Clinical burden of obstructive hypertrophic cardiomyopathy: insights from a nationwide study in France

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Introduction

- Hypertrophic cardiomyopathy (HCM) is the most commonly inherited cardiovascular disease and is defined by left ventricular hypertrophy not solely explained by abnormal loading conditions. This chronic, progressive myocardial disease occurs as obstructive and nonobstructive subtypes[1,2]
- Past studies have shown high unmet needs of HCM. While previous studies have estimated the global burden of HCM, little is known about obstructive HCM and how the disease and its outcomes differ by New York Heart Association (NYHA) class in France[3,4]
- Studies have shown that obstructive HCM, if not well-controlled, is associated with increased risks of downstream cardiovascular (CV) conditions, symptoms, and impaired quality of life, resulting in substantial economic burden.[1,2,5] The effect of NYHA classes, and related economical burden, have been poorly studied

Objectives

- To describe the clinical and economic burden of obstructive HCM from a nationwide study in France

Methods

Data source

- This study analyzed data from the French National Health Data System (Système National des Données de Santé [SNDS]) belonging to the National Health Insurance (**Figure 1**)
- The SNDS contains individual-level data for health-expenditure billing and reimbursement purposes for outpatient and healthcare facilities (DCIR [outpatient healthcare consumption data]), linked to the hospitalization database (PMSI [hospital discharge database]) with a unique, anonymous identifier, the social security number. Therefore, it encompasses anonymous, individual-level data for all healthcare claims for more than 99% of the population residing in France, regardless of the insurance scheme (i.e. close to 65 million people)[6]

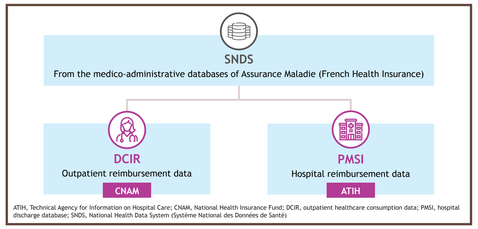
Study population

- All adult patients (≥ 18 years) with at least one hospital stay or long-term disease status (affection longue durée) related to an HCM code (International Classification of Diseases 10th Revision [ICD-10] codes I42.1, I42.2, or I42.9, associated with septal reduction therapy [SRT]) between January 1, 2012, and December 31, 2018, were included (**Figure 2**)
- Obstructive HCM was identified as:
  - at least one diagnosis code for obstructive HCM (ICD-10 I42.1)
  - at least one diagnosis code for HCM (ICD-10 code I42.2 and/or I42.9) and at least one code for SRT
- Patients with less than 1 year of follow-up data available, as well as patients with aortic stenosis, hypertensive heart disease, storage disease, and/or amyloidosis, were excluded
- Patients with obstructive HCM were further divided into subgroups by NYHA class, using a baseline and time-varying proxy algorithm based on treatments and symptoms

Analysis procedure

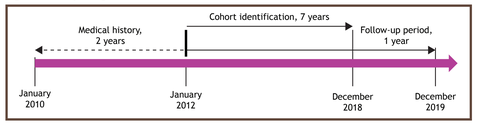
- Baseline patient characteristics, including demographics, comorbidities, and current treatments, were identified
- Health outcomes, healthcare resource utilization, and costs were analyzed for the obstructive HCM study population and the subgroups
- Results were attributed to the subgroup that the patient was in at the time of the documented outcome
- To account for differences in patient follow-up times, costs were annualized based on patient year

Figure 1. SNDS presentation



ATIH, Technical Agency for Information on Hospital Care; CNAM, National Health Insurance Fund; DCIR, outpatient healthcare consumption data; PMSI, hospital discharge database; SNDS, National Health Data System (Système National des Données de Santé)

Figure 2. Study design

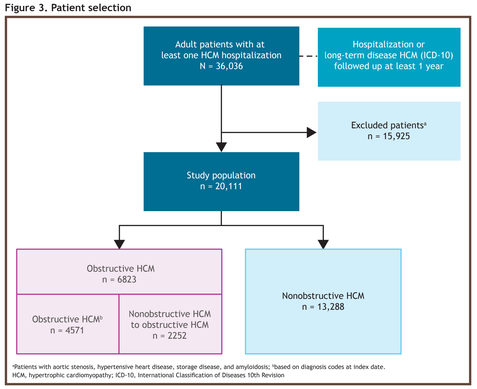


Results

Patient population

- Between 2012 and 2018, 20,111 adult patients met the eligibility criteria (**Figure 3**)
- Overall, there were 6823 patients (34%) with obstructive HCM during the study period; 4571 patients had obstructive HCM as the first HCM diagnosis during the study period, and an additional 2252 patients were initially diagnosed with nonobstructive HCM and were later diagnosed with obstructive HCM
- Of the total obstructive HCM group, 54.7% were male, with a mean (standard deviation [SD]) age of 66.2 (16.7) years, and mean (SD) follow-up of 4.4 (2.5) years (**Table 1**)
- At the index obstructive HCM diagnosis and during the baseline period, patients in higher NYHA classes had greater comorbidity burden based on both a higher Charlson Comorbidity Index score and greater percentage of other CV comorbidities, in particular hypertension, heart failure, and atrial fibrillation/flutter

Figure 3. Patient selection



[a]Patients with aortic stenosis, hypertensive heart disease, storage disease, and amyloidosis; [b]based on diagnosis codes at index date.
HCM, hypertrophic cardiomyopathy; ICD-10, International Classification of Diseases 10th Revision

Table 1. Baseline characteristics[a] by NYHA class for patients with obstructive HCM

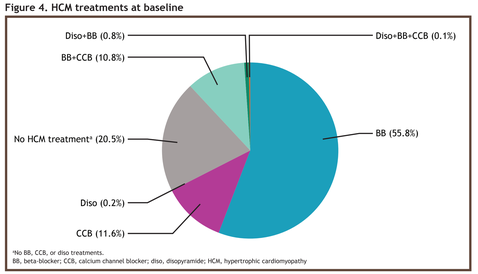
Variable	Total obstructive HCM (N = 6823)	NYHA class I (n = 294)	NYHA class II (n = 2150)	NYHA class III (n = 4102)	NYHA class IV (n = 277)
Male, %	54.7	58.8	60.5	51.1	57.4
Age, years, mean (SD)	66.2 (16.7)	56.9 (21.8)	59.6 (16.8)	70.3 (14.7)	67.2 (15.8)
CCI score, mean (SD)	3.8 (2.3)	2.7 (2.4)	2.8 (2.1)	4.5 (2.2)	4.6 (2.1)
Follow-up duration, years, mean (SD)	4.4 (2.5)	4.6 (2.5)	4.9 (2.5)	4.2 (2.5)	4.2 (2.4)
Comorbidities, devices, and procedures, %					
Atrial fibrillation/flutter	27.5	5.8	12.9	36.0	37.2
Coronary artery disease	17.1	7.1	15.0	18.4	26.0
Conduction disorders[b]	8.7	3.4	6.4	9.8	15.2
Cardiac dysrhythmias[c]	33.6	9.9	20.7	41.3	45.1
Depression	16.0	12.9	15.0	16.9	13.4
Diabetes	19.1	9.5	13.4	22.3	26.7
Hypertension	86.0	21.4	80.9	92.6	96.4
Heart failure	24.5	4.8	9.5	31.2	63.2
Hyperlipidemia	19.5	7.5	17.9	21.0	20.9
Hypercholesterolemia	9.0	3.7	7.4	10.0	11.6
Pacemaker - defibrillator	7.7	7.9	7.5	7.6	9.4
Previous SRT	0.3	0.3	0.3	0.2	0.4
Stroke	6.1	4.8	5.3	6.8	4.7
Myocardial infarction	2.5	2.0	2.2	2.6	3.3
Deep vein thrombosis/ pulmonary embolism	1.8	1.7	1.6	1.9	2.2
Cardiac arrest	0.7	0	0.7	0.6	1.4

[a]Baseline comorbidities were searched 2 years before index date; [b]defined by ICD-10 I44-45, and includes conditions such as atrioventricular block, fascicular block, and bundle-branch block; [c]defined by ICD-10 I46-49, and includes conditions such as cardiac arrest, tachycardia, atrial and ventricular fibrillation, and premature depolarization.
CCI, Charlson Comorbidity Index; HCM, hypertrophic cardiomyopathy; ICD-10, International Classification of Diseases 10th Revision; NYHA, New York Heart Association; SRT, septal reduction therapy

Treatment patterns

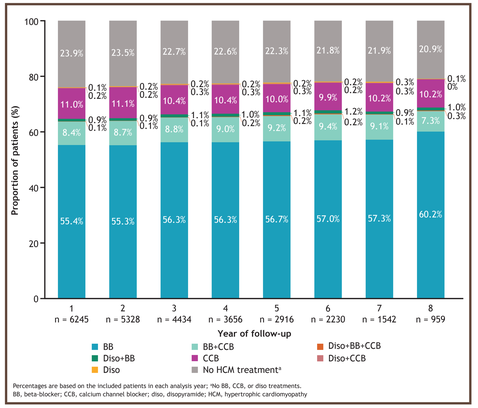
- At baseline, 21% of obstructive HCM patients were not prescribed any HCM-related treatments
- The HCM-related treatments identified at baseline were mainly beta-blockers (56%), calcium channel blockers (12%), or a combination of both (11%) (**Figure 4**)
- During follow-up, few patients switched to other therapies (**Figure 5**)

Figure 4. HCM treatments at baseline



[a]No BB, CCB, or diso treatments.
BB, beta-blocker; CCB, calcium channel blocker; diso, disopyramide; HCM, hypertrophic cardiomyopathy

Figure 5. Evolution of HCM treatments over the study by year of follow-up



Percentages are based on the included patients in each analysis year; [a]No BB, CCB, or diso treatments.
BB, beta-blocker; CCB, calcium channel blocker; diso, disopyramide; HCM, hypertrophic cardiomyopathy

Health outcomes

- NYHA class distribution at baseline was 4%, 32%, 60%, and 4%, for classes I, II, III, and IV, respectively; at the end of follow-up, distribution was, respectively, 2%, 33%, 62%, and 3% (**Table 2**). The majority (73%) of the study patients started and ended the study in the same NYHA class; 13% improved and 14% worsened from their baseline to their end of follow-up. Of the patients who started and ended the study in the same NYHA class, 79% remained in the same NYHA class throughout the study period
- **Table 3** shows the evolution of NYHA class over the years of follow-up throughout the study. Most patients remained in the same NYHA class over time. Among patients who changed NYHA class, they generally transitioned to a higher class or reached the end of their follow-up period
- In general, the risk of CV outcomes increases with higher NYHA classes (**Table 4**)

Table 2. NYHA class at index date and end of follow-up period

		NYHA class at end of follow-up, n				Total, n (%)
		I	II	III	IV	
NYHA class at index date, n	I	141	93	60	0	294 (4)
	II	5	1432	698	15	2150 (32)
	III	7	676	3304	115	4102 (60)
	IV	1	17	189	70	277 (4)
Total, n (%)		154 (2)	2218 (33)	4251 (62)	200 (3)	6823 (100)

NYHA, New York Heart Association

Table 3. NYHA class over the study by year of follow-up

Time since the inclusion, years	Baseline NYHA = class I, n					Baseline NYHA = class II, n				
	Prev. NYHA/Total	I	II	III	IV	Prev. NYHA/Total	I	II	III	IV
0	294	-	-	-	-	2150	-	-	-	-
1	283	283	0	0	0	2002	0	2002	0	0
2	236	184	37	15	0	1767	15	1524	226	2
3	193	130	38	25	0	1531	2	1210	314	5
4	155	79	50	26	0	1323	3	973	344	3
5	124	56	46	22	0	1101	1	754	339	7
6	101	45	41	15	0	859	2	567	284	6
7	75	29	32	14	0	598	0	390	201	7

Time since the inclusion, years	Baseline NYHA = class III, n					Baseline NYHA = class IV, n				
	Prev. NYHA/Total	I	II	III	IV	Prev. NYHA/Total	I	II	III	IV
0	4102	-	-	-	-	277	-	-	-	-
1	3697	0	0	3697	0	262	0	0	0	262
2	3099	7	437	2604	51	214	0	11	123	80
3	2538	3	402	2088	45	161	0	7	104	50
4	2036	1	364	1616	55	129	0	11	86	32
5	1578	2	326	1215	35	105	0	8	72	25
6	1187	0	267	893	27	78	0	9	53	16
7	808	3	178	611	16	57	0	6	39	12

NYHA, New York Heart Association; Prev., previous

Table 4. CV outcomes

Outcome	NYHA class I (PY = 857)		NYHA class II (PY = 11,104)		NYHA class III (PY = 17,484)		NYHA class IV (PY = 783)	
	Events, n	IR[a]	Events, n	IR[a]	Events, n	IR[a]	Events, n	IR[a]
Death[b]	34	3967	344	3098	1452	8305	56	7155
Composite of death or heart transplant	35	4083	351	3161	1516	8671	86	10,967
MACE[c]	72	8400	925	8330	2686	15,362	122	15,587
CV-related hospitalization	654	76,301	9064	81,629	23,692	135,505	2,026	258,845
Any hospitalization	**1520**	**177,335**	**22,425**	**201,955**	**53,690**	**307,078**	**2902**	**370,764**
Heart transplant	1	117	7	63	64	366	30	3833
Heart failure	68	8275	587	5930	4565	34,755	502	126,649
SRT	7	817	281	2531	334	1910	15	1916
ASA	7	817	230	2071	247	1413	8	1022
SM	0	0	51	459	88	503	7	894
Stroke/TIA	32	3733	454	4089	927	5302	50	6388
Atrial fibrillation/flutter	81	9891	1349	13,957	5448	44,497	417	76,809
Pacemaker - defibrillator	74	8633	2430	21,884	6102	34,900	267	34,112
Myocardial infarction	6	700	127	1144	307	1756	16	2044
Ischemic heart disease	59	6883	1328	11,960	3731	21,339	355	45,355

[a]Per 100,000 patient-years; [b]mortality that occurred between index date up to 1 year is not captured; [c]composite of all-cause mortality, myocardial infarction, or stroke.
ASA, alcohol septal ablation; CV, cardiovascular; IR, incidence rate; MACE, major adverse cardiovascular event; NYHA, New York Heart Association; PY, patient-years; SM, surgical septal myectomy; SRT, septal reduction therapy; TIA, transient ischemic attack

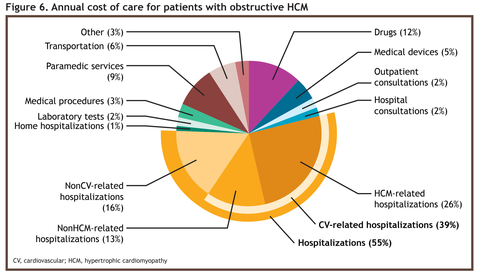
Economic burden

- Among all obstructive HCM patients, total cost for patient management was €386 million, among which 55% was related to hospitalization, 12% to drugs, and 9% to paramedic services (**Figure 6**)
- Average annual costs per patient year gradually increased with increasing NYHA class, from €8881 for class I to €22,818 for class IV (**Table 5**)
- A large part of hospitalization cost was due to CV-related hospitalizations

Limitations

- The study was based on French National Health Database (secondary data), which was originally developed for the reimbursement of healthcare costs. The quality of claims data is dependent on the individual completeness and quality of coding for billing purposes, and on the existing classification systems; therefore, this study has all the limitations of similar studies based on administrative data
- Because only patients with a hospitalization for HCM could be identified, patients with HCM that did not experience a hospitalization are not included. Therefore, results are not representative of all patients with HCM
- NYHA class and symptoms are not coded in the database. A proxy algorithm was developed with expert clinical input and used to assign an NYHA class to each patient. This algorithm should be considered a proxy for actual NYHA class and needs to be validated
- Only patients with at least 1 year of follow-up (and thus still alive at 1 year) were included in this study

Figure 6. Annual cost of care for patients with obstructive HCM



CV, cardiovascular; HCM, hypertrophic cardiomyopathy

Table 5. Annualized cost of care by NYHA class, by utilization category[a]

Cost per PY, €	NYHA class I (PY = 857)	NYHA class II (PY = 11,104)	NYHA class III (PY = 17,484)	NYHA class IV (PY = 783)	Total (PY = 30,228)
Drugs	949	1192	1673	2446	1495
Medical devices	517	402	791	961	645
Outpatient consultations	172	250	340	362	303
Paramedic services	554	597	1423	1255	1091
Hospital consultations	193	264	294	424	283
Hospitalizations	4782	5011	7928	14,746	6944
CV-related hospitalizations	3097	3290	5629	12,764	4883
Including HCM-related hospitalizations	2319	2475	3534	6983	3200
NonCV-related hospitalizations	1685	1721	2299	1982	2061
Home hospitalizations	299	44	65	24	63
Laboratory tests	104	153	277	363	229
Medical procedures	240	365	396	420	381
Transportation	482	597	835	962	741
Other	305	243	366	316	318
All costs	8881	9535	14,658	22,818	12,824

[a]Categories represent all utilization unless otherwise specified.
CV, cardiovascular; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; PY, patient-year

Conclusions

- This is the first nationwide study in France to demonstrate that patients with obstructive HCM have a high clinical and economic burden
- Patients with obstructive HCM in higher NYHA classes have greater risk of CV outcomes, including death, hospitalization, major adverse CV events, heart failure, and other CV conditions
- Similarly, patients in worse NYHA classes also have higher costs of medical care, especially CV-related hospitalizations
- Our results suggest the clinical burden of symptomatic obstructive HCM remains high during follow-up in the context of currently available therapeutics, thus supporting the need for additional treatments

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