# Meta-analysis of Atrial Fibrillation in Patients With Various Cardiomyopathies

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**Patients with cardiomyopathy are at risk of developing atrial fibrillation (AF) which is a strong risk factor for thromboembolic events, progression to heart failure, and mortality or heart transplantation. This systematic review and meta-analysis sought to estimate the prevalence of AF in a global population with cardiomyopathy. PubMed and EMBASE were searched from inception until June 30, 2017 for published articles on AF and major cardiomyopathies without language restrictions. Eligible papers were independently assessed for methodological qualities. The prevalence of AF in patients with cardiomyopathy was estimated using a random-effect model. The chi-square test on Cochrane's Q statistics was used to evaluate heterogeneity across studies. In total 220 full texts representing a population of 118,668 participants were included in the meta-analysis. The ages of the participants ranged from a median of 31 to 72 years. The proportion of males ranged from 3% to 97%. Considering only cardiomyopathies with more than one contributing study, the prevalence of AF was highest in participants with dilated (24% [95% confidence interval: 21 to 28]), ischemic (20% [8 to 35]), and hypertrophic (19% [17 to 21]) cardiomyopathies, and lowest in patients with peripartum cardiomyopathies (5% [1 to 11]). In conclusion, with the exception of peripartum cardiomyopathy, an average of 1 to 2 in every 10 patients with a cardiomyopathy had AF, with no gender difference. Future guidelines need to take into consideration the management of AF in all the forms of cardiomyopathy.** **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:262−269)**

Cardiomyopathies represent a group of disorders characterized by structurally and functionally abnormal myocardium in the absence of hypertension, pericardial disease, valvular, or congenital heart disease sufficient to cause the observed myocardial dysfunction.[1,2] They are an important cause of heart failure and are associated with a high incidence of arrhythmias including ventricular tachycardias and atrial fibrillation (AF).[1] AF is the most prevalent cardiac arrhythmia and is a major public health problem.[3] Mostly asymptomatic, the importance of AF lies in its complications such as heart failure, tachycardia-induced cardiomyopathy, and cardio-embolic events such as stroke and premature mortality.[3] AF has been shown to be frequent in patients with cardiomyopathies and associated with poor outcomes. For instance, AF is the most prevalent arrhythmia in patients with hypertrophic cardiomyopathy (HC), affecting up to 1 in 4 of these patients.[4] AF in HC is associated with increased risk of stroke, heart failure, cardiac, and all-cause mortality.[4,5] AF also seems to be frequent in dilated cardiomyopathy (DC), and is associated to heart failure and a poor survival.[6] Despite the importance of AF in cardiomyopathies, except for HC,[4] pooled estimations of the burden of AF are not available for the other forms of cardiomyopathies including DC, Takotsubo, arrhythmogenic cardiomyopathy, restrictive cardiomyopathy, left ventricular noncompaction (LVNC), peripartum cardiomyopathy (PPCM), or inflammatory cardiomyopathies. This review summarizes the published data on the prevalence of AF in patients with all the major forms of cardiomyopathies.

## Methods

This review is reported in accordance with the Meta-analyses and Systematic reviews of Observational Studies guidelines. We performed a comprehensive search of PubMed/MEDLINE and Excerpta Medica Database (EMBASE) to identify all relevant studies published until June 30, 2017, estimating the prevalence of AF in patients with cardiomyopathies, without language restriction. We conceived and applied a search strategy based on the combination of relevant terms such as "cardiomyopathy" and the specific names of all the forms of cardiomyopathies, and "AF". The search strategies are available in the Appendix. The last electronic search was run on July 15, 2017. The reference lists of all relevant research articles and

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reviews were scrutinized to identify potential additional data sources.

To be included in this systematic review, primary studies had to be observational studies reporting the prevalence of AF in patients with any form of cardiomyopathy or enough data to compute these estimates. We excluded case series with a small sample size (<30 participants), letters, editorials, reviews, and studies without primary data or clear description of methods. For studies published in more than one report (duplicates), the most comprehensive reporting the largest sample size was considered.

Two investigators (JJN and VNA) independently screened the titles and abstracts of articles retrieved from literature search, and the full-texts of articles found potentially eligible were obtained and further assessed for final inclusion (Supplementary Figure 1). Disagreements were resolved through discussions between investigators until a consensus was reached.

We used the tool developed by Hoy et al to evaluate the methodological quality of included studies.[7] Each item was assigned a score of 1 (yes) or 0 (no), and scores were summed across items to generate an overall quality score that ranged from 0 to 10. According to the overall score, we classified studies as having high (≤5), moderate (6 to 8), and low (>8) risk of bias. Two investigators (JRN and AK) independently assessed study quality, with disagreements resolved by consensus.

Five investigators (UFN, ALN, JRN, AK, and CM) independently extracted relevant data from included studies using a preconceived and standardized abstraction form. Information extracted included first author's name, year of publication, study design, sampling method, type of cardiomyopathy, sample size, proportion of male participants, mean or median age, ascertainment of AF, and number of participants with AF. All the extracted data were cross checked for consistency and correctness by a sixth investigator (JJN).

Data analyses used the "meta" packages version 4.9-2 of the statistical software R (version 3.5.1, The R Foundation for statistical computing, Vienna, Austria). Unadjusted prevalence estimates of AF were calculated based on the information of crude numerators and denominators provided by individual studies. To keep the effect of studies with extremely small or extremely large prevalence estimates on the overall estimate to a minimum, the variance of the study-specific prevalence was stabilized with the Freeman-Tukey double arc-sine transformation before pooling the data with the random-effects meta-analysis model.[8] When data were available by gender group, we compared proportions between males and females. Egger test was done to assess the presence of publication and selective reporting bias.[9] A p value <0.10 was considered indicative of statistically significant publication bias. Heterogeneity across included studies was assessed using the chi-square test for heterogeneity with a 5% level of statistical significance,[10] and using the $I^2$ statistic for which a value of 50% was considered to imply moderate heterogeneity.[11] Inter-rater agreements between investigators for study inclusion and methodological quality assessment were assessed using Kappa Cohen's coefficient.[12]

## Results

Initially, 6,337 records were identified. After elimination of duplicates, 6,134 records remained. Titles and abstracts were screened, and 5,747 irrelevant records were excluded. Agreement between investigators on abstract selection was $\kappa = 0.73$. Full-texts, of the remaining 387 papers were scrutinized for eligibility, in which 167 were excluded with reasons. Finally, 220 full texts were included in the meta-analysis (Supplementary Figure 1). The list of references of included studies is provided in the Appendix. The inter-rater agreement for final study inclusion between investigators was $\kappa = 0.94$. In the assessment of methodological quality of included studies, 59 (27%), 125 (57%), and 36 (16%) studies had low, moderate, and high risk of bias. Data were from 39 countries including 118,668 patients from all WHO regions. Most of the studies were from Europe (44%), were cohort studies (68%), were conducted in single site (48%), and were prospective (43%) (Supplementary Table 2, Appendix). Individual characteristics of each included study are shown in the Appendix (Supplementary Table 3).

The number of studies reporting the prevalence of AF in cardiomyopathy varied widely from 119 studies for HC to one study for restrictive, unspecified nondilated, and alcoholic cardiomyopathies (Table 1). The prevalence of AF varied widely in types of cardiomyopathies from 5% in PPCM to 75% in restrictive cardiomyopathy with significant difference ($p < 0.0001$; Table 1).

One type of cardiomyopathy presented a prevalence <10%: PPCM (5%; Figure 1). Seven types of cardiomyopathies had a prevalence between 10% and 20%: Chagas (9%; Figure 1), Takotsubo (11%; Figure 2), amyloid (15%; Figure 1), arrhythmogenic cardiomyopathy (15%; Figure 1), LVNC (15%; Figure 3), Keshan (18%; Figure 3), and HC (19%; Figure 4). The prevalence was between 20% and 30% for 3 types of cardiomyopathies: ischemic (20%; Figure 3), unspecified DC (24%; Figure 5), and alcoholic (27%; Figure 3). Two presented with prevalence higher than 40%: unspecified nondilated (42%; Figure 3) and restrictive (75%; Figure 3). There was substantial heterogeneity except for PPCM, LVNC, and Keshan disease (Table 1). There was no publication bias except for HC, arrythmogenic, and Chagas cardiomyopathies.

There was no difference between males and females for all cardiomyopathies when the prevalence of AF was compared by gender (arrythmogenic, unspecified DC, HC, Takotsubo, and LVNC; Supplementary Table 4).

## Discussion

There exists a complex relation between AF and cardiomyopathy. On one hand, patients with a long-standing AF are prone to tachycardia-induced cardiomyopathy leading to myocardial dysfunction, which consequently results in heart failure.[13,14] In contrast, patients with cardiomyopathies are at an increased risk of developing AF.[15] This review focuses on patients with cardiomyopathy concomitantly diagnosed with AF at the time of recruitment or during follow-up. We found a broad variation of the prevalence of AF across the different forms of cardiomyopathy, with no significant gender predilection. Except for PPCM, our findings depict that at an average of

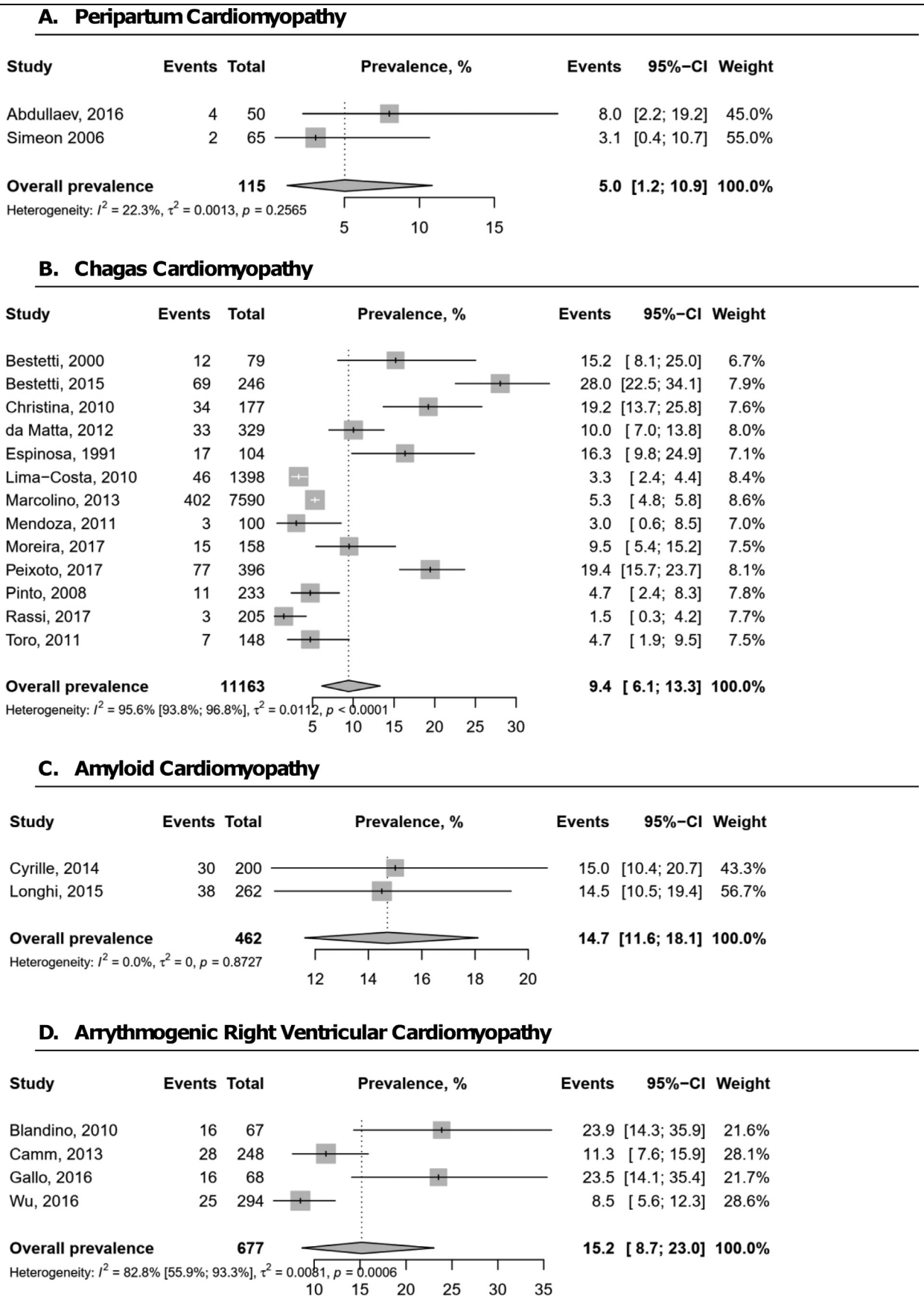


Figure 1. Prevalence of overall cases of peripartum, Chagas, amyloid, and arrythmogenic right ventricular cardiomyopathies.

Table 1
Meta-analysis prevalence of atrial fibrillation in the global population with cardiomyopathies

| Cardiomyopathies | Prevalence (95% confidence interval) | N studies | N participants | H (95% confidence interval) | $I^2$ (95% confidence interval) | p Heterogeneity | p Egger test | p Difference |
|---|---|---|---|---|---|---|---|---|
| Restrictive | 75 (65-83) | 1 | 94 | NA | NA | NA | NA | <0.0001 |
| Unspecified nondilated | 42 (30-55) | 1 | 57 | NA | NA | NA | NA | |
| Alcoholic | 27 (12-44) | 1 | 30 | NA | NA | NA | NA | |
| Unspecified dilated | 24 (21-28) | 42 | 9012 | 4 (4-5) | 94 (93-95) | <0.0001 | 0.279 | |
| Ischemic | 20 (9-35) | 4 | 1602 | 5 (4-7) | 97 (94-98) | <0.0001 | 0.730 | |
| Hypertrophic | 19 (17-21) | 119 | 67032 | 6 (6-7) | 97 (97-98) | <0.0001 | 0.025 | |
| Keshan disease | 18 (13-23) | 2 | 221 | 1.0 | 0.0 | 0.397 | NA | |
| Arrythmogenic right ventricular | 15 (9-23) | 4 | 677 | 2 (2-4) | 83 (56-93) | 0.0006 | 0.014 | |
| Left ventricular noncompaction | 15 (11-19) | 6 | 664 | 1 (1-2) | 46 (0-79) | 0.100 | 0.816 | |
| Amyloid | 15 (12-18) | 2 | 462 | 1.0 | 0 | 0.873 | NA | |
| Takotsubo | 11 (8-13) | 20 | 26921 | 4 (4-5) | 94 (92-96) | <0.0001 | 0.178 | |
| Chagas | 9 (6-13) | 13 | 11163 | 5 (5-6) | 96 (94-97) | <0.0001 | 0.085 | |
| Peripartum | 5 (1-11) | 2 | 115 | 1 | 22 | 0.257 | NA | |

1 to 2 in 10 patients with any major form of cardiomyopathy have AF. This is particularly concerning because even though AF significantly increases the patient's risk of thromboembolic events, heart failure, and mortality or heart transplant,[15–17] most of the attention has been limited to AF in patients with HC. The bias toward HC is evident as over 50% of the included studies reported on HC, Table 1. In fact, guidelines on the management of patients with AF only mentioned guidelines on the management of HC in other cardiomyopathies.[18–20] Evidently, the high prevalence of AF in other cardiomyopathies such as DC and ischemic heart disease is a call for concern.

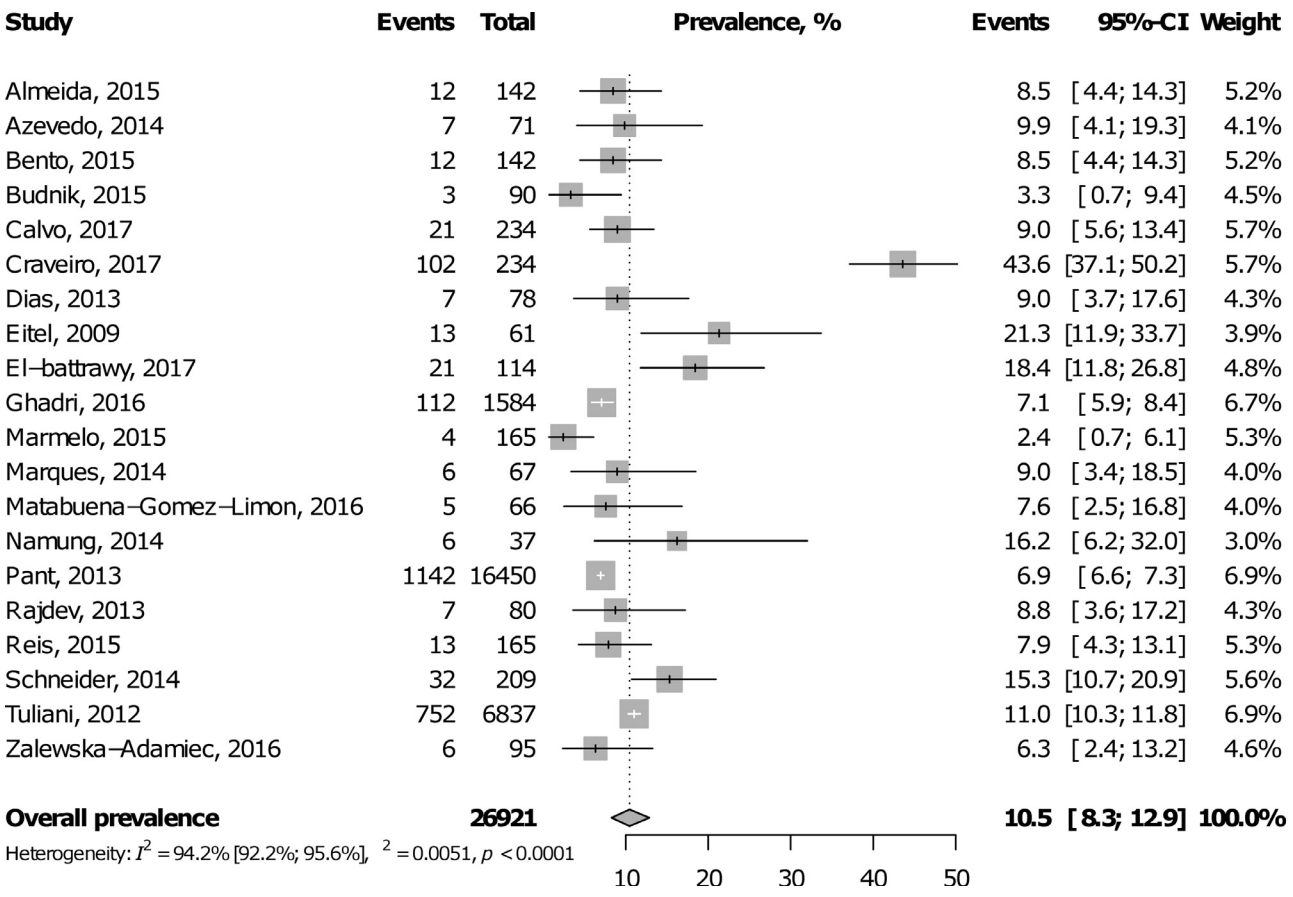


Figure 2. Prevalence of overall cases of takutsubo cardiomyopathy.

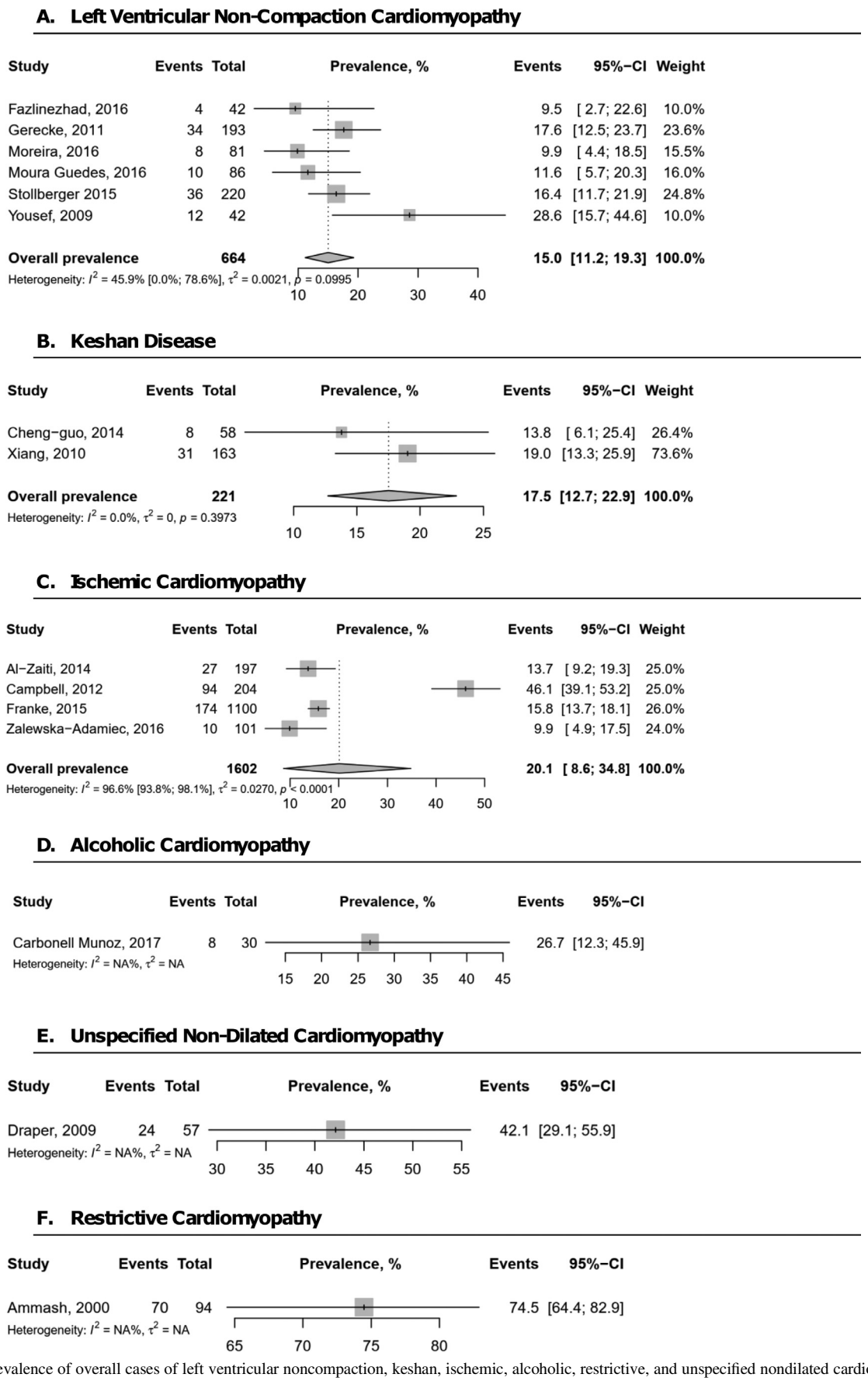


Figure 3. Prevalence of overall cases of left ventricular noncompaction, keshan, ischemic, alcoholic, restrictive, and unspecified nondilated cardiomyopathies.

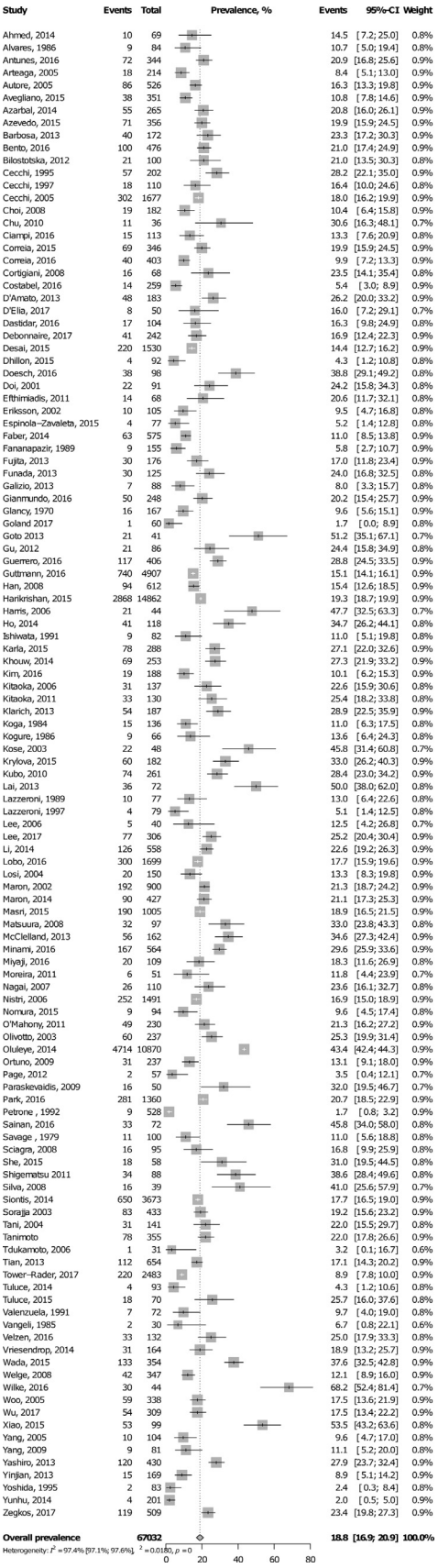


Figure 4. Prevalence of overall cases of hypertrophic cardiomyopathy.

Specifically, our review presents an estimation of the prevalence of AF in the largest reported pooled population of patients with HC: 67,032 versus 7,381 as compared with the study by Guttmann et al.[4]. We found a prevalence of 19% which is lower than the 23% reported by Guttmann et al. We found a higher prevalence (24%) in patients with DC. AF was half less frequent in patients with Takotsubo and Chagas cardiomyopathies (prevalence ∼ 10%). The current knowledge of the pathophysiology of AF in patients with cardiomyopathies is limited. However, it is postulated that increased atrial size and stretch are important mechanisms leading to AF in these populations. Indeed, several studies have shown that left atrial size and volume are independent predictors of atrial arrhythmia.[4] Perhaps the difference in the prevalence rates of AF across the different forms of cardiomyopathy could be explained anatomically, with the forms of cardiomyopathy which depicts the largest increase in left atrial size and volume having the highest prevalence of AF.

The lowest prevalence of AF (5%) was observed in women with PPCM. Although this estimate is derived from only 2 studies with a pooled population of 115 patients, this relatively low prevalence compared with the other forms of cardiomyopathy might be due to the short duration of the disease in these patients, where it improves in the majority. The atrial involvement is a less important feature as compared with the ventricular dysfunction.

Evidence on gender predilection of AF in patients with cardiomyopathy is uncertain. Some authors have highlighted an association between the female gender and AF in the context of cardiomyopathies[4] while others have reported no association.[21,22] However, our findings show no gender disparities in the prevalence of AF in patients with major cardiomyopathies.

This review should be interpreted in the context of its limitations. The prevalence of AF in some cardiomyopathies like restrictive and non-DC was reported by a single study, limiting the generality of such findings. Therefore, the prevalence of AF in these populations needs to be confirmed by further studies. Consequently, these studies will not be taken into consideration during comparison of prevalence rates henceforth. We noted significant heterogeneity across studies most likely due to various sociodemographic and clinical diversities in the study populations and difference in the study designs and diagnosis of the main outcomes (AF and respective cardiomyopathies). Nevertheless, this study is the first attempt to summarize the prevalence of AF in patients with major cardiomyopathies.

In this meta-analysis of over 100,000 participants, an average of 1 to 2 in every 10 patients with a cardiomyopathy had AF, with no gender difference. The high prevalence rates call for guidelines for the diagnosis and management of AF in all the major forms of cardiomyopathies. In future studies, it would be imperative to investigate and compare the clinical outcomes of patients with AF across different cardiomyopathies.

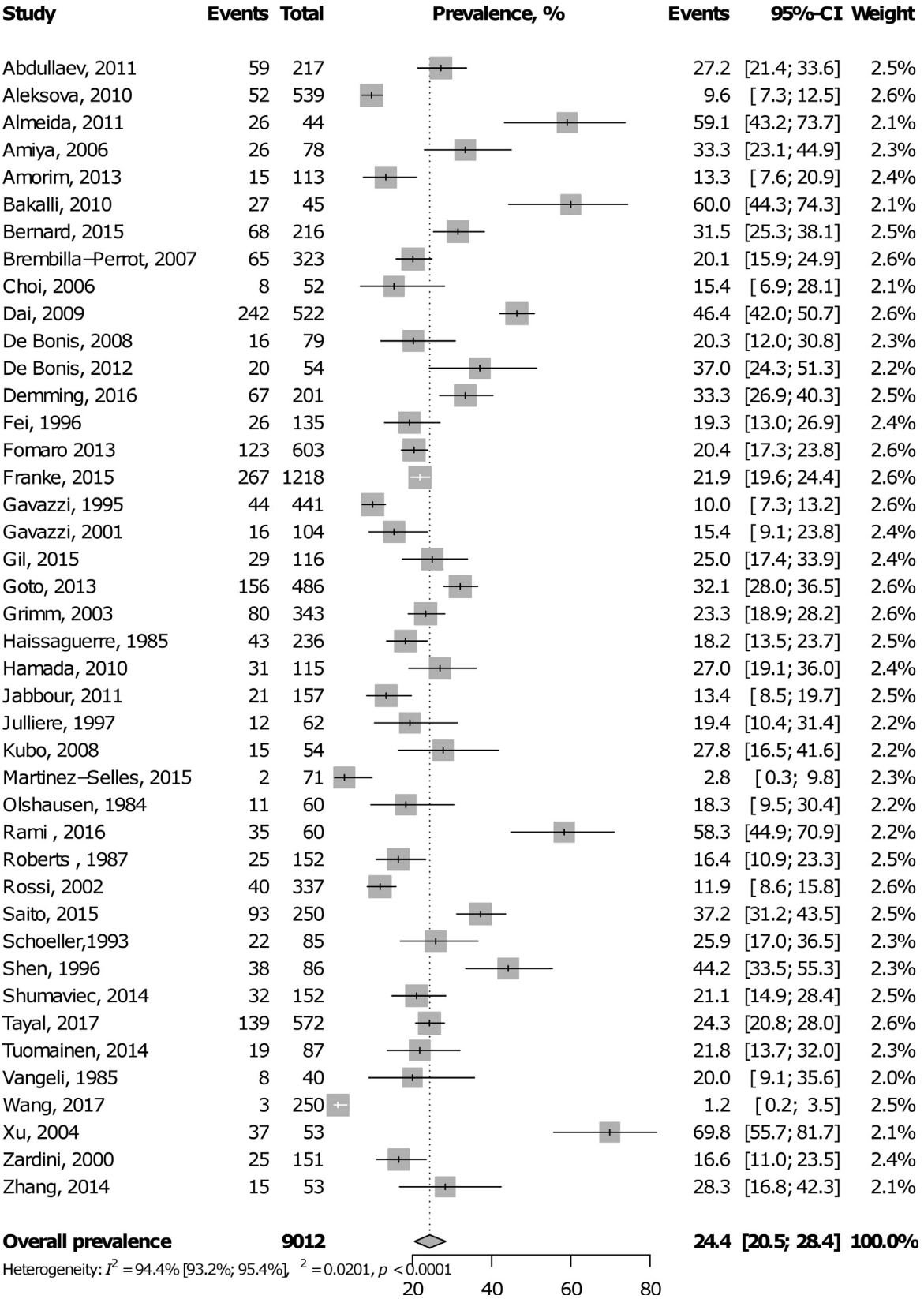


Figure 5. Prevalence of overall cases of dilated cardiomyopathy.

## Disclosures

The authors have no conflicts of interest to disclose.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.04.028.


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