UNIVERSIDADE FEDERAL DE MINAS GERAIS
FACULDADE DE FARMÁCIA

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AVALIAÇÃO DA QUALIDADE DO CONTROLE DA ANTICOAGULAÇÃO ORAL DE ACORDO COM O SEXO: REVISÃO SISTEMÁTICA E META-ANÁLISE

Belo Horizonte

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Dissertação apresentada ao Programa de Pós-Graduação em Medicamentos e Assistência Farmacêutica da Faculdade de Farmácia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Mestre em Medicamentos e Assistência Farmacêutica.

Orientadora: Prof.ª Dra. Maria Auxiliadora Parreiras Martins.

Coorientador: Prof. Dr. Marcus Fernando da Silva Praxedes.

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RESUMO

O aumento da prevalência das doenças cardiovasculares observado nos últimos anos tem ocasionado o aumento do número de pessoas com indicação de uso de anticoagulantes orais (ACO). Os ACO com maior experiência de uso são os inibidores da vitamina K, sendo a varfarina o derivado cumarínico mais utilizado no Brasil. O tratamento com varfarina apresenta difícil manejo relacionado ao seu estreito índice terapêutico e ampla variabilidade dose-resposta. A monitorização laboratorial periódica torna-se fundamental para guiar os ajustes de dose. O *time in therapeutic range* (TTR) é um dos métodos utilizados para avaliar a qualidade da anticoagulação, sendo recomendado que seja mantido acima de 60%. Nessa faixa, o risco de sangramento e complicações tromboembólicas é minimizado. Estudos anteriores mostraram diferenças na qualidade do controle da anticoagulação oral entre homens e mulheres, embora essas evidências sejam controversas. Dessa forma, o objetivo deste estudo foi realizar uma revisão sistemática com meta-análise para avaliar a associação entre sexo e controle da anticoagulação oral com derivados cumarínicos. Consultou-se as bases de dados MEDLINE, BVS, CINAHL, EMBASE, Cochrane Central e Web of Science para analisar estudos observacionais e experimentais, com participantes de ambos os sexos, com idade >18 anos, em anticoagulação oral crônica com derivados cumarínicos. Foram incluídos quatorze estudos que estavam de acordo com os critérios de elegibilidade. *Odds ratios* (OR) para variáveis binárias e diferenças médias (DM) para variáveis contínuas foram agrupados usando os modelos de efeitos aleatórios. Nove estudos foram avaliados na meta-análise a partir de variáveis binárias (OR=0,89; IC 95%=0,80,1,00; z=-1,96; p=0,05; I^2=74%) e cinco estudos com variáveis contínuas (DM=-4.03; 95% CI=-5.74, -2.31; z=-4.61; p<0.0001; I^2=49%). As estimativas combinadas indicaram que o sexo feminino estava associado a menor TTR do que o sexo masculino, sendo um fator de risco (mediador) para pior controle da anticoagulação. As mulheres em anticoagulação oral frequentemente são idosas, com quadro frágil de saúde e dependentes de cuidadores. Nossos resultados sinalizam a necessidade de estudos futuros delineados para melhor compreensão dos aspectos envolvidos a esse pior controle. Além disso, nossos resultados podem contribuir para subsidiar o desenvolvimento de estratégias centradas no paciente e para adaptação de cuidados a fim de aumentar a efetividade e segurança do tratamento, contribuindo para redução de complicações nesse subgrupo de pacientes.

Palavras-chave: Cumarínicos. Qualidade da terapia. Sexo. Tromboembolismo. Varfarina.

ABSTRACT

The increased prevalence of cardiovascular diseases observed in recent years has enhanced the number of people using oral anticoagulants (OAC). Warfarin is a vitamin K inhibitor with most experience use as an OAC, being the main coumarin derivative distributed in Brazil. Warfarin therapy presents difficult management related to its narrow therapeutic index and wide dose-response variability. Frequent laboratory monitoring becomes fundamental to guide dose adjustments. The time therapeutic range (TTR) is one of the methods used to evaluate the quality of anticoagulation, and it is recommended to be maintained above 60%. In this range, the risk of bleeding and thromboembolic complications is minimized. Previous studies have shown differences in the quality of oral anticoagulation control between men and women, although this evidence is controversial. Thus, the purpose of this study was to perform a systematic review and meta-analysis to assess the association between sex and oral anticoagulation control in patients on coumarin derivatives. The MEDLINE, BVS, CINAHL, EMBASE, Cochrane Library and Web of Science databases were consulted to analyze observational and experimental studies, involving patients of both sexes, aged over 18 years, on chronic oral anticoagulation with coumarin derivatives. Fourteen studies met the eligibility criteria and were included in the review. The data were synthesized and then compiled results were used to develop a meta-analysis. Odds ratios (OR) for binary variables and mean differences (MD) for continuous variables were grouped using randomized effect models. Nine studies were evaluated in the meta-analysis from binary variables (OR=0.89; CI 95%=0.80, 1.00; z=-1.96; p=0.05; I^2=74%) and five studies with continuous variables (MD=-4.03; 95% CI=-5.74, -2.31; z=-4.61; p<0.0001; I^2=49%). The combined estimates indicated that the female sex was associated with lower TTR than the male sex being a risk factor (mediator) for worse control of anticoagulation. Women in oral anticoagulation are often elderly, with poor health and dependent on caregivers. Our results signal the need for future studies designed to better understand the aspects involved in this worse control. Besides, our results may contribute to subsidize the development of patient-centered strategies and adaptation of care in order to increase the effectiveness and safety of treatment, contributing to reduce complications in this subgroup of patients.

Keywords: Coumarins. Quality of therapy. Sex. Thromboembolism. Warfarin**.**

LISTA DE ABREVIATURAS E SIGLAS

ACO	Anticoagulantes orais
AVC	Acidente vascular cerebral
DCV	Doenças cardiovasculares
FA	Fibrilação atrial
IC	Intervalo de confiança
IRR	*Incidence rate ratio*
OMS	Organização Mundial de Saúde
OR	*Odds Ratio*
RNI	Relação Normalizada Internacional
RENAME	Relação Nacional de Medicamentos Essenciais
RR	Risco Relativo
SUS	Sistema Único de Saúde
TP	Tempo de protrombina
TTR	*Time in therapeutic range*
VKORC1	Vitamina K epóxido redutase

SUMÁRIO

1 INTRODUÇÃO

A prevalência das doenças cardiovasculares (DCV) tem aumentado nos últimos anos, representando uma das principais causas de mortalidade no mundo. Em 2016, estima-se que 41 milhões de pessoas morreram devido a doenças não transmissíveis, representando 71% do total geral de 57 milhões de mortes no mundo. As DCV representaram 17,9 milhões de mortes (WORLD HEALTH ORGANIZATION, 2018) e no Brasil, em 2017, as DCV representaram 28,8% das mortes no país (GLOBAL HEALTH DATA EXCHANCE, 2019).

A prevalência global observada em 2017 para doença cardíaca isquêmica foi 1,72% e de acidente vascular cerebral (AVC) foi 1,41%, enquanto no Brasil essa prevalência foi de 1,75% e de 1,27%, respectivamente (GLOBAL HEALTH DATA EXCHANCE, 2019). Já a prevalência de fibrilação atrial (FA), na população geral, foi estimada entre 0,5% e 1,0%, e no Brasil, estima-se que afete 1,5 milhões de indivíduos, números que podem estar subestimados, uma vez que muitos casos (10 a 25%) não provocam sintomas e permanecem não diagnosticados (MAGALHÃES *et al.*, 2016).

A anticoagulação oral é o tratamento de escolha para pacientes com risco de desenvolver complicações tromboembólicas arteriais e venosas nas DCV, como na fibrilaçao atrial (FA), uma doença que nas últimas décadas, tornou-se um importante problema de saúde pública, com grande consumo de recursos em saúde (PENTILLA *et al*., 2019; AGENO *et al*., 2012, MAGALHÃES *et al.*, 2016). Os anticoagulantes orais (ACO) mais usuais são os inibidores da vitamina K derivados cumarínicos, sendo a varfarina o mais utilizado no mundo, principalmente em países de baixa e média-renda (PRAXEDES, 2015). No entanto, a terapia com derivados cumarínicos é um desafio, devido ao seu índice terapêutico estreito e ampla variabilidade dose-resposta (PARK *et al*., 2017). Assim, é necessária uma monitorização frequente para minimizar o risco de hemorragia e tromboembolismo.

A Relação Normalizada Internacional (RNI), calculada a partir do tempo de protrombina, é utilizada para monitorização do tratamento, e a qualidade da anticoagulação oral pode ser avaliada pelo *time in therapeutic range* (TTR). O TTR é frequentemente calculado pelo método Rosendaal e varia de 0-100% (ROSENDAAL *et al*., 1993). Valores inferiores a 60% foram classificados como controle inadequado

apresentando maior risco de complicações relacionadas com a anticoagulação (SENOO; LIP, 2015).

Estudos prévios sobre fatores associados ao controle da anticoagulação demonstraram uma relação entre o TTR e o sexo, porém as conclusões desses estudos são discrepantes. O sexo feminino tem sido associado a menor valor de TTR do que o sexo masculino por alguns autores, enquanto outros encontraram menor controle para o sexo masculino (PRAXEDES *et al*., 2020; WHITE *et al*., 2016; GAMERO *et al*., 2017). Há ainda, estudos que não demonstraram diferenças significativas no TTR entre homens e mulheres (FARSAD *et al*., 2016; KOSE *et al*., 2015).

Os aspectos relacionados com o sexo que podem afetar o TTR, tais como fatores comportamentais e fisiológicos, não são totalmente compreendidos até o momento. Estudos amplos que visam investigar a relação do sexo com a qualidade do controle da anticoagulação oral são escassos na literatura. Diante das discrepâncias observadas nos resultados dos estudos, foi proposta a presente pesquisa para investigar a associação entre o sexo e o controle da anticoagulação oral com varfarina e outros derivados cumarínicos. Esse trabalho poderá auxiliar a prática clínica, com o objetivo de melhorar a efetividade e a segurança do tratamento dos pacientes.

2. REVISÃO DA LITERATURA

2.1 Indicações clínicas para uso de derivados cumarínicos

Os inibidores de vitamina K derivados da cumarina são eficazes na tromboprofilaxia primária e secundária, sendo usados por milhões de pacientes em todo o mundo (AGENO *et al*., 2012). Nessa classe, encontram-se os fármacos varfarina, femprocumona e acenocumarol, dentre outros (AGENO *et al.*, 2012; VAN GEEST-DAALDEROP; PÉQUÉRIAUX; VAN DEN BESSELAAR, 2009).

Varfarina é o derivado cumarínico com a maior experiência clínica acumulada até o momento (PERK *et al.*, 2012). É amplamente utilizado na prevenção primária e secundária de eventos tromboembólicos por pacientes com FA para reduzir o risco de AVC (HART; PEARCE; AGUILAR, 2007), em tratamentos do tromboembolismo venoso (GARCIA *et al.*, 2008) e em pacientes com prótese de valva cardíaca (GRZYMALA-LUBANSKI *et al.*, 2017).

A FA é uma doença cardiovascular que, nas últimas décadas, tornou-se importante problema de saúde pública, com grande consumo de recursos em saúde. Essa condição apresenta importante repercussão na qualidade de vida, em especial devido às suas consequências clínicas, risco para ocorrência de fenômenos tromboembólicos e alterações cognitivas (MAGALHÃES *et al*., 2016). O risco de AVC cardioembólico é aumentado em pessoas com FA, apresentando maior gravidade clínica quando comparado a outros tipos de AVC (BEST *et al*., 2019; SACHDEVA *et al*., 2016). Esse fato é preocupante, uma vez que o AVC tem ocupado o terceiro lugar nas causas de morte no mundo e o segundo lugar no Brasil (GLOBAL HEALTH DATA EXCHANCE, 2017). Os coágulos na FA tendem a ser grandes, podendo obstruir vasos de diâmetros maiores, causando complicações neurológicas mais graves, e o uso de varfarina previne a formação desses coágulos (BEST *et al*., 2019; SACHDEVA *et al*., 2016; HART; PEARCE; AGUILAR, 2007). Foi demonstrado em meta-análise que reuniu 29 ensaios clínicos randomizados e um total de 28.044 participantes com FA, que a terapia com varfarina reduziu o risco de AVC em 64% em comparação com o placebo e em 39% em comparação com ácido acetilsalícilico (HART; PEARCE; AGUILAR, 2007).

O risco de embolia sistêmica de válvulas cardíacas protéticas depende do tipo de válvula, sua posição e outros fatores que contribuem para o risco de

desenvolvimento de trombose, como ritmo cardíaco e dilatação (CARNICELLI, 2015). Já foi demonstrado que o risco relatico de um evento tromboembólico em pacientes com válvula cardíaca mecânica com o uso de varfarina em comparação com nenhuma terapia antitrombótica é de 0,21 (95% IC 0,16-0,27), e 0,11 (95% CI 0,07-0,2) para trombose de válvula cardíaca. Esses dados sugerem que a anticoagulação tem benefícios para esses pacientes (WHITLOCK *et al*., 2012).

No Brasil, a anticoagulação oral com varfarina é recomendada para pessoas com doença de Chagas, nas quais os eventos embólicos que acometem o sistema nervoso central constituem a forma mais grave de tromboembolismo, e contribuem para elevada morbimortalidade nesses pacientes (LOPES *et al.*, 1991; DIAS *et al.*, 2016). A varfarina também é utilizada de forma crônica por pacientes com valvulopatia reumática e implantação de prótese mecânica valvar devido ao alto risco de ocorrência de fenômenos embólicos. A sequela valvar reumática incide majoritariamente em jovens e possibilita um incremento progressivo de valvopatias degenerativas na população idosa, associado a índices elevados de calcificação e disfunção valvar (TARASOUTCHI *et al.*, 2017).

2.2 Propriedades farmacológicas dos derivados cumarínicos

Os derivados cumarínicos produzem seu efeito anticoagulante interferindo na interconversão cíclica da vitamina K e seu 2,3-epóxido (epóxido da vitamina K), inibindo a gama-carboxilação dos fatores dependentes da vitamina K (II, VII, IX e X). A carboxilação é necessária para alteração conformacional que ocorre nas proteínas da coagulação e leva à ligação a cofatores nas superfícies fosfolipídicas nos locais de lesão vascular. O tratamento com anticoagulantes derivados cumarínicos resulta na produção hepática de proteínas parcialmente carboxiladas e descarboxiladas com reduzida atividade coagulante (ANSELL *et al.*, 2008; AGENO *et al.*, 2012; LIMA, 2008).

O derivado cumarínico varfarina é uma mistura racêmica de dois isômeros opticamente ativos, os enantiômeros R e S, sendo a (S)-varfarina de 2,7 a 3,8 vezes mais potente que o enantiômero R. A varfarina é altamente solúvel em água, é rapidamente absorvida pelo trato gastrointestinal, tem alta biodisponibilidade, e atinge concentrações sanguíneas máximas em torno de 90 minutos após a administração

oral (ANSELL *et al.*, 2008; AGENO *et al.*, 2012). A varfarina possui meia-vida de 36 a 42 horas [(R)-varfarina, 45 horas e (S)-varfarina, 29 horas], circula ligada às proteínas do plasma e acumula-se no fígado, onde cerca de 90% do enantiômero S da varfarina sofre metabolismo oxidativo pela enzima CYP2C9 do sistema do citocromo P450 e em menor grau pela CYP3A4 (MINEIRS; BIRKETT, 1998). O enantiômero R sofre em torno de 60% do metabolismo oxidativo pelas enzimas do citocromo P450, CYP1A2 e CYP3A4, e, em menor extensão, pela CYP2C9. O metabolismo restante de ambos os enantiômeros envolve a redução de álcoois diastereoisômeros (AGENO *et al*., 2012).

Esses agentes terapêuticos possuem índice terapêutico estreito e flutuação constantes na anticoagulação que se deve às múltiplas interações dos derivados cumarínicos com alimentos, medicamentos, álcool e também às características farmacocinéticas do fármaco e peculiaridades genéticas individuais (NUTESCU *et al*., 2006; MARTINS *et al*., 2011; PARK *et al*., 2017; ROTH *et al*., 2015). Os óleos vegetais e as hortaliças verde-escuras são as fontes mais significativas de vitamina K. Deste modo, a quantidade ingerida dessa vitamina influencia na ação dos derivados cumarínicos, tendo em vista que, a quantidade prescrita desses fármacos procura se adequar à quantidade de vitamina K disponível no sangue (HOLBROOK *et al.,* 2005; NUTESCU *et al*., 2006; MIRANDA *et al*., 2017). A ingestão aguda e excessiva de álcool está relacionada ao risco de hemorragia, enquanto o uso crônico pode induzir enzimas hepáticas e resultar em aumento do risco de tromboembolismo (NUTESCU *et al*., 2006).

As interações dos derivados cumarínicos com medicamentos podem reduzir ou aumentar o efeito anticoagulante. Martins *et al*. (2011) identificaram 573 interações, das quais 243 foram consideradas significativas em pelo menos uma base de dados. Identificou-se nesse estudo a falta de terminologia padrão, imprecisão das avaliações e documentação de gravidade dessas interações, o que pode levar a procedimentos heterogêneos e potenciais consequências clínicas graves. A redução do efeito anticoagulante da varfarina pode ocorrer devido à interação com colestiramina, que ao se ligar ao trato gastrintestinal, provoca redução da absorção deste derivado cumarínico. Outra interação que pode ocorrer é o aumento da depuração metabólica, em decorrência da indução de enzimas hepáticas, particularmente a CYP2C9, por barbitúricos, carbamazepina e rifampicina (WEITZ, 2012; NUTESCU *et al*., 2006).

Os medicamentos que podem aumentar o efeito da varfarina incluem aqueles que inibem as enzimas hepáticas, em especial a CYP2C9, como a amiodarona, antifúngicos azólicos, cimetidina, clopidogrel, clotrimazol, dissulfiram, fluoxetina, isoniazida e metronidazol. O efeito da varfarina pode também ser aumentado com o uso de medicamentos que participam do deslocamento dos locais de ligação das proteínas como o diurético de alça furosemida (WEITZ, 2012). Podem ocorrer, ainda, interações farmacodinâmicas com medicamentos que inibem a agregação plaquetária, causando aumento do risco de sangramento, por exemplo, ácido acetilsalicílico, clopidogrel e antiinflamatórios não esteroidais (AGENO *et al.*, 2012; NUTESCU *et al*., 2006).

Vários fatores genéticos e clínicos contribuem para a variação interindividual dos requerimentos de dose de manutenção de derivados cumarínicos. Pacientes idosos, em geral, requerem dose diária menor de ACO, enquanto os pacientes de maior estatura e com sobrepeso requerem uma dose maior. Poderá haver variação da dose diária intraindividual devido à alteração no padrão de uso de medicamentos, modificações na ingestão de vitamina K, alterações no estado de saúde do paciente (por exemplo, febre, vômitos) e devido a não adesão ao tratamento (VERHOEF *et al.*, 2014; AGENO *et al.,* 2012).

Polimorfismos nas isoformas da CYP2C9 e vitamina K epóxido redutase (VKORC1) são as principais variações genéticas que podem alterar as doses requeridas para anticoagulação. A associação de fatores clínicos com as variações genéticas na CYP2C9 e na VKORC1 é responsável por aproximadamente 50% da variabilidade da dose-resposta da varfarina (JOHNSON *et al*., 2011). Já foi demonstrado que pacientes com mutações em CYP2C9 podem requerer menores doses de varfarina para anticoagulação adequada (LINDH *et al*., 2009), enquanto as mutações em VKORC1 podem induzir a resistência farmacodinâmica à varfarina (HARRINGTON *et al*., 2008).

2.3 Monitorização da anticoagulação oral

O manejo dos derivados cumarínicos é complexo devido à estreita faixa terapêutica e ampla variabilidade dose-resposta, o que aumenta o risco de sangramentos (PARK *et al*., 2017). A monitorização laboratorial se faz necessária para auxiliar nos ajustes de

dose desses fármacos. O método indicado para monitorização da anticoagulação é o tempo de protrombina (TP) descrito por Quick, em 1935, que avalia a atividade da protrombina na presença dos fatores II, VII, IX, X da vitamina K e posterior medida do tempo de formação de coágulo. Devido às diferenças de resultados de TP entre diferentes laboratórios, houve necessidade de padronização do teste para solucionar essa questão. Essas diferenças foram padronizadas pela Relação Normalizada Internacional (RNI), instituída pela Organização Mundial de Saúde (OMS), em 1983 (QUICK, 1935; WORLD HEALTH ORGANIZATION, 1983). O cálculo da RNI é feito de acordo com a seguinte fórmula:

$$RNI = \left[\frac{TP\ paciente}{TP\ referência} \right]^{ISI}$$

ISI, Relação Normalizada Internacional

A faixa terapêutica recomendada da RNI para a maioria das indicações é de 2,00 a 3,00 que representa ponto ótimo no qual há proteção contra eventos tromboembólicos e risco minimizado de sangramentos. Valores da RNI <2,00 aumentam o risco de eventos tromboembólicos e valores da RNI >3,00 aumentam o risco de sangramento. A RNI deve ser verificada diariamente até que o intervalo terapêutico recomendado tenha sido alcançado e mantido por dois dias consecutivos, depois duas ou três vezes por semana durante uma a duas semanas e, depois, com menor frequência, de acordo com a estabilidade dos resultados. Uma vez atingida a RNI estável, a frequência de testes pode ser reduzida a intervalos de até quatro a seis semanas. Quando são necessários ajustes de dose, a monitorização frequente é retomada (HIRSH *et al.*, 2003; MEARNS *et al.*, 2014; VERHOEF *et al.*, 2014).

Para a maioria dos pacientes, os inibidores de vitamina K devem ser iniciados com uma dose de manutenção de 5mg por dia (WIGLE; HEIN; BERNHEISEL, 2019). Porém, a dose deve ser ajustada de acordo com características dos pacientes e resultados da RNI. Pacientes idosos e pessoas com doenças hepáticas ou estado nutricional inadequado, por exemplo, podem exigir doses mais baixas (WIGLE; HEIN; BERNHEISEL, 2019).

Apesar do advento dos anticoagulantes orais diretos, que têm como uma das vantagens não necessitar de monitorização laboratorial, os inibidores de vitamina

K continuam a ser amplamente utilizados em países de baixa e média renda por pacientes com fatores de risco para tromboembolismo por razões de custo (DE LIMA SILVA, 2017; MASSARO; LIP, 2016; KO *et al*., 2017). Além disso, os anticoagulantes orais diretos ainda não têm aplicação para válvula de prótese mecânica, estenose mitral moderada a grave (geralmente de origem reumática) (STEFFEL *et al*., 2018) e há poucas evidências sobre a sua efetividade e segurança na síndrome antifosfolipídica (TEKTONIDOU *et al*., 2019). Varfarina é o único anticoagulante oral que consta na Relação Nacional de Medicamentos Essenciais (RENAME) com ampla distribuição pelo Sistema Único de Saúde (SUS) no Brasil (PRAXEDES, 2015; RENAME, 2020).

2.4 Principais eventos adversos dos derivados cumarínicos

A complicação mais comum relacionada ao uso de derivados cumarínicos é a hemorragia, e o risco está associado com dose excessiva do anticoagulante ou predisposição do paciente, como a idade acima de 65 anos, insuficiência renal ou anemia, e ainda a interações com medicamentos (HIRSH *et al*., 2003; TELES *et al*., 2012). Esses eventos podem ser classificados em hemorragia grave, hemorragia não grave clinicamente relevante e hemorragia não grave (PATEL *et al*., 2011; SILVA, 2016).

Hemorragias graves são aquelas que resultam em morte, causam sequelas crônicas ou consomem grandes recursos de saúde. Há envolvimento de sítio anatômico crítico (intracraniano, espinhal, pericárdico, articular, retroperitonial, ou intramuscular); queda de 2 g/dL ou mais na concentração de hemoglobina ou transfusão de duas ou mais unidades de sangue total ou concentrado de hemácias, ou invalidez permanente (PATEL *et al*., 2011; SILVA, 2016).

A hemorragia não grave clinicamente relevante é aquela que não atende aos critérios para sangramentos graves, mas que necessita de intervenção médica, contato não agendado (presencial ou por telefone) com o profissional de saúde, interrupção temporária do tratamento, ou que interfere negativamente nas atividades diárias. Hemorragia não grave são eventos que não atendem aos critérios de

hemorragia grave e não grave clinicamente relevante (PATEL *et al*., 2011; SILVA, 2016).

O evento adverso não hemorrágico mais importante dos derivados cumarínicos é o tromboembolismo, que pode estar associado à falha terapêutica ou dose insuficiente do anticoagulante (MEARNS *et al*., 2014; ESMERIO *et al*., 2009). Seu uso pode ocasionar ainda, complicações trombóticas agudas, como necrose da pele e síndrome do dedo roxo. Estas complicações, incomuns, são geralmente observadas do terceiro ao oitavo dia de terapia e são causadas por trombose extensa das vênulas e capilares dentro da gordura subcutânea (no caso de necrose da pele) e obstrução do fluxo da circulação venosa do membro (AGENO *et al*., 2012; KAKAGIA *et al*., 2014).

2.5 Qualidade da anticoagulação oral

A qualidade da terapia com derivados cumarínicos pode ser avaliada pelo cálculo do TTR que pode ser obtido pelo método de Rosendaal. Esse método utiliza a interpolação linear, a partir de uma série histórica de resultados da RNI, e consiste em uma proporção de tempo em que o paciente permaneceu dentro da faixa da RNI recomendada no período analisado (ROSENDAAL *et al*., 1993).

O TTR varia de 0% a 100%, sendo recomendado que permaneça acima de 60%, o que favorece o alcance dos objetivos terapêuticos. Valores abaixo de 60% representam controle inadequado e risco aumentado de complicações associados à anticoagulação (WHITE *et al*., 2007; GALLAGHER, *et al*., 2011; SENOO; LIP, 2015).

White *et al*. (2007), em estudo randomizado, dividiram 3.587 pacientes com FA em três grupos iguais, de acordo com o controle da anticoagulação: controle adequado (TTR >75%), controle moderado (TTR 60-75%), e controle inadequado (TTR <60%). Os pacientes com TTR <60% apresentaram taxas de mortalidade anual (4,20%) e hemorragia grave (3,85%) mais elevadas quando comparadas com pacientes do grupo de controle moderado (1,84% e 1,96%, respectivamente) e com pacientes de controle adequado (1,69% e 1,58%, respectivamente) ($p<0,01$). O grupo de controle inadequado também apresentou maiores taxas de infarto do miocárdio (1,38% vs 0,62%, $p=0,04$) e de AVC ou embolia sistêmica (2,10% vs 1,07%, $p=0,02$) quando comparado com o grupo de TTR >75%.

Connolly *et al*. (2008) em estudo randomizado com 6.706 pacientes com FA, também observaram que para os pacientes com maior TTR (acima de 65%), a anticoagulação oral foi associada a redução de eventos vasculares em mais de duas vezes, em relação à terapia com antiagregante plaquetário [risco relativo (RR)=2,14; IC 95% 1,61-2,85; p<0,0001].

Um estudo de coorte multicêntrico com 3.831 pacientes com válvulas cardíacas mecânicas, tratados com varfarina, mostrou que o TTR <70% foi significativamente associado a taxas (por 100 tratamentos-ano) mais altas de complicações quando comparado com um TTR ≥70%. A taxa de trombose nos pacientes com TTR ≥70% foi 2,13 (95% IC 1,86-41) e nos pacientes com TTR <70% foi 3.05 (95% IC 2,58-3,59) e a taxa de morte foi, respectivamente, 1,68 (95% IC 1,47, 1,93) e 4,00 (95% IC 3,50-4,54). Já a taxa de sangramentos foi, respectivamente, 2,30 (95% IC 2,0-2,60) e 5,13 (4,51-5,82). O risco de hemorragia também foi superior no grupo com menor TTR [*Hazard Ratio* (HR)=2,43; 95% CI 2,02-2,89; p<0,001] (GRZYMALA-LUBANSKI *et al*., 2017). Com esses resultados, os autores demostraram a importância da manutenção dos níveis adequados de TTR para que o tratamento possa ser efetivo e seguro para os pacientes.

Investigações prévias sobre fatores associados ao controle da anticoagulação demonstraram uma relação entre TTR e sexo, embora essas evidências sejam controversas. Melamed *et al.* (2011), em estudo transversal realizado em Israel com 906 participantes (59,1% mulheres), com diagnóstico de FA tratados com varfarina, investigaram os fatores que influenciam o controle da anticoagulação oral. Os autores estratificaram os pacientes de acordo com o nível de TTR, como segue: controle da anticoagulação deficiente (TTR <60%), controle da anticoagulação bom (TTR 60%-75%) e controle da anticoagulação excelente (TTR >75%). Neste estudo, o grupo de pacientes com excelente controle teve a menor proporção de mulheres (42,6%), seguido pelo grupo com bom controle (47,6%). A maior proporção de mulheres foi encontrada no grupo com controle deficiente (54,8%). TTR <60% foi significativamente associado ao sexo feminino (p=0,02).

Gamero *et al*. (2017) mostraram em estudo retrospectivo realizado em um hospital universitário do Peru com 143 pacientes (idade ≥65 anos; 51,75% mulheres) que o sexo feminino foi associado a ótimo controle da anticoagulação (TTR ≥60%) (OR=3,0; IC 95%=1,62-5,81; p<0,001). Por outro lado, em um estudo de coorte realizado no Canadá com 1.059 pacientes (idade média=71 anos, 62% homens) o

sexo não teve associação significativa com controle da anticoagulação deficiente, definido no estudo como um TTR <60% (OR=1,09; IC 95% 0,80-1,47; p=0,59) (PERREAULT *et al*., 2018).

Além da avaliação do TTR, outros fatores relacionados ao sexo devem ser avaliados, a fim de otimizar a terapia anticoagulante dos pacientes. Há diferenças entre homens e mulheres sobre a apresentação clínica das DCV, bem como em relação à fisiopatologia e resposta ao tratamento (NEWSON, 2018). Estudos têm demonstrado que as mulheres vivem mais tempo do que os homens e o risco de desenvolver DCV com a idade aumenta (STEENMAN; LANDE, 2017; ZARULLI *et al*., 2018). Um estudo mostrou que a prevalência de FA na população geral aumenta com o avanço da idade, chegando a 0,12-0,16% em pessoas com menos de 49 anos, e a 3,7-4,2% naquelas com idade entre 60-70 anos. A partir de 80 anos, a taxa estimada é de 10-17% (ZONI-BERISSO *et al*., 2014).

Estudos mostraram que as mulheres com FA tendem a apresentar piores sintomas, pior qualidade de vida e maior suscetibilidade a fenômenos tromboembólicos, principalmente AVC, do que os homens (PANCHOLY *et al*., 2014; KO *et al*., 2016; KO *et al*., 2017). Em uma meta-análise realizada por Pancholy *et al*. (2014), com seis estudos e amostra total de 26.260 pacientes (9.500 mulheres), as mulheres com FA em varfarina apresentaram maior risco residual de AVC ou embolia sistêmica do que os homens (OR=1,28; IC 95%=1,11-1,47; p=0,001). Em um estudo de revisão realizado por KO *et al*. (2016), os autores concluíram que na FA, o sexo feminino tinha maior risco de AVC, risco de infarto do miocárdio e mortalidade. A prevalência de hipertensão arterial e cardiopatia valvular também foi maior entre as mulheres.

Por outro lado, evidências recentes sugeriram que o sexo feminino com FA, na ausência de outros fatores de risco, tem um baixo risco de AVC, que é semelhante ao do sexo masculino. Com avaliação por meio do CHA_2DS_2-VASc (escore 0 para homens e 1 para mulheres), o risco aumentado foi evidente entre aquelas mulheres com fatores de risco de AVC não relacionados com o sexo (escore ≥2). Os resultados mostraram que o sexo feminino é um modificador de risco e é idade dependente (JANUARY *et al*., 2019). A pontuação CHA_2DS_2-VASc é recomendada para estratificação do risco de AVC em pacientes com FA. Esse escore considera os fatores insuficiência cardíaca congestiva, hipertensão, idade ≥75 anos (duplicado), diabetes

mellitus, AVC prévio ou ataque isquêmico transitório ou tromboembolismo (duplicado), doença vascular, idade 65 a 74 anos e categoria de sexo (JANUARY *et al*., 2019).

Outros fatores que podem causar alterações no controle da anticoagulação no sexo feminino e devem ser avaliados são o uso de anticoncepcionais e a menopausa. Já foi documentado que os contraceptivos hormonais combinados aumentam o risco de tromboembolismo venoso (HUGON-RODIN; GOMPEL; PLU-BUREAU, 2014, STEGEMAN *et al*., 2013). Uma meta-análise com 26 estudos demonstrou que a utilização de contraceptivos orais combinados aumentou o risco de trombose venosa em comparação com a não utilização (RR=3,5; IC 95%=2,9-4,3) (STEGEMAN *et al*., 2013). A menopausa aumenta os riscos de DCV, principalmente quando as mulheres entram na menopausa antes dos 45 anos. Um dos problemas que ocorre nesse período é a queda dos níveis de estrogênios, hormônios que possuem papéis importantes sobre o sistema cardiovascular, como no relaxamento e expansão dos vasos sanguíneos, contribuindo para manutenção adequada da pressão arterial (NEWSON, 2018; MUKA *et al*., 2016). Além disso, o estrogênio tem papel direto na redução da incidência de FA nas mulheres. Porém, os efeitos fisiológicos do estradiol que interagem para modificar o risco de FA no sexo feminino ainda não estão completamente esclarecidos (KO *et al.,* 2016).

A terapia de reposição hormonal tem sido associada à proteção cardiovascular (NEWSON, 2018), porém, seu efeito sobre a anticoagulação oral precisa ser melhor estudado. Um estudo realizado no Reino Unido com 80.396 mulheres (40-79 anos) mostrou que a exposição à reposição hormonal estava associada a um risco significativamente maior de tromboembolismo venoso em comparação com a ausência de exposição [OR ajustado=1,58; IC 95%=1,52-1,64]. Esse risco foi maior tanto para as preparações apenas com estrogênios (OR ajustado=1,40; IC 95%=1,32-1,48) como para as preparações combinadas (OR ajustado=1,73; 1,65-1,81) (VINOGRADOVA; COUPLAND; HIPPISLEY-COX, 2019).

Quanto aos fatores hormonais do sexo masculino que atuam no sistema cardiovascular, foi documentado que testosterona e estradiol estão associados com a incidência de FA em homens com idade mais avançada (KO *et al.,* 2016; MAGNANI *et al.,* 2014). O estudo de coorte realizado por Magnani *et al.* (2014), com 1.251 pacientes do sexo masculino mostrou que a cada desvio padrão de diminuição nos níveis de testosterona em homens com 55 a 69 anos de idade houve aumento do risco de incidência de FA (HR=1,30, IC 95%=1,07-1,59; p=0,008). Em homens com idade

≥80 anos, esse risco foi ainda maior (HR=3,53, 95% IC=1,96-6,37). A associação entre estradiol com incidência de FA foi HR=1,12 (IC 95%=1,01-1,26) (MAGNANI *et al.,* 2014).

Pelo exposto, observa-se resultados divergentes quanto à associação do sexo e controle da anticoagulação oral. Os fatores relacionados ao sexo que podem afetar a manutenção de níveis adequados de TTR não estão totalmente esclarecidos na literatura. Além disso, os estudos foram realizados com diferentes metodologias e populações, o que inviabiliza a generalização desses resultados, tornando necessário, portanto, a realização de estudos mais abrangentes sobre o tema.

3 JUSTIFICATIVA

Devido à alta prevalência das DCV associada ao envelhecimento populacional nos últimos anos, observa-se indicação crescente de ACO. A FA, que é um problema de saúde pública no Brasil e no mundo, é a principal indicação para o uso de ACO principalmente por mulheres, pois elas apresentam maior sobrevida em comparação aos homens. As mulheres com FA apresentam pior prognóstico, maior incidência de AVC e maior taxa de mortalidade em relação aos homens, o que pode estar relacionado a um pior controle de anticoagulação.

No Brasil, a varfarina é o ACO mais amplamente distribuído pelo SUS, o que torna importante acompanhar a utilização desse medicamento considerado de risco devido ao índice terapêutico estreito. O entendimento de aspectos relacionados ao uso do medicamento e, especificamente, à qualidade do controle da anticoagulação oral pode ser útil para melhorar o cuidado prestado ao paciente em países de baixa e média rendas.

Há estudos que abordam a diferença no controle da anticoagulação entre os sexos, sugerindo que as mulheres têm pior controle (medido pelo TTR), porém os dados são controversos e não há estudos abrangentes relacionados a esse tema. A realização de uma revisão sistemática com meta-análise sobre associação entre o sexo e o controle da anticoagulação oral poderá contribuir para avanços nos conhecimentos e perspectivas de melhorias do processo assistencial. Poderá favorecer, ainda, a criação de subsídios para adaptação dos protocolos assistenciais e maior qualificação do processo de cuidado centrado no paciente, de acordo com as necessidades individuais.

4 OBJETIVOS

Realizar uma revisão sistemática com meta-análise para avaliar a associação do sexo com o controle da anticoagulação oral em pacientes tratados com derivados cumarínicos.

5 METODOLOGIA

Esta revisão sistemática foi desenvolvida em conformidade com as orientações do *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA-P) (MOHER *et al*., 2015) e com a *Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence* (MOOLA *et al*., 2017). O protocolo foi registrado no PROSPERO (https://www.crd.york.ac.uk/prospero/) sob código RD42019128329 (**Anexo A**).

5.1 Métodos de pesquisa para identificação dos estudos

A questão norteadora foi "Há interferência do sexo na qualidade do controle da anticoagulação oral com derivados cumarínicos?". Foi aplicada a estratégia PICO para planejar os métodos de revisão que compunham: P, pacientes - pessoas com qualquer indicação de anticoagulação oral prolongada; I, intervenção - anticoagulação oral com qualquer derivado da cumarina; C, comparação - subgrupos de homens e mulheres; O, resultado - qualidade da anticoagulação oral medida pelo TTR. A estratégia de pesquisa foi desenvolvida com o apoio de um bibliotecário experiente. Foi realizada uma pesquisa inicial na base de dados MEDLINE para identificar artigos sobre o tema. Palavras-chaves em títulos e resumos de artigos relevantes foram identificadas, bem como termos de indexação para construir a estratégia de pesquisa completa da base de dados MEDLINE (**Apêndice A**). Foram incluídos os termos "*warfarin"*, "*coumarins"*, "*sex"*, "*quality of therapy*" e "*time in therapeutic range*". A estratégia de pesquisa, incluindo todas as palavras-chaves e termos de indexação identificados, foi adaptada para as demais bases de dados: BVS, CINAHL, EMBASE, Cochrane Central e Web of Science (**Apêndice A**). As fontes de estudos não publicados e de literatura cinzenta pesquisadas incluíram MedNar, *OpenGrey*, *Google Scholar* e *ProQuest Dissertations and Theses*. Foi realizada busca manual nas listas de referências citadas pelos artigos selecionados para identificação de estudos adicionais.

5.2 Tipos de estudos e critérios de inclusão e exclusão

Esta revisão considerou estudos observacionais e experimentais que incluíram pacientes de ambos os sexos, com idade superior a 18 anos com anticoagulação oral com varfarina ou outros derivados cumarínicos, por mais de três meses, para qualquer indicação de uso crônico. Foram incluídos estudos que compararam o TTR, avaliado pelo método de ROSENDAAL *et al.* (1993), entre os sexos. Foram excluídos artigos em duplicata, revisão narrativa ou sistemática e meta-análise, relatos de casos, séries de casos, estudos incluindo apenas homens ou apenas mulheres, e estudos experimentais envolvendo animais. Foram selecionados estudos sem qualquer restrição linguística e sem limites de tempo de publicação.

5.3 Seleção dos estudos

Após a remoção das duplicatas, por meio do *software* EndNote X5 (*Clarivate Analytics*, PA, USA), a seleção dos estudos foi realizada em duas etapas. Primeiramente, títulos e resumos foram avaliados e a segunda etapa envolveu a recuperação e avaliação do texto integral, de acordo com os critérios de elegibilidade. As duas etapas foram realizadas por dois revisores de modo independente. A taxa de concordância entre os avaliadores foi >80%. Os desacordos que surgiram entre os revisores em cada fase da seleção dos estudos foram resolvidos com auxílio de um terceiro revisor. As referências que não cumpriram os critérios de elegibilidade foram excluídas e as razões de exclusão foram documentadas e comunicadas. As etapas da pesquisa foram apresentadas no diagrama *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) (MOHER *et al*., 2009).

5.4 Extração de dados

Os dados dos estudos incluídos foram extraídos por dois revisores de modo independente. Os desacordos foram resolvidos com auxílio de um terceiro revisor. Os dados extraídos foram:

1) Detalhes do estudo: autor, ano de publicação, revista.
2) Método/características do estudo: desenho do estudo, participantes (idade, sexo, tamanho da amostra, país/localidade, indicação para anticoagulação oral); ambiente do estudo (hospital ou comunidade); procedimentos de recrutamento utilizados; acompanhamento ou duração do estudo; exposição (uso de varfarina ou outros derivados da cumarina).
3) Resultados: valores de TTR calculados pelo método Rosendaal (ROSENDAAL *et al*., 1993).
4) Métodos de análise de dados: estimativas estatísticas expressas por RR, OR, valor-p e 95% IC.

A incidência de resultados definitivos, tais como eventos tromboembólicos e hemorrágicos foram de interesse, se disponíveis nos artigos selecionados. Foram considerados eventos tromboembólicos diagnosticados por imagem e qualquer gravidade de hemorragias relatadas nos estudos.

5.5 Avaliação da qualidade dos estudos

Dois revisores de modo independente avaliaram a qualidade metodológica e o risco de viés dos estudos selecionados. Os estudos de coorte foram avaliados por meio da ferramenta *Newcastle-Ottawa Scale* (**Anexo B**) (WELLS *et al*., 2020). Essa escala contempla domínios de avaliação relacionados à adequação da seleção dos pacientes, comparabilidade dos grupos estudados, e comprovação da exposição ou desfecho. Os estudos foram considerados de qualidade alta (8-9 estrelas), média (6-7 estrelas) ou baixa (<6 estrelas).

A avaliação dos estudos transversais foi realizada por meio da ferramenta *Agency for Research and Health Quality (ARHQ) Methodology Checklist for Cross-sectional Study* (**Anexo C**) (ROSTON *et al*., 2004). Esse checklist consiste em 11

itens, com classificações de respostas "sim", "não" ou "pouco claro". Neste estudo, os artigos foram avaliados como de qualidade baixa (zero a três “sim”), qualidade moderada (quatro a sete “sim”), qualidade alta (oito a onze “sim”).

5.6 Síntese de dados e análise estatística

Os dados extraídos dos estudos selecionados foram sintetizados em tabelas e os resultados compilados foram utilizados para desenvolver uma meta-análise. O OR foi a principal medida de efeito de interesse. Para cada estudo primário, foram extraídos OR e seu erro padrão. Para os estudos que reportaram TTR dicotomizados, tais estimativas (ajustadas ou não ajustadas) foram obtidas a partir dos resumos dos modelos de regressão logística, teste qui-quadrado ou teste exato de Fisher, ou quando não estavam diretamente disponíveis foram calculadas utilizando dados brutos. Para os estudos primários que realizaram a regressão linear para TTR contínua, as estimativas OR foram obtidas através de transformação dos resultados da regressão linear de acordo com a relação conhecida entre as distribuições normal e logística.

Os valores de OR para variáveis binárias e diferenças médias (DM) para variáveis contínuas foram agrupados usando os modelos de efeitos aleatórios com estimativa através do método DerSimonian-Laird da variância entre estudos. Todas as estimativas de modelos foram apresentadas com 95% de IC e as estatísticas Q-estatística, I^2 e tau-quadrado foram utilizadas para avaliar a heterogeneidade entre os estudos.

Foi planeado, previamente, que na presença de diferenças de subgrupos, seriam utilizados métodos de meta-regressão para investigar os efeitos de covariáveis categóricas ou contínuas. Foram realizadas análises de sensibilidade excluindo estudos com menor tamanho amostral (<200 participantes) e estudos com baixa qualidade metodológica. A meta-regressão foi realizada com o ano de publicação dos estudos. O viés de publicação foi investigado utilizando o gráfico de funil e o teste Begg and Mazumdar. Estimativa de valores $p<0,05$ foi considerada estatisticamente significativa. Todas as análises foram realizadas utilizando a versão R 4.0.0 expandida por pacotes adequados.

6 RESULTADOS

Os resultados deste trabalho foram apresentados na forma de dois artigos científicos. O primeiro artigo abordou o protocolo da revisão sistemática e meta-análise que foi intitulado ”*Assessment of the influence of sex on oral anticoagulation control in patients taking coumarin derivatives: a systematic review protocol”*. Esse artigo foi submetido ao periódico *JBI Evidence Synthesis* (ISSN 2689-8381) (**Anexo D**) seguindo normas específicas (**Anexo E**) e foi aceito para publicação.

O segundo artigo abordou a revisão sistemática e meta-análise e foi intitulado *“Assessment of the influence of sex on oral anticoagulation control in patients treated with coumarin derivatives: a systematic review and meta-analysis”.* Esse artigo foi submetido ao periódico *Clinical Research in Cardiology* (ISSN=1861-0692; Fator de Impacto=4.907) (**Anexo F**) seguindo normas específicas (**Anexo G**).

O resumo da revisão sistemática e meta-análise foi submetido para apresentação como pôster no congresso virtual da *American Heart Association Scientific Sessions 2020* com o título *“Female Sex And Its Relation With Poor Control Of Oral Anticoagulation With Coumarin Derivatives: A Systematic Review And Meta-analysis”* (**Anexo H**).

ARTIGO 1

Assessment of the influence of sex on oral anticoagulation control in patients taking coumarin derivatives: a systematic review protocol

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Assessment of the influence of sex on oral anticoagulation control in patients taking coumarin derivatives: a systematic review protocol

Abstract

Objective: To present the protocol of a systematic review aiming to assess the influence of sex on oral anticoagulation control in patients taking coumarin derivatives.

Introduction: Coumarin derivatives, such as warfarin, have a narrow therapeutic index, requiring frequent monitoring to achieve adequate anticoagulation control which can be assessed by the time in therapeutic range (TTR). Differences in the quality of oral anticoagulation control between men and women have been reported, although the current evidence is controversial. A systematic review on this topic would be useful to provide results that could be incorporated into clinical practice to enhance oral anticoagulation control and treatment outcomes.

Inclusion criteria: Observational and experimental studies were assessed for eligibility, with participants aged ≥18 years of both sexes, on oral anticoagulation other coumarin derivatives ≥3 months for any indication of chronic use who had oral anticoagulation control evaluated by TTR.

Methods: Electronic databases will be MEDLINE, BVS, CINAHL, EMBASE, Cochrane CENTRAL and Web of Science. Two reviewers will independently perform title/abstract selection and screening, and then full text retrieval and screening of articles that meet the inclusion criteria. The evaluation of methodological quality and data extraction will be also performed by two independent reviewers. Data will be synthesized in tables and then compiled results will be meta-analyzed. In the presence of subgroup differences, meta-regression methods will be used to investigate the effects of categorical or continuous covariates. If statistical pooling is not possible, a narrative synthesis will be presented.
Systematic review registration number: PROSPERO CRD42019128329.

Keywords: coumarins; quality of health care; sex; thromboembolism; warfarin

Introduction

The population aging observed in the last years has raised the prevalence of cardiovascular diseases and consequently the number of people with risk factors for thromboembolism.[1] In Australia, Europe and the Unites States of America, the current estimated prevalence of atrial fibrillation (AF) is between 1% and 4%, and lower prevalence is estimated in Asia (0.49%-1.9%).[2] AF prevalence in the general population increases with advancing age, reaching 0.12-0.16% in people younger than 49 years to 3.7-4.2% in those aged 60-70 years. Beyond 80 years, it can become as high as 10-17%.[3] In Western Europe, Australia and North America, 70% of people with AF are aged above 65 years.[2]

Oral anticoagulation with coumarin derivatives is indicated for primary and secondary thromprophylaxis. It has been described that AF is a strong independent risk factor for stroke and warfarin therapy can reduce the risk by 64%.[4] Warfarin is widely used in low- and middle-income countries by patients with cardiovascular diseases and risk factors for thromboembolism. However, the management of the therapy with coumarin derivatives is challenging due to their narrow therapeutic index, wide variability in dose-response, influence of genetic polymorphisms and interactions with numerous drugs, foods, and alcohol.[5-9] Thus, frequent monitoring is required to minimize the risk of bleeding and thromboembolism.

The International Normalized Ratio (INR), calculated from the prothrombin time, is used for treatment monitoring and the quality of oral anticoagulation can be assessed by the time in therapeutic range (TTR).[5] TTR is frequently calculated by the Rosendaal method[10] that applies a linear interpolation using at least two INR values with a range of 0-100%.[10] Values below 60% have been classified as inadequate control presenting higher risk of anticoagulation-related complications.[11-13]

Sex-differences in oral anticoagulation control have been reported by previous studies, although with conflicting results.[14,15] In a cross-sectional study conducted in Botswana with 410 participants (68.8% women, median age 46 years), women presented lower TTR than men (Ajusted Odds Ratio (OR) 1.54, 95% Confidance Intervals (CI) 0.84-2.83, p=0.16). The indications for warfarin use were AF, mechanical heart valves and deep vein thrombosis.[16] In a meta-analysis conducted by Pancholy *et al*.[17], women with AF on warfarin had higher residual risk of stroke or systemic embolism than men (OR=1.28; 95% CI=1.11-1.47; p=0.001), which may be associated with worse anticoagulation control.

Conversely, other studies showed better oral anticoagulation control in women than in men. In a cross-sectional study conducted in Finland with 54,568 participants with AF (47.0% women, mean age 73.1 years), the mean TTR was significantly higher among women than men (62.5±23.6% vs. 59.8±26.4%, p<0.001). Cardiovascular mortality (Hazard Ratios (HR) 0.82, 95% CI 0.78-0.88, p<0.001) and all-cause mortality (HR 0.79, 95% CI 0.75-0.83, p<0.001) were lower in women that men.[15] In addition, a retrospective observational study performed in Korea including 1,230 participants with AF (mean age 70.1 years) identified that men had worse anticoagulation control (TTR<60%) than women (n=851, women=44.4%, men=55.6%, OR=1.31, 95% IC=1.02-1.67, p=0.04).[18]

Some studies have reported no difference in the oral anticoagulation control between men and women. In a retrospective cohort study developed in Saudi Arabia with 110 patients with nonvalvular AF (60.9% women, mean age 64.9 years), there was no significant differences in TTR between sexes (p=0.83).[19] In a multicenter prospective study conducted in Turkey including 4,987 patients (59.1% women, mean age 60.7 years), there was no significant difference in TTR between men (49.9±22.9%) and women (49.2±22.8%), p=0.283. The main indications for the use of warfarin were nonvalvular AF and mechanical heart valves.[20]

It is noteworthy that the physiopathology of cardiovascular diseases may change according to sex.[15,21] Studies have shown that women are older when suffering a stroke, are more likely to live alone or widowed before the event[22] and suffer from greater neurological deficits after a stroke.[23] Women with AF still tend to have worse symptoms and worse quality of life and greater susceptibility to thromboembolic phenomena, especially stroke, and higher mortality rate than men.[17,24] Broad studies investigating the oral anticoagulation control, according to sex, are scarce in the literature. The performance of a systematic review would help expanding knowledge on this topic, especially on sex specificities The results could be useful to clinical practice to improve anticoagulation control and treatment outcomes. We described the protocol of a systematic review aimed to assess the influence of sex on oral anticoagulation control in patients taking coumarin derivatives, considering TTR as an intermediate treatment outcome. A preliminary search was conducted on PROSPERO, MEDLINE, Cochrane CENTRAL and the JBI Database of Systematic Reviews and Implementation Reports with no detection of current or underway systematic reviews on the topic.

Review question

Are there sex-differences in oral anticoagulation control, evaluated by TTR, in patients taking coumarin derivatives?

Inclusion criteria

Participants

This review will consider for eligibility assessment studies including patients aged ≥18 years of both sexes.

Exposure

The exposure will be oral anticoagulation with warfarin or other coumarin derivatives used for more than three months for any indication of chronic use.

Comparator

This review will compare TTR between men and women.

Outcomes

TTR, calculated by the Rosendaal method[10], will be considered as an intermediate outcome used to measure the quality of oral anticoagulation control. The incidence of definitive outcomes, such as thromboembolic and bleeding events will be of interest, if available in the selected articles. We will consider thromboembolic events diagnosed by imaging and any severity of bleedings reported in the studies.

Types of studies

This review will consider experimental studies, such as randomized controlled trials and non-randomized controlled trials, as well as prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies. Duplicate articles, narrative or systematic review and meta-analysis, case reports, case series and experimental studies involving animals will be excluded. Studies will be selected with no language restriction and no time limit.

Methods

The proposed systematic review will be conducted in accordance to the manual of the Joanna Briggs Institute (JBI) applied for systematic reviews assessing etiology and risk.[26] The systematic review protocol has been registered on PROSPERO, under the code CRD42019128329.

Search strategy

The search strategy was focused on published studies, being developed with the support of an experienced librarian. An initial search on MEDLINE database was undertaken to identify articles on the topic. We identified text words in titles and abstracts of relevant articles, and also index terms to build the full search strategy for MEDLINE database (see Appendix I). The specific medical subject headings (MeSH) terms "warfarin", “coumarins” and "sex" and keywords as “quality of therapy” and “time in therapeutic range” were selected. The development of the search strategies will be tailored for each additional information source. The reference list of the selected articles for critical appraisal will be screened for additional studies. Unpublished studies and gray literature will also be searched for relevant studies.

Information sources

We will consider the following databases as information sources: MEDLINE (Pubmed), Biblioteca Virtual em Saúde (BVS), Cochrane CENTRAL, EMBASE (OVID), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO), and Web of Science (ISI). Sources of unpublished studies and gray literature to be searched include MedNar, OpenGrey, Google Scholar and ProQuest Dissertations and Theses.

Study selection

The search records will be managed by the EndNote X5 software (Clarivate Analytics, PA, USA) in which the duplicates will be identified and removed. Title/abstract screening and selection will be performed by two independent reviewers. Abstracts providing insufficient information with regard to the inclusion and exclusion criteria will be downloaded for full-text analysis. The full text screening and retrieval will be assessed independently by two reviewers, according to eligibility criteria. The agreement rate between the reviewers must be >80%. Disagreements that arise between the reviewers at each stage of the selection of articles will be solved by consensus, or with a third reviewer. References that do not meet eligibility criteria will be excluded and the reasons for exclusion will be documented and reported. The steps of the search will be presented in the flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[25].

Assessment of methodological quality

The two independent reviewers will use the standardized instruments from JBI to develop a critical appraisal of experimental studies (randomized controlled trials and non-randomized controlled trials) and prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies.[26] Authors of papers will be contacted to request missing or additional data for clarification at any stage, if necessary. Any disagreements between the reviewers will be discussed and solved. The results of the assessment of methodological quality of studies will be reported in a narrative format and added to a table. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). The results of the critical appraisal by means of JBI tool will be described in the review in a descriptive format. We will address how these results could influence the interpretation of the study evidence.

Data extraction

Data will be extracted from selected studies independently by two reviewers using the standardized JBI data extraction tool.[26] The data extracted will include details about the population, study methods, exposures, and outcomes, as following:

- Study details: author, year of publication, journal.
- Study method/characteristics: study design, participants (age, sex, sample size, country/location, indication for oral anticoagulation); s**tudy setting (**hospital or community); recruitment procedures utilized; follow-up or study duration; **exposure (the use of** warfarin or other coumarin derivatives).
- Outcomes: TTR values calculated by Rosendaal method.[10] Thromboembolic and bleeding events, if available.
- Data analysis methods: statistical estimates expressed by risk ratio, relative risk ratio, odds ratio, p values and confidence intervals.

Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. We will analyze the available data, and the impact of missing data will be considered as a study limitation, when applicable.

Data synthesis

Data extracted from selected studies will be synthesized in tables and the compiled results will be used to develop a meta-analysis. Data synthesis and analysis will be designed to address the research question on the assessment of the influence of sex on oral anticoagulation control. As sex is a possible modifier of TTR, we will perform the analysis with stratification by sex. The summary OR will be the primary measure of interest. For each primary study, OR and its standard error will be extracted. For studies reporting dichotomized TTR such estimates (adjusted or unadjusted) will be obtained from the summaries of logistic regression models, chi-square tests or Fisher's exact test, or when not directly available they will be calculated using raw data. For primary studies that performed linear regression for continuous TTR, the OR estimates will be obtained through transformations of the results of the linear regression according to the known relationship between the normal and logistic distributions.

The results of studies will be pooled and an overall estimate of OR will be obtained from random-effects models to account for study heterogeneity. The DerSimonian and Laird estimator of between-study variance will be used. All model estimates will be shown with 95% CIs and the Q-statistic, I^2 statistic and tau-squared statistic will be used for assessing the heterogeneity between studies. Forest plots for all meta-analyses will be provided.

In the presence of subgroup differences, meta-regression methods will be used to investigate the effects of categorical or continuous covariates. Publication bias will be investigated using the funnel plot and Egger’s regression test. A p-value <0.05 will be considered statistically significant. All analyses will be conducted using R version 4.0.0 expanded by appropriate packages. If metaanalysis is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Topics of interest, such as TTR, will be identified and discussed. We will perform a comprehensive assessment of the methodological quality of the studies. The results of this systematic review will provide useful data on the assessment of the influence of sex on the oral anticoagulation control. These results may guide the future design of adapted strategies focused on improvements in patient care.

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Conflicts of interest

The authors declare they have no conflict of interest.

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Appendix I: Search strategy to MEDLINE (PUBMED) database.

Database	Strategy	Records retrieved
MEDLINE (PUBMED)	((((("Time in therapeutic range"[Title/Abstract] OR "Quality of Anticoagulation"[Title/Abstract] OR "International Normalised Ratio"[Title/Abstract] OR "Quality of therapy"[Title/Abstract])))) AND ((((("Warfarin"[Mesh]) OR "Coumarins"[Mesh])) OR ("Warfarin"[Title/Abstract] OR "Coumarins"[Title/Abstract] OR aldocumar[Title/Abstract] OR "Apo-Warfarin"[Title/Abstract] OR coumadin[Title/Abstract] OR coumadine[Title/Abstract] OR "Gen-Warfarin"[Title/Abstract] OR marevan[Title/Abstract] OR tedicumar[Title/Abstract] OR warfant[Title/Abstract] OR Aldocumar[Title/Abstract] OR "Apo-Warfarin"[Title/Abstract] OR Coumadin[Title/Abstract] OR Coumadine[Title/Abstract] OR "Gen-Warfarin"[Title/Abstract] OR Marevan[Title/Abstract] OR Tedicumar[Title/Abstract] OR Warfant[Title/Abstract] OR "Warfarin Potassium"[Title/Abstract] OR "Warfarin Sodium"[Title/Abstract] OR "Potassium, Warfarin"[Title/Abstract] OR "Sodium, Warfarin"[Title/Abstract] OR "1,2-Benzopironas"[Title/Abstract] OR Cumarinas[Title/Abstract] OR "Benzopiran-2-Onas"[Title/Abstract] OR "1,2-Benzo-Pyrones"[Title/Abstract] OR "1,2-Benzopyrone Derviatives"[Title/Abstract] OR "Benzopyran-2-ones"[Title/Abstract] OR "Coumarin Derivatives"[Title/Abstract] OR Coumarines[Title/Abstract] OR "1,2 Benzo Pyrones"[Title/Abstract] OR "1,2 Benzopyrone Derviatives"[Title/Abstract] OR "1,2 Benzopyrones"[Title/Abstract] OR "Benzopyran 2 ones"[Title/Abstract] OR "Derivatives, Coumarin"[Title/Abstract] OR "Derviatives, 1,2-Benzopyrone"[Title/Abstract] OR "1,2-Benzopyrones"[Title/Abstract])))) AND ((((((("Sex"[Mesh]) OR "Women"[Mesh]) OR "Female"[Mesh]) OR "Male"[Mesh])) OR ("Sex"[Title/Abstract] OR "Women"[Title/Abstract] OR "Female"[Title/Abstract] OR "Male"[Title/Abstract]))	546

ARTIGO 2

Assessment of the influence of sex on oral anticoagulation control in patients treated with coumarin derivatives: a systematic review and meta-analysis

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Abstract

Background Previous studies showed sex-differences in oral anticoagulation control, although the current evidence is conflicting. We sought to develop a systematic review and meta-analysis to assess the association of sex with oral anticoagulation control employing coumarin derivatives.

Methods Electronic sources were MEDLINE, Biblioteca Virtual em Saúde (BVS), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Cochrane Central and Web of Science. Inclusion criteria were: observational and experimental studies; age ≥18 years; both sexes; treatment with any coumarin derivative for ≥3 months; any indication of long-term use; quality of oral anticoagulation measured by TTR, calculated by the Rosendaal method. The meta-analysis was developed with odds ratios (OR) for binary variables and mean differences (MD) for continuous variables using the random-effects models (DerSimonian and Laird) with 95% confidence intervals (CI).

Results Ten cohort studies and four cross-sectional studies were included with a participant range of 110-57669 (90672; women: 45%). The main indication of oral anticoagulation was atrial fibrillation. All studies reported the use of warfarin. Nine studies were assessed with binary variables in the meta-analysis (OR=0.89; 95% CI=0.80, 1.00; z=-1.96; p=0.05; I^2=74%) and five studies with continuous variables (MD=-4.03; 95% CI=-5.74, -2.31; z=-4.61; p<0.0001; I^2=49%). The pooled estimates indicated that women were associated with lower TTR than men.

Conclusions We found that women had worse oral anticoagulation control than men. Further studies are needed to investigate sex-related factors that influence the quality of oral anticoagulation control and innovative strategies to improve patient care. (Registration number: PROSPERO CRD42019128329)

Keywords Coumarins · Quality of health care · Sex · Thromboembolism · Warfarin

Introduction

Coumarin derivatives have proved to be effective in primary and secondary prevention of thromboembolic events in people with cardiovascular diseases, such as atrial fibrillation (AF) which is a major cause of stroke [1-3]. Warfarin has been reported to reduce the risk of stroke by 64% in patients with AF [1]. However, coumarin derivatives present a narrow therapeutic index and a wide dose-response variability, requiring the need of frequent laboratory monitoring to guide dose adjustments and to reduce the risks of bleeding and thromboembolic events [4-6].

The introduction of direct oral anticoagulants (DOACs) has broaden therapeutic options for oral anticoagulation, bringing advantages over coumarin derivatives, such as improved safety profile and no recommendation of regular monitoring. However, the access to DOACs is limited in low- and middle-income countries, due to cost issues [4,7,8]. In addition, DOACs have no application yet for mechanical prosthetic valve, moderate to severe mitral stenosis (usually of rheumatic origin) [9] and there is limited evidence about their effectiveness and safety in antiphospholipid syndrome [10].

The achievement of oral anticoagulation control is required to ensure the achievement of therapeutic goals with coumarin derivatives and it can be assessed by the time in therapeutic range (TTR). The Rosendaal method [11] has been widely used by a linear interpolation of sequential values of International Normalized Ratio (INR) ranging from 0 to 100% [11]. TTR <60% has been associated with higher mortality rates, severe bleeding, myocardial infarction, stroke and systemic embolism events than TTR >60% [12].

Previous investigations on factors associated with anticoagulation control demonstrated a relationship between TTR and sex, even though with conflicting evidence. Some authors reported that the association of female sex with poorer TTR than the male sex and other authors found opposite results [13-15]. No statistical significant differences in TTR have been reported in the comparison of oral anticoagulation control between men and women [16,17]. Sex-related aspects that may affect TTR, such as behavioral and physiological factors, are not fully understood so far. Broad studies aiming to investigate the sex-related aspects with the quality of oral anticoagulation control are scarce in the literature. We sought to perform a systematic review and meta-analysis to assess the association of sex with the oral anticoagulation control in patients treated with coumarin derivatives, considering TTR as the study outcome.

Methods

This systematic review followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) [18]. We complied with Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence [19] and the study protocol has been described elsewhere. The protocol was published in PROSPERO website (https://www.crd.york.ac.uk/prospero/) with the registration code CRD42019128329.

Search strategy and selection of articles

It was performed a search on MEDLINE, Biblioteca Virtual em Saúde (BVS), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Cochrane Central and Web of Science databases. The search strategy combining free and indexing terms was developed primarily to search for articles on MEDLINE applying Medical Subject Heading (MESH) terms (Supplementary) and then it was adapted to the other databases. Unpublished studies and gray literature was searched in MedNar, OpenGrey, Google Scholar and ProQuest Dissertations and Theses. Databases were screened to identify studies no time limit of time. It was applied the PICO strategy to plan the review methods that comprised: P, patients - people with any indication of long-term oral anticoagulation; I, intervention - oral anticoagulation with any coumarin derivative; C, comparison - subgroups of men and women; O, outcome - quality of oral anticoagulation, measured by TTR.

Inclusion criteria included: (1) experimental and observational studies; (2) no language restriction; (3) age ≥18 years; (4) both sexes; (5) oral anticoagulation with warfarin or other coumarin derivative used for ≥3 months; (6) any indication for long-term use; (7) quality of oral anticoagulation measured by TTR, calculated by the Rosendaal method [11]. We excluded duplicate articles, narrative or systematic reviews and meta-analysis, case reports, case series, studies including only men or only women and experimental studies involving animals.

The selection of the studies was performed in two steps using the PRISMA flow diagram [20]. In the first step, titles and abstracts were screened. In the second step, a full reading of the articles was carried out. Manual search was performed in the reference list of the selected articles was screened for evaluation of additional studies. Two reviewers (MFSP and CCV) performed independently all steps of article selection and disagreements were resolved by a third reviewer (MAPM).

Data extraction and study quality

Two independent authors (MFSP and CCV) performed data extraction in accordance with the eligibility criteria, using a predefined form. Data extracted were: (1) study design, author, journal and year of publication; (2) age of participants, percentage of women, sample size, country and indication for anticoagulation and TTR values; (3) **data analysis methods** risk ratio (RR), relative RR, odds ratio (OR), p-value and 95% Confidence Intervals (CI). The incidence of definitive outcomes, such as thromboembolic and bleeding events were of interest, if available in the selected articles. It were considered thromboembolic events diagnosed by imaging and any severity of bleedings reported in the studies.

Two authors (MFSP and CCV) assessed independently the methodological quality of the selected studies. The cohort studies were assessed as proposed by Newcastle-Ottawa Scale [21], considering high quality (8–9 stars), medium (6–7 stars) or low quality (<6 stars). The evaluation of cross-sectional studies was performed using the tool Agency for Research and Health Quality (ARHQ) Methodology Checklist for Cross Sectional/Prevalence Studies [22], that consists of 11 items with answers as “yes”, “no”, or “unclear”. The studies were rated with “low quality” (0–3 “yes”), “moderate quality” (4–7 “yes”) or “high quality” (8–11 “yes”).

Data synthesis and statistical analysis

The analysis was performed with stratification by sex, considering that sex is a possible modifier of TTR. The summary OR was the primary measure of interest. For each primary study, OR and its standard error were extracted. For studies reporting dichotomized TTR, such estimates (adjusted or unadjusted) were obtained from the summaries of logistic regression models, chi-square tests or Fisher's exact test, or when not directly available, they were calculated using raw data. For primary studies that performed linear regression for continuous TTR, the OR estimates were obtained through transformations of the results of the linear regression according to the known relationship between the normal and logistic distributions.

Results expressed in OR and mean differences (MD) for continuous variables were pooled using the random-effects models with estimation via the DerSimonian-Laird method. All model estimates were shown with 95% CI and the Q-statistic, I^2 statistic and tau-squared statistic were used for assessing the heterogeneity between studies. Forest plots for all meta-analysis were provided.

We planned the investigation of the effects of categorical or continuous covariates by meta-regression methods in the presence of subgroup differences. A sensitivity analysis was conducted excluding studies with small sample sizes (<200 participants) and only studies with low methodological quality. The meta-regression was performed with the year of publication of the studies. Bias of publication was investigated using the funnel plot and Begg and Mazumdar test. A p-value <0.05 was considered statistically significant. All analysis were conducted using R version 4.0.0 (Auckland, New Zealand, 2018) expanded by appropriate packages.

Results

Search results and study characteristics

A total of 3127 records were retrieved after running the initial search. After the removal of duplicates, 1864 articles were screened by titles and abstracts. After this step, 148 articles were considered for full-text evaluation. Fourteen studies met the inclusion criteria of this systematic review, being selected for qualitative synthesis and meta-analysis [16,23-35]. No unpublished article on the topic was found. We performed a manual search and screened the grey literature without identification of any study meeting the eligibility criteria. The flowchart of the selection process of studies is presented in Figure 1.

Data extracted from the selected studies are summarized in Table 2. Ten cohort studies and four cross-sectional studies were included with publication range from 2011 to 2020. The number of participants ranged from 110 to 57669, in aggregate (90672; women: 45%). The average age in the studies was >57 years, excepting for two studies [32,33] that presented age of participants by categories and with no report of averages. The main indication of long-term oral anticoagulation was AF. Warfarin use was reported in all studies and acenocoumarol also appeared in the studies performed by Lobos-Bejarano et al. [30] and Corrochano *et al*. [35]. The incidence of definitive outcomes, such as thromboembolic and bleeding events, has not been reported due to their absence in the selected studies.

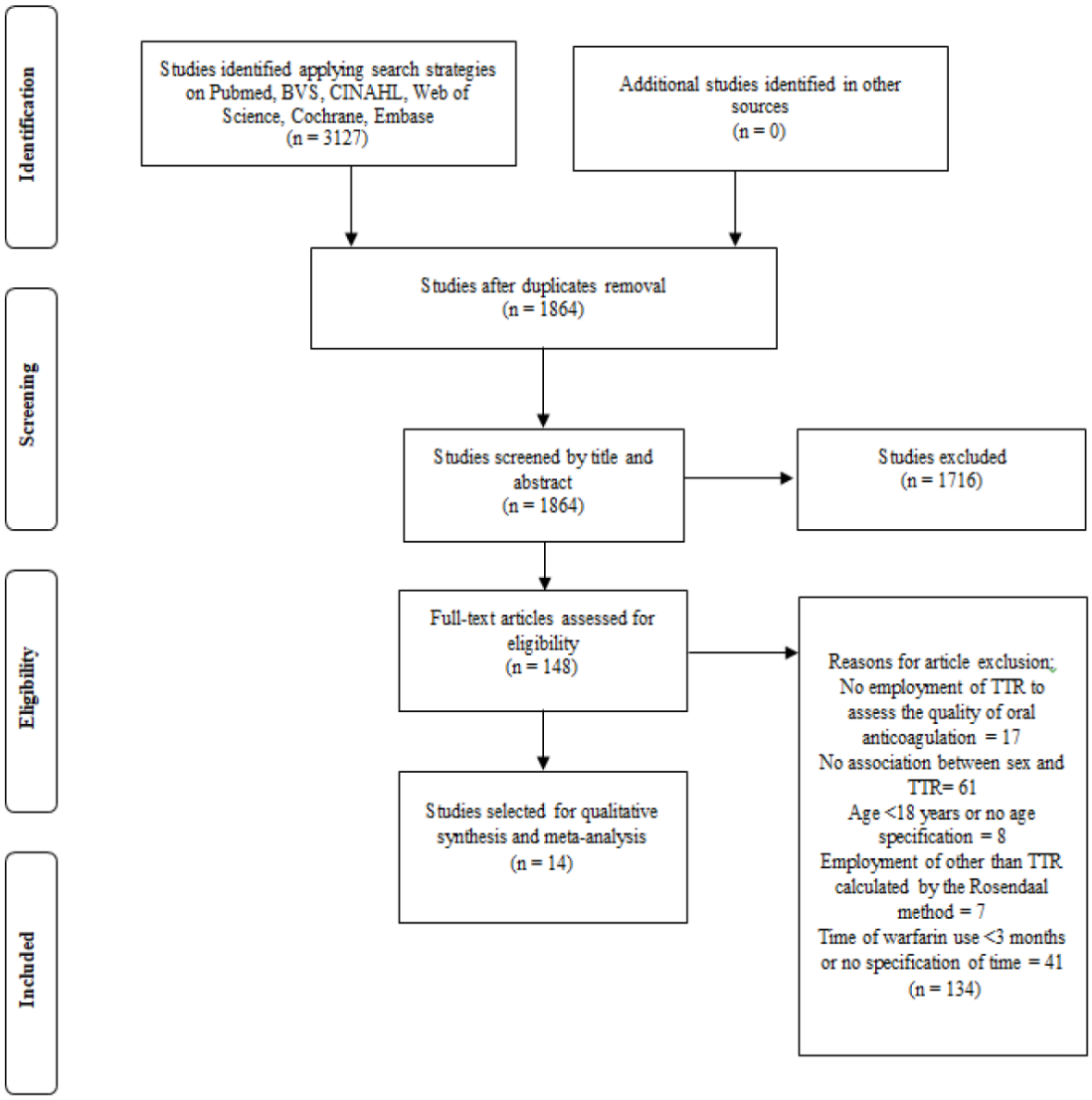

Fig. 1 Selection process of articles about the oral anticoagulation control assessed by TTR in men and women on coumarin derivatives.

There was a discrepancy regarding TTR cutoff values to classify the adequacy of oral anticoagulation control in the studies selected for this systematic review (Table 2). For instance, Lobos-Bejarano et al. [30] applied two TTR categories encompassing good control (TTR ≥65%) and poor anticoagulation control (TTR <65%). On the other hand, Farsad et al. [16] considered three categories, including good control (TTR >70%), intermediate control (50%<TTR<70%), and poor control (TTR <50%). All studies considered p value <0.05 as statistical significant in their analysis. There was also a variation in sex-related TTR in the studies. In six studies [23,24,27,29,16,33], no significant difference in TTR between men and women was observed, and eight studies [25,26,28,30-32,34,35] reported female sex with association with lower TTR than male sex (Table 2).

Using the Newscastle-Otawa Scale [21], three studies [25,29,32] were deemed to be of high quality. Five studies were judged with medium quality [23,28,31,33,35], and two studies were classified as having low quality [27,34] (Table 3). The four studies assessed by the tool ARHQ Methodology Checklist for Cross Sectional/Prevalence Studies were considered of moderate quality [16,24,26,30] (Table 4).

Table 2 Characteristics of included studies in the systematic review and meta-analysis with TTR results, according to sex.

Author/ year	Country	Study design	Sample size (N)	Age	Female sex (%)	Coumarin derivative	Main indications for anticoagulation	TTR (female sex)	TTR (male sex)
Corrochano et al., 2020 [35]	Spanish	Cohort	927	58.1	46.5%	Acenocumarol andwarfarin	Mechanical heart valve	60,6±13,2%	66,2±13,1%
Henderson et al., 2019 [31]	North Carolina	Cohort	121	57±13	20.7	Warfarin	Implantation of CF-LVAD	In the multivariable analysis, female sex was associated with 10.1% decrease in TTR (p=0.04).	-
Cosansu et al., 2018 [24]	Turkey	Cross-sectional	271	70.25±9.35	60.5	Warfarin	NVAF	TTR≥65 (n=132)=76 (58%) TTR<65 (n=139)=82 (59%)	-
McAlister; Wiebe; Hemmelgarn, 2018 [32]	Canada	Cohort	57669	65-74=22.7% 75–84=26.5% ≥85=50.8%	44.5	Warfarin	NVAF	Adjusted OR associated with TTR (7-12 months): n=42011=aOR (95% CI)=0.95 (0.91-1.00)	-
Perreault et al., 2018 [29]	Canada	Cohort	1059	70.7±11.8	38.0	Warfarin	Paroxysmal AF Chronic AF	-	TTR<60% (n=243)=144 (59.3%)[a] TTR≥60% (n=599)=367 (61.3%)[b]
Alyousif; Alsailee, 2016 [23]	Saudi Arabia	Cohort	110	64.9±16.5	60.9	Warfarin	NVAF	TTR<50 (n=36)=21 (58.3%) TTR50–75 (n=45)=27 (60.0%) TTR>75 (n=29)=19 (65.6%)	-
Dallalzadeh et al., 2016 [33]	Northern California	Cohort	2841	<75=56.8% ≥75=43.2%	43.8	Warfarin	NVAF	TTR≥70% (n=1244)=506 (40.7%)[c] TTR≥70% (n=435)=242 (55.6%)[e]	TTR≥70% (n=1597)=650 (40.7)[d] TTR≥70% (n=552)=320 (58%)[f]
Dumas et al., 2016 [25]	Canada	Cohort	1069	70.4±11.7	38.2	Warfarin	AF	Women had significantly lower TTR than men (-3.70±1.67; p=0.027)	-
Farsad et al., 2016 [16]	Japan	Cross-sectional	470	58.0±14.2	60.2	Warfarin	NVAF	TTR>70% (n=283)=101 (35.7%) TTR50%-70% (n=283)=76 (26.9%) TTR<50% (n=283)=106 (37.5%)	TTR>70% (n=187)=74 (36.9%) TTR50%-70% (n=187)=40 (21.4%) TTR<50% (n=187)=73 (39.0%)
Lobos-Bejarano et al., 2016 [30]	Spain	Cross-sectional	1524	77.4±8.7	48.6	Acenocumarol and warfarin	NVAF	TTR, mean (SD): Present factor: 67.9% (17.3%) Absent factor: 70.0% (18.0%)	-
Gomez et al., 2014 [27]	Uruguay	Cohort	117	67.3±14	61.5	Warfarin	FA/Flutter and Valvular	TRT≥65% (n=44)=28 (24%) TRT<65% (n=73)=44 (38%)	-
Nelson et al., 2013 [28]	United States	Cohort	23425	74.8±9.7	46.4	Warfarin	NVAF	-	Men (vs women): OR=0.78; 95% CI=0.73-0.83; p<0.001
Tomita et al., 2013[34]	Japan	Cohort	163	74.4±8.8	38.0	Warfarin	NVAF	TTR=75.2±21.3	TTR=82.1 ± 19.0
Melamed et al., 2011 [26]	Israel	Cross-sectional	906	71.7±9.0	51.9	Warfarin	AF	TTR<60 (n=611)=54.8% TTR60-75 (n=187)=47.6% TTR>75 (n=108)=42.6%	-

Abbreviations: AF, atrial fibrillation; *aOR,* adjusted odds ratio; CF-LVAD, continuous-flow left ventricular assist device; *CI* confidence interval; *NVAF,* non-valvular atrial fibrillation; *OR,* odds ratio; *TTR,* time in therapeutic range.
[a, b] Anticoagulation control from 3 to 12 months after initiation of warfarin therapy.
[c, d] Patients with TTR ≥70% in months 4-9 (Months 4–9 are the first 6-month period after the initial 3-month period to establish a stable warfarin dose).
[e, f] Patients that persisted with TTR ≥70% in months 10-15.

Table 3 Newcastle-Ottawa scale for methodological quality evaluation

Cohort studies									
Study	Selection				Comparability	Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
Corrochano *el al*. 2020 [35]	1	1	1	1	0	0	1	1	6
Henderson et al., 2019 [31]	1	1	1	1	0	0	1	1	6
McAlister; Wiebe; Hemmelgarn, 2018 [32]	1	1	1	1	2	0	1	1	8
Perreault et al., 2018 [29]	1	1	2	1	0	1	1	1	8
Alyousif; Alsaileek, 2016 [23]	1	1	1	1	0	0	1	1	6
Dallalzadeh et al., 2016 [33]	1	1	1	1	0	0	1	1	6
Dumas et al., 2016 [25]	1	1	1	1	2	0	1	1	8
Gomez et al., 2014 [27]	0	1	1	1	0	0	1	1	5
Nelson et al., 2013 [28]	1	1	1	1	1	0	1	1	7
Tomita et al., 2013 [34]	0	1	0	1	0	0	1	1	4

Table 4 Agency for Research and Health Quality (AHRQ) Methodology Checklist for Cross-Sectional to assess quality of the included studies.

Item/Study	Cosansu et al., 2018 [24]			Lobos-Bejarano et al., 2016 [30]			Farsad et al., 2016 [16]			Melamed et al., 2011 [26]		
	Yes	No	Unclear	Yes	No	Unclear	Yes	No	Unclear	Yes	No	Unclear
1) Define the source of information (survey, record review)	1			1			1			1		
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	1			1			1			1		
3) Indicate time period used for identifying patients		0		1			1			1		
4) Indicate whether or not subjects were consecutive if not population-based	1				0		1			1		
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants		0			0			0			0	
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)		0			0		1				0	
7) Explain any patient exclusions from analysis		0			0		1			1		
8) Describe how confounding was assessed and/or controlled.		0			0			0			0	
9) If applicable, explain how missing data were handled in the analysis		0			0			0			0	
10) Summarize patient response rates and completeness of data collection	1			1			1			1		
11)) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained		0			0				0			0

Meta-analysis

Nine studies with a total of 86.868 patients (45% women) were included in the meta-analysis from binary variables considering OR with effect measure (Fig. 2). The pooled estimate indicated that female sex was associated with lower TTR than men (OR=0.89; 95% CI=0.80, 1.00; p=0.05). These studies presented evidence of heterogeneity with significant p value (τ^2=0.0135; p<0.01; I^2=74%). In the sensitivity analysis, when studies with small sample size, the female sex was associated with lower TTR than men (OR=0.88; 95% CI=0.78, 0.99; p=0.04; I^2=80%). This result was observed, in analysis without studies with low methodological quality (OR=0.89; 95% CI=0.79, 1.00; p=0.05; I^2=77%) (Fig. 2). However, in the two analyses there was an increase of heterogeneity.

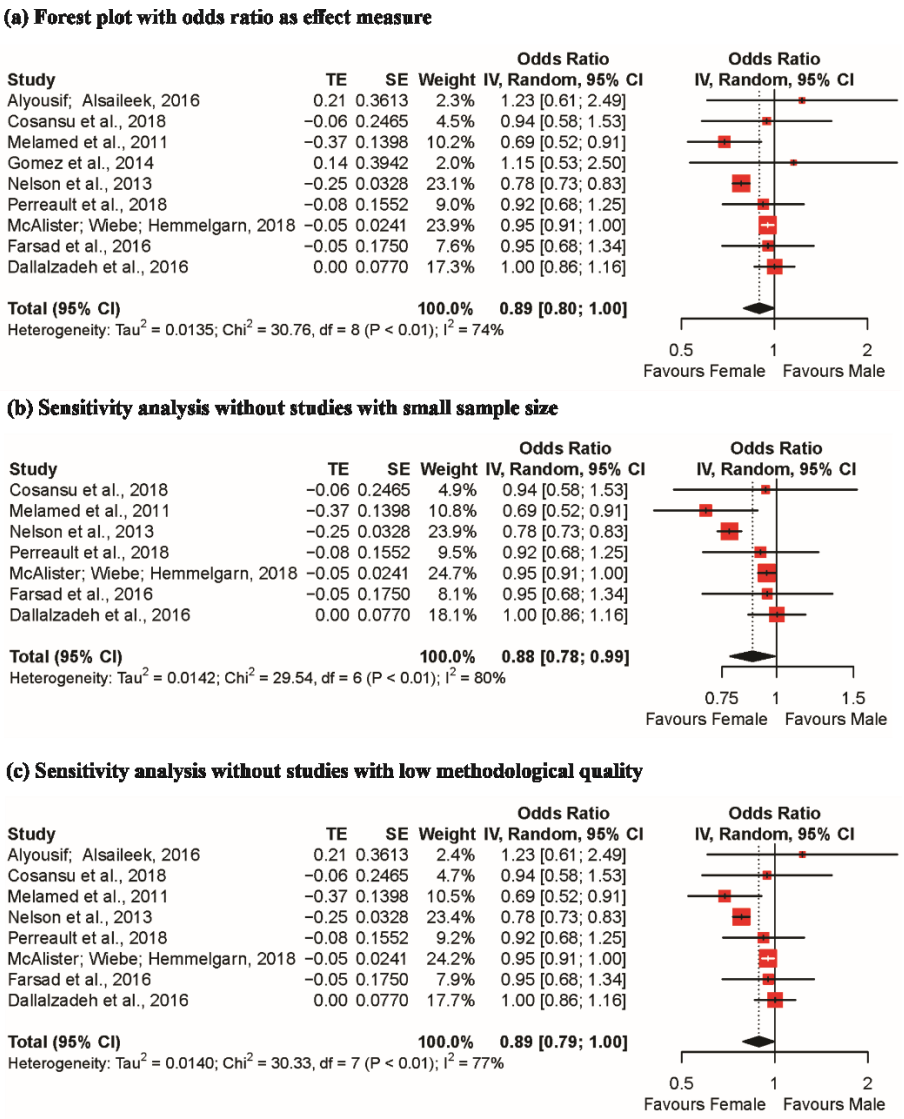

Fig. 2 Forest plot with odds ratio for effect of sex in the anticoagulation control

The mean difference of TTR in men and women was assessed using five studies with 3804 participants (44.0% women) in total (Fig. 3). The pooled estimate indicated that female sex was significant associated with lower TTR that male sex (MD=-4.03; 95% CI=-5.74, -2.31; p<0.0001). These studies presented low heterogeneity with no significant p value (τ^2=0.6778; p=0.10; I^2=49%). In the sensitivity analysis with exclusion of studies with small

sample size (MD=-3.85; 95% CI=-5.53, -2.17; p<0.0001; I^2=52%) or studies with low methodological quality (MD=-4.27; 95% CI=-6.42, -2.12; p<0.0001; I^2=59%), the female sex continued with significant association with low TTR than male sex (Fig. 3). These two analyses showed an increase of heterogeneity.

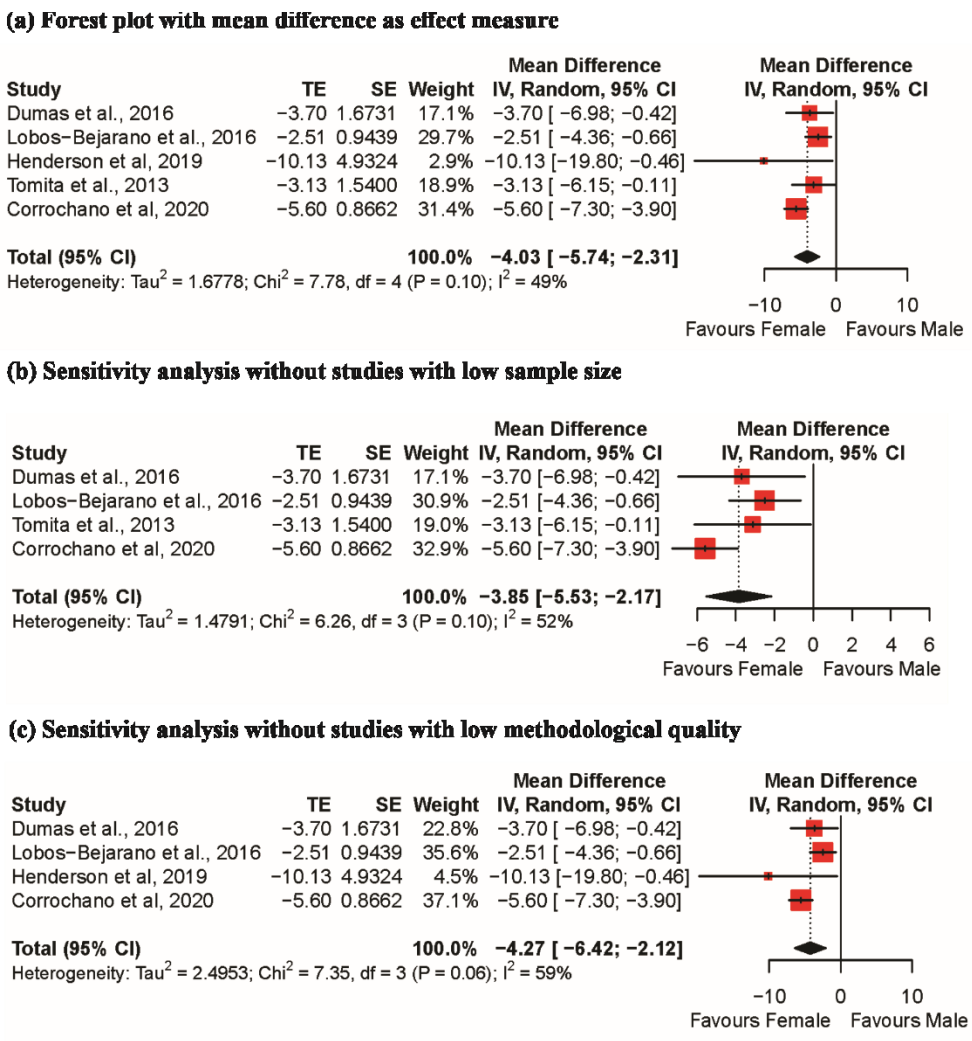

Fig. 3 Forest plot with mean difference for effect of sex in the anticoagulation control

Publication bias evaluation

The funnel plots of nine studies and of five studies (Fig. 4) showed asymmetrical distributions, suggesting the possibility of publication bias. Thehe Begg's and Mazundar Test showed a no significant p-value (p=0.6767 and p=0.6242, respectively). This analysis was limited due to the low number of studies.

Meta-regression

The meta-regression with the year of publication of study as covariate showed that effect was significant in both analysis for the binary response (p<0.0001) and for the continuous response (p=0.0246) (Fig. 5). This result suggested that the difference of effect increased over time.

Discussion

This systematic review developed to assess the association of sex with the oral anticoagulation control in patients on coumarin derivatives revealed that women presented lower TTR than men. This result confirmed the findings of previous studies [15,36], showing consistency according to the performance of meta-analysis results. The female sex is a possible modifier of TTR and the reasons for worse control of oral anticoagulation in women may be related to hormonal effect, pharmacokinetic changes, social and family aspects and less access to health services [8]. However, these factors are not fully understood. Warfarin was the coumarin derivative used by patients in all studies included in this analysis, and the main indication was AF. Previous evidences reported that women are older that men at the first diagnosis of AF [37], tend to live longer alone and to be less educated than men [38]. These aspects may contribute to lower adherence to drug therapy [39]. The use of oral contraceptives have been described to increase the risk of venous thrombosis, myocardial infarction, strokes and peripheral arterial diseases, and hormone replacement therapy, has been associated with an increased risk of thromboembolism [40,41].

The authors of included studies in this systematic review varied in TTR cutoff points and applied different analysis methodologies to assess the association between TTR and sex. Thus, we conducted two meta-analysis. The first estimate was performed with a combination of odds ratio and the second with mean differences. For both, the results suggested the control of anticoagulation for women . In addition, the authors used different populations and different sample sizes, which resulted in great heterogeneity in the studies.

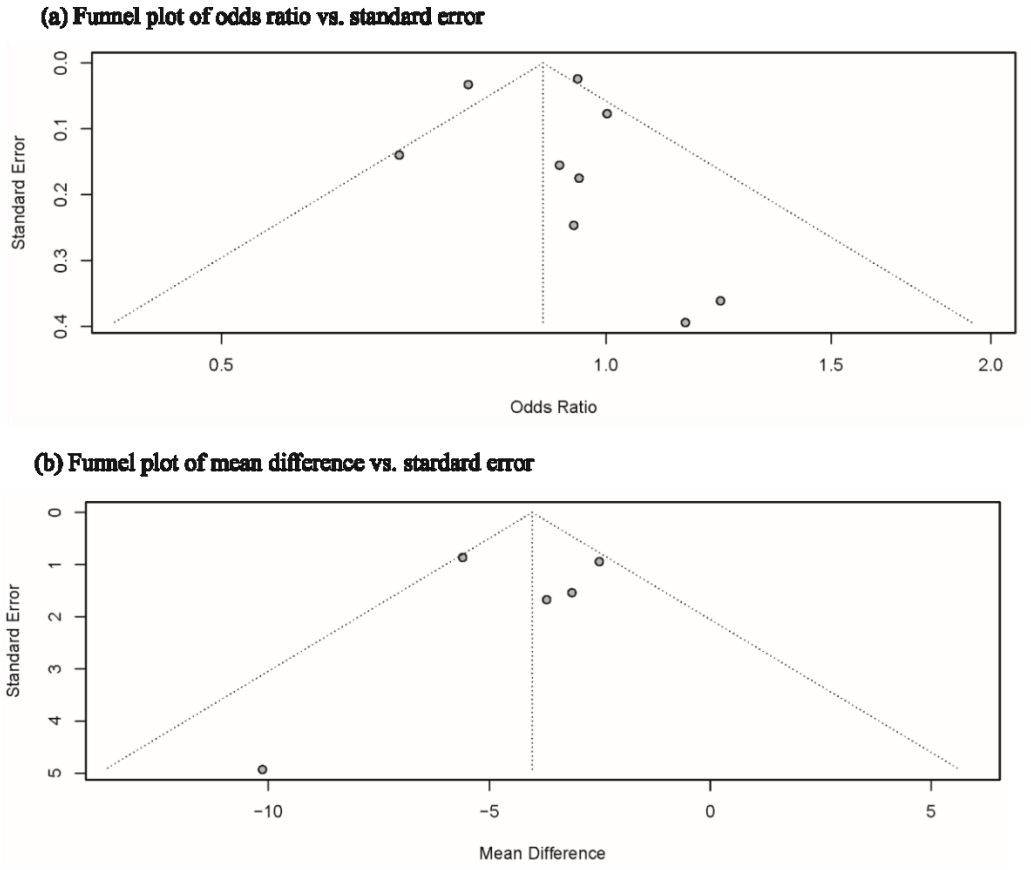

Fig.4 Funnel plots of the comparisons of TTR between female sex and male sex

The results of sensitivity analysis replicated the results of the studies analyzed altogether. The exclusion of two studies [23,27] with lower weights in the meta-analysis, resulted in changes in the overall OR in favor of the lowest TTR for women with statistical significance. However, there was an increase in heterogeneity (I^2) from 0.74% to 80% (p<0.001). The exclusion of a study with low quality [27] and similar OR to the overall result, however the heterogeneity (I^2) also increased from 74% to 77% (p<0.001). In the sensitivity analysis using MD, with exclusion of the study of lower weight [31], there was a reduction of the difference in the TTR between the sexes (MD=-4.03 to MD=-3.85), but the women continued with significant association with lower TTR than men (p<0.0001). The heterogeneity increased from 49% to 52% (p=0.10). Removing a study [34] with low quality, the MD changed from -4.03 to -4.27 in favor of lower TTR for females than males (p<0.0001). The heterogeneity increased to 50% (p=0.06). In summary, the heterogeneity assessed by Q-statistic, I^2 statistic and tau-squared statistic was greater than in the analysis including all the studies. The analysis of the risk of bias showed that there is a possibility of publication bias and the meta-regression with the year of publication of the studies suggested that the difference in effect increased over time. It was not possible to perform the meta-regression with the age of participants because not all studies presented the mean ages.

To the best of our knowledge, this is the first study that directly approached the influence of sex on the control of oral anticoagulation in patients on coumarin derivatives. New investigations should be carried out to evaluate the association between sex and the quality of oral anticoagulation control, using primary data, since our study was based on sub-analysis from other studies.

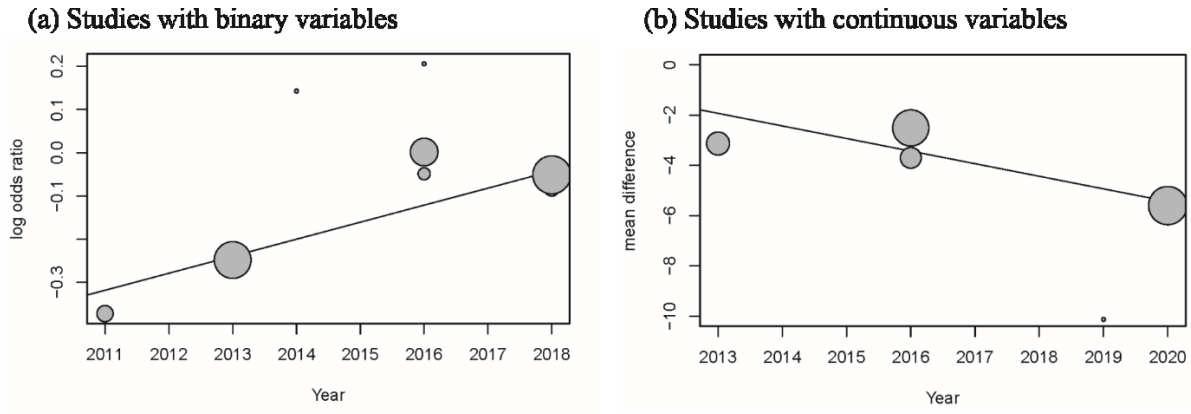

Fig. 5 Meta-regression with the year of study

We should address some limitations of our study. Relevant articles may have not been captured by our search, despite following the rigorous methodology recommended for systematic reviews. Non-indexed articles or those employing very specific terms related to TTR or to oral anticoagulation control could not have been detected by our search strategy. Only observational studies were included in this systematic review and our results depended on the methodological quality of these studies. In addition, the findings of our study referred to AF, despite the many indications for oral anticoagulation. We should also consider the wide clinical and methodological heterogeneity in the selected studies and the possibility of publication bias, which may have limited the strength of our conclusions.

The factors related to sex are complex and their associations with TTR have not been fully described. Women carry several factors that may be related to the worst control of anticoagulation, such as hormonal factors, and more detailed research should be carried out on this subject. In view of this, the healthcare system should develop targeted care strategies for these patients to promote the effectiveness and safety of treatment, contributing to reduce the burden of complications in women undergoing oral anticoagulation.

Conclusion

This systematic review with meta-analysis showed that women were associated with a lower TTR than men. High heterogeneity was observed in the studies and the results showed that there is a possibility of publication bias. Thus, more comprehensive studies are needed to evaluate this association as well as factors that may be related to anticoagulation control in women. In addition, innovative strategies could be useful to adapt care protocols to provide care focused on these patients.

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Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethical standards Not applicable, as it is a secondary study.

Authors contributions CCV, MFSP, JLPS and MAPM participated of the conception and design of the study; CCV and MFSP independently screened articles according to inclusion criteria. MAPM acted as the third reviewer of article selection. CCV and MFSP extracted data from selected articles. CCV, MFSP, JLPS and MAPM participated of the plan and conduction of statistical analysis. CCV drafted the manuscript. CCV, MFSP, WJFNS, FB, JLPS and MAPM interpreted results. All authors reviewed and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

SEARCH STRATEGIES

PUBMED

No	Search items
1	Time in therapeutic range
2	Quality of Anticoagulation
3	International Normalised Ratio
4	Quality of therapy
5	Warfarin
6	Warfarina
7	Marevan
8	Warfant
9	Coumadin
10	Coumarins
11	Sex
12	Women
13	Female
14	Male
15	#1 OR #2 OR #3 OR #4
16	#5 OR #6 OR #7 OR #8 OR #9 OR #10
17	#11 OR #12 0R #13 OR #14
18	#15 AND #16 AND #17

EMBASE

No	Query Results
#1.	'time in therapeutic range':ti,ab,kw
#2.	'quality of anticoagulation':ti,ab,kw
#3.	'international normalised ratio':ti,ab,kw
#4.	'quality of therapy':ti,ab,kw
#5.	warfarin:ti,ab,kw
#6.	warfarina:ti,ab,kw
#7.	marevan:ti,ab,kw
#8.	warfant:ti,ab,k
#9.	coumadin:ti,ab,kw
#10.	coumarins:ti,ab,kw
#11.	sex:ti,ab,kw
#12.	women:ti,ab,kw
#13.	male:ti,ab,kw
#14.	female:ti,ab,kw
#15.	#1 OR #2 OR #3 OR #4
#16.	#5 OR #6 OR #7 OR #8 OR #9 OR #10
#17.	#11 OR #12 OR #13 OR #14
#18.	#15 AND #16 AND #17

CINAHL

CINAHL	("Time in therapeutic range" OR "Quality of Anticoagulation" OR "International Normalised Ratio" OR "Quality of therapy") AND (Warfarin OR Warfarina OR Varfarina OR Aldocumar OR "Apo-Warfarin" OR Coumadin OR Coumadine OR "Gen-Warfarin" OR Marevan OR Tedicumar OR Warfant OR Coumarins) AND (Sex OR Women OR Female OR Male)

WEB OF SCIENCE

Web of Science (ISI)	("Time in therapeutic range" OR "Quality of Anticoagulation" OR "International Normalised Ratio" OR "Quality of therapy") AND (Warfarin OR Warfarina OR Varfarina OR Aldocumar OR "Apo-Warfarin" OR Coumadin OR Coumadine OR "Gen-Warfarin" OR Marevan OR Tedicumar OR Warfant OR Coumarins) AND (Sex OR Women OR Female OR Male)

COCHRANE

ID	Search Hits
#1	Time in therapeutic range
#2	Quality of Anticoagulation
#3	International Normalised Ratio
#4	Quality of therapy
#5	Warfarin
#6	Warfarina
#7	Marevan
#8	Warfant
#9	Coumadin
#10	Coumarins
#11	Sex
#12	Women
#13	Female
#14	Male
#15	#1 OR #2 OR #3 OR #4
#16	#5 OR #6 OR #7 OR #8 OR #9 OR #10
#17	#11 OR #12 0R #13 OR #14
#18	#15 AND #16 AND #17

7 CONCLUSÕES

Nesta revisão sistemática da literatura com meta-análise, para avaliar a influência do sexo no controle da anticoagulação oral em pacientes tratados com derivados cumarínicos, observou-se que o sexo feminino esteve associado a menores valores de TTR do que os homens.

Esta é a primeira revisão sistemática com meta-análise que aborda diretamente a associação entre sexo e o controle da anticoagulação oral com derivados cumarínicos. Nossos resultados podem contribuir para melhor compreensão dos fatores que podem interferir com a anticoagulação no sexo feminino. As mulheres que utilizam anticoagulantes orais são frequentemente idosas, com condição de saúde precária e dependem de cuidados especializados. Diante disso, o sistema de saúde deve desenvolver estratégias de cuidados adaptadas para esse subgrupo, a fim de aumentar a efetividade e segurança do tratamento, contribuindo para a redução da morbidade e mortalidade das pacientes.

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APÊNDICES

APÊNDICE A – Estratégias de busca para revisão de literatura.

PUBMED

No	Search items
1	Time in therapeutic range
2	Quality of Anticoagulation
3	International Normalised Ratio
4	Quality of therapy
5	Warfarin
6	Warfarina
7	Marevan
8	Warfant
9	Coumadin
10	Coumarins
11	Sex
12	Women
13	Female
14	Male
15	#1 OR #2 OR #3 OR #4
16	#5 OR #6 OR #7 OR #8 OR #9 OR #10
17	#11 OR #12 0R #13 OR #14
18	#15 AND #16 AND #17

EMBASE

No	Query Results
#1.	'time in therapeutic range':ti,ab,kw
#2.	'quality of anticoagulation':ti,ab,kw
#3.	'international normalised ratio':ti,ab,kw
#4.	'quality of therapy':ti,ab,kw
#5.	warfarin:ti,ab,kw
#6.	warfarina:ti,ab,kw
#7.	marevan:ti,ab,kw
#8.	warfant:ti,ab,k
#9.	coumadin:ti,ab,kw
#10.	coumarins:ti,ab,kw
#11.	sex:ti,ab,kw
#12.	women:ti,ab,kw
#13.	male:ti,ab,kw
#14.	female:ti,ab,kw
#15.	#1 OR #2 OR #3 OR #4
#16.	#5 OR #6 OR #7 OR #8 OR #9 OR #10
#17.	#11 OR #12 OR #13 OR #14
#18.	#15 AND #16 AND #17

CINAHL

CINAHL	("Time in therapeutic range" OR "Quality of Anticoagulation" OR "International Normalised Ratio" OR "Quality of therapy") AND (Warfarin OR Warfarina OR Varfarina OR Aldocumar OR "Apo-Warfarin" OR Coumadin OR Coumadine OR "Gen-Warfarin" OR Marevan OR Tedicumar OR Warfant OR Coumarins) AND (Sex OR Women OR Female OR Male)

WEB OF SCIENCE

Web of Science (ISI)	("Time in therapeutic range" OR "Quality of Anticoagulation" OR "International Normalised Ratio" OR "Quality of therapy") AND (Warfarin OR Warfarina OR Varfarina OR Aldocumar OR "Apo-Warfarin" OR Coumadin OR Coumadine OR "Gen-Warfarin" OR Marevan OR Tedicumar OR Warfant OR Coumarins) AND (Sex OR Women OR Female OR Male)

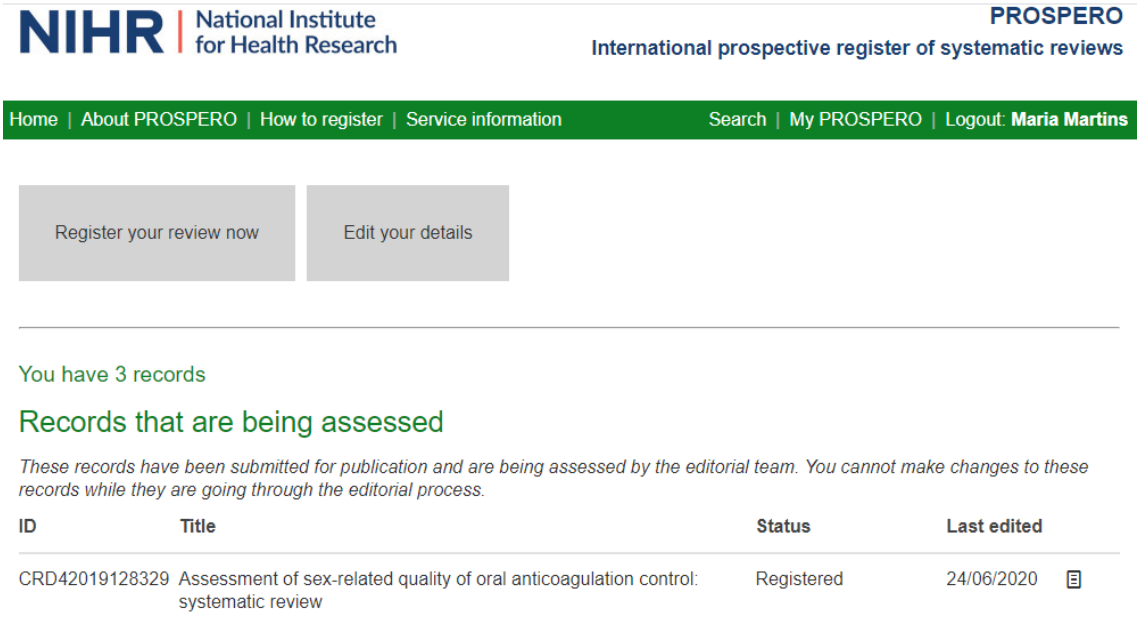
APÊNDICE A – Estratégias de busca para revisão de literatura (continuação).

COCHRANE

ID	Search Hits
#1	Time in therapeutic range
#2	Quality of Anticoagulation
#3	International Normalised Ratio
#4	Quality of therapy
#5	Warfarin
#6	Warfarina
#7	Marevan
#8	Warfant
#9	Coumadin
#10	Coumarins
#11	Sex
#12	Women
#13	Female
#14	Male
#15	#1 OR #2 OR #3 OR #4
#16	#5 OR #6 OR #7 OR #8 OR #9 OR #10
#17	#11 OR #12 0R #13 OR #14
#18	#15 AND #16 AND #17

ANEXOS

ANEXO A - Cadastro do protocolo na base de registro de revisões sistemáticas *International prospective register of ongoing systematic reviews* (PROSPERO).



ANEXO B – Escala de Newcastle-Ottawa para avaliação de estudos de coorte.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✱
   b) somewhat representative of the average _____ in the community ✱
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✱
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✱
   b) structured interview ✱
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✱
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✱
   b) study controls for any additional factor ✱ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✱
   b) record linkage ✱
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✱
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✱
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✱
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

ANEXO C – Agency for Research and Health Quality (ARHQ) Methodology Checklist for Cross-sectional Study

Item	Yes	No	Unclear
1) Define the source of information (survey, record review)			
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications			
3) Indicate time period used for identifying patients			
4) Indicate whether or not subjects were consecutive if not population-based			
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants			
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)			
7) Explain any patient exclusions from analysis			
8) Describe how confounding was assessed and/or controlled.			
9) If applicable, explain how missing data were handled in the analysis			
10) Summarize patient response rates and completeness of data collection			
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained			

ANEXO D – Artigo submetido ao periódico *JBI Evidence Synthesis*.

JBI EVIDENCE SYNTHESIS

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Role: Author Username: AUXILIADORA

Submissions with an Editorial Office Decision for Author Maria Auxiliadora Parreiras Martins, Ph.D.

Page: 1 of 1 (1 total completed submissions) Display 10 results per page.

Action	Manuscript Number	Title	Initial Date Submitted	Status Date	Current Status	Date Final Disposition Set	Final Disposition
View Submission Author Status Author Response View Decision Letter Send E-mail	JBIES-20-00168	Assessment of the influence of sex on oral anticoagulation control in patients taking coumarin derivatives: a systematic review protocol	29 Apr 2020	20 Jul 2020	Accept		

ANEXO E – Normas do periódico *JBI Evidence Synthesis*.

Disponível em: http://edmgr.ovid.com/jbisrir/accounts/ifauth.htm.

Information for authors

About the Journal

Scope

JBI Evidence Synthesis (*JBI Evidence Synthesis*) is an official journal of JBI. It is an international peer-reviewed, online journal that publishes manuscripts encompassing evidence synthesis and health care. *JBI Evidence Synthesis* seeks to disseminate rigorous, high-quality research that provides the best available evidence to inform policy and practice through the science and conduct of systematic and scoping reviews.

The journal publishes systematic and scoping review protocols, diverse types of systematic reviews, and scoping reviews covering multi-disciplinary healthcare-related topics that follow methodology and methods developed by JBI. The journal also publishes editorials, letters to the editor as well as original applied research and discussion papers examining synthesis methods. *JBI Evidence Synthesis* does not accept systematic reviews of in *vitro* or animal studies.

Publication frequency

Issues of *JBI Evidence Synthesis* are published monthly in annual volumes. The journal also offers online publication of accepted manuscripts prior to assignment and publication in an issue (see 'Online First' below).

Indexing

Scopus, MEDLINE, Embase, Mosby's Index, EmCare, CINAHL (EBSCO), HINARI, Epistemonikos, KSR Evidence, Zetoc, PsycInfo.

Publishing model, article access and author fees

JBI Evidence Synthesis is a hybrid open access journal and publishes subscription-based, free access and open access articles. Readers can access systematic reviews via paid subscriptionto the journal or via pay-per-view, which provides paid access to a single article. If authors have paid an article processing charge to make their systematic reviews open access, it will be freely accessible to readers upon publication. OPEN Editorials and systematic review protocols are permanently free to access. FREE

Authors are not required to pay any fees to have their manuscript processed or published in *JBI Evidence Synthesis*, however, authors of systematic reviews have the option to pay an article processing charge to make their manuscript 'Open access' and freely available. For more information please read our detailed 'Open access' section below.

Online First

JBI Evidence Synthesis offers online publication of accepted manuscripts prior to publication in an issue. ***Disclaimer****:* Articles appearing in the 'Online First' section have been peer-reviewed and accepted for publication in this journal and posted online before publication in an issue. Articles appearing here may contain statements, opinions, and information that have errors in facts, figures, or interpretation. Accordingly, Lippincott Williams & Wilkins, the editors and authors and their respective employees are not responsible or liable for the use of any such inaccurate or misleading data, opinion or information contained in the articles in this section.

Affiliated society

JBI is a research and development organization based within the Faculty of Health and Medical Sciences at The University of Adelaide, South Australia. JBI works with over 70 Collaborating Entities (comprising JBI Centres of Excellence and Affiliated Groups) around the world, who together as the JBI Collaboration (JBC), collaborate to promote and support evidence informed approaches to the delivery of healthcare policy and practice globally.

The Editor-in-Chief of *JBI Evidence Synthesis* is employed and appointed by JBI, however, the organisation follows the principles of editorial independence advocated for by the World Association of Medical Editors and grants the Editor-in-Chief editorial freedom in decision-making processes associated with the operation and development of the journal, including full authority over the editorial content of the journal and the appointment of members to *JBI Evidence Synthesis* Editorial Advisory Board and panel of Senior Associate Editors and Associate Editors.

Journal history

JBI Evidence Synthesis evolved from the *JBI Library of Systematic Reviews* (first available online in 1998) and

ANEXO F - Artigo submetido ao periódico *Clinical Research in Cardiology*

Submissions Being Processed for Author Maria Auxiliadora Parreiras Martins, Ph.D.

Page: 1 of 1 (1 total submissions) Display 10 results per page.

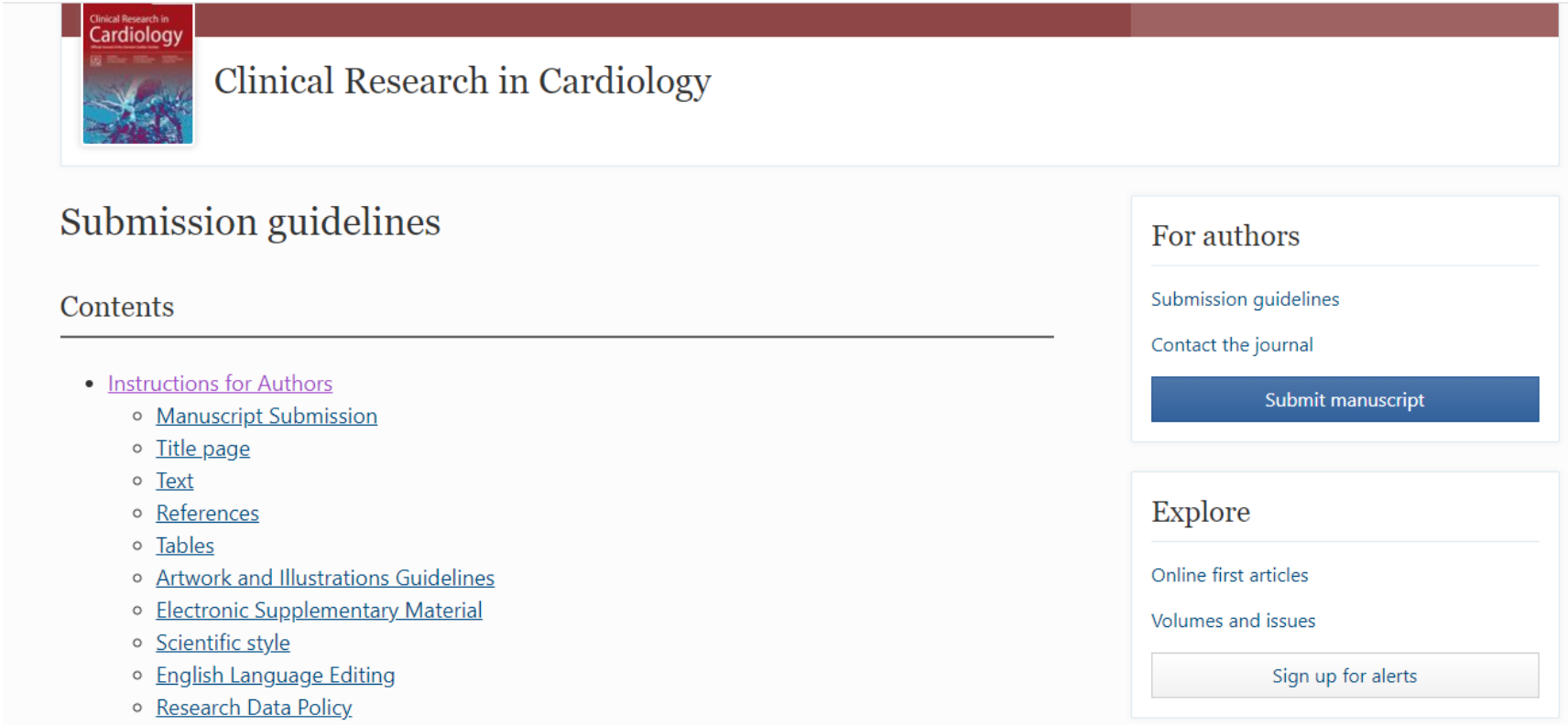
Action	Manuscript Number	Title	Initial Date Submitted	Status Date	Current Status
Action Links	CRCD-D-20-01078	Assessment of the influence of sex on oral anticoagulation control in patients treated with coumarin derivatives: a systematic review and meta-analysis	15-08-2020	15-08-2020	Submitted to Journal

Page: 1 of 1 (1 total submissions) Display 10 results per page.

<< Author Main Menu

ANEXO G - Normas do periódico *Clinical Research in Cardiology*.

Disponível em: https://www.springer.com/journal/392/submission-guidelines#Instructions%20for%20Authors



Clinical Research in Cardiology

Submission guidelines

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ANEXO H - Resumo submetido ao congresso *American Heart Association Scientific Sessions 2020*.

De: AHAScientificSessions@abstractmanagement.com <AHAScientificSessions@abstractmanagement.com>
Enviado: quarta-feira, 5 de agosto de 2020 17:07
Para: auxiliadorapmartins@hotmail.com <auxiliadorapmartins@hotmail.com>
Assunto: AHA Scientific Sessions 2020 Notification Letter for Abstract #16815

Maria Martins:
We are pleased to inform you that your abstract, #16815: Female Sex And Its Relation With Poor Control Of Oral Anticoagulation With Coumarin Derivatives: A Systematic Review And Meta-analysis, has been accepted for virtual presentation at Scientific Sessions 2020 scheduled for November 13-17. All participation will be done virtually. You will be receiving additional information soon outlining the details of your acceptance and how to preparing for you participation.
Information on registration will be available soon. We look forward to your participation, and congratulations.
With sincere thanks,
Committee on Scientific Sessions Program