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Temporal trends of hypertrophic cardiomyopathy in Denmark

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TITLE:

Temporal trends of hypertrophic cardiomyopathy in Denmark

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KEY MESSAGES:

What is already known about the topic:

- Hypertrophic cardiomyopathy (HCM) is a hereditary cardiovascular disease with a suspected phenotypic incidence of 1:500
- While only few patients develop symptoms, HCM is associated with many cardiovascular complications such as atrial fibrillation, heart failure and sudden cardiac death.
- Current evidence suggests that HCM is highly underdiagnosed, especially in women.

What does this study add:

- This nationwide study is one of the largest epidemiological studies on HCM and includes comprehensive data on patient characteristics, pharmacotherapy and patient resource utilization.
- Trend and changes within these characteristics are analyzed on a yearly basis and quantify advancements within the field of inherited cardiovascular disease.

How might this impact clinical practice:

- While detection rated are improving, the problem of women being diagnosed at later stages than men remains a challenge.

ABSTRACT:

Aim:

To describe the population of patients diagnosed with hypertrophic cardiomyopathy (HCM) in Denmark and determine temporal trends in incidence and patient characteristics over time.

Methods:

All patients aged ≥16 years diagnosed with HCM from 2005 - 2018 were identified in the Danish National Registers. Time trends in HCM diagnosis, patient characteristics, comorbidities, and pharmacotherapy were identified and tested for significance using the Cochran-Armitage trend test.

Results:

In this study 3,856 HCM patients were included (median age 68 years [IQR 56-78]). Although there were more males (53%), females were older (72 years vs. 63 years) and more likely to have their type of HCM classified as obstructive (54% vs. 38%). A consistent rise in HCM cases per year was detected and there was a significant decline in prevalence of HF (2005: 20% to 2018: 12%, p <0.001) and ischemic heart disease (2005: 31% to 2019: 16%, p = <0.001). Prevalence of atrial fibrillation and stroke remained notable and unchanged. Lastly, the rate of hospitalizations decreased over time (2005: 64% to 2016: 46%, p <0.001), while the rate of outpatient follow-up increased (2005: 81% to 2016: 87%, p 0.003).

Conclusion:

There is a consistent rise in HCM cases with decreasing morbidity burden. Females are older at diagnosis and more likely to classifies as obstructive HCM. Moreover, the rate of outpatient follow-up is increasing.

Key Words:
Hypertrophic Cardiomyopathy; Atrial Fibrillation; Epidemiology

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a hereditary heart disease caused by a multitude of mutations integral to the structure and function of the cardiac muscle tissue, and it is one of the most common genetic cardiovascular diseases worldwide (1,2). It is a condition that affects patients irrespective of age, ethnicity, and sex, but the penetrance of the disease can vary by age (2,3). However, the absolute number of patients diagnosed and registered with HCM suggests that the condition is highly underdiagnosed (1). Furthermore, several epidemiological studies have shown this is especially prevalent in females, where HCM detection rates are significantly lower than in males (4–9).

The presence of functional obstruction of the left ventricular outflow tract referred to as hypertrophic obstructive cardiomyopathy (HOCM), increases the probability of developing symptoms compared to non-obstructive HCM (1,10).

Patients with HCM have an increased risk of cardiovascular complications, such as atrial fibrillation (AF), stroke, heart failure (HF), and sudden cardiac death (11-13). Especially AF in HCM patients can be challenging since symptoms, and hemodynamic changes, are often poorly tolerated. Moreover, HCM patients with AF have an elevated risk of thromboembolic events compared with AF patients without HCM (12–15).

Given the relative rarity of the condition, few large-scale epidemiological studies pertaining to the demographics and morbidity burden of the HCM population exist so far. Hence in this study we sought to describe the population of patients diagnosed with HCM in Denmark and determine temporal trends in incidence and patient characteristics over time.

METHODS:

Study Design:

This study was designed as a nationwide cohort study aiming to identify all Danish adults diagnosed for the first time with HCM between January 1st 2005, and December 31th 2018, describe their characteristics, comorbidities, and pharmacotherapy, and identify changes and trends within these parameters over time.

Concomitant Pharmacotherapy was analyzed both prevalent at baseline and during the first two years after initial diagnosis, and the changes over time were compared.

To quantify resource utilization of HCM patients, hospitalizations and outpatient visits up to two years following inclusion were analyzed, and changes over time were described.

Data Sources:

All Danish residents are provided with a unique civil registration number, enabling linkage between the individual national Danish registries for research purposes. For this register-based cohort study 3 register were used; 1) The Civil Registration System holds data on age, gender, and vital status, and all deaths are registered within 14 days. 2) The Danish National Patient Register holds information on every hospitalization in Denmark since 1978. Primary diagnosis is registered according to the International Classification of Diseases, the 10th revision (ICD-10) since 1994. The database further holds information on operations and procedures performed in Denmark. These procedures have been registered since 1996 and coded according to the Nordic Classification of Surgical Procedures (NCSP) by The Nordic Medico-Statistical Committee.

3) The Danish National Prescriptions Registry contains data on all prescriptions dispensed by Danish pharmacies since 1994. Pharmaceuticals are registered in accordance with the Anatomical Therapeutic Chemical (ATC) classification system

Inclusion

All Danish patients of 16 years or more, diagnosed with first-time HCM (ICD-10: DI421, DI422) between January 1st 2005, and December 31th 2018 were included. All patients with incomplete data and those without a history of permanent residence in Denmark during the observation period were excluded from the analysis.

Variables and factors of interest

Patient characteristics more closely analyzed were gender, age, and type of HCM (obstructive and non-obstructive). For analytical purposes, patients were divided into two groups according to age: those over 60 and those younger.

Comorbidities included AF, HF, ischemic heart disease (IHD), hypertension, ischemic stroke, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD) and were registered five years before study inclusion. ICD-10 codes used for these comorbidities are provided in **Supplementary Table 1**.

Concomitant pharmacotherapy at baseline was defined as any claimed prescription 180 days prior to the date of study inclusion. Additionally, pharmacotherapy was also analyzed for a follow-up period of two years after the initial HCM diagnosis. In order to ensure complete follow-up, this analysis included only patients diagnosed with HCM in the years 2005 – 2016. Medications included in the analysis were beta-blockers, calcium channel blockers (CCB), ACE inhibitors, loop diuretics, spironolactone, oral anticoagulant therapy (OAC), digoxin, and amiodarone. OAC comprised warfarin, phenprocoumon, dabigatran, rivaroxaban, apixaban, and edoxaban. ATC codes used for these pharmaceuticals are provided in **Supplementary Table 2**.

Implantable cardioverter defibrillator (ICD) implantations were analyzed at inclusion and separately during a follow-up period of two years after the initial HCM diagnosis. Procedural codes used for ICD implantation are provided in Supplementary Table 1.

Hospitalizations and outpatient visits were solely analyzed for the two-year follow-up after inclusion at initial HCM diagnosis. Hospitalizations were defined as any admission to a Danish hospital, regardless of diagnosis, within these two years. Likewise, outpatient visits were defined as any outpatient visit at a Danish hospital, regardless of diagnosis within the same follow-up period.

Statistical Analysis

Descriptive tables were employed to describe the study population by morbidity burden with continuous variables reported as medians and interquartile ranges [IQRs] and categorical variables summarized with counts and corresponding percentages. Statistical differences were calculated using the Chi-squared test, for categorical variables the Kruskal-Wallis test was employed. Time trends were calculated for gender, age, HCM sub-type, comorbidities, and concomitant pharmacotherapy. Significant changes in trends over time were tested using the Cochran-Armitage trend test and linear regression. A two-sided p-value of <0.05 was considered significant.

Statistical analysis and programming were conducted using R statistical software (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Ethics:

According to Danish legislation, retrospective studies using administrative health databases do not need ethical approval in Denmark. The Danish Data Protection Agency has approved the use of registry data, and the current project is registered with the responsible data institute (Approval number: P-2019-408).

RESULTS:

Baseline characteristics of HCM patients:

A total of 3,856 patients were included in the study between 2005 and 2018. The median age was 68 years (IQR 56-78), with a slight majority of males (53%). (**Table 1)** Cardiovascular morbidity and prevalent use of concomitant pharmacotherapy were frequent in the population, with more than 50% having concurrent hypertension. IHD, AF, and HF were also frequently observed comorbidities with a prevalence of 22%, 14%, and 17%, respectively. Beta-blockers and ACE inhibitors were prescribed to more than one-third of the population, and OAC and loop diuretics were common, being prescribed to 12% and 22% of patients. (Table 1)

Table 1: Baseline characteristics of all patients included 2005 - 2018

	Overall	Male	Female
Number of patients	3856 (100%)	2060 (53%)	1796 (47%)
Age median (median [IQR])	68 [56, 78]	63 [52, 74]	72 [62, 81]
HCM type: obstructive (%)	1717 (45)	789 (38)	928 (54)
Age over 60 (%)	2610 (68)	1199 (58)	1411 (82)
Comorbidities			
Hypertension (%)	1944 (50)	940 (46)	1004 (56)
IHD (%)	859 (22)	490 (24)	369 (21)
AF (%)	656 (17)	386 (19)	270 (15)
Heart failure (%)	523 (14)	292 (14)	231 (13)
Stroke (%)	288 (7)	136 (7)	152 (9)
Chronic obstructive pulmonary disease (%)	313 (8)	124 (6)	189 (11)
Chronic kidney disease (%)	193 (5)	113 (6)	80 (5)
Concomitant pharmacotherapy			
Beta-blockers (%)	1413 (37)	691 (34)	722 (40)
ACE inhibitors (%)	971 (25)	556 (27)	415 (23)
Oral anticoagulant therapy (%)	454 (12)	271 (13)	183 (10)
Loop diuretics (%)	847 (22)	396 (19)	451 (25)
Spironolactone (%)	293 (8)	152 (7)	141 (8)

	Angiotensin II inhibitors (%)	758 (20)	349 (17)	402 (22)
	Calcium channel blockers (%)	1023 (25)	469 (23)	554 (31)
	Digoxin (%)	198 (5)	102 (5)	96 (5)
	Amiodarone (%)	41 (1)	22 (1)	19 (1)
Implantable cardioverter-defibrillator (%)		62 (2)	44 (2)	18 (1)

Gender comparison:

In this cohort, 47% of patients diagnosed with HCM were female. Female patients were in general older (median age 72 years [IQR 62, 81] vs. 63 years [52, 74]) than their male counterparts and their type of HCM was more likely to be classified as obstructive (54% vs. 38%). Regarding concurrent comorbidity, both groups were comparable, although hypertension was more commonly associated with female gender (56% vs. 46%) and AF with males (15% vs. 19%). At time of diagnosis, female patients received more treatment with beta-blockers (40% vs. 34%), CCB (31% vs. 23%) and loop diuretics (25% vs. 19%). (Table 1)

Time trends:

Between 2005 and 2018, the number of patients diagnosed with HCM increased steadily from 207 to 256 annually, with a maximum of 361 patients diagnosed in 2012 (**Figure 1, Supplementary Table 3**). In the context of the Danish population for each year, these numbers correspond to a rise in incidence of 3.1 per 100,000 people in 2005 to 4.4 newly diagnosed HCM patients per 100,000 in 2018. In 2012, the year with the highest number of newly detected patients, the yearly incidence estimates 6.4/100,000. (Supplementary Table 3)

The number of patients classified as having an obstructive HCM type decreased from 58% in 2005 to 40% in 2018 (p-value < 0.001, Figure 1).

Furthermore, there was a decreasing proportion of patients with prevalent IHD (31% in 2005 to 16% in 2018, p-value < 0.001 for time trends), HF (20% in 2005 to 12% in 2018, p-value < 0.001 for time

trends), and COPD (9% in 2005 to 7% in 2018, p-value 0.04 for time trends). Though, prevalent hypertension, AF, and stroke remained high and unchanged. (Supplementary Table 3) Analyzing active pharmacotherapy at inclusion, there was a decrease in loop diuretics (26% in 2005 to 16% in 2018, p-value < 0.001) and ACE inhibitors (from 30% in 2005 to 18% in 2018, p-value <0.001) (**Supplementary Table 4**).

Two-year follow-up of use of concomitant pharmacotherapy and ICD implantations

Up to two years following HCM diagnosis, prescription with beta-blockers increased from 36% of patients at baseline to 63% of all HCM patients, while CCB treatment increased from 26% to 35%. Similarly, treatment with ACE inhibitors rose from 26% to 33%, and loop diuretic use increased from 23% to 35%. OACs were prescribed to 20% of patients two years after diagnosis, an increase from 11% at baseline. While at the time of inclusion, 2% of patients had received an ICD prior to diagnosis with HCM, and two years after diagnosis, 5% of all patients had received an ICD. (**Figure 2, Table 2**)

While there was a noticeable increase in active pharmacotherapy following HCM diagnosis in all years combined, trend analysis for pharmacotherapy in this follow-up period in year-by-year comparison revealed that the use of ACE inhibitors and loop diuretics decreased from 2004-2016, while there was an increase in the use of OAC in the same period (Figure 2, **Supplementary Table 5**).

Table 2: Analysis of concomitant pharmacotherapy and ICD up to two years after HCM diagnosis in the years 2005-2016.

	Baseline (2005-2016)	Follow up (2 years)
Number of patients	3266	
Beta-blockers (%)	1183 (36)	2058 (63)
ACE inhibitors (%)	853 (26)	1088 (33)
Oral anticoagulant therapy (%)	364 (11)	663 (20)
Loop diuretics (%)	744 (23)	1133 (35)
Spironolactone (%)	246 (8)	473 (15)
Calcium channel blockers (%)	856 (26)	1129 (35)
Digoxin (%)	177 (5)	215 (7)
Amiodarone (%)	36 (1)	130 (4)

Implantable cardioverter-defibrillator (%)	49 (2)	161 (5)

Resource utilization:

Finally, the rate of hospitalizations and outpatient follow-up were analyzed. In the two years following HCM diagnosis, trend analysis revealed a significant fall in hospitalization from 2005 to 2016 (64% in 2005 to 46% in 2016, p-trend = <0.001). During the same time, outpatient follow-up was significantly increased (81% in 2005 to 87% in 2016, p-trend = 0.003) (Figure 2, Supplementary table 5).

DISCUSSION:

Overall, this study identified a large cohort of HCM patients with a steady and consistent yearly increase in detected HCM cases and a decreased morbidity-burden over time. Gender distribution in this cohort revealed a near equal distribution of males and females; however, females were older and more likely to have their type of HCM classified as obstructive at first diagnosis.

While HCM is often thought of as a disease of the young, most epidemiological studies place the typical age of patients at initial HCM diagnosis well over 60 (16–20). This study is no exception, with a median age of 68 years at the time of diagnosis and without major change comparing individual years. While the patients' age remained stable, there was a significant decrease in the prevalence of comorbidities such as HF, IHD, and COPD. Notably, the prevalence of IHD decreased markedly in this study, and this was the case despite the general prevalence of IHD increasing from 1980 to 2009 (21).

Several factors can be attributed to this rise in detection. For one there have been considerable advances in both availability and capability of imaging modalities such as cardiac magnetic resonance imaging and echocardiography. Especially cardiac magnetic resonance imaging has gained a more prominent role in classification of HCM (22, 23).

Further the importance and availability of genetic testing and counseling has only increased over time. An increasing number of genes have been associated with the development of HCM making it possible

to classify patients and their relatives with less severe HCM phenotypes more accurately (24, 25). This coupled with the practice of cascade genetic screening can be expected to contribute to the rising number of detected HCM cases.

Lastly advances in the organized management of HCM patients and increased general awareness for rare and genetic diseases cannot be underestimated. The European Society of Cardiology recommended its 2014 guidelines on managing HCM genetic testing patients suspected of HCM (12). In Denmark, this practice is predated by establishing specialized clinics for inherited heart diseases in which clinical and genetic screening are performed based on the first national recommendation for management of inherited heart diseases from 2003. Both factors likely contributed to the rise in detection rate and awareness of HCM in the Danish population.

While the prevalence of cardiovascular comorbidity among the newly diagnosed decreased markedly, this was notably not the case for AF and stroke. There is a well-documented strong association between HCM, AF, and stroke (15,16,26-28), and therefore unsurprising to see a stable prevalence of both conditions, despite a rising detection rate. International guidelines in the treatment of HCM recommend aggressive treatment of AF in the presence of HCM since stroke risk is higher and symptoms of AF can be aggravated in these patients (12–14). The general advances in AF treatment, especially in the context of HCM, were emphasized in the detectable increase of patients in active OAC treatment, both prevalent at baseline and follow-up. In Denmark, a general trend toward increased prescription of OAC in AF patients could previously be detected and attributed to mounting evidence supporting the safety and efficacy of direct oral anticoagulant treatment in this group (29). The increase in OAC treatment following the years after diagnosis with HCM could be explained by increased awareness of the importance of sufficient anticoagulation within the context of HCM, as highlighted by international guidelines (12,14).

Despite a significant gender gap reported in numerous studies (4-9), showing a lower HCM detection rate in females, the distribution between the genders in this cohort of Danish HCM patients was near equal. There was a slight majority of male patients (53%) in this cohort, although this difference was

far less pronounced than in comparable studies and did not prove statistically significant (17-20). In terms of temporal changes, although in most years, the detection rate of HCM in females was slightly below that of males, the difference was not significant and did not alter over time. Females, however, were older at the diagnosis and more likely to be classified as obstructive. This is consistent with other large studies examining HCM cohorts (17-20). Whether this difference is due to differences in penetrance or bias in screening/referral remains controversial (4-9).

Arguments to support the case for a bias in screening and detection between the genders can be found in this Danish cohort. There was an overweight of AF among males in this HCM cohort. Diagnosis with AF would, in accordance with current guidelines, result in the patients referral to follow-up, including procedures such as echocardiography, in which previously unknown HCM would be more likely to be detected. With ever-increasing options for screening and follow-up for AF, this or comparable processes with other cardiovascular comorbidities could explain the difference in age and severity between the genders. However, more research is warranted to explain this disparity between the genders in HCM diagnosis sufficiently.

Limitations:

Given the relative rarity of HCM, large nationwide databases are well suited for research on this topic; however, this method is not without limitations. The Danish National Patient Registry and the general completeness of data in the Danish nationwide registries ensure minimal missing data and a complete follow-up (30). The main limitations are all inherent to the observational study design, and the possibility of residual confounding remains. Most notably, the utilized registries do not contain data on echocardiography or genetic testing, which limits the ability of detailed cohort description. HCM diagnosis and type classification (obstructive vs. non-obstructive) is solely based on ICD-10 coding within the registries and hereby judgment of the treating physician. Since diagnosis of HCM can be challenging and easily mistaken for other conditions presenting with left ventricular hypertrophy, this approach is inherently prone to misdiagnosis and error. This especially applies for patients with hypertension. Prevalence of hypertension in this cohort was high, with 50% opening possibility for misclassification. However, given the low positive predictive value for hypertension within the Danish

registries, hypertension was classified as active treatment with two or more antihypertensive pharmaceuticals in this study. This included ACE inhibitors and beta blockers which are often prescribed for HF, AF and other conditions often seen in conjunction with HCM. Therefore, with this method misclassification of hypertension cannot be excluded in this context and the percentage of patients classified as hypertensive might be inflated.

The positive predictive value for HCM within the Danish National Patient Registry, has been shown to be 90% in a study validating a variety of cardiovascular diagnosis within the Danish registries from 2016 (31). This study however only analyzed 20 patients with HCM, possibly necessitating further validation of HCM within the Danish registries. For the purpose of this study the authors have decided to rely on currently available data.

CONCLUSION:

This large epidemiological study of Danish HCM patients could determine a steady increase in detected HCM patients.

The previously described gender gap in HCM detection was less pronounced in these groups with near equal distribution between the genders; however, females remained older and more likely to have their type of HCM classified as obstructive at first diagnosis.

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Conflict of interest statement:

No conflict of interest to declare.

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DATA AVAILABILITY:

Data for this study are derived from and accessed through Statistics Denmark. By law, these data are not allowed to be shared. For this reason, data cannot not be made available to other researchers.

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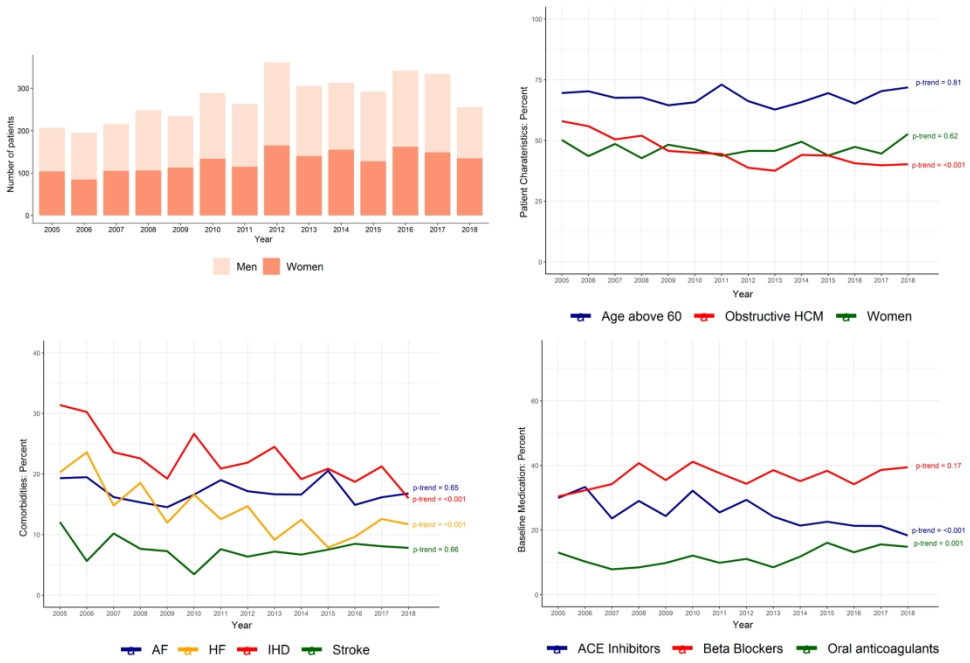
FIGURE LEGENDS:

Figure 1: Temporal trends of yearly detection rate, baseline patient characteristics, comorbidities and concomitant pharmacotherapy (2005 - 2018), (Scale: 1771 x 1181)

Figure 2: Temporal trends of concomitant pharmacotherapy and resource utilization identified in the follow up period (2005 – 2016) (Scale: 1771 x 1181)



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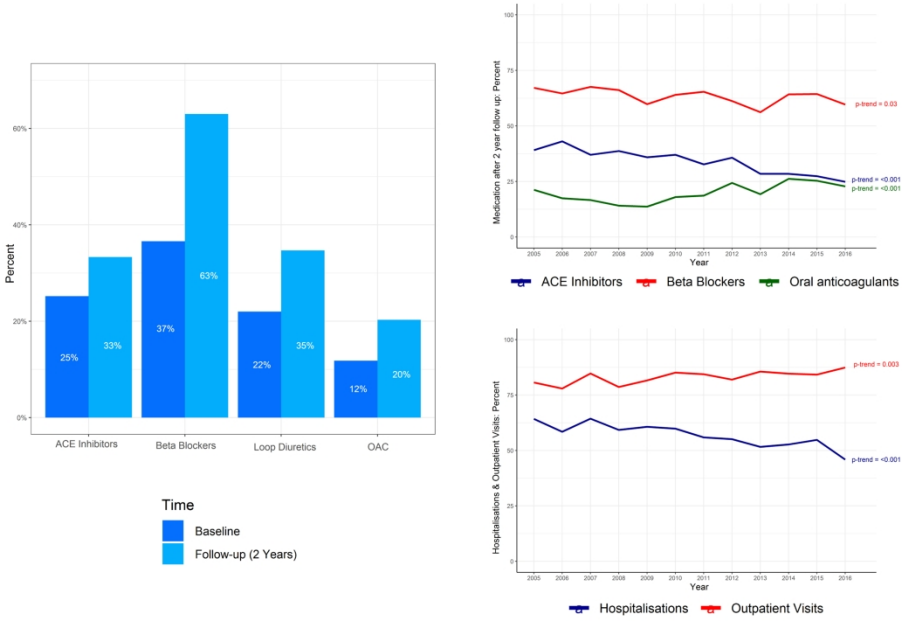

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Supplementary appendix

Supplementary table 1: Diagnostic and procedural codes used to identify comorbidity
Supplementary table 2: ATC-codes used to define medical therapy
Supplementary table 3: Temporal trends of patient characteristics and comorbidities at baseline
Supplementary table 4: Temporal trends of concomitant pharmacotherapy at baseline
Supplementary table 5: Temporal trends of concomitant pharmacotherapy and resource utilization during follow up, up to two years after inclusion (2005-2016).

Supplementary table 1

Diagnostic and procedural codes used to identify comorbidity

Comorbidity	
Atrial fibrillation / Atrial flutter	*ICD-10: I48*
Chronic Obstructive Pulmonary Disease	*ICD-10: J42-J44*
Ischemic heart disease	*ICD-10: I20-I25*
Pacemaker / implantable cardioverter defibrillator	*BFCA0-3, BFCA6, BFCA6, BFCA7, BFCB0, BFCB2, BFCB3, BFCB5, BFCB7, ZZ4050, ZZ4051*
Hypertension	*Treatment with more than one anti-hypertensive medication.*
Congestive heart failure	*ICD-10: I50*
Ischemic stroke / TIA / systemic embolism	*ICD-10: I63, I64, I74, G458, G459*
Chronic Kidney Disease	*ICD-10: N02-N08, N11-N14, N18, N19, N26, N158-N160, N 162, N163, N164, N168, Q61, E102, E112, E132, E142, I120, M321B*

Supplementary table 2: ATC-codes used to define medical therapy

Oral anticoagulatnt treatment (Warfarin, phenprocoumon, dabigatran, rivaroxaban, apixaban, edoxaban)	*ATC-codes: B01AA03, B01AA04, B01AE07, B01AF01, B01AF02, B01AF03*
Beta-blockers	*C07A, C07B, C07C, C07D, C07F*
Calcium channel antagonist	*C08C, C08D, C08E, C08G, C09BB, CO9DB*
Spironolactone	*C03D, C03E, C03EB*
Loop diuretics	*C03C, C03EB*
Non-loop diuretics	*C02L, C02DA, C07D, C09XA52, C03A, C03EA, C03B, C03X, C07C, C08G, C09BA, C09DA, C03D, C03E, C03EB*
ACE inhibitors	*C09A, C09B*
Digoxin	*C01AA*
Amiodarone	*C02BD01*

Supplementary table 3: Temporal trends of patient characteristics and comorbidities at baseline

Year		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P - trend
Number		207	195	216	248	234	289	263	361	306	317	292	342	334	256	
Incidence per 100,000		3.8	3.6	3.9	4.5	4.3	5.3	4.7	6.4	5.5	5.6	5.1	6	5.8	4.4	
Median age [IQR]		67 [57, 78]	69[58, 79]	68 [56, 77]	66[58, 78]	66 [55, 77]	68 [55, 77]	68[59, 78]	66 [56, 77]	67 [53, 78]	68 [57, 78]	69[54, 78]	67[55, 78]	70 [57, 78]	70 [58, 78]	0.56
Gender (%)	Male	103 (50)	110 (56)	111 (51)	142 (57)	121 (52)	155 (54)	148 (56.)	196 (54)	166 (54)	155 (51)	164 (56)	180 (53)	185 (55)	121 (47)	0.62
	Female	104 (50)	85 (43)	105 (49)	106 (42)	113 (48)	134 (46)	115 (44)	165 (46)	140 (46)	152 (50)	128 (44)	162 (47)	149 (45)	135 (53)	
Age (%)	Above or 60	144 (70)	137 (70)	146 (68)	168 (68)	151 (65)	190 (68)	192 (73)	239 (66)	192 (63)	201 (66)	203 (70)	223 (65)	235 (70)	184 (72)	0.81
HCM type (%)	Non-obstructive HCM	87 (42)	86 (44)	107 (49)	119 (48)	127 (54)	159 (55)	146 (56)	221 (61)	191 (62)	177 (60)	164 (56)	203 (59)	201 (60)	153 (60)	<0.001
	Obstructive HCM	120 (58)	109 (56)	109 (51)	129 (52)	107 (46)	130 (45)	117 (45)	140 (39)	115 (38)	139 (44)	128 (44)	139 (41)	133 (40)	103 (40)	
Ischemic heart disease (%)		65 (31)	59 (30)	51 (24)	56 (23)	45 (20)	77 (27)	55 (21)	79 (22)	75 (25)	60 (20)	61 (21)	64 (19)	71 (21)	41 (16)	<0.001
Chronic obstructive pulmonary disease (%)		19 (9)	18 (9)	16 (7)	24 (9)	23 (10)	33 (11)	24 (9)	32 (9)	17 (6)	14 (5)	31 (11)	16 (5)	27 (8)	19 (7)	0.04
Chronic kidney disease (%)		11 (5)	9 (5)	11 (5)	9 (4)	9 (4)	13 (5)	15 (6)	25 (7)	10 (3)	13 (4)	14 (5)	14 (4)	18 (5)	22 (9)	0.3
Hypertension (%)		109 (53)	98 (50)	105 (49)	134 (54)	110 (47)	156 (54)	125 (48)	188 (52)	147 (48)	159 (50)	151 (52)	155 (45)	171 (51)	136 (53)	0.6
Heart Failure (%)		42 (20)	46 (24)	32 (15)	46 (19)	28 (12)	48 (17)	33 (13)	53 (13)	28 (9)	39 (13)	23 (8)	33 (10)	42 (13)	30 (12)	<0.001
Stroke (%)		25 (12)	11 (6)	22 (10)	19 (8)	17 (7)	10 (4)	20 (8)	23 (6)	22 (7)	21 (7)	22 (9)	29 (9)	27 (8)	20 (8)	0.66
Atrial fibrillation (%)		40 (19)	38 (20)	35 (16)	38 (15)	34 (15)	48 (17)	50 (19)	62 (17)	51 (17)	52 (17)	60 (21)	51 (15)	54 (16)	43 (17)	0.65

Supplementary table 4: Temporal trends of concomitant pharmacotherapy at baseline

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P - trend
Number	207	195	216	248	234	289	263	361	306	313	295	342	334	256	
Beta-blockers (%)	63 (30)	63 (32)	74 (34)	101 (41)	83 (36)	119 (41)	99 (38)	124 (34)	118 (39)	110 (35)	113 (38)	117 (34)	129 (39)	101 (40)	0.17
Oral anticoagulant therapy (%)	27 (13)	20 (10)	17 (8)	21 (9)	23 (10)	35 (12)	26 (10)	40 (11)	26 (9)	37 (12)	47 (16)	45 (13)	52 (16)	38 (15)	0.01
Calcium channel blockers (%)	53 (26)	39 (20)	51 (24)	63 (25)	53 (23)	85 (29)	56 (21)	102 (28)	97 (32)	89 (28)	91 (31)	77 (23)	97 (29)	70 (27)	0.03
Spironolactone (%)	28 (14)	19 (10)	21 (10)	15 (6)	16 (7)	23 (8)	20 (8)	23 (6)	13 (4)	29 (9)	14 (5)	25 (7)	23 (7)	24 (9)	0.04
Loop Diuretics (%)	53 (26)	53 (27)	57 (26)	65 (26)	46 (20)	74 (26)	62 (24)	84 (23)	57 (19)	76 (24)	57 (20)	60 (18)	62 (19)	41 (16)	<0.001
Digoxin (%)	18 (9)	20 (10)	13 (6)	13 (5)	20 (9)	20 (7)	17 (7)	14 (4)	14 (5)	8 (3)	11 (4)	9 (3)	12 (4)	9 (4)	<0.001
Amiodarone (%)	6 (3)	<3 (1)	<3 (1)	4 (2)	3 (1)	<3 (1)	4 (2)	<3 (1)	<3 (1)	5 (2)	3 (1)	<3 (1)	3 (1)	<3 (1)	0.1
ACE inhibitors (%)	62 (30)	65 (33)	51 (24)	72 (29)	57 (24)	93 (32)	67 (26)	106 (29)	74 (24)	67 (21)	66 (23)	73 (21)	71 (21)	47 (18)	<0.001
Implantable cardioverter-defibrillator (%)	3 (1)	5 (3)	<3 (1)	4 (2)	6 (3)	5 (2)	6 (2)	5 (1)	<3 (1)	4 (1)	4 (1)	4 (1)	7 (2)	6 (2)	0.98

Supplementary table 5: Temporal trends of concomitant pharmacotherapy and resource utilization during follow up, up to two years after inclusion (2005-2016).

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	P -trend
Number	207	195	216	248	234	289	263	361	306	342	292	342	
Beta-blockers (%)	139 (67)	126 (65)	146 (68)	164 (66)	140 (60)	185 (64)	172 (65)	221 (61)	172 (56)	211 (62)	188 (64)	204 (60)	0.03
Calcium channel blockers (%)	77 (37)	65 (33)	72 (33)	82 (33)	83 (36)	102 (35)	73 (28)	136 (38)	101 (33)	131 (38)	116 (40)	104 (30)	0.87
Oral Anticoagulant therapy (%)	44 (21)	34 (17)	36 (17)	35 (14)	32 (14)	52 (18)	49 (19)	88 (24)	59 (19)	82 (24)	74 (25)	78 (23)	<0.001
Spironolactone (%)	38 (18)	32 (16)	36 (17)	42 (17)	30 (13)	39 (14)	39 (15)	51 (14)	34 (11)	54 (16)	37 (13)	41 (12)	0.02
Loop Diuretics (%)	85 (41)	77 (39)	90 (42)	94 (38)	71 (30)	111 (38)	89 (34)	141 (39)	86 (28)	115 (34)	83 (28)	91 (27)	<0.001
ACE inhibitors (%)	81 (39)	84 (43)	80 (37)	96 (39)	84 (36)	107 (37)	86 (33)	129 (36)	87 (28)	89 (26)	80 (27)	85 (25)	<0.001
Digoxin (%)	20 (10)	24 (12)	20 (9)	16 (7)	22 (9)	15 (5)	20 (8)	30 (8)	14 (5)	13 (4)	11 (4)	12 (4)	<0.001
Amiodarone (%)	15 (7)	6 (3)	9 (4)	9 (4)	9 (4)	8 (3)	14 (5)	15 (4)	14 (5)	15 (4)	9 (3)	6 (2)	0.11
Implantable cardioverter-defibrillator (%)	6 (3)	9 (5)	8 (4)	19 (8)	10 (4)	18 (6)	27 (10)	15 (4)	16 (5)	13 (4)	9 (3)	12 (4)	0.34
Hospitalizations (%)	133 (64)	114 (59)	139 (64)	147 (59)	142 (61)	173 (60)	147 (60)	199 (55)	158 (52)	165 (53)	160 (55)	157 (46)	<0.001
Outpatient Visits (%)	167 (81)	152 (78)	183 (85)	195 (79)	191 (82)	246 (85)	222 (84)	296 (82)	262 (85)	265 (85)	246 (84)	299 (87)	0.003

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 -2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Temporal trends of hypertrophic cardiomyopathy in Denmark: a nationwide retrospective cohort study

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Temporal trends of hypertrophic cardiomyopathy in Denmark: a nationwide retrospective cohort study

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ABSTRACT

Objectives

To describe the population of patients diagnosed with hypertrophic cardiomyopathy (HCM) in Denmark and determine temporal trends in incidence and patient characteristics over time.

Design

Nationwide retrospective cohort study.

Setting

Danish nationwide administrative and clinical registers and databases.

Participants

All patients aged ≥16 years diagnosed with HCM from 2005 to 2018.

Outcomes measures

Time trends in HCM diagnosis, patient characteristics, comorbidities, and pharmacotherapy were identified and tested for significance using the Cochran-Armitage trend test.

Results

3,856 HCM patients were included (median age 68 years [IQR 56-78]). Although there were more males (53%), females were older (72 years vs. 63 years) and more likely to have their type of HCM classified as obstructive (54% vs. 38%). A consistent rise in HCM cases per year was detected and there was a significant decline in prevalence of HF (2005: 20% to 2018: 12%, p <0.001) and ischemic heart disease (2005: 31% to 2019: 16%, p = <0.001). Prevalence of atrial fibrillation and stroke remained notable and unchanged. Lastly, the rate of hospitalizations decreased over time (2005: 64% to 2016: 46%, p <0.001), while the rate of outpatient follow-up increased (2005: 81% to 2016: 87%, p 0.003).

Conclusion

There was a consistent rise in HCM cases with decreasing morbidity burden. Females were older at diagnosis and more likely to have their type of HCM classified as obstructive. The rate of outpatient follow-up is increasing.

Keywords:
Hypertrophic Cardiomyopathy; Atrial Fibrillation; Epidemiology

Strengths and limitations of this study

- Large nationwide cohort study design capturing all Danish adults diagnosed with hypertrophic cardiomyopathy (HCM) over a 14-year period.
- Utilization of comprehensive national registries for data collection, ensuring minimal missing data and a complete follow-up.
- Lack of specific data on echocardiographic features, genetic testing, and implementation rate of genetic counseling.
- Reliance on ICD-10 coding for HCM diagnosis and classification, which may vary between healthcare institutions.
- Absence of long-term outcome analysis, limiting assessment of the impact of HCM on morbidity and mortality beyond the 2-year follow-up period.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a hereditary heart disease caused by a multitude of mutations integral to the structure and function of the cardiac muscle tissue, and it is one of the most common genetic cardiovascular diseases worldwide (1,2). It is a condition that affects patients irrespective of age, ethnicity, and sex, but the penetrance of the disease can vary by age (2,3). However, the absolute number of patients diagnosed and registered with HCM suggests that the condition is highly underdiagnosed (1). Furthermore, several epidemiological studies have shown this is especially prevalent in females, where HCM detection rates are significantly lower than in males (4–9).

The presence of functional obstruction of the left ventricular outflow tract referred to as hypertrophic obstructive cardiomyopathy (HOCM), increases the probability of developing symptoms compared to non-obstructive HCM (1,10).

Patients with HCM have an increased risk of cardiovascular complications, such as atrial fibrillation (AF), stroke, heart failure (HF), and sudden cardiac death (11-13). Especially AF in HCM patients can be challenging since symptoms, and hemodynamic changes, are often poorly tolerated. Moreover, HCM patients with AF have an elevated risk of thromboembolic events compared with AF patients without HCM (12–15).

Given the relative rarity of the condition, few large-scale epidemiological studies pertaining to the demographics and morbidity burden of the HCM population exist so far. Hence, in this study, we sought to describe the population of patients diagnosed with HCM in Denmark and determine temporal trends in incidence and patient characteristics over time.

METHODS

Study design

This study was designed as a nationwide retrospective cohort study aiming to identify all Danish adults diagnosed for the first time with HCM between January 1st 2005, and December 31th 2018, describe their characteristics, comorbidities, and pharmacotherapy, and identify changes and trends within these parameters over time.

Concomitant Pharmacotherapy was analyzed both prevalent at baseline and during the first two years after initial diagnosis, and the changes over time were compared.

To quantify resource utilization of HCM patients, hospitalizations and outpatient visits up to two years following inclusion were analyzed, and changes over time were described.

Data sources

All Danish residents are provided with a unique civil registration number, enabling linkage between the individual national Danish registries for research purposes. For this register-based cohort study 3 register were used:

1) The Civil Registration System holds data on age, gender, and vital status, and all deaths are registered within 14 days.

2) The Danish National Patient Register holds information on every hospitalization in Denmark since 1978. Primary diagnosis is registered according to the International Classification of Diseases, the 10th revision (ICD-10) since 1994. The database further holds information on operations and procedures performed in Denmark. These procedures have been registered since 1996 and coded according to the Nordic Classification of Surgical Procedures (NCSP) by The Nordic Medico-Statistical Committee.

3) The Danish National Prescriptions Registry contains data on all prescriptions dispensed by Danish pharmacies since 1994. Pharmaceuticals are registered in accordance with the Anatomical Therapeutic Chemical (ATC) classification system.

Inclusion

All Danish patients of 16 years or more, diagnosed with first-time HCM (ICD-10: DI421, DI422) between January 1st 2005, and December 31th 2018 were included. All patients with incomplete data and those without a history of permanent residence in Denmark during the observation period were excluded from the analysis.

Variables and factors of interest

Patient characteristics more closely analyzed were gender, age, and type of HCM (obstructive and non-obstructive). For analytical purposes, patients were divided into two groups according to age: those over 60 and those younger.

Comorbidities included AF, HF, ischemic heart disease (IHD), hypertension, ischemic stroke, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD) and were registered five years before study inclusion. ICD-10 codes used for these comorbidities are provided in **Supplementary Table 1**.

Concomitant pharmacotherapy at baseline was defined as any claimed prescription 180 days prior to the date of study inclusion. Additionally, pharmacotherapy was also analyzed for a follow-up period of two years after the initial HCM diagnosis. In order to ensure complete follow-up, this analysis included only patients diagnosed with HCM in the years 2005 – 2016. Medications included in the analysis were beta-blockers, calcium channel blockers (CCB), ACE inhibitors, loop diuretics, spironolactone, oral anticoagulant therapy (OAC), digoxin, and amiodarone. OAC comprised warfarin, phenprocoumon, dabigatran, rivaroxaban, apixaban, and edoxaban. ATC codes used for these pharmaceuticals are provided in **Supplementary Table 2**.

Implantable cardioverter defibrillator (ICD) implantations were analyzed at inclusion and separately during a follow-up period of two years after the initial HCM diagnosis. Procedural codes used for ICD implantation are provided in Supplementary Table 1.

Hospitalizations and outpatient visits were solely analyzed for the two-year follow-up after inclusion at initial HCM diagnosis. Hospitalizations were defined as any admission to a Danish

hospital, regardless of diagnosis, within these two years. Likewise, outpatient visits were defined as any outpatient visit at a Danish hospital, regardless of diagnosis within the same follow-up period.

Statistical analysis

Descriptive tables were employed to describe the study population by morbidity burden with continuous variables reported as medians and interquartile ranges [IQRs] and categorical variables summarized with counts and corresponding percentages. Statistical differences were calculated using the Chi-squared test, for categorical variables the Kruskal-Wallis test was employed. Time trends were calculated for gender, age, HCM sub-type, comorbidities, and concomitant pharmacotherapy. Significant changes in trends over time were tested using the Cochran-Armitage trend test and linear regression. A two-sided p-value of <0.05 was considered significant.

Statistical analysis and programming were conducted using R statistical software (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Patient and public involvement

None.

RESULTS

Baseline characteristics of HCM patients

A total of 3,856 patients were included in the study between 2005 and 2018. The median age was 68 years (IQR 56-78), with a slight majority of males (53%) (**Table 1**). Cardiovascular morbidity and prevalent use of concomitant pharmacotherapy were frequent in the population, with more than 50% having concurrent hypertension. IHD, AF, and HF were also frequently observed comorbidities with a prevalence of 22%, 14%, and 17%, respectively. Beta-blockers and ACE inhibitors were prescribed to more than one-third of the population, and OAC and loop diuretics were common, being prescribed to 12% and 22% of patients (Table 1).

Table 1. Baseline characteristics of all patients included, 2005 to 2018

	Overall	Male	Female
Number of patients	3856 (100%)	2060 (53%)	1796 (47%)
Age median (median [IQR])	68 [56, 78]	63 [52, 74]	72 [62, 81]
HCM type: obstructive (%)	1717 (45)	789 (38)	928 (54)
Age over 60 (%)	2610 (68)	1199 (58)	1411 (82)
Comorbidities			
Hypertension (%)	1944 (50)	940 (46)	1004 (56)
IHD (%)	859 (22)	490 (24)	369 (21)
AF (%)	656 (17)	386 (19)	270 (15)
Heart failure (%)	523 (14)	292 (14)	231 (13)
Stroke (%)	288 (7)	136 (7)	152 (9)
Chronic obstructive pulmonary disease (%)	313 (8)	124 (6)	189 (11)
Chronic kidney disease (%)	193 (5)	113 (6)	80 (5)
Concomitant pharmacotherapy			
Beta-blockers (%)	1413 (37)	691 (34)	722 (40)
ACE inhibitors (%)	971 (25)	556 (27)	415 (23)
Oral anticoagulant therapy (%)	454 (12)	271 (13)	183 (10)
Loop diuretics (%)	847 (22)	396 (19)	451 (25)
Spironolactone (%)	293 (8)	152 (7)	141 (8)

	Angiotensin II inhibitors (%)	758 (20)	349 (17)	402 (22)
	Calcium channel blockers (%)	1023 (25)	469 (23)	554 (31)
	Digoxin (%)	198 (5)	102 (5)	96 (5)
	Amiodarone (%)	41 (1)	22 (1)	19 (1)
Implantable cardioverter-defibrillator (%)		62 (2)	44 (2)	18 (1)

Gender comparison

47% of patients diagnosed with HCM were female. Female patients were in general older (median age 72 years [IQR 62, 81] vs. 63 years [52, 74]) than their male counterparts and their type of HCM was more likely to be classified as obstructive (54% vs. 38%). Regarding concurrent comorbidity, both groups were comparable, although hypertension was more commonly associated with female gender (56% vs. 46%) and AF with males (15% vs. 19%). At time of diagnosis, female patients received more treatment with beta-blockers (40% vs. 34%), CCB (31% vs. 23%) and loop diuretics (25% vs. 19%) (Table 1).

Time trends

Between 2005 and 2018, the number of patients diagnosed with HCM increased steadily from 207 to 256 annually, with a maximum of 361 patients diagnosed in 2012 (**Figure 1, Supplementary Table 3**). In the context of the Danish population for each year, these numbers correspond to a rise in incidence of 3.1 per 100,000 people in 2005 to 4.4 newly diagnosed HCM patients per 100,000 in 2018. In 2012, the year with the highest number of newly detected patients, the yearly incidence estimates 6.4/100,000 (Supplementary Table 3).

The number of patients classified as having an obstructive HCM type decreased from 58% in 2005 to 40% in 2018 (p-value < 0.001, Figure 1).

Furthermore, there was a decreasing proportion of patients with prevalent IHD (31% in 2005 to 16% in 2018, p-value < 0.001 for time trends), HF (20% in 2005 to 12% in 2018, p-value < 0.001 for time trends), and COPD (9% in 2005 to 7% in 2018, p-value 0.04 for time trends). Though, prevalent hypertension, AF, and stroke remained high and unchanged (Supplementary Table 3). Analyzing

active pharmacotherapy at inclusion, there was a decrease in loop diuretics (26% in 2005 to 16% in 2018, p-value < 0.001) and ACE inhibitors (from 30% in 2005 to 18% in 2018, p-value <0.001) (**Supplementary Table 4**).

Two-year follow-up of use of concomitant pharmacotherapy and ICD implantations

Up to two years following HCM diagnosis, prescription with beta-blockers increased from 36% of patients at baseline to 63% of all HCM patients, while CCB treatment increased from 26% to 35%. Similarly, treatment with ACE inhibitors rose from 26% to 33%, and loop diuretic use increased from 23% to 35%. OACs were prescribed to 20% of patients two years after diagnosis, an increase from 11% at baseline. While at the time of inclusion, 2% of patients had received an ICD prior to diagnosis with HCM, and two years after diagnosis, 5% of all patients had received an ICD (**Figure 2, Table 2**). While there was a noticeable increase in active pharmacotherapy following HCM diagnosis in all years combined, trend analysis for pharmacotherapy in this follow-up period in year-by-year comparison revealed that the use of ACE inhibitors and loop diuretics decreased from 2004-2016, while there was an increase in the use of OAC in the same period (Figure 2, **Supplementary Table 5**).

Table 2. Analysis of concomitant pharmacotherapy and ICD up to two years after HCM diagnosis in the years 2005 to 2016

	Baseline (2005-2016)	Follow up (2 years)
Number of patients	3266	
Beta-blockers (%)	1183 (36)	2058 (63)
ACE inhibitors (%)	853 (26)	1088 (33)
Oral anticoagulant therapy (%)	364 (11)	663 (20)
Loop diuretics (%)	744 (23)	1133 (35)
Spironolactone (%)	246 (8)	473 (15)
Calcium channel blockers (%)	856 (26)	1129 (35)
Digoxin (%)	177 (5)	215 (7)
Amiodarone (%)	36 (1)	130 (4)
Implantable cardioverter-defibrillator (%)	49 (2)	161 (5)

Resource utilization

Finally, the rate of hospitalizations and outpatient follow-up were analyzed. In the two years following HCM diagnosis, trend analysis revealed a significant fall in hospitalization from 2005 to 2016 (64% in 2005 to 46% in 2016, p-trend = <0.001). During the same time, outpatient follow-up was significantly increased (81% in 2005 to 87% in 2016, p-trend = 0.003) (Figure 2, Supplementary Table 5).

DISCUSSION

Overall, this study identified a large cohort of HCM patients with a steady and consistent yearly increase in detected HCM cases and a decreased morbidity-burden over time. Gender distribution in this cohort revealed a near equal distribution of males and females; however, females were older and more likely to have their type of HCM classified as obstructive at first diagnosis.

While HCM is often thought of as a disease of the young, most epidemiological studies place the typical age of patients at initial HCM diagnosis well over 60 (16–20). This study is no exception, with a median age of 68 years at the time of diagnosis and without major change comparing individual years. While the patients' age remained stable, there was a significant decrease in the prevalence of comorbidities such as HF, IHD, and COPD. Notably, the prevalence of IHD decreased markedly in this study, and this was the case despite the general prevalence of IHD increasing from 1980 to 2009 (21).

Several factors can be attributed to this rise in detection. For one there have been considerable advances in both availability and capability of imaging modalities such as cardiac magnetic resonance imaging and echocardiography. Especially cardiac magnetic resonance imaging has gained a more prominent role in classification of HCM (22, 23).

Further the importance and availability of genetic testing and counseling has only increased over time. An increasing number of genes have been associated with the development of HCM making it possible to classify patients and their relatives with less severe HCM phenotypes more accurately (24, 25). This coupled with the practice of cascade genetic screening can be expected to contribute to the rising number of detected HCM cases.

Lastly advances in the organized management of HCM patients and increased general awareness for rare and genetic diseases cannot be underestimated. The European Society of Cardiology recommended its 2014 guidelines on managing HCM genetic testing patients suspected of HCM (12). In Denmark, this practice is predated by establishing specialized clinics for inherited heart diseases in which clinical and genetic screening are performed based on the first national recommendation for management of inherited heart diseases from 2003. Both factors likely contributed to the rise in detection rate and awareness of HCM in the Danish population.

While the prevalence of cardiovascular comorbidity among the newly diagnosed decreased markedly, this was notably not the case for AF and stroke. There is a well-documented strong association between HCM, AF, and stroke (15,16,26-28), and therefore unsurprising to see a stable prevalence of both conditions, despite a rising detection rate. International guidelines in the treatment of HCM recommend aggressive treatment of AF in the presence of HCM since stroke risk is higher and symptoms of AF can be aggravated in these patients (12–14). The general advances in AF treatment, especially in the context of HCM, were emphasized in the detectable increase of patients in active OAC treatment, both prevalent at baseline and follow-up. In Denmark, a general trend toward increased prescription of OAC in AF patients could previously be detected and attributed to mounting evidence supporting the safety and efficacy of direct oral anticoagulant treatment in this group (29). Looking at the individual temporal trends of warfarin and direct oral anticoagulant treatment in these Danish patients, a clear shift can be detected in which from 2012 onward direct oral anticoagulants increase in usage, while prescriptions of warfarin decline. This was both the case at baseline and follow up analysis and this data is summarized in Supplementary Tables 4 and 5.

The increase in OAC treatment following the years after diagnosis with HCM could be explained by increased awareness of the importance of sufficient anticoagulation within the context of HCM, as highlighted by international guidelines (12,14).

Despite a significant gender gap reported in numerous studies (4-9), showing a lower HCM detection rate in females, the distribution between the genders in this cohort of Danish HCM patients

was near equal. There was a slight majority of male patients (53%) in this cohort, although this difference was far less pronounced than in comparable studies and did not prove statistically significant (17-20). In terms of temporal changes, although in most years, the detection rate of HCM in females was slightly below that of males, the difference was not significant and did not alter over time. Females, however, were older at the diagnosis and more likely to be classified as obstructive. This is consistent with other large studies examining HCM cohorts (17-20). Whether this difference is due to differences in penetrance or bias in screening/referral remains controversial (4-9).

Arguments to support the case for a bias in screening and detection between the genders can be found in this Danish cohort. There was an overweight of AF among males in this HCM cohort. Diagnosis with AF would, in accordance with current guidelines, result in the patient's referral to follow-up, including procedures such as echocardiography, in which previously unknown HCM would be more likely to be detected. With ever-increasing options for screening and follow-up for AF, this or comparable processes with other cardiovascular comorbidities could explain the difference in age and severity between the genders. However, more research is warranted to explain this disparity between the genders in HCM diagnosis sufficiently.

Strengths and limitations

Given the relative rarity of HCM, large nationwide databases are well suited for research on this topic; however, this method is not without limitations. The Danish National Patient Registry and the general completeness of data in the Danish nationwide registries ensure minimal missing data and a complete follow-up (30). The main limitations are all inherent to the observational study design, and the possibility of residual confounding remains. Most notably, the utilized registries do not contain data on echocardiography or genetic testing, which limits the ability of detailed cohort description. HCM diagnosis and type classification (obstructive vs. non-obstructive) is solely based on ICD-10 coding within the registries and hereby judgment of the treating physician. The specific criteria or definition used for HCM in Denmark during the study period were not explicitly stated or standardized. Therefore, with this data we can solely distinguish between obstructive and non-obstructive HCM as classified at time of inclusion. Since diagnosis of HCM can be challenging and easily mistaken for

other conditions presenting with left ventricular hypertrophy, this approach is inherently prone to misdiagnosis and error. This especially applies for patients with hypertension. Prevalence of hypertension in this cohort was high, with 50% opening possibility for misclassification. However, given the low positive predictive value for hypertension within the Danish registries, hypertension was classified as active treatment with two or more antihypertensive pharmaceuticals in this study. This included ACE inhibitors and beta blockers which are often prescribed for HF, AF and other conditions often seen in conjunction with HCM. Therefore, with this method misclassification of hypertension cannot be excluded in this context and the percentage of patients classified as hypertensive might be inflated.

The positive predictive value for HCM within the Danish National Patient Registry, has been shown to be 90% in a study validating a variety of cardiovascular diagnosis within the Danish registries from 2016 (31). This study however only analyzed 20 patients with HCM, possibly necessitating further validation of HCM within the Danish registries. For the purpose of this study the authors have decided to rely on currently available data.

CONCLUSION

This large epidemiological study of Danish HCM patients identified a steady increase in detected HCM patients. The previously described gender gap in HCM detection was less pronounced, with near equal distribution between the genders; however, females were older and more likely to have their type of HCM classified as obstructive at first diagnosis.

COMPETNG INTERESTS

No conflict of interest to declare.

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This project was funded through the Gentofte University Hospital Department of Cardiovascular Research.

DATA AVAILABILITY STATEMENT

Data for this study are derived from and accessed through Statistics Denmark. By law, these data are not allowed to be shared. For this reason, data cannot not be made available to other researchers.

CONTRIBUTORS

Christopher Ryan Zörner MD: study concept and design, data analysis, drafting manuscript. Jannik Pallisgaard: study concept and design, data analysis, critical revision of the manuscript drafts. Anne-Marie Schjerning: study concept and design, critical revision of the manuscript drafts. Morten Kvistholm Jensen: study concept and design, critical revision of the manuscript drafts. Jacob Tønnesen: critical revision of the manuscript drafts. Lise Da Riis-Vestergaard: critical revision of the manuscript drafts. Charlotte Middelfart: critical revision of the manuscript drafts. Peter Vibe Rasmussen: critical revision of the manuscript drafts. Gunnar Gislason: critical revision of the manuscript drafts. Morten Lock Hansen: study concept and design, critical revision of the manuscript drafts.

ETHICS STATEMENT

According to Danish legislation, retrospective studies using administrative health databases do not need ethical approval in Denmark. The Danish Data Protection Agency has approved the use of registry data, and the current project is registered with the responsible data institute (approval number: P-2019-408).

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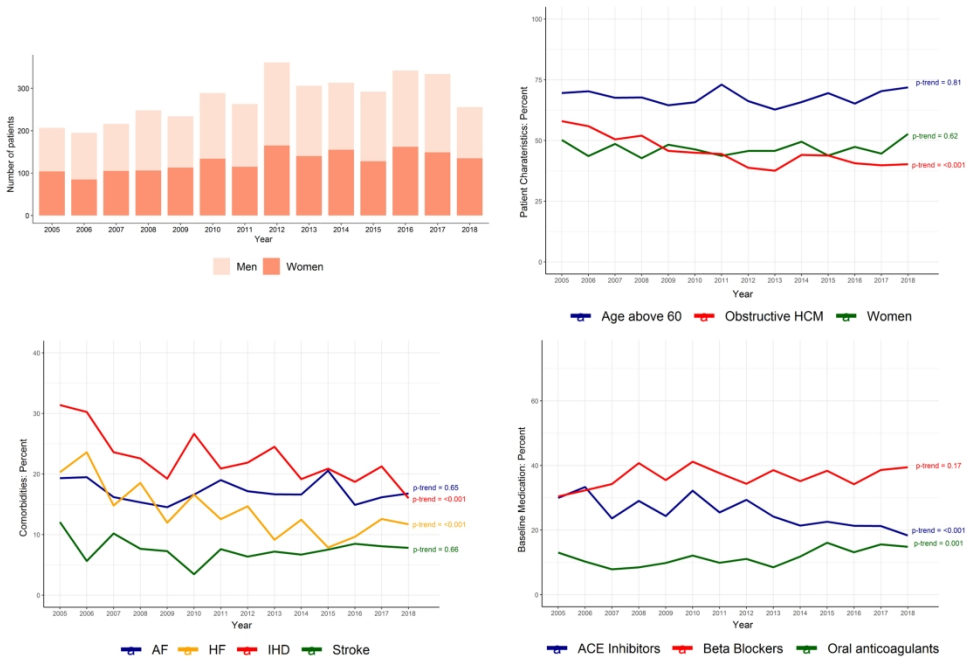
FIGURE TITLES/LEGENDS:

Figure 1. Temporal trends of yearly detection rate, baseline patient characteristics, comorbidities and concomitant pharmacotherapy (2005 to 2018) (scale: 1771 x 1181)

Figure 2. Temporal trends of concomitant pharmacotherapy and resource utilization identified in the follow up period (2005 to 2016) (scale: 1771 x 1181)



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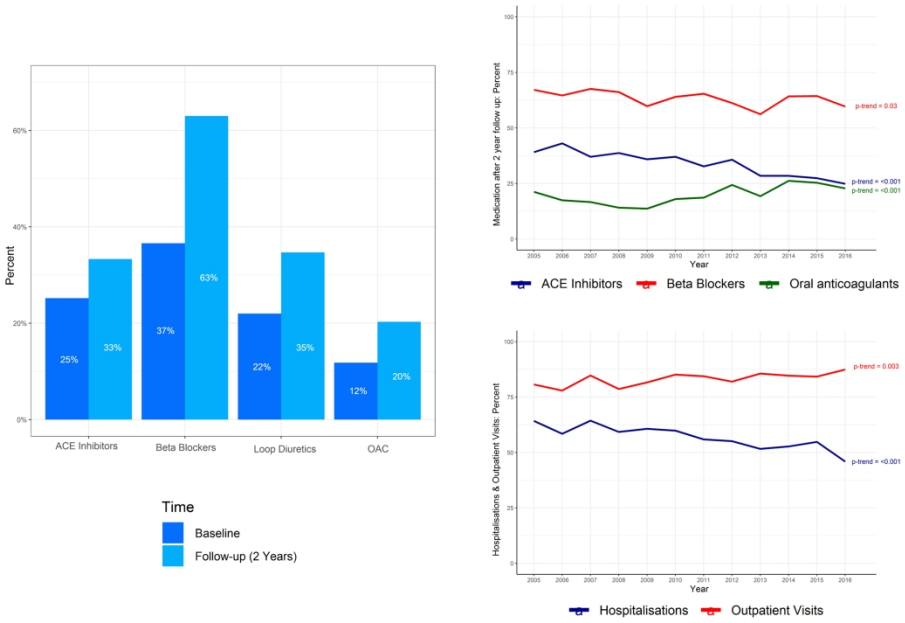

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Supplementary appendix

Supplementary table 1: Diagnostic and procedural codes used to identify comorbidity
Supplementary table 2: ATC-codes used to define medical therapy
Supplementary table 3: Temporal trends of patient characteristics and comorbidities at baseline
Supplementary table 4: Temporal trends of concomitant pharmacotherapy at baseline
Supplementary table 5: Temporal trends of concomitant pharmacotherapy and resource utilization during follow up, up to two years after inclusion (2005-2016).

Supplementary table 1

Diagnostic and procedural codes used to identify comorbidity

Comorbidity	
Atrial fibrillation / Atrial flutter	*ICD-10: I48*
Chronic Obstructive Pulmonary Disease	*ICD-10: J42-J44*
Ischemic heart disease	*ICD-10: I20-I25*
Pacemaker / implantable cardioverter defibrillator	*BFCA0-3, BFCA6, BFCA6, BFCA7, BFCB0, BFCB2, BFCB3, BFCB5, BFCB7, ZZ4050, ZZ4051*
Hypertension	*Treatment with more than one anti-hypertensive medication.*
Congestive heart failure	*ICD-10: I50*
Ischemic stroke / TIA / systemic embolism	*ICD-10: I63, I64, I74, G458, G459*
Chronic Kidney Disease	*ICD-10: N02-N08, N11-N14, N18, N19, N26, N158-N160, N 162, N163, N164, N168, Q61, E102, E112, E132, E142, I120, M321B*

Supplementary table 2: ATC-codes used to define medical therapy

Oral anticoagulatnt treatment (Warfarin, phenprocoumon, dabigatran, rivaroxaban, apixaban, edoxaban)	*ATC-codes: B01AA03, B01AA04, B01AE07, B01AF01, B01AF02, B01AF03*
Beta-blockers	*C07A, C07B, C07C, C07D, C07F*
Calcium channel antagonist	*C08C, C08D, C08E, C08G, C09BB, CO9DB*
Spironolactone	*C03D, C03E, C03EB*
Loop diuretics	*C03C, C03EB*
Non-loop diuretics	*C02L, C02DA, C07D, C09XA52, C03A, C03EA, C03B, C03X, C07C, C08G, C09BA, C09DA, C03D, C03E, C03EB*
ACE inhibitors	*C09A, C09B*
Digoxin	*C01AA*
Amiodarone	*C02BD01*

Supplementary table 3: Temporal trends of patient characteristics and comorbidities at baseline

Year		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P - trend
Number		207	195	216	248	234	289	263	361	306	317	292	342	334	256	
Incidence per 100,000		3.8	3.6	3.9	4.5	4.3	5.3	4.7	6.4	5.5	5.6	5.1	6	5.8	4.4	
Median age [IQR]		67 [57, 78]	69[58, 79]	68 [56, 77]	66[58, 78]	66 [55, 77]	68 [55, 77]	68[59, 78]	66 [56, 77]	67 [53, 78]	68 [58, 78]	69[54, 78]	67[55, 78]	70 [57, 78]	70 [58, 78]	0.56
Gender (%)	Male	103 (50)	110 (56)	111 (51)	142 (57)	121 (52)	155 (54)	148 (56.)	196 (54)	166 (54)	159 (51)	164 (56)	180 (53)	185 (55)	121 (47)	0.62
	Female	104 (50)	85 (43)	105 (49)	106 (42)	113 (48)	134 (46)	115 (44)	165 (46)	140 (46)	158 (50)	128 (44)	162 (47)	149 (45)	135 (53)	
Age (%)	Above or 60	144 (70)	137 (70)	146 (68)	168 (68)	151 (65)	190 (68)	192 (73)	239 (66)	192 (63)	208 (66)	203 (70)	223 (65)	235 (70)	184 (72)	0.81
HCM type (%)	Non-obstructive HCM	87 (42)	86 (44)	107 (49)	119 (48)	127 (54)	159 (55)	146 (56)	221 (61)	191 (62)	177 (60)	164 (56)	203 (59)	201 (60)	153 (60)	<0.001
	Obstructive HCM	120 (58)	109 (56)	109 (51)	129 (52)	107 (46)	130 (45)	117 (45)	140 (39)	115 (38)	139 (44)	128 (44)	139 (41)	133 (40)	103 (40)	
Ischemic heart disease (%)		65 (31)	59 (30)	51 (24)	56 (23)	45 (20)	77 (27)	55 (21)	79 (22)	75 (25)	60 (20)	61 (21)	64 (19)	71 (21)	41 (16)	<0.001
Chronic obstructive pulmonary disease (%)		19 (9)	18 (9)	16 (7)	24 (9)	23 (10)	33 (11)	24 (9)	32 (9)	17 (6)	14 (5)	31 (11)	16 (5)	27 (8)	19 (7)	0.04
Chronic kidney disease (%)		11 (5)	9 (5)	11 (5)	9 (4)	9 (4)	13 (5)	15 (6)	25 (7)	10 (3)	13 (4)	14 (5)	14 (4)	18 (5)	22 (9)	0.3
Hypertension (%)		109 (53)	98 (50)	105 (49)	134 (54)	110 (47)	156 (54)	125 (48)	188 (52)	147 (48)	158 (50)	151 (52)	155 (45)	171 (51)	136 (53)	0.6
Heart Failure (%)		42 (20)	46 (24)	32 (15)	46 (19)	28 (12)	48 (17)	33 (13)	53 (13)	28 (9)	39 (13)	23 (8)	33 (10)	42 (13)	30 (12)	<0.001
Stroke (%)		25 (12)	11 (6)	22 (10)	19 (8)	17 (7)	10 (4)	20 (8)	23 (6)	22 (7)	21 (7)	22 (9)	29 (9)	27 (8)	20 (8)	0.66
Atrial fibrillation (%)		40 (19)	38 (20)	35 (16)	38 (15)	34 (15)	48 (17)	50 (19)	62 (17)	51 (17)	52 (17)	60 (21)	51 (15)	54 (16)	43 (17)	0.65

Supplementary table 4: Temporal trends of concomitant pharmacotherapy at baseline

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P - trend
Number	207	195	216	248	234	289	263	361	306	313	295	342	334	256	
Beta-blockers (%)	63 (30)	63 (32)	74 (34)	101 (41)	83 (36)	119 (41)	99 (38)	124 (34)	118 (39)	110 (35)	113 (38)	117 (34)	129 (39)	101 (40)	0.17
Oral anticoagulant therapy, all (%)	27 (13)	20 (10)	17 (8)	21 (9)	23 (10)	35 (12)	26 (10)	40 (11)	26 (9)	37 (12)	47 (16)	45 (13)	52 (16)	38 (15)	0.01
Warfarin (%)	0	0	0	0	0	0	0	8 (2)	5 (2)	12 (4)	25 (8)	25 (7)	34 (10)	29 (11)	<0.001
Direct-acting oral anticoagulants (%)	26 (13)	20 (10)	17 (8)	20 (8)	23 (10)	35 (12)	25 (10)	35 (10)	22 (7)	27 (9)	23 (8)	19 (6)	21 (6)	9 (4)	0.01
Calcium channel blockers (%)	53 (26)	39 (20)	51 (24)	63 (25)	53 (23)	85 (29)	56 (21)	102 (28)	97 (32)	89 (28)	91 (31)	77 (23)	97 (29)	70 (27)	0.03
Spironolactone (%)	28 (14)	19 (10)	21 (10)	15 (6)	16 (7)	23 (8)	20 (8)	23 (6)	13 (4)	29 (9)	14 (5)	25 (7)	23 (7)	24 (9)	0.04
Loop Diuretics (%)	53 (26)	53 (27)	57 (26)	65 (26)	46 (20)	74 (26)	62 (24)	84 (23)	57 (19)	76 (24)	57 (20)	60 (18)	62 (19)	41 (16)	<0.001
Digoxin (%)	18 (9)	20 (10)	13 (6)	13 (5)	20 (9)	20 (7)	17 (7)	14 (4)	14 (5)	8 (3)	11 (4)	9 (3)	12 (4)	9 (4)	<0.001
Amiodarone (%)	6 (3)	<3	<3	4 (2)	3 (1)	<3	4 (2)	<3	<3	5 (2)	3 (1)	<3	3 (1)	<3	0.1
ACE inhibitors (%)	62 (30)	65 (33)	51 (24)	72 (29)	57 (24)	93 (32)	67 (26)	106 (29)	74 (24)	67 (21)	66 (23)	73 (21)	71 (21)	47 (18)	<0.001
Implantable cardioverter-defibrillator (%)	3 (1)	5 (3)	<3	4 (2)	6 (3)	5 (2)	6 (2)	5 (1)	<3 (1)	4 (1)	4 (1)	4 (1)	7 (2)	6 (2)	0.98

Supplementary table 5: Temporal trends of concomitant pharmacotherapy and resource utilization during follow up, up to two years after inclusion (2005-2016).

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	P -trend
Number	207	195	216	248	234	289	263	361	306	342	292	342	
Beta-blockers (%)	139 (67)	126 (65)	146 (68)	164 (66)	140 (60)	185 (64)	172 (65)	221 (61)	172 (56)	204 (60)	188 (64)	204 (60)	0.03
Calcium channel blockers (%)	77 (37)	65 (33)	72 (33)	82 (33)	83 (36)	102 (35)	73 (28)	136 (38)	101 (33)	132 (39)	116 (40)	104 (30)	0.87
Oral Anticoagulant therapy (%)	44 (21)	34 (17)	36 (17)	35 (14)	32 (14)	52 (18)	49 (19)	88 (24)	59 (19)	82 (24)	74 (25)	78 (23)	<0.001
Warfarin (%)	43 (21)	33 (17)	35 (16)	34 (14)	32 (14)	50 (17)	41 (14)	66 (18)	43 (16)	48 (14)	33 (11)	23 (8)	<0.001
Direct-acting oral anticoagulants (%)	0	0	<3	<3	0	3 (1)	11 (4)	32 (9)	23 (8)	43 (13)	49 (17)	55 (16)	0.001
Spironolactone (%)	38 (18)	32 (16)	36 (17)	42 (17)	30 (13)	39 (14)	39 (15)	51 (14)	34 (11)	54 (16)	37 (13)	41 (12)	0.02
Loop Diuretics (%)	85 (41)	77 (39)	90 (42)	94 (38)	71 (30)	111 (38)	89 (34)	141 (39)	86 (28)	115 (34)	83 (28)	91 (27)	<0.001
ACE inhibitors (%)	81 (39)	84 (43)	80 (37)	96 (39)	84 (36)	107 (37)	86 (33)	129 (36)	87 (28)	89 (26)	80 (27)	85 (25)	<0.001
Digoxin (%)	20 (10)	24 (12)	20 (9)	16 (7)	22 (9)	15 (5)	20 (8)	30 (8)	14 (5)	12 (4)	11 (4)	12 (4)	<0.001
Amiodarone (%)	15 (7)	6 (3)	9 (4)	9 (4)	9 (4)	8 (3)	14 (5)	15 (4)	14 (5)	19 (6)	9 (3)	6 (2)	0.11
Implantable cardioverter-defibrillator (%)	6 (3)	9 (5)	8 (4)	19 (8)	10 (4)	18 (6)	27 (10)	15 (4)	16 (5)	12 (4)	9 (3)	12 (4)	0.34
Hospitalizations (%)	133 (64)	114 (59)	139 (64)	147 (59)	142 (61)	173 (60)	147 (60)	199 (55)	158 (52)	165 (53)	160 (55)	157 (46)	<0.001
Outpatient Visits (%)	167 (81)	152 (78)	183 (85)	195 (79)	191 (82)	246 (85)	222 (84)	296 (82)	262 (85)	265 (85)	246 (84)	299 (87)	0.003

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 -2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.