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Outcomes of Patients With Hypertrophic Obstructive Cardiomyopathy and Pacemaker Implanted After Alcohol Septal Ablation

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ABSTRACT

BACKGROUND Atrioventricular block is a frequent major complication after alcohol septal ablation (ASA).

OBJECTIVES The aim of this study was to evaluate the outcomes of patients with implanted permanent pacemaker (PPM) related to a high-grade atrioventricular block after ASA for hypertrophic obstructive cardiomyopathy.

METHODS We used a multinational registry (the Euro-ASA registry) to evaluate the outcome of patients with PPM after ASA.

RESULTS A total of 1,814 patients were enrolled and followed up for 5.0 ± 4.3 years (median = 4.0 years). A total of 170 (9.4%) patients underwent PPM implantation during the first 30 days after ASA. Using propensity score matching, 139 pairs (278 patients) constituted the matched PPM and non-PPM groups. Between the matched groups, there were no long-term differences in New York Heart Association functional class (1.5 ± 0.7 vs 1.5 ± 0.9, $P = 0.99$) and survival (log-rank $P = 0.47$). Patients in the matched PPM group had lower long-term left ventricular (LV) outflow gradient (12 ± 12 mm Hg vs 17 ± 19 mm Hg, $P < 0.01$), more pronounced LV outflow gradient decrease (81% ± 17% vs 72% ± 35%, $P < 0.01$), and lower LV ejection fraction (64% ± 8% vs 66% ± 8%, $P = 0.02$) and were less likely to undergo reintervention (re-ASA or myectomy) (log-rank $P = 0.02$).

CONCLUSIONS Patients with hypertrophic obstructive cardiomyopathy treated with ASA have a 9% probability of PPM implantation within 30 days after ASA. In long-term follow-up, patients with PPM had similar long-term survival and New York Heart Association functional class but lower LV outflow gradient, a more pronounced LV outflow gradient decrease, a lower LV ejection fraction, and a lower likelihood of reintervention compared with patients without PPM.
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ABBREVIATIONS AND ACRONYMS

ASA = alcohol septal ablation

AV = atrioventricular

BBB = bundle branch block

CCS = Canadian Cardiovascular Society

HOCM = hypertrophic obstructive cardiomyopathy

ICD = implantable cardioverter-defibrillator

LV = left ventricular

NYHA = New York Heart Association

PPM = permanent pacemaker

Alcohol septal ablation (ASA) is used to treat symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM).[1-4] Because of the proximity of the perfusion territory of the coronary artery septal branches to the cardiac conduction system (especially the right bundle branch), a significant complication of ASA-induced targeted myocardial necrosis is periprocedural atrioventricular (AV) block requiring implantation of a permanent pacemaker (PPM) in 7% to 20% of cases.[5-9]

Currently, very limited evidence is available on the outcomes of these patients.[10,11] Based on a multinational European registry (the Euro-ASA registry) of patients who underwent ASA for HOCM, we determined the short- and long-term outcomes of patients with PPM implanted for high-grade ASA-related AV block. Furthermore, we used propensity score matching analysis to compare the outcomes of patients with and without PPM.

METHODS

DIAGNOSIS AND PATIENTS. The diagnosis of HOCM was established by experienced cardiologists based on typical clinical, electrocardiographic, and echocardiographic features; patients had to have a left ventricular (LV) outflow tract gradient ≥30 mm Hg at rest and/or ≥50 mm Hg after provocation.

TABLE 1 Clinical and Echocardiographic Characteristics of Study Patients at Baseline and at the Last Clinical Checkup

	Unmatched Cohort			Matched Cohort		
	PPM Group (N = 170)	Non-PPM Group (N = 1,644)	*P* Value	PPM Group (N = 139)	Non-PPM Group (N = 139)	*P* Value
Age, years	62.5 ± 12.1	57.5 ± 13.6	<0.001	60.6 ± 11.8	60.1 ± 11.6	0.713
Females	85 (50)	839 (51)	0.809	71 (51)	72 (52)	1.000
ASA alcohol dose, mL	2.2 ± 1.1	2.1 ± 1.2	0.038	2.2 ± 1.1	2.0 ± 1.1	0.059
Alcohol dose during the first ASA, mL	2.1 ± 1.0	2.0 ± 0.9	0.021	2.1 ± 1.0	1.9 ± 0.8	0.031
Bundle branch block before ASA	55 (33)	203 (12)	<0.001	45 (33)	26 (19)	0.013
Basal septum thickness (mm)						
Baseline	20.1 ± 3.3	20.7 ± 3.8	0.101	20.2 ± 3.3	20.0 ± 2.7	0.982
Last clinical checkup	14.9 ± 4.1	15.7 ± 4.0	0.013	15.0 ± 4.1	15.7 ± 3.6	0.069
NYHA functional class						
Baseline	2.8 ± 0.5	2.7 ± 0.6	0.017	2.8 ± 0.5	2.7 ± 0.5	0.497
Last clinical checkup	1.5 ± 0.8	1.4 ± 0.9	0.030	1.5 ± 0.7	1.5 ± 0.9	0.989
NYHA functional class III/IV						
Baseline	129 (77)	1111 (68)	0.018	106 (76)	104 (75)	0.889
Last clinical checkup	17 (11)	141 (11)	0.782	10 (8)	21 (18)	0.021
Angina, CCS class						
Baseline	1.1 ± 1.2	1.0 ± 1.1	0.471	1.2 ± 1.2	1.1 ± 1.1	0.367
Last clinical checkup	0.4 ± 0.7	0.5 ± 0.8	0.089	0.5 ± 0.7	0.5 ± 0.7	0.854
LV outflow gradient at rest, mm Hg						
Baseline	76.6 ± 41.9	67.5 ± 35.1	0.015	71.8 ± 37.5	69.7 ± 34.0	0.737
Last clinical checkup	13.2 ± 20.2	17.6 ± 19.8	<0.001	11.9 ± 12.3	17.1 ± 18.9	0.002
>30 mm Hg	13 (8)	260 (16)	0.003	12 (9)	23 (17)	0.069
Percent LV outflow gradient decrease at last clinical checkup, %	80.9 ± 17.3	70.4 ± 30.8	<0.001	80.8 ± 16.6	71.7 ± 35.2	0.001
LV diameter, mm						
Baseline	44.2 ± 6.3	44.3 ± 6.3	0.857	44.5 ± 6.2	45.5 ± 6.4	0.389
Last clinical checkup	46.7 ± 6.0	46.0 ± 5.9	0.209	46.8 ± 6.1	46.9 ± 5.8	0.986
LV ejection fraction, %						
Baseline	67.7 ± 8.8	69.7 ± 8.4	0.015	68.4 ± 7.9	67.8 ± 8.0	0.395
Last clinical checkup	63.3 ± 9.2	66.5 ± 8.0	<0.001	63.5 ± 8.4	66.1 ± 7.9	0.022
Left atrium diameter, mm						
Baseline	46.8 ± 6.2	45.7 ± 6.4	0.016	46.8 ± 6.1	46.1 ± 5.3	0.205
Last clinical checkup	46.2 ± 7.1	44.6 ± 6.7	0.003	46.3 ± 7.2	45.1 ± 6.3	0.127
Mean follow-up duration, years Median	4.8 ± 4.1 4.0 (1.5, 7.6)	5.0 ± 4.4 4.0 (1.3, 7.8)		4.9 ± 4.1 4.1 (1.9, 7.6)	4.7 ± 4.0 4.0 (1.3, 6.7)	

Values are mean ± SD, n (%), or median (quartile 1, quartile 3).

ASA = alcohol septal ablation; CCS = Canadian Cardiovascular Society; LV = left ventricular; NYHA = New York Heart Association; PPM = pacemaker.

The indication for ASA was intractable clinical symptoms despite maximal pharmacotherapy. The decision regarding septal reduction therapy (ASA vs myectomy) was made after detailed multidisciplinary discussions and shared decision making with the patients.

INTERVENTIONS. Procedures were performed in tertiary invasive centers in 6 European countries. All patients had been prospectively included in institutional registries and subsequently in the Euro-ASA registry.[8] ASA procedures were performed by experienced interventional cardiologists, with only 1 or 2 interventionalists performing all procedures in each center. Details of the technique have been published in the past[4,12]; the indication and procedural technique were at the discretion of the participating centers. There were no major differences in the technique or methodology of performing ASA among sites. The post-ASA patients were observed in the coronary care unit for ≥48 hours. If no episodes of AV block occurred, the periprocedural temporary pacemaker was removed. The indication and technique for PPM implantation was at the discretion of the treating clinicians, and PPMs were usually implanted if high-grade AV block persisted for ≥24 hours or occurred later after the procedure.[5-7,13]

STUDY DESIGN AND OUTCOMES. Clinical, demographic, and echocardiographic data and symptoms were recorded at baseline and during follow-up. Patients underwent a clinical examination 1 to 6 months after ASA and every year thereafter. The follow-up program included recording of symptoms, physical and echocardiographic examination, and electrocardiography. All clinical adverse events were confirmed by reviewing the medical records. The survival of patients treated in the Czech Republic, Russia, and Denmark were confirmed by the National Database of Deaths. The survival of patients treated in the other countries was recently updated by clinical examination, telephone call, or mail communication. The study was performed in compliance with the Declaration of Helsinki.

We identified patients with PPM implanted for high-grade periprocedural AV block (**Table 1**) and used the propensity score to match each patient with a comparable patient without PPM. We then compared both short- and long-term outcomes in all groups of patients.

We assessed the following outcomes: 1) 30-day all-cause mortality rate, 2) long-term all-cause mortality rate, 3) long-term New York Heart Association (NYHA) functional class, 4) long-term LV outflow gradient and percent LV gradient decrease, 5) long-term LV ejection fraction, and 6) long-term rate of reintervention (re-ASA or myectomy).

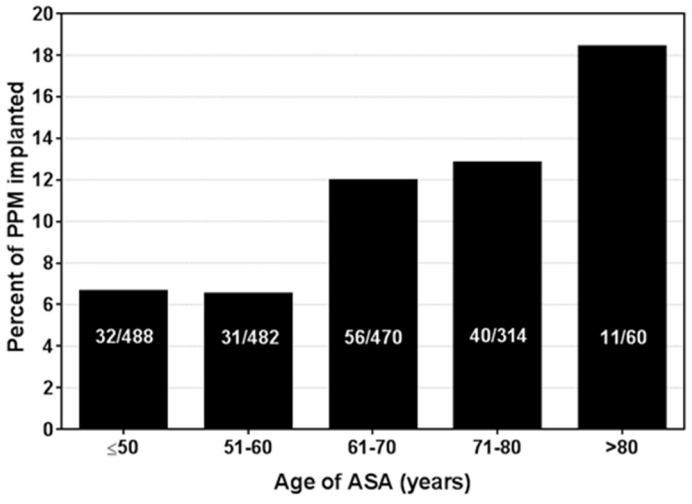
TABLE 2 Predictors of Pacemaker Implantation During 30 Days After Alcohol Septal Ablation

	Odds Ratio	95% CI	*P* Value
NYHA functional class III/IV (reference category: NYHA functional class I/II)	1.63	1.07-2.49	0.024
Age (per a unit increase [ie, 1 year of age])	1.02	1.00-1.03	0.029
LV ejection fraction at baseline (per a unit increase [ie, 1 percentage point increase])	0.97	0.95-1.00	0.014
IVS thickness at baseline (per a unit increase [ie, 1 mm if thickness increase])	0.94	0.89-0.99	0.026
BBB before ASA (reference category: no BBB before ASA)	3.56	2.38-5.31	<0.001
Alcohol dose during the first ASA (per a unit increase [ie, 1-mL increase])	1.36	1.14-1.63	0.001

BBB = bundle branch block; IVS = interventricular septum; LV = left ventricular; NYHA = New York Heart Association.

STATISTICAL ANALYSIS. All data were assessed and edited by 2 research statisticians. Data are presented as mean ± SD or median and quartiles (Q1, Q3) in case of the follow-up duration and numbers and proportions for categoric variables, respectively. The Mann-Whitney *U* test was used to assess the difference between continuous variables, and the Fisher exact test was used for categoric variables. We compared patients with PPMs implanted during 30 days after ASA (the PPM group) and patients without PPMs implanted during this period (the non-PPM group). We calculated a propensity score for the following baseline variables: sex, age, LV outflow gradient, LV end-diastolic diameter, basal interventricular septum thickness, LV ejection fraction, and NYHA functional class. The propensity score matching was performed using the PSMATCH procedure (SAS software, version 9.4; SAS) (Supplemental Figure 1). Records with missing observations for key variables were not entered into the matching. The calculation yielded 139 patients with PPM (the matched PPM group) and matched them with 139 patients without PPM (the matched non-PPM group). To find risk predictors of all-cause mortality in the matched cohort, the following baseline variables were evaluated in a multivariable model using a backward stepwise algorithm for the Cox proportional hazards survival model: sex, age, LV outflow gradient, LV end-diastolic diameter, interventricular septum thickness, LV ejection fraction, NYHA functional class I/II or III/IV, bundle branch block (BBB) before ASA, total alcohol dose, and distinguishing of the PPM and non-PPM groups of patients. The same variables were used in a logistic regression to find risk predictors of PPM implantation

FIGURE 1 Percent of Permanent Pacemakers (PPMs) Implanted



Relationship between the patient's age and the probability of PPM implantation within 30 days after alcohol septal ablation (ASA).

in which the year of ASA also was performed as a predictor in the form of 2 categories (ASA in 1996-2009 and ASA in 2010 and later), and instead of the total alcohol dose, the alcohol dose during the first ASA was used. Estimates for long-term outcomes were performed using the Kaplan-Meier method (including 95% CIs), and differences were assessed by the log-rank test. $P < 0.05$ was considered statistically significant. All reported P values were 2-sided. All analyses were performed using SAS software (version 9.4).

RESULTS

A total of 1,977 consecutive patients with symptomatic HOCM underwent ASA between 1996 and 2021 and were registered in the Euro-ASA registry, which is a multinational European registry of ASA patients.[8] For the analysis, we excluded 163 (8.2%) patients, including 15 (0.8%) patients with myectomy before ASA, 126 (6.4%) patients with a PPM or implantable cardioverter-defibrillator (ICD) implanted before ASA, and 22 (1.1%) patients with an ICD implanted for the prevention of sudden cardiac death during 30 days after ASA. The mean follow-up duration of these patients (n = 163) was 5.3 ± 5 years, and a total of 22 of these patients died, which translated to an all-cause mortality rate of 2.5 per 100 patient-years.

UNMATCHED COHORT. We analyzed 1,814 ASA patients (Table 1). A total of 16 (0.9%) patients died during 30 days after ASA, including 2 (1%) in the PPM group and 14 (0.9%) in the non-PPM group ($P = 0.66$) (Supplemental Table 1).

The PPM group was composed of 170 (9.4%) patients, 150 (88%) of whom received a PPM during the first post-ASA week and 20 (12%) a PPM between day 8 and day 30 after the procedure. Later, PPMs were implanted in a further 56 (3%) patients at a mean of 3.6 ± 3.7 years after ASA.

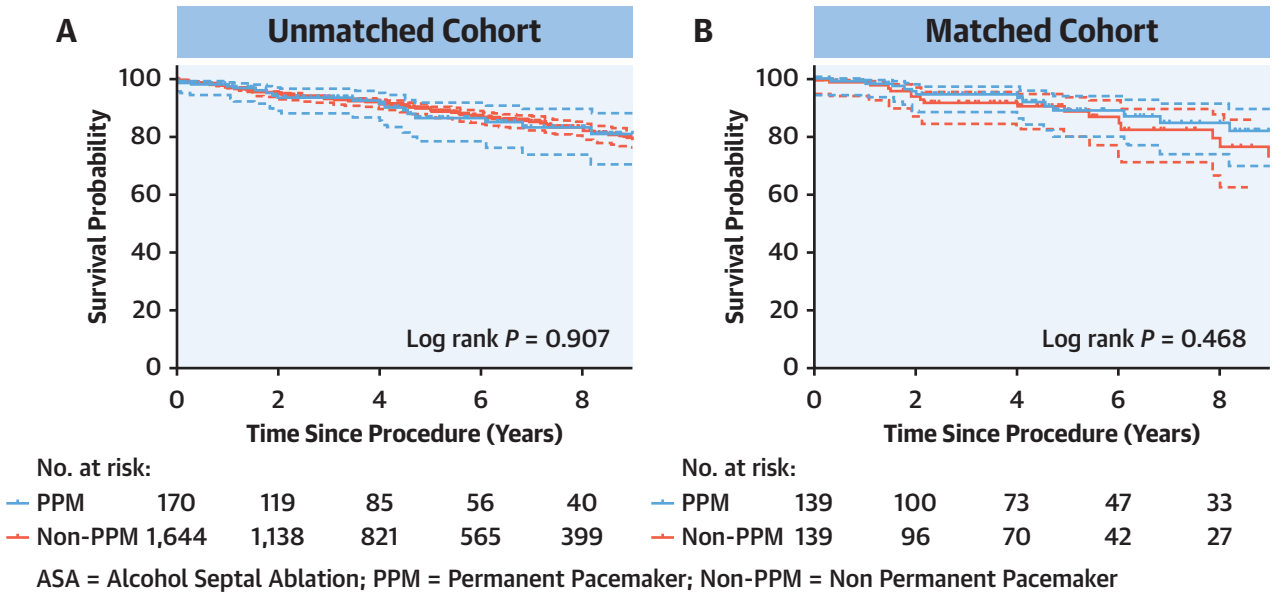
Patients in the PPM group were older ($P < 0.01$), more often had a BBB before ASA ($P < 0.01$), had a higher NYHA functional class before ASA and at the last clinical checkup ($P = 0.02$ and $P = 0.03$), received a higher total alcohol dose ($P = 0.04$), had a higher LV outflow gradient before ASA ($P = 0.02$) and a lower LV outflow gradient at the last clinical checkup ($P < 0.01$), had a lower basal septum thickness at the last clinical checkup ($P = 0.01$), had a larger left atrial diameter before ASA and at the last clinical checkup ($P = 0.02$ and $P = 0.003$), and a lower LV ejection fraction before ASA and at the last clinical checkup ($P = 0.02$ and $P < 0.01$) (Table 1). In multivariable analysis, the predictors of PPM implantation were older age at baseline, worse NYHA functional class (III/IV), lower LV ejection fraction, lower basal septum thickness, higher alcohol dose during the first ASA, and a BBB before ASA (Table 2). Patients ≤60 years were less likely to undergo PPM implantation than older patients (6.5% vs 12.7%, $P < 0.01$) (Figure 1).

Overall, the mean duration of follow-up was 5.0 ± 4.3 years, and a total of 245 deaths occurred during 9,066 patient-years, which translated to an all-cause mortality rate of 2.7 per 100 patient-years. Freedom from all-cause mortality in the PPM group (N = 170) at 1, 5, and 10 years was 98% (95% CI: 94%-99%), 88% (95% CI: 79%-92%), and 78% (95% CI: 65%-86%), respectively. This observed mortality was comparable with the mortality of the non-PPM group (N = 1,644) (log-rank $P = 0.91$, Central Illustration).

A total of 194 (11%) patients underwent repeated septal reduction procedures (re-ASA or myectomy) attributable to persisting symptoms and/or LV outflow gradient. The Kaplan-Meier curves describing reinterventions rates are shown in Figure 2A; patients in the PPM group were less likely to undergo reinterventions (log-rank $P = 0.03$).

MATCHED COHORT. The matched cohort analysis comprised 278 patients with 139 patients in the matched PPM group and 139 in the matched non-PPM group. One (0.4%) patient died during 30 days after ASA, including 0 patients and 1 patient in the matched PPM group and the non-PPM group ($P = 1.00$), respectively (Supplemental Table 1).

CENTRAL ILLUSTRATION **Survival of Paced Versus Nonpaced Patients After Alcohol Septal Ablation**



ASA = Alcohol Septal Ablation; PPM = Permanent Pacemaker; Non-PPM = Non Permanent Pacemaker

Veselka J, et al. J Am Coll Cardiol Intv. 2022;■(■):■-■.

Kaplan-Meier survival curves with 95% CIs describing the freedom from all-cause mortality in **(A)** the permanent pacemaker (PPM) versus the non-PPM groups and **(B)** the matched PPM versus the matched non-PPM groups.

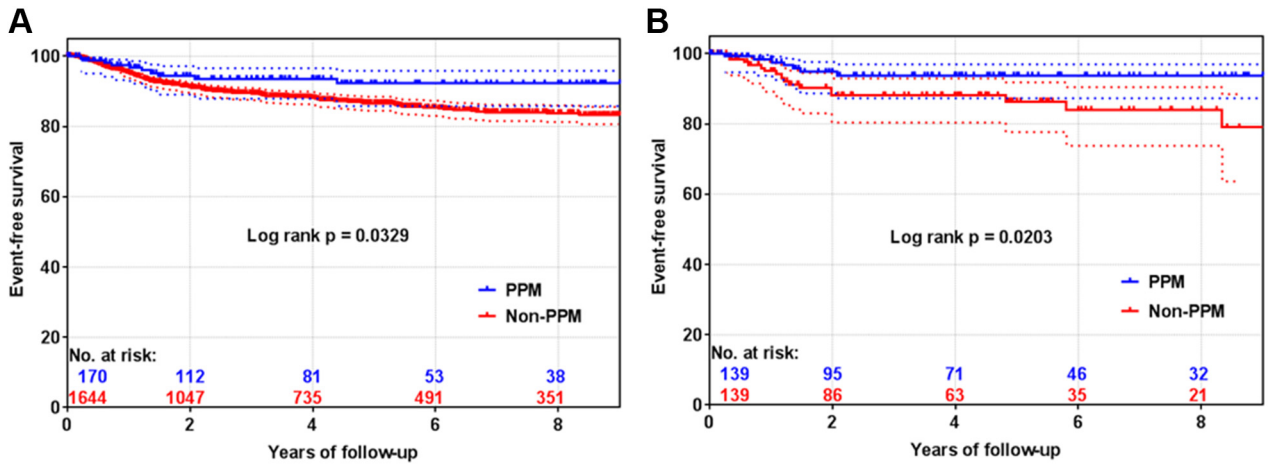
Patients in the matched PPM group more often had a BBB before ASA ($P = 0.01$), were treated with a higher dose of alcohol during the first ASA ($P = 0.03$), had a more pronounced reduction of LV outflow gradient and a lower LV outflow gradient at the last clinical checkup ($P < 0.01$ for both), had a lower LV ejection fraction at the last clinical checkup ($P = 0.02$), and had a lower proportion of patients who had NYHA functional class III/IV in comparison to the non-PPM group ($P = 0.02$) (Table 1). The mean duration of follow-up was 4.9 ± 4.1 years, and a total of 33 deaths occurred during 1,335 patient-years, translating to an all-cause mortality rate of 2.5 per 100 patient-years.

Freedom from all-cause mortality in the matched PPM group at 1, 5, and 10 years was 98% (95% CI: 94%-100%), 89% (95% CI: 80%-94%), and 78% (95% CI, 61%-88%), respectively. This observed mortality was comparable with the survival of the matched non-PPM group ($P = 0.47$) (Central Illustration). In multivariable analysis, the predictors of all-cause mortality were older age at baseline ($P < 0.01$) and BBB before ASA ($P = 0.01$). A total of 24 (9%) patients underwent repeated septal reduction procedures. Patients in the matched PPM group were less likely to undergo reinterventions (log-rank $P = 0.02$, Figure 2B).

DISCUSSION

To our knowledge, this is the first study with propensity score matching analysis evaluating short- and long-term outcomes of patients with HOCM who underwent ASA and received a PPM for periprocedural AV block. We report the following principal findings: 1) PPMs were implanted in 9.4% of patients during 30 days after ASA and in addition in 3.1% of patients during follow-up; 2) baseline predictors of PPM implantation within 30 days of ASA were older age, worse NYHA functional class (III/IV), lower LV ejection fraction, lower basal septum thickness, higher alcohol dose during the first ASA, and BBB before ASA; 3) short- and long-term mortality rates were similarly low in all evaluated groups; 4) in the long-term follow-up, patients in the matched PPM group had a lower LV ejection fraction (still in the normal range), lower LV outflow gradient, more pronounced reduction of LV outflow gradient, and a lower proportion of patients had NYHA functional class III/IV in comparison to the non-PPM group; and

FIGURE 2 **Repeated Reduction Procedures After Alcohol Septal Ablation**



Kaplan-Meier curves with 95% CIs describing the freedom from repeated septal reduction therapy in **(A)** the permanent pacemaker (PPM) versus the non-PPM groups and **(B)** the matched PPM versus the matched non-PPM groups.

5) the rate of reinterventions was significantly lower in the paced patients.

The most frequent significant post-ASA complication is high-grade AV block requiring PPM implantation.[4-8] The cause for this lies in the anatomical proximity of the target perfusion territory of the coronary artery septal branches to the conduction system. In this regard, our current results are in line with previous reports indicating that the occurrence of post-ASA high-grade AV block requiring PPM placement is approximately 10%,[7-9,14] with 97% of these AV blocks occurring within 5 days after ASA.[7,12]

In the past, it has been convincingly shown that certain factors play a key role in the risk of PPM implantation after ASA. Among the most important factors are preprocedural conduction abnormalities, especially a left BBB.[4-6,11] Also, it has been demonstrated that the age of patients is a significant factor contributing to post-ASA conduction disturbances. For example, Batzner et al[15] recently reported ASA-related PPM ratios of 4%, 9%, and 14% in patients <40 years, 40 to 60 years, and ≥60 years of age, respectively. Interestingly, the procedural experience of the center performing ASA may significantly influence these results. Along this line, we have reported that centers with an overall volume >50 ASA procedures implanted fewer postprocedure PPMs than centers with less experience (9% vs 15%, $P < 0.01$).[16] Another factor influencing the likelihood of PPM implantation is the type of financial ownership of the hospital where the procedure is performed. Lam et al[13] identified in the 2010 to 2015 U.S. Nationwide Readmissions Databases 1,296 patients who underwent ASA; 14% of these received PPMs and 11% ICDs during the index hospitalization. Notably, private hospital ownership independently predicted a 2 times increased probability of PPM or ICD implantation. Moreover, both devices were mostly implanted within 3 days after ASA. Thus, a "watch-and-wait" strategy may be used more in governmentally owned hospitals and may reduce the rate of implanted PPM after ASA.[13]

In the present study, we confirmed the results of previous studies regarding the higher risk of ASA-related PPM implantation in elderly patients, and we found that patients ≤60 years of age were almost half as likely to undergo PPM implantation than patients >60 years of age (7% vs 13%). Furthermore, we found additional independent predictors of PPM implantation, including a worse NYHA functional class (III/IV), lower LV ejection fraction, and lower basal septum thickness, respectively. Alcohol dose during the procedure also plays a role because on average a 10% higher dose was used in patients requiring PPMs compared with those who did not receive PPM.

The long-term implications of PPM implantation after ASA are scarcely reported.[10,11,17,18] In terms of long-term outcomes of patients with PPM after ASA, 3 results of the present study are of special importance. First, PPM implantation did not translate into worsened long-term mortality. Second, PPM patients had a more pronounced decrease in the LV outflow gradient during long-term follow-up, which may be caused by both the more aggressive ASA (higher dose of alcohol used during the procedure and smaller

septal thickness, Table 1) and the long-term synergistic effects of PPM pacing on LV hypercontractility and LV ejection fraction.[18] This highlights the difficult clinical choice between more ablation with better gradient reduction but a higher pacemaker rate. Third, the lower LV outflow gradient after ASA in patients with PPM was linked with a lower probability of reintervention.

STUDY LIMITATIONS. The limitations of this study include the following: first, we did not have functional pacing data, but from our previous study of a smaller number of patients, it appears that two-thirds of patients were mostly independent of PPM pacing.[10] Second, although patients in this study were followed for an average of more than 5 years, some complications of PPM can occur later, which could affect future longer-term outcomes. Third, this study was based on the currently largest reported registry of ASA patients. Nevertheless, the sample size of PPM patients (N = 170) was limited, and only 278 patients (139 pairs) were included in propensity score matching. These 2 factors somewhat limit the predictive value of survival-related parameters as well as propensity score matching, which included only 15% of the 1,814 enrolled patients.

CONCLUSIONS

Patients with HOCM treated with ASA have a 9.4% probability of PPM implantation within 30 days after ASA. In this long-term follow-up, patients with PPMs had lower LV outflow gradient, more pronounced LV outflow gradient decrease, lower LV ejection fraction, and lower likelihood of reintervention but similar long-term survival and mean NYHA functional class compared with patients without PPMs.

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PERSPECTIVES

WHAT IS KNOWN? Because of the proximity of the perfusion territory of the coronary artery septal branches to the cardiac conduction system, a significant complication of ASA is a periprocedural atrioventricular block requiring implantation of a permanent pacemaker in 7% to 20% of cases. The long-term implications of PPM implantation after ASA are scarcely reported.

WHAT IS NEW? PPMs were implanted in 9% of patients during 30 days after ASA and in addition in 3% of patients during the 5-year follow-up. There were the following baseline predictors of PPM implantation within 30 days of ASA: older age, worse NYHA functional class (III/IV), lower LV ejection fraction, lower basal septum thickness, higher alcohol dose during the first ASA, and BBB before ASA. Patients with and without PPM after ASA did not have different survival rates. However, in the long-term follow-up, patients with PPM had a lower LV ejection fraction (still in the normal range), lower LV outflow gradient, and more pronounced reduction of LV outflow gradient, and a lower proportion of patients had NYHA functional class III/IV. Also, the rate of reinterventions was significantly lower in the paced patients.

WHAT IS NEXT? It should be clarified why PPM patients had a more pronounced decrease in the LV outflow gradient during long-term follow-up.

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KEY WORDS alcohol septal ablation, permanent pacemaker, prognosis

APPENDIX For supplemental tables and figures, please see the online version of this paper.