Comparison of Effectiveness of Alcohol Septal Ablation Versus Ventricular Septal Myectomy on Acute Care Use for Cardiovascular Disease in Patients With Hypertrophic Cardiomyopathy

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Alcohol septal ablation (ASA) and ventricular septal myectomy (VSM) are 2 options of ventricular septal reduction therapy (VSRT) for obstructive hypertrophic cardiomyopathy (HC). We hypothesized that patients with HC who underwent ASA have a higher risk of acute care use (i.e., emergency department [ED] visit or unplanned hospitalization) for cardiovascular disease (CVD) than VSM. We performed a comparative effectiveness study of ASA versus VSM (reference group) among patients with HC who underwent VSRT, using population-based ED and inpatient databases in 3 states, 2005 to 2014. The outcome was acute care use for CVD during a 2-year post-VSRT period. We constructed univariable and multivariable logistic regression models to compare the risk during sequential 6-month periods. We also performed sensitivity analysis with propensity score-matching at 1:1 ratio. We identified 850 patients with HC who underwent VSRT, including 393 with ASA and 457 with VSM. During 13 to 18 months after VSRT, there was a nonsignificantly higher risk with ASA than VSM (adjusted odds ratio [OR] 1.73; 95% confidence interval [CI] 0.83 to 3.60; p = 0.14). Patients who had ASA had a significantly higher risk in the 19 to 24 months post-VSRT period (adjusted OR 2.12; 95% CI 1.06 to 4.23; p = 0.03). Similarly, the propensity score-matched analysis demonstrated a higher risk with ASA than VSM during 13 to 18 months (OR 2.97; 95% CI 1.04 to 8.46; p = 0.04) and 19 to 24 months (OR 7.06; 95% CI 2.04 to 24.36; p = 0.002) after VSRT. In conclusion, among 850 patients with HC who underwent VSRT, the risk of acute care use for CVD was higher after ASA than VSM during the second post-VSRT year. **(Am J Cardiol 2019;124:1272−1278)**

Left ventricular outflow tract (LVOT) obstruction is observed in 70% of patients with hypertrophic cardiomyopathy (HC) and can result in a variety of acute cardiovascular events.[1] Ventricular septal reduction therapy (VSRT) alleviates LVOT obstruction by reducing interventricular septal thickness.[2,3] There are currently 2 options of VSRT − ventricular septal myectomy (VSM) and alcohol septal ablation (ASA).[4] VSM has been considered as the gold standard VSRT technique for over a half century,[4] whereas ASA has gained popularity over the last 2 decades and overtaken VSM as the most commonly performed VSRT for obstructive HC.[5] However, past studies comparing ASA and VSM have focused on either surrogate of clinical end points (e.g., reduction in LVOT gradient), procedure-related complications, or postprocedural mortality.[3,6,7] To date, no studies have compared the risk of acute care use for all cardiovascular manifestations of HC. To address the knowledge gap, we designed a comparative effectiveness study to test the hypothesis that, among patients with HC, ASA is associated with a higher risk of acute care use for cardiovascular disease (CVD) compared with VSM.

Methods

We performed a comparative effectiveness study of ASA versus VSM on the risk of acute care use (i.e., emergency department [ED] visit or unplanned hospitalization) for CVD in patients with HC. We used population-based datasets − the Healthcare Cost and Utilization Project (HCUP)

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State Emergency Department Databases (SEDD) and State Inpatient Databases (SID) − from 3 states (California, Florida, and Nebraska) from 2005 to 2014.[8,9] We chose these states because of geographic diversity and unique patient identifiers which enabled us to perform longitudinal follow-up across the study years. The HCUP is the largest longitudinal hospital care database in the United States.[8,9] In the participating states, all ED visits regardless of disposition were captured in the HCUP SEDD,[8] and all inpatient discharges regardless of source of hospitalization were recorded in the SID.[9] By integrating the HCUP SEDD and SID, we identified all ED visits and hospitalizations within the 3 study states.[8,9] Details of the databases have been published previously.[8−14] The institutional review boards of Massachusetts General Hospital and Columbia University Medical Center approved this study.

We took the following steps to identify all patients with HC who underwent either ASA or VSM within the study states. First, we identified adults (aged ≥18 years) with HC using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code 425.1x. Second, among these patients with HC, we further identified patients who underwent either ASA or VSM, using the ICD-9-CM procedure code 37.34 for ASA and the code 37.33 for VSM.[15] We included patients who had either ASA or VSM from January 1, 2005 to December 31, 2012 to allow for a 2-year follow-up period. Lastly, among these patients with HC who underwent either ASA or VSM, we further identified patients with at least 1 ED visit or unplanned hospitalization for CVD during the study period (i.e., from January 1, 2005 to December 31, 2014). We excluded patients who died during the index hospitalization for VSRT and those who had 2 or more VSRTs during the study period.[10−14,16] We also excluded residents outside the study states.[10−14,16]

We retrieved data from the HCUP SEDD and SID on the patient demographics (age, gender, and race/ethnicity), primary insurance type, quartiles for estimated median household income of residents in the patient's ZIP code, *ICD-9-CM* diagnoses, procedures, season, and year of VSRT, state, and co-morbidities defined by Elixhauser co-morbidity measures.[10−14,16] We used the baseline characteristics information recorded during the index hospitalization for VSRT.

The primary outcome measure was acute care use for CVD defined as ED visit or unplanned hospitalization with a primary diagnosis of CVD. The ICD-9-CM diagnosis codes for CVD were 390-459.9.[14] The secondary outcome measures were acute care use for each of the 3 most common CVD categories − dysrhythmia, heart failure, and procedure-related complication. The 3 most common CVD categories were identified based on the risk of acute care use during the 2-year post-VSRT period according to the Clinical Classifications Software (CCS) categories for CVDs (i.e., *CCS* categories 96 to 121).[14,17]

For comparisons of the baseline characteristics between patients with ASA and those with VSM, Mann-Whitney-Wilcoxon or chi-squared test was used, as appropriate. The number of patients and risk of the outcome event was determined for 0 to 6 months, 7 to 12 months, 13 to 18 months, and 19 to 24 months after VSRT. Unadjusted and adjusted odds ratios (ORs) were computed by fitting logistic regression models − with VSM group as the reference − for each corresponding 6-month period with generalized estimating equations to account for patient clustering within hospitals. Multivariable models adjusted for age, gender, race/ethnicity, insurance type, median household income quartile, season and year of VSRT, state, and Elixhauser co-morbidity measures.

Several sensitivity analyses were performed to determine the robustness of our inferences. First, the analysis was repeated after stratifying by age group (18 to 44, 45 to 59, and ≥60 years) or gender.[18] Second, by fitting negative binomial regression models, the event rate of outcomes was modeled as a count, instead of a binary, variable. Third, to address the possibility of loss to follow-up (e.g., out-of-hospital deaths, emigration from the study states), a subgroup analysis was conducted by limiting the population to those with any ED visit or hospitalization during 25 to 36 months after VSRT. Lastly, propensity score (PS)-matched analysis was performed to address possible confounding by indication. PS was computed with the use of a logistic regression model to estimate the propensity that a patient would undergo ASA.[19] The variables included in the propensity model were the selected variables above and hospital sites. Patients who underwent ASA were matched to patients who received VSM according to PS at a 1:1 ratio. The matching was performed without replacement, using calipers (width = 0.1) of the standard deviation of the logit of the PS. Although PS-matching may lead to a smaller sample size, it provides a clinically relevant estimate of the effects since patients in the matched sample are potential candidates for either VSRT.[19] In the PS-matched groups, the risk and ORs were also calculated.

Additionally, E-values were computed for significant associations in the multivariable and PS-matched analyses. The E-value is a method to gauge the evidence for causality.[20] The E-value shows how strong an unmeasured confounder would have to be associated with the exposure and outcome in order for the observed association not to be causal.[20] For example, an E-value of 3.0 means that the ORs for the associations of an unmeasured confounder with both the exposure and outcome would have to be >3.0 to explain away the observed exposure-outcome association.[20]

All analyses were performed at a 2-sided significance level of 0.05, and all confidence intervals (CIs) were reported as 2-sided values with a confidence level of 95%. Statistical analyses were performed using STATA 14.1 (StataCorp; College Station, TX).

Results

A total of 850 patients − 393 with ASA and 457 with VSM − met the inclusion and exclusion criteria and were included in the analysis. The median follow-up duration was 6.4 years (interquartile range, 4.5 to 8.5). The baseline characteristics are described in Table 1 and Supplemental Table 1. At baseline, patients who underwent ASA had a significantly lower prevalence of heart failure, valvular heart disease, hypertension, chronic pulmonary disease, and obesity (all p <0.005).

The number and risk of acute care use for CVD according to the type of VSRT are displayed in Figure 1. The

Table 1
Baseline characteristics of patients with hypertrophic cardiomyopathy who underwent alcohol septal ablation or ventricular septal myectomy

Characteristics	Alcohol septal ablation (n = 393)	Ventricular septal myectomy (n = 457)	p Value
Age ± standard deviation (year)	62 ± 15	61 ± 16	0.23
Female sex	218 (56%)	249 (54%)	0.71
Race/ethnicity*			0.18
Non-Hispanic white	274 (70%)	312 (68%)	
Non-Hispanic black	23 (6%)	27 (6%)	
Hispanic	46 (12%)	49 (11%)	
Asian	28 (7%)	24 (5%)	
Other	22 (6%)	45 (10%)	
Primary insurance			0.21
Medicare	197 (50%)	224 (49%)	
Medicaid	17 (4%)	32 (7%)	
Private	160 (41%)	176 (39%)	
Self-pay	≤10 (<3%)	≤10 (<3%)	
Other	17 (4%)	17 (4%)	
Quartiles for median household income			0.67
1 (lowest)	87 (23%)	107 (24%)	
2	97 (25%)	102 (23%)	
3	93 (24%)	119 (27%)	
4 (highest)	109 (28%)	116 (26%)	
Season of ventricular septal reduction therapy			0.49
January-March	108 (28%)	112 (25%)	
April-June	89 (23%)	122 (27%)	
July-September	92 (23%)	110 (24%)	
October-December	104 (26%)	113 (25%)	
Year of ventricular septal reduction therapy			0.22
2005	56 (14%)	58 (13%)	
2006	56 (14%)	70 (15%)	
2007	71 (18%)	52 (11%)	
2008	51 (13%)	64 (14%)	
2009	67 (17%)	88 (19%)	
2010	24 (6%)	29 (6%)	
2011	33 (8%)	50 (11%)	
2012	35 (9%)	46 (10%)	
Hospital state			<0.001
California	188 (48%)	170 (37%)	
Florida	194 (49%)	252 (55%)	
Nebraska	11 (3%)	35 (8%)	
Selected comorbidities†			
Heart failure	102 (26%)	171 (37%)	<0.001
Arrhythmia	280 (71%)	301 (66%)	0.09
Valvular heart disease	96 (24%)	347 (76%)	<0.001
Hypertension	227 (58%)	307 (67%)	0.005
Chronic pulmonary disease	73 (19%)	143 (31%)	<0.001
Diabetes mellitus	60 (15%)	84 (18%)	0.23
Obesity	41 (10%)	89 (20%)	<0.001

Exact numbers in cells with ≤10 patients were not shown according to the Healthcare Cost and Utilization Project Data Use Agreement.
* Race/ethnicity data were not available in Nebraska.
† Defined by Elixhauser co-morbidity measures. Full list of co-morbidities is displayed in Supplemental Table 1.

univariable analysis showed that the risk was significantly lower in ASA group during the first 6 post-VSRT months (Figure 1). There were no significant differences in the risk during the 7 to 12 and 13 to 18 post-VSRT months (both p >0.10). The risk was significantly higher in ASA group during 19 to 24 months after VSRT.

In the multivariable analysis adjusting for 23 potential confounders and patient clustering (Figure 1), there were no significant differences in the risk of acute care use for CVD between the 2 groups during the first 6 months, 7 to 12 months, and 13 to 18 months after VSRT. In contrast, the patients who received ASA had a significantly higher risk of the outcome in the 19 to 24 months post-VSRT period (adjusted OR 2.12; 95% CI 1.06 to 4.23; p = 0.03; E-value = 3.66) compared with those who had VSM.

The sensitivity analyses demonstrated the robustness of the findings. In the stratified analyses by age group (Supplemental Figure 1) and gender (Supplemental Figure 2) as well as the sensitivity analysis using negative binomial regression model with the outcome as a count variable (Supplemental Figure 3), the findings were similar. Furthermore, the subgroup analysis limiting to the patients with any healthcare utilization

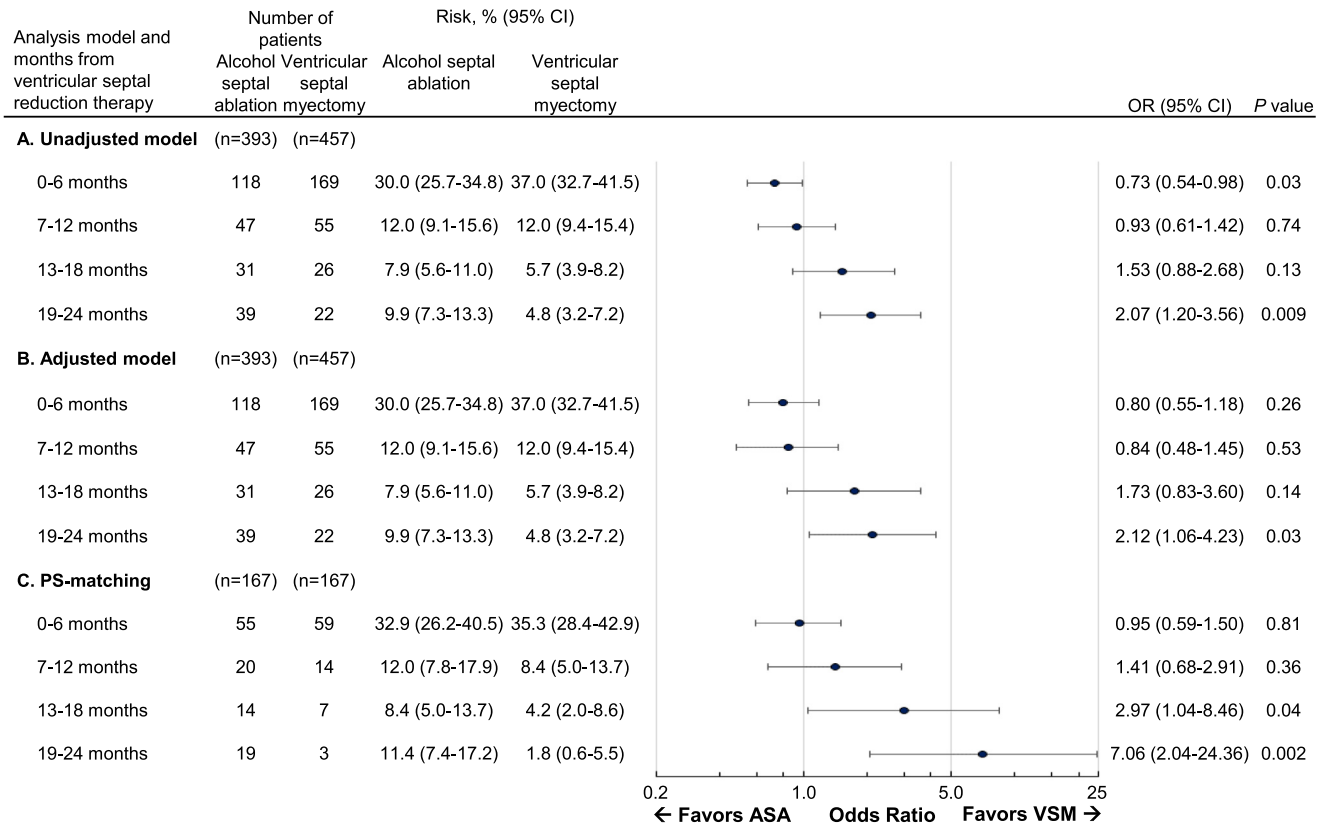

Figure 1. Acute care use for cardiovascular disease in 6-month intervals among patients with hypertrophic cardiomyopathy who underwent alcohol septal ablation or ventricular septal myectomy. Shown are the number of patients with an ED visit or unplanned hospitalization for CVD, risk of the outcome event, and odds ratio in 6-month intervals, using (*A*) unadjusted model, (*B*) multivariable model adjusting for age, gender, race/ethnicity, insurance type, household income quartile, season and year of ventricular septal reduction therapy, state, and Elixhauser co-morbidity measures, and (*C*) PS-matching. Odds ratios were calculated for each 6-month period with VSM group as the reference, using logistic regression model with generalized estimating equations to account for patient clustering within hospitals. Co-morbidities with prevalence <0.5% in both groups were excluded from the multivariable model.
ASA = alcohol septal ablation; CI = confidence interval; CVD = cardiovascular disease; ED = emergency department; OR = odds ratio; PS = propensity score; VSM = ventricular septal myectomy.

during 25 to 36 months after VSRT replicated the results (Supplemental Figure 4).

In the PS-matched cohort, the baseline characteristics of 2 patient groups were all balanced as indicated by p value >0.25 in all covariates (Table 2 and Supplemental Table 2). Consistent with the main analysis, patients who underwent ASA had a significantly higher risk of acute care use for CVD during 13 to 18 (OR 2.97; 95% CI 1.04 to 8.46; p = 0.04; E-value = 5.39) and 19 to 24 months (OR 7.06; 95% CI 2.04 to 24.36; p = 0.002; E-value = 13.6) after VSRT (Figure 1).

With further classification according to the CVD categories (Figure 2), the risk of acute care use for dysrhythmia was significantly higher in patients with ASA during the second post-VSRT year. Approximately 65% of these dysrhythmia events were related to atrial fibrillation (AF). In contrast, there was a nonsignificantly lower risk of acute care use for heart failure and procedure-related complication in ASA group during the first post-VSRT year.

Discussion

In this comparative effectiveness study using population-based data of 850 patients with HC, patients who underwent ASA had a significantly higher risk of acute care use for CVD compared with those who had VSM in the 19 to 24 months after VSRT despite the higher burden of cardiopulmonary disease in the VSM group. The difference persisted across several analytical assumptions and was consistently observed with PS-matching. The between-group difference was primarily driven by the higher risk of acute care use for dysrhythmia in ASA group during the second post-VSRT year. In contrast, there was a nonsignificantly higher risk of acute care use for heart failure and procedure-related complication with VSM in the early post-VSRT period. To the best of our knowledge, this is the first study that has examined the effectiveness of the 2 different types of VSRT (i.e., ASA and VSM) on all acute CV manifestations of HC.

HC manifests itself with a variety of cardiovascular conditions − for example, heart failure, AF and related stroke, and ventricular tachycardia/fibrillation. However, the currently-available evidence on the effects of VSRT is mainly focused on reductions in LVOT gradient, complications, and mortality.[3,6,7] For instance, recent meta-analyses have shown that VSM results in greater reduction in LVOT gradient.[3,6,7] The risk of conduction abnormality and the need

Table 2
Baseline characteristics of patients with hypertrophic cardiomyopathy who underwent alcohol septal ablation and propensity score-matched patients who underwent ventricular septal myectomy

Characteristics	Alcohol septal ablation n = 167	Ventricular septal myectomy n = 167	p Value
Age ± standard deviation (year)	61 ± 15	61 ± 15	0.92
Female sex	97 (58%)	92 (55%)	0.58
Race/ethnicity*			0.80
Non-Hispanic white	112 (67%)	115 (69%)	
Non-Hispanic black	13 (8%)	≤10 (<6%)	
Hispanic	16 (10%)	18 (11%)	
Asian	14 (8%)	12 (7%)	
Other	12 (7%)	14 (8%)	
Primary insurance			0.89
Medicare	82 (49%)	81 (49%)	
Medicaid	11 (7%)	≤10 (<6%)	
Private	64 (38%)	68 (41%)	
Self-pay	≤10 (<6%)	≤10 (<6%)	
Other	≤10 (<6%)	≤10 (<6%)	
Quartiles for median household income			0.98
1 (lowest)	40 (25%)	37 (23%)	
2	38 (24%)	39 (24%)	
3	35 (22%)	34 (21%)	
4 (highest)	49 (30%)	51 (32%)	
Season of ventricular septal reduction therapy			0.94
January-March	40 (24%)	38 (23%)	
April-June	48 (29%)	46 (28%)	
July-September	39 (23%)	38 (23%)	
October-December	40 (24%)	45 (27%)	
Year of ventricular septal reduction therapy			0.98
2005	25 (15%)	22 (13%)	
2006	25 (15%)	23 (14%)	
2007	24 (14%)	24 (14%)	
2008	23 (14%)	23 (14%)	
2009	32 (19%)	37 (22%)	
2010	≤10 (<6%)	≤10 (<6%)	
2011	13 (8%)	17 (10%)	
2012	19 (11%)	16 (10%)	
Hospital state			0.90
California	77 (46%)	81 (49%)	
Florida	82 (49%)	78 (47%)	
Nebraska	≤10 (<6%)	≤10 (<6%)	
Selected comorbidities†			
Heart failure	56 (34%)	56 (34%)	>0.99
Arrhythmia	121 (72%)	113 (68%)	0.34
Valvular heart disease	86 (51%)	87 (52%)	0.91
Hypertension	109 (65%)	100 (60%)	0.31
Chronic pulmonary disease	39 (23%)	37 (22%)	0.79
Diabetes mellitus	32 (19%)	30 (18%)	0.78
Obesity	20 (12%)	20 (12%)	>0.99

Exact numbers in cells with ≤10 patients were not shown according to the Healthcare Cost and Utilization Project Data Use Agreement.
* Race/ethnicity data were not available in Nebraska.
† Defined by Elixhauser co-morbidity measures. Full list of co-morbidities is displayed in Supplemental Table 2.

for permanent pacemaker placement are higher after ASA than VSM, whereas mortality rate is similar.[3,7] Yet, no previous studies have examined whether such differences are translated into differential risk of acute care use for the overall CVD. In this context, the current study provides the most comprehensive evidence on the comparative CV effectiveness of ASA versus VSM.

There was a nonsignificantly higher risk of heart failure-related acute care use and procedure-related complication with VSM during the first postoperative year. Compared with ASA, VSM is more invasive as it involves general anesthesia, sternotomy, and cardiopulmonary bypass.[4] These can result in fluid retention and heart failure due to neurohormonal changes. It is also known that the risk of certain post-VSRT complications – for example, infection, bleeding – is higher after VSM.[4] These unfavorable factors unique to open heart surgery may have contributed to the observed higher risk in VSM group in the short term. In contrast, ASA was associated with a significantly higher risk of acute care use for dysrhythmia during the second

CVD category and months from ventricular septal reduction therapy	Number of patients: Alcohol septal ablation (n=393)	Number of patients: Ventricular septal myectomy (n=457)	Risk, % (95% CI): Alcohol septal ablation	Risk, % (95% CI): Ventricular septal myectomy	OR (95% CI)	*P* value
Dysrhythmia						
0-12 months	34	30	8.7 (6.2-11.9)	6.6 (4.6-9.2)	1.33 (0.79-2.25)	0.29
13-24 months	16	6	4.1 (2.5-6.6)	1.3 (0.6-2.9)	3.65 (1.32-10.05)	0.01
Heart failure						
0-12 months	17	31	4.3 (2.7-6.9)	6.8 (4.8-9.5)	0.59 (0.32-1.08)	0.09
13-24 months	9	6	2.3 (1.2-4.3)	1.3 (0.6-2.9)	1.67 (0.59-4.74)	0.33
Procedure-related complication						
0-12 months	18	37	4.6 (2.9-7.2)	8.1 (5.9-11.0)	0.56 (0.31-1.02)	0.06
13-24 months	3	9	0.8 (0.2-2.3)	2.0 (1.0-3.7)	0.36 (0.10-1.35)	0.13

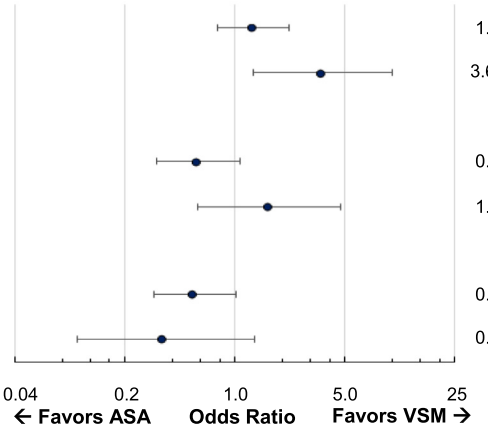

Figure 2. Acute care use for 3 most common categories of cardiovascular disease in 12-month intervals among patients with hypertrophic cardiomyopathy who underwent alcohol septal ablation or ventricular septal myectomy. Shown are the number of patients with an ED visit or unplanned hospitalization for CVD, risk of the outcome event, and odds ratio in 12-month intervals for each of the 3 most common categories of CVD. Odds ratios were calculated for each 12-month period with VSM group as the reference, using logistic regression model with generalized estimating equations to account for patient clustering within hospitals.

ASA = alcohol septal ablation; CI = confidence interval; CVD = cardiovascular disease; ED = emergency department; OR = odds ratio; VSM = ventricular septal myectomy.

post-VSRT year. Potential explanations include the smaller reduction in the degree of LVOT obstruction achieved with ASA,[3,6,7] which can in turn aggravate some of the potential triggers of AF − for example, LV filling pressures, left atrial size, and adverse left atrial remodeling. These factors may have contributed to the increased risk of dysrhythmia-related acute event in ASA group in the long run.

A large-scale, high-quality randomized controlled trial (RCT) would be ideal to compare the efficacy and safety of ASA versus VSM. However, such an RCT would be resource- and time consuming. Approximately 34,000 patients with HC would need to be screened and ~1,000 to be randomized to perform such a trial, which was deemed "virtually insurmountable."[21] In this context, the present study provides the most robust evidence on the comparative effectiveness of ASA and VSM as it included 850 patients who underwent VSRT. Indeed, this sample size is larger than any of the previous meta-analyses.[3,6,7] Additionally, participants enrolled in an RCT may be different or behave differently than the general population because of vigorous selection processes and highly controlled environment.[22,23] In contrast, the present study captured all ED visits and hospitalizations of racially/ethnically-, socioeconomically-, and geographically diverse population in the natural setting. These factors strengthen the external validity of the study.

In addition to the rigorous adjustment for potential confounders in the adjusted models, the PS-matched analysis augments the internal validity as it reduces intergroup differences at baseline and enables a more precise assessment of the effectiveness of different interventions.[19] Indeed, the PS-matched groups in our dataset had similar characteristics at baseline, addressing the possibility of confounding by indication. Additionally, the E-values in the present study were all >3.5. This indicates that, in order for an unmeasured confounder to bring the observed exposure-outcome association to null, the confounder would have to be associated with both the exposure and the outcome by an OR of >3.5-fold each.[20] Such a "substantial"[20] unmeasured confounding would be necessary to explain away the observed associations.[20]

Our study has several potential limitations. First, due to the use of administrative data, misclassification could have occurred. However, the quality of the HCUP datasets has been extensively tested in previous studies.[10−14,16,24] Further, our inclusion criteria required both the diagnostic code for HC and the procedure code for VSRT, thereby increasing the specificity.[25] Regarding the outcome, previous studies have shown that administrative data have high specificity and positive predictive value to identify CVD-related acute care use. For example, most studies reported values of >95% for identifying acute heart failure exacerbation and dysrhythmia.[14,26,27] Second, there were variables not collected a priori (e.g., echocardiographic measurements). Yet, the high E-values indicated that the evidence for causality was "reasonably strong."[20] Last, time-to-event analysis with the Cox proportional hazards method could not be performed as the proportional hazards assumption did not hold true.

In this comparative effectiveness study of 850 patients with HC using large population-based datasets from 3 diverse states in the United States, we found that ASA is associated with a significantly higher risk of CVD-related acute care use when compared with VSM in the second year after VSRT. In conjunction with the physiological

studies reporting smaller reduction in LVOT obstruction with ASA, the present study lends support to the concept that ASA offers less cardioprotective effects than VSM in the long run.

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.2019.07.031.

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