JOHANA ALEJANDRA MORENO DRADA

SAÚDE BUCAL EM PACIENTES EM TERAPIA ANTICOAGULANTE E EFETIVIDADE DAS TERAPIAS HEMOSTÁTICAS PARA A PREVENÇÃO DO SANGRAMENTO

Faculdade de Odontologia
Universidade Federal de Minas Gerais
Belo Horizonte
2020

Johana Alejandra Moreno Drada

SAÚDE BUCAL EM PACIENTES EM TERAPIA ANTICOAGULANTE E EFETIVIDADE DAS TERAPIAS HEMOSTÁTICAS PARA A PREVENÇÃO DO SANGRAMENTO

Tese apresentada ao Colegiado de Pós-Graduação da Faculdade de Odontologia da Universidade Federal de Minas Gerais, como requisito para obtenção do grau de Doutor em Odontologia.
Área de concentração: Saúde Coletiva
Orientador: Prof. Mauro Henrique Nogueira Guimarães de Abreu
Co-orientadora: Profa. Isabela Almeida Pordeus

Belo Horizonte
2021

Ficha Catalográfica

D757s 2021 T

Drada, Johana Alejandra Moreno.
Saúde bucal em pacientes em terapia anticoagulante e efetividade das terapias hemostáticas para a prevenção do sangramento / Johana Alejandra Moreno Drada. -- 2021.

186 f. : il.

Orientador: Mauro Henrique Nogueira Guimarães de Abreu.
Coorientadora: Isabela Almeida Pordeus.

Tese (Doutorado) -- Universidade Federal de Minas Gerais, Faculdade de Odontologia.

1. Anticoagulantes. 2. Saúde bucal. 3. Qualidade de vida. 4. Procedimentos cirúrgicos operatórios. 5. Hemostáticos. I. Abreu, Mauro Henrique Nogueira Guimarães de. II. Pordeus, Isabela Almeida. III. Universidade Federal de Minas Gerais. Faculdade de Odontologia. IV. Título.

BLACK - D047

Elaborada por: Miriam Cândida de Jesus - CRB: 6/2727.

Biblioteca Faculdade de Odontologia - FAO UFMG

UNIVERSIDADE FEDERAL DE MINAS GERAIS

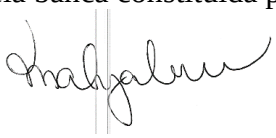
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

FOLHA DE APROVAÇÃO

SAÚDE BUCAL E ASSISTÊNCIA ODONTOLÓGICA EM PACIENTES EM TERAPIA ANTICOAGULANTE

JOHANA ALEJANDRA MORENO DRADA

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em Odontologia, como requisito para obtenção do grau de Doutor, área de concentração Saúde Coletiva.
Aprovada em 27 de maio de 2021, pela banca constituída pelos membros:



Prof(a). Mauro Henrique Nogueira Guimaraes de Abreu

Prof(a). Isabela Almeida Pordeus

Prof(a). Saul Martins de Paiva

Prof(a). Maria Esperanza Cortes Segura

Prof(a). Adolfo Contreras Rengifo

Prof(a). Marina Helena Cury Gallottini

Defesa Homologada pelo Colegiado de Pós-Graduação em Odontologia em ____/____/2020.

Profa. Isabela Almeida Pordeus
Coordenadora
Programa de Pós-Graduação em Odontologia da UFMG

Dedico este trabalho a minha família e namorado que tanto me apoiaram e incentivaram meu crescimento profissional e a todos meus amigos que me ajudaram e torceram.

AGRADECIMENTOS

Em primeiro lugar, agradeço a Deus por me permitir viver esta experiência e alcançar esta conquista. Meus agradecimentos são uma longa lista e provavelmente esquecerei personagens que foram importantes durante meu doutorado, desde já peço desculpas sinceras a eles.

Sou colombiana, orgulhosamente colombiana, e deixar minha terra foi uma experiência forte, mas enriquecedora. Agradeço a Maira Alejandra Moreno por ter iniciado essa ideia maluca de estudar no exterior, foi por causa dela que tudo começou. Agradeço aos meus professores da Universidad del Valle por acreditarem em minhas habilidades e me encorajarem a continuar com a loucura do doutorado, especialmente à professora Martha Lucía Rodriguez e o professor Adolfo Contreras. Agradeço a minha família do Hospital San Juan de Dios de Cali (Sonia, Leidy, Juan David, Juan Manuel e Verónica), é a melhor equipe de trabalho que Deus pôde me dar, obrigada pelo apoio. Obrigada aos meus amigos da minha amada terra. Jessica Delgado, as longas conversas com você nunca me deixaram sozinha, obrigada por sempre me ajudar e me apoiar em todos os momentos, você sabe que é minha irmã. Juan Pablo Pava sua visita e o passeio pelo Rio de Janeiro recarregou minhas energias. Daniela Angulo as visitas a São Paulo foram maravilhosas e também gostei muito de suas visitas aqui em BH, “nuestras tertúlias” são incomparáveis. Alejandro não vou esquecer seu apoio no momento mais difícil. Graças aos meus novos amigos, aqueles que tive a oportunidade de conhecer neste país maravilhoso, foram minha família e continuarão sendo parte dela, são presentes da vida. Obrigada Richard, Catalina, Lisandra, Omar, Daniel, Manuel, Alfonso e Lida porque estamos longe de nossa terra, mas com ela em nossos corações. Agradeço também ao Wilmer por abrir meus olhos quando era necessário, você é um 10. Obrigada Helena, Rafaela, Alex, Heloisa e Leo porque me mostraram suas belas terras, sua comida gostosa e o calor das pessoas neste lindo país, vocês fizeram minha estadia muito agradável. Vou sentir saudade de todos vocês.

Agradeço aos meus professores da Universidade Federal de Minas Gerais por acreditarem em mim, mesmo sem saber falar ao princípio. Obrigada professor Lucas e professoras Isabela, Maria Auxiliadora, Fabiana e Ana Cristina, por toda a colaboração durante o meu crescimento. Obrigada ao Matheus e à equipe da Clínica

de Anticoagulação do Hospital das Clínicas (HC) da Universidade Federal de Minas Gerais (UFMG) e seus pacientes, sem eles a pesquisa não teria sido possível.

Obrigada Professora Maria Esperanza Cortés e Professor Rubén, não só consegui um lar, mas também encontrei duas grandes pessoas que me acolheram e apoiaram, especialmente quando a situação se tornou difícil devido à pandemia.

Quero deixar um agradecimento especial ao meu orientador Mauro Henrique Abreu, sua paciência, dedicação e calor humano são admiráveis, tive a sorte de contar com sua guia e seus conhecimentos. Obrigada por tanta paciência, mesmo quando me sentia impotente por não conseguir me expressar como queria devido à linguagem. Obrigada por me receber, por acreditar em mim e por ser um excelente profissional e ser humano.

Principalmente, agradeço a toda minha família e namorado. Meu pai Ernesto Moreno, minha mãe María Drada e meu irmão Julian Moreno são minha força motriz, minha inspiração, meu exemplo a seguir. Obrigada por estar sempre ao meu lado, por me levantar naqueles momentos difíceis, pela educação que me deram e por me amar, sinto orgulho da minha família. Eu amo vocês profundamente. Obrigada ao meu namorado, Luís Eduardo Pedraza, amor sem você teria sido extremamente difícil, você é um dos muitos presentes que o Brasil me deu, obrigada pelo seu apoio, por me ajudar na adaptação, por compartilhar seu conhecimento em línguas estrangeiras, seu conhecimento em computação e acima de tudo por ser uma das pessoas mais bonitas que já conheci.

Finalmente, agradeço à OEA e ao Programa de Alianças para Educação e Capacitação - PAEC OEA-GCUB. Agradeço também ao Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) pelo apoio financeiro.

Muchas Gracias a todos por ser parte de este hermoso proceso y ayudar a lograrlo.

“A mente é um fogo a ser aceso, não um vaso a preencher/*El conocimiento no es una vasija que se llena, sino un fuego que se enciende*”.

Plutarco

RESUMO

O objetivo deste trabalho foi determinar a efetividade das terapias hemostáticas em indivíduos sob terapia anticoagulante a fim de evitar o sangramento por procedimentos odontológicos e descrever os fatores associados à qualidade de vida e saúde bucal entre pacientes em terapia anticoagulante oral com varfarina. Inicialmente foi desenvolvida uma revisão sistemática e meta-analise em rede que revisou os ensaios clínicos em diferentes bases de dados para determinar a efetividade das terapias hemostáticas. A extração de dados, a avaliação do risco de viés dos artigos incluídos (ferramentas de JBI e Cochrane) e a avaliação da certeza das evidências (GRADE) foram realizadas. Como resultados, foi verificado que o N-butil-2-cianoacrilato [RR -35,00 (95% CI - 107,12, -5,78)], sulfato de cálcio ($CaSO_4$) [RR -5,62 (95% CI -11,41, -1,03)], e Ácido tranexâmico (TXA) [RR -3,46 (95% CI -7,63, -0,77)] mostraram efeitos benéficos em comparação com o placebo. No entanto, apenas o TXA apresentou efeitos benéficos com evidência de certeza moderada. N-butil-2-cianoacrilato e $CaSO_4$ apresentaram evidência de certeza muito baixa. Não foram observadas diferenças entre agentes hemostáticos na prevenção de eventos de sangramento. Concluindo, os eventos de sangramento em indivíduos em anticoagulação oral diminuíram com o uso de TXA em comparação com o placebo. O N-butil-2-cianoacrilato e o $CaSO_4$ também foram superiores ao placebo, mas a certeza das evidências era baixa. Para o tempo médio de sangramento, não foi observada diferença significativa nos agentes hemostáticos.

Por outro lado, foi desenvolvido um estudo transversal, questionários validados avaliaram doença periodontal auto-relatada, variáveis demográficas e qualidade de vida relacionada à saúde bucal (QVRSB), usando a versão curta do instrumento Oral Health Impact Profile (OHIP-14), em pacientes anticoagulados de um Hospital de Belo Horizonte, Brasil. Após a calibração intra-examinador (Kappa = 0,95), um examinador avaliou a experiência dos pacientes com cárie dentária e a necessidade de próteses dentárias. A análise estatística envolveu proporções e medidas de tendência central. Modelos de regressão binomial negativos foram usados para estimar as razões de taxas (RR) e os intervalos de confiança de 95% (IC) correspondentes. A média do OHIP-14 foi de 10,62 (DP = 10,92). Um escore total do OHIP-14 mais alto (baixa QVRSB) foi associado ao grupo étnico, idade, auto-relato de doença periodontal, cárie dentária e auto-relato de saúde bucal. Concluindo, as doenças bucais entre indivíduos submetidos a terapia anticoagulante oral com varfarina é preocupante. Os fatores demográficos e clínicos têm uma influência na percepção de pacientes anticoagulados na QVRSB.

Palavras chave: Anticoagulante. Saúde bucal. Qualidade de vida. Procedimentos Cirúrgicos Operatórios. Hemostáticos.

ABSTRACT

Oral health in patients under anticoagulant therapy and effectiveness of hemostatic therapies for bleeding prevention.

This study aimed to determine the effectiveness of hemostatic protocols in anticoagulated patients to prevent bleeding in dental procedures and describe the factors associated with quality of life and oral health-related to patients undergoing oral anticoagulant therapy with warfarin. In the first instance, in the systematic review and network meta-analysis, a search of the literature was conducted in different databases where clinical trials were evaluated to determine the effectiveness of hemostatic protocols. Data extraction and assessment of the risk of bias (JBI and Cochrane tools) of the included articles were performed. Assessment of the certainty of the evidence (GRADE) was also performed. As results we find that the N-butyl-2-cyanoacrylate [RR -35.00 (95% CI - 107.12, -5.78)], calcium sulfate ($CaSO_4$) [RR -5.62 (95% CI -11.41, -1.03)], and tranexamic acid (TXA) [RR -3.46 (95% CI -7.63, -0.77)] showed beneficial effects compared to placebo. However, only TXA presented beneficial effects with moderate certainty evidence. N-butyl-2-cyanoacrylate and $CaSO_4$ presented very low certainty evidence. No differences were observed between hemostatic agents in preventing bleeding events. Concluding, the bleeding events in individuals on oral anticoagulation decreased with the use of TXA compared to placebo. N-butyl-2-cyanoacrylate and $CaSO_4$ were also superior to placebo, but the certainty of the evidence was low. For the mean bleeding time, no significant difference in hemostatic agents was observed.

On the other hand, a the cross-sectional study was performed, validated questionnaires assessed self-reported periodontal disease, demographic variables, and OHRQoL, using the short version of the Oral Health Impact Profile (OHIP-14) instrument in anticoagulated patients at a Belo Horizonte, Brazil. After calibration (Kappa = 0,95), an examiner evaluated patients' experience with dental caries and the need for dental prostheses. Statistical analysis involved proportions and measures of central tendency. Negative binomial regression models were used to estimate the rate ratios (RR) and the corresponding 95% confidence interval (CI). The OHIP-14 mean was 10.62 (SD = 10.92). A higher OHIP-14 total score (low OHRQoL) was associated with an ethnic group, age, periodontal disease self-report, dental caries, and oral health self-report. Concluding, the burden of oral diseases among individuals undergoing OAT is worrisome. Additionally, demographic and clinical factors have an influence on the perception of anticoagulated patients on OHRQoL.

Keywords: Anticoagulants. Oral health. Quality of life. Oral Surgical Procedures. Hemostatics.

LISTA DE ILUSTRAÇÕES
FIGURAS, GRÁFICOS E QUADROS

METODOLOGIA

ARTIGO 1

ARTIGO 2

Informações de Apoio Artigo 2

LISTA DE TABELAS

ARTIGO 2

Informações de Apoio Artigo 2

ARTIGO 3

ARTIGO 4

LISTA DE ACRÔNIMOS E ABREVIATURAS

AHA	*American Heart Association* (Associação Americana do Coração)
AVK	Antagonistas da Vitamina K
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CENTRAL	*Cochrane Controlled Trials Register Center*
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
DCV	Doenças Cardiovasculares
DMFT/CPO-D	Decayed, Missing, and Filled Teeth - Dentes Cariados, Perdidos e Obturados
DTEV	Doença Tromboembólica Venosa
EACA	Ácido Épsilon-Aminocapróico
GRADE	*Grading of Recommendations Assessment, Development and Evaluation* - Classificação de Recomendações, Avaliação, Desenvolvimento e Análises.
IBGE	Instituto Brasileiro de Geografia e Estatística
JBI	*Joanna Briggs Institute*
LILACS	*Latin American and Caribbean Literature in Health Sciences*
NMA	*Network Meta-analysis* - Meta-analise em Rede
NOAC/DOAC	Anticoagulantes Orais Diretos ou Novos Anticoagulantes Orais
OHIP	Perfil de Impacto Sobre a Saúde Bucal - *Oral Health Impact Profile*
OHRQoL/QVRSB	*Oral Health-Related Quality of Life* - Qualidade de Vida Relacionada à Saúde Bucal
OMS	Organização Mundial da Saúde
OR	*Odds Ratio* - Razão de Chances
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-analysis*

PROSPERO	*International Prospective Register of Systematic Reviews*
PRSF	*Potential Scale Reduction Factor*
RAR	Raspagem e Alisamento Radicular
RNI	Razão Normalizada Internacional
RR	*Risk Ratio or Relative Risk* – Risco Relativo
RR	*Rate Ratios* - Razão de Taxas
SS	Sangramento à Sondagem
SUCRA	*Surface Under the Cumulative Ranking Curve* - Superfície Sob a Curva Cumulativa de Classificação
TAO	Terapia Anticoagulante Oral
TXA	Ácido Tranexâmico
UFMG	Universidade Federal de Minas Gerais

SUMÁRIO

1 CONSIDERAÇÕES INICIAS

Os anticoagulantes orais são medicamentos usados na prevenção e tratamento da doença tromboembólica (BAJKIN; POPOVIC; SELAKOVIC, 2009; JIMÉNEZ *et al.*, 2008; RIPOLLES-DE RAMON *et al.*, 2014). A terapia anticoagulante oral (TAO) é indicada para pacientes ambulatoriais com fibrilação atrial ou outras arritmias cardíacas, válvulas cardíacas protéticas, tromboembolismo venoso, síndrome coronariana aguda ou infarto do miocárdio, hipertensão pulmonar, valvulopatia e substituição de válvula para prevenção e tratamento, reduzindo o risco de acidente vascular cerebral, morbidade e mortalidade (BONED-OMBUENA *et al*., 2017; EICHHORN *et al*., 2012; KÄMMERER *et al*., 2015; LEH-CHING NG *et al*., 2019; RIPOLLÉS *et al*., 2012; ROCHA *et al*., 2018).

A Organização Mundial da Saúde comenta que a cada ano, 16,7 milhões ou 29,2% do total de mortes no mundo são resultado de doenças cardiovasculares (DCV), com os países em desenvolvimento respondendo por 80% das mortes no mundo. No município de Ribeirão Preto, interior do estado de São Paulo, por exemplo, foram registrados 1.050 óbitos por doenças cardiovasculares, representando uma taxa de mortalidade de 13,81% em 2007 (PELEGRINO *et al.*, 2010). A doença tromboembólica é um distúrbio comum, com incidência anual de aproximadamente um caso por 1.000 pessoas-ano, associada à alta mortalidade em curto prazo (SÁNCHEZ-SILES *et al.*, 2015). A fibrilação atrial é a arritmia cardíaca sustentada que afeta aproximadamente 1,5-2% da população nos países desenvolvidos. A prevalência desta patologia é de 4,4% na população espanhola. No Brasil, estima-se que aproximadamente 1,5 milhão de pessoas tenham fibrilação atrial e seja responsável por 33% de todas as internações por arritmia (BARTHOLOMAY *et al.*, 2014).

Em relação à TAO, não há dados disponíveis sobre a prevalência atual para Brasil. Segundo a Sociedade Espanhola de Cardiologia, 700.000 pacientes recebem terapia de anticoagulação oral (ALMIÑANA-PASTOR *et al.*, 2017). De acordo com um estudo recente realizado naquele país, a prevalência de pacientes com essa terapia é de 1,3 casos por 100 habitantes com 18 anos ou mais. A prevalência aumentou progressivamente com a idade, atingindo uma proporção de 6,9 casos por 100 habitantes com 80 anos ou mais (BONED-OMBUENA *et al.*, 2017).

Quanto às terapias com anticoagulantes orais, podemos encontrar os derivados cumarínicos ou também conhecidos como antagonistas da vitamina K (AVK) (ALMIÑANA-PASTOR *et al*., 2017; BARTHOLOMAY *et al*., 2014; EICHHORN *et al*., 2012) são os mais utilizados no mundo, principalmente em países de baixa e média renda (MARTINS *et al*., 2017). Atuam diminuindo os níveis plasmáticos dos fatores de coagulação dependentes da vitamina K (fatores II, VII, IX e X e proteínas S e C). Esses medicamentos exercem seu efeito nos microssomas das células hepáticas, inibindo a redutase necessária para transformar a vitamina K inativa em vitamina K ativa (ALMIÑANA-PASTOR *et al.*, 2017). Varfarina e acenocumarol são exemplos de tais medicamentos. O efeito anticoagulante tem uma meia-vida de pelo menos 48 horas e leva de 4 a 5 dias para ficar totalmente ativo (KÄMMERER *et al.*, 2015). A eficácia e a segurança desses medicamentos dependem da manutenção do paciente dentro da faixa terapêutica adequada à sua patologia, medida pela Razão Normalizada Internacional (RNI) (BONED-OMBUENA *et al*., 2017; PURCELL, 1997).

Nos últimos anos, os chamados "novos anticoagulantes orais" ou "anticoagulantes orais diretos" (DOAC) foram desenvolvidos (TOMASELLI *et al.*, 2017). Em comparação com os derivados cumarínicos, esses fármacos têm objetivos particulares na cascata da coagulação, são inibidores do fator Xa, como exemplo desses fármacos é o rivaroxaban e o apixaban, o dabigatran é um inibidor direto da trombina (SERRANO-SÁNCHEZ *et al.*, 2017). É importante ter em consideração que tanto o defeito quanto o excesso da anticoagulação podem ser prejudiciais, aumentando o risco tromboembólico e hemorrágico, respectivamente (BONED-OMBUENA *et al*., 2017).

Para os pacientes em TAO, alguns procedimentos odontológicos, como extrações dentárias, tratamentos periodontais, cirurgias a retalho ou procedimentos de implantodontia, podem resultar em hemorragias, além de lesões de tecidos moles ou duros no sítio tratado (BAJKIN; POPOVIC; SELAKOVIC, 2009; JIMÉNEZ *et al.*, 2008; RIPOLLES-DE RAMON *et al.*, 2014).

Devido ao risco de sangramento, tem uma falta de consenso sobre a realização de extrações dentárias ou outras cirurgias bucais para pacientes em uso de anticoagulantes. Uma variedade de protocolos, intervenções ou abordagens terapêuticas para o atendimento odontológico deste grupo de pacientes foi apresentada na literatura. Sugere-se desde uma suspensão temporária de TAO (MULLIGAN; WEITZEL, 1988) ou uma diminuição na dosagem de TAO entre 2 a 7

dias antes de uma extração dentária, para obter uma RNI subterapêutica ou normal; a substituição de TAO por heparina; uma continuação do TAO com ênfase na hemostasia local (BAJKIN; POPOVIC; SELAKOVIC, 2009) ou nenhuma mudança no regime de TAO, sem hemostasia local (WAHL, 1998). Alguns autores sugerem uma abordagem individualizada para cada paciente (BAJKIN; POPOVIC; SELAKOVIC, 2009) e outros relatam que os procedimentos são seguros em indivíduos altamente anticoagulados com RNI entre 3,5 e 4,2, se as medidas hemostáticas locais eficazes forem fornecidas (BRANISLAV *et al.*, 2015). Os agentes hemostáticos locais mais comumente usados são gelatina absorvente ou esponjas de colágeno, celulose oxidada regenerada, cola de fibrina e antifibrinolíticos aplicados diretamente na ferida ou na forma de uma solução como o ácido tranexâmico (BRANISLAV *et al.*, 2015).

Um aspecto importante na saúde bucal dos pacientes em TAO é a possível implicação dos anticoagulantes como modificadores do sangramento positivo a sondagem (SS) e a relação entre doença tromboembólica venosa (DTEV) e doença periodontal (SÁNCHEZ-SILES *et al.*, 2015). Mesmo assim, são poucas as publicações sobre a saúde bucal de pacientes submetidos à TAO ou seus hábitos de higiene bucal (ALMIÑANA-PASTOR *et al.*, 2017). Embora sem muitos estudos anteriores, a saúde bucal tem um papel essencial em indivíduos anticoagulados. O tratamento odontológico em pacientes com qualquer doença periodontal demonstrou aumentar significativamente a RNI (MOREIRA *et al*., 2007), enquanto a raspagem e a limpeza resultaram na redução da RNI (PURCELL, 1997). Meurman *et al.*, (2003), identificaram que parte dos pacientes em anticoagulação oral não escovaram os dentes diariamente nem limparam os espaços interdentais em seu estudo. O medo de sangramento gengival provavelmente poderia induzir os indivíduos a escovar os dentes com menor frequência, aumentando o número de dentes recobertos por placa e causando bolsas periodontais profundas (MEURMAN *et al.*, 2003; MOREIRA *et al.*, 2007; PADRÓN *et al.*, 2003).

Por outro lado, a literatura científica é também deficiente quanto à qualidade de vida relacionada a saúde bucal (QVRSB) dos pacientes anticoagulados. A pesquisa tem dado pouca atenção ao impacto na QVRSB, apesar da interação que pode ter o tratamento complexo a longo prazo, como a TAO e os cuidados de saúde bucal adicionais, para evitar riscos de sangramento (MOLINO- PAGAN; ANDUJAR-MATEOS; JORNET, 2015; PADRÓN *et al.*, 2003). Estudos anteriores identificaram que a QVRSB pode ser afetada por doença periodontal, condições dentárias (dentes

cariados, perdidos ou restaurados), lesões da mucosa e problemas com prótese dentária (BAIJU *et al*., 2019; ORTÍZ-BARRIOS *et al*., 2019; WONG; NG; KEUNG LEUNG, 2019). Apesar das publicações sobre o tema, pouco se sabe sobre os comportamentos, percepções ou repercussões das condições bucais em indivíduos em TAO.

O risco de sangramento, restrições na ingestão alimentar e possíveis interações de anticoagulantes orais, como a varfarina, com outros medicamentos podem interferir nas atividades diárias em pessoas submetidas à TAO (LEH-CHING NG *et al*., 2019; MOLINO- PAGAN; ANDUJAR- MATEOS; JORNET, 2015; TRULLAS-VILA *et al*., 2009). Além das incertezas associadas ao TAO, existe um risco aumentado de sangramento bucal devido a doenças bucais (MOLINO- PAGAN; ANDUJAR- MATEOS; JORNET, 2015; PADRÓN *et al.*, 2003) que podem causar insatisfação e ter um impacto negativo na QVRSB.

Então, é relevante realizar um estudo analítico transversal primário para obter informações sobre a qualidade de vida relacionada à saúde bucal em pacientes com terapia anticoagulante oral e uma revisão sistemática da literatura sobre terapias hemostáticas para a prevenção de sangramento em pacientes anticoagulados (ANTMAN EM, LAU J, KUPELNICK B, MOSTELLER F, 1992; HIGGINS; GREEN, 2011; OXMAN; GUYATT, 1993).

2 JUSTIFICATIVA

Tanto no contexto hospitalar quanto na atenção primária à saúde, é frequente o atendimento odontológico de pacientes tratados com anticoagulantes. Apesar da frequência desta situação nos serviços de saúde, pouco se conhece na literatura sobre a saúde bucal desses pacientes.

Os tratamentos cirúrgicos odontológicos podem ser realizados se os valores da RNI estiverem dentro do intervalo terapêutico (BAJKIN *et al.*, 2015; BAJKIN; POPOVIC; SELAKOVIC, 2009). No entanto, os novos anticoagulantes não se refletem nesses tempos de coagulação, e o risco de sangramento é ainda maior, então outros protocolos são recomendados para continuar com a terapia anticoagulante, mas com ênfase na hemostasia local. Alguns estudos descrevem extrações dentárias bem-sucedidas sem interrupção da terapia anticoagulante, usando medidas hemostáticas locais e se não houver outras coagulopatias presentes (BAJKIN *et al.*, 2015; BAJKIN; POPOVIC; SELAKOVIC, 2009). Existem diferentes alternativas ou terapias hemostáticas para evitar possíveis sangramentos de difícil controle (BRANISLAV *et al.*, 2015; CARTER *et al.*, 2003; ISOLA *et al.*, 2015; PIPPI; SANTORO; CAFOLLA, 2015; SACCO *et al.*, 2007; SOUTO *et al.*, 1996). Apesar da variedade dos agentes hemostáticos locais (BRANISLAV *et al.*, 2015), nenhum deles demonstrou ser mais efetivo em comparação com outros (BAJKIN *et al.*, 2014; HALFPENNY; FRASER; ADLAM, 2001).

Cada procedimento odontológico invasivo realizado em pacientes anticoagulados representa um risco; o principal problema que surge é alterar ou suspender a terapia anticoagulante oral que pode resultar em risco de tromboembolismo ou deixar o paciente com terapia anticoagulante, mas com possibilidade de sangramento durante ou após o procedimento oral (BAJKIN; POPOVIC; SELAKOVIC, 2009). As informações fornecidas são diversas, não há uma abordagem padronizada para o tratamento de pacientes anticoagulados durante o procedimento cirúrgico bucal, resultando em incertezas sobre qual manejo pode ser apropriado, e como podem ser usadas intervenções eficazes para prevenir o sangramento após procedimentos odontológicos (BAJKIN; POPOVIC; SELAKOVIC, 2009).

Por outro lado, a qualidade de vida é um componente importante na avaliação de resultados de programas de atenção médica e saúde pública, levando em consideração o conceito de que a saúde é um recurso e não simplesmente a ausência de doença (SLADE, 1997). Segundo a Organização Mundial da Saúde, a qualidade de vida foi definida em termos do modo como o indivíduo percebe o lugar que ocupa no ambiente cultural e no sistema de valores em que vive, assim como em relação aos seus objetivos, expectativas, critérios e preocupações. Tudo isso é qualificado, naturalmente, por sua saúde física, seu estado psicológico, seu grau de independência, suas relações sociais, os fatores ambientais e suas crenças pessoais (WHO QUALITY OF LIFE ASSESSMENT GROUP, 1996). Em termos de qualidade de vida de pacientes anticoagulados, o manejo do paciente é complexo e requer frequentes consultas de controle analítico para monitorar e regular os valores do RNI, restrições na dieta e certas atividades, possível preocupação com sangramento ou hematomas, interações com outros medicamentos (TRULLAS-VILA *et al.*, 2009).

Tendo em conta as dificuldades acima mencionadas que podem levar a um desacordo com o tratamento de anticoagulantes orais, para este tipo de população que geralmente pertence a uma faixa etária de idosos e adicionalmente com as condições inerentes à velhice, como a doença periodontal, diminuição do fluxo salivar e a redução das defesas do hospedeiro que podem levar a diferentes tipos de doenças bucais. Tudo isso e o pouco conhecimento sobre saúde bucal entre os idosos, bem como as preocupações com o sangramento, podem contribuir para uma inadequada higiene bucal (PADRÓN *et al.*, 2003). A higiene bucal adequada é importante para prevenir a colonização microbiana ou placa bacteriana que pode levar a infeções, bolsas gengivais profundas ou exodontias (ALMIÑANA-PASTOR *et al.*, 2017; PADRÓN *et al.*, 2003), aumentando a possibilidade de sangramento no paciente anticoagulado (ROCHA *et al.*, 2018). Esses eventos podem afetar a qualidade de vida da população em anticoagulação oral.

Com o aumento da expectativa de vida das populações, há uma tendência de aumento no número de indivíduos que utilizará da terapia anticoagulante. Portanto, um maior conhecimento do assunto é essencial para proporcionar o manejo ideal na área da saúde bucal a essa população que aumenta gradativamente (BONED-OMBUENA *et al.*, 2017). Quando há evidências científicas insuficientes, há uma incapacidade de obter conclusões ou informações atualizadas que possam ajudar os profissionais de saúde a tomar decisões e melhorar os cuidados reduzindo riscos ou

complicações. É necessário contribuir para estudos primários que constroem o conhecimento e para os estudos secundários que sintetizam e promovem o progresso do conhecimento científico.

3 OBJETIVOS

3.1 Geral

Determinar a efetividade da terapia hemostática para prevenção de sangramento em procedimentos odontológicos e descrever a qualidade de vida relacionada à saúde bucal entre pacientes com terapia anticoagulante oral e.

3.2 Específicos

- Desenvolver uma revisão sistemática para determinar o mecanismo hemostático mais efetivo na prevenção do sangramento em indivíduos anticoagulados.
- Identificar os efeitos adversos da realização de diferentes intervenções hemostáticas em indivíduos submetidos a procedimentos orais.
- Determinar a frequência de cárie dentária e de uso e necessidade de prótese em pacientes com terapia anticoagulante oral.
- Descrever o auto relato para doença periodontal em pacientes anticoagulados.
- Descrever e analisar os fatores associados à qualidade de vida relacionada à saúde bucal de pacientes em terapia anticoagulante oral.

4 METODOLOGIA.

Uma revisão sistemática da literatura sobre terapias hemostáticas para a prevenção de sangramento em pacientes anticoagulados e um estudo primário transversal foi realizado para obter informações sobre a qualidade de vida relacionada à saúde bucal em pacientes com terapia anticoagulante oral.

4.1 Revisão Sistemática

4.1.1 Protocolo e registro

A revisão sistemática foi conduzida de acordo com a metodologia do Instituto Joanna Briggs para revisões sistemáticas de evidências de efetividade (TUFANURU *et al.*, 2017) e do Cochrane (HIGGINS; GREEN, 2011). O protocolo foi registrado no Registro Prospectivo Internacional de Revisões Sistemáticas (PROSPERO), sob o número de registro CRD42019136744. O relato dessa revisão sistemática seguiu o Preferred Reporting Items for Systematic Reviews and Meta-analyses (MOHER *et al.*, 2009), segundo heterogeneidade dos estudos, apresentando as evidências científicas até o momento sobre a efetividade dos procedimentos hemostáticos utilizados no manejo de pacientes anticoagulados para evitar o sangramento por via oral. O protocolo desta revisão sistemática está publicado no JBI Evidence Synthesis (Ver artigo 1).

4.1.2 Pergunta de pesquisa

A pergunta respondida pela revisão sistemática foi: Qual é a efetividade das terapias hemostáticas no manejo de paciente anticoagulado para a prevenção de sangramentos após procedimentos bucais? Seguindo a pergunta PICO [P=patients (pacientes), I=intervention (intervenção), C=comparison (comparação), O=outcome (desfecho).

4.1.3 Critérios de inclusão e exclusão

4.1.3.1 Participantes ou pacientes

Esta revisão sistemática considerou ensaios clínicos com participantes de 18 anos de idade ou mais submetidos a terapia de anticoagulação oral, como derivados cumarinicos e DOACs, que necessitaram de procedimentos orais, 1) procedimentos

odontológicos, como extrações dentárias, cirurgias periodontais ou endodônticas, 2) cirurgia de tecidos moles (biópsias) e 3) cirurgia em tecidos ósseos, como aumento do rebordo alveolar foram incluídos. Artigos que avaliaram procedimentos extraorais foram excluídos.

4.1.3.2 Intervenções

Estudos que avaliaram a efetividade de terapias hemostáticas para a prevenção de sangramentos, como ácido tranexâmico, epsilon ou soluções antifibrinolíticas locais, celulose oxidada, gelfoam, esponjas de gelatina reabsorvíveis, esponjas de colágeno absorvíveis, cola de fibrina, cola de cianoacrilato, gel de plasma rico em plaquetas, trombina tópica, alginato de cálcio e meios mecânicos como sutura, grampo cirúrgico, pressão da gaze e agentes vasoconstritores. Foram excluídos os estudos com informações insuficientes para determinar a efetividade da terapia hemostática avaliada.

4.1.3.3 Comparação

As comparações apresentadas na revisão foram 1) Pacientes com TAO e intervenção hemostática versus pacientes com TAO e sem intervenção hemostática ou pressão de gaze. 2) Pacientes com TAO e intervenção hemostática versus pacientes com TAO e placebo. 3) Pacientes com TAO e intervenção hemostática versus pacientes com TAO e outro tipo de intervenção hemostática.

4.1.3.4 Desfechos

Esta revisão sistemática considerou estudos que avaliaram a efetividde na prevenção de sangramentos pós-operatórios como desfecho primário, mensurada pelo número de eventos de sangramento e o tempo de sangramento. Os desfechos secundários foram os efeitos adversos das terapias hemostáticas (consequência indesejável ou não intencional durante a administração de hemostático) e o tipo de terapia anticoagulante à qual os participantes foram submetidos.

Resumos de congressos e revisões da literatura, opinião de especialistas e editoriais também foram excluídos.

4.1.4 Fontes de informações

A pesquisa cobriu a literatura existente desde a data de início das bases de dados até setembro de 2020. Foram realizadas buscas nas seguintes bases de dados: PubMed, Medline Ovid, EMBASE, Web of Science, Cochrane Controlled Trials Register Center, LILACS- Literatura Latino-Americana e do Caribe em Ciências da Saúde e Scopus. Buscas manuais na lista de referências dos artigos incluídos também foram realizadas. Os estudos não publicados foram pesquisados no banco de dados ProQuest Dissertations and Theses e no Clinicaltrials.gov. Também foram realizadas pesquisas no Google Scholar e OpenGrey limitadas aos 200 primeiros hits. A lista de referências dos artigos incluídos foi rastreada para identificar referências perdidas durante as pesquisas nos bancos de dados eletrônicos. Os resultados das pesquisas foram verificados para eliminação das duplicatas.

4.1.5 Estratégias de busca

As estratégias de busca foram construídas de acordo com cada base de dados utilizada.

a) Estratégia de busca PubMed Medline (Mesh):

(6-aminohexanoic acid OR 6 aminohexanoic acid OR epsilon-aminocaproic acid OR epsilon aminocaproic acid OR 6-aminocaproic acid OR 6 aminocaproic acid OR “capralense” OR capramol OR caproamin OR “caprocid” OR “hexalense” OR CY-116 OR CY 116 OR CY116 OR epsamon OR epsikapron OR hemocaprol OR amicar OR “caprolest” OR AMCHA OR trans-4-(Aminomethyl)cyclohexanecarboxylic Acid OR t-AMCHA OR AMCA OR anvitoff OR cyklokapron OR “ugurol” OR KABI 2161 OR “spotof” OR “transamin” OR “amchafibrin” OR “exacyl” OR oxidized Cellulose OR oxycellulose OR cellulosic Acid OR absorbable Cellulose OR carboxycellulose OR oxycel OR absorbable gelatin sponge OR absorbable gelatin sponges OR gelfoam OR gelaspon OR absorbable collagen sponge OR fibrin glue OR fibrin adhesive OR fibrin sealant OR fibrin seal OR tisseel OR “tissel” OR tissucol OR beriplast OR fibrin Seal OR cyanoacrylate glue OR ethyl cyanoacrylate OR ethyl-2-cyanoacrylate OR ethyl alpha-cyanoacrylate OR epiglue OR “krazy glue” OR “cyacrine” OR cyano-veneer OR platelet-rich plasma OR topical thrombin OR suture OR surgical staple OR stitch OR gauze pressure OR vasoconstrictor) **AND** (oral bleeding OR oral bleeding management OR oral blood OR oral blood management OR oral bleeding hemostasis

OR oral blood hemostasis OR oral hemostasis OR oral surgery OR oral hemorrhage) **AND** (anticoagulants OR “factor xa inhibitor” OR “factor xa inhibitors” OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR savaysa OR betrixaban OR bevyxxa OR “thrombin inhibitor” OR “thrombin inhibitors” OR dabigatran OR pradaxa OR melagatran OR ximelagatran OR exanta OR heparin OR coumarin OR warfarin OR 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one OR apo-warfarin OR aldocumar OR gen-warfarin OR “warfant” OR coumadin OR “marevan” OR warfarin potassium OR warfarin sodium OR “coumadine” OR “tedicumar”) **AND** (randomized controlled trial OR clinical trial)

Ovid Medline (Mesh):

6-aminohexanoic acid.mp OR exp Aminocaproic Acid/ OR 6 aminohexanoic acid.mp OR epsilon-aminocaproic acid.mp OR epsilon aminocaproic acid.mp OR 6-aminocaproic acid.mp OR 6 aminocaproic acid.mp OR capramol.mp OR caproamin.mp OR epsamon.mp OR epsikapron.mp OR hemocaprol.mp OR amicar.mp OR AMCHA.mp OR exp Tranexamic Acid/ OR t-AMCHA.mp OR AMCA.mp OR anvitoff.mp OR cyklokapron.mp OR ugurol.mp OR KABI 2161.mp OR transamin.mp OR exacyl.mp OR oxidized Cellulose.mp OR exp Cellulose, Oxidized/ OR oxycellulose.mp OR cellulosic Acid.mp OR absorbable Cellulose.mp OR carboxycellulose.mp OR oxycel.mp OR absorbable gelatin sponge.mp OR exp Gelatin Sponge, Absorbable/ OR absorbable gelatin sponges.mp OR gelfoam.mp OR gelaspon.mp OR absorbable collagen sponge.mp OR fibrin glue.mp OR exp Fibrin Tissue Adhesive/ OR fibrin adhesive.mp OR fibrin sealant.mp OR fibrin seal.mp OR tisseel.mp OR tissel.mp OR tissucol.mp OR beriplast.mp OR fibrin Seal.mp OR cyanoacrylate glue.mp OR exp Cyanoacrylates/ OR ethyl cyanoacrylate.mp OR ethyl-2-cyanoacrylate.mp OR ethyl alpha-cyanoacrylate.mp OR epiglue.mp OR krazy glue.mp OR cyacrine.mp OR cyano-veneer.mp OR platelet-rich plasma.mp OR exp Platelet-Rich Plasma/ OR topical thrombin.mp OR exp Thrombin/ OR suture.mp OR exp Sutures/ OR surgical staple.mp OR stitch.mp OR gauze pressure.mp OR vasoconstrictor.mp OR exp Vasoconstrictor Agents/ **AND** oral bleeding.mp OR exp Oral Hemorrhage/ OR oral blood.mp OR oral hemostasis.mp OR exp Hemostasis/ OR oral surgery.mp OR exp Surgery, Oral/ OR oral hemorrhage.mp **AND** anticoagulants.mp OR exp Anticoagulants/ OR factor xa inhibitor.mp OR exp Factor Xa Inhibitors/ OR factor xa inhibitors.mp OR rivaroxaban.mp OR exp Rivaroxaban/ OR

xarelto.mp OR apixaban.mp OR eliquis.mp OR edoxaban.mp OR lixiana.mp OR savaysa.mp OR betrixaban.mp OR bevyxxa.mp OR thrombin inhibitor.mp OR thrombin inhibitors.mp OR exp Antithrombins/ OR dabigatran.mp OR exp Dabigatran/ OR pradaxa.mp OR melagatran.mp OR ximelagatran.mp OR exanta.mp OR heparin.mp OR exp Heparin/ OR coumarin.mp OR exp Coumarins/ OR warfarin.mp OR exp Warfarin/ OR apo-warfarin.mp OR aldocumar.mp OR Coumadin.mp OR marevan.mp OR warfarin potassium.mp OR warfarin sodium.mp OR coumadine.mp. **AND** exp randomized controlled trial/ OR exp clinical trial/

b) Lilacs:

("6-aminohexanoic acid " OR "6 aminohexanoic acid" OR "epsilon-aminocaproic acid" OR "epsilon aminocaproic acid" OR "6-aminocaproic acid" OR "6 aminocaproic acid" OR capralense OR capramol OR caproamin OR caprocid OR hexalense OR "CY-116" OR "CY 116" OR "CY116" OR epsamon OR epsikapron OR hemocaprol OR amicar OR caprolest OR "AMCHA" OR "trans-4-(Aminomethyl)cyclohexanecarboxylic Acid" OR "t-AMCHA" OR "AMCA" OR anvitoff OR cyklokapron OR ugurol OR "KABI 2161" OR spotof OR transamin OR amchafibrin OR exacyl OR "oxidized Cellulose" OR oxycellulose OR "cellulosic Acid" OR "absorbable Cellulose" OR carboxycellulose OR oxycel OR "absorbable gelatin sponge" OR "absorbable gelatin sponges" OR gelfoam OR gelaspon OR "absorbable collagen sponge" OR "fibrin glue" OR "fibrin adhesive" OR "fibrin sealant" OR "fibrin seal" OR tisseel OR tissel OR tissucol OR beriplast OR "fibrin Seal" OR "cyanoacrylate glue" OR "ethyl cyanoacrylate" OR "ethyl-2-cyanoacrylate" OR "ethyl alpha-cyanoacrylate" OR epiglue OR "krazy glue" OR cyacrine OR "cyano-veneer" OR "platelet-rich plasma" OR "topical thrombin" OR suture OR "surgical staple" OR stitch OR "gauze pressure" OR vasoconstrictor) **AND** ("oral bleeding" OR "oral bleeding management" OR "oral blood" OR "oral blood management" OR "oral bleeding hemostasis" OR "oral blood hemostasis" OR "oral hemostasis" OR "oral surgery" OR "oral hemorrhage") **AND** (anticoagulants OR "factor xa inhibitor" OR "factor xa inhibitors" OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR savaysa OR betrixaban OR bevyxxa OR "thrombin inhibitor" OR "thrombin inhibitors" OR dabigatran OR pradaxa OR melagatran OR ximelagatran OR exanta OR heparin OR coumarin OR warfarin OR "4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one" OR "apo-warfarin" OR aldocumar OR "gen-warfarin" OR warfant OR coumadin OR marevan OR "warfarin

potassium" OR "warfarin sodium" OR coumadine OR tedicumar) **AND** (randomized controlled trial OR clinical trial)

c) Embase (Emtree)

('aminocaproic acid'/exp OR 'aminocaproic acid' OR 'aminocaproic acid derivative'/exp OR 'aminocaproic acid derivative' OR 'tranexamic acid'/exp OR 'tranexamic acid' OR 'oxidized cellulose'/exp OR 'oxidized cellulose' OR 'gelatin sponge'/exp OR 'gelatin sponge' OR 'gelfoam'/exp OR 'gelfoam' OR 'gelaspon'/exp OR 'gelaspon' OR 'absorbable collagen sponge'/exp OR 'absorbable collagen sponge' OR 'fibrin glue'/exp OR 'fibrin glue' OR 'fibrin seal'/exp OR 'fibrin seal' OR 'cyanoacrylate glue'/exp OR 'cyanoacrylate glue' OR 'ethyl 2 cyanoacrylate'/exp OR 'ethyl 2 cyanoacrylate' OR 'platelet-rich plasma cell'/exp OR 'platelet-rich plasma cell' OR 'thrombin'/exp OR 'thrombin' OR 'suture'/exp OR 'suture' OR 'surgical staple'/exp OR 'surgical staple' OR 'gauze dressing'/exp OR 'gauze dressing' OR 'vasoconstrictor agent'/exp OR 'vasoconstrictor agent') **AND** ('oral bleeding'/exp OR 'oral bleeding' OR 'oral bleeding management' OR 'oral blood' OR 'oral blood management' OR 'oral bleeding hemostasis' OR 'oral blood hemostasis' OR 'oral hemostasis' OR 'oral surgery'/exp OR 'oral surgery' OR 'oral hemorrhage'/exp OR 'oral hemorrhage') **AND** ('anticoagulant agent'/exp OR 'anticoagulant agent' OR 'factor xa inhibitor'/exp OR 'factor xa inhibitor' OR 'blood clotting factor 10a inhibitor'/exp OR 'blood clotting factor 10a inhibitor' OR 'rivaroxaban'/exp OR 'rivaroxaban' OR 'xarelto'/exp OR xarelto OR 'apixaban'/exp OR 'apixaban' OR 'eliquis'/exp OR eliquis OR 'edoxaban'/exp OR 'edoxaban' OR 'lixiana'/exp OR lixiana OR 'savaysa'/exp OR savaysa OR 'betrixaban'/exp OR 'betrixaban' OR 'bevyxxa'/exp OR bevyxxa OR 'thrombin inhibitor'/exp OR 'thrombin inhibitor' OR 'thrombin inhibitors'/exp OR 'thrombin inhibitors' OR 'dabigatran'/exp OR 'dabigatran' OR 'pradaxa'/exp OR pradaxa OR 'melagatran'/exp OR 'melagatran' OR 'ximelagatran'/exp OR 'ximelagatran' OR 'exanta'/exp OR exanta OR 'heparin'/exp OR 'heparin' OR 'coumarin'/exp OR 'coumarin' OR 'warfarin'/exp OR 'warfarin' OR 'apo warfarin' OR 'aldocumar'/exp OR aldocumar OR 'gen warfarin' OR 'warfant' OR 'coumadin'/exp OR coumadin OR 'marevan'/exp OR 'marevan' OR 'warfarin potassium'/exp OR 'warfarin potassium' OR 'warfarin sodium'/exp OR 'warfarin sodium' OR 'coumadine'/exp OR 'coumadine' OR 'tedicumar') **AND** ('randomized controlled trial'/exp OR 'clinical trial'/exp)

d) Scopus (Emtree)

("aminocaproic acid" OR "aminocaproic acid derivative" OR "tranexamic acid" OR "oxidized cellulose" OR "gelatin sponge" OR gelfoam OR gelaspon OR "absorbable collagen sponge" OR "fibrin glue" OR "fibrin seal" OR "cyanoacrylate glue" OR "ethyl 2 cyanoacrylate" OR "platelet-rich plasma cell" OR thrombin OR suture OR "surgical staple" OR "gauze dressing" OR "vasoconstrictor agent") AND ("oral bleeding" OR "oral bleeding management" OR "oral blood" OR "oral blood management" OR "oral bleeding hemostasis" OR "oral blood hemostasis" OR "oral hemostasis" OR "oral surgery" OR "oral hemorrhage") AND ("anticoagulant agent" OR "factor xa inhibitor" OR "blood clotting factor 10a inhibitor" OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR savaysa OR betrixaban OR bevyxxa OR "thrombin inhibitor" OR "thrombin inhibitors" OR dabigatran OR pradaxa OR melagatran OR ximelagatran OR exanta OR heparin OR coumarin OR warfarin OR "apo-warfarin" OR aldocumar OR "gen-warfarin" OR warfant OR Coumadin OR marevan OR "warfarin potassium" OR "warfarin sodium" OR coumadine OR tedicumar) **AND** (randomized controlled trial OR clinical trial)

e) Cochrane Controlled Trials Register Center

6 aminohexanoic acid OR epsilon aminocaproic acid OR 6 aminocaproic acid OR capralense OR capramol OR caproamin OR caprocid OR hexalense OR CY 116 OR CY116 OR epsamon OR epsikapron OR hemocaprol OR amicar OR caprolest OR AMCHA OR t AMCHA OR AMCA OR anvitoff OR cyklokapron OR ugurol OR KABI 2161 OR spotof OR transamin OR amchafibrin OR exacyl OR oxidized Cellulose OR oxycellulose OR cellulosic Acid OR absorbable Cellulose OR carboxycellulose OR oxycel OR absorbable gelatin sponge OR absorbable gelatin sponges OR gelfoam OR gelaspon OR absorbable collagen sponge OR fibrin glue OR fibrin adhesive OR fibrin sealant OR fibrin seal OR tisseel OR tissel OR tissucol OR beriplast OR fibrin Seal OR cyanoacrylate glue OR ethyl cyanoacrylate OR ethyl alpha cyanoacrylate OR epiglue OR krazy glue OR cyacrine OR cyano veneer OR platelet rich plasma OR topical thrombin OR suture OR surgical staple OR stitch OR gauze pressure OR vasoconstrictor **AND** oral bleeding OR oral bleeding management OR oral blood OR oral blood management OR oral bleeding hemostasis OR oral blood hemostasis OR oral hemostasis OR oral surgery OR oral hemorrhage **AND** anticoagulants OR factor xa inhibitor OR factor xa inhibitors OR rivaroxaban OR xarelto OR apixaban OR eliquis

OR edoxaban OR lixiana OR savaysa OR betrixaban OR bevyxxa OR thrombin inhibitor OR thrombin inhibitors OR dabigatran OR pradaxa OR melagatran OR ximelagatran OR exanta OR heparin OR coumarin OR warfarin OR apo warfarin OR aldocumar OR gen warfarin OR warfant OR coumadin OR marevan OR warfarin potassium OR warfarin sodium OR coumadine OR tedicumar **AND** randomized controlled trial OR clinical trial

f) Web of Science

1. TS=(6-aminohexanoic acid OR 6 aminohexanoic acid OR epsilon-aminocaproic acid OR epsilon aminocaproic acid OR 6-aminocaproic acid OR 6 aminocaproic acid OR “capralense” OR capramol OR caproamin OR “caprocid” OR “hexalense” OR CY-116 OR CY 116 OR CY116 OR epsamon OR epsikapron OR hemocaprol OR amicar OR “caprolest” OR AMCHA OR trans-4-(Aminomethyl)cyclohexanecarboxylic Acid OR t-AMCHA OR AMCA OR anvitoff OR cyklokapron OR “ugurol” OR KABI 2161 OR “spotof” OR “transamin” OR “amchafibrin” OR “exacyl” OR oxidized Cellulose OR oxycellulose OR cellulosic Acid OR absorbable Cellulose OR carboxycellulose OR oxycel OR absorbable gelatin sponge OR absorbable gelatin sponges OR gelfoam OR gelaspon OR absorbable collagen sponge OR fibrin glue OR fibrin adhesive OR fibrin sealant OR fibrin seal OR tisseel OR “tissel” OR tissucol OR beriplast OR fibrin Seal OR cyanoacrylate glue OR ethyl cyanoacrylate OR ethyl-2-cyanoacrylate OR ethyl alpha-cyanoacrylate OR epiglue OR “krazy glue” OR “cyacrine” OR cyano-veneer OR platelet-rich plasma OR topical thrombin OR suture OR surgical staple OR stitch OR gauze pressure OR vasoconstrictor)

2. TS=(oral bleeding OR oral bleeding management OR oral blood OR oral blood management OR oral bleeding hemostasis OR oral blood hemostasis OR oral hemostasis OR oral surgery OR oral hemorrhage)

3. TS=(anticoagulants OR “factor xa inhibitor” OR “factor xa inhibitors” OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR savaysa OR betrixaban OR bevyxxa OR “thrombin inhibitor” OR “thrombin inhibitors” OR dabigatran OR pradaxa OR melagatran OR ximelagatran OR exanta OR heparin OR coumarin OR warfarin OR 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one OR apo-warfarin OR aldocumar OR gen-warfarin OR “warfant” OR coumadin OR

“marevan” OR warfarin potassium OR warfarin sodium OR “coumadine” OR “tedicumar”)

4. TS= (randomized controlled trial OR clinical trial)
5. #4 AND #3 AND #2 AND #1

4.1.6 Seleção dos estudos

As referências recuperadas nas pesquisas foram exportadas para o software Endnote (Clarivate Analytics, Filadélfia, EUA). As duplicatas foram removidas após a identificação. Dois autores avaliaram títulos/resumos de forma independente. Referências cujos títulos/resumos preencherem os critérios de elegibilidade foram incluídas. As referências cujos títulos/resumos contiveram informações insuficientes para uma decisão de inclusão ou exclusão tiveram os textos completos recuperados. Os mesmos autores avaliaram os textos completos. Referências cujos textos completos preencheram os critérios de elegibilidade também foram incluídas. Discordâncias entre os dois autores foram resolvidas através da opinião do pesquisador sênior. As informações detalhadas dos estudos incluídos foram importadas para o Sistema JBI de Gerenciamento Unificado, Avaliação e Revisão de Informações (JBI SUMARI) (Joanna Briggs Institute, Adelaide, Austrália). O texto completo dos estudos que não se enquadraram nos critérios de elegibilidade foi excluído. Os resultados da pesquisa foram relatados na íntegra na revisão sistemática final e apresentados em um diagrama de fluxo Itens Preferidos para Relatórios para Revisões Sistemáticas e Meta-análises (PRISMA) (MOHER *et al.*, 2009).

4.1.7 Extração de dados

Os dados dos estudos incluídos foram extraídos usando a ferramenta padronizada de extração de dados do Instituto Joanna Briggs. Dois pesquisadores extraíram dados dos artigos incluídos. Os avaliadores confirmaram a entrada de dados e verificaram os dados pelo menos duas vezes para constatar sua exatidão. Discordâncias entre os dois pesquisadores foram resolvidas pelo pesquisador sênior.

4.1.8 Dados a serem extraídos

Os seguintes dados foram extraídos: nome dos autores e data da publicação, país onde o estudo foi conduzido, número de participantes, características dos participantes (sexo e idade), tipo de anticoagulante usado pelos participantes,

terapiass hemostáticas avaliadas, desfechos avaliados e resultados das comparações da efetividade das terapias hemostáticas avaliadas. Para os dados ausentes, os autores dos estudos incluídos cujos dados estavam faltando foram contatados.

4.1.9 Risco de viés dos estudos incluídos

A avaliação da qualidade metodológica dos estudos incluídos foi obtida por dois autores da revisão e as discrepâncias entre os dois foram resolvidas por meio da opinião do pesquisador sênior. A qualidade metodológica dos estudos selecionados e incluídos foi avaliada de acordo com as ferramentas Cochrane (HIGGINS; GREEN, 2011) e do Instituto Joanna Briggs para ensaios clínicos randomizados (TUFANURU *et al.*, 2017). Os seguintes itens foram avaliados e foram gerados gráficos de risco de viés para cada estudo e para todos os estudos incluídos: geração da sequência aleatória, alocação oculta, cegamento dos participantes/pessoal, cegamento do avaliador do desfecho, dados de resultados incompletos, relato seletivo de resultados e outras fontes de viés (HIGGINS; GREEN, 2011). Enquanto que uma tabela foi gerada para a avaliação dos 13 itens a seguir com a ferramenta do Instituto Joanna Briggs: randomização verdadeira para atribuição de participantes a grupos de tratamento, ocultação de alocação a grupos de tratamento, similaridade de grupos de tratamento na linha de base, ocultação de participantes para atribuição de tratamento, ocultação de distribuidores de tratamento para atribuição de tratamento, ocultação de avaliadores de resultado para atribuição de tratamento, tratamento que não seja intervenção de interesse idêntico em grupos de tratamento, conclusão do acompanhamento e, caso contrário, descrição adequada e análise das diferenças entre os grupos em termos de acompanhamento, análise dos participantes nos grupos em que foram randomizados, mesma medida dos resultados para os grupos de tratamento, avaliação confiável dos resultados, uso de análise estatística adequada e desenho do estudo apropriado ou análise de quaisquer desvios de um padrão aleatório ensaio clínico especializado (TUFANURU *et al.*, 2017). Cada item podia receber "sim" (baixo risco de viés), "não" (alto risco de viés) ou "incerto" (risco pouco claro de viés).

Todos os estudos incluídos foram submetidos à extração de dados. A síntese dos dados (quando possível) e a avaliação da certeza das evidências foram realizadas com a ferramenta de Classificação de Recomendações, Avaliação, Desenvolvimento

e Análises, em inglês Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (GUYATT *et al.*, 2008).

4.1.10 Medidas de associação

Para estudos com dados dicotômicos, foi obtido o risco relativo (RR), intervalo de confiança e valores de *p*. Para estudos com dados contínuos, a diferença de média com seu respectivo desvio padrão foi coletada.

4.1.11 Síntese dos resultados.

A síntese de dados foi realizada para uma meta-analise em rede ou em inglês network meta-analysis (NMA) devido à quantidade de intervenções. Para a NMA, definimos os nós como o número de estudos que pesquisam as intervenções hemostáticas. Definimos as bordas como o número de comparações entre os tratamentos. O grupo designado como "fibrina" foi aquele relacionado a toda intervenção com este composto, tais como a cola de fibrina e a esponja. O placebo foi definido como uma substância que não tinha um ingrediente ativo ou um efeito clínico esperado nos desfechos de sangramento. Utilizamos o JBI SUMARI e o software Review Manager [Review Manager (RevMan) - Programa de computador. Versão 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]. Também usamos a versão R 3.6.2 (R Core Team) para desenhar e analisar a rede com o pacote BUGSnet para NMA. Para cada resultado, realizamos uma NMA de efeitos aleatórios bayesianos. Os resultados da NMA foram fornecidos em risco relativo (RR) para estudos com dados dicotômicos e em diferença de média para estudos com dados contínuos. Os intervalos de credibilidade de 95% (IC) também foram fornecidos.

Quando comparamos uma intervenção com outra intervenção, medidas de resultados negativos indicaram efeitos benéficos ou uma maior redução nos eventos de sangramento (dados dicotômicos) ou tempo médio de sangramento (dados contínuos). Para cada análise, especificamos quatro cadeias de Markov Monte Carlo, com *burn-in* de 50.000 iterações seguidas por 100.000 iterações com 10.000 adaptações (BÉLIVEAU *et al.*, 2019; DIAS *et al.*, 2013). A convergência foi avaliada usando *trace plots, leverage plots* e a identificação de possíveis *outliers* (BÉLIVEAU *et al.*, 2019). Uma forma alternativa de avaliar a convergência foi por meio do valor do Fator de Redução da Escala Potencial, em inglês o *Potential Scale Reduction Factor*

(PRSF) (HARRER *et al.*, 2019). Na convergência, o PRSF deve ser gradualmente reduzido com um número crescente de interações e também deve ser inferior a 1,05. A inconsistência foi testada usando o modelo de inconsistência (ou modelo de efeitos médios não relacionados) (DIAS *et al.*, 2011; EFTHIMIOU *et al.*, 2016). Também foi implementada a comparação do desvio da média de cada ponto de dados entre o modelo da consistência e inconsistência. Fornecemos a classificação relativa dos agentes hemostáticos por meio do gráfico de superfície sob a curva cumulativa de classificação, em inglês, *Surface Under the Cumulative Ranking Curve* (SUCRA). Um valor mais alto de SUCRA denota uma maior probabilidade de efetividade de uma intervenção no controle do sangramento do que outras intervenções (BÉLIVEAU *et al.*, 2019; SALANTI; ADES; IOANNIDIS, 2011). Os resultados da NMA foram relatados em gráficos de floresta e no gráfico de calor de liga mostrando estimativas de efeito e IC (HIGGINS; GREEN, 2011).

4.1.12 Risco de viés entre os estudos

Avaliamos a heterogeneidade estatística da NMA por meio da estatística I^2 (HIGGINS; GREEN, 2011), avaliando a heterogeneidade entre os estudos com cada comparação possível pareada dentro da rede onde a evidência direta tinha ocorrido. Da mesma forma, avaliamos a heterogeneidade usando estatísticas globais I^2, considerando a variável idade dos participantes dentro de cada braço de tratamento do estudo (BÉLIVEAU *et al.*, 2019).

A unidade de análise nesta revisão sistemática foi o estudo e não a publicação. Quando um estudo tinha originado mais de uma publicação com os mesmos participantes e avaliando o mesmo desfecho, uma publicação somente foi incluída.

A avaliação da certeza das evidências foi realizada com GRADE para NMA e um resumo das descobertas foi criado (GUYATT *et al.*, 2008). No início da análise, cada comparação direta tinha uma alta certeza de evidência. Em seguida, as comparações diretas foram examinadas e determinamos se ocorreram preocupações sérias ou muito sérias de risco de viés, imprecisão, inconsistência, indireta e/ou viés de publicação. Depois, a evidência indireta foi reduzida se houvesse sérias preocupações de intransitividade. Ao final, a certeza da evidência foi rebaixada se fosse observada qualquer imprecisão ou incoerência para a estimativa final da NMA (BRIGNARDELLO-PETERSEN *et al.*, 2018; GUYATT *et al.*, 2008; PUHAN *et al.*,

2014). Com base nessa avaliação, a certeza das evidências poderia ser muito baixa, baixa, moderada ou alta.

4.1.13 Análise de sensibilidade

A robustez dos achados foi avaliada por meio da análise de sensibilidade, na qual os ensaios clínicos com alto risco de viés foram removidos e foram repetidos os cálculos para verificar e determinar a possível influência desses estudos no resultado.

4.2 Estudo transversal

Descrição da metodologia parcial de um estudo transversal que foi realizado com a intenção de descrever os fatores associados ao impacto da saúde bucal na qualidade de vida, bem como as condições de saúde bucal de um grupo de pacientes em tratamento com anticoagulante oral.

4.2.1 Local do estudo

O estudo foi realizado em pacientes que estão em tratamento com anticoagulantes orais durante o ano de 2019, em regime ambulatorial, na Clínica de Anticoagulação do Hospital das Clínicas (HC) da UFMG. A clínica de anticoagulação é multidisciplinar totalmente inserida no Sistema Único de Saúde Brasileiro, com protocolos estabelecidos para educação do paciente e ajuste de dose (MARTINS *et al.*, 2017). A clínica é orientada pelos farmacêuticos, eles têm protocolos institucionais que permitem que funcionem independentemente dos médicos. A entrevista do paciente é guiada pelo protocolo que recomenda perguntas padronizadas sobre adesão à medicação, ingestão de vitamina K, eventos adversos da varfarina (sangramento ou tromboembolismo), mudanças em outras terapias medicamentosas em andamento e o uso de medicamentos de venda livre. Os pacientes têm acesso a materiais escritos e são orientados oralmente durante consultas individuais que ocorrem pelo menos uma vez a cada seis semanas (DE LIMA SILVA *et al.*, 2017).

4.2.2 Tamanho da amostra

A partir da lista de pacientes cadastrados no serviço, foi selecionada uma amostra aleatória simples. Um cálculo de amostra foi feito por comparação de médias tendo em conta o estudo de De Oliveira *et al.*, 2005, que analisou a QVRSB por meio da forma abreviada da versão Brasileira do perfil de impacto sobre a saúde bucal -

Oral Health Impact Profile - (OHIP-14) entre mulheres adultas com cárie dentária não tratada e sem cárie dentária não tratada. O estudo de De Oliveira *et al.*, 2005, é a validação do instrumento OHIP-14 no Brasil. Observou-se no grupo com cárie dentária não tratada, um valor médio de OHIP-14 de 9,3 (± 11,3) [mediana 4,5], no grupo sem cárie dentária não tratada, o valor médio do OHIP-14 foi 4,4 (± 7,4) [mediana 2,0]. O cálculo amostral foi realizado com nível de confiança de 95% e poder de 80% com base nas informações de cárie dentária não tratada em relação à qualidade de vida, obtendo-se 120 pacientes, portanto, foi escolhido como o tamanho amostral.

4.2.2.1 Critérios de inclusão e exclusão

Como foi mencionado anteriormente, este estudo avaliou os pacientes ambulatoriais com 18 anos ou mais em tratamento com anticoagulante oral durante o ano de 2019 na Clínica de Anticoagulação do Hospital das Clínicas da UFMG. Foram avaliados pacientes anticoagulados com Varfarina, pois os novos anticoagulantes não são comumente utilizados por causa de seu alto custo. Foram excluídos os seguintes pacientes: com histórico médico sem as informações necessárias para o estudo; que não deram seu consentimento para participar; cujo estado cognitivo não podia responder às perguntas feitas; ou com sangramento espontâneo mesmo antes do exame odontológico.

4.2.3 Trabalho de campo

Assim que o Comitê de Ética da UFMG e o parecer da Diretoria de Ensino, Pesquisa e Extensão do HC-UFMG aprovou a pesquisa os prontuários clínicos dos pacientes com anticoagulante oral foram revisados para complementar as informações. O formato de coleta de dados para estudo transversal analítico está anexado (Apêndice A), no qual as variáveis estudadas foram identificadas. Os pacientes foram identificados e foi realizado um levantamento que complementa as informações para obtenção das variáveis e que permite avaliar a QVRSB por meio do OHIP-14 (Anexo A) (DE OLIVEIRA; NADANOVSKY, 2005). OHIP-14 demonstrou boa confiabilidade e validade (SLADE, 1997). OHIP-14 possui uma sólida base conceitual e empírica, com facilidade de aplicação (GONZALES-SULLCAHUAMÁN *et al.*, 2013), e é um indicador específico da qualidade de vida relacionado à saúde, que considera o impacto de condições mais definidas no campo da saúde bucal (CASTRO; PORTELA; LEÃO, 2007). O instrumento foi testado e validado para uso na língua

portuguesa e na cultura brasileira, e possui boas propriedades psicométricas, semelhantes às da versão original (DE OLIVEIRA; NADANOVSKY, 2005; MOIMAZ *et al.*, 2016). O OHIP-14 avalia 7 subescalas conceituais dos acontecimentos nos últimos seis meses, com duas perguntas para cada domínio em relação ao impacto: limitação funcional (dificuldade de mastigar), dor física (sensibilidade dos dentes), desconforto psicológico (consciência de si), incapacidade física (mudanças na dieta), incapacidade psicológica (a redução da capacidade de concentração), incapacidade social (evitando interação social) e incapacidade (incapacidade de trabalhar de forma produtiva) (DE OLIVEIRA; NADANOVSKY, 2005). As notas foram feitas em uma escala Likert de 5 pontos: 0 = "nunca"; 1 = "raramente"; 2 = " Às vezes "; 3 = "repetidamente"; e 4 = "sempre". O escore total pode ir de 0 até 56. O maior escore do OHIP-14 indicou pior qualidade de vida (MASOOD *et al.*, 2019).

4.2.3.1 Exame clínico

4.2.3.1.1 Experiência de cárie

Um exame clínico foi realizado, onde a experiência de cárie na população foi avaliada através do CPO-D (dentes cariados, perdidos e obturados), seu valor se expressou pela soma de dentes cariados, perdidos e obturados para obter um índice individual, e para o índice de comunidade, representará a média. Apenas 28 dentes foram considerados (ORGANIZATION, 2013).

Quadro 1. Critério diagnostico para CPOD

Condição	**Critérios de diagnostico**
Cariado	Um dente cariado foi considerado quando estiver presente uma lesão em um sulco ou fissura, em uma superfície lisa do dente ou raiz, com cavidade evidente, esmalte sem suporte, fundo ou parede amolecidos de modo detectável. Um dente com uma restauração temporária, ou que está selado mas também cariado, também é considerado como cariado.

Restaurado ou obturado com cárie	Uma coroa ou raiz é considerada restaurada, com cárie, quando possui uma ou mais restaurações permanentes e uma ou mais áreas estão cariadas.
Restaurado ou obturado sem cárie	Uma coroa ou raiz é considerada restaurada, sem cárie, quando uma ou mais restaurações permanentes estão presentes e não há cárie em nenhuma parte.
Perdido devido à cárie	Dentes que foram extraídos devido à cárie.

Fonte: World Health Organization. *Oral health surveys. Basic methods*, 2013.

4.2.3.1.2 Avaliação periodontal

A periodontite é caracterizada por uma inflamação mediada pelo hospedeiro e associada a bactérias que resulta na perda do ligamento periodontal e osso alveolar (CATON *et al.*, 2018; TONETTI; GREENWELL; KORNMAN, 2018). O padrão ouro para o diagnóstico de periodontite segue sendo o exame clínico com sondagem periodontal (CYRINO *et al.*, 2011). No entanto, a maioria dos pacientes anticoagulados são pacientes com certas formas de doença cardíaca (LASKIN, 2011), como pacientes com válvula protética ou material protético (ANDERSON *et al.*, 2005; LALANI *et al.*, 2006), pacientes com endocardite infecciosa prévia (CHU *et al.*, 2005) ou pacientes com cardiopatia congênita (TAKEDA; NAKANISHI; NAKAZAWA, 2005) submetidos a procedimentos. O comitê de prevenção de endocardite infecciosa da Associação Americana do Coração (AHA) recomenda a profilaxia em pacientes de alto risco antes de procedimentos odontológicos que envolvam manipulação do tecido gengival, região periapical dos dentes ou perfuração da mucosa oral (NISHIMURA *et al.*, 2008), aumentando o custo de pesquisas e o risco para pacientes no programa de atendimento periodontal (CYRINO *et al.*, 2011).

Essas circunstâncias criaram a necessidade de explorar novas abordagens para a pesquisa epidemiológica de doenças periodontais e suas associações e tornaram as medidas periodontais auto-referidas (CYRINO *et al.*, 2011). Questionários, incluindo medidas de auto-relato, tornaram-se eficazes como meio de acessar muitas doenças. Devido ao anterior, foi utilizado o questionário desenvolvido

por Cyrino *et al*., (2011). (CYRINO *et al.*, 2011). A estrutura final do questionário foi composta por um total de 18 questões sendo: 4 questões sócio-demográficas – idade, sexo, escolaridade e renda; 2 questões de fatores de risco – diabetes, fumo; 9 questões de auto-relato de saúde bucal e periodontite – escovação, uso de fio dental, última visita ao dentista, doença gengival, migração dental, mobilidade, perda dental, número de dentes presentes na boca e saúde bucal; 2 questões de história pregressa de tratamento periodontal – ser submetido a procedimentos de raspagem e alisamento radicular (RAR) e cirurgia gengival; 1 questão de relato profissional de doença periodontal – ocorrência de perda óssea (CYRINO *et al.*, 2011).

O instrumento de auto-relato da doença periodontal (CYRINO *et al.*, 2011) tem boa acurácia para identificação de indivíduos não doentes. A soma da sensibilidade e da especificidade apresentou um valor de moderado a bom para identificação da doença periodontal em diferentes modelos preditivos, especialmente para doença periodontal moderada a grave. Além disso, o estudo avaliou a população de Belo Horizonte, Brasil, a mesma cidade em que esta tese está sendo realizada (CYRINO *et al.*, 2011).

4.2.3.1.3 Uso de prótese dentária

O uso ou não de próteses e o tipo de próteses dentárias utilizadas foram clinicamente estabelecidos, levando-se em consideração se é prótese fixa, prótese parcial removível ou prótese total, seja prótese mandibular ou maxilar (ORGANIZATION, 2013).

4.2.4 Construção do banco de dados

Os pesquisadores desenvolveram um instrumento para a coleta de informação identificando as variáveis sociodemográficas, aquelas relacionadas à saúde bucal, auto-relato periodontal, e qualidade de vida relacionada à saúde bucal, que foram coletadas e analisadas no pacote estatístico SPSS versão 25.0.

4.2.5 Variáveis

Para atingir as metas propostas, foram estimadas variáveis dependentes e independentes. A variável dependente foi OHIP-14. Quanto às variáveis independentes, são aquelas relacionadas à saúde bucal, o auto-relato periodontal e para uma caracterização das variáveis sociodemográficas da população.

Quadro 2. Variáveis de pesquisa.

VARIÁVEIS				
Nome da variável	**Definição operacional**	**Tipo de variável**	**Valores possíveis**	**Fonte de informação**
Variável dependente				
OHIP-14 Perfil de Impacto na Saúde Bucal	Medição total do impacto da saúde bucal na qualidade de vida	Quantitativa contínua	Qualquer valor numérico de acordo com Perfil de Impacto na Saúde Oral (OHIP-14)	Questionário
Variáveis independentes				
Variáveis sociodemográficas				
Idade	Idade em anos	Quantitativa discreta	Qualquer idade	História clínica
Sexo	Sexo biológico do paciente	Qualitativa nominal	0= Feminino 1 = Masculino	História clínica
Cor da pele auto-relatada.	Etnia a que o paciente pertence segundo as características etno-raciais da população do Instituto Brasileiro de Geografia e Estatística (IBGE, 2013)	Qualitativa nominal	1. Branco 2. Preto 3. Pardo 4. Amarelo 5. Indígena 6. Outro	Questionário
Lugar onde mora	Cidade onde mora o paciente	Qualitativa nominal	1. BH 2. Fora da BH	Questionário
Escolaridade	Anos de estudo de acordo com a Pesquisa Nacional de Saúde Bucal. (2010)	Quantitativa discreta	Qualquer ano de estudo	Questionário
Educação	Educação máxima obtida de acordo com a síntese dos indicadores sociais do Instituto Brasileiro de Geografia e Estatística (IBGE. 2017)	Qualitativa nominal	1. Sem educação 2. Ensino fundamental incompleto 3. Ensino fundamental completo 4. Ensino Médio incompleto 5. Ensino Médio completo 6. Ensino superior incompleto 7. Ensino superior completo	Questionário
Renda mensal em reais	Faixa de Renda (em reais) de acordo com a Pesquisa Nacional de Saúde Bucal. (2010)	Qualitativa ordinal	1. Até 3 salários mínimos 2. Até 3 a 5 salários mínimos	Questionário

			3. mais que 5 salários mínimos	
Instrumento de Medidas Periodontais Auto-Relatadas				
Consumo de álcool	Consumir bebida alcoólica frequentemente ou anteriormente nos últimos 3 meses	Qualitativa nominal	1. Sim 2. Não	Questionário
Fumante	Você fuma ou você já fumou?	Qualitativa nominal	1. Sim 2. Não	Questionário
Número de cigarros ao dia	Quantos cigarros ao dia?_____	Quantitativa discreta	Qualquer número de cigarros	Questionário
Tempo de ser fumante	Há quanto tempo você fuma?	Quantitativa contínua	Qualquer número segundo o tempo em anos	Questionário
Tempo que parou de fumar	Se ex-fumante, parou a quanto tempo?	Quantitativa contínua	Qualquer número segundo o tempo em anos	Questionário
Diabetes	Você tem diabetes?	Qualitativa nominal	1. Sim 2. Não	Questionário
Fio dental	Você faz uso do fio ou fita dental?	Qualitativa nominal	1. Sim 2. Não	Questionário
Frequência de fio dental	Você usa fio dental, qual a frequência?	Qualitativa ordinal	1. 1 x por semana 2. Diariamente 3. Dia sim, dia não 4. Outros	Questionário
Frequência de escova dental	Com que frequência você geralmente escova os dentes?	Qualitativa ordinal	1. 1 x ao dia 2. 2 x ao dia 3. 3 ao dia ou mais	Questionário
Última visita ao dentista	Quando foi a sua última visita ao dentista para controle ou tratamento?	Qualitativa ordinal	1. Até 6 meses 2. 1 ano 3. 2-3 Anos 4. Mais que 3 anos 5. Nunca foi ao dentista	Questionário
Doença gengival	A doença gengival é um problema relativamente comum que ocorre em nossa boca. Pessoas com doença gengival devem ter sangramento ao redor dos dentes, gengivas inchadas, machucadas ou infeccionadas, que permanece por 2 semanas ou mais e não é causada por próteses removíveis parciais ou totais. Você acha que pode ter doença gengival?	Qualitativa nominal	1. Sim 2. Não	Questionário

Espaços entre dentes	Você notou nos últimos anos que seus dentes anteriores se projetaram para frente ou que surgiram espaços entre seus dentes da frente?	Qualitativa nominal	1. Sim 2. Não	Questionário
Dente bambo	Você já teve algum dente que se tornou bambo na boca por si só, sem nenhum trauma ou injúria?	Qualitativa nominal	1. Sim 2. Não	Questionário
Dente permanente perdido sozinho	Você já teve algum dente permanente que foi perdido sozinho, sem que houvesse nenhum traumatismo e sem ter ido ao dentista para fazer extração?	Qualitativa nominal	1. Sim 2. Não	Questionário
Dentes naturais em boca	Consideramos como dentes naturais, aqueles que ainda apresentam raízes dentro do osso, mesmo que estes dentes possuam, pinos, obturações, coroas, ‘‘pivôs’’, blocos metálicos ou sejam apoio de pontes fixas. Faça uma análise cuidadosa em sua boca e responda: quantos dentes naturais você possui? (caso possua próteses removíveis como “rôte” ou “dentadura” retire-as da boca antes de contar)	Quantitativa discreta	Qualquer quantidade de dentes	Questionário
Saúde dos dentes e gengivas	De um modo geral, como você poderia classificar a saúde de seus dentes e gengivas?	Qualitativa ordinal	1. Excelente 2. Muito boa 3. Boa 4. Ruim 5. Muito ruim	Questionário
Raspagem ou alisamento radicular	Você já fez raspagem ou alisamento radicular, algumas vezes chamado de limpeza profunda ou curetagem gengival?	Qualitativa nominal	1. Sim 2. Não	Questionário
Cirurgia das gengivas	Você já se submeteu a alguma cirurgia para limpar por baixo de suas gengivas?	Qualitativa nominal	1. Sim 2. Não	Questionário

Perda óssea	Algum dentista já lhe disse que você teve perda óssea ao redor dos dentes?	Qualitativa nominal	1. Sim 2. Não	Questionário
Avaliação normativa dos agravos bucais				
Índice CPO-D: dentes cariados, perdidos, obturados	É obtido a partir da soma dos dentes permanentes cariados, perdidos e obturados, incluindo as extrações indicadas, dentre o total de indivíduos examinados	Quantitativa discreta	CPOD = Cariado + perdido + obturado	Exame clínico
Uso de prótese	Uso de prótese dentária superior ou inferior	Qualitativa nominal	1. Superior 2. Inferior 3. Não usa	Exame clínico
Tipo de prótese	Tipo de prótese dentária de acordo com o Manual OMS, Pesquisas de saúde bucal (2013) e o Pesquisa Nacional de Saúde Bucal. (2010)	Qualitativa nominal	0. Não usa 1. Uma prótese fixa 2. Mais de que uma prótese fixa 3. prótese parcial removível 4. Uma ou mais prótese fixa e uma ou mais prótese removíveis 5. Prótese dentária total	Exame clínico
Necessidade de Prótese	Necessidade de prótese dentária de acordo com a Pesquisa Nacional de Saúde Bucal (2010).	Qualitativa nominal	0. Não necessita prótese 1. Necessita uma prótese, fixa ou removível para substituição de um elemento 2. Necessita uma prótese, fixa ou removível para substituição de mais de um elemento 3. Necessita uma combinação de próteses fixas e/ou removíveis para substituição de um e/ou mais de um elemento 4. Necessita prótese total	Exame clínico

Fonte: Elaboração própria (DE OLIVEIRA; NADANOVSKY, 2005; CYRINO *et al.*, 2011; ORGANIZATION, 2013).

4.2.6 Análise estatística

Foi realizado um estudo piloto antes do trabalho de campo com dez pacientes que não entraram na amostra total. Observamos o nível de consistência por uma

calibração intraexaminador, comparando o observador consigo mesmo para estudar o grau de concordância de suas decisões, e por meio do coeficiente Kappa de Cohen, que é uma estatística que relaciona a concordância que os observadores exibem, além do acaso, com a concordância potencial também além do acaso. O Kappa foi acima de 0,60, considerado adequado.

Para realizar a análise estatística, uma análise univariada foi realizada para estimar as medidas de tendência central e dispersão, as proporções foram dadas com seus IC95% e as frequências estabelecidas. Com esta análise, a população estudada foi descrita.

As respostas do OHIP-14 foram tomadas como nunca (0), raramente (1), às vezes (2), repetidamente (3) e sempre. Houve uma contagem individual dos pontos obtidos pelas respostas, que, por método aditivo, podem dar um valor entre 0 e 56. Para estas respostas, um modelo de regressão binomial negativa foi utilizado para estimar as razões de taxas não ajustadas e ajustadas (RR) e correspondentes intervalos de confiança de 95%. Foram desenvolvidos modelos de regressão binomial negativa não ajustados para estimar o RR não ajustado (IC95%) e os valores de *p* para cada uma das 35 covariáveis. Nessa primeira etapa, qualquer covariável com valor de *p* inferior a 0,25 foi uma candidata a ser testada no modelo final de regressão binomial negativa ajustado. O interesse se concentrou nos efeitos independentes de cada covariável, todas as variáveis potenciais foram incluídas no modelo não ajustado, que incluiu idade, sexo, cor da pele auto relatada, lugar onde mora, fumante, uso de fio dental, doença gengival, espaços entre dentes, dente bambo, saúde dos dentes e gengiva, raspagem ou alisamento radicular, cirurgia das gengivas, perda óssea, número de dentes naturais em boca, dentes cariados, perdidos e obturados, extração indicada, uso de prótese inferior e necessidade de prótese. Apenas as covariáveis com valor de *p* menor que 0,05 permaneceram no modelo final. Para a avaliação da adequação do ajuste do modelo final, foi indicada a razão entre o desvio residual e o grau de liberdade e o teste do qui-quadrado dos resultados do desvio residual (HOSMER; LEMESHOW; STURDIVANT, 2013; LONG, 1997)

4.2.7 Considerações éticas

Este estudo foi apresentado e aceito pelo Comitê de Ética em Pesquisa da UFMG e o parecer da Diretoria de Ensino, Pesquisa e Extensão do HC-UFMG. Nesta

pesquisa, nenhuma intervenção intencional ou modificação das variáveis biológicas, fisiológicas ou sociais dos indivíduos participantes foi realizada.

Uma gestão da informação foi realizada tendo em conta a confidencialidade dos dados, cada paciente foi explicado em termos simples e comuns o que foi feito, os fins para os quais a pesquisa foi realizada, o tempo que levaria a participação, os possíveis riscos (mínimo) e benefícios, a fim de compreender, aceitar e dar seu consentimento livre e esclarecido (Apêndice B). Somente os indivíduos que desejaram participar foram incluídos e poderiam retirar-se do estudo sempre que desejaram, sem qualquer consequência ou inconveniência.

5 ARTIGOS

5.1 Artigo 1

Johana Alejandra Moreno-Drada, Lucas Guimarães Abreu, Maria Auxiliadora Parreiras Martins, Isabela Almeida Pordeus, Mauro Henrique Nogueira Guimarães de Abreu. Effectiveness of hemostatic protocols for the prevention of bleeding during oral procedures in anticoagulated individuals: a systematic review protocol. JBI Evid Synth 2020; 18(0):1–8. doi: 10.11124/JBISRIR-D-19-00342. Artigo publicado na revista JBI Evidence Synthesis anteriormente denominada JBI Database of Systematic Reviews and Implementation Reports. Cite Score 0.42 (2019) Q2 (Nursing) and Q3 (Medicine) no Scimago Journal & Country Rank, e Qualis Capes B2 para Enfermagem e B4 para Medicina.

SYSTEMATIC REVIEW PROTOCOL

Effectiveness of hemostatic protocols for the prevention of bleeding during oral procedures among individuals receiving anticoagulation therapy: a systematic review protocol

Johana Alejandra Moreno-Drada[1] • Lucas Guimarães Abreu[2] • Maria Auxiliadora Parreiras Martins[3] • Isabela Almeida Pordeus[2] • Mauro Henrique Nogueira Guimarães de Abreu[1]

[1]Department of Community and Preventive Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [2]Department of Pediatric Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, and [3]Department of Pharmaceutical Products, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

ABSTRACT

Objective: The objective of this review is to determine the effectiveness of hemostatic protocols for the prevention of bleeding during dental procedures among individuals receiving oral anticoagulation therapy.

Introduction: Dental procedures may increase the chance of bleeding in individuals receiving oral anticoagulation therapy. The literature suggests different hemostatic protocols for the prevention of bleeding in these individuals but offers no consensus regarding their effectiveness.

Inclusion criteria: Randomized controlled clinical trials comparing the effectiveness of different hemostatic protocols for the prevention of bleeding during oral procedures among individuals 18 years or older receiving oral anticoagulation therapy will be included.

Methods: Computerized searches will be conducted in seven electronic databases. Gray literature and searches in the reference lists of the included articles will also be screened. Two independent reviewers will assess titles/abstracts for potential inclusion against the eligibility criteria. References that meet the eligibility criteria will be included without restriction on the language or date of publication. Assessment of the methodological quality of the included articles and data extraction will be performed. Statistical heterogeneity of meta-analysis will be assessed. In the event of high statistical heterogeneity, sensitivity analysis will be performed. Subgroup analysis will be planned. The certainty of the evidence will be evaluated with the Grading of Recommendations, Assessment, Development and Evaluation.

Systematic review registration number: PROSPERO CRD42019136744

Keywords anticoagulants; hemorrhage; hemostatics; oral surgical procedures

JBI Evid Synth 2020; 18(11):2409–2415.

Introduction

Oral anticoagulants are used to prevent and treat thromboembolic events. Some dental procedures may result in a soft- or hard-tissue injury with consequent bleeding,[1] in particular in individuals using anticoagulants.[1-3]

Correspondence: Johana Alejandra Moreno-Drada, joalmodra@hotmail.com

The authors declare no conflict of interest.

DOI: 10.11124/JBISRIR-D-19-00342

Atrial fibrillation and other diseases require that individuals receive oral anticoagulant therapy (OAT) to reduce the risk of stroke, morbidity, and mortality.[4-7] A recent study from the Valencia region of Spain demonstrated that the percentage of individuals aged 18 years or older receiving OAT is 1.3%.[6] The prevalence increases progressively with age, reaching 6.9% among individuals aged 80 years or older.[6]

Vitamin K antagonists (VKA) are the most commonly used oral anticoagulants. The use of VKA reduces stroke rates by 30% in high-risk

individuals.[8] Warfarin is the most commonly used medication among VKAs and has a long half-life (48 hours).[4,5,9] Therefore, the pharmacological action of this anticoagulant after discontinuation of therapy may last between two and five days.[4]

The efficacy and safety of these medications depend on the maintenance of the patient within the therapeutic value of the international normalized ratio (INR), which must be compatible with the patient's pathology. In an individual who does not receive OAT, the INR usually has a value of 1.0, while among those who receive OAT, the value ranges between 2.0 and 3.0.[6,9]

Alternatively, the new oral anticoagulants (NOACs), such as dabigatran (a thrombin inhibitor), as well as rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors), have been used.[10] New oral anticoagulants have a short onset of action and achieve their maximum plasma level between one and four hours. Also, they present a short half-life ranging from five to 17 hours.[11,12] Because NOACs are short-lived, some authors have stated that these medications could be discontinued for one or two days.[12] However, other authors have stated that clinicians are reluctant to discontinue these medications; therefore, an assertive protocol for the management of individuals undergoing therapy with NOACs during tooth extractions remains uncertain.[11,12] In a retrospective study with individuals who had undergone tooth extractions without discontinuation of NOAC treatment, a significant increase in postoperative bleeding was observed.[11]

More recently, the literature has reported that the use of OAT should be reduced or even suspended before tooth extractions.[13] The literature reports that OAT could be replaced with heparin (low molecular weight heparin has smaller molecules, making it less cell-bound). The OAT could also be continued with emphasis on local hemostasis methods, such as the use of adjuvants and regulators[1,2]; alternatively, the OAT could be continued without changes in its regimen and without local hemostasis, taking into consideration INR values.[2]

The critical question is whether to continue, modify, or discontinue OAT before any dental treatment. The suspension or reduction of anticoagulant doses before dental procedures may expose these individuals to the risk of thromboembolism.[14] In contrast, maintenance of the OAT increases the risk of bleeding during or after the procedure.[2,15]

Results from other reports show that dental procedures may be performed if the INR values are within the acceptable therapeutic range, which is below 4.0.[16] Conversely, some authors have suggested that these procedures are safe in individuals receiving anticoagulation therapy whose INR values range between 3.5 and 4.2, since effective local hemostatic measurements are provided.[16] A meta-analysis on individuals treated with warfarin showed that the risk of bleeding increased for individuals with an INR greater than 3.0, but the authors of another study reported that even INR values up to 5.5 are acceptable.[17] In these cases, alternative protocols to avoid difficulties in controlling bleeding are highly recommended.[16,18,19]

Different authors confirm that tooth extraction in patients receiving OAT may be performed safely without changing the regimen if local hemostatic measures are used.[14,20] Among the hemostatic agents used to control bleeding in individuals receiving OAT, the literature has highlighted oxidized cellulose, resorbable gelatin sponges, collagen sponges, fibrin glue, cyanoacrylate glue, platelet-rich plasma gel, calcium alginate, and topical thrombin.[17,19,21] Local interventions, such as sutures, sealants, adhesives, ligating clips, vasoconstrictor agents, or a combination of these measures, have also been used to control bleeding.[21] Hemostatic interventions also include antifibrinolytic agents. The importance of antifibrinolytic mouthwash solutions in the prevention of post-extraction bleeding has been observed in several articles.[22-24]

Epsilon-aminocaproic acid and tranexamic acid (TXA) are the most commonly used antifibrinolytic agents. Tranexamic acid and epsilon-aminocaproic acid work by blocking the interaction of plasminogen with fibrin, precluding the degradation of the fibrin clot.[23,24] Antifibrinolytic agents are used to mitigate bleeding in surgical procedures because they stabilize and inhibit the breakdown of blood clots.[23]

Systematic reviews on the effectiveness of local hemostatic protocols for the prevention of bleeding in individuals receiving OAT who underwent tooth extraction have been reported in the literature, but no meta-analysis with pooled data has been found.[25] The multiple interventions, heterogeneity of the studies, and the quality of the documents make quantitative analysis complex. Moreover, the prevention of bleeding in individuals receiving OAT undergoing other dental procedures, such as

periodontal procedures or endodontic surgery, has been poorly documented.[21,25] Different systematic reviews and meta-analyses have assessed VKAs and warfarin,[25,26] but there is a shortage of information concerning NOACs. Recently, a systematic review and meta-analysis was carried out with studies assessing individuals receiving OAT with both VKAs and NOACs. However, only TXA and epsilon-aminocaproic acid were evaluated, and the effectiveness of TXA was demonstrated compared to placebo in patients receiving VKAs, but no results are available for individuals receiving NOACs.[24] The results of the systematic reviews reported are diverse; one of them indicates greater effectiveness of TXA,[25] but the other suggests greater effectiveness of Histoacryl glue.[26] Therefore, this systematic review aims to compare the effectiveness of different hemostatic protocols for the prevention of bleeding during oral procedures among individuals receiving OAT (VKAs or NOACs).

Review question

What is the effectiveness of hemostatic protocols for the prevention of bleeding during oral procedures among individuals receiving anticoagulation therapy?

Inclusion criteria

Participants

This systematic review will consider studies with participants 18 years of age or older who receive OAT such as VKA and NOAC, and who need oral procedures including i) dental procedures, such as dental extractions, periodontal surgeries, or endodontic surgeries; ii) soft-tissue surgery (biopsies); or iii) procedures on bone tissues, such as alveolar bone flange surgeries. Articles evaluating extraoral procedures will be excluded.

Interventions

Studies in which the effectiveness of hemostatic protocols for the prevention of bleeding, such as TXA, epsilon or local antifibrinolytic solutions, oxidized cellulose, gel foam, resorbable gelatin sponges, collagen sponges or fleeces, fibrin glue, cyanoacrylate glue, platelet-rich plasma gel, topical thrombin, calcium alginate, and mechanical means such as suture, ligating clips, gauze pressure, and vasoconstrictor agents will be evaluated. Studies with insufficient information to determine the effectiveness of the hemostatic protocol assessed will be excluded.

Comparators

The comparisons presented in the review can be i) patients with OAT and hemostatic intervention versus patients with OAT and without hemostatic intervention or gauze pressure; ii) patients with OAT and hemostatic intervention versus patients with OAT and placebo; iii) patients with OAT and hemostatic intervention versus patients with OAT and another type of hemostatic intervention.

Outcomes

This systematic review will consider studies in which the effectiveness in preventing intraoperative and postoperative bleeding was evaluated as a primary outcome. The secondary outcomes to be assessed in this systematic review will be the adverse effects of hemostatic protocols and the type of anticoagulant therapy to which participants had been submitted.

Types of studies

Randomized controlled clinical trials will be included without restriction on the language or date of publication. Meeting abstracts, literature reviews, expert opinions, and editorials will be excluded.

Methods

This systematic review will be conducted in accordance with the JBI methodology for systematic reviews of effectiveness.[27] The protocol was registered in PROSPERO: CRD42019136744.

Search strategy

A preliminary search was conducted in PubMed. Text words in the titles/abstracts and keywords of the references retrieved will be used to tailor the search strategy for each electronic database. The search strategy for PubMed is displayed in Appendix I.

Computerized searches will be performed in the following electronic databases: MEDLINE (PubMed, Ovid), Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS (Latin American and Caribbean Literature in Health Sciences), and Scopus. Unpublished studies will be searched in the ProQuest Dissertations and Theses database and in ClinicalTrials.gov. Searches in Google Scholar and OpenGrey limited to the first 100 hits will also be conducted. The reference lists of the included articles will be screened to identify references that might be missed during the searches in the electronic databases.

Study selection

The references retrieved in the searches will be uploaded to EndNote Basic (Clarivate Analytics, PA, USA), and duplicates removed. To select the studies, two independent review authors will assess the titles/abstracts of the references retrieved. References whose titles/abstracts meet the eligibility criteria will be included. For the references whose titles/abstracts contain insufficient information for a decision on inclusion or exclusion, the full texts will be retrieved. The same two review authors will evaluate the full texts. References whose full texts meet the eligibility criteria will also be included. Detailed information of the included studies will be imported to the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia). The full text of studies that do not fit the eligibility criteria will be excluded. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[28] Discrepancies between review authors during study selection will be resolved via a senior researcher.

Assessment of methodological quality

The assessment of the methodological quality of the included studies will be obtained by two review authors and discrepancies will be resolved via a senior researcher. The assessment of the methodological quality will be carried out using the JBI appraisal checklist for randomized controlled trials.[27] Each item may be awarded "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (unclear risk of bias).

All included studies will be submitted to data extraction.

Data extraction

Data of the included studies will be extracted using the standardized JBI data extraction tool.[27] Data will be extracted by two review authors and any disagreements will be resolved via a senior researcher. These two evaluators will check the data extracted twice to verify accuracy. The following data will be extracted: last name of the first authors and date of publication of the study, country where the study was conducted, number of participants, characteristics of the participants (sex and age), type of anticoagulant used by participants, hemostatic protocols evaluated, outcomes evaluated, and comparisons of the effectiveness of the hemostatic protocols evaluated. In the case of missing data, the authors of the included studies will be contacted for further information.

Data synthesis

JBI SUMARI and RevMan v5.3 (Copenhagen, The Nordic Cochrane Centre, Cochrane) will be used. Results of the meta-analysis will be provided in risk ratio for studies with dichotomous data and mean difference for studies with continuous data. Confidence intervals (95%) will also be provided. Statistical heterogeneity of the meta-analysis will also be evaluated by means of the I^2 statistic. If the meta-analysis presents high statistical heterogeneity, the random effects model will be used; if the meta-analysis presents low statistical heterogeneity, the fixed effects model will be used.[27] For meta-analysis with high statistical heterogeneity, sensitivity analysis will be performed, removing studies one by one, repeating the calculations to check for similar results and determining the possible influence of each study. A funnel plot will be generated: for meta-analysis of continuous outcomes, the assessment of funnel plot asymmetry will be performed with the Egger test; for the meta-analysis of dichotomous outcomes, the Harbord test will be employed for funnel plot asymmetry evaluation.[30] The results will be displayed as forest plots. Subgroup analyses will be planned considering the characteristics of participants (according to age and INR), methodological quality, type of interventions, and the outcome measures of the studies. If possible, the authors will perform a meta-regression analysis to compare the effects of the interventions according to the risk of bias. If necessary, the authors will develop the network meta-analysis that allows the identification of the results. A Bayesian structure will be carried out through statistical packages in Software R v3.6.2 (R Core Team). The network description, network graph, evaluation of the convergence, assessment of inconsistencies, and results of the network meta-analysis will be delivered. If data pooling is unfeasible, a narrative synthesis presenting data in tables and figures will be carried out instead.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach

for grading the certainty of evidence will be followed and a Summary of Findings will be created using GRADEpro (McMaster University, ON, Canada).[29] For the outcomes assessed, GRADE evaluates the number of studies incorporated into the analysis, studies' design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. For risk of bias, inconsistency, indirectness, imprecision, and publication bias, the certainty of the evidence may be downgraded one or two levels. Based on this evaluation, the certainty of the evidence for each outcome may be very low, low, moderate, or high.

Funding

This study was supported by the Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior (CAPES). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Ripolles-De Ramon J, Muñoz-Corcuera M, Bravo-Llatas C, Bascones-Martinez A. Aplicacion de un gel de Acido tranexamico en pacientes tratados con anticoagulantes orales [Tranexamic acid gel in patients treated with oral anticoagulants]. Med Clin (Barc) 2014;143(11):484–8; Spanish.
2. Bajkin BV, Popovic SL, Selakovic SDJJ. Randomized, prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. J Oral Maxillofac Surg 2009;67(5):990–5.
3. Jiménez Y, Poveda R, Gavaldá C, Margaix M, Sarrión G. An update on the management of anticoagulated patients programmed for dental extractions and surgery. Med Oral Patol Oral Cir Bucal 2008;1313(33):176–9.
4. Kämmerer PW, Frerich B, Liese J, Schiegnitz E, Al-Nawas B. Oral surgery during therapy with anticoagulants—a systematic review. Clin Oral Investig 2015;19(2):171–80.
5. Eichhorn W, Burkert J, Vorwig O, Blessmann M, Cachovan G, Zeuch J, *et al.* Bleeding incidence after oral surgery with continued oral anticoagulation. Clin Oral Investig 2012;16(5):1371–6.
6. Boned-ombuena A, Pérez-panadés J, López-maside A. Prevalencia de la anticoagulación oral y calidad de su seguimiento en el ámbito de la atención primaria: estudio de la Red Centinela Sanitaria de la Comunitat Valenciana [Prevalence of oral anticoagulation and quality of its management in primary healthcare: a study by the Health Sentinel Network of the Region of Valencia (Spain)]. Atención Primaria 2017;49(9):534–48; Spanish.
7. Rocha AL, Souza AF, Martins MAP, Fraga MG, Travassos DV, Oliveira ACB, *et al.* Oral surgery in patients under antithrombotic therapy: perioperative bleeding as a significant risk factor for postoperative hemorrhage. Blood Coagul Fibrinolysis 2018;29(1):97–103.
8. Bartholomay E, Polli I, Borges A, Kalil C, Arroque A, Kohler I, *et al.* Prevalence of oral anticoagulation in atrial fibrillation. Clinics 2014;69(9):615–20.
9. Almiñana-Pastor PJ, Segarra-Vidal M, López-Roldán A, Alpiste-Illueca FM. A controlled clinical study of periodontal health in anticoagulated patients: assessment of bleeding on probing. J Clin Exp Dent 2017;9(12):e1431–8.
10. Serrano-Sánchez V, Ripollés-de-Ramón J, Collado-Yurrita L, Vaello-Checa I, Colmenero-Ruiz C, Helm A, *et al.* New horizons in anticoagulation: direct oral anticoagulants and their implications in oral surgery. Med Oral Patol Oral Cir Bucal 2017;22(5):e601–8.
11. Hanken H, Gröbe A, Heiland M, Smeets R, Kluwe L, Wikner J, *et al.* Postoperative bleeding risk for oral surgery under continued rivaroxaban anticoagulant therapy. Clin Oral Investig 2016;20(6):1279–82.
12. Miclotte I, Vanhaverbeke M, Agbaje JO, Legrand P, Vanassche T, Verhamme P, *et al.* Pragmatic approach to manage new oral anticoagulants in patients undergoing dental extractions: a prospective case-control study. Clin Oral Investig 2017;21(7):2183–8.
13. Mulligan R, Weitzel KG. Pretreatment management of the patient receiving anticoagulant drugs. J Am Dent Assoc 1988;117(3):479–83.
14. Bajkin BV, Selakovic SD, Mirkovic SM, Sarcev IN, Tadic AJ, Milekic BR. Comparison of efficacy of local hemostatic modalities in anticoagulated patients undergoing tooth extractions. Vojnosanit Pregl 2014;71(12):1097–101.
15. Dudek D, Marchionni S, Gabriele M, Iurlaro A, Helewski K, Toti P, *et al.* Bleeding rate after tooth extraction in patients under oral anticoagulant therapy. J Craniofac Surg 2016;27(5):1228–33.
16. Branislav V, Sanja B, Bojana R, Biljana A. Risk factors for bleeding after oral surgery in patients who continued using oral anticoagulant therapy. JADA 2015;146(6):375–81.
17. Febbo A, Cheng A, Stein B, Goss A, Sambrook P. Postoperative bleeding following dental extractions in patients anticoagulated with warfarin. J Oral Maxillofac Surg 2016;74(8):1518–23.
18. Carter G, Goss A, Lloyd J, Tocchetti R. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. J Oral Maxillofac Surg 2003;61(12):1432–5.
19. Pippi R, Santoro M, Cafolla A. The effectiveness of a new method using an extra-alveolar hemostatic agent after dental extractions in older patients on oral anticoagulation

treatment: an intrapatient study. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120(1):15–21.
20. Ferrieri GB, Castiglioni S, Carmagnola D, Cargnel M, Strohmenger L, Abati S. Oral surgery in patients on anticoagulant treatment without therapy interruption. J Oral Maxillofac Surg 2007;65(6):1149–54.
21. Nagraj SK, Prashanti E, Aggarwal H, Lingappa A, Muthu MS, Krishanappa SKK, *et al*. Interventions for treating post-extraction bleeding. Cochrane Database Syst Rev 2018;(3):CD011930.
22. Carter G, Goss A. Tranexamic acid mouthwash–a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int J Oral Maxillofac Surg 2003;32(5):504–7.
23. de Vasconcellos SJ, de A, de Santana Santos T, Reinheimer DM, Faria-e-Silva AL, de Melo M, de FB, Martins-Filho PRS. Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery: a systematic review and meta-analysis of randomized clinical trials. J Craniomaxillofac Surg 2017;45(1):20–6.
24. Engelen ET, Schutgens RE, Mauser-bunschoten EP, Van Es RJ, Van Galen KP. Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions. Cochrane Database Syst Rev 2018;(7):CD012293.
25. Ockerman A, Miclotte I, Vanhaverbeke M, Verhamme P, Poortmans L-L, Vanassche T, *et al*. Local haemostatic measures after tooth removal in patients on antithrombotic therapy: a systematic review. Clin Oral Investig 2019;23(4):1695–708.
26. Weltman NJ, Al-Attar Y, Cheung J, Duncan DPB, Katchky A, Azarpazhooh A, *et al*. Management of dental extractions in patients taking warfarin as anticoagulant treatment: a systematic review. J Can Dent Assoc 2015;81:f20.
27. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z, editors. JBI Reviewer's Manual [Internet]. Adelaide: JBI, 2017 [cited 2019 Sep 5]. Available from: https://reviewersmanual.joannabriggs.org/.
28. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Chinese edition). J Chinese Integr Med 2009;7(9):889–96.
29. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924–6.
30. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration. 2011 [cited 2019 Sep 5]. Available from: https://training.cochrane.org/handbook/current.

Appendix I: Search strategy

MEDLINE (PubMed)
Search conducted October 2019.

Search	Query	Records retrieved
#1	6-aminohexanoic acid [tw] OR 6 aminohexanoic acid [Mesh] OR 6 aminocaproic acid [tw] OR capramol [tw] OR caproamin [tw] OR epsamon [tw] OR epsikapron [tw] OR hemocaprol [tw] OR amicar [tw] OR AMCHA [tw] OR trans-4-(Aminomethyl)cyclohexane-carboxylic Acid [tw] OR t-AMCHA [tw] OR Tranexamic Acid [Mesh] OR AMCA [tw] OR anvitoff [tw] OR cyklokapron [tw] OR ''ugurol'' [tw] OR KABI 2161 [tw] OR ''transamin'' [tw] OR ''exacyl'' [tw] OR oxidized Cellulose [tw] OR Cellulose, Oxidized [Mesh] OR oxycellulose [tw] OR cellulosic Acid [tw] OR absorbable Cellulose [tw] OR carboxycellulose [tw] OR oxycel [tw] OR absorbable gelatin sponge [tw] OR absorbable gelatin sponges [tw] OR Gelatin Sponge, Absorbable [Mesh] OR gelfoam [tw] OR gelaspon [tw] OR absorbable collagen sponge [tw] OR fibrin glue [tw] OR Fibrin Tissue Adhesive [Mesh] OR fibrin adhesive [tw] OR fibrin sealant [tw] OR fibrin seal [tw] OR tisseel [tw] OR ''tissel'' [tw] OR tissucol [tw] OR beriplast [tw] OR fibrin Seal [tw] OR cyanoacrylate glue [tw] OR Cyanoacrylates [Mesh] OR ethyl cyanoacrylate [tw] OR ethyl-2-cyanoacrylate [tw] OR ethyl alpha-cyanoacrylate [tw] OR epiglue [tw] OR ''krazy glue'' [tw] OR ''cyacrine'' [tw] OR cyano-veneer [tw] OR Platelet-Rich Plasma [Mesh] OR topical thrombin [tw] OR Thrombin [Mesh] OR suture [tw] OR Sutures [Mesh] OR surgical staple [tw] OR stitch [tw] OR gauze pressure [tw] OR vasoconstrictor [tw] OR Vasoconstrictor Agents [Mesh]	530,104
#2	oral bleeding [tw] OR Oral Hemorrhage [Mesh] OR oral blood [tw] OR Hemostasis [Mesh] OR oral surgery [tw] OR Surgery, Oral [Mesh] OR oral hemorrhage [tw]	525,067
#3	Anticoagulants [Mesh] OR ''factor xa inhibitor'' [tw] OR ''factor xa inhibitors'' [Mesh] OR Rivaroxaban [Mesh] OR xarelto [tw] OR apixaban [tw] OR eliquis [tw] OR edoxaban [tw] OR lixiana [tw] OR savaysa [tw] OR betrixaban [tw] OR bevyxxa [tw] OR ''thrombin inhibitor'' [tw] OR ''thrombin inhibitors'' [tw] OR Antithrombins [Mesh] OR Dabigatran [Mesh] OR pradaxa [tw] OR melagatran [tw] OR ximelagatran [tw] OR exanta [tw] OR Heparin [Mesh] OR coumarin [tw] OR Coumarins [Mesh] OR Warfarin [Mesh] OR apo-warfarin [tw] OR aldocumar [tw] OR coumadin [tw] OR ''marevan'' [tw] OR warfarin potassium [tw] OR warfarin sodium [tw] OR ''coumadine'' [tw]	39,683
#4	randomized controlled trial [Mesh] OR clinical trial [Mesh]	1,171,406
#5	#1 AND #2 AND #3 AND #4	315

5.2 Artigo 2

Johana Alejandra Moreno-Drada, Lucas Guimarães Abreu, Patrícia Azevedo Lino, Maria Auxiliadora Parreiras Martins, Isabela Almeida Pordeus, Mauro Henrique Nogueira Guimarães de Abreu. Effectiveness of local hemostatic to prevent bleeding in dental patients on anticoagulation. A systematic review and network meta-analysis.

Artigo aceito na revista Journal of Cranio-Maxillofacial Surgery. Cite Score 0.94 (2019) Q1 (Dentistry) no Scimago Journal & Country Rank, e Qualis Capes A2 para Odontologia.

Journal of Cranio-Maxillo-Facial Surgery

EFFECTIVENESS OF LOCAL HEMOSTATIC TO PREVENT BLEEDING IN DENTAL PATIENTS ON ANTICOAGULATION: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

--Manuscript Draft--

Manuscript Number:	JCMS-D-21-00043R1
Article Type:	Review article
Keywords:	Anticoagulants; Warfarin; Hemorrhage; Hemostatics; Oral Surgical Procedures
Corresponding Author:	Johana Alejandra Moreno Drada Universidade Federal de Minas Gerais Belo Horizonte, MG BRAZIL
First Author:	Johana Alejandra Moreno-Drada
Order of Authors:	Johana Alejandra Moreno-Drada
	Lucas Guimarães Abreu
	Patrícia Azevedo Lino
	Maria Auxiliadora Parreiras Martins
	Isabela Almeida Pordeus
	Mauro Henrique Nogueira Guimarães de Abreu
Abstract:	This study aimed to determine the effectiveness of hemostatic protocols to prevent bleeding in dental procedures among individuals undergoing oral anticoagulation therapy. A systematic review and network meta-analysis were accomplished. Searches of literature and grey literature were performed in different electronic databases. Clinical trials were considered as part of the inclusion criteria. Data extraction and assessment of the risk of bias of the included articles were performed. Assessment of the certainty of evidence was also performed. As results we find that the N-butyl-2-cyanoacrylate [RR -35.00 (95% CI - 107.12, -5.78)], CaS [RR -5.62 (95% CI -11.41, -1.03)], and TXA [RR -3.46 (95% CI -7.63, -0.77)] showed beneficial effects compared to placebo. However, only TXA presented beneficial effects with moderate certainty evidence. N-butyl-2-cyanoacrylate and CaS presented very low certainty evidence. In the comparisons between the hemostatic agents, no differences were observed. For the mean bleeding time, no significant difference in the comparisons was observed as well. Concluding, bleeding events in individuals on oral anticoagulation decreased with the use of TXA compared to placebo. N-butyl-2-cyanoacrylate and CaS were also superior to placebo, but the certainty of evidence was low. For the mean bleeding time, no significant difference in hemostatic agents was observed.
Response to Reviewers:	Comments: Section editor: The authors have to follow the guidelines for authors in every detail. The authors should also follow the PRISMA guidelines in every detail (for example it seems that PICOS is missing). If the authors are not willing to perform a comprehensive revision, they should not resubmit the manuscript. Author response: According to Journal of Cranio-Maxillofacial Surgery, we have provided numbers for the sections and subsections of the manuscript. The manuscript conforms with the PRISMA statement. In the “Materials and Methods” section, the follow subitems have been provided. Protocol and registration Eligibility criteria Information sources Search Study selection Data extraction Data items Risk of bias in individual studies

	Summary measures Synthesis of results Risk of bias across studies Additional analysis (sensitivity analysis) Grading of recommendations assessment development and evaluation (GRADE) In the “Results” section, the following subitems have been provided. Study selection Characteristics of the included studies Risk of bias within studies Synthesis of results and risk of bias across studies Sensitivity analysis Grading of recommendations assessment development and evaluation (GRADE) The PRISMA checklist has been provided as Tab A.1. We have highlighted the PICO strategy used in the article in the “Eligibility criteria” subsection of the “Materials and Methods” section. We have applied the guidelines for authors. We make minor corrections according to those guidelines and performed modifications in the abstract and references. The abstract became unstructured, and the references were organized alphabetically, as indicated by the journal.

Title Page (with Author Details)

EFFECTIVENESS OF LOCAL HEMOSTATIC TO PREVENT BLEEDING IN DENTAL PATIENTS ON ANTICOAGULATION: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Authors

Johana Alejandra Moreno-Drada[1]. – 1. School of Dentistry, Universidade Federal de Minas Gerais. Belo Horizonte, Brazil.

Corresponding author

E-mail: joalmodra@hotmail.com

Postal address: 31270-901

Lucas Guimarães Abreu[1]. 1. School of Dentistry, Universidade Federal de Minas Gerais. Belo Horizonte, Brazil

Patrícia Azevedo Lino[1]. 1. School of Dentistry, Universidade Federal de Minas Gerais. Belo Horizonte, Brazil

Maria Auxiliadora Parreiras Martins[2]. 2. Professor, Department of Pharmaceutical Products, Universidade Federal of Minas Gerais. Belo Horizonte, Brazil.

Isabela Almeida Pordeus[1]. 1. School of Dentistry, Universidade Federal de Minas Gerais. Belo Horizonte, Brazil

Mauro Henrique Nogueira Guimarães de Abreu[1]. 1. School of Dentistry, Universidade Federal de Minas Gerais. Belo Horizonte, Brazil

1

ABSTRACT

This study aimed to determine the effectiveness of hemostatic protocols to prevent bleeding in dental procedures among individuals undergoing oral anticoagulation therapy. A systematic review and network meta-analysis were accomplished. Searches of literature and grey literature were performed in different electronic databases. Clinical trials were considered as part of the inclusion criteria. Data extraction and assessment of the risk of bias of the included articles were performed. Assessment of the certainty of evidence was also performed. As results we find that the N-butyl-2-cyanoacrylate [RR -35.00 (95% CI - 107.12, -5.78)], calcium sulfate ($CaSO_4$) [RR -5.62 (95% CI -11.41, -1.03)], and tranexamic acid (TXA) [RR -3.46 (95% CI -7.63, -0.77)] showed beneficial effects compared to placebo. However, only TXA presented beneficial effects with moderate certainty evidence. N-butyl-2-cyanoacrylate and $CaSO_4$ presented very low certainty evidence. In the comparisons between the hemostatic agents, no differences were observed. For the mean bleeding time, no significant difference in the comparisons was observed as well. Concluding, bleeding events in individuals on oral anticoagulation decreased with the use of TXA compared to placebo. N-butyl-2-cyanoacrylate and $CaSO_4$ were also superior to placebo, but the certainty of evidence was low. For the mean bleeding time, no significant difference in hemostatic agents was observed.

Keywords: Anticoagulants; Warfarin; Hemorrhage; Hemostatics; Oral Surgical Procedures.

2

1. INTRODUCTION

Some dental procedures may result in soft or hard tissue injury with consequent bleeding *(Ripollés-de Ramón et al*., 2014), in particular in individuals using anticoagulants *(Jiménez et al.*, 2008; *Bajkin, Popovic, & Selakovic*, 2009; *Ripollés-de Ramón et al.*, 2014). Oral anticoagulants are indicated for primary and secondary thromboprophylaxis *(Ripollés-de Ramón et al*., 2014). Atrial fibrillation is an example of pro-thrombotic disease that require the use of oral anticoagulation (OAT) to reduce the risk of stroke, related morbidity, and mortality (*Kämmerer et al.*, 2015; *Rocha et al.*, 2018; *Chan et al*., 2019). Coumarin derivatives (*Bartholomay et al*., 2014) and direct oral anticoagulants (DOACs) are classes of oral anticoagulants widely prescribed worldwide (*Serrano-Sánchez et al*., 2017; *Giustozzi et al.*, 2019). The critical question is whether to continue, modify, or discontinue OAT before any dental treatment. The suspension or reduction of the dose of the anticoagulant before dental procedures may expose the patient to increased risk of thromboembolism (*Bajkin et al*., 2014). In contrast, maintenance of OAT may increase the risk of bleeding during or after the procedure (*Bajkin et al*., 2009; *Dudek et al.*, 2016). Thus, some studies have indicated that OAT should be stopped before tooth extractions to avoid bleeding (*Mulligan & Weitzel,* 1988). However, the underlying premise that the OAT could be continued with emphasis being placed on local hemostasis protocols is also acknowledged in the literature (*Ferrieri et al*., 2007; *Bajkin et al.*, 2009, 2014; *Ripollés-de Ramón et al*., 2014).

Among the hemostatic agents used to control bleeding in individuals undergoing OAT, the literature has highlighted the oxidized cellulose, resorbable gelatin sponges, collagen sponges, fibrin glue, cyanoacrylate glue, platelet-rich plasma gel, calcium alginate, and topical thrombin (*Pippi, Santoro, & Cafolla*, 2015; *Febbo et al*., 2016; *Nagraj et al*., 2018). Local interventions, such as sutures, sealants, adhesives, ligating clips, vasoconstrictor agents, or the combination of these measures have also been used to control bleeding (*Nagraj et al.*, 2018). Hemostatic interventions also include antifibrinolytic agents, such as tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA). The importance of antifibrinolytic mouthwash solutions in the prevention of post-extraction bleeding has been observed in several studies (*G Carter & Goss*, 2003; *Engelen et al*., 2018). They

are used to mitigate bleeding in surgical procedures because they stabilize and inhibit the break-down of blood clots (*de Vasconcellos et al*., 2017).

Nevertheless, none of these hemostatic agents has been shown to be superior compared to others (*Halfpenny, Fraser, & Adlam*, 2001; *Bajkin et al.*, 2014). Due to the variety of hemostatic interventions reported in the literature, we decided to conduct a systematic review and network meta-analysis (NMA). Therefore, following the clinical question on the effectiveness of hemostatic protocols for preventing bleeding during oral procedures on anticoagulated individuals, this systematic review and NMA aimed to compare the effectiveness of different hemostatic protocols for the prevention of bleeding during oral procedures among individuals undergoing OAT.

2. MATERIALS AND METHODS

2.1. Protocol and registration

This study was performed according to the Cochrane and Joanna Briggs Institute (JBI) recommendations. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) extension statement for reporting NMAs (Table A.1) has been followed (*Moher et al*., 2009; *Hutton et al*., 2015). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42019136744.

2.2. Eligibility criteria

The search covered the existing literature from the databases' date of inception until September 2020. No restrictions on language or date of publication were imposed. The inclusion criteria follow the PICOS strategy. The participants (P) were male and female ≥18 years undergoing OAT while submitted to oral procedures. The oral procedures could be 1) dental procedures, such as dental extractions, periodontal surgeries or endodontic surgeries, 2) soft-tissue surgery (biopsies), and 3) procedures on bone tissues, such as alveolar bone surgeries. We excluded articles in which extraoral procedures had been evaluated. We also excluded studies assessing patients with hereditary blood disorders. Meeting abstracts, editorials and expert opinions were also excluded.

For the intervention (I), we evaluated studies in which the effectiveness of hemostatic for the prevention of bleeding, such as TXA, EACA, oxidized cellulose, gel foam, gelatin sponges, collagen

sponges, fibrin glue, cyanoacrylate glue, topical thrombin, calcium alginate, platelet-rich plasma (PRP), calcium sulfate ($CaSO_4$), chitosan, n-butyl-2-cyanoacrylate surgical adhesive (histoacryl), blue-violet LED or other products had been assessed. Mechanical means, such as suture, ligating clips, gauze pressure, and vasoconstrictor agents were also evaluated. We evaluated the following comparisons (C) in the selected articles: i) Patients undergoing OAT submitted to hemostatic intervention versus patients undergoing OAT submitted to gauze pressure. ii) Patients undergoing OAT submitted to hemostatic intervention versus patients undergoing OAT and placebo. iii) Patients undergoing OAT using a hemostatic intervention versus patients undergoing OAT using another type of hemostatic intervention. We excluded studies in which the effectiveness of the hemostatic protocol had not been described.

The primary outcomes (O) were the effectiveness in preventing postoperative bleeding by means of the measurement of bleeding events and the mean bleeding time. We included clinical trial studies (S)

2.3. Information sources

We searched the studies in the following electronic databases: MEDLINE via PubMed, Ovid, EMBASE, Web of Science, Cochrane Controlled Trials Register Center (CENTRAL), LILACS (Latin American and Caribbean Literature in Health Sciences), and Scopus. We explored the grey literature in the ProQuest Dissertations and Theses database and Clinicaltrials.gov. Searches in Google Scholar and OpenGrey limited to the first 200 hits were also conducted. The searches were updated in September 2020. We screened the reference list of the included articles to identify references that might have been missed during the searches in the electronic databases.

We exported the references retrieved in the searches to the software Endnote (Clarivate Analytics, Philadelphia, USA). Duplicates were removed upon identification.

2.4. Search

A search strategy was tailored for each database. The search strategy employed in the MEDLINE database via PubMed is displayed in Appendix A.

2.5. Study selection

5

Two review authors participated in the selection of the studies independently. They assessed the titles/abstracts of the references retrieved. References whose titles/abstracts met the eligibility criteria were included straight away. For the references whose titles/abstracts did not contain sufficient information for a precise decision, the full text was assessed. The eligibility criteria were applied and those references whose full texts fulfilled the eligibility criteria were also included. Detailed information of the included studies was imported to the JBI System for the Unified Management, Assessment, and Review of Information (JBI SUMARI) (Joanna Briggs Institute, Adelaide, Australia). If any divergence between review authors took place, a third author decided. The process of selection of studies is depicted in a flow diagram (Fig 1).

2.6. Data extraction

We extracted data from the included studies using the standardized JBI data extraction tool (*Tufanaru et al.*, 2017).

2.7. Data items

The following data were extracted: the last name of the first author and date of publication, country where the study had been conducted, number of participants, participants' age and sex, type of anticoagulant used, hemostatic protocols, outcomes evaluated and comparisons of the effectiveness of the hemostatic protocols evaluated. For greater accuracy, two review authors extracted data independently. Discrepancies between the two review authors were resolved by means of a discussion. If the divergence persisted, a third author decided.

2.8. Risk of bias in individual studies

The assessment of risk of bias of individual and across included studies was carried out with the Cochrane tool (*Higgins & Green*, 2011) and the Joanna Briggs Institute tool for randomized controlled trials (*Tufanaru et al*., 2017). The following items were evaluated with the Cochrane tool: random sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases (*Higgins & Green*, 2011). Graphs of risk of bias were generated for each study and all included studies. The following 13 items were assessed with the Joanna Briggs Institute tool: true randomization used for assigning participants to treatment groups, allocation to groups concealed, treatment groups similar

at the baseline, participants blind to treatment assignment, researcher who is delivering treatment blinded to treatment assignment, outcome assessors blind to treatment assignment, treatment groups treated identically other than the intervention of interest, follow-up complete and if not, differences between groups in terms of their follow-up adequately described and analyzed, participants analyzed in the groups to which they were randomized, outcome measured in the same way for treatment groups, outcomes measured in a reliable way, appropriate statistical analysis used, trial design appropriate for the topic, and any deviations from the standard RCT design accounted for in the conduct and analysis (*Tufanaru et al*., 2017). A table for the evaluation of risk of bias with the Joanna Briggs Institute tool was generated

2.9. Summary measures

For studies with dichotomous data, the relative risk was obtained. For studies with continuous data, the mean difference was retrieved though.

2.10. Synthesis of results

Data synthesis was performed. For the NMAs, we defined the nodes as the number of studies examining hemostatic interventions. We define the edges as the number of comparisons between treatments. The "fibrin" was the group to which the fibrin glue, fibrin glue, and fibrin sponge were assigned. Placebo was defined as substances that did not have an active ingredient or an expected clinical effect on bleeding outcomes. We used the JBI SUMARI and the Review Manager software [Review Manager (RevMan) - Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]. We also used the R version 3.6.2 (R Core Team) to draw the network graphics with the BUGSnet package for NMA. For each outcome, we carried out a Bayesian random effects NMA. NMA results were provided in relative risk for studies with dichotomous data and mean difference for studies with continuous data. The 95% credible intervals (CI) were also provided.

When we compared one intervention with another intervention, negative outcome measures indicated beneficial effects or a greater reduction in bleeding events (dichotomous data) or mean bleeding time (continuous data). We employed default vague priors, which allowed us to easily calculate a prior variance from the data without any user input (*van Valkenhoef et al.*, 2012; *Béliveau*

et al., 2019). For each analysis, we specified four chains with a burn-in of 50,000 iterations followed by 100,000 iterations with 10,000 adaptations (*Dias et al*., 2013; *Béliveau et al.*, 2019). Convergence was evaluated using trace plots, the leverage plots and the identification of possible outliers (*Béliveau et al.*, 2019). An alternative way to evaluate convergence was by means of the Potential Scale Reduction Factor (PRSF) value (*Harrer et al.*, 2019). In convergence, the PRSF should be gradually reduced with an increasing number of interactions and should also be below 1.05. Inconsistency was tested using the inconsistency model (or unrelated mean effects model) (*Dias et al*., 2011; *Efthimiou et al*., 2016). Comparison of each data point's posterior mean deviation between the consistency and the inconsistency model was also deployed. We provided the relative ranking of the hemostatic agents by means of the surface under the cumulative ranking curve (SUCRA) plot. A higher value of SUCRA denotes a greater probability of effectiveness of an intervention in controlling bleeding than other interventions (*Salanti, Ades, & Ioannidis*, 2011; *Béliveau et al*., 2019). The results of the NMA were reported in forest plots and in a league heat plot showing effect estimates and CI (*Higgins & Green*, 2011).

2.11. Risk of bias across studies

We evaluated the statistical heterogeneity of the NMA by means of the I statistics (*Higgins & Green*, 2011), assessing heterogeneity between/among studies within each possible pairwise comparison within the network where direct evidence had taken place. Similarly, we evaluated heterogeneity using global I statistics, considering the variable participants' age within each study's treatment arm (*Béliveau et al*., 2019).

2.12. Additional analysis

The robustness of the findings was evaluated by means of sensitivity analysis, in which clinical trials with high risk of bias were removed.

2.13. Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

The assessment of the certainty of the evidence was carried out with the GRADE for NMA. A summary of findings was created using GRADEPro GDT (McMaster University, ON, Canada). At the onset of analysis, each direct comparison had a high certainty of evidence. Thereupon the direct comparisons were scrutinized and we determined whether serious or very serious concerns of risk of

bias, imprecision, inconsistency, indirectness, and/or publication bias had taken place. Then, the indirect evidence was rated down if there were serious concerns of intransitivity. At the end, the certainty of evidence was downgraded if any imprecision or incoherence for the final NMA estimate was observed (*Guyatt et al*., 2008; *Puhan et al.*, 2014; *Brignardello-Petersen et al.*, 2018).

3. RESULTS

3.1. Study selection

We found 1,229 references across the databases. Twenty-one were selected for inclusion in the qualitative analyses and 16 were incorporated into the quantitative analyses (*Sindet-Pedersen et al.,* 1989; *Ramström et al.*, 1993; *Souto et al*., 1996; *Blinder et al*., 1999; *Halfpenny et al*., 2001; *Al-Belasy & Amer*, 2003; *G Carter & Goss*, 2003; *Glen Carter et al*., 2003; *Giuffrè et al.*, 2006; *Al-Mubarak et al.*, 2007; *Çakarer et al.*, 2013; *Bajkin et al.,* 2014; *Ripollés-de Ramón et al*., 2014; *Scarano et al.*, 2014; *Soares et al.*, 2014; *Okamoto et al*., 2014; *Pippi et al.*, 2015; *Kumar et al*., 2016; *da Silva et al*., 2018; *Queiroz et al*., 2018; *Baldoni & Lauritano*, 2019).

We excluded duplicates and articles that did not comply with the inclusion criteria. Five studies were excluded from the quantitative analysis due to the following reasons: the first study presented a measure of effect different from the other studies *(Ripollés-de Ramón et al.*, 2014). The second study did not provide outcome data (*Scarano et al*., 2014). In the third study, the unit of analysis was different; the study analyzed number of teeth with bleeding instead of number of individuals (*da Silva et al.*, 2018). The fourth presented groups of interventions not comparable to the groups of the other articles (*Giuffrè et al.*, 2006), and the fifth study compared the same hemostatic intervention at two different times; the TXA after two days and five days after tooth extraction (*G Carter & Goss*, 2003) (Fig 1).

3.2. Characteristics of included studies

In the 21 included studies, 1,237 individuals were assessed. In 16 studies (*Sindet-Pedersen et al.*, 1989; *Ramström et al.*, 1993; *Souto et al*., 1996; *Blinder et al.*, 1999; *Halfpenny et al.*, 2001; *Al-Belasy & Amer*, 2003; *G Carter & Goss*, 2003; *Glen Carter et al*., 2003; *Giuffrè et al.*, 2006; *Al-Mubarak et al*., 2007; *Bajkin et al*., 2014; *Okamoto et al.,* 2014; *Scarano et al*., 2014; *Soares et al.*,

2014; *da Silva et al.*, 2018; *Baldoni & Lauritano*, 2019), the outcome evaluated was the number of individuals with bleeding. In two studies (*Pippi et al*., 2015; *Santhosh Kumar*, 2016), the outcome evaluated was bleeding time. In two studies, both outcomes were assessed (*Çakarer et al*., 2013; *Queiroz et al*., 2018). *Ripollés-de Ramón et al.*, 2014 evaluated the clotting time. Regarding the type of procedure performed, the study of *Sindet-Pedersen et al.*, 1989 examined tooth extraction, surgically treated teeth or removal of impacted teeth, periapical surgery, and surgery for gingival hyperplasia. The study by *Ramström et al.*, 1993 evaluated tooth extraction and surgically treated teeth, while *Giuffrè et al.*, 2006 investigated tooth extraction and cystectomies. In the other studies, only surgeries for tooth extractions were reported (*Souto et al.*, 1996; *Blinder et al*., 1999; *Halfpenny et al.*, 2001; *Al-Belasy & Amer*, 2003; *G Carter & Goss,* 2003; *Glen Carter et al.*, 2003; *Al-Mubarak et al*., 2007; *Çakarer et al*., 2013; *Bajkin et al.*, 2014; *Okamoto et al.*, 2014; *Ripollés-de Ramón* et al., 2014; *Scarano et al*., 2014; *Soares et al*., 2014; *Pippi et al.*, 2015; *Kumar et al*., 2016; *da Silva et al.,* 2018; *Queiroz et al*., 2018; *Baldoni & Lauritano*, 2019).

The most used hemostatic type was TXA, followed by the gelatin sponge and fibrin hemostatic. We also found other hemostatic measures, such as EACA, chitosan, suture, n-butyl-2-cyanoacrylate surgical adhesive, PRP, $CaSO_4$, oxidized cellulose, collagen sponge, blue-violet LED and an herbal product called Ankaferd blood stopper (ABS). Comparisons between interventions or between an intervention and a control group were made. Controls used were gauze pressure and placebo (Table 1). Only one article (*Ramström et al*., 1993) reported adverse effects. The other studies did not present data on adverse effects. All studies were carried out in patients undergoing OAT with coumarin derivatives. Studies evaluating DOACs were not found.

3.3. Risk of bias within studies

The assessment of the risk of bias of individual and across included studies according to the Cochrane tool is displayed in Fig 2 and Fig 3. For sequence generation, 11 studies presented low risk of bias. For allocation concealment, 14 studies were awarded unclear risk of bias. For blinding of participants/personnel, three studies presented low risk of bias. For blinding of the outcome assessor, five studies were awarded low risk of bias. Most studies presented a low risk of bias for incomplete outcome data and selective reporting. As regards other sources of bias, 16 studies presented high

risk of bias. The JBI tool and its criteria for the assessment of the risk of bias can be found in the Table A.2.

3.4. Synthesis of results and risk of bias across studies

3.4.1 Studies included in NMA and Network geometry.

We performed NMA for two outcomes; bleeding events and mean bleeding time. Fig 4 shows the NMA geometry. For bleeding events, most patients were treated with TXA. For the mean bleeding time, most patients were treated with chitosan and gauze was the comparison most used. The numbers of direct comparisons and the characteristics that make up the NMA are displayed in Table 2.

In the evaluation of the model, we obtained a convergent random-effects model for both outcomes (Fig A.1, Fig A.2, and Appendix B). We observed moderate statistical heterogeneity in the analysis regarding bleeding events (I^2= 41.9%) and high heterogeneity in the analysis of the outcome mean bleeding time (I^2 > 75%) (Fig A.3, Fig A.4). Reviewing the inconsistency for bleeding events, we concluded that even though treatment arms that tended towards the inconsistency model had been observed, there is a lack of evidence of inconsistencies within the network (Fig A.5, Fig A.6). For the mean bleeding time, consistency was observed in the network, despite the existing heterogeneity (Fig A.7, Fig A.8).

3.4.2 Bleeding events

We incorporated 14 studies (*Sindet-Pedersen et al.*, 1989; *Ramström et al.,* 1993; *Souto et al.*, 1996; *Blinder et al.*, 1999; *Halfpenny et al*., 2001; *Al-Belasy & Amer*, 2003; *Glen Carter et al.*, 2003; *Al-Mubarak et al.*, 2007; *Çakarer et al.*, 2013; *Bajkin et al.*, 2014; *Okamoto et al.*, 2014; *Soares et al.*, 2014; *Queiroz et al*., 2018; *Baldoni & Lauritano*, 2019) with 12 interventions (suture, gelatin sponge, gauze, TXA, fibrin, EACA, LED, oxidized cellulose, n-butyl-2-cyanoacrylate, $CaSO_4$, ABS and placebo) and 781 patients in the network. N-butyl-2-cyanoacrylate [RR -35.00 (95% CI - 107.12, -5.78)], $CaSO_4$ [RR -5.62 (95% CI -11.41, -1.03)], and TXA [RR -3.46 (95% CI -7.63, -0.77)] showed beneficial effects compared to placebo (Fig 5, Fig 6, Fig 7 and Fig A.9).

3.4.3 Mean bleeding time

11

We incorporated four studies (Çakarer et al., 2013; *Pippi et al.*, 2015; *Kumar et al.*, 2016; *Queiroz et al.*, 2018) with five interventions (TXA, ABS, chitosan, collagen sponge and gauze) and 162 patients in the network. No significant difference between the interventions and gauze was observed (Fig 8, Fig 9, Fig 10 and Fig A.10).

3.5. Sensitivity analysis

The sensitivity analysis, excluding studies with a high risk of bias (*Souto et al*., 1996; *Blinder et al.*, 1999; *Al-Belasy & Amer*, 2003; *Glen Carter et al.*, 2003; *Al-Mubarak et al.*, 2007; *Çakarer et al*., 2013; *Bajkin et al.*, 2014; *Okamoto et al*., 2014; *Kumar et al.*, 2016; *Baldoni & Lauritano,* 2019;), showed a significant beneficial effect of TXA compared to placebo for bleeding events [RR -3.72 (95% CI -8.39, -0.53)] (Appendix C). In the sensitivity analysis for the mean bleeding time, the result persisted. No significant difference between the interventions and gauze was observed (Appendix D).

3.6. Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

The GRADE assessment of the certainty of the evidence for each comparison is provided in Appendix E. The comparisons that presented statistical significance were TXA, N-butyl-2-cyanoacrylate, and $CaSO_4$ compared with placebo.

For the direct comparison of TXA and placebo, indirectness was downgraded by one level because serious concern due to the variety of procedures performed. Therefore, the level of certainty of the evidence was moderate.

In the indirect comparison of N-butyl-2-cyanoacrylate with placebo, the certainty of the evidence was very low. Imprecision was downgraded by one level because serious concern due to the wide confidence interval. Intransitivity was downgraded by one level due to the variety of procedures in the comparison TXA vs. placebo and taking the indirectness through a second-order loop via gelatin sponge, and TXA (N-butyl-2-cyanoacrylate vs. gelatin sponge, gelatin sponge vs. TXA and TXA vs. placebo), a downgrade by one level was also set in place.

For the indirect comparison of $CaSO_4$ with placebo, the certainty of the evidence was also very low. Imprecision was downgraded by one level because serious concern due to the wide confidence interval. Intransitivity was downgraded by one level due to the variety of procedures in the

comparison TXA vs. placebo and taking into account the indirectness through a first-order loop via TXA ($CaSO_4$ vs. TXA and TXA vs. placebo), a downgrade by one level was also set in place.

4. DISCUSSION

Compared to placebo, we found a reduction in the risk of bleeding when TXA is used as a hemostatic agent before oral procedures in patients undergoing OAT with moderate certainty of evidence. We also found beneficial effects in the risk of bleeding for N-butyl-2-cyanoacrylate and $CaSO_4$ compared to placebo. Due to serious concerns regarding risk of bias, indirectness and imprecision, the certainty of the evidence for the comparisons of the mentioned interventions was very low, with an imprecise magnitude of the effect. However, we did not find differences in the comparisons of bleeding events between hemostatic interventions (one hemostatic agent against another hemostatic agent). We also did not observe differences in the mean bleeding time for the comparisons between hemostatic interventions (TXA, ABS, chitosan) and gauze pressure.

In this systematic review and NMA, TXA was the only hemostatic agent in direct comparison with placebo. Taking into account that placebo substance does not have an expected clinical effect on bleeding outcomes, one can conclude that TXA shows significant effectiveness. Herein, no hemostatic measure showed greater effectiveness than other hemostatic intervention. Similar to the systematic review carried out by *Weltman et al.*, 2015, who had also reported that there is no evidence to indicate the superiority of one hemostatic agent over another. Our results and the findings of *Engelen et al*., 2018, who had also reported, in their systematic review, the effectiveness of TXA versus placebo and similarities regarding the effectiveness of different hemostatic agents are very much alike. However, unlike *Engelen et al*., 2018 who had only evaluated the effectiveness of antifibrinolytic agents (TXA or EACA), our study assessed any hemostatic intervention. *Nagraj et al.*, 2018 tried to carry out a similar evaluation with different interventions. Nevertheless, they did not find studies that could be included according to their eligibility criteria. Our study succeeded in evaluating various interventions due to the implemented methodology. Indirect treatment comparisons and NMA are approaches to quantitatively summarize the evidence when there are more than two treatments of interest. The NMA allowed us to compare two or more treatments that had not been directly

compared. Furthermore, it can provide greater statistical precision by incorporating indirect evidence that is not considered in the paired meta-analysis (*Béliveau et al.*, 2019).

Despite being used as a control group in many studies, pressure with gauze without hemostatic agents continues to represent a helpful mechanical hemostatic measure. This finding is supported by the results of studies in which no statistical differences between pressure with gauze and other hemostatic agents with respect to the control of bleeding events and the mean bleeding time were observed. The mean bleeding time indicates the time in minutes for clot stabilization and the cessation of bleeding visually assessed by the evaluator (*Queiroz et al*., 2018). This type of outcome should be addressed in future research because few clinical trials (*Çakarer et al.*, 2013; *Pippi et al*., 2015; *Kumar et al.*, 2016; *Queiroz et al.*, 2018) have evaluated it.

When the mean bleeding time was assessed, high statistical heterogeneity was observed (I^2 >75%). For the analysis of this outcome, few studies with small sample sizes have been included in this systematic review and NMA. Three studies compared different hemostatic interventions with gauze, and one study compared two interventions. For this NMA, heterogeneity with respect to the age of the participants was observed. In one of the studies (*Pippi et al*., 2015), participants with a higher mean age were recruited (70.45 ±10.56), and in another study (*Kumar et al.,* 2016), the mean age of participants was not reported, which would explain the high heterogeneity. In this systematic review and NMA, we compared the proportion of bleeding events among individuals using different hemostatic interventions. We observed moderate statistical heterogeneity with I^2 = 41.9% in the comparisons between the interventions. The moderate heterogeneity may be explained by the similarity of populations evaluated in the included studies. Most studies applied hemostatic interventions in patients undergoing tooth extractions. Only in the comparison of TXA and placebo, other dental procedures in addition to tooth extraction were performed. Likewise, other articles also point out that the prevention of bleeding in anticoagulated individuals undergoing dental procedures other than tooth extraction, such as periodontal procedures or endodontic surgery, has been poorly documented thus far (*Nagraj et al*., 2018; *Ockerman et al.*, 2019).

Some methodological procedures of the studies included in this systematic review and NMA have not been adequately described; consequently, the risk bias may have been over or

underestimated. However, the Cochrane and JBI tools for experimental studies are instruments that allow one to perform a consistent assessment of the risk of bias within studies (*Higgins & Green*, 2011; *Tufanaru et al*., 2017). Based on the risk of bias analysis, we strongly recommend the accomplishment of high quality studies with larger sample sizes allowing researchers to evaluate the effectiveness of hemostatic agents in patients undergoing OAT after different types of oral procedures. We observed that the reporting of outcomes regarding risk of bleeding among smokers or individuals with systemic conditions, such as immunosuppression and diabetes mellitus has been poorly documented in literature as well. Only two studies reported the inclusion of smokers (*Ramström et al*., 1993; *Giuffrè et al*., 2006), three studies included diabetic patients (*Okamoto et al.*, 2014; *da Silva et al.*, 2018; *Queiroz et al.*, 2018) and *Okamoto et al*., 2014 reported the inclusion of a patient with chronic myelocytic leukemia. We strongly suggest randomized controlled experimental studies assessing this type of population to determine the most effective hemostatic intervention to prevent bleeding. Similarly, reporting of adverse effects of hemostatic medications is necessary, as only one study has reported this outcome (*Ramström et al.*, 1993).

As regards the type of local hemostatic used, at least half of the included studies used TXA. Some articles also identified TXA as the most used antifibrinolytic agent (*de Vasconcellos et al*., 2017; *Ockerman et al.*, 2019). Concerning the type of oral anticoagulant, all participants used coumarin derivatives, mostly warfarin. We found no information related to DOAC medications, similar to *Engelen et al*., 2018, who suggested future research on this issue. The OAT doses or duration were not mentioned. This is a significant limitation, since these variables can alter the International Normalized Ratio (INR) and the bleeding time. In addition to the afore-mentioned statement, studies with a small sample size were included in our systematic review and NMA, and a limited number of direct comparisons was identified (15 of 66 for bleeding events and 4 of 10 for mean bleeding time). The shortage of direct comparisons explains the very low or low certainty of the evidence. For this reason and due to the inconsistencies presented, results should be interpreted cautiously.

5. CONCLUSION

In conclusion, one can state that the number of individuals on anticoagulation with bleeding events reduced with the use of TXA compared to placebo when oral procedures were carried out. This outcome presented moderate certainty of evidence. In contrast, no differences regarding bleeding or mean bleeding time was observed when two hemostatic agents were compared. N-butyl-2-cyanoacrylate and $CaSO_4$ were superior to placebo to reduce bleeding events in anticoagulated individuals, but the certainty of the evidence was very low.

Acknowledgments and funding

This study was supported by the Brazilian agencies: *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) and *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES).

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Author contributions

All authors contributed to the study conception, design, material preparation, data collection, and analysis. All authors commented on previous versions of the manuscript, read and approved the final manuscript.

Johana Alejandra Moreno-Drada: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Roles/Writing - original draft; Writing - review & editing. **Lucas Guimarães Abreu:** Formal analysis; Investigation; Methodology; Roles/Writing - original draft; Writing - review & editing. **Patrícia Azevedo Lino:** Conceptualization; Data curation; Formal analysis. **Maria Auxiliadora Parreiras Martins:** Conceptualization; Investigation; Roles/Writing - original draft; Writing - review & editing. **Isabela Almeida Pordeus:** Funding acquisition; Project administration; Resources; Software; Supervision; Validation; Visualization. **Mauro Henrique Nogueira Guimarães de Abreu:** Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

16

REFERENCES

Al-Belasy, F. A., & Amer, M. Z: Hemostatic effect of n-butyl-2-cyanoacrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. J Oral Maxillofac Surg 61(12), 1405-1409, 2003. Retrieved from https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00459412/full

Al-Mubarak, S., Al-Ali, N., Abou-Rass, M., Al-Sohail, A., Robert, A., Al-Zoman, K., … Ciancio, S: Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. Br Dent J 203(7), E15; discussion 410-1, 2007. https://doi.org/10.1038/bdj.2007.725

Bajkin B V., Popovic SL, Selakovic SDJ: Randomized, Prospective Trial Comparing Bridging Therapy Using Low-Molecular-Weight Heparin With Maintenance of Oral Anticoagulation During Extraction of Teeth. J Oral Maxillofac Surg 67(5):990–5, 2009. Available from: http://dx.doi.org/10.1016/j.joms.2008.12.027

Bajkin B V, Selakovic SD, Mirkovic SM, Sarcev IN, Tadic AJ, Milekic BR: Comparison of efficacy of local hemostatic modalities in anticoagulated patients undergoing tooth extractions. Vojnosanit Pregl 71(12):1097–101, 2014. https://doi.org/http://dx.doi.org/10.2298/VSP1412097B

Baldoni M, Lauritano D: Bleeding control with calcium sulphate after oral surgery in anticoagulant therapy patients. J Biol Regul Homeost Agents 33((6 Suppl. 1)):41–7, 2019.

Bartholomay E, Polli I, Borges A, Kalil C, Arroque A, Kohler I, et al.: Prevalence of oral anticoagulation in atrial fibrillation. Clinics (Sao Paulo) 69(9):615–20, 2014. Available from:https://doi.org/10.6061/clinics/2014(09)07

Béliveau A, Boyne DJ, Slater J, Brenner D, Arora P.: BUGSnet: An R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. BMC Med Res Methodol 19(1):196, 2019. Available from: https://doi.org/10.1186/s12874-019-0829-2

Blinder D, Manor Y, Martinowitz U, Taicher S, Hashomer T: Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88(2):137–40, 1999. Retrieved from https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00387180/full

17

Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al.: Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol 93:36–44, 2018. Available from: https://doi.org/10.1016/j.jclinepi.2017.10.005

Çakarer S, Eyüpoğlu E, Günes ÇÖ, Küseoğlu BG, Berberoğlu HK, Keskin C: Evaluation of the hemostatic effects of ankaferd blood stopper during dental extractions in patients on antithrombotic therapy. Clin Appl Thromb 19(1):96–9, 2013. https://doi.org/10.1177/1076029611435836

Carter G, Goss A: Tranexamic acid mouthwash--a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int J Oral Maxillofac Surg 32(5):504–7, 2003. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14759109

Carter G, Goss A, Lloyd J, Tocchetti R: Tranexamic Acid Mouthwash Versus Autologous Fibrin Glue in Patients Taking Warfarin Undergoing Dental Extractions: A Randomized Prospective Clinical Study. J Oral Maxillofac Surg 61(12):1432–5, 2003. https://doi.org/10.1016/j.joms.2003.01.001

Chan YH, Lee HF, See LC, Tu HT, Chao TF, Yeh YH, et al: Effectiveness and Safety of Four Direct Oral Anticoagulants in Asian Patients With Nonvalvular Atrial Fibrillation. Chest 156(3):529–43, 2019. https://doi.org/10.1016/j.chest.2019.04.108

da Silva R V, Gadelha TB, Luiz RR, Torres SR: Intra-alveolar epsilon-aminocaproic acid for the control of post-extraction bleeding in anticoagulated patients: randomized clinical trial. Int J Oral Maxillofac Surg 47(9):1138–44, 2018. Available from: https://doi.org/10.1016/j.ijom.2018.02.013

de Vasconcellos SJ, de Santana Santos T, Reinheimer DM, Faria-e-Silva AL, de Melo MF, Martins-Filho PR: Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery: A systematic review and meta-analysis of randomized clinical trials. J Cranio-Maxillofacial Surg 45(1):20–6, 2017. Available from: https://doi.org/10.1016/j.jcms.2016.10.001

Dias S, Sutton AJ, Ades AE, Welton NJ: Evidence synthesis for decision making 2: A generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled

trials. Med Decis Mak 33(5):607–17, 2013. Available from: https://doi.org/10.1177/0272989X12458724

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE: NICE DSU technical support document 4: inconsistency in networks of evidence based on randomised controlled trials report by the decision support unit. 2011. Retrieved from www.nicedsu.org.uk

Dudek D, Marchionni S, Gabriele M, Iurlaro A, Helewski K, Toti P, et al: Bleeding Rate After Tooth Extraction in Patients Under Oral Anticoagulant Therapy. J Craniofac Surg 27(5):1228–33, 2016. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27380567

Efthimiou O, Debray TPA, van Valkenhoef G, Trelle S, Panayidou K, Moons KGM, et al: GetReal in network meta-analysis: a review of the methodology. Res Synth Methods 7(3):236–63, 2016. Available from: https://doi.org/10.1002/jrsm.1195

Engelen ET, Schutgens RE, Mauser-bunschoten EP, Van Es RJ, Van Galen KP: Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions (Review). Cochrane Database Syst Rev (7):1–45, 2018. https://doi.org/10.1002/14651858.CD011385.pub2.www.cochranelibrary.com

Febbo A, Cheng A, Stein B, Goss A, Sambrook P: Postoperative Bleeding Following Dental Extractions in Patients Anticoagulated With Warfarin. J Oral Maxillofac Surg 74(8):1518–23, 2016. Available from: https://doi.org/10.1016/j.joms.2016.04.007

Ferrieri GB, Castiglioni S, Carmagnola D, Cargnel M, Strohmenger L, Abati S: Oral Surgery in Patients on Anticoagulant Treatment Without Therapy Interruption. J Oral Maxillofac Surg 65(6):1149–54, 2007. Available from: https://doi.org/10.1016/j.joms.2006.11.015

Giuffrè G, Caputo G, Misso S, Peluso F: Platelet-rich plasma treatment and hemostasis in patients with hemorrhagic risk. Minerva Stomatol 55(11-12):599-609, 2006. Retrieved from https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00586488/full

Giustozzi M, Franco L, Vedovati MC, Becattini C, Agnelli G: Safety of direct oral anticoagulants versus traditional anticoagulants in venous thromboembolism. J Thromb Thrombolysis 48(3):439–53, 2019. https://doi.org/10.1007/s11239-019-01878-x

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al.: GRADE: an emerging

consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–6, 2008. Available from: https://doi.org/10.1136/bmj.39489.470347.AD

Halfpenny W, Fraser JS, Adlam DM: Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 92(3):257–9, 2001. https://doi.org/10.1067/moe.2001.115463

Harrer M, Cuijpers P, Furukawa T, Ebert D: Doing Meta-Analysis in R: A Hands-on Guide. https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/. 2019.

Higgins J, Green S: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. 2011. www. cochrane-handbook.org

Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al.: The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. Ann Intern Med 162(11):777–84, 2015. Available from: https://pubmed.ncbi.nlm.nih.gov/26030634/.

Jiménez Y, Poveda R, Gavaldá C, Margaix M, Sarrión G: An update on the management of anticoagulated patients programmed for dental extractions and surgery. Med Oral Patol Oral y Cir Bucal 13(3):E176-9, 2008. Retrieved from http://www.medicinaoral.com/medoralfree01/v13i3/medoralv13i3p176.pdf

Kämmerer PW, Frerich B, Liese J, Schiegnitz E, Al-Nawas B: Oral surgery during therapy with anticoagulants—a systematic review. Clin Oral Investig 19(2):171–80, 2015. Available from: https://doi.org/10.1007/s00784-014-1366-3

Kumar KR, Kumar J, Sarvagna J, Gadde P, Chikkaboriah S: Hemostasis and post-operative care of oral surgical wounds by hemcon dental dressing in patients on oral anticoagulant therapy: A split mouth randomized controlled clinical trial. J Clin Diagnostic Res 10(9):ZC37-ZC40, 2016. https://doi.org/10.7860/JCDR/2016/17275.8462

Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al.: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 6(7):e1000097, 2009. https://doi.org/10.1371/journal.pmed.1000097

Mulligan R, Weitzel KG: Pretreatment management of the patient receiving anticoagulant drugs. J

Am Dent Assoc 117(3):479–83, 1988. Available from: https://doi.org/10.1016/S0002-8177(88)73021-4

Nagraj KS, Prashanti E, Aggarwal H, Lingappa A, Ms M, Krishanappa KK, et al.: Interventions for treating post-extraction bleeding (Review). Cochrane Database Syst Rev (3):1–26, 2018. https://doi.org/10.1002/14651858.CD011930.pub3.www.cochranelibrary.com

Ockerman A, Miclotte I, Vanhaverbeke M, Verhamme P, Poortmans L-L, Vanassche T, et al.: Local haemostatic measures after tooth removal in patients on antithrombotic therapy: a systematic review. Clin Oral Investig 23(4):1695–708, 2019. https://doi.org/10.1007/s00784-018-2576-x

Okamoto T, Ishikawa I, Kumasaka A, Morita S, Katagiri S, Okano T, et al.: Blue-violet light-emitting diode irradiation in combination with hemostatic gelatin sponge (Spongel) application ameliorates immediate socket bleeding in patients taking warfarin. Oral Surg Oral Med Oral Pathol Oral Radiol 117(2):170-177, 2014. Available from: https://doi.org/10.1016/j.oooo.2013.09.009

Pippi R, Santoro M, Cafolla A: The effectiveness of a new method using an extra-alveolar hemostatic agent after dental extractions in older patients on oral anticoagulation treatment: an intrapatient study. Oral Surg Oral Med Oral Pathol Oral Radiol 120(1):15-21, 2015. Available from: https://doi.org/10.1016/j.oooo.2015.02.482

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al.: A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 349(g5630), 2014. Available from: https://doi.org/10.1136/bmj.g5630

Queiroz SIML, Silvestre VD, Soares RM, Campos GBP, Germano AR, da Silva JSP: Tranexamic acid as a local hemostasis method after dental extraction in patients on warfarin: a randomized controlled clinical study. Clin Oral Investig 22(6):2281–9, 2018. Available from: https://doi.org/10.1007/s00784-017-2327-4

Ramström G, Sindet-Pedersen S, Hall G, Blombäck M, Alander U: Prevention of postsurgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. J oral Maxillofac Surg 51(11):1211-1216, 1993. Retrieved from https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00096963/full

Ripollés-de Ramón J, Muñoz-Corcuera M, Bravo-Llatas C, Bascones-Martínez A: Aplicación de un gel de ácido tranexámico en pacientes tratados con anticoagulantes orales. TT - [Tranexamic acid gel in patients treated with oral anticoagulants]. Med Clin (Barc) 143(11):484–8, 2014. Retrieved from http://dx.doi.org/10.1016/j.medcli.2013.07.028

Rocha AL, Souza AF, Martins MAP, Fraga MG, Travassos D V, Oliveira ACB, et al.: Oral surgery in patients under antithrombotic therapy: Perioperative bleeding as a significant risk factor for postoperative hemorrhage. Blood Coagul Fibrinolysis 29(1):97–103, 2018. Available from: https://doi.org/10.1097/MBC.0000000000000677

Salanti G, Ades AE, Ioannidis JPA: Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. J Clin Epidemiol 64(2):163–71, 2011. Available from: https://doi.org/10.1016/j.jclinepi.2010.03.016

Santhosh Kumar MP: Local hemostatic agents in the management of bleeding in oral surgery. Asian J Pharm Clin Res 9(3):35-41, 2016. Retrieved from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84969194599&partnerID=40&md5=d94ea8ff9815155dc8f948ff8ad84a71

Scarano A, Sinjari B, Murmura G, Mijiritsky E, Iaculli F, Mortellaro C, et al.: Hemostasis control in dental extractions in patients receiving oral anticoagulant therapy: an approach with calcium sulfate. J Craniofac Surg 25(3):843-846, 2014. Available from: https://doi.org/10.1097/SCS.0000000000000824

Serrano-Sánchez V, Ripollés-de-Ramón J, Collado-Yurrita L, Vaello-Checa I, Colmenero-Ruiz C, Helm A, et al.: New horizons in anticoagulation: Direct oral anticoagulants and their implications in oral surgery. Med Oral Patol Oral Cir Bucal 22(5):e601–8, 2017. https://doi.org/10.4317/medoral.21862

Sindet-Pedersen S, Ramström G, Bernvil S, Blombäck M: Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 320(13):840-843, 1989. Available from: https://doi.org/10.1056/NEJM198903303201305

Soares ECS, Costa FWG, Bezerra TP, Nogueira CBP, de Barros Silva PG, Batista SHB, et al.: Postoperative hemostatic efficacy of gauze soaked in tranexamic acid, fibrin sponge, and dry

gauze compression following dental extractions in anticoagulated patients with cardiovascular disease: a prospective, randomized study. Oral Maxillofac Surg 19(2):209-216, 2014. Available from: https://doi.org/10.1007/s10006-014-0479-9

Souto JC, Oliver A, Zuazu-Jausoro I, Vives A, Fontcuberta J: Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: A prospective randomized study. J Oral Maxillofac Surg 54(1):27–32, 1996. Available from: https://doi.org/10.1016/S0278-2391(96)90297-9

Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L: Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute; 2017. Available from: https://wiki.joannabriggs.org/display/MANUAL/Chapter+3%3A+Systematic+reviews+of+effectiveness

van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ: Automating network meta-analysis. Res Synth Methods 3(4):285–99, 2012. Available from: https://doi.org/10.1002/jrsm.1054

Weltman J, Al-Attar, Cheung, Duncan, Katchky, Azarpazhooh, et al.: Management of dental extractions in patients taking warfarin as anticoagulant treatment: A systematic review. J Can Dent Assoc (Tor) 81:f20, 2015. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-84979950764&partnerID=40&md5=031b910e828e211ab2290b94cbdee1c9

23

Table 1. Characteristics of included studies.

Authors	M	F	Treatment	Group 1 (G1)	Group 2 (G2)	Group 3 (G3)	Outcome	Event G1	n G1	EventG 2	n G2	Event G3	n G3	Mean G1	SD	Mean G2	SD	*p*
Al-Belasy et al., 2003 (Egypt)	19	11	Dental extraction	**N-butyl-2-cyanoacrylate** INR: 2.51 (1.9-4.3) Gender (m/f): 10/5 Age: 56.47 (50-64)	**Gelatin sponge** INR: 2.42 (1.7-4.1) Gender (m/f): 9/6 Age: 58 (53-65)		Bleeding events	0	15	5	15	_	_	_	_	_	_	0.016
Al-Mubarak et al., 2007 (Saudi Arabia)	51	59	Dental extraction	**Suture** INR: 2.7 ±0.6 Gender (m/f): 24/28 Age: 53.1 ±13.7	**Gauze** INR: 2.4 ±0.5 Gender (m/f): 27/31 Age: 51.7 ±14.7		Bleeding events	29	52	21	58	_	_	_	_	_	_	>0.05
Bajkin et al., 2014 (Serbia)	55	35	Dental extraction	**Suture** INR: 2.35 ± 0.37 (<=3.0) Gender (m/f): 19/11	**Gelatin sponge** INR: 2.43 ± 0.4 (<=3.0) Gender (m/f): 16/14	**Gauze** INR: 2,36 ± 0,34 (<=3.0) Gender (m/f): 20/10	Bleeding events	1	30	2	30	2	30	_	_	_	_	0.811

24

				Age: 65.5 ± 11.1 (23-78)	Age: 66.9 ± 9.8 (41–81)	Age: 65.8 ± 11.2 (36–85)												
Baldoni M, Lauritano D, 2019 (Italy)	14	6	Dental extraction	**$CaSO_4$** INR: > 3.0 Gender (m/f): 14/6 Age: 54.3 ± 10.3	**TXA**		Bleeding events	0	10	5	10	_	_	_	_	_	_	0.0055
Blinder et al., 1999 (Israel)	86	64	Dental extraction	**Gelatin sponge + suture** INR: 2.38 (1.5-3.6) Gender (m/f): 35/15 Age: 56 (40-86)	**Fibrin glue +gelatin sponge+suture** INR: 2.7 (1.9-4) Gender (m/f): 33/17 Age: 61 (35-79)	**TXA +gelatin sponge+suture** INR: 2.19 (1.5-3.58) Gender (m/f): 18/32 Age: 64 (40-93)	Bleeding events	3	50	6	50	4	50	_	_	_	_	0.54
Cakarer et al., 2013 (Turkey)	13	12	Dental extraction	**ABS** INR: 1.49 ±0.56 Gender (m/f): 8/7 Age: 56.2 ±12.86	**Gauze** INR: 1.24 ±150.44 Gender (m/f): 5/5 Age: 47.60 ±15.88		Bleeding events The mean bleeding time	0	15	1	10	_	_	0.93	0.39	3.4	1.57	0.0001

25

Carter et al., 2003 (Australia)	31	18	Dental extraction	**TXA** INR: 3.0 (2.3-4.0) Gender (m/f): 16/10 Age: 65 (24-85)	**Fibrin glue** INR: 3.1 (2.1-4.0) Gender (m/f): 15/8 Age: 65 (40-83)		Bleeding events	0	26	2	23	_	_	_	_	_	_	0.12
Carter, Goss., 2003 (Australia)	54	31	Dental extraction	**TXA 2 days** INR: 2.7 Gender (m/f): 22/21 Age: 65.2 (21-77)	**TXA 5 days** INR: 2.8 Gender (m/f): 32/10 Age: 65.7 (24-86)		Bleeding events	2	43	1	42	_	_	_	_	_	_	0.57
da Silva et al., 2018 (Brazil)	24	28	Dental extraction	**EACA** INR: 2.8±0.525 (2.0-4.0) Age: 61.9± 12.1 (40-93)	**Gauze** INR: 2.6±0.541 (2.0-4.0)		Bleeding events	11	70	12	70	_	_	_	_	_	_	0.871 OR: 1.08 (0.40-2.92)
Giuffre et al., 2006 (Italy)	84	124	Dental extraction, cystectomies	**PRP + Suture** INR: 2.7 ±0.6 Gender (m/f): 23/29	**PRP + Suture + haemostatic sponges** INR: 2.6 ±0.5 Gender (m/f): 26/26	**PRP + Suture + haemostatic sponges + TXA** INR: 2.7 ±0.3 Gender (m/f): 20/32	Bleeding events	2	52	0	52	9	52	_	_	_	_	_

26

				Age: 59±7 (51-78)	Age: 53±7 (51-78)	Age: 55±5 (51-78)														
Halfpenny et al., 2001 (UK)	30	26	Dental extraction	**Fibrin adhesive** INR: 2.7 (2-4.1) Gender (m/f): 13/17 Age: 66.5 (33.4-83.4)	**Oxidized cellulose** INR: 2.9 (2.1-4.1) Gender (m/f): 17/9 Age: 64.8 (38.2-79.3)		Bleeding events	2	26	1	20	_	_	_	_	_	_	_
Kumar et al., 2016 (India)	12	18	Dental extraction	**Chitosan** Gender (m/f): 12/18 Age:18-90	**Gauze**		The mean bleeding time	_	30	_	30	_	_	1.49	0.39	4.06	1.85	0.001
Okamoto et al., 2014 (Japan)	28	20	Dental extraction	**Blue-violet LED (A)** INR: 1.951±0.338 (1.64-3.01) Gender (m/f): 4/11 Age: 67.5±7.2 (44-81)	**Gelatin sponge + Blue-violet LED (B)** INR: 2.009±0.376 (1.64-3.01) Gender (m/f): 8/7 Age: 65.8±9.2 (44-81)	**Gelatin sponge (C)** INR: 2.032±0.402 (1.64-3.01) Gender (m/f): 8/10 Age: 69.7 ±10.9 (44-81)	Bleeding events	7	15	2	15	13	18	_	_	_	_	A/B: 0.14 A/C: 0.40 B/C: 0.002

27

Pippi et al., 2015 (Italy)	15	5	Dental extraction	**Chitosan** INR: 2.53 ±0.47 (1.6-3.36) Age: 70.45 ±10.56 (40-80)	**Collagen sponge**	The mean bleeding time	_	20	_	20	_	_	4.66	3.37	4.08	2.24	0.8813
Queiroz et al., 2018 (Brazil)	14	23	Dental extraction	**TXA** INR: 2.6 (2.2–2.9) Gender (m/f): 8/9 Age: 50.5 (41.4–59.3)	**Gauze** INR: 2.2 (1.8–2.5) Gender (m/f): 6/14 Age: 41.4 (34.9–47.8)	Bleeding events The mean bleeding time	0	17	3	20	_	_	5.9	1.4	11.9	2.5	Bleeding 0.059 Bleeding Time: <0.001
Ramstrom et al., 1993 (Denmark /Sweden)	53	36	Dental extraction/ Surgically treated teeth	**TXA** INR: 2.10-4.00 Gender (m/f): 25/19 Age: 69.8 ±7.9 (53-87)	**Placebo** Gender (m/f): 28/17 Age: 67.1 ±10.5 (35-83)	Bleeding events	0	44	10	45	_	_	_	_	_	_	< 0.01
Ripollés et al., 2013 (Spain)	_	_	Dental extraction	**TXA** INR: 2-3 Age: 18-65	**Gauze**	The median clotting time	_	8	_	8	_	_	Median: 30	Interval: (15-45)	Median: 90	Interval: (45-180)	0.024
	8	22		**$CaSO_4$**	**Suture**		_	_	_	_	_	_	_	_	_	_	0.0056

28

Scarano et al., 2014 (Italy)			Dental extraction	INR: 2.0-3.0 Gender (m/f): 8/22 Age: 54.6 ±9.2	INR: 2.0-3.0 Gender (m/f): 8/22 Age: 54.6 ±9.2		Bleeding events											
Sindet-Pedersen et al., 1989 (Denmark /Sweden)	22	17	Dental extraction, Surgically treated teeth, Removal of retained teeth, Periapical surgery, Excesional gingival hyperplasia	**TXA** INR: 2.5-4.8 Gender (m/f): 11/9 Age: 58 (20-72)	**Placebo** Gender (m/f): 11/8 Age: 55.65 (19-77)		Bleeding events	1	19	8	20	_	_	_	_	_	_	0.01
Soares et al., 2014 (Brazil)	56	28	Dental extraction	**TXA** INR: 2.52±0.16 (2.1-3.1) Gender (m/f): 18/10 Age: 51.0 ±2.9 (44-56)	**Fibrin sponge** INR: 2.51±0.16 (2.1-3.1) Gender (m/f): 20/8 Age: 51.1±3.0 (44-56)	**Gauze compression** INR: 2.51±0.13 (2.1-3.1) Gender (m/f): 18/10 Age: 51.1±2.8 (44-56)	Bleeding events	1	12	2	13	1	13	_	_	_	_	Surgical site (28 per group): 0.769

29

				TXA **EACA**													
Souto et al., 1996 (Spain)	30	34	Dental extraction	INR: 3.29 INR: 3.5 Gender (m/f): 30/34 Age: 59.7±9.8		Bleeding events	10	12	9	13	_	_	_	_	_	_	G1/OR: 0.88 (0.09-8,75) G2/OR: 1.64 (0.20-13.5)

30

Table 2. Characteristic of Network Meta-analysis

Characteristic of NMA	**Bleeding Events**	**Mean Bleeding time**
Number of Interventions	12	5
Number of Studies	14	4
Total Number of Patients in Network	781	162
Total Possible Pairwise Comparisons	66	10
Total Number of Pairwise Comparisons With Direct Data	15	4
Total Number of Events in Network or Average Outcome	149	4.491

Figures

*Each node represents an intervention where Ga: Gauze; Fi: Fibrin treatment; EACA: Epsilon-aminocaproic acid; CO: Oxidized cellulose; CaS: $CaSO_4$ (Calcium sulfate); ABS: Ankaferd blood stopper; TXA: Tranexamic acid; Su: Suture; H: N-butyl-2-cyanoacrylate; Ge: Gelatin sponge; LED: Blue-violet LED; P: Placebo; Chi: Chitosan; Co: Collagen sponge.

*The treatments are ABS: Ankaferd blood stopper; CaS: $CaSO_4$ (Calcium sulfate); CO: Oxidized cellulose; EACA: Epsilon-aminocaproic acid; Fi: Fibrin treatment; Ga: Gauze; Ge: Gelatin sponge; H: N-butyl-2-cyanoacrylate; LED: Blue-violet LED; P: Placebo; Su: Suture; TXA: Tranexamic acid.

*Treatments and comparisons are ABS: Ankaferd blood stopper; CaS: $CaSO_4$ (Calcium sulfate); CO: Oxidized cellulose; EACA: Epsilon-aminocaproic acid; Fi: Fibrin treatment; Ga: Gauze; Ge: Gelatin sponge; H: N-butyl-2-cyanoacrylate; LED: Blue-violet LED; P: Placebo; Su: Suture; TXA: Tranexamic acid.

*Treatments are ABS: Ankaferd blood stopper; CaS: $CaSO_4$ (Calcium sulfate); CO: Oxidized cellulose; EACA: Epsilon-aminocaproic acid; Fi: Fibrin treatment; Ga: Gauze; Ge: Gelatin sponge; H: N-butyl-2-cyanoacrylate; LED: Blue-violet LED; P: Placebo; Su: Suture; TXA: Tranexamic acid.

*Treatments are ABS: Ankaferd blood stopper; Chi: Chitosan; Co: Collagen sponge; Ga: Gauze; TXA: Tranexamic acid.

*Treatments and comparators are ABS: Ankaferd blood stopper; Chi: Chitosan; Co: Collagen sponge; Ga: Gauze; TXA: Tranexamic acid.

Fig 10. Forest plot for mean bleeding time

*Treatments are ABS: Ankaferd blood stopper; Chi: Chitosan; Co: Collagen sponge; Ga: Gauze; TXA: Tranexamic acid.

Tables

Table 1. Characteristics of included studies.

*INR: International Normalized Ratio; TXA: Tranexamic acid; CaS: $CaSO_4$ (Calcium sulfate); ABS: Ankaferd blood stopper; EACA: Epsilon-aminocaproic acid; PRP: platelet-rich plasma.

Table 2. Characteristic of Network Meta-analysis

Supporting information

Table A.1. PRISMA NMA Checklist.

Appendix A. Search strategy

Table A.2. The assessment of risk of bias with the Joanna Briggs Institute (JBI) tool for randomized controlled trials

Fig A.1. Leverage plots for convergent of model for bleeding events

Fig A.2. Leverage plots for convergent of model for mean bleeding time

Appendix B. Trace plots for convergent model

Fig A.3. Heterogeneity for bleeding events

*ABS: Ankaferd blood stopper; CaS: $CaSO_4$ (Calcium sulfate); CO: Oxidized cellulose; EACA: Epsilon-aminocaproic acid; Fi: Fibrin treatment; Ga: Gauze; Ge: Gelatin sponge; H: N-butyl-2-cyanoacrylate; LED: Blue-violet LED; P: Placebo; Su: Suture; TXA: Tranexamic acid.

Fig A.4. Heterogeneity for mean bleeding time

*ABS: Ankaferd blood stopper; Chi: Chitosan; Co: Collagen sponge; Ga: Gauze; TXA: Tranexamic acid.

Fig A.5. Inconsistency model for bleeding events

Fig A.6. Leverage plots for inconsistency model in bleeding events

Fig A.7. Inconsistency model for mean bleeding time

Fig A.8. Leverage plots for inconsistency model in mean bleeding time

Fig A.9. Rankogram of interventions for bleeding events

*Where the treatments are ABS: Ankaferd blood stopper; CaS: $CaSO_4$ (Calcium sulfate); CO: Oxidized cellulose; EACA: Epsilon-aminocaproic acid; Fi: Fibrin treatment; Ga: Gauze; Ge: Gelatin sponge; H: N-butyl-2-cyanoacrylate; LED: Blue-violet LED; P: Placebo; Su: Suture; TXA: Tranexamic acid.

Fig A.10. Rankogram of interventions for mean bleeding time

*Where the treatments are ABS: Ankaferd blood stopper; Chi: Chitosan; Co: Collagen sponge; Ga: Gauze; TXA: Tranexamic acid.

Appendix C. Sensitivity analysis for bleeding events

*Where the treatments are TXA: Tranexamic acid; Ga: Gauze; Fi: Fibrin treatment; CO: Oxidized cellulose; P: Placebo.

Appendix D. Sensitivity analysis for mean bleeding time

**Where the treatments are Chi: Chitosan; Co: Collagen sponge; Ga: Gauze; TXA: Tranexamic acid.

Appendix E. GRADE evaluation

*Where the comparisons are Ga: Gauze; Fi: Fibrin treatment; EACA: Epsilon-aminocaproic acid; CO: Oxidized cellulose; CaS: $CaSO_4$ (Calcium sulfate); ABS: Ankaferd blood stopper; TXA: Tranexamic acid; Su: Suture; H: N-butyl-2-cyanoacrylate; Ge: Gelatin sponge; LED: Blue-violet LED; Chi: Chitosan; Co: Collagen sponge; P: Placebo

Fig 1

Click here to access/download;Figure;S1_Fig.eps

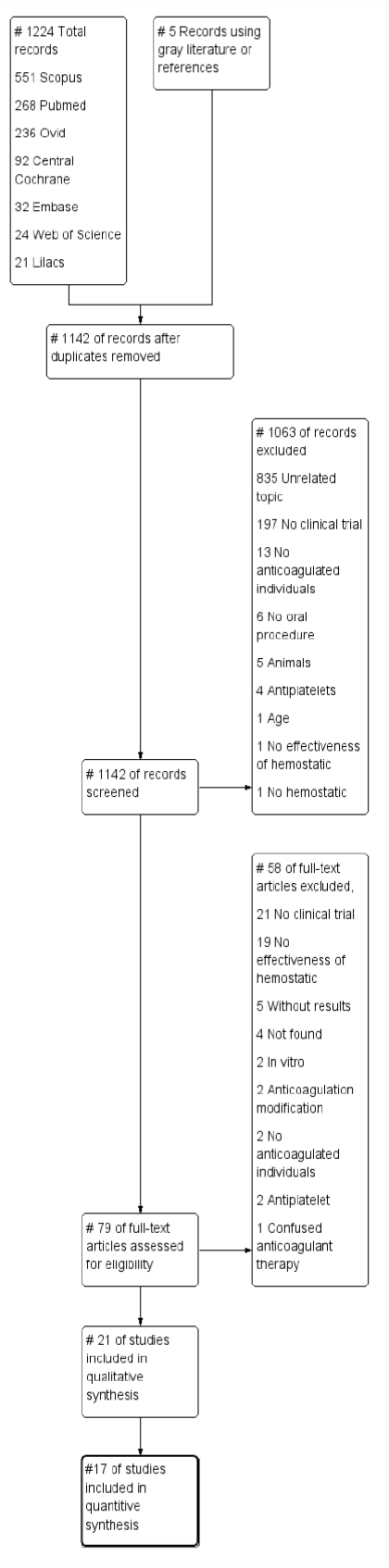


Fig 2

Click here to access/download;Figure;Fig2.eps

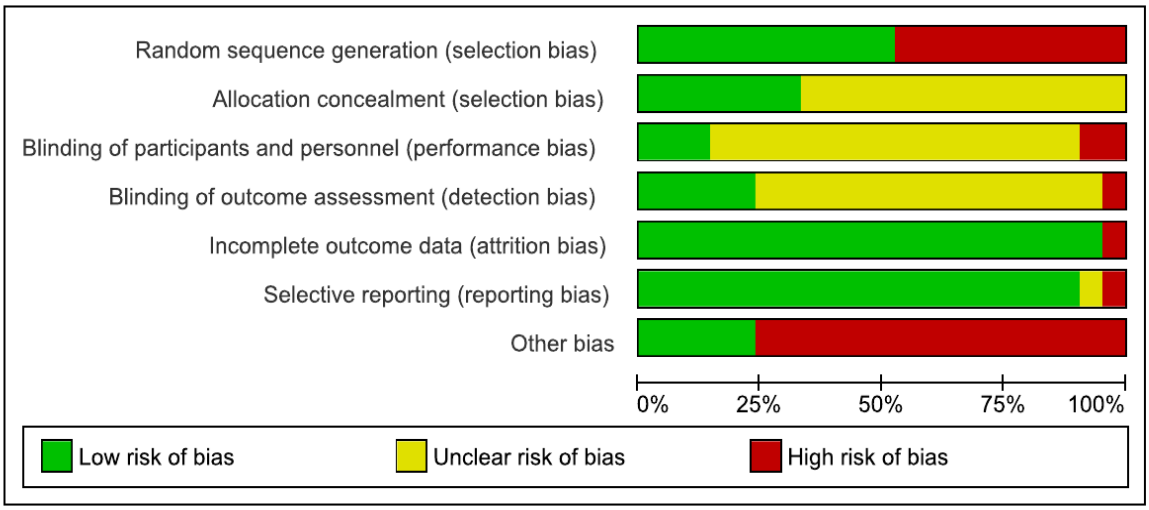


Fig 3

Click here to access/download;Figure;Fig3.eps

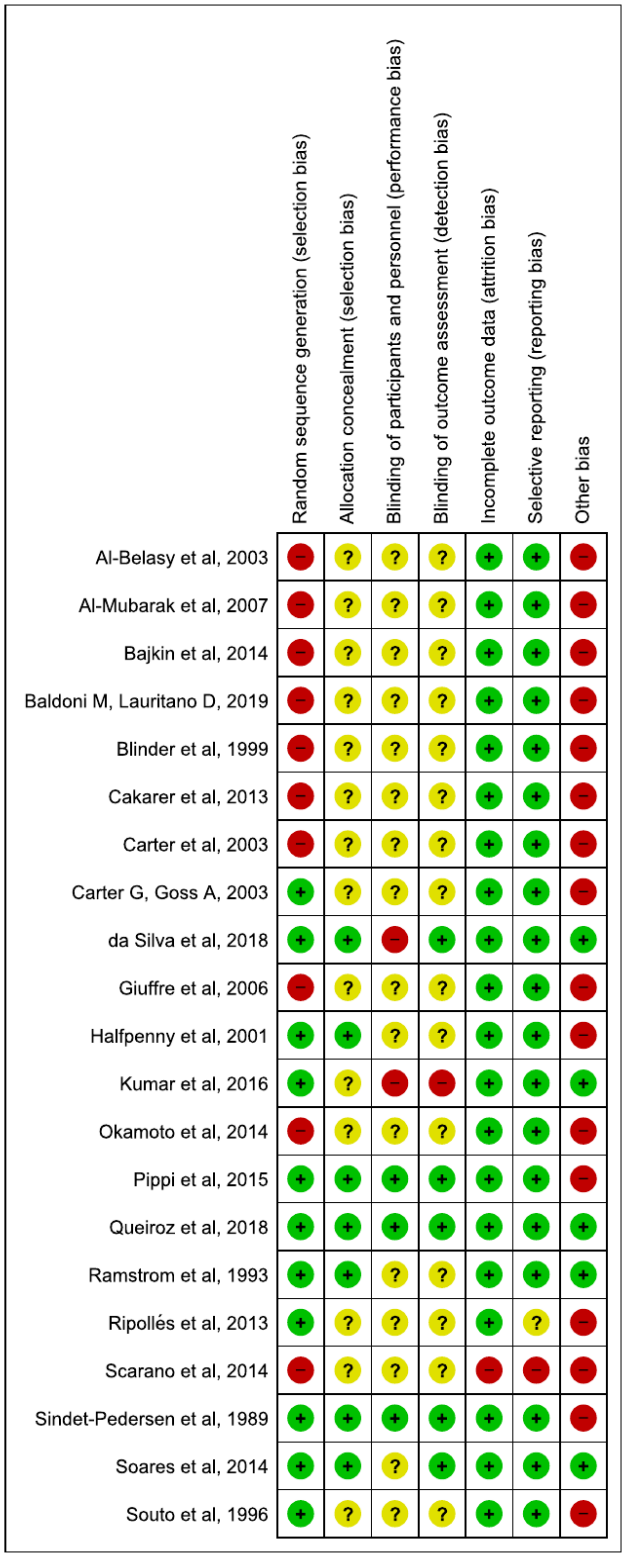


Fig 4

Click here to access/download;Figure;Fig 4.tiff

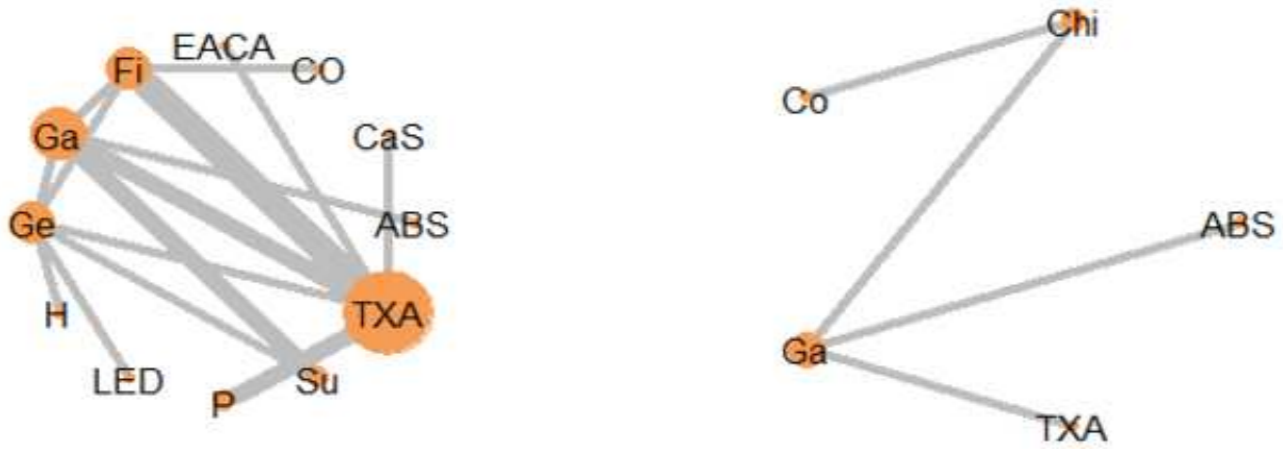


Fig 5

Click here to access/download;Figure;Fig 5.eps

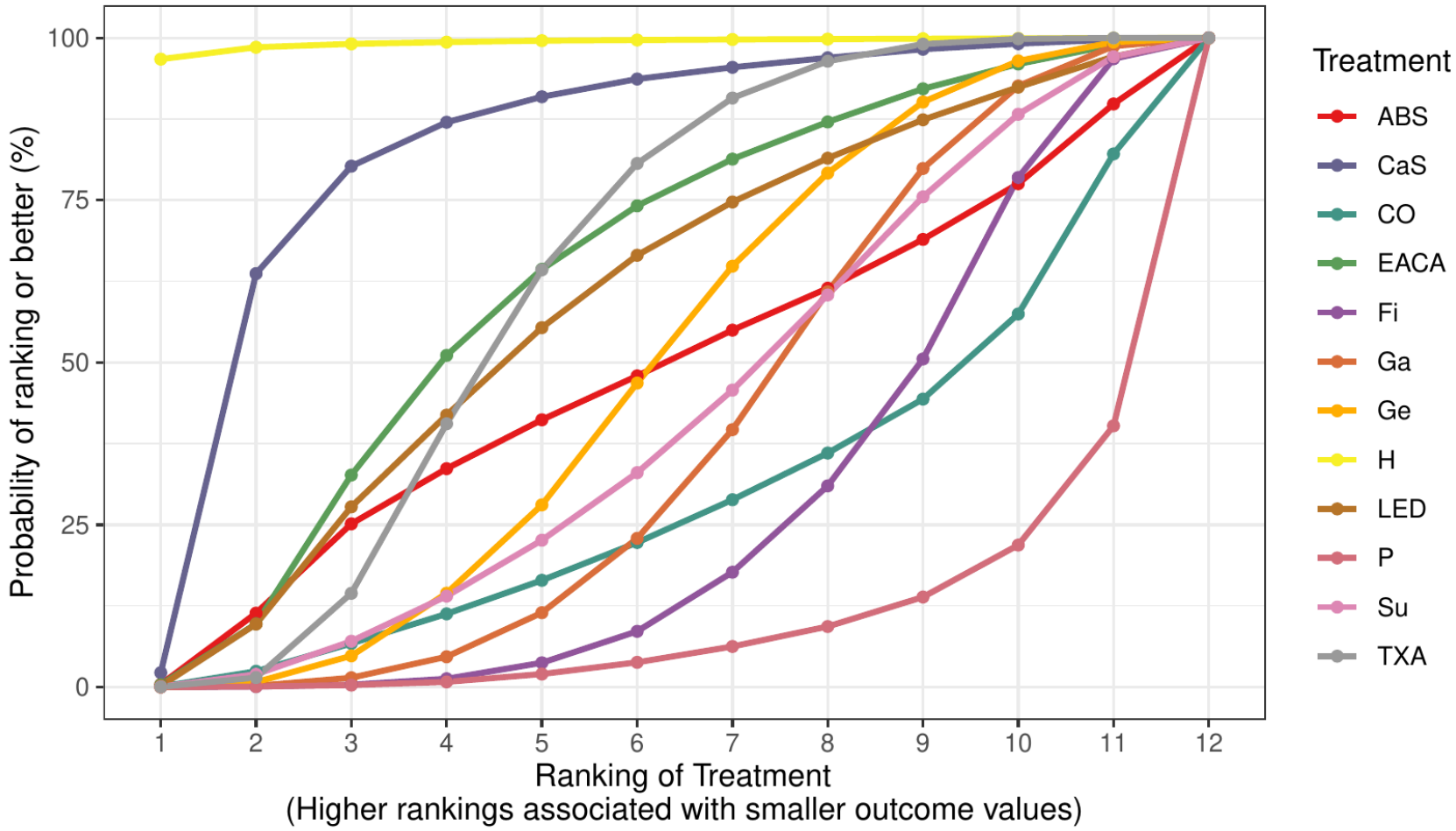


Fig 6

Click here to access/download;Figure;Fig 6.eps

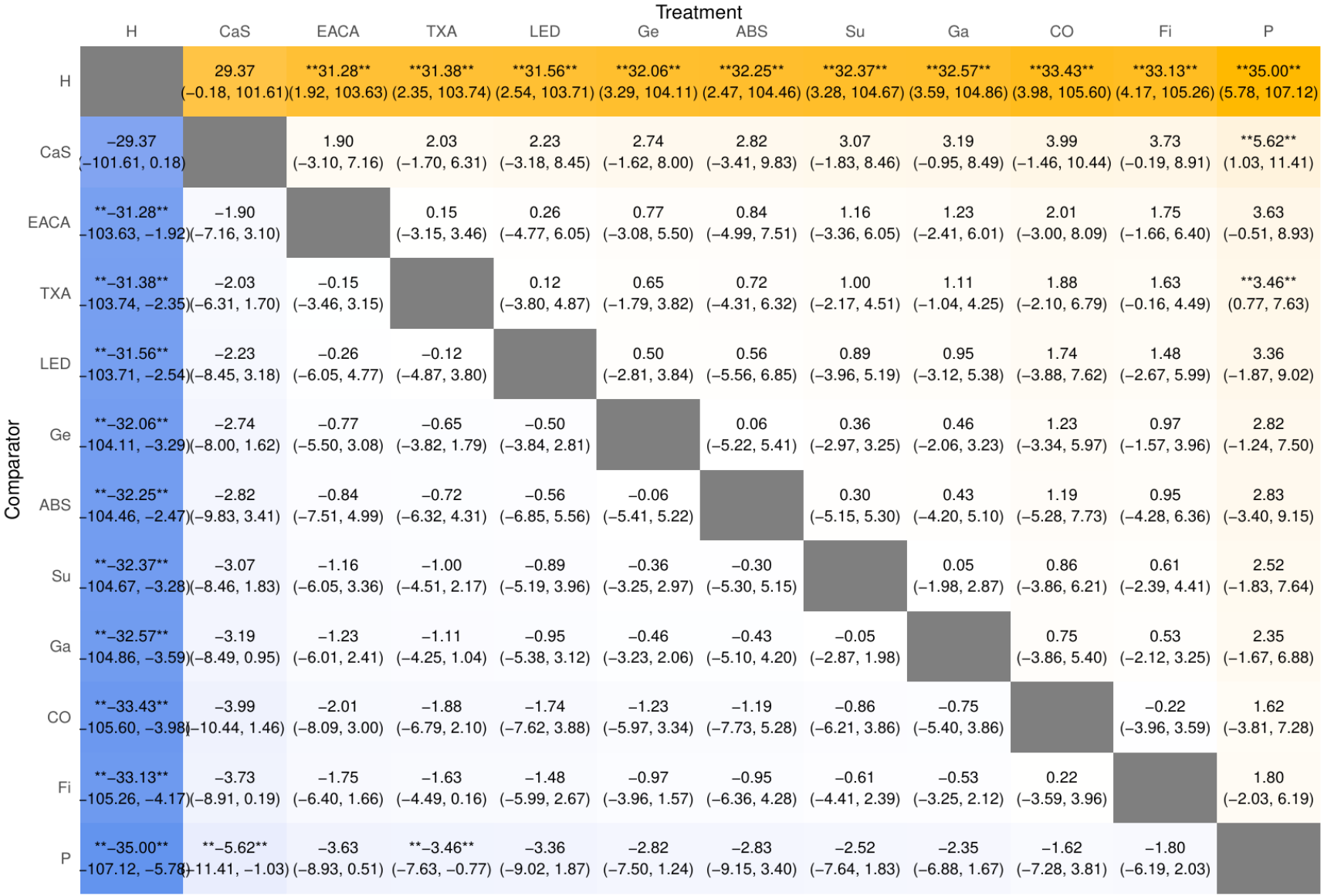


Fig 7

Click here to access/download;Figure;Fig 7.eps

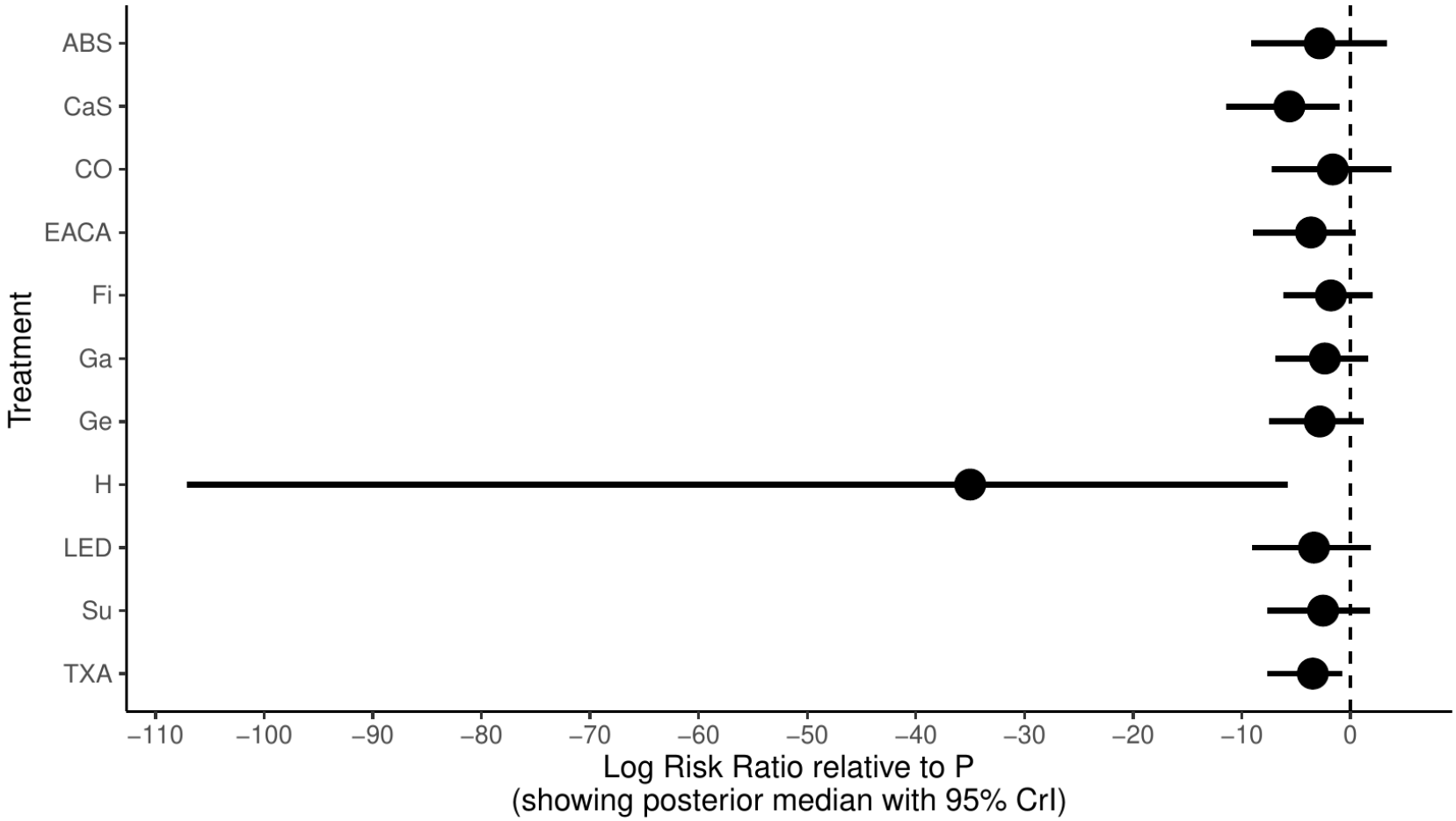


Fig 8

Click here to access/download;Figure;Fig 8.eps

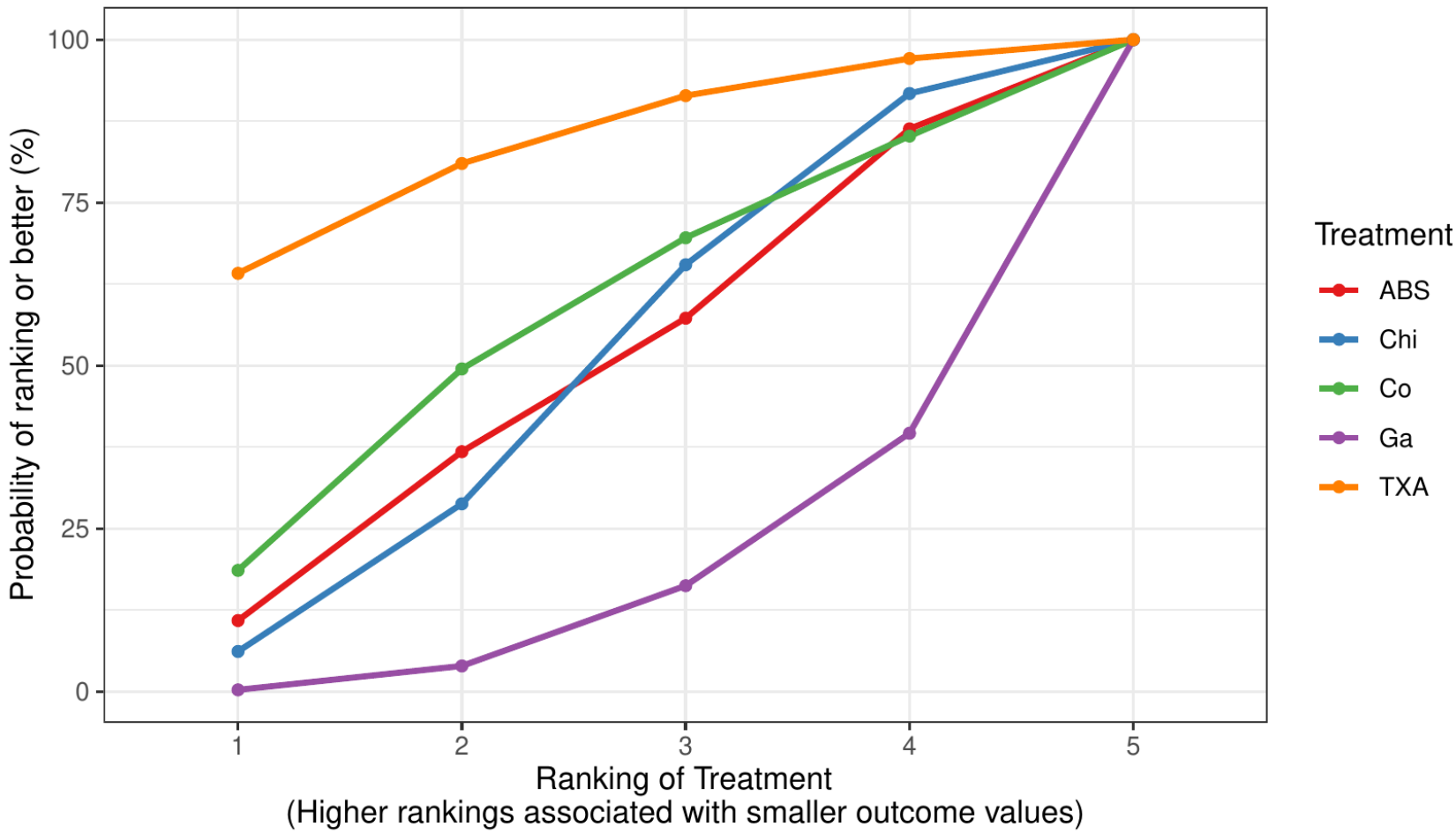


Fig 9

Click here to access/download;Figure;Fig 9.eps

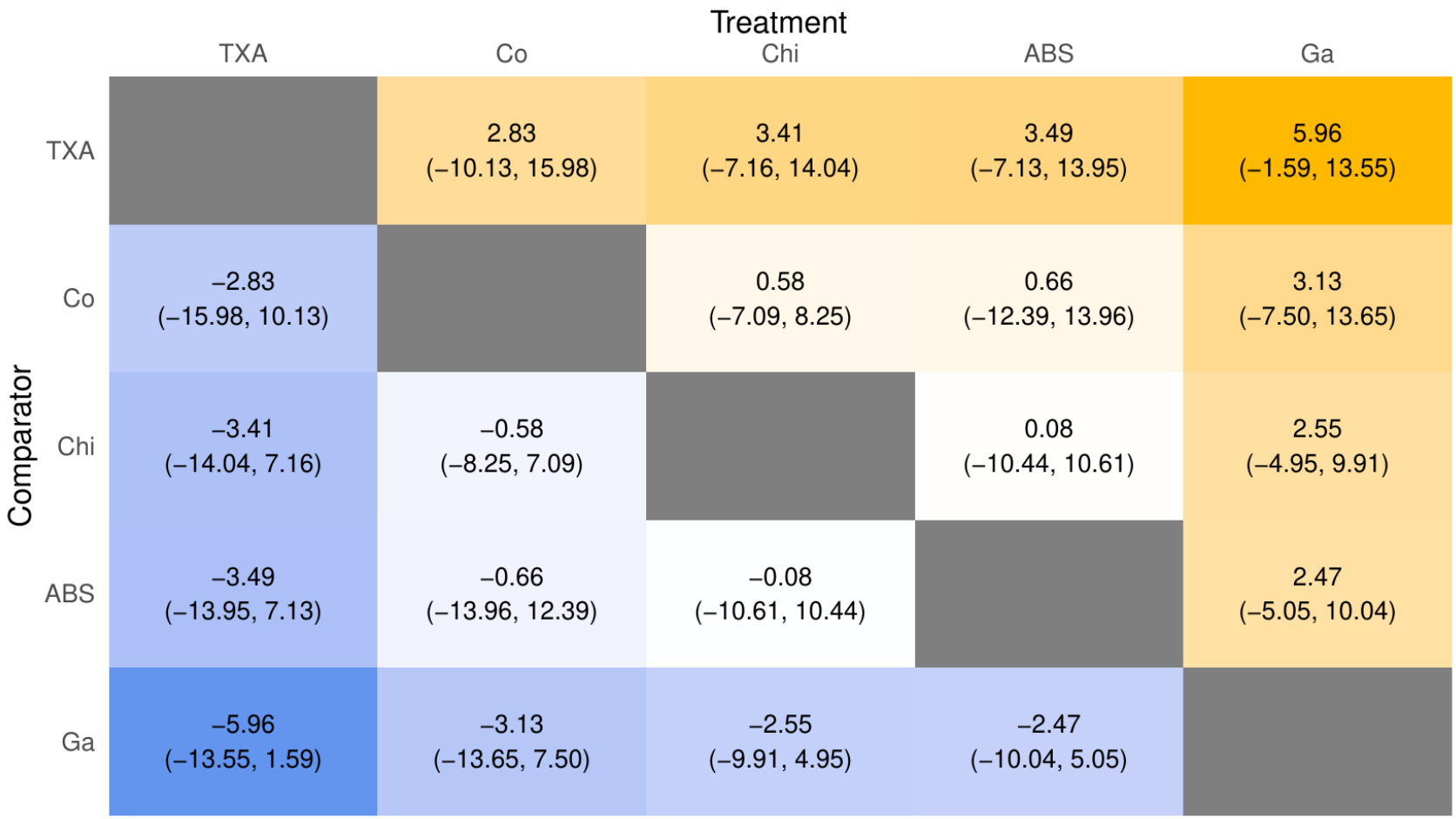


Fig 10

Click here to access/download;Figure;Fig 10.eps

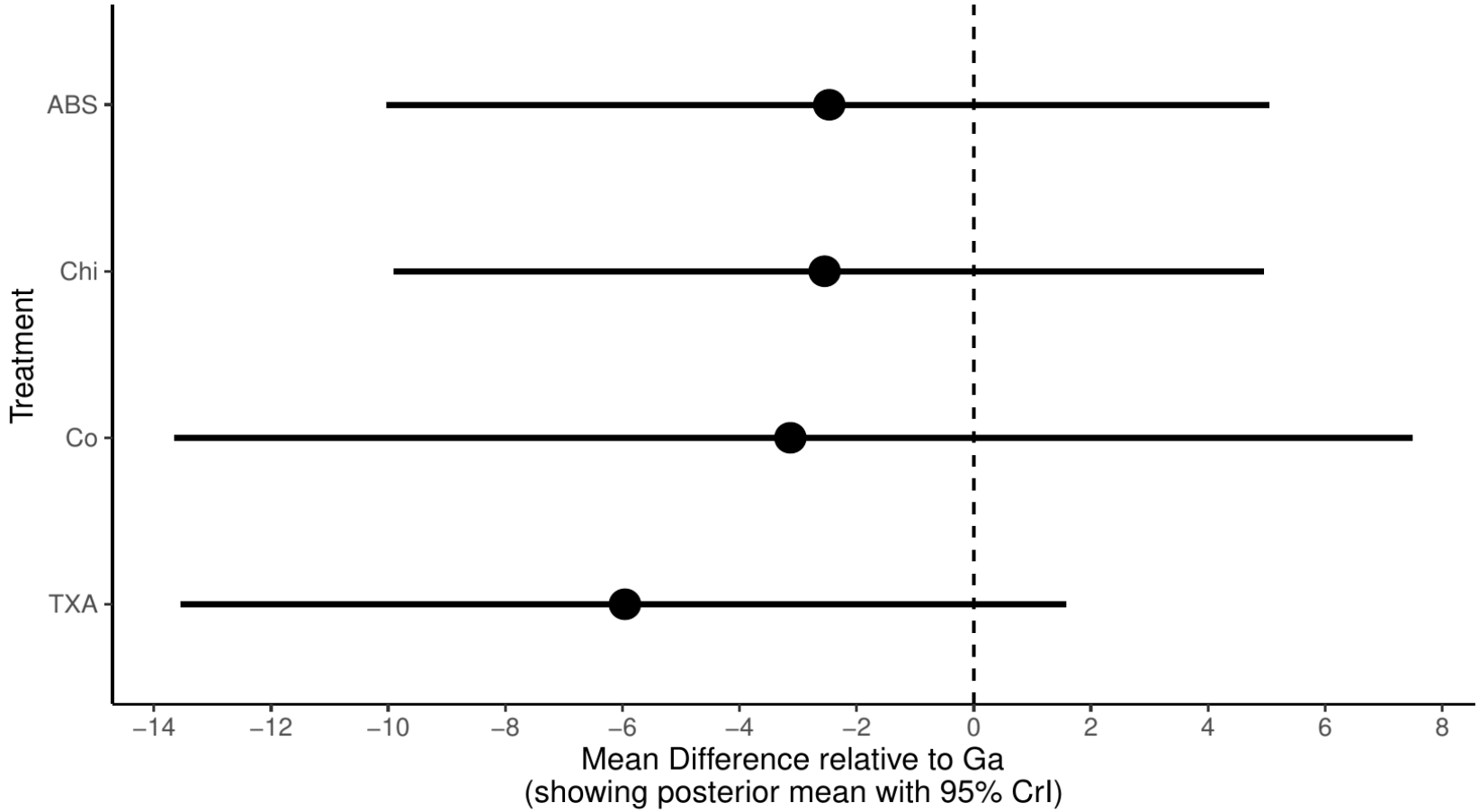


Table A.1: PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	Tittle page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta- analysis has been conducted.*	2
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 (Appendix A)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	6
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	6
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; And Assessment of model fit.*	6
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement studied. Describe efforts taken to address its presence when found.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses if done, indicating, which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	7

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	10
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	10 (Table 2)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9 (Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	10
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	10
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	13-14

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	14-15

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix A: Search strategy

MEDLINE (PubMed)

Search conducted on September 2020

Search	Query
#1	6-aminohexanoic acid [tw] OR 6 aminohexanoic acid [Mesh] OR 6 aminocaproic acid [tw] OR capramol [tw] OR caproamin [tw] OR epsamon [tw] OR epsikapron [tw] OR hemocaprol [tw] OR amicar [tw] OR AMCHA [tw] OR trans-4-(Aminomethyl)cyclohexanecarboxylic Acid [tw] OR t-AMCHA [tw] OR Tranexamic Acid [Mesh] OR AMCA [tw] OR anvitoff [tw] OR cyklokapron [tw] OR "ugurol" [tw] OR KABI 2161 [tw] OR "transamin" [tw] OR "exacyl" [tw] OR oxidized Cellulose [tw] OR Cellulose, Oxidized [Mesh] OR oxycellulose [tw] OR cellulosic Acid [tw] OR absorbable Cellulose [tw] OR carboxycellulose [tw] OR oxycel [tw] OR absorbable gelatin sponge [tw] OR absorbable gelatin sponges [tw] OR Gelatin Sponge, Absorbable [Mesh] OR gelfoam [tw] OR gelaspon [tw] OR absorbable collagen sponge [tw] OR fibrin glue [tw] OR Fibrin Tissue Adhesive [Mesh] OR fibrin adhesive [tw] OR fibrin sealant [tw] OR fibrin seal [tw] OR tisseel [tw] OR "tissel" [tw] OR tissucol [tw] OR beriplast [tw] OR fibrin Seal [tw] OR cyanoacrylate glue [tw] OR Cyanoacrylates [Mesh] OR ethyl cyanoacrylate [tw] OR ethyl-2-cyanoacrylate [tw] OR ethyl alpha-cyanoacrylate [tw] OR epiglue [tw] OR "krazy glue" [tw] OR "cyacrine" [tw] OR cyano-veneer [tw] OR Platelet-Rich Plasma [Mesh] OR topical thrombin [tw] OR Thrombin [Mesh] OR suture [tw] OR Sutures [Mesh] OR surgical staple [tw] OR stitch [tw] OR gauze pressure [tw] OR vasoconstrictor [tw] OR Vasoconstrictor Agents [Mesh]
#2	oral bleeding [tw] OR Oral Hemorrhage [Mesh] OR oral blood [tw] OR Hemostasis [Mesh] OR oral surgery [tw] OR Surgery, Oral [Mesh] OR oral hemorrhage [tw]
#3	Anticoagulants [Mesh] OR "factor xa inhibitor" [tw] OR "factor xa inhibitors" [Mesh] OR Rivaroxaban [Mesh] OR xarelto [tw] OR apixaban [tw] OR eliquis [tw] OR edoxaban [tw] OR lixiana [tw] OR savaysa [tw] OR betrixaban [tw] OR bevyxxa [tw] OR "thrombin inhibitor" [tw] OR "thrombin inhibitors" [tw] OR Antithrombins [Mesh] OR Dabigatran [Mesh] OR pradaxa [tw] OR melagatran [tw] OR ximelagatran [tw] OR exanta [tw] OR Heparin [Mesh] OR coumarin [tw] OR Coumarins [Mesh] OR Warfarin [Mesh] OR apo-warfarin [tw] OR aldocumar [tw] OR coumadin [tw] OR "marevan" [tw] OR warfarin potassium [tw] OR warfarin sodium [tw] OR "coumadine" [tw]
#4	randomized controlled trial [Mesh] OR clinical trial [Mesh]
#5	#1 AND #2 AND #3 AND #4

Table A.2: The assessment of risk of bias with the Joanna Briggs Institute (JBI) tool for randomized controlled trials

Authors	Was true randomization used for assignment of participants to treatment groups?	Was allocation to treatment groups concealed?	Were treatment groups similar at the baseline?	Were participants blind to treatment assignment?	Were those delivering treatment blind to treatment assignment?	Were outcomes assessors blind to treatment assignment?	Were treatment groups treated identically other than the intervention of interest?	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Were participants analyzed in the groups to which they were randomized?	Were outcomes measured in the same way for treatment groups?	Were outcomes measured in a reliable way?	Was appropriate statistical analysis used?	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?
Al-Belasy et al, 2003	Unclear	Unclear	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Al-Mubarak et al, 2007	Unclear	Unclear	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bajkin et al, 2014	Unclear	Unclear	Yes	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Baldoni M & Lauritano D, 2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Blinder et al, 1999	Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Cakarer et al, 2013	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Carter et al, 2003	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Carter, Goss., 2003	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
da Silva et al, 2018	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Soares et al, 2014	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Giuffre et al, 2006	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Halfpenny et al, 2001	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes
Kumar et al, 2016	Yes	Unclear	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Okamoto et al, 2014	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pippi et al, 2015	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Queiroz et al, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ramstrom et al, 1993	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ripollés et al, 2013	Yes	Yes	Unclear	No	No	No	Yes	Yes	Yes	Yes	Unclear	Yes	No
Scarano et al, 2014	Unclear	Unclear	Unclear	NA	NA	NA	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Sindet-Pedersen et al, 1989	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Souto et al, 1996	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Fig A.1. Leverage plots for convergent of model for bleeding events

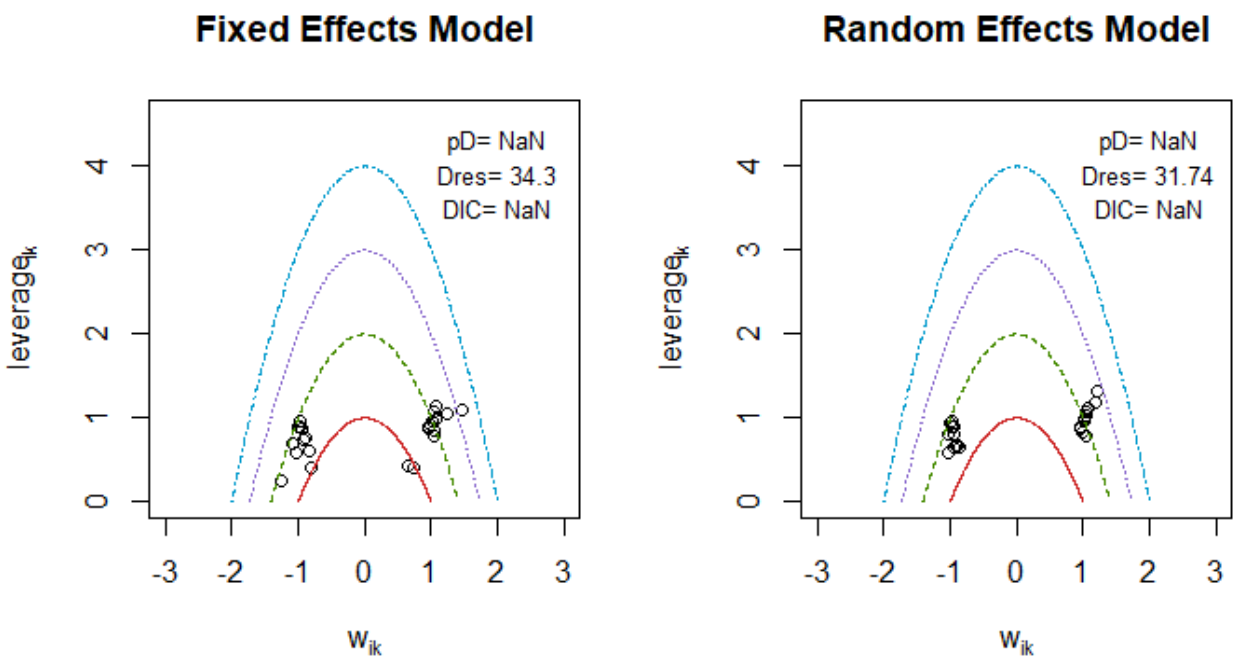
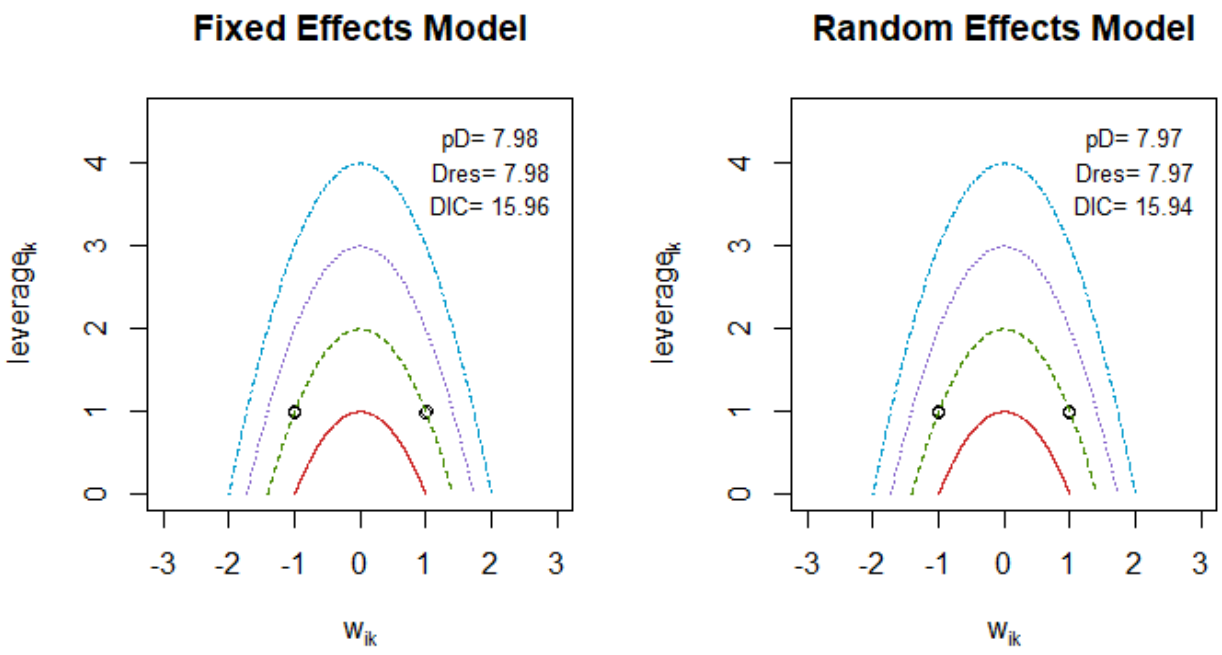


Fig A.2. Leverage plots for convergent of model for mean bleeding time



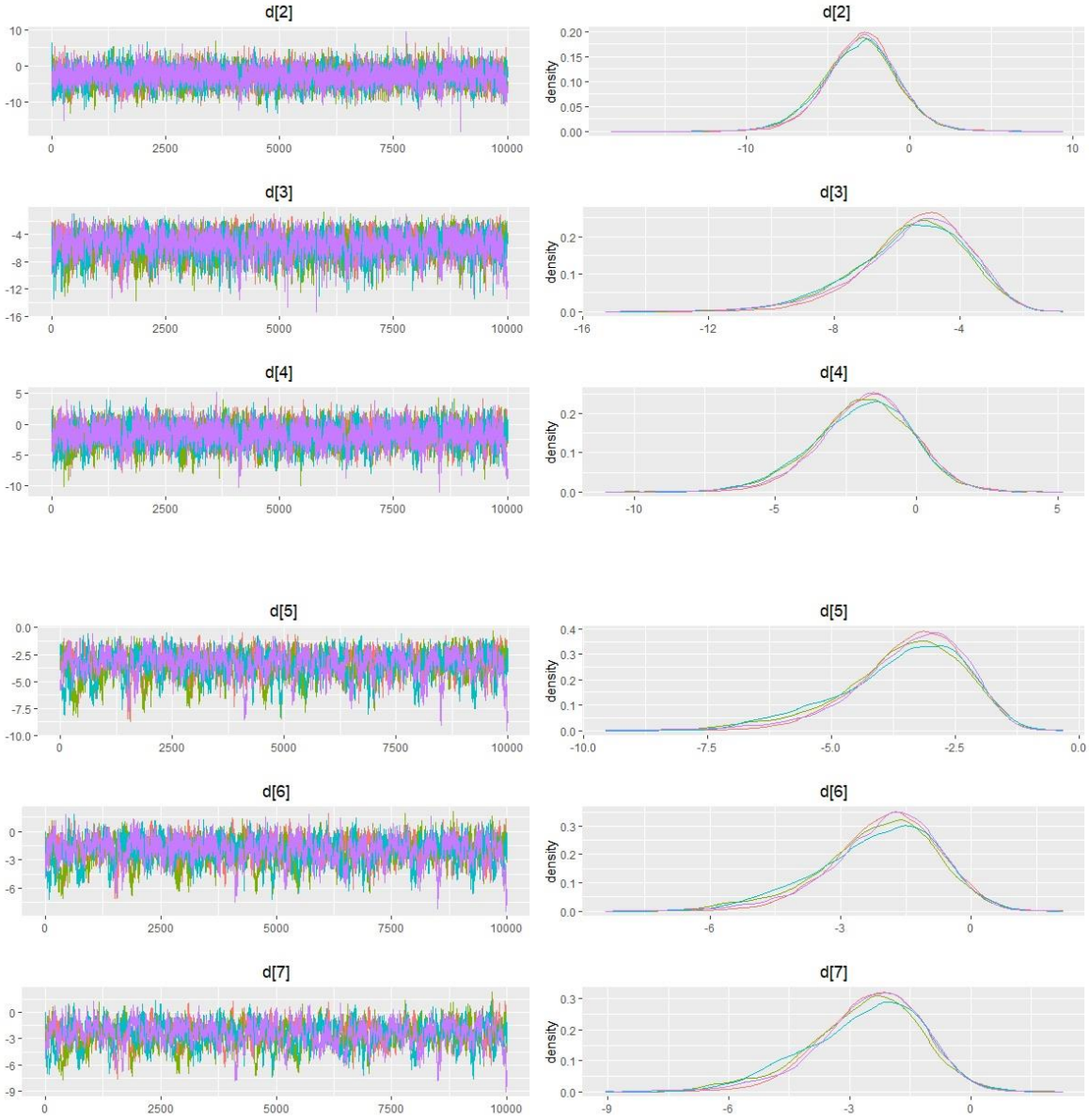
Appendix B. Trace plots for convergent model

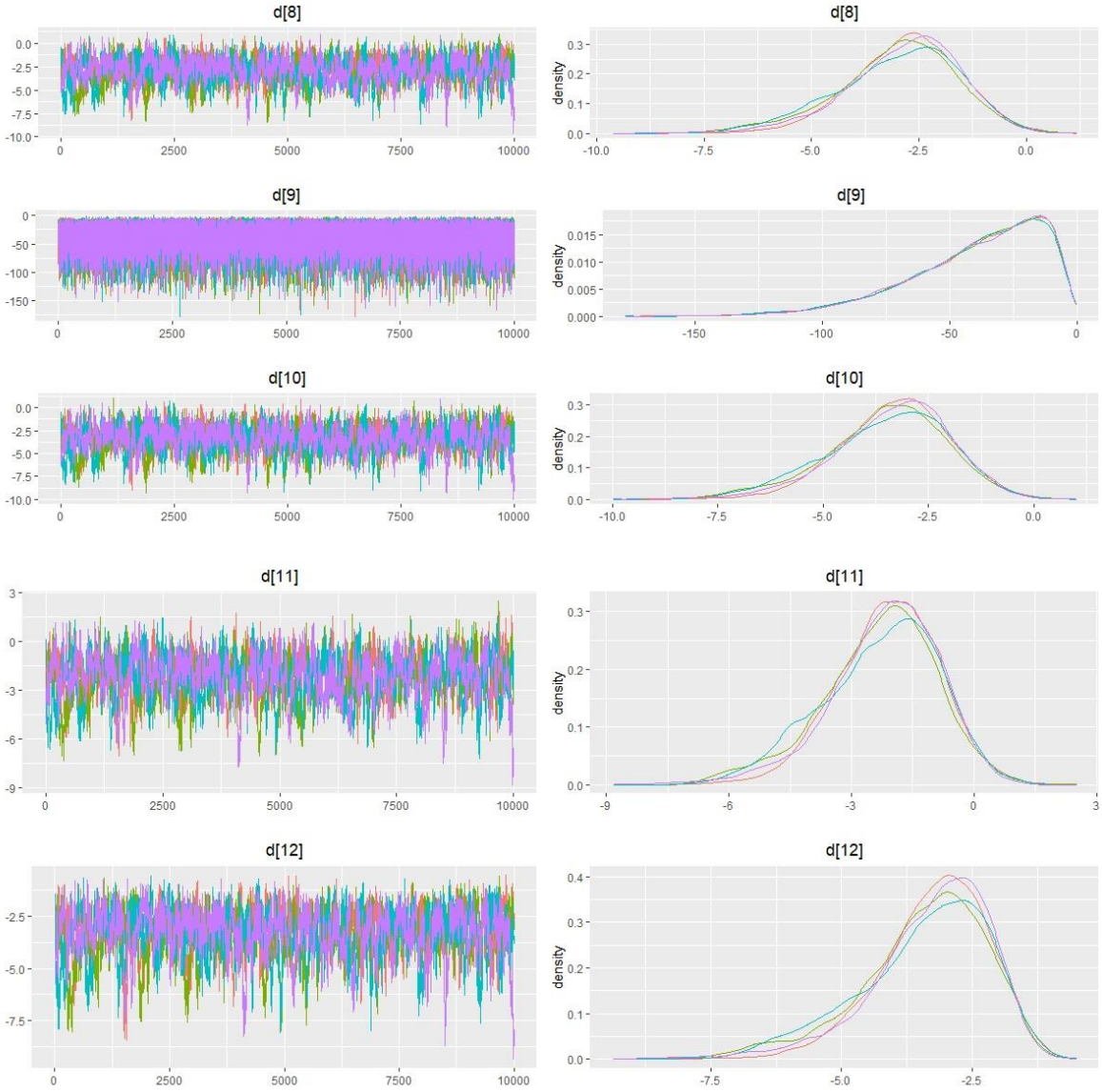
Trace plots

Evaluation of model

1. **Bleeding events**

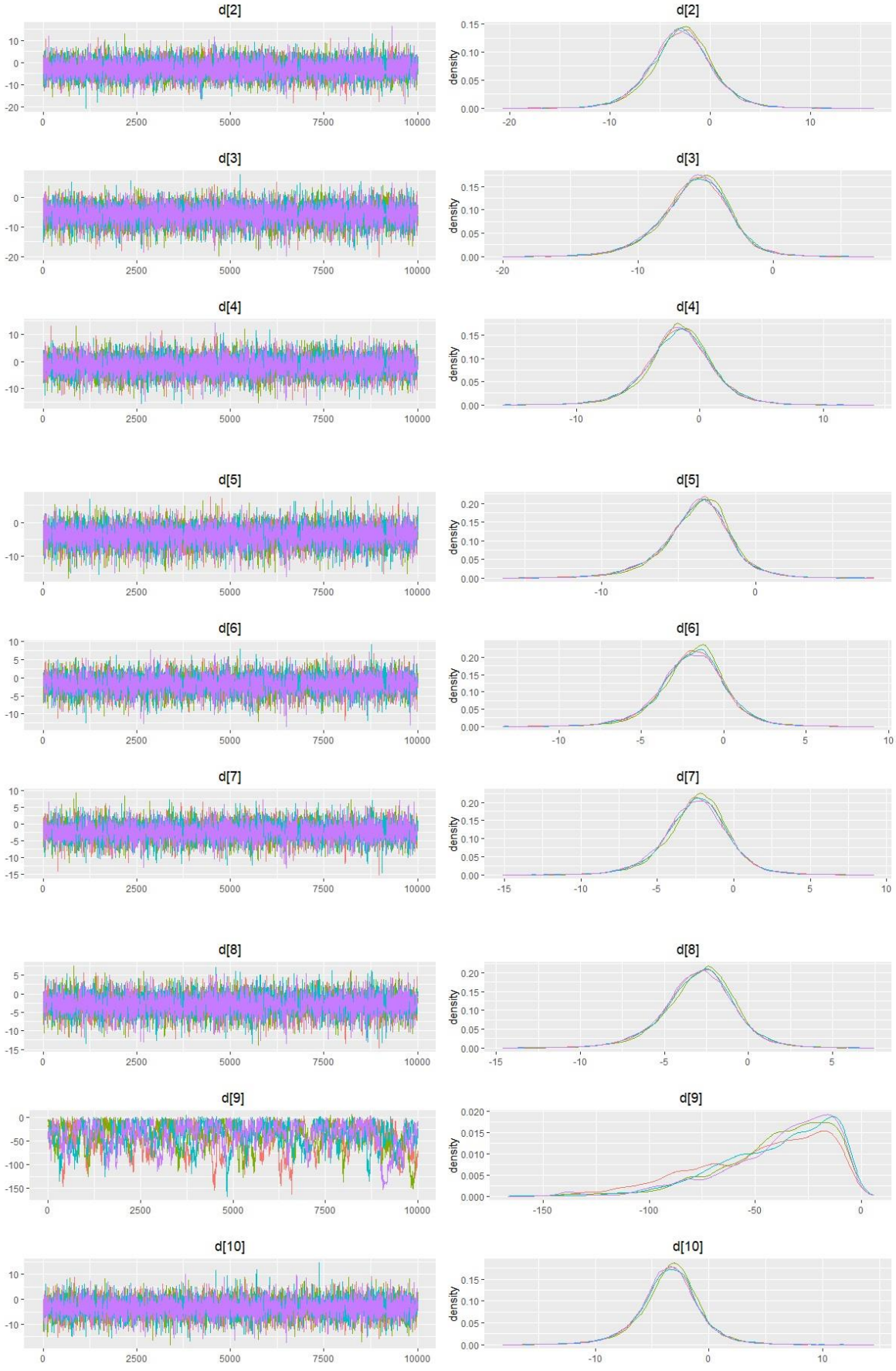
- Convergent fixed-effects model

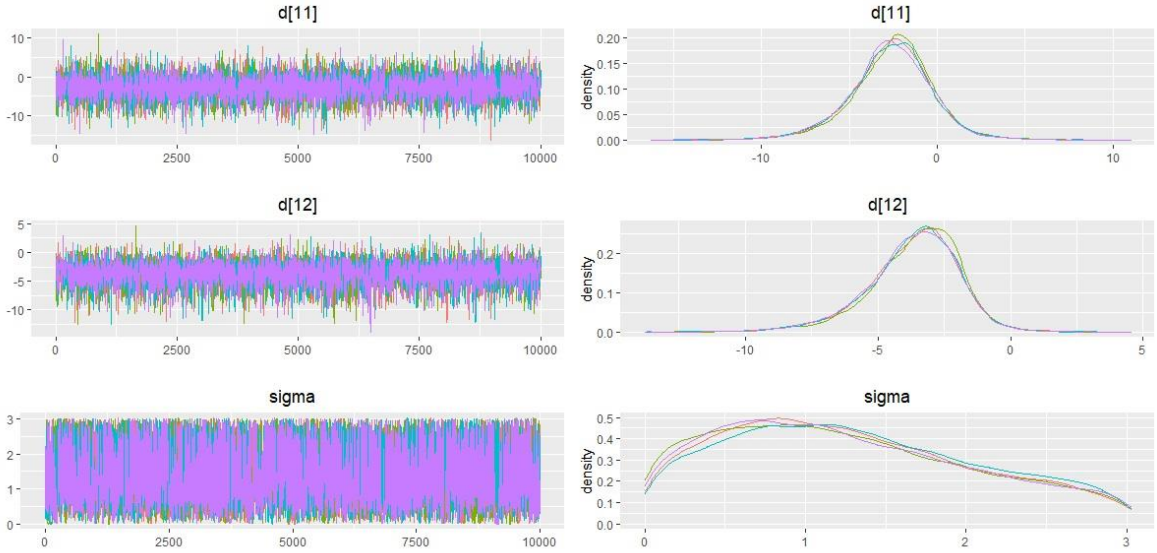




PRSF: 1.004927

- Convergent random-effects model

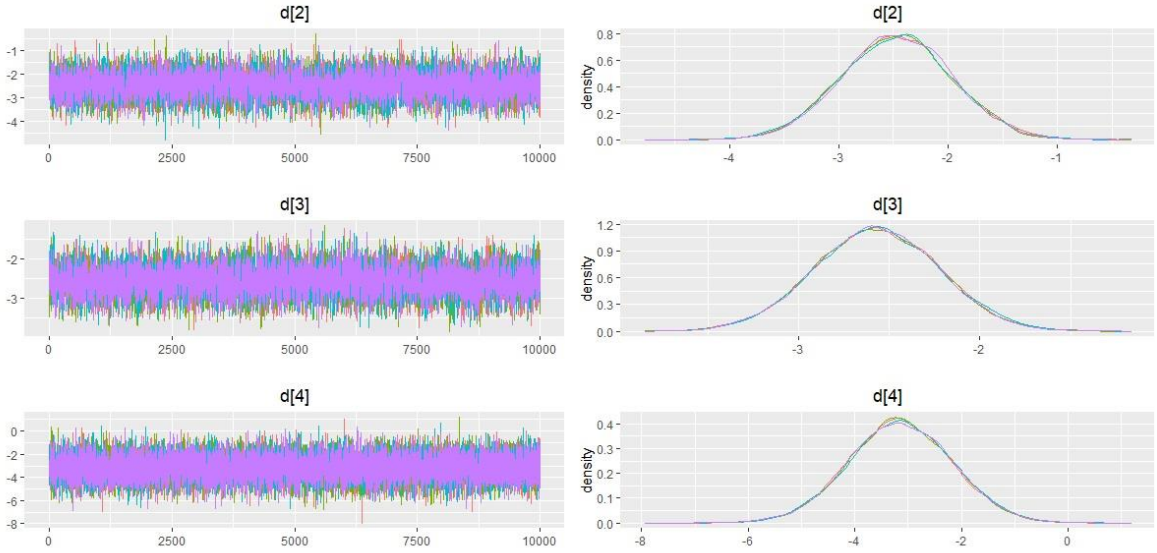

d[2]
d[2]
density
d[3]
d[3]
density
d[4]
d[4]
density
d[5]
d[5]
density
d[6]
d[6]
density
d[7]
d[7]
density
d[8]
d[8]
density
d[9]
d[9]
density
d[10]
d[10]
density

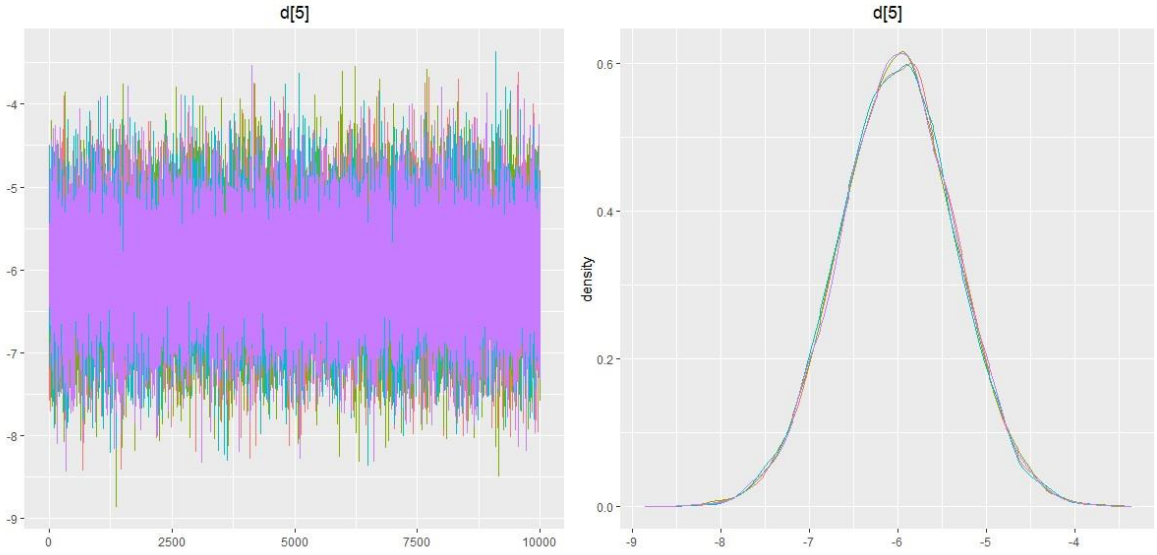


PRSF: 1.021224

2. Mean Bleeding time

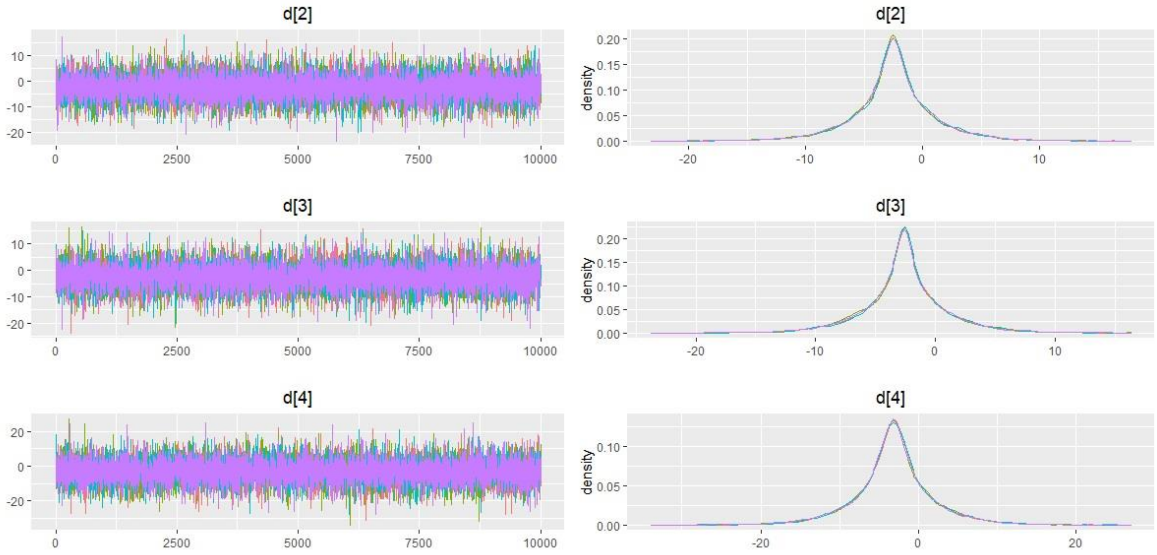
- Convergent fixed-effects model

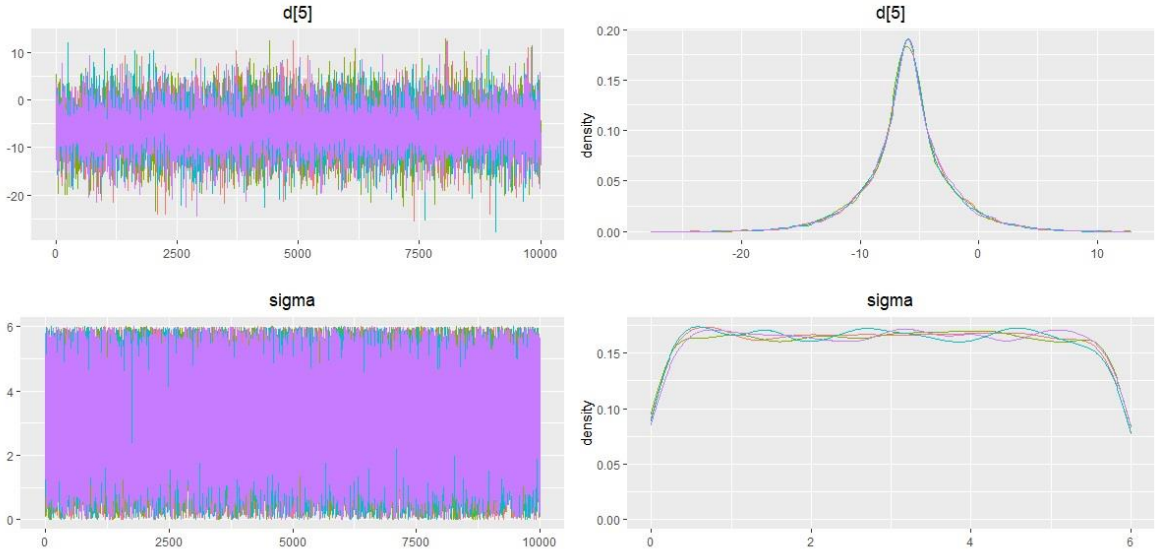




PRSF: 1.000174

- Convergent random-effects model





PRSF: 1.000265

Fig A.3. Heterogeneity for bleeding events

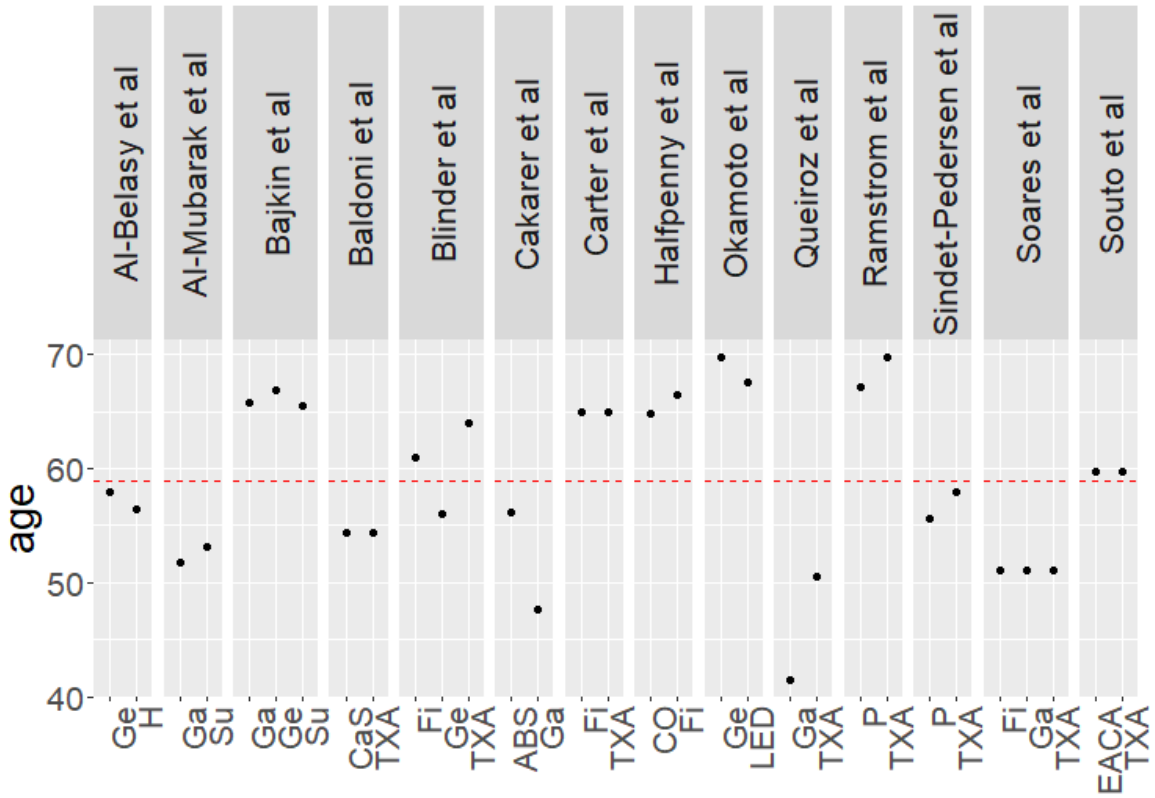


Fig A.4. Heterogeneity for mean bleeding time

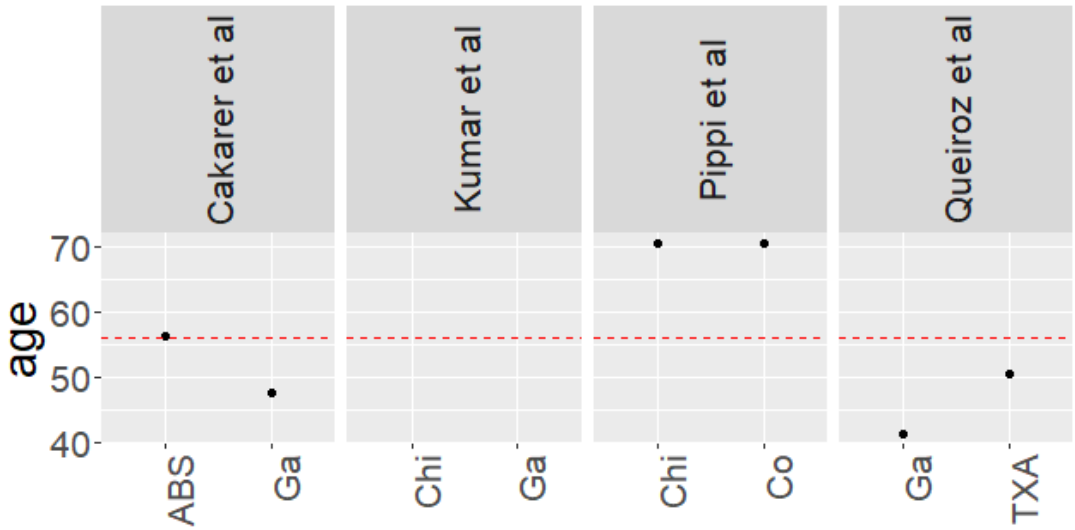


Fig A.5. Inconsistency model for bleeding events

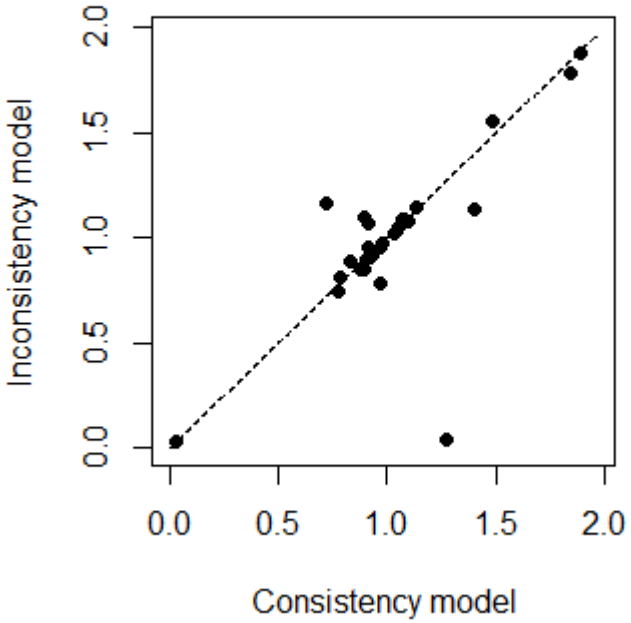


Fig A.6. Leverage plots for inconsistency model in bleeding events

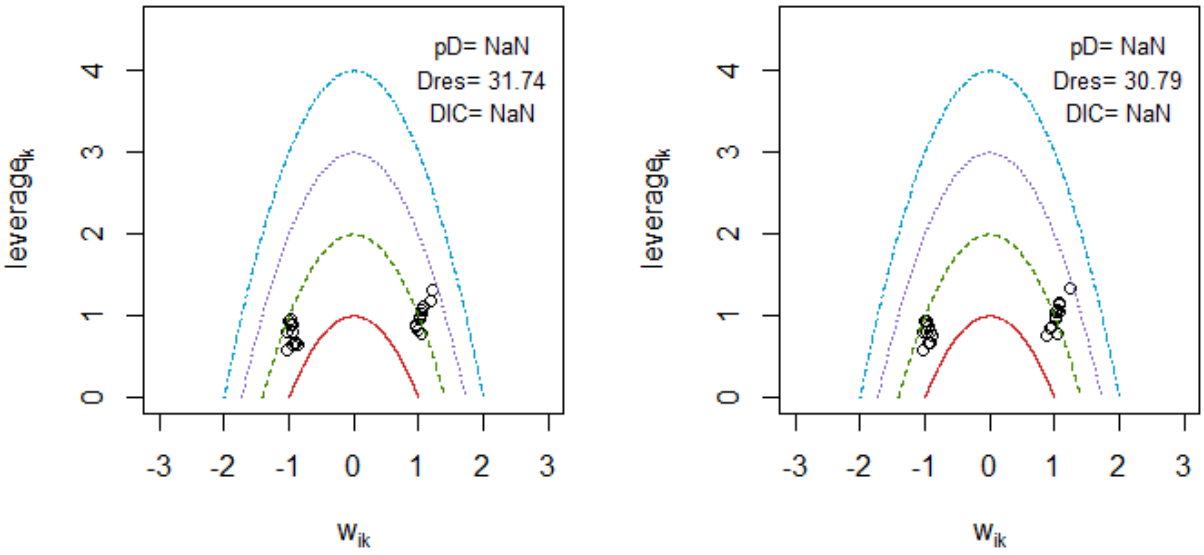


Fig A.7. Inconsistency model for mean bleeding time

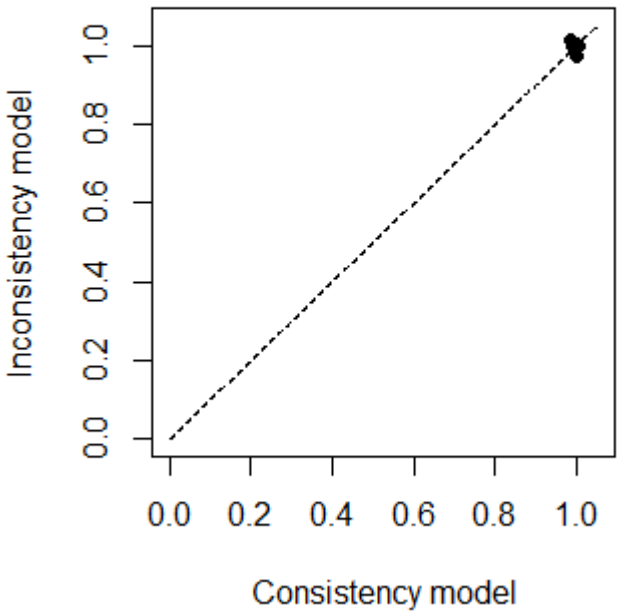


Fig A.8. Leverage plots for inconsistency model in mean bleeding time

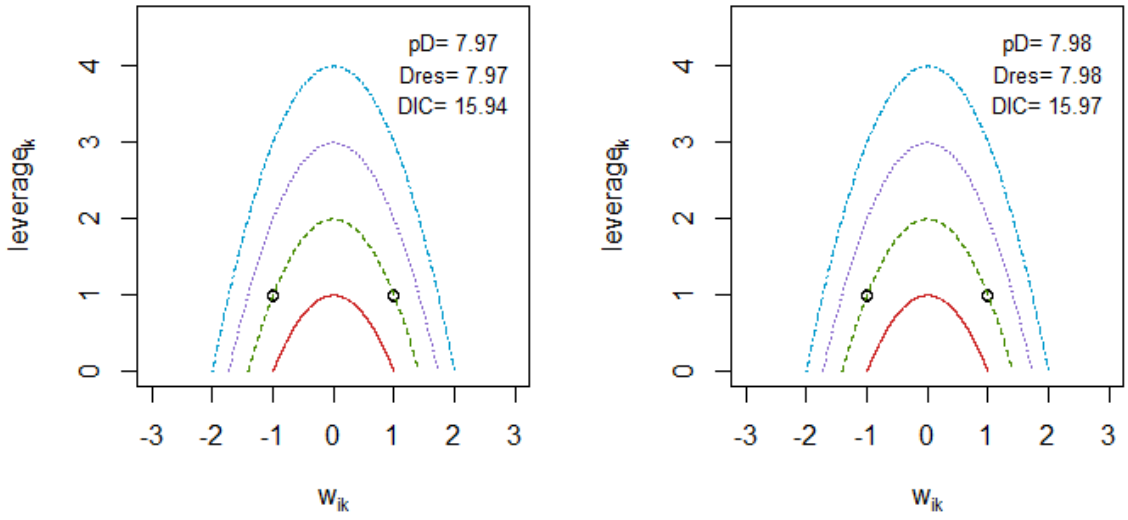


Fig A.9. Rankogram of interventions for bleeding events

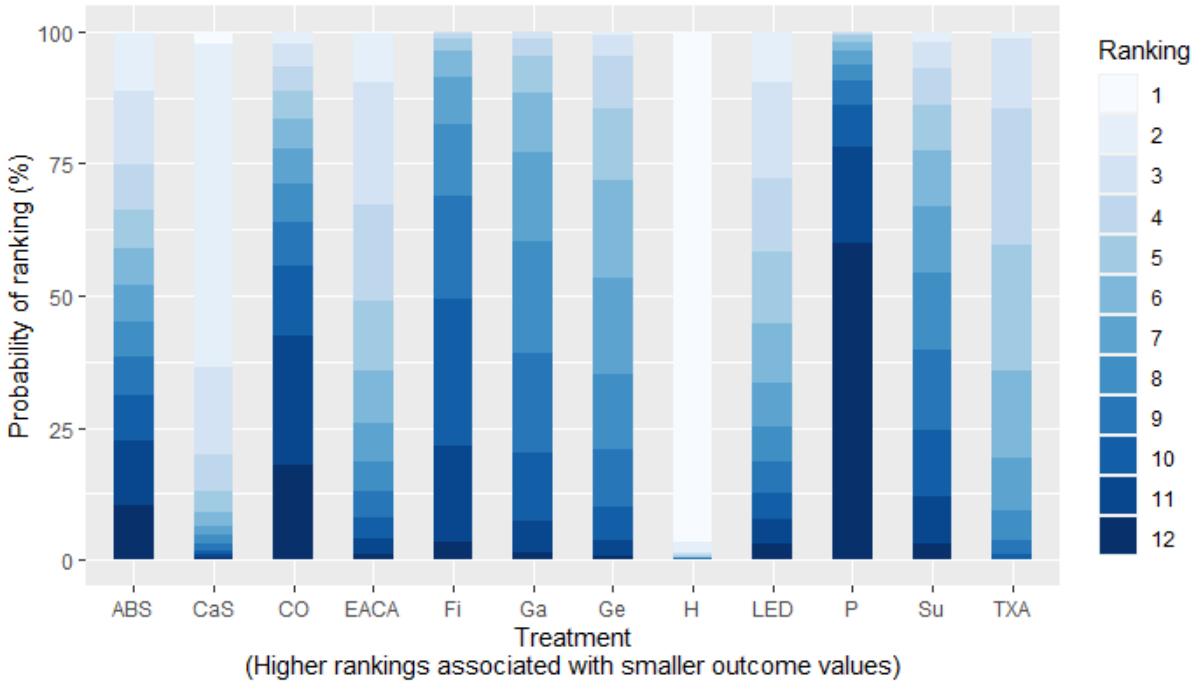
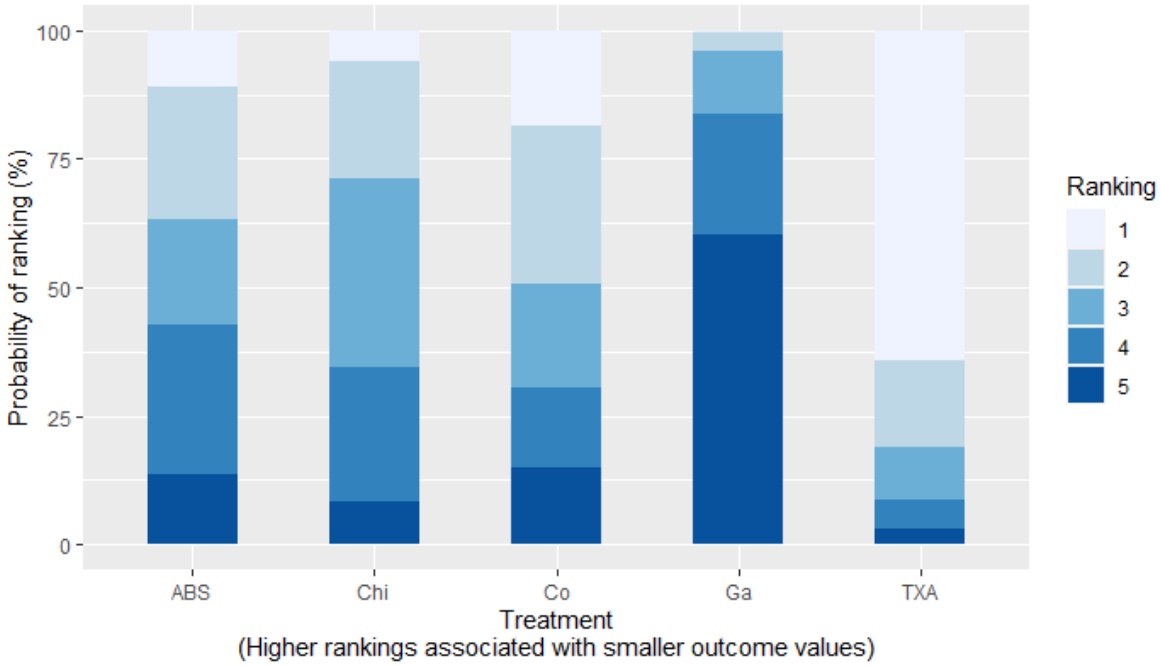
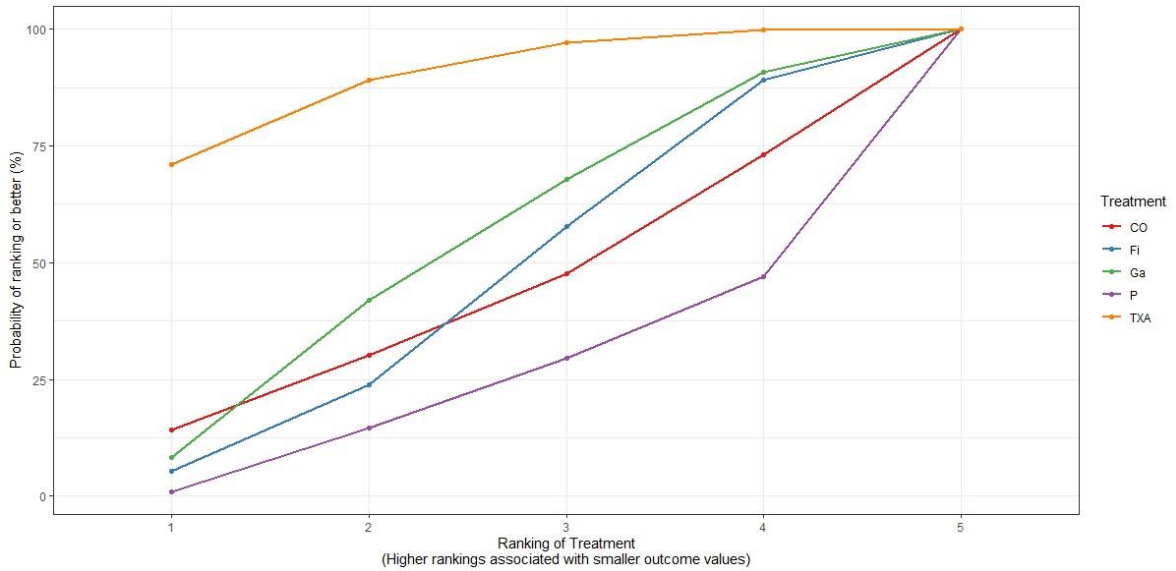


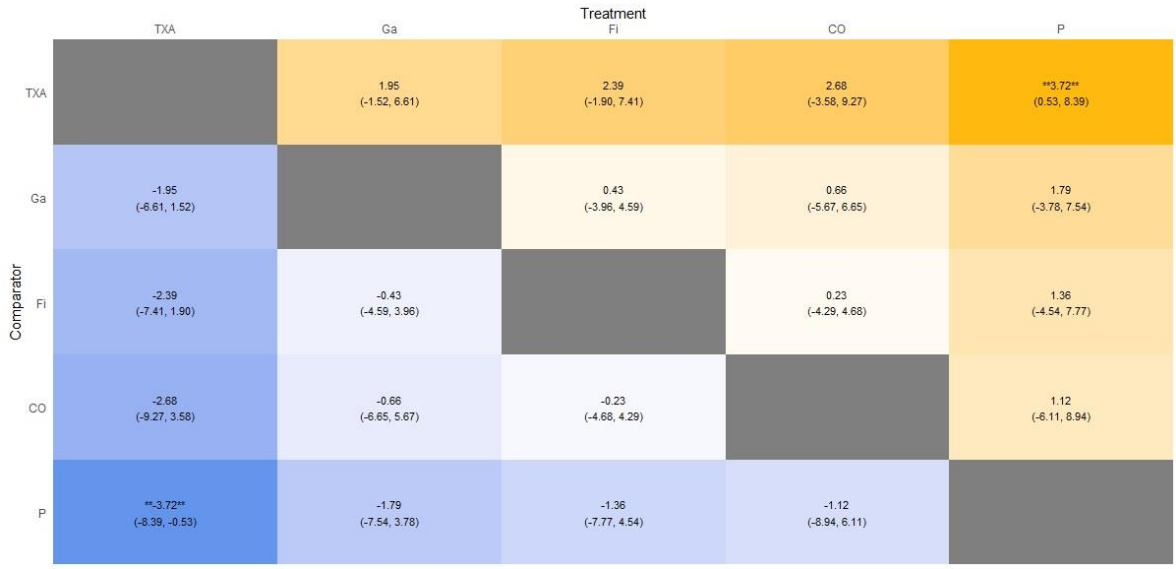
Fig A.10. Rankogram of interventions for mean bleeding time

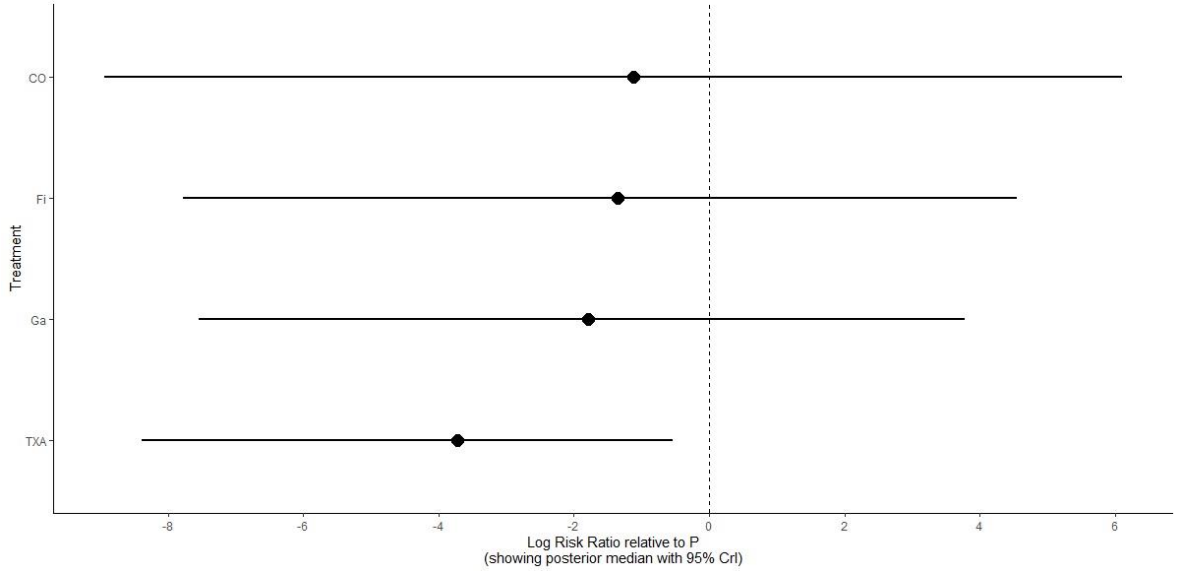


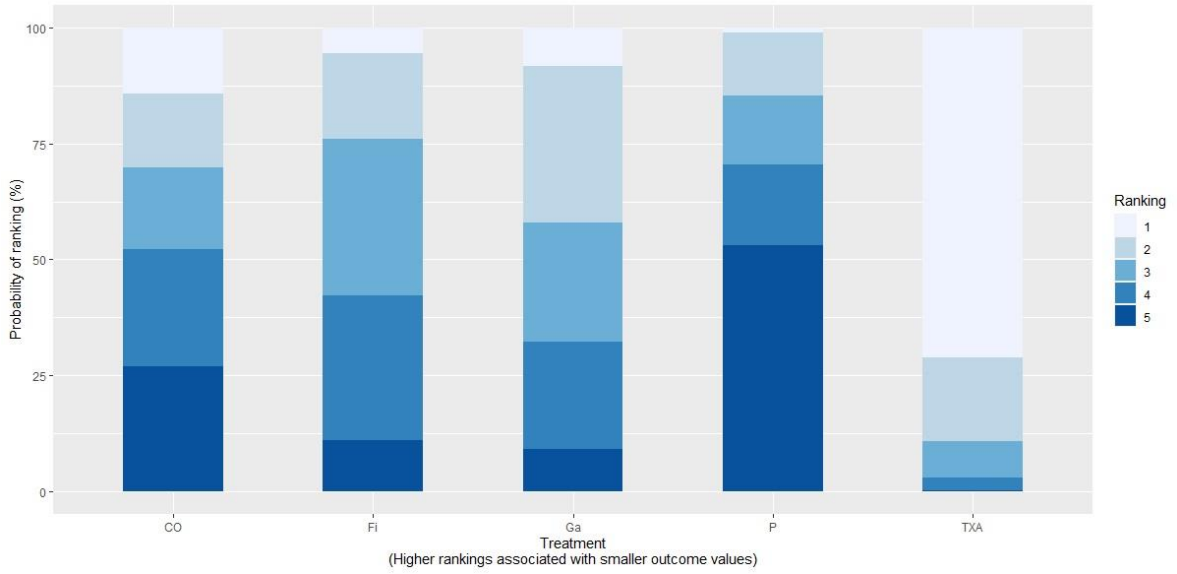
Appendix C. Sensitivity analysis for bleeding events

Sensitivity analysis- Bleeding events



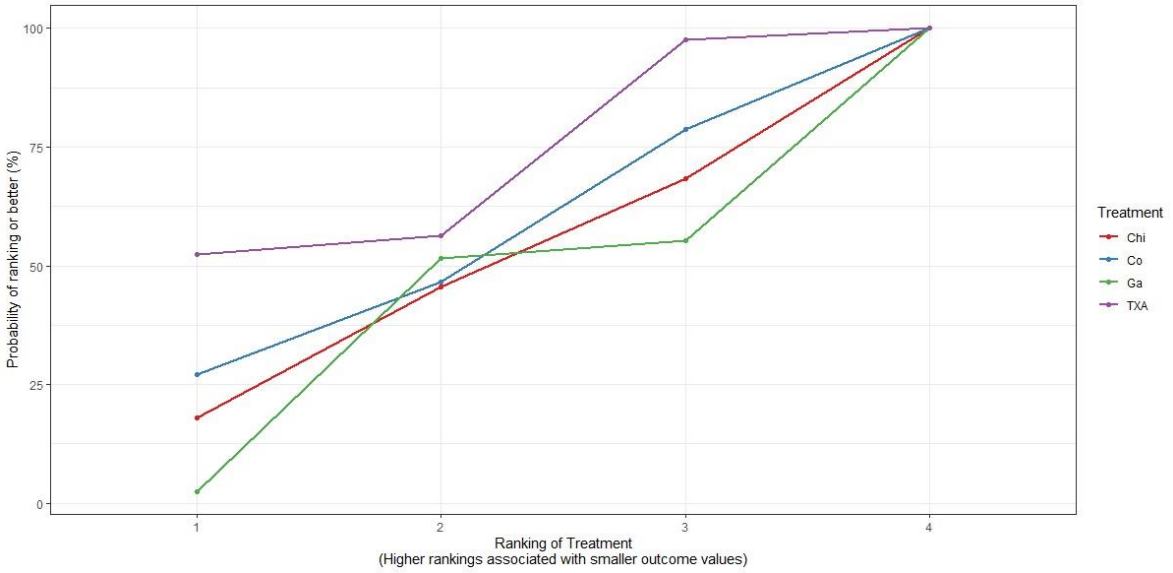


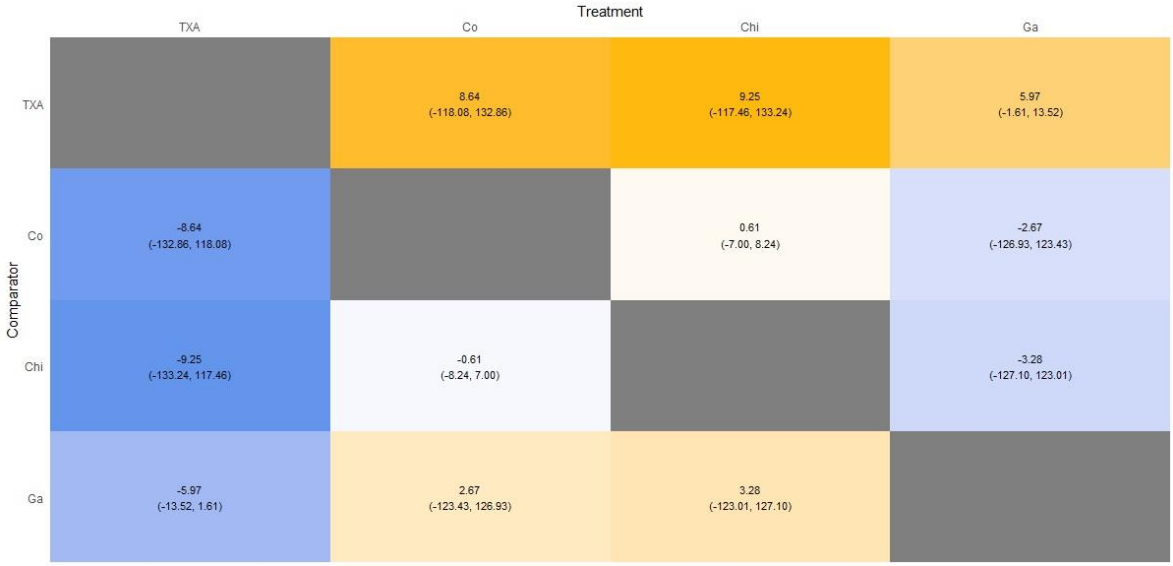

CO
Fi
Ga
TXA
Treatment
-8
-6
-4
-2
0
2
4
6
Log Risk Ratio relative to P
(showing posterior median with 95% CrI)

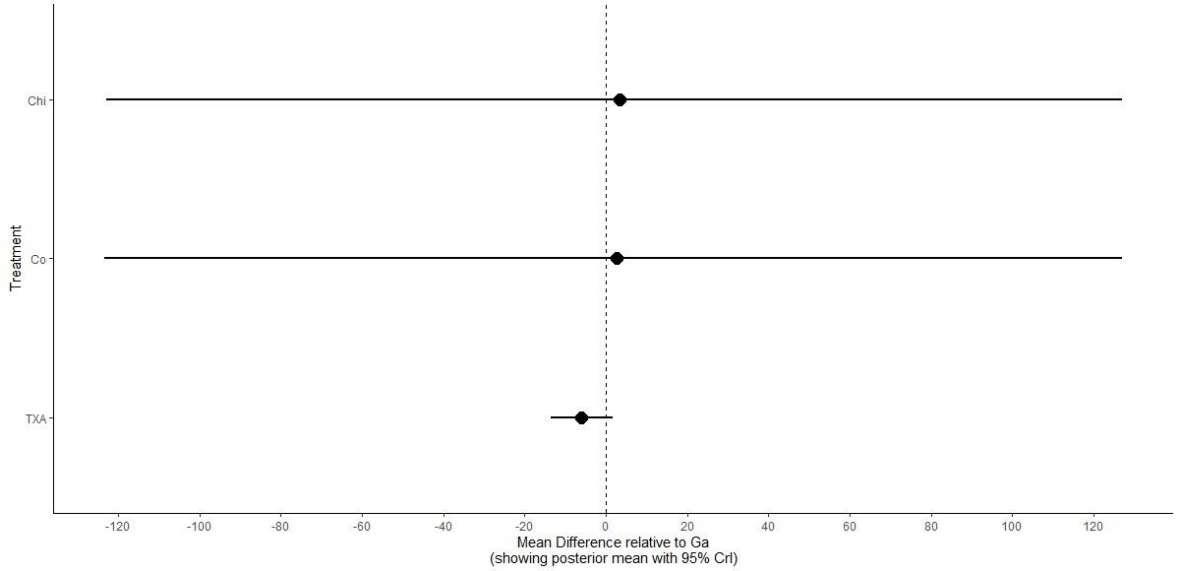

100
75
50
25
0
Probability of ranking (%)
CO
Fi
Ga
P
TXA
Treatment
(Higher rankings associated with smaller outcome values)
Ranking
1
2
3
4
5

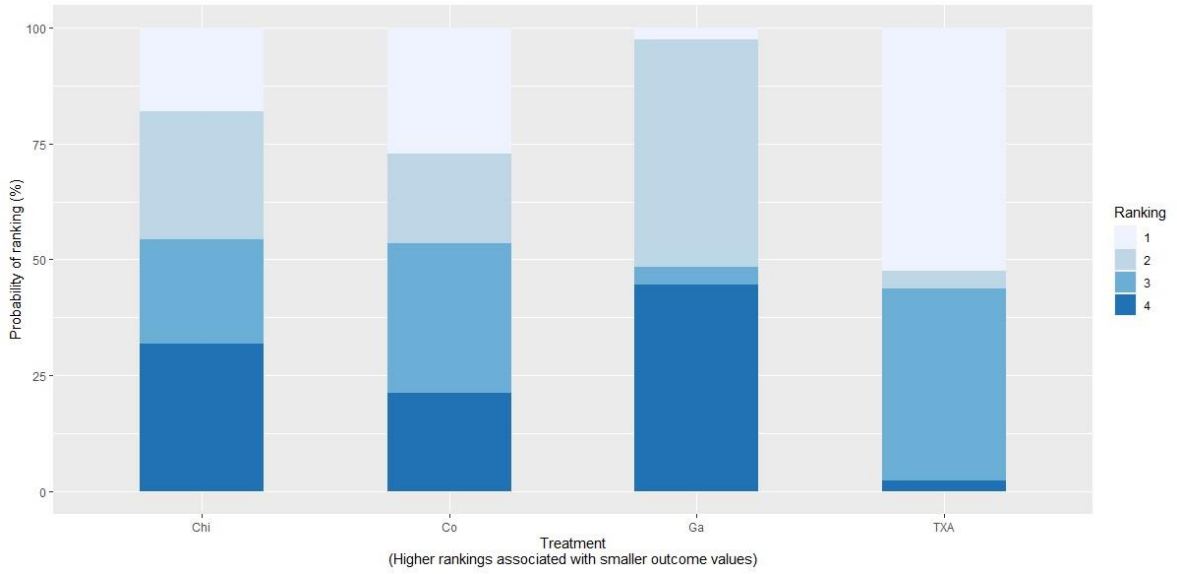
Appendix D. Sensitivity analysis for mean bleeding time

Sensitivity analysis- Mean Bleeding time






Chi
Co
TXA
Treatment
-120
-100
-80
-60
-40
-20
0
20
40
60
80
100
120
Mean Difference relative to Ga
(showing posterior mean with 95% CrI)


100
75
50
25
0
Probability of ranking (%)
Chi
Co
Ga
TXA
Treatment
(Higher rankings associated with smaller outcome values)
Ranking
1
2
3
4

Appendix E. GRADE evaluation

Table 1. GRADE evaluation of the analysis of the direct comparisons between hemostatic agents for the prevention of bleeding events during oral procedures of individuals on oral anticoagulant treatment (OAT).

Comparison	NMA RR 95%IC	Risk of bias	Inconsistency	Indirectness	Publication bias	Imprecision	Incoherence	Quality of evidence
ABS vs Ga	-0.43 (-5.10;4.20)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
TXA vs. CaS	2.03 (-1.70;6.31)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
CO vs. Fi	0.22 (-3.59;3.96)	No	No	No	Undetected	Serious	No	⊕⊕⊕◯ Moderate
TXA vs. EACA	0.15 (-3.15;3.46)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
Fi vs. Ga	0.53 (-2.12;3.25)	No	No	No	Undetected	Serious	No	⊕⊕⊕◯ Moderate
Fi vs. Ge	0.97 (-1.57;3.96)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
TXA vs. Fi	-1.63 (-4.49;0.16)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
Ga vs. Ge	-0.46 (-3.23;2.06)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
Su vs. Ga	-0.05 (-2.87;1.98)	Serious	No	No	Undetected	No	No	⊕⊕⊕◯ Moderate

TXA vs. Ga	-1.11 (-4.25;1.04)	No	No	No	Undetected	Serious	No	⊕⊕⊕◯ Moderate
Ge vs. H	32.06 (3.29:104.11)	Serious	Serious	No	Undetected	Serious	No	⊕◯◯◯ Very low
LED vs. Ge	-0.50 (-3.84;2.81)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
Ge vs. Su	-0.36 (-3.25;2.97)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
TXA vs. Ge	-0.65 (-3.82;1.79)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
TXA vs. P	-3.46 (-7.63;-0.77)	No	No	Yes	Undetected	No	No	⊕⊕⊕◯ Moderate

Table 2. GRADE evaluation of the analysis of the direct comparisons between hemostatic agents for the mean bleeding time during oral procedures of individuals on oral anticoagulant treatment (OAT).

Comparison	NMA Mean DS	Risk of bias	Inconsistency	Indirectness	Publication bias	Imprecision	Incoherence	Quality of evidence
ABS vs. Ga	-2.47 (-10.04;5.05)	Serious	No	No	Undetected	Serious	No	⊕⊕◯◯ Low
Chi vs. Co	0.58 (-7.09;8.25)	No	No	Serious	Undetected	Serious	No	⊕⊕◯◯ Low
Chi vs. Ga	-2.55 (-9.91;4.95)	Serious	No	Serious	Undetected	Serious	No	⊕◯◯◯ Very low
Ga vs. TXA	5.96 (-1.59;13.55)	No	No	No	Undetected	Serious	No	⊕⊕⊕◯ Moderate

Table 3. GRADE evaluation of the analysis of the indirect comparisons between hemostatic agents for the prevention of bleeding events during oral procedures of individuals on oral anticoagulant treatment (OAT).

Comparison	NMA RR 95%IC	Intransitivity	Imprecision	Incoherence	Quality of evidence
ABS vs. CO	-1.19 (-7.73;5.28)	No	Serious	No	⊕⊕◯◯ Low
Su vs. CO	-0.86 (-6.21;3.86)	No	Serious	No	⊕⊕◯◯ Low
Su vs. P	-2.52 (-7.64;1.83)	Serious	Serious	No	⊕◯◯◯ Very low
Su vs. Fi	-0.61 (-4.41;2.39)	No	Serious	No	⊕⊕◯◯ Low
ABS vs. Su	-0.30 (-5.30;5.15)	No	Serious	No	⊕⊕◯◯ Low
ABS vs. P	-2.83 (-9.15;3.40)	Serious	Serious	No	⊕◯◯◯ Very low
ABS vs. Fi	-0.95(-6.36;4.28)	No	Serious	No	⊕⊕◯◯ Low
LED vs. ABS	-0.56 (-6.85;5.56)	No	Serious	No	⊕⊕◯◯ Low
LED vs. Su	-0.89 (-5.19;3.96)	No	Serious	No	⊕⊕◯◯ Low
LED vs. CO	-1.74 (-7.62;3.88)	No	Serious	No	⊕⊕◯◯ Low
LED vs. Fi	-1.48 (-5.99;2.67)	No	Serious	No	⊕⊕◯◯ Low
LED vs. P	-3.36 (-9.02;1.87)	Serious	Serious	No	⊕◯◯◯ Very low
LED vs. Ga	-0.95 (-5.38;3.12)	No	Serious	No	⊕⊕◯◯ Low
Ge vs. ABS	-0.06 (-5.41;5.22)	No	Serious	No	⊕⊕◯◯ Low
Ge vs. CO	-1.23 (-5.97;3.34)	No	Serious	No	⊕⊕◯◯ Low

TXA vs. CO	-1.88 (-6.79;2.10)	No	Serious	No	⊕⊕◯◯ Low
TXA vs. Su	-1.00 (-4.51;2.17)	No	Serious	No	⊕⊕◯◯ Low
TXA vs. ABS	-0.72 (-6.32;4.31)	No	Serious	No	⊕⊕◯◯ Low
TXA vs. LED	-0.12 (-4.87;3.80)	No	Serious	No	⊕⊕◯◯ Low
P vs. EACA	3.63 (-0.51;8.93)	Serious	Serious	No	⊕◯◯◯ Very low
Fi vs. EACA	1.74 (-1.66;6.40)	No	Serious	No	⊕⊕◯◯ Low
CO vs. EACA	2.01 (-3.00;8.09)	No	Serious	No	⊕⊕◯◯ Low
Ga vs. EACA	1.23 (-2.41;6.01)	No	Serious	No	⊕⊕◯◯ Low
Su vs. EACA	1.16 (-3.36;6.05)	No	Serious	No	⊕⊕◯◯ Low
ABS vs. EACA	0.84 (-4.99;7.51)	No	Serious	No	⊕⊕◯◯ Low
Ge vs. EACA	0.77 (-3.08;5.50)	No	Serious	No	⊕⊕◯◯ Low
LED vs. EACA	0.26 (-4.77;6.05)	No	Serious	No	⊕⊕◯◯ Low
P vs. H	35.00 (5.78;107.12)	Serious	Serious	No	⊕◯◯◯ Very low
Fi vs. H	33.13 (4.17;105.26)	No	Serious	No	⊕◯◯◯ Very low
CO vs. H	33.43 (3.98;105.60)	No	Serious	No	⊕◯◯◯ Very low
Su vs. H	32.37 (3.28;104.67)	No	Serious	No	⊕◯◯◯ Very low
ABS vs. H	32.25 (2.47;104.46)	No	Serious	No	⊕◯◯◯ Very low

LED vs. H	31.56 (2.54;103.71)	No	Serious	No	⊕◯◯◯ Very low
TXA vs. H	31.38 (2.35;103.74)	No	Serious	No	⊕◯◯◯ Very low
EACA vs. H	31.28 (1.92;103.63)	No	Serious	No	⊕◯◯◯ Very low
EACA vs. CaS	1.90 (-3.10;7.16)	No	Serious	No	⊕⊕◯◯ Low
LED vs. CaS	2.23 (-3.18;8.45)	No	Serious	No	⊕⊕◯◯ Low
Ge vs. CaS	2.74 (-1.62;8.00)	No	Serious	No	⊕⊕◯◯ Low
Su vs. CaS	3.07 (-1.83;8.46)	No	Serious	No	⊕⊕◯◯ Low
ABS vs. CaS	2.82 (-3.41;9.83)	No	Serious	No	⊕⊕◯◯ Low
Ga vs. CaS	3.19 (-0.95;8.49)	No	Serious	No	⊕⊕◯◯ Low
Fi vs. CaS	3.73 (-0.19;8.91)	No	Serious	No	⊕⊕◯◯ Low
P vs. CaS	5.62 (1.03;11.41)	Serious	Serious	No	⊕◯◯◯ Very low
CO vs. CaS	3.99 (-1.46;10.44)	No	Serious	No	⊕⊕◯◯ Low
CaS vs. H	29.37 (-0.18;101.61)	No	Serious	No	⊕◯◯◯ Very low
CO vs. P	-1.62 (-7.28;3.81)	Serious	Serious	No	⊕◯◯◯ Very low
Fi vs. P	-1.80 (-6.19;2.03)	Serious	Serious	No	⊕◯◯◯ Very low
Ga vs. CO	-0.75 (-5.40;3.86)	No	Serious	No	⊕⊕⊕◯ Moderate
Ga vs. P	-2.35 (-6.88;1.67)	Serious	Serious	No	⊕◯◯◯ Very low

Ge vs. P	-2.82 (-7.50;1.24)	Serious	Serious	No	⊕◯◯◯ Very low

Table 4. GRADE evaluation of the analysis of the indirect comparisons between hemostatic agents for the mean bleeding time during oral procedures of individuals on oral anticoagulant treatment (OAT).

Comparison	**NMA Mean DS**	**Intransitivity**	**Imprecision**	**Incoherence**	**Quality of evidence**
TXA vs. ABS	-3.49 (-13.95;7.13)	No	Serious	No	⊕⊕◯◯ Low
TXA vs. Chi	-3.41 (-14.04;7.16)	Serious	Serious	No	⊕◯◯◯ Very low
TXA vs. Co	-2.83 (-15.98;10.13)	Serious	Serious	No	⊕◯◯◯ Very low
ABS vs. Co	0.66 (-12.39;13.96)	Serious	Serious	No	⊕◯◯◯ Very low
Chi vs. ABS	-0.08 (-10.61;10.44)	Serious	Serious	No	⊕◯◯◯ Very low

5.3 Artigo 3

Johana Alejandra Moreno-Drada, Alex Junio Silva da Cruz, Luis Otávio de Miranda Cota, Maria Auxiliadora Parreiras Martins, Isabela Almeida Pordeus, Mauro Henrique Nogueira Guimarães de Abreu. Describing the oral health of warfarin users.

Artigo sometido na revista Brazilian Dental Journal. Cite Score 0.61 (2019) Q2 (Dentistry) no Scimago Journal & Country Rank, e Qualis Capes A2 para Odontologia.

Brazilian Dental Journal

BRAZILIAN DENTAL JOURNAL

Describing the oral health of warfarin users

Journal:	*Brazilian Dental Journal*
Manuscript ID	Draft
Manuscript Type:	Original Article
Keyword:	Anticoagulants, Dental Caries, Dental prosthesis, Oral Health, Periodontal Diseases

Describing the oral health of warfarin users

ABSTRACT

Aim: To describe the oral health and the self-reported periodontal disease in patients under Oral Anticoagulation Therapy (OAT) with warfarin.

Methods: A cross-sectional study was conducted. Validated questionnaires assessed self-reported periodontal disease and demographic variables. After calibration (Kappa>0.60), an examiner evaluated dental caries and the need for dental prostheses. Statistical analysis involved proportions and measures of central tendency.

Results: The sample consisted of 158 individuals, with a mean age of 58.8 years (SD=12.1), of which 62.7% of the participants were women. The average DMFT index was 22.9 (SD=7.6), with the component missing being higher (Mean =16.23). The use of maxillary prosthesis (53.2%) was higher than mandibular (32.3%). The need for mandibular prosthesis reached 66.5%. The percentage of participants that referred gum disease, tooth migration, and tooth mobility was 29.6%, 37.4%, and 30.40%, respectively.

Conclusions: The burden of oral diseases among individuals undergoing OAT is worrisome.

Keywords: Anticoagulants, Dental Caries, Dental prosthesis, Oral Health, Periodontal Diseases.

RESUMO

Objetivo**:** Descrever a saúde bucal e a doença periodontal auto-relatada em pacientes em uso de anticoagulação oral com varfarina**.**

Métodos: Foi realizado um estudo transversal. Questionários validados avaliaram doença periodontal auto-relatada e variáveis demográficas. Após a calibração (Kappa> 0,60), um examinador avaliou a cárie dentária e a necessidade de próteses dentárias. A análise estatística envolveu proporções e medidas de tendência central.

Resultados: A amostra foi composta por 158 indivíduos, com média de idade de 58,8 anos (DP = 12,1), dos quais 62,7% dos participantes eram mulheres. O índice CPOD médio foi de 22,9 (DP = 7,6), com o componente perdido sendo o que mais contribuiu para o índice (Média = 16,23). O uso de prótese maxilar (53,2%) foi maior do que mandibular (32,3%). A necessidade de prótese mandibular atingiu 66,5%. O percentual de participantes que referiram doença gengival, migração dentária e mobilidade dentária foi igual a 29,6%, 37,4% e 30,40%, respectivamente.

Conclusões: A carga de doenças bucais entre indivíduos submetidos à anticoagulação oral com varfarina foi preocupante.

INTRODUCTION

Oral Anticoagulation Therapy (OAT) with warfarin has been widely prescribed for people at high risk or who have had thromboembolic diseases (1,2). Despite the effectiveness of anticoagulants to prevent stroke, heart attack, and other embolic complications, individuals under OAT have an increased risk for bleeding during surgical procedures, including those performed by oral health practitioners (2). Whilst there is extensive literature discussing whether to continue or discontinue OAT in patients undergoing dental surgery and the effectiveness of local measures for bleeding control (2-4), little is known about the oral health status of the population receiving anticoagulants.

With the growth of both life expectancy and the prevalence of cardiovascular diseases (5), there is a tendency for further increase in the number of individuals who will use anticoagulants. OAT is frequently prescribed to elders who present with periodontal disease, dental caries, decreased salivary flow, and reduced host defenses leading to a range of oral diseases (2,6). In this manner, we expect that the number of patients under OAT seeking dental care will increase in the next years, either in primary health care or hospital settings. This fact highlights the rationale for investigation about the oral health conditions of individuals undergoing OAT. Data produced by these studies could provide some insights on organizing the access of this increasing population to oral health care services. This research aimed to describe the burden of oral diseases and the self-reported periodontal disease of patients under OAT with warfarin.

METHODS

The Research Ethics Committee from Universidade Federal de Minas Gerais (UFMG) approved this cross-sectional study. Protocol number CAAE 17726219.0.0000.5149.

We recruited outpatients from the Brazilian National Health System (SUS in Portuguese) attending the anticoagulation clinic of the Hospital das Clínicas from October 2019 to March 2020. Hospital das Clínicas is the teaching hospital of UFMG, the main campus is located at Belo Horizonte, capital of the state of Minas Gerais, Brazil.

The anticoagulation clinic is multidisciplinary, with established protocols for patient counseling and dose adjustments (7). A convenience sample was selected. We highlight that our sample size is acceptable for this study since there is no literature evidence. Eligible patients at the clinic who gave authorization (participation was voluntary, and participants could refuse to answer any question) were consecutively recruited.

Eligibility criteria were patients over 18 years old undergoing OAT with warfarin. Exclusion criteria were patients with insufficient information about their medical history, individuals that could not communicate their answers to the questions asked, or patients with spontaneous bleeding before the dental examination.

Data collection comprised face-to-face interviews using structured questionnaires and oral examination. Before fieldwork, a team composed of an examiner (dental surgeon) and two assistants were trained on the criteria for assessing oral conditions and the approach to conduct the interviews. The examiner underwent a training and calibration exercise to diagnose dental caries. Calibration was carried out using images from different clinical situations on two separate occasions. A pilot study was conducted before the main study, where we evaluated ten adult patients from School of Dentistry at UFMG. The agreement level was observed through Cohen's Kappa coefficient above 0.60, which is considered adequate.

Oral examinations were performed according to the World Health Organization (WHO) standards for epidemiological studies [8]. To measure the participants' caries experience, the DMFT index was used. Its value was expressed by the sum of Decayed, Missing, and Filled Teeth to obtain an individual index. The use or not of prosthesis and the type of prosthesis were clinically established (8).

In the interview, each patient was asked about sociodemographic characteristics and self-perception of periodontal disease. The self-reported periodontal disease instrument evaluated risk

factors for periodontal disease, self-reported oral health measures, and periodontal status. Although the gold standard for periodontitis diagnosis is still the clinical examination with periodontal probing [9], it was not recommended in this group of participants. Many patients on warfarin have heart diseases with a risk for infective endocarditis requiring antibiotic prophylaxis before invasive dental procedures. Moreover, the self-report within the periodontal disease instrument has shown good accuracy in identifying non-diseased individuals. The sum of sensitivity and specificity showed a moderate to good value in identifying periodontal disease in different predictive models (9). Edentulous were not asked about periodontal disease.

Descriptive statistics were performed using Statistical Package for Social Sciences (SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). The characteristics of the sample are presented by frequency. Measures of central tendency and variability were calculated for dental caries severity (DMFT and its components), stratifying by sociodemographic conditions and habits. Self-reported periodontal disease is presented by frequency and proportion. No confidence interval was calculated taking into account that this sample is not at random.

RESULTS

The surveyed sample included 158 patients. The mean age was 58.8 (SD=12.1) years, with a predominance of the female sex (62.7%), and 26.6% of the participants reported that their skin color was white. The evaluated population presented low educational level (60.8%) and majority (93%) reported that household income was one, or more, minimum wage. The majority (61.1%) of the patients take a year or more to have a dental check-up. The average DMFT index was 22.9 (SD=7.6; Table 1), with the component missing being higher (Mean =16.23). Patients among 59-91 years of age had a higher DFMT index (mean 26.8, SD=5.2) compared to those under 58 years of age (mean 19.1, SD=7.6), with a higher index of missing teeth in those over 59 years old (mean 22.5, SD=8.9) compared with those under 58 years old (mean 10.0, SD=9.1). Moreover, a higher DMFT index was observed in patients who did not floss (mean 27.0, SD=7.2) or brushed only once a day (mean 28.0, SD=6.2). Similar behavior was detected for patients with more missing teeth who did not floss (mean 24.1, SD=10.1) or brush only once a day (mean 25.2, SD=9.6).

The use of maxillary prosthesis (53.2%) was higher than the mandibular one (32.3%). The need for prosthesis in both arches was 44.9%, and the need for mandibular prosthesis reached 66.5%. The percentage of participants that referred gum disease, tooth migration, and tooth mobility was 29.6%, 37.4%, and 30.40%, respectively. In addition, participants that did not use floss were 41.1%, while 10.5% reported tooth loss due to periodontal diseases (Table 2).

DISCUSSION

This study described the oral health and the self-reported periodontal disease from 158 individuals under OAT with warfarin. The majority was female, and participants age was close to 60 years old. The prevalence of dental caries was high, and severity increased with age, lower educational level, poor oral hygiene habits, and time since the last dental checkup. Moreover, a substantial percentage of the patients evaluated required a mandibular prosthesis.

In our study, the surveyed sample presented high DMFT values. Findings have shown that patients under OAT present a higher number of dental surfaces covered with biofilm and a lower number of filled teeth than healthy controls (6,10). Some factors might explain these findings. Individuals under OAT, by fear of gingival bleeding, might brush their teeth less often, resulting in great biofilm deposits or plaque (6,11) what is a risk factor for dental caries. Oral hygiene has been linked to plaque and caries experience (12). Similar to our findings, a previous study showed that flosser patients had fewer caries and fewer missing teeth than nonflossers (13). Furthermore, there is still limited recognition by oral health care practitioners about the management of patients under OAT (e.g., which dental procedures are at low risk for bleedings and do not require anticoagulation interruption or the effectiveness of the different local measures to control bleeding during dental procedures). Although most procedures, such as root canal treatment, restorations, and dental extractions that are not surgically complex, can be safely performed at the dental office, the concern of bleedings might be a barrier to oral health practitioners to attend patients under OAT (3).

Previous research reported that patients under OAT had worse oral health status than the healthy control group (6,10). Similarly, data from the general population in Brazil shows that adults had better DMFT values (16.75; IC 95%: 16.29-17.21) (14), compared to individuals under OAT from the age group of 27-58 years. Conversely, elders from the general population had worse DMFT (27.53; IC 95%: 27.03-28.04) (14) than individuals using anticoagulants in the age group of 59-91 years. Discrepancies in dental caries experience may be explained by different studied populations, methodologies, and age groups. Nonetheless, it is noteworthy that Padrón *et al*. (2003) and Meurman JH *et a*l. (2003) (6,10) did not present DMFT values impairing direct comparisons with our findings. This limited information underlines the rationale for further research in this field.

The prevalence of tooth loss in the studied population reflects the abundant demand for oral prostheses. Rehabilitation, both with a removable or fixed prosthesis, can reestablish masticatory function and improve oral health-related quality of life. However, the small provision of this procedure in the Brazilian primary health care contributes to the great demand for oral prostheses observed in this study (15).

Considering the periodontal disease, it comes to our attention that 70% of participants reported been submitted to scaling and root planning; however, only 29.6% acknowledged having gum disease. In Spain, the mean values of plaque index in a sample of patients receiving OAT were 86.3%, and the prevalence of gingival bleeding was 58.3% (11). Untreated, periodontal diseases seem a risk factor for the recurrence of thromboembolic events (16). It is important, though, to develop strategies to improve oral health literacy in the population under OAT. An educational program based on routine dental care could increase oral hygiene habits and self-perception of oral diseases.

In this cross-sectional study, a convenience sample was evaluated. Therefore, it is not possible to extrapolate our findings to the whole anticoagulated population in Brazil and the generalizability of the results should be performed with caution. Moreover, we did not have a control group in our study. Apart from the addressed limitations, the study provide contributions to the scarce literature on the subject. Furthermore, we emphasize the need for further researches. Analytical epidemiological studies could improve understanding of the factors associated with the oral health status of the anticoagulated population. This is important to nurture policymakers' decisions in the provision of oral healthcare for this growing population.

CONCLUSIONS

Individuals undergoing OAT with warfarin showed a high burden of the DFMT index and the need for prosthesis. The great number of tooth loss and the demand for oral rehabilitation highlight the comprehensive dental care need of this population.

Acknowledgements: We thank Matheus Luis Soares de Faria for the collaboration during the project. His contribution was essential to carry out the data collection. We also thank the patients for their participation.

Author contributions: Johana Alejandra Moreno-Drada: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Roles/Writing - original draft; Writing - review & editing. Alex Junio Silva da Cruz: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Roles/Writing - original draft; Writing - review & editing. Luis Otávio de Miranda Cota: Conceptualization; Investigation; Methodology. Maria Auxiliadora Parreiras Martins: Conceptualization; Investigation; Roles/Writing - original draft; Writing - review & editing. Isabela Almeida Pordeus: Funding acquisition; Project administration; Resources; Software; Supervision; Validation; Visualization. Mauro Henrique Nogueira Guimarães de Abreu: Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. All authors have read and agreed to the published version of the manuscript.

Data availability statement: All data and materials, as well as a software application or custom code, support the published claims and comply with field standards.

Conflict of Interest: Johana Alejandra Moreno-Drada declares that he has no conflict of interest. Alex Junio Silva da Cruz declares that he has no conflict of interest. Luis Otávio de Miranda Cota declares that he has no conflict of interest. Maria Auxiliadora Parreiras Martins declares that he has no conflict of interest. Isabela Almeida Pordeus declares that he has no conflict of interest. Mauro Henrique Nogueira Guimarães de Abreu declares that he has no conflict of interest.

Funding: The work was supported by the Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (financial number 001).

Ethical approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institution and approved by The Research Ethics Committee from Universidade Federal de Minas Gerais (UFMG). Protocol number CAAE 17726219.0.0000.5149. The study was conducted according to the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Table 1- Decayed, Missing, Indicated for extraction and Filled Teeth (DMF-T) index of the patients under anticoagulation therapy with warfarin, Belo Horizonte, Brazil, 2019-2020.

Variables	Decayed Teeth Me (SD)	Missing Teeth Me (SD)	Teeth indicated for extraction Me (SD)	Filled Teeth Me (MSD	DMFT index Me (SD)
Sex (N=158)					
Male (n=59)	1.2 (1.5)	17.6 (10.3)	0.3 (0.7)	4.2 (5.3)	23.3 (7.5)
Female (n=99)	1.1 (2.0)	15.4 (11.3)	0.3 (1.8)	6.2 (5.9)	22.7 (7.6)
Age (N=158)					
27 to 58 (n=79)	1.4 (2.3)	10.0 (9.1)	0.4 (0.1)	7.5 (6.1)	19.1 (7.6)
59 to 91 (n= 79)	0.8 (1.3)	22.5 (8.9)	0.1 (0.5)	3.3 (4.6)	26.8 (5.2)
Skin color (N=158)					
White (n=42)	1.1 (1.5)	18.3 (11.4)	0.2 (0.4)	5.0 (5.9)	24.5 (7.5)
Others (n=116)	1.1 (2.0)	15.5 (10.7)	0.3 (1.7)	5.6 (5.7)	22.4 (7.6)
Place of residence (N=158)					
Small cities near of Belo Horizonte (n= 75)	1.1 (1.4)	16.0 (11.2)	0.2 (0.6)	5.5 (6.0)	22.8 (7.9)
Belo Horizonte (n= 83)	1.1 (2.2)	16.5 (10.8)	0.4 (1.9)	5.3 (5.6)	23.1 (7.3)
Educational level- years of formal education (N=158)					
Up to 8 years (n= 96)	1.1 (2.2)	18.4 (10.9)	0.3 (1.8)	4.6 (5.5)	24.2 (7.3)
More than 8 years (n=62)	1.2 (1.2)	12.9 (10.3)	0.2 (0.7)	6.7 (5.9)	21.0 (7.7)
Household Income (N=158)					
<1 Minimum wage* (n=11)	0.6 (1.0)	11.9 (11.4)	0 (0)	7.9 (7.8)	20.5 (9.8)
>1 Minimum wage (n= 147)	1.1 (1.9)	16.6 (10.9)	0.3 (1.5)	5.2 (5.6)	23.1 (7.4)

Alcohol consumption (N=158)					
Yes (n=22)	1.0 (1.5)	17.5 (10.9)	0.3 (0.8)	4.4 (5.3)	23.1 (7.6)
No (n= 136)	1.1 (1.9)	16.0 (11.0)	0.3 (1.5)	5.6 (5.8)	22.9 (7.6)
Smoking (N=158)					
Yes (n= 13)	0.9 (1.6)	19.5 (10.7)	0.1 (0.3)	4.3 (6.5)	24.8 (5.3)
No (n= 145)	1.1 (1.9)	15.9 (11.0)	0.3 (1.5)	5.5 (5.7)	22.8 (7.7)
Diabetes (N=157)					
Yes (n=21)	1.0 (1.3)	16.2 (10.4)	0.1 (0.7)	5.6 (5.5)	23.0 (7.0)
No (n=136)	1.1 (1.9)	16.1 (11.0)	0.3 (1.5)	5.4 (5.8)	22.9 (7.7)
Dental flossing (N=158)					
Yes (n=93)	1.2 (1.3)	10.7 (7.7)	0.1 (0.5)	8.0 (5.9)	20.1 (6.5)
No (n= 65)	1.0 (2.4)	24.1 (10.1)	0.5 (2.2)	1.7 (2.8)	27.0 (7.2)
Tooth brushing frequency (N=158)					
Once a day (n=10)	1.2 (1.8)	25.2 (9.6)	0.8 (1.5)	0.8 (1.8)	28.0 (6.2)
Twice a day or more (n=148)	1.1 (1.9)	15.6 (10.8)	0.2 (1.5)	5.7 (5.8)	22.6 (7.6)
Last dental checkup (N=157)					
Up to 6 months (n=61)	1.3 (1.4)	12.1 (8.2)	0.2 (0.6)	7.0 (5.5)	20.6 (6.9)
1 year or more (n=96)	1.0 (2.1)	19.0 (11.7)	0.3 (1.8)	4.4 (5.8)	24.5 (7.6)

*Minimum wage in Brazil is R$1,100.00 (Real) what is equivalent to US$ 210.00 (American Dollar).

Table 2- Self-reported periodontal diseases of the patients under anticoagulation therapy with warfarin, Belo Horizonte, Brazil, 2019-2020.

Categorical variables (Yes)	Frequency	%
Gum disease (N=125)	37	29.6
Tooth migration (N=123)	46	37.4
Tooth mobility (N=125)	38	30.4
Tooth loss (N=124)	13	10.5
Scaling and root planning (N=124)	87	70.2
Periodontal surgery (N=125)	10	8.0
Bone loss (N=125)	24	19.2

REFERENCES

1. Francis CW. Warfarin: an historical perspective. Hematology Am Soc Hematol Educ Program 2008; 251. DOI: 10.1182/asheducation-2008.1.251.
2. Yang S, Shi Q, Liu J, Li J, Xu J. Should oral anticoagulant therapy be continued during dental extraction? A meta-analysis. BMC Oral Health 2016; 16(1):81. DOI: 10.1186/s12903-016-0278-9.
3. Kaplovitch E, Dounaevskaia V. Treatment in the dental practice of the patient receiving anticoagulation therapy. J Am Dent Assoc 2019; 150(7):602-608. DOI: 10.1016/j.adaj.2019.02.011.
4. Wahl MJ. The mythology of anticoagulation therapy interruption for dental surgery. J Am Dent Assoc 2018; 149(1):e1-e10. DOI: 10.1016/j.adaj.2017.09.054.
5. Deaton C, Froelicher ES, Wu LH, Ho C, Shishani K, Jaarsma T. The global burden of cardiovascular disease. J Cardiovasc Nurs 2011; 26(4 Suppl):S5-14. DOI: 10.1097/JCN.0b013e318213efcf.
6. Padrón N, Limeres J, Tomás I, Diz Dios P. Oral health and health behavior in patients under anticoagulation therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 96(5):519-20. DOI: 10.1016/j.tripleo.2003.08.021.
7. Martins MAP, Costa JM, Mambrini JVM, Ribeiro ALP, Benjamin EJ, Brant LCC, Paasche-Orlow MK, Magnani JW. Health literacy and warfarin therapy at two anticoagulation clinics in Brazil. Heart 2017; 103(14):1089-1095. DOI: 10.1136/heartjnl-2016-310699.
8. World Health Organization. Oral Health Surveys: basic methods. 5 ed. 2013. pp 125.
9. Cyrino RM, Miranda Cota LO, Pereira Lages EJ, Bastos Lages EM, Costa FO. Evaluation of self-reported measures for prediction of periodontitis in a sample of Brazilians. J Periodontol 2011; 82(12):1693-704. DOI: 10.1902/jop.2011.110015.
10. Meurman JH, Qvarnstrom M, Janket S, Nuutinen P. Oral health and health behavior in patients referred for open-heart surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 95: 300-7.
11. López-Lacomba D, Roa-López A, González-Jaranay M, Gómez-Moreno G, Moreu G. Periodontal and biochemical bone metabolism assessment on a chronic oral anticoagulation

population treated with dicoumarins. Med Oral Patol Oral Cir Bucal 2017; 22(2):e258-e263. DOI: 10.4317/medoral.21567.

12. Laajala A, Pesonen P, Anttonen V, Laitala ML. Association of Enamel Caries Lesions with Oral Hygiene and DMFT among Adults. Caries Res 2019; 53(4):475-481. doi: 10.1159/000497358.
13. Marchesan JT, Byrd KM, Moss K, Preisser JS, Morelli T, Zandona AF, Jiao Y, Beck J. Flossing Is Associated with Improved Oral Health in Older Adults. J Dent Res 2020; 99(9):1047-1053. doi: 10.1177/0022034520916151.
14. Brasil. Ministério da Saúde (MS). Projeto SB Brasil 2010: condições de saúde bucal da população brasileira, resultados principais. [SB Brasil 2010 Project: oral health conditions of the Brazilian population, main results] Brasília: MS; 2012.
15. Cunha MAGM, Matta-Machado ATG, Lucas SD, Abreu MHNG. Availability of Dental Prosthesis Procedures in Brazilian Primary Health Care. Biomed Res Int 2018; 2018:4536707. DOI: 10.1155/2018/4536707.

Sánchez-Siles M, Rosa-Salazar V, Salazar-Sánchez N, Camacho-Alonso F. Periodontal disease as a risk factor of recurrence of venous thromboembolic disease: a prospective study. Acta Odontol Scand 2015; 73(1):8-13. DOI: 10.3109/00016357.2014.920514.

5.4 Artigo 4

Moreno-Drada JA, Silva da Cruz AJ, Soares de Faria ML, Miranda Cota LO, Parreiras Martins MA, Almeida Pordeus I, Nogueira Guimarães de Abreu MH. Oral Health-Related Quality of Life in Anticoagulated Patients with Warfarin Treatment: A Cross-Sectional Study. International Journal of Environmental Research and Public Health. 2021; 18(7):3714. https://doi.org/10.3390/ijerph18073714.

Artigo publicado na revista International Journal of Environmental Research and Public Health. Cite Score 0.74 (2019) Q2 (Public health) no Scimago Journal & Country Rank, e Qualis Capes B1 para Odontologia.

International Journal of
Environmental Research and Public Health

MDPI

Article

Oral Health-Related Quality of Life in Anticoagulated Patients with Warfarin Treatment: A Cross-Sectional Study

Johana Alejandra Moreno-Drada [1,*], Alex Junio Silva da Cruz [1], Matheus Luis Soares de Faria [1], Luís Otávio Miranda Cota [1], Maria Auxiliadora Parreiras Martins [2], Isabela Almeida Pordeus [1] and Mauro Henrique Nogueira Guimarães de Abreu [1]

[1] School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte CEP 31270-901, Brazil; junio.alex@hotmail.com (A.J.S.d.C.); matheuslsfaria@gmail.com (M.L.S.d.F.); luisotaviocota@gmail.com (L.O.M.C.); isabela.pordeus@gmail.com (I.A.P.); maurohenriqueabreu@gmail.com (M.H.N.G.d.A.)
[2] Department of Pharmaceutical Products, Universidade Federal of Minas Gerais, Belo Horizonte CEP 31270-901, Brazil; auxiliadorapmartins@hotmail.com
* Correspondence: joalmodra@hotmail.com

Abstract: To evaluate factors associated with oral health-related quality of life (OHRQoL) in patients under oral anticoagulant therapy with warfarin, a cross-sectional study was conducted. Validated questionnaires assessed self-reported periodontal disease, demographic variables, and OHRQoL using the short version of the Oral Health Impact Profile (OHIP-14) instrument. After calibration (Kappa > 0.60), an examiner evaluated patients' experience with dental caries and the need for dental prostheses. Statistical analysis involved proportions and measures of central tendency. Negative binomial regression models were used to estimate the rate ratios (RR) and the corresponding 95% confidence interval (CI). The sample consisted of 158 individuals, with a mean age of 58.8 years (SD = 12.1), of which 62.7% of the participants were women. The OHIP-14 mean was 10.62 (SD = 10.92). A higher OHIP-14 total score (worse OHRQoL) was associated with ethnic group, age, periodontal disease self-report, dental caries, and oral health self-report. Demographic and clinical factors can negatively influence the perception of anticoagulated patients on OHRQoL.

Keywords: anticoagulants; oral health; quality of life; oral health-related quality of life

Citation: Moreno-Drada, J.A.; Silva da Cruz, A.J.; Soares de Faria, M.L.; Miranda Cota, L.O.; Parreiras Martins, M.A.; Almeida Pordeus, I.; Nogueira Guimarães de Abreu, M.H. Oral Health-Related Quality of Life in Anticoagulated Patients with Warfarin Treatment: A Cross-Sectional Study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 3714. https://doi.org/10.3390/ijerph18073714

Academic Editors: Katherine Chiu Man Leung and Chun Hung Chu

Received: 20 February 2021
Accepted: 30 March 2021
Published: 2 April 2021

1. Introduction

Oral anticoagulant therapy (OAT) has increased in recent years [1,2], especially due to the increase in life expectancy [3]. OAT is recommended for outpatients with atrial fibrillation, prosthetic heart valves, venous thromboembolism, acute coronary syndrome or myocardial infarction, and pulmonary hypertension for prevention and treatment, reducing the risk of stroke-related morbidity and mortality [2,4–8]. Coumarin derivatives, such as warfarin, are the most commonly used drugs, especially in low and middle-income countries [6,9–11]. The efficacy and safety of warfarin depend on achieving the desired therapeutic range, monitored by the international normalized ratio (INR) [2,12]. Both insufficient and excessive anticoagulation effects can be harmful, increasing thromboembolic and hemorrhagic risks, respectively [2].

Although prior studies are scarce in the literature, oral health plays an essential role in individuals on oral anticoagulation. Meurman et al. [13] identified that part of the OAT patients had never brushed their teeth. The fear of gingival bleeding may well induce individuals to brush their teeth less frequently, increasing the number of plaque-covered teeth and causing deep gingival pockets [13,14]. Moreover, the population undergoing OAT tends to be older [3,15]. Other conditions increase their prevalence and severity in aged patients, such as periodontal disease, decreased salivary flow, and reduced host defenses, leading to different oral diseases. These conditions and insufficient knowledge

of oral health may contribute to inadequate oral hygiene [14]. As a result, extractions in patients undergoing OAT are frequent [7,9,14]. The loss of teeth may also negatively influence essential oral functions [16].

The interest in Patient-Reported Outcome Measures (PROMs) in clinical research has been growing lately. The use of PROMs to assess the oral health related quality of life (OHRQoL) allows us to understand the impact of oral conditions on the subjects' daily lives, a perspective that would probably not be achieved by clinical indicators [17]. Previous studies identified that the OHRQoL could be affected by sociodemographic factors, such as age, sex, ethnicity, and socioeconomic level [18–20]. Similarly, periodontal disease, teeth (decayed, missing, or filled), mucosal lesions, and denture problems were prevalent and showed a negative association with OHRQoL [19,21,22]. By contrast, a systematic review stated no consensus in the literature on the association between edentulism, caries, and periodontal conditions and OHRQoL [23]. Despite the increasing publications about this topic, there is limited knowledge about the behaviors, feelings, or repercussions of oral conditions in individuals undergoing OAT.

The risk of bleeding, dietary intake restrictions, and possible interactions of oral anticoagulants, such as warfarin, with other medications can interfere with daily activities in people undergoing OAT [8,24,25]. These events can affect the general quality of life of the population that uses oral anticoagulants. In addition to the uncertainties associated with OAT, there is an increased risk of oral bleeding due to oral diseases that can cause dissatisfaction and have a significant negative impact upon OHRQoL [14,25]. However, the scientific community has paid little attention to the interaction between complex long-term treatments, such as OAT and oral health care, and the impact oral health has on one's quality of life [14,25]. Considering that most patients who receive oral anticoagulation suffer from chronic diseases that may be severe or life-threatening and undergo continuous drug treatment throughout their lives, the role of oral health and its impact on the quality of life in this population is unclear. Thus, this study aims to analyze the factors associated with OHRQoL in patients on OAT with warfarin.

2. Materials and Methods

The Ethics Committee for Human Research from Universidade Federal de Minas Gerais (UFMG) (logged under protocol number CAAE 17726219.0.0000.5149) approved the conduction of this study. Patients signed an informed consent form; participation was voluntary, and patients could refuse to answer any questions.

2.1. Participants and Data Collection

Outpatients from the Brazilian National Health System (SUS in Portuguese) undergoing oral anticoagulant treatment during 2019 at the Anticoagulation Clinic of the Hospital das Clínicas of UFMG were evaluated. The anticoagulation clinic is multidisciplinary, with established protocols for patient education and dose adjustments [11]. A consecutive sample of patients was selected. The patients under medical treatment at the Anticoagulation Clinic of the Hospital das Clínicas of UFMG and those who were eligible and gave authorization were recruited consecutively. The sample calculation was performed with a 95% confidence level (CI) and an 80% power and the comparison of means on the information about the impact of untreated dental caries on the quality of life, considering the study of De Oliveira et al. [26], resulting in a minimum of 120 patients for the sample size. Considering the possibility of missing data for some variables, we added 30% to this sample size, resulting in a minimum of 156 patients.

This study included patients of $\geq$18 years of age on oral anticoagulation with warfarin. Exclusion criteria were: patients with insufficient information in their medical history, individuals that could not communicate their answers to the questions asked, or patients with spontaneous bleeding before the dental examination.

Data were collected from October 2019 to February 2020. Each patient was asked to answer a structured questionnaire with a combination of sociodemographic questions:

the Brazilian version of the Oral Health Impact Profile (OHIP-14) [26], which has been designed to measure the perception of the social impact of oral disorders [27,28], together with the periodontal disease self-report instrument [29].

2.2. Instruments

The self-reported periodontal disease instrument evaluated sociodemographic information, risk factors for periodontal disease, self-reported oral health measures, and periodontal status. The preferred clinical examination is periodontal probing, and although it remains the gold standard for the diagnosis of periodontitis [29], it was not considered in this group of patients. The explanation is given because many patients on warfarin have heart diseases [30] or prosthetic heart valves with a risk for infective endocarditis [31], treated with the recommendation of antibiotic prophylaxis before dental procedures involving the manipulation of the gingival tissue, the periapical region of the teeth, or perforation of the oral mucosa [32]. The clinical evaluation would imply a risk of gingival bleeding that is difficult to control or a risk of endocarditis, in addition to the need to implement prophylactic antibiotic therapy. Moreover, the self-reported periodontal disease instrument has shown good accuracy in identifying sick individuals, especially those with severe periodontitis. The sensitivity and specificity showed a moderate to good value in identifying periodontal disease in different predictive models [29].

The OHIP-14 is a specific indicator of OHRQoL, which demonstrated good reliability and validity [28]. The OHIP-14 items involved the evaluation of seven conceptual subscales: functional limitation, physical pain, psychological distress, physical disability, psychological disability, social disability, and handicap [26]. The dependent variable analyzed in this study was the OHIP-14, with 14 questions and an answer possibility from 0 to 4. The total score range was 0 to 56, where the highest OHIP-14 score indicated a worse quality of life. The mean and median values of OHIP-14 were calculated for each covariate.

2.3. Face-to-Face Interviews and Clinical Examination

Trained researchers conducted face-to-face interviews. Prior to the fieldwork, an examiner underwent a training and calibration exercise to diagnose dental caries. Calibration was carried out using images from different clinical situations on two separate occasions. A pilot study was conducted before the fieldwork, where ten adult patients were evaluated at the School of Dentistry at Universidade Federal de Minas Gerais. The calibration level was observed through a Cohen's Kappa coefficient above 0.60, which is considered adequate. A clinical examination was performed using DMFT index (decayed, missing, and filled teeth index) to assess the patients' caries experience. Its value was expressed by the sum of decayed, missing, and filled teeth to obtain an individual index. The use or not of prostheses and the type of prostheses were clinically established [33].

2.4. Statistical Analysis

This analysis involved descriptive analysis, together with the calculation of proportions and central tendency and variability measures. Negative binomial regression models were used to estimate the unadjusted and adjusted rate ratios (RR) and corresponding 95% CI. First, unadjusted negative binomial regression models were carried out to estimate unadjusted RR (95% CI) and p-values for each of the 35 covariates included one by one. In this first step, any covariate with a p-value of less than 0.25 was a candidate to be tested in the final adjusted negative binomial regression model. As the focus of interest was on the independent effects of each covariate, all potential variables were included in the unadjusted model, which had age, sex, self-reported skin color, place of residence, smoking, tooth brushing frequency, gum disease, tooth migration, oral health, periodontal surgery, decayed (DMFT index) tooth indicated for extraction, and need for a prosthesis. Only covariates with a p-value lower than 0.05 were maintained in the final model when all variables would be presented together. The ratio between residual deviance and degree of freedom, as well as results from the chi-squared test of the residual deviance, was indicated

to evaluate the goodness of fit of the final model [34,35]. Missing data were not computed in the statistical analysis. Variation Inflation Factor (VIF) was calculated for multicollinearity diagnosis. Statistical analyses were carried out in SPSS statistics software Version 24 (IBM, Chicago, IL, USA).

3. Results

The surveyed sample included 158 patients. The mean age (SD) was 58.8 (12.0) years, with a predominance of the female sex (62.7%), and 26.6% of the individuals reported that their skin color was white. We found ten patients who reported being smokers. The range number of cigarettes per day was 7 to 20, with a mean of 7.2 and a standard deviation of 5.96.

Regarding the indications for OAT, the results showed that the majority of patients had some fibrillation (19.7% non-valve atrial fibrillation/flutter and 23.7% valve atrial fibrillation/flutter) or some prosthetic heart valves (4.6% with biological valve prosthesis (mitral), 27.0% with mechanical valve prosthesis (aortic) and 34.2% with mechanical valve prosthesis (mitral)). The sum of these diagnoses was higher than 100%, considering that the same patient could have more than one OAT indication.

The mean of the years of school of the included patients was 6.63 (±3.87). The mean OHIP-14 of the sample was 10.6 (±10.9). The descriptive characteristics of the patients included in this study are presented in Table 1.

Table 1. Characteristics of the patients under anticoagulation therapy with warfarin, Belo Horizonte, Brazil, 2019–2020.

Quantitative Variables	**Mean (SD)**	**Minimum–Maximum**
OHIP14- Oral Health Impact Profile (*N* = 158)	10.62 (10.92)	0–53
Functional limitation (*N* = 158)	1.35 (2.03)	0–8
Physical pain (*N* = 158)	2.48 (2.35)	0–8
Psychological discomfort (*N* = 158)	2.35 (2.70)	0–8
Physical disability (*N* = 158)	1.53 (2.19)	0–8
Psychological disability (*N* = 158)	1.52 (2.07)	0–8
Social disability (*N* = 158)	0.54 (1.30)	0–8
Handicap (*N* = 158)	0.85 (1.59)	0–8
Age (*N* = 158)	58.80 (12.05)	27–91
Years of school (*N* = 158)	6.63 (3.87)	0–20
INR-International normalized ratio (*N* = 157)	2.61 (0.82)	1.06–5.40
Number of teeth self-report (*N* = 154)	14.94 (11.02)	0–36
DMFT index- Decayed, missing, and filled teeth index (*N* = 158)	22.92 (7.57)	1–32
Decayed (DMFT index) (*N* = 158)	1.10 (1.85)	0–18
Missing (DMFT index) (*N* = 158)	16.23 (10.96)	0–32
Tooth indicated for extraction (*N* = 158)	0.27 (1.45)	0–17
Filled teeth (DMFT index) (*N* = 158)	5.43 (5.75)	0–24
Categorical Variables	**Frequency**	**%**
Sex (*N* = 158)		
Male	59	37.3
Female	99	62.7
Skin color (*N* = 158)		
White	42	26.6
Others	116	73.4
Place of residence (*N* = 158)		
Belo Horizonte	83	52.5
Small cities near Belo Horizonte	75	47.5

Table 1. *Cont.*

Categorical Variables	Frequency	%
Education level (*N* = 158)		
Up to 8 years of formal education	96	60.8
More than 8 years of formal education	62	39.2
Household Income (*N* = 158)		
<1 Minimum wage	11	7.0
>1 Minimum wage	147	93.0
Alcohol consumption (*N* = 158)	22	13.9
Smoking (*N* = 158)	13	8.2
Diabetes (*N* = 157)	21	13.4
Dental flossing (*N* = 158)	93	58.9
Dental flossing frequency (*N* = 93)		
Occasionally	44	47.3
Daily	49	52.7
Tooth brushing frequency (*N* = 158)		
Once a day	10	6.3
Twice a day or more	148	93.7
Last dental checkup (*N* = 157)		
Up to 6 months	61	38.9
1 year or more	96	61.1
Gum disease (*N* = 125)	37	29.6
Tooth migration (*N* = 123)	46	37.4
Tooth mobility (*N* = 125)	38	30.4
Tooth loss (*N* = 124)	13	10.5
Oral health (*N* = 157)		
Excellent/Very Good/Good	114	72.6
Poor/Fair	43	27.4
Scaling and root planing (*N* = 124)	87	70.2
Periodontal surgery (*N* = 125)	10	8.0
Bone loss (*N* = 125)	24	19.2
Use of maxillary prostheses (*N* = 158)	84	53.2
Use of mandibular prostheses (*N* = 158)	51	32.3
Need for general prostheses (*N* = 158)		
Needs maxillary and mandibular prostheses	71	44.9
Needs only maxillary prosthesis or only mandibular prosthesis	43	27.2
None required	44	27.8
Need for maxillary prostheses (*N* = 158)	80	50.6
Need for mandibular prostheses (*N* = 158)	105	66.5

Minimum wage in Brazil is BRL 1100.00 (Real), which is approximately equivalent to USD 200.00 (American Dollar).

The final multivariate-adjusted model consisted of ten variables. Individuals from other races were more likely to have poor OHRQoL than white individuals (RR = 1.047; 95% CI 1.024–1.070). Older individuals were less likely to have poor OHRQoL (RR = 0.998; 95% CI 0.997–0.999). Patients who reported poor or fair oral health were more likely to have poor OHRQoL (RR = 1.055; 95% CI 1.028–1.083) than those who reported excellent, very good, or good oral health. Patients who reported gingival disease (RR = 1.031; 95% CI 1.013–1.048), dental migration (RR = 1.034; 95% CI 1.011–1.057), scaling and root planing (RR = 1.027; 95% CI 1.006–1.048), and periodontal surgery (RR = 1.032; 95% CI 1.010–1.055) had poor OHRQoL. Likewise, the individuals that presented more decayed (RR = 1.006;

95% CI 1.003–1.008), missing (RR = 1.002; 95% CI 1.001–1.004), and filled teeth (RR = 1.004; 95% CI 1.002–1.006) also had poor OHRQoL (Table 2). Parameters of the goodness of fit were adequate. The chi-squared test of the residual deviance results, with a *p*-value equal to 0.997, and the ratio between residual deviance and degree of freedom resulted in 1.078, indicating that the model fit well. VIF values were all lower than 10, showing no problem with collinearity.

Table 2. Factors associated with oral health related quality of life among patients under anticoagulation therapy with warfarin. Belo Horizonte, Brazil, 2019–2020.

Variable	OHIP-14 Scores (Mean; Median)	Unadjusted Rate Ratio (95% CI)	*p* Value	Adjusted Rate Ratio (95% CI)	*p* Value
Sex (*N* = 158)					
Male (*N* = 59)	6.2; 4.0	1	<0.001		
Female (*N* = 99)	10.3; 9.0	1.079 (1.036–1.126)			
Skin color (*N* = 158)					
White (*N* = 42)	5.9; 4.0	1	0.004	1	<0.001
Others (*N* = 116)	12.3; 8.0	1.081 (1.025–1.142)		1.047 (1.024–1.070)	
Age (*N* = 158)		0.998 (0.997–0.999)	<0.001	0.998 (0.997–0.999)	<0.001
INR- International normalized ratio (*N* = 157)		0.999 (0.978–1.019)	0.895		
Place of residence (*N* = 158)					
Belo Horizonte (*N* = 83)	9.4; 7.0	1	0.140		
Small cities near of Belo Horizonte (*N* = 75)	11.9; 8.0	1.021 (0.993–1.049)			
Education level (*N* = 158)					
Up to 8 years of formal education (*N* = 96)	10.5; 7.0	1	0.808		
More than 8 years of formal education (*N* = 62)	10.9; 9.0	1.003 (0.976–1.031)			
Household Income (*N* = 158)					
<1 Minimum wage (*N* = 11)	10.9; 6.0	1	0.945		
>1 Minimum wage (*N* = 147)	10.6; 7.0	0.998 (0.930–1.069)			
Alcohol consumption (*N* = 158)					
No (*N* = 136)	10.5; 7.0	1	0.826		
Yes (*N* = 22)	11.2; 8.0	1.005 (0.961–1.051)			
Smoking (*N* = 158)					
No (*N* = 145)	11.2; 8.0	1	0.005		
Yes (*N* = 13)	4.1; 4.0	0.878 (0.801–0.962)			
Diabetes (*N* = 157)					
No (*N* = 136)	10.6; 7.0	1	0.756		
Yes (*N* = 21)	11.3; 9.0	1.005 (0.973–1.039)			
Dental flossing (*N* = 158)					
No (*N* = 65)	8.0; 6.0	1	0.010		
Yes (*N* = 93)	12.4; 9.0	1.040 (1.009–1.073)			
Dental flossing frequency (*N* = 158)					
Occasionally or not use (*N* = 109)	10.1; 6.0	1	0.345		
Daily (*N* = 49)	11.8; 9.0	1.013 (0.986–1.040)			
Tooth brushing frequency (*N* = 158)					
Once a day (*N* = 10)	10.3; 7.0	1	0.926		
Twice a day or more (*N* = 148)	10.6; 7.0	1.003 (0.944–1.065)			
Last dental checkup (*N* = 157)					
Up to 6 months (*N* = 61)	10.3; 7.0	1	0.739		
1 year or more (*N* = 96)	10.9; 7.0	0.995 (0.968–1.023)			
Gingival disease (*N* = 125)					
No (*N* = 88)	8.6; 6.0	1	<0.001	1	0.001
Yes (*N* = 37)	17.0; 13.0	1.054 (1.026–1.083)		1.031 (1.013–1.048)	
Dental migration (*N* = 123)					
No (*N* = 77)	7.8; 6.0	1	<0.001	1	0.003
Yes (*N* = 46)	16.9; 16.5	1.066 (1.034–1.098)		1.034 (1.011–1.057)	
Tooth mobility (*N* = 125)					
No (*N* = 87)	9.3; 6.0	1	0.003		
Yes (*N* = 38)	15.7; 12.5	1.013 (1.013–1.069)			

Table 2. *Cont.*

Variable	OHIP-14 Scores (Mean; Median)	Unadjusted Rate Ratio (95% CI)	*p* Value	Adjusted Rate Ratio (95% CI)	*p* Value
Tooth loss (*N* = 124)					
No (*N* = 111)	10.9; 7.0	1	0.364		
Yes (*N* = 13)	12.8; 9.0	1.013 (0.985–1.042)			
Oral health (*N* = 157)					
Excellent/Very Good/Good (*N* = 114)	7.0; 5.0	1	<0.001	1	<0.001
Poor/Fair (*N* = 43)	20.4; 19.0	1.090 (1.061–1.120)		1.055 (1.028–1.083)	
Scaling and root planing (*N* = 124)					
No (*N* = 37)	9.1; 6.0	1	0.174	1	0.011
Yes (*N* = 87)	12.2; 9.0	1.026 (0.989–1.064)		1.027 (1.006–1.048)	
Periodontal surgery (*N* = 125)					
No (*N* = 115)	10.6; 7.0	1	0.003	1	0.004
Yes (*N* = 10)	18.0; 21.0	1.036 (1.012–1.061)		1.032 (1.010–1.055)	
Bone loss (*N* = 125)					
Yes (*N* = 24)	14.2; 10.0	1	0.074		
No (*N* = 101)	10.5; 7.0	1.023 (0.998–1.049)			
Number of teeth self-reported (*N* = 154)		1.001 (1.000–1.002)	0.188		
Use of maxillary prostheses (*N* = 158)					
No (*N* = 74)	10.8; 8.0	1	0.859		
Yes (*N* = 84)	10.5; 6.0	0.998 (0.971–1.026)			
Use of mandibular prostheses (*N* = 158)					
No (*N* = 107)	11.6; 8.0	1	0.107		
Yes (*N* = 51)	8.5; 6.0	0.972 (0.939–1.006)			
Need for general prostheses (*N* = 158)					
Needs maxillary and mandibular prostheses (*N* = 71)	12.7; 8.0	1			
Needs only maxillary prosthesis or only mandibular prosthesis (*N* = 43)	10.0; 8.0	0.981 (0.951–1.013)	0.238		
None required (*N* = 44)	7.9; 4.5	0.957 (0.919–0.997)	0.035		
Need for maxillary prostheses (*N* = 158)					
No (*N* = 78)	9.1; 6.0	1	0.091		
Yes (*N* = 80)	12.1; 8.0	1.024 (0.996–1.054)			
Need for mandibular prostheses (*N* = 158)					
No (*N* = 53)	7.8; 6.0	1	0.029		
Yes (*N* = 105)	12.1; 8.0	1.042 (1.004–1.081)			
DMFT index-Decayed, missing, and filled teeth index (*N* = 158)		1.000 (0.998–1.001)	0.788		
Decayed (DMFT index) (*N* = 158)		1.004 (1.003–1.005)	<0.001	1.006 (1.003–1.008)	<0.001
Missing (DMFT index) (*N* = 158)		0.999 (0.998–1.000)	0.190	1.002 (1.001–1.004)	0.007
Tooth indicated for extraction (*N* = 158)		1.004 (1.003–1.005)	<0.001		
Filled Teeth (DMFT) (*N* = 158)		1.001 (0.999–1.003)	0.190	1.004 (1.002–1.006)	<0.001

Minimum wage in Brazil is BRL 1100.00 (Real), which is approximately equivalent to USD 200.00 (American Dollar).

4. Discussion

We found that the OHRQoL is associated with some sociodemographic factors, periodontal self-reported factors, and other clinical factors. White and older individuals were less likely to have poor OHRQoL. Patients who reported gingival disease, dental migration, scaling and root planing, periodontal surgery, poor or fair oral health, and more decayed, missing, and filled teeth had poor OHRQoL.

Almost half of the OHIP-14 value refers to the dimensions of psychological discomfort and pain. We must bear in mind that most oral problems do not represent an immediate risk of death; however, they are responsible for reducing the quality of life of individuals, prolonging pain states, causing functional, aesthetic, and nutritional problems, and due to everything above, leading to psychological issues [36]. High levels of stress, anxiety, and depression have been reported in patients with dental pain in the literature, reducing the quality of life [37].

Some authors have discussed the relationship between ethnic groups and OHRQoL. White individuals tend to show better oral status than other ethnic groups. This situation occurs because they tend to exhibit the highest social grade [38–40]. Ethnicity was the only social factor associated with OHRQoL in our study, which is different from that observed in other studies [18,19]. This is possibly because the present study was performed in a public hospital where most of the population presented low income and education levels.

Oral health problems have become a significant issue in old age. These problems include tooth loss, edentulism, clinical attachment loss, coronal and root caries, oral mucosa lesions, the use of non-functional dental prostheses (partial or total), chewing problems, among other conditions [21,41]. As seen in other studies, we expected a greater impact on OHRQoL in older people [18,42]; however, our findings showed the opposite. Some feasible explanations prove that dental esthetics is related to a person's self-esteem and social interaction. Older adults seem more likely to be satisfied with their dental appearance than younger individuals [43]. Since dental esthetics may not be of primary concern among elders, this fact does not necessarily impact or impact the OHRQoL less in this age group. Moreover, dental perceptions are subjective and are associated with cultural characteristics and personality profiles [44]. This result was expected due to a variance in OHIP-14 scores, depending on the societal values where the construct was applied.

Severe periodontitis has been related to the OHRQoL [45–48]. The literature showed that the difference in OHIP-14 scores for patients with a probing depth > 6 mm was statistically more significant than for patients with a probing depth < 6 mm. Likewise, periodontal surgery was a statistically significant predictor for the OHIP-14 score [45]. Similarly, this study demonstrated the importance of gingival disease, tooth migration, scaling and root planing, and periodontal surgery related to OHRQoL. Moreover, the self-reported periodontal disease instrument allows one to understand the perception that individuals have regarding their oral and periodontal health. This perspective could be relevant to understand the impact of oral conditions on one's quality of life. It is important to reinforce that a high percentage of patients in our study would need antibiotic prophylaxis before clinical examination considering their health condition [30–32]. In this clinical situation, the utility of self-report measures for periodontal disease is once more justified.

Untreated dental caries, poor self-perception of oral health, and tooth loss have already been associated with poor OHRQoL [27,49,50]. Even a meta-analysis reported that tooth loss is associated with unfavorable OHRQoL scores, regardless of the study location and the OHRQoL instrument [49]. These are consistent with our findings. Individuals with untreated dental caries may experience pain, mouth infection, and tooth loss, affecting adults' productivity at work, social interaction, and other daily activities. Furthermore, untreated caries represent a significant social, biological, and financial burden on individuals [51], negatively impacting OHRQoL and needing to be controlled using a population approach [52].

Our study identified that patients using warfarin have factors associated with OHRQoL, similar to the general population, as shown by a systemic review. This review indicates that different studies reported poor OHRQoL in individuals with tooth loss, periodontal disease, and dental caries in the general population [53]. Even though our research did not analyze a group without OAT, we consider that this study provides information on the impact of oral health on the daily life of patients undergoing OAT. Despite the fact that taking warfarin was not a covariate in our study, future investigations that allow such a comparison are recommended. Some tested covariates were not associated with OHRQoL. Alcohol consumption, smoking, and diabetes were not associated with OHRQoL. Associations of these variables and quality of life have been reported in the literature; however, these associations are directed to alcohol abuse [54], impaired glycemic control or complications of diabetes [55], and the number of cigarettes smoked [56]. In our study, the details of these variables were not analyzed according to the amount of alcohol or cigarettes, nor were glycemic control or diabetes complications analyzed.

Subjective perceptions linked to culture and personality [44] may have altered the association of OHRQoL with sex and dental prostheses. Some studies related that women had a poorer OHRQoL compared to men [18,42], most likely explained by the fact that women are more affected by their physical appearance [57]. On the other hand, OHRQoL has been better in people who use dental prostheses than those who do not use and/or need them [19,57–59]. However, this study found no associations between sex or dental prostheses and OHRQoL. Perhaps, similar to age, dental esthetics played an essential role in the non-association of these variables. For this sample on oral anticoagulation, dental esthetics may not have been a primary concern. Nevertheless, most of the partial dentate and edentulous rehabilitated subjects used removable prostheses in the analyzed sample. A prior study reported that removable prostheses did not constitute an essential factor in determining good or bad OHRQoL [60]. Furthermore, a systematic review noted that in longer follow-ups (>9 months), removable partial dentures did not improve OHRQoL [61].

Some limitations of this study need to be acknowledged. First, this study uses a cross-sectional design, and the temporal relationship and causality between the outcome and the exposure cannot be determined. In this way, it cannot be guaranteed that the exposure preceded the outcome because there was no follow-up. In other words, it will be difficult to determine whether a particular factor is a cause or the result of another element. Longitudinal studies are needed to assess the temporality and causality of exposure [62,63]. Our sample is not selected at random, and our results have no external validity. Moreover, despite the fact that some values of RR are statistically significant, their effect on OHRQoL could be considered small. Despite the limitations, some strengths should also be highlighted. This study provides information on the impact of oral health on the daily life of patients undergoing OAT. This information can contribute to the decisions of public policymakers regarding the oral health of the population using oral anticoagulants. The impact of OHRQoL was also evaluated in a group of patients undergoing chronic medical treatment, and this evaluation is not common in the literature. Therefore, we recommend conducting future longitudinal research that improves the knowledge of oral conditions and the OHRQoL of this population. This study expands one's understanding of the impact that oral diseases and other variables have on the OHRQoL of anticoagulated patients. It is important to highlight the importance of an interdisciplinary team focused on a comprehensive approach to the patient with systemic pathologies. This information, which is a rare topic of discussion in the literature, may well be useful when organizing oral health care in this growing population.

5. Conclusions

Demographic and oral health condition factors can influence poor OHRQoL among anticoagulated patients with warfarin. Oral health and psychological factors are important for a better OHRQoL in this type of increasing population.

Author Contributions: Conceptualization, J.A.M.-D., A.J.S.d.C., L.O.M.C., M.A.P.M. and M.H.N.G.d.A.; data curation, J.A.M.-D., A.J.S.d.C. and M.L.S.d.F.; formal analysis, J.A.M.-D. and M.H.N.G.d.A.; investigation, J.A.M.-D., A.J.S.d.C., M.L.S.d.F., L.O.M.C., M.A.P.M. and M.H.N.G.d.A.; methodology, J.A.M.-D., A.J.S.d.C., M.L.S.d.F., L.O.M.C. and M.H.N.G.d.A.; software, I.A.P.; validation, I.A.P. and M.H.N.G.d.A.; resources, I.A.P.; writing—original draft preparation, J.A.M.-D., A.J.S.d.C., M.A.P.M. and M.H.N.G.d.A.; writing—review and editing, J.A.M.-D., A.J.S.d.C., M.A.P.M. and M.H.N.G.d.A.; visualization, I.A.P. and M.H.N.G.d.A.; supervision, I.A.P. and M.H.N.G.d.A.; project administration, I.A.P.; funding acquisition, I.A.P. All authors contributed to the study conception, design, material preparation, data collection, and analysis. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Institutional Review Board Statement: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee for Human Research of the Universidade Federal de Minas Gerais (protocol no. CAAE 17726219.0.0000.5149).

Informed Consent Statement: Informed consent was obtained from all individual participants included in the study.

Data Availability Statement: All data and materials, as well as a software application or custom code, support the published claims and comply with field standards.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kaplovitch, E.; Dounaevskaia, V. Treatment in the Dental Practice of the Patient Receiving Anticoagulation Therapy. *J. Am. Dent. Assoc.* **2019**, *150*, 602–608. Available online: https://pubmed.ncbi.nlm.nih.gov/31109636/ (accessed on 15 January 2021). [CrossRef] [PubMed]
2. Boned-Ombuena, A.; Pérez-Panadés, J.; López-Maside, A.; Miralles-Espí, M.; Vilarroig, S.G.; Ruiz, D.A.; Zurriaga, O. Prevalencia de la anticoagulación oral y calidad de su seguimiento en el ámbito de la atención primaria: Estudio de la Red Centinela Sanitaria de la Comunitat Valenciana [Prevalence of oral anticoagulation and quality of its management in primary healthc. *Atención Primaria* **2017**, *49*, 534–548. [CrossRef]
3. Lee, J.K. Dental Management of Patients on Anti-Thrombotic Agents. *J. Korean Assoc. Oral Maxillofac. Surg.* **2018**, *44*, 143–150. Available online: https://pubmed.ncbi.nlm.nih.gov/30181980/ (accessed on 15 January 2021). [CrossRef] [PubMed]
4. Ripollés de, R.J.; Gómez, F.R.; Muñoz-Corcuera, M.; Bascones, M.A. Actualización en Los Protocolos de Extracción Dental en Pacientes Anticoagulados [Update in Dental Procedures in Patients Receiving Oral Anticoagulated Therapy]. *Av. Odontoestomatol.* **2012**, *28*, 311–320. Available online: http://scielo.isciii.es/pdf/odonto/v28n6/original5.pdf (accessed on 15 January 2021). [CrossRef]
5. Kämmerer, P.W.; Frerich, B.; Liese, J.; Schiegnitz, E.; Al-Nawas, B. Oral Surgery during Therapy with Anticoagulants—A Systematic Review. *Clin. Oral Investig.* **2015**, *19*, 171–180. Available online: http://link.springer.com/10.1007/s00784-014-1366-3 (accessed on 15 January 2021). [CrossRef]
6. Eichhorn, W.; Burkert, J.; Vorwig, O.; Blessmann, M.; Cachovan, G.; Zeuch, J.; Eichhorn, M.; Heiland, M. Bleeding Incidence after Oral Surgery with Continued Oral Anticoagulation. *Clin. Oral Investig.* **2012**, *16*, 1371–1376. Available online: http://link.springer.com/10.1007/s00784-011-0649-1 (accessed on 15 January 2021). [CrossRef]
7. Rocha, A.L.; Souza, A.F.; Martins, M.A.; Fraga, M.G.; Travassos, D.V.; Oliveira, A.C.; Ribeiro, D.D.; Silva, T.A. Oral surgery in patients under antithrombotic therapy: Perioperative bleeding as a significant risk factor for postoperative hemorrhage. *Blood Coagul. Fibrinolysis* **2018**, *29*, 97–103. [CrossRef]
8. Ng, D.L.C.; Gan, G.G.; Chai, C.S.; Chee, K.H.; Tan, K.L.; Tan, S.B.; Bee, P.C. Comparing quality of life and treatment satisfaction between patients on warfarin and direct oral anticoagulants: A cross-sectional study. *Patient Prefer. Adherence* **2019**, *13*, 1363–1373. [CrossRef]
9. Almiñana-Pastor, P.J.; Segarra-Vidal, M.; López-Roldán, A.; Alpiste-Illueca, F.M. A controlled clinical study of periodontal health in anticoagulated patients: Assessment of bleeding on probing. *J. Clin. Exp. Dent.* **2017**, *9*, e1431–e1438. [CrossRef] [PubMed]
10. Bartholomay, E.; Polli, I.; Borges, A.P.; Kalil, C.; Arroque, A.; Kohler, I.; Danzmann, L.C. Prevalence of Oral Anticoagulation in Atrial Fibrillation. *Clinics* **2014**, *69*, 615–620. Available online: http://clinics.org.br/article.php?id=1372 (accessed on 15 January 2021). [CrossRef]
11. Martins, M.A.P.; Costa, J.M.; de Melo Mambrini, J.V.; Ribeiro, A.L.P.; Benjamin, E.J.; Brant, L.C.C.; Paasche-Orlow, M.K.; Magnani, J.W. Health literacy and warfarin therapy at two anticoagulation clinics in Brazil. *Heart* **2017**, *103*, 1089–1095. [CrossRef]
12. Purcell, C.A. Dental Management of the Anticoagulated Patient. *N. Z. Dent. J.* **1997**, *93*, 87–92. Available online: https://pubmed.ncbi.nlm.nih.gov/9323898/ (accessed on 15 January 2021).
13. Meurman, J.H.; Qvarnström, M.; Janket, S.J.; Nuutinen, P. Oral Health and Health Behavior in Patients Referred for Open-Heart Surgery. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol.* **2003**, *95*, 300–307. Available online: https://pubmed.ncbi.nlm.nih.gov/12627100/ (accessed on 15 January 2021). [CrossRef]
14. Padrón, N.; Limeres, J.; Tomás, I.; Diz Dios, P. Oral Health and Health Behavior in Patients under Anticoagulation Therapy. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol.* **2003**, *96*, 519–520. Available online: http://www.ncbi.nlm.nih.gov/pubmed/14658438 (accessed on 15 January 2021). [CrossRef]
15. Hanon, O.; Jeandel, C.; Jouanny, P.; Paccalin, M.; Puisieux, F.; Krolak-Salmon, P.; Berrut, G. Traitement Par Anticoagulants Chez Les Patients Atteints de Fibrillation Atriale: Un Consensus [Anticoagulant Treatment in Elderly Patients with Atrial Fibrillation: Position Paper]. *Gériatrie Psychol. Neuropsychiatr. Vieil.* **2019**, *17*, 341–355. Available online: https://pubmed.ncbi.nlm.nih.gov/31848123/ (accessed on 15 January 2021).
16. Sharka, R.; Abed, H.; Hector, M. Oral health-related quality of life and satisfaction of edentulous patients using conventional complete dentures and implant-retained overdentures: An umbrella systematic review. *Gerodontology* **2019**, *36*, 195–204. [CrossRef]

17. Perazzo, M.F.; Serra-Negra, J.M.; Firmino, R.T.; Pordeus, I.A.; Martins-JÚnior, P.A.; Paiva, S.M. Patient-centered assessments: How can they be used in dental clinical trials? *Braz. Oral Res.* **2020**, *34*, e075. [CrossRef] [PubMed]
18. Abdelrahim, R.; Delgado-Angulo, E.K.; Gallagher, J.E.; Bernabé, E. Ethnic Disparities in Oral Health Related Quality of Life among Adults in London, England. *Community Dent Health* **2017**, *34*, 122–127. Available online: https://pubmed.ncbi.nlm.nih.gov/28573845/ (accessed on 15 January 2021). [PubMed]
19. Wong, F.M.F.; Ng, Y.T.Y.; Keung Leung, W. Oral Health and Its Associated Factors among Older Institutionalized Residents—A Systematic Review. *Int. J. Environ. Res. Public Health* **2019**, *16*, 4132. Available online: https://pubmed.ncbi.nlm.nih.gov/31717812/ (accessed on 15 January 2021). [CrossRef] [PubMed]
20. Schuster, A.; Pastorino, D.; Marcello-Machado, R.; Faot, F. Influence of Age and Time since Edentulism on Masticatory Function and Quality of Life in Implant-Retained Mandibular Overdenture Wearers: 1-year Results from a Paired Clinical Study. *Int. J. Oral Maxillofac. Implant.* **2019**, *34*, 1466–1474. Available online: https://pubmed.ncbi.nlm.nih.gov/31711087/ (accessed on 15 January 2021). [CrossRef]
21. Ortíz-Barrios, L.B.; Granados-García, V.; Cruz-Hervert, P.; Moreno-Tamayo, K.; Heredia-Ponce, E.; Sánchez-García, S. The impact of poor oral health on the oral health-related quality of life (OHRQoL) in older adults: The oral health status through a latent class analysis. *BMC Oral Health* **2019**, *19*, 141. [CrossRef] [PubMed]
22. Baiju, R.; Peter, E.; Varghese, N.; Varughese, J.; Sivaram, R.; Narayan, V. Development and initial validation of an oral health-related quality of life scale for older adolescents. *Indian J. Dent. Res.* **2019**, *30*, 826–833. [CrossRef]
23. van de Rijt, L.J.; Stoop, C.C.; Weijenberg, R.A.; de Vries, R.; Feast, A.R.; Sampson, E.L.; Lobbezoo, F. The Influence of Oral Health Factors on the Quality of Life in Older People: A Systematic Review. *Gerontologist* **2019**, *60*, e378–e394. Available online: https://pubmed.ncbi.nlm.nih.gov/31729525/ (accessed on 15 January 2021). [CrossRef]
24. Trullas-Vila, J.C.; Freitas-Ramírez, A.; Soler-Simon, S.; Roncero-Vidal, J.M.; Gispert-Magarolas, R. Ten-Year Experience with Acenocoumarol Treatment in an Ambulatory Cohort of Spanish Patients. *J. Thromb. Thrombolysis* **2009**, *28*, 436–443. Available online: http://www.ncbi.nlm.nih.gov/pubmed/19225864 (accessed on 15 January 2021). [CrossRef] [PubMed]
25. Molino-Pagan, D.; Andujar- Mateos, P.; Jornet, P. Analysis of General and Oral Quality of Life and Satisfaction with Treatment among Anticoagulated Patients. *J. Dent. Oral Health* **2015**, *1*, 1–4.
26. De Oliveira, B.H.; Nadanovsky, P. Psychometric properties of the Brazilian version of the Oral Health Impact Profile—Short form. *Community Dent. Oral Epidemiol.* **2005**, *33*, 307–314. [CrossRef]
27. Ulinski, K.G.B.; do Nascimento, M.A.; Lima, A.M.C.; Benetti, A.R.; Poli-Frederico, R.C.; Fernandes, K.B.P.; Fracasso, M.L.C.; Maciel, S.M. Factors Related to Oral Health-Related Quality of Life of Independent Brazilian Elderly. *Int. J. Dent.* **2013**, *2013*, 705047. [CrossRef]
28. Slade, G.D. Derivation and validation of a short-form oral health impact profile. *Community Dent. Oral Epidemiol.* **1997**, *25*, 284–290. [CrossRef]
29. Cyrino, R.M.; Miranda Cota, L.O.; Pereira Lages, E.J.; Bastos Lages, E.M.; Costa, F.O. Evaluation of Self-Reported Measures for Prediction of Periodontitis in a Sample of Brazilians. *J. Periodontol.* **2011**, *82*, 1693–1704. [CrossRef]
30. Laskin, D.M. Should prophylactic antibiotics be used for patients having removal of erupted teeth? *Oral Maxillofac. Surg. Clin.* **2011**, *23*, 537–539. Available online: http://www.ncbi.nlm.nih.gov/pubmed/21982605 (accessed on 15 January 2021). [CrossRef]
31. Chu, V.H.; Sexton, D.J.; Cabell, C.H.; Barth, R.L.; Pappas, P.A.; Singh, R.K.; Fowler, V.G., Jr.; Ralph, C.G.; Aksoy, O.; Woods, C.W. Repeat Infective Endocarditis: Differentiating Relapse from Reinfection. *Clin. Infect. Dis.* **2005**, *41*, 406–409. Available online: http://www.ncbi.nlm.nih.gov/pubmed/16007540 (accessed on 15 January 2021). [CrossRef] [PubMed]
32. Nishimura, R.A.; Carabello, B.A.; Faxon, D.P.; Freed, M.D.; Lytle, B.W.; O'Gara, P.T.; O'Rourke, R.A.; Shah, P.M. ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Endorsed by the Society of Cardiovascular Anest. *Circulation* **2008**, *118*, 887–896. Available online: http://www.ncbi.nlm.nih.gov/pubmed/18663090 (accessed on 15 January 2021). [CrossRef] [PubMed]
33. Petersen, P.E.; Baez, R.J.; World Health Organization. *Oral health Surveys: Basic Methods*, 5th ed.; World Health Organization: Geneva, Switzerland, 2013; Available online: http://apps.who.int/iris/handle/10665/97035 (accessed on 15 January 2021).
34. Hosmer, D.W.; Lemeshow, S.; Sturdivant, R.X. *Applied Logistic Regression*, 3rd ed.; Wiley: New York, NY, USA, 2013; p. 500.
35. Long, J.S. *Regression Models for Categorical and Limited Dependent Variables*, 1st ed.; Sage Publications: Thousand Oaks, CA, USA, 1997; p. 297.
36. Spanemberg, J.C.; Cardoso, J.A.; Slob, E.M.G.B.; López-López, J. Quality of Life Related to Oral Health and Its Impact in Adults. *J. Stomatol. Oral Maxillofac. Surg.* **2019**, *120*, 234–239. Available online: https://pubmed.ncbi.nlm.nih.gov/30763780/ (accessed on 15 January 2021). [CrossRef] [PubMed]
37. Yang, S.E.; Park, Y.G.; Han, K.; Min, J.A.; Kim, S.Y. Dental Pain Related to Quality of Life and Mental Health in South Korean Adults. *Psychol. Health Med.* **2016**, *21*, 981–992. Available online: https://pubmed.ncbi.nlm.nih.gov/26456324/ (accessed on 15 January 2021). [CrossRef]
38. Dye, B.A.; Tan, S.; Smith, V.; Barker, L.K.; Thornton-Evans, G.; Eke, P.I.; Beltraán-Aguilar, E.D. Trends in oral health status: United States, 1988–1994 and 1999–2004. *Vital Health Stat.* **2007**, *11*, 1–92.
39. Elani, H.W.; Harper, S.; Allison, P.J.; Bedos, C.; Kaufman, J.S. Socio-Economic Inequalities and Oral Health in Canada and the United States. *J. Dent. Res.* **2012**, *91*, 865–870. Available online: https://pubmed.ncbi.nlm.nih.gov/22837551/ (accessed on 15 January 2021). [CrossRef]

40. Hjern, A.; Grindefjord, M. Dental health and access to dental care for ethnic minorities in Sweden. *Ethn. Health* **2000**, *5*, 23–32. Available online: https://pubmed.ncbi.nlm.nih.gov/10858936/ (accessed on 15 January 2021). [CrossRef]
41. Sánchez-García, S.; Juárez-Cedillo, T.; Reyes-Morales, H.; De La Fuente-Hernández, J.; Solórzano-Santos, F.; García-Peña, C. State of Dentition and Its Impact on the Capacity of Elders to Perform Daily Activities. *Salud Publica Mex.* **2007**, *49*, 173–181. Available online: https://pubmed.ncbi.nlm.nih.gov/17589771/ (accessed on 15 January 2021). [CrossRef]
42. Cho, M.J.; Kim, E.K. Subjective Chewing Ability and Health-Related Quality of Life among the Elderly. *Gerodontology* **2019**, *36*, 99–106. Available online: https://pubmed.ncbi.nlm.nih.gov/30565311/ (accessed on 15 January 2021). [CrossRef]
43. Alkhatib, M.N.; Holt, R.; Bedi, R. Age and Perception of Dental Appearance and Tooth Colour. *Gerodontology* **2005**, *22*, 32–36. Available online: https://pubmed.ncbi.nlm.nih.gov/15747896/ (accessed on 15 January 2021). [CrossRef]
44. Karasneh, J.; Al-Omiri, M.K.; Al-Hamad, K.Q.; Al Quran, F.A.M.A. Relationship between Patients' Oral Health-Related Quality of Life, Satisfaction with Dentition, and Personality Profiles. *J. Contemp. Dent. Pract.* **2009**, *10*, 49–56. Available online: https://pubmed.ncbi.nlm.nih.gov/20020081/ (accessed on 15 January 2021).
45. Sonnenschein, S.K.; Betzler, C.; Kohnen, R.; Krisam, J.; Kim, T.S. Oral health-related quality of life in patients under supportive periodontal therapy. *Acta Odontol. Scand.* **2018**, *76*, 572–579. [CrossRef] [PubMed]
46. Llanos, A.H.; Benítez Silva, C.G.; Ichimura, K.T.; Rebeis, E.S.; Giudicissi, M.; Romano, M.M.; Saraiva, L. Impact of aggressive periodontitis and chronic periodontitis on oral health-related quality of life. *Braz. Oral Res.* **2018**, *32*, 1–7. [CrossRef]
47. Durham, J.; Fraser, H.M.; McCracken, G.I.; Stone, K.M.; John, M.T.; Preshaw, P.M. Impact of periodontitis on oral health-related quality of life. *J. Dent.* **2013**, *41*, 370–376. [CrossRef] [PubMed]
48. Masood, M.; Younis, L.T.; Masood, Y.; Bakri, N.N.; Christian, B. Relationship of periodontal disease and domains of oral health-related quality of life. *J. Clin. Periodontol.* **2019**, *46*, 170–180. [CrossRef]
49. Gerritsen, A.E.; Allen, P.F.; Witter, D.J.; Bronkhorst, E.M.; Creugers, N.H.J. Tooth Loss and Oral Health-Related Quality of Life: A Systematic Review and Meta-Analysis. *Health Qual. Life Outcomes* **2010**, *8*, 126. Available online: http://www.hqlo.com/content/8/1/126 (accessed on 15 January 2021). [CrossRef]
50. Oliveira, D.C.; Ferreira, F.M.; Morosini, I.D.A.; Torres-Pereira, C.C.; Paiva, S.M.; Fraiz, F.C. Impact of oral health status on the oral health-related quality of life of Brazilian male incarcerated adolescents. *Oral Health Prev. Dent.* **2015**, *13*, 417–425.
51. Kassebaum, N.J.; Bernabé, E.; Dahiya, M.; Bhandari, B.; Murray, C.J.L.; Marcenes, W. Global Burden of Untreated Caries: A Systematic Review and Metaregression. *J. Dent. Res.* **2015**, *94*, 650–658. Available online: https://pubmed.ncbi.nlm.nih.gov/25740856/ (accessed on 15 January 2021). [CrossRef]
52. Baelum, V. Dentistry and population approaches for preventing dental diseases. *J. Dent.* **2011**, *39* (Suppl. S2), S9–S19. [CrossRef]
53. Haag, D.G.; Peres, K.G.; Balasubramanian, M.; Brennan, D.S. Oral Conditions and Health-Related Quality of Life: A Systematic Review. *J. Dent. Res.* **2017**, *96*, 864–874. Available online: https://pubmed.ncbi.nlm.nih.gov/28581891/ (accessed on 15 January 2021). [CrossRef]
54. Ugochukwu, C.; Bagot, K.S.; Delaloye, S.; Pi, S.; Vien, L.; Garvey, T.; Bolotaulo, N.I.; Kumar, N.; IsHak, W.W. The Importance of Quality of Life in Patients with Alcohol Abuse and Dependence. *Harv. Rev. Psychiatry* **2013**, *21*, 1–17. Available online: https://pubmed.ncbi.nlm.nih.gov/23656759/ (accessed on 15 January 2021). [CrossRef] [PubMed]
55. Rodríguez-Almagro, J.; García-Manzanares, Á.; Lucendo, A.J.; Hernández-Martínez, A. Health-Related Quality of Life in Diabetes Mellitus and Its Social, Demographic and Clinical Determinants: A Nationwide Cross-Sectional Survey. *J. Clin. Nurs.* **2018**, *27*, 4212–4223. Available online: https://pubmed.ncbi.nlm.nih.gov/29987853/ (accessed on 15 January 2021). [CrossRef] [PubMed]
56. Goldenberg, M.; Danovitch, I.; IsHak, W.W. Quality of Life and Smoking. *Am. J. Addict.* **2014**, *23*, 540–562. Available online: https://pubmed.ncbi.nlm.nih.gov/25255868/ (accessed on 15 January 2021). [CrossRef] [PubMed]
57. Faot, F.; Martins, A.P.P.; Marcello-Machado, R.M.; Schuster, A.J.; Bielemann, A.M.; Nascimento, G.G.; Melo, A.C.M.; de Rezende Pinto, L. Influence of Facial Patterns on the Masticatory Function and Quality of Life of Completely Edentulous Patients during the Transition to Implant-Retained Mandibular Overdentures. *J. Prosthet. Dent.* **2019**, *122*, 450–458. Available online: https://pubmed.ncbi.nlm.nih.gov/30948299/ (accessed on 15 January 2021). [CrossRef] [PubMed]
58. Figueredo, O.M.C.; Câmara-Souza, M.B.; Carletti, T.M.; Rodrigues Garcia, R.C.M. Chewing Ability and Oral Health-Related Quality of Life in Frail Elders after New Complete Dentures Insertion: A Paired Controlled Clinical Trial. *Spec. Care Dent.* **2020**, *40*, 168–174. Available online: https://pubmed.ncbi.nlm.nih.gov/31943301/ (accessed on 15 January 2021). [CrossRef] [PubMed]
59. Myint Oo, K.Z.; Fueki, K.; Yoshida-Kohno, E.; Hayashi, Y.; Inamochi, Y.; Wakabayashi, N. Minimal Clinically Important Differences of Oral Health-Related Quality of Life after Removable Partial Denture Treatments. *J. Dent.* **2020**, *92*, 103246. Available online: https://pubmed.ncbi.nlm.nih.gov/31738967/ (accessed on 15 January 2021). [CrossRef]
60. Bagewitz, I.; Söderfeldt, B.; Palmqvist, S.; Nilner, K. Oral prostheses and oral health-related quality of life: A survey study of an adult Swedish population. *Int. J. Prosthodont.* **2007**, *20*, 134–142.
61. Ali, Z.; Baker, S.R.; Shahrbaf, S.; Martin, N.; Vettore, M.V. Oral health-related quality of life after prosthodontic treatment for patients with partial edentulism: A systematic review and meta-analysis. *J. Prosthet. Dent.* **2019**, *121*, 59–68.e3. [CrossRef] [PubMed]
62. Olsen, J.; Christensen, K.; Murray, J.; Ekbom, A. The Cross-Sectional Study. In *An Introduction to Epidemiology for Health Professionals*; Springer: New York, NY, USA, 2010; Available online: https://link.springer.com/chapter/10.1007/978-1-4419-1497-2_11 (accessed on 15 January 2021).
63. Arnett, D.K.; Claas, S.A. Introduction to Epidemiology. In *Clinical and Translational Science: Principles of Human Research*, 2nd ed.; Robertson, D., Gordon, H.W., Eds.; Academic Press: Cambridge, MA, USA; Elsevier Inc.: London, UK, 2017; pp. 53–69.

6 CONSIDERAÇÕES FINAIS

Os resultados da revisão sistemática e meta-analise em rede apresentada no artigo 2, determinaram que os eventos de sangramento em indivíduos em anticoagulação oral diminuíram com o uso de TXA em comparação com o placebo. O N-butil-2-cianoacrilato e o $CaSO_4$ também foram superiores ao placebo. Porém, apenas o TXA apresentou efeitos benéficos com evidência de certeza moderada. N-butil-2-cianoacrilato e $CaSO_4$ apresentaram evidência de certeza muito baixa. Não foram observadas diferenças entre agentes hemostáticos na prevenção de eventos de sangramento. Para o tempo médio de sangramento, também não foi observada diferença significativa nas comparações. O ácido tranexâmico foi o agente hemostático mais estudado e o único para o qual foram feitas comparações diretas com o placebo. A falta de comparações diretas no estudo pode levar a uma certeza baixa ou muito baixa das evidências para a maioria dos resultados. Por este motivo, para futuras pesquisas, sugere-se a realização de estudos com as intervenções estudadas, a fim de se obter comparações diretas e, assim, evitar superestimar ou subestimar os efeitos dos tratamentos.

Observamos na literatura, estudos com alto risco de viés. Com base na análise do risco de viés, recomenda-se fortemente a realização de estudos de alta qualidade com amostras calculadas, permitindo aos pesquisadores avaliar efetivamente os agentes hemostáticos. Ressaltamos que ainda há muita pouca informação na literatura sobre pacientes submetidos a TAO após outro tipo de procedimentos odontológicos, além da extração dentária. Além disso, os efeitos do risco de sangramento entre fumantes ou portadores de doenças sistêmicas, como imunossupressão e diabetes mellitus, ainda são incipientes na literatura científica. Esses avanços metodológicos permitirão a construção de protocolos clínicos para os serviços de saúde, visando a segurança e efetividade do cuidado em saúde bucal a esse grupo populacional.

Países em crescimento, como a maioria dos países latino-americanos, não dispõem de grandes recursos para a disponibilidade de alguns medicamentos no mercado. Os estudos em que é avaliada a efetividade dos medicamentos permitem saber onde o orçamento deve ser alocado e evitar gastos desnecessários em saúde. Portanto, consideramos que este estudo deixa resultados a serem considerados para

a implementação de políticas públicas de medicamentos respeito aos hemostáticos locais.

Mais pesquisas sobre os anticoagulantes tipo DOAC são importantes. É possível que os resultados mudem devido aos mecanismos de ação diferentes. Os DOAC apresentam inibição dos fatores Xa e IIa. Os derivados cumarinicos inibem os fatores dependentes da vitamina K (II, VII, IX, X, proteínas S e C). Os desfechos avaliados neste estudo dos hemostáticos locais podem ser alterados, em relação ao número de eventos de sangramento e tempo médio de sangramento.

Por outro lado, o estudo transversal (artigos 3 e 4) descreveu que a carga de doenças bucais entre indivíduos submetidos a terapia anticoagulante oral com varfarina é preocupante. O índice CPOD apresentou um componente perdido alto. Há, ainda, uma possibilidade de que indivíduos em TAO, por medo de sangramento gengival, possam escovar os dentes com menor frequência, resultando em grande depósito de biofilme ou placa, fator de risco para cárie dentária e posterior necessidade de extração.

Consequentemente, o uso de prótese também foi alto, sendo maior o uso de prótese maxilar do que mandibular. No entanto, a necessidade de uma prótese mandibular observada clinicamente é ainda maior. A reabilitação, tanto com prótese removível quanto fixa, pode restabelecer a função mastigatória e melhorar a qualidade de vida relacionada à saúde bucal. Porém, a pequena oferta desse procedimento na atenção primária no Brasil contribui para a grande demanda por próteses bucais observada neste estudo.

O número de perdas dentárias e a demanda por reabilitação oral evidenciam a necessidade de assistência odontológica integral a essa população. É importante, no entanto, desenvolver estratégias para melhorar a alfabetização em saúde bucal na população sob TAO. Um programa educacional baseado no atendimento odontológico de rotina pode melhorar a auto-percepção de doenças bucais, bem como os hábitos de higiene bucal.

Os fatores demográficos e clínicos podem influenciar negativamente a percepção de pacientes anticoagulados na QVRSB. Um escore total do OHIP-14 mais alto (pior QVRSB) foi associado a um grupo étnico, idade, auto-relato de doença periodontal, cárie dentária e auto-relato de saúde bucal. Quase metade do valor do OHIP-14 refere-se às dimensões de desconforto psicológico e dor. Devemos ter em mente que a maioria dos problemas bucais são responsáveis por reduzir a qualidade

de vida dos indivíduos, prolongando estados de dor, problemas funcionais, estéticos e nutricionais, levando a altos níveis de estresse, ansiedade e depressão.

O impacto da QVRSB foi avaliado em um grupo de pacientes em tratamento médico crônico, sendo esta avaliação pouco comum na literatura. Portanto, recomendamos a realização de futuras pesquisas longitudinais com validade externa que aprimorem o conhecimento das condições bucais e da QVRSB dessa população. É necessário o acompanhamento para definir se um determinado fator é uma causa ou o resultado de outro elemento. Este estudo amplia o conhecimento na compreensão do impacto que as doenças bucais e outras variáveis na QVRSB de pacientes anticoagulados. Destacamos a importância de uma equipe interdisciplinar voltada para uma abordagem integral ao paciente com patologias sistêmicas. Essas informações são tema de discussão pouco comum na literatura, e podem ser úteis na organização da atenção à saúde bucal dessa população em crescimento.

REFERÊNCIAS

ALMIÑANA-PASTOR, P.J. *et al.* A controlled clinical study of periodontal health in anticoagulated patients: Assessment of bleeding on probing. *Journal of Clinical and Experimental Dentistry*, v. 9, n. 12, p. e1431-8, 2017.

ANDERSON, D J *et al.* Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the International Collaboration on Endocarditis-merged database. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*, v. 24, n. 10, p. 665–70, 2005. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/16244853>.

ANTMAN EM, LAU J, KUPELNICK B, MOSTELLER F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. *Journal of the American Medical Association*, v. 268, p. 240–248, 1992. Disponível em: <http://www.jameslindlibrary.org/antman-em-lau-j-kupelnick-b-mosteller-f-chalmers-tc-1992/>.

BAIJU, Radhamoni *et al.* Development and initial validation of an oral health-related quality of life scale for older adolescents. *Indian Journal of Dental Research*, v. 30, n. 6, p. 826–833, 2019.

BAJKIN, Branislav V. *et al.* Risk factors for bleeding after oral surgery in patients who continued using oral anticoagulant therapy. *Journal of the American Dental Association*, v. 146, n. 6, p. 375–381, 2015. Disponível em: <http://dx.doi.org/10.1016/j.adaj.2015.01.017>.

BAJKIN, Branislav V.; POPOVIC, Stevan L.; SELAKOVIC, Srecko D.J. J. Randomized, Prospective Trial Comparing Bridging Therapy Using Low-Molecular-Weight Heparin With Maintenance of Oral Anticoagulation During Extraction of Teeth. *Journal of Oral and Maxillofacial Surgery*, v. 67, n. 5, p. 990–995, 2009. Disponível em: <http://dx.doi.org/10.1016/j.joms.2008.12.027>.

BAJKIN, Branislav V *et al.* Comparison of efficacy of local hemostatic modalities in anticoagulated patients undergoing tooth extractions. *Vojnosanitetski pregled*, v. 71, n. 12, p. 1097–1101, 2014.

BARTHOLOMAY, E *et al.* Prevalence of oral anticoagulation in atrial fibrillation. *Clinics (Sao Paulo, Brazil)*, v. 69, n. 9, p. 615–620, 2014. Disponível em: <http://clinics.org.br/article.php?id=1372>.

BÉLIVEAU, Audrey *et al.* BUGSnet: An R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. *BMC Medical Research Methodology*, v. 19, n. 1, p. 196, 2019. Disponível em: <https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-019-0829-2>.

BONED-OMBUENA, Ana *et al.* Prevalencia de la anticoagulación oral y calidad de su seguimiento en el ámbito de la atención primaria : estudio de la Red Centinela Sanitaria de la Comunitat Valenciana [Prevalence of oral anticoagulation and quality of its management in primary healthc. *Atención Primaria*, v. 49, n. 9, p. 534–548, 2017. Disponível em: <http://dx.doi.org/10.1016/j.aprim.2016.11.015>.

BRANISLAV, VB *et al.* Risk factors for bleeding after oral surgery in patients who continued using oral anticoagulant therapy. *JADA*, v. 146, n. 6, p. 375–381, 2015. Disponível em: <http://sci-hub.io/10.1016/j.adaj.2015.01.017>.

BRIGNARDELLO-PETERSEN, Romina *et al.* Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of Clinical Epidemiology*, v. 93, p. 36–44, 2018. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/29051107/>.

CARTER, Glen *et al.* Tranexamic Acid Mouthwash Versus Autologous Fibrin Glue in Patients Taking Warfarin Undergoing Dental Extractions: A Randomized Prospective Clinical Study. *Journal of Oral and Maxillofacial Surgery*, v. 61, n. 12, p. 1432–1435, 2003.

CASTRO, Rodolfo De Almeida Lima; PORTELA, Margareth C.; LEÃO, Anna Thereza. Adaptação transcultural de índices de qualidade de vida relacionada à saúde bucal [Cross-cultural adaptation of quality of life indices for oral health]. *Cadernos de Saude Publica*, v. 23, n. 10, p. 2275–2284, 2007.

CATON, Jack G. *et al.* A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification. *Journal of Clinical Periodontology*, v. 45, n. March, p. S1–S8, 2018.

CHU, Vivian H *et al.* Repeat infective endocarditis: differentiating relapse from reinfection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, v. 41, n. 3, p. 406–9, 2005. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/16007540>.

CYRINO, Renata Magalhães *et al.* Evaluation of Self-Reported Measures for Prediction of Periodontitis in a Sample of Brazilians. *Journal of Periodontology*, v. 82,

n. 12, p. 1693–1704, 2011.

DE LIMA SILVA, Rogério Guimarães *et al.* Assessment of oral anticoagulation control at two pharmacist-managed clinics in Brazil. *International Journal of Clinical Pharmacy*, v. 39, n. 6, p. 1157–1161, 2017.

DE OLIVEIRA, Branca Heloisa; NADANOVSKY, Paulo. Psychometric properties of the Brazilian version of the Oral Health Impact Profile - Short form. *Community Dentistry and Oral Epidemiology*, v. 33, n. 4, p. 307–314, 2005.

DIAS, Sofia *et al.* Evidence synthesis for decision making 2: A generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical Decision Making*, v. 33, n. 5, p. 607–617, 2013. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/23104435/>.

DIAS, Sofia *et al. NICE DSU technical support document 4: inconsistency in networks of evidence based on randomised controlled trials report by the decision support unit*, 2014. Disponível em: <www.nicedsu.org.uk>.

EFTHIMIOU, Orestis *et al.* GetReal in network meta-analysis: a review of the methodology. *Research Synthesis Methods*, v. 7, n. 3, p. 236–263, 2016. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/26754852/>.

EICHHORN, Wolfgang *et al.* Bleeding incidence after oral surgery with continued oral anticoagulation. *Clinical Oral Investigations*, v. 16, n. 5, p. 1371–1376, 2012. Disponível em: <http://link.springer.com/10.1007/s00784-011-0649-1>.

GONZALES-SULLCAHUAMÁN, Judith A. *et al.* Oral health-related quality of life among Brazilian dental students. *Acta odontológica latinoamericana : AOL*, v. 26, n. 2, p. 76–83, 2013.

GUYATT, Gordon H *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, v. 336, n. 7650, p. 924–926, 2008. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/18436948>.

HALFPENNY, Wayne; FRASER, Julian S; ADLAM, David M. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, v. 92, n. 3, p. 257–259, 2001.

HARRER, Mathias *et al. Doing Meta-Analysis in R: A Hands-on Guide*.

HIGGINS, J.; GREEN, S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, 2011.

HOSMER, David W.; LEMESHOW, Stanley.; STURDIVANT, Rodney X. *Applied logistic regression.* 3rd. ed ed. New York: Wiley, 2013.

ISOLA, G *et al.* Anticoagulant therapy in patients undergoing dental interventions: a critical review of the literature and current perspectives. *Minerva stomatologica*, v. 64, n. 1, p. 21–46, 2015. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/25660591>.

JIMÉNEZ, Yolanda *et al.* An update on the management of anticoagulated patients programmed for dental extractions and surgery. *Medicina Oral Patologia Oral y Cirugia Bucal*, v. 13, n. 3, p. E176-9, 2008. Disponível em: <http://www.medicinaoral.com/medoralfree01/v13i3/medoralv13i3p176.pdf>.

KÄMMERER, Peer W. *et al.* Oral surgery during therapy with anticoagulants—a systematic review. *Clinical Oral Investigations*, v. 19, n. 2, p. 171–180, 22 mar. 2015. Disponível em: <http://link.springer.com/10.1007/s00784-014-1366-3>.

LALANI, T *et al.* Prosthetic valve endocarditis due to coagulase-negative staphylococci: findings from the International Collaboration on Endocarditis Merged Database. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*, v. 25, n. 6, p. 365–8, 2006. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/16767483>.

LASKIN, Daniel M. Should prophylactic antibiotics be used for patients having removal of erupted teeth? *Oral and maxillofacial surgery clinics of North America*, v. 23, n. 4, p. 537–9, vi, 2011. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/21982605>.

LEH-CHING NG, Diana *et al.* Comparing quality of life and treatment satisfaction between patients on warfarin and direct oral anticoagulants: A cross-sectional study. *Patient Preference and Adherence*, v. 13, p. 1363–1373, 2019.

LONG, J. Scott. *Regression models for categorical and limited dependent variables*. 1st ed ed. Thousand Oaks: Sage Publications, 1997.

MARTINS, M. *et al.* Health literacy and warfarin therapy at two anticoagulation clinics in Brazil. *Heart (British Cardiac Society)*, v. 103, n. 14, p. 1089–1095, 2017.

MASOOD, Mohd *et al.* Relationship of periodontal disease and domains of oral health-related quality of life. *Journal of Clinical Periodontology*, v. 46, p. 170–180, 2019.

MEURMAN, Jukka H. *et al.* Oral health and health behavior in patients referred for open-heart surgery. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, v. 95, n. 3, p. 300–307, 2003. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/12627100/>.

MOHER, David *et al.* Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement (Chinese edition). *Journal of Chinese Integrative Medicine*, v. 7, n. 9, p. 889–896, 2009.

MOIMAZ, Suzely A S *et al.* Influence of Oral Health on Quality of life in pregnant women. *Acta Odontol. Latinoam*, v. 29, n. 2, p. 186–193, 2016.

MOLINO- PAGAN, Diana; ANDUJAR- MATEOS, Paz; JORNET, Pia. Analysis of General and Oral Quality of Life and Satisfaction with Treatment among Anticoagulated Patients. *Journal of Dental and Oral Health*, v. 1, n. 5, p. 1–4, 2015.

MOREIRA, P *et al.* Interferência da doença periodontal na anticoagulaç ão oral em pacientes cardiopatas: Efeito do tratamento periodontal na anticoagulação oral [Effect of periodontal treatment on oral anticoagulation in patients with heart disease]. *Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology*, v. 26, n. 10, p. 977–989, 2007. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/18232621/>.

MULLIGAN, Roseann; WEITZEL, Karen Gjerde. Pretreatment management of the patient receiving anticoagulant drugs. *The Journal of the American Dental Association*, v. 117, n. 3, p. 479–483, 1988. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/S0002817788730214>.

NISHIMURA, Rick A *et al.* ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: endorsed by the Society of Cardiovascular Anest. *Circulation*, v. 118, n. 8, p. 887–96, 2008. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/18663090>.

ORGANIZATION, World Health. *Oral health surveys. Basic methods*, 2013.

ORTÍZ-BARRIOS, Lyzbeth Beatriz *et al.* The impact of poor oral health on the oral health-related quality of life (OHRQoL) in older adults: The oral health status through a latent class analysis. *BMC Oral Health*, v. 19, n. 1, p. 141, 2019.

OXMAN, A D; GUYATT, G H. The science of reviewing research. *Annals of the New York Academy of Sciences*, v. 703, p. 125- 33; discussion 133–4, 1993. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/8192290>.

PADRÓN, N *et al.* Oral health and health behavior in patients under anticoagulation therapy. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*, v. 96, n. 5, p. 519–20, 2003. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/14658438>.

PELEGRINO, Flávia Martinelli *et al.* Perfil sócio demográfico e clínico de pacientes em uso de anticoagulantes orais [Socio-demographic and clinical profile of patients using oral anticoagulants]. *Revista Gaúcha de Enfermagem*, v. 31, n. 1, p. 123–128, 2010.

PIPPI, Roberto; SANTORO, Marcello; CAFOLLA, Arturo. The effectiveness of a new method using an extra-alveolar hemostatic agent after dental extractions in older patients on oral anticoagulation treatment: An intrapatient study. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, v. 120, n. 1, p. 15–21, 2015. Disponível em: <http://dx.doi.org/10.1016/j.oooo.2015.02.482>.

PUHAN, Milo A. *et al.* A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Online)*, v. 349, n. g5630, 2014. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/25252733/>.

PURCELL, C. A. Dental management of the anticoagulated patient. *The New Zealand dental journal*, v. 93, n. 413, p. 87–92, 1997. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/9323898/>.

RIPOLLES-DE RAMON, Jorge *et al.* Aplicacion de un gel de Acido tranexamico en pacientes tratados con anticoagulantes orales. *Medicina Clinica*, v. 143, n. 11, p. 484–488, 2014.

RIPOLLÉS, De Ramón J *et al.* Actualización en los protocolos de extracción dental en pacientes anticoagulados [Update in dental procedures in patients receiving oral anticoagulated therapy]. *Avances en Odontoestomatología*, v. 28, n. 6, p. 311–320,

2012. Disponível em: <http://scielo.isciii.es/pdf/odonto/v28n6/original5.pdf>.

ROCHA, Amanda L. *et al.* Oral surgery in patients under antithrombotic therapy: Perioperative bleeding as a significant risk factor for postoperative hemorrhage. *Blood Coagulation and Fibrinolysis*, v. 29, n. 1, p. 97–103, 2018.

SACCO, R. *et al.* Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different intensity targets. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, v. 104, n. 1, p. e18–e21, 2007. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/17482846>.

SALANTI, Georgia; ADES, A. E.; IOANNIDIS, John P.A. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *Journal of Clinical Epidemiology*, v. 64, n. 2, p. 163–171, 2011. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/20688472/>.

SÁNCHEZ-SILES, Mariano *et al.* Periodontal disease as a risk factor of recurrence of venous thromboembolic disease: A prospective study. *Acta Odontologica Scandinavica*, v. 73, n. 1, p. 8–13, 2015.

SERRANO-SÁNCHEZ, Víctor *et al.* New horizons in anticoagulation: Direct oral anticoagulants and their implications in oral surgery. *Medicina Oral, Patologia Oral y Cirugia Bucal*, v. 22, n. 5, p. e601–e608, 2017.

SLADE, Gary D. Derivation and validation of a short-form oral health impact profile. *Community dentistry and oral epidemiology*, v. 25, n. 4, p. 284–290, 1997.

SOUTO, J C *et al.* Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: a prospective randomized study. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*, v. 54, n. 1, p. 27–32; discussion 323, 1996. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/8530996>.

TAKEDA, Sho; NAKANISHI, Toshio; NAKAZAWA, Makoto. A 28-year trend of infective endocarditis associated with congenital heart diseases: a single institute experience. *Pediatrics international : official journal of the Japan Pediatric Society*, v. 47, n. 4, p. 392–6, 2005. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/16091075>.

TOMASELLI, Gordon F. *et al.* 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the

American College of Cardiology Task Force on Expert Consensus Decision Pathways. *Journal of the American College of Cardiology*, v. 70, n. 24, p. 3042–3067, 2017. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/29203195/>.

TONETTI, Maurizio S.; GREENWELL, Henry; KORNMAN, Kenneth S. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *Journal of Clinical Periodontology*, v. 45, n. February, p. S149–S161, 2018.

TRULLAS-VILA, Joan-Carles *et al.* Ten-year experience with acenocoumarol treatment in an ambulatory cohort of Spanish patients. *Journal of Thrombosis and Thrombolysis*, v. 28, n. 4, p. 436–443, 2009. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/19225864>.

TUFANURU, C *et al.* Chapter 3: Systematic reviews of effectiveness - JBI Reviewer's Manual. In: AROMATARIS, E; MUNN, Z (Org.). . *The Joanna Briggs Institute*. The Joanna Briggs Institute, 2017. Disponível em: <https://wiki.joannabriggs.org/display/MANUAL/Chapter+3%3A+Systematic+reviews+of+effectiveness>.

VAN VALKENHOEF, Gert *et al.* Automating network meta-analysis. *Research Synthesis Methods*, v. 3, n. 4, p. 285–299, 2012. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/26053422/>.

WAHL, Michael J. Dental Surgery in Anticoagulated Patients. *Archives of Internal Medicine*, v. 158, n. 15, p. 1610, 1998. Disponível em: <http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.158.15.1610>.

WHO QUALITY OF LIFE ASSESSMENT GROUP. Que calidad de vida? La gente y la salud. *Foro mundial de la salud*, v. 17, n. 4, p. 385–387, 1996. Disponível em: <https://apps.who.int/iris/bitstream/handle/10665/55264/WHF_1996_17_n4_p385-387_spa.pdf?sequence=1&isAllowed=y>.

WONG, Florence M.F.; NG, Yannies T.Y.; KEUNG LEUNG, W. Oral health and its associated factors among older institutionalized residents—a systematic review. *International journal of environmental research and public health*, v. 16, n. 21, p. 4132, 2019. Disponível em: <https://pubmed.ncbi.nlm.nih.gov/31717812/>.

APÊNDICES E ANEXOS

APÊNDICE A - Formato de coleta de dados para estudo transversal analítico

Coleta de dados para estudo transversal analítico

Esta informação é muito importante para conhecer sobre a sua saúde. Obrigado pela sua ajuda.

Este documento será confidencial.

Nome: Código de identificação:

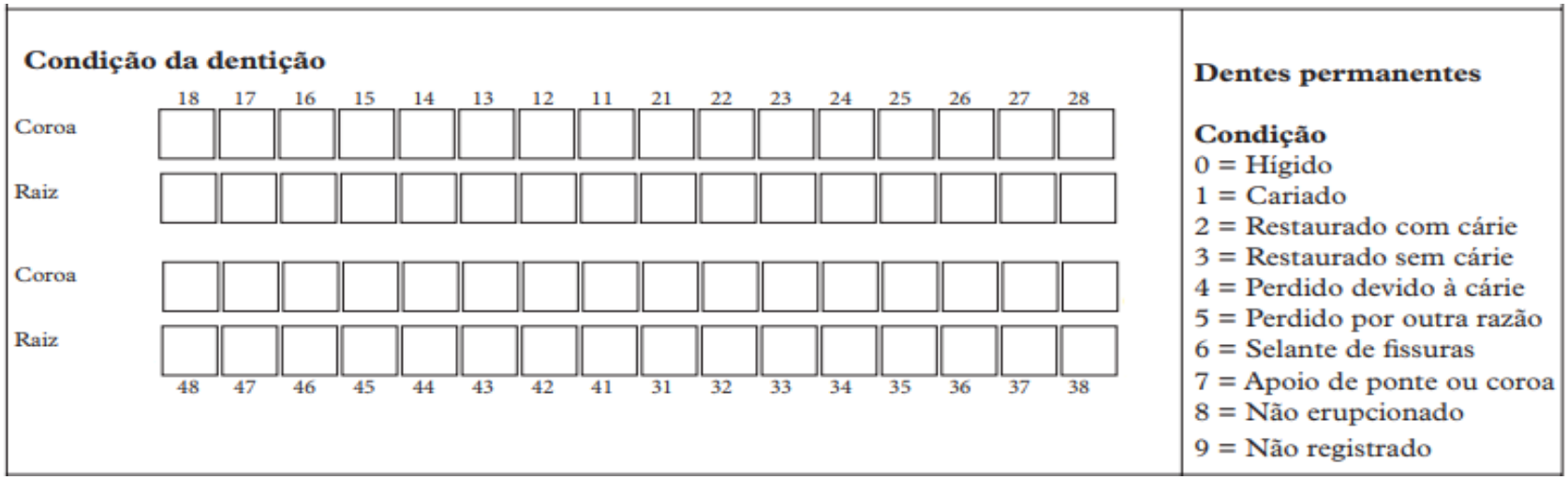
1. Data (DD/MM/ANO):	_____/_____/20__	**RNI no dia do exame:**_____	**Razão de anticoagulação:**	
2. Quantos anos você tem?		_____		
3. Sexo	( ) Feminino ( ) Masculino			
4. Qual é sua cor de pele?	( )Branco/a ( )Preto/a	( )Pardo/a ( )Amarelo/a	( ) Indígena ( ) Outros	
5. Onde você mora?	( ) Belo Horizonte ( ) Fora de Belo Horizonte			
6. Quantos anos de estudo você tem?	_____			
7. Qual é a faixa de renda mensal?	( ) Até 1 a 3 salários mínimos ( ) até 3 a 5 salários mínimos		( ) mais que 5 salários mínimos	
8. Você consome álcool?	( ) Sim ( ) Não			
9. Você é um fumante?	( ) Sim ( ) Não	Quantos cigarros ao dia? _____	Há quanto tempo você fuma? _____	Se ex-fumante, parou a quanto tempo? _____

Nome: Código de identificação:

10. Você tem diabetes?	( ) Sim		
	( ) Não		
11. Você faz uso do fio ou fita dental?	( ) Sim	( ) Não	
12. Se usa fio dental, qual a frequência?	( ) 1 x por semana	( ) Diariamente	
	( ) Dia sim, dia não	( ) Outros _____	
13. Com que frequência você geralmente escova os dentes?	( ) 1 x ao dia	( ) 3 x ao dia ou mais	
	( ) 2 x ao dia		
14. Quando foi a sua última visita ao dentista para controle ou tratamento?	( ) até 6 meses	( ) 2 – 3 anos	
	( ) 1 ano	( ) mais que 3 anos	
15. A doença gengival é um problema relativamente comum que ocorre em nossa boca. Pessoas com doença gengival devem ter sangramento ao redor dos dentes, gengivas inchadas, machucadas ou infeccionadas, que permanece por 2 semanas ou mais e não é causada por próteses removíveis parciais ou totais. Você acha que pode ter doença gengival?	( ) Sim		
	( ) Não		
16. Você notou nos últimos anos que seus dentes anteriores se projetaram para frente ou que surgiram espaços entre seus dentes da frente?	( ) Sim		
	( ) Não		
	( ) Sim		

17. Você já teve algum dente que se tornou bambo na boca por si só, sem nenhum trauma ou injúria?	( ) Não		
18 Você já teve algum dente permanente que foi perdido sozinho, sem que houvesse nenhum traumatismo e sem ter ido ao dentista para fazer extração?	( ) Sim ( ) Não		
19. Consideramos como dentes naturais, aqueles que ainda apresentam raízes dentro do osso, mesmo que estes dentes possuam, pinos, obturações, coroas, ‘‘pivôs’’, blocos metálicos ou sejam apoio de pontes fixas. Faça uma análise cuidadosa em sua boca e responda: quantos dentes naturais você possui? (caso possua próteses removíveis como “rôte” ou “dentadura” retire-as da boca antes de contar)	_____		
20. De um modo geral, como você poderia classificar a saúde de seus dentes e gengivas?	( ) Excelente ( ) Muito boa	( ) Boa ( ) Ruim	( ) Muito ruim
21. Você já fez raspagem ou alisamento radicular, algumas vezes chamado de limpeza profunda ou curetagem gengival?	( ) Sim ( ) Não		
22. Você já se submeteu a alguma cirurgia para limpar por baixo de suas gengivas?	( ) Sim ( ) Não		
23. Algum dentista já lhe disse que você teve perda óssea ao redor dos dentes?	( ) Sim ( ) Não		

Condição da dentição.



Uso e necessidade de prótese dentária.

Uso de próteses dentaria	( ) Superior	
	( ) Inferior	
	( ) Não usa prótese	
Tipo de prótese dentária	Maxila	Mandíbula
	( ) Não usa prótese	( ) Não usa prótese
	( ) Usa uma ponte fixa	( ) Usa uma ponte fixa
	( ) Usa mais que uma ponte fixa	( ) Usa mais que uma ponte fixa
	( ) Usa prótese parcial removível	( ) Usa prótese parcial removível
	( ) Usa uma ou mais pontes fixas e uma ou mais prótese removíveis	( ) Usa uma ou mais pontes fixas e uma ou mais prótese removíveis
	( ) Usa prótese dentária total	( ) Usa prótese dentária total
Necessidade de prótese	Maxila	Mandíbula
	( ) Não necessita de prótese dental	( ) Não necessita de prótese dental
	( ) Necessita de uma prótese, fixa ou removível para substituição de um elemento	( ) Necessita de uma prótese, fixa ou removível para substituição de um elemento
	( ) Necessita de uma prótese, fixa ou removível para substituição de mais de um elemento	( ) Necessita de uma prótese, fixa ou removível para substituição de mais de um elemento
	( ) Necessita de uma combinação de próteses fixas e/ou removíveis para substituição de um e/ou mais de um elemento	( ) Necessita de uma combinação de próteses fixas e/ou removíveis para substituição de um e/ou mais de um elemento
	( ) Necessita de prótese total	( ) Necessita de prótese total

ANEXO A - Versão brasileira da forma abreviada do Perfil de Impacto da Saúde Bucal (OHIP14)

Nos últimos seis meses, por causa de problemas com seus dentes, sua boca ou dentadura:

QUESTÕES	Nunca (0)	Raramente (1)	Às vezes (2)	Repetidamente (3)	Sempre (4).
1. Você teve problemas para falar alguma palavra?					
2. Você sentiu que o sabor dos alimentos tem piorado?					
3. Você sentiu dores em sua boca ou nos seus dentes?					
4. Você se sentiu incomodada ao comer algum alimento?					
5. Você ficou preocupado/a?					
6. Você se sentiu estressado/a?					
7. Sua alimentação ficou prejudicada?					
8. Você teve que parar suas refeições?					
9. Você encontrou dificuldade para relaxar?					
10. Você se sentiu envergonhado/a?					
11. Você ficou irritado/a com outras pessoas?					
12. Você teve dificuldade para realizar suas atividades diárias?					
13. Você sentiu que a vida, em geral, ficou pior?					
14. Você ficou totalmente incapaz de fazer suas atividades diárias?					

APÊNDICE B - Termo de consentimento livre e esclarecido

Projeto: Saúde bucal em pacientes com terapia anticoagulante e efetividade das terapias hemostáticas para a prevenção do sangramento.

Prezado Senhor (a)
Você está sendo convidado para uma pesquisa realizada nesta Clínica de Anticoagulação. O objetivo do estudo é verificar como está a saúde dos seus dentes e boca e se isso interfere na sua vida.

Se você concordar em participar do estudo, ocorrerá o seguinte:
Vamos fazer-lhe algumas perguntas sobre o seu estado de saúde, tais como o tipo de tratamento ou o tipo de medicamento que você toma, se apresenta ou tem outras doenças, como está a sua satisfação com a saúde da sua boca ou dentes e também faremos perguntas sobre questões gerais como idade, raça, renda e outras. A entrevista ou o questionário da pesquisa durará entre 10 a 15 minutos. A entrevista será conduzida de acordo com sua disponibilidade no dia do seu atendimento na Clínica de Anticoagulação. O questionário será completado por você, se desejar, ou será feita uma entrevista se você preferir não preencher os documentos. Após o questionário ou entrevista, será realizado exame dos seus dentes e boca, onde serão observados cárie, a saúde das gengivas e se você utiliza alguma prótese (dentadura, por exemplo). A avaliação clínica pode durar de 15 a 20 minutos, não irá causar dor ou qualquer incômodo. Será utilizado apenas um espelho, e uma sonda periodontal (um instrumento usado pelo dentista) será colocada levemente na sua gengiva. Você não receberá benefício financeiro direto pela sua participação no estudo. No entanto, se concordar em participar, estará colaborando com a ciência, fornecendo informações básicas sobre o estado de saúde bucal em pacientes tratados com medicamentos anticoagulantes para obter uma melhoria da atenção à saúde bucal. Todas as informações que você nos fornece para o estudo serão estritamente confidenciais, ou seja, ninguém, além de você saberá como estão as condições dos seus dentes e boca. Essas informações serão usadas somente pela equipe de pesquisa do projeto e não estarão disponíveis para nenhuma outra finalidade. Você será identificado com um número e não com o seu nome. Os resultados deste estudo serão publicados para fins científicos, mas serão apresentados de forma que ninguém será identificado. Sua participação neste estudo apresenta riscos mínimos. Esses riscos podem estar relacionados a algum desconforto durante o exame ou entrevista. Para diminuir os riscos, faremos os procedimentos com equipe experiente, dentro de sua disponibilidade e de forma rápida. Se alguma das perguntas fizer você se sentir um pouco desconfortável ou se você se sentir desconfortável na avaliação clínica, você tem o direito de não responder ou desistir da pesquisa.

Você não receberá nenhum pagamento pela participação no estudo e nem pagará nada para participar. Você é livre para se recusar a participar ou retirar sua participação a qualquer momento. Sua decisão de participar ou não, não afetará de maneira alguma como você é tratado no hospital ou centros de saúde. Se você tiver quaisquer perguntas, comentários ou preocupações sobre o projeto, entre em contato com a pesquisadora: Johana Alejandra Moreno Drada pelo telefone 31 999445248 de segunda a sexta-feira das 7:00 às 17:00 horas ou com seu orientador Prof. Mauro Henrique Nogueira Guimarães de Abreu pelo telefone 31 34092434. Se você tem perguntas gerais sobre os seus direitos com o estudo de pesquisa, você pode contatar o Comitê de Ética da Universidade Federal de Minas Gerais no telefone 3409-4592 de segunda a sexta-feira em uma programação das 08:00-16:00 horas.

Se você concordar em participar do estudo, nós lhe daremos uma via deste documento que pedimos a gentileza de assiná-lo. Consentimento para participação no estudo sobre “Saúde bucal em pacientes com terapia anticoagulante e efetividade das terapias hemostáticas para a prevenção do sangramento". Sua assinatura indica sua aceitação em participar voluntariamente deste estudo.

Nome do participante:
_____
Data: _____ Dia / Mês / Ano
Assinatura: _____
Endereço ou contato:

Johana Alejandra Moreno Drada
Nome da pessoa que obtém o consentimento:
_____
Data: _____ Dia / Mês / Ano

ATIVIDADES ACADÉMICAS E PRODUÇÃO INTELECTUAL

Artigo 5

Silva da Cruz AJ, **Moreno-Drada JA**, Santos JS, Nogueira Guimaraes de Abreu MH, Dental caries remains a significant public health problem for South American Indigenous peoples, The Journal of Evidence-Based Dental Practice (2020), doi: https://doi.org/10.1016/j.jebdp.2020.101418.

Artigo publicado na revista The Journal of Evidence-Based Dental Practice. Cite Score 0.65 (2019), impact factor 2.426, Q1 (Dentistry) no Scimago Journal & Country Rank e Qualis Capes B1 para Odontologia.

Outras atividades acadêmicas: Colaboração no Trabalho de tese de doutorado do estudante Ricardo Luiz de Barreto Aranha. Is Stress at Work Associated with Temporomandibular Disorders? A Systematic Review:

Ricardo Aranha, Renata Martins, Diego Aguilar, Johana Drada, Woosung Sohn, Carolina Martins, Mauro Henrique Nogueira Guimarães Abreu. Association between Stress at Work and Temporomandibular Disorders: A Systematic Review, BioMed Research International, 2021,2021.

Artigo publicado na revista BioMed Research International. Cite Score 0.68 (2019), impact factor 2.276, Q2 (Medicine) no Scimago Journal & Country Rank e Qualis Capes B1 para Odontologia.