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PII: S0828-282X(20)31068-0

DOI: https://doi.org/10.1016/j.cjca.2020.10.013

Reference: CJCA 3898

To appear in: *Canadian Journal of Cardiology*

Received Date: 17 September 2020

Revised Date: 6 October 2020

Accepted Date: 20 October 2020

Please cite this article as: Samuel M, Khairy P, Mongeon F-P, Andrade J, Gomes S, Galvan Z, Weerasooriya R, Novak P, Nault I, Arentz T, Deisenhofer I, Veenhuyzen GD, Jaïs P, Parkash R, Verma A, Menon S, Puererfellner H, Scavée C, Talajic M, Guerra PG, Rivard L, Dubuc M, Dyrda K, Thibault B, Mondesert B, Tadros R, Cadrin-Tourigny J, Aguilar M, Tardif J-C, Levesque S, Roy D, Nattel S, Macle L, Pulmonary Vein Stenosis after Atrial Fibrillation Ablation: Insights from the Adenosine following pulmonary Vein Isolation to target dormant Conduction Elimination Trial, *Canadian Journal of Cardiology* (2020), doi: https://doi.org/10.1016/j.cjca.2020.10.013.

Pulmonary Vein Stenosis after Atrial Fibrillation Ablation: Insights from the Adenosine following pulmonary Vein Isolation to target dormant Conduction Elimination Trial

Short Title: Pulmonary Vein Stenosis after AF Ablation

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Word count: 5,504 words

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BRIEF SUMMARY

The incidence of pulmonary vein (PV) stenosis after AF ablation remains unclear and is limited to single-center studies. The present study determines the incidence and predictors of PV stenosis following radiofrequency ablation in the ADVICE trial. In the first multicenter systematic evaluation of post-ablation PV stenosis, no patients acquired severe PV stenosis. Although the results are encouraging, 20.8% of patients had mild or moderate PV stenosis, in which the long-term effects are unknown.

ABSTRACT

BACKGROUND: Pulmonary vein (PV) stenosis is a complication of atrial fibrillation (AF) ablation. The incidence of PV stenosis after routine post-ablation imaging remains unclear and is limited to single-center studies. Our objective was to determine the incidence and predictors of PV stenosis following circumferential radiofrequency ablation in the multicenter **Ad**enosine Following Pulmonary **V**ein **I**solation to Target Dormant **C**onduction **E**limination (ADVICE) trial.

METHODS: Patients with symptomatic AF underwent circumferential radiofrequency ablation in one of 13 trial centers. Computed tomography (CTA) or magnetic resonance (MRA) angiography was performed pre-ablation and at 90-days post-ablation. Two blinded reviewers measured PV diameters and areas. PVs with stenosis were classified as severe (>70%), moderate (50-70%), or mild (<50%). Predictors of PV stenosis were identified by multivariable logistic regression.

RESULTS: A total of 197 patients (median age 59.5 years, 29.4% women) were included in the present sub-study. PV stenosis was identified in 41 patients (20.8%) and 47 (8.2%) of 573 ablated PVs. PV stenosis was classified as mild in 42 PVs (7.3%) and moderate in 5 PVs (0.9%). No PVs had severe stenosis. Both cross-sectional area and diameter yielded similar classifications for severity of PV stenosis. Diabetes was associated with a statistically significant increased risk of PV stenosis [OR 4.91 (95% CI 1.45-16.66)].

CONCLUSION: In the first systematic multicenter evaluation of post-ablation PV stenosis, no patient acquired severe PV stenosis. Although the results are encouraging for the safety of AF ablation, 20.8% of patients had mild or moderate PV stenosis, in which the long-term effects are unknown.

KEYWORDS: pulmonary vein stenosis, atrial fibrillation, catheter ablation

ABBREVIATIONS

AF= atrial fibrillation

CT= computed tomography

LA= left atrial

LVEF= left ventricular ejection fraction

MPR= multiplanar reconstruction

MRI= magnetic resonance imaging

PV= pulmonary vein

TEE= transesophageal echocardiography

INTRODUCTION

Atrial fibrillation (AF) ablation is a minimally invasive intervention aimed to restore and maintain sinus rhythm in patients with drug refractory AF.[1] AF ablation is relatively safe to perform, however, a substantial risk of complications, such as pulmonary vein (PV) stenosis, remains.[1-3] PV stenosis is defined as a reduction in PV diameter.[1] It is a consequence of thermal injury in the PV-antral junction or inside the PV ostia due to catheter ablation.[4] Subsequently, intimal proliferation is initiated, which results in narrowing of the PV from endovascular contraction, myocardial collagen replacement, and irreversible damage to venous tissue.[4] Depending on the severity, PV stenosis may cause severe dyspnea, cough, chest pain, hemoptysis, and pulmonary arterial hypertension.[1,5]

Randomized trials and observational studies reported an incidence of PV stenosis following AF ablation between <1% to 6%.[1,2] However, studies that performed routine post-procedure imaging have reported incidences ranging from <1% to 100%.[6-11] Reductions in PV diameter post-ablation are detected from computed tomography angiography (CTA), magnetic resonance angiography (MRA), or transesophageal echocardiography (TEE).[10,12,13] However, post-procedural imaging is not commonly performed in asymptomatic patients. Less than 25% of the Heart Rhythm Society (HRS) task force members screen asymptomatic patients for PV stenosis.[14] As an estimated 65% of patients with PV stenosis are asymptomatic, it is likely an underdiagnosed complication.[4,5]

The utilization of AF ablation as a treatment option has increased in recent years [2]. Indications have expanded to include challenging subpopulations, such as patients with persistent AF or comorbid heart failure,[1] who may be at an increased risk of PV stenosis due to more lesions and longer ablations. Despite the increasing number of patients undergoing AF ablation, current evidence of post-ablation PV stenosis from routine screening is limited to surveys and single center studies.[6-11] Therefore, the primary objective of the present study was to determine the incidence and predictors of PV stenosis following circumferential radiofrequency ablation in the multicenter **Ad**enosine Following Pulmonary

Vein **I**solation to Target Dormant **C**onduction **E**limination (ADVICE) trial. In addition, we compared the magnitude and severity of PV stenosis measured from cross-sectional area and diameter.

METHODS

Clinical Trial

Detailed descriptions of the trial design, ablation procedure, and protocol have been previously published.[3,15] In summary, the ADVICE trial was a multicenter, single-blind, randomized controlled trial in which symptomatic paroxysmal AF patients undergoing AF ablation were enrolled. Patients who underwent AF ablation and tested positive for dormant conduction with adenosine were randomized (1:1) to adenosine guided ablation or no further ablation. Patients who underwent AF ablation but did not have dormant conduction were prospectively followed in a registry for atrial tachyarrhythmia recurrence.

AF ablation was conducted in accordance with standard clinical practice. Irrigated-tip ablation catheters, guided by 3-D non-fluoroscopy mapping, were used to perform circumferential ablation lesions 1 to 2 cm from the PV ostia to electrically isolate the PVs. Radiofrequency energy was delivered at a target temperature of 50 °C and a power of 25-35 watts. Following PV isolation, intravenous adenosine (≥12 mg) was administered to test for dormant conduction. Patients with dormant conduction who were randomized to the adenosine guided ablation arm underwent additional targeted ablations delivered at reconnection sites. Targeted ablations were conducted until dormant conduction was no longer detected by adenosine testing.

The ADVICE study protocol did not mandate routine post-ablation CTA or MRA. Thirteen of 18 centers participating in the ADVICE trial performed post-procedural imaging. All patients undergoing a post-procedural CTA or MRA were included in this pre-specified sub-study of the ADVICE trial. The study was approved by the institutional review boards of all 13 centers.

Detection of PV Stenosis

Systematic imaging of the left atrium and PVs were performed by MRA or CTA at baseline (prior to AF ablation) and 90-days post-AF ablation. Measurements of PV dimensions between MRA and CTA are moderate to highly correlated (R=0.60-0.90).[16,17] Multiplanar reconstruction (MPR) of 3D angiographic images was used to identify the PV long-axis on oblique coronal and axial orientations (Figure 1a and 1b) and to reconstruct a cross-sectional view of the PV from two orthogonal planes (Figure 1c). The minor and major axis luminal diameters were measured, as well as the luminal cross-sectional area (Figure 1c and 1d). The PV was measured at the hinge point between the vein and the left atrial border or at the narrowest diameter identified on the long-axis views. Only clearly visualized PVs on pre- and post-ablation CTA or MRA images were included in the present analyses. Individual PVs were excluded due to poor image quality on either the pre- or post-ablation image. All images were stored in a core lab and each image was independently analyzed by two blinded reviewers (imaging cardiologists). An interclass correlation coefficient was calculated to compare the consistency of measurements by reviewers.

PV stenosis was defined as the reduction in PV diameters or cross-sectional area post-ablation compared to pre-ablation and was represented as a percentage of the pre-ablation diameter or cross-sectional area, respectively. Based on the 2017 Heart Rhythm Society/European Heart Rhythm Association/ European Cardiac Arrhythmia Society Expert Consensus statements, reductions in the PV diameter or cross-sectional area of <50% was classified as mild PV stenosis, 50-70% as moderate PV stenosis, and >70% as severe PV stenosis.[1] If classification of stenosis severity (mild, moderate, or severe) differed based on the dimension measured (major axis diameter, minor axis diameter, or cross-sectional area), stenosis severity was determined from 2 of 3 dimensions which categorized the PV stenosis as the same severity.

Statistical Analysis

In descriptive analyses, distributions of continuous variables were summarized with medians and interquartile range (IQR) and categorical variables were described by frequency and percentages.

Univariate logistic regression models were used to identify potential predictors of any PV stenosis (mild, moderate, or severe). Predictors included demographic, clinical, and procedural variables. Potential predictors with a $p<0.2$ in univariate logistic regression models were incorporated into the final multivariable logistic regression model. To assess potential associations between PV size at baseline and PV stenosis in each individual PV, univariate logistic regressions were performed. Results of predictor analyses were summarized by Odds Ratios with 95% confidence intervals. For all analyses, p-values <0.05 were considered statistically significant. Stata (Version 16, StataCorp, College Station, Texas) was employed for all analyses.

RESULTS

Baseline characteristics

Of the 401 patients with dormant conduction or in the registry of the ADVICE trial, 197 patients from 13 (of 18) centers had pre- and post- MRAs or CTAs and were, therefore, included in the present sub-study. A total of 573 PVs were evaluated for stenosis. Fifty-four right PVs and 75 left PVs were excluded due to poor image quality of the individual PV. Most PVs excluded due to poor image quality were acquired by CTA (65.3% of excluded PVs). Patients were a median age of 59.5 (IQR 53.4-65.1) years, 71% male, and 88% of patients had a $CHADS_2$ score ≤1 (Table 1).

Freedom from atrial tachyarrhythmia (AF, atrial flutter, atrial tachycardia)

Of 147 patients with dormant PV conduction who received additional adenosine-guided ablation, 69.4% remained free from symptomatic atrial tachyarrhythmia between 91 and 365 days after the ablation procedure compared with 42.3% of 137 patients with no further ablation (HR 0.44, 95% CI 0.31–0.64, P <0.0001). In patients without dormant conduction, 55.7% were free from symptomatic atrial tachyarrhythmia during the study period.

Incidence of PV stenosis

PV imaging was performed at a mean of 103 days (SD 33) after AF ablation. A total of 131 patients had a MRA at baseline and at 90 days and 65 patients had a CTA at baseline and 90 days. One patient had a CTA at baseline and an MRA at 90 days.

PV stenosis was identified in 41 (20.8%) patients and 47 (8.2%) of 573 ablated PVs. PV stenosis was classified as mild in 42 PVs (7.3%; 36 (18.2%) patients) and moderate in 5 PVs (0.9% of PVs; 5 (2.5%) patients). No PVs had severe stenosis. The most common sites for PV stenosis were common ostium (4 of 21 PVs, 19.0%), left inferior (22 of 122 PVs, 18.0%) and left superior (8 of 122 PVs, 6.5%) PVs (Table 2). Moderate stenosis (N=5 PVs) only developed in left inferior PVs. Although PV stenosis was more frequent in the left PVs, there was a greater median reduction in PV size post-ablation in right PVs with stenosis (Table 2). All patients with PV stenosis were asymptomatic and none required an intervention (percutaneous balloon angioplasty or stent implantation).

Comparison of cross-sectional area and diameter for the measurement of PV stenosis

There was a high degree of consistency in measurements between blinded reviewers (interclass correlation coefficient=0.92) and percent stenosis of the PVs determined by diameter or circumferential area were highly correlated [Supplementary Figure S1; correlation coefficients between 64-94%, $p<0.001$ for all]. Overall, classifications of PV stenosis severity were consistent between dimensions measured, however, the mean percent stenosis was greater with the measurement of cross-sectional area (Table 2). Subsequently, circumferential area overestimated severity in 2 PVs and minor axis diameter underestimated the severity in 4 PVs (Figure 2).

Predictors of PV stenosis

In multivariable analyses, the presence of diabetes mellitus was associated with a statistically significant increased risk of PV stenosis [OR 4.91 (95% CI 1.45-16.66)] (Table 3a). No other clinical or procedural variables, including radiofrequency energy or procedure times, were identified as predictors for PV stenosis (Table 3a). In addition, there was no statistically significant association detected between pre-ablation PV size and incident PV stenosis for all PVs investigated (Table 3b).

DISCUSSION

In the first multicenter systematic assessment of post-ablation PV stenosis, salient findings include the following: 1) PV stenosis was identified in 20.8% of patients and 8.2% of PVs; 2) no patient had severe PV stenosis; 3) all patients remained asymptomatic; 4) the most frequent sites for PV stenosis were the common ostium and left PVs; and 5) diabetes was a predictor of PV stenosis.

To our knowledge, the present study was also the first study to compare the reduction in PV size and classification of PV stenosis by cross-sectional area and diameter measurements. Although the magnitude of the reduction in PV size differed, the classification of severity of PV stenosis was relatively consistent between approaches.

Incidence of PV Stenosis

There is a wide variation in the incidence of post-ablation PV stenosis reported in published literature. Randomized trials and observational studies estimate an incidence between <1% to 6%.[1,2] However, only symptomatic patients typically undergo the subsequent CTA or MRA imaging necessary to diagnose PV stenosis in standard clinical practice. In contrast, single-center studies that performed routine systematic imaging post-ablation on all patients report an incidence between <1% to 100% (Table 4).[6-11] The incidence of any PV stenosis in the present ADVICE sub-study (20.8%) is within the range.

In the largest single center study (N=11,103) to identify the incidence of post-ablation PV stenosis, Schoene et al reported an incidence of 0.78%[6] All patients had a TEE to screen for post-ablation PV narrowing and a CT or MRI was conducted if the patient was symptomatic or PV stenosis was identified by the TEE.[6] This was the only study which used TEEs to screen patients for PV stenosis. TEEs may underestimate the incidence of PV stenosis as diagnosis is based on reductions in Doppler velocity, instead of decreased luminal diameter and area.[6] Further, the incidence rate of 0.78% is more consistent with the rate of severe stenosis in other systematic assessments (0-4%).[7,9,10]

Additional differences in the incidence rates of prior studies compared to the present ADVICE sub-study may be reflective of more operators performing AF ablations, timing and type of post-ablation imaging, and more recently performed ablation procedures (i.e. improvements in ablation techniques or technology reduce occurrence of PV stenosis).

Severity of PV Stenosis

All patients with PV stenosis in the ADVICE sub-study were asymptomatic. In prior studies, symptoms were only reported in some patients with severe PV stenosis.[6,7,9-11] As no patient in the ADVICE trial had severe PV stenosis, the absence of symptoms is consistent with the milder forms of PV stenosis observed.

Similar to the present sub-study, most patients with PV stenosis in other systematic assessments had a mild or moderate degree of disease (Table 4).[6-11] Limited evidence exists about the progression of PV stenosis in moderate and mild patients and thus, the long-term effects are unknown. In a small sub-study by Schoene et al (N=54 patients), classification of PV stenosis was shown to improve (i.e. classification changed from moderate to mild) from diagnosis of PV stenosis to a mean of 43 months after diagnosis (p=0.001).[18] Subsequently, symptoms also reduced over follow-up.[18] Only patients that underwent repeat AF ablation had a further reduction in the PV diameter. However, older studies by Baranowski and Saad et al indicated that few patients with mild or moderate PV stenosis at diagnosis progressed to more severe PV stenosis after a few months.[9,10]

In addition, long-term outcomes for patients with moderate or mild PV stenosis remain uncertain. A few studies have suggested that patients with moderate PV stenosis may develop pulmonary hypertension, progress to complete PV occlusion, or become susceptible to recurrent or drug resistant pneumonia over long-term follow-up.[19-21] Hemodynamic changes from PV stenosis, such as increased pulmonary capillary pressure or right ventricular systolic pressure, may underlie the development of pulmonary hypertension.[19,20] Congestion upstream from the obstruction has been proposed to explain the increased susceptibility to recurrent pneumonia.[21-23] Although studies by Yang

and Di Biase indicate that early intervention for severe symptomatic PV stenosis may improve long-term clinical outcomes and symptoms,[24,25] there is no evidence that intervening in patients with mild to moderate PV stenosis is of value. Thus, additional long-term studies are warranted to determine if mild or moderate PV stenosis poses a risk for patients in the long-term and subsequently, if routine post-procedural imaging to screen for PV stenosis is necessary.

Classification of PV stenosis by cross-sectional area versus diameter

It has been suggested that classification of the severity of PV stenosis may differ by the PV dimension measured, either diameter or area.[26] A comparison of the incidence of severe PV stenosis in cryoballoon ablation studies showed that the incidence was approximately 0% when PV diameter was used to identify PV stenosis;[1,27] however, the Sustained Treatment Of Paroxymal Atrial Fibrillation (STOP AF) trial used reduction in PV cross-sectional area to detect PV stenosis and found an incidence rate of 3.1%.[26] The results of the present study also suggest that classification of PV stenosis based on cross-sectional area may overestimate the percent stenosis and severity of PV stenosis compared to diameter measurements. Nevertheless, misclassification based on cross-sectional area was marginal (1.2% vs 0.8% of PVs with moderate stenosis, cross-sectional area versus diameter, respectively).

Increased risk in common ostium and left PVs

PV stenosis has been shown to occur more frequently in the left PVs; an observation which is confirmed by the present multicenter study.[6,7] The left inferior PV is the smallest PV, lies anterior to the descending aorta, and often appears compressed.[5] It is hypothesized that the small diameter of left inferior PVs and ablation sites for the left superior PVs positioned closer to the ostium due to the steep coumadin ridge may render left PVs more susceptible to stenosis.[5,6] Further, the instability of the coumadin ridge may explain the higher incidence of PV stenosis in the common ostium. There is also evidence that PVs undergo mild reverse atrial remodeling and tissue shrinkage from ablation-induced fibrosis after radiofrequency ablation.[12] Therefore, it is possible that the post-ablation structural changes occur differentially in PVs, such as the common ostium. However, the limited number of

patients with pre- and post-imaging of the common ostium and potential differences in the measurement of area and diameter of the common ostium suggest a larger study is required to confirm these results.

Diabetes as a potential predictor for PV stenosis

Due to the relatively low incidence of PV stenosis, studies had limited power to detect predictors. Only prior AF ablation has been identified as a predictor of PV stenosis in patients who underwent radiofrequency ablation.[18] The present study suggests that diabetes mellitus may be a predictor of post-ablation PV stenosis. Diabetes is strongly associated with an increased risk of microvascular and macrovascular complications[28] and has also been shown to be involved in atrial structural and electrical remodeling in AF patients.[29] Resulting endothelial dysfunction, collagen disposition, inflammatory response, and reduced fibrinolysis may be potential mechanisms for the link between diabetes and PV stenosis.[29] In addition, a study by Gibson et al found that patients with diabetes who underwent AF ablation were at an increased risk of pulmonary hypertension (N=1,058, multivariable OR 9.29 (95% CI 2.0-44.2)).[30] Pulmonary hypertension is also a complication of PV stenosis.[1,5] With the results of the present study, it is possible that milder PV stenosis may be part of the causal pathway between diabetes and pulmonary hypertension. Further investigations are warranted to determine the potential relationship between diabetes and PV stenosis.

Limitations

Although the present study is externally generalizable as the first multicenter assessment of post-ablation PV stenosis, several limitations need to be considered. First, the sample size was relatively small (<200 patients) with relatively few (47) events. As a result, few predictors were included in the multivariable model and results for the predictor analysis were hypothesis generating. Only a subset of patients enrolled in the ADVICE trial qualified for inclusion in the present sub-study (i.e. those with pre- and post- imaging of PVs). This carries the potential to introduce a selection bias at entry. However, this potential bias is unlikely to have a major impact on the results considering that the

distribution of baseline characteristics in the sub-study population was similar to the overall trial population.[3] In addition, we defined PV stenosis anatomically in this study, the hemodynamic consequences and clinical implications of a minimal reductions in PV area and diameter are unknown. Although no patient developed symptoms related to PV stenosis during the 12-month study period, longer-term outcomes associated with PV stenosis were not captured by the ADVICE trial. Finally, as patients had either a CTA or MRA, measurements of PVs may have differed between imaging modalities.

CONCLUSION

In the first multicenter systematic evaluation of post-ablation PV stenosis, none of the patients who underwent AF ablation acquired severe PV stenosis or required an intervention. Although the results are encouraging for the safety of AF ablation, nearly 21% of patients had a mild or moderate degree of PV stenosis, in which the long-term effects are unknown. Further, the approach used to classify severity of PV stenosis, cross-sectional area or diameter, yielded similar results and thus, either approach seems reasonable to detect PV stenosis. A larger study is required to determine whether certain patient or procedural factors are associated with a higher risk of any PV stenosis.

FUNDING SOURCES: The ADVICE trial was funded by grants from the Canadian Institutes of Health Research (CIHR), St Jude Medical, Biosense Webster, and M Lachapelle (Montreal Heart Institute Foundation). Dr. Samuel is supported by a post-doctoral fellowship training award from Fonds de recherché du Québec-Santé (FRQS). Dr. Khairy is supported by the André Chagnon Research Chair. Dr. Andrade is supported by a Michael Smith Foundation for Health Research Scholar Award.

DISCLOSURES: Dr. Khairy receives consulting fees from Boehringer Ingelheim and grant support from Boehringer Ingelheim, Actelion, Bayer, Medtronic, and St Jude Medical Dr. Andrade reports grants and personal fees from Medtronic, grants from Baylis, personal fees from Biosense-Webster. Dr. Weerasooriya has received lecture fees from Boehringer Ingelheim, Bpfizer, Bayer, and Biotronik. Dr. Nault has received honoraria/research support from Bayer, BMS/Pfizer, and Servier. Dr. Jaïs receives lecture fees from Biosense Webster and Abbott. Dr. Parkash receives grant support from St. Jude Medical and Medtronic. Dr. Verma has received grant support and fees for serving on advisory boards from Bayer, Boehringer Ingelheim, Medtronic, Biosense Webster, and St. Jude Medical. Dr. Puererfellner receives consulting fees from Medtronic. Dr. Thibault reports personal feels and other from Medtronic, Abbott, and St. Jude Medical. Dr. Tardif reports receiving grant support from Amarin, Esperion, and Ionis Pharmaceuticals, receiving grant support and honoraria from AstraZeneca, Pfizer, Sanofi, and Servier, receiving grant support and honoraria from and having equity in DalCor Pharmaceuticals. Dr. Macle reports personal fees from Medtronic, grants and personal fees from St. Jude Medical/Abbott and Biosense-Webster. All other authors have nothing to disclose.

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FIGURE LEGENDS

Figure 1. Measurements of Pulmonary Vein Diameters

PV long axis in multiplanar reconstruction of the pulmonary veins in the (A) coronal and (B) axial orientations. (C) Cross-sectional view of the luminal diameter. (D) Circumferential area and diameter measurements for pulmonary veins in the cross-sectional view.

Figure 2. Classification of PV stenosis by measurement type

PV stenosis classifications were compared between the percent stenosis from cross-sectional area, major axis diameter, minor axis diameter measures.

Table 1. Baseline characteristics

Patient characteristics	N=197
Age, years*	59.5 (53.4-65.1)
Women, N (%)	58 (29.4)
Number of failed antiarrhythmic medications, N (%)	3 (2-4)
Hypertension, N (%)	68 (34.5)
Dyslipidemia, N (%)	74 (37.6)
Diabetes mellitus, N (%)	13 (6.6)
Ischemic heart disease, N (%)	17 (8.6)
Congestive heart failure, N (%)	8 (4.1)
Prior stroke or transient ischemic attack, N (%)	9 (4.6)
Chronic obstructive lung disease (COPD), N (%)	6 (3.1)
$CHADS_2$ Score*	
0	110 (55.8)
1	67 (34.0)
≥2	20 (10.2)
Left atrial size, parasternal long axis, mm*[+]	39 (36-43)
Left atrial volume, mL/m^2*[‡]	27 (21-32)
Left ventricular ejection fraction (LVEF), %*[‡]	60 (58-63)
Treatment arm, N (%)	
Dormant conduction- no further ablation	79 (40.1)
Dormant conduction- additional ablation	73 (37.1)
No dormant conduction- registry	45 (22.8)
Type of sedation (conscious sedation vs general anesthesia), N (%)	56 (28.4)
Procedure time, min*	159 (110-208)
Radiofrequency energy time, min*	44 (27-64)
Fluoroscopy time, min*	28 (21-38)

*Continuous variables are summarized by median (IQR).
[+]Measured by transthoracic echocardiogram (TTE).

Table 2. Size of narrowed pulmonary veins pre- and post-AF ablation

Pulmonary Vein (N=573)	Pre-ablation			Post-ablation			% Reduction		
	Diameter-minor axis (mm)	Diameter-major axis (mm)	Cross-sectional Area (mm^2)	Diameter-minor axis (mm)	Diameter-major axis (mm)	Cross-sectional Area (mm^2)	Diameter-minor axis (%)	Diameter-major axis (%)	Cross-sectional Area (%)
Common Ostium (4/21 PVs, 19.0%)	13.9 (12.9-15.0)	25.6 (24.4-26.8)	3.3 (3.0-3.5)	11.9 (11.2-12.7)	22.6 (19.3-26.0)	2.2 (2.2-2.2)	12.0 (2.8-21.1)	14.3 (13.2-15.3)	32.1 (25.4-28.8)
RSPV (7/143 PVs, 4.9%)	16.8 (16.1-18.9)	20.9 (16.7-22.1)	3.2 (2.5-3.3)	13.3 (11.1-15.9)	18.6 (16.1-18.6)	1.9 (1.8-2.5)	11.4 (10.9-12.5)	17.3 (16.3-17.3)	25.5 (20.6-26.3)
RIPV (6/143 PVs, 4.2%)	16.6 (15.8-18.6)	19.3 (19.6-19.1)	2.7 (2.6-3.3)	15.2 (13.4-16.5)	16.6 (16.2-17.1)	2.2 (1.9-2.4)	13.0 (11.4-16.4)	11.2 (5.3-19.3)	27.4 (17.1-29.4)
LSPV (8/122 PVs, 6.5%)	12.7 (12.1-13.8)	18.5 (16.9-20.1)	1.9 (1.7-2.5)	11.9 (10.6-15.1)	16.2 (15.9-18.9)	1.7 (1.3-1.9)	8.7 (0.3-17.3)	9.2 (0.5-19.9)	16.1 (2.1-28.9)
LIPV (22/122 PVs, 18.0%)	9.3 (7.4-11.8)	16.1 (14.4-18.0)	1.2 (1.0-1.7)	9.5 (7.8-10.2)	15.9 (14.5-17.5)	1.2 (1.0-1.4)	6.8 (0.9-13.2)	8.3 (0.0-18.1)	10.9 (3.8-17.9)

*Presented as median (IQR).

[+]The % reduction in PVs was calculated per patient. The median (IQR) was calculated based on the per patient % reduction in PV.

[§]There was no PV stenosis in the 22 RMPVs ablated.

Table 3a. Predictors of any pulmonary vein stenosis

Potential predictors	Odds ratio (95% CI)	P-value
Univariate Analysis		
Age, years	1.00 (0.96-1.03)	0.86
Female	0.99 (0.46-2.11)	0.98
Time between diagnosis of paroxysmal AF and ablation, years	0.97 (0.92-1.04)	0.33
Number of prior antiarrhythmic medications	0.96 (0.73-1.26)	0.42
Comorbidities		
Hypertension	1.12 (0.55-2.30)	0.75
Diabetes mellitus	3.65 (1.15-11.53)	0.03
Congestive heart failure	1.28 (0.25-6.60)	0.77
Prior stroke or transient ischemic attack	0.46 (0.06-3.81)	0.43
$CHADS_2$ Score >= 2	1.08 (0.69-1.68) 1.74 (0.62-4.85)	0.73 0.31
Imaging characteristics		
Left atrial size, mm	0.98 (0.92-1.05)	0.65
Left atrial volume, cc/m^2	0.96 (0.90-1.02)	0.16
Left ventricular ejection fraction (LVEF), %	0.97 (0.92-1.02)	0.25
Ablation characteristics		

Randomization group Adenosine guided ablation (dormant conduction) Adenosine guided ablation (dormant conduction) Registry group (no dormant conduction)	 0.94 (0.40-2.21) 0.64 (0.25-1.59) 1.11 (0.47-2.63)	 0.89 0.34 0.81
Sinus rhythm prior to ablation	0.84 (0.42-1.67)	0.23
Procedure time, min	1.00 (0.99-1.01)	0.81
Radiofrequency energy time, min	1.00 (0.99-1.01)	0.74
Fluoroscopy time, min	0.98 (0.93-1.05)	0.62
Type of sedation (conscious sedation vs general anesthesia)	0.65 (0.28-1.47)	0.30
Multivariable analysis*$^{\gamma}$		
Diabetes mellitus	4.91 (1.45-16.66)	0.01
Left atrial volume, cc/m^2	0.97 (0.90-1.04)	0.42

*Only potential predictors with a $p<0.2$ in univariate logistic regression models were included in multivariable analysis.
$^{+}$Potential predictors with $p<0.05$ in multivariable analyses were considered statistically significant.

Table 3b. Association between PV size at baseline and incident PV stenosis by individual PV

Pulmonary Vein	Cross sectional Area OR (95% CI), p-value	Major Axis Diameter OR (95% CI), p-value	Minor Axis Diameter OR (95% CI), p-value
Common Ostium (N=21 PVs)	0.79 (0.24-2.56) p=0.69	0.87 (0.65-1.17) p=0.36	1.01 (0.67-1.52) p=0.98
RSPV (N= 143 PVs)	1.74 (0.72-4.21) p=0.22	1.08 (0.82-1.43) p=0.60	1.17 (0.87-1.58) p=0.29
RIPV (N=143 PVs)	0.97 (0.33-2.85) p=0.95	0.85 (0.65-1.12) p=0.26	1.06 (0.77-1.44) p=0.74
LSPV (N= 122 PVs)	0.78 (0.17-3.44) p=0.74	0.92 (0.69-1.23) p=0.57	0.95 (0.72-1.25) p=0.72
LIPV (N=22)	0.36 (0.12-1.02) 0.06	0.87 (0.73-1.03) p=0.11	0.90 (0.75-1.08) p=0.26

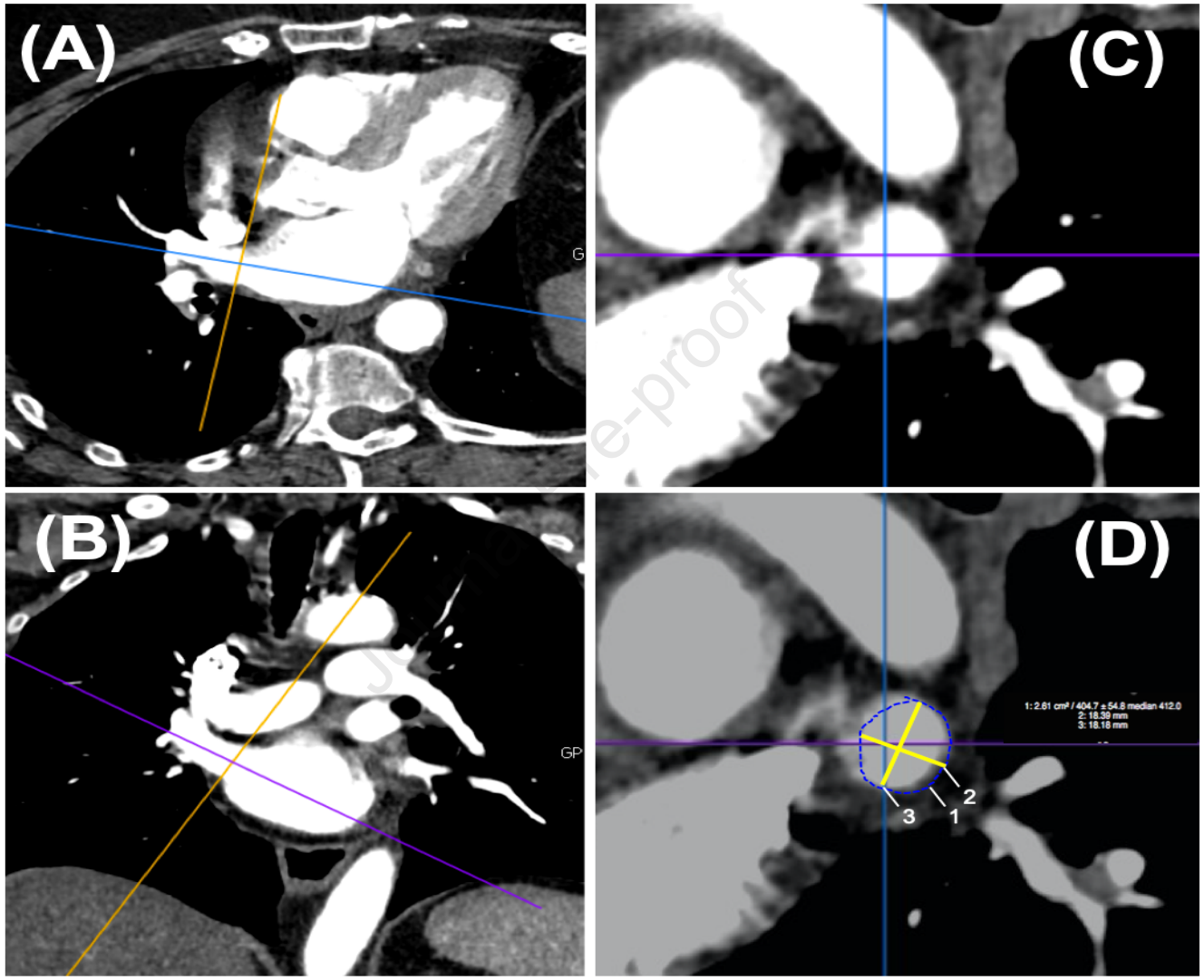
* PV size was not a predictor for PV stenosis in any PV (P<0.05 was considered statistically significant).

Table 4. Incidence of pulmonary vein stenosis in studies with routine post-ablation screening (radiofrequency ablation only)

Study	Study Type	Multicenter/ Single center	Sample Size	Screening for PV stenosis	Primary ablation strategy	Timing of post-ablation imaging	Incidence of PV stenosis	Proportion PV stenosis patients with symptoms
ADVICE sub-study (2020)	RCT	Multicenter (13 centers)	197	CT or MRI	RF circumferential ablation	3-months	41 (20.8%) patients 47 of 570 PVs Severe= 0 PVs Moderate= 5 PVs Mild=42 PVs	0 (0.0%)
Schoene et al. (2018)[6]	Observational	Single center	11,103	TEE and MRI or CT	RF or cryoballoon ablation	6 to 12-months	105 (0.78%) patients	35 (33.3%)
Teunissen et al. (2017)[7]	Observational	Single center	976	MRI or CT	RF PV antrum isolation	6-months	335 (36.4%) patients 572 of 4,171 PVs Severe= 9 PVs Moderate= 50 PVs Mild= 513 PVs	1 (0.3%)
De Greef et al. (2012)[8]	Observational	Single center	50	CT	RF circumferential ablation	3-months	50 (100%) patients 127 of 200 PVs Mild=64 PVs Moderate=55 PVs Severe=8 PVs	Not reported
Baranowski et al. (2010)[9]	Observational	Single center	501	CT	RF circumferential ablation	3-months	57 (11.4%) patients	3 (0.5%)
Dong et al. (2005)[11]	Observational	Single center	41	MRI	RF circumferential ablation	Mean 5.7-months	30 (73%) patients 60 of 157 PVs Mild=54 PVs Moderate=5 PVs Severe=1 PV	0 (0.0%)
Saad et al. (2003)[10]	Observational	Single center	608	CT	RF circumferential ablation	Mean 3.5-months	95 (15.6%) patients Severe= 36 PVs	13 (2.1%)

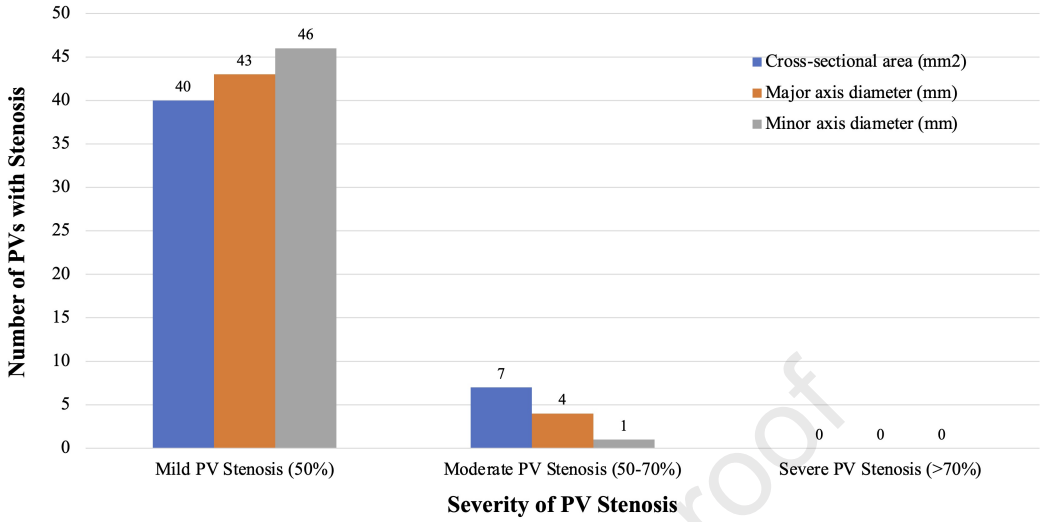
*For classifications, patients may have ≥1 PV with stenosis

Figure 1. Measurements of Pulmonary Vein Dimensions



PV long axis in multiplanar reconstruction of the pulmonary veins in the (A) coronal and (B) axial orientations. (C) Cross-sectional view of the luminal diameter. (D) Circumferential area and diameter measurements for pulmonary veins in the cross-sectional view.

Figure 2. Classification of PV stenosis by measurement type



*A total of 47 PVs had stenosis: 5 had moderate and 42 mild PV stenosis.