Epidemiology of cardiomyopathies and incident heart failure in a population-based cohort study

Jack RW Brownrigg MD PhD[1], Vincenzo Leo PhD[1], Joel Rose[2], Eric Low[3], Sarah Richard[3], Gerry Carr-White MD PhD[4], Perry M Elliott MD FRCP[5]

(1) Pfizer, Surrey, United Kingdom

(2) Cardiomyopathy UK, Chesham, United Kingdom

(3) Amyloidosis Research Consortium, Edinburgh, United Kingdom

(4) St Thomas' Hospital, London, United Kingdom

(5) University College London & St Bartholomew's Hospital, London, United Kingdom

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Address for correspondence: Perry Elliott

Institute of Cardiovascular Science

University College London

Paul O'Gorman Building

72 Huntley Street

London

WC1E 6AG

United Kingdom

Email: Perry.Elliott@ucl.ac.uk

Tel: 0044 (0)207 6796500

Abstract

Aims: The population prevalence of cardiomyopathies and the natural history of symptomatic heart failure (HF) and arrhythmia across cardiomyopathy phenotypes is poorly understood. Study aims were to estimate the population diagnosed prevalence of cardiomyopathies and describe the temporal relationship between a diagnosis of cardiomyopathy with HF and arrhythmia.

Methods: People with cardiomyopathy (n=4116) were identified from linked electronic health records (~9 million individuals; 2000-2018) and categorised into hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM) and cardiac amyloidosis (CA). Cardiomyopathy point prevalence, rates of symptomatic HF and arrhythmia, and timing relative to a diagnosis of cardiomyopathy were determined.

Results: In 2018, DCM was the most common cardiomyopathy. DCM and HCM were twice as common among men, with the reverse trend for ARVC. Between 2010 and 2018, prevalence increased for ARVC by 180% and HCM by 9%. At diagnosis, more patients with CA (57%), DCM (48%) and RCM (44%) had pre-existing HF compared to ARVC (31%) and HCM (19%). Among those free of HF at diagnosis of cardiomyopathy, annualised HF incidence was greatest in CA and DCM. Diagnoses of all cardiomyopathies clustered around the time of HF onset.

Conclusions

The recorded prevalence of all cardiomyopathies increased over the past decade. Recognition of CA is generally preceded by HF whereas individuals with ARVC or HCM more often developed HF after their cardiomyopathy diagnosis suggesting a more indolent course or better asymptomatic recognition. The clustering of HF and cardiomyopathy diagnoses suggests opportunities for pre-symptomatic or earlier diagnosis

What is already known on this topic

- Cardiomyopathies are under-recognised, and diagnoses are often delayed.
- Cardiomyopathies frequently cause heart failure and arrhythmia, yet the natural history of incident events is poorly understood.

What this study adds

- The study indicates differences in the natural history of incident heart failure and arrhythmia across cardiomyopathy phenotypes. Hypertrophic cardiomyopathy is generally recognised before the onset of heart failure and arrhythmia whereas arrhythmogenic right ventricular cardiomyopathy and cardiac amyloidosis are diagnosed later. Cardiomyopathy diagnoses for all phenotypes clustered around the time of onset of HF and arrhythmia.
- A significant increase in the prevalence of ARVC was observed during the past decade, particularly among women.

How might this impact on clinical practice

- Improved understanding of the epidemiology of cardiomyopathies and heart failure will guide rational selection of diagnostic tests in heart failure services and accelerate the recognition of underlying causes of heart failure.
- Further studies are warranted to better understand the reasons underlying the observed recent increase in diagnosed ARVC, particularly among women in whom diagnoses increased four-fold during the past decade.

Abbreviations

AL	light chain
ARVC	arrhythmogenic right ventricular cardiomyopathy
ATTR-CM	transthyretin amyloid cardiomyopathy

CA	cardiac amyloidosis
CAD	Coronary artery disease
CPRD	Clinical Practice Research Datalink
DCM	dilated cardiomyopathy
HER	electronic health record
HCM	hypertrophic cardiomyopathy
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with preserved ejection fraction
ICD-10	International Classification of Diseases version 10
ONS	Office for National Statistics
OPCS-4	Operating Procedure Codes version 4
RCM	restrictive cardiomyopathy

Introduction

Cardiomyopathies are disorders defined by structural and functional abnormalities of the ventricular myocardium that are unexplained solely by coronary artery disease (CAD) or abnormal loading conditions. Patients with cardiomyopathy can present with symptoms of heart failure (HF), arrhythmia, syncope, chest pain, and even sudden cardiac death (SCD). In the long-term patients experience premature mortality yet cardiomyopathies remain under-recognised, and diagnoses are often delayed.[1,2]

Cardiomyopathies frequently cause HF and arrhythmia, yet little is known about the natural history of these conditions across the spectrum of cardiomyopathy phenotypes. The timelines to the onset of HF are thought to vary among cardiomyopathies;[3] however, observational data suggest it often precedes diagnosis of the underlying cardiomyopathy.[4-6] Accordingly, improved understanding of the natural history of each cardiomyopathy subtype will help guide rational selection of diagnostic tests and increase diagnostic accuracy. Furthermore, earlier recognition of underlying causes of HF may assist in prevention of downstream complications, better targeting of treatment and improved classification of HF populations to inform trial design and enrolment.

Our objectives were to estimate the prevalence of cardiomyopathy phenotypes and describe the temporal relationship between each specific cardiomyopathy diagnosis with symptomatic HF and arrhythmia.

Methods

Study design and data sources

This population-based cohort study used the Clinical Practice Research Datalink (CPRD), a research database that includes a representative sample of the UK population[7,8] which has been validated for use in epidemiology research of HF and hypertrophic cardiomyopathy.[9-11] CPRD contains anonymised electronic health records (EHRs) with information on clinical diagnoses, laboratory tests, and prescription data coded with the Read clinical terminology

system that is used in UK primary care. We used data from GP practices in England that consented to data linkage with Hospital Episodes Statistics (HES), providing information on every hospital admission, including diagnoses recorded with the International Classification of Diseases 10th revision (ICD-10) codes. The STROBE checklist[12] is shown in online supplemental Table 1.

Study population

The data extract included patients ≥18 years of age on 1 January 2000 (study start). The follow-up period extended to 31 March 2019, the date of patient transfer from an included practice, or death. Individuals with cardiomyopathy were classified by a specific diagnostic code for one of the phenotypes described in the classification scheme of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease, with no contradictory code describing another cardiomyopathy phenotype.[13] We were unable to validate the diagnoses recorded in the EHR due to data anonymisation; however, code lists used to classify cardiomyopathieswere developed from established criteria where available[9] or using published guidance (online supplemental Table 2).[14,15] Data from contributing practices are accepted in CPRD only when they meet standards of data completeness, and at the patient-level data are labelled as acceptable for research through an algorithmic process that excludes patients with noncontinuous follow-up or poor data according to a predefined list of quality metrics.

Cardiomyopathies were grouped into the following morphological and functional phenotypes: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and restrictive cardiomyopathy (RCM). An additional subtype of cardiac amyloidosis (CA) included individuals with light chain (AL) amyloidosis or transthyretin amyloid cardiomyopathy (ATTR-CM) and was reported separately in light of recent evidence suggesting relatively high prevalence among people with HF and preserved ejection fraction (HFpEF) and HCM.[2,16] When a diagnostic code specific to CA was present,

contradictory codes suggesting another cardiomyopathy were discounted given the aetiological diagnosis of CA. A random sample of one million patients ≥30 years of age at the study start provided a control group of patients with HF attributed to aetiologies other than cardiomyopathy.

Study approval was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol number 19_013RMn).

Definition of baseline characteristics

Comorbidities were defined using algorithms combining Read, ICD-10, drug, and Operating Procedure Codes (OPCS-4) across linked primary and secondary care data. We used phenotyping algorithms that follow CALIBER (CArdiovascular disease research using LInked Bespoke studies and Electronic health Records) guidelines, including those for valvular heart disease, CAD and hypertension (www.caliberresearch.org/portal/phenotypes). Baseline characteristics were defined as those recorded before a diagnosis of cardiomyopathy with numerical data derived from the nearest value recorded before a diagnosis. Medication use at baseline was noted for prescriptions in the 6 months preceding diagnosis.

Statistical analyses

An index date at first diagnosis of HF and arrhythmia was determined and the time from/to first diagnosis of cardiomyopathy calculated relative to the index date. Individual timelines to a diagnosis of cardiomyopathy from the onset of HF and arrhythmia were plotted alongside the standard deviation for the overall population. Event rates for HF and arrhythmia among individuals free of each at cardiomyopathy diagnosis were calculated as the number of events divided by the person-years of follow-up and expressed per 1000 person-years.

Point prevalence was estimated for each cardiomyopathy subtype for consecutive years throughout the study period. Our inclusion criteria specified individuals ≥18 years of age at the study start (2000) which meant the denominator population were ≥36 years of age at the

study end (2018). For consistency all our prevalence estimates therefore reflect a denominator population aged ≥36years. To align with Office of National Statistics (ONS) estimates which are applied mid-year, cases were removed if they died or left the practice prior to the index date of 30th June in each year. Population estimates were derived from the number of active prevalent cases in each year (numerator) and denominators counts (by age and sex) for the entire CPRD population in the corresponding year. We then used ONS estimates of the size of the UK population by single year of age and sex to scale the ratio of the CPRD population to estimate population prevalence for each cardiomyopathy subtype. Data were analysed using R version 2.15.2.

Results

Patient characteristics

We categorised 4116 patients with cardiomyopathy (17,348 person-years of follow-up) and excluded 122 individuals with contradictory codes allocating them to >1 cardiomyopathy subtype (Figure 1). Compared with other cardiomyopathy subtypes, individuals with ARVC were younger at diagnosis and mostly female whereas those with CA were older and predominantly male (Table 1). Non-cardiac comorbidities were found at higher rates among people with RCM and CA compared to other cardiomyopathy phenotypes, which may reflect their more elderly populations (Online supplemental Figure 1). The use of blood pressure lowering medication was comparable across cardiomyopathy subtypes except for CA where use of both beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was higher (Table 1).

Compared with individuals with HF not attributed to cardiomyopathy, those with cardiomyopathy at diagnosis of HF were younger and more likely to be male, with lower blood pressure despite lower use of antihypertensives (online supplemental Table 3). The prevalence of CAD and atrial fibrillation were higher among those with cardiomyopathy. We

also observed higher rates of pacemaker and implantable cardiac defibrillator implantation in all cardiomyopathy cohorts at diagnosis relative to the general HF population.

Prevalence of cardiomyopathies

Table 2 shows the diagnosed prevalence of cardiomyopathy phenotypes in 2018. DCM was the most common among women and men with 2.7 and 5.9 cases per 10,000 population, respectively. The 2-fold greater prevalence among men was consistent across DCM and HCM; however, the reverse trend was observed for ARVC, found in 1.9 per 10,000 women and 1.0 per 10,000 men.

Compared with 2010, data for 2018 (Figure 2 and online supplemental Figures 2 and 3) show a significant increase in ARVC prevalence among women from 0.5 to 1.9 per 10,000. Prevalence of DCM fell between 2010 and 2018 (5.7 and 4.3 per 10,000 respectively), whereas the recording of HCM increased by 9%, primarily driven by men.

Natural history of heart failure and arrhythmia in cardiomyopathies

At the time of first diagnosis of cardiomyopathy, more patients with CA (56.9%) had pre-existing HF compared to ARVC (47.9%), DCM (47.9%), HCM (18.9%) and RCM (43.9%). Pre-existing arrhythmia at diagnosis of cardiomyopathy was most common in RCM and CA and lowest in HCM.

Figures 3 and 4 show the temporal relation between onset of symptomatic HF or arrhythmia and first diagnosis of cardiomyopathy where patients experienced both during the study period. A diagnosis of HCM and DCM were recorded earliest at a mean -1.7 years (SE 0.2) and -0.2 years (SE 0.1) relative to the onset of symptomatic HF, respectively. The same pattern was observed relative to the onset of arrhythmia where HCM and DCM were diagnosed earliest.

Annualised event rates for symptomatic HF and arrhythmia among individuals free of each at diagnosis of cardiomyopathy are shown in Table 1 and corresponding Kaplan-Meier estimates for cumulative incidence of HF and arrhythmia in Figure 3.

Discussion

This study is the first to report simultaneous population prevalence and natural history data for all types of cardiomyopathies. It provides novel insights into recent changes in diagnosed prevalence of specific cardiomyopathies and differences in characteristics among patients with cardiomyopathy and HF resulting from other aetiologies. Our study found that diagnoses of CA and ARVC rose significantly between 2010 and 2018 by 100% and 180%, respectively. We observed important sex differences in the change in prevalence over time; the increase in CA was driven by men whereas women accounted for most of the increase in ARVC.

An important advance of this study was our ability to interrogate the natural history of HF in cardiomyopathies. EHR algorithms have been extensively applied in CPRD to conduct research in HF, identifying similar patients to traditional HF registries and European EHR cohorts.[10] Most cases of CA in our study were preceded by clinical expression of HF and a significant proportion of those with DCM and RCM also had pre-existing HF at diagnosis. This finding suggests that opportunities exist for earlier diagnosis of cardiomyopathies in HF services. Conversely, most patients with ARVC or HCM developed HF following a cardiomyopathy diagnosis, suggesting these phenotypes may have a more indolent natural history with respect to cardiac function. Alternatively, there may be a bias in our findings (and clinical practice) towards increased and earlier detection in subtypes with a strong genetic predisposition such as HCM or ARVC, resulting from cardiac or genetic screening of asymptomatic relatives.

The clustering of diagnoses we observed for all cardiomyopathy phenotypes around the onset of HF underscores the benefit of adopting a cardiomyopathy-focussed approach in HF clinics. It is possible that recording of incident HF may precede a subsequent diagnosis of cardiomyopathy by weeks to months by virtue of its relative ease of diagnosis. Confirmatory investigations and specialist assessment required for definitive diagnosis of some cardiomyopathy subtypes may occur later in the clinical pathway and in this circumstance, HF may not be a true antecedent of cardiomyopathy. Once diagnosed, a systematic approach to identify the mechanism of HF should combine conventional cardiac assessments with a search for diagnostic clues to guide the use of additional tests including genetic analysis.[17] Given that a large proportion of cardiomyopathies are genetic in origin, an index case should prompt consideration of cardiac screening in 1st-degree relatives where no mutation is identified and predictive genetic testing in 1st-degree relatives where a mutation is identified.[18]

One potential barrier to a specific diagnosis of cardiomyopathy is the long-standing emphasis on left ventricular ejection fraction (LVEF), which does not provide any specific information on causation of HF[18] and promotes a protocol- rather than hypothesis-driven approach, particularly in patients with HFpEF where better biological and phenotypic characterisation has the potential to improve implementation of targeted therapies.[19]

In UK practice, many patients with HFpEF are discharged from specialist care after a single clinic visit in contrast to counterparts with HFrEF who receive routine access to a multidisciplinary service.[20] Given that several cardiomyopathy phenotypes (HCM, RCM, CA) are generally associated with HFpEF and may have tailored treatment options available, further discrimination is imperative in those with clinical suspicion of a heart muscle disorder. It is important to note that DCM typically manifests with HFrEF and these patients will also benefit from early identification and prompt treatment with standard HF therapies such as ACE inhibitors and β blockers. Unexpectedly, we observed the highest use of these therapies in CA which may be explained by the elderly population with a high burden of

arrhythmia, or alternatively by indiscriminate use of secondary prevention despite the absence of direct benefit supporting its use, given that rates of CAD and hypertension were lower than other subtypes.

Consistent with our findings in HF, the highest prevalence of arrhythmia at diagnosis of cardiomyopathy was seen in DCM, CA and RCM. In DCM, first recognition of arrhythmia clustered around the time of diagnosis of cardiomyopathy and >40% of individuals had a pre-existing record of arrhythmia. DCM is known to be associated with an increased risk for cardiac arrhythmias and SCD, requiring surveillance and often device management. The burden of arrhythmia prior to diagnosis of DCM suggests a missed opportunity to manage the risk of potentially life-threatening arrhythmias with an earlier cardiomyopathy diagnosis. This is particularly relevant in genetic subtypes such as Lamin A/C-related DCM where conduction system disease often precedes the development of LV dilatation and dysfunction.[21] Rates of incident arrhythmia after diagnosis of DCM were comparable with those for other cardiomyopathy phenotypes (≈55 per 1000 person years), with the exception of CA where rates were approximately 2-fold higher. Our study confirms others that have reported AF prevalence of ≈20% in HCM patients,[22] however we provide additional insight into the timing of arrhythmia. We observed the diagnosis of HCM precedes the development of arrhythmia in most patients, although 20% of those free of arrhythmia at diagnosis will still go on to develop arrhythmia within 5-years of diagnosis. This underscores the need for routine evaluation of arrhythmias given their prognostic significance in HCM.[22]A comparison of our diagnosed prevalence findings with screening studies suggests they may be underestimates of overall prevalence. Our estimates reflect the disease population with symptoms interacting with the healthcare service so will inevitably be smaller than those derived from population screening that includes asymptomatic individuals. Our prevalence estimate for HCM (3.5 in 10,000) is comparable with another UK population study,[9] however it falls short of those from dedicated screening studies such as CARDIA (Coronary Artery Risk Development in Young Adults) where HCM was reported in 17 per 10,000.[23] The latter

enrolled fit young adults, whereas this study captures individuals who, for whatever reason, have encountered the healthcare system. We observed an increase in HCM diagnoses over time, primarily driven by men. This could be due to under-recognition of early, familial disease that has been partly addressed by greater uptake of genetic counselling and testing in recent years.

Prevalence of DCM in the general population is poorly defined. Clinically expressed DCM was found in 3.7 per 10,000 in the Rochester Epidemiology Project which is lower than our estimate of 4.3.[24] Our study reflects a more contemporary cohort as the Rochester study examined healthcare records between 1975 and 1984. Other DCM screening studies have been limited to those investigating familial DCM in relatives of affected individuals and are not comparable to our population estimates of all recorded DCM (familial and non-familial) given the familial type accounts for only a proportion (20% to 80%) of overall cases.[25]

We observed a significant rise in the diagnosis of ARVC during the observation period, particularly among women. Specific diagnostic imaging parameters introduced by the Task Force Criteria in 2010,[26] and expanded use of cardiac magnetic resonance (CMR) may have resulted in an increase in overall detection and this trend is consistent with other observational reports.[27] The reasons behind sex differences observed in our study are unclear although it is possible that survival bias is a contributory factor and that women have hitherto been underrepresented in reports. Studies conducted in Europe suggest a male predominance; however, those from the United States report more comparable estimates across women and men.[28] Interestingly, in large population genotyping studies examining ARVC-associated variants, a relative underrepresentation of males suggests a potential mismatch between genetic epidemiology and cases ascertained using diagnostic criteria in previous reports.[29]

We found an unexpectedly high burden of CAD among individuals with cardiomyopathy relative to those with HF attributed to causes other than cardiomyopathy. Other EHR studies

in cardiomyopathy have also reported excess rates of myocardial infraction and coronary revascularisation compared to population controls.[9] For CAD it is possible that information recorded in the EHR may result from misdiagnosis in patients with elevated serum troponin levels or ischaemic-type pain in the presence of angiographically normal coronary arteries.[30] Verifying the burden of CAD in cardiomyopathy subtypes warrants further investigation in prospective studies.

Study limitations

Limitations of the study include our reliance on comprehensive code lists for identifying individuals with cardiomyopathy. A lack of corroborative imaging data or genetic testing are inherent limitations in EHRs. Despite this, a diagnosis of a cardiomyopathy subtype is sufficiently specific that it is likely only used where there is a confirmed diagnosis. Consistent with a previous study that sought to validate an algorithm to identify HCM cases in CPRD,[9] we observed high rates of pre-existing and incident HF and arrhythmias in patients with cardiomyopathy, providing indirect evidence of the validity of our code lists. We were unable to sub-classify cardiomyopathies into familial and non-familial forms and our estimates therefore pool patients within each morphological and functional phenotype. Our data were subject to limitations in the amount of clinical detail recorded in administrative population datasets such as the CPRD, which offer the benefit of large cohorts at the expense of granularity common to bespoke epidemiological studies. In this regard, the indication for overlapping medicines used in both blood pressure and HF management were not available and would have allowed us to comment on adequacy of guideline-directed medical therapy. New York Heart Association classification and LVEF were not available meaning that it was not possible to identify the severity or type of HF. The difficulty with which the diagnosis of a particular cardiomyopathy is made could bias our estimates of prevalence and the analysis of the timing of cardiomyopathy diagnosis relative to incident HF, and it was not possible to adjust for this confounder. Finally, ethical approval for mortality outcomes analyses was not sought which precluded reporting on SCD and a competing risks analysis for cumulative

incidence of HF and arrhythmia. Our Kaplan-Meier function for onset of symptomatic HF and arrhythmia could therefore result in estimates of incidence that are biased upward.

Conclusions

This population study characterises the prevalence of five cardiomyopathy phenotypes, the most common of which are HCM and DCM. HF and arrhythmia are more prevalent at diagnosis in CA, DCM, and RCM than in ARVC or HCM. Incident HF after diagnosis of cardiomyopathy is also highest in CA, DCM, and RCM, suggesting a more aggressive course of cardiac dysfunction. The temporal clustering of HF and cardiomyopathy diagnoses suggests a need for greater awareness of specific aetiologies of HF in routine practice and opportunities for pre-symptomatic diagnosis.

Author contribution*:* JB is the guarantor of the study, had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors
Acquisition, analysis, or interpretation of data: All authors
Drafting of the manuscript: Brownrigg, Elliott
Critical revision of manuscript for important intellectual content: All authors
Statistical analysis: Brownrigg, Hurst, Mason
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Patient involvement: Representatives from two patient organisations (Cardiomyopathy UK, Amyloidosis Research Consortium) were members of the study steering committee and participated in developing the design of the study, interpretation of results and drafting the manuscript.

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Table 1. Clinical characteristics of patients with cardiomyopathy

	DCM n=1,840	ARVC n=726	p value †	CA n=123	p value †	HCM n=1,320	p value †	RCM n=107	p value †
Women	582 (31.6)	457 (62.9)	<0.001	31 (25.2)	0.165	502 (38.0)	<0.001	48 (44.9)	0.006
Age, years (SD)	60.4 (13.9)	60.2 (15.8)	0.746	74.0 (11.3)	<0.001	61.2 (14.6)	0.139	68.7 (14.7)	<0.001
Known ethnicity= White	383 (48.9)	126 (45.3)	0.337	20 (41.7)	0.409	251 (47.1)	0.553	17 (43.6)	0.628
Ethnicity missing	1,057 (57.4)	448 (61.7)	0.054	75 (61.0)	0.501	787 (59.6)	0.235	68 (63.6)	0.253
BMI, kg/m^2 (SD)	28.9 (6.2)	26.7 (5.7)	<0.001	25.4 (3.9)	<0.001	28.3 (5.8)	0.012	28.3 (6.7)	0.437
BMI missing	301 (16.4)	177 (24.4)	<0.001	11 (8.9)	0.04	281 (21.3)	<0.001	26 (24.3)	0.045
Systolic BP, mm Hg (SD)	124.1 (18.9)	129.3 (20.0)	<0.001	119.4 (16.9)	0.007	132.7 (18.2)	<0.001	123.8 (18.2)	0.9
Diastolic BP, mm Hg (SD)	76.0 (12.9)	76.2 (11.5)	0.789	71.1 (8.7)	<0.001	76.6 (11.1)	0.34	73.8 (12.1)	0.169
BP missing	653 (35.5)	399 (55.0)	<0.001	13 (10.6)	<0.001	581 (44.0)	<0.001	50 (46.7)	0.024
Comorbidities									
Atrial Fibrillation	759 (41.2)	195 (26.9)	<0.001	63 (51.2)	0.038	345 (26.1)	<0.001	66 (61.7)	<0.001
Coronary Artery Disease	615 (33.4)	247 (34.0)	0.808	27 (22.0)	0.012	399 (30.2)	0.063	50 (46.7)	0.007
Chronic Kidney Disease	473 (25.7)	149 (20.5)	0.007	57 (46.3)	<0.001	290 (22.0)	0.017	49 (45.8)	<0.001
COPD	363 (19.7)	125 (17.2)	0.16	25 (20.3)	0.965	217 (16.4)	0.021	21 (19.6)	1
Diabetes	330 (17.9)	93 (12.8)	0.002	16 (13.0)	0.205	220 (16.7)	0.379	20 (18.7)	0.945
Hypertension	951 (51.7)	351 (48.3)	0.139	57 (46.3)	0.292	708 (53.6)	0.295	76 (71.0)	<0.001
ICD	211 (11.5)	91 (12.5)	0.492	7 (5.7)	0.068	70 (5.3)	<0.001	24 (22.4)	0.001
Malignancy	132 (7.2)	38 (5.2)	0.091	22 (17.9)	<0.001	74 (5.6)	0.091	11 (10.3)	0.314
Pacemaker	258 (14.0)	100 (13.8)	0.92	17 (13.8)	1	96 (7.3)	<0.001	24 (22.4)	0.024
Valvular Heart Disease	432 (23.5)	151 (20.8)	0.16	21 (17.1)	0.128	224 (17.0)	<0.001	49 (45.8)	<0.001
CV preventive treatment in 3 months before study entry									
ACEI/ARB	911 (49.5)	161 (22.2)	<0.001	64 (52.0)	0.654	344 (26.1)	<0.001	31 (29.0)	<0.001
Anticoagulants	337 (18.3)	55 (7.6)	<0.001	44 (35.8)	<0.001	102 (7.7)	<0.001	32 (29.9)	0.004

Any BP lowering*	749 (40.7)	120 (16.5)	<0.001	90 (73.2)	<0.001	286 (21.7)	<0.001	45 (42.1)	0.861
Beta-blockers	741 (40.3)	121 (16.7)	<0.001	53 (43.1)	0.602	381 (28.9)	<0.001	32 (29.9)	0.042
Heart failure events									
Pre-existing heart failure at diagnosis of cardiomyopathy	1022 (55.5)	209 (28.8)	<0.001	81 (65.9)	0.066	354 (26.8)	<0.001	66 (61.7)	0.479
No. of symptomatic heart failure after diagnosis	271	64	<0.001	11	0.101	130	<0.001	13	0.553
Symptomatic heart failure rate per 1000 person years	99.8	58.0		114.2		54.1		59.6	
Arrhythmia events									
Pre-existing arrythmia at diagnosis of cardiomyopathy	759 (41.2)	243 (33.5)	<0.001	63 (51.2)	0.034	354 (26.8)	<0.001	66 (61.7)	<0.001
No. of incident arrythmia after diagnosis	170	56	0.25	4	0.036	153	0.036	7	0.441
Incident arrythmia rate per 1000 person years	54.7	53.2		116.2		51.4		54.9	

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARVC: arrhythmogenic right ventricular cardiomyopathy; ATTR-CM: transthyretin amyloid cardiomyopathy; BMI: body mass index; BP: blood pressure; CA: cardiac amyloidosis; CD: cardiac defibrillator; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; HF: heart failure; ICD: implantable cardioverter-defibrillator; RCM: restrictive cardiomyopathy

† Compared with dilated cardiomyopathy referent

* Includes aldosterone antagonists, alpha-1 blockers, potassium sparing diuretics, loop diuretics, thiazides, vasodilators.

Table 2. Estimated point prevalence of cardiomyopathy phenotypes for a population aged ≥36* in 2018

	Estimated prevalent cases in UK			Estimated UK prevalence† per 10,000 population		
	Women	**Men**	**All**	**Women**	**Men**	**All**
ARVC	3,594	1,772	5,365	1.9	1.0	1.4
CA	179	495	674	0.1	0.3	0.2
DCM	5,207	10,528	15,735	2.7	5.9	4.3
HCM	4,435	8,302	12,737	2.3	4.7	3.5
RCM	229	259	488	0.1	0.1	0.1

ARVC: arrhythmogenic right ventricular cardiomyopathy; ATTR-CM: transthyretin amyloid cardiomyopathy; CA: cardiac amyloidosis; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy

* Patient inclusion criteria were defined as patients aged 18 as of 2000-01-01. Prevalence calculated based on eligible active patients as of 2018-06-30 with pre-existing cardiomyopathy. Active defined as patients who had not yet reached follow-up (consisting of earliest of death, 2019-03-31, transfer out of participating practice or practice stopped participating in CPRD).

† UK prevalence within 2018 assessed by scaling up the number of active patients with the condition utilising CPRD denominator data and Office for National Statistics population estimates as of 2018, adjusted by sex and age.

Figure 1. Study flow diagram

ARVC: arrhythmogenic right ventricular cardiomyopathy; CA: cardiac amyloidosis; CPRD: Clinical Practice Research Datalink; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; HF: heart failure; RCM: restrictive cardiomyopathy

Figure 2: Sex based differences in diagnosed prevalence of cardiomyopathies between 2000 and 2018

ARVC: arrhythmogenic right ventricular cardiomyopathy; CA: cardiac amyloidosis; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy

Figure 3: Diagnosis of cardiomyopathies relative to diagnosis of heart failure (n=2221)

ARVC: arrhythmogenic right ventricular cardiomyopathy; CA: cardiac amyloidosis; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy

Figure 4: Diagnosis of cardiomyopathies relative to diagnosis of arrhythmia (n=1870)

ARVC: arrhythmogenic right ventricular cardiomyopathy; CA: cardiac amyloidosis; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy

Figure 5: Onset of symptomatic heart failure among individuals free of heart failure at diagnosis of cardiomyopathy (n=2384)

ARVC: arrhythmogenic right ventricular cardiomyopathy; CA: cardiac amyloidosis; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy; NAR: number at risk.

Individuals were censored at study end defined as the 31 March 2019, the date of patient transfer from an included practice or death.

Figure 6: Onset of arrhythmia among individuals free of arrhythmia at diagnosis of cardiomyopathy (n=2636)

ARVC: arrhythmogenic right ventricular cardiomyopathy; CA: cardiac amyloidosis; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy; NAR: number at risk.

Individuals were censored at study end defined as the 31 March 2019, the date of patient transfer from an included practice or death.