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Terapia anticoagulante precoce após implante de prótese valvar mecânica: revisão sistemática e meta-análise.

LUIZ GUILHERME PASSAGLIA

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Realizou-se, no dia 14 de abril de 2015, às 10:00 horas, Sala 029, andar térreo da Faculdade de Medicina, da Universidade Federal de Minas Gerais, a defesa de dissertação, intitulada **TERAPIA ANTICOAGULANTE PRECOCE APÓS IMPLANTE DE VALVA CARDÍACA COM PRÓTESE MECÂNICA: REVISÃO SISTEMÁTICA E META-ANÁLISE**, apresentada por **LUIZ GUILHERME PASSAGLIA**, número de registro 2013709166, graduado no curso de MEDICINA, como requisito parcial para a obtenção do grau de Mestre em CIÊNCIAS APLICADAS À SAÚDE DO ADULTO, à seguinte Comissão Examinadora: Prof. Marcos Roberto de Sousa - Orientador (UFMG), Dr. Daniel Dias Ribeiro (UFMG.

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Aos meus queridos pais, pelo eterno exemplo de vida e caráter.

Á minha esposa e filhos, pelo apoio e sonhos compartilhados.

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“Há 25 anos, eu gostaria que alguém me tivesse dado a ‘Prece da Serenidade’. Por meio dela, peço ***a serenidade para aceitar as coisas que não podem ser mudadas, a coragem para mudar as coisas que posso*** e, o mais importante, ***a sabedoria para saber a diferença entre as duas***.” (Pat Riley)

RESUMO

Fundamento: a abordagem da anticoagulação no pós-operatório precoce da cirurgia cardíaca valvar com prótese mecânica permanece controversa. A maioria das diretrizes descreve sobre a anticoagulação no longo prazo, ao passo que as evidências são escassas sobre as estratégias de terapia de ponte com anticoagulante parenteral até que o RNI atinja sua faixa terapêutica.
Objetivo: realizar revisão sistemática e meta-análise de estudos com e sem anticoagulação parenteral como terapia de ponte no pós-operatório precoce após implante de valva cardíaca mecânica.
Métodos: cinco bases de dados da literatura foram pesquisadas para avaliar a segurança (taxa de sangramento) e eficácia (taxa de eventos tromboembólicos) da Anticoagulação Oral (ACO) sem ou com ponte com Heparina não-Fracionada (HNF) ou Heparina de Baixo Peso Molecular (HBPM). Mortalidade como desfecho também foi avaliada. O Software Comprehensive Meta Analysis foi utilizado para combinar os resultados dos estudos e grupos de estudos pelo modelo de efeitos mistos (modelo de efeitos aleatórios entre os estudos de cada grupo e modelo de efeitos fixos para comparação entre os grupos). Heterogeneidade e viés de publicação foram avaliados através do I^2 e Teste de Egger, respectivamente. Quando o teste de Egger foi positivo, o método Trim e Fill foi utilizado para avaliar o impacto teórico do viés de publicação.
Resultados: Vinte e três estudos com 9534 pacientes foram incluídos. A taxa de sangramento foi de 1,8% (IC 95% 1,0-3,3) no grupo que recebeu ACO, 2,2% (IC 95% 0,9-5,3) no grupo ACO+HNF e 5,5% (95% IC 2,9-10,4) no grupo ACO+HBPM (p = 0,042). A taxa de eventos tromboembólicos foi de 2,1% (IC 95% 1,5-2,9) no grupo que recebeu ACO versus 1,1% (IC 95% 0,7-1,8) ao combinar os grupos de terapia de ponte ACO+HNF e ACO+HBPM (p = 0,035). A mortalidade não foi diferente entre os grupos. A maioria das análises tinha heterogeneidade moderada e teste negativo para o viés de publicação.
Conclusão: a terapia de ponte após a cirurgia cardíaca valvar com prótese mecânica provavelmente reduz a taxa de eventos tromboembólicos, embora a diferença seja pequena e com intervalos de confiança sobrepostos. A terapia de ponte com HNF parece ser segura neste contexto (mas com risco de viés), enquanto a HBPM esteve associada com altas taxas de sangramento nos estudos avaliados. Mais estudos são necessários para determinar a relevância clínica da terapia ponte e a segurança da HBPM neste contexto.

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1 CONSIDERAÇÕES INICIAIS

1.1 As doenças cardíacas valvares

O coração, órgão situado no mediastino médio, possui em sua anatomia interna um aparato denominado aparelho valvar com objetivo de direcionar o fluxo sanguíneo, sendo dois pares de valvas na entrada dos ventrículos e dois pares de valvas na saída destes (1). Doença Valvar (DV) é uma condição patológica envolvendo qualquer uma das quatro valvas cardíacas e suas estruturas associadas, como os músculos papilares e cordas tendíneas (2).

Na Europa, a DV é menos prevalente do que outras importantes patologias cardiovasculares como a hipertensão, a doença coronariana e a insuficiência cardíaca (3). Dados coletados de 75 centros em 25 países europeus demonstram uma maior prevalência da estenose de valva aórtica (43,1%), seguidos pela regurgitação da valva mitral (31,5%), regurgitação da valva aórtica (13,3%) e estenose da valva mitral (12,1%), sendo a etiologia degenerativa predominante nas três primeiras disfunções valvares citadas. A valvopatia reumática teve maior importância apenas na estenose da valva mitral (4).

Nos Estados Unidos, a DV é responsável por 10 a 20% de todas as cirurgias cardíacas (5), com uma prevalência estimada de doença moderada a grave de 2,5% na população geral, 8,5% em indivíduos entre 65-74 anos de idade e 13,2% naqueles com $\geq$ 75 anos de idade. Nesse país, a regurgitação da valva mitral e a estenose da valva aórtica também são as patologias valvares mais comuns, enquanto a estenose da valva mitral, a menos comum (6).

Na Europa, assim como nos Estados Unidos, a prevalência da DV aumenta progressivamente com a idade, tanto em homens quanto em mulheres. Outro ponto em comum é a sobrevida reduzida dos pacientes com DV comparados com grupos semelhantes da população em geral sem a presença desta doença (6).

No Brasil, apesar de dados limitados, a DV representa uma importante parcela das internações por doença cardiovascular (7). Em contraste com países mais desenvolvidos, palco de uma marcada mudança na etiologia da DV com predomínio atual de causas degenerativas relacionadas ao aumento da expectativa de vida, a cardiopatia reumática é ainda

extremamente prevalente em países emergentes (8, 9). Uma estimativa mostra que 79% de dos casos são oriundos de países menos desenvolvidos, com uma prevalência estimada no Brasil de 1 a 3 casos por 1000 habitantes (10). Em Salvador (Brasil), entre os anos de 2002 e 2005, 60.3% das cirurgias cardíacas valvares tiveram como patologia de base a etiologia reumática (11).

Diante do cenário da alta prevalência da doença reumática associada à crescente presença das DV degenerativas com o envelhecimento da população, a cirurgia cardíaca valvar possui um destaque particular no Brasil. Dados do DATASUS mostram que de 2010 a 2013 foram realizadas 43.241 cirurgias cardíacas valvares pelo SUS. Em 2013, foram 10.853 cirurgias cardíacas valvares, a um custo total de R$ 556.129.232,25 reais e uma permanência média hospitalar de 13,6 dias (12).

1.2 Cirurgia cardíaca valvar

Até o presente momento, nenhum fármaco se mostrou eficaz em prevenir ou alterar a evolução natural do acometimento valvar na estenose aórtica (13-15). Do mesmo modo, dados contraditórios ou de importância clínica duvidosa não justificam o emprego rotineiro de vasodilatadores em pacientes assintomáticos e com função ventricular preservada na insuficiência mitral e aórtica (16). Diante desse cenário, o manejo clínico da DV grave continua dependente da escolha do momento ideal para o tratamento intervencionista (7).

Diversas diretrizes sumarizam as indicações de intervenção na DV guiadas pela presença de sintomas e/ou dados ecocardiográficos de repercussão hemodinâmica (3, 7, 16). No entanto, quando comparados com outras doenças cardiovasculares também prevalentes, existem escassos estudos de intervenção aleatorizados sobre o tema. A partir do momento em que existe indicação de intervenção cirúrgica, a escolha da prótese valvar a ser implantada associada ao adequado manejo do paciente no pós-operatório é essencial para a redução das complicações relacionadas às próteses.

As primeiras trocas bem sucedidas de valva cardíaca foram realizadas somente após o aprimoramento da cirurgia a céu aberto. A cirurgia cardíaca, guardada as devidas proporções com outras especialidades e procedimentos médicos, “pode ser considerada um dos mais importantes avanços médicos do século XX” (17). Naquela época, o desenvolvimento de

próteses cardíacas valvares do modelo bola-gaiola (ou valva esférica) possibilitou o início do tratamento cirúrgico definitivo para os pacientes com DV (18-21).

Atualmente, dois principais tipos de próteses valvares cardíacas estão disponíveis: prótese mecânica e prótese biológica. Como não há um substituto valvar perfeito, a escolha do tipo de prótese recai na ponderação de vantagens e desvantagens de cada modelo: a prótese mecânica tem vantagem na durabilidade e desvantagens no maior risco tromboembólico e nos riscos do tratamento anticoagulante; já a prótese biológica, tem vantagem na baixa trombogenicidade e desvantagem na durabilidade (22), o que poderá resultar em reoperações mais precoces para troca da prótese em caso de sua disfunção.

As próteses mecânicas, ao longo dos anos, foram aperfeiçoadas em suas características hemodinâmicas com um crescente esforço para redução dos eventos tromboembólicos relacionados (trombose de prótese e embolia) (23). A introdução do carbono pirolítico na confecção das próteses otimizou os seus resultados, especialmente no que se refere à durabilidade estrutural e ao risco de complicações tromboembólicas (7). As próteses mecânicas de duplo disco, com excelente performance hemodinâmica, são hoje em dia as próteses valvares cardíacas mais utilizadas e mais seguras (24-30).

Apesar de grande evolução, todas as valvas mecânicas ainda são “imperfeitas” (31) e os maiores riscos compreendem o contínuo contraponto entre os eventos tromboembólicos devido à presença da prótese e os sangramentos pelo uso dos anticoagulantes (32).

Por definição (32), trombose de prótese é qualquer trombo, não causado por infecção, preso ao tecido protético ou próximo deste que obstrui parte do fluxo sanguíneo, interfere no funcionamento da valva e/ou é suficientemente grande para justificar tratamento. Embolia valvar é qualquer evento decorrente do desprendimento de trombo ou debris do material valvar, que ocorre na ausência de infecção, podendo se manifestar como evento neurológico ou como um evento embólico vascular não cerebral.

Os trombos podem ocorrer tanto ao nível do anel do tecido da prótese como na junção dos discos semicirculares, provocando aumento do gradiente transprotético por redução orificial e/ou regurgitação pelo incompleto fechamento dos folhetos. Sua incidência é relatada em torno de 0,1% pacientes/ano e os eventos tromboembólicos de 1,3% a 3,19% pacientes/ano

(7), taxas bem inferiores às apresentadas nos estudos iniciais quando não se usavam anticoagulantes para as valvas mecânicas (2,5 a 10% pacientes/ano) (31).

1.3 Próteses mecânicas, anticoagulação e terapia de ponte

É consenso que todos os pacientes com prótese mecânica necessitam de algum esquema anticoagulante por tempo indefinido para o correto funcionamento do dispositivo e para redução das graves complicações secundárias aos eventos tromboembólicos (16, 31, 33, 34).

O esquema de terapia anticoagulante oral com cumarínico, associado ou não ao uso do ácido acetilsalicílico (AAS), varia de acordo com o tipo de prótese, grau de trombogenicidade do dispositivo e da posição do seu implante. A associação com antiplaquetário em dose baixa, apesar de controversa, é recomendada por grande parte dos autores (16, 33, 35-37), a menos que haja uma contraindicação ao seu uso. É importante destacar que a Sociedade Europeia de Cardiologia (3) considera que a associação do antiplaquetário deve ocorrer apenas nos pacientes com doença coronariana concomitante ou após evento tromboembólico ocorrido em paciente já em uso de anticoagulante oral na faixa terapêutica apropriada.

O risco tromboembólico é aumentado no período precoce após o implante da valva cardíaca, particularmente para próteses mecânicas (38-40). Como a terapia com cumarínico demora 7 a 14 dias para atingir o nível terapêutico adequado, uma terapia de ponte com heparinas parenterais é usualmente prescrita para este período de transição. A opção tradicional inclui o uso de Cumarínico associado à Heparina Não-Fracionada (HNF) (41-46), ou mais recentemente, à Heparina de Baixo Peso Molecular (HBPM) (47-53).

As recomendações das principais sociedades quanto ao uso da terapia de ponte são contraditórias e limitadas a um baixo nível de evidência:

A) A recomendação do Colégio Americano de Cirurgiões Torácicos (33) é que se faça a terapia de ponte preferencialmente com HNF (dose profilática) ou HBPM (dose profilática ou terapêutica) em detrimento do uso de HNF intravenosa terapêutica (Grade 2C).
B) A Sociedade Europeia de Cardiologia (3), sem descrever o grau de recomendação e o nível de evidência, orienta que o início do anticoagulante oral deverá ocorrer nos primeiros dias do pós-operatório associado ao anticoagulante parenteral, preferencialmente HNF intravenosa, até a adequação da Razão Internacional

Normalizada (RNI). O uso da HBPM é colocado como "*off-label*" devido a ausência de estudos aleatorizados, preocupações quanto a farmacocinética em pacientes obesos, contraindicação na presença de doença renal severa e dificuldade em neutralizar seus efeitos anticoagulantes quando indicado. O termo "*off-label*" refere-se ao uso não aprovado de um medicamento, que não consta em bula. Segundo a ANVISA, caracteriza-se como o uso "feito por conta e risco do médico que o prescreve, e pode eventualmente vir a caracterizar um erro médico, mas em grande parte das vezes trata-se de uso essencialmente correto, apenas ainda não aprovado" (54).

C) A última publicação da Diretriz de DV do Colégio Americano de Cardiologia (16) não traz recomendações quanto ao tema, apenas destacando que muitos centros iniciam a heparina antes do RNI terapêutico, alguns com uso de HBPM e outros com HNF. A recomendação anterior (55) coloca o uso de HNF como controversa.
D) A Diretriz de terapia antitrombótica da *Scottish Intercollegiate Guidelines Network* (SIGN) (56), a Diretriz da Sociedade Europeia de Cirurgia Cardiotorácica (37) e a Diretriz Brasileira de Valvopatias (7) não fazem recomendações específicas sobre o tema.

Se o uso do anticoagulante precoce após a cirurgia cardíaca valvar teoricamente reduz o risco dos eventos tromboembólicos relacionados à prótese mecânica, em contrapartida, o seu uso neste cenário também aumenta o risco de sangramentos. Por definição (32), sangramento maior no pós-operatório de cirurgia cardíaca é qualquer evento, interno ou externo, que cause morte, hospitalização, dano permanente ou necessidade de hemotransfusão, podendo ser de causa cirúrgica (mecânica) e/ou não cirúrgica (coagulopatia) (57, 58).

Os sangramentos de maior porte, que exigem transfusões, são descritos a uma taxa de 0,6% pacientes/ano (7), mas são mais significativos no pós-operatório imediato e apesar de diferentes definições ocorrem em aproximadamente 5% dos casos (57). O sangramento e, particularmente a reexploração cirúrgica por sangramento excessivo, são fatores independentes para eventos adversos (57) como morte, tempo prolongado de terapia intensiva e uso de balão de intra-aórtico (59).

Não existem estudos randomizados para terapia de ponte para próteses mecânicas. Além disso, apesar de existir um movimento de melhoria das diretrizes (60), nem todas as recomendações específicas são baseadas em revisões sistemáticas de cada pergunta. Uma

revisão sobre o tema realizada em 2006 (61) encontrou poucos estudos que comparassem as terapias anticoagulantes precoces após implante de prótese valvar, de forma que uma meta-análise não foi possível. Em uma análise apenas qualitativa, o autor encontrou os achados descritos na **Tabela 1**. No entanto, dos 28 artigos utilizados, diversos estudos apresentam dados de difícil separação entre desfechos de curto prazo (menos de 30 dias de pós-operatório ou intra-hospitalares) e desfechos de médio / longo prazo (62-76).

TABELA 1: Eventos Tromboembólicos e Sangramentos – Revisão Sistemática (61)

	Eventos Tromboembólicos	**Sangramentos**
Anticoagulação oral isolada	0,9%	3,3%
Anticoagulação oral associada à HNF	1,1%	7,2%
Anticoagulação oral associada à HBPM	0,6%	4,8%

Observação: HNF – heparina não-fracionada; HBPM – heparina de baixo peso molecular.

Como não existe consenso nas recomendações, um estudo transversal publicado também em 2006 traduziu a grande variabilidade dos esquemas utilizados (77). Nesta avaliação, questionários foram enviados a 100 cirurgiões cardíacos canadenses (57 cirurgiões responderam) sobre a estratégia de anticoagulação utilizada no pós-operatório de cirurgia valvar mecânica. O resultado mostrou que, como terapia de ponte, a HNF foi rotineiramente administrada após troca aórtica (63%) e troca mitral (68%), mais comumente no primeiro dia de pós-operatório, por via subcutânea (28% para prótese aórtica e 25% para prótese mitral) ou intravenosa (33% para prótese aórtica e 42% para prótese mitral). A HBPM foi utilizada em 21% das trocas aórticas e 23% das trocas mitrais. O cumarínico, isoladamente ou associado à terapia de ponte, foi iniciado no primeiro dia de pós-operatório em 72% dos pacientes com prótese aórtica e 68% dos com prótese mitral, sendo que o antiplaquetário foi acrescido ao esquema em 61% e 65% dos pacientes, respectivamente.

Na prática, alguns serviços iniciam a anticoagulação parenteral no 1º ou 2º dia de pós-operatório (41, 43, 48, 50-53, 78, 79), enquanto outros iniciam somente após 48h da cirurgia (42, 47, 80). Alguns serviços usam cumarínico precocemente (26, 42, 50, 51, 53, 80-85), outros, apenas após 48 h (23, 30, 43, 44, 48, 49, 52, 78, 79, 86-88). No Hospital das Clínicas

da Universidade Federal de Minas Gerais, iniciamos o uso do cumarínico associado ao antiplaquetário e a heparina em doses profiláticas para prevenção de trombose venosa no 2ª dia de pós-operatório, geralmente após a retirada dos drenos; já a anticoagulação parenteral plena com HBPM, apenas no 5º dia de pós-operatório caso o RNI não atinja a faixa terapêutica estabelecida. Esse modelo é similar ao utilizado em uma coorte prospectiva de 460 valvas mecânicas implantadas em 391 cirurgias valvares entre 1983 e 1994 no *Massachusetts General Hospital* (80).

Para estimar os efeitos benéficos e eventos adversos do uso da terapia anticoagulante precoce após implante valvar com prótese mecânica é preciso revisar a literatura de forma sistemática (89, 90), avaliar a qualidade dos estudos de forma criteriosa (91) e estabelecer os riscos de viés (92), e se possível, combinar resultados de diferentes estudos, comparando indiretamente as taxas de cada terapia. Diante de todas as incertezas que envolvem esse tema e diante das poucas recomendações pela grande limitação de literatura disponível, é necessária uma análise de todos os trabalhos científicos existentes para uma melhor definição de conduta.

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2 OBJETIVOS

2.1 Objetivo Geral

Realizar revisão sistemática e comparar os resultados com meta-análise das estratégias de anticoagulação no pós-operatório precoce de cirurgia cardíaca valvar com prótese mecânica.

2.2 Objetivos Específicos

- Realizar revisão sistemática dos estudos que utilizaram apenas anticoagulantes orais (cumarínicos) no pós-operatório precoce de cirurgia cardíaca valvar com prótese mecânica, mesmo que não tenham realizado comparação com o esquema de uso de anticoagulantes parenterais como terapia de ponte, quantificando resultados para possíveis comparações indiretas.
- Realizar revisão sistemática dos estudos que utilizaram anticoagulantes parenterais (HNF e HBPM) associados ao anticoagulante oral no pós-operatório precoce de cirurgia cardíaca valvar com prótese mecânica, mesmo que não tenham realizado comparação entre os diferentes tipos de anticoagulantes e possíveis esquemas terapêuticos.
- Realizar meta-análise dos estudos e braços de estudos que descreveram ou compararam os diferentes esquemas de anticoagulantes orais e a parenterais no pós-operatório precoce de cirurgia cardíaca valvar com prótese mecânica.

3 ARTIGO

EARLY POSTOPERATIVE BRIDGING ANTICOAGULATION AFTER MECHANICAL HEART VALVE REPLACEMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

Corresponding author:
Luiz Guilherme Passaglia
Avenida Alfredo Balena, 110 – Santa Efigênia – Belo Horizonte, MG – Brazil - CEP: 30.130-100
Phone: +55 31 3409-9437 or 3409-9972
E-mail: lg.passaglia@uol.com.br

Luiz Guilherme Passaglia[1]
Guilherme Monteiro de Barros[2]
Marcos Roberto de Sousa[3]

School of Medicine[1,2,3], Hospital das Clínicas[1,3] and Postgraduate Program in Adult Health Sciences[1,3]
Universidade Federal de Minas Gerais[1,2,3] (UFMG). Belo Horizonte, Minas Gerais, Brazil.

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ABSTRACT

Objective: To perform a systematic review and meta-analysis of studies evaluating anticoagulation during the early postoperative period following mechanical heart valve implantation.

Methods: Five literature databases were searched to assess the rates of bleeding and thromboembolic events among patients receiving oral anticoagulation (OAC), both with and without bridging anticoagulation therapy with unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH). The studies' results were pooled via a mixed effects meta-analysis. Heterogeneity (I^2) and publication bias were both evaluated.

Results: Twenty-three studies including 9534 patients were included. The bleeding rate was 1.8% (95%CI 1.0-3.3) in the group receiving OAC, 2.2% (95%CI 0.9-5.3) in the OAC+UFH group and 5.5% (95%CI 2.9-10.4) in the OAC+LMWH group (p=0.042). The thromboembolic event rate was 2.1% (95%CI 1.5-2.9) in the group receiving OAC compared with 1.1% (95%CI 0.7-1.8) when combining the bridging therapy groups as follows: OAC+UFH and OAC+LMWH (p=0.035). Most of the analyses exhibited moderate heterogeneity and negative tests for publication bias.

Conclusions: Bridging therapy following cardiac valve surgery was associated with a lower thromboembolic event rate, although the difference was small, with considerable overlap of the confidence intervals. Direct comparisons are missing. Bridging therapy with UFH appears to be safe; however, this observation has a risk of bias. Early bridging therapy with LMWH appears to be associated with consistently high bleeding rates across multiple analyses. Based on the quality of the included studies, more trials are necessary to establish the clinical relevance of bridging therapy and the safety of LMWH.

INTRODUCTION

The optimal approach to early postoperative anticoagulation following mechanical valve replacement remains controversial. Most guidelines pertaining to this subject have focused on long-term anticoagulation following mechanical valve replacement [1, 2], as only scarce evidence supports the use of specific strategies in the management of anticoagulation during the early postoperative period [3]. The primary purpose of early anticoagulation initiation is the prevention of valve thrombosis or embolism (thromboembolic events) [4]. The rate of thromboembolic events is higher during the first days following surgery compared with later time periods [5, 6], as demonstrated by transesophageal echocardiography [7, 8]. Some guidelines suggest administering intravenous unfractionated heparin (UFH) [1] or prophylactic doses of subcutaneous UFH or subcutaneous low molecular weight heparin (LMWH) [4] as bridging therapy until patients' oral anticoagulation reaches a therapeutic level as determined via the international normalized ratio (INR). Some guidelines do not provide explicit recommendations pertaining to this issue, however [2, 9, 10].

To provide more evidence based information for clinicians caring for patients during the first days following surgical valve replacement, a systematic review was performed. The purpose of this review was to appraise the studies evaluating oral anticoagulation, both with and without early bridging anticoagulant therapy, focusing on both thromboembolic event rates and bleeding rates. Mortality was also analysed.

METHODS

Search strategy and study selection

The methodology of this review was previously registered in the PROSPERO database (CRD42014013432) [11] and will be briefly described herein. According to the PRISMA statement [12] for systematic reviews, as well as specific guidelines for non-randomized studies [13, 14], a literature search was performed for articles published from the beginning of each database until August 30th 2014 in PubMed, Web of Knowledge, LILACS, SCOPUS, and EMBASE, using the following terms: "early anticoagulation," "early anticoagulants," "bridging anticoagulant," "early antiplatelet," “valve replacement," "heart valve surgery," "cardiac surgery," "prosthetic valve surgery," "anticoagulants"[Mesh], "heart valve prosthesis implantation"[Mesh], and "heart valve prosthesis"[Mesh]. A hand search of each paper references and "*related citations*" in PubMed [15] were used to increase the sensitivity. We expected to find scarce evidence, so we included all types of study design, without starting limit of publication date until the final date of the search, including studies with at least 10 patients that evaluated UFH, LMWH or oral anticoagulation (OAC) following mechanical heart valve implantation. Studies must have reported thromboembolic and bleeding event numbers in explicitly defined period such as during the first six weeks or until hospital discharge. Paper languages were restricted to English, Spanish and Portuguese. The Newcastle Ottawa Scale (NOS) [16] was used to evaluate each study’s quality.

Groups and outcomes

The three study groups were defined as OAC alone (OAC), OAC plus bridging therapy with UFH (OAC+UFH) or OAC plus bridging therapy with LMWH (OAC+LMWH). Additionally, OAC+UFH and OAC+LMWH were grouped to assess the effects of OAC with and without bridging anticoagulation on patient outcomes. The outcomes of interest included thromboembolic and bleeding events, although mortality was also analysed.

For data extraction, one thromboembolic event was defined as a valve thrombosis or embolism (only embolic events from the valves were considered). Bleeding was defined as intracranial bleeding or a fall of haemoglobin greater than 2.0 g/dL or requiring transfusion or requiring anticoagulant withdrawal. Early mortality was reported as all-cause mortality in the hospital or during the first month following the initiation of therapy [17].

Statistical analysis

The event rates (percentages with confidence intervals) in each group or arm (with and without bridging) were pooled and compared using Comprehensive Meta-analysis® software (version 2.2.064). A one group meta-analysis with subgroup comparisons was performed via a "mixed effects meta-analysis" (“random-effects within” and “fixed-effects between”) meaning that a random effects model was used to combine the studies within each subgroup with 95% confidence intervals and two sided p values for each comparison [18]. A p-value <0.05 was considered statistically significant. The study-to-study variance (tau-squared) was not assumed to be the same for all subgroups; this value was computed within the subgroups. The heterogeneity in event rates noted among the studies was assessed using the Inconsistency (I^2) statistic. Sensitivity analyses were performed by two methods: excluding outliers using the Box Plot method and excluding older studies by publication date (studies before 2000). Exploration of sources of heterogeneity was also performed via a meta-regression analysis (unrestricted maximum likelihood) and a subgroup analysis using the time to the onset of anticoagulant in each event rate. Egger's test [19] was used to evaluate publication bias. Positive tests for publication bias were subsequently evaluated via the Trim and Fill method to evaluate the impact of the publication bias [20, 21].

RESULTS

Study characteristics

The study selection process is depicted in **Figure 1**. Twenty-three studies and 9534 patients were included. The characteristics of each study are described in **Table 2**.

FIGURE 1: The study selection process.

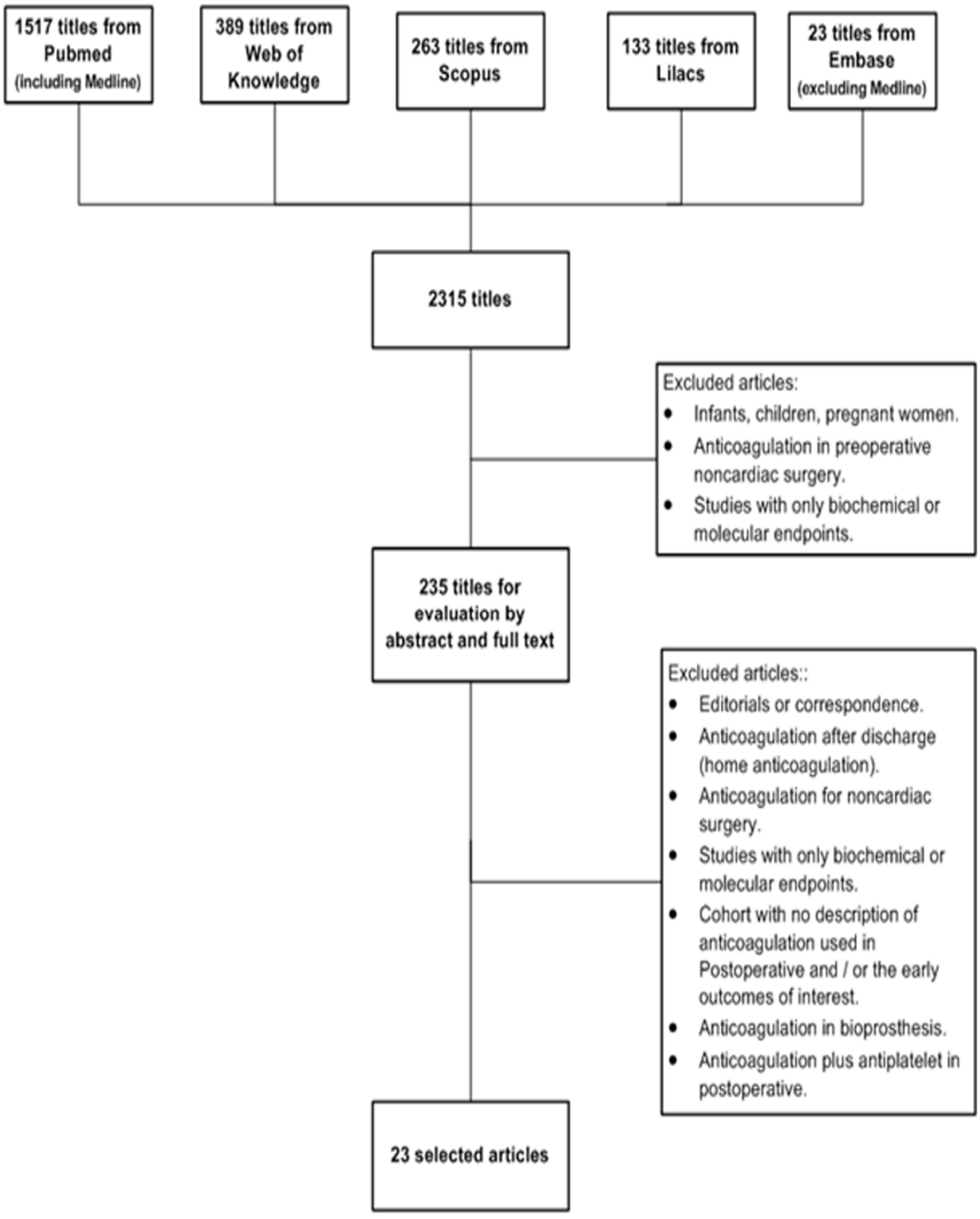


TABLE 2: The characteristics of the selected studies.

Author / year	Study design	Enrolment period	Reference period for early outcome	NOS (stars)	n	Mean age	Anticoagulation regimen
Akins et al. 1996 [22]	Cohort (single arm)	1983-1994	Hospitalization period	5	391	59.5	OAC+UFH
Allou et al. 2009 [6]	Cohort (single arm)	2005-2007	30 days	6	300	57.7	OAC+UFH
Alsaddique et al. 2002 [23]	Cohort (single arm)	1989-1993	30 days	5	130	36	OAC
Antilla et al. 2002 [24]	Cohort (single arm)	1978-1982	30 days	5	91	47.9	OAC
Arrigoni et al. 1973 [25]	Cohort (single arm)	1969-1970	30 days	6	70	57	OAC
Baudet et al. 1995 [26]	Cohort (single arm)	1978-1987	30 days	6	1112	55.9	OAC+UFH
Copeland et al. 1984 [27]	Cohort (single arm)	1988-1992	30 days	6	786	57.3	OAC
Coutinho et al. 2010 [28]	Cohort (single arm)	1988-1995	Hospitalization period	6	144	67.7	OAC
De Feo et al. 2003 [29]	Cohort (single arm)	1998-1999	31 days	6	338	56.6	OAC
De La Fuente et al. 2000 [30]	Cohort (single arm)	1988 e 1998	Hospitalization period	6	321	57	OAC
Debetaz et al. 1997 [31]	Cohort (single arm)	1979-1984	30 days	6	192	57	OAC+UFH
Fanikos et al. 2004 [32]	Case control	1999-2001	30 days	8	34	58.7	OAC+UFH
					29	52.9	OAC+LMWH
Fernandez et al. 1994 [33]	Cohort (single arm)	1982-1991	Hospitalization period	6	1200	58	OAC
Kindo et al. 2014 [34]	Cohort (single arm)	2000-2010	42 days	6	1063	59.2	OAC+LMWH
Kure et al. 1986 [35]	Cohort (single arm)	1981-1984	30 days	3	486	62	OAC+UFH
Messmer et al. 1972 [36]	Cohort (single arm)	1969-1971	30 days	6	460	52	OAC
Meurin et al. 2006 [37]*	Cohort (single arm)	2000-2005	30 days	6	250	60	OAC+LMWH
Minakata et al. 2000 [38]	Cohort (single arm)	1994-2000	30 days	6	590	61.6	OAC
Montalescot et al. 2000 [39]	Cohort (two arms at different times)	ND	Hospitalization period	9	106	55.3	OAC+UFH
					102	59.8	OAC+LMWH
Puri et al. 2008 [40]**	Cohort (three arms)	2001-2006	Hospitalization period and 6 months	9	221	45.4	OAC
					159	43.7	OAC+LMWH
					123	44.7	OAC+UFH
Remadi et al. 2001 [41]	Cohort (single arm)	1979-1987	30 days	6	440	60	OAC+UFH
Rivas-Gándara et al.2008 [42]	Cohort (single arm)	2003-2004	Hospitalization period	6	140	66	OAC+LMWH
Steger et al. 2008 [43]*	Cohort (single arm)	2000-2004	Hospitalization period	6	256	ND	OAC+LMWH

Footnote: LMWH - low molecular weight heparin, NOS - Newcastle Ottawa Scale, OAC - oral anticoagulation, UFH - unfractionated heparin, NA - not applicable, ND - not described, n - sample size
* These studies used UFH during the postoperative period but only reported outcomes for LMWH.
** Reported bleeding during hospitalization. Thromboembolic events reported within 6 months.

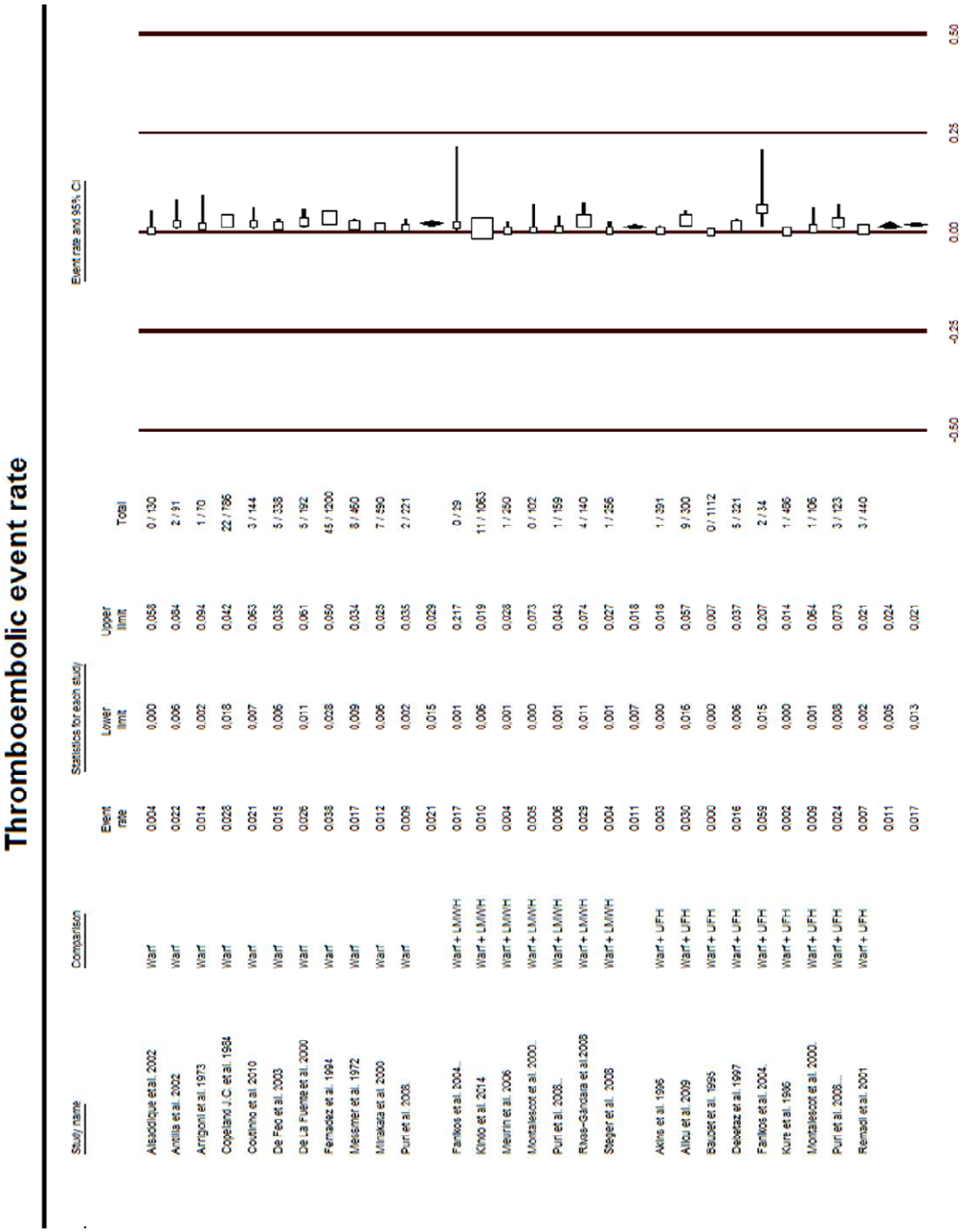
There were 11 studies or arms evaluating the outcomes of patients receiving OAC without bridging therapy (4222 patients) [23-25, 27-30, 33, 36, 38, 40]. There were 9 studies or arms evaluating the outcomes of patients receiving bridging therapy with UFH (3313 patients) [6, 22, 26, 31, 32, 35, 39-41] and 7 studies or arms evaluating the outcomes of patients receiving bridging therapy with LMWH (1999 patients) [32, 34, 37, 39, 40, 42 43]. The studies evaluating OAC+LMWH were more recently published (median 2008; interquartile range 2005-2008) compared with the studies in which OAC was used alone (median 2000; interquartile range of1989-2002) and OAC+UFH (median 2000; interquartile range of 1996-2004).

Only three studies used antiplatelet medication in combination with anticoagulants in their protocol: two studies added aspirin [7, 44], and the other study added aspirin plus dipyridamole [45]. To avoid the introduction of confounding variables, these three studies were excluded. The mean age of the sample was 55 ± 7 years. The study quality analysis by NOS varied from 3 to 9, with a median of 6 stars. The meta-regression analysis data between the NOS and the outcomes are included in the appendix (supplementary material). In some of the studies, parenteral anticoagulation was initiated on either the 1st or the 2nd day following surgery [6, 26, 31, 34, 37, 40, 42 43], whereas in other studies, therapy was initiated only at 48 hours following surgery [22, 32, 35, 39]. Some studies used early OAC [22, 23, 28-30, 34, 35, 38, 40, 42], whereas other studies used OAC only at 48 h following surgery [6, 24-26, 32, 33, 36, 37, 39, 41, 43].

Outcomes and the subgroup analysis

The thromboembolic event rate and the bleeding rate are included in **Figures 2 and 3, respectively.** The thromboembolic event rates, the bleeding rates and the mortality rates for the three groups, as well as the comparison between OAC with and without bridging therapy (combining groups OAC+UFH and OAC+LMWH), are included in **Table 3**.

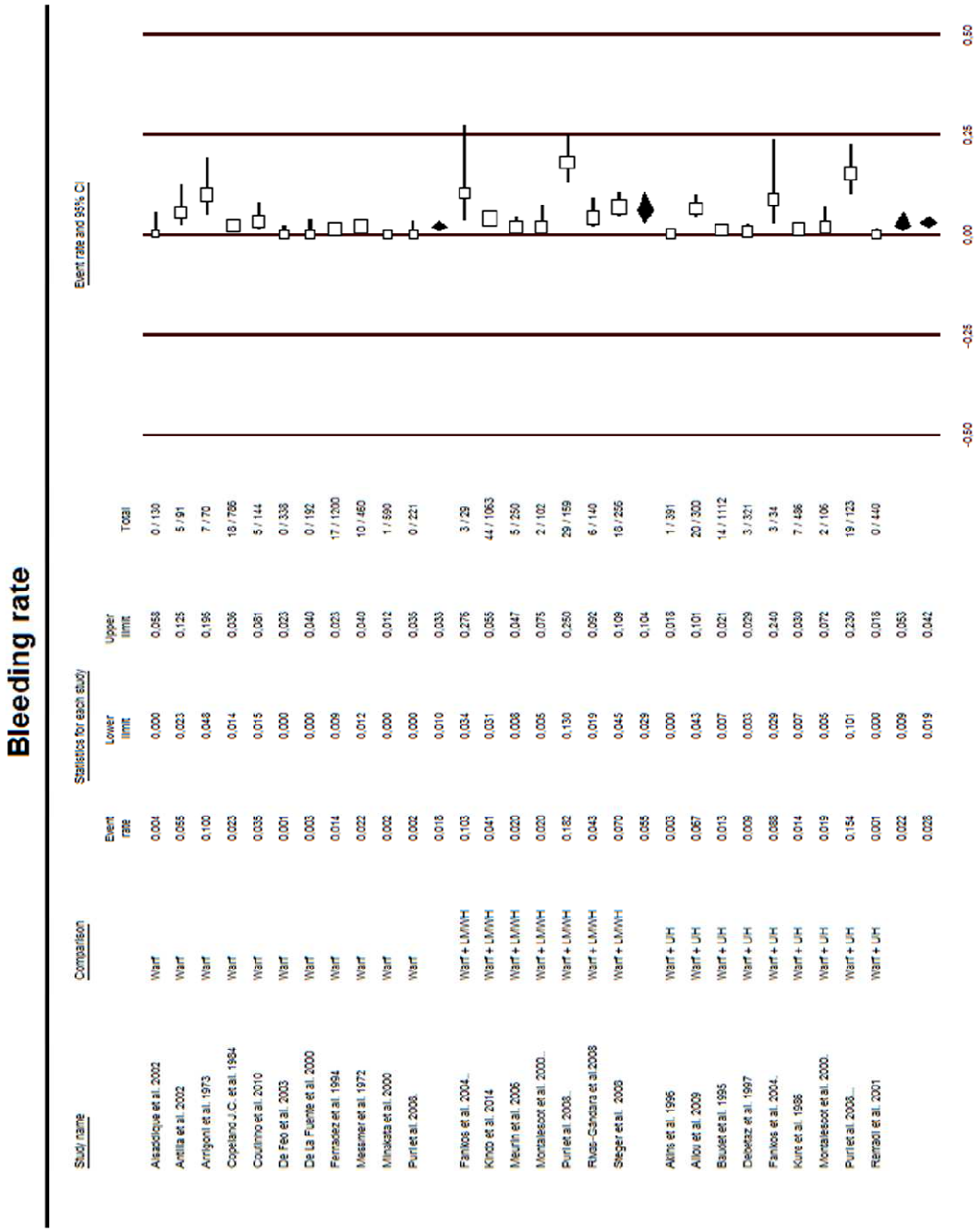
FIGURE 2: The thromboembolic rates by group.



Footnote:

1) LMWH - low molecular weight heparin, OAC - oral anticoagulation, UFH - unfractionated heparin.
2) Previous studies considered only the thromboembolic events that were clinically diagnosed, as was the case in the Allou et al. 2009 study (1) the thromboembolic events diagnosed via echocardiography were excluded (of the 24 events reported, only 9 were clinical events, and 15 were echocardiographic diagnoses).

FIGURE 3: The bleeding rates by group.



Footnote: LMWH - low molecular weight heparin, OAC - oral anticoagulation, UFH - unfractionated heparin.

TABLE 3: The outcomes of each therapy.

Outcome	Group	n	Events	Sample size	Pooled rate (95% CI)	I^2 (%)	p
Thromboembolic event rate (Groups)	**OAC**	11	100	4222	2.1% (1.5-2.9)	45.6	0.062
	OAC+UFH	9	25	3313	1.1% (0.5-2.4)	66.9	
	OAC+LMWH	7	18	1999	1.1% (0.7-1.8)	8.7	
Thromboembolic event rate (Bridging)	**OAC**	11	100	4222	2.1% (1.5-2.9)	45.6	0.035
	OAC+Bridging	16	43	5312	1.1% (0.7-1.8)	53.5	
Bleeding rate (Groups)	**OAC**	11	63	4222	1.8% (1.0-3.3)	75.9	0.042
	OAC+UFH	9	69	3313	2.2% (0.9-5.3)	91.2	
	OAC+LMWH	7	107	1999	5.5% (2.9-10.4)	88.9	
Bleeding rate (Bridging)	**OAC**	11	63	4222	1.8% (1.0-3.3)	75.9	0.117
	OAC+Bridging	16	176	5312	3.5% (2.0-5.9)	90.3	
Mortality (Groups)	**OAC**	11	223	4222	4.0% (2.8-5.9)	76.9	0.069
	OAC+UFH	9	108	3313	3.3% (2.6-4.3)	30.0	
	OAC+LMWH	7	9	1999	0.5% (0.1-2.9)	77.1	
Mortality (Bridging)	**OAC**	11	223	4222	4.0% (2.8-5.9)	76.9	0.109
	OAC+Bridging	16	117	5312	2.6% (1.8-3.8)	60.5	

Footnote: LMWH - low molecular weight heparin, OAC - oral anticoagulation,UFH - unfractionated heparin, n - number of studies

A higher thromboembolic event rate was observed in the group receiving only OAC (2.1%; CI 95% 1.5-2.9) compared with the group receiving bridging therapy (1.1%; CI 95% 0.7-1.8) (p=0.035). When comparing the subgroups of studies using early anticoagulation (less than 48 hours) with those using late anticoagulation (more than 48 hours), there was no difference in the rate of thromboembolic events **(Table 5 in Appendix).** In the meta-regression analysis, the year of publication (p=0.698), age (p=0.706) and the quality evaluated by NOS (p=0.454) were not associated with changes in the embolic event rates. In a sensitivity analysis that excluded two arms as outliers, including one arm in the OAC+UFH group [32] and another in the OAC+LMWH subgroup [42], the results were similar to those of the primary analysis, with confidence intervals overlapping in the comparison of OAC with OAC+UFH **(Table 4)**. In a sensitivity analysis that excluded older studies [22, 25, 26, 27, 31, 33, 35, 36] there was no difference in the rate of thromboembolic events **(Table 6 in Appendix).**

TABLE 4: A sensitivity analysis – the outcomes of each therapy following the exclusion of outliers.

Outcome	Group	n	Events	Sample size	Pooled rate (95% CI)	I^2(%)	p
Thromboembolic event rate (Groups)	OAC alone	11	100	4222	2.1% (1.5-2.9)	45.6	0.006
	OAC + UFH	8	22	3279	0.9% (0.4-2.0)	66.0	
	OAC + LMWH	6	14	1859	0.9% (0.5-1.4)	0.0	
Thromboembolic event rate (Bridging)	OAC alone	11	100	4222	2.1% (1.5-2.9)	45.6	0.006
	OAC + Bridging	14	37	5138	0.9% (0.5-1.5)	48.3	
Bleeding rate (Groups)	OAC alone	10	56	4152	1.6% (0.9-2.7)	63.6	0.005
	OAC + UFH	8	50	3190	1.7% (0.7-3.8)	85.0	
	OAC + LMWH	6	78	1840	4.4% (2.9-6.6)	55.0	
Bleeding rate (Bridging)	OAC alone	10	56	4152	1.6% (0.9-2.7)	63.6	0.132
	OAC + Bridging	14	128	5030	2.8% (1.7-4.3)	80.7	

Footnote 1: LMWH - low molecular weight heparin, OAC - oral anticoagulation, UFH - unfractionated heparin, n - number of studies.
Footnote 2: The Box plot graphical technique was used to identify outliers.

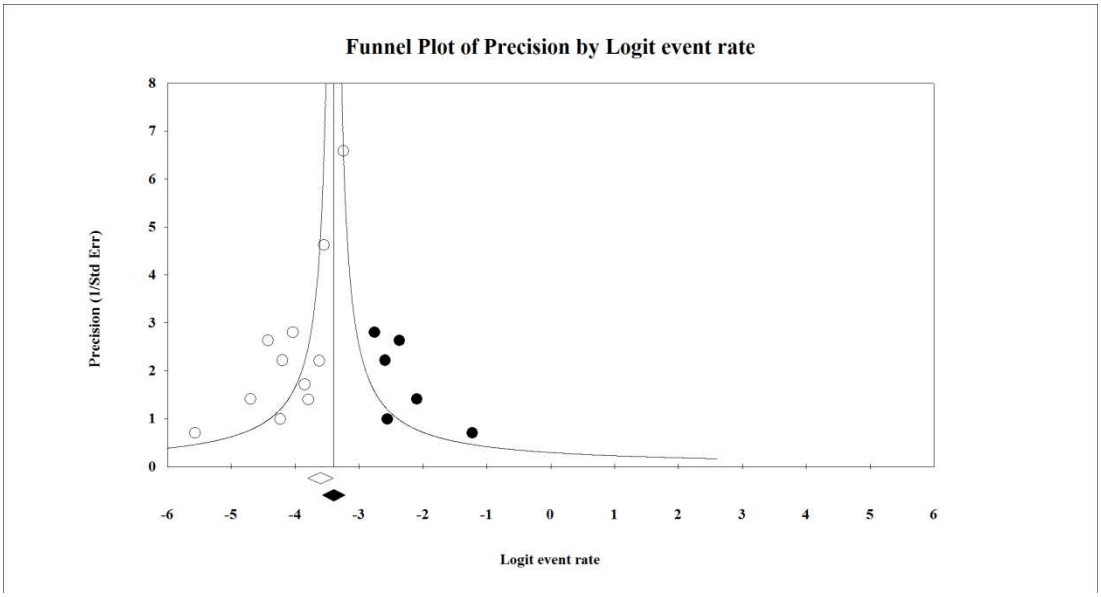
There appeared to be a higher bleeding rate in the group receiving OAC+LMWH (5.5%; CI 95% 2.9-10.4) compared with the other groups as follows: OAC (1.8%; CI 95% 1.0-3.3) and OAC+UFH (2.2%; CI 95% 0.9-5.3) (p=0.042).There was also no difference in the subgroup analysis stratified based on either the early (less than 48 hours) or the late (more than 48 hours) implementation of an anticoagulation regimen **(Table 5 in Appendix).** In meta-regression analysis, the year of publication (p=0.341) and age (p=0.170) were not associated with this outcome. The meta-regression analysis demonstrated a relationship between bleeding and study quality as determined via NOS (p=0.018), as a higher bleeding rate was noted among the studies with more stars (**Figure 6 in Appendix**). In a sensitivity analysis that excluded three outlier studies, including one in the OAC group [25] and two arms of the study comparing OAC+UFH and OAC+LMWH [40], the results were similar to those of the primary analysis, with overlapping confidence intervals **(Table 3).** In a sensitivity analysis that excluded older studies [22, 25, 26, 27, 31, 33, 35, 36] there was more bleeding events events in the group receiving OAC+LMWH (5.5%; CI 95% 2.9-10.4) and in the group receiving OAC+UFH (5.2%; CI 95% 2.1-12.4) compared with OAC (0.8%; CI 95% 0.2-2.7) (p=0.018). There was also more bleeding events in the bridging group (5.6%; CI 95% 3.4-9.0) compared with OAC (0.8%; CI 95% 0.2-2.7) (p=0.004). **(Table 6 in Appendix)**.

There was no significant difference in the mortality noted by both analyses, either by group (p=0.069) or by bridging therapy (p=0.109). In the meta-regression analysis, age was not associated with mortality (p=0.082), although publication year appeared to influence mortality, as the more recently published studies exhibited lower mortality rates than the older studies (p=0.001) **(Figure 7 in Appendix).**

Publication Bias

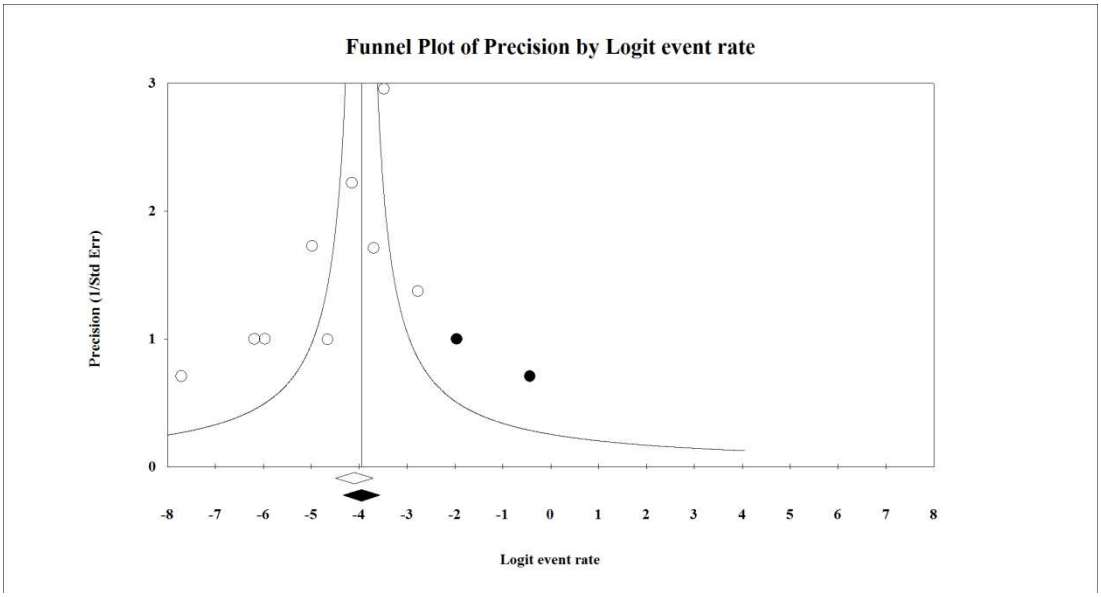
The publication bias evaluation was negative for the following outcomes: bleeding in the OAC group (Egger's test p=0.237), bleeding in the OAC+UFH group (Egger's test p=0.251), bleeding in the OAC+LMWH group (Egger's test p=0.707), the thromboembolic event rate in the OAC+LMWH group (Egger's test p=0.174), and the mortality rate in the OAC+UFH group (Egger's test p=0.094). The Egger's test demonstrated the possibility of publication bias for the mortality outcome in two groups (OAC p<0.001 and OAC+LMWH p=0.002) and for the thromboembolic event rate outcome in both the OAC group (p=0.003) and the OAC+UFH group (p=0.030). The Trim and Fill evaluation of the positive tests for the thromboembolic event rate may be found in **Figures 4 and 5**.

FIGURE 4: A funnel plot of the thromboembolic event rate with OAC.



Footnote: A point estimate via random effects for the observed values, 0.021 (0.015-0.029). Six studies trimmed; a point estimate was performed via random effects for adjusted values, 0.031 (0.022-0.043).

FIGURE 5: A funnel plot of the thromboembolic event rate with OAC+UFH.



Footnote: A point estimate via random effects for the observed values, 0.011 (0.005-0.023). Two studies trimmed; a point estimate was performed via random effects for the adjusted values, 0.016 (0.007-0.035).

DISCUSSION

The primary finding of this study was the high bleeding rates observed in the group receiving early bridging therapy with OAC+LMWH. Although limited evidence and overlapping confidence intervals hampered our conclusions, this group exhibited higher bleeding rates compared with either OAC alone or OAC+UFH. It was consistent with the results of studies evaluating bridging therapy for device implantation in chronically anticoagulated patients receiving implantable cardiac arrhythmia devices [44-47]. Each of these studies observed higher bleeding rates in the setting of OAC+LMWH bridging compared with maintaining OAC at therapeutic levels during either pacemaker or defibrillator implantation, as demonstrated by a recent meta-analysis [48]. Additionally, two studies [37, 39] that started bridging therapy at the end of the first week following surgery exhibited lower numbers of bleeding events with LMWH (2%). Starting the full dose of LMWH later appears to be an attractive strategy. Although it was not firmly conclusive, this finding generated several interesting hypotheses.

There appeared to be a small reduction in the thromboembolic event rate secondary to early bridging therapy. This benefit was marginal, as there was considerable overlap of the confidence intervals. Additionally, there may have been publication bias regarding the thromboembolic event rate in OAC+UFH group, which suggests that this rate was underestimated. Mortality was not different among the groups. In the meta-regression analysis of the relationship between publication year and mortality, the reduction in mortality observed with newer publications was both a plausible and an expected finding. The studies of higher quality (NOS in stars) [32, 39, 40] were recent studies that used LMWH. These findings may be explained by progressive improvements in the results of cardiac surgery as a means of introducing a competing risk (patients who die less have a higher chance of bleeding due to the use of the anticoagulant). Several conditions affect mortality in addition to anticoagulation; therefore, the primary focus of this review was the comparison between bleeding and thromboembolic events.

We decided to exclude studies that did not simultaneously evaluate the early outcomes of safety and efficacy to allow for a balance between the risks of thromboembolic events and bleeding as a result of using the same treatment strategy in the same group of patients. The inclusion of studies published after 2006 and the differences in either the inclusion criteria or

the inclusion of studies presenting data pertaining to short-term outcomes that were difficult to distinguish from either the medium or the long term results [49-65] distinguished the systematic review completed in 2006 [3] from our study. Significant differences in the inclusion criteria were also noted compared with the meta-analysis completed in 2014 [66], which included studies that utilized bridging therapy for noncardiac surgery (such as tooth extraction and pregnant women receiving long term anticoagulation). Additionally, there were only four studies comparing oral anticoagulation with low molecular weight heparin; two did not include events.

Each study was analysed to evaluate the causes of heterogeneity observed in the results, including study quality and clinical characteristics. Two studies evaluating bridging therapy demonstrated outlier rates pertaining to thromboembolic events as follows: (a) one study exhibited a rate of 5.9% in the arm that used OAC+UFH [32], most likely as a result of the use of subtherapeutic doses of medication. A second study presented an event rate of 4.3% with the use of OAC+LMWH [42], most likely because fixed and subtherapeutic doses were utilized. However, the year of publication was not associated with different thromboembolic event rates in the meta-regression analysis and in sensitivity analysis that excluded older studies (studies before 2000), in spite of improvements in both prosthesis and surgical technology.

Some studies in different groups have demonstrated bleeding rates higher than 5% [6, 24, 25, 32, 40, 43]. One study demonstrated OAC alone was associated with a high rate of bleeding (10%) [25], an unexpected occurrence with the isolated use of an oral anticoagulant; said study was characterized as an outlier. Another outlier was a study with a 15.4% bleeding rate with OAC+UFH and 18.2% with OAC+LMWH [40], which also reported increased drainage by surgical drains as part of its bleeding rates (not included in other studies). This study started parenteral anticoagulation too early (between 6 and 12 hours following surgery), which suggests that when deciding to use bridging therapy, it is prudent to start after any drains have been removed. Sensitivity analysis excluding these arms and also the sensitivity analysis that excluded studies before 2000 reinforced the primary finding of more bleeding events with LMWH. However, the following question is important: is it possible that the bleeding rates observed in the primary analysis with UFH were lower because in most centres UFH is rarely introduced immediately at therapeutic doses as suggested [67]?

The limitations of these analyses included moderate heterogeneity in most groups and high heterogeneity in some of the groups. Said heterogeneity may be attributed to the following: limited descriptions of the short-term outcomes, doses of drugs, a temporal relationship between the onset of the anticoagulation and outcomes, different types of OAC control, and the evolution of valve technology and surgical technology. Another limitation was the lack of standardization of the criteria used for the definition of a thromboembolic event or bleeding, although only four articles in our review were published before 1988 [25, 27, 35, 36], the date of the first publication of the "Guidelines for Reporting Mortality and Morbidity after Cardiac Valve Interventions" [17].

The type of mechanical prosthesis is an important factor with respect to the rates of thromboembolic events, but a subgroup analysis of the type of prosthesis was not possible, as 34% of the studies or arms evaluated herein either did not describe this variable or used more than one type of prosthesis, without separating the results. The use of prophylactic heparin may also have introduced confounding variables with respect to the event rates reported by some studies (confounding by indication); unfortunately, this bias cannot be measured by limiting the description of the data in the primary studies. In spite of these limitations, sources of heterogeneity were evaluated by several analyses and a thorough evaluation of study characteristics. Meta-regression analysis and sensitivity analysis reinforced findings of the primary analysis.

CONCLUSIONS

Early bridging anticoagulation therapy following cardiac valve surgery appeared to reduce the thromboembolic event rate to 1%, with considerable overlap of the confidence intervals. Bridging therapy with UFH appears to be safe, but this observation carries a risk of bias. Early bridging therapy with LMWH appears to be associated with a higher rate of bleeding compared with either OAC or OAC+UFH. Considering the available evidence, the following suggestions may be made:

Implications for practice: Bridging therapy should be started later and after any drains have been removed. The early initiation of full dose LMWH will most likely result in increased bleeding. Based on the available evidence, we recommend that bridging therapy be initiated with either UFH or low dose LMWH to minimize the risk of bleeding. Following either the fourth or fifth postoperative day, full dose bridging therapy may be safely used.

Implications for research: Future studies may be used to determine the clinical relevance of early bridging therapy during the postoperative period following heart valve surgery when comparing different anticoagulation regimens. A better understanding of the ideal time at which to start oral and parenteral anticoagulation is essential. A randomized clinical trial comparing the thromboembolic event rate of OAC (2.1%) versus that of OAC+UFH or LMWH (1.1%) would, given an alpha error of 5%, and a power of 80%, require 2667 patients in each arm (a sample of 5334 patients). Faced with this potential limitation, a multicentre prospective registry may be useful.

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Disclosures

The authors report no conflicts of interest regarding the publication of this manuscript.

Addendum

L. G. Passaglia performed the study's conception and design, analysed and interpreted the data, wrote and revised the article and provided final approval of the version to be published. M. R. Sousa performed the study's conception and design, analysed and interpreted the data, wrote and revised the article and provided final approval of the version to be published. G. M. de Barros participated in the study's design, literature review and data extraction, revised the article and provided final approval of the version to be published.

APPENDIX

TABLE 5: Subgroup analysis by time to onset of anticoagulant in each event rate

Outcome	Group	n	Events	Sample size	Pooled rate (95% CI)	I^2(%)	p
Thromboembolic event rate (oral anticoagulation)	Less than 48h	13	45	4011	1.4% (1.0-2.1)	37.7	0.825
	More than 48h	12	71	4416	1.3% (0.7-2.4)	65.4	
Thromboembolic event rate (parenteral anticoagulation)	Less than 48h	11	36	3932	1.3% (0.7-2.1)	49.4	0.722
	More than 48h	4	4	940	0.9% (0.1-5.4)	71.8	
Bleeding rate (oral anticoagulation)	Less than 48h	13	115	4011	2.3% (1.1-4.7)	90.3	0.468
	More than 48h	12	103	4416	3.2% (1.9-5.3)	84.5	
Bleeding rate (parenteral anticoagulation)	Less than 48h	11	162	3932	4.2% (2.3-7.4)	91.7	0.599
	More than 48h	4	14	940	2.8% (0.7-10.9)	83.5	

Footnote: n - number of studies.

TABLE 6: A sensitivity analysis after exclusion of studies published before 2000.

Outcome	Group	n	Events	Sample size	Pooled rate (95% CI)	I^2(%)	p
Thromboembolic event rate (Groups)	OAC alone	7	24	1706	1.6% (1.1-2.3)	0.0	0.326
	OAC + UFH	5	18	1003	2.1% (1.0-4.2)	48.6	
	OAC + LMWH	7	18	1999	1.1% (0.7-1.8)	8.6	
Thromboembolic event rate (Bridging)	OAC alone	7	24	1706	1.6% (1.1-2.3)	0.0	0.842
	OAC + Bridging	12	36	3002	1.5% (0.9-2.4)	42.4	
Bleeding rate (Groups)	OAC alone	7	21	1706	0.8% (0.2-2.7)	72.9	0.018
	OAC + UFH	5	44	1003	5.2% (2.1-12.4)	82.7	
	OAC + LMWH	7	107	1999	5.5% (2.9-10.4)	88.9	
Bleeding rate (Bridging)	OAC alone	7	21	1706	0.8% (0.2-2.7)	72.9	0.004
	OAC + Bridging	12	151	3002	5.6% (3.4-9.0)	86.3	

Footnote 1: LMWH - low molecular weight heparin, OAC - oral anticoagulation, UFH - unfractionated heparin, n - number of studies.

FIGURE 6: Meta-regression between bleeding rate and Newcastle Ottawa scale.

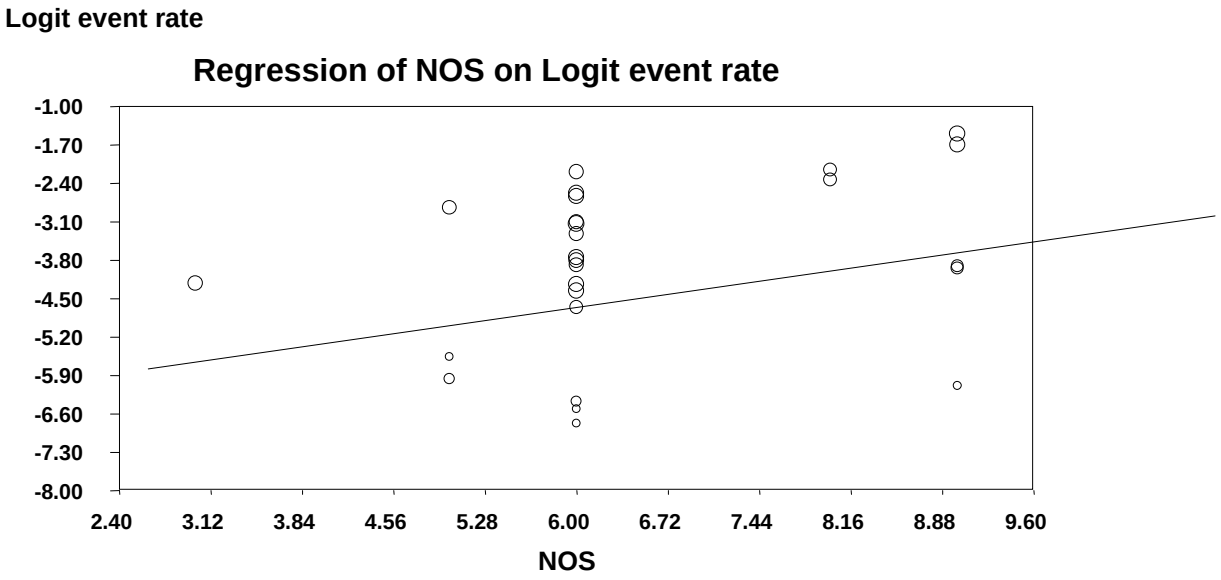
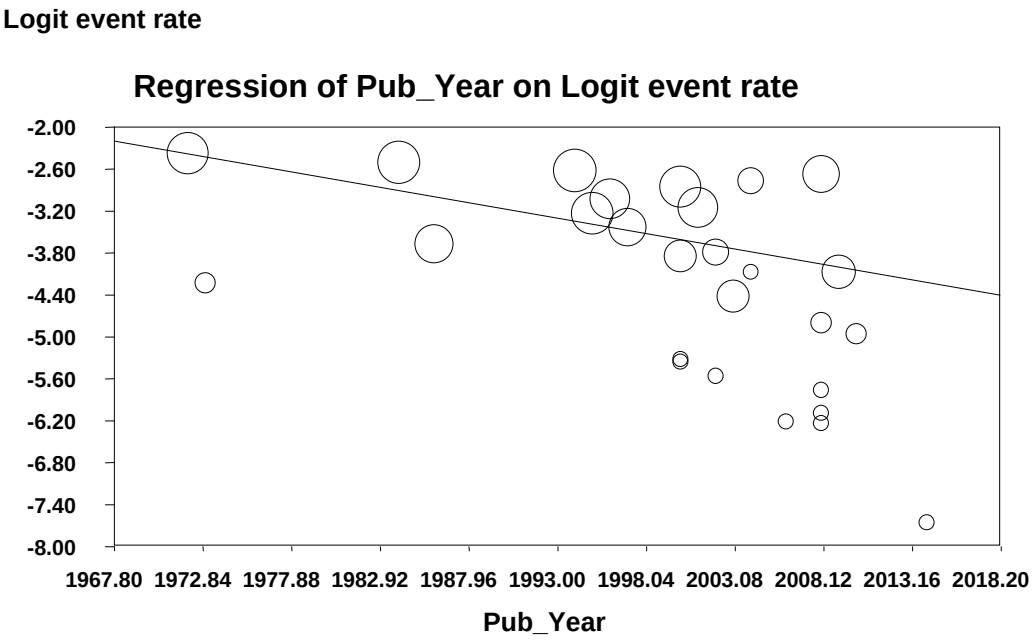


FIGURE 7: Meta-regression of mortality by publication year.



Footnote: p=0.001

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4 CONSIDERAÇÕES FINAIS

A DV é uma condição patológica prevalente e representa uma importante parcela das cirurgias cardíacas realizadas, particularmente no Brasil. No entanto, as recomendações das principais diretrizes das sociedades de cardiologia quanto ao uso da terapia de ponte após o implante da valva cardíaca mecânica são contraditórias. Diante desse cenário de incerteza, o presente estudo objetivou realizar uma revisão sistemática e meta-análise quanto aos riscos e benefícios do uso do anticoagulante parenteral como terapia de ponte no pós-operatório.

No estudo apresentado, a taxa de eventos tromboembólicos no grupo que recebeu apenas o Anticoagulante Oral (ACO) foi discretamente superior quando comparada ao uso da terapia de ponte combinada (ACO+HNF e ACO+HBPM), sugerindo que o uso do anticoagulante parenteral reduz a taxa desses eventos. A análise de sensibilidade também encontrou mais eventos tromboembólicos com o uso isolado do ACO. Entretanto, é importante destacar que a diferença estatística é pequena e que os intervalos de confiança são sobrepostos, o que reforça a necessidade de novos estudos para avaliar a real relevância clínica deste benefício.

Quanto às taxas de sangramento, o grupo que recebeu ACO+HBPM sangrou significativamente mais que o grupo com ACO isolado. A análise de sensibilidade corroborou com este achado. Na análise qualitativa dos estudos, 5 dos 7 estudos com HBPM apresentaram taxas de sangramento maiores do que 4%. Estes dados questionam a real segurança do uso da HBPM neste cenário. Ao mesmo tempo em que a diferença nas taxas de sangramento que comparam ACO isolado com ACO+HPBM é estatisticamente e, possivelmente, clinicamente relevante, o mesmo não pode ser dito na comparação entre ACO+HNF e ACO+HBPM. Além de taxas mais próximas, é notório que apenas um estudo[1] registrou a porcentagem de pacientes que alcançaram o nível terapêutico com o uso da HNF: no 2º dia de tratamento, 87% dos pacientes com HBPM tinham a dosagem do fator Xa ativado na faixa de eficácia enquanto que apenas 9% dos pacientes com HNF tinha um Tempo de Tromboplastina Ativado (PTTa) na faixa terapêutica. Esse fato gera uma pergunta que a princípio permanece sem resposta: as taxas de sangramento menores com o uso de ACO+HNF não ocorreram simplesmente porque o uso da HNF estava em doses subterapêuticas do medicamento?

Adicionalmente, em uma análise crítica dos estudos, apenas duas coortes realizaram comparação direta de grupos entre as duas heparinas citadas. O estudo[2] com taxas de sangramento de 18,2% para o uso da HBPM e de 15,4% para o uso da HNF iniciou o anticoagulante parenteral num momento extremamente precoce do pós-operatório (dentro das primeiras 6h). Já o estudo[3] com taxas de sangramento de 2% para HBPM e de 1,9% para HNF usou o anticoagulante parenteral apenas após o 2º dia de pós-operatório. Dois estudos iniciaram o anticoagulante parenteral mais tardiamente, um estudo[4] com HNF apresentou taxa de sangramento de 0,3% (início do anticoagulante parenteral após o 5º dia) e o outro estudo[5] com HBPM teve taxa de sangramento de 2% (início do anticoagulante parenteral apenas após a primeira semana de cirurgia), ambos com baixas taxas de eventos tromboembólicos. Apesar de não ter ocorrido diferença estatística na comparação de subgrupos de início do anticoagulante parenteral com menos de 48h comparados com o início com mais de 48h, talvez a diferença do "extremamente precoce" (6-12h) possa ser relevante com o grupo "extremamente tardio" (mais de 5 dias). Este cálculo estatístico não foi realizado por representar a minoria (6) do total de estudos apresentados (23).

Por fim, as maiores taxas de sangramento nos estudos com HBPM não se refletiram em maior mortalidade. Uma possível explicação para a discrepância sangramento x mortalidade é a evolução do cuidado em cirurgia cardíaca, resultando em menor mortalidade ao longo do tempo, como sugere a metarregressão.

Diante do que foi exposto, podemos sumarizar algumas implicações:

Implicações para a prática: preferencialmente, as heparinas devem ser introduzidas após a retirada dos drenos. Este momento ocorre, na maioria das instituições, e na ausência de complicações, entre o 1º e 3º dia de pós-operatório. A princípio, além do dado de segurança do uso da HNF em dose de anticoagulação plena poder estar enviesado, o seu uso possui a desvantagem de necessitar de uma via de infusão venosa continua (interferindo negativamente na liberdade de movimento do paciente) e acrescenta infusão de solução salina em uma fase "pró-inflamatória" (na qual a sobrecarga volêmica pode ser um problema clínico de difícil manejo em pacientes cardiopatias). Com relação ao uso da HBPM, mais estudos são necessários para avaliação da sua segurança neste cenário. Caso a HBPM venha a ser utilizada para anticoagulação plena, é prudente ser introduzida somente após uma redução substancial do risco de complicações hemorrágicas. A proposta do seu início pleno e não mais apenas

profilático após o 5º dia de pós-operatório (caso o RNI ainda não esteja terapêutico) possivelmente pode vir a reduzir as taxas de sangramento do seu uso.

Implicações para a investigação: estudos futuros poderiam servir para determinar a relevância clínica da terapia de ponte no período pós-operatório precoce de cirurgia cardíaca valvar ao comparar diferentes regimes de anticoagulação. Um melhor entendimento de qual anticoagulante parenteral é mais seguro, eficiente e custo-efetivo, assim como de qual o momento ideal para iniciar o anticoagulante oral e parenteral a fim de minimizar o risco de sangramento e otimizar a redução de eventos tromboembólicos são questões pertinentes no processo assistencial.

Como um estudo aleatorizado sobre o tema é pouco prático, particularmente pelo tamanho da amostra necessária para uma correta análise dos desfechos de interesse, a proposta de um registro de dados prospectivo e multicêntrico de pós-operatório das cirurgias cardíacas valvares torna possível a confecção de um banco de informações válidas para um melhor esclarecimento desta lacuna no conhecimento científico.

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