronic medical records, clinical multidisciplinary teams, clinical pathways and multifaceted interventions, such as audit and feedback, might be effective.[29] However, before widespread implementation of such interventions is recommendable, additional research of higher methodological quality on the effectiveness of quality improvement strategies is warranted.[30] This study may contribute to

providing an overview and highlighting important aspects that are needed for future research to establish potential underlying causal mechanisms of the poor guideline adherence.

***Limitations***

Our study lacked detailed patient-level data at the time of the diagnosis of HF, such as EF, NYHA classification, vital signs or biochemistry, which are important clinical characteristics for determining the recommended treatment. We may have included HF patients with preserved EF in whom optimal pharmacological treatment remains to be determined. Validation studies of the HF diagnosis in the Danish National Patient Registry have reported varying positive predictive values from 76% to 88%.[31, 32] We cannot rule out that the variation reflects geographical differences. Accordingly, at least 1 in 10 patients may have a false positive record of HF and therefore the real utilisation may be higher. We cannot rule out that some patients were in treatment for HF without registration in the National Patient Registry. However, in Denmark, patients with suspected HF are recommended to be referred to a hospital for a thorough diagnostic work-up. Diagnosis codes were also used to retrieve information on all comorbidities. The validity of several diagnoses in the registry has been examined, and in general, the validity appears high.[33]However, we cannot rule out that there has been variation over time. Systematic changes in data quality in the databases used in our study period may have occurred; however, we have no evidence to support that. Accordingly, we expect the misclassification to be constant over time.

We were unable to examine the association between cardiac recovery and discontinuation because we had no serial data on the patients. Our analysis on dosages was based on assumptions from redemptions, and information on the actual utilisation is unknown. As our analysis approach combined adherence and quality of prescribing, a patient taking the right dose but not every day would not be classified as using the recommended dosage. Furthermore, we were unable to include combination drugs in the dosage analysis because of inaccessible information on the related tablet strength. Our results may not be generalizable to other European countries because the national clinical guidelines and clinical practice may be different.

# Conclusion

There has been a substantial progression in the HF treatment among patients with incident HF since 1997. The publication of landmark Phase III clinical trials appears to have influenced the

pattern of utilisation of pharmacological therapy for HF. Today, approximately two out of three patients receive ACEI/ARB and beta-blocker, respectively, within 3 months after the diagnosis of HF. This pattern remains 1 year after the diagnosis. However, a high proportion of patients appear not to receive the recommended target dosages. Despite improvements over time, the real-life pharmacological treatment still seems far from the evidence-based recommendations.

## Conflict of interest

NV, MJ, LF: nothing to disclose; FS: personal fees from Bayer, outside the submitted work; TBL: personal fees from Bayer, personal fees from Pfizer/BMS, personal fees from Boehringer Ingelheim, outside the submitted work; SPJ: grants and personal fees from Pfizer, grants and personal fees from Bristol-Myers Squibb, personal fees from Bayer, outside the submitted work.

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# Tables

**Table 1. Patients died within 1 year after the diagnosis of heart failure.**

| Year | Number | Proportion, % |
|---|---|---|
| 1997 | 3640 | 32.4 |
| 1998 | 3884 | 32.5 |
| 1999 | 3913 | 30.8 |
| 2000 | 4211 | 29.8 |
| 2001 | 4080 | 29.2 |
| 2002 | 4024 | 28.9 |
| 2003 | 3802 | 29.2 |
| 2004 | 3467 | 27.1 |
| 2005 | 3316 | 27.6 |
| 2006 | 3146 | 27.5 |
| 2007 | 3097 | 27.1 |
| 2008 | 2998 | 27.2 |
| 2009 | 2803 | 26.0 |
| 2010 | 2807 | 25.4 |
| 2011 | 2652 | 24.4 |
| 2012 | 2586 | 24.4 |
| 2013 | 2494 | 23.0 |
| 2014 | 2483 | 23.4 |

| | | |
|---|---|---|
| 2015 | 2551 | 23.3 |

# Figure legends

**Figure 1. Baseline characteristics of patients with incident heart failure by year of diagnosis.**
Abbreviations: CAD = coronary artery disease; MI = myocardial infarction; CKD = chronic kidney disease; ACEI = angiotensin-converting enzyme inhibitor; OAC = Oral anticoagulants; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist;

**Figure 2. Age- and sex-standardised cumulative incidences of drug dispensing 3 months (line) and 12 months (dot)* after the diagnosis of heart failure.**
*Cumulative incidence of drug dispensing was estimated among patients alive 9 months after the diagnosis. Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist.

**Figure 3. Age- and sex-standardised proportion of patients dispensing classes of heart failure treatment 0-3 months and 9-12 months after the diagnosis of heart failure.**
Main classes included diuretics, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists, ivabradine, digoxin, and angiotensin receptor neprilysin inhibitor (ARNI).

**Figure 4. Age- and sex-standardised proportion of patients (95% confidence intervals) alive 1 year after the diagnosis of heart failure who received the recommended dosage.***
*Denominator is the number of patients who redeemed at least two prescriptions within 180 days prior to day 365 after baseline, by year of HF. Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist.

**Figure 5. Age- and sex-standardised cumulative incidence of dispensing after 3 months after the diagnosis of heart failure and landmark studies.**
All references are given in Supplementary Tables 4-11.
Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; ARNI = angiotensin receptor neprilysin inhibitor; H-ISDN = hydralazine and isosorbide dinitrate; ARNI = angiotensin receptor neprilysin inhibitor.

**Figure 1**

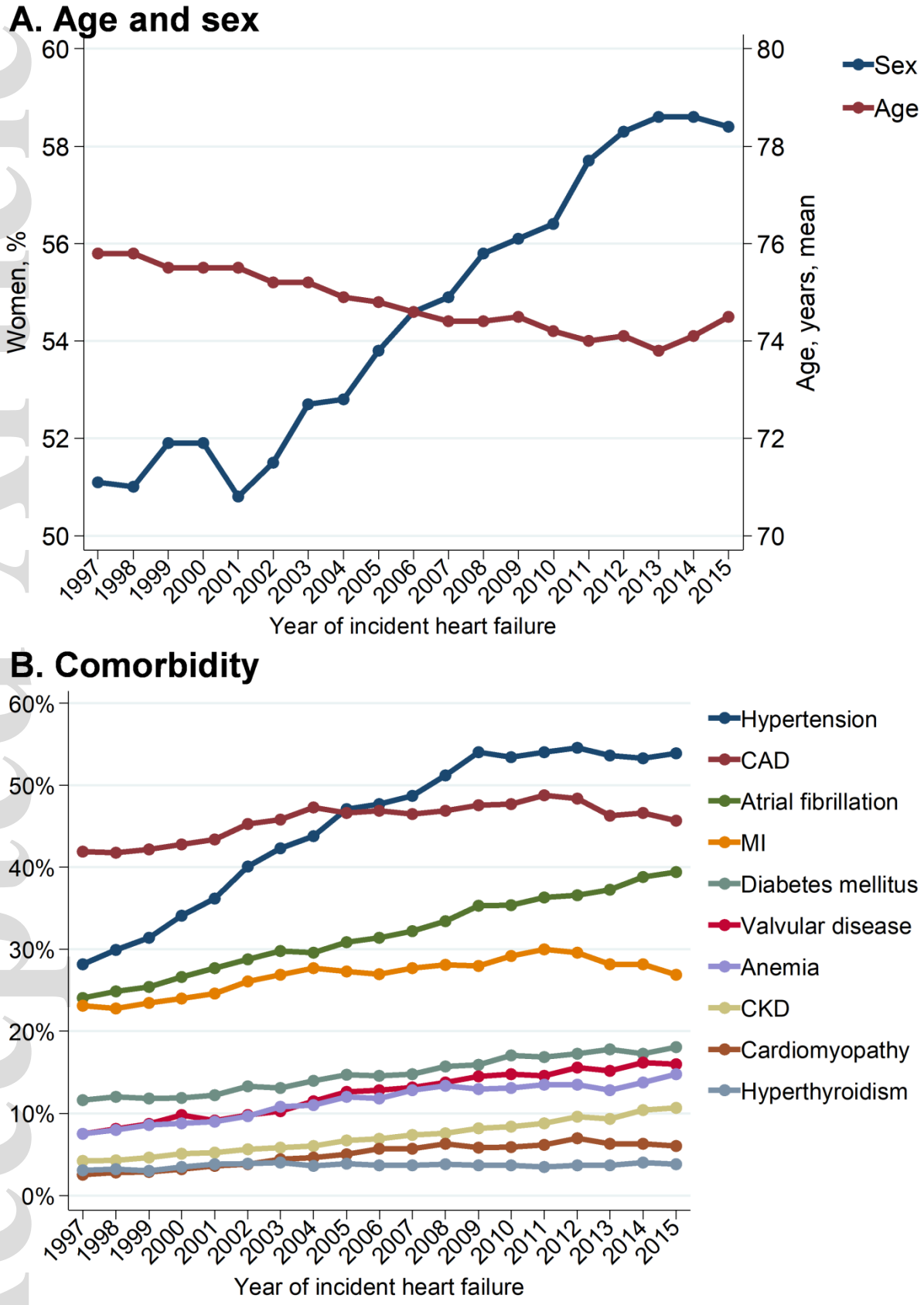

**Figure 2**

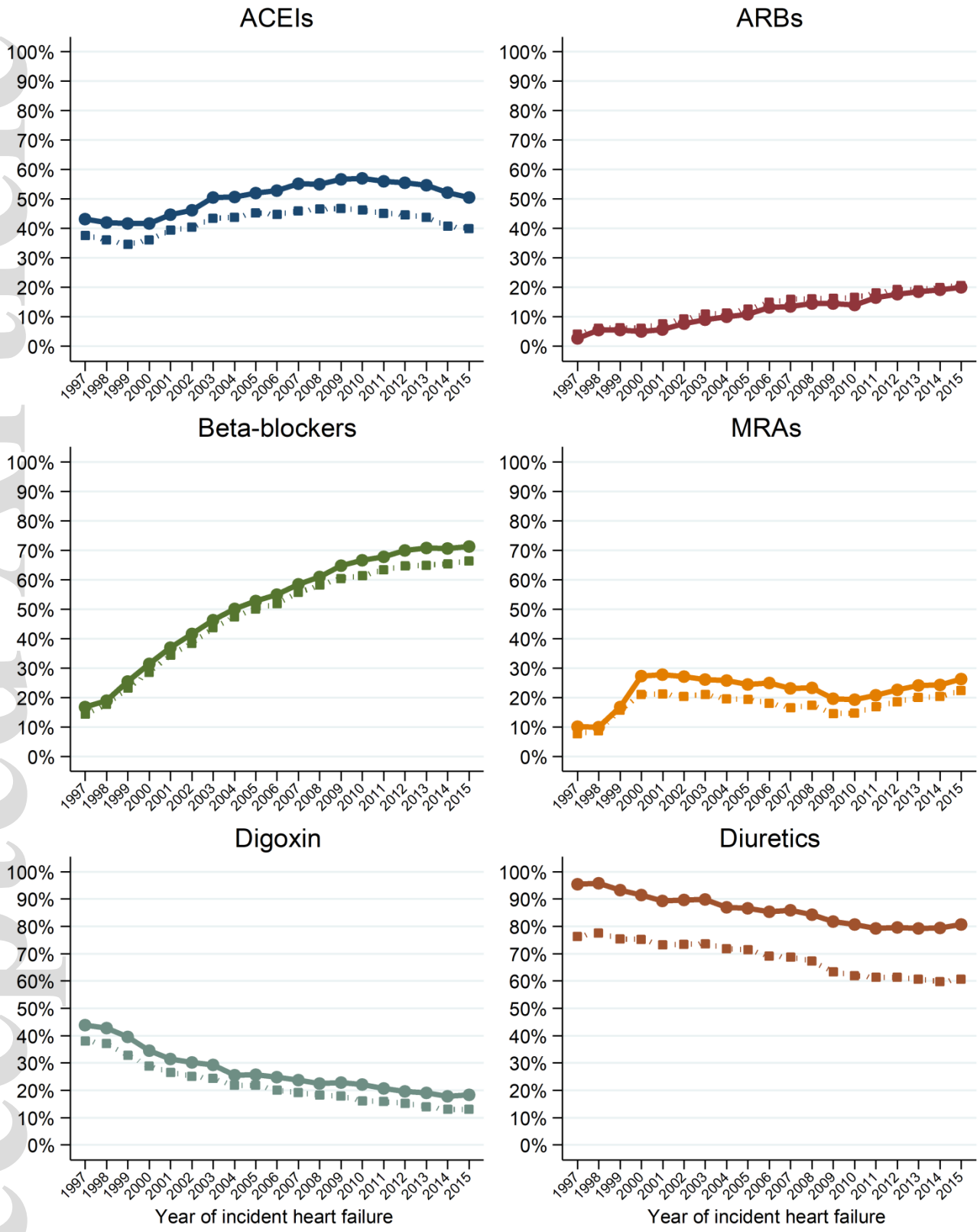

**Figure 3**

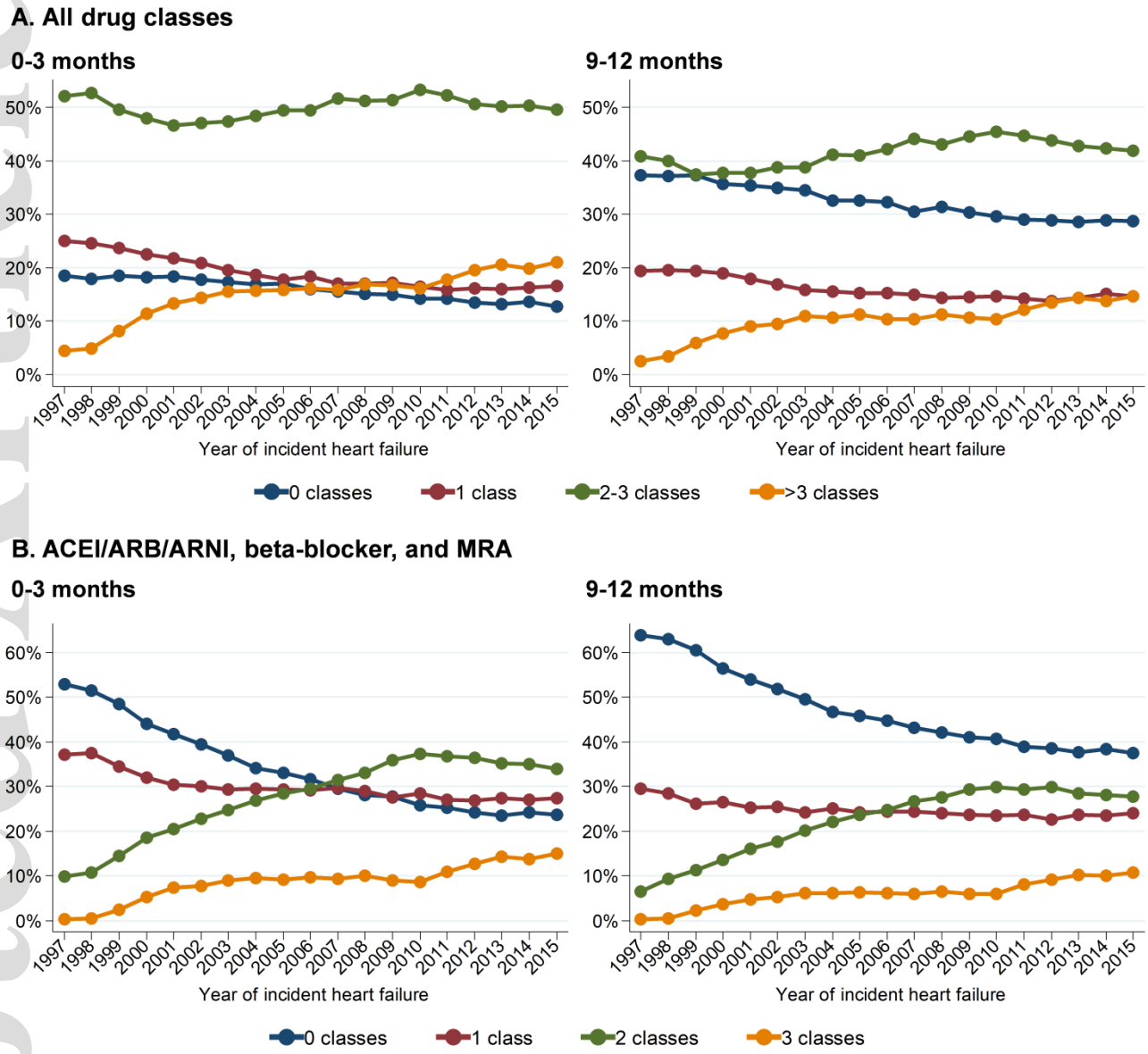

**Figure 4**

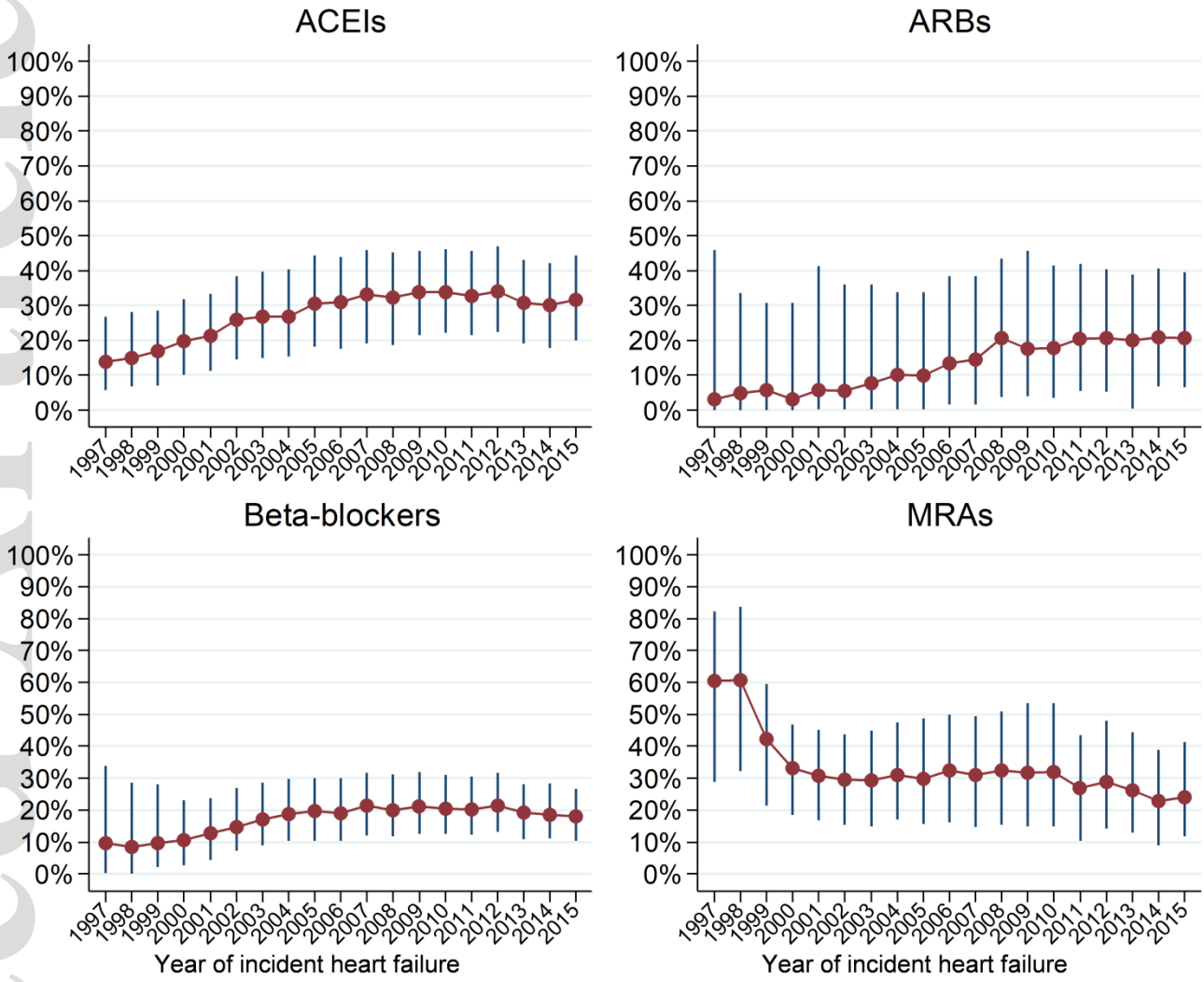

**Figure 5**