REVIEW ARTICLE

Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation

A Systematic Review

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Background: Circumferential pulmonary vein ablation (CPVA) has become common therapy for atrial fibrillation (AF), but results of large randomized controlled trials comparing this procedure with antiarrhythmic drug therapy (ADT) have not been published to date. We conducted a systematic literature review to assess whether CPVA is superior to ADT for the management of AF.

Methods: We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for relevant randomized controlled trials. Data were abstracted to construct a 2×2 table for each trial. Recurrence of any atrial tachyarrhythmia (AT) was considered the primary end point of the trials. The estimate and confidence interval for the pooled risk ratio of AT recurrence–free survival in the CPVA group vs the ADT group were obtained using the random-effects model.

Results: Four trials qualified for the meta-analysis. In total, 162 of 214 patients (75.7%) in the CPVA group had AT recurrence–free survival vs 41 of 218 patients (18.8%) in the ADT group. The random-effects pooled risk ratio for AT recurrence–free survival was 3.73 (95% confidence interval, 2.47-5.63). In addition, fewer adverse events were reported in the CPVA group compared with that in the ADT group.

Conclusions: We observed statistically significantly better AT recurrence–free survival with CPVA than with ADT. These results highlight the need for larger trials to determine the appropriate role for CPVA in the management of AF. Ongoing clinical trials may provide further guidance on these treatment options for AF.

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ATRIAL FIBRILLATION (AF) IS the most common sustained atrial arrhythmia and is present in 0.4% of the population.[1,2] It affects 4% of patients older than 60 years and 15% of patients older than 70 years.[1,2] Atrial fibrillation is associated with a 2-fold risk of cardiac and overall mortality.[1] Antiarrhythmic drug therapy (ADT) is widely used in the treatment of AF, but it has demonstrated limited efficacy in controlled trials and the potential for significant toxic effects.[3,4] Widely publicized trials have shown that a rhythm control strategy for management of AF may carry no benefit over rate control.[5,6] However, in subgroup analyses of these trials, survival is improved in patients who achieve sinus rhythm, and the poor efficacy of ADT in maintaining sinus rhythm is highlighted.[7] Radiofrequency catheter ablation for substrate modification or electrical isolation of pulmonary veins (circumferential pulmonary vein ablation [CPVA]) is a new but widely adopted technique for the treatment of AF that provides an alternate approach for maintaining sinus rhythm.[8-12]

We found several moderate-sized randomized clinical trials that we discuss in the "Results" and "Comment" sections of this article that have been conducted to evaluate the efficacy of CPVA compared with ADT for rhythm control of AF.[13-18] The participants in the trials range from patients with a first episode of symptomatic AF to those with drug-resistant persistent and chronic AF. The outcomes evaluated range from quality of life to number of hospitalizations to survival free of atrial arrhythmias during the follow-up period. However, a large randomized trial or a comprehensive meta-analysis on the issue is lacking to date. Therefore, we conducted a meta-analysis on the published trials to assess whether CPVA is superior to ADT for the management of AF. We assessed atrial tachyarrhythmia (AT) recurrence–free survival in the 12-month follow-up period after intervention (CVPA vs ADT) in accord with the recommendations of the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society's expert consensus statement.[19]

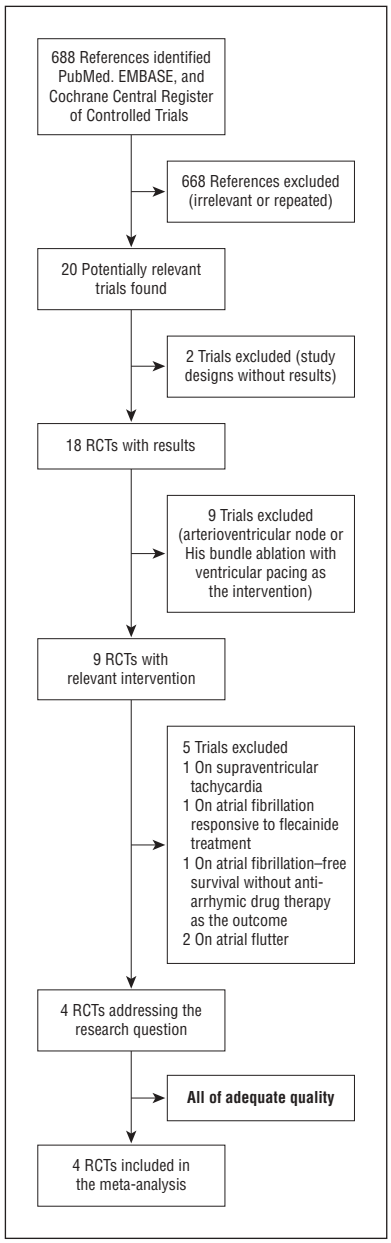

Figure 1. Flow diagram of the stages of the literature search to find relevant randomized controlled trials (RCTs).

METHODS

SEARCH STRATEGY

We searched the electronic databases of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for all randomized trials published until June 30, 2007, evaluating the efficacy of CPVA for the treatment of AF. The search strategy included *atrial tachyarrhythmia*, *atrial fibrillation*, *atrial flutter*, *ablation*, and *catheter ablation* as Medical Subject Headings and text words. Abstracts of all randomized clinical trials identified were independently screened by 2 reviewers (A.N. and A.K.) to assess the relevance to the research question.

STUDY ELIGIBILITY

We included all studies in which an intervention group comprising patients receiving CPVA for management of AF was compared with a control group comprising patients managed solely using ADT, and for which adequate information was available to construct a 2×2 table for AT recurrence–free survival during the 12-month follow-up period. Atrial tachyarrhythmia included AF, atrial flutter, and atrial tachycardia. We excluded trials that did not compare CPVA with ADT and trials that had atrioventricular node or His bundle ablation with ventricular pacing as the intervention of interest.

ASSESSMENT OF STUDY QUALITY

Both reviewers independently assessed trial validity and quality. Using a component approach, we checked the individual trials for the following 5 characteristics: appropriate allocation sequence generation, no exclusions after randomization, attrition less than 15%, blinded assessment, and intent-to-treat analysis.[20] We decided to exclude from our meta-analysis the trials not fulfilling at least 3 of these 5 criteria. Failure to mention the quality measure in the articles was considered a failure to fulfill the criterion.

DATA ABSTRACTION

Data were abstracted by both reviewers (A.N. and A.K.) independently to construct a 2×2 table for each trial, and disagreements were resolved by discussion. Other variables abstracted included the year of publication, country of trial, study size, study subject definition, mean age and sex distribution of study participants, number of total participants and number having AT recurrence–free survival in the intervention and control arms, and number of patients having adverse events during the procedure or follow-up period.

STATISTICAL ANALYSIS

Data were analyzed using commercially available software (STATA for Windows, version 9; StataCorp LP, College Station, Texas). Heterogeneity between individual trial estimates was assessed using Q statistic (χ^2) and I^2 statistic.[21] We obtained the combined pooled estimate using the random-effects model by DerSimonian and Laird,[22] which considers the heterogeneity among trials. We obtained a forest plot showing the individual trials with the pooled estimate. Publication bias was assessed with the funnel plot and using tests by Begg and Mazumdar[23] and Egger et al,[24] respectively.[23-25] We also used meta regression analysis to identify causes of heterogeneity among the trials.

RESULTS

The electronic search identified 263 references in PubMed, 255 references in EMBASE, and 170 references in the Cochrane Central Register of Controlled Trials. The review of abstracts from the 3 sources showed that there were 20 potentially relevant randomized trials. Of these, we excluded a further 16 because the interventions or study outcomes were inconsistent with those of the present review and included 4 trials in our meta-analysis by Krittayaphong et al,[13] Wazni et al,[14] Stabile et al,[15] and Pappone et al.[16] We included the trial by Stabile et al[15] in which the participants in the intervention arm received ADT in addition to the intervention of interest (ie, CPVA). We excluded the trial by Oral et al[17] in which the outcome pursued in the control group was AT recurrence–free survival in the absence of ADT because we were interested in comparing CPVA with ADT as the control treatment. Another study by Stabile et al[18] examining outcomes only in patients with AF responsive to flecainide acetate infusion (conversion of AF to atrial flutter by flecainide treatment) was excluded. A flow diagram showing studies excluded at each stage is shown in **Figure 1**.[26]

The individual trial characteristics are given in **Table 1**, and the assessment of study quality is given in **Table 2**. Combining the 4 studies, there were 214 patients in the intervention arm, of whom 162 (75.7%) had AT recurrence–free survival during the 12-month follow-up period, whereas there were 218 patients in the control arm, of which 41 (18.8%) had AT recurrence–free survival (**Table 3**). The statistical test for heterogeneity among the studies was not significant (P=.13, Q test; I^2=46% [95% confidence interval, 0%-82%]). The

Table 1. Individual Trial Characteristics

Source	Patient Age, Mean, y	Baseline Diagnosis	First-line Therapy		Follow-up Period	Primary Outcome
			Intervention Arm	Control Arm		
Pappone et al,[16] 2006 (Italy)	56	Drug-refractory paroxysmal AF ≥6 mo	LACA	Flecainide acetate, propafenone hydrochloride, or sotalol hydrochloride	12 mo After randomization	AF, AFL, ATach, or repeated procedure
Stabile et al,[15] 2006 (Italy)	62	Drug-refractory or drug-intolerant paroxysmal or persistent AF	LACA plus amiodarone or other drugs	Amiodarone or other drugs	12 mo, With 1-mo blanking period	AF, AFL, or ATach
Wazni et al,[14] 2005 (United States)	54	Drug-naive monthly symptomatic AF ≥3 mo	Pulmonary vein isolation	Flecainide, propafenone, or sotalol; amiodarone if needed	2-12 mo After randomization	AF
Krittayaphong et al,[13] 2003 (Thailand)	52	Drug-refractory amiodarone-naive paroxysmal or persistent AF ≥6 mo	LACA[a]	Amiodarone	12 mo After randomization	AF

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; ATach, atrial tachycardia; LACA, left atrial catheter ablation.
[a]The intervention ablation technique was not clearly defined.

Table 2. Quality Assessment of Individual Trials

Source	Appropriate Allocation of Participants	No Exclusions After Randomization	Blinded Assessment	Attrition <15% in Both Study Arms	Intent-to-Treat Analysis
Pappone et al,[16] 2006	Not mentioned	Yes	Not mentioned	Yes	Yes
Stabile et al,[15] 2006	Yes	Yes	Yes	Yes	Yes
Wazni et al,[14] 2005	Yes	Yes	Not mentioned	Yes	Yes
Krittayaphong et al,[13] 2003	Not mentioned	Yes	Not mentioned	Yes	Yes

Table 3. Results From the Individual Trials

Source	Intervention Arm			Control Arm			RR for AT Recurrence–Free Survival (95% CI)
	Total	AT Recurrence–Free Survival	Adverse Clinical Events[a]	Total	AT Recurrence–Free Survival	Adverse Clinical Events[a]	
Pappone et al,[16] 2006	99	85	5	99	22	23	3.86 (2.65-5.63)
Stabile et al,[15] 2006	68	38	3	69	6	4	6.43 (2.91-14.21)
Wazni et al,[14] 2005	32	27[b]	4	35	7[b]	4	4.22 (2.14-8.32)
Krittayaphong et al,[13] 2003	15	12[b]	5	15	6[b]	7	2.00 (1.02-3.91)
Total	**214**	**162**	**17**	**218**	**41**	**38**	3.73 (2.47-5.63)[c]

Abbreviations: AT, atrial tachyarrhythmia; CI, confidence interval; RR, relative risk.
[a]All complications due to the intervention, major drug adverse effects, deaths, and others.
[b]Atrial fibrillation recurrence–free survival.
[c]DerSimonian and Laird[22] random-effects pooled estimate.

DerSimonian and Laird[22] random-effects pooled estimate for the risk ratio for AT recurrence–free survival was 3.73 (95% confidence interval, 2.47-5.63) ($P<.001$). The forest plot is shown in **Figure 2**. Using meta regressions individually with mean age of trial participants, percentage of men in the trial, and trial size on trial estimates, there was no statistical evidence for heterogeneity due to mean age of trial participants ($P=.18$), percentage of males in the trial ($P=.75$), or trial size ($P=.47$). The Begg and Egger tests for publication bias showed no statistical evidence for significant publication bias ($P=.31$ and $P=.95$, respectively). The funnel plot is shown in **Figure 3**. There were 2 deaths within the 12-month follow-up period, 1 each in the intervention and the control arms, in the trial by Stabile et al,[15] while the other trials[13,14,16] did not report any death during the follow-up period. Reported adverse events and adverse effects were statistically significantly higher in the ADT group compared with the CPVA group ($P=.02$, DerSimonian and Laird[22] random-effects pooled estimate) for the 4 trials. However, some of the ad-

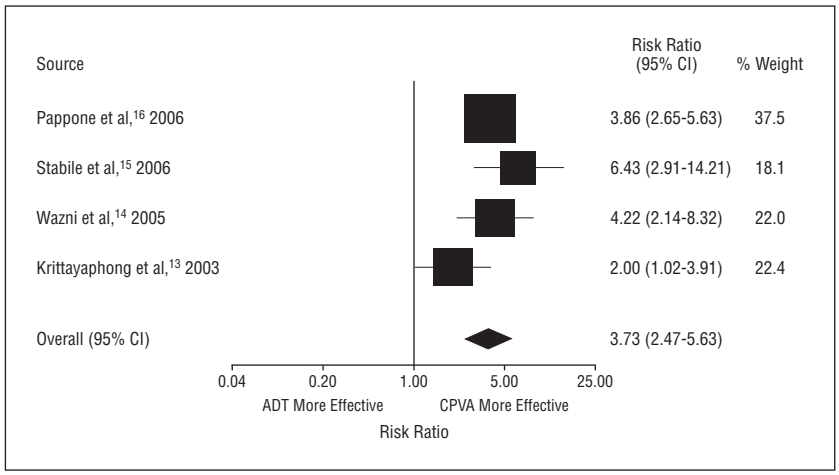

Figure 2. Forest plot of the 4 randomized controlled trials evaluating circumferential pulmonary vein ablation (CPVA) vs antiarrhythmic drug therapy (ADT) for atrial tachyarrhythmia recurrence–free survival during the follow-up period. The DerSimonian and Laird[22] random-effects model is used for the pooled estimate. CI indicates confidence interval; square, the area is proportional to the weight assigned to the trial; and diamond, the overall summary estimate for the analysis (width of the diamond represents the 95% CI).

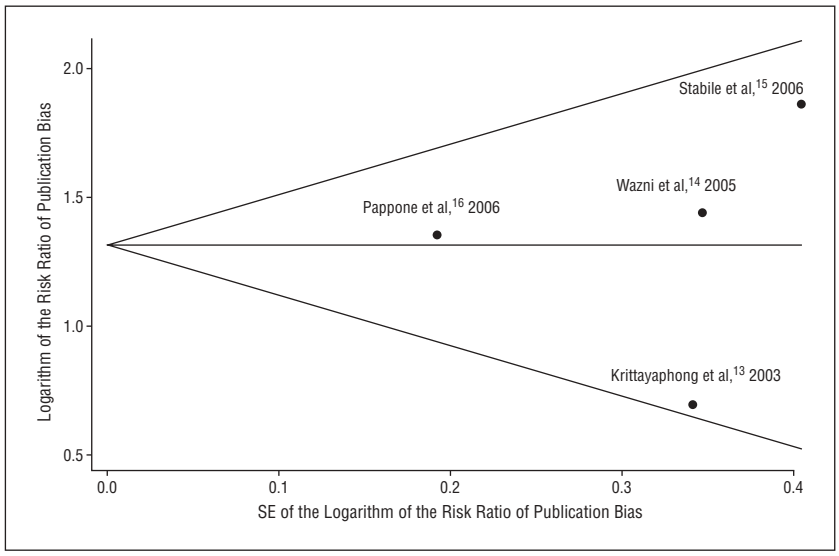

Figure 3. Funnel plot (with pseudo 95% confidence limits) for assessing publication bias.

verse events in the CPVA group (eg, stroke) were much more severe than those in the ADT group.

COMMENT

In this meta-analysis, we report statistically significantly better AT recurrence–free survival with CPVA than with ADT. The relative risk for recurrence of AT within 12 months of the follow-up period was 3.73 (95% confidence interval, 2.47-5.63) for CPVA compared with ADT. Despite the fact that the studies included are from different parts of the world and use somewhat different ablation techniques, the results are remarkably consistent. In addition, the adverse event rate associated with CPVA was statistically significantly lower than that associated with ADT.

THE 4 RANDOMIZED CONTROLLED TRIALS

Although *circumferential pulmonary vein ablation* is used as a general term to describe catheter ablation of AF, different ablation strategies were used in the 4 studies. Wazni et al[14] used electrical isolation of the pulmonary veins (pulmonary vein isolation) as the end point of ablation, while in the other 3 studies[13,15,16] the goal of ablation was substrate modification of the left atrium, commonly referred to as *left atrial catheter ablation* (LACA). Because of the small number of studies, subgroup analysis was not performed. In the trial by Stabile et al,[15] the intervention group received ADT in addition to CPVA, whereas the other 3 studies[13,14,16] assessed outcome for CPVA without ADT as the intervention. In contrast to the other 2 trials,[15,16] the trials by Krittayaphong et al[13] and Wazni et al[14] did not have any repeated procedures performed in the CPVA arm and evaluated the results of a single ablation procedure. The trial by Wazni et al[14] was unique in that it enrolled ADT-naive patients and was evaluating CPVA vs ADT for first-line treatment of AF, while the other trials[13,15,16] enrolled only those patients that had been treated with ADT and their results might not be generalizable to the population diagnosed as having symptomatic AF for the first time.

In the trial by Krittayaphong et al,[13] the CPVA group compared with the ADT group had a higher probability of being free from recurrent AF (80% vs 40%), a decrease in symptoms related to AF, and an improvement in quality of life. In the trial by Wazni et al,[14] the pulmonary vein isolation group had fewer cases of symptomatic AF recurrence (13% vs 63%) and fewer hospitalizations (9% vs 54%) compared with the ADT group. In the trial by Stabile et al,[15] 44% of the patients undergoing LACA in addition to ADT had recurrence of AF, much lower than the 91% recurrence rate among patients receiving only ADT. Compared with the ADT group, the LACA group in the trial by Pappone et al[16] had a higher percentage of patients free from recurrent AT (86% vs 22%), and the hospitalization rates were much lower.

Many trials of catheter ablation of AF have lacked ambulatory monitoring to detect asymptomatic AF, which is observed in a significant number of patients after CPVA and may lead to overestimates of procedural success.[27] However, Holter monitoring was used for outcome assessment in all 4 trials included in our analysis at 3, 6, and 12 months during the follow-up period. Twelve-lead electrocardiograms were also

obtained in the trials by Pappone et al,[16] Stabile et al,[15] and Krittayaphong et al.[13] The trial by Wazni et al[14] used a loop event–recorder worn for 1 month during the first month of the follow-up period, which was repeated at 3 months and thereafter at recurrence of symptoms.

CLINICAL IMPLICATIONS

The role that CPVA should have in the treatment of AF continues to evolve as the technique becomes more refined. Some investigators have proposed that catheter ablation should be offered to patients as first-line treatment for AF,[28] but this argument has not been settled.[29] There is a sense of hesitancy in recommending catheter ablation as a first-line treatment in the absence of definitive evidence because it is associated with a complication rate as high as 6% according to a worldwide survey.[30] The current American College of Cardiology/American Heart Association/European Society of Cardiology guidelines[31] recommend an initial trial of ADT for most patients with symptomatic AF pursuing a rhythm control strategy and reserve catheter ablation for patients who have received no benefit from medical therapy.

A finding of this review was the scarcity of trials comparing CPVA with ADT. Catheter ablation of AF has rapidly grown in popularity during the past 10 years and has entered into widespread use in the United States and Europe. Numerous trials have demonstrated the efficacy of this procedure in the treatment of AF, but few trials have compared it with standard treatment for ADT. Despite this lack of data, some electrophysiologists advocate CPVA for first-line therapy of AF.[28] Because 3 of 4 trials in this meta-analysis did not look at first-line therapy, it is difficult to say based on our results whether using catheter ablation therapy as the first-line treatment is a reasonable approach. Nevertheless, the conclusions of this analysis at least seem to be in agreement with the hypothesis that CPVA may be more efficacious therapy than ADT. This study also confirms the need for larger randomized trials to evaluate the strategy of offering CPVA as first-line therapy for carefully selected patients with AF.

Although the Atrial Fibrillation Follow-up Investigation of Rhythm Management[6] trial is frequently cited in arguments against a rhythm control strategy for management of AF, a primary finding of that trial is the poor efficacy of ADT in maintaining sinus rhythm. In a similar fashion, this analysis highlights the low efficacy of ADT in preventing recurrent AT. In addition, patients in the Atrial Fibrillation Follow-up Investigation of Rhythm Management[7,32] trial who achieved sinus rhythm had improved survival and quality of life. The lack of effective medications emphasizes the need for improved therapies for AF and explains why many clinicians have embraced CPVA for management of AF, despite the absence of concrete evidence in its favor. Although CPVA seems to be significantly superior to ADT in this analysis, only 75.7% of patients undergoing CPVA in these trials were free of recurrent AT during the 1-year follow-up period. This finding allows for substantial improvements in current techniques.

LIMITATIONS

We did not find statistically significant heterogeneity among the published trials; however, the test for heterogeneity would not be powerful enough in light of the small number of studies included in the meta-analysis. There could still be some heterogeneity among the 4 trials owing to differences in the subject populations on the basis of the country of origin, differences in the inclusion and exclusion criteria, disparity in the interventions and the control treatments, and variation in expertise of the physicians. Also contributing to the lack of finding statistically significant heterogeneity are the remarkably consistent results from these trials, despite the obvious dissimilarities. Similarly, with 4 trials we had little power to detect any publication bias, and we did not find any evidence for it.

The ablation technique assessed varied among the trials. The trial by Wazni et al[14] assessed pulmonary vein isolation, while the remaining trial techniques were more consistent with LACA. Stabile et al[15] used amiodarone and other drugs in conjunction with LACA, while Krittayaphong et al[13] prescribed amiodarone for 3 months following the procedure. In view of the few available studies, this analysis was unable to assess the individual techniques separately. The results reflect the efficacy of the most commonly used techniques as a group and are consistent with the significant variation among procedural techniques in current clinical practice. We used the random-effects model to obtain the estimate and confidence interval of the relative risk, which allows for variation due to heterogeneity among the trials. However, this leads to disproportionately more weight being given to small studies.

The few published trials comparing CPVA with ADT is a significant limitation of this analysis. The numbers of participants in the trials are limited as well, ranging from 30 to 198. As already noted, the widespread and growing use of CPVA for treatment of AF warrants further research on this question. Furthermore, whether the results of small controlled trials of procedures performed by experienced operators can be generalized to the population of patients undergoing CPVA for AF remains an open question.

CONCLUSIONS

The recent Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society's expert consensus statement[19] outlines the current recommendations for ablation therapy in AF. This consensus statement reaffirms the role of CPVA as second-line therapy after failure of at least 1 antiarrhythmic medication.[19] Two trials that are recruiting patients, Radiofrequency Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment[33] in the Canada, Europe, and Australia and the Catheter Ablation for the Cure of Atrial Fibrillation–2 study[34] in Europe, could provide a more definitive answer regarding the relative efficacy of catheter ablation for management of AF. Findings from this meta-analysis suggest that CPVA for treat-

ment of AF is not inferior to ADT and may be associated with better outcomes up to 1 year after the procedure. The significant limitations of this analysis already outlined must be stressed when evaluating these results in a clinical context. Particularly when considering first-line therapy options, the conclusions of this study must be taken as confirmation of the need for further trials and not as a guide for clinical practice because of the limited number of studies addressing this issue.

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Author Contributions: Dr Noheria had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Noheria and Kumar. *Acquisition of data:* Noheria and Kumar. *Analysis and interpretation of data:* Noheria, Kumar, Wylie, and Josephson. *Drafting of the manuscript:* Noheria, Kumar, and Wylie. *Critical revision of the manuscript for important intellectual content:* Noheria, Kumar, Wylie, and Josephson. *Statistical analysis:* Noheria and Kumar. *Administrative, technical, and material support:* Josephson. *Study supervision:* Wylie and Josephson.

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