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Meta-Analysis of Catheter Ablation versus Medical Therapy in Patients with Atrial Fibrillation Without Heart Failure

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Abstract

Introduction: Catheter ablation has shown to reduce mortality in patient with atrial fibrillation (AF) and heart failure (HF) with reduced ejection fraction. Its effect on mortality in patients without HF has not been well elucidated.

Methods: Thirteen randomized controlled trials encompassing 3856 patients were selected using PubMed, Embase and the CENTRAL till April 2019. Estimates were reported as random effects risk ratio (RR) with 95% confidence intervals (CI).

Results: Compared with medical therapy, catheter ablation did not reduce the risk of all-cause mortality (RR, 0.86, 95% CI, 0.62-1.19, P=0.36; I^2=0), stroke (RR, 0.55, 95% CI, 0.18-1.66, P=0.29; I^2=0), need for cardioversion (RR, 0.84, 95% CI, 0.66-1.08, P=0.17; I^2=0) or pacemaker (RR, 0.59, 95% CI, 0.34-1.01, P=0.06; I2=0). However, ablation reduced the RR of cardiac hospitalization (0.37, 95% CI, 0.18-0.77, P=0.01; I^2=86), and recurrent atrial arrhythmia (0.46, 95% CI, 0.35-0.60, P<0.001; I^2=87). There were non-significant differences among treatment groups with respect to major bleeding (RR, 1.89, 95% CI, 0.59-6.08, P=0.29; I^2=15), and pulmonary vein stenosis (RR, 3.00, 95% CI, 0.83-10.87, P=0.09; I^2=0), but had significantly higher rates of pericardial tamponade (RR, 4.46, 95 % CI, 1.70-11.72, P<0.001; I^2=0).

Conclusions: Catheter ablation did not improve survival compared with medical therapy in patients with AF without HF. Catheter ablation reduced cardiac hospitalization and recurrent atrial arrhythmia at the expense of pericardial tamponade.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac rhythm disorder, associated with increased morbidity and mortality [1–3]. AF has an estimated prevalence of ~ 34 million people worldwide [4]. Guidelines for the management of AF recommends medical therapy (MT) (rate control or rhythm control) as an initial management, however in case of unstable, symptomatic or drug refractory conditions, catheter ablation (CA) is the recommended management [5,6]. MT for sinus rhythm (SR) restoration has not shown significant survival advantage over a rate-control strategy [7]. Moreover, literature adds that use of antiarrhythmic drugs is associated with increased re-hospitalization. [7–10]. Since anti arrhythmic drugs show moderate results in maintaining SR, pro arrhythmic, and causes significant side effects, therefore, physicians need to focus on the safety profile other than efficacy while prescribing them [5]. Moreover, the selection of antiarrhythmic drug becomes limited when the comorbidity, cardiovascular risk, side effects, and preference of the patient is taken into account. Literature has shown significant efficacy of CA both as an initial and secondary approach in management to maintain SR in case of MT failure, improvement in functional status, and cardiac function [11–15]. Catheter ablation has shown reduction in mortality with AF and systolic heart failure (HF), however no survival benefit in patients without HF has been observed [16]. Since previous meta-analysis [16], new randomized data has provided further insight on this topic and has the potential to impact clinical outcomes [17, 18]; therefore, we sought to update the meta-analysis in subjects with AF without HF.

Key Words

Catheter Ablation; Atrial Fibrillation; Medical Therapy; Meta-Analysis.

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Table 1: Baseline characteristics of the randomized clinical trials.

First Author/Study (Year)	Groups (Ablation vs AAD Class)	N	Mean Age (yrs)	Male (%)	SHD (%)	LAD (mm)	DM (%)	CAD (%)	Prior Stroke (%)	LVEF (%)	Cross over to RFA (%)	AF Pattern (%)		Blanking (weeks)	Follow-Up (months)
												Paroxysmal	Persistent		
Krittayaphong et al. (2003)	Ablation	15	55	73	13	40	6.7	NR	NR	64	NR	73	27	NR	12
	Amio	15	49	53	13	39	20	NR	NR	62		60	40		
Wazni et al. (2005)	Ablation	33	53	NR	28	41	NR	NR	NR	53	NR	97	3	8	12
	Class I, III	37	54	NR	28	42	NR	NR	NR	54		95	5		
Oral et al. (2006)	Ablation	77	55	87	08	45	NR	NR	NR	55	77	95	5	12	12
	Amio	69	58	90	09	45	NR	NR	NR	56		0	100		
APAF (2006)	Ablation	99	55	70	07	40	5.1	NR	NR	60	42	100	0	6	12
	Class I, III	99	57	65	04	38	4	NR	NR	61		100	0		
Stabile et al. (2006)	Ablation	68	62	62	63	46	NR	NR	NR	59	52	62	38	4	12
	Class I, III	69	62	64	62	45	NR	NR	NR	58		72	28		
A4 study (2008)	Ablation	53	50	85	19	39	1.9	5.7	NR	63	63	100	0	12	12
	Class I, III	59	52	83	24	40	3.4	10	NR	66		100	0		
Forleo et al. (2009)	Ablation	35	63	57	46	44	NR	20	NR	55	NR	46	54	5	12
	Class I, III	35	65	66	54	45	NR	20	NR	53		37	63		
Wilber et al. (2010)	Ablation	106	55.5	68.9	9.5	NR	9.5	NR	1.9	62.3	NR	NR	NR	12	9
	Class I, III	61	56.1	62	15	NR	12	NR	3	62.7		NR	NR		
MANTRA PAF (2012)	Ablation	146	56	68	5	40	4	4	NR	NA	36	100	0	12	24
	Class I, III	148	54	72	10	40	7	1	NR	NA		100	0		
SARA (2014)	Ablation	98	55	76	NR	NR	NR	3.1	3.1	61.1	47.9	NR	NR	12	12
	Class I, III	48	55	37	NR	NR	NR	2.1	2.1	60.8		NR	NR		
RAAFT2 (2014)	Ablation	66	56	77	NR	40	1.5	9.1	4.6	61.4	47	98.5	96.7	12	21
	Class I, III	61	54	74	NR	43	6.6	3.3	6.6	60.8		1.5	3.3		
CAPTAF (2019)	Ablation	79	55.8	73.4	1.3	41.7	3.8	2.5	5.1	56.2	10.1	70.9	29.1	12	12
	Class I, III	76	56.3	81.6	1.3	41.7	3.9	3.9	0	56.1		75	19		
CABANA (2019)	Ablation	1108	68	62.7	NR	NR	25.3	18.8	6.1	-	27.1	42.4	47.3	12	12
	Class I, III	1096	67	63	NR	NR	25.7	19.7	5.3	-		43.5	47.3		

A4 Study=A Comparison of Antiarrhythmic Drug Therapy and Radio Frequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation; AF = atrial fibrillation; Amio = amiodarone; APAF=Ablation for Paroxysmal Atrial Fibrillation; CABANA= The Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial; CAD=coronary artery disease; CAPTAF= Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation; class I, III = class I, III antiarrhythmic agents; DM = diabetes mellitus; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; MANTRA-PAF = Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation: A Randomized Prospective Multicenter Study; NA = not available; NR = not reported; RAAFT2 = Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation; RFA = radiofrequency ablation; SARA = Study of Ablation Versus antiarrhythmic Drugs in Persistent Atrial Fibrillation; SHD = structural heart disease

Methods

This meta-analysis was conducted as per the guidelines of Cochrane Collaboration [19], and it is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report [20].

Data Sources And Searches

An updated literature search was conducted to select randomized controlled trials using PubMed, Embase and the CENTRAL till April 2019 using key search terms, "atrial fibrillation", "catheter ablation", "pulmonary vein isolation" and "antiarrhythmic drugs". The PubMed search algorithm is reported in the [Table]. A gray literature [21,22] search was carried out by searching www.clinicaltrialresults.com, www.clinicaltrials.gov, www.cardiosource.org, www.esccardio.org, and abstracts and presentations from major cardiovascular meetings. Reference lists of the relevant articles were also reviewed. All citations were downloaded into EndNote X7 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania), and duplicates were removed electronically and manually.

Study Selection

Two independent reviewers (M.Z.K. and M.Z.) analyzed the citations at the level of title and abstract, and the studies were considered on the basis of following criteria: 1) RCTs investigating CA versus MT (rhythm- or rate-control medications) in patients with AF; and 2) studies reporting at least 1 event for outcomes of interest in an adult population. Moreover, the inclusion criteria for studies was not limited to sample size, language preference, follow up duration or availability of the full text. The whole process was supervised by a third author (S.U.K.), and any discrepancies were resolved by consensus.

Quality Assessment And Data Extraction

Two independent authors (M.U.K and A.A.) used a structured data collection form to abstract the data for baseline characteristics, techniques of the procedure, events, nonevents, mode of medical treatment, sample size, mean, standard deviations, crude point estimates or standard error estimates, and follow-up duration. Additionally, the continuous outcomes were extracted as per the differences between the 2 groups during the follow up in addition

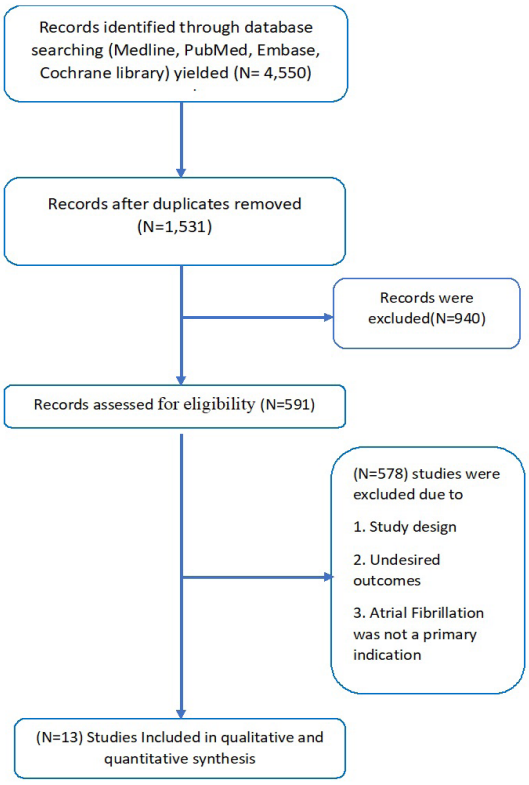


Figure 1: **Flow Chart of our study**

to any changes from baseline. For all estimates, adjusted estimates were extracted. Intention-to-treat principle was used as basis for the acquisition of data. Data adjudication was done by 1 author (S.U.K.). Methodological quality or risk bias assessment was done at study level using the Cochrane bias risk assessment tool [23] (Table).

Outcome Measures

The primary endpoint was all-cause mortality. The secondary endpoints were stroke, cardiac hospitalization, recurrent atrial arrhythmia, need for cardioversion or pacemaker, major bleeding, pulmonary vein stenosis and pericardial complications. The definitions of the endpoints were taken as reported in the included trials.

Statistical Analysis

Estimates were assessed by using a DeSermonian and Laird random effects model. We preferred a random effects model to account for any study heterogeneity [24]. Binary outcomes were calculated as risk ratio (RR) or risk difference, and continuous estimates were expressed as mean difference (MD) with 95% confidence interval (CI). Because both the RR and risk difference represent the same data, we focused on RR estimates in this review. A p value of 0.05 was set as significant. Heterogeneity was assessed using Q statistics and quantified by I2 with values >50% consistent with a high degree of heterogeneity [25]. Publication bias was assessed using Egger's regression test. All analyses were conducted using Comprehensive Meta-analysis software version 3.0 (Biostat, Englewood, New Jersey).

Results

The initial search yielded 4,550 records, of which 3,019 citations were removed as duplicates; of the remaining 1,531 articles, 940 studies were excluded if the title and/or abstract suggested that the studies were not relevant. A total of 591 records were assessed for eligibility, of which 578 studies were excluded because of their study design or undesired outcomes or when AF was not a primary indication. Ultimately, 13 RCTs (3856) met the inclusion criteria (Figure 1). Baseline characteristics of the trials are shown in Table 1 [18,19,26–36].

In 13 trials (3856 patients), the pooled mean age of patients was 56.8±4.8 years, 69% were males and 8.8% had coronary artery disease. The mean left ventricular ejection fraction (LVEF) was 59.1±3.8%, 67% patients had paroxysmal AF and 33% had persistent AF. The average follow-up duration was 19 months. Compared with medical therapy, ablation did not reduce the RR of all-cause mortality (0.86 [95% CI, 0.62-1.19], P=0.36; I^2=0; Figure 2) and stroke (0.55 [95% CI, 0.18-1.66], P=0.29; I^2=0). However, ablation reduced the RR of cardiac hospitalization (0.37 [95% CI, 0.18-0.77], P=0.01; I^2=86), and recurrent atrial arrhythmia (0.46 [95% CI, 0.35-0.60], P<0.001; I^2=87). There were non-significant differences among treatment groups with respect to safety outcomes (figure 3) such as major bleeding (1.89 [95% CI, 0.59-6.08], P=0.29; I^2=15), need for cardioversion (0.84 [95% CI, 0.66-1.08], P=0.17; I^2=0) or pacemaker (0.59 [95% CI, 0.34-1.01], P=0.06; I^2=0) and pulmonary vein stenosis (3.01 [95% CI, 0.83-10.92], P=0.09; I^2=0). However, pericardial complications were more common among the ablation group (4.44 [95% CI, 1.69-11.68], P<0.001; I^2=0). Egger's regression test did not detect publication bias for primary endpoint (P=0.94).

Discussion

In this meta-analysis, ablation did not reduce the risk of total mortality, stroke, need for cardioversion or pacemaker compared with medical therapy in patients with AF without HF. However, ablation was associated with 63% RR reduction of for cardiac hospitalization and 54% for recurrent atrial arrhythmia. Previous meta-analysis [13-16] addressed a mix of both HF and non-HF population, however those studies were limited by low power for hard outcomes and brief follow-ups of non-HF trials. Whereas, current meta-analysis was updated with the CABANA (Catheter Ablation Vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial, the largest and longest follow-up study powered to assess effect of catheter ablation on mortality in subjects with AF without HF [17], and the CAPTAF (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation) trial [18] to confirm catheter ablation's lack of benefit on hard clinical endpoints in this subset of patients. Ablation was not significantly associated with stroke prevention but most of the patients with stroke risk factors were on anticoagulation even after ablation, therefore, making it difficult to assess actual stroke risk change with ablation. It remains uncertain whether after ablation anticoagulation can be safely discontinued. Ongoing the OCEAN (Optimal Anticoagulation for Higher Risk Patients Post Catheter Ablation for Atrial Fibrillation) trial (NCT02168829) will shed further light on this issue. Our analysis showed ablation had statistically significance reduction for cardiac hospitalization, the persistent benefits of having reduced risk for cardiac hospitalization

Group by Outcome	Study name	Events / Total		Statistics for each study			
		CA	MT	Risk ratio	Lower limit	Upper limit	p-Value
All-cause mortality	CABANA	58 / 1108	67 / 1096	0.86	0.61	1.20	0.37
	MANTRA PAF	3 / 146	4 / 148	0.76	0.17	3.34	0.72
	Stabile et al	2 / 68	1 / 69	2.03	0.19	21.86	0.56
	The AF4 study	0 / 53	2 / 59	0.22	0.01	4.53	0.33
	Wilber et al.	1 / 106	0 / 61	1.74	0.07	42.02	0.73
				0.86	0.62	1.19	0.36
Cardiac hospitalization	CABANA	556 / 1108	605 / 1096	0.91	0.84	0.98	0.02
	Wazni et al.	3 / 32	19 / 35	0.17	0.06	0.53	0.00
	MANTRA PAF	0 / 146	2 / 148	0.20	0.01	4.19	0.30
	CAPTAF	0 / 79	2 / 76	0.19	0.01	3.95	0.28
	Forleo et al	3 / 35	12 / 35	0.25	0.08	0.81	0.02
	The APAF study	24 / 99	67 / 99	0.36	0.25	0.52	0.00
				0.37	0.18	0.77	0.01
Recurrence of atrial arrythmia	CABANA	305 / 1108	437 / 1096	0.69	0.61	0.78	0.00
	Wazni et al.	4 / 33	22 / 37	0.20	0.08	0.53	0.00
	Krittayaphong et al	3 / 15	9 / 15	0.33	0.11	0.99	0.05
	Oral H et al	25 / 77	53 / 69	0.42	0.30	0.60	0.00
	RAAFT 2	36 / 66	44 / 61	0.76	0.58	0.99	0.04
	SARA study	29 / 98	27 / 48	0.53	0.35	0.78	0.00
	MANTRA PAF	22 / 138	42 / 148	0.56	0.35	0.89	0.01
	Stabile et al	30 / 68	63 / 69	0.48	0.37	0.64	0.00
	The AF4 study	7 / 53	42 / 59	0.19	0.09	0.38	0.00
	Wilber et al.	35 / 103	47 / 56	0.40	0.30	0.54	0.00
	CAPTAF	56 / 75	52 / 74	1.06	0.87	1.30	0.55
	Forleo et al	7 / 35	20 / 35	0.35	0.17	0.72	0.00
	The APAF study	14 / 99	75 / 99	0.19	0.11	0.31	0.00
				0.46	0.35	0.60	0.00
Stroke	CABANA	3 / 1108	7 / 1096	0.42	0.11	1.64	0.21
	Stabile et al	1 / 68	0 / 69	3.04	0.13	73.43	0.49
	CAPTAF	1 / 79	2 / 76	0.48	0.04	5.20	0.55
				0.55	0.18	1.66	0.29

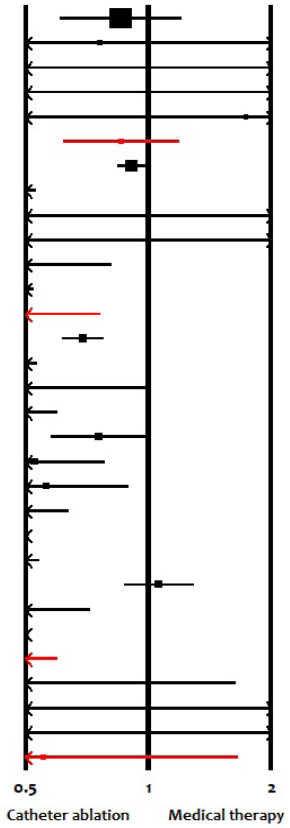


Figure 2: **Forest Plot Showing Results of Catheter Ablation versus Medical Therapy in Patients with Atrial Fibrillation Without Heart Failure**

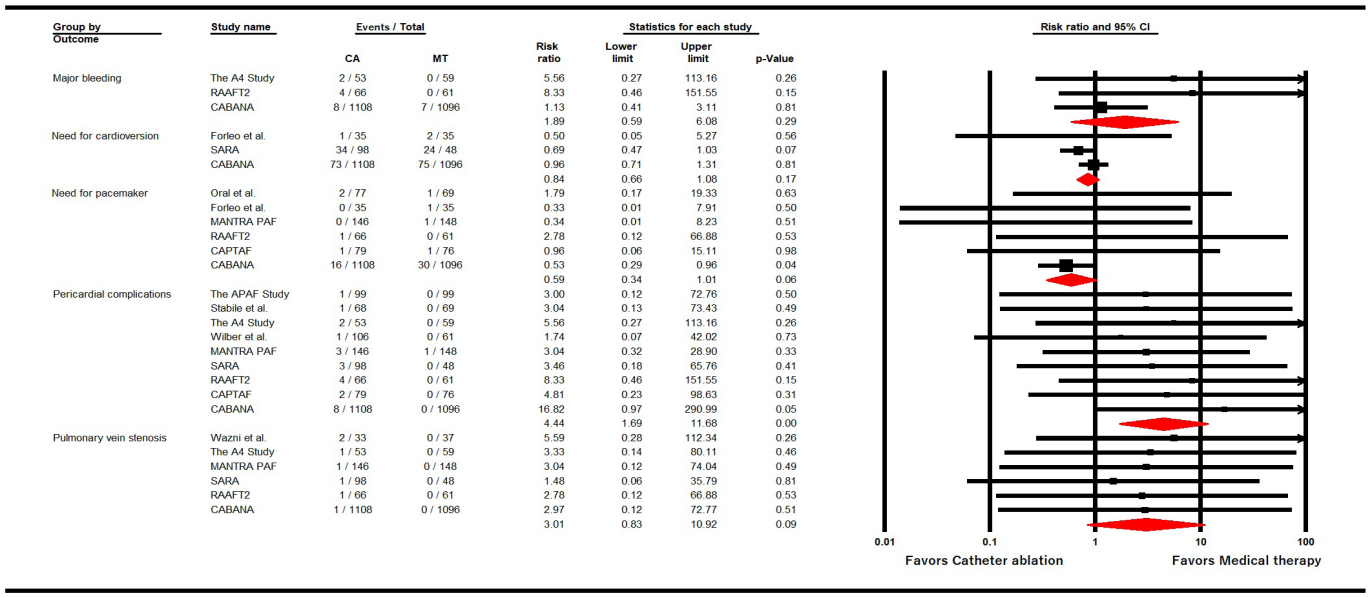
and recurrent atrial arrhythmia with ablation are reassuring and carry significant implications for quality of life and health care expenditures. Finally, although, ablation was generally safe in terms of major bleeding or pulmonary vein stenosis, the benefits of reduced hospitalization and recurrent arrythmias were somewhat counterbalanced by higher rates of pericardial complications like cardiac tamponade, although infrequent, can be serious complications with significant mortality and morbidity [36].

Study Limitations

Considerable limitations of this meta-analysis include variations in ablation strategies, duration of treatment, post ablation antiarrhythmic therapy, methods of AF surveillance, CHA_2D-VAS_2c scores and follow-up durations. In addition to lack of blinding, protocol adherence and cross over were not random across most of the trials, therefore a high degree of selection bias was noticed. All-cause mortality was not adequately powered in any of the included individual trials. We refrained from assessment of Quality of Life due to paucity of data and heterogeneity in measurement scales. The safety endpoints were not powered and lacked precision. Moreover, this analysis is mainly driven by the CABANA trial as it had the highest number of participants.

Conclusions

Although among patients with AF without HF, ablation was associated with lower rates of cardiac hospitalization and recurrent atrial arrhythmia compared with medical therapy, subjects receiving ablation did not experience mortality benefit. Therefore, perceived advantages of ablation in "healthy" subjects with AF must be closely weighed against potential complications and health care use costs [37].



Group by Outcome	Study name	Events / Total		Statistics for each study			
		CA	MT	Risk ratio	Lower limit	Upper limit	p-Value
Major bleeding	The A4 Study	2 / 53	0 / 59	5.56	0.27	113.16	0.26
	RAAFT2	4 / 66	0 / 61	8.33	0.46	151.55	0.15
	CABANA	8 / 1108	7 / 1096	1.13	0.41	3.11	0.81
				1.89	0.59	6.08	0.29
Need for cardioversion	Forleo et al.	1 / 35	2 / 35	0.50	0.05	5.27	0.56
	SARA	34 / 98	24 / 48	0.69	0.47	1.03	0.07
	CABANA	73 / 1108	75 / 1096	0.96	0.71	1.31	0.81
				0.84	0.66	1.08	0.17
Need for pacemaker	Oral et al.	2 / 77	1 / 69	1.79	0.17	19.33	0.63
	Forleo et al.	0 / 35	1 / 35	0.33	0.01	7.91	0.50
	MANTRA PAF	0 / 146	1 / 148	0.34	0.01	8.23	0.51
	RAAFT2	1 / 66	0 / 61	2.78	0.12	66.88	0.53
	CAPTAF	1 / 79	1 / 76	0.96	0.06	15.11	0.98
	CABANA	16 / 1108	30 / 1096	0.53	0.29	0.96	0.04
				0.59	0.34	1.01	0.06
Pericardial complications	The APAF Study	1 / 99	0 / 99	3.00	0.12	72.76	0.50
	Stabile et al.	1 / 68	0 / 69	3.04	0.13	73.43	0.49
	The A4 Study	2 / 53	0 / 59	5.56	0.27	113.16	0.26
	Wilber et al.	1 / 106	0 / 61	1.74	0.07	42.02	0.73
	MANTRA PAF	3 / 146	1 / 148	3.04	0.32	28.90	0.33
	SARA	3 / 98	0 / 48	3.46	0.18	65.76	0.41
	RAAFT2	4 / 66	0 / 61	8.33	0.46	151.55	0.15
	CAPTAF	2 / 79	0 / 76	4.81	0.23	98.63	0.31
	CABANA	8 / 1108	0 / 1096	16.82	0.97	290.99	0.05
				4.44	1.69	11.68	0.00
Pulmonary vein stenosis	Wazni et al.	2 / 33	0 / 37	5.59	0.28	112.34	0.26
	The A4 Study	1 / 53	0 / 59	3.33	0.14	80.11	0.46
	MANTRA PAF	1 / 146	0 / 148	3.04	0.12	74.04	0.49
	SARA	1 / 98	0 / 48	1.48	0.06	35.79	0.81
	RAAFT2	1 / 66	0 / 61	2.78	0.12	66.88	0.53
	CABANA	1 / 1108	0 / 1096	2.97	0.12	72.77	0.51
				3.01	0.83	10.92	0.09

Figure 3: **Forest Plot showing safety analysis between Catheter Ablation versus Medical Therapy in Patients with Atrial Fibrillation Without Heart Failure**

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