Occurrence of Clinically Diagnosed Hypertrophic Cardiomyopathy in the United States

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Hypertrophic cardiomyopathy (HC) is the most common genetic heart disease and an important cause of sudden death and heart failure symptoms. The current prevalence for HC (1:500) is based on echocardiographic population studies in which a substantial proportion of affected subjects have not come to clinical recognition. Therefore, we sought to define the subset of patients with HC who are diagnosed in the US. A proprietary integrated claims database including medical condition *International Classification of Diseases, Ninth Revision* diagnostic codes for over 160 million individual patients in the US was interrogated for 2013 to identify the prevalence of clinically recognized HC. Patients with ≥1 claim for any of the HC *International Classification of Diseases, Ninth Revision* diagnosis codes from January to December 2013 were identified. The combined occurrence rate of HC was stratified by age and gender and multiplied by the 2013 United States population in the same age/gender categories to produce the final projected prevalence. The analysis was performed on 169,089,614 patients, of whom 59,009 unique patients were identified with ≥1 claim for HC. The projected estimated occurrence of diagnosed HC in the US in 2013 was 1:3,195 for a total of 98,958 subjects. Average age at HC diagnosis was in the fifth decade of life, with 43% of the cohort composed of women. In conclusion, leveraging a claims-based data analytic technique, about 100,000 patients are diagnosed clinically with HC in the US, an occurrence which is less than the prevalence reported in systematic population studies based on echocardiographic diagnosis. This observation supports the view that many patients with HC are undiagnosed throughout life and enhances our understanding of the burden of this genetic heart disease on the health care system. **(Am J Cardiol 2016;117:1651 1654)**

Hypertrophic cardiomyopathy (HC) is a common genetically inherited heart disease and represents an important cause of cardiovascular morbidity and mortality in patients of all ages.[1] The prevalence of HC in the general population has been estimated at 1:500, based on numerous epidemiologic studies in the United States (US) and globally, in which unrelated subjects were randomly selected from the general population to undergo echocardiographic evaluation.[2] However, these estimated figures largely represent clinically unrecognized disease in the general population because most patients in these studies were not known to be affected. In addition, most patients with HC never develop (or recognize) cardiovascular symptoms, experience an adverse disease-related event or are identified with another clinical marker (e.g., abnormal electrocardiogram and family history) which could lead to clinical recognition.[3] Thus, we sought to define the subset of patients with HC who are clinically diagnosed (and treated) in the US, with important implications to our understanding of the burden of this disease on the health care system.

Methods

We queried a large proprietary integrated claims database (Symphony Health Solutions [SHS], Phoenix, Arizona), which includes medical condition diagnostic codes (*International Classification of Diseases, Ninth Revision* [ICD-9]) for over 160 million individual patients (>1/2 census population of 316,159,818 in 2013[4]) in the United States. These claims are captured in each of the US states and include all insurance types, including Medicare and Medicaid. The database is composed of electronically submitted private practitioner (Centers for Medicare and Medicaid Services 1500) claims and hospital and facility (uniform bill 04) claims within a given year. The private practitioner claims include diagnostic, therapeutic, and procedure information from over 860,000 practitioners of all medical and surgical specialties, and practices of all sizes. The institutional claims encompass diagnostic, therapeutic, and procedure information, including administered medications, from hospitals and clinics and are inclusive of inpatient and outpatient encounters, including emergency department care.

To identify patients with diagnosed HC, subjects with ≥1 claim for the ICD-9 diagnosis codes for HC (i.e., 425.1, 425.11, 425.18) from January 1, 2013 to December 31, 2013 were searched. To avoid double counting of individual patients, patient-level records from each data source were

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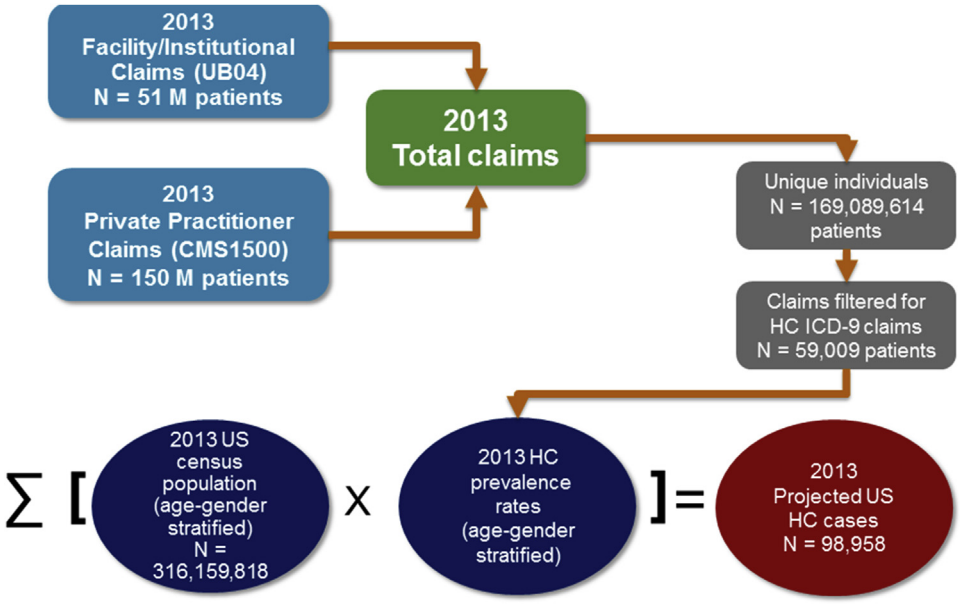

Figure 1. Flow diagram of 2013 claims data analysis. ∑ represents sum of the 2013 US census population stratified by gender and age, multiplied by crude prevalence of HC in respective gender and age matched strata, to generate the final estimated prevalence of diagnosed HC in the US. CMS Centers for Medicare and Medicaid services; UB uniform billing.

linked longitudinally across settings of care through a Health Insurance Portability and Accountability Act-compliant, deidentified unique patient identifier that matched patients using a hash generated from the patient's first name, last name, gender, and date of birth. Because HC is a lifelong condition, period prevalence, which reflects both the incidence and duration of disease, was selected as the most appropriate measure of disease frequency in this analysis. In light of recently published clinical guidelines for HC recommending annual surveillance visits, the period prevalence was defined as the number of individual patients with HC identified during 2013 divided by the total United States population alive at the end of this year (reported as cases per 100,000 subjects).[1,5] Crude prevalence of HC was then stratified by dividing the number of patients with ≥1 HC claim in each age and gender category by the total number of patients in that stratum and then multiplied by the 2013 United States population to produce the final projected estimated prevalence of diagnosed HC.

Results

Over the study period, 169,089,614 unique patients were identified, of which 59,009 had ≥1 HC diagnostic claim (Figure 1). The final occurrence of diagnosed HC in the United States for 2013 was estimated to be 1:3,195. This prevalence estimate yielded a total of 98,958 patients with HC, approximately half of whom are presumed to be symptomatic based on previous large HC cohort studies.[3,6] The average age of HC diagnosis was in the fifth decade of life, with 43% of the HC cohort comprised women. There were no age differences seen across the 3 diagnostic codes, which appeared to be internally consistent (Figure 2).

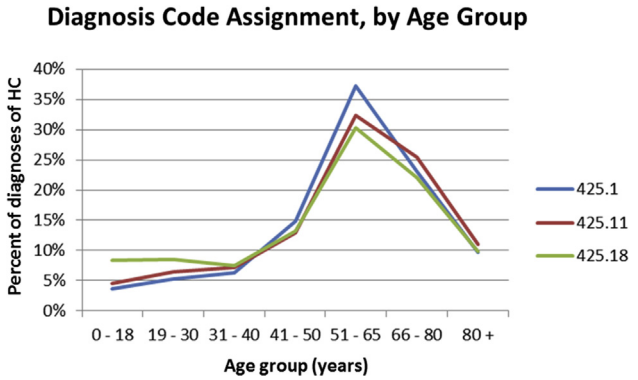

Figure 2. Differences in HC ICD codes by age. ICD 9 code 425.1—HC, 425.11—hypertrophic obstructive cardiomyopathy, 425.18—other HC.

Discussion

Leveraging a claims-based analytic technique, the number of patients with HC in the US is estimated to be about 100,000 patients. This figure represents the first reasonable estimate on which nationwide resource allocation and health care burden related to HC can be evaluated. Of note, although considerable in absolute terms, the frequency with which patients are diagnosed with HC and seek medical care contrasts sharply with the much higher estimated occurrence of unrecognized disease identified in the general population. Overall, the number of patients with ≥1 HC diagnostic claim represents a fraction of the global estimated HC population based on large population studies and can be considered to represent the "tip of the iceberg" of the disease spectrum (Figure 3).

These observations support the view that many patients with HC are undiagnosed throughout life, potentially missing the opportunity for appropriate therapies and management. What fraction of these undiagnosed patients with HC may be candidates for major therapeutic interventions

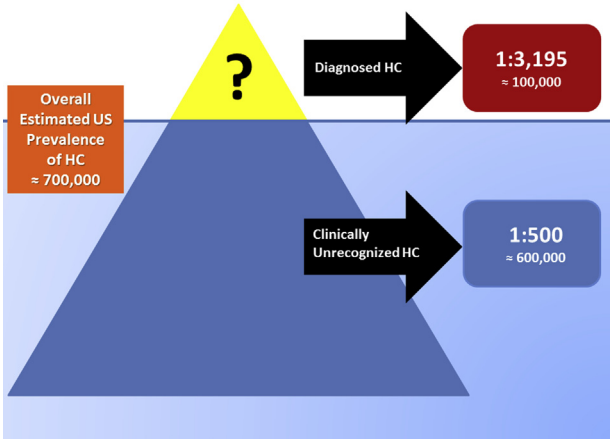

Figure 3. Prevalence of HC in the United States. Overall estimated prevalence of HC in US is 1:500 yielding ~700,000 cases *(left)*.[2] The prevalence of clinically diagnosed HC is 1:3,195 *(above right)*, yielding ~100,000 patients with the remaining ~600,000 patients likely remaining undiagnosed *(below right)*.

cause sudden death in asymptomatic patients as the initial manifestation of disease,[7] and that 10% of clinically identified patients with HC are considered at high arrhythmic risk,[8] together suggest that a significant proportion of these unrecognized patients may be at risk and benefit from early recognition and treatment strategies.

A major advantage of claims data analysis is the inclusion of much larger and more diverse sample sizes across a wider geographic region than is possible with single-center referral studies or epidemiologic cohort studies, and to our knowledge, this is the first time this type of analysis has been performed in a genetic heart disease such as HC. Indeed, our analysis comprised more than 169 million unique patients, which represents over 50% of the US census population in 2013.[4] The claims used in this analysis leverage data from all 50 states and encompass a wide payer mix. Furthermore, these data are contemporaneous and reflect current clinical practice, with 95% of claims available for analysis within 6 weeks of the medical encounter. As compared with a closed payer database, patients in the SHS database are generally tracked for a longer period of time and are not lost to follow-up when their health plan changes. In addition, despite different sampling techniques and methods, the results of our analysis validate the findings of the seminal The Coronary Artery Risk Development in Young Adults Study.[2] The established prevalence of 1:500 (0.2%) in that study projects a total of 700,000 subjects with HC in the United States. When this number is then multiplied by the proportion of symptomatic patients in The Coronary Artery Risk Development in Young Adults Study of 1 of 7, this also yields approximately 100,000 patients with symptomatic, or clinically evident, HC.

We note that the average age in our analysis was in the fifth decade life, which is older than that described in published studies of the fourth decade of life.[3] This likely reflects the historical referral bias of tertiary referral centers whereby younger and more symptomatic patients were referred for expert care. However, more recently HC has largely as a result of increased clinical recognition, wider distribution of centers of excellence and improved diagnostic imaging methods.[7] The upward shift in average age of our analysis might also be explained by the inverse relation between advanced age and disease-related risk in HC, whereby achieving older age in HC is associated with low risk for adverse disease-related complications, including sudden cardiac death.[8]

There are several limitations of the present analysis which reflect the inherent constraints in accessing claims data. For example, the SHS database does not fully represent certain segments of the population, such as the uninsured, prisoners, or the Veterans' Administration population. Likewise, out of network care and cash payments for private practitioner and institutional care are not captured, as claims are not generated for reimbursement purposes. Although the 3 ICD-9 diagnostic codes used in our study are unambiguous and exhaustive for HC, it is not possible to verify diagnosis in each patient. However, the unique strengths of accessing a large national claims database, which includes over 50% of the US population, provide a large measure of compensation for these issues and for this reason, we consider our estimates for the number of clinically diagnosed HC in the US to be robust and relevant.

In conclusion, the occurrence of clinically identified patients with HC in the US (~100,000) contrasts with the higher prevalence based on echocardiographic-based population studies. These data support the concept that many patients with HC remain undiagnosed and emphasize the need for concentrated efforts to increase awareness among the general public and the clinical practicing community regarding symptoms and clinical presentation of HC, as well as future efforts to develop rapid noninvasive diagnostic markers, which could potentially lead to enhanced recognition in the population.

Disclosures

Dr. Maron had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The study was funded by Gilead Sciences, Inc. The sponsor was involved in design and conduct of the study; interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication. Drs. Maron, Olivotto, and Lucove report receiving consulting fees from Gilead Sciences, Inc. Drs. Hellawell and Farzaneh-Far are employees of Gilead Sciences, Inc and hold equity in the company.

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