TESE DE DOUTORADO

Ablação de Fibrilação Atrial: Eficácia entre Técnicas com Cateter de Radiofrequência, Repercussões na Insuficiência Cardíaca e Preditores de Recorrência do Registro SBR-AF

por
Caique Martins Pereira de Moura Ternes

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

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"Para se conhecer a sabedoria e a instrução;
para se entenderem as palavras da prudência;
para se receber a instrução do entendimento,
a justiça, o juízo e a equidade"

Provérbios 1:2–3

"Make the impossible possible,
the possible easy, &
the easy elegant"

Moshe Feldenkrais

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ABREVIATURAS

AAD – antiarrhythmic drug

AF – atrial fibrillation

ATA – atrial tachyarrhythmia

CA – catheter ablation

CI – confidence interval

ECR – ensaio clínico randomizado

EHRA – European Heart Rhythm Association

ESC – European Society of Cardiology

IC – insuficiência cardíaca

FA – fibrilação atrial

HF – heart failure

MD – mean difference

OR – odds ratio

PAF – paroxysmal atrial fibrillation

PeAF – persistent atrial fibrillation

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO – International Prospective Register of Systematic Reviews

PVI – pulmonary vein isolation

PWI – posterior wall isolation

RCT – randomized controlled trial

RoB2 – Risk of Bias Assessment Tool

VP – veias pulmonares

RESUMO

Introdução: A fibrilação atrial (FA) é a taquiarritmia sustentada mais prevalente, podendo ser paroxística, persistente, ou persistente de longa duração. O controle de ritmo apresenta melhores resultados clínicos e pode ser realizado com medicamentos de uso contínuo ou por meio de um procedimento eletivo de ablação, que visa isolar as veias pulmonares (VPs) e restabelecer o ritmo sinusal sem a necessidade de medicamentos. Dados sobre a segurança e a eficácia da ablação de FA na América Latina são escassos. **Objetivos:** Estruturamos um registro multicêntrico prospectivo dedicado a avaliar desfechos relacionados à ablação de FA no Brasil, e realizamos análises sistemáticas dos dados existentes sobre o procedimento na população com insuficiência cardíaca (IC) e nas formas não-paroxísticas de FA. **Métodos:** O *Estudo I* é um registro multicêntrico prospectivo que incluiu 1.043 pacientes submetidos à uma primeira ablação de FA no Brasil. O *Estudo II* é uma revisão sistemática e meta-análise de ensaios clínicos randomizados (ECRs) que incluiu 1.055 pacientes com FA e IC, dos quais 50,2% foram submetidos à ablação. O *Estudo III* é uma revisão sistemática e meta-análise de ECRs que incluiu 1.104 pacientes com FA persistente, submetidos à ablação com isolamento das VPs versus isolamento das VPs associado à ablação da parede posterior do átrio esquerdo. **Resultados:** O *Estudo I* demonstrou que, com uma mediana de acompanhamento de 1,4 (1,0 - 3,4) anos, 78,6% dos pacientes permaneceram livres de recorrência de taquiarritmia atrial após a primeira ablação de FA em centros brasileiros. Os preditores independentes de recorrência foram características de pacientes em estágios mais avançados da doença (maiores diâmetros do átrio esquerdo, FA persistente de base e escores EHRA de sintomas de FA avançados). A taxa de complicações foi de 2,1%, e não houve óbito relacionado ao procedimento. O *Estudo II* demonstrou, nas análises combinadas de 6 ECRs que incluíram pacientes com FA e IC, que os pacientes randomizados para ablação apresentaram menor razão de risco para morte cardiovascular, hospitalização por IC, menor carga de arritmia e melhora na fração de ejeção e na qualidade de vida em comparação ao controle de ritmo com fármacos. Não houve diferença significativa em eventos adversos graves entre os grupos ($p=0,14$). O *Estudo III* demonstrou que, em uma análise combinada de 8 ECRs em pacientes com FA persistente, a ablação complementar da parede posterior do átrio esquerdo reduziu a recorrência de taquiarritmias atriais em comparação aos pacientes que receberam apenas o isolamento das VPs. Uma meta-regressão demonstrou que o fator de maior impacto para a recorrência após a ablação foi o tempo de diagnóstico da FA até o procedimento índice ($p<0,01$). **Conclusões:** Este registro multicêntrico prospectivo de centros brasileiros demonstrou que a ablação de FA é um procedimento com baixa taxa de complicações e eficácia semelhante à dos ECRs e registros de países de alta renda. Preditores independentes de recorrência são característicos de pacientes em estágios avançados da FA. O maior benefício clínico para o paciente com FA está associado ao controle de ritmo com ablação realizada o mais precocemente possível. O benefício clínico se estende à população com IC concomitante, sem aumento na taxa de eventos adversos graves. Em pacientes com FA não-paroxística, associar a ablação da parede posterior do átrio esquerdo ao isolamento das VPs aumentou a eficácia do procedimento.

Palavras-chave: fibrilação atrial, insuficiência cardíaca, ablação por radiofrequência, ablação por cateter, dados de registro

ABSTRACT

Introduction: Atrial fibrillation (AF) is the most prevalent sustained tachyarrhythmia, and may present in paroxysmal, persistent, or long-standing persistent forms. Rhythm control shows better clinical outcomes and can be achieved with continuous-use medications or through an elective ablation procedure aimed at isolating the pulmonary veins (PVI) and restoring sinus rhythm without the need for medications. Data on the safety and efficacy of AF ablation in Latin America are scarce. **Objectives:** Our aim was to build a prospective multicenter registry dedicated to evaluating outcomes related to AF ablation in Brazil, as well as to conduct a systematic analysis of existing data on ablation outcomes in patients with heart failure (HF) and in non-paroxysmal forms of AF. **Methods:** *Study I* is a prospective multicenter registry that included 1,043 patients undergoing a first AF ablation in Brazil. *Study II* is a systematic review and meta-analysis of randomized controlled trials (RCTs) that included 1,055 patients with AF and HF, of whom 50.2% underwent ablation. *Study III* is a systematic review and meta-analysis of RCTs that included 1,104 patients with persistent AF, who underwent ablation with PVI versus PVI combined with posterior wall ablation of the left atrium. **Results:** *Study I* demonstrated with a median follow-up of 1.4 (1.0 - 3.4) years, that 78.6% of patients remained free from atrial tachyarrhythmia (ATA) recurrence after the first AF ablation in Brazil. Independent predictors of recurrence were characteristics of patients in more advanced stages of AF (larger left atrial diameters, baseline persistent AF, and high EHRA scores of AF symptoms). The complication rate was 2.1%, with no procedure-related deaths. *Study II* in the pooled analysis of 6 RCTs that included patients with AF and HF, showed that patients randomized to ablation had a lower risk ratio for cardiovascular death, HF hospitalization, lower arrhythmia burden, improved ejection fraction and quality of life compared to rhythm control with medical therapy alone. There was no significant difference in serious adverse events between the groups ($p=0.14$). *Study III* showed in a pooled analysis of 8 RCTs in patients with persistent AF, additional ablation of the left atrial posterior wall reduced the recurrence of ATA compared to patients who received only PVI. A meta-regression demonstrated that the most significant factor for recurrence was AF duration prior to index procedure ($p<0.01$). **Conclusions:** This prospective multicenter registry of Brazilian centers demonstrated that AF ablation is a procedure with a low complication rate and efficacy similar to RCTs and registries from high-income countries. Independent predictors of recurrence are characteristic of patients in advanced stages of AF. The greatest clinical benefit for AF patients is associated with early rhythm control through ablation. The clinical benefit extends to the population with concomitant HF, without an increase in the rate of serious adverse events. In patients with non-paroxysmal AF, adding posterior wall ablation of the left atrium to PVI increased the procedure's efficacy.

Keywords: atrial fibrillation, heart failure, radiofrequency ablation, catheter ablation, registry data

1 Introdução e Marco Teórico

A fibrilação atrial (FA) é a taquiarritmia cardíaca sustentada mais comum, com uma prevalência global estimada de 59,7 milhões de pacientes em 2019. (1–5) Indivíduos com FA enfrentam um aumento no risco de eventos tromboembólicos, disfunção ventricular esquerda progressiva e deterioração da qualidade de vida. (6–8) O manejo da fibrilação atrial baseia-se em dois pilares principais: controle de frequência e controle de ritmo – uma discussão tradicionalmente conhecida como '*rate vs rhythm*' na cardiologia. No início dos anos 2000, o estudo clínico randomizado AFFIRM (*Atrial Fibrillation Follow-up Investigation of Rhythm Management*), foi desenhado com o objetivo de avaliar mortalidade como o desfecho primário em 4.060 pacientes com FA. Os resultados não demonstraram benefício significativo do controle de ritmo em comparação ao controle de frequência. Entretanto, no grupo que recebeu controle de ritmo, as estratégias utilizadas limitaram-se a cardioversão e fármacos antiarrítmicos, e apenas 0,7% (14/2.033) da população recebeu ablação por cateter. (9) Embora as primeiras observações do uso de lesões por radiofrequência em focos arritmogênicos nas veias pulmonares para o tratamento da FA datem do final da década de 1990, realizadas por Haïssaguerre et al., foi apenas em 2005 que a ablação por cateter de radiofrequência foi testada como estratégia de primeira linha para controle de ritmo da FA no estudo RAAFT-1. (10,11)

Apesar de o primeiro ECR que avaliou a ablação por cateter como primeira linha de tratamento ter sido realizado há duas décadas, esse tratamento não foi adotado como rotina no manejo inicial da FA por vários anos. As diretrizes de 2006 ACC/AHA/ESC para o manejo da fibrilação atrial classificaram a ablação como uma recomendação de classe 2A, sendo indicada como segunda linha de tratamento para o controle do ritmo em casos refratários ao uso de drogas antiarrítmicas. (12) O uso cauteloso nos estágios iniciais da ablação ocorreu principalmente devido aos estudos com um número limitado de participantes e eficácia relativamente baixa para um procedimento invasivo, com cerca de 60% dos pacientes que receberam ablação permanecendo livres de taquiarritmias atriais em 12 meses de acompanhamento. (13,14)

Diversos estudos demonstraram resultados promissores na escolha da ablação como primeira linha de controle de ritmo no manejo da FA. O estudo MANTRA-PAF demonstrou que a ablação por cateter comparada à terapia medicamentosa apresentou maior percentual em 24 meses de pacientes livres de arritmias taquiatrias (85% vs. 71%, p=0.004) e livres de FA sintomática (93% vs. 84%, p=0.01). (15) O benefício se manteve na análise de follow-up estendido por 5 anos, com menor taxa de recorrência e menor carga de FA no grupo randomizado para ablação. (16) O RAAFT-2 demonstrou que a ablação reduziu significativamente a recorrência de FA em comparação com a terapia medicamentosa (HR 0,56; IC 95%, 0,35-0,90; p = 0,02). (17) No entanto, os resultados do estudo CABANA geraram controvérsia a respeito da escolha da ablação como primeira linha para controle de ritmo no manejo da FA. Publicado em 2019, o CABANA foi o estudo randomizado com o maior número de participantes com FA alocados entre ablação por cateter vs. fármacos antiarrítmicos até o momento. (18) Entre 2.204 pacientes incluídos entre 2009 e 2016, o desfecho primário composto de morte, acidente vascular cerebral incapacitante, sangramento grave ou parada cardíaca não apresentou diferença estatisticamente significativa entre os dois grupos, com

uma redução de 14% nos eventos para o grupo de ablação, mas sem significância estatística (HR 0,86; p = 0,30). No entanto, diversos fatores podem ter influenciado a análise de intenção de tratar do CABANA; 57,1% dos pacientes possuíam FA persistente na linha de base, 9,2% dos pacientes randomizados para ablação não foram submetidos ao procedimento, houve uma taxa de crossover de 27,5% dos pacientes no grupo farmacológico que realizaram ablação, e 89,3% dos pacientes completaram o acompanhamento do estudo. O grupo que recebeu ablação apresentou melhor resultado quanto à recorrência de FA (HR 0,52; IC 95%, 0,45-0,60; p < 0,001), e uma análise exploratória de mortalidade por qualquer causa, dividindo os grupos por tratamento recebido, demonstrou desfecho favorável no grupo que recebeu ablação (HR 0,60; IC 95%, 0,42-0,86; p = 0,005). (18) Análises post hoc do estudo CABANA forneceram insights adicionais. A análise de qualidade de vida confirmou melhora sustentada com a ablação, (7) enquanto a análise de follow-up estendido por 5 anos mostrou uma redução significativa da recorrência e da carga de FA no grupo ablação (19). Em pacientes com insuficiência cardíaca, a ablação apresentou redução relativa em morte por todas as causas (HR 0,57; IC 95%, 0,33-0,96) e na recorrência de FA (HR 0,56; IC 95%, 0,42-0,74). (20) Além disso, a ablação mostrou ser custo-efetiva a longo prazo devido à redução nas hospitalizações e ao melhor controle dos sintomas. (21)

O aprimoramento das tecnologias de ablação da FA foi essencial para a transição desse tratamento, que inicialmente era utilizado como segunda linha em casos refratários a antiarrítmicos (12), para indicação de classe I com nível de evidência A na Diretriz de 2024 ESC/EHRA/ESO (22), como terapia inicial de manutenção do ritmo sinusal em pacientes com fibrilação atrial, em decisão compartilhada com o paciente, para reduzir sintomas, recorrência de taquiarritmias atriais e mitigar a progressão da FA. Dentre as técnicas que revolucionaram a ablação por cateter de radiofrequência, destacam-se o mapeamento eletroanatômico 3D e os cateteres irrigados com sensor de força de contato. (23–25) O procedimento de ablação de FA por cateter de radiofrequência

consiste principalmente no isolamento elétrico das veias pulmonares, podendo incluir a ablação de focos arritmogênicos complementares, como a parede posterior do átrio esquerdo, em casos não-paroxísticos com atriopatia avançada. (26–28) O objetivo do procedimento é que o paciente se mantenha em ritmo sinusal permanente após a ablação, sendo a falha da ablação definida como uma recorrência de taquiarritmia atrial por mais de 30 segundos após um período de 60 dias do procedimento. (29) Além da ablação por cateter de radiofrequência, o procedimento pode ser realizado por crioablação. Ambas técnicas geram lesões termais direcionadas ao isolamento das veias pulmonares e à eliminação de focos arritmogênicos, com resultados semelhantes em termos de eficácia e segurança. (30) A técnica mais recente para ablação de FA descrita é a por campo pulsado (31), que utiliza pulsos elétricos de alta intensidade, em vez de energia térmica, para criar poros nas membranas das células cardíacas, causando morte celular seletiva e com o potencial de evitar complicações raras da termoablação, como fístulas esofágicas. (32) O estudo ADVENT, publicado em 2023, foi o primeiro a comparar a ablação por campo pulsado com a ablação térmica convencional em pacientes com fibrilação atrial paroxística, demonstrando que a PFA foi não inferior em eficácia (73,3% vs. 71,3%) e teve taxas semelhantes de eventos adversos graves (2,1% vs. 1,5%) em um ano. (33)

Resultados de ensaios clínicos recentes indicam benefícios clínicos significativos para pacientes com FA submetidos a controle precoce do ritmo por ablação por cateter, em comparação com estratégias baseadas no controle da frequência ou no uso exclusivo de drogas antiarrítmicas. (34,35) O estudo EAST-AFNET 4, um dos primeiros a incluir a ablação no grupo de controle de ritmo, incluiu 2.789 pacientes diagnosticados com FA há menos de 12 meses, randomizados para controle de ritmo precoce ou controle de frequência e tratamento sintomático. O estudo foi interrompido precocemente devido à eficácia do controle de ritmo precoce, com uma redução

significativa no desfecho composto de morte cardiovascular, acidente vascular cerebral ou hospitalização por insuficiência cardíaca ou síndrome coronariana aguda (3,9 vs. 5,0 por 100 pessoas-ano; HR 0,79; IC 96%, 0,66–0,94; p = 0,005). (36) A ablação por cateter demonstra superioridade na manutenção do ritmo sinusal e na prevenção da progressão da FA paroxística para a forma persistente da doença, em comparação com o tratamento com medicamentos antiarrítmicos. (16,37) No estudo EARLY-AF, com 303 pacientes com FA paroxística sintomática randomizados para ablação por cateter ou controle de ritmo farmacológico, a ablação como primeira estratégia resultou em uma redução significativa na recorrência de taquiarritmias atriais (42,9% vs. 67,8%, HR 0,48; IC 95%, 0,35–0,66; p < 0,001). As complicações graves ocorreram de forma semelhante entre os grupos (3,2% vs. 4,0%). (38) Uma análise de follow-up prolongado mostrou que os pacientes do EARLY-AF submetidos à ablação tiveram uma menor progressão para FA persistente em comparação com a terapia medicamentosa (1,9% vs. 7,4%, HR 0,25; IC 95%, 0,09–0,70). (39)

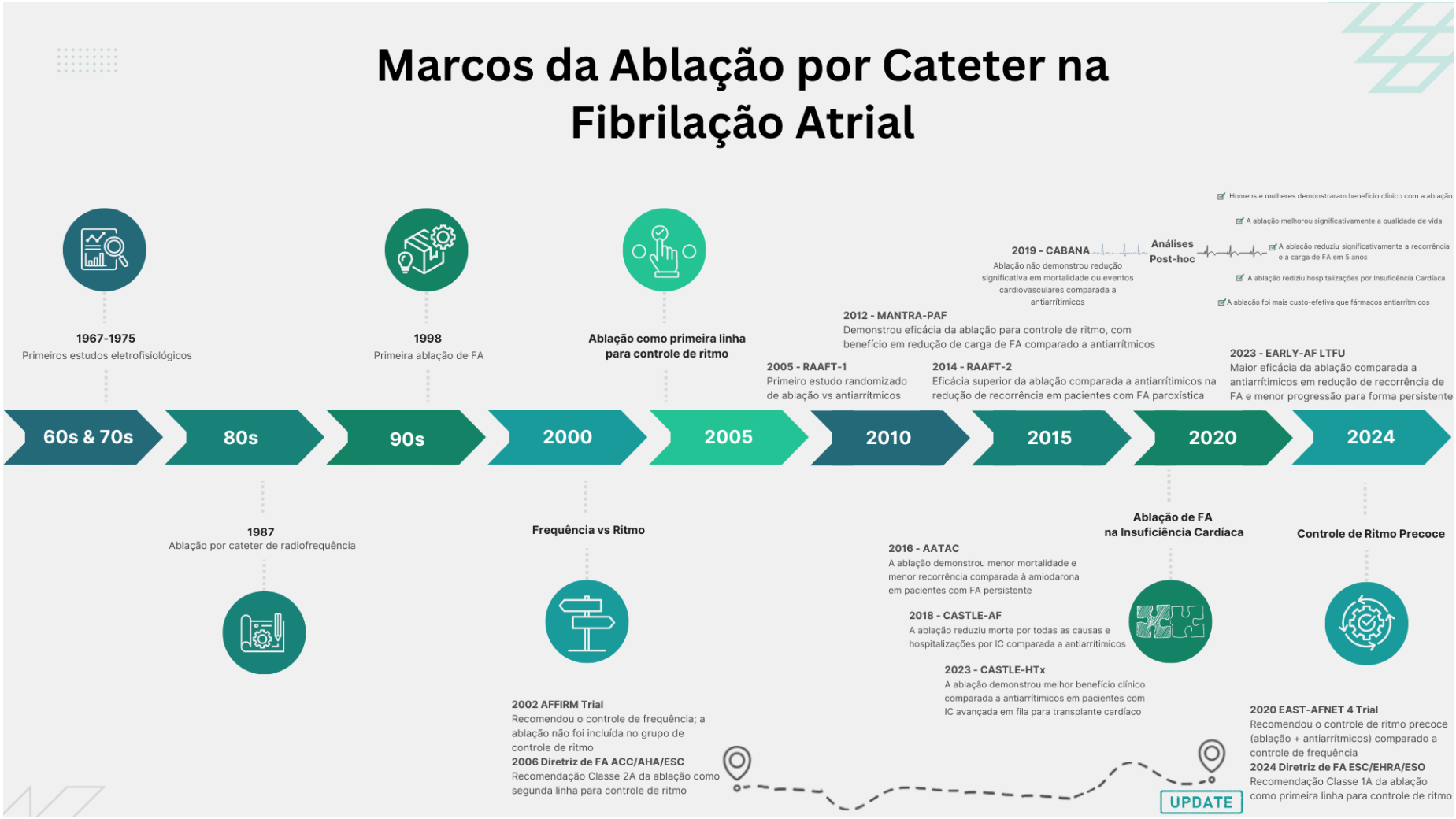
A Diretriz ESC 2024 para o manejo da FA recomenda uma abordagem multifatorial baseada no acrônimo *AF-CARE (Comorbidity and risk factor management; Avoid stroke and thromboembolism; Reduce symptoms by rate and rhythm control; Evaluation and dynamic reassessment*). (22) Entre as comorbidades mais impactantes na morbi-mortalidade e risco cirúrgico dos pacientes com FA está a coexistência com insuficiência cardíaca (IC). Em 2008, Roy et al. conduziram um estudo com 1.376 pacientes com FA e IC, randomizados para controle de ritmo ou frequência. A estratégia de controle de ritmo não reduziu significativamente a mortalidade cardiovascular em comparação com o controle de frequência (27% vs. 25%, HR 1,06; IC 95%, 0,86–1,30; p = 0,59), sugerindo preferência pelo controle de frequência para evitar cardioversão nestes pacientes de alto risco. No entanto, este estudo não incluiu ablação como parte da estratégia do controle de ritmo.(40) Dez anos depois, Marrouche et al. no estudo CASTLE-AF, com 363 pacientes com IC e FA refratária a antiarrítmicos, demonstraram que a ablação por cateter reduziu significativamente o desfecho composto de morte

por qualquer causa ou hospitalização por IC em comparação à terapia medicamentosa (28,5% vs. 44,6%, HR 0,62; IC 95%, 0,43–0,87; p = 0,007). (41) Em 2023, Sohns et al. no estudo CASTLE-HTx, com 194 pacientes com IC em estágio terminal e FA, mostraram que a ablação por cateter reduziu significativamente o desfecho composto de morte, implantação de dispositivo de assistência ventricular esquerda ou transplante cardíaco urgente (8% vs. 30%, HR 0,24; IC 95%, 0,11–0,52; p < 0,001), com 2.1% de complicações não-fatais periprocedimento. (42)

Além das evidências de estudos randomizados (**Figura Central**), diversos registros multicêntricos demonstraram a alta eficácia da ablação de FA, associada a uma baixa taxa de complicações. (43–45) Nos Estados Unidos, o NCDR AFib Ablation Registry incluiu 76.219 pacientes submetidos à ablação de FA entre 2016 e 2020. O sucesso do isolamento elétrico das veias pulmonares foi de 92,4%, com uma taxa geral de complicações de 2,5% durante a hospitalização, complicações graves de 0,9% e mortalidade associada ao procedimento de 0,05%. (43) O *ESC-EORP EHRA Atrial Fibrillation Ablation Long-Term Registry* incluiu 3.593 pacientes submetidos a ablação de FA em 27 países europeus, demonstrando que teve uma taxa de sucesso do procedimento após 12 meses foi de 69-71%, com uma taxa de complicações graves de 0,03%. (46)

Apesar do crescente respaldo em ECRs a favor do controle do ritmo com ablação como tratamento de primeira linha para a FA, é crucial reconhecer que os resultados em contextos do mundo real, especialmente em países de baixa e média renda per capita, podem não reproduzir os mesmos níveis de eficácia observados em estudos realizados em centros acadêmicos de alto volume, com operadores experientes e acesso às tecnologias mais avançadas. (45)

Figura Central. Evidências de estudos randomizados na ablação de Fibrilação Atrial.



Os registros de eficácia e eficiência da ablação de FA em centros localizados em países de baixa e média renda per capita, como na América Latina, são escassos. O primeiro registro de ablação por cateter na América Latina analisou procedimentos para taquiarritmias supraventriculares realizados no ano de 2012. A taxa de sucesso foi de 89% em 1.161 casos de FA, com uma taxa de complicações de 8,3%. No entanto, o registro não especificou os critérios de sucesso do procedimento e não realizou acompanhamento dos pacientes após a ablação. (47) No Brasil, o registro oficial de ablação da Sociedade Brasileira de Arritmias Cardíacas (SOBRAC) remonta a 2007, abrangendo 755 pacientes com menos de 1 ano de seguimento. (48) Recentemente, os resultados primários do Estudo RECALL (Registro Cardiovascular Brasileiro de Fibrilação Atrial) revelaram que, no início do estudo, apenas 4,4% da população havia sido submetida a ablação por cateter, com uma incidência de 1,8 ablações por 100 pacientes-ano durante o acompanhamento. No entanto, a efetividade das ablações no Brasil não foi avaliada no estudo. (49)

Dessa forma, há uma lacuna significativa no entendimento sobre se, em regiões de baixa e média renda per capita, o risco de complicações perioperatório e a eficácia prevalecem sobre os benefícios clínicos associados à ablação para FA. (20,43,50,51) Considerando que as ablações de FA continuarão a ser amplamente adotadas, abrangendo a América do Sul, e demais países de baixa e média renda, é essencial estabelecer registros estruturados. Esses registros permitirão rastrear sistematicamente os pacientes com FA, coletando dados perioperatórios e de longo prazo sobre aqueles submetidos à ablação por cateter. Isso se torna essencial para obter uma compreensão clara das lacunas entre as recomendações das diretrizes e os dados do mundo real sobre o manejo da FA em países de baixa e média renda.

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2 Justificativa e Objetivos

2.1 JUSTIFICATIVA

A ablação por cateter, constituída predominantemente pelo isolamento das veias pulmonares, tem se mostrado mais eficaz do que o tratamento medicamentoso na manutenção do ritmo sinusal e na prevenção da progressão da fibrilação atrial (FA) para formas mais graves da doença. As diretrizes atuais para o manejo da FA são baseadas em estudos randomizados e registros multicêntricos realizados predominantemente em países de alta renda. Em contraste, há uma escassez significativa de dados provenientes de países de baixa e média renda, como os da América Latina, onde as características populacionais e o acesso a cuidados de saúde podem influenciar substancialmente os resultados do procedimento. Além disso, há divergências no entendimento sobre a relação risco-benefício do procedimento em pacientes com insuficiência cardíaca e sobre a eficácia do uso de técnicas de ablação em focos complementares em casos não-paroxísticos com arteriopatia avançada.

Esta Tese surge da percepção de que a ablação de FA apresenta benefícios clínicos com uma baixa taxa de complicações no Brasil, e da hipótese de que esses benefícios superam os riscos do procedimento, incluindo pacientes com insuficiência cardíaca. Propõe-se a construção de um registro brasileiro dedicado à ablação de FA, com o objetivo de avaliar a segurança e a eficácia do procedimento em centros brasileiros. Além disso, esta pesquisa busca investigar as repercussões da ablação de FA na população com insuficiência cardíaca, assim como a eficácia da ablação da parede posterior do átrio esquerdo em casos não-paroxísticos. Este projeto visa fornecer dados essenciais para adaptar as diretrizes internacionais às especificidades da população brasileira, contribuindo para um manejo mais eficaz e seguro da FA em nosso país.

2.2 OBJETIVOS

2.2.1 Objetivo Geral

Conduzir um registro multicêntrico no Brasil para avaliar os desfechos clínicos, eficácia e segurança da ablação por cateter de radiofrequência em pacientes com fibrilação atrial.

2.2.2 Objetivos específicos

a) Descrever as características demográficas, o uso de medicamentos, as características ecocardiográficas e os escores de sintomas clínicos em pacientes com fibrilação atrial submetidos à primeira ablação em centros brasileiros.

b) Avaliar a recorrência de taquiarritmias atriais após 12 meses da primeira ablação de FA.

c) Identificar preditores independentes de recorrência de FA na população brasileira após a primeira ablação.

d) Avaliar a segurança do procedimento e os desfechos clínicos da ablação por cateter de radiofrequência em pacientes com fibrilação atrial e insuficiência cardíaca.

e) Comparar os resultados de ablação complementar da parede posterior do átrio esquerdo em pacientes com fibrilação atrial na forma não-persistente.

f) Promover colaboração acadêmica entre centros brasileiros na construção do registro SBR-AF.

3 Artigo I.

THE SOUTHERN BRAZILIAN REGISTRY OF ATRIAL FIBRILLATION (SBR-AF):

PREDICTORS OF ATRIAL ARRHYTHMIA RECURRENCE AFTER FIRST-TIME CATHETER ABLATION

Aceito para publicação nos *Arquivos Brasileiros de Cardiologia, impact factor 2.6*.

Arquivos Brasileiros de Cardiologia

Decision Letter (ABC-2024-0246.R1)

From: rochitte@cardiol.br

To: caiqueternes@gmail.com

CC:

Subject: Arquivos Brasileiros de Cardiologia - Decision on Manuscript ID/Decisão sobre ID do Manuscrito ABC-2024-0246.R1

Body: Dear Mr. M P Ternes:

It is a pleasure to accept your manuscript entitled "The Southern Brazilian Registry of Atrial Fibrillation (SBR-AF): Predictors of atrial arrhythmia recurrence after first-time catheter ablation" in its current form for publication in the Arquivos Brasileiros de Cardiologia. The comments of the reviewer(s) who reviewed your manuscript are included at the bottom of this letter.

Send the following forms below completed and signed to revista@cardiol.br and inform the Manuscript ID:

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Thank you for your fine contribution. On behalf of the Editors of the Arquivos Brasileiros de Cardiologia, we look forward to your continued contributions to the journal.

Sincerely,
Dr. Carlos Rochitte
Editor-in-Chief
rochitte@cardiol.br
Arquivos Brasileiros de Cardiologia

Associate Editor
Comments to the Author:
(There are no comments.)

Prezado(a) Mr. M P Ternes:

É uma satisfação aceitar seu manuscrito intitulado "The Southern Brazilian Registry of Atrial Fibrillation (SBR-AF): Predictors of atrial arrhythmia recurrence after first-time catheter ablation" na sua forma atual para publicação nos Arquivos Brasileiros de Cardiologia. Os comentários dos avaliadores que revisaram seu manuscrito estão ao fim desta carta.

Envie os seguintes formulários abaixo preenchidos e assinados para revista@cardiol.br, informando o ID do Manuscrito:

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Todos os formulários podem ser acessados em https://abccardiol.org/formularios-para-publicacao/

Obrigado por sua excelente contribuição. Em nome dos editores dos Arquivos Brasileiros de Cardiologia, aguardamos suas novas contribuições para o periódico.

Atenciosamente,
Dr. Carlos Rochitte
Editor-Chefe
rochitte@cardiol.br
Arquivos Brasileiros de Cardiologia

The Southern Brazilian Registry of Atrial Fibrillation (SBR-AF Registry):
Predictors of atrial arrhythmia recurrence after first-time catheter ablation

SBR-AF Registry:
Preditores de recorrência de taquiarritmia atrial após primeira ablação por cateter

Caique M P Ternes, MD[1,2*], Luis E Rohde, MD, ScD[1,3*], Alexander Dal Forno, MD[2], Andrei Lewandowski MD [2], Helcio Garcia Nascimento, MD[2], Gabriel Odozynski MD[2], Claudio Ferreira, MD[4] Enrico G Ferro, MD[5], Carisi A Polanczyk, MD, ScD[1,3], André Zimerman, MD, ScD[6], Lucas S Faganello, MD, MHS[3], Eric Pasqualotto[2], Grazyelle Damasceno[2], Leandro I Zimerman, MD, ScD[1,3], Andre d'Avila, MD, ScD[2,5]

[1]Post-Graduate Program in Cardiology and Cardiovascular Sciences, Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.
[2]Cardiac Arrhythmia Service, Hospital SOS Cardio, Florianópolis, Brazil.
[3]Cardiology Division, Hospital Moinhos de Vento, Porto Alegre, Brazil.
[4]Cardiac Arrhythmia Service, Hospital Unimed, Chapecó, Brazil
[5]Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.
[6]TIMI Study Group, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts,USA.

* Both authors contributed equally for this study

Short title (50 characters): SBR-AF Registry
Southern Brazilian Registry of Atrial Fibrillation

Word count: 3,552 words

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Address for correspondence: Andre d'Avila, MD, ScD
Director - Cardiac Arrhythmia Service
Hospital SOS Cardio, Florianópolis, Brazil.
Rodovia, SC-401, 121 - Itacorubi, Florianópolis - SC, 88030-000
Email: adavila@bidmc.harvard.edu

ABSTRACT

Background: Treatment of atrial fibrillation (AF) with catheter ablation (CA) has evolved significantly. However, real-world data on long-term outcomes are limited, particularly in low- and middle-income countries.

Objective: This multicenter prospective cohort of consecutive patients aimed to evaluate the safety and efficacy of first-time CA for AF in Southern Brazil from 2009 to 2024.

Methods: The primary outcome was any atrial tachyarrhythmia (ATA) recurrence. Multivariable Cox proportional hazards model assessed independent predictors of recurrence.

Results: Among 1,043 patients (mean age 67.3 ± 11.3 years, 27.9% female), 75.5% had paroxysmal AF. At a median follow-up of 1.4 (1.0 - 3.4) years, 21.4% had ATA recurrence. Recurrence rates were 18.6% for paroxysmal and 29.8% for persistent AF, and 67.3% of events occurred within the first year after CA. Predictors of recurrence were persistent AF at baseline (hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.15-2.13; p = 0.004), left atrial size for each millimeter diameter enlargement (HR 1.03, 95% CI 1.00-1.05; p = 0.033), and higher EHRA score of AF symptoms (HR 1.60, 95% CI 1.18-2.18; p = 0.003). Recurrence rates decreased over time according to the procedure's calendar year, with a 9% relative reduction per consecutive year (HR 0.91; p < 0.001). There were 2.1% procedure-related adverse events.

Conclusions: In the largest cohort of consecutive AF ablations in Latin America, predictors of ATA recurrence were related to later stages of AF. Complication and recurrence rates were comparable to those in high-income countries, underscoring the global applicability of CA for AF management.

Keywords: Atrial Fibrillation; Catheter Ablation; Prognosis

NON-STANDARD ABBREVIATIONS AND ACRONYMS

CFS – contact force-sensing

LA – left atrial

LCPV – left common pulmonary vein

LMICs – low and middle-income countries

RF – radiofrequency

INTRODUCTION

Atrial fibrillation (AF) estimated global prevalence was of 44 million people in 2016.[1–4] AF patients are at increased risk for thromboembolic events, progressive left ventricular dysfunction, and worsening quality of life.[5,6] Contemporary trials support early rhythm control to improve clinical outcomes and quality of life compared with rate control.[7,8] Catheter ablation (CA) of AF is superior to anti-arrhythmic drugs (AAD) in maintaining sinus rhythm and delaying progression from paroxysmal to persistent AF.[9,10] Therefore, CA is increasingly performed as the first-line rhythm control therapy for patients with recently diagnosed AF.[11-13] Despite increasing evidence favoring rhythm control in randomized clinical trials (RCTs), real-world scenarios may not replicate the same levels of efficacy from studies in which high-volume centers with experienced operators are commonly overrepresented.[14] Furthermore, the promising efficacy profile of AF ablation needs to be matched by an equally appealing safety profile, especially as this procedure is adopted by operators and hospitals with heterogeneous experience and expertise around the world. The risk of peri-procedural complications might reduce the overall net clinical benefit of ablation techniques for rhythm control in AF patients.[15] In this scenario, much of the evidence is drawn from RCTs and registries conducted either in high-income countries or in reference/academic centers in low and middle-income countries (LMICs).[16-19] In Brazil, the most recent official registry on CA outcomes sponsored by *the Brazilian Society of Cardiac Arrhythmias* dates back to 2007.[20] Recently, the RECALL Study (*Brazilian Cardiovascular Registry of Atrial Fibrillation*) primary results showed that at baseline, only 4.4% of the population had undergone CA. During follow-up, there were 1.8 ablations per 100 patients-years. However, the effectiveness of CA was not assessed in the study.[21]

Thus, to gain a clear understanding of gaps between guideline recommendations and real-world data on AF management in LMICs, there is an urgent need for structured registries to

systematically track AF patients and collect peri-operative and long-term outcomes of CA. The current Southern Brazilian Registry of Atrial Fibrillation (SBR-AF) study is the largest multicenter prospective cohort in Latin America to date dedicated to assessing the peri-procedural safety, efficacy, and long-term clinical outcomes of consecutive ablations.

MATERIAL AND METHODS

Study design and eligibility criteria

We conducted a prospective multicenter cohort study of 1,043 consecutive patients ≥ 18 years of age, with paroxysmal, persistent, or longstanding persistent AF who underwent a first-time radiofrequency (RF) CA from January 2009 to January 2024. The study included patients with symptomatic and documented AF in 3 centers in Brazil (SOS Cardio, Florianopolis, SC; Hospital Unimed, Chapecó, SC; and Hospital Moinhos de Vento, Porto Alegre, RS).

Baseline sociodemographic and clinical characteristics were collected before each procedure, together with the Canadian Cardiovascular Society Severity of AF (CCS-SAF) score and the European Heart Rhythm Association score of AF-related symptoms (hereafter referred to as EHRA Score).[22,23] All data was stored in Syscardio® software, preserving the patient's identity. Local Ethics Committees approved the study, and patients provided informed consent in accordance with the Helsinki Declaration.

Procedural protocol and follow-up

All patients underwent RFCA under general anesthesia. All procedures were performed with different versions of an *EnSite Navx - Abbott®*. *Figure 1* illustrates the ablation approach for paroxysmal a non-paroxysmal AF. Briefly, only pulmonary vein isolation (PVI) was performed in patients with paroxysmal AF, whereas the posterior wall was included in most patients with

non-paroxysmal AFib. In patients with paroxysmal AF, the posterior wall was also isolated using a posterior wall single line contralateral to the position of the esophagus when high esophageal temperatures were deemed too risky and prevented PVI. The posterior was included in all patients with areas of low voltage identified in sinus rhythm or when 3 cardioversion attempts did not restore sinus rhythm. In those patients in whom areas of low voltage were not present, ablation of the posterior wall of the left atrium was performed according to the operator's discretion. Esophageal temperature was continuously monitored in all cases using coated sensors (Circa®), and ablation was immediately stopped if the esophageal temperature exceeded 38°C. After June 2016, ablation procedures were performed with contact-force sensing catheters. RF applications were delivered for 8-12 sec along the posterior wall and 15-30 sec everywhere else with a current ranging between 650-700 *m*Amperes. When available, this approach would typically result in an ablation index of 3.5-4 for the posterior wall and 4.5 to 5.5 along the anterior wall and roof of the left atrium. Isoproterenol infusion (up to 20 mcg/min) and adenosine infusion were used at the operators' discretion until 2018 but not after that. Demonstration of PV (all patients) and posterior wall (when performed) bidirectional block was the endpoint of the procedure. After CA, patients were kept on antiarrhythmic drugs for 30 days. Amiodarone was prescribed or kept in place for patients with LVEF ≤ 40% and/or coronary artery disease. Patients with a normal LVEF were prescribed 25 mg of metroprolol once a day and 150 mg of profanenone twice a day. Anticoagulation medications were recommended for at least 3 months. Beyond the initial 3 months, oral anticoagulation was utilized as a function of the CHA2DS2-VASc score but ultimately left at the physician's discretion. Follow-up was conducted with in-person visits after ablation within 30, 180, and 360 days. Subsequently, patients were recommended for yearly visits. Upon failure to return for a yearly visit, additional contact was made by phone contacts throughout the study period, using a pre-specified query to assess arrhythmia symptoms. In cases of symptomatic arrhythmia identified in phone

contacts, patients were asked to provide an EKG and schedule a Holter to monitor

Primary outcome

The primary outcome was defined as the recurrence of any documented atrial tachyarrhythmia (ATA) assessed by either an EKG, Holter monitor, or a cardiac stress test showing AF or atrial flutter. We allowed a blanking period of 60 days, i.e., events occurring less than 60 days from the index procedure were not included in the current analysis.[13] Patients were censored at the last available contact, either by phone or in-person visit, and they were considered free of ATA if no records of arrhythmia were made after CA.

Statistical analysis

Data are expressed as mean ± standard deviation, median and interquartile range (IQR), or absolute numbers and percentages. Data normality was assessed using the Shapiro-Wilk test, and variables were considered normally distributed when their significance p-value was > 0.05. Comparisons between groups (with and without ATA recurrence) were performed using the Student's t-test test for normally distributed variables or the Wilcoxon-Mann-Whitney and Kruskal-Wallis test for variables with non-normal distribution. The chi-square test was used to assess the significance of the association between frequencies of variables. Univariable predictors of recurrent arrhythmic events (p-value < 0.10) and baseline characteristics were evaluated with the multivariable Cox proportional hazards model. Mean values were interpolated for missing values in body mass index, glomerular filtration rate, and left atrial (LA) diameter to allow adequate statistical modeling for multivariable analysis. Longstanding persistent AF patients were incorporated with the persistent AF group. Survival analyses were performed using Kaplan-Meier curves and the log-rank test. All statistical analyses used Stata (version 18). A two-tailed p-value of 0.05 was considered statistically significant.

RESULTS

Patient characteristics

From January 2009 through January 2024, a total of 1,043 patients underwent first-time CA for paroxysmal (n = 788), persistent (n = 230), and longstanding persistent AF (n=25) patients). Mean age was 67.3 ± 11.3 years, and 27.9% were female. Most patients (79.0%) reported AF-related symptoms, with 23.8% classified with EHRA Score class III or IV. Most patients had CHA_2DS_2-VASc scores ≥2, and 79.1% were on anticoagulants. Table 1 describes baseline clinical characteristics stratified by ATA recurrence during follow-up.

Procedural characteristics

Pulmonary vein isolation (PVI) was performed in all patients using radiofrequency CA, with a mean fluoroscopy time of 10.6 ± 7.3 minutes and radiation dose of 93 ± 121 mSv (data available for 639 and 622 patients, respectively). The anatomical variation of the left common pulmonary vein (LCPV) was determined in cases where the two left pulmonary veins (PVs) fused at least 10 mm before their common ostium insertion into the left atrium (*Figure 1*), with 26.6% (n=277) exhibiting this characteristic. Adjunctive posterior wall isolation (PWI - 199 patients [19.1%]) was performed in patients with non-paroxysmal AF patients and in those paroxysmal AF patients in whom high esophageal temperatures prevented PVI.

Follow-up and atrial tachyarrhythmia recurrence

The mean follow-up time was 2.5 ± 2.3 years (median 1.4 [IQR 1.0 – 3.4] years). Overall, 223 (21.4%) patients had ATA recurrence, 67.3% of which (n=150) occurred within the first year following the procedure. *Figure 2* illustrates the rate of ATA recurrence after 12 months following a first-time CA for AF according to the year of procedure. We observed a significant stepwise

decrease in ATA recurrences in temporal analysis (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.90 to 0.99; p = 0.01), reaching 1-year recurrence rates as low as 7.5% in 2017. *Supplementary Figure 1* depicts the absolute numbers of AF ablations and ATA recurrences according to the year the procedure was performed. Patients with paroxysmal AF had a 12.8% ATA recurrence rate at 1 year and an overall rate of 18.6%. The ATA recurrence rate for patients with persistent AF was 19.2% at 1 year and 29.8% during long-term follow-up. A survival analysis comparing paroxysmal vs non-paroxysmal AF found significantly higher freedom from ATA in paroxysmal AF, as shown in *Figure 3* for both (A) 12 months and (B) overall follow-up. Patients with LCPV anatomy had an overall 81.6% freedom from ATA (226/277, p=0.08). Freedom from ATA in paroxysmal and non-paroxysmal AF who received adjunctive PWI was 87.2% (82/94, p = 0.11) and 77.1% (81/105, p = 0.04), respectively. Survival analysis comparing ablation techniques with and without contact force-sensing (CFS) catheters shown in *Figure 4A* found a higher rate of freedom from ATA during follow-up in patients who underwent ablation using CFS catheters (log-rank p = 0.03).

Univariable and multivariable analysis

Univariable analysis and Cox proportional hazards model to assess predictors of ATA recurrence following CA for AF are presented in *Table 2*. Independent predictors of ATA recurrence after a first-time ablation included persistent AF at baseline (HR 1.57, 95% CI 1.15 to 2.13; p = 0.004), larger LA diameter in millimeters (HR 1.03, 95% CI 1.00 to 1.05; p = 0.033), and patients with an EHRA Score of AF Symptoms class III or IV (HR 1.60, 95% CI 1.18 to 2.18; p = 0.003) as shown in *Central Figure*. The procedure year was an independent protective factor, with a 9% relative reduction in recurrence for each new calendar year of the ablation program (*Figure 2* and *Table 2*). These findings were consistent in an analysis restricted to patients with paroxysmal AF, as shown in *Supplementary Table 1*. A subgroup analysis of ATA recurrence across different age ranges, sex, BMI categories, hypertension, type 2 diabetes, glomerular filtration rate, left ventricular ejection fraction,

and LA diameter is shown in *Figure 5*. Among the subgroups, patients older than 75 years (HR 1.77, 95% CI 1.28-2.45; p = 0.001) and with a larger LA diameter (45-49mm, p = 0.020; >50mm, p = 0.003) had statistically significant worse outcomes regarding ATA. Overall, LA diameter ≥ 45mm (n=211) was associated with more ATA events (HR 1.55, 95% CI 1.15-2.10, p = 0.004). The multivariable analysis only identified age (HR 1.03, 95% CI 1.00 – 1.05, p = 0.01) as an independent predictor of ATA recurrence when restricted to patients with persistent AF (*Supplementary Table 2).* *Figure 4B* illustrates survival analysis in persistent AF patients with and without LCPV (log-rank p = 0.30).

Safety and adverse events

Over 15 years of procedures, among 1,043 consecutive ablations on aggregate, the complication rate during the index admission was 2.1% as shown in *Supplementary Table 3*. Notably, patients older than 75 years represented only 0.8% of the overall complications. Severe adverse events included two cases of cardiac tamponade (one successfully managed during the procedure and one requiring cardiac surgery), one non-fatal stroke during admission for index procedure, and one esophageal perforation without fistula successfully treated conservatively. There were no phrenic nerve injuries, clinically relevant pulmonary vein stenosis, or procedure-related deaths (*Central Figure*).

DISCUSSION

This multicenter prospective cohort evaluated over one thousand consecutive AF patients undergoing first-time CA in Brazil and provides long-term data about efficacy, safety, and predictors of arrhythmia recurrence. The key findings of the current analysis include: (i) overall efficacy and safety were comparable to clinical trials and high-income countries registries in Europe and North America[14,17]; (ii) long-term efficacy increased over time, with a 9% relative risk reduction of ATA recurrence for each consecutive year that CA was performed; (iii) adopting contact force-sensing catheters improved the outcomes after first-time ablation (iv) most ATA recurrences occurred within one year following ablation; and (v) ATA recurrence was more frequently observed in procedures performed on patients with advanced disease (severe EHRA score of AF symptoms, larger LA and persistent AF). Additionally, our findings highlight the low rate of complications of consecutive CAs in a prospective cohort in Latin America.

International registries play a crucial role in understanding disparities between guidelines and AF management in daily clinical practice. An initial report of the *Atrial Fibrillation Ablation Pilot Registry of the European Society* (EORP-AF) demonstrated 1-year success rates after ablation ranging from 69% to 74.7% in different countries.[24] The EORP-AF has also contributed significantly to the understanding of real-world data related to AF.[25] Within the EORP-AF Long-Term Registry, outcomes were documented for 9,663 AF patients based on their antithrombotic therapy.[26] While 42% and 33% of EORP-AF patients used vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs), respectively, our cohort exhibited a different pattern, with 15% on VKA and 64% on DOACs. Gender-based ablation outcomes have also been reported in this European collaboration, with a similar gender representation to that observed in our study, where only about 30% of patients were female. At baseline, female patients were more symptomatic than male

patients, with mean EHRA scores of 2.6 vs. 2.4 in Europe ($p<0.001$)[27] and 2.2 vs. 2.0 in Brazil ($p<0.001$). Importantly, neither study found statistically significant gender-based differences in 12-month recurrence rates (34.4% vs. 34.2% in Europe; 16.1% vs. 13.7% in Brazil, $p=0.3$), highlighting the need for equitable access to ablation as a treatment option for women.[27]

This study represents the largest cohort to this date designed to assess ablation outcomes in AF patients in Latin America. Data on Brazilian patients with AF have recently been described in the RECALL Study, although ablation outcomes were not assessed.[21] The last multicenter registry dedicated to ablation outcomes published in Brazil was conducted by *the Brazilian Society of Cardiac Arrhythmias* between 2005 and 2006.[20] In that registry, 755 AF patients were included, and a complication rate of 14.3% was reported, which included 1.4% transient neurologic ischemic events, 0.4% pulmonary vein stenosis, 3.8% groin hematomas, and 2.3% other complications. The 2.1% complication rate observed in the current cohort highlights the learning curve associated with ablation procedures and demonstrates how technological advances, especially contact force-sensing catheters, have made these procedures safer and more reliable in clinical practice. Similar findings were observed in the largest global cohort, the *NCDR AFib Ablation Registry*, with a 2.5% complication rate among 76,219 AF patients over 5 years.[17]

Previous studies have addressed predictors of recurrence after CA for AF. The current analysis demonstrates that persistent AF and larger LA have been consistently reported as independent risk factors.[28,29] Several scores have been developed to predict rhythm outcomes after AF ablation. The APPLE score (one point for age >65 years, persistent AF, impaired eGFR [<60 ml/min/1.73 m^2], LA diameter ≥ 43 mm, LVEF < 50%) had suboptimal performance (AUC = 0.64),[30] while the AFA-Recur web calculator based on a random forest model of 19 variables achieved an acceptable discriminative performance (AUC 0.72).[31] Our Cox

model also incorporated the EHRA score of AF symptoms class III-IV as an independent predictor of risk. The EHRA AF score is commonly used to assess clinical response following CA,[32] and might also signal the severity and longer duration of the disease. Compared to previous registries, our cohort also showed higher ATA rates following CA in older patients, although there was no significant difference in outcomes across BMI categories.[33,34]

It is reasonable to propose that paroxysmal AF patients exposed to longer arrhythmia burdens experience progressive remodeling of the atrium. This possibly leads to worsening of underlying atriopathy and progression to the persistent or more severe forms of the disease. Ultimately, this expected progression of AF leads to worse clinical outcomes in procedures performed later in the natural history of the arrhythmia. This proposition was substantiated in the EARLY-AF trial, where paroxysmal AF patients were followed for 3 years.[35] This study revealed that patients who underwent initial CA had a lower progression to persistent AF and fewer ATA recurrences when compared with those treated solely with antiarrhythmic drugs. While it seems evident that earlier ablations could yield better results, achieving high efficacy in persistent AF ablations remains a challenge. Adjunctive ablation sites, such as posterior wall isolation, have been suggested recently as a potential strategy for managing this challenging condition.[36,37] In the current cohort, posterior wall isolation was performed in approximately one-fifth of enrolled patients at the operator's discretion but was not an independent predictor of ATA recurrence.

Strengths and limitations.

Our cohort comprises consecutive AF patients undergoing their first-time ablation, making it Latin America's largest dataset dedicated to evaluating the safety and efficacy of CA for AF. These findings are particularly relevant in the context of LMICs, providing valuable insights into real-world clinical safety in these settings. Residual confounding is a potential concern, as we lacked data to adjust for

AF duration. We did not analyze the outcomes of redo ablations in this study. This multicenter cohort was conducted only in private centers and might not reflect the reality of public centers in Brazil. Most patients were white and did not represent the population in Latin America. Additionally, patients were censored at the last follow-up, which could have underestimated the ATA recurrence rate.

CONCLUSION

In the largest cohort in Latin America of consecutive first-time ablations for AF, ATA recurrence is associated with interventions conducted at later stages of the disease's progression, highlighting the significance of early intervention for improved clinical outcomes. Peri-procedural complications and ATA recurrence rates were comparable to those in high-income countries, underscoring the global applicability of CA for AF management. Overall, these data highlight the outstanding performance of CA in AF management in Latin American centers, suggesting that this treatment option should be expanded to the public health system in Brazil.

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TABLES AND FIGURES

Table 1: Baseline characteristics of patients with atrial fibrillation undergoing first-time catheter ablation.

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Figure 5. Cox proportional hazards model for the risk of ATA recurrence after first-time CA stratified by subgroups.

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Table 1: Baseline characteristics of patients with atrial fibrillation undergoing first-time catheter ablation.

Clinical Characteristic	**All** *(n=1,043)*	**ATA-Free** *(n = 820)*	**ATA recurrence** *(n = 223)*	**P value**
Age (years), mean ± SD	67.3 ± 11.3	66.8 ± 11.3	69.0 ± 11.2	0.01
Male, n (%)	752 (72.1)	598 (72.9)	154 (69.1)	0.25
White, n (%)	1,027 (98.5)	806 (98.3)	221 (99.1)	0.10
BMI (kg/m^2), mean ± SD	27.8 ± 4.1	27.8 ± 4.0	27.7 ± 4.3	0.91
History and Comorbidities, n (%)				
Hypertension	578 (55.4)	452(55.3)	126 (55.8)	0.80
Diabetes mellitus	162 (15.5)	124 (14.9)	38 (17.4)	0.42
Coronary artery disease	126 (12.1)	99 (12.2)	27 (11.6)	0.96
Previous stroke or TIA	50 (4.8)	34 (4.1)	16 (7.0)	0.07
Family history of AF	137 (13.1)	110 (13.4)	27 (12.4)	0.59
Prior direct cardioversion	529 (50.7)	404 (48.5)	125 (57.4)	0.08
Prior bleeding	24 (2.3)	18 (2.0)	6 (3.1)	0.67
Type of AF, n (%)				<0.001
Paroxysmal	788 (75.5)	641 (79.0)	147 (65.1)	
Persistent	255 (24.5)	179 (21.0)	76 (34.9)	
EHRA Score of AF Symptoms, n (%)				0.003
Class I	219 (21.0)	188 (22.9)	31 (15.1)	
Class II	576 (55.2)	451 (55.4)	125 (54.7)	
Class III-IV	248 (23.8)	181 (21.7)	67 (30.2)	
CCS-SAF Symptom Score, n (%)				0.002
Class 0	129 (12.4)	110 (13.2)	19 (9.7)	
Class 1-2	578 (55.4)	469 (57.7)	109 (48.4)	
Class 3-4	336 (32.2)	241 (29.1)	95 (41.9)	
CHA2DS2-VASc, n (%)				0.07
Median (Q1, Q3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	
0-1	460 (44.1)	376 (45.5)	84 (40.0)	
2	222 (21.3)	168 (20.5)	54 (23.6)	

3	145 (13.9)	108 (13.0)	37 (16.7)	
4	83 (8.0)	65 (7.9)	20 (8.1)	
≥ 5	48 (4.6)	37 (4.6)	11 (4.6)	
Drugs, n (%)				
Amiodarone	666 (63.8)	511 (62.4)	155 (68.2)	0.07
ß blockers	537 (51.5)	413 (50.3)	124 (55.0)	0.17
Aspirin	108 (10.3)	76 (8.5)	32 (15.9)	0.03
Diuretics	152 (14.6)	106 (12.5)	46 (20.9)	0.004
Anticoagulation, n (%)	825 (79.1)	636 (76.9)	189 (85.6)	<0.001
Warfarin	157 (15.0)	102 (11.8)	55 (24.8)	<0.001
DOACs	668 (64.0)	534 (65.1)	134 (60.9)	<0.001
Exams, median(Q1, Q3)				
LVEF, %	64 (57-69)	65 (57-69)	63 (56-70)	0.97
LA diameter, mm	40 (36-43)	40 (36-43)	40 (37-45)	0.02
Creatinine, mg/dl	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.9-1.1)	0.93
GFR, ml/min//1.72 m2	78 (66-88)	78 (65-88)	78 (66-89)	0.80

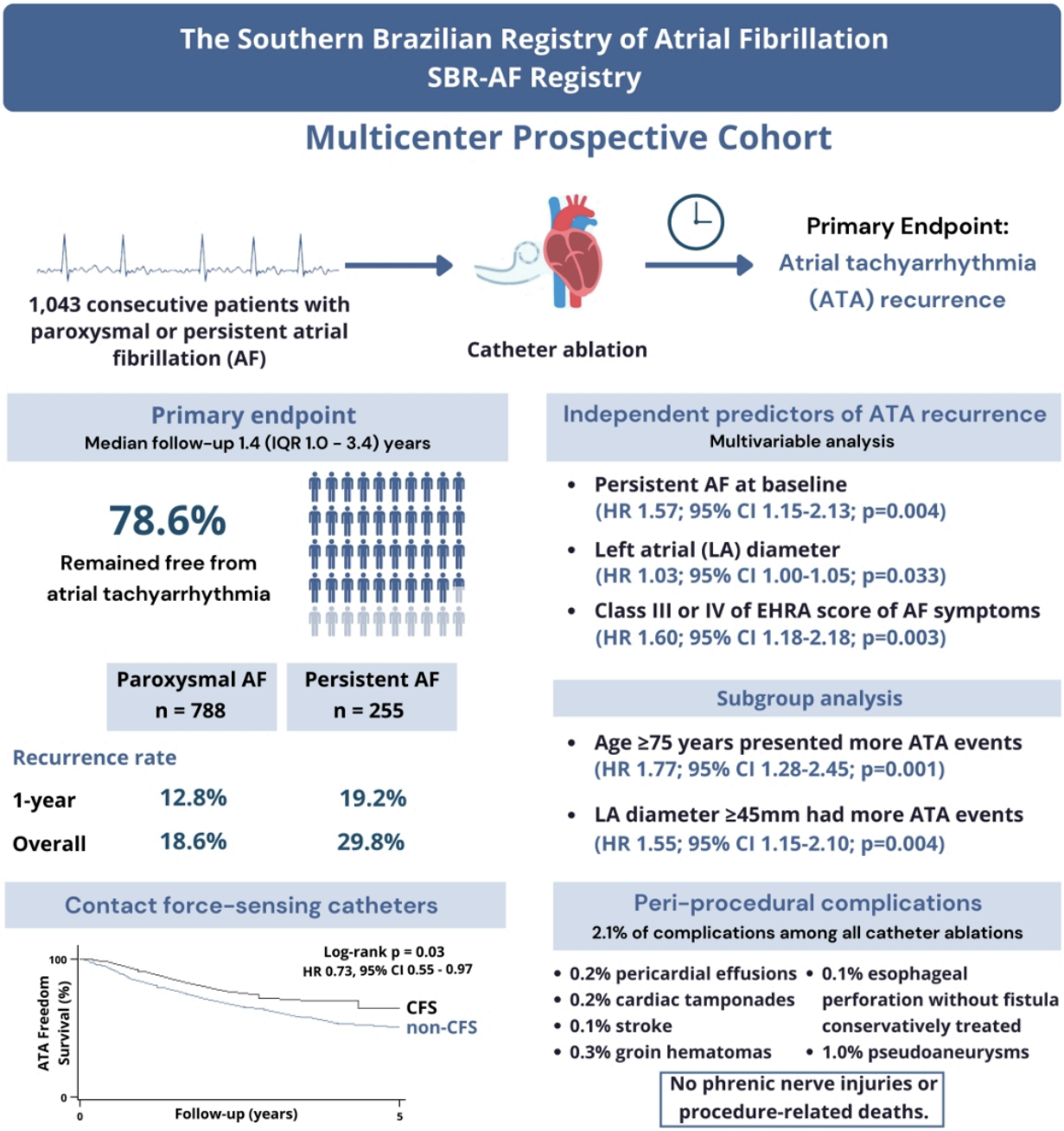
AF – atrial fibrillation; ATA – atrial tachyarrhythmia; BMI – body mass index; creatinine (7.6% N/A); CHA2DS2-VASc Score (8.1% N/A); CCS-SAF – Canadian Cardiovascular Society Severity of atrial fibrillation; DOAC – direct oral anticoagulant; EHRA – European Heart Rhythm Association; GFR – glomerular filtration rate (7.6% N/A); Q1 and Q3, quartiles (25th and 75th percentiles); SD – standard deviation; TIA – transient ischemic attack; LA – left atrial; LVEF – left ventricular ejection fraction.

Table 2: Univariable analysis and Cox proportional hazards model for risk of atrial tachyarrhythmia recurrence after radiofrequency catheter ablation.

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
*Procedure c*onsecutive year	0.94	0.90 – 0.99	0.010	0.91	0.87 – 0.96	<0.001
Persistent atrial fibrillation	1.72	1.30 – 2.28	<0.001	1.57	1.15 – 2.13	0.004
Left atrial diameter enlargement (mm)	1.03	1.01 – 1.05	0.002	1.03	1.00 – 1.05	0.033
EHRA Score of AF Symptoms Class III-IV	1.94	1.26 – 2.97	0.002	1.60	1.18 – 2.18	0.003
Sex	0.82	0.62 – 1.09	0.172			
Age	1.01	1.00 – 1.03	0.027			
Hypertension	1.08	0.82 – 1.42	0.590			
Type 2 diabetes	1.26	0.88 – 1.79	0.205			
Previous stroke	1.74	1.04 – 2.90	0.033			
Beta-blockers use	1.20	0.92 – 1.57	0.172			
Diuretics use	1.38	1.00 – 1.91	0.052			
Left common pulmonary vein	0.91	0.66 – 1.24	0.548			
Use of CFS catheter	0.73	0.55 – 0.97	0.030			
Prior direct cardioversion	1.28	0.96 – 1.70	0.088			

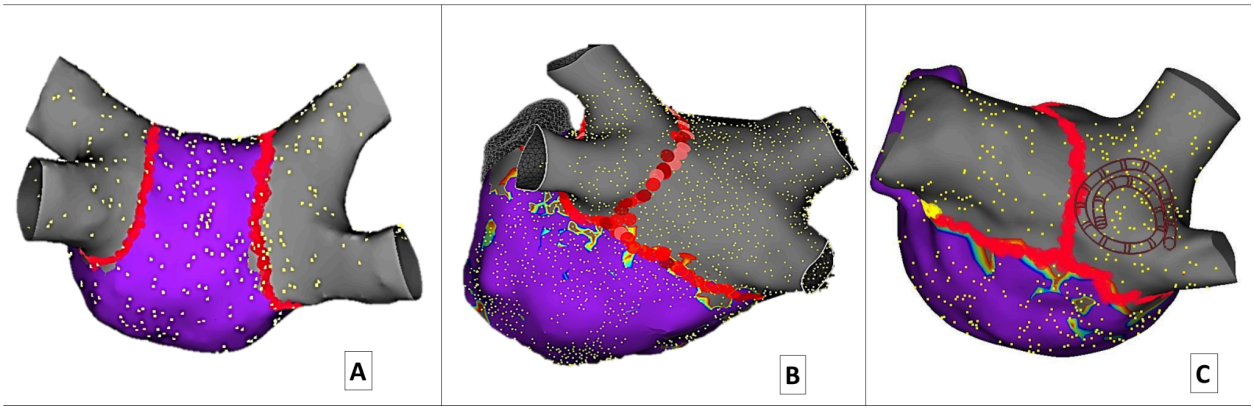
AF – atrial fibrillation; CFS – contact force sensing EHRA – European Heart Rhythm Association;

Central figure: Southern Brazilian Registry of Atrial Fibrillation, periprocedural complications, and ATA recurrence in long-term clinical follow-up.



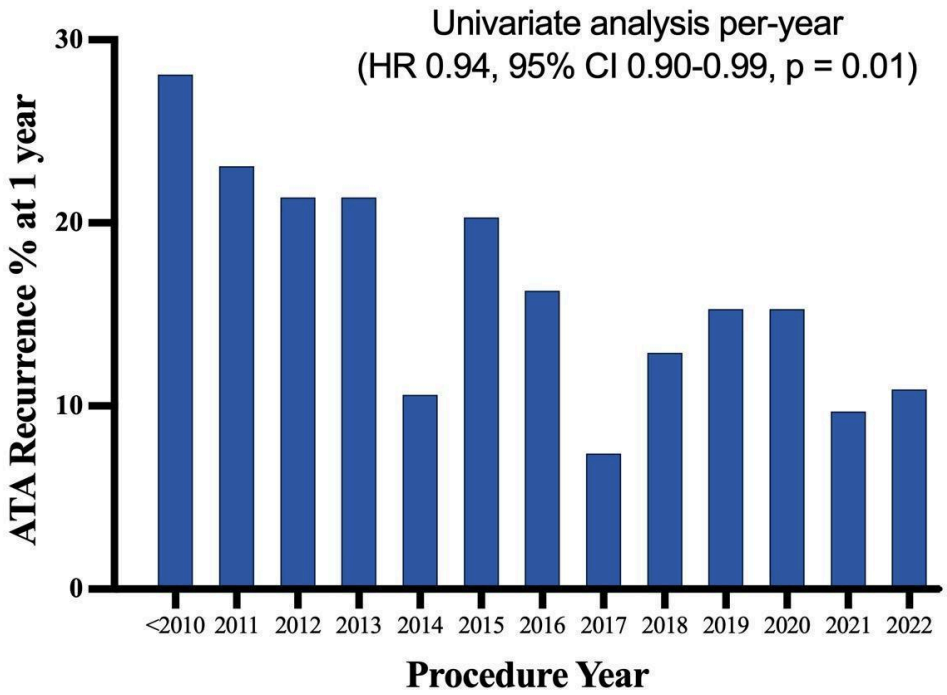
Notes: AF – atrial fibrillation; ATA – atrial tachyarrhythmia; CFS – contact force-sensing.

Figure 1. Illustrative examples of the ablation approach utilized during the study period.



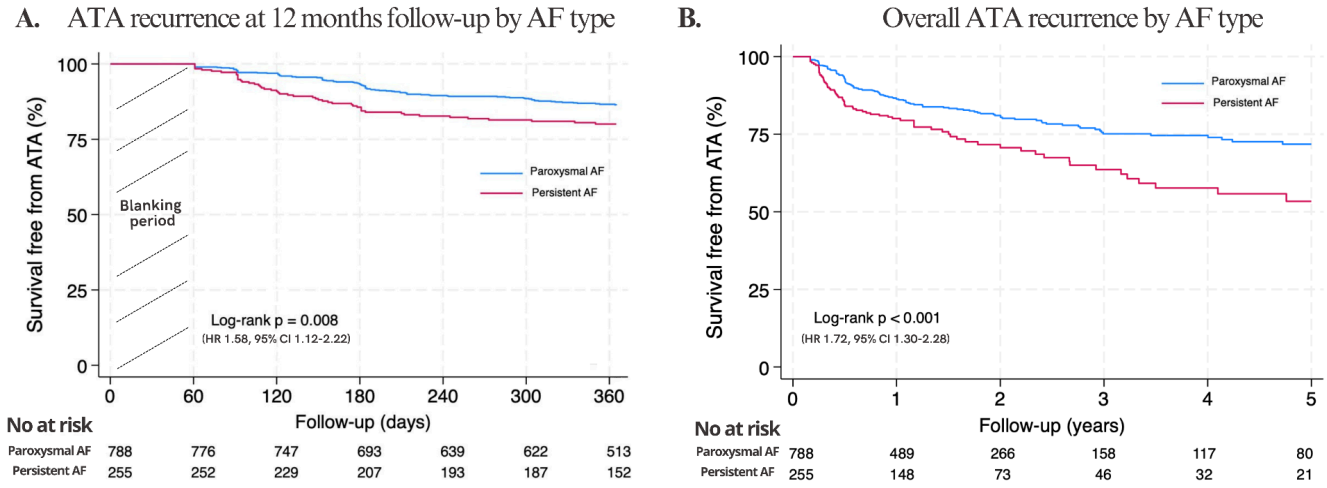
Notes: Only Pulmonary vein isolation was performed in patients with paroxysmal atrial fibrillation (A). In all other non-paroxysmal patients, the posterior wall was also isolated when areas of low voltage were present in normal sinus rhythm or when patients could not be successfully cardioverted (B). In patients with a left common trunk (C), the posterior wall of the left atrium was ablated according to the type of atrial fibrillation. The red dots represent the ablation lesion. Areas in gray represent the absence of electrical activity after ablation whereas areas in pink represent normal atrial voltage in sinus rhythm.

Figure 2. 1-year ATA recurrence rate following first-time catheter ablation according to the year of procedure.



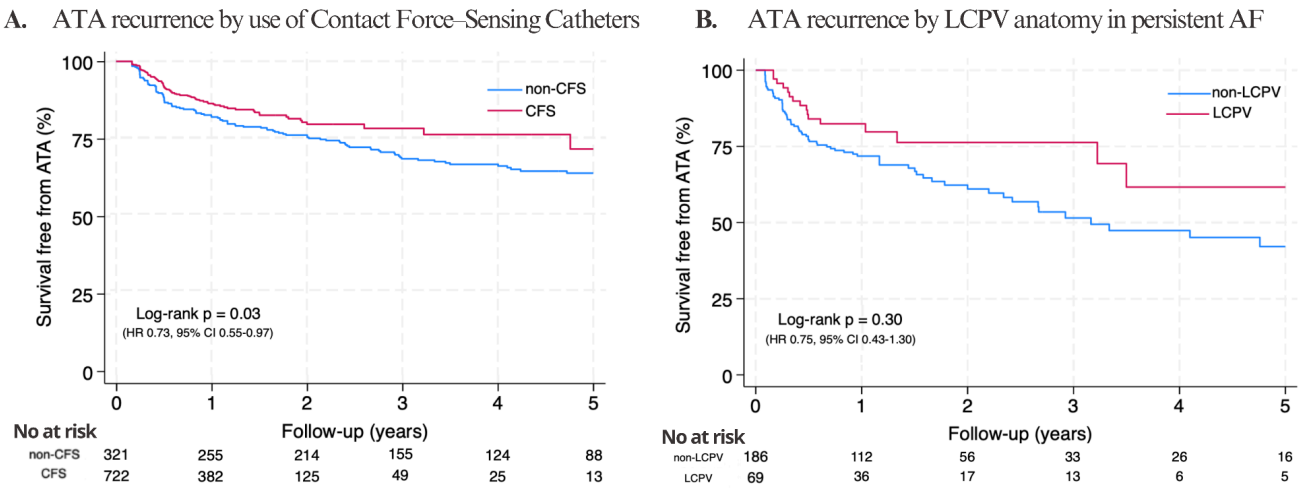
Notes: ATA – atrial tachyarrhythmia recurrence; CI – confidence interval; HR – hazard ratio.

Figure 3. Kaplan-Meier curve illustrating ATA recurrence in patients with paroxysmal and non-paroxysmal atrial fibrillation at (A) 12 months and (B) the end of long-term follow-up.



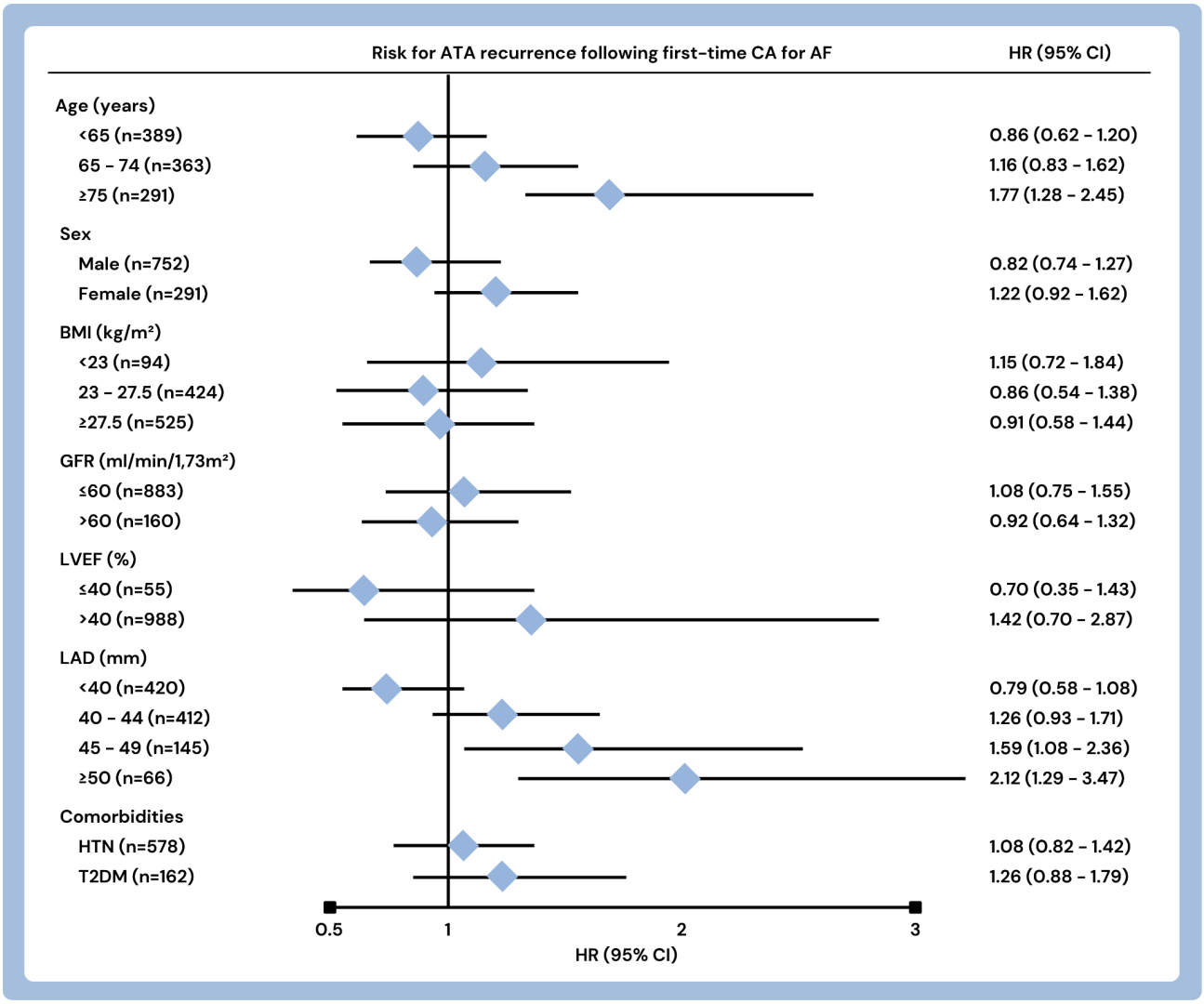
Notes: AF – atrial fibrillation; ATA – atrial tachyarrhythmia.

Figure 4. Kaplan-Meier curves for ATA recurrence according to (A) contact force-sensing catheter use in first-time CA and (B) presence of LCPV anatomy in patients with persistent AF.



Notes: AF – atrial fibrillation; ATA – atrial tachyarrhythmia; CA – catheter ablation; CFS – contact force sensing; LCPV – left common pulmonary vein.

Figure 5. Cox proportional hazards model for the risk of ATA recurrence after first-time CA stratified by subgroups.



Notes: AF – atrial fibrillation; ATA – atrial tachyarrhythmia; BMI - body mass index; CA – catheter ablation; CI – confidence interval; HR – hazard ratio; HTN - hypertension. T2DM - type 2 diabetes; GFR - glomerular filtration rate.

SUPPLEMENTARY APPENDIX

Supplementary Table 1. Univariable analysis and Cox proportional hazards model for risk of atrial tachyarrhythmia recurrence after radiofrequency catheter ablation in *paroxysmal atrial fibrillation*.

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Procedure consecutive year	0.93	0.88 – 0.98	0.006	0.91	0.86 – 0.96	<0.001
Left atrial diameter (mm)	1.03	1.00 – 1.06	0.024	1.03	1.00 – 1.07	0.028
EHRA Score of AF Symptoms Class III-IV	2.00	1.16 – 3.43	0.012	1.51	1.04 – 2.21	0.032
CHA2DS2-VASc	1.12	1.00 – 1.25	0.046			
Aspirin use	1.33	0.86 – 2.06	0.210			
Anticoagulation therapy	1.15	0.89 – 1.47	0.294			
Left common pulmonary vein	0.97	0.66 – 1.42	0.881			
Prior direct current cardioversion	1.10	0.78 – 1.55	0.575			

EHRA – European Heart Rhythm Association

Supplementary Table 2: Univariable analysis and Cox proportional hazards model for risk of atrial tachyarrhythmia recurrence after radiofrequency catheter ablation in *persistent atrial fibrillation* (n=255).

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.03	1.01 – 1.05	0.010	1.03	1.00 – 1.05	0.010
EHRA Score of AF Symptoms Class III-IV	1.95	0.97 – 3.90	0.060			
Procedure consecutive year	0.97	0.90 – 1.04	0.405			
Left atrial diameter enlargement (mm)	1.01	0.97 – 1.05	0.539			
Posterior wall isolation	0.94	0.56 – 1.55	0.797			
LCPV	0.75	0.43 – 1.30	0.304			

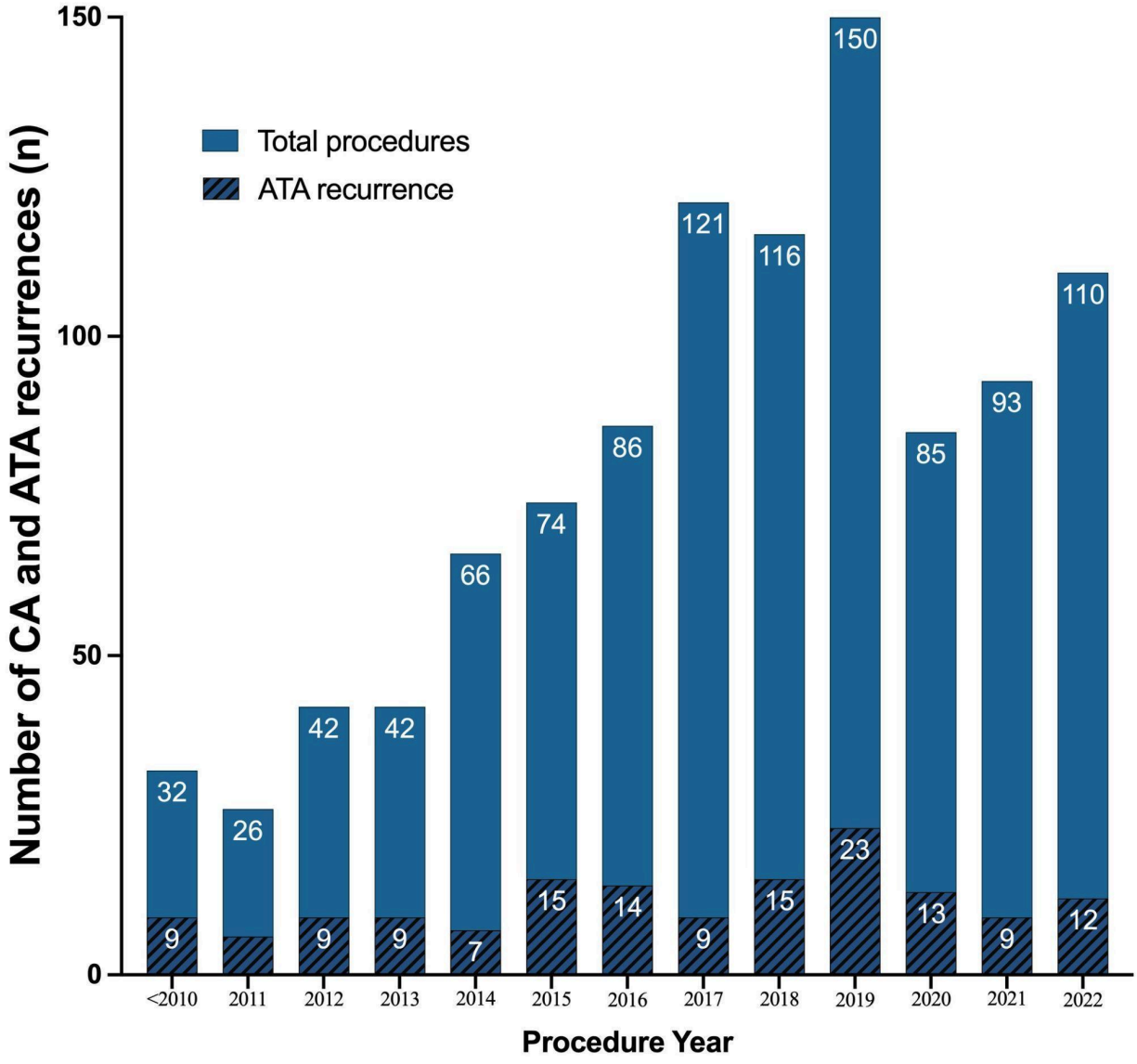
AF – atrial fibrillation; EHRA – European Heart Rhythm Association; LCPV – left common pulmonary vein;

Supplementary Table 3: Procedure-related complications occurred in 1,043 consecutive catheter ablations

Adverse events	Events, n (%)
Cardiac tamponade	2 (0.19)
Pericardial effusion †	2 (0.19)
Esophageal perforation without fistula	1 (0.09)
Stroke during admission	1 (0.09)
Gastroparesis	2 (0.19)
Femoral AV fistula	1 (0.09)
Pseudoaneurysm	10 (0.95)
Groin hematoma	3 (0.28)

† transient effusion without tamponade; AV – arteriovenous

Supplementary Figure 1. Absolute number of procedures and ATA recurrences within 12 months following a first-time catheter ablation for AF according to the year of procedure.



4 Artigo II.

CATHETER ABLATION FOR ATRIAL FIBRILLATION IN HEART FAILURE WITH REDUCED EJECTION FRACTION PATIENTS: A META-ANALYSIS

Versão manuscrita submetida ao periódico *Heart Rhythm Journal (Impact Factor 5.6)*

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Heart Rhythm

Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction patients: A meta-analysis

--Manuscript Draft--

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Keywords:	Catheter ablation, Heart failure, Atrial fibrillation, Heart failure hospitalization, Cardiovascular mortality, All-cause mortality.
Corresponding Author:	Eric Pasqualotto Universidade Federal de Santa Catarina Florianópolis, Santa Catarina BRAZIL
First Author:	Eric Pasqualotto
Order of Authors:	Eric Pasqualotto
	Caique M P Ternes, MD
	Matheus Pedrotti Chavez
	Carisi A Polanczyk, MD, ScD
	Rafael Oliva Morgado Ferreira
	Thiago Faraco Nienkötter
	Gustavo de Oliveira Almeida
	Edmundo Bertoli
	Mariana R. C. Clemente
	Andre d'Avila, MD, ScD
	Luis E Rohde, MD, ScD
Manuscript Region of Origin:	BRAZIL
Abstract:	Background: The optimal treatment for atrial fibrillation (AF) in patients with heart failure with reduced ejection fraction (HFrEF) remains unsettled. Objectives: To assess the efficacy of catheter ablation (CA) and medical therapy compared to medical therapy alone in patients with AF and HFrEF. Methods: We performed a systematic review of randomized controlled trials (RCTs) comparing CA versus guideline-directed medical therapy for AF in patients with HFrEF (left ventricular ejection fraction (LVEF) ≤40%). We systematically searched PubMed, Embase, and Cochrane for eligible trials. A random-effects model was used to calculate the risk ratios (RRs) and mean differences (MDs), with 95% confidence intervals (CIs). Results: Six RCTs comprising 1,055 patients were included, of whom 530 (50.2%) were randomized to CA. Compared with medical therapy, CA was associated with a significant reduction in heart failure (HF) hospitalization (RR 0.57; 95% CI 0.45-0.72; p<0.01), cardiovascular mortality (RR 0.46; 95% CI 0.31-0.70; p<0.01), all-cause mortality (RR 0.53; 95% CI 0.36-0.78; p<0.01), and AF burden (MD –29.8%; 95% CI –43.73,–15.90; p<0.01). Also, there was a significant improvement in LVEF (MD 3.8%; 95% CI 1.6,6.0; p<0.01) and quality of life (Minnesota living with HF questionnaire; MD –4.92 points; 95% CI –8.61,–1.22; p<0.01) in the ablation group. Conclusion: In this meta-analysis of RCTs of patients with AF and HFrEF, CA was associated with a reduction in HF hospitalization and cardiovascular and all-cause mortality, as well as a significant improvement of LVEF and quality of life.

Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction patients: A meta-analysis

Eric Pasqualotto[a*], Caique M P Ternes, MD[b*], Matheus Pedrotti Chavez[a], Carisi A Polanczyk, MD, ScD[b,c], Rafael Oliva Morgado Ferreira[a], Thiago Nienkötter[d], Gustavo de Oliveira Almeida[e], Edmundo Bertoli[d], Mariana Clemente[f], Andre d'Avila, MD, ScD[g], Luis E Rohde, MD, ScD[b,c]

[a] Division of Medicine, Universidade Federal de Santa Catarina, Florianópolis-SC, Brazil
[b]Postgraduate Program in Cardiology and Cardiovascular Sciences, Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre-RS, Brazil.
[c] Division of Cardiology, Hospital Moinhos de Vento, Porto Alegre-RS, Brazil.
[d] Division of Medicine, Universidade do Sul de Santa Catarina, Palhoça-SC, Brazil.
[e] Division of Medicine, Universidade Federal do Triângulo Mineiro, Uberaba-MG, Brazil.
[f] Division of Medicine, Arthur Sá Earp Neto Medical School, Petrópolis-RJ, Brazil.
[g] Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston-MA, EUA.

* Both authors contributed equally for this study

Running title: Catheter ablation for AF in HFrEF patients

Corresponding author
Name: Luis Eduardo Rohde
Address: Hospital de Clinicas de Porto Alegre - Ramiro Barcelos, 2350. CEP 90000-000, Porto Alegre, RS - Brasil
E-mail address:
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Tweet: In a meta-analysis by Pasqualotto et al, catheter ablation was associated with a reduction in heart failure hospitalization and cardiovascular and all-cause mortality in patients with atrial fibrillation and heart failure with reduced ejection fraction. #ACCIntl #CVD #HeartFailure

ABSTRACT

Background: The optimal treatment for atrial fibrillation (AF) in patients with heart failure with reduced ejection fraction (HFrEF) remains unsettled.

Objectives: To assess the efficacy of catheter ablation (CA) and medical therapy compared to medical therapy alone in patients with AF and HFrEF.

Methods: We performed a systematic review of randomized controlled trials (RCTs) comparing CA versus guideline-directed medical therapy for AF in patients with HFrEF (left ventricular ejection fraction (LVEF) ≤40%). We systematically searched PubMed, Embase, and Cochrane for eligible trials. A random-effects model was used to calculate the risk ratios (RRs) and mean differences (MDs), with 95% confidence intervals (CIs).

Results: Six RCTs comprising 1,055 patients were included, of whom 530 (50.2%) were randomized to CA. Compared with medical therapy, CA was associated with a significant reduction in heart failure (HF) hospitalization (RR 0.57; 95% CI 0.45-0.72; $p<0.01$), cardiovascular mortality (RR 0.46; 95%CI 0.31-0.70; $p<0.01$), all-cause mortality (RR 0.53; 95% CI 0.36-0.78; $p<0.01$), and AF burden (MD –29.8%; 95% CI –43.73,–15.90; $p<0.01$). Also, there was a significant improvement in LVEF (MD 3.8%; 95% CI 1.6-6.0; $p<0.01$) and quality of life (Minnesota living with HF questionnaire; MD –4.92 points; 95%CI –8.61,–1.22; $p<0.01$) in the ablation group.

Conclusion: In this meta-analysis of RCTs of patients with AF and HFrEF, CA was associated with a reduction in HF hospitalization and cardiovascular and all-cause mortality, as well as a significant improvement of LVEF and quality of life.

Key words: Catheter ablation, Heart failure, Atrial fibrillation, Heart failure hospitalization, Cardiovascular mortality, All-cause mortality.

ABBREVIATIONS

AF=atrial fibrillation

AMICA=Atrial Fibrillation Management in Congestive Heart Failure With Ablation
CA=catheter ablation

CASTLE-AF=Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation

CASTLE-HTx=Catheter Ablation for Atrial Fibrillation in Patients with End-Stage Heart Failure and Eligibility for Heart Transplantation

CI=confidence interval

GRADE=Grading of Recommendation, Assessment, Development, and Evaluation

HF=heart failure

HFrEF=heart failure reduced ejection fraction

LV=left ventricular

LVEF=left ventricular ejection fraction

MD=mean difference

MLHFQ=Minnesota Living with Heart Failure Questionnaire

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO=International Prospective Register of Systematic Reviews

QoL=quality of life

RCT=randomized controlled trial

Rob-2=Cochrane Collaboration tool for assessing risk of bias in randomized trials

RR=risk ratio

TSA=trial sequential analysis

TSMB=trial sequential monitoring boundaries

6-MWT=6-minute walk test

1. INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) often coexist and are closely connected by their pathophysiology, with each condition mutually aggravating the progression of the other.[1] Both entities are main contributors to the economic burden through healthcare costs and have a substantial impact on patients' morbidity and mortality.[2]

Management of patients with concomitant AF and HF with left ventricular (LV) systolic dysfunction is challenging. In this scenario, rhythm control has been an elusive treatment target until the advent of contemporary ablation techniques. Catheter ablation (CA) in HF with reduced ejection fraction (HFrEF) patients has shown improvements in quality of life (QoL), left ventricular ejection fraction (LVEF), and functional capacity in isolated randomized controlled trials (RCTs).[3–6] This prompted international clinical practice guidelines to consider CA as a potentially recommended approach for selected patients with concomitant AF and HFrEF, although there is substantial uncertainty which subset of patients would get the best benefit.[7,8]

The recent CASTLE-HTx (Catheter Ablation for Atrial Fibrillation in Patients with End-Stage Heart Failure and Eligibility for Heart Transplantation) trial presented extended and robust benefits of adding CA to guideline-directed medical therapy.[9] Therefore, this systematic review and meta-analysis of RCTs along with a trial sequential analysis (TSA), aimed to assess the efficacy of CA and medical therapy compared to medical therapy alone in patients with AF and HFrEF.

2. METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[10] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023462252.[11]

2.1 Search strategy and data extraction

PubMed, Embase, and Cochrane Library were systematically searched from inception to September 05, 2023, with the following search terms: "catheter ablation", "atrial fibrillation", "heart failure", "medical therapy", "medical treatment", and “treatment”. The references from all included studies, previous systematic reviews, and meta-analyses were also searched manually for any additional studies. Two authors (E.B. and T.N.) independently extracted baseline characteristics and data outcomes following predefined search criteria. Disagreements were resolved by consensus among three authors (E.P., M.P.C., and L.R.).

2.2 Eligibility criteria

Studies with the following criteria were included: (1) RCTs; (2) comparing CA with medical therapy; (3) enrolling patients with AF and HFrEF; and (4) reporting at least one outcome of interest. We excluded: (1) non-RCTs; and (2) overlapping populations.

2.3 Endpoints and Subgroup Analysis

The main outcome of interest was HF hospitalization. Other analyzed outcomes were: (1) LVEF change, (2) 6-minute walk test (6-MWT) distance, (3) AF burden, (4) QoL, (5)

cerebrovascular accident, (6) cardiovascular mortality, (7) all-cause mortality, and (8) severe adverse events. QoL was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Two pre-defined subgroup analyses were performed with (1) patients with LVEF ≤35%, and (2) patients with persistent AF.

2.4 Risk of bias and quality assessment

The Cochrane Collaboration tool for assessing risk of bias in randomized trials (Rob-2) was used to assess the quality of individual RCTs.[12] Each trial received a high, low, or unclear risk of bias score in five domains: randomization process; deviations from the intended interventions; missing outcomes; measurement of the outcome; and selection of reported results. Two independent authors conducted the risk of bias assessment (E.P. and T. N.), and disagreements were resolved unanimously with the senior author (L.R.). In addition, potential publication bias was judged by visual inspection of contour-enhanced funnel plots.[13]

Quality of evidence was assessed according to the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines.[14,15] Very low, low, moderate, or high-quality evidence grades were designed for the outcomes based on the risk of bias, inconsistency of results, imprecision, publication bias, and magnitude of treatment effects.

2.5 Statistical analysis

The treatment effects for continuous outcomes were compared using mean differences (MDs), and binary endpoints were evaluated using risk ratios (RRs), with 95% confidence intervals (CIs). Heterogeneity was assessed with the Cochrane Q-test and I^2 statistics; P values >0.10 and I^2 values >25% were considered significant for heterogeneity.[16] DerSimonian and Laird random-effects models were used for all endpoints.[17] Cochrane Handbook for Systematic Reviews of Interventions

was used for data handling and conversion.[18] Statistical analyses were performed using R statistical software, version 4.2.3 (R Foundation for Statistical Computing) and the Trial Sequential Analysis software, version 0.9.5.10, for statistical analysis.[19]

2.6 Sensitivity analysis

"Leave-one-out procedures" were used to identify influential studies and their effect on the pooled estimates, evaluating heterogeneity. This procedure was carried out by removing data from one study and reanalyzing the remaining data. When pooled effect size p-values changed from significant to non-significant, or vice-versa, study dominance was assigned. In addition, we performed a meta-regression analysis for LVEF change, all-cause mortality, and cardiovascular mortality outcomes to assess any interaction with the proportion of patients with ischemic cardiomyopathy.

2.7 Trial sequential analysis

A TSA was conducted on the included studies to assess whether the cumulative evidence had sufficient statistical power in the main outcomes. Our statistical plan involved two-sided testing with a type I error of 5% and a type II error of 20%. Both conventional and trial sequential monitoring boundaries (TSMBs) were generated for the CA and medical therapy groups. A heterogeneity correction was applied in the TSA using the variance-based approach and random effects model.[19] A z-score curve was generated to assess the confidence and adequacy of evidence. Additionally, an analysis to determine the required number of patients in a meta-analysis was performed to either accept or reject the intervention. By definition, a TSA analysis provides firm evidence when the patient sample size exceeds the necessary for achieving a definitive conclusion, or when z-curves cross the TSMBs before attaining the essential patient count for conclusive evidence.

3. RESULTS

3.1 Study selection and characteristics

The initial search yielded 3,099 results, as detailed in Figure 1. After removing duplicate records and assessing the studies based on title and abstract, 13 full text remained and were thoroughly reviewed according to inclusion and exclusion criteria. Of these, six RCTs comprising 1,055 patients were included.[4,9,20–23] 530 (50.2%) patients were randomized to CA. The mean age was 63.4 years and 77.9% were male. The mean AF duration ranged from 8.6 to 51 months. Study and participant characteristics are summarized in Table 1.

3.2 Pooled analysis of all studies

HF hospitalization was significantly reduced in the CA group compared to medical therapy (RR 0.57; 95% CI 0.45-0.72; p<0.01; I^2=0%; Fig. 2A). We also observed a significant reduction in cardiovascular mortality (RR 0.46; 95% CI 0.31-0.70; p<0.01; I^2=0%; Fig. 2B), and all-cause mortality (RR 0.53; 95% CI 0.36-0.78; p<0.01; I^2=13%; Fig. 2C) in the CA group. There was no significant difference between groups in cerebrovascular accident rates (RR 0.57; 95% CI 0.19-1.66; p=0.30; I^2=4%; Fig. 3A) and severe adverse events (RR 1.10; 95% CI 0.94-1.27; p=0.23; I^2=16%; Fig. 3B).

There was a significant increase in LVEF after AF CA (MD 3.82%; 95% CI 1.64-6.01; p<0.01; I^2=70%; Fig. 3C) and a significant reduction in AF burden (MD -29.82%; 95% CI -43.73,-15.90; p<0.01; I^2=80%; Fig. 4A) when compared to medical therapy. In addition, QoL assessed by the MLHFQ improved (MD -4.92 points; 95% CI -8.61,-1.22; p<0.01; I^2=14%; Fig. 4B) with CA. There was no significant difference between groups in functional capacity assessed by 6-WMT (MD 12.57 meters; 95% CI -7.43,32.56; p=0.22; I^2=73%; Fig. 4C).

3.3 Subgroup analysis

In the subgroup analysis of patients with LVEF ≤ 35%, benefit of CA was maintained for most outcomes analyzed, such as HF hospitalization (RR 0.59; 95% CI 0.42-0.83; p<0.01; I^2=0%; Supplementary Material 1, Fig. S1B), cardiovascular mortality (RR 0.46; 95% CI 0.31-0.70; p<0.01; I^2=0%; Fig. 2B), all-cause mortality (RR 0.57; 95% CI 0.34-0.96; p=0.04; I^2=31%; Supplementary Material 1, Fig. S1C), LVEF (MD 4.80%; 95% CI 2.92-6.67; p<0.01; I^2=29%; Supplementary Material 1, Fig. S1A), and AF burden (MD -29.82%; 95% CI -43.73,15.90; p<0.01; I^2=80%; Fig. 4A). There was no significant difference between groups in 6-MWT distance (MD 10.42 meters; 95% CI -24.90,45.74; p=0.56; I^2=76%; Supplementary Material 1, Fig. S2A), QoL (MD -5.44 points; 95% CI -11.99,1.10; p=0.10; I^2=42%; Supplementary Material 1, Fig. S2B), cerebrovascular accident rates (RR 0.57; 95% CI 0.19-1.66; p=0.30; I^2=4%; Fig. 3A), and severe adverse events (RR 1.07; 95% CI 0.98-1.17; p=0.14; I^2=0%; Supplementary Material 1, Fig. S2C).

In the subgroup analysis of patients with persistent AF, we observed a statistically significant reduction in HF hospitalization (RR 0.56; 95% CI 0.40-0.77; p<0.01; I^2=0%; Supplementary Material 1, Fig. S3A) and improvement in QoL (MD -4.92 points; 95% CI -8.61,-1.22; p<0.01; I^2=14%; Fig. 4C). There was no significant difference between groups in all other analyzed outcomes (LVEF: MD 4.44%; 95% CI -0.83,9.71; p=0.10; I^2=96%; Supplementary Material 1, Fig. S3B; 6-MWT: MD 3.97 meters; 95% CI -22.95,30.88; p=0.77; I^2=60%; Supplementary Material 1, Fig. S3C; cardiovascular mortality: RR 0.68; 95% CI 0.19-2.49; p=0.56; I^2=3%; Supplementary Material 1, Fig. S4A; all-cause mortality: RR 0.70; 95% CI 0.33-1.50; p=0.36; I^2=27%; Supplementary Material 1, Fig. S4B; and severe adverse events: RR 1.39; 95% CI 0.75-2.56; p=0.29; I^2=8%; Supplementary Material 1, Fig. S4C).

3.4 Sensitivity analysis

We performed a leave-one-out sensitivity analysis for all endpoints. There was a significant improvement in functional capacity assessed by the 6-MWT with the removal of the AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) trial.[21] Change in the QoL lost statistical significance between groups when omitting the AATAC (Ablation vs. Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device) trial.[20] All-cause mortality also lost significance between groups when excluding the CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial.[23] For all other outcomes, there were no major changes in significance with the removal of each individual study. The leave-one-out analysis is shown for the endpoint of HF hospitalization in Supplementary Material 1, Fig. S5.

3.5 Metaregression

The benefit of CA in LVEF change was attenuated in patients with ischemic cardiomyopathy when compared with medical therapy (p=0.02; Supplementary Material 1, Fig. S6). There were no significant interactions between ischemic cardiomyopathy and all-cause mortality (p=0.33; Supplementary Material 1, Fig. S7), and cardiovascular mortality (p=0.65; Supplementary Material 1, Fig. S8).

3.6 Risk of bias and quality assessment

Fig. 5A outlines individual assessment of each RCT included in the meta-analysis. Five studies were classified as having a low risk of bias.[4,9,20–22] Meanwhile, one RCT was classified as having some concerns of risk of bias due to deviations from intended interventions, in which a considerable percentage of patients from the medical therapy group crossed over to CA.[23] As shown

in Figure 5B, funnel plots presented a symmetrical distribution of similar weight studies, indicating no evidence of publication bias.

According to the GRADE assessment, two outcomes evaluated in this study were classified as high-quality evidence: cardiovascular mortality and QoL. Two outcomes had moderate quality of evidence: HF hospitalization and all-cause mortality. Three outcomes were classified as having low-quality evidence: LVEF, 6-MWT, and AF burden. The main domains responsible for reducing the quality of evidence of the outcomes were: risk of bias and inconsistency. Quality assessment is detailed in Supplementary Material 2.

3.7 Trial sequential analysis

TSA showed that enough evidence exists for the benefit of CA over medical therapy regarding improvement in LVEF, QoL, reduction of HF hospitalization, cardiovascular mortality and all-cause mortality. However, TSA demonstrated that there is not enough evidence for the outcome of functional capacity assessed by the 6-MWT. The trial sequential graphs are detailed in Supplementary Material 1, Fig. S9, S10, S11, S12, S13, and S14.

4. DISCUSSION

In this systematic review and meta-analysis of 6 RCTs including 1,055 patients, we compared data on CA and medical therapy to medical therapy alone for AF in patients with HFrEF. Our main findings demonstrate a consistent benefit of adding AF CA to guideline directed medical therapy in reducing HF hospitalization, cardiovascular mortality and all-cause mortality, and significantly improving LVEF and scores of HF-related QoL. Our finding remained mostly unaltered in patients with severe LV dysfunction (LVEF < 35%), although the benefits were attenuated in subjects with

persistent AF. Overall, these results strengthen the recommendation of adopting and earlier and more aggressive approach when facing patients with concomitant AF and HFrEF.

Previous meta-analyses have evaluated AF ablation in individuals with HF and showed a significant improvement in mortality and HF-related hospitalizations.[1,24,25] Nevertheless, a high proportion of patients in this analyses pertained to studies that assessed HF individuals with both preserved and reduced ejection fraction. These subgroups have shown significant differences after AF ablation, and the included trials exhibited conflicting outcomes in the HFrEF population.[1,24–27] Our study adds considerably to this topic providing pooled data of RCTs demonstrating the clinical benefit of AF ablation in HFrEF.

Currently, three long-term follow-up RCTs have shown the value of CA compared to medical therapy for AF in patients with HFrEF.[9,20,23] The AATAC trial showed a reduction in unplanned hospitalizations and all-cause mortality, with a 56% decrease in the relative risk of mortality in patients receiving CA.[20] In the CASTLE-AF trial, the composite outcome of death or hospitalization for worsening HF was significantly reduced in the ablation group compared with medical therapy.[23] Finally, the CASTLE-HTx trial included patients with end-stage HF and showed that the combination of CA and guideline-directed medical therapy reduced the incidence of a composite outcome of all-cause mortality, implantation of a LV assist device, or urgent heart transplantation, compared with medical therapy alone.[9] However, studies with follow-up limited to 12 months did not demonstrate a statistically significant change in LVEF change between groups.[4,21,22] It is reasonable to infer from these results that a longer follow-up duration might be necessary to discern the clinical benefits of CA in clinical studies.

CA has been associated with improved and sustained echocardiographic outcomes, LVEF change, functional capacity, and rhythm control. Our findings showed no significant difference between groups in cerebrovascular accidents, although the individual studies were underpowered for

this outcome. In our study, significant effects favoring CA for improvement in LVEF, reduction of cardiovascular mortality, and all-cause mortality were corroborated by the TSA findings, as the z–curves crossed the TSMBs or the number of patients estimated to fulfill the information was successfully obtained.

Adequate selection and implementation of AF CA for potentially eligible patients with HFrEF will be challenging, as ablation techniques and operator skills are not necessarily homogeneous in all settings. HF and arrhythmia specialists will have to work together to identify the precise moment to intervene to ensure efficacy and safety, considering factors as AF duration, left atrium and ventricular remodeling, and local expertise. Cost-utility analysis might help to define the best profile of patients that could benefit from AF ablation while keeping system sustainability and equitable choices.

This study must be interpreted considering its limitations. First, the CASTLE-AF and AMICA trials had significant post-randomization follow-up patient lost. Second, the AMICA trial was terminated early due to apparent futility by the Steering Committee and Data Safety Monitoring Board. However, we performed sensitivity analysis to assess the influence of these trials on our findings. Third, all included trials were not double-blinded by design and we cannot exclude the possibility that different or more aggressive approaches in certain situations could have influenced our results. This seems unlikely because our main results showed low heterogeneity. Fourth, the trials had slightly different inclusion criteria for AF duration. We performed a subgroup analysis to specifically evaluate patients with persistent AF.

5. CONCLUSIONS

In conclusion, our meta-analysis of RCTs of patients with concomitant AF and HFrEF indicates CA was associated with a reduction in HF hospitalizations and overall mortality, as well as improved LVEF and HF-related QoL. These results reinforce the recommendation of CA as first-line management strategy for patients affected by these two morbid conditions.

6. CLINICAL PERSPECTIVES

- Catheter ablation was associated with a reduction in heart failure hospitalization and cardiovascular and all-cause mortality in patients with atrial fibrillation and heart failure with reduced ejection fraction.
- Catheter ablation was associated with an improvement in left ventricular eject fraction and quality of life in patients with atrial fibrillation and heart failure with reduced ejection fraction.
- The results of this meta-analysis reinforce the recommendation of catheter ablation as first-line management strategy for patients with atrial fibrillation and heart failure with reduced ejection fraction.

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FIGURES

Figure 1. PRISMA Flow Diagram of Study Screening and Selection

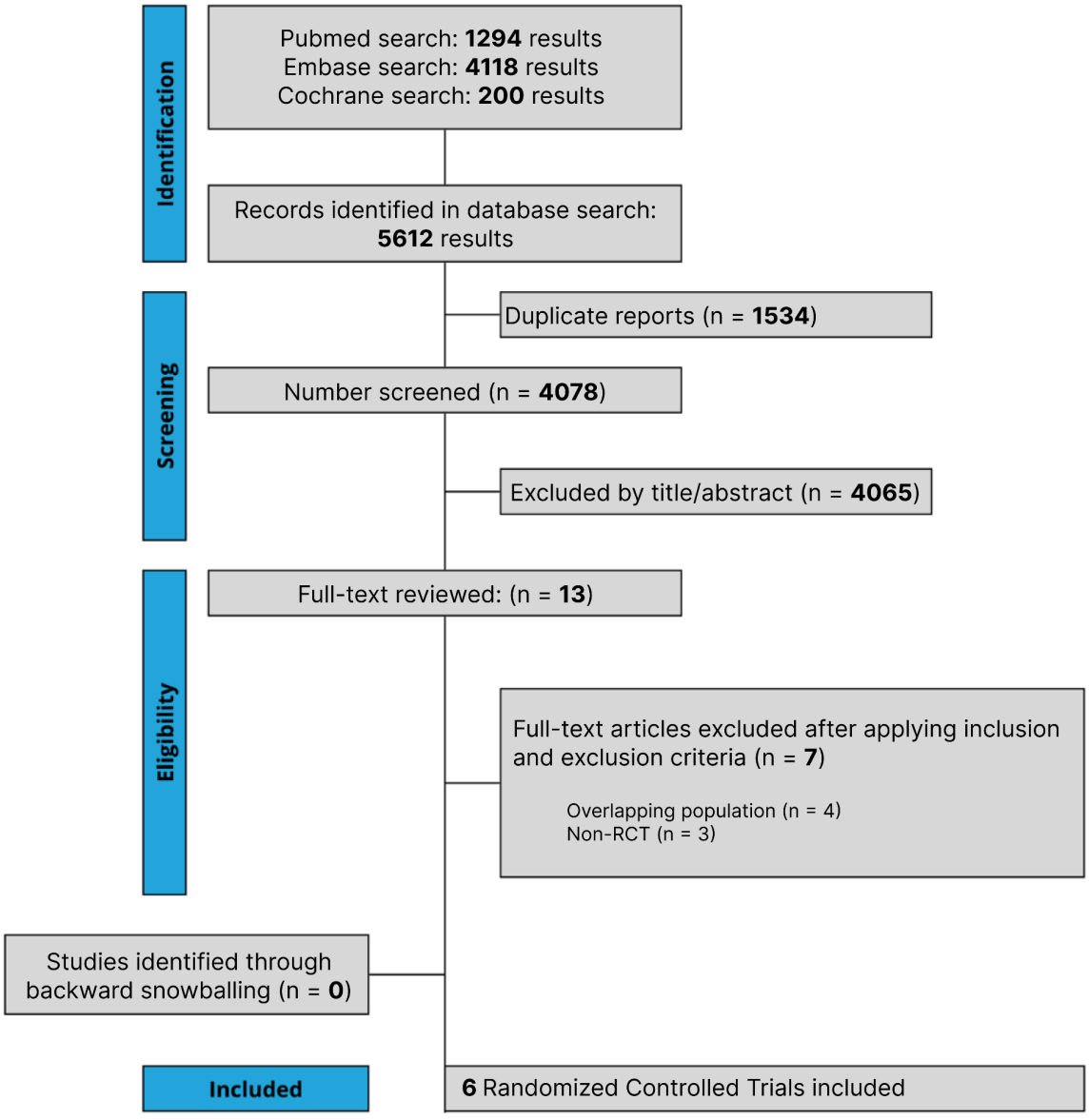
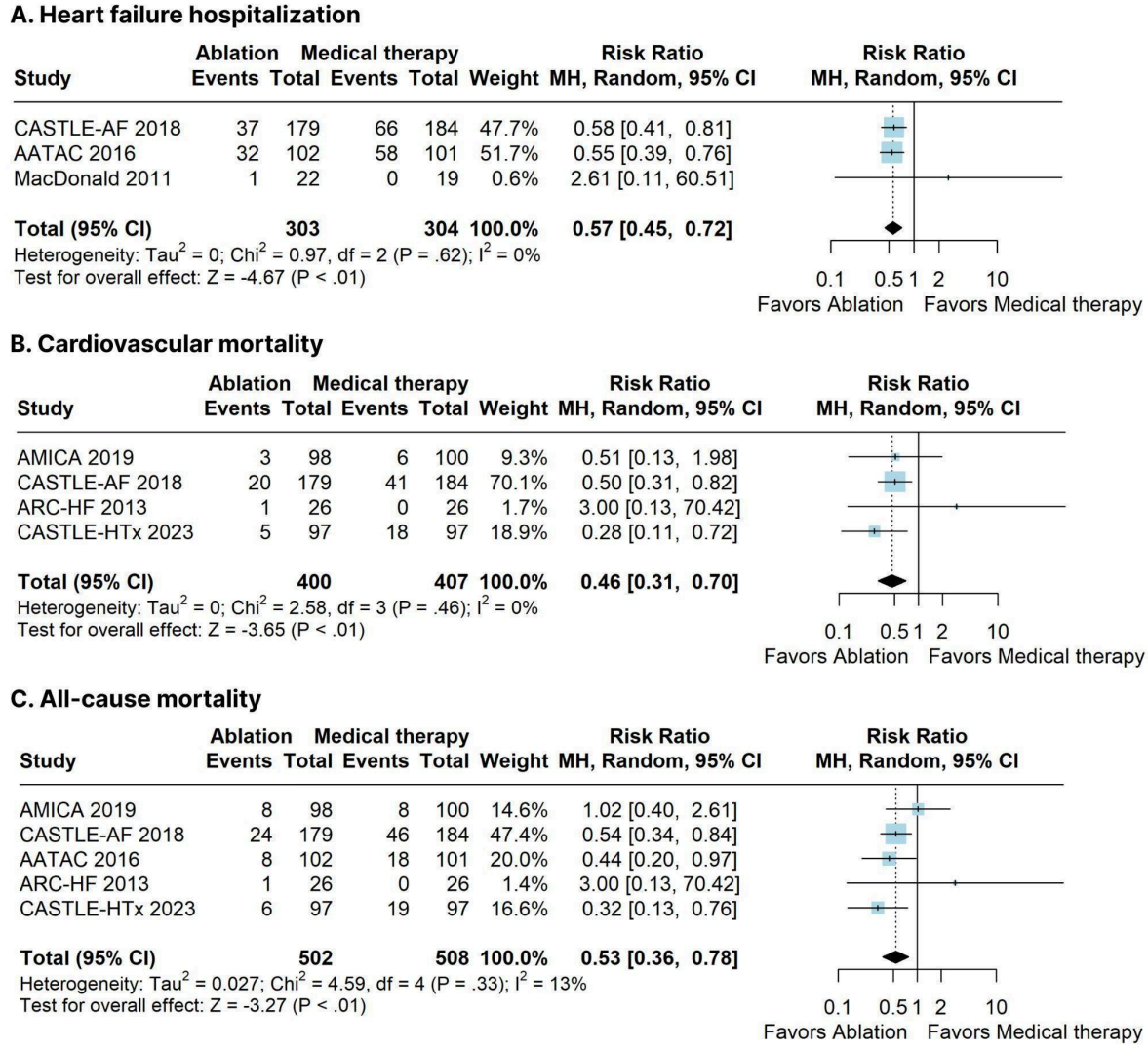
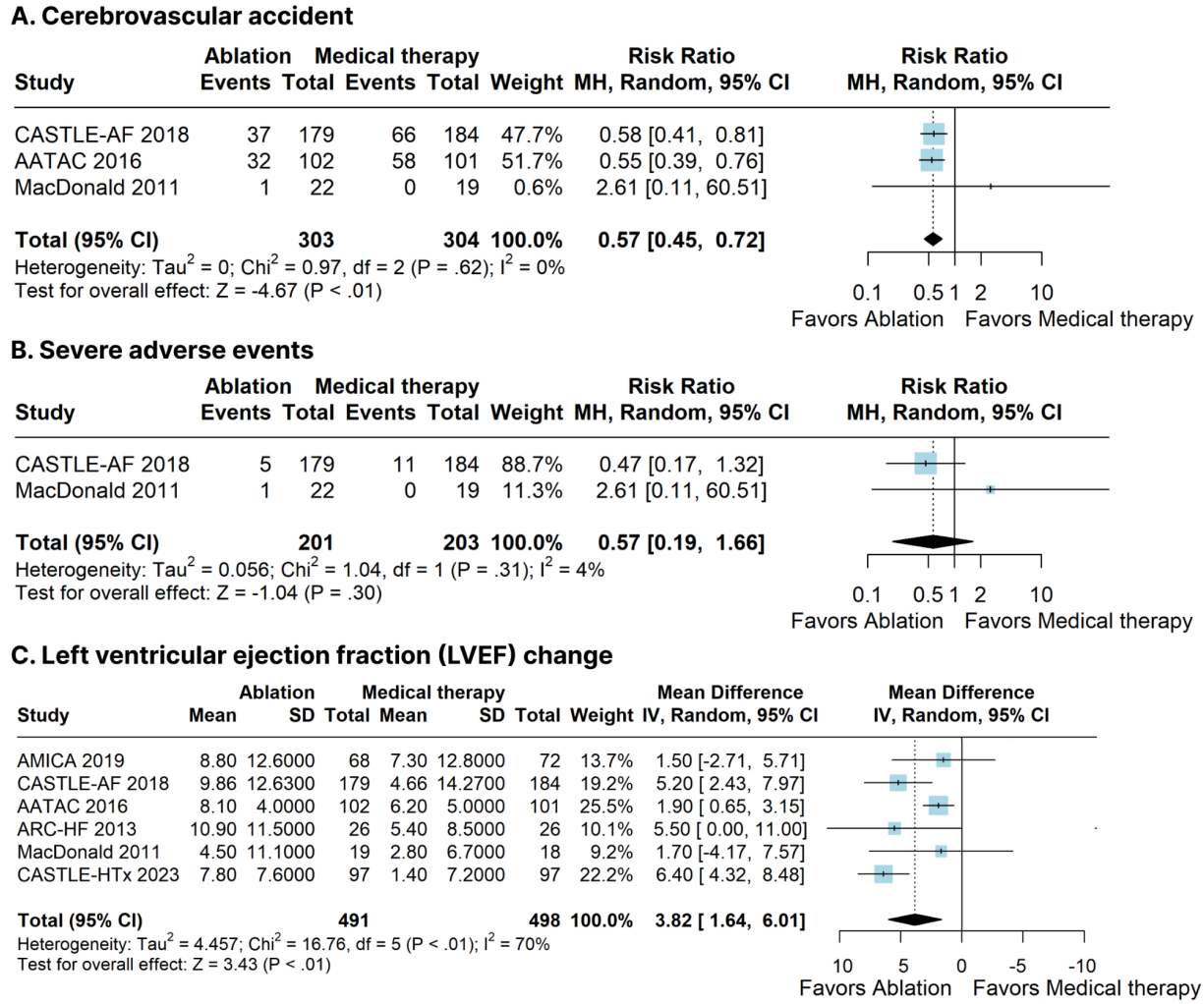


Figure 2. Forest plots of comparison between catheter ablation and medical therapy



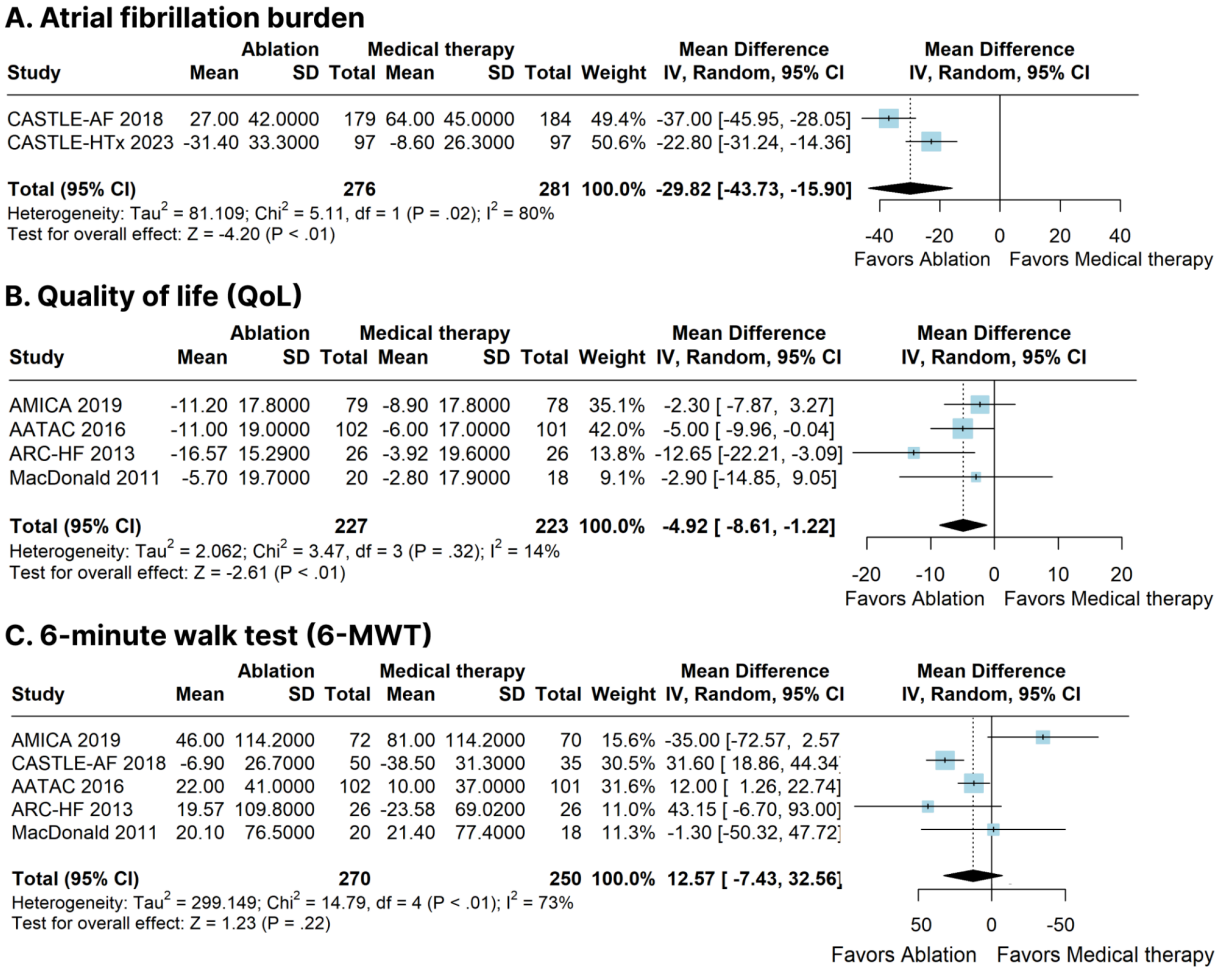
Forest plots of comparison between catheter ablation and medical therapy for atrial fibrillation in patients with heart failure with reduced ejection fraction. **A.** Heart failure hospitalization. **B.** Cardiovascular mortality. **C.** All-cause mortality.

Figure 3. Forest plots of comparison between catheter ablation and medical therapy



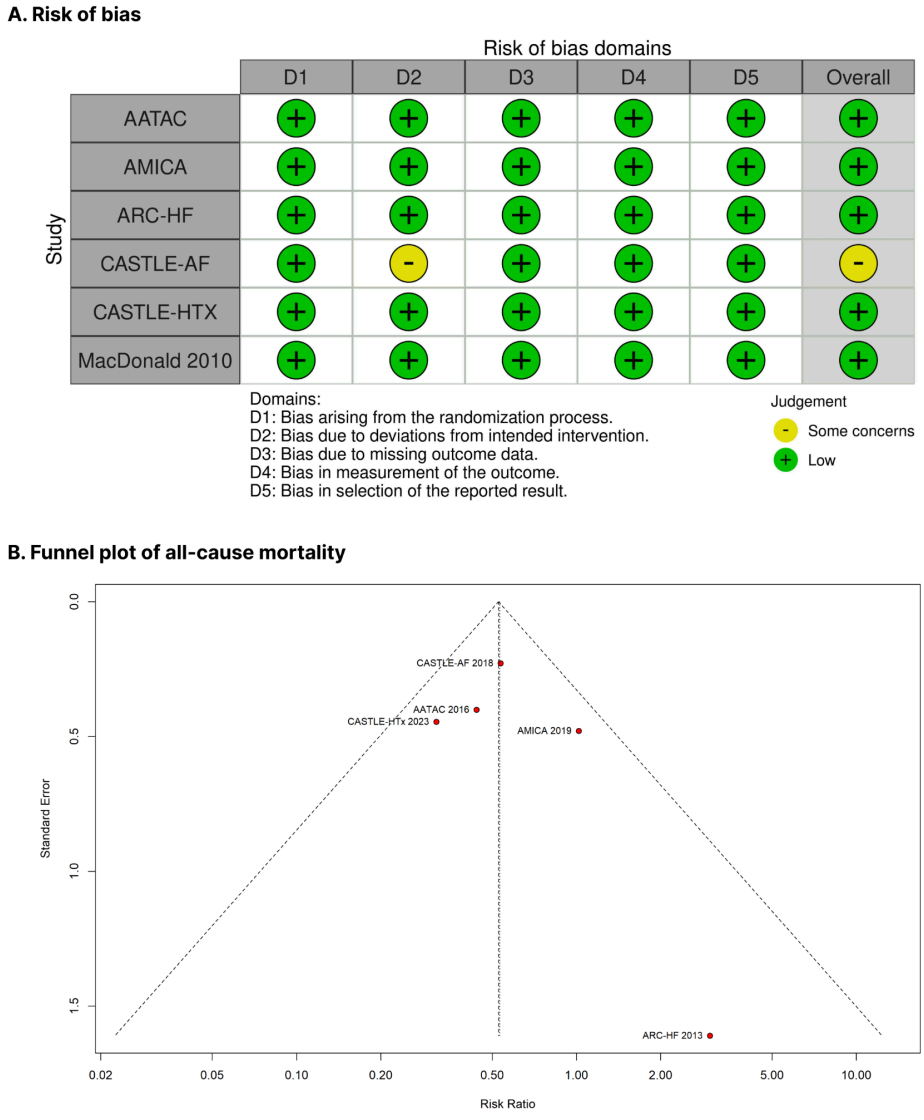
Forest plots of comparison between catheter ablation and medical therapy for atrial fibrillation in patients with heart failure with reduced ejection fraction. **A.** Cerebrovascular accident. **B.** Severe adverse events. **C.** Left ventricular ejection fraction (LVEF) change.

Figure 4. Forest plots of comparison between catheter ablation and medical therapy



Forest plots of comparison between catheter ablation and medical therapy for atrial fibrillation in patients with heart failure with reduced ejection fraction. **A.** Atrial fibrillation burden. **B.** Quality of life (QoL). **C.** 6-minute walk test (6-MWT).

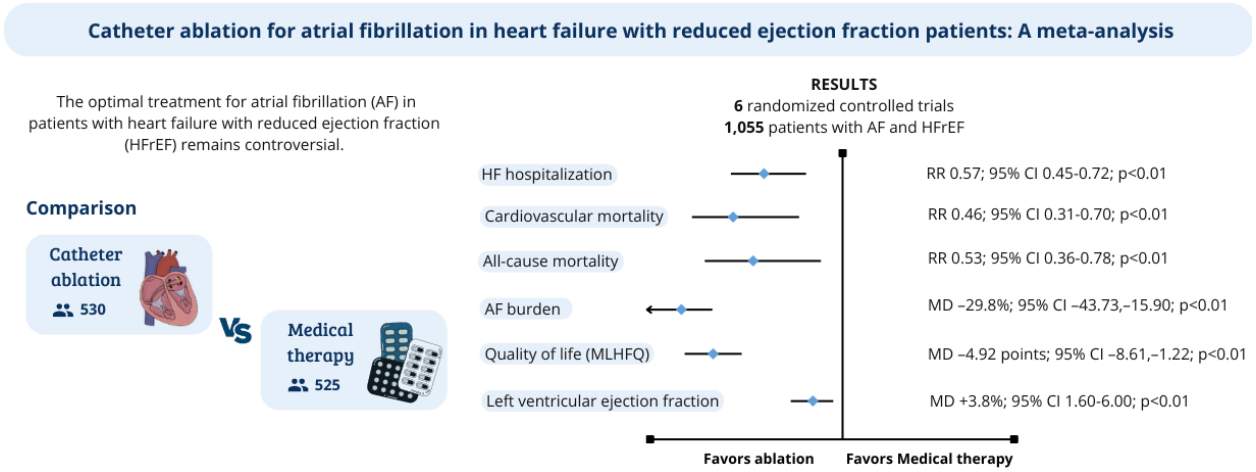
Figure 5. Risk of bias and publication bias assessment



A. Critical appraisal of randomized controlled trials according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. **B.** Funnel plot analysis of the all-cause mortality shows no evidence of publication bias.

CENTRAL ILLUSTRATION

Catheter ablation for AF in HFrEF patients



AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MD, mean difference; MLHFQ, Minnesota Living with Heart Failure Questionnaire; RR, risk ratio.

TABLES

Table 1. Design and Characteristics of Studies Included in the Meta-analysis

Study	Follow-up (months)	Characteristics	Intervention	Sample size, n CA/MT	Age, years CA/MT	Male, n CA/MT	LVEF, % CA/MT	AF duration, mo or yr CA/MT	AF persistent, n (%) CA/MT	Ischemic cardiomyopathy, n (%) CA/MT	6-MWT, meters CA/MT	N-terminal pro-BNP level, pg/mL CA/MT
MacDonald 2011	6 months	LVEF ≤35%	PVI + linear ablation + CFAEs	22/19	62.3 (6.7)/ 64.4 (8.3)	17/15	36.1 (11.9)/ 42.9 (9.6)	44 (36.5)/ 64 (47.6) mo	22 (100)/ 19 (100)	NA/NA	317.5 (125.8)/ 351.8 (117.1)	2550 (2150)/ 1846 (1687)
ARC-HF 2013	12 months	LVEF ≤35%	PVI + linear ablation + CFAEs	26/26	64 (10)/ 62 (9)	21/24	NA/NA	51 (39)/ 51 (76) mo	26 (100)/ 26 (100)	7 (27)/ 10 (38)	416 (78)/ 411 (109)	412 (324)/ 283 (285)
AATAC 2016	24 months	LVEF <40%	PVI + PWI + linear ablation + CFAEs	102/101	62 (10)/ 60 (11)	77/74	29 (5)/ 30 (8)	8.6 (3.2)/ 8.4 (4.1) mo	102 (100)/ 101 (100)	NA/NA	348 (111)/ 350 (130)	NA/NA
CASTLE-AF 2018	60 months	LVEF ≤35%	PVI + optional additional lesions	179/184	64.0 (2.8)/ 64.1 (3.2)	156/155	32.5 (25.0-38.0)/ 31.5 (27.0-37.0)	NA/NA	125 (70)/ 120 (65)	72 (40)/ 96 (52)	NA/NA	NA/NA
AMICA 2019[a]	12 months	LVEF ≤35%	PVI + linear ablation + CFAEs	68/72	65 (8)/ 65 (8)	60/66	27.8 (9.5)/ 24.8 (8.8)	NA/NA	104 (100)/ 98 (100)	30 (44)/ 40 (56)	NA/NA	NA/NA
CASTLE-HTx 2023	18 months	LVEF ≤35%	PVI + optional additional lesions	97/97	62 (12)/ 65 (10)	85/72	29 (6)/ 25 (6)	4 (5)/ 3 (4) yr	54 (56) / 54 (56)	37 (38)/ 39 (40)	308 (69)/ 299 (66)	3852 (3261)/ 4461 (5191)

Data are presented as mean (SD) or median (IQR). [a]104 patients were randomized to catheter ablation and 98 to best medical therapy, however, only 140 patients were evaluated for the primary outcome at the 1-year follow-up. AATAC, ablation vs. amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device; AF, atrial fibrillation; ARC-HF, a randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure; AMICA, atrial fibrillation management in congestive heart failure with ablation; CASTLE-AF, catheter ablation versus standard conventional therapy in patients with left ventricular dysfunction and atrial fibrillation; CASTLE-HTx, catheter ablation for atrial fibrillation in patients with end-stage heart failure and eligibility for heart transplantation; BNP, B-natriuretic peptide; CA, catheter ablation group; CFAE, complex fractionated atrial electrogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; MT, medical therapy group; NA, not available; PVI, pulmonary vein isolation; PWI, posterior wall isolation; SD, standard deviation; 6-MWT, 6-minute walk test.

SUPPLEMENTARY MATERIAL (A)

Figure S1. Forest plots of comparison between catheter ablation and medical therapy for atrial fibrillation in patients with left ventricular ejection fraction ≤35%. **A.** Left ventricular ejection fraction (LVEF) change. **B.** Heart failure hospitalization. **C.** All-cause mortality.

Figure S2. Forest plots of comparison between catheter ablation and medical therapy for atrial fibrillation in patients with left ventricular ejection fraction ≤35%. **A.** 6-minute walk test (6-MWT). **B.** Quality of life (QoL). **C.** Severe adverse events.

Figure S3. Forest plots of comparison between catheter ablation and medical therapy in patients with persistent atrial fibrillation. **A.** Heart failure hospitalization. **B.** Left ventricular ejection fraction (LVEF) change. **C.** 6-minute walk test (6-MWT).

Figure S4. Forest plots of comparison between catheter ablation and medical therapy in patients with persistent atrial fibrillation. **A.** Cardiovascular mortality. **B.** All-cause mortality. **C.** Severe adverse events.

Figure S5. Leave-one-out sensitivity analyses of heart failure hospitalization outcome.

Figure S6. Meta-regression assessing the impact of proportion of patients with ischemic cardiomyopathy on left ventricular ejection fraction (LVEF) change.

Figure S7. Meta-regression assessing the impact of proportion of patients with ischemic cardiomyopathy on all-cause mortality.

Figure S8. Meta-regression assessing the impact of proportion of patients with ischemic cardiomyopathy on cardiovascular mortality.

Figure S9. Trial sequential analysis for left ventricular ejection fraction (LVEF) change**.**

Figure S10. Trial sequential analysis for cardiovascular mortality.

Figure S11. Trial sequential analysis for all-cause mortality.

Figure S12. Trial sequential analysis for heart failure hospitalization.

Figure S13. Trial sequential analysis for quality of life.

Figure S14. Trial sequential analysis for 6-minute walk test distance.

Figure S1. Forest plots of comparison between catheter ablation and medical therapy for atrial fibrillation in patients with left ventricular ejection fraction ≤35%. **A.** Left ventricular ejection fraction (LVEF) change. **B.** Heart failure hospitalization. **C.** All-cause mortality.

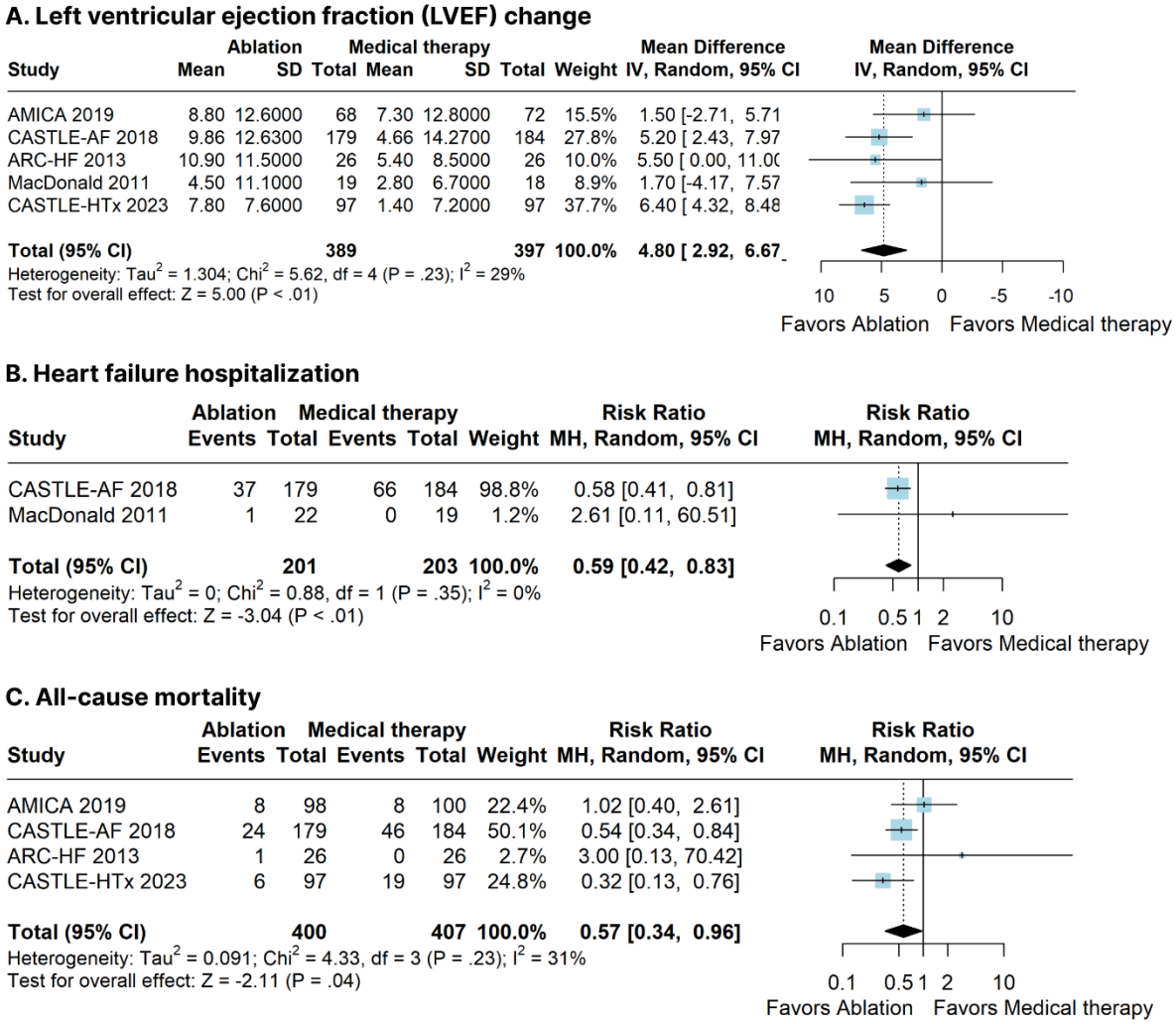


Figure S2. Forest plots of comparison between catheter ablation and medical therapy for atrial fibrillation in patients with left ventricular ejection fraction ≤35%. **A.** 6-minute walk test (6-MWT). **B.** Quality of life (QoL). **C.** Severe adverse events.

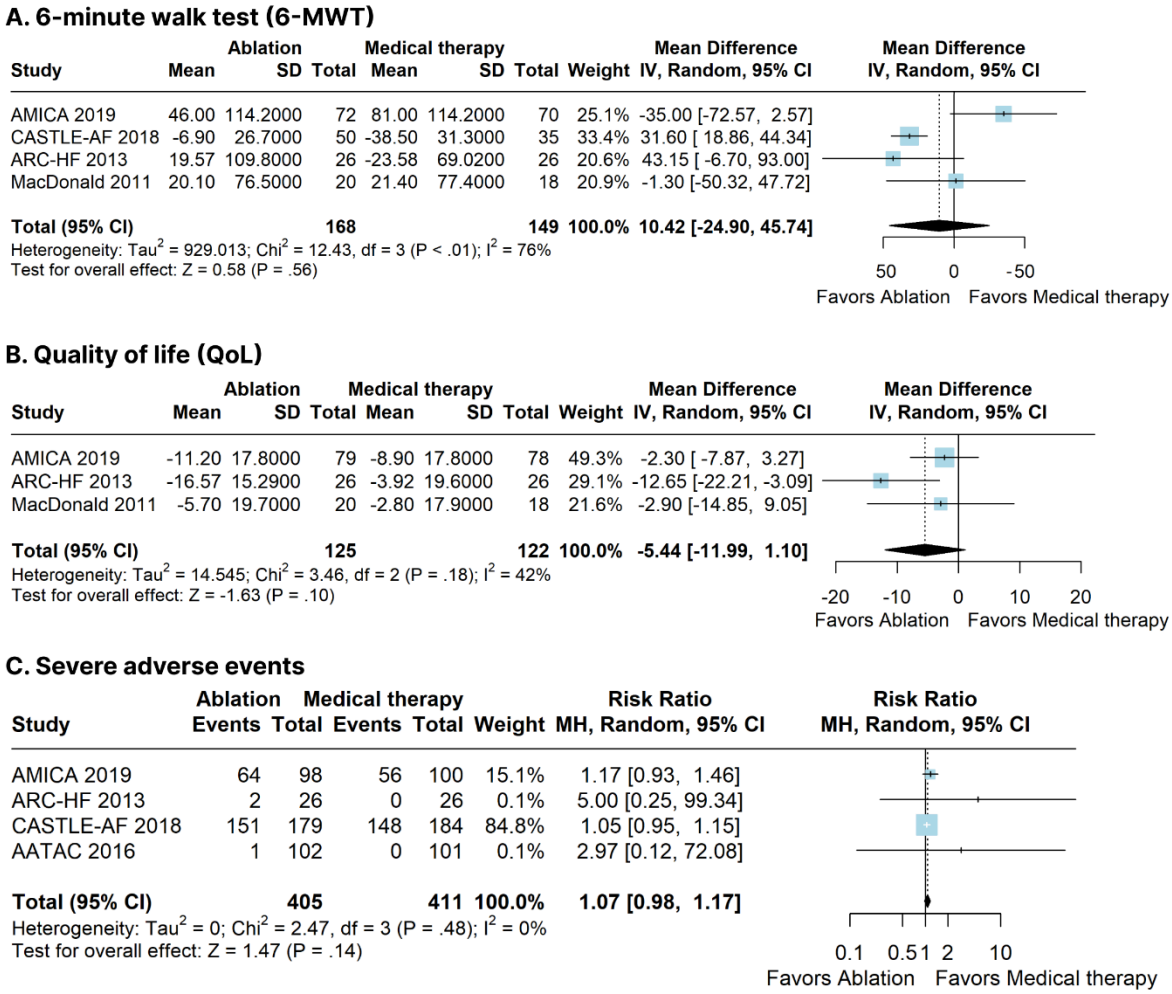


Figure S3. Forest plots of comparison between catheter ablation and medical therapy in patients with persistent atrial fibrillation. **A.** Heart failure hospitalization. **B.** Left ventricular ejection fraction (LVEF) change. **C.** 6-minute walk test (6-MWT).

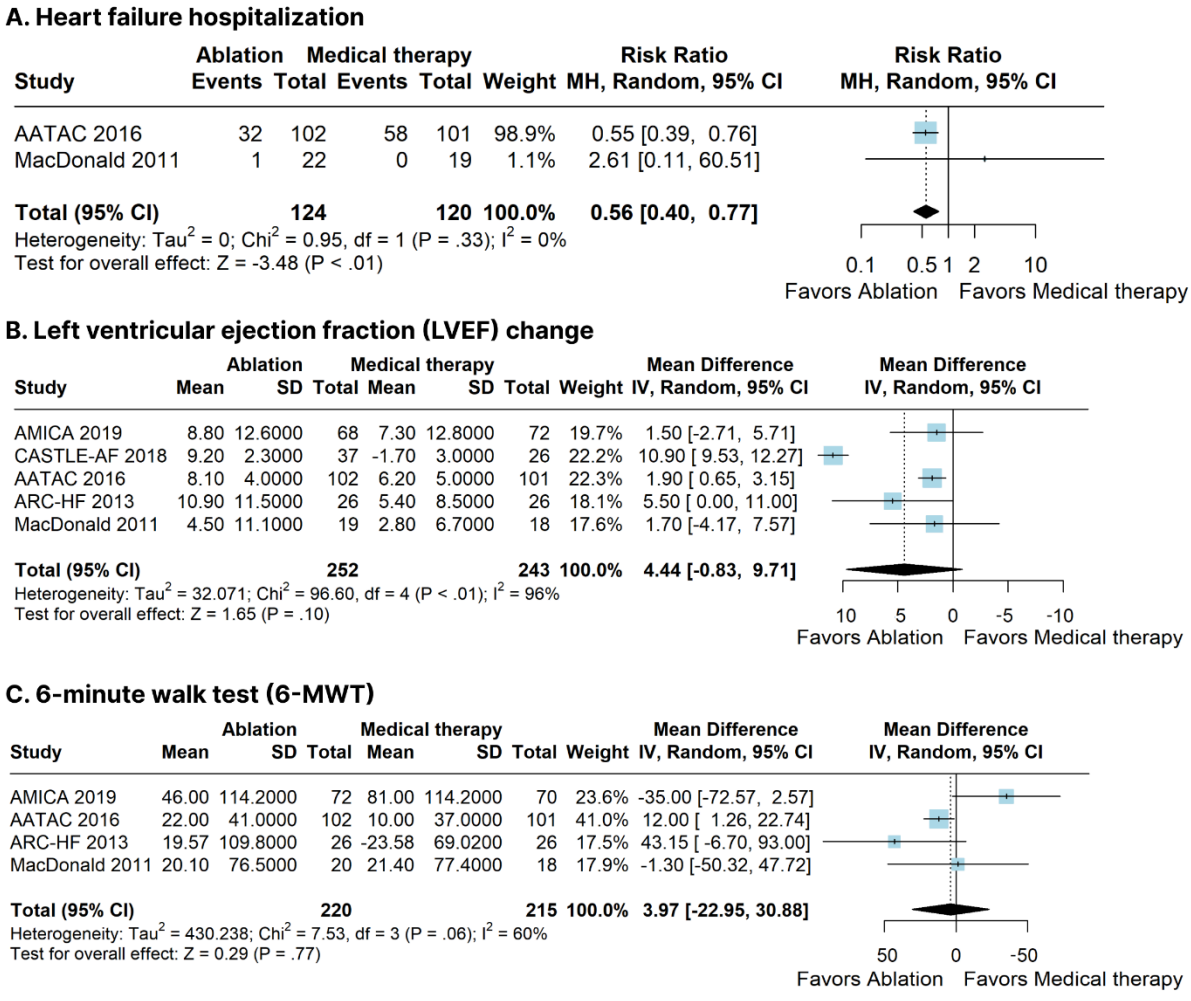


Figure S4. Forest plots of comparison between catheter ablation and medical therapy in patients with persistent atrial fibrillation. **A.** Cardiovascular mortality. **B.** All-cause mortality. **C.** Severe adverse events.

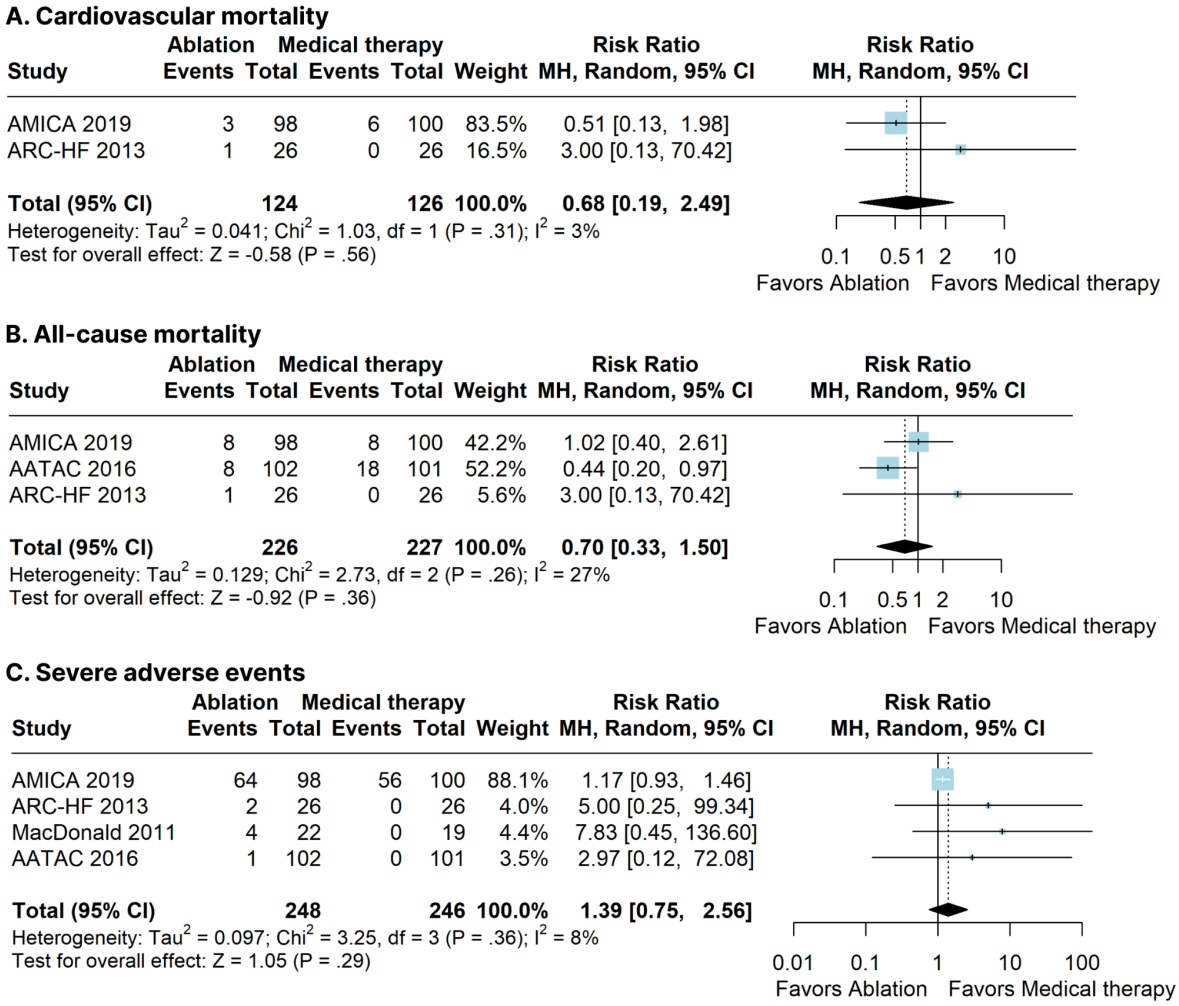


Figure S5. Leave-one-out sensitivity analyses of heart failure hospitalization outcome.

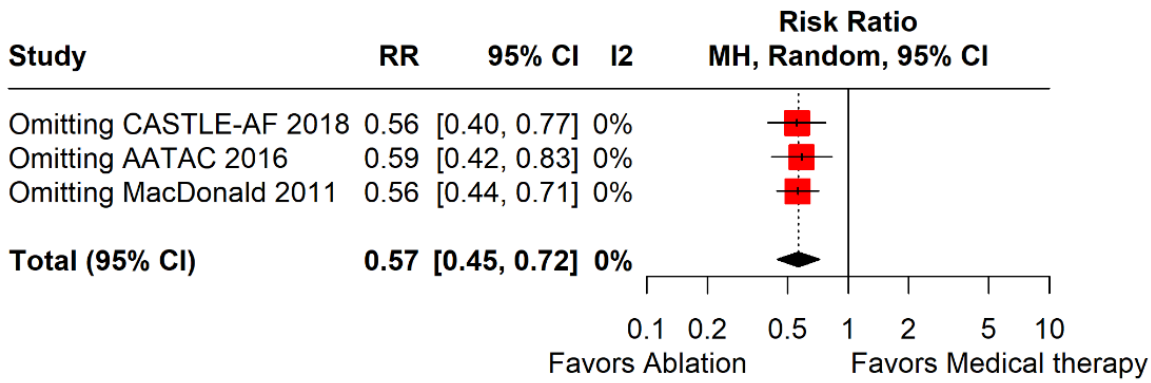
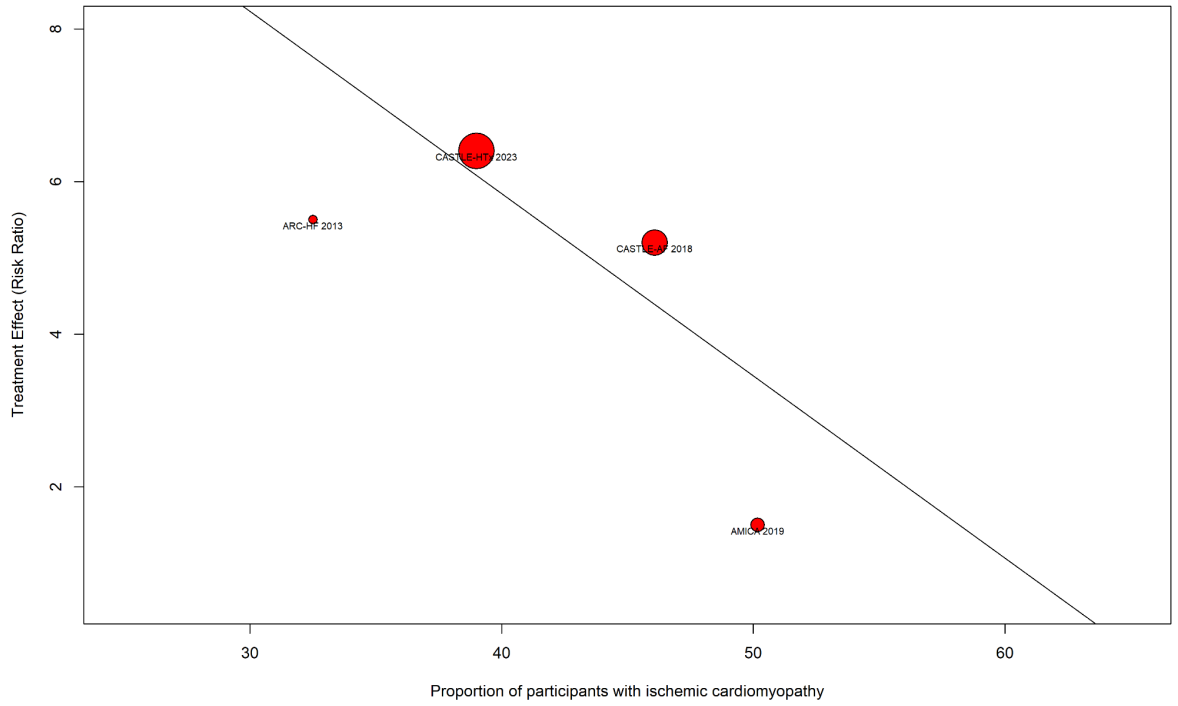
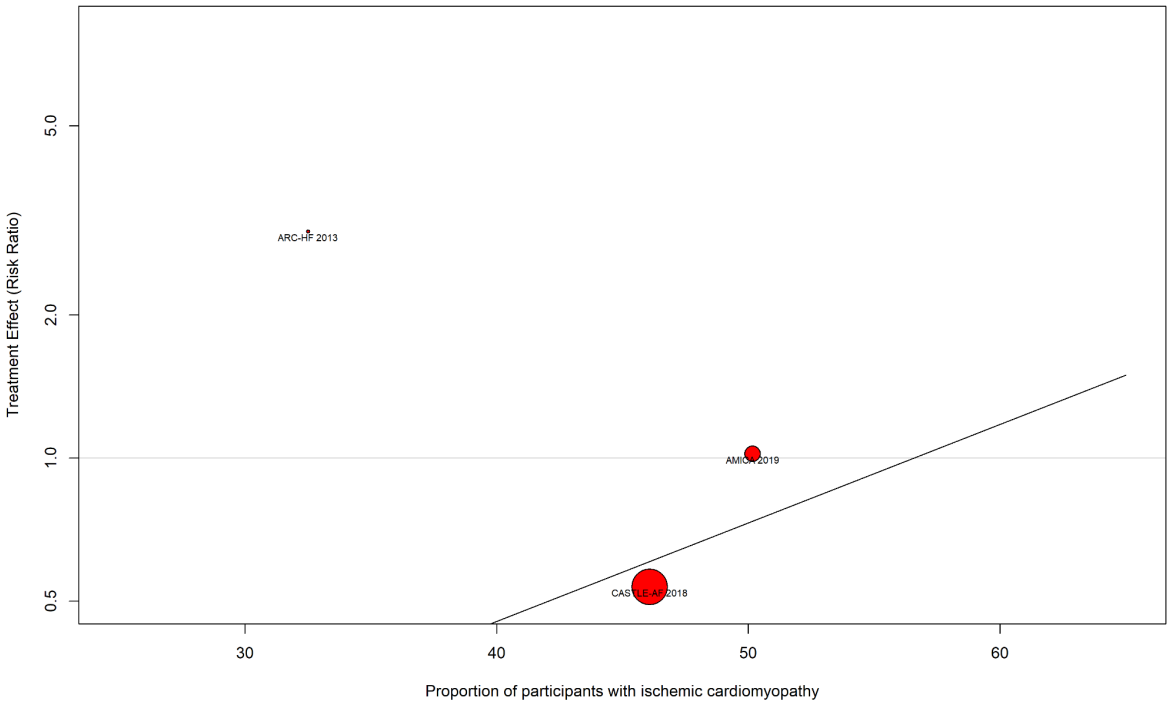


Figure S6. Meta-regression assessing the impact of proportion of patients with ischemic cardiomyopathy on left ventricular ejection fraction (LVEF) change.



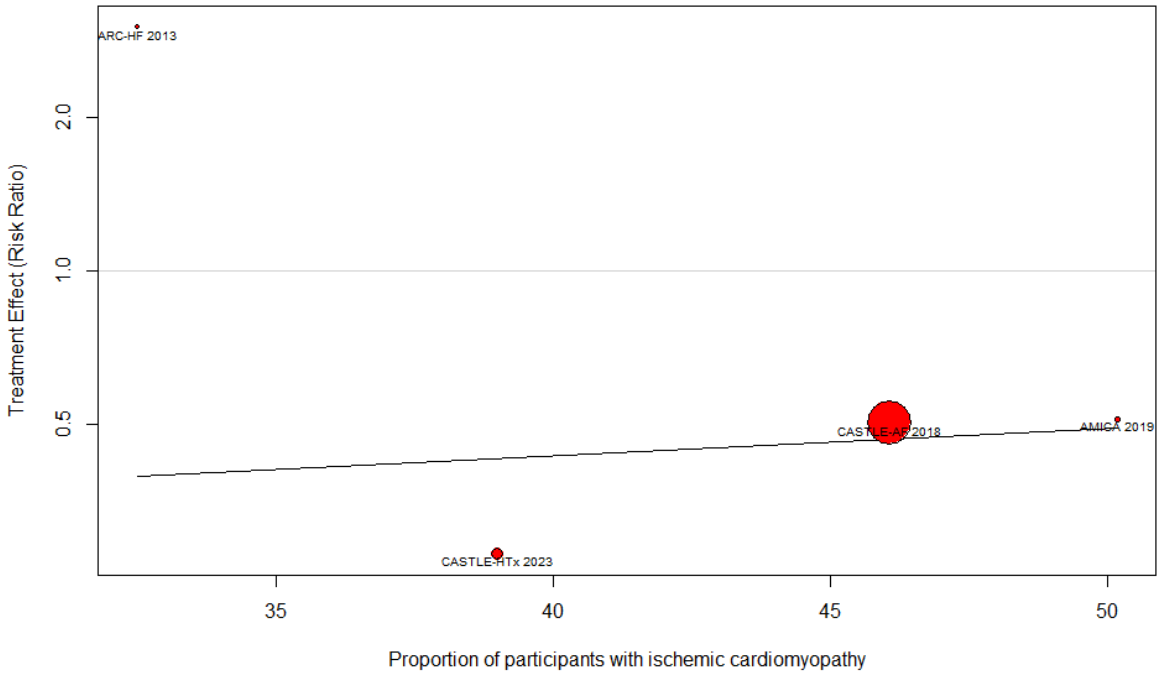
	Effect estimate	p-value	I^2	Test for residual heterogeneity
Intercept	15.4008	0.0178	0%	P = 0.4083
Ischemic cardiomyopathy	-0.2389	0.1203		

Figure S7. Meta-regression assessing the impact of proportion of patients with ischemic cardiomyopathy on all-cause mortality.



	Effect estimate	p-value	I^2	Test for residual heterogeneity
Intercept	-2.7005	0.3302	34.63%	P = 0.2166
Ischemic cardiomyopathy	0.0477	0.4381		

Figure S8. Meta-regression assessing the impact of proportion of patients with ischemic cardiomyopathy on cardiovascular mortality.



	Effect estimate	p-value	I^2	Test for residual heterogeneity
Intercept	-1.3315	0.6495	17.84%	P = 0.2961
Ischemic cardiomyopathy	0.0123	0.1873		

Figure S9. Trial sequential analysis for left ventricular ejection fraction (LVEF) change.

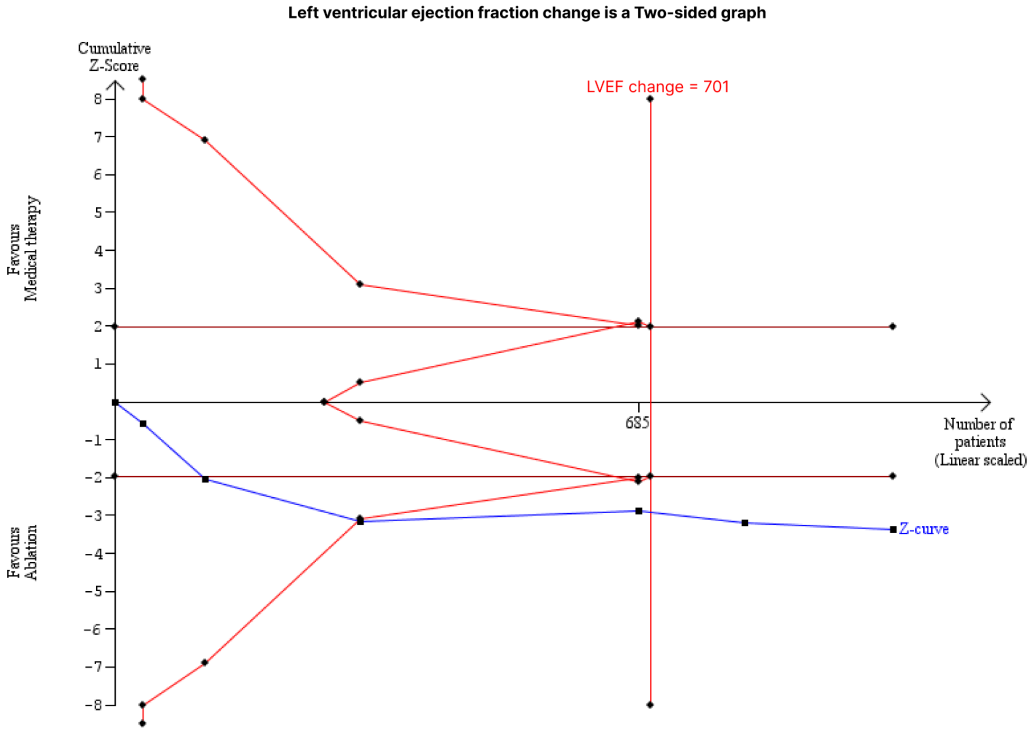


Figure S10. Trial sequential analysis for cardiovascular mortality.

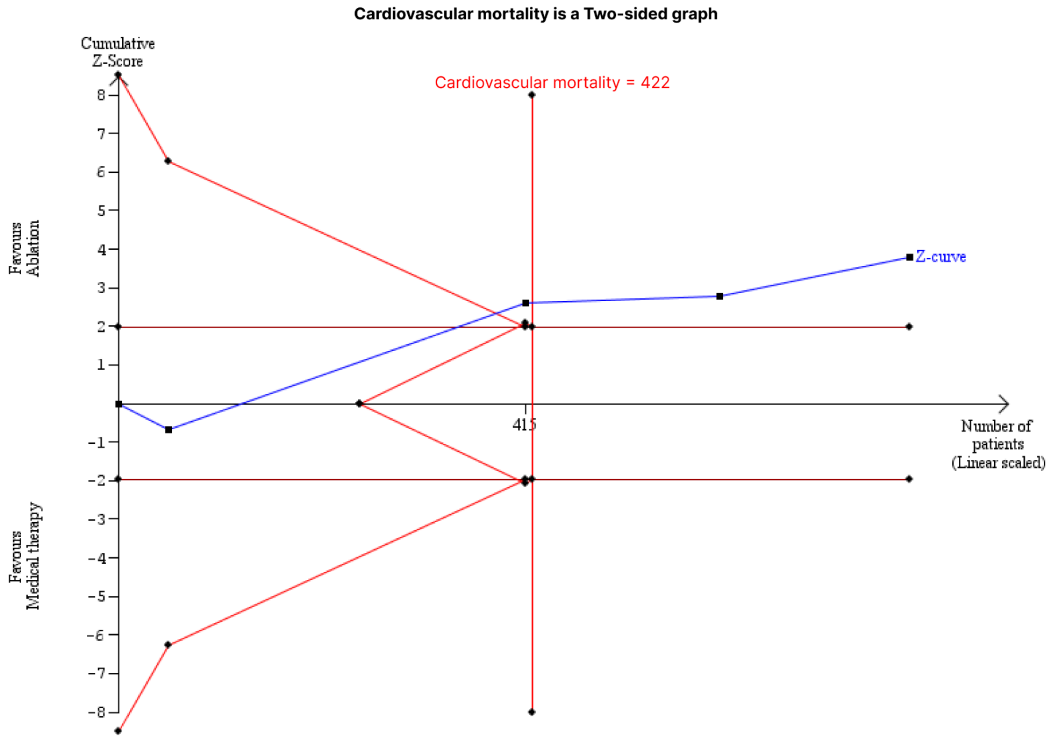


Figure S11. Trial sequential analysis for all-cause mortality.

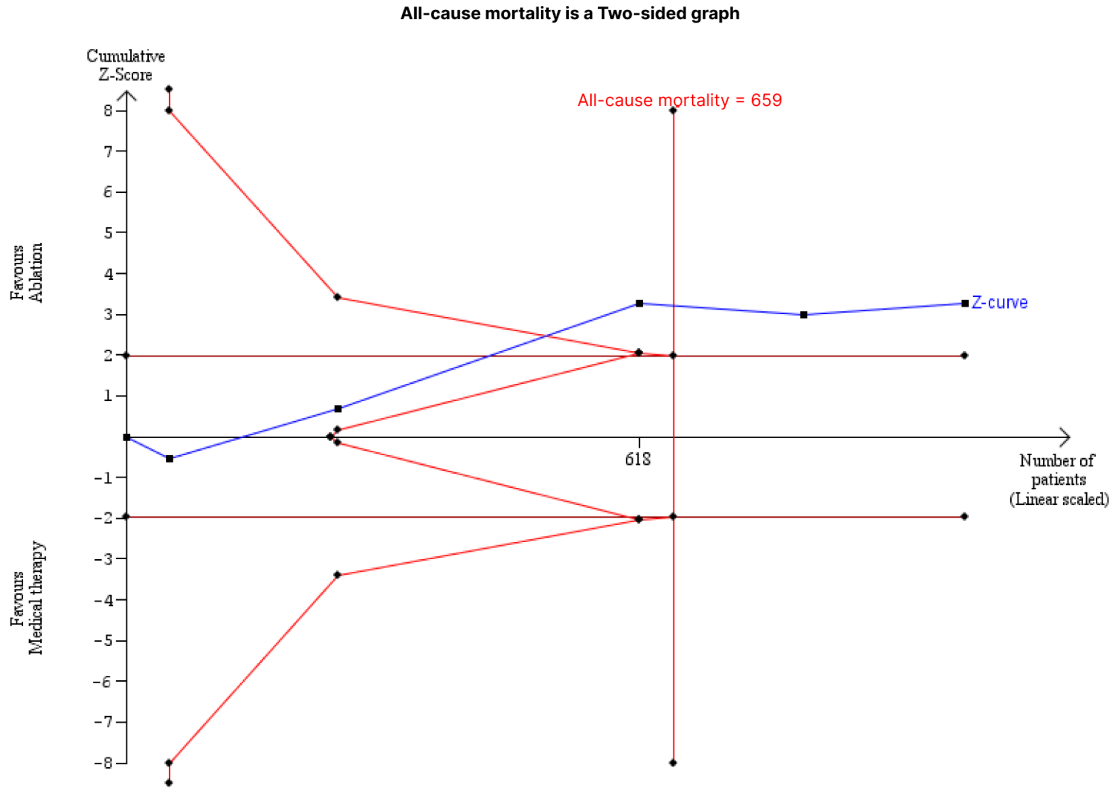


Figure S12. Trial sequential analysis for heart failure hospitalization.

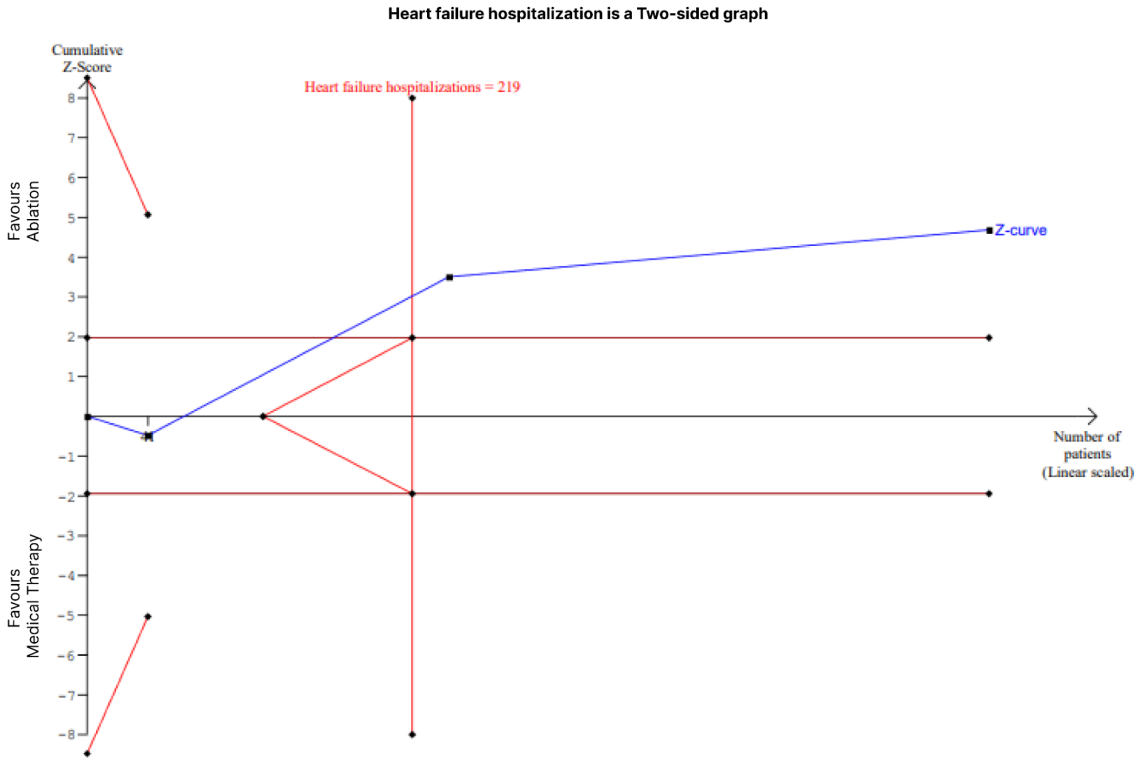


Figure S13. Trial sequential analysis for quality of life.

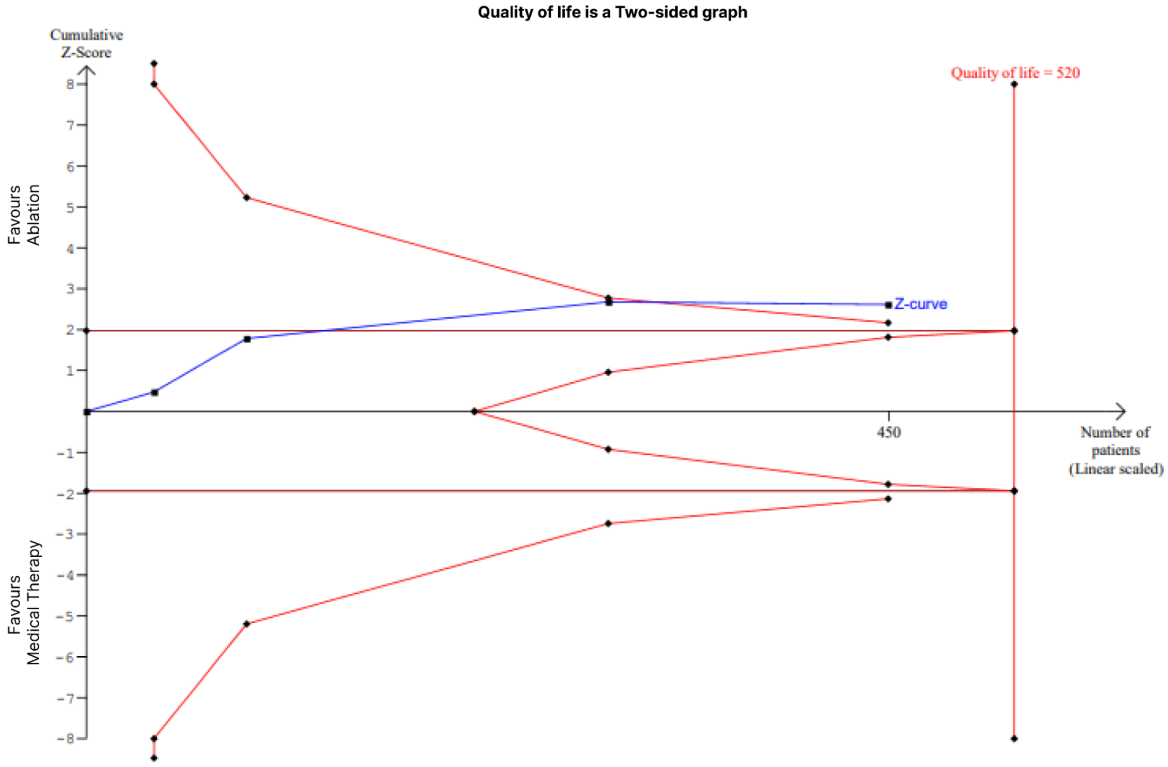
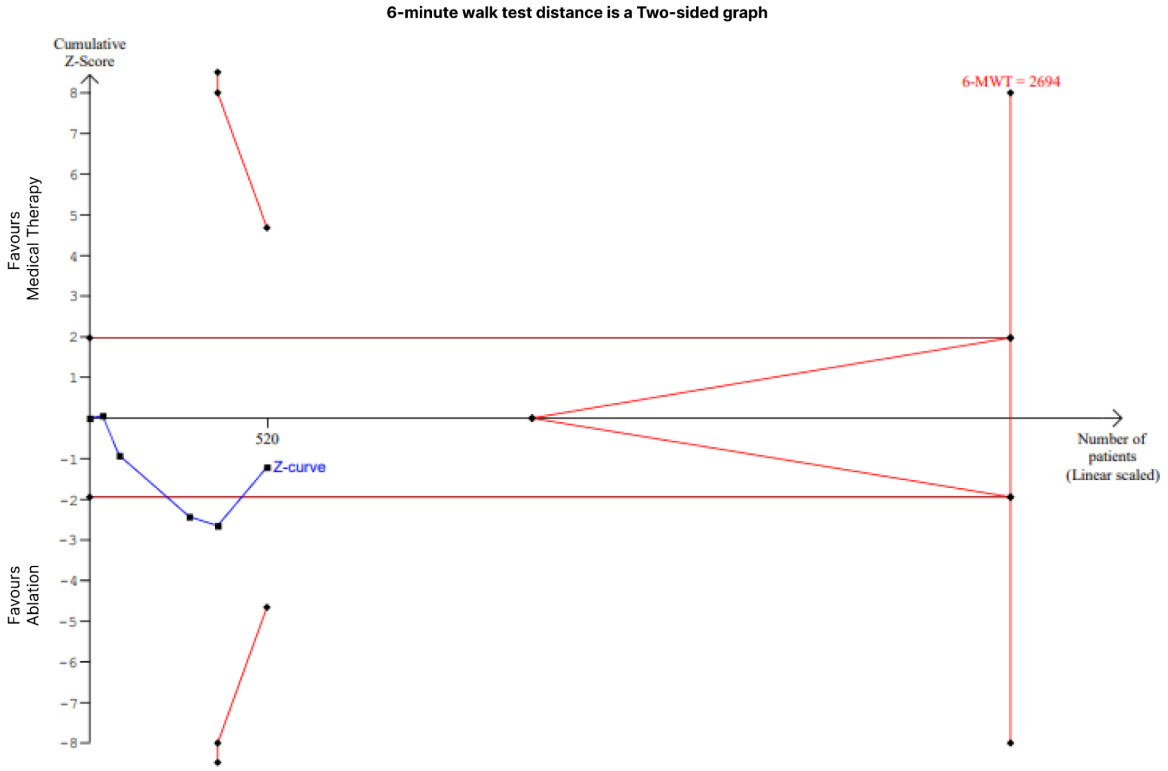


Figure S14. Trial sequential analysis for 6-minute walk test distance.



SUPPLEMENTARY MATERIAL (B)

Catheter ablation compared to medical therapy for atrial fibrillation in patients with heart failure with reduced ejection fraction

Bibliography: Pasqualotto, Ternes et al.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With medical therapy	With Catheter ablation		Risk with medical therapy	Risk difference with Catheter ablation
Left Ventricular Ejection Fraction (LVEF)											
989 (6 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	498	491	-	498	MD **3.82 higher** (1.64 higher to 6.01 higher)
Six Minute Walking Test (6-MWT)											
520 (5 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	250	270	-	250	MD **12.57 higher** (7.43 lower to 32.56 higher)

Atrial Fibrillation burden

557 (2 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	281	276	-	281	MD **29.82 lower** (43.73 lower to 15.9 lower)

Heart Failure hospitalization

607 (3 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	124/304 (40.8%)	70/303 (23.1%)	**RR 0.57** (0.45 to 0.72)	124/304 (40.8%)	**175 fewer per 1.000** (from 224 fewer to 114 fewer)

Cardiovascular mortality

807 (4 RCTs)	serious[a]	not serious	not serious	not serious	strong association	⨁⨁⨁⨁ High	65/407 (16.0%)	29/400 (7.2%)	**RR 0.46** (0.31 to 0.70)	65/407 (16.0%)	**86 fewer per 1.000** (from 110 fewer to 48 fewer)

All-cause mortality

1010 (5 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	91/508 (17.9%)	47/502 (9.4%)	**RR 0.53** (0.36 to 0.78)	91/508 (17.9%)	**84 fewer per 1.000** (from 115 fewer to 39 fewer)

Quality of Life (QoL)

450 (4 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	223	227	-	223	MD **4.92 lower** (8.61 lower to 1.22 lower)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. One study with some concerns for risk of bias

b. High heterogeneity

5 Artigo III.

ADJUNCTIVE POSTERIOR WALL ISOLATION FOR PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION:

AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

Em processo no periódico *Heart Rhythm 02*

Adjunctive Posterior Wall Isolation for Patients with Persistent Atrial Fibrillation: An Updated Systematic Review and Meta-Analysis

André Rivera,[1] Antônio S. Menezes, MD, PhD,[2] Douglas Mesadri Gewehr, MD,[3,4] Bárbara Nascimento, MD,[5] Isabele Ayumi Miyawaki,[6] Luís E. Rohde, MD, PhD,[5] Caique M. P. Ternes, MD,[5] Arash Aryana, MD, PhD,[7] André d'Avila, MD, PhD[8]

[1]Department of Medicine, Nove de Julho University, São Bernardo do Campo, Brazil
[2]Federal University of Goiás, Goiânia, Brazil
[3]Curitiba Heart Institute, Curitiba, Brazil
[4]Denton Cooley Institute of Research, Science, and Technology, Curitiba, Brazil
[5]Federal University of Rio Grande do Sul, Porto Alegre, Brazil
[6]Federal University of Paraná, Curitiba, Brazil
[7]Mercy General Hospital and Dignity Health Heart and Vascular Institute, Sacramento, California, USA
[8]Harvard Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Short title: PVI with versus without PWI in Persistent AF

Word count: 3,690 words

Disclosures: none

Corresponding Author: André d'Avila, MD, PhD
Harvard Thorndike Electrophysiology Institute,
Beth Israel Deaconess Medical Center, Harvard Medical School
185 Pilgrim Road, Boston, Massachusetts 02215, USA
Email: adavila@bidmc.harvard.edu

ABSTRACT

Background: Pulmonary vein isolation (PVI) is the cornerstone of atrial fibrillation (AF) ablation. Its effectiveness for persistent AF (PeAF) is limited, and the benefits of adjunctive posterior wall ablation are uncertain.

Objective: We aimed to perform a systematic review and meta-analysis of PVI with/without adjunctive PWI in patients with persistent AF.

Methods: We systematically searched PubMed, EMBASE, Cochrane, and ClinicalTrials.gov databases for randomized controlled trials (RCTs) comparing PVI with/without PWI in patients with PeAF. Random-effects model was used for the meta-analysis. Atrial tachyarrhythmia (ATA) was a composite of AF, atrial flutter, or atrial tachycardia.

Results: Our meta analysis included eight RCTs with 1,104 patients (PVI=546). Compared to PVI alone, adjunctive PWI significantly increased freedom from ATA recurrence (RR: 1.13; 95% CI 1.01–1.27; p=0.03), and this benefit was even greater when restricted to patients in the advanced stage of long-standing persistent AF (RR 1.76; 95% CI 1.02-3.03; p=0.04). A subgroup analysis of PWI techniques indicated no significant difference for ATA recurrence with box-isolation alone (RR: 1.13, 95% CI 0.97-1.33, p=0.124), whereas a pooled analysis using only studies with direct posterior wall ablation favored the adjunctive PWI group (RR: 1.39; 95% CI 1.11-1.74, p=0.004). Adverse events did not significantly differ between groups.

Conclusions: Our findings support that adjunctive PWI to PVI is an effective strategy compared to PVI alone for reducing ATA recurrence in patients with PeAF without compromising safety. Notably, patients with longer AF duration appeared to benefit more from PWI. Direct posterior wall ablation results in superior clinical outcomes compared to posterior wall box isolation alone.

Keywords: pulmonary vein isolation; atrial fibrillation; persistent; posterior wall isolation; catheter ablation; BOXI

NON-STANDARD ABBREVIATIONS AND ACRONYMS

BOXI – box isolation

CAPLA – Effect of Catheter Ablation Using PVI With vs. Without Posterior Left Atrial Wall Isolation on Atrial Arrhythmia Recurrence in Patients with Persistent Atrial Fibrillation

CBA – cryoballoon ablation

RFCA – radiofrequency ablation

RR – risk ratio

INTRODUCTION

Atrial fibrillation (AF) ablation is an effective strategy for treating symptomatic AF as it has been shown to be superior to medical therapy in reducing AF recurrence, symptomatic AF, and AF burden.[1] Pulmonary vein isolation (PVI) has been the cornerstone of AF ablation,[2] but its efficacy in patients with persistent AF (PeAF) is inferior to those with paroxysmal AF.[3] Ablation strategies beyond PVI have emerged as frequently used adjunctive approaches particularly in scenarios of reduced likelihood of success. However, the enthusiasm for extra-PVI ablation in patients with AF has been dampened due to the limited efficacy in several clinical trials.[4–6] Accordingly, the 2020 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of AF has assigned a class 2B recommendation for additional ablation strategies beyond PVI.[1]

Prior meta-analyses have investigated the role of adjunctive posterior wall isolation (PWI) and shown lower recurrence of atrial tachyarrhythmias (ATA) in patients with PeAF.[7] However, the recent "Effect of Catheter Ablation Using PVI With versus Without Posterior Left Atrial Wall Isolation on Atrial Arrhythmia Recurrence in Patients With Persistent Atrial Fibrillation" (CAPLA) trial found that PVI had similar endpoints at 12 months, regardless PWI.[8]

Given this uncertainty, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to further investigate the efficacy and safety of PVI with adjunctive PWI compared with PVI alone in patients with PeAF.

MATERIAL AND METHODS

The systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions[9] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines (*Supplemental Methods 1*).[10] The prospective meta-analysis protocol was uploaded to the International

Prospective Register of Systematic Reviews (PROSPERO; CRD42023397998).

Data Source and Search Strategy

We systematically searched PubMed (MEDLINE), Scopus, Cochrane, and ClinicalTrials.gov from inception to January 2023. The search terms used included "pulmonary vein isolation", "posterior wall isolation", and "atrial fibrillation". The complete search strategy is provided in *Supplemental Methods 2*. Two authors (A.R. and B.N.) independently screened titles and abstracts and evaluated the articles in full for eligibility based on prespecified criteria. Discrepancies were resolved in a panel discussion with the senior author (A.R., B.N., and A.S.M.). Moreover, we used backward snowballing (i.e., review of references) to identify relevant texts from articles identified in the original search.

Eligibility Criteria

We considered studies eligible for inclusion if they (1) were RCTs; (2) compared PVI alone versus PVI plus adjuvant PWI; (3) enrolled patients with PeAF (defined as a sustainable episode lasting ≥ 7 days) or long-standing PeAF (defined as continuous AF >12 months duration); (4) *de novo* ablation; and (5) presented data regarding prespecified efficacy and safety endpoints. We excluded non-randomized studies, studies including exclusively patients with paroxysmal AF, studies using surgical or hybrid approaches. There was no restriction of follow-up, publication date, or status.

Data Extraction

Two authors (A.R. and B.N.) independently extracted the data for each study using a standardized study form to determine: authors, clinical trial registration number, enrollment period *(Supplemental Methods 3)*, study publication year, main exclusion criteria *(Supplemental Methods 4)*, sample size, follow-up period, baseline patient characteristics, antiarrhythmic drug (AAD) use at baseline, PVI and PWI techniques employed, endpoint definitions, the methods used to confirm electrical isolation during ablation *(Supplemental Methods 5),* and the posterior wall reconnection rates at repeated catheter ablation. Discrepancies were resolved in a panel discussion with the senior author.

Endpoints

Our primary efficacy endpoint was freedom from ATA, defined as AF, atrial flutter, or atrial tachycardia. Prespecified secondary efficacy endpoints included (1) freedom from AF; (2) freedom from atrial flutter/tachycardia; (3) freedom from ATA after a single ablation procedure; (4) freedom from ATA without AAD; (5) freedom from ATA after a single ablation procedure without AAD; (6) need for cardioversion; and (7) need for repeat ablation. Prespecified procedure- related endpoints consisted of (1) total procedure time; (2) ablation time; and (3) fluoroscopy time. Prespecified safety endpoints included (1) pericarditis; (2) cardiac tamponade; (3) phrenic nerve injury; and (4) atrioesophageal fistula. Other secondary endpoints were (1) short- (<12 months) and long-term (≥12 months) AAD use and (2) change in left atrial diameter (mm). *Supplemental Methods 6* comprehensively describes the endpoint definitions and methods used for each study.

Subgroup and Meta-regression Analysis

We conducted prespecified subgroup and meta-regression analyses for the primary endpoint. Studies were grouped based on (1) PWI technique (direct posterior wall ablation vs. box isolation); (2) the technique employed for catheter ablation (radiofrequency catheter ablation (RFCA) vs. cryoballoon ablation (CBA) vs. CBA with adjunct RFCA); (3) overall risk of bias; and (4) study location. In addition, we added a sensitivity analysis (1) restricted to studies published after 2015, given that technological advances in catheter ablation could perhaps limit the applicability of older data to current practice, and (2) omitting studies which performed an additional mitral linear ablation in the adjunctive PWI group. We performed a meta-regression to assess for interactions between the outcomes and study-patient characteristics, including (1) duration of AF; (2) left atrial diameter; and (3) mean age of patients.

Quality Assessment

Two independent authors assessed the risk of bias in the included RCTs using the Cochrane tool for assessing the risk of bias in randomized trials (RoB 2).[11] Any disagreements were resolved by consensus. We explored the potential for publication bias through funnel plots and Egger's test for the primary endpoint.

Statistical Analysis

We summarized binary endpoints using the Mantel-Haenszel random-effects model (restricted maximum likelihood estimator for τ^2) with risk ratio (RR) and 95% confidence interval (CI) as a measure of effect size. Furthermore, we utilized weighted mean differences (MD) to pool continuous endpoints. We assessed heterogeneity with Cochrane's Q statistic and Higgins and Thompson's I^2 statistic with $p \leq 0.10$, indicating statistical significance. We determined the consistency of the studies based on I^2 values of 0%, ≤ 25%, ≤ 50%, and > 50%, indicating no observed low, moderate, and substantial heterogeneity, respectively. All tests were two-tailed, and a p-value of < 0.05 was considered statistically significant. If necessary, means and standard deviations were estimated.[12] We used R version 4.2.2 and the extension packages "meta" for all calculations and graphics.[13] An in-depth description of the statistical analyses is available in *Supplemental Methods 7*.

RESULTS

Our systematic search yielded 1,831 potential articles (*Figure 1*). After removing duplicates, 50 articles were retrieved and reviewed in full for possible inclusion. Of these, eight RCTs met all inclusion criteria and were included in the primary analysis.[8,14–20] We included 1,104 patients, with 546 patients (49.5%) assigned to PVI alone and 558 patients (50.5%) assigned to PVI with PWI. *Table 1* summarizes the main characteristics of the included studies, and *Supplemental Tables 1-2*

summarize the clinical baseline characteristics of the patients and the AADs used before randomization. The mean age of the patients was 62.7 years (range: 52.7–65.6 years), and 76% (range: 52–84%) were male. Two RCTs included both paroxysmal and persistent AF.[18,19] In these cases, we only included data on patients with PeAF. Obesity and hypertension were the predominant comorbidities. The AF duration ranged from 12–64 months. The mean left atrial diameter was 43.5 mm (range: 39.5–48.3 mm). RFCA was predominantly used with only two RCTs utilizing CBA as the primary strategy.[14,15] Follow-up ranged from 10 to 23.8 months. During data collection, three authors were contacted for additional data, and one provided the information.

Efficacy Endpoints

PVI with adjunctive PWI overall resulted in a significantly higher rate of freedom from ATA (13% increase), as compared to PVI alone (RR 1.13; 95% CI 1.01-1.27; p=0.03; I2=32%; *Figure 2A*), mainly due to improved freedom from AF (RR 1.17; 95% CI 1.02-1.36; p=0.03; I2=66%; *Figure 2B*). There was no statistical difference between groups for freedom from atrial flutter/tachycardia (RR 0.96; 95% CI 0.89-1.03; p=0.22; I2=0%; *Supplemental Figure 1A*). Freedom from ATA after a single ablation procedure was significantly higher among patients receiving PVI with adjunctive PWI, as compared to PVI alone (RR 1.16; 95% CI 1.03- 1.30; p=0.02; I2=13%; *Figure 2C*). When restricted to patients with long-standing persistent AF, adjunctive PWI also significantly increased freedom from ATA (RR 1.76; 95% CI 1.02-3.03; p=0.04; I2=0%; *Figure 3*). There was no significant difference between groups regarding freedom from ATA without AAD (RR 1.12, 95% CI 0.99-1.27; p=0.06; I2=21%; *Supplemental Figure 1B*), freedom from ATA after a single procedure without AAD (RR 1.10; 95% CI 0.97- 1.26; p=0.14; I2=32%; *Supplemental Figure 1C*), and need for cardioversion (RR 1.30; 95% CI 0.64-2.60; p=0.47; I2=57%; *Supplemental Figure 1D*). Also, the need for repeat ablation was not significantly different between groups (RR 1.38; 95% CI 0.63-3.01; p=0.42;

I2=34%; *Supplemental Figure 1E*). However, in patients who received PVI with PWI, 19/29 patients (65.6%) exhibited posterior wall reconnection at repeat catheter ablation.

Procedural Endpoints

PVI with adjunctive PWI was associated with a significantly higher total procedural time (MD 23.8 min; 95% CI 15.7-31.9 min; p<0.01; I^2=54%; *Figure 4A*), ablation time (MD 14.5 min; 95% CI 9.0-20.0 min; p<0.01; I^2=82%; *Figure 4B*), and fluoroscopy time (MD 1.3 min; 95% CI 0.3-2.4 min; p=0.01; I^2=0%; *Figure 4C*).

Safety Endpoints

There was no significant difference between groups concerning atrioesophageal fistula (RR 1.06; 95% CI 0.11-10.11; p=0.96; I^2=0%; *Supplemental Figure 2A*), pericarditis (RR 0.78; 95% CI 0.15-4.03; p=0.77; I^2=0%; *Supplemental Figure 2B*), cardiac tamponade (RR 1.13; 95% CI 0.12-10.47; p=0.92; I^2=35%; *Supplemental Figure 2C*), and phrenic nerve injury (RR 1.29; 95% CI 0.28-5.93; p=0.745; I^2=0%; *Supplemental Figure 2D*).

Secondary Endpoints

There was no significant difference between groups regarding change in left atrial diameter (MD –1.07 mm; 95% CI [–2.30]-[0.17] mm; p=0.09; I^2=0%; *Supplemental Figure 3A*) and short- term (RR 0.79; 95% CI 0.62-1.00; p=0.05; I^2=0%; *Supplemental Figure 3B*) and long-term AAD therapy (RR 0.80; 95% CI 0.64-1.01; p=0.06; I^2=0%; *Supplemental Figure 3C*). These secondary outcomes, however, are likely underpowered to rule out a significant difference between groups, given the fewer number of studies that reported on these results. Nonetheless, as seen, there were trend toward a benefit associated with PVI plus PWI.

Subgroup and Sensitivity Analysis

Freedom from ATA remained similar between PVI and PVI with adjunctive PWI when stratified by posterior wall isolation technique (*Figure 5*), energy source used (*Supplemental Figure 4A*), overall risk of bias (*Supplemental Figure 4B*), and study location (*Supplemental Figure 4C*). After omitting studies published before 2015, We found that the primary outcome remained statistically significant after omitting studies published before 2015 (RR 1.15; 95% CI 1.002-1.319; p=0.046; I^2=50%; *Supplemental Figure 5A*) and studies performing an additional mitral isthmus ablation (RR 1.19; 95% CI 1.03-1.36; p=0.016; I^2=36%; *Supplemental Figure 5A*)

Meta-regression Analysis

We performed meta-regression analyses to assess the impact of study-level characteristics and to explore potential sources of heterogeneity among the studies. Our analysis revealed that a longer duration of AF was significantly associated with a more favorable effect of PVI with adjunctive PWI relative to PVI alone for the outcome of freedom from ATA (p<0.01), accounting for 92% of the heterogeneity in results among studies (R^2). However, we found no significant association between left atrial diameter (p=0.61; *Supplemental Figure 6A*) or mean age (p=0.92; *Supplemental Figure 6B*) and the effectiveness of PVI with/without adjunctive PWI.

Addressing Heterogeneity

We conducted a Graphic Display of Heterogeneity (GOSH) analysis to investigate the moderate to high heterogeneity in our findings. Our results were consistent across multiple simulations and remained stable after random exclusion of studies. A comprehensive explanation of statistical protocols to explore heterogeneity is available in *Supplementary Results 1* and *Supplemental Figures 7-9*

Quality Assessment

The RoB 2 results identified five RCTs at some concerns for bias[14,16,18–20] and four at low risk of bias[8,15,17,21] (*Supplemental Figure 10*). Funnel plot analysis and Egger regression test for the primary efficacy endpoint detected no evidence of publication bias for the included studies (*Supplemental Figure 11*). However, the funnel plots should be interpreted with caution given the imprecision related to the small number of studies included in the meta-analysis.

DISCUSSION

This comprehensive meta-analysis of eight RCTs enrolling 1,243 patients examined the efficacy of PVI with adjunctive PWI in patients with PeAF. The main findings are as follows. First, PVI with adjunctive PWI was associated with a higher rate of freedom from ATA, primarily due to freedom from AF. Second, PVI with adjunctive PWI was also found to be superior to PVI alone for freedom from ATA after just a single ablation procedure. Third, the two strategies had no significant difference in the incidence of procedure-related adverse events. Lastly, the observed benefit of PVI with adjunctive PWI was superior among patients with a longer AF duration.

Despite its superiority in maintaining sinus rhythm over AAD therapy, catheter ablation for the treatment of AF still has limited success rates, particularly in patients with PeAF.[1,2] Previous clinical trials have reported single ablation procedure success rates of PVI in patients with PeAF ranging between 47% and 69% at 12 months, highlighting the suboptimal results of this technique in this challenging patient population.[22,23] These results contrast the previously- studied strategies, such as MRI-guided ablation, complex fractionated electrogram ablation, and double wide-area circumferential ablation.[4–6] The efficacy of PWI combined with PVI might stem from (1) the shared embryological origin of the posterior left atrial wall and the pulmonary veins; (2) the housing of the septopulmonary bundle within the posterior left atrium, a site of wave-front (2) the housing of the

septopulmonary bundle within the posterior left atrium, a site of wave-front collision, facilitating formation of reentrant circuits;[24–27] and (3) the potential for structural remodeling in the left atrial posterior wall promoting AF substrates.[28]

It should be highlighted that the RCTs included in our analysis did not verify the isolation of the posterior wall during long-term follow-up. However, 29 patients treated with PVI with PWI who experienced recurrent AF did undergo a repeat ablation, and approximately two-thirds exhibited posterior wall reconnection. Similarly, Bulava et al. reported 77% PWI reconnection rate
3 months following RFCA.[29] Since the cardiac autonomic nerves contribute to AF trigger mechanisms and are located on the subepicardial surface, it is believed that a transmural-plus lesion may be necessary during endocardial ablation.[30,31] Hence, we can hypothesize that residual cardiac autonomic nerves could play a role in reconnection of the posterior wall and perhaps the recurrence of AF.

Of note, the remote date of conduction and publication of studies by Pappone et al. (2004) and Tamborero et al. (2009) are of concern.[18,19] The applicability of these studies' findings may be limited due to significant advances that have been made in catheter ablation techniques over the past two decades (e.g., contact force, high-density mapping, etc.). To address this issue, we performed a sensitivity analysis excluding studies published prior to 2015. However, the results remained unchanged as compared to the pooled analysis (*Supplemental Figure 4*). In addition, meta-regression analysis revealed that the duration of AF could be a significant element affecting the efficacy of adjunctive PWI. Specifically, patients with longer AF durations may benefit more from this procedural strategy compared to those with shorter AF durations. While the success rates of standard PVI decrease as the duration of AF increases, the addition of adjunctive PWI could have a greater effect on the outcomes of AF ablation. This could explain why the CAPLA trial was

identified as an outlier, considering the shorter mean duration of AF reported (26.3 months).

The subgroup analysis comparing direct posterior wall ablation versus posterior box isolation yielded intriguing findings. Pooled data from studies employing posterior box isolation showed no significant difference in freedom from ATA (RR 1.13; 95% CI 0.97-1.33; I^2=21%), while those employing a direct posterior wall ablation approach demonstrated statistically significant results without heterogeneity (RR 1.39; 95% CI 1.11-1.74; I^2=0%), despite no significant subgroup interaction (p=0.14). It is important to mention that CAPLA and Pappone et al. trials were excluded from this subgroup analysis due to their extremes in atrial fibrillation duration, which could have introduced unwarranted heterogeneity. These findings contribute to the ongoing discussion regarding the varying effectiveness of PWI techniques when employed alongside PVI in the treatment of AF.[32] Direct posterior wall ablation could potentially offer increased reliability compared to box isolation.[33]

Although previous meta-analyses also found a benefit of PVI with adjunctive PWI in reducing the recurrence of ATA in patients with both paroxysmal and persistent AF,[7,34] in the current study, we decided to limit inclusion to patients with only PeAF for consistency and RCTs to minimize confounding variables in the analyses. Furthermore, we incorporated four additional RCTs (n = 692 patients), which were not included in the prior meta-analysis,[7] including the CAPLA trial, representing the largest multicenter RCT of PVI against PVI with PWI to date. Moreover, additional endpoints and analyses were performed in our study, such as (1) the finding of superior efficacy of PVI with adjunctive PWI for freedom from ATA after a single ablation and (2) meta-regression analysis showing a more favorable effect of PVI with PWI in studies with longer duration of AF.

Study Limitations

This study has several limitations. First, the mean AF duration varied significantly among RCTs. Despite the heterogeneity, this created an important finding of the improved relative benefit of PVI with PWI relative to PVI alone with a longer AF duration. Second, the primary endpoint reported was based on the currently accepted standard of 30 seconds of arrhythmia recurrence, with a slight variation among the studies. The AF burden has recently been increasingly considered a more clinically meaningful endpoint than the conventional recurrence definition.[35] Nevertheless, the AF burden was only assessed in one of the included studies. Thus, it was not possible to perform a meta-analysis of AF burden as an endpoint. Third, there was moderate heterogeneity for the primary endpoint of freedom from ATA. However, we addressed increased heterogeneity by performing dedicated subgroup and meta-regression analyses, meticulously exploring the potential study-level and patient-level characteristics, as reported in *Supplementary Appendix*. Fourth, the sample size in comparing subgroups and secondary endpoints is relatively small, potentially resulting in an underpowered analysis. Fifth, the studies did not assess the durability of posterior wall isolation during follow-up in sinus rhythm, limiting our findings' mechanistic evaluation. Lastly, there were variations in the PWI techniques, as outlined in *Table 1*.

CONCLUSION

In this meta-analysis of RCTs, PVI with adjunctive PWI in patients with PeAF resulted in a higher rate of freedom from ATA, including AF, without an increase in procedure-related adverse events, compared with PVI alone. This benefit was particularly notable in patients with longer AF durations. These findings support the routine use of PWI as an adjunct strategy to PVI in patients with PeAF and longer AF durations. Direct posterior wall ablation results in superior clinical outcome as compared to posterior wall box isolation alone.

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TABLES AND FIGURES

Table 1. Baseline characteristics of included studies.

Central Figure. Graphic Abstract PVI with adjunctive PWI.

Figure 1. PRISMA flow diagram of study screening and selection.
Abbreviations: RCT, randomized controlled trial.

Figure 2. Meta-analysis of efficacy endpoints in patients with AF undergoing PVI with adjunctive PWI.

Caption: Forest plots presenting the risk ratio (RR) and 95% confidence interval (CI) for each treatment strategy on (A) freedom from atrial tachyarrhythmia, (B) freedom from atrial fibrillation, and (C) freedom from atrial tachyarrhythmia after a single ablation procedure.

Abbreviations: CI, confidence interval; MH, Mantel-Haenszel; PVI, pulmonary vein isolation; PWI, posterior wall isolation; RR, risk ratio.

Figure 3. Meta-analysis of efficacy endpoints in patients with long-standing persistent AF undergoing PVI with adjunctive PWI.

Caption: Forest plots presenting the risk ratio (RR) and 95% confidence interval (CI) for each treatment strategy on (A) total procedure time, (B) ablation time, and (C) fluoroscopy time.

Abbreviations: CI, confidence interval; IV, inverse-variance; MD, mean difference; PVI, pulmonary vein isolation; PWI, posterior wall isolation.

Figure 4. Meta-analysis of procedural endpoints in patients with AF undergoing PVI with adjunctive PWI

Caption: Forest plots presenting the risk ratio (RR) and 95% confidence interval (CI) for each treatment strategy on (A) total procedure time, (B) ablation time, and (C) fluoroscopy time.

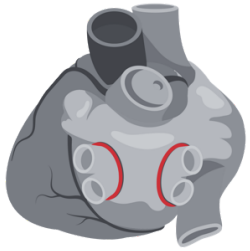
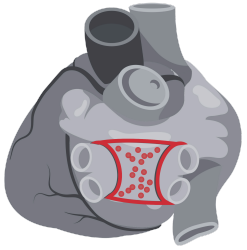
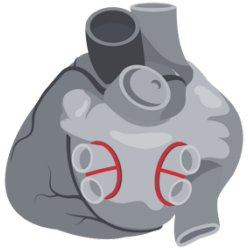
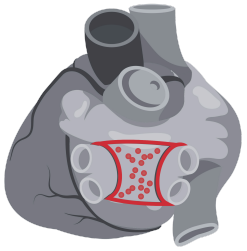
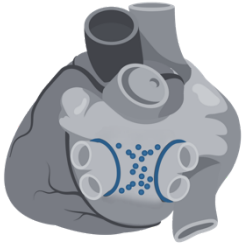
Abbreviations: CI, confidence interval; IV, inverse-variance; MD, mean difference; PVI, pulmonary vein isolation; PWI, posterior wall isolation.

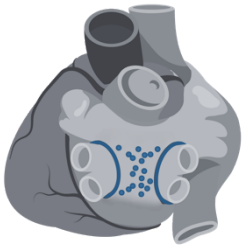
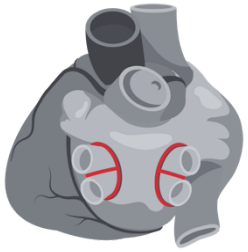
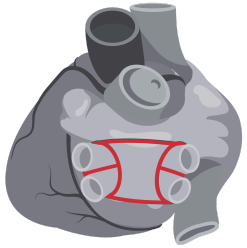
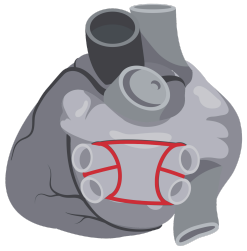
Figure 5. Subgroup analysis of the primary outcome in patients with AF undergoing PVI with adjunctive PWI stratified by PWI technique.

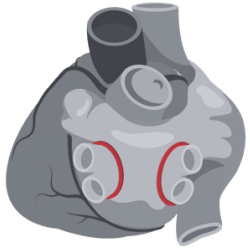
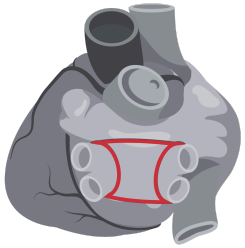
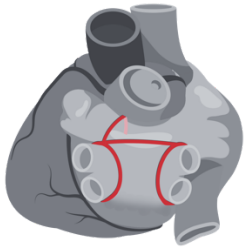
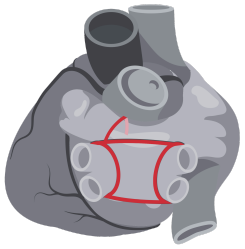
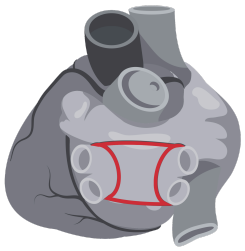
Caption: Forest plots presenting the risk ratio (RR) and 95% confidence interval (CI) for each subgroup strategy on freedom from ATA recurrence stratified by (1) direct PWI and (2) box isolation.

Abbreviations: CI, confidence interval; MH, Mantel-Haenszel; PVI, pulmonary vein isolation; PWI, posterior wall isolation; RR, risk ratio; BOXI, box isolation.

Table 1. Baseline characteristics of included studies.

First Author, Year (Study Acronym or Registry)	**Country** (RCT identifier)	**Number of Patients**	**Ablation Procedure**	**PVI Group Ablation Technique**	**Adjunctive PWI Group Ablation Technique**	**Mean Duration of AF** (months)	**Follow-up**† (months)
Kistler, 2023 (CAPLA)	AUS, CA, and UK (ACTRN12616001436460)	338	Radiofrequency ablation	 Circumferential PVI without interpulmonary isthmus line	 BOX isolation ± debulking (red points on LA posterior wall)	26.29	12
Wong, 2023 (PEF-HOT)	US (--)	67	High-power short duration	 Circumferential PVI with interpulmonary isthmus line	 BOX isolation ± debulking (red points on LA posterior wall)	12	12.4
Ahn, 2022	Korea (KCT0004149)	100	Cryoballoon ablation	 Circumferential PVI without interpulmonary isthmus line	 Direct PWI	56.15	15

Aryana, 2021	Japan and US (NCT03057548)	110	Cryoballoon ablation with adjunct radiofrequency ablation	 Circumferential PVI without interpulmonary isthmus line + CTI	 Direct PWI	NA	21
Pak, 2021 (PEACEFUL)	Korea (NCT02176616)	114	Radiofrequency ablation	 Circumferential PVI with interpulmonary isthmus line + CTI	 BOX isolation	31.74	23.8
Lee, 2019 (POBI-AF)	Korea (NCT02721121)	207	Radiofrequency ablation	 Circumferential PVI with interpulmonary isthmus line + CTI	 BOX isolation	38.5	16.2

Yu, 2017	Korea (NCT02176616)	113	Radiofrequency ablation	 Circumferential PVI without interpulmonary isthmus line + CTI	 BOX isolation	42.8	18.6
Kim, 2015	Korea (--)	120	Radiofrequency ablation	 Circumferential PVI without interpulmonary isthmus line + LA roof line + anterior wall LA + CTI	 BOX isolation	NA	12
Tamborero, 2009	Spain (--)	48	Radiofrequency ablation	 Circumferential PVI without interpulmonary isthmus line + LA roof line ablation + mitral isthmus ablation	 BOX isolation	63.9*	10

†DataExpressed as mean or median; *data from the entire study.

Abbreviations: AUS, Australia; CA, Canada; mo, months; CTI, cavotricuspid isthmus; LA, left atrium; PVI, pulmonary vein isolation; PWI, posterior wall isolation; RCT, randomized controlled trial; UK, United Kingdom.

Central Figure. Graphic Abstract PVI vs PVI with adjunctive PWI.

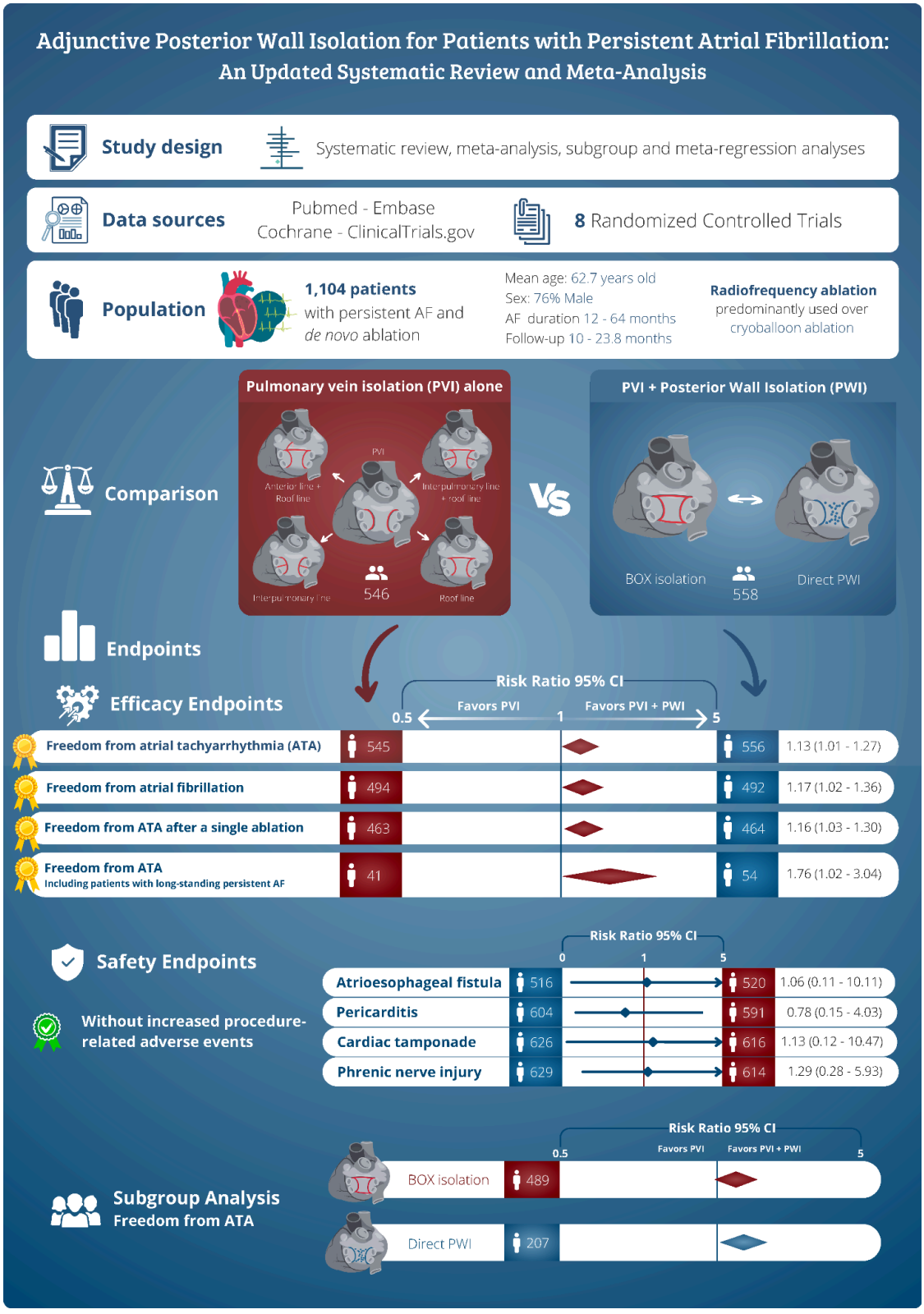


Figure 1. PRISMA flow diagram of study screening and selection.

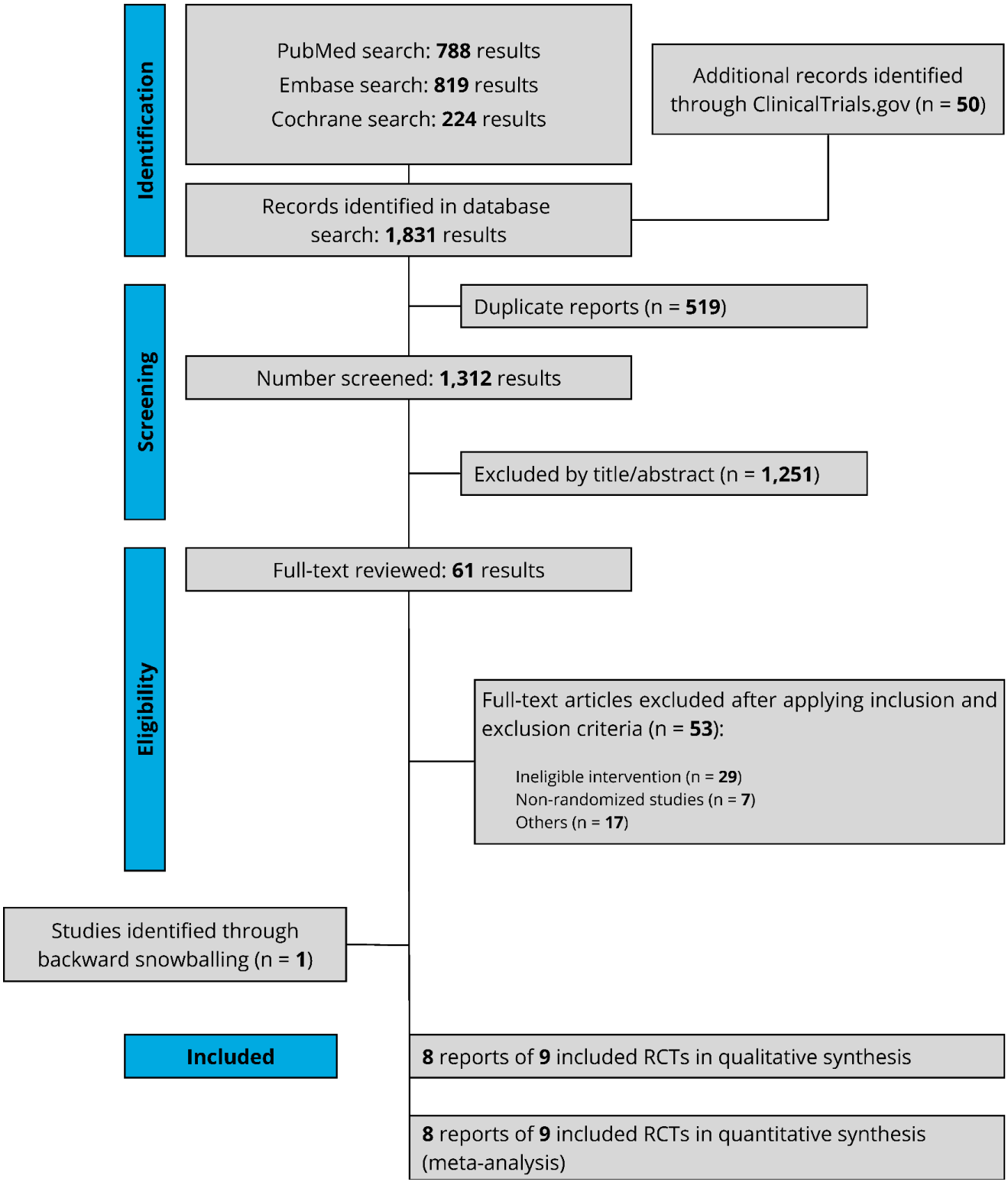


Figure 2. Meta-analysis of efficacy endpoints in AF patients undergoing PVI with adjunctive PWI.

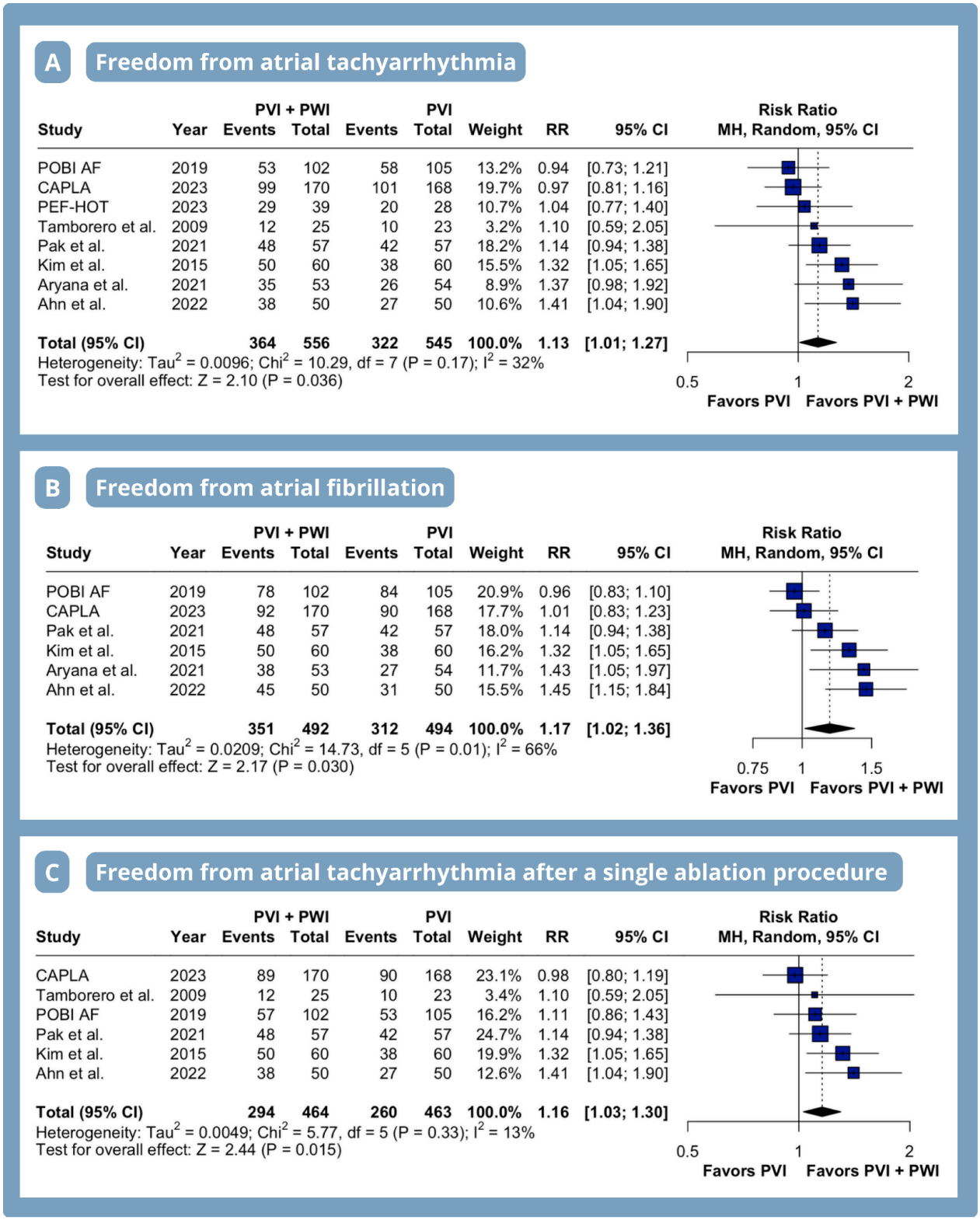


Figure 3. Meta-analysis of efficacy endpoints in patients with long-standing persistent AF undergoing PVI with adjunctive PWI.

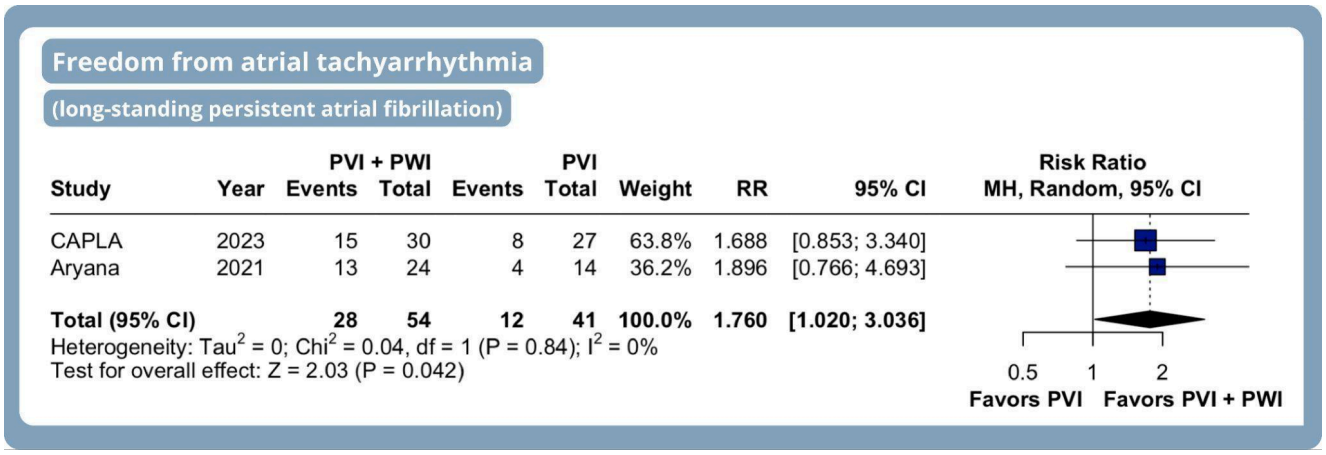


Figure 5. Subgroup analysis of the primary outcome in patients with AF undergoing PVI with adjunctive PWI stratified by PWI technique.

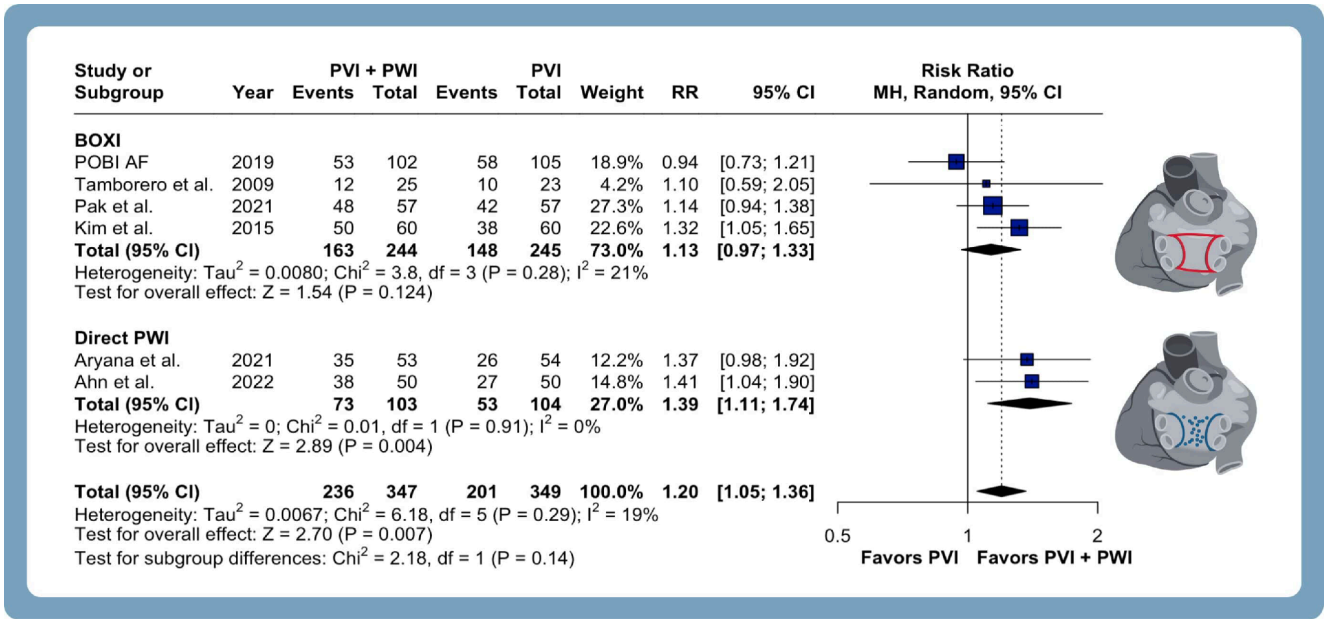
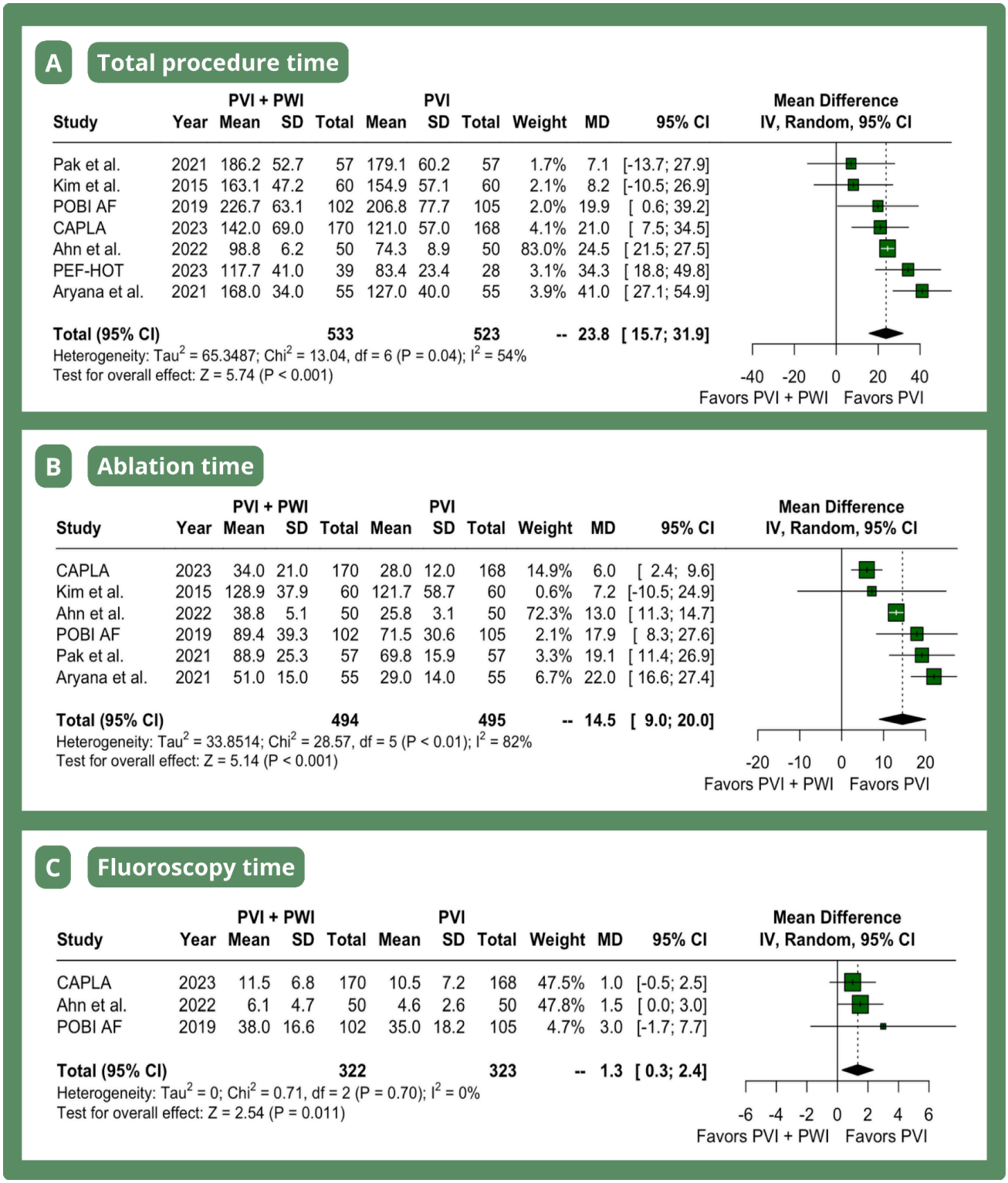


Figure 4. Meta-analysis of procedural endpoints in patients with AF undergoing PVI with adjunctive PWI.



SUPPLEMENTARY APPENDIX

Supplemental Methods 1. PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1 at MS
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 4 at MS
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 4 at MS
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg 5-8 at MS
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg. 5 at MS
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pg. 6 at sup
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 5-6 at MS
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 6 at MS
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 6-7 at MS
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg. 6 at MS
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 7 at MS
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg 7 at MS
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Table 1

Topic	No.	Item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg. 7-8 at MS
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg. 8 at MS, Pg. 12-13 at sup.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg. 7-8 at MS, Pg. 12-13 at sup.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg. 7-8 at MS
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg. 12-13 at sup.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg. 7 at MS
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Table 1, Pg. 7-10, 14-15 at sup.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pg. 11 at MS, Pg. 29 at sup.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig. 2-4 at MS, Pg. 16-18 at sup.
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Pg. 11 at MS, Pg. 19 at sup.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg 9-10 at MS
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg. 11 at MS, Pg. 12-13 at sup.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg. 12-13 at sup.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 29-30 at sup.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA

Topic	No.	Item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg. 12-14 at MS
	23b	Discuss any limitations of the evidence included in the review.	Pg. 14 at MS
	23c	Discuss any limitations of the review processes used.	Pg. 14 at MS
	23d	Discuss implications of the results for practice, policy, and future research.	Pg. 15 at MS
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	PROSPERO; CRD42023397998
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=397998
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	More outcomes were available and main outcome was changed.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	Pg. 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Non-Available

Abbreviations: MS, manuscript; sup., supplement.

Supplemental Methods 2. Details of the Search Strategy

Search Strategy for all databases
("atrial fibrillation" OR AF OR A-fib OR Afib) **AND** (PWI OR "posterior wall" OR "posterior left atrial wall" OR "posterior LA wall" OR "LA posterior wall" OR "left atrial posterior wall" OR "posterior left atrium" OR box OR "posterior box" OR "single ring" OR debulking) **AND** (PVI OR pulmonary vein) **AND** (ablation OR isolation)

Supplemental Methods 3. Enrollment Period by Study

Study	Enrollment Period
Kistler, 2023 (CAPLA)	July 2018 - March 2021
Wong, 2023 (PEF-HOT)	NA
Ahn, 2022	December 2019 - July 2020
Aryana, 2021	February 2017 – April 2019
Pak, 2021 (PEACEFUL)	June 2014 - ongoing
Lee, 2019 (POBI-AF)	March 2016 – January 2019
Yu, 2017	June 2014 - ongoing
Kim, 2015	January 11 – August 2012
Tamborero, 2009	NA

Supplemental Methods 4. Main Exclusion Criteria Used by Study

Study and year	Main exclusion criteria
Kistler, 2023 (CAPLA)	Long-standing persistent AF > 3 years; AF secondary to reversible cause; severe valvular heart disease or cyanotic; congenital heart disease; hypertrophic cardiomyopathy
Wong, 2023 (PEF-HOT)	Long-standing persistent AF > 3 years and LAD > 60 mm
Ahn, 2022	Prior AF ablation or cardiac surgery; CKD with clearance rate <30mL/min
Aryana, 2021	AF with a reversible cause; prior LA ablation; LVEF < 40%; LAD > 50 mm; prior MI; congenital heart disease; hypertrophic cardiomyopathy; LVEF < 40%; class IV HF
Pak, 2021 (PEACEFUL)	AF with rheumatic valvular disease; LAD ≥ 55 mm; prior AF ablation or cardiac surgery; valvular AF; structural heart disease
Lee, 2019 (POBI-AF)	AF with rheumatic valvular disease; LAD ≥ 60 mm; prior AF ablation or cardiac surgery; valvular AF
Kim, 2015	Prior AF ablation or cardiac surgery, cardiomyopathy, or congenital heart disease
Tamborero, 2009	Prior AF ablation

LVEF, left ventricular ejection fraction; HF, heart failure; CKD, chronic kidney disease; LAD, left atrial diameter; MI, myocardial infarction.

Supplemental Methods 5. Methods Used to Confirm Isolation During Ablation

Study	Methods used for ablation confirmation	
Kistler, 2023 (CAPLA)	Presence of entrance and exit block, along with the presence of spontaneous potentials or the complete absence of local electrograms without any response to high-output pacing.	
Wong, 2023 (PEF-HOT)	Presence of entrance block (noise floor 0.04 mV) and exit block pacing at 20 mA at 2 milliseconds	
Ahn, 2022	Confirmed by high-density voltage mapping.	
Aryana, 2021	A detailed post-ablation 3-dimensional electroanatomic map was recreated in each patient using the high-density mapping catheter to confirm PVI or PVI with PWI, as applicable (cutoff 0.10 to 0.50 mV). In addition to detailed voltage mapping in sinus rhythm, PVI and PVI with PWI were confirmed using high-output pacing (>10 mA) within the PVs to test for entrance or exit block before and after intravenous drug stimulation (adenosine). Pacing maneuvers to confirm PWI were also performed extensively from multiple sites within the area of isolation (the PV component) before and after intravenous drug stimulation.	
Pak, 2021 (PEACEFUL)	For PVI, electrical isolation of PV potentials and bidirectional block were confirmed.	For PWI, successful bidirectional block of the roof line, (2) voltage abatement of <0.1 mV in the LA posterior wall, and (3) entrance and exit block.
Lee, 2019 (POBI-AF)	For PVI, verified during an isoproterenol infusion after a 30-min waiting time.	For PWI, 1) successful bidirectional block of the roof line; 2) voltage abatement of <0.1 mV in the LA posterior wall; and 3) entrance and exit block.
Yu, 2017	For PVI, electric isolation of PV potentials and bidirectional block of PVs.	For PWI, no endocardial electrogram in the LA posterior wall with a roof line block.
Kim, 2015	For PVI differential pacing maneuver on either side of the linear lesions after the restoration of sinus rhythm.	For PWI, defined as the absence of local potentials or dissociation potentials in the posterior wall of the LA and lack of LA capture by pacing maneuver.
Tamborero, 2009	For PVI, local electrogram inside the encircled area disappeared or was dissociated or, when this was not possible, until the bipolar voltage amplitude dropped to 0.15 mV; electric block was confirmed by the inability to conduct to the LA after pacing at several sites within the PV antrum.	For PWI, confirmed by the inability to conduct to the remaining atria after pacing at several sites within the surrounded LA posterior region with the ablation catheter, observing the local capture in the proximal bipole of the pacing catheter when possible.

Supplemental Methods 6. Endpoint Definitions and Methods used by Study

Study	Atrial tachyarrhythmia (ATA)	Method	Clinical ATA recurrence
Kistler, 2023 (CAPLA)	AF, AFL, or AT	ILR or CIED: 53 (15.7%) Frequent ECG monitoring: 237(70.1%) 24-h Holter each visit (3, 6, 9, and 12 months): 47 (13.9%)	ATA lasting > 30 seconds and occurring after a 3-month blanking period after a single ablation procedure.
Wong, 2023 (PEF-HOT)	AF, AFL, or AT	Follow-up at 1, 3, 6, and 12 months, with 2-week continuous ECG monitoring at 3 and 12 months	
Ahn, 2022	AF, AFL, or AT	ECG each visit and 24h-Holter at 3, 6, and 12 months ECG whenever a patient presented with palpitations	
Aryana, 2021	AF, AFL, or AT	ECG each visit. Mobile cardiac telemetry at 3-, 6-, and 9-months post-ablation unless pre-existing CIED	
Pak, 2021 (PEACEFUL)	AF or AFL	ECG each visit. 24-hour Holter at 3 and 6 months, then every 6 months	
Lee, 2019 (POBI-AF)	AF or AFL	ECG each visit. 24-hour Holter at 3 and 6 months, then every 6 months	
Yu, 2017	AF or AFL	ECG each visit. 24-hour Holter at 3 and 6 months, then every 6 months	
Kim, 2015	AF or AFL	ECG each visit and whenever patients reported palpitations. 48-hour Holter at 1-, 3-, 6- and 12-months post-ablation	Any patient with documented AF or atrial flutter (AFL) during the follow-up period was diagnosed as having a clinical arrhythmia recurrence.
Tamborero, 2009	AF or AFL	48-hour Holter before each visit at 1, 4, and 7 months, then every 6 months if asymptomatic	AF recurrences or LA flutter after a blanking period of 3 months.
Abbreviations: ATA, atrial tachyarrhythmia; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; ILR, implantable loop recorder; CIED, cardiac implantable electronic device; ECG, electrocardiography; LA, left atrium			

Supplemental Methods 7. Addressing Heterogeneity

To ensure the reliability and robustness of our findings, we conducted a thorough analysis to identify potential outliers and influential studies for the primary outcome. This included the use of a Graphic Display of Heterogeneity (GOSH) analysis, in which we performed multiple random simulations and exclusions. The GOSH plot was generated, and three unsupervised machine learning (ML) algorithms were applied to detect clusters in the data, namely the k-means algorithm, density-based spatial clustering of applications with noise (DBSCAN), and Gaussian mixture models.

We created a Baujat plot and performed a leave-one-out sensitivity analysis to investigate potential outliers for the primary efficacy endpoint. The leave-one-out sensitivity analysis removed one study at a time to ensure that our results were not reliant on a single study. These methods helped to identify any potential outliers.

It is worth noting that the MH default continuity correction of 0.5 (default behavior in metabin function [R meta package]) is only necessary when one specific cell is zero in all included studies in the meta-analysis. However, its use in other scenarios has been discouraged by Efthimiou et al. [7], as it can lead to biased results. Therefore, we only applied the continuity correction in the specific situation mentioned above, and when it was not fitted, we used the exact MH method without continuity correction.

Supplemental Results 1. Addressing Heterogeneity

Hence, due to the moderate heterogeneity of the results, we performed Graphical Display of Study Heterogeneity (GOSH) analyses for the primary endpoint. The GOSH plot illustrates the effect size plotted against the I^2 for all possible combinations of studies. The 255 possible subsets of meta-analysis (2^k – 1 possible combinations) for freedom from atrial tachyarrhythmia recurrence (ATA) are presented as a GOSH plot in Supplementary Figure 7A. By analyzing the pattern in our data, we find that most values are concentrated in a cluster with high heterogeneity and a symmetrical distribution along the overall estimate axis. The distribution of I^2 is relatively bimodal, with clusters following a moderate I^2 sparse and considerable number of study combinations for which the estimated heterogeneity was null. To find out which studies cause this shape, we applied three unsupervised machine learning (ML) algorithms, detailed in methods, to detect clusters in the GOSH plot data (Supplemental Figures 7B-D*)*. Ultimately, one potential outlier was identified similarly by the three unsupervised ML algorithms. The corresponding subset, including this potential outlier, is demonstrated in Supplemental Figure 7E-F. In summary, the GOSH analysis showed that heterogeneity significantly changed when the CAPLA trial was excluded from the analysis. The overall effect did not change significantly before and after excluding random studies in the GOSH plot. However, results also show that the results are stable on multiple simulations, despite significant heterogeneity. We further explored each study`s influence by performing a Baujat plot leave-one-out sensitivity analysis (Supplemental Figure 8) and plotting the leave-one-out sensitivity analysis (Supplementary Figure 9). The analyses showed that most of the heterogeneity was carried out by CAPLA trial, as already identified by GOSH analysis. By inspecting the leave-one-out sensitivity analysis, when the CAPLA trial is omitted, the pooled effect estimates (RR) varied from 1.13 to 1.18, accompanied by a significant decrease of heterogeneity (I^2) from 32% to 13%. The CAPLA trial had the second smallest AF duration period and the largest sample size, contributing to the heterogeneity in the meta-analytic summary estimates.

Supplemental Table 1. Clinical Baseline of the Patients Included in the Primary Analysis

Study	Patients PWI (-)/PWI(+)	Age† , y	Male, n (%)	AF duration †, months	LVEF†, %	LAD†, mm	HTN, n (%)	HF, n (%)	CHA2DS2-VASc score†	Follow-up† (months)
Kistler, 2023 (CAPLA)	168/170	65.6	259 (76%)	26.29	55.5	45	159 (47%)	98 (29%)	2	12
Wong, 2023 (PEF-HOT)	28/39	68.4	51 (76.1)	8.4 (3–25)	52.1	47	49 (73.1)	21 (31.3%)	2.7	12.4
Ahn, 2022	50/50	65.5	84 (84%)	56.15	58	48.3	83 (83%)	45 (45%)	3	15
Aryana, 2021	55/55	68.5	68 (61.8%)	NA	60.5	44	62 (53.3%)	29 (26.4%)	2.6	21
Pak, 2021 (PEACEFUL)	57/57	60.1	82 (71.9%)	24 (10–60)	60.5	42	58 (50.9%)	23 (20.2%)	2	23.8
Lee, 2019 (POBI-AF)	105/102	58.7	172 (83.1%)	38.5 ± 38.8	59	44.8	97 (46.9%)	47 (22.7%)	1.72	16.2
Yu, 2017	59/54	60.4	85 (75%)	42.8 ± 44.4	62	42.7	28 (52%)	19 (17%)	2.2	18.6
Kim, 2015	60/60	57.2	87 (72.5%)	NA	63.7	42.2	54 (45%)	23 (19.2%)	NA	12
Tamborero, 2009	23/25	52.7*	92* (76.7%)	63.9*	59.6*	41.3*	55* (45.8%)	NA	NA	10±4

*Data from the entire study population, not just in persistent atrial fibrillation; †Mean or median; AAD: anti-arrhythmic drugs; LSP-AF, long-standing persistent atrial fibrillation; HTN, hypertension; HF, heart failure; PWI, posterior wall isolation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; CHA2DS2-VASC, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female)

Supplemental Table 2. Baseline Patients' Antiarrhythmic Drugs

Study	Class 1	Class 3
Kistler, 2023 (CAPLA)	48 (14.2%)	186 (55%)
Wong, 2023 (PEF-HOT)	NA	
Ahn, 2022	36 (36%)	64 (64%)
Aryana, 2021	35(31.8%)	
Pak, 2021 (PEACEFUL)	47 (41.2%)	67 (58.8%)
Lee, 2019 (POBI-AF)	NA	
Yu, 2017	64 (56.6%)	49 (43.3%)
Kim, 2015	NA	
Tamborero, 2009		

Supplemental Figure 1. Secondary Efficacy Endpoints

Figure 1A. Freedom from Atrial Flutter/Tachycardia

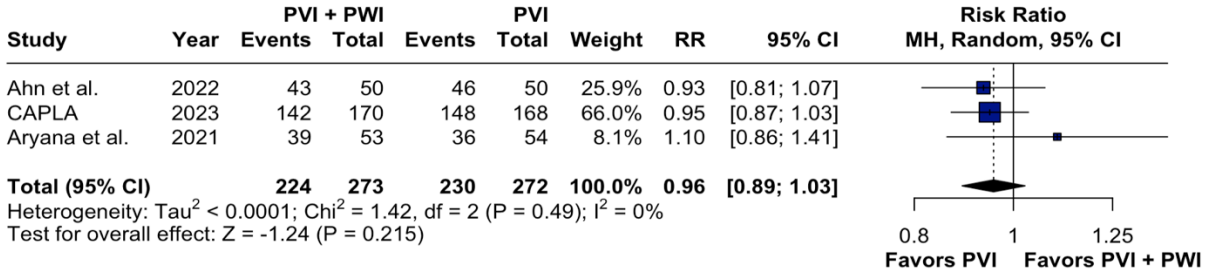


Figure 1B. Freedom from ATA without AAD

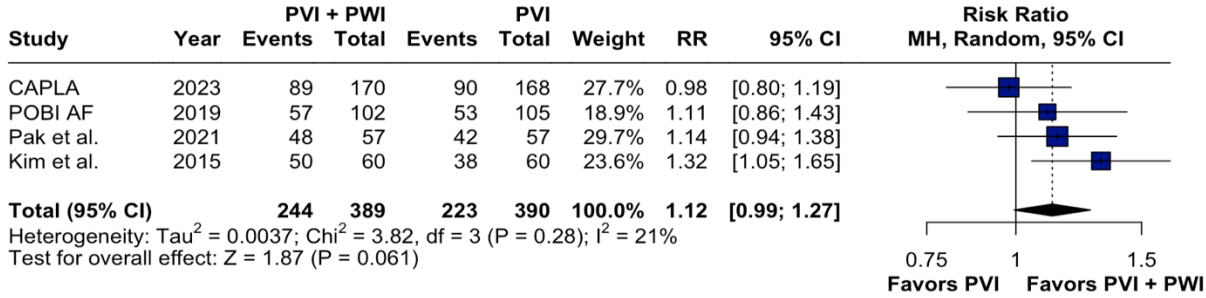


Figure 1C. Freedom from ATA after a Single Procedure without AAD

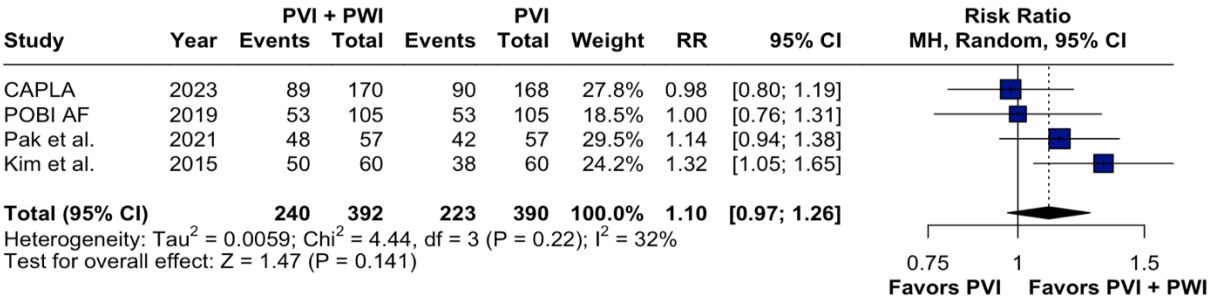


Figure 1D. Need for Cardioversion

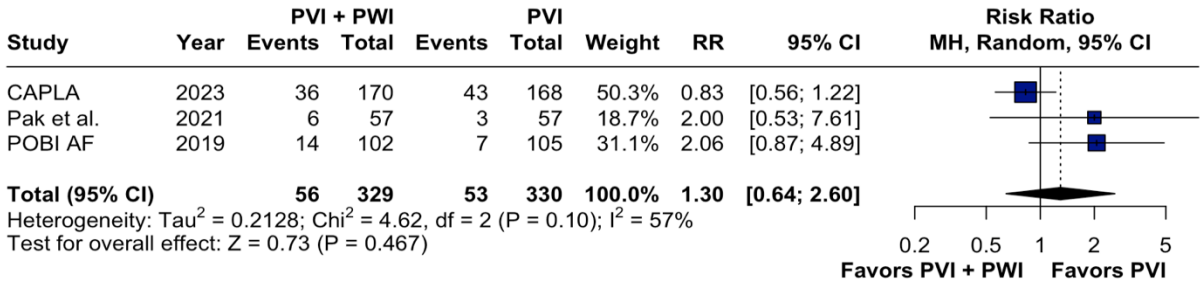
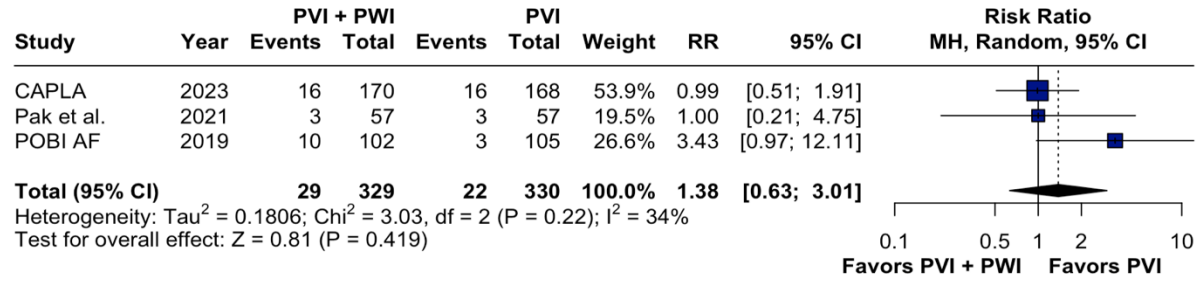


Figure 1E. Need for Repeated Ablation



Supplemental Figure 2. Safety Endpoints

Figure 2A. Atrioesophageal fistula

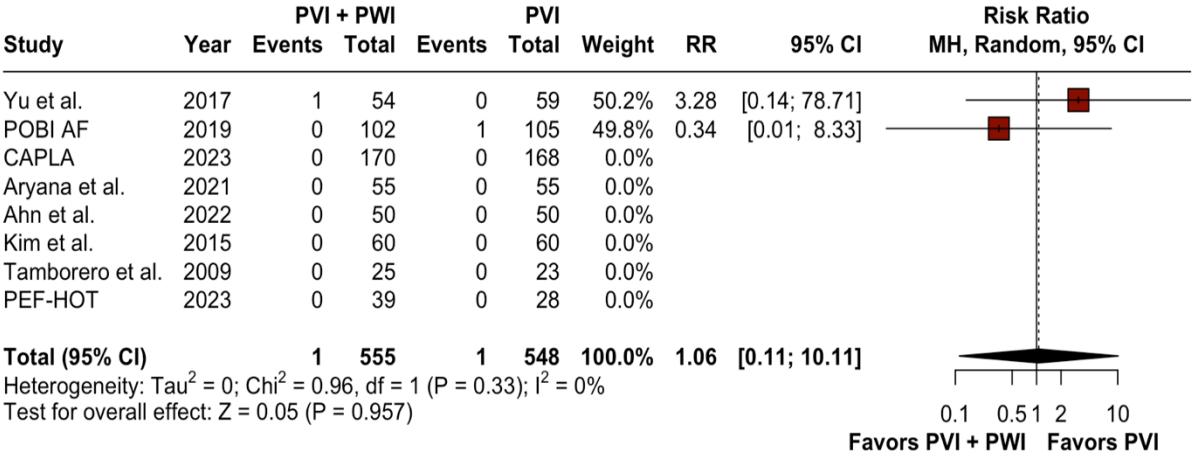


Figure 2B. Pericarditis

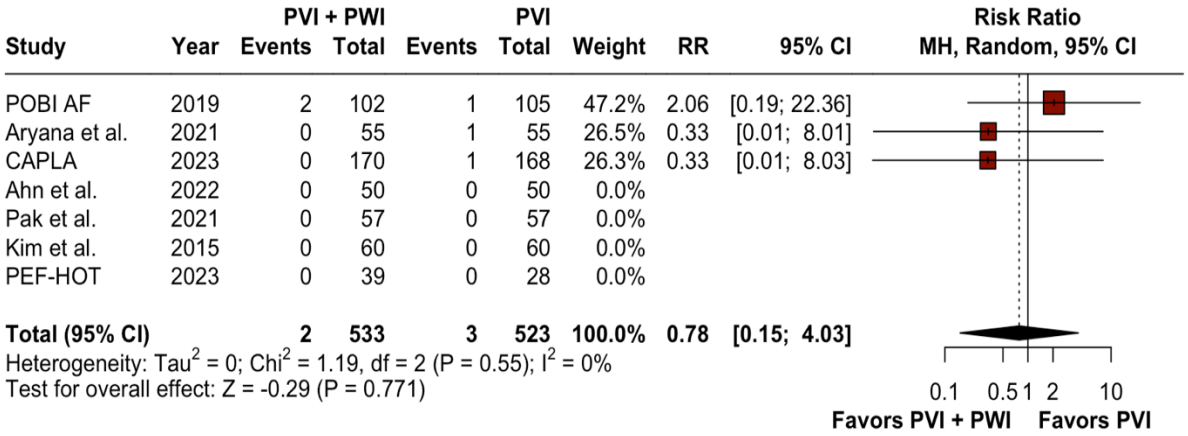


Figure 2C. Cardiac tamponade

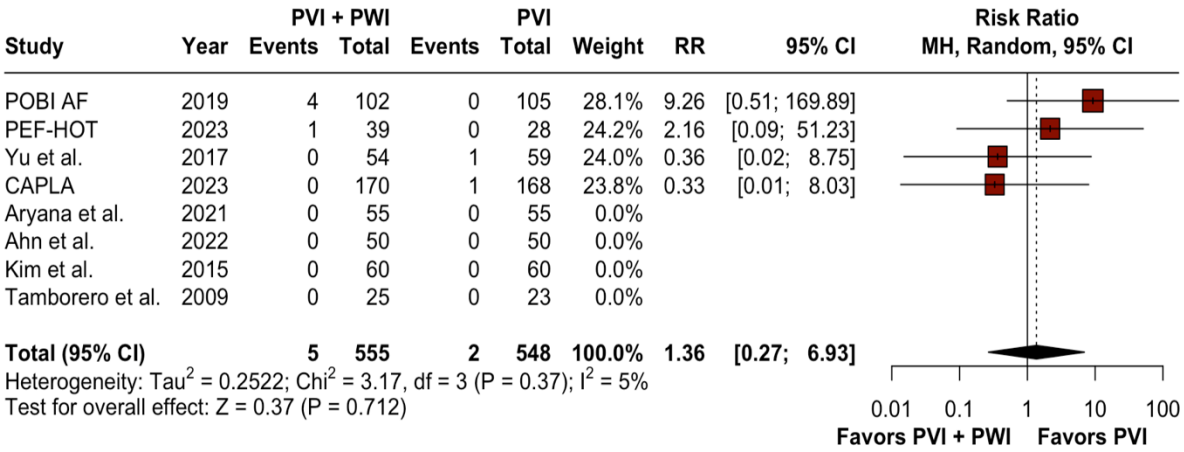
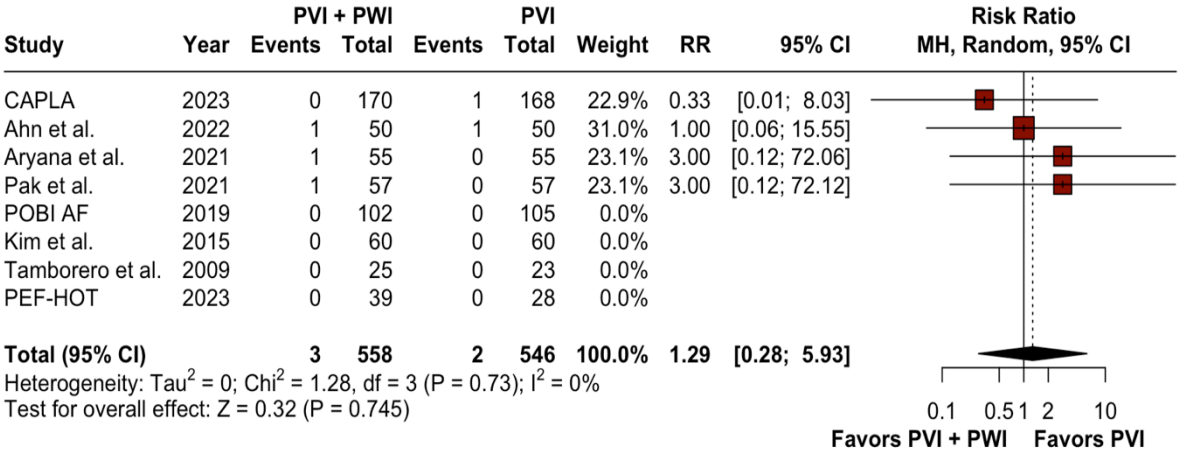


Figure 2D. Phrenic nerve injury



Supplemental Figure 3. Secondary Endpoints

Figure 3A. Left atrial diameter change (mm)

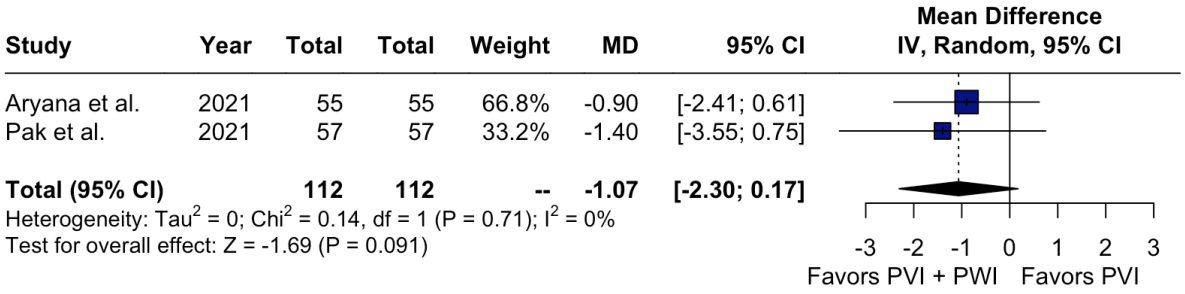


Figure 3B. Short-term AAD prescription (<12 months)

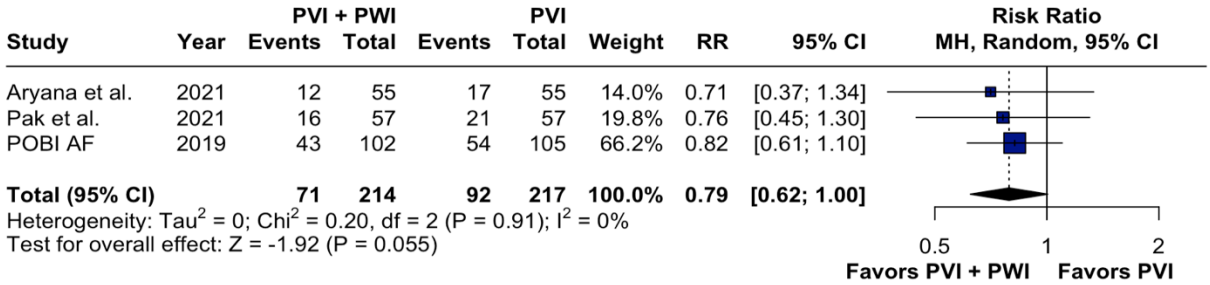
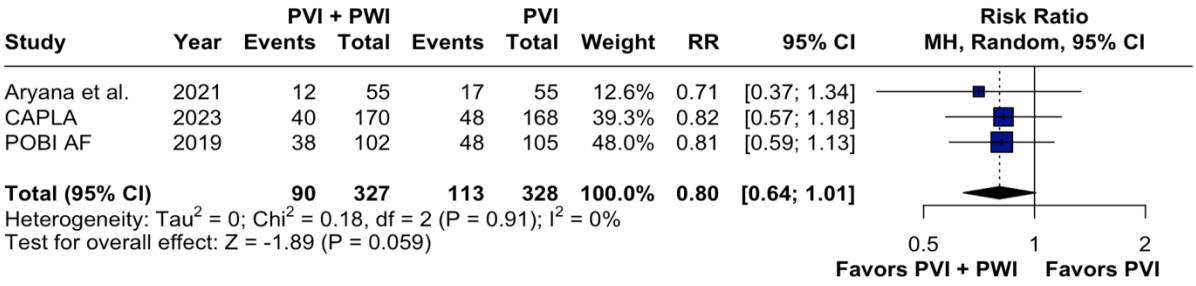


Figure 3C. Long-term AAD prescription (≥12 months)



Supplemental Figure 4. Subgroup Analysis for the Primary Efficacy Endpoint

Figure 4A. Primary Efficacy Endpoint Stratified by Energy Source Used.

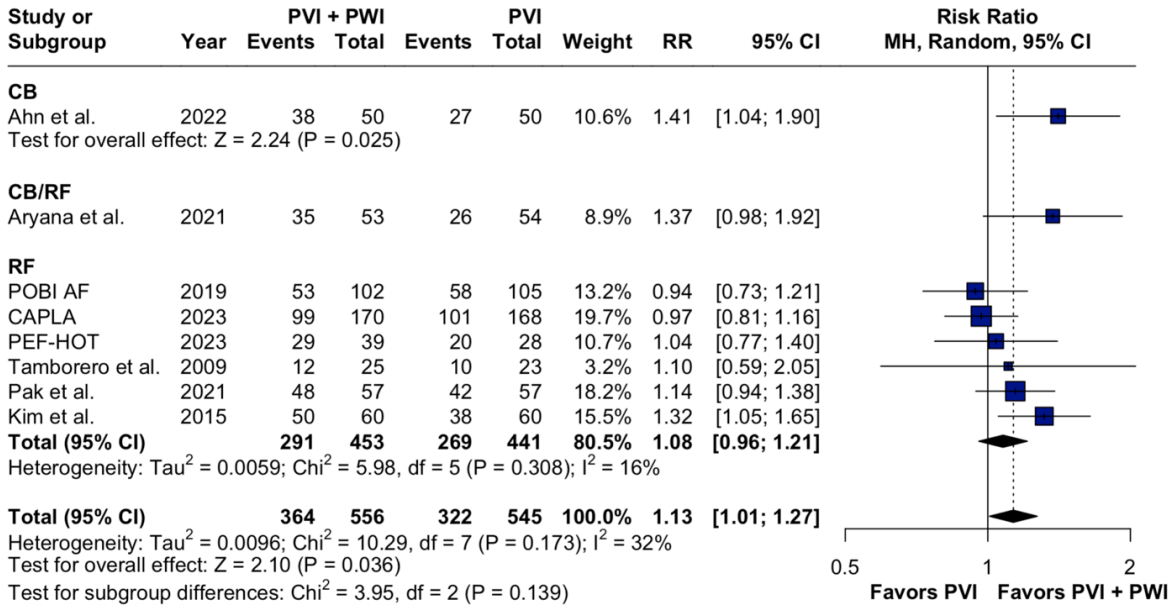


Figure 4B. Primary Efficacy Endpoint Stratified by Overall Risk of Bias.

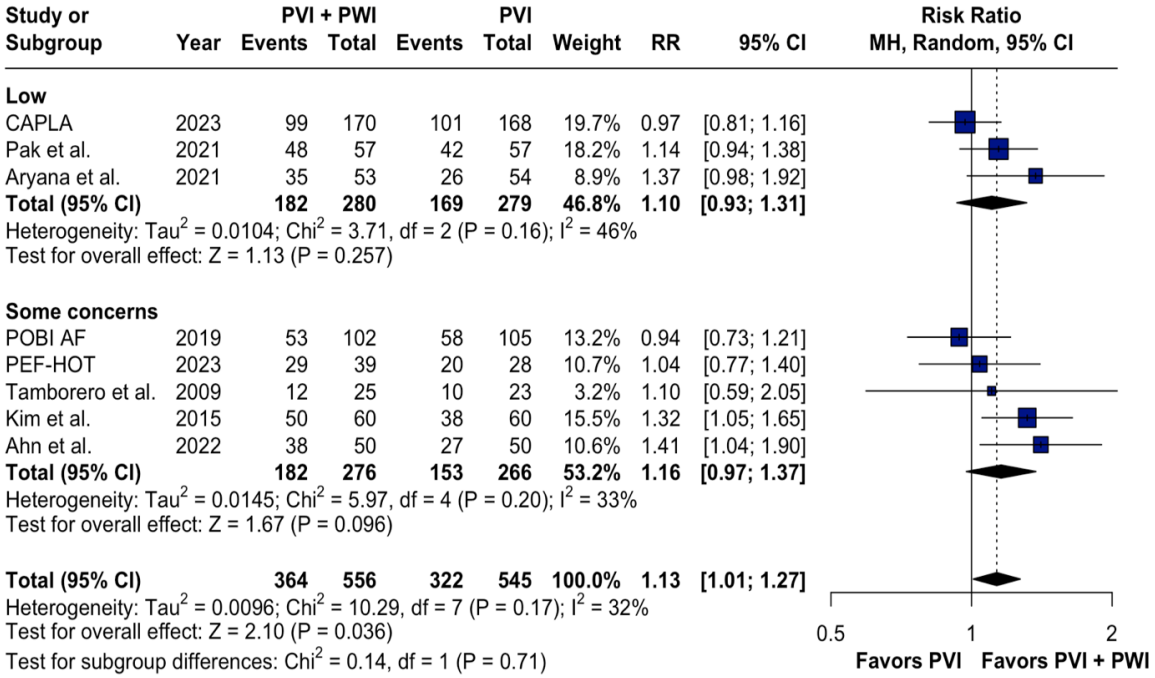
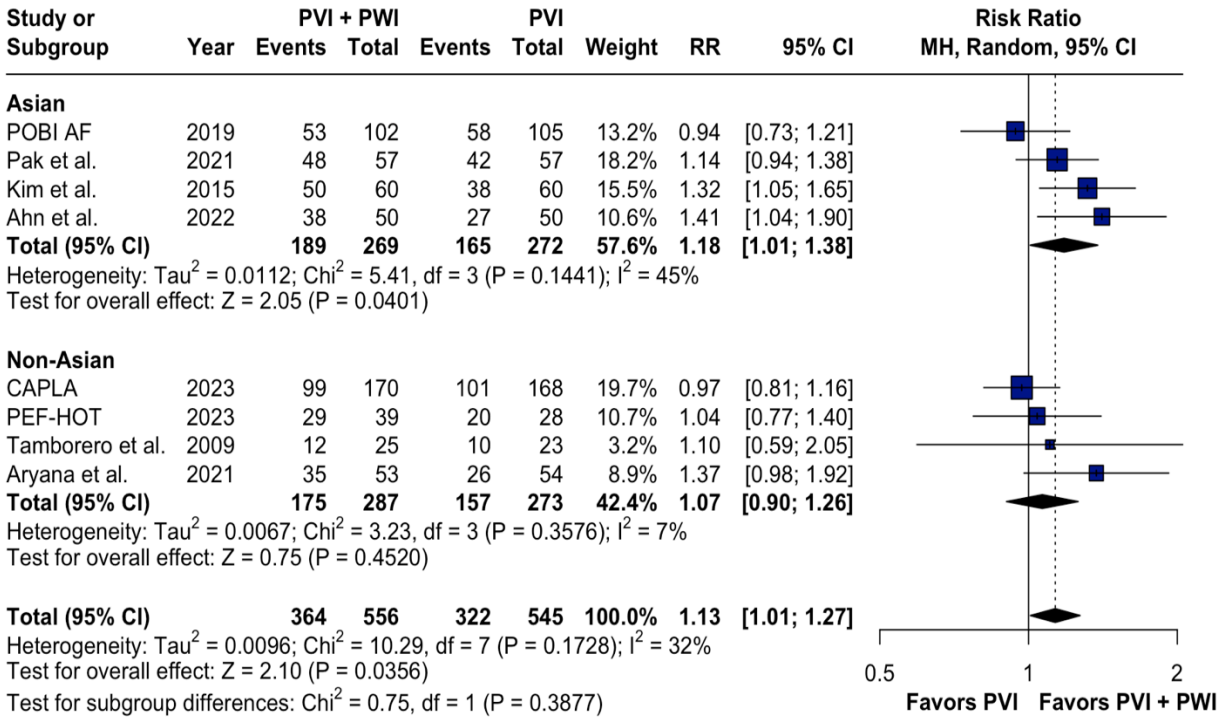
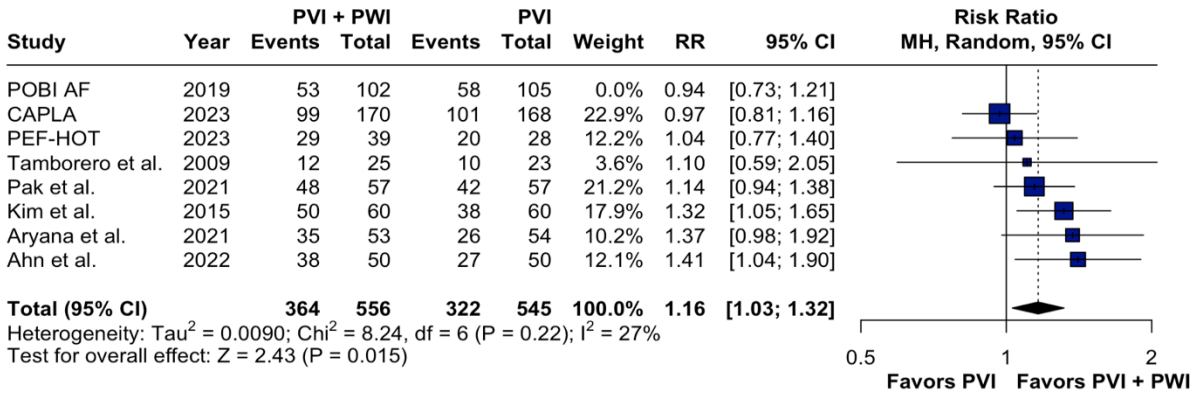


Figure 4C. Primary Efficacy Endpoint Stratified by Country.



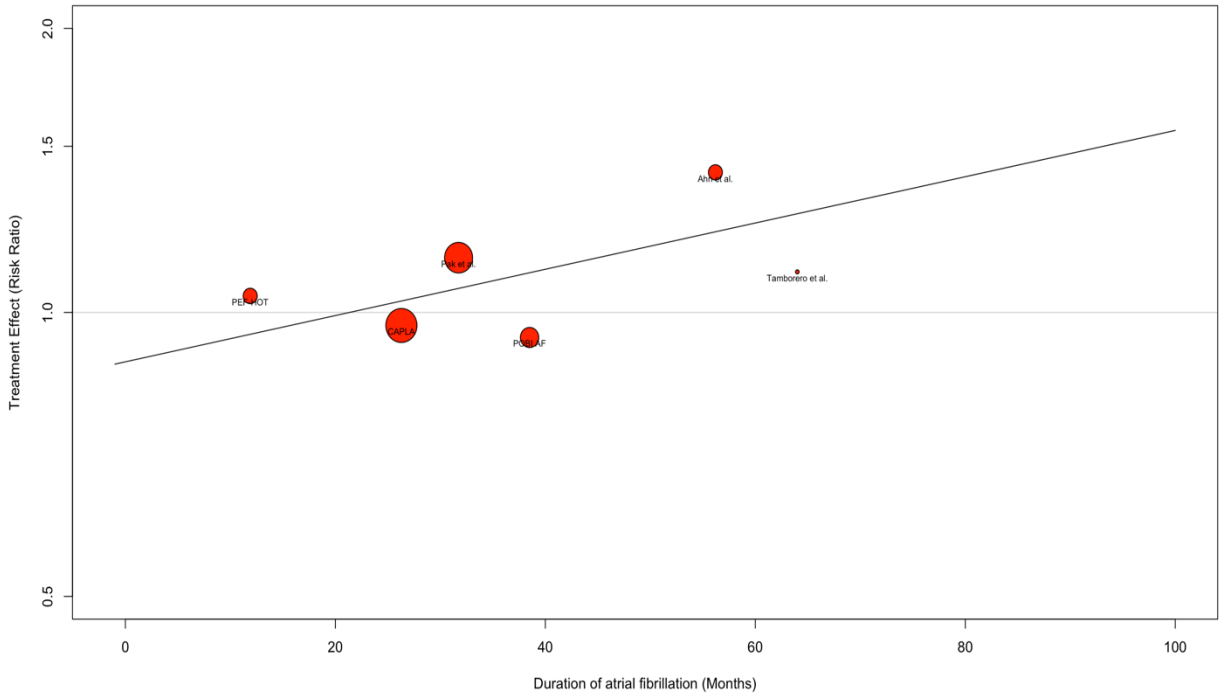
Supplemental Figure 5. Sensitivity Analysis of the Primary Outcome

Primary Efficacy Endpoint Omitting Studies Performing an Additional Mitral Isthmus Ablation in PWI Group.



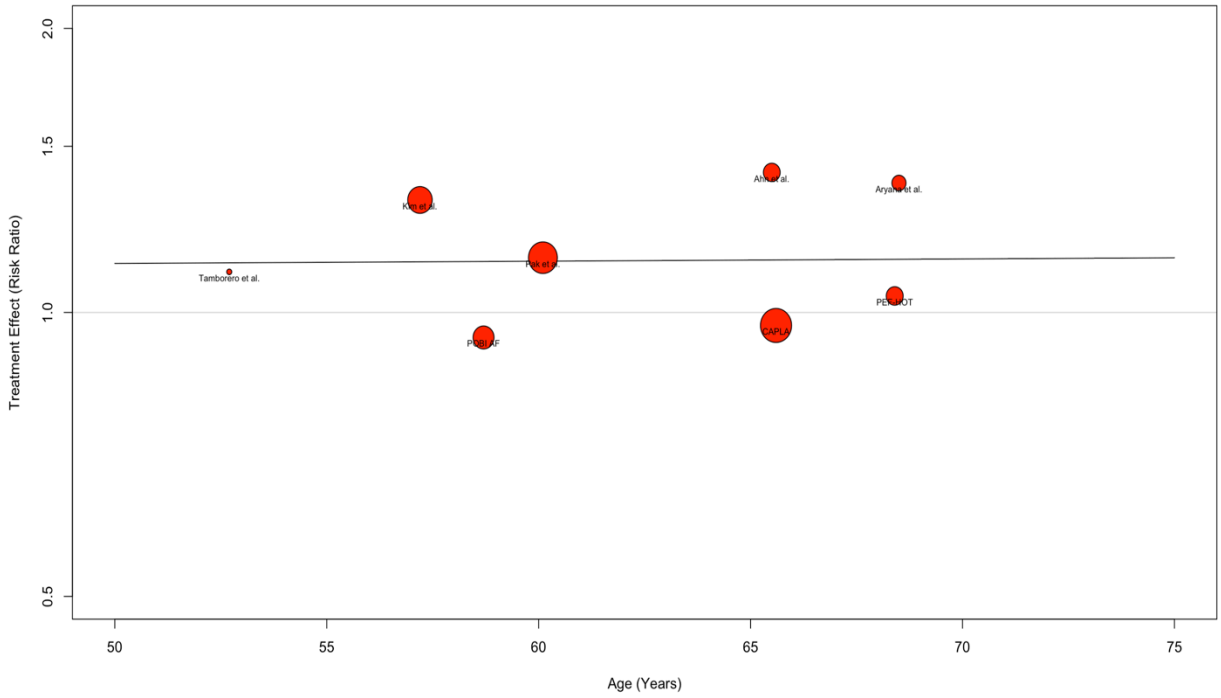
Supplemental Figure 6. Meta-Regressions and Bubble Plots

Figure 6A. Meta-regression and bubble plot assessing the impact of AF duration on freedom from atrial tachyarrhythmias in all studies that reported this covariable.



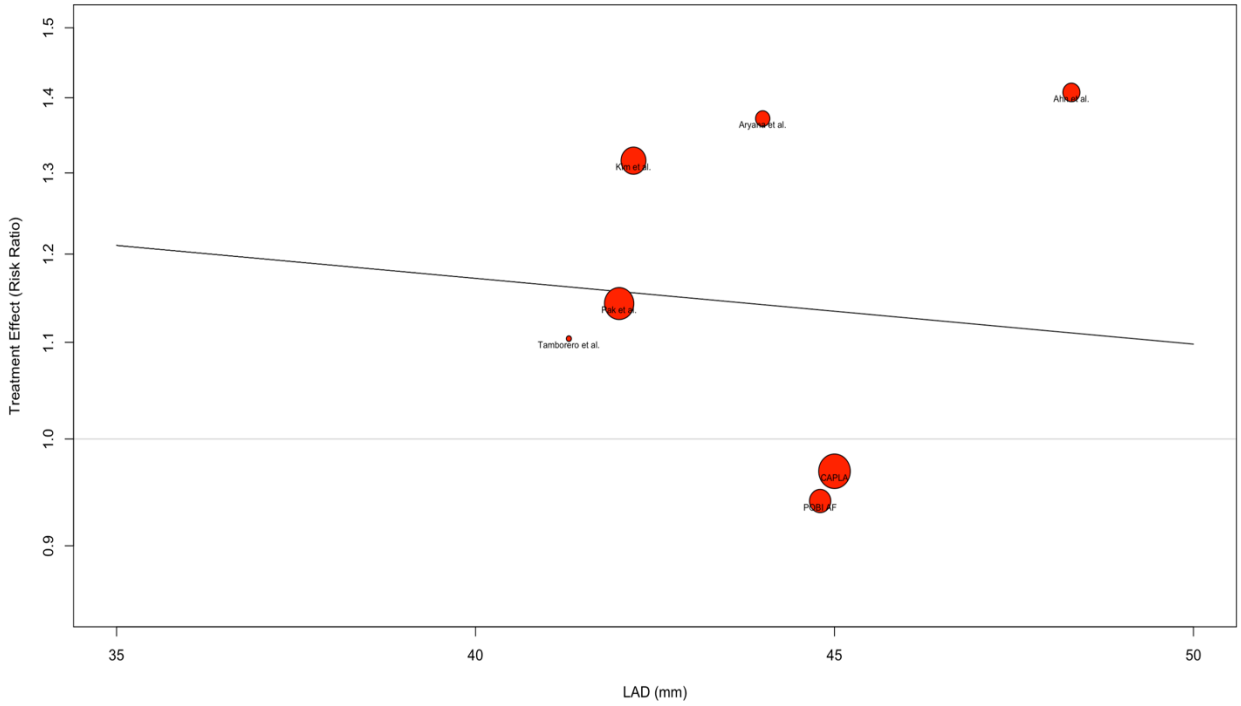
	Effect Estimate	p-value	I^2	Test for Residual Heterogeneity
Intercept	-0.1206	0.4038	89.11%	p=0.4071
AF duration	0.0057	0.1732		

Figure 6B. Meta-regression and bubble plot assessing the impact of mean age on freedom from atrial tachyarrhythmias in all studies that reported this covariable.



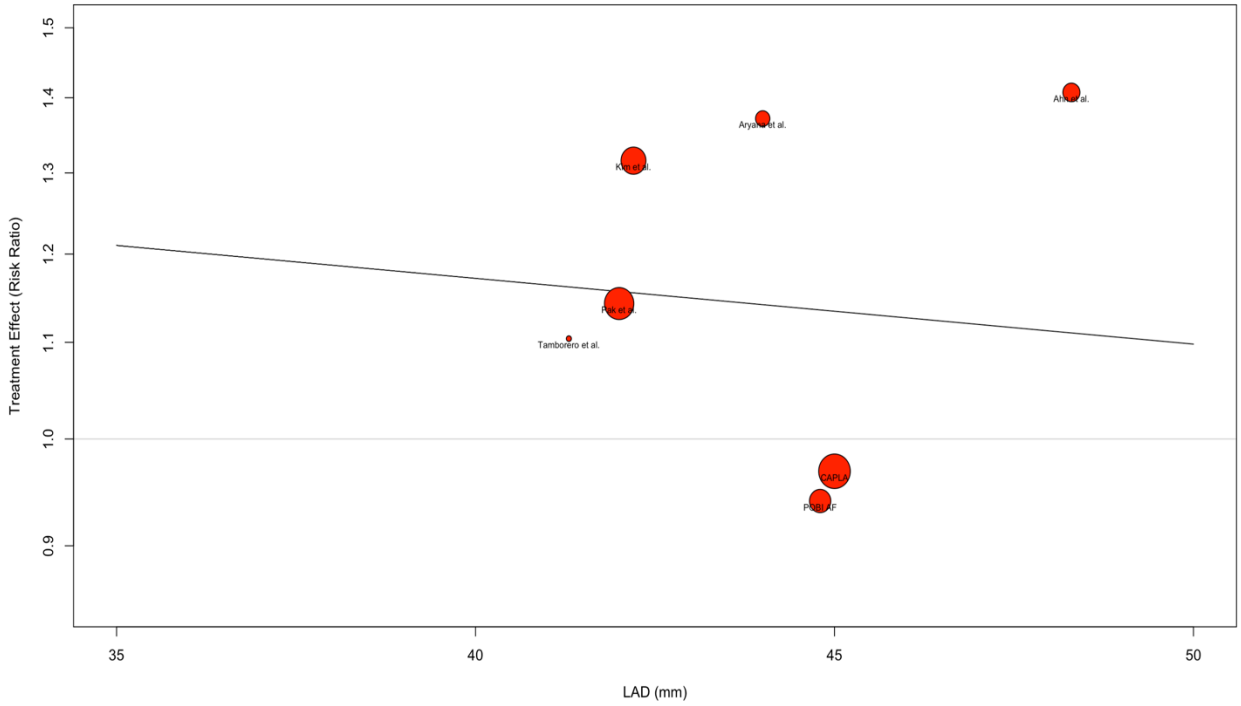
	Effect Estimate	p-value	I^2	Test for Residual Heterogeneity
Intercept	0.0912	0.9172	0.00%	p=0.1179
Mean age	0.0006	0.9677		

Figure 6C. Meta-regression and bubble plot assessing the impact of left atrial diameter (LAD) on ATA recurrence in all studies that reported this covariable.



	Effect Estimate	p-value	I^2	Test for Residual Heterogeneity
Intercept	0.4184	0.6282	0%	p=0.1250
LAD	-0.0065	0.7345		

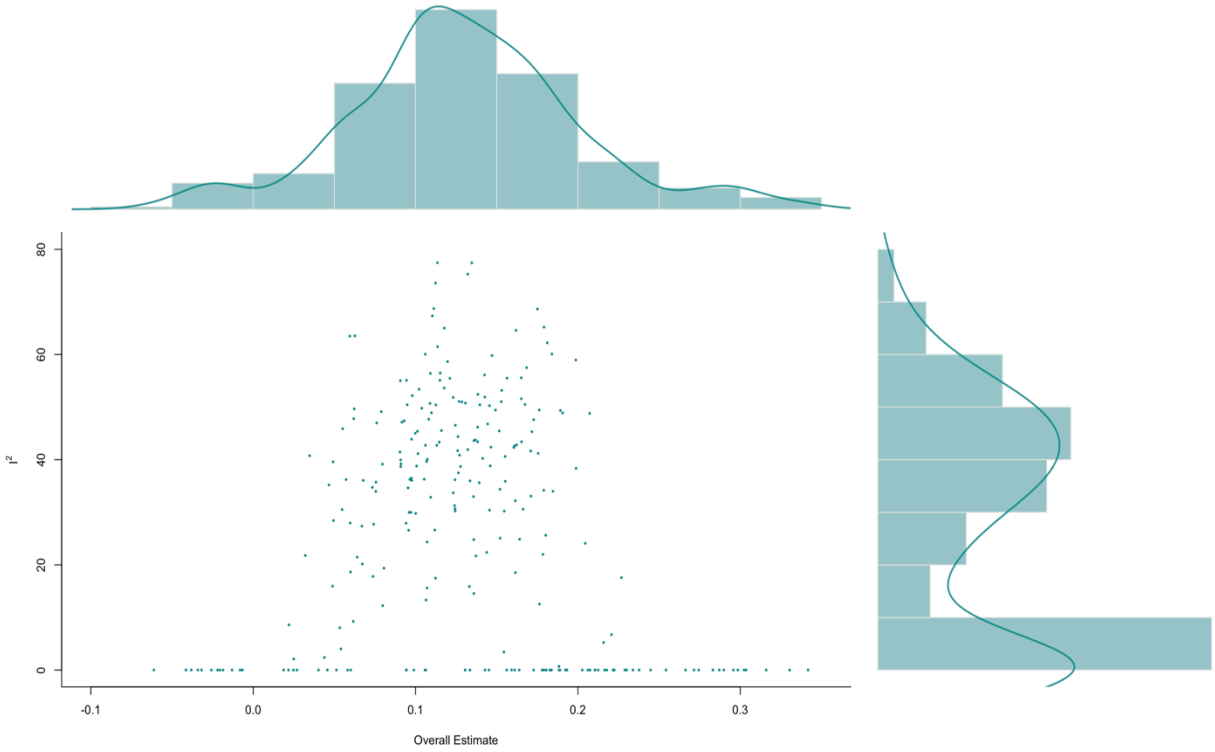
Figure 6D. Meta-regression and bubble plot assessing the impact of left ventricular ejection fraction (LVEF) on ATA recurrence in all studies that reported this covariable.



	Effect Estimate	p-value	I^2	Test for Residual Heterogeneity
Intercept	-1.4117	0.0833	90.60%	p=0.3743
LVEF	0.0260	0.0608		

Supplemental Figure 7. Graphical Display of Study Heterogeneity (GOSH)

Figure 7A. GOSH plot.



Legend: GOSH plot of I^2 against summary effect sized (log risk ratio).

Figure 7B. K-means Algorithm

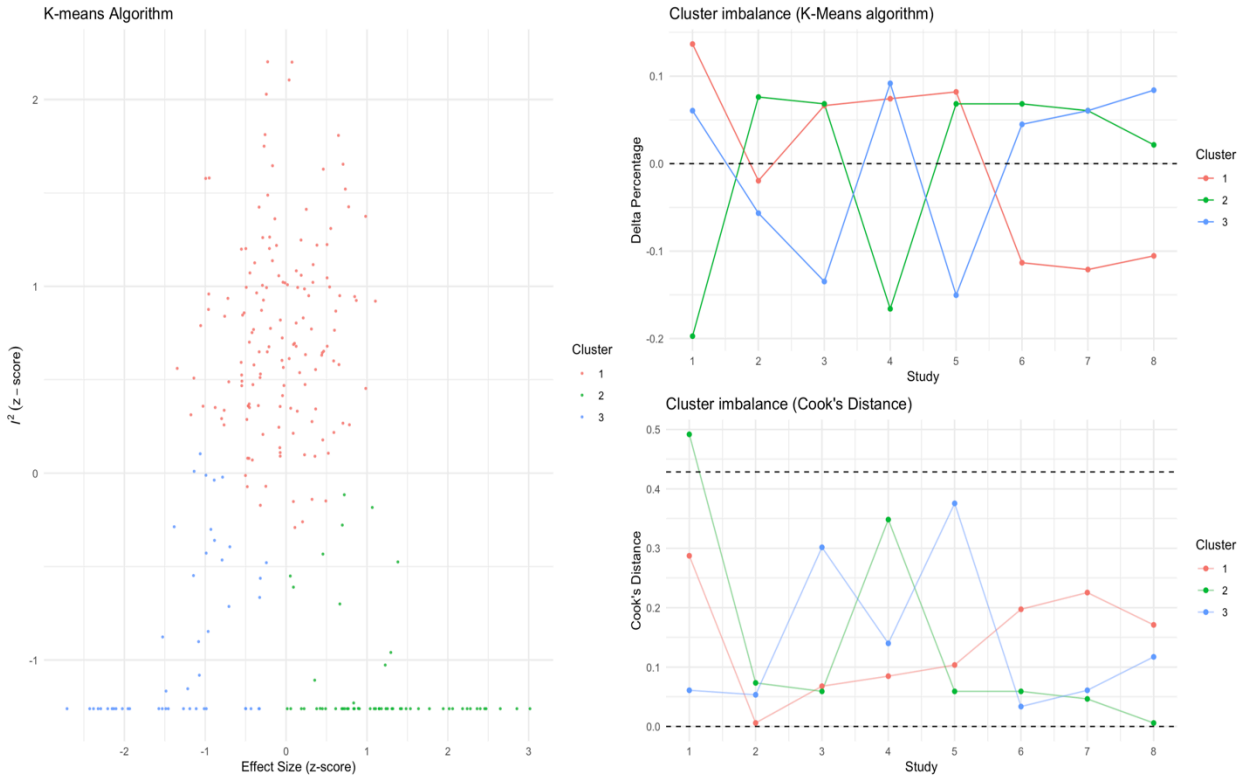


Figure 7C. Density-based spatial clustering of applications with noise (DBSCAN) Algorithm

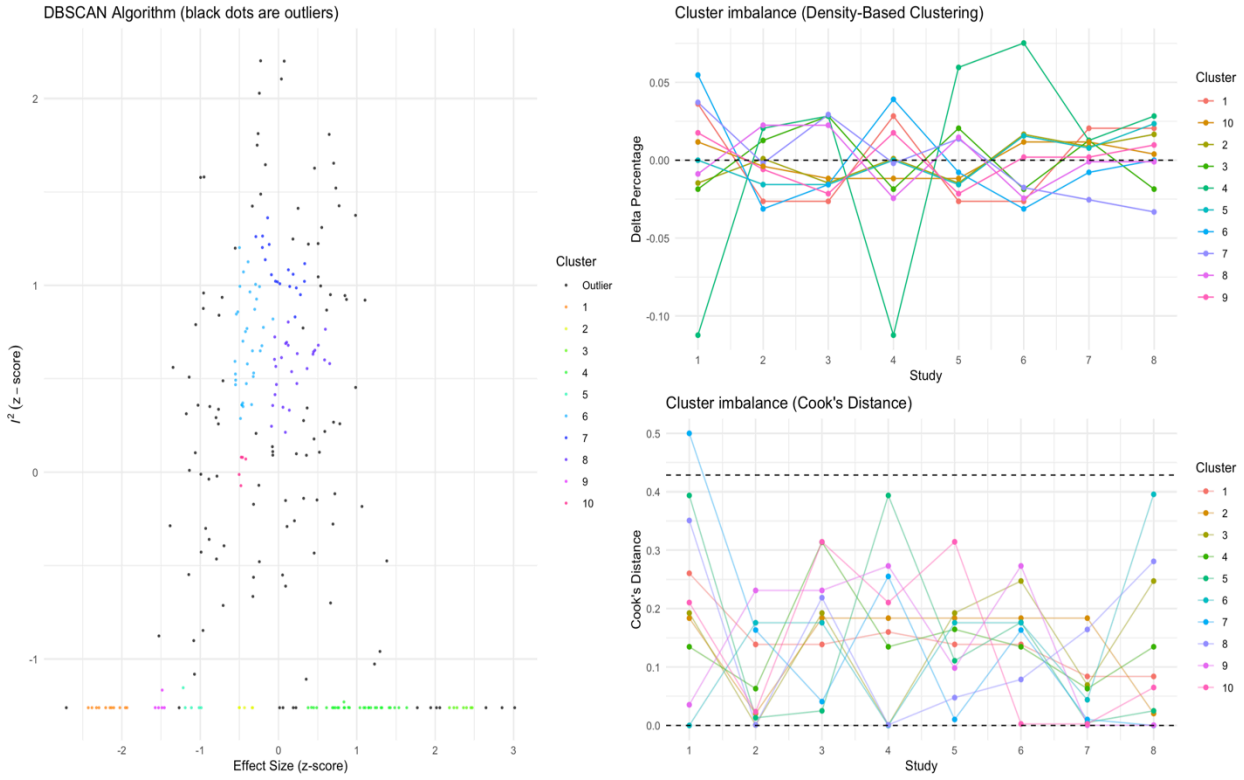


Figure 7D. Gaussian Mixture Model

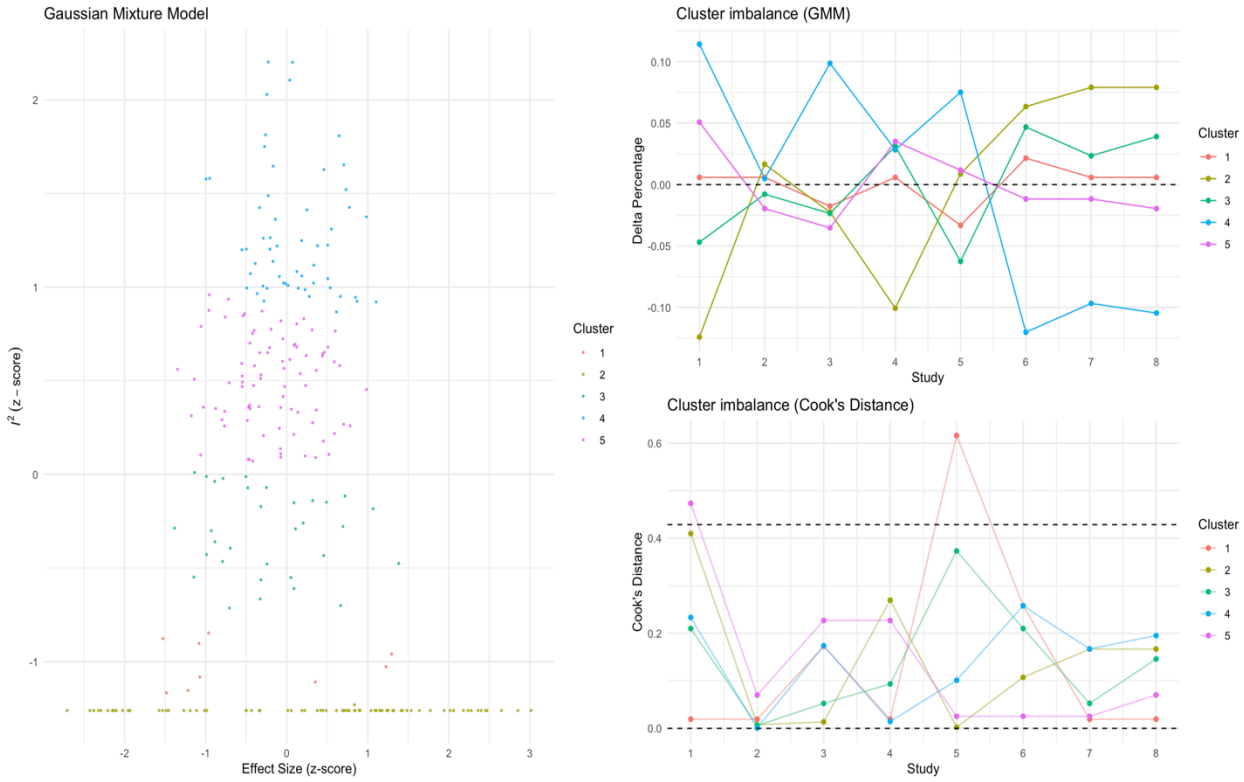
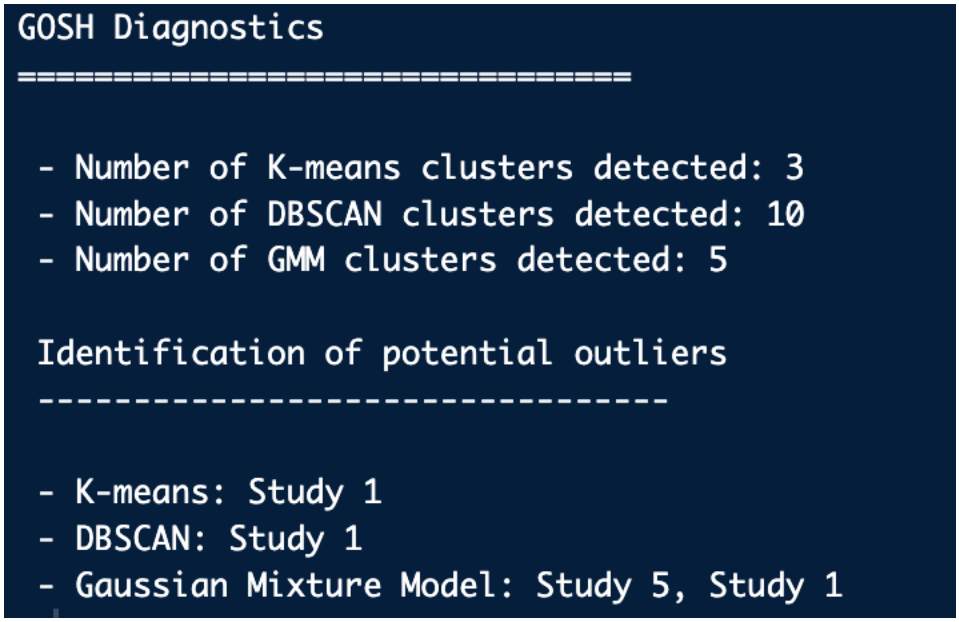
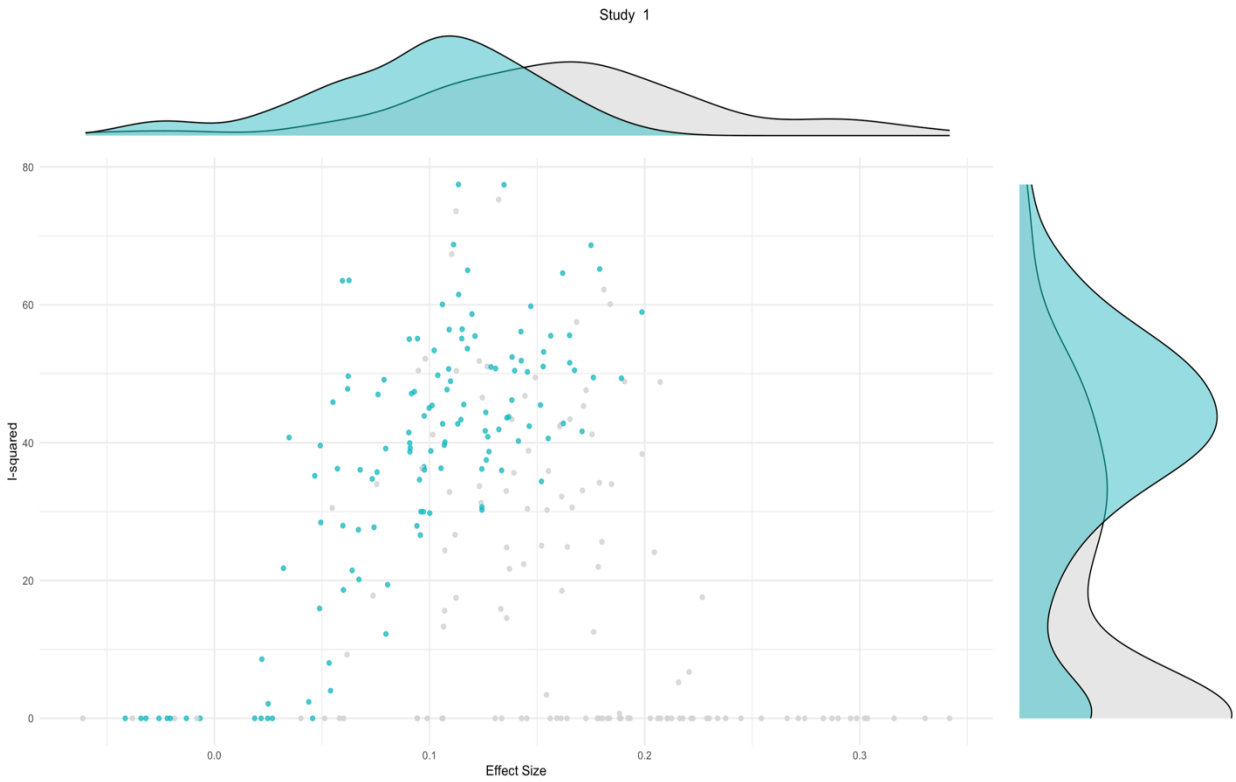


Figure 7E. GOSH Plot Analysis R Output for Primary Endpoint – Identification of Potential Outliers



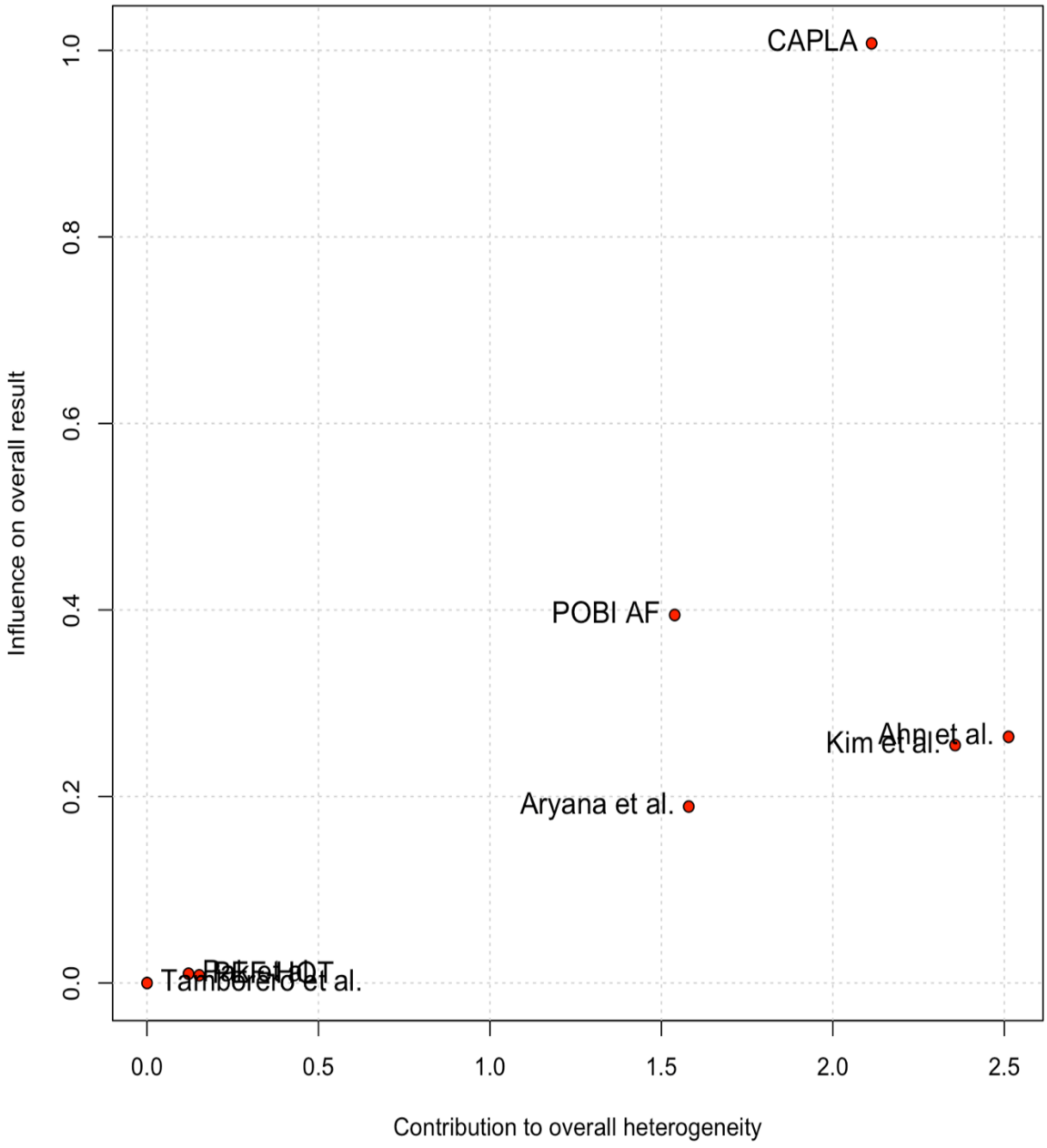
Study 1 = CAPLA 2023

Figure 7F. GOSH plots with the corresponding subset



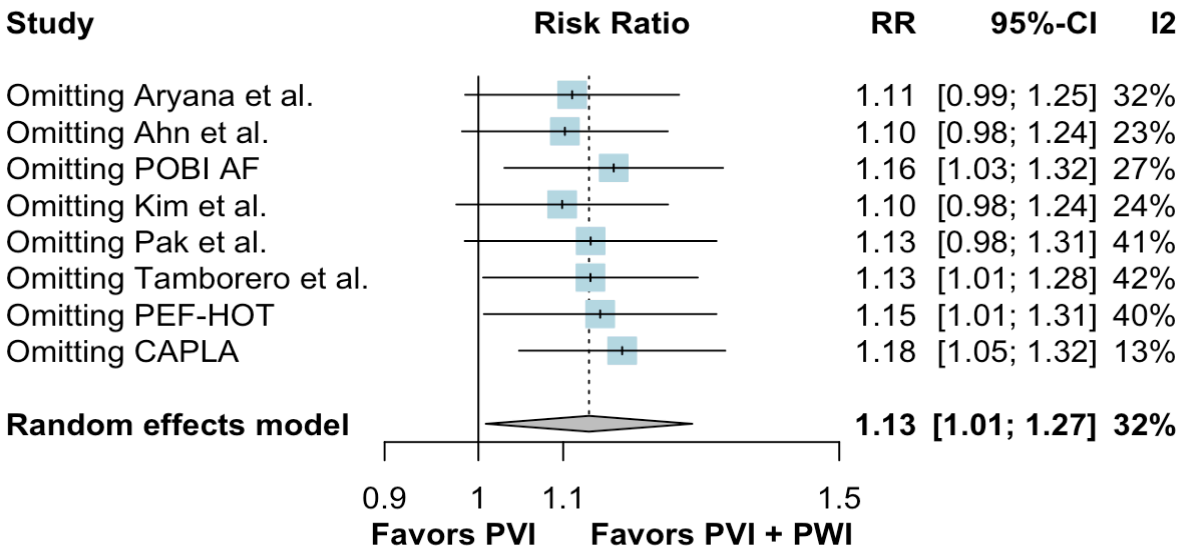
Legend: GOSH plots with the corresponding subset, including the potential outlier (CAPLA trial) colored in cyan.

Supplemental Figure 8. Baujat Plot for the Primary Efficacy Endpoint



Legend: Baujat plot depicting the contribution of individual studies to overall heterogeneity on the x-axis (i.e., relative contribution to the Q-statistic) plotted against influence on the overall result on the x-axis (i.e., leave-one-out method).

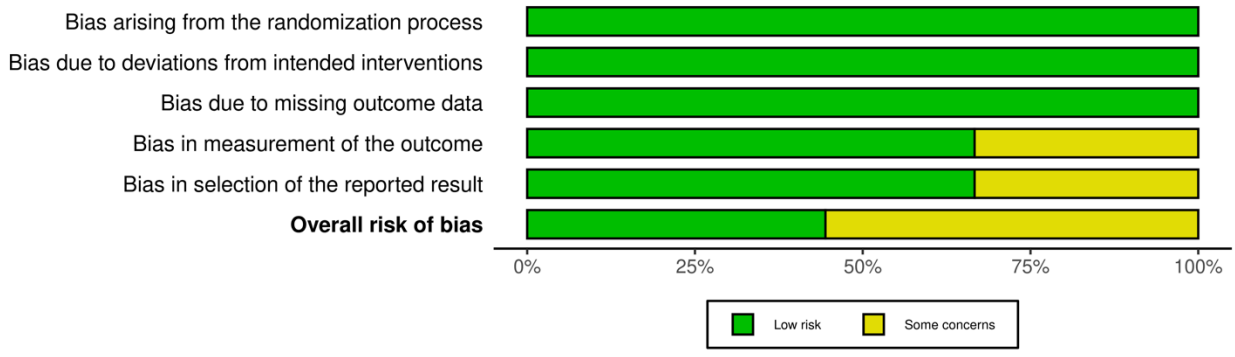
Supplemental Figure 9. Leave-one-out Analysis Sensitivity Analysis for the Primary Efficacy Endpoint



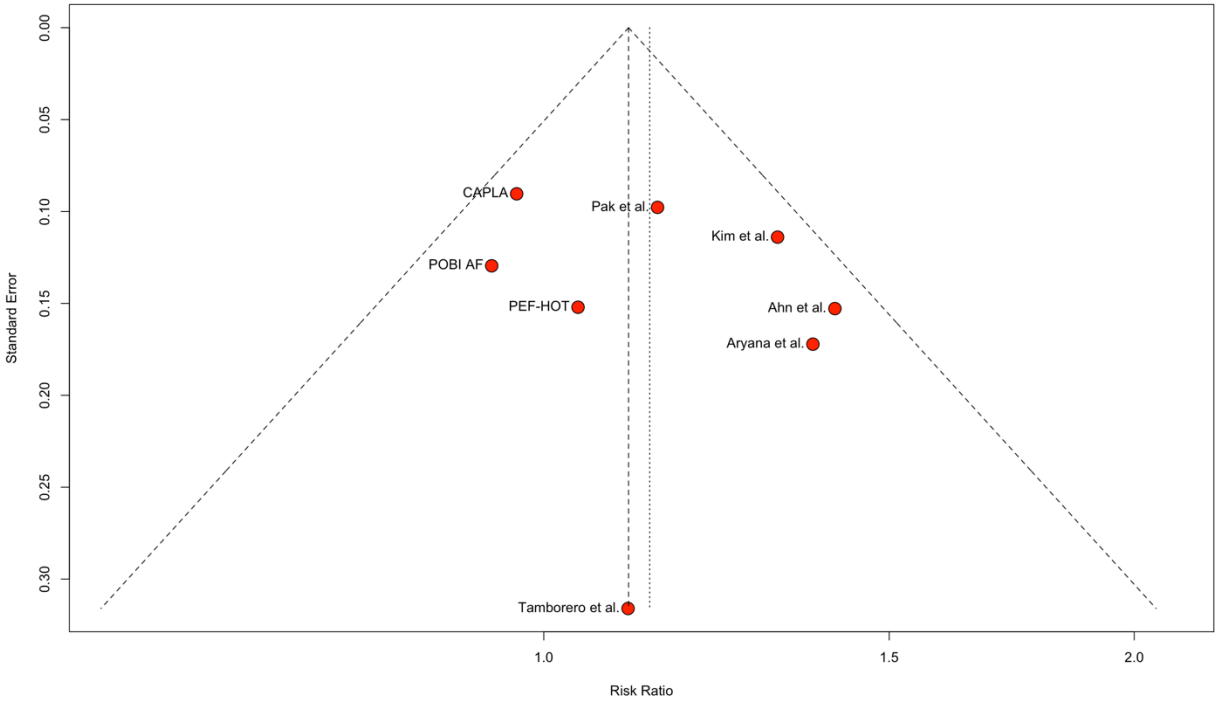
Supplemental Figure 10. RoB 2 - Cochrane tool for assessing the risk of bias in randomized clinical trials

Figure 10A. Traffic light plot

Figure 10B. Summary plot



Supplemental Figure 11. Funnel Plot and Egger's Test for the Primary Efficacy Endpoint



Egger's Regression Test for Freedom from Atrial Tachyarrhythmia			
Intercept	**95% CI**	**t**	**p-value**
0.163	-1.68 – 4.01	0.8	0.454

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6 CONCLUSÕES & IMPLICAÇÕES CLÍNICAS

Nesta tese, avaliamos a assistência médica em ablação de fibrilação atrial em centros brasileiros, buscando preencher a lacuna de dados sobre segurança e eficácia no país em comparação com centros de alta renda, que fundamentam diretrizes de cardiologia. Com um registro prospectivo de mais de mil pacientes submetidos à primeira ablação de FA e acompanhados por mediana de 1,4 anos, analisamos a recorrência de taquiarritmias, aplicando modelos de Cox para identificar preditores de recorrência. Os resultados indicaram menor eficácia em pacientes com FA persistente, aumento do diâmetro atrial e sintomas avançados, com taxa de complicação de 2,1% e nenhum óbito relacionado ao procedimento. Além disso, revisões sistemáticas e meta-análises com pacientes de insuficiência cardíaca e FA não-paroxística mostraram que, na IC, a ablação resultou em menor risco de mortalidade cardiovascular e hospitalizações, sem aumento de eventos adversos graves em comparação ao tratamento medicamentoso; na FA não-paroxística, a ablação com abordagem complementar na parede posterior do átrio esquerdo mostrou-se mais eficaz. Esses achados sustentam importantes implicações clínicas da ablação por cateter no manejo da fibrilação atrial:

A ablação demonstrou segurança e eficácia robustas em todos os cenários.

A avaliação de segurança da ablação nesta tese mostrou baixas taxas de eventos adversos e ausência de aumento significativo na morbi-mortalidade associada ao procedimento. A análise abrangeu três esferas: a) revisão de literatura de ensaios clínicos randomizados e registros de países de alta-renda, b) dados do registro SBR-AF, com mais de mil primeiras ablações desde 2009, e c) os artigos II e III, que reuniram 15 estudos totalizando mais de dois mil pacientes com insuficiência cardíaca ou FA não-paroxística. Em todos os cenários, o procedimento manteve uma baixa taxa de complicações, sem eventos com risco de vida. Embora a eficácia tenha variado entre grupos específicos de pacientes com fibrilação atrial, a extensa maioria apresentou benefício clínico com a ablação.

A intervenção precoce proporciona maior benefício clínico.

Embora o controle de ritmo seja amplamente preferido ao controle de frequência no manejo da FA, há um intenso debate sobre o momento ideal para indicar a ablação — recomendada desde o primeiro episódio sintomático ou em casos subclínicos diagnosticados por dispositivos de monitoramento, até a FA persistente de longa duração. Nesse contexto, é fundamental orientar os pacientes que o tratamento da FA vai além do resultado imediato do procedimento; a doença segue um curso progressivo, com dilatação do átrio esquerdo, aumento da carga arrítmica, evolução para formas não paroxísticas e mais sintomáticas, maior suscetibilidade a episódios de alta resposta ventricular e risco tromboembólico. Essa deterioração clínica implica em menor eficácia da ablação, conforme demonstrado no registro SBR-AF, onde os preditores de recorrência após a primeira ablação foram associados a estágios mais avançados da doença — FA persistente, dilatação do átrio esquerdo e sintomas limitantes. Assim, em decisão compartilhada

com o paciente, visando aumentar a probabilidade de eficácia da ablação e mitigar os danos associados à progressão da FA, a indicação precoce do procedimento oferece o maior benefício clínico.

FA avançada, ablação ampliada.

Ao passo que a intervenção precoce na FA oferece maior probabilidade de manter o ritmo sinusal e retardar a progressão da doença, a ablação em estágios não-paroxísticos da FA permanece um desafio. Os resultados do registro SBR-AF, consistentes com estudos randomizados, mostram que a taxa de sucesso em pacientes com FA persistente é substancialmente menor que em pacientes paroxísticos, sem diferença nas complicações relacionadas ao procedimento. Esse cenário reflete as mudanças estruturais, como a dilatação e fibrose do átrio esquerdo, além do surgimento de focos arritmogênicos secundários em áreas fora do contato com as veias pulmonares. Embora seja lógica a hipótese de que a presença de focos arritmogênicos suplementares exija ablação complementar, essa abordagem foi pouco explorada. O número restrito de estudos randomizados testando a eficácia de lesões na parede posterior do atrio esquerdo pode ser justificado pela cautela em evitar lesões esofágicas que podem resultar de lesões termais nesta região. Contudo, a análise agrupada dos estudos randomizados incluídos no Artigo III não demonstrou aumento na taxa de complicação em pacientes que receberam protocolo de ablação ampliado com lesões na parede posterior. Um refinamento desta análise demonstrou que, entre as técnicas de ablação da parede posterior do átrio esquerdo, a aplicação de lesões mais extensas, além das linhas de isolamento em caixa, resultou em uma menor taxa de recorrência de taquiarritmias atriais. Desta forma, visando potencializar a eficácia da ablação em casos avançados de FA não-paroxística, a ablação complementar da parede posterior aumenta a eficácia do procedimento.

Ablação de FA na Insuficiência Cardíaca – o 5º pilar da terapia otimizada.

A coexistência da FA com a insuficiência cardíaca está associada a uma elevada morbidade. Nessa população, é comum que o controle de ritmo seja exclusivamente farmacológico, devido ao pressuposto de maior risco cirúrgico e à ausência de diferença estatisticamente significativa em mortalidade na maioria dos estudos randomizados. No entanto, o estudo CASTLE-Htx, publicado em 2023, trouxe resultados surpreendentes com um desenho intrépido: pacientes com FA e IC classe funcional NYHA IV, em fila para transplante cardíaco, foram randomizados para ablação ou terapia medicamentosa. O estudo foi interrompido precocemente devido à eficácia superior no grupo que recebeu ablação, sem aumento nas complicações associadas ao procedimento. Nossos achados no Artigo II corroboram esses resultados, mostrando que a análise combinada de estudos randomizados indica uma redução na mortalidade entre pacientes com FA e IC tratados com ablação concomitante à terapia farmacológica otimizada. Diante do benefício clínico substancial, sem aumento significativo de eventos adversos graves, a ablação desempenha um papel essencial no manejo de pacientes com disfunção sistólica e fibrilação atrial – possivelmente se consolidando como o 5º pilar no tratamento da IC.

Considerações Finais

Perspectivas futuras para o registro SBR-AF

O registro SBR-AF desenvolvido nesta tese representa, até o momento, a maior base de dados no Brasil dedicada a desfechos clínicos em pacientes com fibrilação atrial submetidos a ablação. A métrica criada para coleta de dados padronizados em uma interface que permite a exportação de dados

anônimos, sem informações sensíveis dos participantes, configura um modelo replicável e com potencial de expansão para outros centros. Espera-se que esta linha de pesquisa continue após a conclusão do doutorado e, através da colaboração entre pares e entidades como a Sociedade Brasileira de Arritmias Cardíacas (SOBRAC), que este registro possa se consolidar como a base de dados nacional de ablação por cateter no manejo da FA.

Relevância social e Summarium Ultimum desta Tese

Além dos pilares de ensino e pesquisa, as Universidades Federais possuem o pilar da extensão, idealmente pautado por uma relação transformadora entre Universidade e Sociedade. Os resultados do registro SBR-AF demonstram a segurança e eficácia da ablação por cateter no manejo da FA em centros brasileiros. Uma limitação relevante do estudo é que, até o momento, a base de dados é composta exclusivamente por centros terciários privados. As ponderações sobre este viés foram devidamente discutidas pelos autores no Artigo I, aceito para publicação nos Arquivos Brasileiros de Cardiologia. Ainda assim, estes resultados são os que mais se aproximam da realidade brasileira, dada a lacuna de registros com este desenho no país. Esses achados têm o potencial de capitanear e embasar o delineamento de políticas públicas de saúde, com o objetivo de tornar o tratamento da fibrilação atrial por ablação amplamente acessível aos pacientes do Sistema Único de Saúde. A incorporação da ablação como opção de controle de ritmo para fibrilação atrial no SUS transcende o âmbito acadêmico dos benefícios clínicos demonstrados neste estudo, traduzindo esses achados em redução de formas limitantes da doença, diminuição de AVCs criptogênicos e melhora na qualidade de vida de milhares de brasileiros acometidos pela fibrilação atrial.

ANEXO I: PUBLICAÇÕES REALIZADAS DURANTE O DOUTORADO

1. Cardoso R, Graffunder FP, **Ternes CMP,** Fernandes A, Rocha AV, Fernandes G, Bhatt DL. SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis. *E Clinical Medicine*. 2021 Jun 5:36:100933. doi: 10.1016/j.eclinm.2021.100933.

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3. Cardoso R, **Ternes CMP,** Justino GB, Fernandes A, Rocha AV, Knijnik L, d'Avila A, Lopes RD. Non-Vitamin K Antagonists Versus Warfarin in Patients with Atrial Fibrillation and Bioprosthetic Valves: A Systematic Review and Meta-Analysis. *Am J Med*. 2022 Feb;135(2):228-234.e1. doi: 10.1016/j.amjmed.2021.08.026.

4. Maher TR, Rech JVT, **Ternes CMP**, Dal Forno A, d'Avila A. Esophageal Perforation Following Radiofrequency Catheter Ablation for Atrial Fibrillation: A Conservative Approach. *J Innov Card Rhythm Manag*. 2022 Sep 15;13(9):5154-5158. doi: 10.19102/icrm.2022.130904.

5. Forno ARJD, **Ternes CMP**, Rech JVT, Nascimento HG, Lewandowski A, Damasceno G, d'Avila A. Left Bundle Branch Pacing of His-Purkinje Conduction System: Initial Experience. *Arq Bras Cardiol.* 2022 Feb;118(2):505-516. doi: 10.36660/abc.20201085.

6. Kim JA, Najam US, **Ternes CMP**, Marashly Q, Chelu MG. Clinical Outcomes of Early Rhythm or Rate Control for New Onset Atrial Fibrillation Following Transcatheter Aortic Valve Replacement. *Cardiovasc Drugs Ther*. 2024 Jun 13. doi: 10.1007/s10557-024-07577-x.

7. Rivera A, Braga MAP, **Ternes CMP**, Gewehr DM, Villa Martignoni F, Dal Forno A, Locke AH, d'Avila A. Hybrid ablation for persistent/long‐standing persistent atrial fibrillation: a meta‐analysis and trial sequential analysis of randomized controlled trials. *J Interv Card Electrophysiol*. 2024 Jun 21. doi: 10.1007/s10840-024-01839-2.

8. Rivera A, Gewehr DM, Braga MAP, Carvalho PEP, **Ternes CMP**, Pantaleao AN, Hincapie D, Serpa F, Romero JE, d'Avila A. Adjunctive low‐voltage area ablation for patients with atrial fibrillation: An updated meta‐analysis of randomized controlled trials. *J Cardiovasc Electrophysiol*. 2024 Jul;35(7):1329-1339. doi: 10.1111/jce.16290.

9. **Ternes CMP**, Zimerman A. Conduction System Pacing: Redefining Resynchronization Therapy in Heart Failure. *ABC Heart Failure & Cardiomyopathy*. [aceito para publicação].

ANEXO I: PREMIAÇÕES DURANTE O DOUTORADO

THE BEST ARTICLES OF 2022 IN THE ARQUIVOS BRASILEIROS DE CARDIOLOGIA

Table 1 – List of the 10 best articles published in *Arquivos Brasileiros de Cardiologia* in 2022

Authors	Article title (link)
Forno et al.[11]	Left Bundle Branch Pacing of His-Purkinje Conduction System: Initial Experience (https://abccardiol.org/article/estimulacao-do-ramo-esquerdo-do-sistema-his-purkinje-experiencia-inicial/)

Arrhythmia

Right ventricular pacing is the most widely used pacing modality to correct atrioventricular conduction disorders. However, it increases the risk of atrial fibrillation, could worsen heart failure functional class, and could increase hospitalization for heart failure in up to 20% of patients over 4 years, especially when ventricular pacing is required > 40% of the time and in patients with ventricular dysfunction prior to implantation.[35] Pacing the left bundle branch of the His-Purkinje system can prevent unwanted outcomes from right ventricular pacing. Forno et al.[11] retrospectively evaluated intraoperative, electrocardiographic, and clinical data from the initial follow-up of 50 patients who underwent a successful left bundle branch pacing procedure (n = 52): mostly men (69.2%) with a median age of 73.5 years (65.0-80.0). The authors concluded that pacing the left bundle branch of the His-Purkinje system is a safe and feasible technique with a high success rate that involves low procedure and fluoroscopy time, short left ventricular activation time, and adequate electronic measurements.

Arq Bras Cardiol. 2023; 120(7):e20230342

Original Article

Left Bundle Branch Pacing of His-Purkinje Conduction System: Initial Experience

Alexander Romeno Janner Dal Forno,[1] Caique M. P. Ternes,[1] João Vítor Ternes Rech,[1] Helcio Garcia Nascimento,[1] Andrei Lewandowski,[1] Grazyelle Damasceno,[1] Andre d'Avila[1]

Hospital SOS Cardio,[1] Florianópolis, SC – Brazil

ANEXO I: PREMIAÇÕES DURANTE O DOUTORADO

SESSÃO EDUARDO SOSA DE MELHOR TEMA LIVRE
SOCIEDADE BRASILEIRA DE ARRITMIAS CARDÍACAS 2023

3º LUGAR - PRÊMIO EDUARDO SOSA DE MELHOR TEMA LIVRE ORAL

2070

ADJUNCTIVE POSTERIOR WALL ISOLATION FOR PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

ANDRÉ LUCAS CALLEJAS RIVERA[1]; ANTONIO DA SILVA MENEZES JUNIOR[2]; DOUGLAS MESADRI GEWEHR[3]; BÁRBARA NASCIMENTO[4]; ISABELE AYUMI MIYAWAKI[5]; CAIQUE MARTINS PEREIRA DE MOURA TERNES[6].

1. UNIVERSIDADE NOVE DE JULHO, SÃO BERNARDO DO CAMPO - SP - BRASIL; 2. UNIVERSIDADE FEDERAL DE GOIÁS, GOIÂNIA - GO - BRASIL; 3. INSTITUTO DO CORAÇÃO DE CURITIBA, CURITIBA - PR - BRASIL; 4. UFRGS, PORTO ALEGRE - RS - BRASIL; 5. UFPR, CURITIBA - PR - BRASIL; 6. UFRGS, RIBEIRAO PRETO - SP - BRASIL.

Background: The efficacy and safety of adjunctive posterior wall isolation (PWI) to the standard pulmonary vein isolation (PVI) for patients with persistent atrial fibrillation (PeAF) is still unclear. **Methods:** We systematically searched PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov databases for randomized controlled trials (RCTs) comparing PVI alone versus PVI with PWI in patients with PeAF. Risk ratios (RR) with 95% confidence intervals (CI) were pooled with a random-effects model. Our primary endpoint was freedom from atrial tachyarrhythmia (ATA), a composite of atrial fibrillation (AF), atrial flutter, or atrial tachycardia. We used R version 4.3.1 for all statistical analyses. **Results:** Our meta-analysis included 8 RCTs, compromising 1,243 patients assigned to PVI (n=614) or PVI with PWI (n=629). Compared to PVI alone, the adjunctive PWI significantly increased freedom from ATA recurrence (RR 1.18; 95% CI: 1.05–1.32; p=0.006; Figure 1A). The benefit was mainly driven by freedom from AF recurrence (RR 1.17; 95% CI 1.02–1.36; p=0.03). A meta-regression showed a significant correlation between freedom from ATA recurrence and AF duration (i.e., time since diagnosis of AF)(p<0.01; Figure 1B). The adjunctive PWI group had longer total procedure, ablation, and fluoroscopy times. However, no significant difference in adverse events was found between the two groups. **Conclusion:** Our findings support that adjunctive PWI to PVI is an effective strategy compared to PVI alone for reducing ATA recurrence in patients with PeAF without compromising safety. Notably, patients with longer AF duration appeared to benefit more from PWI.

40º Congresso Brasileiro de Arritmias Cardíacas SOBRAC 2023
30 de novembro a 2 de dezembro
RIO DE JANEIRO RJ

Arq Bras Cardiol 2023;120(12Supl.1):1-24

40º Congresso Brasileiro de
Arritmias Cardíacas
SOBRAC 2023

30 de novembro a 2 de dezembro
Centro de Convenções & Hotéis Windsor · Ala Oceânico
RIO DE JANEIRO · RJ

CERTIFICADO

Certificamos que o trabalho

ADJUNCTIVE POSTERIOR WALL ISOLATION FOR PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Foi apresentado como **TEMA LIVRE ORAL** na **Sessão Melhor Tema Livre** como finalista do **Prêmio Eduarda Sosa** durante o **40º Congresso Brasileiro de Arritmias Cardíacas - SOBRAC 2023,** realizado de 30 de novembro a 02 de dezembro.

Rio de Janeiro, 02 de dezembro de 2023.

Para validar este certificado, acesse: https://icongresso.sobrac.itarget.com.br//certificado/auth/validar - Código de validação: VCbtMvbf3t

PROMOÇÃO

FÁTIMA DUMAS CINTRA LUIZ
Presidente da SOBRAC

CRISTIANO FARIA PISANI
Diretor Científico

SILVIA HELENA CARDOSO BOGHOSSIAN
Presidente do Congresso

ANEXO I: APRESENTAÇÕES DURANTE O DOUTORADO

AMERICAN COLLEGE OF CARDIOLOGY 2021

[ORAL PRESENTATION] Cardoso R, Graffunder FP, **Ternes CMP**, Fernandes G, Rocha AV, Bhatt D. SGLT2 INHIBITORS DECREASE CARDIOVASCULAR MORTALITY OR HEART FAILURE HOSPITALIZATIONS IN HEART FAILURE SUBGROUPS: A SYSTEMATIC REVIEW AND META-ANALYSIS. J Am Coll Cardiol. 2021;77(18):655. doi:10.1016/S0735- 1097(21)02014-3

[POSTER] Cardoso R, **Ternes CMP,** Knijnik L et al. NON-VITAMIN K ANTAGONISTS SHOULD BE PREFERRED OVER WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION AND BIOPROSTHETIC VALVES: A SYSTEMATIC REVIEW AND META-ANALYSIS. J Am Coll Cardiol. 2021;77(18):1693. doi:10.1016/S0735-1097(21)03049-7

BEST OF ACC CHAPTER HONG KONG 2021

[SPEAKER] Ternes CMP. Non-Vitamin K Antagonists Should Be Preferred Over Warfarin in Patients with Atrial Fibrillation and Bioprosthetic Valves: A Systematic Review and Meta-Analysis (https://hk.bestofcardiology.org/Scientific-Program.php)

AMERICAN COLLEGE OF CARDIOLOGY 2022 – Washington, D.C., USA.

[POSTER] **Ternes CMP,** Justino GB, Justino LB et al. NON-VITAMIN K ANTAGONISTS VS. WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION AND TRANSCATHETER AORTIC VALVE REPLACEMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS. J Am Coll Cardiol. 2022;79(9):676. doi:10.1016/S0735-1097(22)01667-9

AMERICAN COLLEGE OF CARDIOLOGY 2023 – New Orleans, LA, USA.

[ORAL PRESENTATION] **Ternes CMP**, Dan Itaya E, Justino, L. et al. NON-VITAMIN K ANTAGONISTS ARE TIED TO A LOWER INCIDENCE OF DEMENTIA WHEN COMPARED WITH WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS. JACC. 2023 Mar, 81 (8_Supplement) 46. https://doi.org/10.1016/S0735-1097(23)00490-4

[POSTER] **Ternes CMP**, Dal Forno A, Dan Itaya E. et al. CONDUCTION SYSTEM PACING VS BIVENTRICULAR PACING IN CARDIAC RESYNCHRONIZATION THERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS. JACC. 2023 Mar, 81 (8_Supplement) 755. https://doi.org/10.1016/S0735-1097(23)01199-3

[POSTER] **Ternes CMP**, Dan Itaya E, Justino G. et al. CPAP OR NOT CPAP? EFFICACY OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON ATRIAL FIBRILLATION RECURRENCE AFTER CATHETER ABLATION IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: A SYSTEMATIC REVIEW AND META-ANALYSIS. JACC. 2023 Mar, 81 (8_Supplement) 258. https://doi.org/10.1016/S0735-1097(23)00702-7

AMERICAN COLLEGE OF CARDIOLOGY 2024 – Atlanta, GA, USA.

[ORAL PRESENTATION] Pasqualotto E, **Ternes CMP,** Ferreira R. et al. CATHETER ABLATION VERSUS MEDICAL THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION AND HEART FAILURE WITH REDUCED EJECTION FRACTION: A SYSTEMATIC REVIEW AND META ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. JACC. 2024 Apr, 83 (13_Supplement) 389. https://doi.org/10.1016/S0735-1097(24)02379-9

[POSTER] **Ternes CMP,** Pasqualotto E, Wippel C. et al. CLEARING THE ROLE OF BEMPEDOIC ACID FOR DYSLIPIDEMIA IN STATIN-INTOLERANT PATIENTS - A SYSTEMATIC REVIEW AND META-ANALYSIS. JACC. 2024 Apr, 83 (13_Supplement) 2022. https://doi.org/10.1016/S0735-1097(24)04012-9

[POSTER] **Ternes CMP**, Sirena E, Colares, F. et al. GLP-1 RECEPTOR AGONISTS RISING ROLE IN HEART FAILURE MANAGEMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS. JACC. 2024 Apr, 83 (13_Supplement) 391. https://doi.org/10.1016/S0735-1097(24)02381-7

[POSTER] **Ternes CMP,** Sirena E, Rivera A. et al. LONG-TERM EFFICACY AND SAFETY OF PULSED FIELD ABLATION FOR ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS. JACC. 2024 Apr, 83 (13_Supplement) 237. https://doi.org/10.1016/S0735-1097(24)02227-7

[POSTER] Rivera A, Braga M, **Ternes CMP**. et al. HYBRID ABLATION FOR PERSISTENT AND LONG-STANDING PERSISTENT ATRIAL FIBRILLATION: A META-ANALYSIS AND TRIAL SEQUENTIAL ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. JACC. 2024 Apr, 83 (13_Supplement) 235. https://doi.org/10.1016/S0735-1097(24)02225-3

[POSTER] Rivera A, Gewehr D, Braga M, **Ternes CMP**. et al. ADJUNCTIVE LOW-VOLTAGE AREA ABLATION FOR PATIENTS WITH ATRIAL FIBRILLATION: AN UPDATED META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. JACC. 2024 Apr, 83 (13_Supplement) 233. https://doi.org/10.1016/S0735-1097(24)02223-X

ANEXO II: PARTICIPAÇÃO NO ESTUDO PHYSIOSYNC-HF

PROJETO DE PESQUISA PROADI/SUS

Estimulação do sistema His-Purkinje versus estimulação biventricular na ressincronização cardíaca em pacientes com insuficiência cardíaca congestiva

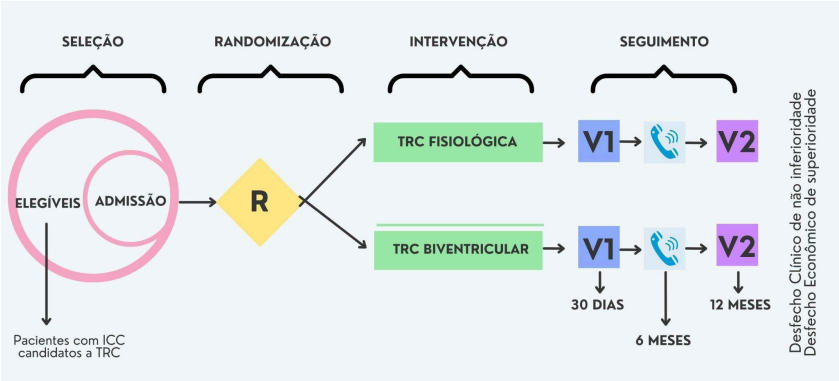
PHYSIOlogic reSYNChronization versus biventricular pacing on Heart Failure patients

COMITÊ DIRETIVO

Carisi Anne Polanczyk (Chair, Investigador Principal)
Alexander Dal Forno (Investigador Principal)
Leandro Zimerman
Luis Eduardo Rohde
André Zimerman
Caique M P Ternes
André d'Ávila

PROTOCOLO DE ESTUDO

Ensaio clínico randomizado de não-inferioridade, cegado, em 14 centros das 5 regiões do Brasil, em pacientes com insuficiência cardíaca congestiva e fração de ejeção do ventrículo esquerdo (FEVE) reduzida (≤35%), com complexo QRS alargado (≥120ms), bloqueio de ramo esquerdo e em tratamento otimizado sem indicação para cardiodesfibrilador implantável. A alocação 1:1 entre grupos que receberão dispositivos terapia de ressincronização cardíaca biventricular (controle) vs estimulação do sistema de condução (intervenção). O desfecho primário é dado por uma escala de *proportional odds* de morte por todas as causas, internação por insuficiência cardíaca, visita de urgência por insuficiência cardíaca e alteração de FEVE em 12 meses.



STATUS DO ESTUDO

Recrutamento: encerrado em Dezembro de 2023

Número de pacientes randomizados: 179

Previsão de término de follow-up: Dezembro de 2024

Previsão de publicação dos resultados: Segundo semestre de 2025

ATUAÇÃO NO ESTUDO (Caique Ternes)

- Colaboração no desenho do Protocolo
- Triagem, credenciamento e contratos com centros participantes
- Visita de ativação presencial a todos os centros participantes
- Validação de critérios de inclusão de pacientes candidatos à randomização
- Apoio clínico aos centros durante o follow-up
- Monitoramento de dados
- Captação e checagem de qualidade dos ecocardiogramas
- Credenciamento dos exames de imagem para adjudicação do CoreLab
- Checagem de eventos reportados para envio aos adjudicadores
- Apresentação em Congressos
- Coordenação dos encontros dos investigadores

ANEXO III: APROVAÇÕES ÉTICAS E REGISTROS DE PROTOCOLOS

ARTIGO I - APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA

INSTITUTO DE CARDIOLOGIA
DE SANTA CATARINA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Preditores de recorrência após ablação por cateter em pacientes com fibrilação atrial - um registro multicêntrico.
Pesquisador: CAIQUE MARTINS PEREIRA DE MOURA TERNES
Área Temática:
Versão: 2
CAAE: 77124424.6.1001.0113
Instituição Proponente: SOS CARDIO SERVICOS HOSPITALARES LTDA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 6.785.240

Apresentação do Projeto:
Projeto de pesquisa original, retrospectivo e multicêntrico com o título de ¿Preditores de recorrência após ablação por cateter em pacientes com fibrilação atrial - um registro multicêntrico.¿

Está sendo considerada uma amostra estimada de 1.500 participantes no Brasil. O estudo será realizado na Instituição SOS CARDIO SERVICOS HOSPITALARES LTDA.

Objetivo da Pesquisa:
Objetivo Primário:

Este estudo retrospectivo em dois centros de eletrofisiologia do Sul do Brasil irá avaliar a segurança e eficácia peri-procedimento de ablação por cateter em pacientes com FA, bem como resultados clínicos durante o seguimento clínico de rotina.

Objetivo Secundário:

Caracterizar aspectos demográficos e clínicos de pacientes com fibrilação atrial submetidos à ablação por cateter de radiofrequência;
Avaliar a segurança peri-procedimento da ablação em pacientes com FA;

Endereço: Rua Adolfo Donato Silva s/n
Bairro: Praia Comprida **CEP:** 88.103-901
UF: SC **Município:** SAO JOSE
Telefone: (48)3664-3016 **E-mail:** treinamentoicsc@gmail.com

Avaliar a recorrência de qualquer taquiarritmia atrial após ablação por cateter;
Avaliar a recorrência de qualquer taquiarritmia atrial de acordo com a classificação do tipo de FA;
Avaliar a recorrência de qualquer taquiarritmia atrial de acordo com o score de sintomas de FA;
Avaliar preditores independentes de recorrência de taquiarritmia atrial após uma primeira ablação.

Avaliação dos Riscos e Benefícios:

Riscos:

Os pacientes que participarem deste estudo estarão exposto a riscos mínimos, uma vez que os pesquisadores somente anotarão as suas informações dos questionários e dos prontuários, e os participantes venham a sentir algum tipo de desconforto relacionado à temática da pesquisa, os pesquisadores (sob a responsabilidade do pesquisador responsável) farão o encaminhamento do participante para um médico cardiologista do local do estudo, que providenciará todas as ações médicas necessárias para ajudar.

Benefícios:

Esta pesquisa tem como benefício indireto a identificação das características clínicas relacionadas com o sucesso do procedimento no tratamento desta arritmia cardíaca. Os resultados irão colaborar para identificar a taxa de complicação do procedimento, bem como a relação de características clínicas com a taxa de sucesso do procedimento - tido como o não-retorno da irregularidade dos batimentos do coração após o procedimento.

Comentários e Considerações sobre a Pesquisa:

Metodologia de Análise de Dados:

A normalidade dos dados será avaliada pelo teste de Shapiro-Wilk. Preditores univariados de eventos arrítmicos recorrentes (valor de $p<0,10$) serão avaliados com modelos multivariáveis de risco proporcional de Cox. Todas as análises estatísticas utilizarão Stata (versão 16 e 17). Um valor p bicaudal de 0,05 será considerado estatisticamente significativo.

O pesquisador solicita dispensa do TCLE com a seguinte justificativa:

Por se tratar de um estudo transversal, com o objetivo de avaliar os resultados do acompanhamento clínico de pacientes submetidos à ablação de fibrilação atrial pelas equipes de eletrofisiologia invasiva dos hospitais SOS Cárdio, em Florianópolis, Santa Catarina, e

Hospital Moinhos de Vento, em Porto Alegre, Rio Grande do Sul. A análise dos fatores preditivos de recorrência de fibrilação atrial dos pacientes tratados nestes centros contribuirá para o planejamento terapêutico e a indicação adequada para essa população. Este estudo não implica em nenhum procedimento adicional ou contato complementar com os pacientes além do acompanhamento clínico habitual realizado pelos médicos assistentes.

Declara que será utilizada fonte secundária de dados como prontuário de pacientes.
Os dados demográficos dos pacientes serão extraídos dos prontuários e os itens de interesse do estudo serão inseridos cuidadosamente na plaforma Syscardio, sistema de amazenamento de dados que permite catalogar as informaações mantendo o anônimato do participante. Os pesquisadores se responsabilizam pela guarda e confidencialidade dos dados.

A pendência foi atendida com a correção do cronograma de atividades ajustada no projeto original, como também, o documento de PB.

O pesquisador apresentou documento de coleta de dados e orçamento.

Considerações sobre os Termos de apresentação obrigatória:
O pesquisador apresenta os termos obrigatórios nas seguintes condições:

- Termo de consentimento livre e esclarecido ¿ TCLE: Presente, mas o pesquisador solicita a dispensa do documento.

- Termo de assentimento livre e esclarecido ¿ TALE: Não se aplica.

- Termo de compromisso para utilização de dados em prontuários de pacientes e de bases de dados em projetos de pesquisa ¿ TCUD: Presente e adequado.

- Termo de anuência institucional ¿ TAI: Presente e adequado.

- Folha de rosto: Presente e adequado.

- Projeto detalhado: Presente e adequado.

Conclusões ou Pendências e Lista de Inadequações:

Este CEP recomenda aprovação após ajuste do cronograma conforme solicitado.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_2200018.pdf	20/04/2024 23:39:57		Aceito
Projeto Detalhado / Brochura Investigador	Brochura_completa_cronograma_ajustado.pdf	20/04/2024 23:39:10	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
Recurso Anexado pelo Pesquisador	Instrumento_de_coleta.pdf	27/01/2024 03:10:19	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	27/01/2024 03:09:06	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
Declaração de Pesquisadores	TCUD_SOSCardio.pdf	27/01/2024 00:38:33	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
Declaração de Instituição e Infraestrutura	Termo_de_anuencia_SOSCardio.pdf	27/01/2024 00:19:56	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
Solicitação Assinada pelo Pesquisador Responsável	Dispensa_TCLE.pdf	27/01/2024 00:18:39	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
Declaração de Pesquisadores	Autorizacao_Submissao_CEP_HMV.pdf	26/01/2024 23:52:48	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
Declaração de Instituição e Infraestrutura	Termo_de_anuencia_HMV.pdf	20/01/2024 21:05:38	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito
Folha de Rosto	Folha_de_rosto.pdf	21/08/2023 19:27:54	CAIQUE MARTINS PEREIRA DE MOURA TERNES	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO JOSE, 24 de Abril de 2024

Assinado por:
Amândio Rampinelli
(Coordenador(a))

Endereço: Rua Adolfo Donato Silva s/n
Bairro: Praia Comprida **CEP:** 88.103-901
UF: SC **Município:** SAO JOSE
Telefone: (48)3664-3016 **E-mail:** treinamentoicsc@gmail.com

ARTIGO I - CARTAS DE ANUÊNCIA

HOSPITAL SOS CÁRDIO, FLORIANÓPOLIS - SC

CARTA DE ANUÊNCIA INSTITUCIONAL

Eu **Fernando Graça Aranha,** na qualidade de diretor técnico do Hospital SOS Cardio, localizado na Rodovia, SC-401, 121 - Itacorubi, Florianópolis - SC, 88030-000, CNPJ 85.307.098/0001-87, autorizo a realização da pesquisa intitulada **"PREDITORES DE RECORRÊNCIA APÓS ABLAÇÃO POR CATETER EM PACIENTES COM FIBRILAÇÃO ATRIAL — UM REGISTRO MULTICÊNTRICO"** a ser conduzida sob a responsabilidade do pesquisador **Caique Martins Pereira de Moura Ternes** e DECLARO que está instituição apresenta infraestrutura necessária à realização da referida pesquisa.

Ciente dos objetivos, métodos e técnicas que serão utilizados nesta pesquisa, concordo em fornecer todos os subsídios para seu desenvolvimento, desde que seja assegurado o que segue:

1) O cumprimento das determinações éticas da Resolução CNS nº 466/2012;

2) A garantia de solicitar e receber esclarecimentos antes, durante e depois do desenvolvimento da pesquisa;

3) Que não haverá nenhuma despesa para esta instituição que seja decorrente da participação nesta pesquisa;

4) No caso do não cumprimento dos itens acima, a liberdade de retirar minha anuência a qualquer momento da pesquisa sem penalização alguma.

O referido projeto será realizado no serviço de arritmia e marcapasso do Hospital SOS Cardio e poderá ocorrer somente a partir da aprovação do Comitê de Ética em Pesquisa (CEP-ICSC/SC).

Florianópolis, 10 de junho de 2021

Fernando Graça Aranha

CRM-SC 12033 RQE 5745 RQE 5746

(48) 3212-5000

HOSPITAL S.O.S. CARDIO

TERMO DE AUTORIZAÇÃO PARA A REALIZAÇÃO DE PESQUISA EM PRONTUÁRIO E COMPROMISSO DE UTILIZAÇÃO DOS DADOS

O Hospital SOS Cardio, localizado na Rodovia, SC-401, 121 - Itacorubi, Florianópolis - SC, 88030-000, CNPJ 85.307.098/0001-87 neste ato através do *Dr. Fernando Graça Aranha* na qualidade de diretor técnico do Hospital SOS Cardio, AUTORIZO os pesquisadores abaixo identificados a terem acesso aos dados dos usuários do serviço desta Instituição em prontuários eletrônicos e físicos para desenvolvimento do projeto de pesquisa intitulado **"PREDITORES DE RECORRÊNCIA APÓS ABLAÇÃO POR CATETER EM PACIENTES COM FIBRILAÇÃO ATRIAL — UM REGISTRO MULTICÊNTRICO"** que tem como objetivo avaliar os resultados do seguimento clínico dos pacientes submetidos a ablação de fibrilação atrial.

A presente autorização é concedida aos pesquisadores, mediante os seguintes compromissos, que expressamente são assumidos pelos mesmos:

1- Iniciar a coleta de dados somente após o Projeto de Pesquisa ser aprovado pelo Comitê de Ética em Pesquisa – CEP;
2- Obedecer às disposições éticas de manter a confidencialidade sobre os dados coletados nos, bem como de manter a privacidade de seus conteúdos, cientes de que poderão responder civil e criminalmente em caso de violação dos mesmos;
3- Utilizar os dados coletados, exclusivamente para embasamento da pesquisa informada no presente termo;
4- Realizar a pesquisa documental mediante coleta de dados do documento original ciente da impossibilidade de reprodução do prontuário, no todo ou em parte, por qualquer tipo de equipamento.

Florianópolis, 10 de junho de 2021

Fernando Graça Aranha

CRM-SC 12033 RQE 5745 RQE 5746

(48) 3212-5000

CARTA DE ANUÊNCIA INSTITUCIONAL

Eu **Mário Goto,** na qualidade de Diretor Hospitalar do Hospital Unimed Chapecó, localizado na Rua Porto Alegre, 132 - D. Centro - Chapecó/SC - CEP: 89802-130, CNPJ 85.283.299/0002-72, autorizo a realização da pesquisa intitulada **"Preditores de recorrência após ablação por cateter em pacientes com fibrilação atrial — um registro multicêntrico"** a ser conduzida sob a responsabilidade do pesquisador **Alexander Romeno Janner Dal Forno** e DECLARO que está instituição apresenta infraestrutura necessária à realização da referida pesquisa.

Ciente dos objetivos, métodos e técnicas que serão utilizados nesta pesquisa, concordo em fornecer todos os subsídios para seu desenvolvimento, desde que seja assegurado o que segue:

1) O cumprimento das determinações éticas da Resolução CNS nº 466/2012;

2) A garantia de solicitar e receber esclarecimentos antes, durante e depois do desenvolvimento da pesquisa;

3) Que não haverá nenhuma despesa para esta instituição que seja decorrente da participação nesta pesquisa;

4) No caso do não cumprimento dos itens acima, a liberdade de retirar minha anuência a qualquer momento da pesquisa sem penalização alguma.

O referido projeto será realizado com núcleo central no serviço de arritmia e marcapasso do Hospital SOS Cardio e poderá ocorrer somente a partir da aprovação do Comitê de Ética em Pesquisa (CEP-ICSC/SC).

Chapecó, 14 de julho de 2021

Dr. Mário Goto
CRM-SC 13525
(49) 3361-1800

Unimed Chapecó

TERMO DE AUTORIZAÇÃO PARA A REALIZAÇÃO DE PESQUISA EM PRONTUÁRIO E COMPROMISSO DE UTILIZAÇÃO DOS DADOS

O Hospital Unimed Chapecó, localizado na Rua Porto Alegre, 132 - D. Centro - Chapecó/SC - CEP: 89802-130, CNPJ 85.283.299/0002-72, neste ato através do *Dr. Mário Goto* na qualidade de Diretor Hospitalar do Hospital Unimed Chapecó, AUTORIZO os pesquisadores abaixo identificados a terem acesso aos dados dos usuários do serviço desta Instituição em prontuários eletrônicos e físicos para desenvolvimento do projeto de pesquisa intitulado **"Preditores de recorrência após ablação por cateter em pacientes com fibrilação atrial — um registro multicêntrico"** que tem como objetivo avaliar os resultados do seguimento clínico dos pacientes submetidos a ablação de fibrilação atrial.

A presente autorização é concedida aos pesquisadores, mediante os seguintes compromissos, que expressamente são assumidos pelos mesmos:

1- *Iniciar* a coleta de dados somente após o Projeto de Pesquisa ser aprovado pelo Comitê de *Ética em Pesquisa – CEP;*
2- *Obedecer* às disposições éticas de manter a confidencialidade sobre os dados coletados nos, bem como de manter a privacidade de seus conteúdos, cientes de que poderão responder civil e criminalmente em caso de violação dos mesmos;
3- Utilizar os dados coletados, exclusivamente para embasamento da pesquisa informada no presente termo;
4- Realizar a pesquisa documental mediante coleta de dados do documento original ciente da impossibilidade de reprodução do prontuário, no todo ou em parte, por qualquer tipo de equipamento.

Chapecó, 14 de julho de 2021

Dr. Mário Goto
CRM-SC 13525
(49) 3361-1800

HOSPITAL MOINHOS DE VENTO

TERMO DE ANUÊNCIA DO CHEFE DO SERVIÇO

Título do projeto: Preditores de recorrência após ablação por cateter em pacientes com fibrilação atrial — um registro multicêntrico.

Eu, Carisi Polanczyk, responsável pelo Serviço de Cardiologia, tenho ciência do protocolo/projeto de pesquisa acima citado, desenvolvido pelo pesquisador Caique Martins Pereira de Moura Ternes, concordando com a realização da pesquisa neste local.

Data 07/07/2022

Assinatura do Chefe de Serviço

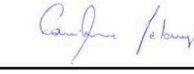
HOSPITAL MOINHOS DE VENTO
Educação e pesquisa

FORMULÁRIO

AUTORIZAÇÃO PARA SUBMISSÃO DE PROJETO DE PESQUISA AO COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS DO INSTITUTO DE EDUCAÇÃO E PESQUISA DO HOSPITAL MOINHOS DE VENTO

Preencha abaixo os dados gerais sobre o seu projeto, utilizando somente os campos azuis.
Após aprovação do seu projeto de pesquisa, uma cópia deste arquivo será enviada para o seu e-mail.

PROJETO DE PESQUISA			
Título	Preditores de recorrência após ablação por cateter em pacientes com fibrilação atrial — um registro multicêntrico		
Finalidade do projeto	Coorte retrospectiva visando avaliar eficácia e eficiência dos procedimentos de ablação por cateter em pacientes com fibrilação atrial		
PESQUISADOR RESPONSÁVEL			
Nome	Caique Martins Pereira de Moura Ternes		
Telefone	(48) 99190-9080	Ramal	
E-mail	caiqueternes@gmail.com		
Vínculo e setor HMV	Pesquisador PROADI-HMV		
Assinatura			

EQUIPE DO ESTUDO				
Nome	Telefone	E-mail	Vínculo HMV	Assinatura
Carisi Polanczyk	(51) 3314-3434	carisi.anne@gmail.com	Chefe de Serviço da Cardiologia	
Luis Eduardo Rohde	(51) 3314-3434	rohde.le@gmail.com	Médico	
Caique Martins Pereira de Moura Ternes	(48) 3212-5055	caiqueternes@gmail.com	Pesquisador Médico	

LOCAL DE ORIGEM E DE REALIZAÇÃO DO ESTUDO	
Instituição ou local de origem	Hospital SOS Cardio, Florianópolis, SC, Brasil.
Instituição ou local de realização	Hospital Moinhos de Vento

RESUMO DO PROJETO DE PESQUISA

Esta coorte retrospectiva multicêntrica tem como objetivo avaliar a segurança e eficácia da primeira ablação por cateter para fibrilação atrial (FA) no Sul do Brasil de 2007 a 2023. Este estudo avaliará os registros de pacientes >18 anos de idade, com FA paroxística, persistente ou persistente de longa duração, submetidos a uma primeira ablação por radiofrequência entre agosto de 2007 e agosto de 2023. Serão avaliados caracteristicas baseline, desfechos de segurança peri-procedimento e taxa de recorrência de arritmias atriais no último seguimento clínico de rotina. Todas as análises serão feitas preservando a identidade do paciente. A normalidade dos dados será avaliada pelo teste de Shapiro-Wilk. Preditores univariados de eventos arrítmicos recorrentes (valor de p<0,10) serão avaliados com modelos multivariáveis de risco proporcional de Cox. Todas as análises estatísticas utilizarão Stata (versão 16 e 17). Um valor p bicaudal de 0,05 será considerado estatisticamente significativo.

ARTIGO II - REGISTRO PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Catheter ablation versus medical therapy in patients with atrial fibrillation and heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials

Review methods were amended after registration. Please see the revision notes and previous versions for detail.

Citation

Eric Pasqualotto, Rafael Oliva Morgado Ferreira, Matheus Pedrotti Chavez, Mariana Clemente, Thiago Nienkötter, Gustavo de Oliveira Almeida, Edmundo Bertoli, Caíque Martins Pereira Ternes. Catheter ablation versus medical therapy in patients with atrial fibrillation and heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. PROSPERO 2023 CRD42023462252 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023462252

Review question

Does catheter ablation for atrial fibrillation in patients with heart failure with reduced ejection fraction have greater benefits than medical therapy?

Searches

We will systematically search PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL). No filters such as publication date or language limitations will be applied in our search.

Types of study to be included

Only randomized controlled trials will be included.

Condition or domain being studied

Catheter ablation for atrial fibrillation has been proposed as a means of improving mortality and morbidity among patients with heart failure, however, the optimal treatment is controversial.

Participants/population

Will we include randomized controlled trials (RCTs) comparing catheter ablation with medical therapy for atrial fibrillation in patients with heart failure with reduced ejection fraction (HFrEF).

Intervention(s), exposure(s)

Catheter ablation

Comparator(s)/control

Medical therapy

Context

We will include only studies that report any of the outcomes of interest.

Main outcome(s) [1 change]

We will extract data for a pooled analysis on the following outcomes: (1) heart failure hospitalization.

Measures of effect

Risk ratio (RR).

Additional outcome(s) [1 change]

(1) left ventricular ejection fraction; (2) 6-minute walk test, (3) quality of life, (4) atrial fibrillation burden, (5) serum B-natriuretic peptide, (6) all-cause mortality, (7) cerebrovascular accident, (8) cardiovascular death, and (9) severe adverse events.

Measures of effect

Weighted mean differences (WMD) and risk ratio (RR).

Data extraction (selection and coding) [1 change]

Data on each of the outcomes described will be collected. In addition, the following baseline characteristics will be collected: (1) follow-up; (2) nº of patients; (3) age; (4) sex; (5) persistent AF; (6) LVEF; (7) NYHA class; (8) Ablation strategy; (9) AF duration; (10) ischemic cardiomyopathy; (11) 6-MWT; (12) N-terminal pro-BNP level. The data will be extracted and recorded on an Excel template by two authors: E.P. and M.P.C.

Risk of bias (quality) assessment

We will use the Cochrane Collaboration's tool for assessing risk of bias in randomized trials for quality assessment of individual randomized studies.

Strategy for data synthesis [1 change]

The systematic review and meta-analysis will be performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. Treatment effects for binary endpoints will be compared using pooled risk ratios (RR), with 95% confidence intervals. Weighted mean differences (WMD) will be used to pool continuous outcomes. Heterogeneity will be evaluated with Cochran Q test and I^2 statistics; p values inferior to 0.10 and I^2>25% will be considered significant for heterogeneity. DerSimonian and Laird random-effects model will be used for all endpoints. Sensitivity analysis will be performed with leave-one-out procedures. A meta-regression analysis will be performed for LVEF change and all-cause mortality outcomes to assess any interaction with the proportion of patients with ischemic cardiomyopathy. The TSA will be conducted on the included studies to assess whether the cumulative evidence had sufficient statistical power in the main outcomes. R software, version 4.2.3 (R Foundation for Statistical Computing), and the Trial Sequential Analysis software, version 0.9.5.10, will be used for statistical analysis.

Analysis of subgroups or subsets [1 change]

Subgroup analysis will be performed for (1) patients with left ventricular ejection fraction (LVEF) ≤35% and (2) patients with persistent atrial fibrillation.

Contact details for further information

Eric Pasqualotto

ericpasqualotto02@gmail.com

Organisational affiliation of the review

Federal University of Santa Catarina

Review team members and their organisational affiliations [1 change]

Mr Eric Pasqualotto. Federal University of Santa Catarina

Mr Rafael Oliva Morgado Ferreira. Federal University of Santa Catarina

Mr Matheus Pedrotti Chavez. Federal University of Santa Catarina

Miss Mariana Clemente. Petrópolis School of Medicine

Mr Thiago Nienkötter. University of South Santa Catarina

Mr Gustavo de Oliveira Almeida. Federal University of Triângulo Mineiro

Mr Edmundo Bertoli. University of South Santa Catarina

Dr Caíque Martins Pereira Ternes. Federal Universisty of Rio Grande do Sul

Type and method of review

Intervention, Meta-analysis, Systematic review

Anticipated or actual start date

07 September 2023

Anticipated completion date

31 December 2023

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Atrial Fibrillation; Catheter Ablation; Heart Failure; Humans; Randomized Controlled Trials as Topic; Stroke Volume; Ventricular Dysfunction, Left

Date of registration in PROSPERO

20 September 2023

Date of first submission

10 September 2023

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note

The changes made refer to the inclusion of information about statistical analysis. We performed sensitivity analyses, meta-regressions and Trial Sequential Analysis (TSA) to better understand the data provided in our meta-analysis.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

20 September 2023

20 September 2023

26 February 2024

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International prospective register of systematic reviews

Pulmonary Vein Isolation with Posterior Wall Isolation Versus Pulmonary Vein Isolation Alone for patients with Persistent Atrial Fibrillation: a systematic review and meta-analysis

Citation

André Rivera, Isabele Ayumi Miyaki, Antonio da Silva Menezes Junior, Bárbara Nunes e Silva Rodrigues do Nascimento. Pulmonary Vein Isolation with Posterior Wall Isolation Versus Pulmonary Vein Isolation Alone for patients with Persistent Atrial Fibrillation: a systematic review and meta-analysis. PROSPERO 2023 CRD42023397998
Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023397998

Review question

Is pulmonary vein isolation with posterior wall isolation more effective than pulmonary vein isolation alone for patients with persistent atrial fibrillation in atrial arrhythmias recurrence?

Searches

The search will be done in PubMed, EMBASE, Cochrane, and ClinicalTrials.gov. There will be no restrictions on language or publication date.

Types of study to be included

Only randomized controlled trials will be included

Condition or domain being studied

Atrial fibrillation (AF) is a prevalent cardiac rhythm disorder that is associated with significant morbidity and mortality. While traditional management of AF typically involves the pharmacological treatment, catheter ablation has emerged as a superior alternative, particularly in restoring and maintaining sinus rhythm. Pulmonary vein isolation (PVI) is considered the cornerstone of AF ablation and is most effective in treating paroxysmal AF compared to persistent AF. However, recent evidence suggests that the left atrial posterior wall (LAPW) plays a role in the maintenance of persistent AF. As a result, a combination of PVI and electrical posterior wall isolation (PWI) is being explored as a potential strategy to improve outcomes. The objective of this systematic review and meta-analysis is to assess the efficacy and safety of PVI combined with PWI compared to PVI alone in the treatment of persistent atrial fibrillation, focusing on endpoints such as atrial arrhythmia recurrence, AF recurrence, and adverse events.

Participants/population

We will include randomized controlled trials (RCTs) comparing pulmonary vein isolation with posterior wall isolation versus pulmonary vein isolation alone in patients with persistent atrial fibrillation, reporting the clinical outcomes of interest. We will exclude studies with overlapping patient populations.

Intervention(s), exposure(s)

Pulmonary vein isolation with posterior wall isolation

Comparator(s)/control

Pulmonary vein isolation alone

Context

We will include only studies that report any of the outcomes of interest, as noted below.

Main outcome(s)

We will extract data for a pooled analysis on the following outcomes: (1) AF recurrence; (2) Any atrial arrhythmia recurrence; (3)Total procedure time; (4) Number of repeated ablation procedures; (5) Ablation time, (6) Discharge rate; and (7) Adverse events

Measures of effect

Risk ratio (RR) and mean difference (MD)

Additional outcome(s)

Recurrence from any atrial arrhythmias after a single procedure, cardioversion required, repeated ablation procedures, early arrhythmia recurrence, and LA indwelling time.

Measures of effect

Risk ratio (RR) and mean difference (MD)

Data extraction (selection and coding)

Data on each of the outcomes described will be collected. In addition, the following baseline characteristics will be collected: (1) number of patients; (2) description of procedure; (3) sex distribution; (4) mean age; (5) race distribution; (6) proportion of patients with long-standing persistent atrial fibrillation; (7) proportion of patients with each type of arrythmia; (8) follow-up in months. The data will be extracted and recorded on an Excel template by two authors: AR and IAM.

Risk of bias (quality) assessment

We will use the Cochrane Collaboration tool for assessing the risk of bias in randomized trials for quality assessment of individual randomized studies. We will use RoB-2 for randomized clinical trials.

Strategy for data synthesis

The systematic review and meta-analysis will be performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. We will extract the data from individual studies using risk ratios (RR). Treatment effects for binary endpoints will be compared using pooled risk ratios (RR) with 95% confidence intervals. Weighted mean differences will be used to pool continuous outcomes. Heterogeneity will be evaluated with the Cochrane Q test and I^2 statistics; p values inferior to 0.10 and I^2>25% will be considered significant for heterogeneity. We will use a fixed-effect model for endpoints with I^2 < 25% (low heterogeneity). In pooled outcomes with high heterogeneity, DerSimonian and Laird random-effects models will be used. Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) will be used for statistical analysis.

Analysis of subgroups or subsets

Subgroup analysis will be performed if considered necessary and if data is available.

Contact details for further information

André Rivera

andre.riveraa01@gmail.com

Organisational affiliation of the review

None

Review team members and their organisational affiliations

André Rivera. Universidade Nove de Julho

Isabele Ayumi Miyaki. Universidade Federal do Parana

Dr Antonio da Silva Menezes Junior. Universidade Federal de Goias

Dr Bárbara Nunes e Silva Rodrigues do Nascimento. Universidade Federal do Rio Grande do Sul

Type and method of review

Intervention, Meta-analysis, Systematic review

Anticipated or actual start date

09 February 2023

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30 March 2023

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Brazil

Stage of review [1 change]

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Atrial Fibrillation; Humans; Pulmonary Veins

Date of registration in PROSPERO

20 February 2023

Date of first submission

08 February 2023

Details of any existing review of the same topic by the same authors

Although there is a previous meta-analysis, new randomized controlled trials were published and may increase the statistical significance. Therefore, we will perform an updated meta-analysis with the latest evidence to date

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

We conducted thorough meta-regressions and statistical analyses to carefully examine the heterogeneity that was identified.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

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