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Thromboembolic Outcomes of Different Anticoagulation Strategies for Patients with Atrial Fibrillation in the Setting of Hypertrophic Cardiomyopathy: A Systematic Review

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Abstract

Objective: Limited data is available assessing the efficacy and safety of different anticoagulation (AC) strategies for prevention of thromboembolic events, major bleeding, and all-cause mortality in patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF). In this systematic review, we conducted a literature search to examine the possible association between different AC strategies and prevention of these adverse outcomes.

Methods: Scientific databases (PubMed, EMBASE, and Scopus) were searched using relevant medical subject headings and keywords to retrieve studies published through September of 2019. Studies assessing the outcomes of interest in patients with HCM and AF receiving AC versus no AC as well as direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) were selected.

Results: This review identified 14 observational studies evaluating thromboembolic events by AC strategies in 8,479 participants with concomitant HCM and AF. The use of AC was associated with a lower pooled incidence rate of total thromboembolic events at 9.5% (112 events in 1,175 patients) compared to 22.1% with no AC (108 events in 489 patients). In addition, the use of DOACs was associated with a lower pooled incidence rate of thromboembolic events at 4.7% (169 events in 3,576 patients) compared to 8.7% with VKAs (281 events in 3,239 patients). Furthermore, the use of DOACs compared to VKAs was associated with a lower pooled incidence rate of major bleeding and all-cause mortality at 3.8% (136 events in 3,576 patients) versus 6.8% (220 events in 3,239 patients) and 4.1% (124 events in 3,008 patients) versus 16.1% (384 events in 2,380 patients), respectively.

Conclusions: AC of patients with concomitant HCM and AF was associated with a lower incidence of thromboembolic events when compared to antiplatelet therapy or no treatment. Treatment with DOACs was also associated with a lower incidence of thromboembolic events, major bleeding, and all-cause mortality when compared to VKAs.

Introduction

Patients with hypertrophic cardiomyopathy (HCM) can range from asymptomatic to a multiplicity of clinical presentations and associated comorbidities.[1-3] Atrial fibrillation (AF) is the most common sustained arrhythmia diagnosed in patients with HCM, occurring in approximately 20-30% of this subpopulation.[4-6] Patients with concomitant AF and HCM tend to have more symptoms and are at an increased risk of stroke, transient ischemic attack, or systemic embolism compared to patients with either condition alone.[7] These findings suggest that both aggressive screening of HCM patients and prophylactic anticoagulation (AC) for all individuals diagnosed with concomitant AF are likely to have a significant prognostic impact on thromboembolic outcomes.[1,4,5,8] Within this subpopulation, AC therapy with a vitamin K antagonist (VKA), such as warfarin, is a Class I recommendation in several guidelines over antiplatelet therapy or no treatment.[9,10] Alternatively, there are no data to suggest that direct oral anticoagulants (DOACs), including a direct thrombin inhibitor or factor Xa inhibitors, cannot be used.[9,10] It is worth noting that these recommendations are based mainly on expert consensus and several relatively small observational studies as there are currently no prospective randomized controlled trials (RCTs) on the subject to date.[1,5,7,11-21]

The aim of this study was to systematically review the literature and objectively quantify the risk associated with different AC strategies in this particular population of interest. This encompasses both a comparison of AC versus no AC and subsequently DOACs versus VKAs for thromboembolic events in patients with concomitant HCM and AF. When available for comparison, major bleeding and all-cause mortality will also be analyzed by the different treatment strategies.

Key Words

Hypertrophic cardiomyopathy, Atrial fibrillation, Vitamin K antagonist, Direct oral anticoagulant, Anticoagulation, Thromboembolism, Major bleeding, All-cause mortality.

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Methods

Literature Search Strategy

Table 1: Characteristics of the individual studies included in the meta-analysis for thromboembolic events (AC vs. No AC).

First Author	Year	Journal	Country	Design	Age (Years)	Female (%)	[a]HCM & AF (n)	[b]AC (n)	[c]No AC (n)	Follow-Up (Years)
[14]Higashikawa et al.	1997	Jpn Circ J	Japan	[d]SC Cohort	55.5 ± 7.8	36.8	19	7	12	7.9 ± 4.6
[15]Doi et al.	2001	J Cardiol	Japan	SC Cohort	51.0 ± 14.0	31.9	22	10	12	6.7 ± 4.8
[2]Olivotto et al.	2001	Circulation	USA, Italy	[e]MC Cohort	45.0 ± 20.0	39.0	107	59	48	9.1 ± 6.4
[7]Maron et al.	2002	JACC	USA, Italy	MC Cohort	46.0 ± 20.0	39.0	190	82	108	7.0 ± 7.0
[17]Inoue et al.	2006	Circ J	Japan	SC Cohort	66.6 ± 10.3	35.2	25	16	9	2.0 ± 0.4
[4]Guttmann et al.	2015	Eur J Heart Fail	UK, Spain, Greece, Italy	MC Cohort	49.0 ± 16.4	36.1	600	471	129	5.9 ± 5.0
[16]Haruki et al.	2016	Stroke	Japan	SC Cohort	51.0 ± 15.6	37.1	162	84	78	10.7 ± 7.5
[18]Lee et al.	2017	Heart	South Korea	SC Cohort	62.0 ± 11.0	32.0	70	53	17	5.5 ± 2.0
[19]Rowin et al.	2017	Circulation	USA	SC Cohort	57.0 ± 14.0	33.0	299	233	66	4.8 ± 3.4
[20]Tsuda et al.	2019	Heart Rhythm	Japan	SC Cohort	71.0 ± 10.0	29.1	170	160	10	2.4 ± 0.9

[a]HCM & AF indicates the number of patients (n) with both HCM and AF from the individual study; [b]AC indicates the number of patients with both HCM and AF from the individual study that received anticoagulation; [c]No AC indicates the number of patients with both HCM and AF from the individual study that did not receive anticoagulation; [d]SC indicates a single-center study design; [e]MC indicates a multi-center study design.

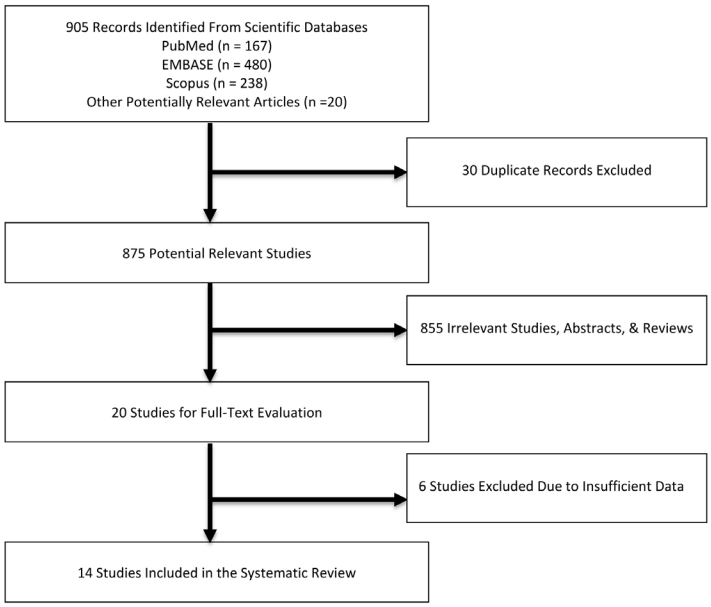

Figure 1: PRISMA flow diagram of the systematic review literature search.

Scientific databases including PubMed, EMBASE, and Scopus were searched through September of 2019 using the terms "hypertrophic cardiomyopathy" AND "atrial fibrillation" AND "stroke." All sets included Medical Subject Heading (MeSH) and free-text terms. No language restrictions were applied. Additionally, relevant publications cited in these studies were assessed to increase the sensitivity of the search. The methodology and presentation of the review are based on the PRISMA guidelines.[22]

Inclusion/Exclusion Criteria & Quality Assessment

Inclusion criteria of interest were: 1) human observational studies in peer-reviewed journals, 2) participants aging ≥ 18 years old, and 3) studies that reported data on thromboembolic events in patients with concomitant HCM and AF receiving AC versus no AC or DOACs versus VKAs. While reporting data on major bleeding or all-cause mortality was not part of the inclusion criteria for this systematic review, these outcomes were compared between the different AC strategies when available. For the comparisons of AC versus no AC or DOACs versus VKAs, thromboembolic events were excluded if they occurred in association with or prior to the initial episode of AF as there was no opportunity for a treatment strategy to be chosen. For the comparison of DOACs versus VKAs, patients were excluded if the etiology of AF was related to valvular causes.

Duplicate publications, irrelevant articles, abstracts, reviews, editorials, and letters were excluded. Two reviewers (MRL and AMS) assessed the titles and abstracts of the identified studies. If the reviewers had inconsistent ideas about an article, it was re-evaluated by a third party (JJL). We also avoided selecting overlapping data by analyzing author names and hospitals in which patients were followed up. Quality assessment was done using Joanna Briggs Institute critical appraisal tool.[23] In addition, the level of evidence for individual studies was assessed using the Oxford Centre of Evidence-Based Medicine – Level of Evidence document (in which a designation of 1A represents the highest level of evidence relative to 5 being the lowest). All studies included in this systematic review received the designation 2b for level of evidence which indicates a well-designed cohort study or low-medium quality RCT. A protocol for this review was submitted and accepted online through the PROSPERO website under the registration number CRD42019127534.

Data Extraction

Critical data extraction was done by MRL; then, the data were entered in Microsoft Office Excel 2016 (Microsoft Corp, Redmon, Washington, USA) and subsequently compared with the original data collected by AMS and JJL to assure the accuracy of the extraction process. The extracted data for each individual study included the following information: first author's last name, journal/year of publication, country, study design, follow-up duration, sample size of the study population, age of the study population, percentage of female patients, sample size of patients with concomitant HCM and AF within the study population, numbers of patients from this subpopulation receiving AC versus no AC or DOACs versus VKAs, and study results (thromboembolic events, major bleeding, and all-cause mortality). Eligible studies for the comparison of AC versus

Table 2: Characteristics of the individual studies included in the meta-analysis for thromboembolic events, major bleeding, and mortality (NOACs vs. VKAs).

First Author	Year	Journal	Country	Design	Age (Years)	Female (%)	[a]HCM & AF (n)	[b]VKA (n)	[c]NOAC (n)	Follow-Up (Years)
[11]Noseworthy et al.	2016	JACC	USA	[d]MC Cohort	67.0 ± 13.3	34.6	1427	859	568	0.56
[12]Dominguez et al.	2017	Int J Card	Spain	MC Cohort	61.6 ± 12.7	34.6	532	433	99	5.25
[13]Jung et al.	2019	Chest	Korea	MC Cohort	69.0 ± 10.9	44.0	2459	955	1504	1.33 ± 1.33
[14]Lee et al.	2019	Stroke	Korea	[e]PB Cohort	67.3 ± 11.2	41.0	2397	1405	992	1.60 ± 1.40

[a]HCM & AF indicates the number of patients (n) with both HCM and AF from the individual study; [b]VKA indicates the number of patients with both HCM and AF from the individual study that received vitamin K antagonists for anticoagulation; [c]NOAC indicates the number of patients with both HCM and AF from the individual study that received non-vitamin K oral anticoagulants; [d]MC indicates a multi-center study design; and [e]PB indicates population-based study design.

no AC and DOACs versus VKAs are qualitatively summarized in [Table 1] and [Table 2], respectively. Due to heterogeneity in baseline characteristics, HCM types, and AC strategies utilized across the included studies, it was not feasible to run a meta-analysis for the outcomes assessed.

Classifications of HCM, AF, and AC Strategies Received

The classification of HCM was variable within the individual full-text studies analyzed. Noseworthy et al., Jung et al., and Lee et al. defined HCM utilizing claims for diagnostic codes (International Classification of Disease, Tenth Revision; ICD-10). The study by Lee et al. also required patients to be registered in the rare intractable disease program where the criteria for HCM was verified by echocardiography. A previous study by Choi et al. demonstrated that the combination of ICD-10 codes and RID codes showed a positive predictive value (PPV) for HCM of 100%.[24] A study by Dominguez et al. utilized a different approach and defined HCM as a maximum LV wall thickness ≥ 15 mm unexplained solely by loading conditions. HCM patients with any type of non-valvular AF (i.e. paroxysmal, persistent, long-standing persistent, and permanent) were included as long as those patients were also diagnosed with HCM based on the above criteria.

For the outcome of thromboembolic events in patients receiving AC versus no AC, participants who received any type of AC during the study period were classified into the AC category. Participants who did not receive any type of AC during the study period or received antiplatelet agents without AC were classified into the no AC category. For the outcome of thromboembolic events in patients receiving DOACs versus VKAs, participants who received apixaban, dabigatran, edoxaban, or rivaroxaban during the study period were classified into the DOACs category and those who received acenocoumarol or warfarin were classified into the VKAs category.

Study Endpoint

There were two primary endpoints of interest. The first primary endpoint assessed the incidence of thromboembolic events in patients with concomitant HCM and AF who received AC versus no AC. The second primary endpoint assessed the incidence of thromboembolic events in patients with concomitant HCM and AF who received DOACs versus VKAs. As stated above, major bleeding and all-cause mortality were also assessed when available for the different AC strategies; however, these two outcomes were not part of the inclusion criteria for this systematic review.

Definitions of Outcomes Assessed

An ischemic stroke was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist, lasting greater than 24 hours, and caused by ischemia. A transient ischemic attack was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist and lasting less than 24 hours. A systemic embolic event was defined as thromboembolism outside of the brain to the heart, eyes, lungs, kidneys, spleen, or limbs. Major bleeding was defined as a decrease in hemoglobin level of at least 2 g/dL and/or hemorrhage leading to an unscheduled visit to a healthcare center or requiring a temporary interruption of AC therapy. All-cause mortality was defined as any death event that occurred during the study period.

Results

Study Selection

The above search strategy yielded 905 publications. Following the exclusion of duplicate and irrelevant records, fourteen papers with a total of 8,479 patients met the inclusion criteria for this systematic review (Refer to [Figure 1]). [1,5,7,11-21] All 14 studies reported data on thromboembolic events such as strokes, transient ischemic attacks, or systemic emboli in patients with concomitant HCM and AF.

Baseline Characteristics

Of the 14 articles retrieved, ten (seven single-center and 3 multi-center observational cohorts) provided data on thromboembolic events in patients with HCM and AF receiving AC (n = 1,175) versus no AC (n = 489). [1,5,7,15-21] The mean age of this population was 54.2 ± 15.6 years old (35.7% females) and the mean duration of follow-up was 6.1 ± 4.7 years. Two of the 10 studies also included data on thromboembolic events in patients who were receiving antiplatelet agents (but no AC).[2,18] Notably, 3 of the 10 studies included data on thromboembolic events occurring before a documented episode of AF - these were not included in the extracted data. Study characteristics are provided in [Table 1].

The remaining four of the 14 retrieved articles provided data on thromboembolic events in patients with HCM and AF receiving DOACs (n = 3,576) versus VKAs (n = 3,239).[11-14] All four studies were propensity-matched observational cohorts. Within the DOAC arm, 874 patients received apixaban, 1,025 patients received dabigatran, 280 patients received edoxaban, and 1,397 patients received rivaroxaban. Within the VKA arm, 433 patients received acenocoumarol and 2,806 patients received warfarin. The mean age of this specific population was 67.4 ± 11.6 years old (40.2% females) and the mean duration of follow-up was 1.57 ± 0.97 years. While major bleeding was reported for all four studies, all-cause mortality

was only reported in three (of the four studies). Study characteristics for these four trials are provided in [Table 2].

Thromboembolic Events (AC versus No AC)

Notably, all ten studies examined for this endpoint were post hoc subgroup analyses of larger cohorts.[1,5,7,15-21] In patients with HCM and AF, the use of AC was associated with a lower pooled incidence rate of total thromboembolic events at 9.5% (112 events in 1,175 patients) compared to 22.1% with no AC (108 events in 489 patients). Eight of the ten studies included in this portion of the analysis reported a lower incidence rate of thromboembolic events in patients receiving AC versus no AC, as expected (refer to [Table 1]). The remaining two studies by Higashikawa et al. and Inoue et al. had a small number of patients that met the inclusion criteria and produced contradictory results with a higher incidence rate of thromboembolic events in patients receiving AC versus no AC. Further analysis of these two studies as well as the studies by Lee et al. and Maron et al. revealed sub-therapeutic international normalized ratios (INRs) at or near the time of certain thromboembolic events in patients classified as receiving AC (Higashikawa et al. 5/6 events; Inoue et al. 5/5 events; Lee et al. 3/6 events, and Maron et al. 9/15 events). Removal of these 22 data points from the current study would result in an even more pronounced difference in the incidence of thromboembolic events in patients receiving AC at 7.8% (90 events in 1,153 patients) versus no AC at 22.1% (108 events in 489 patients).

Thromboembolic Events (DOACs versus VKAs)

As mentioned, this portion of the analysis included four propensity-matched cohorts.[11-14] The use of DOACs in patients with HCM and AF was associated with a lower pooled incidence rate of thromboembolic events at 4.7% (169 events in 3,576 patients) compared to 8.7% with VKAs (281 events in 3,239 patients). In 2016, Noseworthy et al. were the first to compare the two AC strategies and identified a relatively small difference in incidence rate of 3.3% with DOACs (19 events in 568 patients) compared to 4.2% with VKAs (36 events in 859 patients). Since then, three more studies have continued to demonstrate an even more impressive efficacy profile for DOACs relative to VKAs (refer to [Table 2]).

Major Bleeding (DOACs versus VKAs)

The use of DOACs in patients with HCM and AF was associated with a lower pooled incidence rate of major bleeding at 3.8% (136 events in 3,576 patients) compared to 6.8% with VKAs (220 events in 3,239 patients). The study performed by Noseworthy et al. in 2016 demonstrated a minor difference in the incidence rate of major bleeding at 2.3% with DOACs (13 events in 568 patients) compared to 3.0% with VKAs (26 events in 859 patients). Subsequent studies demonstrated slightly larger differences in incidence rates of major bleeding between the AC strategies, also favoring DOACs over VKAs (refer to [Table 2]).

All-Cause Mortality (DOACs versus VKAs)

The use of DOACs in patients with HCM and AF was associated with a lower pooled incidence rate of all-cause mortality at 4.1% (124 events in 3,008 patients) compared to 16.1% with VKAs (384 events in 2,380 patients). One study in particular, performed by Dominguez et al. in 2017 demonstrated an outsized difference in the incidence rate of all-cause mortality at 2.0% with DOACs (2 events in 99 patients) compared to 24.7% with VKAs (107 events in 433 patients). More recent studies demonstrate similar results favoring DOACs over VKAs (refer to [Table 2]) on this endpoint.

Discussion

Experts concur that patients with concomitant HCM and AF are at high risk for strokes, transient ischemic attacks, and systemic embolic events. While this is a valid concern, there is a limited pool of data and no RCTs to provide guidance regarding the value of prophylactic AC, as opposed to no AC. Due to this paucity of evidence and erring on the side of thromboembolic event prevention, AC is recommended within the current guidelines for all patients with concomitant HCM and AF. This systematic review sought to assess the validity of this recommendation and also to compare DOACs to VKAs for superiority between the two available AC options. Importantly, we firmly establish that treatment of patients with AC was associated with a lower incidence rate of thromboembolic events compared to no AC (Refer to [Figure 2A]), and that treatment with DOACs was associated with lower incidence rates of thromboembolic events, major bleeding, and all-cause mortality when compared to VKAs (Refer to [Figure 2B-2D]).

Prevalence and predictors of AF

The estimated prevalence of AF (thought to be 20-30%) in patients with HCM appears to be approximately five times higher than in the age-matched general population.[2] The main pathophysiologic process thought to drive the increased incidence of AF includes hypertrophy and impaired relaxation of the myocardiocytes of the left ventricle.[25] This ultimately leads to some degree of diastolic dysfunction, compromised blood flow, and increased atrial pressure in nearly all patients with HCM.[25] In addition, mitral regurgitation, usually in the setting of outflow tract obstruction, can also cause irregularities in the normal hemodynamics.[5] With these additional stressors placed on the atria, HCM patients are prone to developing AF.

Prevalence and predictors of thromboembolic events

The prevalence of thromboembolic events in patients with HCM and AF is estimated to be approximately 27%.[2] Furthermore, HCM patients that develop AF demonstrated more than a seventeen-fold increased likelihood of developing thromboembolic events when compared to HCM patients in sinus rhythm.[2] While there is a limited pool of data examining the clinical profile of HCM patients experiencing these thromboembolic events and the determinants of an occurrence, previous studies suggest left atrial diameter, left atrial volume, and age as potential predictors.[1,5,6,7] However, due to study heterogeneity and lack of patient-level data, predictive models for development of thromboembolic events in HCM patients with AF are low-yield. Future studies on the topic with propensity-matched baseline characteristics and similar AF burden will help clinicians delineate which individuals are at increased susceptibility for these adverse outcomes.

Unexplained events with prophylactic AC

This study also raises the important consideration that prophylactic

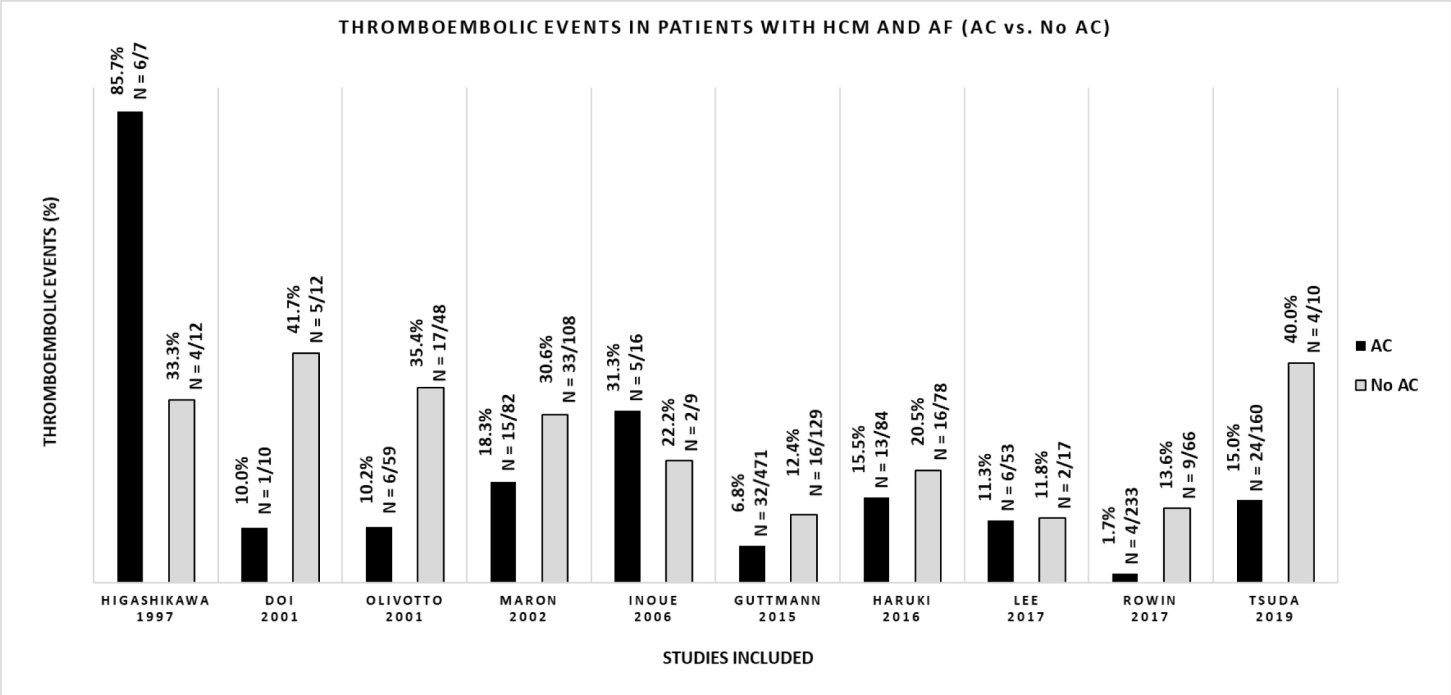

Figure 2A: Percentage of thromboembolic events in patients with HCM and AF who were treated with AC vs. no AC in the individual studies included in this systematic review.

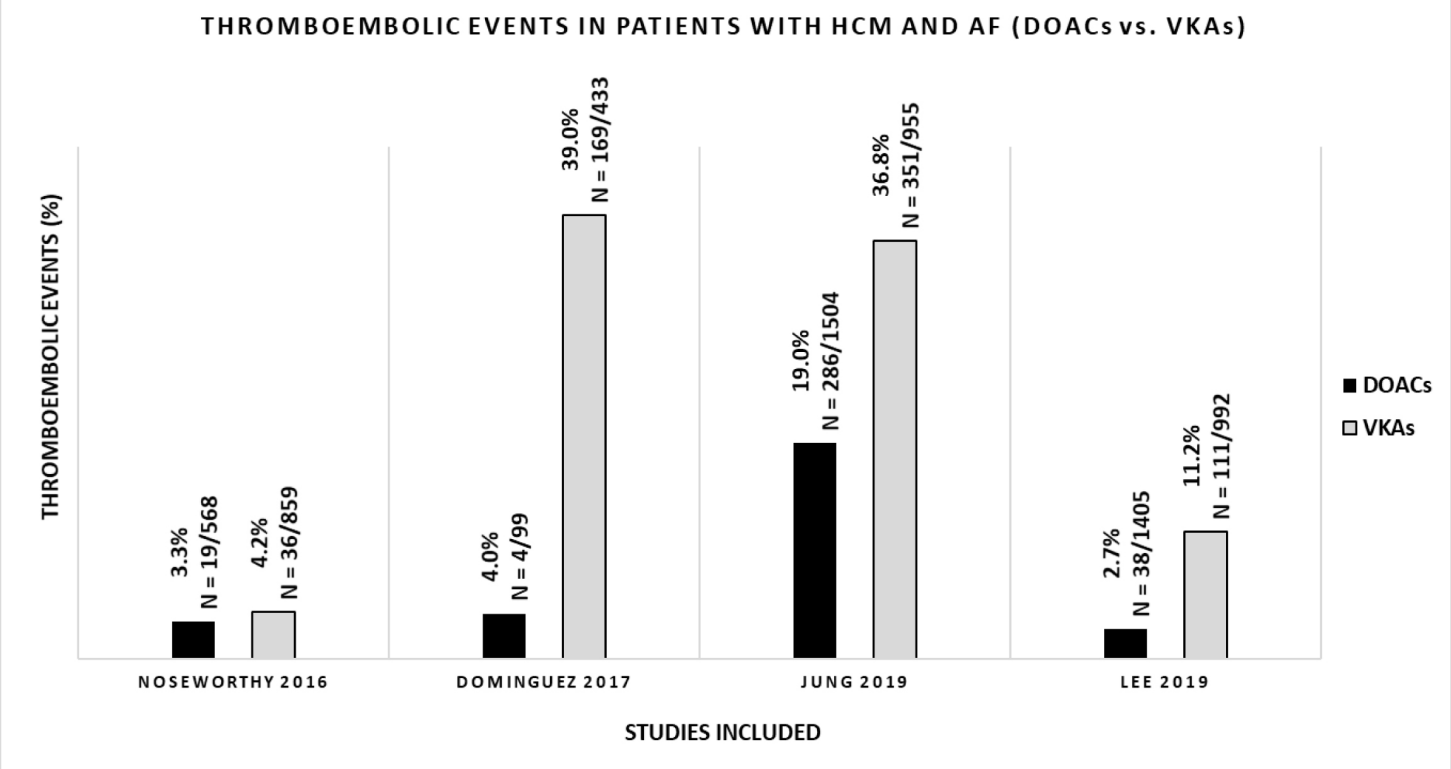

Figure 2B: Percentage of thromboembolic events in patients with HCM and AF who were treated with DOACs vs. VKAs in the individual studies included in this systematic review.

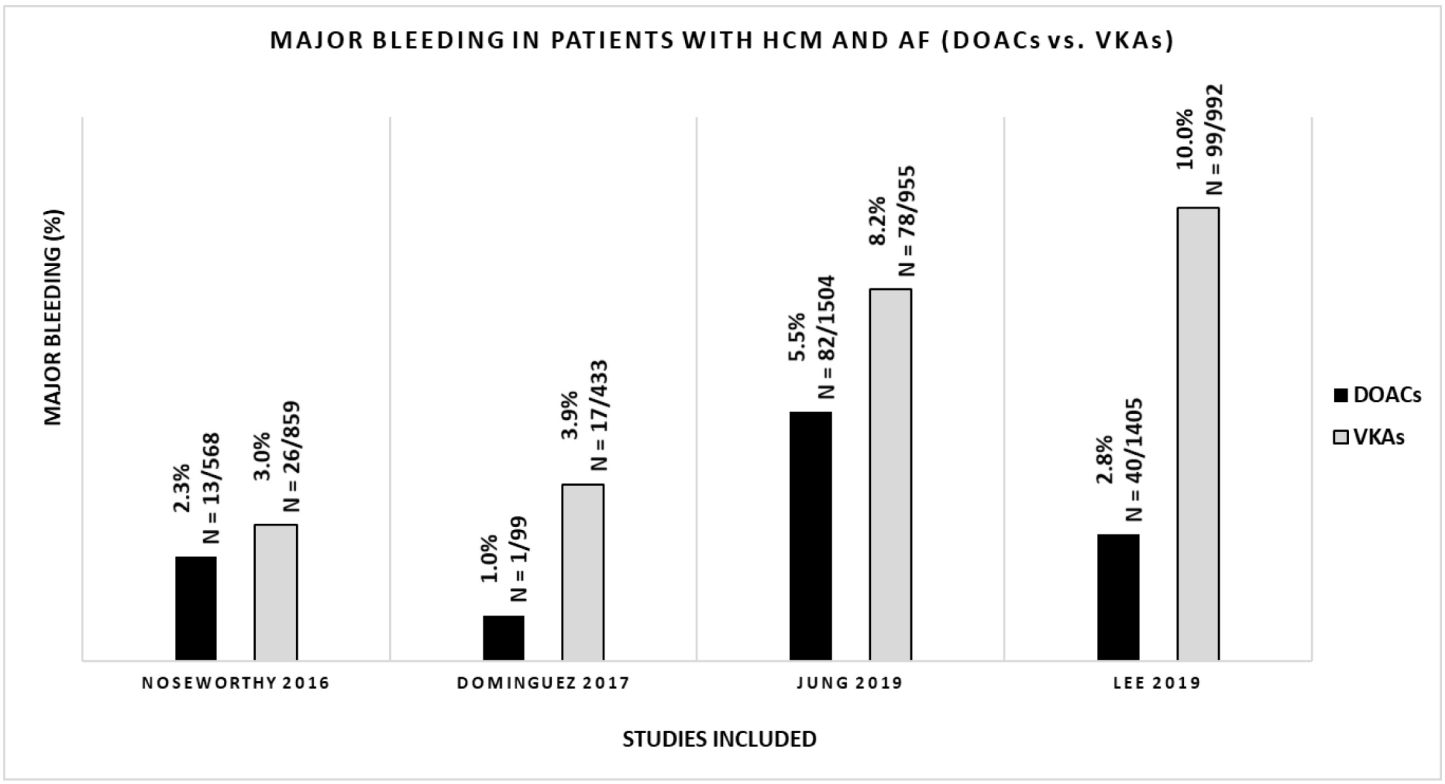

Figure 2C: Percentage of major bleeding events in patients with HCM and AF who were treated with DOACs vs. VKAs in the individual studies included in this systematic review.

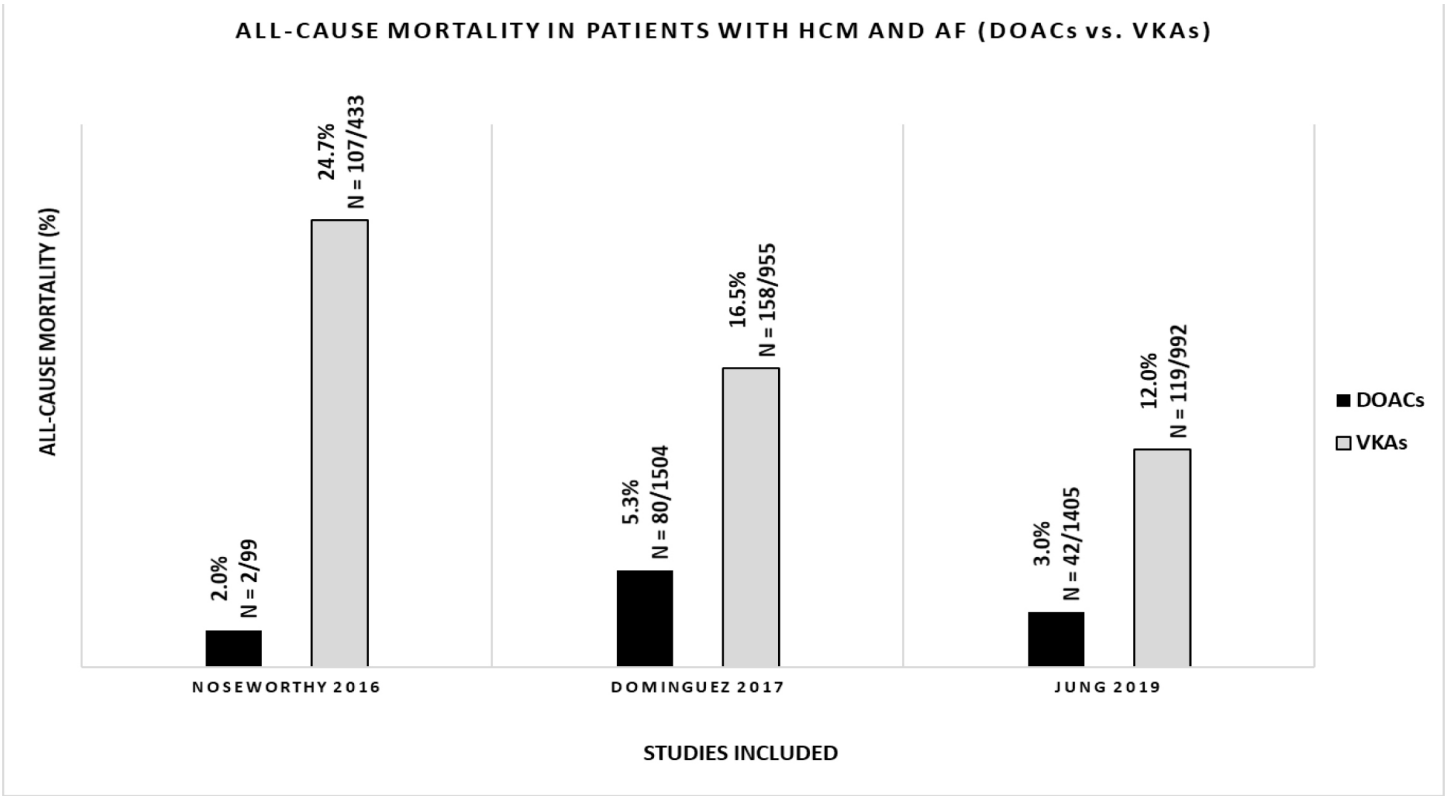

Figure 2D: Percentage of all-cause mortality events in patients with HCM and AF who were treated with DOACs vs. VKAs in the individual studies included in this systematic review.

treatment with AC in this population should not be considered an absolute guardrail against thromboembolic outcomes. Inadequate medication compliance or physician dosing and/or sub-therapeutic INRs in patients taking VKAs could contribute to this, as noted above. However, there were still patients with thromboembolic events from these individual studies that had therapeutic INRs on VKAs at or near the time of thromboembolic events (additionally thromboembolic events occurred in patients receiving appropriate doses of DOACs).

It has been hypothesized that thrombogenesis of the endothelium may be enhanced due to outflow tract obstruction in patients with HCM.[25] This is a possible contributing factor for some of these unexplained events. Another proposed theory suggests thrombosis-inducing anti-cardiolipin antibody is produced by some cell lines of HCM patients when AF occurs.[26] Other pathophysiological factors such as blood stagnation in patients with "end-stage phase" HCM have been implicated.[27] While left ventricular remodeling in children with HCM involves progression of marked wall thickening, the changes seen in some adults can have paradoxically the opposite effect with wall thinning associated with the development of left ventricular cavity enlargement, systolic dysfunction, and eventually congestive heart failure.[28-30] This gradual change in structure of the heart is thought to be the result of extensive myocardiocyte apoptosis and massive replacement fibrosis leading to impaired function and contractility.[27] Standard treatments have not been shown to influence this "end-stage phase" morphologic evolutionary process which may contribute to worse thromboembolic outcomes in HCM patients, especially in the setting of AF. In addition, another study demonstrated that the combination of AF and basal outflow tract obstruction resulting from systolic anterior motion of the mitral valve leaflet can prevent forward flow of blood and possibly contribute to adverse thromboembolic events.[5] This same study eluded to the fact that patients with obstructive HCM may rely on left atrial contraction for left ventricular filling more than non-obstructive patients, and that these same obstructive individuals may be more prone to blood stagnation and development of thrombi.[5]

Utilization of CHA_2DS_2-VASc score

While AC is generally recommended to prevent strokes in the setting of AF with CHA_2DS_2-VASc score ≥ 2, this tool has not been validated in patients with HCM.[1,8] This is due to the many clinical and mechanistic differences inherent to HCM patients.[1,8] Just one study in this systematic review evaluated the utility of this risk stratification tool.[19] Lee et al. found that among HCM patients with AF - those who experienced strokes had a significantly higher CHA_2DS_2-VASc score compared to those who did not have a stroke (5.6 ± 1.7 versus 3.0 ± 1.7, p = 0.002). Interestingly, all patients within this study that had strokes also had CHA_2DS_2-VASc scores greater than two. Inoue et al. recommended modifying the CHA2DS2 -VASc score by adding one point for the presence of HCM as it is an independent risk factor for stroke. A subsequent letter published by Joung et al. in 2019 recommended that HCM be considered as falling into the C criterion of the CHA2 DS2 -VASc score as this cardiac condition typifies heart failure with preserved ejection fraction.[31] While this would be a simple and practical approach to a well-known scoring tool, a HCM population that by itself has a 22.1% incidence of thromboembolic events also supports lifelong anticoagulation without further risk stratification. Future studies further assessing the utility of this adjusted risk stratification tool in this complex subpopulation of HCM patients are warranted, since the statistical weight has not been calculated and validated.

Limitations

Multiple limitations were encountered during this systematic review. First and foremost, this study is based on observational data, with most of the included articles being post hoc subgroup analyses with unmatched cohorts for the AC versus no AC endpoint of thromboembolic events. Potential biases are likely to be greater in these types of studies when compared to RCTs. Second, factors that may predispose patients to thromboembolic events were highly variable and sometimes unable to be accounted for within the individual studies analyzed in this systematic review. These predisposing factors include, but are not limited to, atrial size/stretch, left ventricular outflow tract obstruction, left ventricular mid-cavity obstruction, location predominant/type of hypertrophic cardiomyopathy, history of obstructive sleep apnea or hypertension, diastolic dysfunction, age, or CHA2DS2 VASc score. Moreover, some patients may have been receiving sub-therapeutic doses of VKAs or non-compliant with VKAs and DOACs during the time period that the data was collected. These factors as well as the addition of antiplatelet agents to AC may skew results.

Conclusion

While a relatively small percentage of the HCM population with AF is affected by thromboembolic events, the severity and disabling nature of these events are worth targeting and attempting to eliminate entirely. As we continue in pursuit of optimizing healthcare for HCM patients, implementing evidence-based medicine to improve clinical outcomes, quality of life, and patient satisfaction remain the primary goal. Our study lends additional support to the existing literature that AC is warranted in all patients with concomitant HCM and AF. Furthermore, this is the first systematic review to suggest that DOACs are associated with a lower incidence of thromboembolic events, major bleeding, and all-cause mortality when compared to VKAs. RCTs with larger sample sizes are warranted to help practicing cardiologists further delineate the association of these adverse outcomes and different AC strategies within this complex subpopulation of patients.

References

1. Guttmann O, Pavlou M, et al. Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). Eur J Heart Fail 2015; 17(8): 837-45.
2. Guttmann O, Rahman M, et al. Atrial Fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart 2014; 100(6): 465-72.
3. Vaidya K, Semsarian C, et al. Atrial Fibrillation in Hypertrophic Cardiomyopathy. Heart, Lung, and Circ 2017; 26(9): 975-82.
4. Go A, Hylek E, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285(18): 2370-5.

5. Olivotto I, Cecchi F, et al. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001; 104(21): 2517–24. 1,5,7,11-21
6. Nistri S, Olivotto I, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol 2006; 98(7):960–5.
7. Maron B, Olivotto I, et al. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2002; 39(2): 301–7.
8. Lip G, Lane D. Stroke prevention in atrial fibrillation: a systematic review. JAMA 2015; 313(19): 1950–62.
9. Gersh B, Maron B, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011; 124(24): 2761– 96.
10. Elliott P, Anastasakis A, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014; 35(39):2733–79.
11. Noseworthy P, Yao X, et al. Stroke and bleeding risks in NOAC- and warfarin-treated patients with hypertrophic cardiomyopathy and atrial fibrillation. JACC 2015; 67(25): 3020-3021.
12. Dominguez F, Climent V, et al. Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation. Int J Card 2017; 248: 232-8.
13. Jung H, Yang P, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. Chest 2019; 155(2): 354-63.
14. Lee H-J, Kim H-K, Jung J-H, Han K-D, Lee H, Park J-B, Kim HM, Kim Y-J, Ommen SR. Novel Oral Anticoagulants for Primary Stroke Prevention in Hypertrophic Cardiomyopathy Patients with Atrial Fibrillation. Stroke 2019; 50(9): 2582-2586.
15. Higashikawa M, Nakamura Y, et al. Incidence of ischemic stroke in hypertrophic cardiomyopathy is markedly increased if complicated by atrial fibrillation. Jpn Circ J 1997; 61(8): 673-81.
16. Doi Y, Kitaoka H. Hypertrophic cardiomyopathy in the elderly: significance of atrial fibrillation. J Cardiol 2001; 37(Suppl 1): 133-8.
17. Haruki S, Minami Y, et al. Stroke and embolic events in hypertrophic cardiomyopathy. Stroke 2016; 47(4): 936-42.
18. Inoue H, Nozawa T, et al. Accumulation of risk factors increases risk of thromboembolic events in patients with nonvalvular atrial fibrillation. Circ J 2006; 70(6): 651-656.
19. Lee S, Park J, et al. Impact of atrial fibrillation on the clinical course of apical hypertrophic cardiomyopathy. Heart 2017; 103(19): 1496-1501.
20. Rowin E, Hausvater A, et al. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. Circulation 2017; 136(25): 2420-36.
21. Tsuda T, Hayashi K, et al (in press). Effect of hypertrophic cardiomyopathy on the prediction of thromboembolism in patients with nonvalvular atrial fibrillation. Heart Rhythm 2019; 16(6): 829-37.
22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009; 62(10): e1–e34.
23. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews: Checklist for Systematic Reviews and Research Syntheses. Accessed on September 2nd, 2019 at https://joannabriggs.org/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Systematic_Reviews2017_0.pdf
24. Choi YJ, Choi EK, Han KD, Jung JH, Park J, Lee E, et al. Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among asian patients with hypertrophic cardiomyopathy: A nationwide population-based study. Int J Cardiol 2018; 273: 130-135
25. Borer JS, Atar D, Marciniak T, Kim MH, Serebruany V. Atrial Fibrillation and Stroke in Patients with Hypertrophic Cardiomyopathy: Important New Insights. Thromb Haemost 2019; 119(3): 355-357
26. Barbut D, Borer JS, Wallerson D, Ameisen O, Lockshin M. Anticardiolipin antibody and stroke: possible relation of valvular heart disease and embolic events. Cardiology 1991; 79(2) 99-109
27. Maron B, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol 1998; 81(11): 1339-44.
28. McKenna W, Deanfield J. Hypertrophic cardiomyopathy: an important cause of sudden death. Arch Dis Child 1984; 59(10): 971-975.
29. Maron B, Spirito P, Wesley Y, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. N Engl J Med 1986. 315(10): 610-14.
30. Spirito P, Maron B, Bonow R, Epstein S. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilation in patients with hypertrophic cardiomyopathy. Am J Cardiol 1987; 60(1): 123-29.
31. Joung B, Lip G. To the Editor- Patients with atrial fibrillation with hypertrophic cardiomyopathy: Do we need new stroke risk stratification? Heart Rhythm 2019; 16(8): e56.