Efficacy of Ablation Lesion Sets in Addition to Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation: Findings From the SMASH-AF Meta-Analysis Study Cohort

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Background—The objective was to explore the efficacy of ablation lesion sets in addition to pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation. The optimal strategy for catheter ablation of paroxysmal atrial fibrillation is debated.

Methods and Results—The SMASH-AF (Systematic Review and Meta-analysis of Ablation Strategy Heterogeneity in Atrial Fibrillation) study cohort includes trials and observational studies identified in PubMed, Scopus, and Cochrane databases from January 1 1990, to August 1, 2016. We included studies reporting single procedure paroxysmal atrial fibrillation ablation success rates. Exclusion criteria included insufficient reporting of outcomes, ablation strategies that were not prespecified and uniform, and a sample size of fewer than 40 patients. We analyzed lesion sets performed in addition to PVI (PVI plus) using multivariable random-effects meta-regression to control for patient, study, and procedure characteristics. The analysis included 145 total studies with 23 263 patients (PVI-only cohort: 115 studies, 148 treatment arms, 16 500 patients; PVI plus cohort: 39 studies; 46 treatment arms, 6763 patients). PVI plus studies, as compared with PVI-only studies, included younger patients (56.7 years versus 58.8 years, P=0.001), fewer women (27.2% versus 32.0% women, P=0.002), and were more methodologically rigorous with longer follow-up (29.5 versus 17.1 months, P 0.004) and more randomization (19.4% versus 11.8%, P<0.001). In multivariable meta-regression, PVI plus studies were associated with improved success (7.6% absolute improvement [95% CI, 2.6–12.5%]; P<0.01, I^2=88%), specifically superior vena cava isolation (4 studies, 4 treatment arms, 1392 patients; 15.1% absolute improvement [95% CI, 2.3–27.9%]; P 0.02, I^2=87%). However, residual heterogeneity was large.

Conclusions—Across the paroxysmal atrial fibrillation ablation literature, PVI plus ablation strategies were associated with incremental improvements in success rate. However, large residual heterogeneity complicates evidence synthesis. **(*J Am Heart Assoc*. 2019;8:e009976. DOI: 10.1161/JAHA.118.009976.)**

Key Words: atrial fibrillation • catheter ablation • meta-analysis • success rates • systematic review

Despite almost 20 years of investigation into approaches for catheter ablation for atrial fibrillation (AF),[1] consensus has not been achieved on the utility and efficacy of ablation lesion sets in addition to pulmonary vein isolation (PVI) in patients with paroxysmal AF (PAF). Absence of clarity and agreement on AF mechanisms contributes to the lack of consensus on ablation approach,[2] as does reproducibility issues across the field. Previous attempts at building consensus through evidence synthesis of the AF ablation literature have used limited study cohorts as a result of noncomprehensive search strategies and exclusion of noncontrolled studies. In addition, analyses were confounded by lesion sets not of interest and did not adequately account for the unprecedented degree of variation in the literature with respect to evaluated ablation strategies, study designs and follow-up protocols, and enrolled populations.[3–14]

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Clinical Perspective

What Is New?

- After controlling for patient, study design, and procedural covariates, studies investigating lesion sets in addition to pulmonary vein isolation were associated with modest improvement in success rates for ablation of paroxysmal atrial fibrillation compared with studies on pulmonary vein isolation alone.
- When lesion sets were disaggregated, performing superior vena cava isolation in all study patients in addition to pulmonary vein isolation was associated with the largest improvement in success rates.

What Are the Clinical Implications?

- Large residual heterogeneity limits causal inferences and application of these findings to clinical practice.
- Lack of consensus on the choice of atrial fibrillation ablation lesion set efficacy is driven by evidence incompatibility.
- Lesion sets in addition to pulmonary vein isolation do not appear futile; however, ablation protocol reproducibility across the field needs to be addressed to efficiently determine optimal ablation strategies.

Therefore, we sought to explore the efficacy of ablation lesion sets in addition to PVI in catheter ablation for PAF by performing the most comprehensive attempt, to date, at evidence synthesis through systematic review and meta-analysis. From this cohort of studies, we also sought to explore variation in patient demographics and study design characteristics in the PAF ablation literature.

Methods

The SMASH-AF (Systematic Review and Meta-analysis of Ablation Strategy Heterogeneity in Atrial Fibrillation) study is a comprehensive cohort of trials and observational studies that investigated catheter ablation for AF from January 1, 1990, to August 1, 2016. Included trials met strict criteria for reproducibility of ablation strategy. The full project protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) before data analysis.[15] Methods for cohort creation have been previously described in detail.[16]

Data Sources and Searches

We identified relevant articles in PubMed, Scopus, and Cochrane databases using a sensitive search strategy (Table S1) developed in collaboration with Lane Medical Library (Stanford University), designed to capture both contemporary studies and all studies included in prior AF ablation systematic reviews.[17,18] Search terms were selected to capture the full spectrum of AF ablation approaches, tools, and technologies.

Study Selection

Studies were screened for SMASH-AF cohort inclusion if they reported ablation outcomes of interest, which were defined as AF ablation success rate, safety profile, quality of life postablation, or procedure cost. Major exclusion criteria included: (1) no treatment or outcomes of interest; (2) insufficient reporting of baseline patient demographics, ablation strategy, or outcomes of interest; (3) ablation strategies that were not prespecified and uniform across the treatment arm; and (4) small study size (ie, fewer than 40 patients in a treatment arm). Full exclusion criteria are available in Tables S2 and S3. We screened studies for exclusion criteria in 2 steps: (1) review of title and abstract performed by 1 project member (G.L.); and (2) review of full text performed by 3 project members (G.L., A.C., F.Y.) with 2-reviewer agreement required for final inclusion or exclusion. All exclusion conflicts were settled by a single project member (A.P.).

Data Extraction and Quality Assessment

We identified necessary data assumptions and simplifications (Table S4) and performed data abstraction form optimization through a trial abstraction of 20 random articles. Data abstraction was performed by 3 project members (G.L., A.C., F.Y.) with abstracted data categories available in Table S5. Ablation protocol exclusion criteria (Table S2, criteria 5–11) were used to assess quality, bias, and reproducibility of included studies. All aspects of the SMASH-AF study followed the Standards for Systematic Reviews established by the Institute of Medicine,[19] which has been adopted in the Methodology Standards of the Patient-Centered Outcomes Research Institute.[20] Reporting of results is in accordance with both the Institute of Medicine and PRISMA guidelines.[19,21]

Data Synthesis and Statistical Analysis

For the efficacy of ablation lesion sets in addition to PVI analysis, we excluded treatment arms from the previously described SMASH-AF study cohort that: (1) were not composed exclusively of patients with paroxysmal AF; (2) did not attempt PVI of all pulmonary veins; and (3) did not report a single procedure success rate. The citations of studies included in the analysis cohort are available in the supplemental references. We abstracted success rate as reported single procedure AF recurrence-free survival. If multiple recurrence definitions were reported, the highest priority definition was included in the analysis based on the following priority order: (1) atrial tachyarrhythmia without antiarrhythmic agents; (2) AF without antiarrhythmic agents;

(3) atrial tachyarrhythmia with antiarrhythmic agents; and (4) AF with antiarrhythmic agents. We determined studies' percentage of follow-up with rhythm monitoring based on reported postablation screening protocol.

We performed meta-regressions at the treatment arm level with ablation lesion set as a dichotomous independent variable (PVI only versus PVI with any additional lesion set [PVI plus]) and single procedure success rate as the dependent variable. We did not pool results from studies' treatment and control arms during meta-regression as there is no consistent control arm across the literature and many relevant observational studies are uncontrolled. In a secondary analysis, regression models included separate variables for each ablation lesion set performed in addition to PVI. Multivariable models included covariates selected by face validity for study design (study type [randomized, prospective, retrospective, case control], recurrence definitions [AF or atrial tachyarrhythmia, arrhythmia duration definition], follow-up protocol [duration of follow-up, rhythm monitoring percentage], antiarrhythmic drug prohibition, study size, year published), baseline patient demographics (age, percent of women), and procedure characteristics (ablation energy type, catheter [balloon, contact force, irrigated], cavotricuspid isthmus line).

Meta-regressions used DerSimonian and Laird methodology with random effects, which allows the true effects to vary between studies by assuming that they have a normal distribution around a mean effect. Statistical heterogeneity was assessed using the I^2 statistic. The t test or Mann–Whitney U test were used, depending on variable normality and variance, to compare study design characteristic and patient demographics between PVI plus and PVI-only studies. We used Evidence Partners DistillerSR for: (1) reference management; (2) creation, distribution, and completion of screening and data collection forms; (3) record of exclusion rationale; and (4) storage of abstracted data. All analyses were performed using STATA, version 12.1 (StataCorp).[22,23]

Results

The analysis cohort included 145 studies (194 treatment arms) with 23 263 patients (PVI-only cohort: 115 studies, 148 treatment arms, 16 500 patients; PVI plus cohort: 39 studies, 46 treatment arms, 6763 patients) (Figure 1). Lesion sets performed in addition to PVI in the analysis cohort included 3 linear ablation lesion sets (box lesion, mitral line, and roof line), 3 right atrial ablation lesion sets (coronary sinus isolation, superior vena cava [SVC] isolation in all patients, and SVC isolation in patients with SVC triggers only), complex fractionated atrial electrogram ablation, ectopic foci ablation, and ganglionated plexi/autonomic denervation ablation (Table 1). For PVI-only studies, reported success rates ranged from 29.2% to 93.3%, with a summary estimate of 70.5% (95% CI, 68.4–72.6%; I^2=90%) (Figure S1). For PVI plus studies, reported success rates ranged from 43.0% to 94.0%, with a summary estimate of 73.7% (95% CI, 70.1–77.3%; I^2=92%) (Figure S2).

PVI plus studies, compared with PVI-only studies, included patients who were slightly younger (56.7 versus 58.8 years, P=0.001) and less likely to be women (27.2% versus 32.0% women, P=0.002) and had more rigorous study methodology with a longer mean follow-up (29.5 versus 17.1 months, P=0.004) and more randomization (19.4% versus 11.8%, P<0.001). Individual ablation lesion sets were underpowered to assess for statistical differences in baseline patient demographics and study design characteristics; however, qualitative variation was large (Table 1).

In univariable meta-regressions, PVI plus studies weakly trended towards a 3.2% absolute increase in success rate compared with PVI-only studies (95% CI, −1.0% to 7.3%; P=0.13 [I^2=90%]). Individual ablation lesion sets were not associated with improved success. After controlling for patient demographics, study design, and procedure characteristics, PVI plus studies were associated with a 7.6% absolute increase in success rate compared with PVI-only studies (95% CI, 2.6–12.5%; P<0.01 [I^2=88%]). In multivariable meta-regression of individual ablation lesion sets, as compared with PVI only, SVC isolation in all patients (4 studies, 4 treatment arms, 1392 patients) was associated with a 15.1% absolute improvement in success (95% CI, 2.3–27.9%; P=0.02), while complex fractionated atrial electrogram ablation trended towards a 14.4% absolute improvement in success (95% CI, −2.3% to 31.1%; P=0.09) (Table 2) (Figure 2). The multivariable meta-regression of individual lesion sets had large residual heterogeneity (I^2=87%). A cavotricuspid isthmus line was not associated with success rate in any analysis.

Discussion

In this large and contemporary systematic review and meta-analysis of studies of catheter ablation for PAF, we found an incremental benefit for lesion sets in addition to PVI, specifically SVC isolation. However, we found substantial variation in patient demographics and study design characteristics when studies were stratified by lesion set. Furthermore, there was large residual heterogeneity in treatment effect, which limits evidence synthesis and causal inference.

Variation in study designs, evaluated ablation strategies, and enrolled populations across AF ablation literature is likely driven by the inherent complexity of developing a highly technical procedure-based treatment for a complex disease, for which mechanistic understanding is evolving. An unintended consequence of this variation is the creation of a

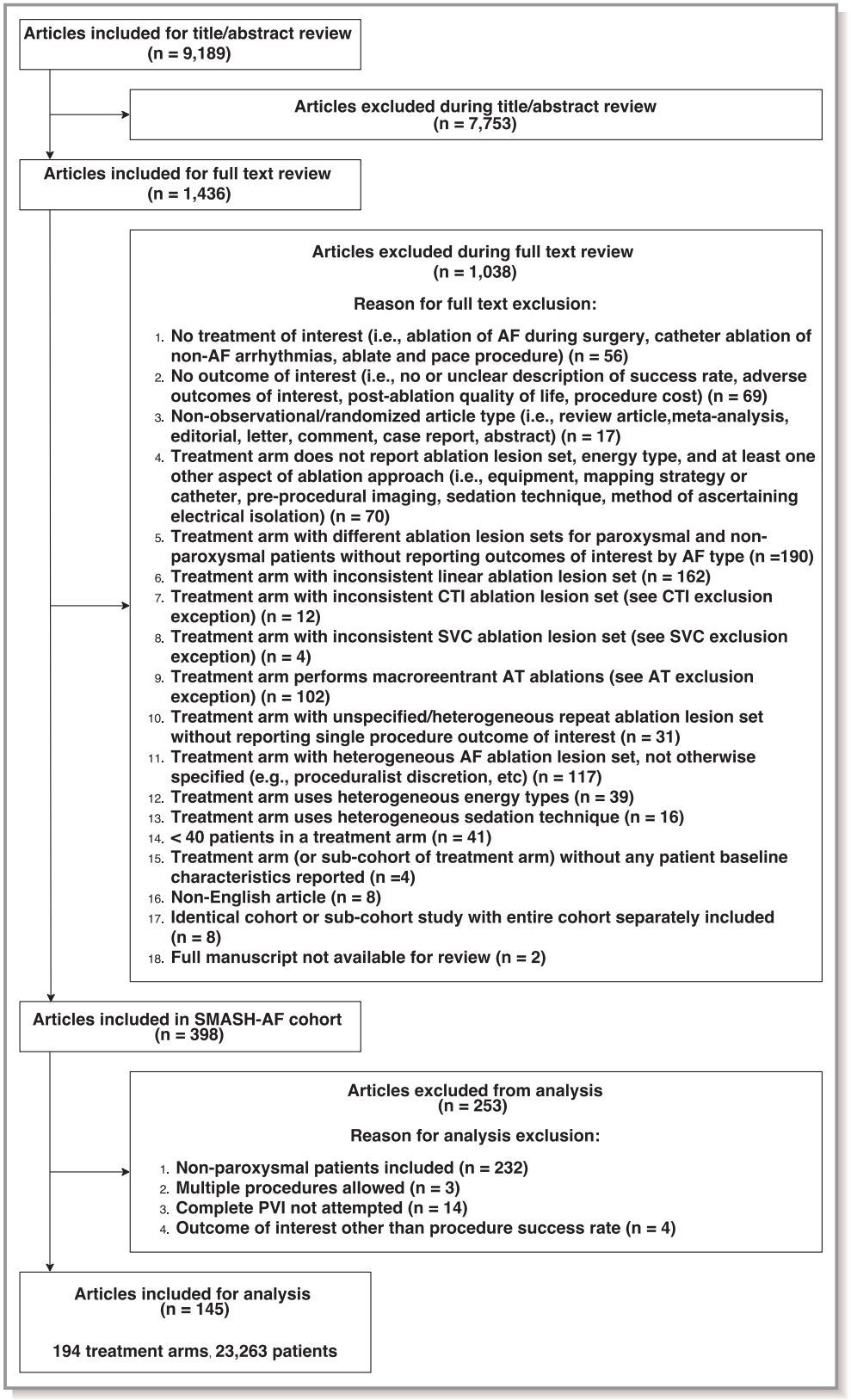

Figure 1. Flow diagram. Inclusion and exclusion criteria used to select analysis cohort. AF indicates atrial fibrillation; AT, atrial tachycardia; CTI, cavotricuspid isthmus; PVI, pulmonary vein isolation; SMASH-AF, Systematic Review and Meta-analysis of Ablation Strategy Heterogeneity in Atrial Fibrillation; SVC, superior vena cava.

Table 1. Patient Demographics, Study Design, and Procedure Characteristics by Ablation Lesion Set in Paroxysmal AF Ablation Studies

Ablation Lesion Set[†,‡]	Treatment Arms, No.	Patient Demographics*			Study Design Characteristics*						Procedure Characteristics*		
		Age, y	Women, %	Hypertension, %[§]	RCT, %	Size, No.[‖]	Follow-Up Duration, mo	Rhythm Monitoring, %[¶]	No AADs, %	Guideline Recurrence Definition, %[#]	RFA, %	CF-Catheter, %[§]	Irrigated-Catheter, %[§]
PVI only	148	58.8	32.0	44.9	11.8	111	17.1	2.6	77.5	66.4	75.6	1.4	53.4
PVI plus**	46	56.7	27.2	40.4	19.4	147	29.5	1.6	82.4	52.1	99.2	1.3	33.0
P value[††]		0.001	0.002	0.28	<0.001	0.85	0.004	0.81	0.83	0.12	<0.001	0.38	0.34
CFAE	3	61.7	38.8	60.0	27.0	94	26.2	1.0	54.4	54.4	100	0	100
Ectopic foci	26	56.9	25.5	37.5	12.6	175	27.9	1.5	96.7	45.2	98.8	0	31.2
Ganglionated plexi	1	56.0	30.0	71.0	100.0	82	24.0	3.3	0.0	100.0	100	0	100
Box lesion	7	55.0	33.8	41.3	50.7	110	13.8	5.4	93.2	50.7	100	17.0	83.0
Mitral line	8	54.0	34.3	45.9	36.0	93	16.6	3.9	93.3	24.0	100	17.8	40.2
Roof line	8	57.9	29.5	51.5	62.7	69	23.5	1.0	58.2	52.2	100	0.0	65.6
Coronary sinus isolation	1	63.5	35.0	64.3	0.0	128	26.3	0.6	0.0	0.0	100	0.0	100
SVC isolation, all[‡‡]	4	54.7	26.9	37.5	10.8	348	54.4	0.4	63.1	44.0	100	0.0	0
SVC isolation, triggered[§§]	11	58.8	25.4	41.7	18.2	217	28.2	2.1	93.3	81.7	100	0.0	43.3

AADs indicates antiarrhythmic drugs; AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; RFA, radiofrequency ablation; RCT, randomized control trial.
*Mean weighted by number of patients per treatment arm.
[†]Ablation lesion sets performed in addition to pulmonary vein isolation (PVI).
[‡]Ablation lesion set groups not mutually exclusive as treatment arm may perform multiple ablation lesion sets.
[§]Percent of PVI-only and PVI plus treatment arms, respectively, reporting hypertension: 87% and 74%; contact force (CF) catheter: 97% and 96%; and irrigated catheter: 97% and 96%.
[‖]Number of patients per treatment arm.
[¶]Percentage of mean follow-up with rhythm monitored.
[#]Recurrence defined as atrial tachyarrhythmia for 30 seconds.
**PVI with any additional lesion sets.
[††]PVI plus as compared with PVI only.
[‡‡]Superior vena cava (SVC) isolation performed in all patients.
[§§]SVC isolation only in patients with SVC triggers.

literature base with an unprecedented degree of heterogeneity. Attempts at evidence synthesis through narrative review and expert opinion are likely to conflict depending on prioritization of study covariates. Similarly, attempts at complex meta-analysis, as evidenced by our study, suffer from large residual heterogeneity despite accounting for many plausible determinants of outcome heterogeneity. In essence, many knowledge gaps in the AF ablation field are no longer sustained by evidence gaps but instead by evidence incompatibility.

Consensus statements on AF ablation have advocated for standardization of outcome definitions to improve reproducibility of results and evidence synthesis.[24–26] Less frequently discussed are issues with ablation protocol reproducibility. In our review, a large proportion of studies were excluded for ablation protocols that were not explicit or consistent (exclusion criteria 5–11 [n=618]; 60% of full text exclusions), making replication and interpretation of results challenging. In the era of clinical outcome testing in AF ablation, trial durations have prolonged increasing the risk of ablation protocol heterogeneity within each individual trial, adding an additional dimension to the field's reproducibility issue.[27,28] Although the effect of ablation protocol reproducibility on our results was limited by strict exclusion criteria, it likely substantially contributes to evidence incompatibility across the field.

Large residual heterogeneity in our analyses prevents confident application of our findings to clinical practice. However, statistical superiority of approaches that utilize lesion sets in addition to PVI in multivariable analysis provides optimism that contemporary ablation strategies can achieve success rates higher than those achieved through PVI alone in patients with PAF. This finding contrasts with the nonparoxysmal AF ablation literature, where randomized trials have

Table 2. Meta-Regressions of Ablation Lesion Sets in Addition to PVI in Paroxysmal AF Ablation Studies

	Univariate Meta-Regression			Multivariate Meta-Regression*,†		
Ablation Lesion Set‡	Coefficient, %§	95% CI	*P* Value	Coefficient, %§	95% CI	*P* Value
PVI plus‖	3.2	−1.0 to 7.3	0.13	7.6	2.6 to 12.5	<0.01
CFAE	7.7	−10.4 to 25.9	0.40	14.4	−2.3 to 31.1	0.09
Ectopic foci	1.3	−4.9 to 7.3	0.70	4.0	−3.1 to 11.0	0.27
Ganglionated plexi	3.7	−21.1 to 28.4	0.77	4.8	−18.0 to 27.6	0.68
Box lesion	9.6	−2.4 to 21.5	0.12	4.6	−8.0 to 17.1	0.47
Mitral line	4.5	−7.6 to 16.6	0.47	10.0	−2.6 to 22.5	0.12
Roof line	5.3	−6.1 to 16.8	0.36	8.9	−2.2 to 20.2	0.12
Coronary sinus isolation	−0.3	−30.2 to 29.6	0.98	−12.8	−40.8 to 15.3	0.37
SVC isolation, all¶	6.0	−6.0 to 18.1	0.32	15.1	2.3 to 27.9	0.02
SVC isolation, triggered#	−3.5	−12.3 to 5.3	0.44	2.0	−9.0 to 13.0	0.72

CFAE indicates complex fractionated atrial electrogram.
*Covariates included study design characteristics (study type [randomized, prospective, retrospective, case control], recurrence definitions [atrial fibrillation (AF) or atrial tachyarrhythmia, arrhythmia duration definition], follow-up protocol [duration of follow-up and rhythm monitoring percentage], antiarrhythmic drug prohibition, study size, year published), patient demographics (age, percentage of women), and procedure characteristics (ablation energy, catheter [balloon, contact force, irrigated], cavotricuspid isthmus line).
†Pulmonary vein isolation (PVI) plus analysis: residual I^2=88%; PVI with individual lesion set analysis: residual I^2=87%.
‡Ablation lesion sets performed in addition to PVI.
§Absolute difference in success rate compared with PVI only.
‖PVI with any additional lesion sets.
¶Superior vena cava (SVC) isolation performed in all patients.
#SVC isolation only in patients with SVC triggers.

provided evidence that ablation beyond PVI with contemporary ablation strategies is not beneficial.[29]

To our knowledge, meta-analysis of studies investigating SVC isolation in addition to PVI in patients with PAF has only been performed once. Three randomized controlled trials were included, with the study finding that SVC isolation strongly trended towards a reduction in AF recurrence (odds ratio, 0.54; 95% CI, 0.29–1.00 [*P* 0.05]).[12] Mechanistically, similar to pulmonary veins, atrial myocardial tissue extends into the SVC,[30] making the SVC a common site of nonpulmonary vein triggers.[31] Interestingly, in our analysis, when SVC isolation was only performed in patients with triggers mapped to the SVC, no reduction in AF recurrence was detected. This finding may be analogous to the early demonstration of inferiority of pulmonary vein ablation approaches that only targeted pulmonary veins with identified triggers, as compared with PVI of all pulmonary veins.

Limitations

Strict exclusion criteria limited the cohort size and resulted in certain ablation lesion sets being underrepresented in the analysis cohort. However, the SMASH-AF study remains the largest systematic review and meta-analysis of AF ablation performed by a large margin. As discussed, large residual heterogeneity requires explanation before definitive evidence synthesis can be achieved. Variable reporting of patient baseline characteristics and operator experience prevented controlling for study characteristics known to impact procedure outcome, which could account for some of the residual heterogeneity. Importantly, ablation approach and intraprocedural end points for adjunctive lesion sets are likely to differ between operators and studies. These factors are difficult to measure and were not reported in the majority of studies and may therefore be contributing to overall heterogeneity. Results may not generalize to patients seen in clinical practice, who may differ from clinical trial populations. Although we controlled for numerous study covariates, it is possible that the quality of PVI itself has improved over time with better technology and procedural maturity. In addition, while we accounted for secular trends, PVI lesion quality and durability could be an unmeasured confounder. Last, as with all systematic reviews and meta-analyses, small study effects may bias results.

Conclusions

In a systematic review and meta-analysis of trials and observational studies that spanned the entire AF ablation literature base, we found substantial variation in study designs. Although statistical superiority of ablation approaches was detected, issues with evidence incompatibility require further examination.

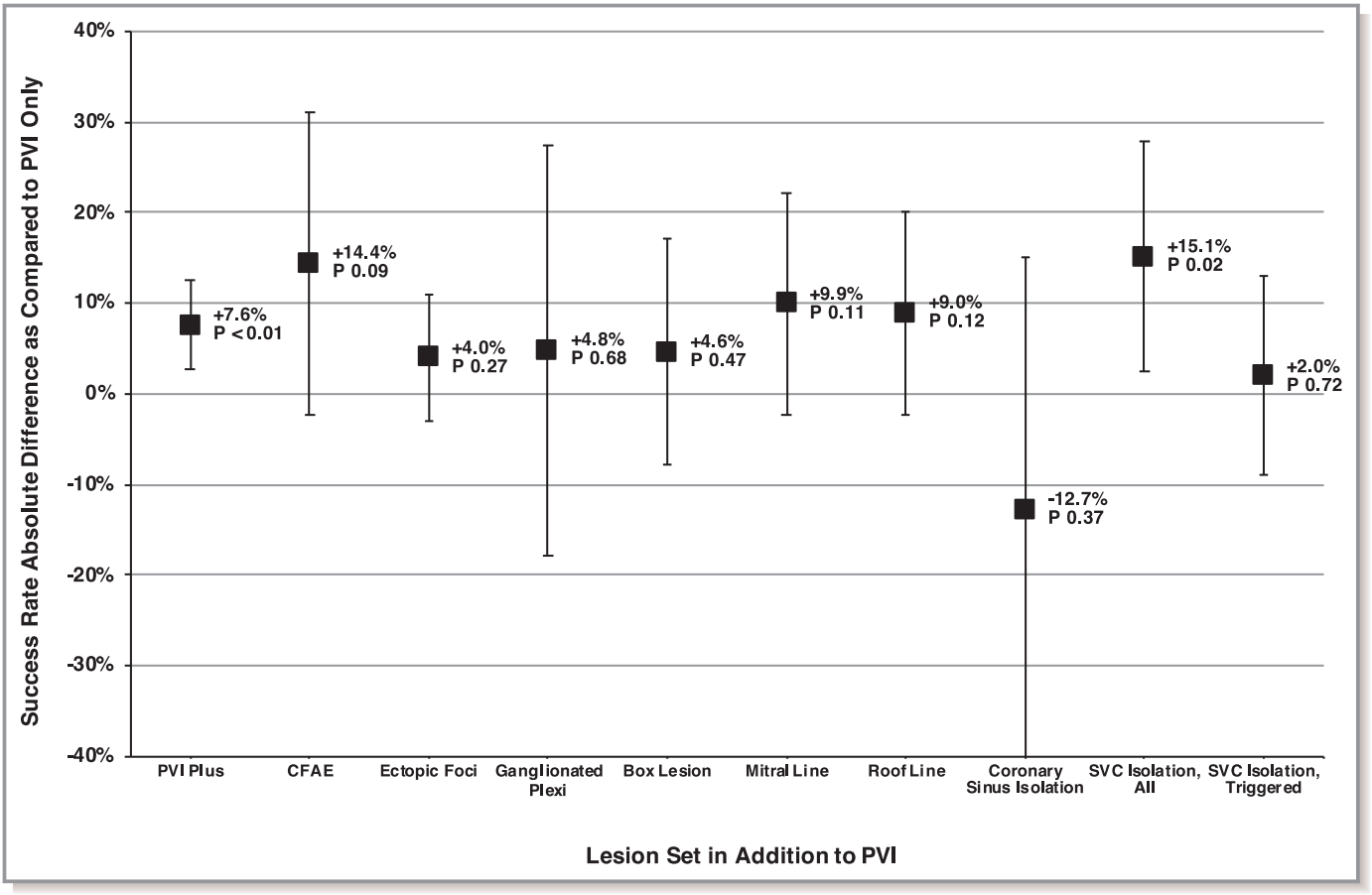

Figure 2. Efficacy of ablation lesion sets in addition to pulmonary vein isolation (PVI) in paroxysmal atrial fibrillation ablation studies. Multivariable meta-regression results are reported. Point estimates represent absolute difference in success rate as compared with PVI only. PVI with any additional lesion sets analysis (PVI plus): residual I^2=88%; individual lesion set analysis: residual I^2=87%. CFAE indicates complex fractionated atrial electrogram; SVC, superior vena cava; SVC isolation, all: SVC isolation performed in all patients; SVC isolation, triggered: SVC isolation only in patients with SVC triggers.

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SUPPLEMENTAL MATERIAL

Table S1. PubMed Search Strategy.

("atrial fibrillation" [mesh] OR "atrial fibrillation" [tw]) AND (ablation [tw] OR "catheter ablation" [mesh] OR "catheter ablation" [tw] OR (ablation [ti] AND "pulmonary veins" [mesh]) OR "pulmonary vein" [tw] OR rotor* [tw] OR FIRM [tw] OR focal impulse [tw] OR driver [tw] OR “complex fractionated atrial electrogram” [tw] OR CFAE [tw] OR “complex fractionated electrogram” [tw] OR CFE [tw] OR “continuous electrical activity” [tw] OR CEA [tw] OR “fractionated electrogram” [tw] OR “ganglionated plexus” [tw] OR “ganglionated plexi” [tw] OR “autonomic denervation” [tw] OR “right atrial” [tw] OR “flutter line” [tw] OR “roof line” [tw] OR “superior vena cava isolation” [tw] OR linear [tw] OR "antral isolation" [tw] OR radiofrequen* [tw] OR cryocatheter* [tw] OR "cryosurgery" [mesh] OR cryosurg* [tw] OR cryoballoon* [tw] OR "cryo-balloon" [tw] OR "laser balloon" [tw] OR "force contact" [tw] OR cryocatheter* [tw]) NOT ("animals" [mesh] NOT "humans" [mesh]) AND english [lang] NOT ("Atrioventricular Node" [mesh] OR "Wolff-Parkinson-White Syndrome" [mesh] OR "Wolff-Parkinson-White" [tw] OR wpw [tw] OR "atrioventricular junction" [tw] OR "Atrioventricular conduction" [tw] OR "accessory pathway" [tw] OR "accessory pathways" [tw] OR "Accessory atrioventricular" [tw] OR maze [tw] OR letter [pt] OR "review" [pt] OR "editorial" [pt] OR "case reports" [pt] OR "case report" [ti]) AND ("1990/01/01"[PDAT] : "3000/12/31"[PDAT])

Table S2. Exclusion Criteria.

1. No treatment of interest (i.e., ablation of AF during surgery, catheter ablation of non-AF arrhythmias, ablate and pace procedure)
2. No outcome of interest (i.e., no/unclear description of success rate, adverse outcomes of interest, post-ablation quality of life, procedure cost)
3. Non-observational/randomized article type (i.e., review article, meta-analysis, editorial, letter, comment, case report, abstract)
4. Treatment arm does not report ablation lesion set, energy type, and at least one other aspect of ablation approach (i.e., equipment, mapping strategy or catheter, pre-procedural imaging, sedation technique, method of ascertaining electrical isolation)
5. Treatment arm with different ablation lesion sets for paroxysmal and non-paroxysmal patients without reporting outcomes of interest by AF type
6. Treatment arm with inconsistent linear ablation lesion set
7. Treatment arm with inconsistent CTI ablation lesion set (see CTI exclusion exception)
8. Treatment arm with inconsistent SVC ablation lesion set (see SVC exclusion exception)
9. Treatment arm performs macroreentrant AT ablations (see AT exclusion exception)
10. Treatment arm with unspecified/heterogeneous repeat ablation lesion set without reporting single procedure outcome of interest
11. Treatment arm with heterogeneous AF ablation lesion set, not otherwise specified (e.g., proceduralist discretion, etc)
12. Treatment arm uses heterogeneous energy types
13. Treatment arm uses heterogeneous sedation technique
14. <40 patients in a treatment arm
15. <30 day follow-up
16. Treatment arm (or sub-cohort of treatment arm) without any patient baseline characteristics reported
17. Non-adult population (any patients <18)
18. Non-English article
19. Non-human study
20. Study published prior to 1990
21. Identical cohort or sub-cohort study with entire cohort separately included
22. Full manuscript not available for review

Table S3. Exclusions Exceptions and Clarifications.

1. If treatment arm employs a clear and consistent single procedure stepwise ablation lesion set or repeat ablation lesion set (including ERAF) to achieve restoration of sinus rhythm (e.g., first PVI, then mitral isthmus), then do NOT exclude for reason "Treatment arm with heterogeneous ablation lesion sets, not otherwise specified."
2. If repeat ablation (including ERAF) meets exclusion criteria, however, initial ablation meets inclusion criteria AND single procedure outcome of interest is reported, include.
3. If treatment arm performs CTI ablation for patients with history of, or inducible, atrial flutter, then do NOT exclude for reason "Treatment arm with inconsistent CTI ablation lesion set."
4. If treatment arm performs SVC ablation/isolation for AF triggers when identified, then do NOT exclude for reason "Treatment arm with inconsistent SVC ablation lesion set."
5. If treatment arm specifies that AT ablations are for focal automaticity, then do NOT exclude for reason “Treatment arm performs macroreentrant AT ablations.”
6. If treatment arm performs ablation of "ectopic foci" when identified, then do NOT exclude for reason "Treatment arm with heterogeneous ablation lesion sets, not otherwise specified."
7. If treatment arm performs additional ablation to complete PVI after balloon ablation, then do NOT exclude for reason "Treatment arm with heterogeneous ablation lesion sets, not otherwise specified " as long as additional ablation approach only differs by ablation catheter type (i.e., if cryoballoon PVI touched up with RFA, exclude).
8. If treatment arm uses varied power settings (watts), then do NOT exclude for reason "Treatment arm with heterogeneous ablation lesion sets, not otherwise specified."
9. If treatment arm uses varied duration of ablation (seconds), then do NOT exclude for reason "Treatment arm with heterogeneous ablation lesion sets, not otherwise specified."
10. If treatment arm uses different sized balloons, then do NOT exclude for reason "Treatment arm with heterogeneous ablation lesion sets, not otherwise specified."
11. If study reports adverse outcomes of interest or procedure cost, then do not exclude for reason follow-up < 30 days.
12. If treatment arm does not report clear duration of follow-up and only outcome of interest is success rate, then exclude for reason "no outcome of interest".
13. If treatment arm only reports adverse outcome that is not of interest (i.e., adverse outcome not defined in adverse outcome abstraction protocol), then exclude for reason "no outcome of interest".
14. If treatment arm only reports outcomes of interest on a sub-cohort of patients stratified after ablation procedure (e.g., AF recurrence rate in the sub-cohort of patients who did not recur by 6 months), then exclude for reason "no outcome of interest".
15. If two studies use identical cohorts and report the same outcome of interest, exclude cohort with shorter follow-up. If equal follow-up, exclude second published.

Table S4. Data Assumptions and Simplifications.

1. For Ablation equipment group, if treatment arm uses different equipment from a single equipment group (e.g., treatment arm uses different sized conventional catheters), abstract as respective equipment group. If treatment arm uses different equipment from different equipment groups (e.g., conventional catheter and contact force catheters), abstract as "heterogeneous equipment groups".
2. For Adverse outcomes, only abstract adverse outcomes if there is at least clear and convincing evidence that adverse outcomes are from single procedure. If beyond a reasonable doubt adverse outcomes are from single procedure (i.e., explicitly stated that results are single procedure), select "beyond a reasonable doubt results single procedure."
3. For AF type, record non-paroxysmal AF that isn't subdivided into persistent, long-standing persistent, and permanent as "non-paroxysmal".
4. For Duration of follow-up, if treatment arm reports success rates at different durations of follow-up, abstract success rate closest to median/mean follow-up.
5. For Electrical isolation/ablation success: procedural success rate, if procedural success rates reported for components of ablation lesion set (e.g., PVI and lines) record composite procedural success rate. If composite procedural success rate cannot be calculate, then select "Not reported."
6. For Procedure success rate, if clear and convincing evidence that multiple ablations were NOT performed (i.e., no mention of repeat ablation procedures, average ablations performed per patient, etc.), abstract as single procedure success rate. If beyond a reasonable doubt (i.e., explicitly stated that results are single procedure), select "beyond a reasonable doubt results single procedure".
7. For Screening method/Interval of ascertaining AF recurrence, if symptoms prompted rhythm analysis, do NOT record subsequent rhythm analysis as a screening method. Record number of times each screening method was checked over mean/median duration of follow-up. If screening frequency range used (e.g., Holter performed every 1-3 months), calculate times checked over mean/median duration of follow-up using most conservative frequency (i.e., every 3 months).

Table S5. Data Abstraction Categories.

Study Level

1. Authors
2. Title
3. Journal of publication
4. Year of publication
5. Total number of patients included
6. Study design
7. Institutional participation
8. Country in which study was performed

Treatment Arm Level

Patient Level

1. Age
2. Sex
3. Comorbidities
4. CHADS2 Score
5. CHA2DS2-VASc Score
6. ECHO Parameters

AF level

1. AF type
2. AF duration
3. AF burden at baseline

Procedure Level

1. Ablation lesion set
2. Ablation energy
3. Ablation equipment group
4. Mapping strategy
5. Mapping catheter
6. Pre-procedure imaging
7. Transeptal puncture
8. Electrical isolation/ablation success: procedural success rate
9. Electrical isolation/Existence of AF triggers: method of assessment
10. Sedation technique
11. Intra-ablation anticoagulation
12. Procedure duration
13. Fluoroscopy time
14. Ablation volume

Outcome Level

1. Duration of follow-up
2. Definition of AF recurrence
3. Screening method/Interval of ascertaining AF recurrence
4. Procedure success rate
5. Adverse outcomes
6. Post-procedure quality of life
7. Procedure cost

Figure S1. Forest Plot of PVI Only Study Arms.[1-148]

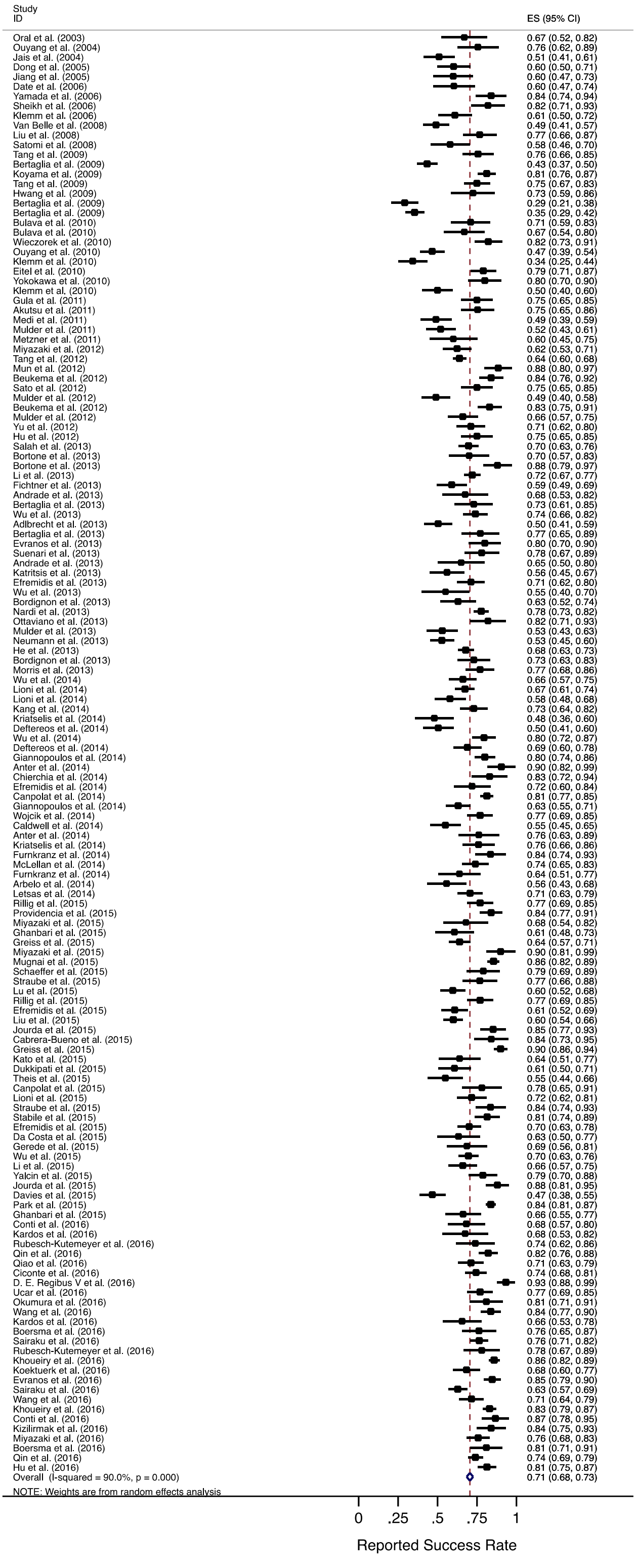
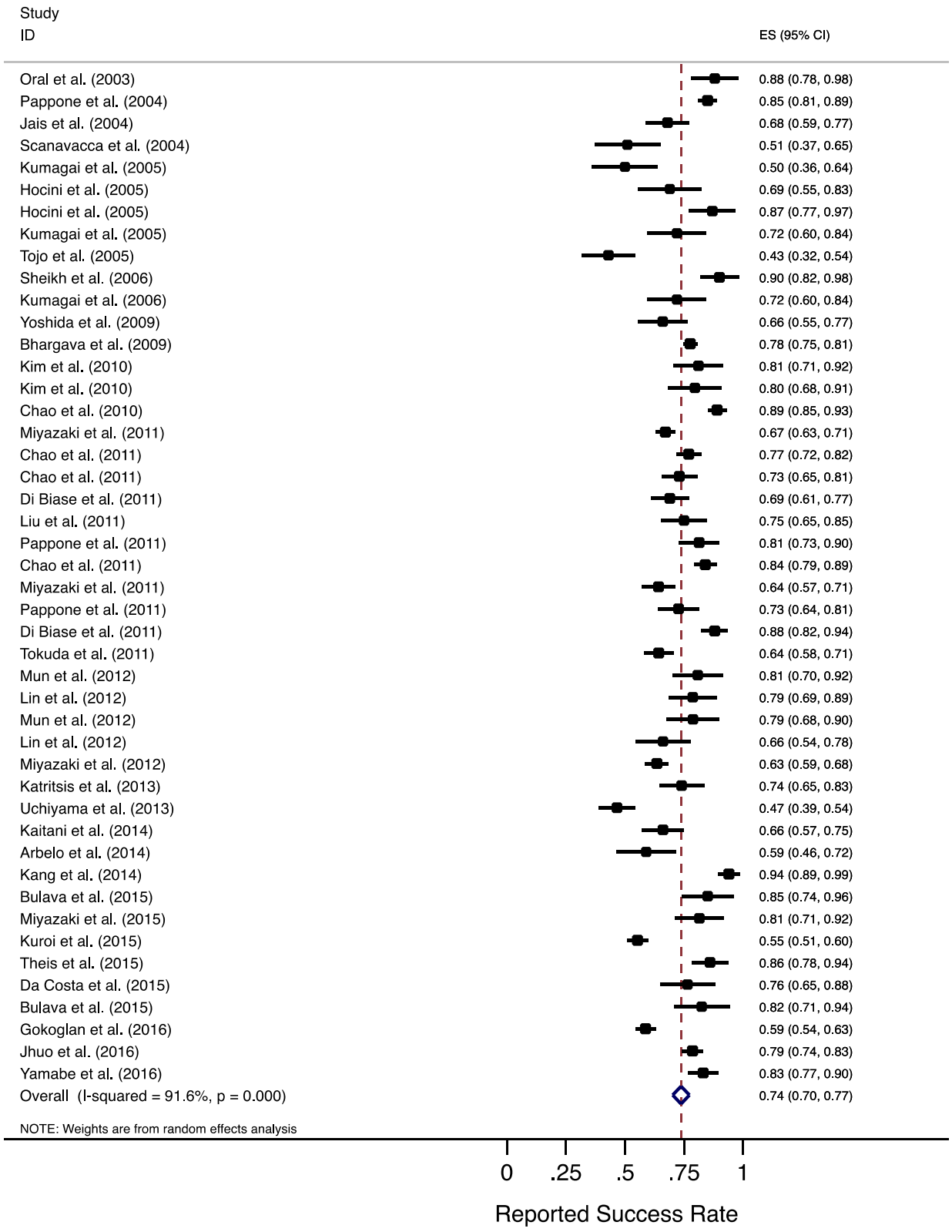


Figure S2. Forest Plot of PVI Plus Treatment Arms.[149-194]



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