Universidade Estadual Paulista “Júlio de Mesquita Filho”

Faculdade de Medicina de Botucatu

Gustavo Muçouçah Sampaio Brandão

PENTASACCHARIDES PARA O TRATAMENTO DA TROMBOSE VENOSA PROFUNDA

Orientador: Prof. Dr. Hamilton Almeida Rollo

Coorientador: Prof. Dr. Marcone Lima Sobreira

Botucatu - SP

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Tese apresentada ao Programa de Pós- Graduação em Bases Gerais da Cirurgia da Faculdade de Medicina de Botucatu-UNESP para a obtenção do título de Doutor.

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Os textos correspondentes à seguinte Tese de Doutoramento foram elaborados de acordo com as recomendações da coordenação do Curso de Pós-graduação da UNESP, tendo como objetivo facilitar a publicação dos trabalhos. A dissertação foi subdividida em três capítulos: o primeiro, redigido como um artigo de revisão, intitulado: *"**Novos anticoagulantes orais para o tratamento da trombose venosa profunda: revisão das revisões sistemáticas**",* o segundo trata-se do protocolo de pesquisa publicado em julho de 2015 pela Cochrane Library e o terceiro redigido conforme um artigo original denominado "***Pentasaccharides* for the treatment of deep vein thrombosis**".

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Gustavo Muçouçah Sampaio Brandão: nada a declarar

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Marcone Lima Sobreira: declara ter recebido pagamento do laboratório farmacêutico Sanofi para ministrar palestras educacionais sobre profilaxia e tratamento do tromboembolismo venoso.

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"A verdadeira felicidade está na própria casa, entre as alegrias da família"

Leon Tolstoi

(1828-1910)

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Capítulo I - ARTIGO DE REVISÃO

"Novos anticoagulantes orais para o tratamento da trombose venosa profunda: revisão das revisões sistemáticas"

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Capítulo I

Novos anticoagulantes orais para o tratamento da trombose venosa profunda: revisão das revisões sistemáticas

New oral anticoagulants for the treatment of deep vein thrombosis: review of systematic reviews

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Resumo

INTRODUÇÃO E OBJETIVOS: A trombose venosa profunda (TVP) é uma doença grave e necessita terapia anticoagulante para seu tratamento. A terapia padrão com warfarina tem uma série de limitações referentes ao seu uso. Nesse contexto, foram desenvolvidos novos anticoagulantes orais (NOACs): inibidores da trombina (dabigatran) e do fator Xa (rivaroxaban, apixaban e edoxaban). Essa revisão das revisões sistemáticas procurou elencar os principais resultados das revisões sistemáticas abordando o tema NOACs em pacientes com TVP. **MÉTODO:** Foram pesquisadas revisões sistemáticas nas bases PubMed e Cochrane Database of Systematic Reviews. A avaliação da qualidade dos estudos foi feita utilizando a ferramenta AMSTAR. **RESULTADOS:** Somente uma revisão foi elegível entre 50 estudos selecionados e descritos os seus resultados. A revisão elegível atingiu escore máximo no AMSTAR e incluiu 7.596 pacientes no grupo de pacientes para análise dos inibidores diretos de trombina e 16.356 pacientes para a análise dos inibidores diretos do fator Xa. Os resultados da meta-

análise realizada indicaram similaridade de eficácia no tratamento do tromboembolismo venoso e de incidência de sangramento maior entre a terapia padrão e os anticoagulantes orais da classe de inibidores diretos da trombina. Os novos anticoagulantes orais inibidores do fator Xa também apresentaram eficácia semelhante à terapia padrão. A incidência de sangramento maior foi um pouco menor nos pacientes recebendo os novos anticoagulantes orais inibidores do fator Xa. **CONCLUSÕES:** O tratamento da TVP com novos anticoagulantes orais, independente da classe, é similar a terapia padrão estabelecida.

ABSTRACT

INTRODUCTION AND OBJECTIVES: Deep vein thrombosis (DVT) is a serious illness and require anticoagulation therapy for their treatment. The standard therapy with warfarin has a number of limitations for its use. In this context, they developed new oral anticoagulants (NOACs): thrombin inhibitors (dabigatran) and factor Xa (rivaroxaban, apixaban and edoxaban). This review of systematic reviews sought to list the main results of systematic reviews addressing the issue NOACs in patients with deep vein thrombosis. **METHOD:** systematic reviews were searched in PubMed and the Cochrane Database of Systematic Reviews. The evaluation of the quality of the studies was done using the AMSTAR tool. **RESULTS:** Only one review was eligible from 50 selected studies and described their results. Eligible review reached maximum score in AMSTAR and included 7,596 patients in the group of patients for analysis of direct thrombin inhibitors and 16,356 patients for the analysis of direct inhibitors of factor Xa. The results of the performed meta-analysis showed efficacy of similarity in preventing venous thromboembolism and incidence of major bleeding between standard therapy and oral anticoagulants of the class of direct thrombin inhibitors. The new oral anticoagulant inhibitors of factor Xa also showed similar efficacy to standard therapy. The incidence of major bleeding was slightly lower in patients receiving oral anticoagulants new inhibitors of factor Xa. **CONCLUSIONS:** The treatment of DVT with new oral anticoagulants, regardless of class, is similar to standard therapy.

Introdução

A trombose venosa profunda (TVP) dos membros inferiores é uma doença grave e potencialmente fatal. Sua incidência na população geral é de cinco casos por dez mil habitantes por ano (1). Cerca de 46% dos casos de trombose venosa profunda proximal (atinge as regiões ílio-femoral, femoral e poplítea) podem evoluir para embolia pulmonar (EP), sendo 4% fatais se não tratados (2) e, segundo Susan Kahn, até 50% podem desenvolver síndrome pós-trombótica (3). Assim, após a confirmação do diagnóstico, torna-se imperativo iniciar a terapia anticoagulante. O objetivo do tratamento é diminuir a extensão do trombo, a possibilidade de EP e impedir a recorrência de nova TVP.

Os antagonistas da vitamina K (AVK) como a warfarina são tradicionalmente utilizados como anticoagulantes orais para tratamento e profilaxia do tromboembolismo venoso (TEV) desde a década de 1950 (4). Apesar de sua eficácia, a warfarina é limitada por fatores como um estreito índice terapêutico, interações medicamentosas, interações com alimentos, início lento, risco de hemorragia, alopecia, necrose de pele e necessidade rigorosa de monitoramento para manter a relação normalizada internacional (RNI) dentro do índice terapêutico. Essas limitações impulsionaram o desenvolvimento de pesquisas com novos anticoagulantes que idealmente deveriam ter baixo risco de sangramento, ausência de efeitos colaterais, ausência de interação com outras medicações ou alimentos, ser de fácil administração, permitir o tratamento domiciliar, não necessitar de controle laboratorial, baixo custo e apresentar um antídoto para reverter anticoagulação nos casos de sangramento maior e clinicamente relevante (5).

Novos anticoagulantes orais

De acordo com as diretrizes do *American College of Chest Physian (6)* duas formas de anticoagulantes orais são indicados para o tratamento da TVP: os inibidores diretos da trombina e os inibidores do fator X ativado (Xa).

Os inibidores orais direto da trombina, como dabigatran, se ligam, diretamente a trombina sem a necessidade de um cofator como a antitrombina. Diferentemente dos AVKs e das heparinas, podem inibir tanto a trombina solúvel quanto a trombina ligada a fibrina (7). Por não se ligarem a outras proteínas, apresentam poucas limitações farmacocinéticas e farmacodinâmicas, tornando mais previsível a resposta anticoagulante, além de não apresentarem efeito antiplaquetário e ausência de trombocitopenia induzida pela heparina (8).

Os inibidores do fator Xa se ligam diretamente ao sítio ativo do fator Xa, bloqueando a atividade do fator de coagulação. Diferentemente dos pentasaccharides (inibidores indiretos do fator Xa), esses medicamentos inativam o fator Xa livre e o fator Xa incorporado ao complexo protrombinase e não interagem com o inibidor

antitrombínico (9). Os inibidores do fator Xa indicados para o tratamento da TVP são: rivaroxaban, apixaban e edoxaban.

A utilização clinica efetiva e segura dos novos anticoagulantes orais requer o acompanhamento das evidências sobre a eficácia clínica desses medicamentos. O estudo dos efeitos adversos, principalmente o sangramento, é também essencial para compreender se os novos anticoagulantes orais têm a possibilidade de serem superiores que os anticoagulantes atualmente utilizados na prática. Portanto, nosso objetivo foi revisar as evidências disponíveis sobre a eficácia dos novos anticoagulantes no tratamento trombose venosa profunda em comparação com a terapia padrão, heparina de baixo peso molecular (HBPM) ou heparina não fracionada (HNF) seguida por AVK.

Método

Nós conduzimos uma revisão de revisões sistemáticas de ensaios clínicos controlados e randomizados sobre o tratamento de pacientes com trombose venosa profunda com terapia padrão em comparação à terapia com novos anticoagulantes orais. Dois desfechos foram considerados essenciais para avaliar a efetividade e segurança clínica dos novos anticoagulantes orais em relação aos AVK: (I) Recorrência de TVP ou tromboembolismo venoso (TEP); e (II) sangramento.

A busca foi realizada nas bases de dados PubMed utilizando um filtro de busca altamente sensível para a recuperação de revisões sistemáticas (10). A busca foi realizada também na Cochrane Database of Systematic Reviews. A estratégia de busca nas duas bases de dados utilizou uma combinação dos seguintes termos com os respectivos símbolos de truncagem: new oral anticoagulant* ou novel oral anticoagulant*, e deep vein thrombosis. Um autor realizou a triagem dos estudos recuperados e extraiu dados dos estudos elegíveis de acordo com os critérios de inclusão: estudos de revisões sistemáticas comparando terapia padrão com novos anticoagulantes orais em pacientes diagnosticados com trombose venosa profunda. Um segundo autor realizou a conferência dos dados extraídos. Revisões narrativas, guidelines e opiniões de especialistas não foram consideradas. Discrepâncias foram resolvidas em reuniões de consenso.

Os dados foram extraídos segundo um formulário de extração de dados descrevendo os estudos de acordo com a data da atualização da busca, população de pacientes estudada, o tipo de anticoagulante oral estudado, a quantidade de ensaios clínicos, os resultados sobre a recorrência de trombose venosa profunda ou embolismo venoso e sangramento maior, e a qualidade dos ensaios clínicos que contribuíram para a análise estatística se realizada (meta-análise).

A validade interna (qualidade metodológica) das revisões sistemáticas foi avaliada com o uso da ferramenta AMSTAR (11, 12). AMSTAR é uma ferramenta validada que consiste de 11 itens de respostas diretas (sim, não, não posso responder ou não aplicável) que avalia, entre outras coisas, a existência de planejamento a priori da revisão sistemática, se a seleção e extração de dados foram realizadas em duplicata, e se o status da publicação foi utilizado como critério de inclusão. A qualidade da revisão pode ser analisada de acordo com a pontuação final atingida.

As revisões sistemáticas incluídas foram descritas em termos de suas características, resultados sobre os desfechos de interesse, e sua qualidade metodológica.

Resultados

No total, 50 artigos foram recuperados. Após a exclusão de duplicadas, 49 artigos foram avaliados de acordo com os critérios de inclusão. Trinta e nove artigos foram excluídos com base na leitura do título e resumo, e 9 artigos considerados potencialmente elegíveis tiveram o artigo completo analisados. Ao final do processo de seleção, uma revisão sistemática foi considerada elegível.

A revisão sistemática conduzida por Robertson e colaboradores (13) comparou o tratamento com inibidores diretos de trombina e inibidores diretos do fator Xa com terapia padrão. Todos os inibidores de trombina e do fator Xa foram comparados com um grupo, e não foi realizada comparação individualizada para cada medicamentos. A comparação relativa aos inibidores de trombina inclui um estudo do medicamento ximelagran, retirado do mercado em 2006 devido ao relato de dano hepático grave durante tratamento continuado (mais de 11 dias) (14).

A revisão atingiu escore máximo no AMSTAR (Tabela 1), e incluiu 7.596 pacientes no grupo de pacientes para análise dos inibidores diretos de trombina e 16.356 pacientes para a análise dos inibidores diretos do fator Xa (Tabela 2). Os resultados da meta-análise realizada indicaram similaridade de eficácia do tratamento do tromboembolismo venoso e de incidência de sangramento maior entre a terapia padrão e os anticoagulantes orais da classe de inibidores diretos da trombina. Os novos anticoagulantes orais inibidores do fator Xa também apresentaram eficácia semelhante à terapia padrão. A incidência de sangramento maior foi um pouco menor nos pacientes recebendo os novos anticoagulantes orais inibidores do fator Xa.

Tabela 1 Descrição da revisão sistemática comparando terapia padrão da trombose venosa profunda com novos anticoagulantes orais.

Autor, Ano	Atualização da busca	População	Anticoagulante oral	Ensaios clínicos incluídos (n)	AMSTAR
Robertson, 2015	28 Janeiro 2015	Pacientes com diagnóstico de trombose venosa profunda confirmado por técnica padrão de imagem (venografia, impedância pletismográfica, ultrassonografia de compressão distal, ultrassonografia de compressão proximal)	Inibidores diretos da trombina e Inibidores diretos do fator Xa	3 estudos comparando inibidores diretos da trombina com terapia padrão; 8 estudos comparando inibidores diretos do fator Xa com terapia padrão	11/11

Tabela 2 Recorrência de tromboembolismo venoso e incidência de sangramento maior em pacientes com trombose venosa profunda recebendo tratamento com novos anticoagulantes orais e comparação com terapia padrão.

Comparação	Pacientes	Recorrência de trombose venosa profunda ou embolismo venoso (OR, 95% IC)	Sangramento Maior	Qualidade dos estudos contribuindo para a meta-análise
Inibidores diretos da trombina (ximelagran, dabigatran)	7.596 pacientes, idade média (min 54,7, máx. 57,1)	≤ 3 meses: OR 1.09 (95% IC 0.62 - 1.91); > 3 meses: OR 1.09 (95% IC 0.76 - 1.58); 6 meses: 1,09 (95% IC 0.80 - 1.49)	≤ 3 meses: (OR 0.54; 95% IC 0.28 - 1.03); > 3 meses: (OR 0.76; 95% IC 0.49 - 1.18); 6 meses: OR 0.68 (95% IC 0.47 - 0.98)	Julgamento dos autores: "*We deemed all included studies to be of high methodological quality and generally low risk of bias*."
Inibidores diretos do fator Xa (apixaban, rivaroxaban, edoxaban)	16.356 pacientes idade média (min 53,1, máx. 60)	≤ 3 meses: OR 0.69 (95% IC 0.48 - 0.99); > 3 meses: OR 0.97 (95% IC 0.78 - 1.22); 6 meses: 0.89 (95% IC 0.73 - 1.07)	≤ 3 meses: OR 0.83 (95% CI 0.47 - 1.45); > 3 meses: OR 0.50 (95% CI 0.36 - 0.71); 6 meses: OR 0.57 (95% IC 0.43 - 0.76)	Julgamento dos autores: "*We deemed all included studies to be of high methodological quality and generally low risk of bias*."

OR: odds ratio; IC: intervalo de confiança.

Discussão

As evidências acumuladas indicam que os novos anticoagulantes orais, tanto inibidores diretos de trombina quanto inibidores diretos de fator Xa, apresentam um balanço de riscos e benefícios semelhantes ao da terapia padrão. Isso significa que esses medicamentos não são melhores nem piores que a combinação de heparinas com AVK no tratamento da trombose venosa profunda.

As evidências encontradas são limitadas a uma revisão sistemática. No entanto a revisão sistemática disponível para essa avaliação foi considerada de alta qualidade metodológica. Portanto, seus resultados tem pouca probabilidade de serem alterados por novas pesquisas. O número de pacientes incluídos na análise quantitativa dos desfechos recorrência de trombose venosa profunda ou embolismo venoso e sangramento maior incluíram um número relevante de pacientes. A qualidade dos ensaios clínicos randomizados incluídos nessa revisão sistemática também foi considerada alta. Uma limitação desses resultados, no entanto, é a análise de eficácia e efeitos adversos ter sido realizada somente para o grupo de medicamentos das duas categorias de novos anticoagulantes orais, inibidores diretos da trombina e inibidores diretos do fator Xa. Apesar de ser provável que medicamentos individuais que compartilham do mesmo mecanismo de ação apresentarem efeitos semelhantes, é útil a comprovação empírica do efeito clínico de cada medicamento.

Os novos anticoagulantes orais apresentam, no entanto, maior facilidade no gerenciamento da terapia, já são administrados em doses fixas, sem necessidade de ajuste pelo peso corporal. Esses medicamentos apresentam um início de ação rápido, não necessitam de controle laboratorial, e apresentam meia-vida curta (o que facilita o manejo dos pacientes quando há necessidade de suspensão dos medicamentos para realização de um procedimento diagnóstico ou cirúrgico). As interações fármaco-fármaco, fármaco-álcool e fármaco-alimentos descritas são poucas e permitem o tratamento ambulatorial.

Um problema prático para utilização dos novos anticoagulantes orais, no entanto, está relacionado às diferentes doses e principalmente posologias desses medicamentos. A terapia padrão, estabelecida como prática clínica há mais de 50 anos, parece

apresentar um esquema terapêutico mais sensível à dinâmica do atendimento ambulatorial, apesar dos ajustes de doses necessários. Outro problema prático relevante é o custo desses novos medicamentos, especialmente em países com baixo nível de desenvolvimento socioeconômico.

Um fator determinante para a utilização clínica rotineira dos novos anticoagulantes orais é a inexistência de um antídoto para essa nova classe de medicamentos. O efeito anticoagulante dos AVK pode ser revertido pela administração de vitamina k, plasma fresco congelado ou complexo protrombínico. Estudos preliminares demonstraram que a tecnologia de recombinação genética tem sido usada para criar e modificar a molécula do fator Xa por meio de uma mutação no seu sítio catalítico que abole a atividade procoagulante do fator Xa, mas mantém a sua estrutura nativa. Isso permite que inibidores do fator Xa se liguem com forte afinidade e neutralize sua atividade anticoagulante. Essa molécula de fator Xa recombinante pode se ligar tanto aos inibidores diretos do fator Xa, como rivaroxaban, apixaban e edoxaban quanto os inibidores do fator Xa que necessitam da ação da antitrombina, como as heparinas de baixo peso molecular e fondaparinux.

Abaixo, apresentamos uma revisão sumarizada do *status* dos estudos de fase III disponíveis sobre os diferentes medicamentos orais inibidores diretos de trombina e inibidores diretos de fator Xa.

Dabigatran

O etexilato de dabigatran (Pradaxa^{R}- Boehringer Ingelhein) é uma pró-droga que é rapidamente metabolizada pelo fígado, transformando-se num composto ativo que se liga de forma competitiva e reversível ao sítio de atividade da trombina, bloqueando sua atividade pró-coagulante. A dabigatrana é absorvida pelo trato gastrointestinal, apresenta uma meia-vida de 12 a 17 horas e excreção renal e fecal. O estudo RE-COVER comparou o tratamento da warfarina com o dabigratran, após o tratamento inicial com uma anticoagulante parenteral, em 2539 pacientes diagnosticados com TEV agudo pelo período de 6 meses. Os resultados mostraram que a administração por via oral de 150 mg duas vezes ao dia de dabigatrana, não apresentou inferioridade em relação a warfarina na prevenção do TEV recorrente ou morte relacionada ao TEV. Um

total de 30 de 1274 pacientes randomizados para receber dabigatran (2,4%), comparados com 27 de 1265 pacientes randomizados para warfarina (2,1%), tiveram TEV recorrente. As taxas de morte relacionadas com TEV foram de 1 paciente para a dabigatran (0,1%) e 3 pacientes para a warfarina (0,2%). Além disso, as taxas de sangramento maior foram semelhantes nos dois grupos: 20 pacientes no grupo do dabigatran (1,6%) e 24 pacientes no grupo da warfarina (1,9%). Porém, as taxas de sangramento no geral foram mais baixas no grupo da dabigatran em relação ao grupo da warfarina: respectivamente 205 pacientes (16,1%) e 277 pacientes (21,7%) (15).

Rivaroxaban

O rivaroxaban (Xarelto^{R} - Bayer Healthcare) é um inibidor oral do fator Xa que se liga de forma reversível ao sítio de atividade do fator Xa. Apresenta metabolização hepática, meia-vida estimada entre 8 e 10 horas e excreção renal e fecal. O estudo EINSTEIN-DVT comparou o tratamento padrão (enoxaparin seguida por AVK- warfarin ou acenocoumarol) realizado em 1718 pacientes com o tratamento realizado em 1731 pacientes com rivaroxaban (total de 3449 pacientes diagnosticados com TVP aguda proximal sem embolia pulmonar sintomática) pelo período de 15 semanas. Os resultados mostraram que a administração de 15 mg de rivaroxaban 2 vezes ao dia pelo período de 3 semanas seguidos pela administração de 20 mg por 12 semanas, não foi inferior à terapia padrão na redução de TEV recorrente. A incidência de TEV recorrente foi de 2,1% no grupo da rivaroxaban em comparação a 3,0% do grupo da terapia padrão. O principal resultado de segurança - sangramento maior e sangramento clinicamente relevante não maior – ocorreu em 139 pacientes (8,1%) do grupo da rivaroxaban e 138 pacientes (8,1%) do grupo tratamento padrão (hazard ratio with rivaroxaban, 0.97; 95% CI, 0.76 a 1.22; P=0.77) (16).

Apixaban

O apixaban (Eliquis^{R}- Bristol Meyer Squibb-Pfizer) é um inibidor oral do fator Xa que inibe a atividade do fator Xa livre e ligado a plaqueta, de forma seletiva e reversível, e bloqueia a atividade do complexo protrombinase. Apresenta metabolização hepática, meia-vida plasmática de 8 a 15 horas e excreção renal e fecal. O estudo AMPLIFY comparou o tratamento de 2704 pacientes usando enoxaparina seguida por warfarina

(tratamento padrão) com 2691 pacientes usando apixaban (total de 5395 pacientes) com TVP sintomática proximal ou EP (com ou sem TVP) pelo período de 6 meses. Os resultados mostraram que a administração de 10 mg de apixaban duas vezes ao dia por 7 dias seguido pela administração de 5 mg de apixaban ao dia por 6 meses, não foi inferior ao tratamento com enoxaparina seguido pela warfarina em relação as taxas de TEV recorrente e de mortalidade relacionada ao tromboembolismo. No entanto, as taxas de sangramento maior foram significativamente mais baixas no grupo do apixaban (0,6%) em comparação ao grupo do tratamento padrão (1,8%) e a associação de sangramento maior com sangramento clinicamente relevante não maior foram respectivamente de 4,3% e 9,7% (risco relativo, 0.44; 95% CI, 0.36 a 0.55; P<0.001) (17).

Edoxaban

O edoxaban (Lixiana^{R}- Daiichi Sankyo) é um inibidor oral do fator Xa que se liga de forma reversível ao sítio de atividade do fator Xa. Apresenta metabolização hepática, meia-vida plasmática de 9 a 11 horas e um terço de excreção renal e o restante fecal. O estudo de fase III Hokusai-VTE comparou o tratamento de 2453 pacientes usando heparina seguida por AVK (tratamento padrão) com o tratamento de 2468 pacientes usando edoxaban (total de 4921 pacientes) pelo período de 12 meses. Os pacientes elegíveis para esse estudo apresentaram TVP aguda sintomática envolvendo as veias ilíaca, femoral e poplítea ou EP aguda sintomática (com ou sem TVP). Os resultados mostraram que a administração de 60 mg de edoxaban uma vez ao dia (ou 30 mg de edoxaban em pacientes com clearence de creatinina entre 30-50 ml/minuto ou com peso corporal menor 60 Kg ou recebendo inibidor da glicoproteína-P) não foi inferior ao tratamento padrão em relação de TEV recorrente. As taxas de TEV recorrente foram de 3,2% (130 pacientes) no grupo do edoxaban e 3,5% no grupo da warfarina (146 pacientes). No entanto, as taxas de sangramento maior e sangramento clinicamente significante não maior, foram significativamente menores no grupo edoxaban em relação ao grupo da warfarina, respectivamente 8,5% (345 pacientes) e 10,3% (423 pacientes). Segundo o laboratório que produz o edoxaban, o medicamento encontra-se em fase final de desenvolvimento para comercialização. Sua primeira aprovação ocorreu em setembro de 2014 no Japão, seguido pela aprovação em janeiro de 2015

nos Estados Unidos e em junho de 2015 na Comissão Européia. No Brasil, ainda não existe disponível (18).

Conclusão

O tratamento da trombose venosa profunda com novos anticoagulantes orais, independente da classe, é similar a terapia padrão estabelecida. No entanto, não existe antídoto para o efeito anticoagulante desses novos medicamentos. Na prática, isso significa que se um sangramento ocorrer não existe esquema terapêutico disponível para a reversão do efeito adverso. Dependendo do local e da gravidade do sangramento, o paciente pode estar sob elevado risco de morrer sem recursos terapêuticos. Atualmente, alguns antídotos para os novos anticoagulantes orais estão em fase de desenvolvimento (19). No entanto, a pergunta a se fazer: é melhor trocar a rotina do tratamento da trombose venosa profunda para uma nova opção com eficácia semelhante, mas problemas práticos de segurança, ou permanecer com estratégias terapêuticas largamente conhecidas, com perfil de segurança conhecido, e igual eficácia aos novos medicamentos atualmente disponíveis?

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Capítulo II

Pentasaccharides for the treatment of deep vein thrombosis (Protocol)

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THE COCHRANE COLLABORATION

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Pentasaccharides for the treatment of deep vein thrombosis (Protocol)
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[Intervention Protocol]

Pentasaccharides for the treatment of deep vein thrombosis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and harms of pentasaccharides for treatment of deep venous thrombosis.

BACKGROUND

Description of the condition

Deep vein thrombosis (DVT) is a severe disorder caused by acute formation of a clot or thrombus in the deep vein system. It results in impaired venous blood flow which may in turn lead to leg swelling, pain, and with propagation of the clot, to pulmonary embolism and death. Clots that form in the deep veins of the lower extremities are more likely to dislodge from the limbs and reach the pulmonary vasculature.

Together, DVT and pulmonary embolism comprise venous thromboembolism (VTE). Between 2007 and 2009, an average 547,596 adults aged 18 years or older were hospitalized with VTE annually in the United States, with confirmed DVT in an estimated annual average of 348,558 hospitalizations (Centers for Disease Control and Prevention 2012). As pointed out in Goldhaber 2012, recurrence is common after a first episode of DVT or pulmonary embolism. Fowkes 2003 described a steep increase in the incidence of DVT with age, from 2 to 3/10,000 in adults aged 30 to 49 years to 20/10,000 in adults aged 70 to 79 years.

DVT may be diagnosed by one of three objective tests: bilateral ascending contrast venography, duplex ultrasound, or color duplex ultrasound (EMA 2007b). Standard treatment is based on antithrombotic therapy (Kearon 2012), initially with parenteral administration (administration through intravenous or subcutaneous injections) of unfractionated heparin or low molecular weight heparins for five to seven days, then subsequent long-term oral vitamin K antagonists (e.g. warfarin) therapy (Erkens 2010). To manage the ideal dose of vitamin K antagonists, it is necessary to reach a therapeutic international normalized ratio (INR) range of 2.0 to 3.0 before the end of heparin treatment (McRae 2004). In the first three months of therapy, the goal of DVT treatment is to prevent the extension and embolization of the thrombus so as to minimize late local effects of venous thrombosis. In patients with pulmonary embolism, the goal is to prevent potentially fatal recurrence. After the third month, the use of continuous anticoagulation therapy is used as a prophylactic measure to prevent late recurrence. However, therapy with warfarin may be problematic and requires monitoring, since individual response to the medicine

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may vary. In addition, hemorrhagic complications (minor as well as major) are a major concern associated with warfarin treatment, and may occur at virtually any site. Indeed, the hemorrhagic risk of warfarin and the required laboratory control remain the Achilles' heel of vitamin K antagonist management.

Description of the intervention

New anticoagulants have been recently developed aiming to improve the profile of harms and efficacy outcomes of DVT treatment. Among them, synthetic pentasaccharides have been modelled on the sequence of the heparin responsible for the binding of a particular coagulation protein, which leads to inhibition of the coagulation cascade and to clot formation and growth (van Boeckel 1993). Pentasaccharides are, therefore, synthetic and selective anticoagulant drugs, in contrast with heparins, which are obtained from animal sources. More specifically, pentasaccharides act indirectly, inhibiting the activated factor X (Xa), thus interrupting the blood coagulation cascade and inhibiting both thrombin formation and thrombus development (EMA 2007a; EMA 2010). Factor X is located at the starting point of the common pathway of the extrinsic and intrinsic coagulation systems and therefore plays a central role in thrombin generation (Bauer 2003).

The advantages attributed to pentasaccharides include a more convenient dosing regimen, a more predictable anticoagulant response, and no need for laboratory monitoring (Bauer 2003; Nutesco 2005; Weitz 2004). In addition, because pentasaccharides are not metabolized in the liver, drug interactions may be reduced. Similarly, adverse reactions that often occur with heparins and vitamin K antagonists, such as bleeding and heparin-induced thrombocytopenia, are expected to be reduced (Nutesco 2005). However, other limitations stand for pentasaccharides:

- there is no antidote to reverse the effect of pentasaccharides if the patient presents any adverse bleeding to treatment or requires an invasive procedure (Gerotziafas 2004);
- the risk-benefit balance of this class of medicines is still under question; and
- financial costs may have significant impact on treatment.

How the intervention might work

The first synthetic pentasaccharide compound granted approval for commercialisation was fondaparinux (approved in 2001 in the United States and 2002 in Europe). Preliminary data have shown that fondaparinux was at least as efficacious as enoxaparin, a low molecular weight heparin, with similar rates of death or clinically relevant bleeding for VTE prophylaxis following orthopedic surgery (Eriksson 2001; Lassen 2002). Nowadays, fondaparinux is widely recommended for VTE prophylaxis (Kearon 2012; Reynolds 2004), having been approved for VTE prophylaxis in a number of different medical interventions. However, questions remain regarding its effectiveness and harms in comparison with low molecular weight heparins. Furthermore, concerns with serious adverse drug reactions involving fondaparinux, including bleeding, have prompted pharmacovigilance alerts and labelling changes since its approval (FDA 2009; Prescrire 2006; Prescrire 2012).

Fondaparinux binds selectively to antithrombin, catalysing factor Xa inhibition. It expresses an elevated affinity for antithrombin, and this specific activity leads to lack of variability in anticoagulation action (Garcia 2012). Even though the administration route is still a limitation - pentasaccharides can only be administered parenterally - fondaparinux exhibits a longer half-life (17 hours) in comparison with heparins, which determines a more convenient posology once a day (Donat 2002). Fondaparinux does not bind to platelets, and so does not cause heparin-induced thrombocytopenia (Reynolds 2004), but renal clearance remains a limitation, contraindicating its use in patients with severe renal insufficiency (creatinine clearance < 20ml/min).

In addition to fondaparinux, other pentasaccharides include idraparinux and idrabiotaparinux, hypermethylated forms of fondaparinux that have longer half-lives (80 to 130 hours). The pharmacokinetic properties of idraparinux were designed to allow weekly dosing by subcutaneous injection without coagulation monitoring (The PERSIST investigators 2004). Idrabiotaparinux is identical to idraparinux but has biotin incorporated to its molecule, so that anticoagulant action can be reversed by avidin injection (Paty 2010; Trellu 2013). However, the development of both idraparinux and idrabiotaparinux was discontinued during phase III trials. A higher risk of bleeding after treatment of VTE and lower efficacy in the treatment of pulmonary embolism compared to standard treatment (enoxaparin followed by warfarin, Harenberg 2008; van Gogh 2007); appear to be the major problems justifying the pharmaceutical industry statement that these compounds do not appear to be able to bring significant improvement in the care of patients (Sanofi-Aventis 2009). Nevertheless, a recent non-Cochrane systematic review has pointed out that the available evidence is still not sufficient to clarify whether or not idraparinux and idrabiotaparinux are as effective and safe as the standard warfarin treatment for VTE treatment (Song 2013).

Why it is important to do this review

The traditional forms of anticoagulation therapy may be associated with major limitations in terms of laboratory monitoring, complications induced by adverse reactions, drug interactions and even dietary aspects (e.g. vitamin K antagonists interaction with food containing elevated levels of vitamin K). Unfractionated heparin is administered exclusively via parenteral route and requires laboratory monitoring of activated partial thromboplastin time and platelet count due to the risk of heparin-induced thrombocytopenia (Junqueira 2012). Since heparins are produced from biological sources, they are also sensitive to contamination (Blossom 2008).

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Vitamin K antagonists may be administered orally, however these agents also require strict laboratory monitoring to ensure that the desired anticoagulation effect occurs during the therapeutic interval. Additional limitations of vitamin K antagonists include interactions with drugs and food, adverse reactions such as skin necrosis, and teratogenic potential (Bauer 2010; Benmira 2010; Garcia 2009; Haas 2008; Laux 2009; Spyropoulos 2008).

Even though monitoring is not required for dose adjustment of low molecular weight heparin, making home treatment possible (Buller 2004), some clinically relevant aspects have not been fully elucidated. For instance, different types of low molecular weight heparin (enoxaparin, tinzaparin, etc) present with different pharmacokinetics properties and thus cannot be promptly interchanged and whether one or another type of heparin is available during the course of a treatment may not be a clinical decision. In countries where public health systems have financial imitations, the type of heparin available depends on costs and may vary on monthly or sometimes weekly basis. Weight adjustment doses required for low molecular weight heparins may also be a limitation in areas with fair resources and in trauma settings. There is conflicting evidence regarding the advantage of one or two daily applications given that the anticoagulant effect of low molecular weight heparins may not always be anticipated (Breddin 2001; Merli 2001), and the best dose for patients with renal failure has not yet been fully defined (Collet 2001; Sanderink 2002). These limitations, together with the motivation for the development of more efficacious and convenient anticoagulants drugs, have driven the search for new agents.

Therefore, determining the efficacy and harms of pentasaccharides will provide useful information to improve the prognosis of patients with DVT.

OBJECTIVES

To assess the efficacy and harms of pentasaccharides for treatment of deep venous thrombosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs).

Types of participants

We will include patients older than 18 years of age with DVT involving popliteal, femoral, iliac veins or calf veins. Diagnosis of DVT should be confirmed by at least one standard imaging technique (venography or duplex venous ultrasonography).

Types of interventions

The treatment of interest is pentasaccharide anticoagulant therapy for DVT.

Despite having their development discontinued in 2009 due to safety issues, a recent non-Cochrane systematic review has pointed out that the available evidence is still insufficient to clarify whether or not idraparinux and idrabiotaparinux are as effective and safe as warfarin for the treatment of VTE (Song 2013). We will include idraparinux and idrabiotaparinux in the review in order to make the results as comprehensive as possible.

We will compare our treatment intervention of interest to standard therapy (low molecular weight heparins, unfractionated heparin or vitamin K antagonists e.g. warfarin) or other treatments identified in RCTs (e.g. placebo, other anticoagulants).

We will exclude studies assessing pentasaccharide anticoagulant therapy for the prevention of VTE as they form part of another Cochrane review (Song 2011).

Types of outcome measures

Primary outcomes

- Main efficacy outcome
  - Any VTE: incidence of symptomatic recurrent VTE during a six-month study period
    - Symptomatic recurrent VTE is defined as objectively documented DVT or pulmonary embolism
- Main harm outcome
  - Major (clinically relevant) and non-major bleeding
    - Major bleeding (as defined by the International Society on Thrombosis and Haemostasis) (Schulman 2005): (i) fatal bleeding; (ii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial bleeding, or intramuscular bleeding progressing to compartment syndrome; (iii) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; (iv) any combination of points 1 to 3.

Secondary outcomes

- Efficacy outcomes
  - All-cause mortality
  - Recurrent DVT: symptomatic DVT confirmed by standard imaging techniques including a new non-compressible

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venous segment or a substantial increase (4 mm or more) in thrombus diameter during full compression in a previously abnormal segment on ultrasonography (Prandoni 1993; Prandoni 2002), or a new intraluminal filling defect found on venograph

◦ Pulmonary embolism (fatal and non-fatal): symptomatic pulmonary embolism confirmed by an intraluminal filling defect on computed tomography or pulmonary angiography; a cut-off vessel of more than 2.5 mm in diameter on pulmonary angiography; a perfusion defect of at least 75% of a segment with corresponding normal ventilation (high-probability lung scan); non-diagnostic lung scan associated with new DVT documented by ultrasonography or venography; or pulmonary embolism confirmed by autopsy (Buller 2004)

• Harm outcomes

◦ Thrombocytopenia (reduction in platelet count above 150 x 10^9 /L)

◦ Heparin-induced thrombocytopenia syndrome defined as a relative reduction in platelet count of about 50% (even if the platelet count at its lowest remains above 150 x 10^9 / L) occurring within 5 to 14 days after the start of heparin therapy (Warkentin 2003)

◊ Clinically suspected cases of heparin-induced thrombocytopenia syndrome should have diagnosis confirmed through functional or immunological laboratory tests to detect platelet activation induced by anti-platelet factor 4 antibodies (Keeling 2006)

◦ All other adverse effects induced by the treatments, including those leading to drop out from the trial including but not limited to anemia, insomnia, increased wound drainage, hypokalemia, dizziness, hypotension, confusion, bullous eruption, hematoma, increase in transaminases, dermatological reactions, others

Search methods for identification of studies

We will perform electronic searches with no restrictions on language.

Electronic searches

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) will search the Group's 'Specialised Register' and the Cochrane Central Register of Controlled Trials (CENTRAL), part of the Cochrane Library (http:// www.cochranelibrary.com/). See Appendix 1 for details of the search strategy which will be used to search CENTRAL. The 'Cochrane Peripheral Vascular Diseases Group Specialised Register' is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the "Specialised Register" section of the Cochrane Peripheral Vascular Diseases Group module in the Cochrane Library (http:// www.cochranelibrary.com/).

In addition, the TSC will search the following trial databases for details of ongoing or unpublished studies using fondaparinux, idraparinux and idrabiotaparinux as search terms:

• World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http:// apps.who.int/trialsearch/);

• ClinicalTrials.gov (http://clinicaltrials.gov/);

• International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.isrctn.com/).

Searching other resources

We will check citations of included studies to identify additional studies not identified in the electronic search.

Data collection and analysis

Selection of studies

Two review authors (GMSB and MLS) will independently screen the titles and abstracts of the identified citations for potential eligibility. We will retrieve full texts of articles judged to be potentially eligible by at least one review author. We will then independently screen the full-text articles for eligibility using a pre-standardized study selection form, which will highlight our inclusion and exclusion criteria. We will resolve disagreement by consensus or by consulting a third review author (DRGJ).

We will attempt to contact authors of the studies retrieved whenever there is insufficient information available to decide whether a study meets the eligibility criteria.

Data extraction and management

We will develop and use a pre-standardized data extraction form. Two review authors (GMSB and MLS) will independently extract data from each included study and we will resolve disagreement by consensus or by consulting a third review author (DRGJ). We will obtain additional information from the authors of the pre-selected studies when necessary.

We aim to describe the studies according to the following characteristics:

• trial design;

• diagnosis of DVT;

• demographic characteristics of participants;

• type of anticoagulant prophylaxis;

• characteristics of the anticoagulant prophylaxis including dose, posology, duration of treatment;

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- co-interventions; and
- frequency of primary and secondary outcomes.

Assessment of risk of bias in included studies

We will assess risk of bias in included studies using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). Two authors (GMSB, MLS) will independently perform this task, with any disagreements resolved by discussion or by consulting a third review author (DRGJ).

We will assess the following domains:

1. sequence generation (selection bias);
2. allocation sequence concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective outcome reporting (reporting bias);
7. other bias.

We will judge bias in each domain as high, low, or unclear risk of bias, and we will provide a statement to support each of our judgement in accordance with the referenced tool.

Measures of treatment effect

Our primary and secondary outcomes are dichotomous variables. We will calculate absolute risks, risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs). When there is a statistical difference for the RR comparing two treatments, we will calculate the expected number of people who need to receive the experimental rather than the comparator intervention for one additional person to either incur or avoid an event through the 'number needed to treat' (NNT) statistic (Higgins 2011). We will apply the 'number needed to treat for an additional beneficial outcome' (NNTB) to estimate the expected number of people who need to receive the test treatment rather than the comparator intervention for one additional person to be successfully treated. The 'number needed to treat for an additional harmful outcome' (NNTH) will compute the number of people who are expected to develop an additional negative outcome (adverse effect) when treated with the test treatment rather than the comparator intervention.

Unit of analysis issues

The unit of analysis will be each patient recruited into a trial.

Dealing with missing data

We will base the analysis on intention-to-treat (ITT) data from the individual clinical trials then accounting for drop-out data. We will obtain incomplete information regarding drop-outs, withdrawals and other missing data not fully reported from the study authors. In the event that data still remain absent after contact with authors, we will take it into consideration in the 'Risk of bias' analysis.

Assessment of heterogeneity

We will asses methodological heterogeneity between studies using the I^2 statistic for quantification of variability. We will also use the Chi^2 test by setting statistical significance at a level of 0.1 to improve power. We will pursue a sensitivity analysis whenever a result demonstrates significant heterogeneity (P value < 0.10 or an I^2 statistic greater than 50%) (Higgins 2011).

We will assess clinical heterogeneity among the studies qualitatively in order balance the strength of the evidence gathered (internal validity) with the extent to which the results can be generalized to the clinical practice (external validity). We will consider the following categories of external validity information (Steckler 2008):

- study participants and delivering settings;
- intervention and treatment consistency across settings, staff and time;
- impact of the outcomes at population, practitioner and decision makers level.

Assessment of reporting biases

For each analysis, we will use funnel plots to investigate the presence of publication bias (the selective publication of trials with positive findings), among the studies included in the review (Higgins 2011). We will only perform this analysis if a sufficient number of trials (10 or more) is included in the meta-analysis, since a funnel plot with fewer studies would lead to a test power without ability to distinguish chance from real asymmetry.

Data synthesis

We will enter data into the Cochrane Collaboration statistical software, Review Manager 2014, and one author will perform data analysis (DRGJ). Whenever appropriate, we will combine the efficacy and harmful effects through a meta-analysis using a fixed-effect model, unless significant heterogeneity (Chi^2 test P value < 0.10 or an I^2 statistic greater than 50%) is detected, in which case we will use a random-effects model.

If it is not possible to pool data using a meta-analysis, we will narratively describe the absolute risks, RRs, RDs, NNTBs, and NNTHs in the text.

Subgroup analysis and investigation of heterogeneity

We will explore potential sources of heterogeneity through stratifying patient subgroups by the following characteristics:

1. age and sex;
2. different types of heparins and pentasaccharides;
3. different treatment duration;
4. previous VTE;
5. provoked and unprovoked VTE;
6. calf vein DVT;

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7. active cancer (treatment within last six months or palliative);
8. pregnancy;
9. major surgery or trauma in the previous 12 weeks;
10. estrogen therapy; and
11. thrombophilia (genetic or acquired).

Sensitivity analysis

If there is an adequate number of studies, we will perform a sensitivity analysis to explore causes of heterogeneity and the robustness of the results. We will re-analyze data by excluding studies that are judged to be at high risk of bias and those in which more than 20% of participants were lost to follow-up.

'Summary of findings' table

We will present the main findings of the review results concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes in a 'Summary of findings' table according to Higgins 2011.

We will describe the following outcomes in the 'Summary of findings' table:

- any VTE;
- deaths;
- major bleeding;
- thrombocytopenia.

Since we plan to assess different interventions and comparators (fondaparinux compared with low molecular weight heparins, unfractionated heparin or vitamin K antagonists or other treatments identified in our included RCTs), we will create one 'Summary of findings' table for each comparison included in the 'Results' section. We will use the GRADEpro (GRADEproGDT) software (http://www.guidelinedevelopment.org/) to assist in the preparation of the 'Summary of findings' tables.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Thrombosis] this term only
#2	MeSH descriptor: [Thromboembolism] this term only
#3	MeSH descriptor: [Venous Thromboembolism] this term only
#4	MeSH descriptor: [Venous Thrombosis] explode all trees
#5	(thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw
#6	MeSH descriptor: [Pulmonary Embolism] explode all trees
#7	PE or DVT or VTE:ti,ab,kw
#8	((vein* or ven*) near thromb*):ti,ab,kw
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	MeSH descriptor: [Anticoagulants] this term only
#11	MeSH descriptor: [Polysaccharides] this term only and with qualifier(s): [Therapeutic use - TU]
#12	fondapar* or Arixtra
#13	Sanorg-34006 or Sanorg34006
#14	SSR-126517* or SSR126517*
#15	pentasac* in Trials
#16	MeSH descriptor: [Factor X] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI]
#17	Factor X* near/4 (antag* or inhib* or block*)
#18	FX* near/4 (antag* or inhib* or block*)
#19	Factor 10* near/4 (antag* or inhib* or block*)
#20	*arinux
#21	ORG31540*
#22	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21

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(Continued)#23 #9 and #22 in Trials (Word variations have been searched)

CONTRIBUTIONS OF AUTHORS

Gustavo MS Brandão conceived the review and wrote the protocol.

Daniela R Junqueira designed the review methods and wrote the protocol together with Gustavo MS Brandão.

Hamilton A Rollo made an intellectual contribution to the protocol, revised and approved the final version of the protocol. Marcone L Sobreira provided clinical knowledge, expert advice, revised and approved the protocol.

Gustavo Brandão, Daniela Junqueira, and Marcone Sobreira take the responsibility to guarantee the completion and updating of the review.

DECLARATIONS OF INTEREST

Gustavo MS Brandão: none known

Daniela R Junqueira: none known

Hamilton A Rollo: none known

Marcone L Sobreira: I have received payment from Sanofi for the development of educational lectures regarding the issue "venous thromboembolism prophylaxis and treatment"

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Capítulo III

Pentasaccharides for the treatment of deep vein thrombosis (Systematic Review)

Brandao GMS, Junqueira DR, Rollo HA, Sobreira ML

THE COCHRANE COLLABORATION

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Pentasaccharides for the treatment of deep vein thrombosis

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ABSTRACT

Background:

Deep vein thrombosis (DVT) is a severe disorder caused by acute formation of a clot or thrombus in the deep vein system. The incidence of DVT increases with age: from 2 to 3/10,000 in adults aged 30 to 49 years to 20/10,000 in adults aged 70 to 79 years. If left untreated, the clot can travel up to the lungs and cause a potentially life-threatening pulmonary embolism (PE). Standard treatment is based on antithrombotic therapy, initially with parenteral administration of unfractionated heparin or low molecular weight heparins (LMWH) for five to seven days, then subsequent long-term oral vitamin K antagonists (e.g. warfarin) therapy. However, hemorrhagic complications are a major concern associated with warfarin treatment. Indeed, the hemorrhagic risk of warfarin and the required laboratory control remain the Achilles' heel of vitamin K antagonist management. The pentasaccharides have characteristics that may be favourable over conventional treatment, including a predictable effect, lack of frequent monitoring or re-dosing and few known drug interactions and absence of heparin-induced thrombocytopenia. To date, no systematic review has measured the effectiveness and safety of these drugs in the treatment of DVT.

Objectives:

To assess the efficacy and harms of pentasaccharides for the treatment of deep venous thrombosis.

Search strategy:

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched July 2015) and the Cochrane Register of Studies (last searched July 2015). We searched clinical trials databases for details of ongoing or unpublished studies and the reference lists of relevant articles retrieved by electronic searches for additional citations.

Selection criteria:

We included randomised controlled trials in which people with a DVTconfirmed by standard imaging techniques, were allocated to receive a pentasaccharide (fondaparinux, idraparinux or idrabiotaparinux) for the treatment of DVT.

Data collection and analysis:

Three review authors (GB, DJ and MS) independently extracted the data and assessed the risk of bias in the trials. Any disagreements were resolved by discussion. We performed meta-analyses when we considered heterogeneity low. The two primary outcomes were recurrent VTE and major (and clinically non-major) bleeding. Other outcomes included all-cause mortality, recurrent DVT, PE, thrombocytopenia, heparin-induced thrombocytopenia syndrome and all other adverse effects induced by the treatments . We calculated all outcomes using a relative risk (RR) with a 95% confidence interval (CI).

Main results:

We included 5 randomised controlled trials of 6981 participants. Two studies tested fondaparinux, while three tested idraparinux (being one tested idrabiotaparinux). We deemed all included studies to be of high methodological quality and generally low risk of bias. The quality of the evidence was generally graded as high as the outcomes were direct and effect estimates were consistent and precise, as reflected in the narrow CIs around the RRs. Meta-analysis of two studies (2658 participants) comparing fondaparinux with standard anticoagulation groups showed no difference in the risk of recurrent VTE (RR 0.88, 95% CI 0.60 to 1.29). The RR of bleeding in the initial period of treatment (RR 0.94, 95% CI 0.73 to 1.22) and three months of follow up (RR 0.61, 95% CI 0.36 to 1.01) were similar comparing both interventions. Two studies comparing idraparinux with standard therapy showed no difference in the risk of recurrent VTE during three months (RR 1.51; 95% CI 0.26, 8.90) and (RR 0.79; 95% CI 0.21; 2.91). The treatment with idraparinux clearly showed a bleeding risk with a pattern dose-response. However, at a dose of 2.5 mg idraparinux, there was no significant difference in the risk of bleeding in patients receiving idrapaparinux in comparison to standard therapy during six

months of follow up (RR 0.92, 95% CI 0.69 to 1.22). One study contributed with data for the analysis (n=741 participants) that there was no significant difference in the risk of recurrent VTE during six months follow-up between idrabiotaparinux compared with idraparinux (RR 0.71, 95% CI 0.30 to 1.66). The risk of bleeding was also similar comparing the two interventions (RR 0.71, 95% CI 0.49 to 1.04).

Authors' conclusions:

The pentasaccharides (fondaparinux, the dose of 2.5 mg idraparinux and equimolar dose of 3.0 mg idrabiotaparinux) may be an effective and safe alternative to conventional anticoagulation treatment for acute DVT.

Background

Description of the condition

Deep vein thrombosis (DVT) is a severe disorder caused by acute formation of a clot or thrombus in the deep vein system. It results in impaired venous blood flow which may in turn lead to leg swelling, pain, and with propagation of the clot, to pulmonary embolism and death. Clots that form in the deep veins of the lower extremities are more likely to dislodge from the limbs and reach the pulmonary vasculature.

Together, DVT and pulmonary embolism comprise venous thromboembolism (VTE). Between 2007 and 2009, an average 547,596 adults aged 18 years or older were hospitalised with VTE annually in the United States, with confirmed DVT in an estimated annual average of 348,558 hospitalizations (Centers for Disease Control and Prevention 2012). As pointed out in Goldhaber 2012, recurrence is common after a first episode of DVT or pulmonary embolism. Fowkes 2003 described a steep increase in the incidence of DVT with age, from 2 to 3/10,000 in adults aged 30 to 49 years to 20/10,000 in adults aged 70 to 79 years.

DVT may be diagnosed by one of three objective tests: bilateral ascending contrast venography, duplex ultrasound, or colour duplex ultrasound (EMA 2007b). Standard treatment is based on antithrombotic therapy (Kearon 2012), initially with parenteral administration (administration through intravenous or subcutaneous injections) of unfractionated heparin or low molecular weight heparins (LMWH) for five to sevendays, then subsequent long-term oral vitamin K antagonists (e.g. warfarin) therapy (Erkens 2010). To manage the ideal dose of vitamin K antagonists, it is necessary to reach a therapeutic international normalized ratio (INR) range of 2.0 to 3.0 before the end of heparin treatment (McRae 2004). In the first three months of therapy, the goal of DVT treatment is to prevent the extension and embolization of the thrombus so as to minimize late local effects of venous thrombosis. In patients with pulmonary embolism, the goal is to prevent potentially fatal recurrence. After the third month, the use of continuous anticoagulation therapy is used as a prophylactic measure to prevent late recurrence. However, therapy with warfarin may be problematic and requires

monitoring, since individual response to the medicine may vary. In addition, hemorrhagic complications (clinically relevant bleeding as well as major bleeding) are a major concern associated with warfarin treatment, and may occur at virtually any site. Indeed, the hemorrhagic risk of warfarin and the required laboratory control remain the Achilles' heel of vitamin K antagonist management.

Description of the intervention

New anticoagulants have been recently developed aiming to improve the profile of harms and efficacy outcomes of DVT treatment. Among them, synthetic pentasaccharides have been modelled on the sequence of the heparin responsible for the binding of a particular coagulation protein, which leads to inhibition of the coagulation cascade and to clot formation and growth (van Boeckel 1993). Pentasaccharides are, therefore, synthetic and selective anticoagulant drugs, in contrast with heparins, which are obtained from animal sources. More specifically, pentasaccharides act indirectly, inhibiting the activated factor X (Xa), thus interrupting the blood coagulation cascade and inhibiting both thrombin formation and thrombus development (EMA 2007a; EMA 2010). Factor X is located at the starting point of the common pathway of the extrinsic and intrinsic coagulation systems and therefore plays a central role in thrombin generation (Bauer 2003).

The advantages attributed to pentasaccharides include a more convenient dosing regimen, a more predictable anticoagulant response, and no need for laboratory monitoring (Bauer 2003; Nutescu 2005; Weitz 2004). In addition, because pentasaccharides are not metabolized in the liver, drug interactions may be reduced. Similarly, adverse reactions that often occur with heparins and vitamin K antagonists, such as bleeding and heparin-induced thrombocytopenia, are expected to be reduced (Nutescu 2005). However, other limitations stand for pentasaccharides:

- there is no antidote to reverse the effect of pentasaccharides if the patient presents any adverse bleeding to treatment or requires an invasive procedure (Gerotziafas 2004);
- the risk-benefit balance of this class of medicines is still under question; and
- financial costs may have significant impact on treatment.

How the intervention might work

The first synthetic pentasaccharide compound granted approval for commercialisation was fondaparinux (approved in 2001 in the United States and 2002 in Europe). Preliminary data have shown that fondaparinux was at least as efficacious as enoxaparin, a LMWH, with similar rates of death or clinically relevant bleeding for VTE prophylaxis following orthopedic surgery (Eriksson 2001; Lassen 2002). Nowadays, fondaparinux is widely recommended for VTE prophylaxis (Kearon 2012; Reynolds 2004), having been approved for VTE prophylaxis in a number of different medical interventions. However, questions remain regarding its effectiveness and harms in comparison with LMWHs. Furthermore, concerns with serious adverse drug reactions involving fondaparinux, including bleeding, have prompted pharmacovigilance alerts and labelling changes since its approval (FDA 2009; Prescrire 2006; Prescrire 2012).

Fondaparinux binds selectively to antithrombin, catalysing factor Xa inhibition. It expresses an elevated affinity for antithrombin, and this specific activity leads to lack of variability in anticoagulation action (Garcia 2012). Even though the administration route is still a limitation - pentasaccharides can only be administered parenterally - fondaparinux exhibits a longer half-life (17 hours) in comparison with heparins, which determines a more convenient posology once a day (Donat 2002). Fondaparinux does not bind to platelets, and so does not cause heparin-induced thrombocytopenia (Reynolds 2004), but renal clearance remains a limitation, contraindicating its use in patients with severe renal insufficiency (creatinine clearance < 20ml/min).

In addition to fondaparinux, other pentasaccharides include idraparinux and idrabiotaparinux, hypermethylated forms of idraparinux that have longer half-lives (80 to 130 hours). The pharmacokinetic properties of idraparinux were designed to allow weekly dosing by subcutaneous injection without coagulation monitoring (The PERSIST investigators 2004). Idrabiotaparinux is identical to idraparinux but has biotin incorporated to its molecule, so that anticoagulant action can be reversed by avidin injection (Paty 2010; Trellu 2013). However, the development of both idraparinux and idrabiotaparinux was discontinued during phase III trials. A higher risk of bleeding after treatment of VTE and lower efficacy in the treatment of pulmonary embolism compared to standard treatment (enoxaparin followed by warfarin, Harenberg 2008; van Gogh 2007); appear to be the major problems justifying the pharmaceutical industry statement that these compounds do not appear to be able to bring significant improvement in the care of patients (Sanofi-Aventis 2009). Nevertheless, a recent non-Cochrane systematic review has pointed out that the available evidence is still not sufficient to clarify whether or not idraparinux and idrabiotaparinux are as effective and safe as the standard warfarin treatment for VTE treatment (Song 2013).

Why it is important to do this review

The traditional forms of anticoagulation therapy may be associated with major limitations in terms of laboratory monitoring, complications induced by adverse reactions, drug interactions and even dietary aspects (e.g. vitamin K antagonists interaction with food containing elevated levels of vitamin K). Unfractionated heparin is administered exclusively via parenteral route and requires laboratory monitoring of activated partial thromboplastin time and platelet count due to the risk of heparin-induced thrombocytopenia (Junqueira 2012). Since heparins are produced from biological sources, they are also sensitive to contamination (Blossom 2008).

Vitamin K antagonists may be administered orally, however these agents also require strict laboratory monitoring to ensure that the desired anticoagulation effect occurs during the therapeutic interval. Additional limitations of vitamin K antagonists include interactions with drugs and food, adverse reactions such as skin necrosis, and teratogenic potential (Bauer 2010; Benmira 2010; Garcia 2009; Haas 2008; Laux 2009; Spyropoulos 2008).

Even though monitoring is not required for dose adjustment of LMWH, making home treatment possible (Buller 2004), some clinically relevant aspects have not been fully elucidated. For instance, different types of LMWH (enoxaparin, tinzaparin, etc) present

with different pharmacokinetics properties and thus cannot be promptly interchanged and whether one or another type of heparin is available during the course of a treatment may not be a clinical decision. In countries where public health systems have financial imitations, the type of heparin available depends on costs and may vary on monthly or sometimes weekly basis. Weight adjustment doses required for LMWHs may also be a limitation in areas with fair resources and in trauma settings. There is conflicting evidence regarding the advantage of one or two daily applications given that the anticoagulant effect of LMWHs may not always be anticipated (Breddin 2001; Merli 2001), and the best dose for patients with renal failure has not yet been fully defined (Collet 2001; Sanderink 2002). These limitations, together with the motivation for the development of more efficacious and convenient anticoagulants drugs, have driven the search for new agents.

Therefore, determining the efficacy and harms of pentasaccharides is important to provide useful information to improve the prognosis of patients with DVT.

Objectives

Our objective was to assess the efficacy and harms of pentasaccharides for the treatment of deep venous thrombosis.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included studies reporting on patients older than 18 years of age with DVT involving popliteal, femoral, iliac veins or calf veins. Diagnosis of DVT should be confirmed by at least one standard imaging technique (venography or duplex venous ultrasonography).

Types of interventions

The treatment of interest was pentasaccharide anticoagulant therapy for DVT.

Despite having their development discontinued in 2009 due to safety issues, a non-Cochrane systematic review has pointed out that the available evidence is still insufficient to clarify whether or not idraparinux and idrabiotaparinux are as effective and safe as warfarin for the treatment of VTE (Song 2013). We therefore included idraparinux and idrabiotaparinux in the review in order to make the results as comprehensive as possible.

We planed to compare our treatment intervention of interest to standard therapy (LMWHs, unfractionated heparin or vitamin K antagonists e.g. warfarin) or other treatments identified in the RCTs (e.g. placebo, other anticoagulants).

We excluded studies assessing pentasaccharide anticoagulant therapy for the prevention of VTE as they form part of another Cochrane review (Song 2011). We also did not consider studies investigating the efficacy and harms of pentasaccharide for the treatment of pulmonary embolism to adhere to our review title and protocol.

Types of outcome measures

Primary outcomes

- Main efficacy outcome:
  - Any VTE: incidence of symptomatic recurrent VTE during a six-month study period;
    - Symptomatic recurrent VTE is defined as objectively documented DVT or pulmonary embolism.
- Main harm outcome:
  - Major bleeding and clinically relevant bleeding;
    - Major bleeding (as defined by the International Society on Thrombosis and Haemostasis) (Schulman 2005): (i) fatal bleeding; (ii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial bleeding, or intramuscular bleeding progressing to compartment syndrome; (iii) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; (iv) any combination of points 1 to 3.

Secondary outcomes

- Efficacy outcomes:
  - All-cause mortality;
  - Recurrent DVT: symptomatic DVT confirmed by standard imaging techniques including a new non-compressible venous segment or a substantial increase (4 mm or more) in thrombus diameter during full compression in a previously abnormal segment on ultrasonography (Prandoni 1993; Prandoni 2002), or a new intraluminal filling defect found on venograph;
  - Pulmonary embolism (fatal and non-fatal): symptomatic pulmonary embolism confirmed by an intraluminal filling defect on computed tomography or pulmonary angiography; a cut-off vessel of more than 2.5 mm in diameter on pulmonary angiography; a perfusion defect of at least 75% of a segment with corresponding normal ventilation (high-probability lung scan); non-diagnostic lung scan associated with new DVT documented by ultrasonography or venography; or pulmonary embolism confirmed by autopsy. (Buller 2004)
- Harm outcomes:
  - Thrombocytopenia (reduction in platelet count above 150 x 10^9/L);
  - Heparin-induced thrombocytopenia syndrome defined as a relative reduction in platelet count of about 50% (even if the platelet count at its lowest remains above 150 x 10^9/L) occurring within 5 to 14 days after the start of heparin therapy (Warkentin 2003);

        - Clinically suspected cases of heparin-induced thrombocytopenia syndrome should have diagnosis confirmed through functional or immunological laboratory tests to detect platelet activation induced by anti-platelet factor 4 antibodies (Keeling 2006).
    - All other adverse effects induced by the treatments, including those leading to drop out from the trial including but not limited to anemia, insomnia, increased wound drainage, hypokalemia, dizziness, hypotension, confusion, bullous eruption, hematoma, increase in transaminases, dermatological reactions, others.

Search methods for identification of studies

We performed electronic searches with no restrictions on language.

Electronic searches

The Cochrane Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Group's Specialised Register (July 2015) and the Cochrane Central Register of Controlled Trials CENTRAL (2015, Issue 6), part of the *Cochrane Library* (http://www.cochranelibrary.com/). See Appendix 1 for details of the search strategy which was used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Vascular Diseases Group module in the *Cochrane Library* (http://www.cochranelibrary.com/).

In addition, the TSC searched the following trial databases (July 2015) for details of ongoing or unpublished studies using fondaparinux, idraparinux and idrabiotaparinux as search terms:

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/);
- ClinicalTrials.gov (http://clinicaltrials.gov/);
- International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.isrctn.com/).

Searching other resources

We checked citations of included studies to identify additional studies not identified in the electronic search. We also searched the Website of the pharmaceutical industry GlaxoSmithKline for non-reported trials of Fondaparinux.

Data collection and analysis

Selection of studies

Two review authors (GB and DJ) independently screened titles and abstracts of the identified citations for potential eligibility. Studies clearly not relevant (e.g. studies investigating the addition of vena cava filter to anticoagulation with fondaparinux) were excluded at this stage, although studies that could have included relevant data or

Information on other studies were initially retained. We retrieved full texts of articles judged to be potentially eligible by at least one review author, and we then independently screened the full-text articles for eligibility using a pre-standardized study selection form. Disagreement were resolved by consensus.

We attempted to contact authors of the studies retrieved whenever there was insufficient information available to decide whether a study met the eligibility criteria.

Data extraction and management

Data extraction was performed by three authors (GB, MS, and DJ) using standardised data extraction form. Where more than one report of a study was identified, data were extracted from the primary report and discrepancies were checked against reports. Reports of subgroup populations had data extracted separately but linked to the primary study report. Trials evaluating patients with DVT and PE were considered if data concerning patients with DVT could be extracted separately. Disagreements were resolved by consensus.

Assessment of risk of bias in included studies

We planned to assess the risk of bias in included studies using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011), which contains the following domains:

1. sequence generation (selection bias);
2. allocation sequence concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective outcome reporting (reporting bias);
7. other bias.

At the review stage, we judged relevant to assess the risk of bias resulting from some domains separately for different groups/outcomes in accordance with the instructions of the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). The following domains were therefore categorised:

- blinding of participants and personnel (performance bias) was assessed separately for (i) participants and (ii) personnel;
- blinding of outcome assessment (detection bias) was assessed separately for (i) efficacy outcomes and (ii) harm outcomes;
- incomplete outcome data (attrition bias) was assessed separately for (i) primary efficacy outcome and (ii) harm outcomes.

Bias was judged in each domain as high, low, or unclear risk of bias, and a statement to support each of our judgement was provided in accordance with the referenced tool.

Measures of treatment effect

Our primary and secondary outcomes were dichotomous variables. For primary efficacy outcomes we calculated risk ratios (RRs) with 95% confidence intervals (CIs). For secondary outcomes, we reported absolute risks (AR, also the incidence) and RRs 95% CIs. Zero events had ARs and CIs estimated considering a one-tailed 97.5% CI (Newcombe 2000).

In our protocol, we planned to calculate risk differences but since relative effect measures are considered more consistent than absolute measures (Deeks 2002; Engels 2000), we calculated only the RRs.

When there was a statistical difference for the RR comparing two treatments, we planned to calculate the expected number of people who needed to receive the experimental rather than the comparator intervention for one additional person to either incur or avoid an event through the 'number needed to treat' (NNT) statistic (Higgins 2011). We applied the 'number needed to treat for an additional beneficial outcome' (NNTB) to estimate the expected number of people who needed to receive the test treatment rather than the comparator intervention for one additional person to be successfully treated. The 'number needed to treat for an additional harmful outcome' (NNTH) computed the number of people who were expected to develop an additional negative outcome (adverse effect) when treated with the test treatment rather than the comparator intervention.

Unit of analysis issues

The unit of analysis was each patient recruited into a trial.

Dealing with missing data

We based our data analysis on intention-to-treat (ITT) data from the individual clinical trials then accounting for drop-out data. We planned to obtain incomplete information regarding drop-outs, withdrawals and other missing data not fully reported from the study authors. In the event that data still remained absent after contact with authors, we analysed the available data and took it into consideration in the 'Risk of bias' analysis

Specifically concerning the analysis of harm outcomes, the included studies analysed only data of those participants who received, at least, one dose of the study medication. Although this could considerable a non-randomised comparison (Higgins 2011), we judged it reasonable to measure adverse effects only in those patients who have received the intervention (CRD' Guidance 2009). To check how robust was this analytical approach, we subsequently performed a sensitivity analysis assuming missing participants as though they experience the negative outcome.

Assessment of heterogeneity

We assessed methodological heterogeneity between studies using the I^2 statistic for quantification of variability. We also used the Chi^2 test by setting statistical significance at a level of 0.1 to improve power. We undertook a sensitivity analysis whenever a result demonstrates significant heterogeneity (P value < 0.10 or an I^2 statistic greater than 50%) (Higgins 2011).

We planned to assess clinical heterogeneity among the studies qualitatively in order balance the strength of the evidence gathered (internal validity) with the extent to which the results can be generalized to the clinical practice (external validity). The following categories of external validity information was planned to be considered (Steckler 2008):

- study participants and delivering settings;
- intervention and treatment consistency across settings, staff and time;
- impact of the outcomes at population, practitioner and decision makers level.

Assessment of reporting biases

For each analysis, we proposed to use a funnel plots to investigate the presence of publication bias (the selective publication of trials with positive findings), among the studies included in the review (Higgins 2011). This analysis would be performed only if a sufficient number of trials (10 or more) were included in the meta-analysis, since a funnel plot with fewer studies led to a test power without ability to distinguish chance from real asymmetry.

Data synthesis

We entered data into the Cochrane Collaboration statistical software, Review Manager 2014, and one author performed data analysis (DJ). Whenever appropriate, we combined the efficacy and harmful effects through a meta-analysis using a fixed-effect model, unless significant heterogeneity (Chi^2 test P value < 0.10 or an I^2 statistic greater than 50%) is detected, in which case we will use a random-effects model.

When it was not possible to pool data using a meta-analysis, we described the estimated ARs.

Subgroup analysis and investigation of heterogeneity

We were able to explore the following sources of heterogeneity through stratifying patients by:

1. body weight;
2. cancer;
3. outpatient treatment.

Data on all the subgroup characteristics we planned in our protocol were not available.

Sensitivity analysis

If there were an adequate number of studies, we planned to perform a sensitivity analysis to explore causes of heterogeneity and the robustness of the results. The re-analysis would be performed by excluding studies judged to be at high risk of bias and those in which more than 20% of participants were lost to follow-up.

'Summary of findings' table

We presented the main findings of the review results concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes in a 'Summary of findings' table according to Higgins 2011.

We planned to describe the following outcomes in the 'Summary of findings' table:

- recurrent VTE;
- deaths;
- major bleeding;
- thrombocytopenia.

However, thrombocytopenia was not reported in the majority of trials. Instead of thrombocytopenia, we described our findings on all harmful outcomes.

We assessed different interventions and comparators, and we created one 'Summary of findings' table for each comparison included in the 'Results' section. We used the GRADEpro (GRADEproGDT) software (http://www.guidelinedevelopment.org/) to assist in the preparation of the ‘Summary of findings’ tables.

Main Results

Description of studies

The the main findings of the review results are described in the Summary of Finding tables: Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4

Summary of findings:

Fondaparinux and vitamin K antagonists compared to standard therapy for deep vein thrombosis

Patient or population: deep vein thrombos is
Setting: Hospitalised and non-hospitalised patients
Intervention: Fondaparinux and vitamin K antagonists
Comparison: standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (s tudies)	Quality of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with Fondaparinux and vitamin K antagonists				
Recurrent venous thromboembolism follow up: 3 months	Study population		RR 0.88 (0.60 to 1.29)	2658 (2 RCTs)	+++/4+ MODERATE [1]	
	42 per 1,000	37 per 1,000 (25 to 54)				
	Moderate					
	46 per 1,000	40 per 1,000 (27 to 59)				
Major bleeding during the initial treatment follow up: 5 days	Study population		RR 1.19 (0.71 to 1.98)	2645 (2 RCTs)	+++/4+ MODERATE [2]	1,2
	21 per 1,000	25 per 1,000 (15 to 42)				
	Moderate					
	12 per 1,000	14 per 1,000 (8 to 23)				
Major bleeding follow up: 3 months	Study population		RR 0.83 (0.22 to 3.16)	453 (1 RCT)	+++/4+ MODERATE 1,2	
	25 per 1,000	21 per 1,000 (6 to 80)				
	Moderate					
	25 per 1,000	21 per 1,000 (6 to 80)				
All-cause mortality follow up: 3 months	Study population		RR 1.06 (0.72 to 1.57)	2645 (2 RCTs)	+++/4+ MODERATE 1,2	
	34 per 1,000	36 per 1,000 (25 to 54)				
	Moderate					
	53 per 1,000	56 per 1,000 (38 to 83)				

All harmful effects follow up: 3 months	Study population		RR 0.62 (0.54 to 0.70)	2205 (1 RCT)	++/4+ LOW [2]
	381 per 1,000	236 per 1,000 (206 to 267)			
	Moderate				
	381 per 1,000	236 per 1,000 (206 to 267)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

C I: Confidence interval; RR: Ris k ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies clos e to that of the es timate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect es timate is limited: The true effect may be s ubs tantially different from the es timate of the effect
Very low quality: We have very little confidence in the effect es timate: The true effect is likely to be s ubs tantially different from the es timate of effect

1. Downgraded due to unclear ris k of s election bias and attrition bias .
2. Downgraded for high ris k of bias of detection bias and attrition bias related to harmful outcomes

Summary of findings:

Idrabiotaprinux compared to Idraparinux for treatment of deep vein thrombosis

Patient or population: treatment of deep vein thrombos is
Setting:
Intervention:Idrabiotaprinux
Comparison: Idraparinux

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (s tudies)	Quality of the evidence (GRADE)	Comments
	Risk with Idraparinux	Risk with Idrabiotaprinux				
Recurrentvenous thromboembolism follow up: 6 months	Study population		RR 0.71 (0.30 to 1.66)	741 (1 RCT)	+++/4+ MODERATE [1]	
	33 per 1,000	24 per 1,000 (10 to 55)				
	Moderate					
	33 per 1,000	24 per 1,000 (10 to 55)				
Recurrent venous thromboembolism follow up: 9 months	Study population		RR 1.53 (0.83 to 2.79)	700 (1 RCT)	+++/4+ MODERATE [1]	
	47 per 1,000	72 per 1,000 (39 to 132)				
	Moderate					
	47 per 1,000	72 per 1,000 (39 to 132)				
Major bleeding follow up: 6 months	Study population		RR 0.21 (0.06 to 0.71)	755 (1 RCT)	+++/4+ MODERATE [1]	
	38 per 1,000	8 per 1,000 (2 to 27)				
	Moderate					
	38 per 1,000	8 per 1,000 (2 to 27)				
Major bleeding follow up: 9 months	Study population		RR 0.64 (0.11 to 3.81)	755 (1 RCT)	+++/4+ MODERATE [1]	
	8 per 1,000	5 per 1,000 (1 to 31)				
	Moderate					
	8 per 1,000	5 per 1,000 (1 to 31)				

All-cause mortality follow up: 6 months	Study population		RR 0.48 (0.18 to 1.27)	755 (1 RCT)	+++/4+ MODERATE [1]
	32 per 1,000	16 per 1,000 (6 to 41)			
	Moderate				
	32 per 1,000	16 per 1,000 (6 to 41)			
All-cause mortality follow up: 9 months	Study population		RR 0.80 (0.25 to 2.60)	755 (1 RCT)	+++/4+ MODERATE [1]
	16 per 1,000	13 per 1,000 (4 to 42)			
	Moderate				
	16 per 1,000	13 per 1,000 (4 to 42)			
All harmful effects follow up: 6 months	Study population		RR 0.92 (0.83 to 1.02)	757 (1 RCT)	++/4+ LOW [2]
	685 per 1,000	630 per 1,000 (568 to 698)			
	Moderate				
	685 per 1,000	630 per 1,000 (568 to 698)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

C I: Confidence interval; RR: Ris k ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies clos e to that of the es timate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect es timate is limited: The true effect may be s ubs tantially different from the es timate of the effect
Very low quality: We have very little confidence in the effect es timate: The true effect is likely to be s ubs tantially different from the es timate of effect

1. Downgraded due to high ris k of attrition bias .
2. Downgraded due to high ris k of detection and attrition bias .

Summary of findings:

LMWH and idraparinux compared to standard treatment for the treatment of deep vein thrombosis

Patient or population: the treatment of deep vein thrombos is
Setting: hospitalised and non-hospitalised patients
Intervention: LMWH and idraparinux
Comparison: standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (s tudies)	Quality of the evidence (GRADE)	Comments
	Risk with standard treatment	Risk with LMWH and idraparinux				
Recurrent venous thromboembolism assessed with: Idraparinux 10 mg follow up: 3 months	Study population		RR 1.51 (0.26 to 8.90)	263 (1 RCT)	+/4+ VERY LOW [1,2]	
	15 per 1,000	23 per 1,000 (4 to 135)				
	Moderate					
	15 per 1,000	23 per 1,000 (4 to 135)				
Major bleeding assessed with: All doses follow up: 3 months	Study population		RR 3.76 (0.50 to 28.19)	659 (1 RCT)	+/4+ VERY LOW [1,2,3]	
	8 per 1,000	28 per 1,000 (4 to 214)				
	Moderate					
	8 per 1,000	29 per 1,000 (4 to 214)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

C I: Confidence interval; RR: Ris k ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies clos e to that of the es timate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect es timate is limited: The true effect may be s ubs tantially different from the es timate of the effect
Very low quality: We have very little confidence in the effect es timate: The true effect is likely to be s ubs tantially different from the es timate of effect

1. Downgraded due to unclear ris k of s election bias and high ris k of detection bias .
2. Analys is include relatively few patients and few events .
3. Downgraded due to high ris k of detection bias and attrition bias concerning harmful outcomes

Summary of findings:

Idraparinux compared to standard therapy for the treatment of deep vein thrombosis

Patient or population: the treatment of deep vein thrombos is
Setting: hospitalised and non-hospitalised patients
Intervention: Idraparinux
Comparison: standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (s tudies)	Quality of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with Idraparinux				
Recurrent venous thromboembolism follow up: 3 months	Study population		RR 0.79 (0.21 to 2.91)	637 (1 RCT)	+++/4+ MODERATE [1]	
	16 per 1,000	13 per 1,000 (3 to 46)				
	Moderate					
	16 per 1,000	12 per 1,000 (3 to 46)				
Recurrent venous thromboembolism follow up: 6 months	Study population		RR 1.00 (0.66 to 1.53)	2267 (1 RCT)	++++/4+ HIGH	
	37 per 1,000	37 per 1,000 (24 to 57)				
	Moderate					
	37 per 1,000	37 per 1,000 (24 to 57)				
Major bleeding follow up: 3 months	Study population		RR 0.39 (0.08 to 2.01)	637 (1 RCT)	+++/4+ MODERATE [1]	
	16 per 1,000	6 per 1,000 (1 to 32)				
	Moderate					
	16 per 1,000	6 per 1,000 (1 to 32)				
Major bleeding follow up: 6 months	Study population		RR 1.24 (0.66 to 2.34)	2267 (1 RCT)	++++/4+ HIGH	
	15 per 1,000	19 per 1,000 (10 to 35)				
	Moderate					
	15 per 1,000	19 per 1,000 (10 to 35)				

All-causes mortality follow up: 3 and 6 months	Study population		RR 1.26 (0.85 to 1.85)	2904 (1 RCT)	++++/4+ HIGH
	54 per 1,000	68 per 1,000 (46 to 99)			
	Moderate				
	39 per 1,000	49 per 1,000 (33 to 72)			
All harmful effects follow up: 3 months	Study population		RR 1.03 (1.00 to 1.06)	2904 (1 RCT)	++/4+ MODERATE [2]
	874 per 1,000	900 per 1,000 (874 to 926)			
	Moderate				
	874 per 1,000	900 per 1,000 (874 to 926)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

C I: Confidence interval; RR: Ris k ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies clos e to that of the es timate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect es timate is limited: The true effect may be s ubs tantially different from the es timate of the effect
Very low quality: We have very little confidence in the effect es timate: The true effect is likely to be s ubs tantially different from the es timate of effect

1. Analys is include relatively few events .
2. Downgraded due to high ris k of attrition bias regarding harmful outcomes .

Results of the search

A total of 729 titles returned from our electronic searches and one additional title was identified through manually searching the reference list of relevant studies. Duplicates accounted for 18 titles. The remaining 712 titles were independently evaluated against the PICOS criteria defined for eligibility into this systematic review. This process led to the identification of 57 titles potentially relevant studies. The potentially relevant abstracts and full texts were further evaluated, and a consensus was agreed through discussion sessions. Five studies were considered eligible, and the results of these studies were reported in a total of 20 published titles. Figure 1 shows the search and selection flow chart.

Included studies

The five included studies comprised multicentric parallel RCTs developed in different countries of South America, North America, Europe, Africa, Asia and Oceania. The 6,981 participants included in the studies were mostly elderly (mean age range 57-62 years old) presenting with acute symptomatic DVT. The setting where the participants were recruited was unclear for most of the studies, though due to the nature of DVT, participants were probably identified during hospitalisation. Profile of risk factors for DVT was very heterogenic among studies but balanced at the baseline.

The trials investigated several comparisons between pentasaccharides and standard or alternative therapies. Details of the study methods, participants, interventions and outcomes are shown in the table Characteristics of included studies and in Table 1; Table 2; Table 3.

Fondaparinux and vitamin K antagonist versus standard therapy

Two studies, the MATISSE-DVT and Rembrandt Trial, compared fondaparinux followed by three months of vitamin K antagonist to standard therapy (LMWH, enoxaparin and dalteparin respectively, followed by three months of vitamin K antagonists).

Fondaparinux was administered once-day during five days in both studies. Vitamin K antagonists were started within 72 hours in both trials and continued during three months. In both trials, the initial treatment with the intervention medications (fondaparinux or LMWH) was discontinued when the INR was maintained >2.0 for two or more consecutive days. In total, these trials randomised 2,658 patients.

The MATISSE-DVT study adjusted doses according to body weight: 5.0 mg if patient weight was <50 kg, 7.5 mg if patient weight was >50 kg but <100 kg, or 10 mg if patient weight was >100 kg. This trial reported data on secondary harmful outcomes only in a summary of results available from the manufacturer Clinical Trial Register, and data on these outcomes were extracted from this source.

The Rembrandt Trial randomised patients for one of the three doses of fondaparinux (5.0 mg, 7.5 mg, or 10 mg) without weight adjustment. The MATISSE-DVT reports an intention-to-treat analysis but does not explain how outcome data for missing participants was analysed. The Rembrandt Trial states that there were no participants lost to follow-up.

Idrabiotaparinux versus idraparinux

One study (EQUINOX) compared idrabiotaparinux 3.0 mg once a week with idraparinux 2.5 mg once a week. Both interventions were administered during six months, and an additional follow-up measurement was undertook three months after the end of treatment. This trial randomised 757 participants. Although the trials' report refers to an intention-to-treat analysis, 88 participants were missing due to withdrawals or lost of follow-up. The report does not clarify how outcome data for missing participants were handled, and contact with authors indicated that these data were considered missing (censored). The analysis performed in the studys' report uses data on 741 participants for whom clinical outcome could be assessed during the six months of follow-up. Analysis of the additional follow-up period of three months included data on 700 patients whose had clinical outcome available.

LMWH and idraparinux versus standard therapy

The PERSIST Trial investigated the effects of an initial treatment with LMWH (enoxaparin) followed by three months of idraparinux as compared to an initial treatment with LMWH followed by warfarin (standard therapy). The LMWH (enoxaparin) was administered during five to 7 days (1 mg kg^{-1}). Thereafter, patients were randomised to receive one of four dosages of idraparinux (2.5 mg, 5 mg, 7.5 mg or 10 mg) without weight adjustment or warfarin target to an INR rate between 2.0 to 3.0. Treatment with idraparinux and warfarin continued for three months. A total of 701 participants were enrolled and received initial treatment with LMWH. After exclusion of 35 patients, 659 participants were randomised. The trial reports two consent withdrawals, 45 missing data due to lost to follow-up, and 66 premature discontinuation of treatment. Analysis considered all randomised participants as the denominator, although the study reports indicates that efficacy analysis included only participants who received treatment and for whom the primary outcome was available.

Idraparinux versus standard therapy

One trial compared therapy with idraparinux to standard therapy (initial therapy with LMWH - tinzaparin or enoxaparin- or unfracionated heparin followed by warfarin or acenocoumarol) (Van Gogh Trial-DVT). Treatment duration was three or six months depending on the judgment of the treating physician. The intervention group received a dose of 2.5 mg of idraparinux administered once a week. The comparison group received heparin for at least five days with doses adjusted for the activated partial-thromboplastin time (ratio, 1.5 to 2.5), and had warfarin or acenocoumarol administered within 24 hours and target to INR 2.0 to 3.0. Heparin was discontinued when the INR was 2.0 or more for two consecutive days.

The Van Gogh Trial-DVT was designed as two separated RCTs, one involving patients with DVT and the other studying patients with pulmonary embolism. We extracted data only of the DVT study comprising 2,904 participants: 637 participants (idraparinux: 321; standard therapy: 316). The totality of the participants were followed by three months and 2,267 (idraparinux: 1,131; standard therapy: 1,136) were followed by six months.

The majority of the participants in the comparison arm received LMWH as initial treatment (1,408, 98.3%).

Excluded studies

We excluded 37 reports referring to six studies. Reasons for exclusions consisted of trials enrolling patients with pulmonary embolism (Cassiopea Investigators, MATISSE-DVT/PE), narrative reviews summarising the results of the DVT study and the pulmonary embolism study of the MATISSE-DVT/PE trial, and trials investigating pentasaccharides for extended prophylaxis of DVT (The Van Gogh Extension). One study was interested in the potential of avidin to reverse the anti-factor Xa activity of idrabiotaparinux and in the bioequipotency of idrabiotaparinux and idraparinux (EQUINOXa). One trial did not diagnose DVT in accordance with standard methods (Nakamura 2011), and one potentially relevant study did not include a control group (Young 2011).

Risk of bias in included studies

Assessement of the risk of bias in individual studies was performed using Cochranes' tool (Higgins 2011). Three domains were assessed taking into consideration different groups (participants and personnel) or outcomes (efficacy and harm outcomes). Summaries of risk of bias assessment are shown in Figure 2; Figure 3.

Allocation (selection bias)

Random sequence generation was considered at low risk of bias in most of the included studies (EQUINOX; MATISSE-DVT; Rembrandt Trial; Van Gogh Trial-DVT). Random sequence generation was unclear in one study (PERSIST Trial).

Allocation concealment was deemed at low risk of bias in two studies (EQUINOX; MATISSE-DVT), and was unclear in three studies (PERSIST Trial; Rembrandt Trial; Van Gogh Trial-DVT).

Blinding (performance bias and detection bias)

Blinding (performance bias) was assessed separately for participants and personnel. This allowed us to make a better judgment on the risk of bias of studies reporting complete and incomplete methods applied to ensure blinding of both participants and personnel.

Blinding of participants was considered at low risk in three studies (EQUINOX; MATISSE-DVT; Rembrandt Trial), and at high risk of bias in one study (PERSIST Trial). In one study, risk of bias of blinding of participants was unclear (Van Gogh Trial-DVT).

Blinding of personnel was judged at low risk of bias in two studies (EQUINOX; MATISSE-DVT), and at high risk of bias in two other studies (PERSIST Trial; Rembrandt Trial). One study was considered unclear in regard to the risk of bias of blinding of personnel (Van Gogh Trial-DVT).

Blinding of outcome assessment (detection bias) was determined separately for efficacy and harmful outcomes. This allowed was to identify that all the included studies were at low risk of bias regarding blinding of efficacy outcome assessment, but only one study (Van Gogh Trial-DVT) was at low risk of bias of blinding of harmful outcome

assessment. In most of the times, this occurred because only bleeding was diagnosed by a committee unaware of treatment assignment.

Incomplete outcome data (attrition bias)

Incomplete outcome data (attrition bias) was assessed separately for primary efficacy outcome and harm outcomes. This methodological option was done to account for differences in the methods specifically related to each type of outcomes.

Two studies were judged at low risk of bias of incomplete outcome data of primary efficacy outcome (Rembrandt Trial; Van Gogh Trial-DVT). Two were judged at high risk of bias (EQUINOX, PERSIST Trial). Bias of incomplete outcome data of the primary efficacy outcome was unclear in one study (MATISSE-DVT).

One study was judged at low risk for bias of incomplete outcome data of harm outcomes (MATISSE-DVT). All the remained trials were considered at high risk of bias (EQUINOX; PERSIST Trial; Rembrandt Trial; Van Gogh Trial-DVT).

Selective reporting (reporting bias)

Selective reporting (reporting bias) could be assessed only for three studies for which trial register could be located or additional information in the form of supplementary material could be accessed online. One study was considered at low risk of bias (EQUINOX) and two studies were rated at high risk of bias (MATISSE-DVT, Van Gogh Trial-DVT).

The other included studies (PERSIST Trial; Rembrandt Trial) were considered at unclear risk of bias for selective reporting bias.

Other potential sources of bias

All included studies disclosed that the investigators responsible for the study or members of the executive committee acted as advisors or employees of the pharmaceutical industry that sponsored the trials. Therefore, the studies were deemed at high risk of bias related to conflict of interests.

Effects of interventions

We group included studies according to comparisons of anticoagulants therapies:

- fondaparinux and vitamin K antagonists versus standard therapy;
- idrabiotaparinux versus idraparinux;
- LMWH and idraparinux versus standard therapy;
- idraparinux versus standard therapy.

In our protocol, we planned to assess our primary efficacy outcome, recurrent VTE, during six-month study period. However, only two studies followed participants during six-months (EQUINOX; Van Gogh Trial-DVT). The remained studies assessed the outcomes after three-months of follow-up. Therefore, we analysed data reported in the included trials according to the time points they measured the outcome.

We planned to assess reporting bias by the use of a funnel plot but the insufficient number of studies included in each analysis did not provide appropriate visual inspection for asymmetry on the scatter plot and therefore the funnel plot was not used.

Primary efficacy outcome

Fondaparinux and vitamin K antagonist versus standard therapy

There was no significant difference in the risk of recurrent VTE during three months of follow-up between fondaparinux compared with LMWH (RR 0.88, 95% CI 0.60 to 1.29, Analysis 1.1, Figure 4). Two studies (n=2,658), with data extracted only from the studies' report, contributed with data to this analysis (MATISSE-DVT; Rembrandt Trial). The results were consistent across studies and independent of the risk of bias of the individual studies. Heterogeneity was detected at 35% (p=0.21) as assessed by the I^2 statistics.

Idrabiotaparinux versus idraparinux

There was no significant difference in the risk of recurrent VTE during six months follow-up between idrabiotaparinux compared with idraparinux (RR 0.71, 95% CI 0.30 to 1.66, Analysis 2.1). One study (EQUINOX) contributed with data for this analysis (n=741). An additional follow-up of three months after the end of treatment (9 months totally) provided data on 361 participants in the idrabitaparinux group and 339 participants in the idraparinux group. This accounts for a degree loss of follow-up of 7.5%. Available data results in a estimated RR 1.53 (95% CI 0.83 to 2.79, Analysis 2.2), demonstrating no difference in the risk of recurrent VTE between groups of intervention after 9-months of follow-up.

LMWH and idraparinux versus standard therapy

The PERSIST Trial compared the effects of an initial treatment with LMWH followed by three months of idraparinux (2.5 mg, 5 mg, 7.5 mg or 10 mg) with therapy with standard therapy. The trials' reports performed an analysis considering as denominator all randomised trials (n=659) although a significant amount of outcome missing data due to exclusions, withdrawals and loss of follow-up. Only 614 participants had data on primary outcome data available but detailswas not provided according to treatment groups. Therefore, we analysed data as available accounting for a high risk of bias in this analysis. Since we do not know the amount of missing data according to allocation treatment, we could not evaluate possible direction of the bias.

No events of recurrent VTE were reported in the groups of participants receiving LMWH followed by idraparinux 2.5 mg, 5 mg or 7.5 mg, three events occurred in patients receiving 10.0 mg of idraparinux, and two events were reported in the group of participants receiving standard therapy. However, two patients receiving 2.5 mg of idraparinux and one receiving 5.0 mg of idraparinux discontinued treatment due to a suspected VTE. Two patients in the standard therapy group were also excluded due to a suspected VTE. Comparing the cases considered as confirmed by the trialists, and excluding the groups with zero outcomes reported, we were able to compare quantitatively the risk of VTE of LMWH followed by 10 mg of idraparinux with standard

Therapy. This analysis did not demonstrated a significant difference in the risk of recurrent VTE comparing these two treatment groups (RR 1.51; 95% CI 0.26, 8.90).

Idraparinux versus standard therapy

There was no significant difference in the risk of recurrent VTE during three months of follow-up when idraparinux was compared to standard therapy (RR 0.79; 95% CI 0.21; 2.91, Analysis 4.1). Six months of follow-up did not change significantly this result (RR 1.00; 95% CI 0.66, 1.53, Analysis 4.2). Only one study (Van Gogh Trial-DVT) contributed with data for this analysis (n=637 and n=2,267, three and six months of follow-up, respectively).

Primary harm outcome

Fondaparinux and vitamin K antagonist versus standard therapy

Events of bleeding were analysed only during the initial treatment period with fondaparinux in the MATISSE-DVT study, and only in participants who received at least on dose of the interventions. The Rembrandt Trial reported bleeding events for the initial period of treatment and the entire study (three months).

Initial period of treatment (approximately 5 days)

Bleeding was a common harmful effect in participants receiving either in fondaparinux and LMWH or standard therapy. The risk of bleeding was equal to 7.89% (95% CI 6.57 to 9.37) in the fondaparinux group, and equal to 8.36% (95% CI 6.94 to 10.05) in the standard therapy group. The RR of bleeding was similar comparing both interventions (RR 0.94, 95% CI 0.73 to 1.22, Analysis 1.2,Figure 5). Heterogeineity was significant in this pooled analysis (I^2 42%, p=0.19). Total of participants included in this analysis was equal to 2,645.

Major bleeding was also a common harmful outcome. Participants receiving fondaparinux presented an absolute risk of major bleeding equal to 2.39% (95% CI 1.71 to 3.32) and this risk was equal to 2.79% (95% CI 2.00 to 3.87) in participants receiving standard therapy. There was no difference in the RR of major bleeding between the two interventions (RR 1.19, 95% CI 0.71 to 1.98, Analysis 1.3, Figure 6). Heterogeineity was estimated as equal to 0% in this pooled analysis by the I^2 statistics (p-0.32). Two studies contributed with data for this analysis (MATISSE-DVT; Rembrandt Trial). Total of participants included in the analysis was equal to 2,645.

Clinically relevant bleeding was reported in one trial (MATISSE-DVT). The absolute risk of clinically relevant bleeding was estimated as equal to 5.50% (95% CI 4.30 to 7.02) in the fondaparinux group and equal to 5.72% (95% CI 4.50 to 7.25) in the standard therapy group. There was no difference in the RR for clinically relevant bleeding (RR 0.96, 95% CI 0.68 to 1.36, Analysis 1.4). Total of participants included in the analysis was equal to 2,192.

Three months of follow-up

Bleeding was a very common outcome during the entire follow-up period of three months in the Rembrandt Trial (n=453). In the fondaparinux arm, the incidence of bleeding was as high as 10.18% (95 CI 7.38 to 13.89) and in the standard therapy group it was similarly high and equal to 16.81% (95% CI 11.15 to 24.54). Although with a marginal significance, the risk of bleeding appeared similar between groups (RR 0.61, 95% CI 0.36 to 1.01).

Major bleeding occurred in 2.10% (95% CI 1.02 to 4.26) of patients receiving fondaparinux and in 2.52% (95% CI 0.86 to 7.15) of patients receiving standard therapy. There was no difference in the risk of major bleeding between groups (RR 0.83, 95% CI 0.22 to 3.16).

Clinically relevant bleeding was not reported.

Idrabiotaparinux versus idraparinux

Six months of follow-up

Bleeding was a very common harmful outcome: incidence of 10.39% (95% CI 7.61 to 13.98) in patients receiving idrabiotaparinux, and of 14.59% (95% CI 11.24 to 18.7) in patients receiving idraparinux.The risk of bleeding was similar comparing both interventions (RR 0.71, 95% CI 0.49 to 1.04, Analysis 2.3).

Major bleeding was not frequent in participants receiving idrabiotaparinux (AR 0.78%, 95% CI 0.27 to 2.27), but was a common harmful outcome in the group of patients receiving idraparinux (AR 3.78%, 95% CI 2.17 to 6.42). The risk of major bleeding was significantly lower in participants receiving idrabiotaparinux compared with participants treated with idraparinux (RR 0.21, 95% CI 0.06 to 0.71, Analysis 2.4).

Clinically relevant bleeding was common in both intervention groups: incidence of 5.19% (95% CI 3.39 to 7.89) in patients receiving idrabiotaparinux, and of 7.30% (95% CI 5.06 to 10.41) in patients receiving idraparinux. The risk of bleeding was similar comparing both interventions (RR 0.70, 95% CI 0.38 to 1.026, Analysis 2.5).

One study (EQUINOX) provided data for these analyses (n=755 participants).

Nine months of follow-up after the end of treatment

For this follow-up period, only data on major and clinically relevant bleeding were reported.

Major bleeding was uncommon and occurred in 0.52% (CI 95% 0.14 to 1.87) of participants in the idrabiotaparinux group and in 0.81% (CI 95% 0.28 to 2.36) of patients in the idraparinux group. Relative analysis did not demonstrate differences in the risk of major bleeding comparing the intervention groups (RR 0.64, 95% CI 0.11 to 3.81, Analysis 2.6).

Remarkbly, clinically relevant bleeding was commonly reported, with an absolute risk of 1.82% (CI 95% 0.88 to 3.88) in patients receiving idrabiotaparinux, and of 2.16% (CI 95% 1.1 to 4.21) in patients receiving idraparinux. Relative analysis did not

demonstrated differences in the risk of major bleeding comparing the intervention groups (RR 2.24, 95% CI 0.58 to 8.61, Analysis 2.7).

Data for these analysis (n=755 participants) were extracted from one study (EQUINOX).

LMWH and idraparinux versus standard therapy

Bleeding was reported as a reason for discontinuation of treatment in 17 patients receiving idraparinux after LMWH (all doses combined). In accordance with what is recommended to an intention-to-treated analysis, we combined these cases with the ones reported in patients not discontinuing treatment (the ones considered by the analysis in the trials' report).

Bleeding was elevated in participants receiving LMWH followed by idraparinux and presented with a dose-response relationship:

- LMWH + idraparinux 2.5 mg: 2.29% (95% CI 0.78 to 6.52);
- LMWH + idraparinux 5.0 mg: 15.56% (95% CI 10.41 to 22.61);
- LMWH + idraparinux 7.5 mg: 15.15% (95% CI 10.03 to 22.25);
- LMWH + idraparinux 10.0 mg: 22.90% (95% CI 16.54 to 30.81);

The RR of bleeding induced by all doses of idraparinux in comparison with standard therapy confirmed the dose-response pattern:

- LMWH + idraparinux 2.5 mg: 0.23 (95% CI 0.07 to 0.80, Analysis 3.2);
- LMWH + idraparinux 5.0 mg: 1.58 (95% CI 0.83 to 3.02, Analysis 3.3);
- LMWH + idraparinux 7.5 mg: 1.54 (95% CI 0.80 to 2.96, Analysis 3.4);
- LMWH + idraparinux 10.0 mg: 2.33 (95% CI 1.27 to 4.26, Analysis 3.5).

Combining participants receiving LMWH and any dose of idraparinux, 14.04% (95% CI 11.34 to 17.26) of patients had an event of bleeding. The occurrence of bleeding was reported in 9.58% (95% CI 5.85 to 16.12) of the participants treated with standard therapy. Overall, there was no significant difference in the relative risk of bleeding comparing participants treated with idraparinux after LMWH, regardless of the dose of idraparinux, with participants receiving standard therapy (RR 1.43, 95% CI 0.82 to 2.49, Analysis 3.6).

Major bleeding was reported in 2.96% (95% CI 1.16, 7.37) of patients treated with 5.0 mg idraparinux, in 1.52 % (95% CI 0.41, 5.36) of patients receiving 7.5 mg of idraparinux, and in 6.87 (95% CI 3.66, 12.54) of patients treated with 10 mg of idraparinux. No major bleeding was reported in patients treated with 2.5 mg of idraparinux. Participants allocated to receive standard therapy presented one event of major bleeding (0.76%, 95% CI 0.14 to 4.16). Overall, there was no significant difference in the risk of major bleeding comparing LMWH followed by idraparinux or standard therapy (RR 3.76; 95% CI 0.50, 28.19, Analysis 3.7).

Clinically relevant bleeding was not reported. Total of participants contributing with data to these analyses was equal to 659 (PERSIST Trial).

Idraparinux and LMWH versus standard therapy

Three months of follow-up

Bleeding occurred with a frequency of 4.05% (CI 95% 2.38, 6.80) in participants receiving idraparinux, and with a frequency of 8.86% (95% CI 6.20, 12.51) in participants receiving standard therapy. There was a significant reduced risk of bleeding in patients receiving idrapaparinux in comparison to standard therapy (RR 0.46, 95% CI 0.24 to 0.87, Analysis 4.3).

Major bleeding appeared to occur with similar risk in the idraparinux group compared with standard therapy (RR 0.39, 95% CI 0.08 to 2.01, Analysis 4.5).

The risk of clinical relevant bleeding was slightly reduced in the idraparinux group compared with the group receiving standard therapy (RR 0.47, 95% CI 0.23 to 0.95, Analysis 4.7). Neverthless, clinically relevant bleeding was a common harmful event in both groups:

- Idraparinux: 3.43% (95% CI 1.92 to 6.03)
- Standard therapy: 7.28% (95% CI 4.90 to 10.68)

Six months of follow-up

Bleeding was common and with a frequency equal to 8.31% (95% CI 95% 6.84 to 10.06) in participants receiving idraparinux, and equal to 8.01% (95% CI 6.65 to 9.83) in participants receiving standard therapy. There was no significant difference in the risk of bleeding in patients receiving idrapaparinux in comparison to standard therapy (RR 0.92, 95% CI 0.69 to 1.22, Analysis 4.4).

Major bleeding and clinical relevant bleeding appeared to occur with similar risks in the idraparinux group compared with standard therapy (RR 1.24, 95% CI 0.66 to 2.34, Analysis 4.6, and RR 0.98, 95% CI 0.72 to 1.34, Analysis 4.8, respectively). Major and clinically relevant bleeding were a common harmful event in both groups:

- Major bleeding:

- Idraparinux: 1.86% (95% CI 1.22 to 2.82)
- Standard therapy: 1.50% (95% CI 0.94 to 2.38)

- Clinically relevant bleeding:

- Idraparinux: 6.45% (95% CI 5.17 to 8.04)
- Standard therapy: 6.60% (95% CI 5.23 to8.20)

Only one study (Van Gogh Trial-DVT) contributed with data for this analysis (n=637 and n=2,267, three months and six months of follow-up, respectively).

Secondary efficacy outcomes

Fondaparinux and vitamin K antagonists versus standard therapy

All-cause mortality was similar in participants treated with fondaparinux and vitamin K antagonists in comparison with participants receiving standard therapy (RR 1.06; 95% CI 0.72, 1.57, Analysis 1.7, Figure 7). Heterogeneity was significant in this pooled analysis (I^2 61%, P=0.11). Two studies contributed with data for this analysis (MATISSE-DVT; Rembrandt Trial). Total of participants analysed was equal to 2,645.

Recurrent DVT was reported only by one study included in this comparison (MATISSE-DVT). In this study, data available from 2,205 participants showed that there was no significant difference comparing both intervention groups (RR 0.65; 95% CI 0.36, 1.16, Analysis 1.8). One study contributed with data to this comparison (n=2,205 (MATISSE-DVT).

There was no significant difference in the risk of pulmonary embolism between fondaparinux compared with standard therapy (RR 1.45; 95% CI 0.83, 2.50, Analysis 1.9, Figure 8). Heterogeneity was not evident in this pooled analysis (I^2 0%, P=0.86). Two studies evaluated this outcome and contributed with data to this comparison (n=2,658) (MATISSE-DVT; Rembrandt Trial).

Idrabiotaparinux versus idraparinux

All-cause mortality was similar in participants treated with idrabiotaparinux in comparison with participants receiving idraparinux regardless the follow-up period: RR 0.48 (95% CI 0.18 to 1.27, Analysis 2.8) for six months of follow-up, and RR 0.80 (95% CI 0.25 to 2.60, Analysis 2.9) for 9 months of follow-up. These analyses were based on data provided by one trial (EQUINOX) and 755 participants.

The risk of recurrent DVT and pulmonary embolism were also similar in both groups of intervention during a period of 6-months of treatment (RR 0.57, 95% CI 0.14, to 2.36, Analysis 2.10, and 0.81, 95% CI 0.27 to 2.39, Analysis 2.11). Data on this outcome was not available for the follow-up of 9 months. These analyses were based on one trial (EQUINOX) and 741 patients.

LMWH and idraparinux versus standard therapy

Mortality for all causes was a rare event reported in participants receiving with an initial treatment with LMWH followed by three months of idraparinux (2.5 mg, 5 mg, 7.5 mg or 10 mg) or warfarin. A total of 7 cases was reported in the group of patients receiving idraparinux after LMWH(1.33%, 95% CI 0.64 to 2.72), and zero events in the group of patients receiving standard therapy.

One event of recurrent DVT were observed in participants receiving 10 mg of idraparinux and in participants receiving standard therapy. The RR was not estimated due to the low number of cases.

All cases of recurrent VTE in this comparison (primary efficacy outcomes) were cases of pulmonary embolism, and there was no difference between the intervention groups (RR 1.51; 95% CI 0.26, 8.90, Analysis 3.1).

These analyses were based on one trial (PERSIST Trial) and 659 randomised patients.

Idraparinux versus standard therapy

There was no difference in the risk of all-cause mortality, recurrent DVT or recurrent pulmonary embolism between patients treated with idraparinux compared with standard therapy, regardless of the duration of the follow-up:

- All-cause mortality:

- 3-months of follow-up: RR 1.12 (95% CI 0.70 to 1.80, Analysis 4.9)
- 6 months of follow-up: RR 1.26 (95% CI 0.85 to 1.85, Analysis 4.10)

- Recurrent DVT

- 3-months of follow-up: RR 0.49 (95% CI 0.04 to 5.40, Analysis 4.11)
- 6 months of follow-up: RR 1.00 (95% CI 0.50 to 2.00, Analysis 4.12)

- Pulmonary embolism

- 3-months of follow-up: RR 0.98 (95% CI 0.20 to 4.84, Analysis 4.13)
- 6 months of follow-up: RR 1.00 (95% CI 0.56 to 1.80, Analysis 4.14).

These analyses were based on one trial (Van Gogh Trial-DVT) comprising 2,267 randomised patients followed by three months, and 637 randomised participants followed by six months.

Secondary harm outcomes

Secondary harmful outcomes were inconsistently reported by the included studies, and detailed only according to the number of participants experiencing a certain type of event. Number of events was not reported in any of the included studies.

Thrombocytopenia and heparin-induced thrombocytopenia

Standard definition for thrombocytopenia is platelet-count less than 150 $x10^9$/L, and heparin-induced thrombocytopenia (HIT) is defined as a relative reduction in platelet count of about 50% (even if the platelet count at its lowest remains above 150 x 10^9/L) occurring within 5 to 14 days after the start of heparin therapy (Warkentin 2003) and should be confirmed through functional or immunological laboratory tests to detect platelet activation induced by anti-platelet factor 4 antibodies (Keeling 2006).

Fondaparinux and vitamin K antagonist versus standard therapy

One trial measured platelet counts at baseline, day 4, and at the end of the trial (MATISSE-DVT). The definition used to classify thrombocytopenia was not documented. HIT was defined as platelet count less than 100 $x10^9$/L or decreased more than 40% from the baseline. Laboratory tests were used to detect HIT antibodies, but were not described in detail. A number of 7 patients in each treatment group developed thrombocytopenia. This represents a frequency of thrombocytopenia approximately equal to 0.64% in both groups. None of the thrombocytopenic patients were reported as

having developed HIT antibodies, and none of the cases were associated with thromboembolism events.

Other comparisons

The other trials did not report a definition nor data on thrombocytopenia and HIT (Rembrandt Trial, EQUINOX, PERSIST Trial, Van Gogh Trial-DVT). The PERSIST Trial stated that no events of HIT were observed although not providing any detail on how it was assessed and diagnosed.

Other harmful effects

Adverse Effects leading to withdrawals or premature discontinuation of treatment

Fondaparinux and vitamin K antagonist versus standard therapy

A number of 46 patients prematurely discontinued treatment due to harmful effects (2.1%). The data were reported inconsistently, though, and was not detailed according to type of adverse effects. The MATISSE-DVT trial had these data described only in non-published reports (GSK Trial Register). No difference was estimated in withdrawals due to harmful effects comparing both treatment groups (RR 0.72, CI 95% 0.40 to 1.32, Analysis 1.10). Number of patients analysed were equal to 2,205.

The Rembrandt Trial trial reported three patients withdrawing the trial due to harmful effects, but did not categorised the data according to treatment groups.

Idrabiotaparinux versus idraparinux

A total of 47 patients enrolled in the EQUINOX prematurely discontinued treatment because of harmful effects. No difference were estimated in withdrawals due to harmful effects comparing both treatment groups (RR 0.71, CI 95% 0.41 to 1.25, Analysis 2.12). Number of patients analysed were equal to 757.

LMWH and idraparinux versus standard therapy

In total, 47 patients discontinued treatment because of bleeding and other harmful effects (PERSIST Trial). The occurrence of all harmful effects leading to withdrawal were dose-related, and achieved a maximum frequency in the group of patients receiving 10 mg of idraparinux:

- LMWH + idraparinux 2.5 mg: 2.29% (95% CI 0.78 to 6.52)
- LMWH + idraparinux 5.0 mg: 9.63% (95% CI 5.71 to 17.78)
- LMWH + idraparinux 7.5 mg: 4.61% (95% CI 2.13 to 9.70
- LMWH + idraparinux 10.0 mg: 15.26% (95% CI 10.11 to 22.84)

The frequency of harmful effects leading to withdrawal in the standard therapy group was equal to 3.79% (95% CI 1.63 to 8.56).

Number of patients analysed was equal to 659.

Idraparinux versus standard heparin

In total, 168 participants were reported as having prematurely discontinued treatment in any moment of the trial (Van Gogh Trial-DVT). The frequency of patients discontinuing treatment because of harmful effects was equal 7.09% (95% CI 5.85 to 8.56) in the idraparinux group and equal to 4.48% (95% CI 3.53 to 5.67) in the standard therapy arm. There was a greater and significant occurrence of adverse effects in the group of participants treated with idraparinux (RR 1.58, 95% CI 1.17 to 2.14, Analysis 4.15).

Number of patients analysed were equal to 2,904.

Other harmful effects during follow-up

Fondaparinux and vitamin K antagonist versus standard therapy

Considering the ten most frequent harmful effects reported in the MATISSE-DVT, the initial treatment of DVT with fondaparinux appears to present a similar safety profile of an initial treatment with LMWH (Table 4). The risk of a harmful effects was increased in the LMWH group for two types of event: (i) bruise (RR 0.94, 95% CI 0.18 to 0.81), and (ii) increased levels of hepatic enzymes (RR 0.08, 95% CI 0.03 to 0.21). Number of patients analysed was equal to 2,192.

Pooling together all harmful effects occurring in the MATISSE-DVT trial (leading to premature discontinuation or during follow-up), the profile of harmful effects significantly favoured fondaparinux (RR 0.62, 95% CI 0.54 to 0.70, Analysis 1.11). Number of patients analysed were equal to 2,205.

Data on harmful effects were not reported by the Rembrandt Trial.

Idrabitaparinux versus idraparinux

Treatment with idrabiotaparinux and idraparinux appears to be comparable in terms of harmful effects (Table 5). Pooling together all harmful effects (leading to premature discontinuation or during follow-up), there was no significant difference comparing both interventions (RR 0.92, 95% CI 0.83 to 1.02, Analysis 2.13). Number of patients analysed were equal to 757 (EQUINOX).

LMWH and idraparinux versus standard therapy

Data on harmful effects were not provided for any of the treatments groups. The published report stated that "adverse effects were distributed similarly between the groups" (PERSIST Trial), although the report of an increase in the alanine aminotransferase levels in patients treated LMWH (15%), and in patients latter allocated to receive idraparinux (0.8%, one patient).

Idraparinux versus standard therapy

Data on harmful effects were detailed for four types of events: cancer; cardiac failure; rash, dermatitis or urticaria, and infection. The risk of cardiac failure was significantly elevated in participants receiving standard therapy in comparison with patients treated with idraparinux (RR 0.33, 95% CI 0.13 to 0.84) (Table 6). Grouping all harmful effects (occurring prematurely or during follow-up), there was no significant difference in the risk

of harmful effects between the treatment groups (RR 1.03, 95% CI 1.00 to 1.06, Analysis 4.16).

Number of patients analysed were equal to 2,904 (Van Gogh Trial-DVT).

Assessment of reporting bias

Reporting bias could not be investigated because of the insufficient number of trials (less than 10).

Subgroup analysis

Available data of the studies included allowed us to perform the following subgroup analysis for a limited number of comparisons:

1. Fondaparinux and vitamin K antagonist versus standard therapy

- obese patients;
- ambulatory patients, and;
- cancer patients.

Obese patients

One study (MATISSE-DVT) had data detailed according to subgroups of patients available from the multiple reports of the study. This trial included 2,205 participants: 55 (2.5%) patients with body weight <50kg; 1,922 (87.2%) patients with body weight between 50kg and 100Kg; and 228 (10.3%) patients with body weight >100kg. The efficacy outcome, recurrent VTE, and the harmful outcome, major bleeding, were reported according to subgroups of body weight.

There was no significant difference in the risk of recurrent VTE between the intervention groups and this result was consisted among subgroups of body weights (I^2=0%, p=0.4, Analysis 1.12, Figure 9). Major bleeding occurred in one patient with body weigh <50kg in the fondaparinux group, and in one patient with body weight >100kg in the LMWH arm. Risks could not be estimated due to sparse number of cases.

Ambulatory patients

In the MATISSE-DVT, 345 of the participants randomised to the group receiving initial treatment with fondaparinux were ambulatory patients, and 374 of the participants randomised to receive initial treatment with LMWH were treated on outpatient basis. There was no significant difference in the risk of recurrent VTE during three months of follow-up between initial treatment fondaparinux compared with initial treatment LMWH (RR 1.04, 95% CI 0.70 to 1.53, Analysis 1.13).

Bleeding was similar

The risk of bleeding and major bleeding during the initial treatment with fondaparinux compared to initial treatment with LMWH were also similar:

- Bleeding: RR 0.94 (95% CI 0.42 to 2.12, Analysis 1.14)
- Major bleeding: RR 4.70, 95% CI 1.35 to 16.34, Analysis 1.15).

Cancer patients

A subgroup of 126 participants randomised to the group receiving initial treatment with fondaparinux and 111 participants randomised to receive initial treatment with LMWH had active cancer. The risk of recurrent VTE was similar in both groups of treatment in this subgroup of patients (RR 2.35, 95% CI 0.95 to 5.79, Analysis 1.17). The analysis also did not demonstrate significant difference in the risk of major bleeding and clinically relevant bleeding comparing initial treatment with fondaparinux to LMWH in patients with active cancer during three-months of treatment:

- Bleeding: RR 0.99 (95% CI 0.40 to 2.48, Analysis 1.18)
- Major bleeding: RR 1.10 (95% CI 0.54 to 2.25, Analysis 1.19).

2. LMWH and Idraparinux versus standard therapy

- Cancer Patients

A subgroup of 186 participants randomised to receive idraparinux and 268 randomised to receive standard therapy had active cancer when enrolled (Van Gogh Trial-DVT). A total of 146 participants treated with idraparinux and 138 patients treated with standard therapy were followed for three months. Six months of followed-up was completed by 140 participants treated with LMWH and idraparinux, and 130 patients treated with standard therapy.

The risk of recurrent VTE did not differ between the intervention groups during three months of follow-up (RR 0.47 (0.17 to 1.35, Analysis 4.17), nor during six months of follow-up (RR 0.46, 0.16 to 1.32, Analysis 4.17). The risk of major bleeding did not differ comparing participants with acute cancer treated with idraparinux to patients on standard therapy during three months (RR 1.43, 95% CI 0.24 to 8.36), and during six months (RR 1.11, 95% CI 0.35 to 3.56) (Analysis 4.20).

Sensitive analysis

We did not performed a sensitive analysis because there were not an adequate number of studies.

Discussion

Summary of main results

The pentasacharide fondaparinux is currently an option for the prevention of DVT and pulmonary embolism in nonsurgical and surgical patients (Kahn 2012, Gould 2012), including orthopaedic surgical patients (Falck-Ytter 2012). Its potential as an effective therapeutic agent with a more convenient posology than the standard therapy of patients at risk of a VTE is therefore recognised. This review complements the evidence on the usefulness of pentasaccharides to prevent DVT.We analysed a group of studies investigating the effects of the pentasaccharides fondaparinux, idraparinux and

idrabiotaparinux, and the evidence suggest that fondaparinux is as effective as the standard treatment to reduce the recurrence of VTE in patients treated for DVT.

Nevertheless, we were disappointed with the paucity of the evidence comparing treatment of DVT with pentasacharides and the standard treatment with LMWH or UFH followed by vitamin K antagonists (standard treatment). We identified in total only five studies, four comprising a direct comparison between one of these new anticoagulants and the typical therapy. Remarkably, the biotinylated molecule of idraparinux, idrabiotaparinux, the only pentasaccharide with an antidote to reverse its anticoagulant effect, has never been compared to standard treatment.

The five studies included in this review encompassed a parallel design and were reported in 20 different publications. Data of 6,981 participants were available from these studies. We assessed recurrent VTE as primary efficacy outcome and bleeding as primary harm outcome according to the reported comparisons between the pentasaccharides and standard or alternative therapies. We planned to assess recurrent VTE after six months of treatment. However, we assessed data reported for three months of study when reported by the trials. Our secondary outcomes for efficacy and harms were: all-cause mortality, recurrent DVT, pulmonary embolism, thrombocytopenia and heparin-induced thrombocytopenia, and other harmful effects.

Primary outcomes

Recurrent venous thromboembolism (VTE)

Results from the meta-analysis demonstrated no significant difference between the risk of recurrent VTE in patients receiving pentasaccharide fondaparinux or lower doses of the long-action pentasacharides in comparison with patients receiving standard therapy. In fact, the frequency of recurrent VTE was lower than the expected incidence of 3.6% in patients treated with LMWH, and 5.3% in patients treated with UFH (Erkens 2010). The treatment duration in the included studies varied from three months (Matisse-VDT e The Rembrandt Trial) to six months (EQUINOX, PERSIST Trial and Van Gogh Trial-DVT). The trial Equinox (EQUINOX) included three months of additional follow-up after the six months of treatment.

Fondaparinux

Our analysis demonstrated that fondaparinux followed by vitamin K antagonists were similar to standard therapy to treat DVT during (three months of follow-up). We judged the quality of the evidence as moderate. The studies included in this analysis (MATISSE-DVT e Rembrandt Trial) enrolled participants with similar demographic characteristics at the baseline and pooled analysis showed no significant heterogeneity.

Idraparinux e Idrabiotaparinux

The studies analysing the effect of idraparinux and its biotinylated molecule, idrabiotaparinux, included diverse comparisons and could not be pooled in one meta-analysis.

Idraparinux (2.5 mg) was not different of an equimolar dose of idrabiotaparinux (3.0 mg) to prevent recurrence of VTE during six and nine months of treatment. We were moderately confident of the quality of the evidence.

Treatment with LMWH and 10 mg of idraparinux was not different from treatment with LMWH followed by warfarin in the prevention of recurrent VTE during three months of treatment. However, we have very little confidence in this estimate and considered the quality of the evidence very low. The results from the single trial providing data to this analysis were influenced by the significant amount of outcome missing data due to exclusions, withdrawals and loss of follow-up. Moreover, patients were excluded due to presumed lack of efficacy (suspected VTE).The few number of accumulated cases of recurrent VTE in the group receiving doses of 2.5 mg, 5.0 mg, and 7.5 mg of idraparinux prevented any quantitative analysis. All subgroup analysis included a relatively few number of cases.

Idraparinux compared to standard treatment showed similar efficacy in the prevention of recurrent VTE during three and six months of treatment of DVT. The quality of the evidence was considered moderate for the three months of follow-up and high for six months of follow-up.

Two trials, PERSIST Trial and van Gogh Trial-DVT, may appear to include two similar intervention groups, which could have allowed us to pursue pooled analysis comparing treatment with 2.5 mg of idraparinux with the standard therapy. In fact, the implemented treatment in the studies was different (Table 3). Participants assigned to the intervention group in the Persist trial received five to 7 days of enoxaparin before being randomised to receive one of three different doses of idraparinux without weight adjustment. Patients enrolled in intervention group of the Van Gogh trial-DVT were treated with idraparinux from day one until the end of the follow-up. For this reason, we did not perform a pooled analysis comparing the data available from these studies.

Bleeding

Fondaparinux

Results from the meta-analysis showed no difference in the risk of bleeding (all events) and major bleeding during the initial five days of treatment when patients receiving fondaparinux were compared to patients receiving LMWH. However, heterogeneity was moderate between studies in the pooled analysis for all cases of bleeding. This heterogeneity may be explained by methodological differences between studies. In addition, both studies were judged at high risk of detection bias related to harm outcomes.

The risk of bleeding and major bleeding was also consistent among interventions, although data for this analysis was provided by only one study. Similarly, one study contributed with data demonstrating that clinical relevant bleeding appeared to occur with no difference between participants receiving fondaparinux followed by vitamin K antagonists and patients receiving standard therapy.

We were moderately confident in the quality of the estimates of the risk of bleeding and major bleeding in participants treated with fondaparinux followed by vitamin K antagonists in comparison with patients receiving standard therapy.

Idraparinux and Idrabiotaparinux

The risk of bleeding during a period of six months of treatment did not differ when comparing idrabiotaparinux and idraparinux. Considering major and clinical relevant bleeding separately, idrabiotaparinux showed a lower risk of bleeding during a period of six months of follow-up. We hypothesised whether the administration of avidin, the antidote for idrabiotaparinux, could have contributed to this lower occurrence of more severe bleeding in patients treated with idrabiotaparinux. Unfortunately, data on the use of avidin was not reported. This lower frequency of major and clinical relevant bleeding in patients receiving idrabiotaparinux was not observed three months after patients stopped treatment (9 months of follow-up). The evidence of major bleeding occurring in patients treated with idrabiotaparinux in comparison with idraparinux was judged moderate.

The incidence of bleeding in participants receiving LMWH followed by idraparinux during three months of treatment demonstrated a clear dose-response relationship when compared to participants receiving standard therapy. The risk of bleeding in patients receiving doses of 10 mg of idraparinux was 10 times fold the risk of bleeding in the group of participants treated with 2.5 mg of idraparinux (absolute risk of 22.9% and 2.29%, respectively). Overall, the risk of bleeding was estimated as similar between the intervention groups, though the absolute risk (incidence) was superior to the expected in both groups (expected incidence of bleeding range from 0.9% to 2.2%) (Hutten 1999). The unacceptable high frequency of bleeding was actually responsible for the withdrawal of the 17 participants in one study (PERSIST Trial). Remarkably, patients receiving the lower dose of 2.5 mg of idraparinux showed a risk of bleeding comparable to the standard therapy. The quality of the evidence related to the outcome of major bleeding between the intervention groups was considered as very low.

Participants receiving 2.5 mg of idraparinux for three months in comparison with standard therapy presented a slight lower overall risk of all cases bleeding and clinically relevant bleeding. After six months of treatment, the risk of bleeding and clinically relevant bleeding was similar between both interventions. After three and six months of treatment, the risk of major bleeding was similar comparing participants receiving 2.5 mg of idraparinux to patients receiving standard treatment. The quality of this evidence was considered moderate for the three months follow-up and high for the six months follow-up.

Secondary outcomes

All-cause mortality

Analyses of all-cause mortality were expected to complement the results of the primary outcome recurrence of VTE. Data on this secondary outcome were available for three comparisons:

- Fondaparinux and vitamin K antagonist versus standard therapy (three months, two trials);
- Idrabiotaparinux versus idraparinux (six and 9 months of follow-up, one trial), and;
- Idraparinux versus standard therapy (three and six months of follow-up, one trial).

The results for all cause-mortality were consistent with those of the primary efficacy outcome recurrent VTE for all the above comparisons, i.e., there was no significant difference in the frequency of mortality between the compared interventions. The meta-analysis comparing all-cause mortality of patients treated with fondaparinux and vitamin K antagonists compared to patients treated with standard therapy exhibited a moderate heterogeneity. We believe this statistical heterogeneity could be explained by the amount of missing data across studies.

We considered the quality of the evidence for this outcome as moderate for the comparison of fondaprinux and AVK versus standard therapy, and idrabiotaparinux versus idraparinux. The quality of the evidence was high for the comparison of idraparinux versus standard therapy.

Recurrent DVT

Recurrent DVT appear to occur with a comparable risk in the following compared groups: (i) patients receiving fondaparinux and AVK to those receiving standard therapy during three months, and (ii) patients receiving idrabiotaparinux to patients receiving idraparinux during six months. These results were analogous to the comparison between idraparinux and standard treatment during three and six months. Data for this analysis were extracted from single studies and no meta-analysis was performed. The confidence intervals for all comparisons were wide thus highlighting a certain level of imprecision in these estimates. There were no data available to compare the risk of recurrent DVT in patients receiving LMWH and idraparinux compared to standard therapy.

Pulmonary embolism

There was a correspondence between results for the risk of pulmonary embolism and those for the risk of DVT. There was no difference in the risk of pulmonary embolism among patients enrolled in the following intervention groups: (i) fondaparinux and LMWH compared to standard treatment (three months of follow-up), (ii) idrabiotaparinux versus idraparinux (six-months follow-up), and (iii) idraparinux versus standard therapy (three and six-months follow-up). Data for this analysis were extracted from single studies and no meta-analysis was performed. The confidence intervals for all comparisons were wide thus highlighting a certain level of imprecision in these estimates. There was no

data available to compare the risk of recurrent DVT in patients receiving LMWH and idraparinux compared to standard treatment.

Secondary harm outcomes

Thrombocytopenia and heparin-induced thrombocytopenia

Only one study reported outcomes associated to the effect of pentasaccharides in the platelets counts. This is very disappointing since there is a need for further studies evaluating the role of fondaparinux in the treatment of heparin-induced thrombocytopenia (HIT) (Linkins 2012).

The incidence of thrombocytopenia defined as platelet count less than 100 x 10^9/L or decreased more than 40% from the baseline was equal to 0.64% in the group of patients exposed to fondaparinux and in the group of patients exposed to LMWH. Nevertheless, which laboratory test was used was not detailed. When the above definition for thrombocytopenia was associated with HIT antibodies detect by laboratory tests, no cases of HIT were identified in 1,098 patients exposed to fondaparinux.

Whether the occurrence of thrombocytopenia and HIT might be low in patients treated with fondaparinux, a finding that could reinforce the potential of fondaparinux as a treatment option for HIT (Badger 2010, Kang 2015), the true effect may also be substantially different from the estimates. The underreported and biased evidence do not allow any definitive conclusion.

All harmful effects

Notably, the reporting of harmful effects was inconsistent and incomplete. Meta-analysis could be performed only for pooled data on all harmful effects combined. Participants withdrawing treatment were mostly not detailed according to treatment and reason leading to withdrawal.

Data available showed that patients receiving fondaparinux and LMWH compared to the group of participants receiving standard treatment withdrew treatment due to harmful effects in comparable proportions. However, a risk of increased levels of hepatic enzymes was observed in the group of patients treated with standard therapy. The overall risk of harm effects was similar in patients assigned to the fondaparinux and LMWH group in comparison to patients assigned to the standard therapy group. The quality of the evidence was deemed low and the true effect may be substantially different from this estimated risk.

Patients receiving idrabiotaparinux compared to participants treated with idraparinux withdrew treatment due to harmful effects in comparable proportions. The overall risk of harm effects was also similar in both groups. The quality of the evidence was judged low.

Comparing the frequency of harmful effects leading to withdrawal in participants receiving LMWH and idraparinux with those receiving standard threatment demonstrated a clear dose-response relationship, with the lower dose of 2.5 mg of idraparinux inducing a almost a 7-fold reduced frequency of harms. Idraparinux was also related to higher frequencies of dropouts when compared to standard therapy. However, data of

Moderate quality provided from one single study contrasting idraparinux with standard therapy did not confirm a higher occurrence of harms in patients treated with idraparinux and followed by three months.

Subgroup analysis

Data evaluating the safety and efficacy of anticoagulant treatment in obese and cancer patients are frequently scarce. Despite of the inclusion of this population in the clinical trials, in general the data are not categorised in a manner allowing data extraction and analysis.

In our review, two studies reported extractable data on obese patients, cancer patients, or patients treated as outpatients (MATISSE-DVT, van Gogh Trial-DVT). Nevertheless, these
studies addressed different comparisons and could not be pooled together. Our analyses suggest that the similar profile of efficacy and harms effects of the pentasaccharides and standard therapy observed for the whole population studies is consistent among the subgroups. However, these results are supported by analysis based on a small sample of these subgroups of patients, and it is still not possible to make a definitive judgment and extrapolate our findings to the clinical practice.

Overall completeness and applicability of evidence

The data gathered in this review led us to conclude that the pentasaccharides fondaparinux, idraparinux and idrabiotaparinux are effective to reduce the recurrence of VTE in patients treated for DVT and as effective as the treatment currently considered as the standard one. All-cause mortality, an important outcome to support the results of the primary efficacy outcome, was also equivalent among patients receiving pentasaccharides or standard treatment. The main harmful effect of anticoagulants, bleeding, was similar between the treatments compared. Finally, the rates of all harm outcomes also appeared to be comparable between the intervention and the control treatment, though incomplete report on this outcome reduces our confidence in this finding. Noticeably, these conclusions are mostly related to fondaparinux and low doses of idraparinux and idrabiotaparinux.

Two of the included studies investigated the effects of fondaparinux, and three evaluated the effects of idraparinux (one of them comparing idraparinux to idrabiotaparinux). Overall, the trials included patients with similar demographic characteristics at the baseline. Most of patients aged 57 to 62 years old, which is the expected population at higher risk of an event of DVT and may represent a relatively good external validity to the evidence.

The observed similar efficacy of idraparinux when compared to standard treatment happened, however, at a cost of an increased risk of harmful effects related to higher doses of idraparinux. Harm outcomes associated to idraparinux showed a clear dose-response relationship and an unacceptable rate of bleeding. These results reveals that doses of idraparinux of 5.0 mg, 7.5 mg e 10.0 mg may not be safe despite of the demonstrated efficacy to treat DVT.

Our results showing the problem with the safety of idraparinux are in agreement with previous observations. In fact, idraparinux and idrabiotaparinux were withdrawn from the

market due to a high risk of bleeding after treatment of VTE (Harenberg 2008; van Gogh 2007). Nevertheless, our results did not identify this safety problem with doses of 2.5 mg of idraparinux and equimolar doses of 3.0 mg of idrabiotaparinux. At these doses, idraparinux and idrabiotaparinux appear to be effective. We regret the lack of data able to justify why research with idraparinux and idrabiotaparinux using these low doses has not evolved, or why further data clarifying the issue have not been published.

Quality of the evidence

Five studies, comprising 6,981 participants, were judged to provide an overall moderate to high quality evidence. As assessed by the GRADE approach, the quality of the evidence provided by the included RCTs was downgraded mostly for unclear or high risk of selection bias, detection bias, and attrition bias related to the efficacy outcome. Key methodological limitations were missing data, withdrawals and loss of follow-up not clearly detailed, and data analysis not consistent with an intention-to treat approach. Some outcomes had the quality of the evidence also downgraded due to the inclusion of relatively few events.

One comparison was particularly problematic and generated low quality evidence (LMWH and idraparinux versus LMWH and warfarin). The study providing data for this analysis (Persist) were judged as potentially flawed since a relevant number of patients were lost to follow-up or discontinued treatment prematurely after randomisation, and even though analysis were carried out considering all randomised participants. The trials' report state that efficacy analysis included only participants who received treatment and for whom the primary outcome was available, but described the analysis as an intention-to-treat approach. The evidence for this comparison was also downgraded for unclear risk of selection bias and for the relatively few patients and few events available.

The quality of the evidence related to harm outcomes were downgraded mostly due to high risk of detection and attrition bias. In general, only the main harm outcome, bleeding, were consistently detected and reported by the included trials.

Potential biases in the review process

We planned and implemented our review methods following high standard guidance to avoid biases in the review process (Higgins 2011). We carried out a comprehensive search strategy at the Cochrane Vascular Group's Specialised Register (July 2015) and the Cochrane Central Register of Controlled Trials CENTRAL. We applied no language restrictions and considered conference abstracts as well as complete articles. This minimizes the risk of missing potential eligible studies.

We used a dual selection and data extraction process, with consensus supported by a third author. Data extraction was also independently checked for agreement by a third author. These processes were guided by the eligibility criteria established in our review protocol to avoid any subjectivity (Brandao 2015).

Therefore, we believe that there are no obvious biases within the review process.

Agreements and disagreements with other studies or reviews

This is the first systematic review evaluating the efficacy and harms of treatment with pentasaccharides in patients with DVT, and our results corroborate international guidelines recommending fondaparinux as a treatment option comparable to LMWH and UFH followed by vitamin K antagonists for DVT and acute pulmonary embolism (Kearon 2012). To our knowledge, only one non-Cochrane review investigated the effects of the pentasaccharides with longer half-lives, idraparinux and idrabiotaparinux. (Song 2013). In this review, Song et al included two studies that were not included in our review: Cassiopea (Cassiopea Investigators) and van Gogh-PE (MATISSE-DVT/PE). We did not include these studies because they investigated patients treat for DVT and pulmonary embolism, and did not report data separately to allow extraction of data only of patients treated for DVT. The review did not find convincing evidence that idraparinux and idrabiotaparinux had a profile of efficacy and harm outcome comparable to standard treatment. This in contrast with our results, since we concluded that appropriate doses of idraparinux and idrabiotaparinux may present similar efficacy and harm effects of the conventional treatment of DVT.

Authors' conclusions

Implications for practice

We found moderate to high quality evidence that fondaparinux at doses of 5.0 mg, 7.5 mg and 10.0 mg has a profile of efficacy similar to standard treatment. The profile of harm outcomes also appear to be comparable between fondaparinux and standard treatment though the quality of the evidence varied from moderate to low. Treatment with fondaparinux is more convenient since it requires only one subcutaneous administration per day, while LMWH requires two subcutaneous injections per day. This convenient posology facilitates outpatient treatment and early discharge from hospital. Fondaparinux also has a more predictable anticoagulant response, and therefore no need for laboratory monitoring of the anticoagulant effect and its profile of drug interactions is more favourable since it is not metabolised in the liver. Moreover, HIT does not appear to be a problem during treatment with fondaparinux. The drawback of fondaparinux is the lack of an antidote capable to reverse its anticoagulant effect.

We found high to very low quality evidence that the dose of 2.5 mg of idraparinux and the equimolar dose of 3.0 mg of idrabiotaparinux were effective to treat DVT and similar to standard therapy. Harm outcomes also appear to be comparable between fondaparinux and standard treatment though the quality of the evidence varied from high to very low. Idraparinux and idrabiotaparinux have the convenience of one weekly subcutaneous administration, and the idrabiotaparinux has an antidote available, avidin. However, these medicines were withdrawn from the market due to a high risk of bleeding. We were disappointed with the lack of data justifying the decision to not further evaluate convenient and potential treatment option at low dose.

Implications for research

Our review showed that the pentasaccharides idraparinux and idrabiotaparinux used in low doses of 2.5 mg and 3.0 mg, respectively, appear to be an alternative to conventional anticoagulants for the

treatment of DVT. However, the pharmaceutical industry has suspended the research on these pentassaccharides during the development of studies of phase III in 2009. We wonder whether this could have been an early decision or whether further data on harmful outcomes have been hidden from the published trials?

The only pentasaccharide with an antidote available to revert its anticoagulant effect is idrabiotaparinux. The molecule of idrabiotaparinux is identical to the one of idraparinux with the addition of biotin. Avidin binds to biotin at the molecule of idrabiotaparinux rapidly reversing is anti-factor Xa activity after an intravenous injection, which is considered safe (Paty 2010). The treatment with fondaparinux does not have an antidote to reverse the anticoagulant effect, which is a matter of concerns to clinicians and patients. An injection of 90 micrograms of recombinant factor VIIa has showed potential to reverse the anticoagulant effect in volunteers who used 10 mg of fondaparinux in emergency situations. Bijsterveld 2002. Idraparinux also does not have an antidote to reverse its anticoagulant effect. It is essential for future research to develop and test candidates to promote the reversal of the anticoagulant effect of fondaparinux and idraparinux.

The thromboembolic disease is a severe and potentially fatal condition. It aetiology is multifactorial, its clinical presentation has a myriad of peculiarities that still deserve continue and improve clarifications, and we are still in the search for an ideal anticoagulant agent. Further randomised studies are expected, particularly to investigate the efficacy and harmful effects of the long-acting pentasaccharides.

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Declarations of interest

Gustavo MS Brandão: none known
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Hamilton A Rollo: none known
Marcone L Sobreira: I have received payment from Sanofi for the development of educational lectures regarding the issue "venous thromboembolism prophylaxis and treatment"

Characteristics of studies

Characteristics of included studies

EQUINOX

Methods	Study design: parallel RCT Duration of follow-up: 6 months after randomisation, plus an additional visit 3 months after the end of treatment Outcome monitoring: Symptoms and signs of thromboembolism and bleeding were monitored using a checklist and instructing patients to report symptoms to the study centre
Participants	Countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Israel, Italy, Mexico, The Netherlands, New Zealand, Poland, Russia, South Africa, Spain, USA Inclusion criteria: Patients who presented with acute symptomatic deep venous thrombosis of the leg Setting: Unclear Total of participants randomised: 757 Mean age: 57 year Sex: 441 (58%) male; 316 (42%) female
Interventions	Intervention group: Idrabiotaparinux Participants randomised: 386 Posology: subcutaneous injections with 3.0 mg idrabiotaparinux in 0.5 mL isotonic sodium chloride once weekly for 6 months Follow-up completion at 6-month: 381 patients (99%) Follow-up completion at 3 months after the study treatment period: 361 (of whom 80 received Vitamin K antagonists) out of 381 patients (95% Comparison group: Idraparinux Participants randomised: 371 Posology: subcutaneous injections with equimolar dose of 2.5 mg idraparinux in 0.5 mL isotonic sodium chloride once weekly for 6 months Follow-up completion at 6-month: 360 patients (97%) Follow-up completion at 3 months after the study treatment period: 339 (of whom 76 received Vitamin K antagonists) out of 360 patients (94%) Staff training: Nurse student under direct supervision of the

	physician investigator; subsequently, the investigator determined if patients would self- inject the medication or continue to receive assistance. Patients were contact by telephone to ensure the second and third injections were administered according to the protocol. Scheduled visits on the second and third days completed the protocol.
Outcomes	Primary outcome: symptomatic recurrent venous thromboembolism Main safety outcome: clinically relevant bleeding (either major or clinically relevant non-major) Death
Notes	Major bleeding: Bleeding associated with a fall in haemoglobin of 2 g/dL or more Bleeding that led to a transfusion of 2 or more units of packed red cells or whole blood Bleeding that involved a critical organ (intracranial, intraocular, intraspinal, retroperitoneal, or pericardial) Bleeding that contributed to death Clinically relevant bleeding: Any bleeding compromising haemodynamics Any bleeding leading to hospitalisation Subcutaneous hematoma larger than 25 cm2, or 100 cm2 if there was a traumatic cause Intramuscular hematoma documented by ultrasonography Epistaxis that lasted for more than 5 minutes, was repetitive (i.e., two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g., packing or electrocoagulation) Gingival bleeding occurring spontaneously (i.e., unrelated to eating or tooth brushing) or lasting for more than 5 minutes Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract Macroscopic gastrointestinal haemorrhage, including at least one episode of melena or hematemesis, if clinically apparent with positive results on a fecal occult-blood test Rectal blood loss, if more than a few spots on toilet paper Hemoptysis, if more than a few speckles in the sputum and not

	occurring within the context of pulmonary embolism Any other bleeding type considered to have clinical consequences for a patient - such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug or associated with pain or impairment of activities of daily life Death was classified as due to pulmonary embolism, bleeding, cancer or other established diagnoses. Pulmonary embolism was considered as the cause of death if objectively documented or if the cause of death was unexplained and pulmonary embolism could not be confidently excluded.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved with the use of a computerized voice-response system. The process was also stratified by centre.
Allocation concealment (selection bias)	Low risk	A computerized voice-response system was used to randomise patients and ensure concealment of allocation.
Blinding of Participants and personnel (performance bias) Participants	Low risk	Identically appearing syringes in isotonic sodium chloride were used.
Blinding of Participants and personnel (performance bias) Personnel	Low risk	The computerized voice-response system used ensures blinding of personnel.
Blinding of outcome assessment (detection bias) Efficacy outcomes	Low risk	Outcomes were classified by an independent central adjudication committee, whose members were unaware of treatment assignment.
Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	Only bleeding was reported to be diagnosed by a committee unaware of treatment assignment.
Incomplete outcome	High risk	Reasons for withdrawals and loss of follow-up may

data (attrition bias) Primary efficacy outcome		be related with efficacy, prognosis, and adverse effects. Analysis was performed using participants whose clinical outcomes were assessed.
Incomplete outcome data (attrition bias) Harm outcomes	High risk	Main harmful effects were reported (bleeding and death) but other harmful effects were reported only if incidence were higher than 2% and data were not available as a supplement material.
Selective reporting (reporting bias)	Low risk	Comparison between the trial register and the full report does not indicate selective reporting bias.
Other bias	High risk	The sponsor, Sanofi-Aventis, had a role in the study design, protocol, study oversight, verification of the data, and statistical analysis since two sponsor-based scientists were part of the executive advisory board.

MATISSE-DVT

Methods	Study design: parallel RCT Duration of follow-up: 3 months Outcome monitoring: Symptoms of thromboembolism and bleeding were monitored daily during initial treatment through contact with patient, and at 1 and 3 months. Patients received instructions to immediately report symptoms to the study centre
Participants	Countries: Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, The Netherlands, New Zealand, Norway, Poland, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, The Netherlands, United Kingdo, USA Inclusion criteria: Patients who presented with acute symptomatic deep venous thrombosis of the the popliteal, femoral, or iliac veins or the trifurcation of the calf veins Setting: Unclear Total of participants randomised: 2,205 Mean age (standard deviation): Fondaparinux group 61.1 (16.7); Enoxaparin group 61.5 (16.5) Female Sex: Fondaparinux group 517 (47%); Enoxaparin group 529 (47.8%)
Interventions	Intervention group: Fondaparinux Participants randomised: 1098 Posology: 5 days of once-daily subcutaneous injection of fondaparinux 5.0 mg if they weighed less than 50 kg, 7.5 mg if

	they weighed between 50 and 100 kg, or 10.0 mg if they weighed more than 100 kg plus vitamin K vitamin antagonist started within 72 hours and continued until 3 months Follow-up completion at 3-month: 1,094 patients (99.6%) Comparison group: Enoxaparin Participants randomised: 1107 Posology: 5 days of twice-daily subcutaneous dose of enoxaparin 1 mg/kg of body weight plus vitamin K vitamin antagonist started within 72 hours and continued until 3 months Follow-up completion at 6-month: 1,096 patients (99%) Staff training: Unclear for hospitalised patients. Home treatment was described as administered by a home care service
Outcomes	Primary efficacy outcome: symptomatic recurrent venous thromboembolism Primary harm outcome: Bleeding
Notes	Death: classified as due to pulmonary embolism, bleeding, cancer, or other established diagnoses, or classified as unexplained. Major bleeding: clinically overt and associated with a decrease in the haemoglobin level of 20 g/L or more, associated with transfusion of two or more units of red blood cells or whole blood cells, retroperitoneal or intracranial, occurring in a critical organ, or contributing to death Clinically relevant bleeding: clinically relevant but not major (for example, epistaxis that required intervention or spontaneous macroscopic hematuria)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved by using a computerized interactive voice response system. Randomisation was stratified by centre in balanced blocks of 4 patients
Allocation concealment (selection bias)	Low risk	A computerized voice-response system was used to randomise patients and ensure concealment of allocation.
Blinding of participants	Low risk	Patients treated with fondaparinux received

and personnel (performance bias) Participants		twice-daily subcutaneous injections of placebo that appeared identical to enoxaparin. Patients treated with enoxaparin received once-daily subcutaneous injection of placebo that appeared identical to fondaparinux.
Blinding of participants And personnel (performance bias) Personnel	Low risk	The computerized voice-response system used ensures blinding of personnel,
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were classified by an independent central adjudication committee, whose members
Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	Only bleeding was reported to be diagnosed by a committee unaware of treatment assignment.
Incomplete outcome data (attrition bias) Primary efficacy outcome	Unclear risk	Reasons for withdrawals and loss of follow-up are not clearly detailed. Authors do not explain how outcome data for 15 missing participants were handled.
Incomplete outcome data (attrition bias)	Low risk	Analysis were performed in all patients who received at least one dose of the interventions.
Selective reporting (reporting bias)	High risk	Results about harmful effects were presented only in the summary of results available in the Clinical Study Register of GSK, the manufacturer of fondaparinux.
Other bias	High risk	Investigators responsible for the study, members of the executive committee, are advisors or employees of the pharmaceutical industry that sponsored the trial.

PERSIST Trial

Methods	Study design: parallel RCT Duration of follow-up: 3 months Outcome monitoring: Patients were asked to report symptoms of thromboembolism and bleeding. At the end of follow-up, ultrasonography and lung scan were performed
Participants	Countries: Austria, Denmark, Italy, The Netherlands, Poland, Spain, Sweden and United Kingdon

	Inclusion criteria: Patients with acute symptomatic proximal DVT confirmed by compression ultrasonography (not compressible) or venography (had an intraluminal filling defect on venography) were potentially eligible for the study Setting: Unclear Total of participants randomised: 659 Mean age (standard deviation): 2.5 mg Idraparinux 58.8 (17.2); 5 mg Idraparinux 59.5 (16.3); 7.5 mg Idraparinux 60.0 (13.5); 10 mg Idraparinux 59.1 (14.7); warfarin, 60.0 (14.8) Male Sex: group 1, 69 (52.7%); group 2, 73 (54.1%); group 3, 85 (65.4%); group 4, 65 (49.6%); warfarin 71 (53.8%)
Interventions	Intervention group: Idraparinux divided in four groups according to dosages received: 2.5 mg; 5 mg; 7.5 mg; 10 mg Participants randomised: 2.5 mg, 131; 5 mg, 135; 7.5 mg, 130; 10 mg, 131; warfarin, 132 Posology: 5 to 7 days of enoxaparin (1 mg kg^{-1}) followed by one of four doses of Idraparinux once a week (2.5 mg, 5.0 mg, 7.5 mg, 10 mg) via subcutaneously injection and without weight adjustment Follow-up completion at 3-months: 614 (93%) of the patients were available for analysis of the primary efficacy outcome Comparison group: Warfarin Participants randomised: Posology: 5-7 days of enoxaparin (1 mg kg^{-1}) followed by warfarin with a target International Normalised Ratio (INR) rate between 2.0 to 3.0 Follow-up completion at 3-month: 614 (93%) of the patients were available for analysis of the primary efficacy outcome Staff training: reported as trained.
Outcomes	Primary efficacy outcome: symptomatic recurrent venous thromboembolism Primary harm outcome: Major bleeding
Notes	The use of clopidogrel and glycoprotein IIb/IIIa antagonist was prohibited during the trial period, and use of aspirin and non-steroidal anti-inflammatory drugs was discouraged. Death: the outcome was evaluated to assess the likelihood of

	pulmonary embolism or bleeding as the cause of death Major bleeding: clinically overt bleeding that was fatal, retroperitoneal, intracranial, within a critical organ, leading to a decrease in haemoglobin of >2 g dL−1, or required a transfusion of ≥2 U of packed cells Thrombocytopenia: defined as platelet count <100 × 10^9 L−1 or a drop of >40%

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Incomplete information about the randomisation method.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of Participants and personnel (performance bias) Participants	High risk	The different doses of Idraparinux was blinded, but the type of drug of the treatment groups was open.
Blinding of Participants and personnel (performance bias) Personnel	High risk	Investigators were blinded to the different doses of Idraparinux, but the type of drug of the treatment groups was open.
Blinding of outcome assessment (detection bias) Efficacy outcomes	Low risk	A central adjudication committee, blinded to treatment allocation, reviewed the diagnosis of the efficacy outcomes.
Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	The safety monitoring committee was only partially blinded to treatment groups.
Incomplete Outcome data (attrition bias)	High risk	A relevant number of patients were lost to follow-up or discontinued prematurely after randomisation (n=113).

Primary efficacy outcome		analysis included only participants who received treatment and for whom the primary outcome was available. Neverthless, estimates considered all randomised participants.
Incomplete Outcome data (attrition bias) Harm outcomes	High risk	A significant number of patients withdrawn enrolment in the studies due to harm outcomes. Appropriate definition and description of other harmful outcomes besides bleeding were not given. Data collection of harmful outcomes a part of bleeding was not detailed.
Selective reporting (reporting bias)	Unclear risk	We could not identify the study trial and, therefore, we were unable to judge selective reporting bias.
Other bias	High risk	Employees of the pharmaceutical industry sponsor were members of the steering committee whose took responsibility for the design, analysis and publication of the trial. Other members of the steering committee have received an honorarium for their activities, and a writing committee was also paid by the sponsor for their role in the study report.

Rembrandt Trial

Methods	Study design: parallel RCT Duration of follow-up: 3 months Outcome monitoring: Symptoms of thromboembolism and bleeding were monitored daily during initial treatment through contact with patient, and at 2 and 3 months. Patients received instructions to immediately report symptoms to the study centre
Participants	Countries: France, Italy, Switzerland, Belgium, Australia, Italy, New Zealand, Canada Inclusion criteria: Patients with acute, symptomatic, proximal deep vein thrombosis, who were older than 18 years old Setting: Consecutive patients referred to hospitals Total of participants randomised: 456, but three patients did not received the study drug and were excluded from further analysis (participants analysed=453) Mean age (standard deviation): Fondaparinux 5mg, 61.0 (17.6); fondaparinux 7.5 mg, 57.8 (18.9); fondaparinux 10 mg, 59.6 (16.4); dalteparin, 69.4 (16.0) Sex: 233 (51.1) males; 220 (48.9) females
Interventions	Intervention group: Fondaparinux

	Participants randomised: 334 Posology: ± 5 days of once-daily subcutaneous injection of one among three dosages of fondaparinux (5.0 mg, 7.5 mg, 10 mg) without body weigh adjustment. Treatment with vitamin K antagonist was started on day 1 or 2 and continued for ±90 days. The study drug was discontinued when the INR was maintained at ±2.0 for 2 consecutive days Follow-up completion at 3-month: 323 (96.7%) of all three dosages completed the follow-up Comparison group: Dalteparin Participants randomised: 119 Posology: ± 5 days of twice-daily subcutaneous injection of dalteparin 100IU/kg. Treatment with vitamin K antagonists was started on day 1 or 2 and continued for ±90 days. The study drug was discontinued when the INR was maintained at ±2.0 for 2 consecutive days Follow-up completion at 3-month: 114 (95.8%) received the study intervention in accordance to the protocol Staff training: not reported. Before randomisation was performed, participants were allowed to received therapeutic dosages of unfractionated or low-molecular-weight heparin for24 hours, provided that it was
Outcomes	Primary efficacy outcome: symptomatic recurrent venous thromboembolism Primary harm outcome: major bleeding
Notes	Major bleeding: clinically overt and associated with a fall in haemoglobin level >2 g/dL or leading to a transfusion of more than 2 units of red cells; if it was intracranial, retroperitoneal, or in a critical organ; or when it was fatal. Minor bleeding: clinically unusual overt bleeding not meeting the criteria for major bleeding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence	Low risk	Randomisation was performed by the use of a

generation (selection bias)		computer algorithm through a central 24-hour telephone service.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of Participants and personnel (performance bias) Participants	Low risk	Participants treated with fondaparinux received twice-daily subcutaneous injection of a placebo matching dalteparin. Participants treated with dalteparin received a once-daily subcutaneous injection of a placebo matching pentasaccharide. The volumes of the syringes were adjusted to obtain the correct dose of the active treatment or its matching placebo.
Blinding of Participants and personnel (performance bias) Personnel	High risk	Not reported.
Blinding of outcome assessment (detection bias) Efficacy outcomes	Low risk	Efficacy outcomes were interpreted by a central committee unaware of treatment allocation.
Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	Data collection of harmful outcomes was not detailed.
Incomplete Outcome data (attrition bias) Primary efficacy outcomes	Low risk	Altough the trial report documents the exclusion of three randomised participants who did not receive treatment, the subsequent analysis was performed using an intention-to treat approach with no patient lost to follow-up. The potential impact on the effect estimates of the three excluded patients appears to be low.
Incomplete Outcome data (attrition bias) Harm outcomes	High risk	Among the harmful outcomes, only major bleeding was reported.
Selective reporting (reporting bias)	Unclear risk	We could not identify the study trial and, therefore, we

Other bias	High risk	Investigators responsible for the study, members of the executive committee, are advisors or employees of

Van Gogh Trial-DVT

Methods	Study design: parallel RCT Duration of follow-up: 3 or 6 months. Randomisation was stratified according to intended treatment duration judged on the basis of the perceived risk of recurrence, as assessed by the treating physician Outcome monitoring: A check list was used in schedule contacts with patients to collect information on symptoms and signs of thromboembolism and bleeding. Patient were instructed to contact the study centre if experiencing any symptoms.
Participants	Countries: Netherlands, United Kingdon, United States of America, France, Australia, Canada, Italy Inclusion criteria: Patients over 18 years of age who presented with a acute symptomatic deep venous thrombosis of lower-extremities Setting: Unclear Total of participants randomised: 2,904 (only participants of the DVT study) Mean age (standard deviation): 58 years Male Sex: 1,568 (54%)
Interventions	Intervention group: Idraparinux Participants randomised: 1,452 (3-months follow-up: 321; 6-months follow-up: 1,131) Posology: Once-weekly subcutaneous dose of 2.5 mg. For patients with a creatinine clearance of less than 30 ml per minute (as calculated with the Cockcroft-Gault formula), the second and subsequent doses were 1.5 mg Follow-up completion: Treatment duration of 3 months was planned for 22% of the participants and for 6 months for the remaining patients. Follow-up was completed for the primary efficacy outcome in 99.3% of patients. Comparison group: Standard therapy (LMWH or Heparin followed by warfarin or acenocoumarol) Participants randomised: 1,452 (3-months follow-up: 316; 6-months follow-up: 1,136)

	Posology: Tinzaparin, enoxaparin, or intravenous heparin adjusted for the activated partial-thromboplastin time (ratio, 1.5 to 2.5), followed by warfarin or acenocoumarol (international normalized ratio, INR, 2.0 to 3.0), which was started within 24 hours after randomisation. Heparin was discontinued when the INR was 2.0 or more for 2 consecutive days and the patient had received at least 5 days of initial treatment. Follow-up completion: Treatment duration of 3 months was planned for 22% of the participants and for 6 months for the remaining patients. Follow-up was completed for the primary efficacy outcome in 99.3% of patients. Staff training: not reported.
Outcomes	Primary efficacy outcome: Symptomatic recurrent venous thromboembolism Primary harm outcome: Clinically relevant bleeding and deaths from all causes
Notes	Major bleeding: Bleeding associated with a fall in haemoglobin of 2 g per decilitre or more Bleeding that led to a transfusion of 2 or more units of packed red cells or whole blood Bleeding that involved a critical organ (intracranial, intraocular, intraspinal, retroperitoneal, or pericardial) Bleeding that contributed to death Clinically relevant bleeding: Any bleeding compromising haemodynamics Any bleeding leading to hospitalisation Subcutaneous hematoma larger than 25 cm2, or 100 cm2 if there was a traumatic cause Intramuscular hematoma documented by ultrasonography Epistaxis that lasted for more than 5 minutes, was repetitive (i.e., two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g., packing or electrocoagulation) Gingival bleeding occurring spontaneously (i.e., unrelated to eating or tooth brushing) or lasting for more than 5 minutes Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g.,

	catheter placement or surgery) of the urogenital tract Macroscopic gastrointestinal haemorrhage, including at least one episode of melena or hematemesis, if clinically apparent with positive results on a fecal occult-blood test Rectal blood loss, if more than a few spots on toilet paper Hemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism Any other bleeding type considered to have clinical consequences for a patient - such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug or associated with pain or impairment of activities of daily life Death: classified as due to pulmonary embolism, bleeding, cancer, or other established diagnoses. Pulmonary embolism: considered the cause of death if there was objective documentation or if the cause of death was unexplained and pulmonary embolism could not be confidently ruled out.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by the use of a computerized voice-response system, and stratified according to centre and intended treatment duration.
Allocation concealment (selection bias)	Low risk	A computerized voice-response system was used to randomise patients and ensure concealment of allocation.
Blinding of participants and personnel (performance bias) Participants	Unclear risk	Not reported, probably not done.
Blinding of participants and personnel (performance bias) Personnel	Unclear risk	Not reported, probably not done.
Blinding of outcome assessment	Low risk	A central adjudication committee unaware of treatment assignments classified all outcomes.

(detection bias) Efficacy outcomes		
Blinding of outcome assessment (detection bias) Harmful outcomes	Low risk	A central adjudication committee unaware of treatment assignments classified all outcomes. An independent data and safety monitoring board periodically reviewed the studies' outcomes and advised the steering committee.
Incomplete outcome data (attrition bias) Primary efficacy outcome	Low risk	The study reports states that all analysis included all randomised patients, and follow-up was successful in 99.1%. Missing data might not have an impact in the study results.
Incomplete outcome data (attrition bias) Harm outcomes	High risk	Reasons for treatment discontinuation comprised harmful outcomes, and only adverse effects with incidence >1% were reported.
Selective reporting (reporting bias)	High risk	The trials protocol does not contain information on planned outcome data to be considered in the study.
Other bias	High risk	Investigators responsible for the study disclosed financial conflict of interest with the pharmaceutical industry that sponsored the trial. The sponsor also had a role in the preparation of the trial report.

Footnotes

Characteristics of excluded studies

Cassiopea Investigators

Reason for exclusion	The trial evaluates the treatment of acute symptomatic pulmonary embolism, not treatment of deep vein thrombosis.

EQUINOXa

Reason for exclusion	These trials from the EQUINOX study aimed to assess the reversibility of the anti-FXa activity of idrabiotaparinux by intravenous avidin infusion and the bioequipotency of idrabiotaparinux and idraparinux.

MATISSE-DVT/PE

Reason for exclusion	These relates to narrative reviews summarising the results of the MATISSE-DVT/PE trial and an abstract presenting the methods applied in the trial.

Nakamura 2011

Reason for exclusion	The diagnosis of deep vein thrombosis was performed by contrast-enhanced multidetector-row computed tomography

	(MDCT). This is not in accordance with our eligibility criteria.

The Van Gogh Extension

Reason for exclusion	These reports from The Van Gogh Trial evaluated the efficacy of pentasaccharides (idraparinux) for extended prophylaxis of deep vein thrombosis.

Young 2011

Reason for exclusion	The study does not have a control group.

Footnotes

Additional tables

1 Characteristics of included studies: Methods

Study	Year	Countries	Funding sources
EQUINOX	2006/2007	Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Israel, Italy, Mexico, The Netherlands, New Zealand, Poland, Russia, South Africa, Spain, USA	Sanofi
MATISSE-DVT	2000/2001	Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, The Netherlands, New Zealand, Norway, Poland, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, The Netherlands, United Kingdom, USA	Sanofi and NV Organon
PERSIST Trial	1999/2001	Austria, Denmark, Italy, The Netherlands, Poland, Spain, Sweden and United Kingdom	Sanofi and NV Organon
The Rembrandt Trial	1997/1998	France, Italy, Switzerland, Belgium, Australia, Italy, New Zealand, Canada	Sanofi and NV Organon
The Van Gogh Trial-DVT	2003/2004	Netherlands, United Kingdom, United States of America, France, Australia, Canada, Italy	Sanofi

Footnotes

2 Characteristics of included studies: Participants

Study	Number of randomised participants	Age (Mean)	Exclusion criteria
EQUINOX	757	57 years	Patients who had presented with or documented: symptomatic pulmonary embolism; active bleeding or high risk of bleeding; creatinine clearance < 30 mL min); severe hepatic disease; bacterial endocarditis; uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg); known allergy to idraparinux, idrabiotaparinux or egg proteins; therapeutic doses of LMWH, unfractionated heparin or fondaparinux given for more than 36 hours before randomisation; initiation of vitamin K antagonist treatment or treatment with thrombolysis, thrombectomy, or a vena cava filter for the current episode of deep venous thrombosis; another indication for prolonged anticoagulant therapy; life expectancy of < 6 months; participation in another pharmacotherapeutic study within the prior 30 days; pregnant women, breast-feeding or premenopausal and not using effective contraceptive measures.
MATISSE-DVT	2,205	61 years	Patients who had presented with or documented: symptomatic pulmonary embolism; received therapeutic doses of low molecular weight heparin or oral anticoagulants for more than 24 hours; required thrombolysis, thrombectomy, or a vena cava filter;

			anticoagulant therapy contraindication (for example, active bleeding, thrombocytopenia [platelet count 100,000 x 10^9/L]); elevated serum creatinine levels above177 mol/L [2 mg/dL]) uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg); pregnancy; had a life expectancy < 3 months.
PERSIST Trial	659	59 years	Patients who had presented with or documented: symptoms for more than 14 days; symptomatic pulmonary embolism; documented DVT within the last 2 years; surgery within the past 10 days; more than 32 hours of therapeutic anticoagulant treatment; contraindications for anticoagulants; life expectancy <3 months; pregnancy; serum creatinine >200 μmol L−1; platelet count <100 × 109 L−1
The Rembrandt Trial	456	62 years	Patients who had presented with or documented: symptomatic pulmonary embolism; previously documented thrombosis in the same leg, unless complete ultrasound normalization had been documented; known bleeding tendency; surgery within the previous 5 days; body weight of <50 kg or > 100 kg; any contraindication for anticoagulant treatment treatment with therapeutic dosages of anticoagulants for >24 hours

			before randomisation; pregnant women, breast-feeding or premenopausal and not using effective contraceptive measures; drug-addictive disorder or alcoholism; known renal insufficiency; life expectancy of <6 months; participation in another clinical drug study within the previous 90 days.
The Van Gogh Trial-DVT	2,904	58 years	Patients who had presented with or documented: receipt of a therapeutic dose of low-molecular-weight heparin or unfractionated heparin administered for more than 36 hours before randomisation; treatment with thrombolysis, embolectomy, or a vena cava filter required for the current episode; another indication for a vitamin K antagonist; pregnancy or breast-feeding; creatinine clearance of less than 10 ml per minute; uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg); life expectancy of less than 3 months.

Footnotes

3 Characteristics of included studies: Outcomes

Study	Intervention	Comparison	Primary efficacy outcome	Primary harm outcome	Time points measured of outcomes
EQUINOX	Idrabiotaparinux: 3.0 mg once a week during 6 months	Idraparinux: 2.5 mg once a week during 6 months	Symptomatic recurrent venous thromboembolism	Clinically relevant bleeding	6 and 9 months
MATISSE-DVT	(1) Fondaparinux: 5.0 mg (weight <50 kg) or 7.5 mg (50 kg> weight <100 kg) or 10 mg (weight >100 kg) once-daily during 5 days; (2) vitamin K antagonists started within 72 hours and continued until 3 months	(1) Enoxaparin: 1 mg/kg twice-daily during 5 days; (2) vitamin K antagonists started within 72 hours and continued until 3 months	Symptomatic recurrent venous thromboembolism	Bleeding	3 months
PERSIST Trial	(1) 5 to 7 days of enoxaparin (1 mg kg−1); (2) Idraparinux: 2.5 mg, 5 mg, 7.5 mg or 10 mg once a week without weight adjustment continued for 3 months	(1) 5 to 7 days of enoxaparin (1 mg kg−1); (2) Warfarin target to a INR rate between 2.0 to 3.0 continued for 3 months	Symptomatic recurrent venous thromboembolism	Major bleeding	3 months
The Rembrandt Trial	(1) Fondaparinux: 5.0 mg, 7.5 mg, or 10 mg once-daily without weigh adjustment during ±5 days; (2) vitamin K antagonists started on day 1 or 2 and continued for ±90 days	(1) Dalteparin: 100IU/kg twice-daily during ±5 days; (2) vitamin K antagonists started on day 1 or 2 and continued for ±90 days	Symptomatic recurrent venous thromboembolism	Major bleeding	3 months

The Van Gogh Trial-DVT	Idraparinux: 2.5 mg once a week during 3 or 6 months, as assessed by the treating physician	(1) Tinzaparin, enoxaparin, or intravenous Heparin: dose adjusted for the activated partial-thromboplastin time (ratio, 1.5 to 2.5); (2) Warfarin or Acenocoumarol started within 24 and target to INR 2.0 to 3.0 during 3 or 6 months, as assessed by the treating physician	Symptomatic recurrent venous thromboembolism	Clinically relevant bleeding and All cause mortality	3 or 6 months

Footnotes

4 Relative risks of the ten most frequent harmful effects during the initial treatment with fondaparinux versus the low molecular heparin, enoxaparin.

Harmful effect, n (%)	Fondaparinux (n=1091)	Enoxaparin (n=1101)	Relative Risk (95% CI)
Nausea	27 (2.5)	29 (2.6)	0.94 (CI 0.56 to 1.58)
Constipation	21 (1.9)	32 (2.9)	0.66 (0.38 to 1.14)
Diarrhoea	15 (1.4)	22 (2.0)	0.69 (0.36 to 1.32)
Vomiting	13 (1.2)	14 (1.3)	0.94 (0.44 to 1.98)
Bruise	9 (0.8)	24 (2.2)	0.38 (0.18 to 0.81)
Hematoma	13 (1.2)	17 (1.5)	0.77 (0.38 to 1.58)
Fever	25 (2.3)	32 (2.9)	0.79 (0.47 to 1.32)
Hepatic enzymes increased	4 (0.4)	52 (4.7)	0.08 (0.03 to 0.21)
SGPT increased	2 (0.2)	47 (4.3)	0.04 (0.01 to 0.18)
SGOT Increased	1 (0.1)	31 (2.8)	0.03 (0.00 to 0.24)
Headache	35 (3.2)	37 (3.4)	0.95 (0.61 to 1.50)
Coughing	14 (1.3)	7 (0.6)	2.02 (0.82 to 4.98)
Pneumonia	13 (1.2)	5 (0.5)	2.62 (0.94 to 7.33)
Insomnia	25 (2.3)	19 (1.7)	1.33 (0.74 to 2.40)
Urinary tract infection	23 (2.1)	29 (1.8)	0.80 (0.47 to 1.37)

Footnotes

CI: confidence interval, SGPT: serum glutamic pyruvic transaminase, SGOT: serum glutamic oxaloacetic transaminase

5 Relative risks of harmful effects induced by idrabiotaparinux versus idraparinux

Harmful effects, n (%)	Idrabiotaparinux (n = 385)	Idraparinux (n = 370)	Relative Risk (95% CI)
All	223 (57.9)	227 (61.4)	0.94 (0.84 to 1.06)
Infections and infestations	68 (17.7)	83 (22.4)	0.79 (0.59 to 1.05)
Nasopharyngitis	12 (3.1)	7 (1.9)	1.65 (0.66 to 4.14)
Urinary tract infection	8 (2.1)	8 (2.2)	0.96 (0.36 to 2.53)
Bronchitis	7 (1.8)	10 (2.7)	0.67 (0.26 to 1.75)
Influenza	6 (1.6)	8 (2.2)	0.72 (0.25 to 2.06)
Musculoskeletal and connective tissue disorders	49 (12.7)	44 (11.9)	1.07 (0.73 to 1.57)
Pain in extremity	14 (3.6)	10 (2.7)	1.35 (0.61 to 2.99)
Arthralgia	8 (2.1)	10 (2.7)	0.77 (0.31 to 1.93)
Gastrointestinal disorders	40 (10.4)	48 (13.0)	0.80 (0.54 to 1.19)
Diarrhoea	9 (2.3)	8 (2.2)	1.08 (0.42 to 2.77)
Vascular disorders	40 (10.4)	35 (9.5)	1.10 (0.71 to 1.69)
Hematoma	15 (3.9)	20 (5.4)	0.72 (0.37 to 1.39)
Hypertension	9 (2.3)	8 (2.2)	0.80 (0.54 to 1.19)
Injury, poisoning and procedural complications	38 (9.9)	44 (11.9)	0.83 (0.55 to 1.25)
Accidental overdose*	21 (5.5)	13 (3.5)	1.55 (0.79 to 3.05)
Fall	5 (1.3)	12 (3.2)	0.40 (0.14 to 1.13)
Nervous system disorders	38 (9.9)	32 (8.6)	1.14 (0.73 to 1.79)
Headache	19 (4.9)	15 (4.1)	1.22 (0.63 to 2.36)
General disorders and administration site conditions	34 (8.8)	42 (11.4)	0.78 (0.51 to 1.19)
Edema peripheral	7 (1.8)	13 (3.5)	0.52 (0.21 to 1.28)

Respiratory, thoracic and mediastinal disorders	32 (8.3)	29 (7.8)	1.06 (0.66 to 1.72)
Epistaxis	12 (3.1)	7 (1.9)	1.65 (0.66 to 4.14)

Footnotes

*Overdose is defined as ‡ 2 injections of study drug in £ 5 days.

CI: confidence interval.

6 Relative risks of harmful effects induced by idraparinux versus standard therapy

Adverse effects (n.%)	Idraparinux (n=1452)	Standard Therapy (n=1452)	Relative Risk (95% CI)
Cancer	97 (6.68)	91 (6.27)	1.07 (0.81 to 1.41)
Cardiac failure	6 (0.41)	18 (1.24)	0.33 (0.13 to 0.84)
Rash, dermatites or urticaria	62 (4.27)	46 (3.17)	1.35 (0.93 to 1.96)
Infection	262 (18.0)	295 (20.31)	0.89 (0.76 to 1.03)
Other event	778 (53.58)	754 (51.92)	1.03 (0.96 to 1.11)

Footnotes

CI: confidence interval.

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Data and analyses

1 Fondaparinux versus LMWH

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Recurrent VTE during 3-months follow-up	2	2658	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.60, 1.29]
1.2 Bleeding [Initial Treatment]	2	2645	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.22]
1.3 Major bleeding [Initial Treatment]	2	2645	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.71, 1.98]
1.4 Clinically relevant Bleeding [Initial Treatment]	1	2192	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.68, 1.36]
1.5 Bleeding [3-months follow-up]	1	453	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.36, 1.01]
1.6 Major bleeding [3-months follow-up]	1	453	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.22, 3.16]
1.7 All-cause mortality during 3-months follow-up	2	2645	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.72, 1.57]
1.8 Recurrent DVT during 3-months follow-up	1	2205	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.16]
1.9 Pulmonary embolism during 3-months follow-up	2	2658	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.83, 2.50]
1.10 Harmful effects leading to premature discontinuation	1	2205	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.40, 1.32]
1.11 All harmful effects	1	2205	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.54, 0.70]
1.12 Recurrent VTE during 3-months follow-up [Body weight]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.12.1 Recurrent VTE during 3-months follow-up [Body weight <50 Kg]	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.33]
1.12.2 Recurrent VTE	1	1922	Risk Ratio (M-H, Fixed,	0.97 [0.63, 1.51]

during 3-months follow-up [Body weight 50-100 Kg]			95% CI)	
1.12.3 Recurrent VTE during 3-months follow-up [Body weight >100 Kg]	1	228	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.37, 6.24]
1.13 Recurrent VTE during 3-months follow-up [Ambulatory patients]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.13.1 Recurrent VTE during 3-months follow-up [Ambulatory patients]	1	719	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.70, 1.53]
1.14 Bleeding [Initial Treatment] [Ambulatory Patients]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.14.1 Bleeding [Initial treatment]	1	1909	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.42, 2.12]
1.15 Major bleeding [Initial treatment] [Ambulatory patients]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.15.1 Major bleeding [Initial treatment] [Ambulatory patients]	1	719	Risk Ratio (M-H, Fixed, 95% CI)	4.70 [1.35, 16.34]
1.17 Recurrent VTE during 3-months follow-up [Patients with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.17.1 Recurrent VTE during 3-months follow-up [Patients with active cancer]	1	237	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.95, 5.79]
1.18 Major bleeding [3-Months follow-up] [Patients with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.18.1 Major bleeding [3-months follow-up] [Patients with active canc	1	237	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.40, 2.48]

1.19 Clinically relevant Bleeding [3-months follow-up] [Patients with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.19.1 Clinically relevant Bleeding [3-months follow-up] [Patients with active cancer]	1	237	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.54, 2.25]

2 Idrabiotaprinux versus Idraparinux

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Recurrent VTE after 6-months follow-up	1	741	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.30, 1.66]
2.2 Recurrent VTE after 9-months follow-up	1	700	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.83, 2.79]
2.3 Bleeding after 6-months follow-up	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.49, 1.04]
2.4 Major bleeding after 6-months follow-up	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.06, 0.71]
2.5 Clinically relevant bleeding after 6-months follow-up	1	755	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.38, 1.26]
2.6 Major bleeding after 9-months follow-up	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.11, 3.81]
2.7 Clinically relevant bleeding after 9-months follow-up	1	755	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [0.58, 8.61]
2.8 All-cause mortality after 6-months follow-up	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.18, 1.27]
2.9 All-cause mortality after 9-months follow-up	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.25, 2.60]
2.10 Recurrent DVT after 6-months follow-up	1	741	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.14, 2.36]
2.11 Pulmonary embolism after 6-months	1	741	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.27, 2.39]

follow-up				
2.12 Harmful effects leading to premature discontinuation	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.25]
2.13 All harmful effects	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.02]

3 LMWH and idraparinux versus LMWH and warfarin

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Recurrent VTE [Idraparinux 10 mg]	1	263	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.26, 8.90]
3.2 Bleeding [Idraparinux 2.5 mg]	1	263	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.80]
3.3 Bleeding [Idraparinux 5.0 mg]	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.83, 3.02]
3.4 Bleeding [Idraparinux 7.5 mg]	1	264	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.80, 2.96]
3.5 Bleeding [Idraparinux 10 mg]	1	263	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [1.27, 4.26]
3.6 Bleeding [All doses]	1	659	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.82, 2.49]
3.7 Major bleeding [All doses]	1	659	Risk Ratio (M-H, Fixed, 95% CI)	3.76 [0.50, 28.19]

4 Idraparinux versus Standard therapy

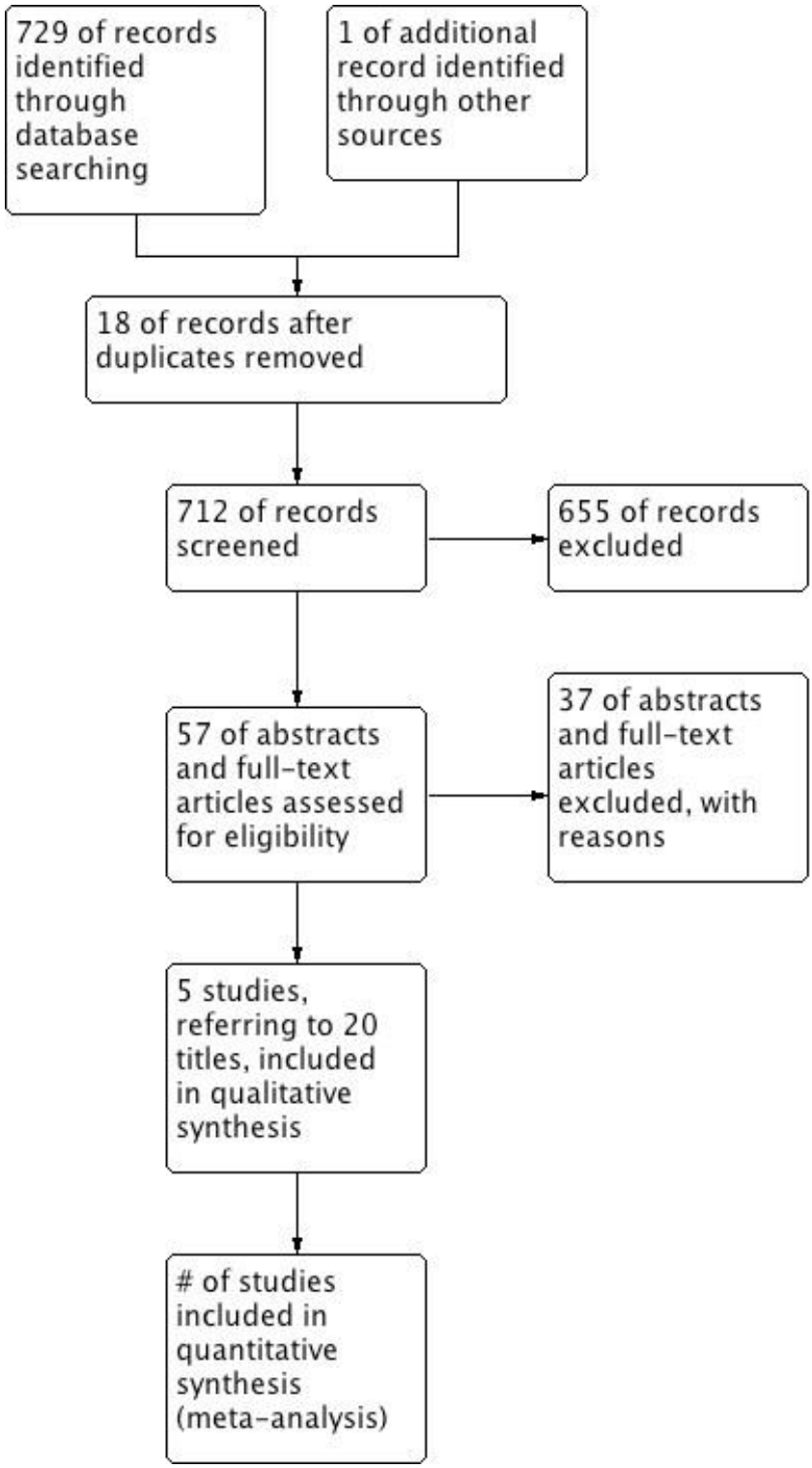
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Recurrent VTE during 3-months follow-up	1	637	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.21, 2.91]
4.2 Recurrent VTE during 6-months follow-up	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.66, 1.53]
4.3 Bleeding, 3-months follow-up	1	637	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.24, 0.87]
4.4 Bleeding, 6-months	1	2267	Risk Ratio (M-H, Fixed,	0.92 [0.69, 1.22]

follow-up			95% CI)	
4.5 Major bleeding, 3-months follow-up	1	637	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 2.01]
4.6 Major bleeding, 6-months follow-up	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.66, 2.34]
4.7 Clinically relevant bleeding, 3-months follow-up	1	637	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.95]
4.8 Clinically relevant bleeding, 6-months follow-up	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.34]
4.9 All-cause mortality during 3-months follow-up	1	637	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.70, 1.80]
4.10 All-cause mortality during 6-months follow-up	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.85, 1.85]
4.11 Recurrent DVT during 3-months follow-up	1	637	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.04, 5.40]
4.12 Recurrent DVT during 6-months follow-up	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.50, 2.00]
4.13 Recurrent PE during 3-months follow-up	1	637	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.20, 4.84]
4.14 Recurrent PE during 6-months follow-up	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.56, 1.80]
4.15 Harmful effects leading to premature discontinuation	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.17, 2.14]
4.16 All harmful effects	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [1.00, 1.06]
4.17 Recurrent VTE [Patients with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.17.1 Recurrent VTE during 3-months follow-	1	284	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.17, 1.35]

follow up				
4.17.2 Recurrent VTE during 6-months follow-up	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.16, 1.32]
4.18 Clinically relevant bleeding [Patients with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.18.1 Bleeding, 3-months follow-up	1	284	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.22, 1.02]
4.18.2 Bleeding, 6-months follow-up	1	270	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.65, 2.99]
4.20 Major bleeding [Patients with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.20.1 Major bleeding, 3-months follow-up	1	284	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.24, 8.36]
4.20.2 Major bleeding, 6-months follow-up	1	270	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.35, 3.56]

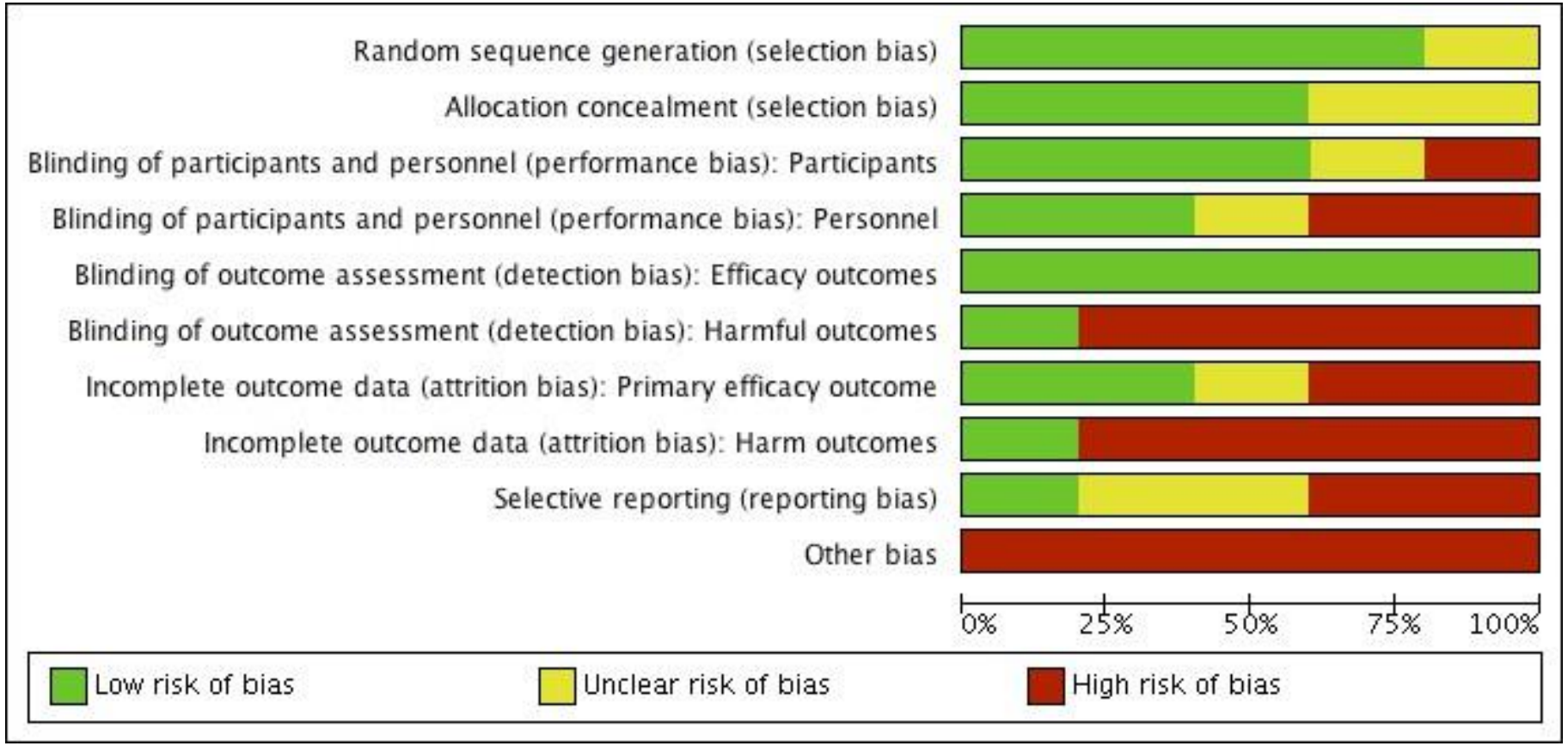
Figures

Figure 1



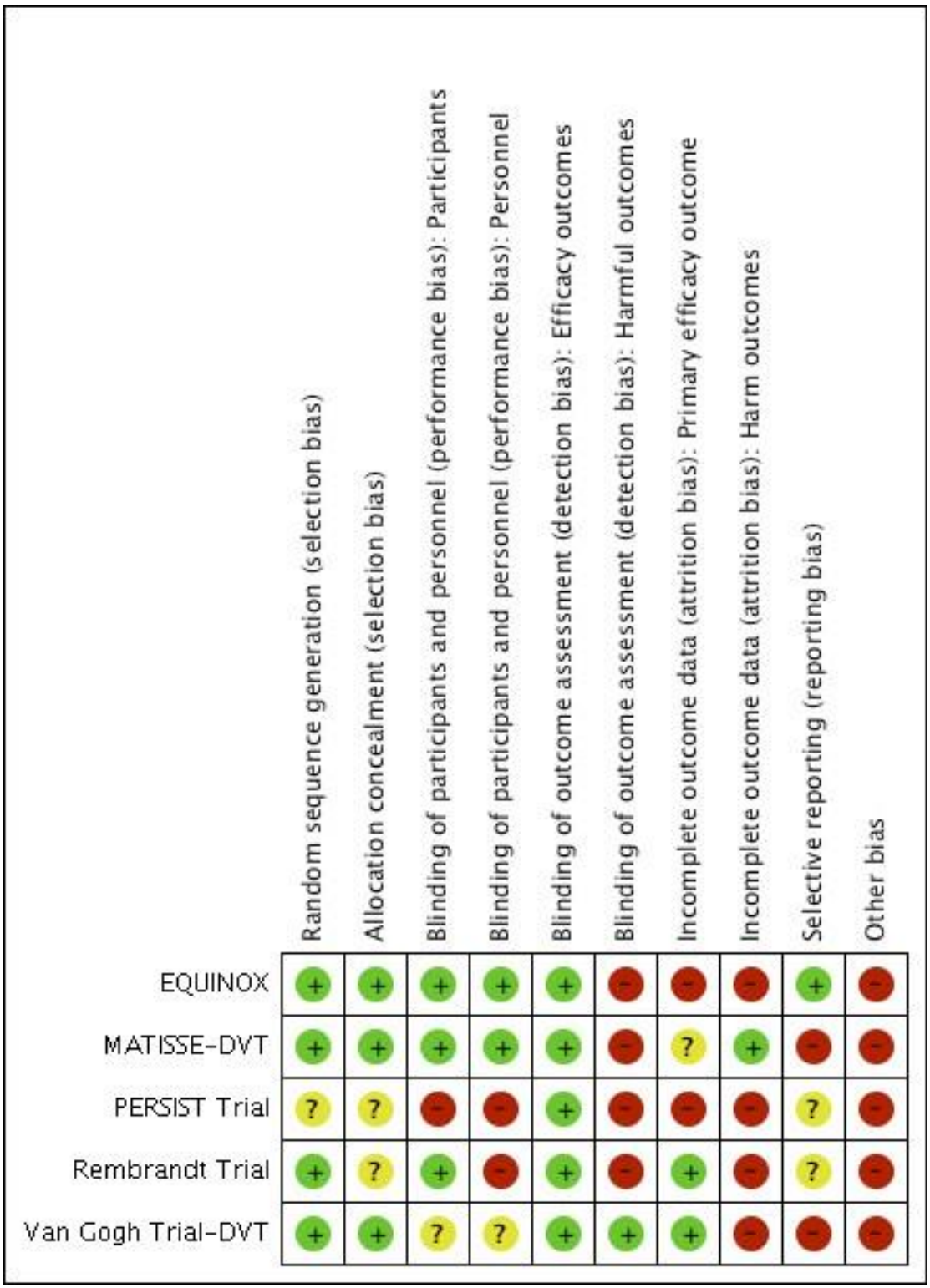
Study flow diagram.

Figure 2



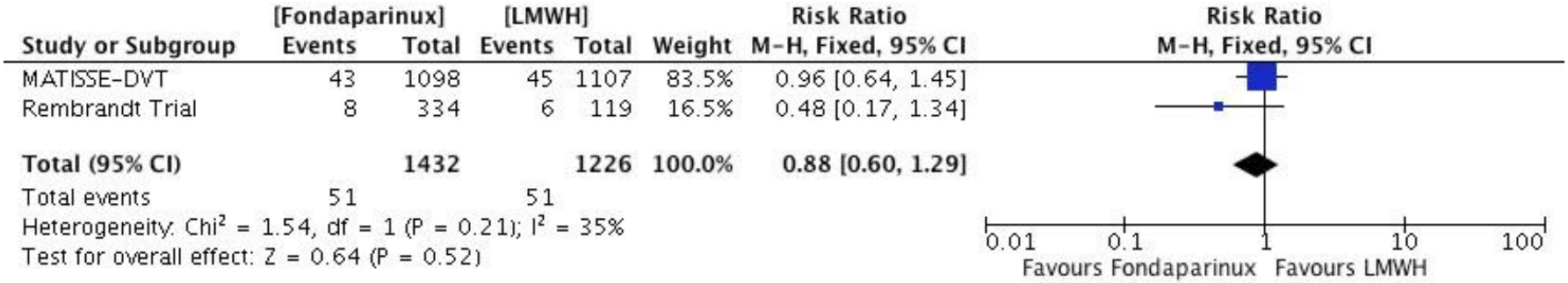
Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3



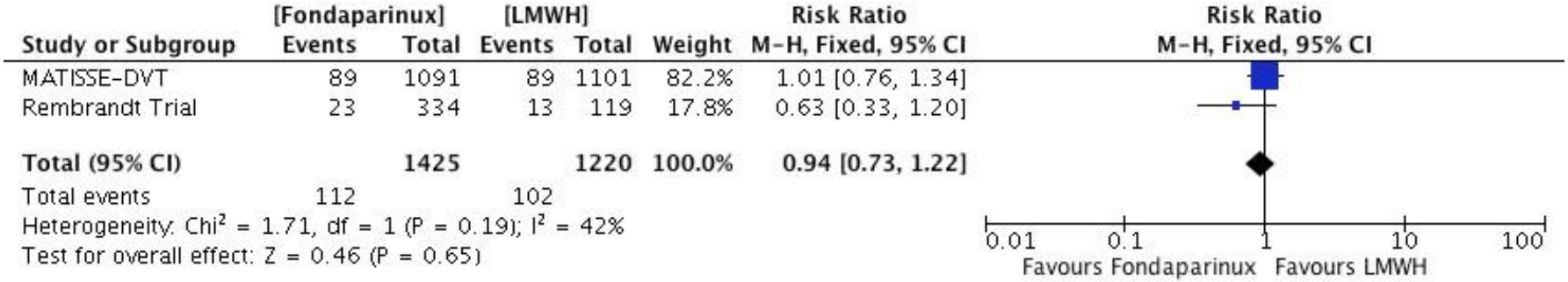
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 4 (Analysis 1.1)



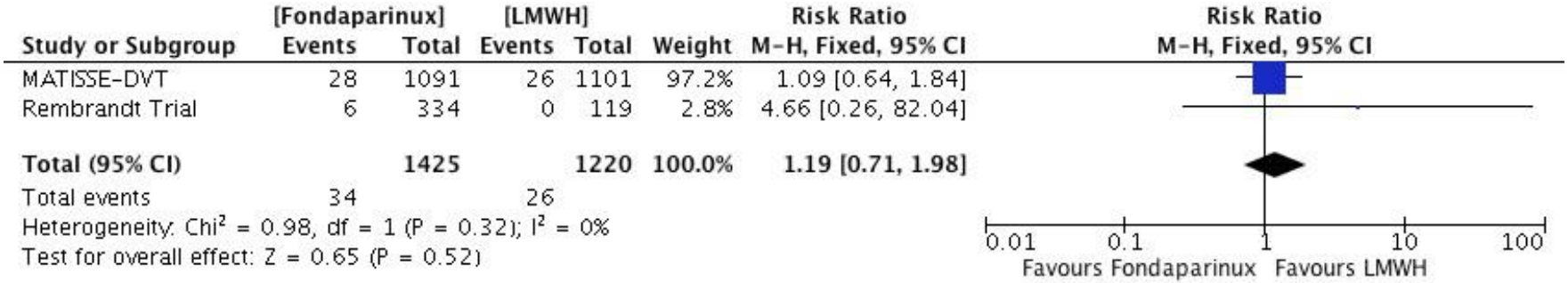
Forest plot of comparison: 1 Fondaparinux versus LMWH, outcome: 1.1 Recurrent VTE during 3-months follow-up.

Figure 5 (Analysis 1.2)



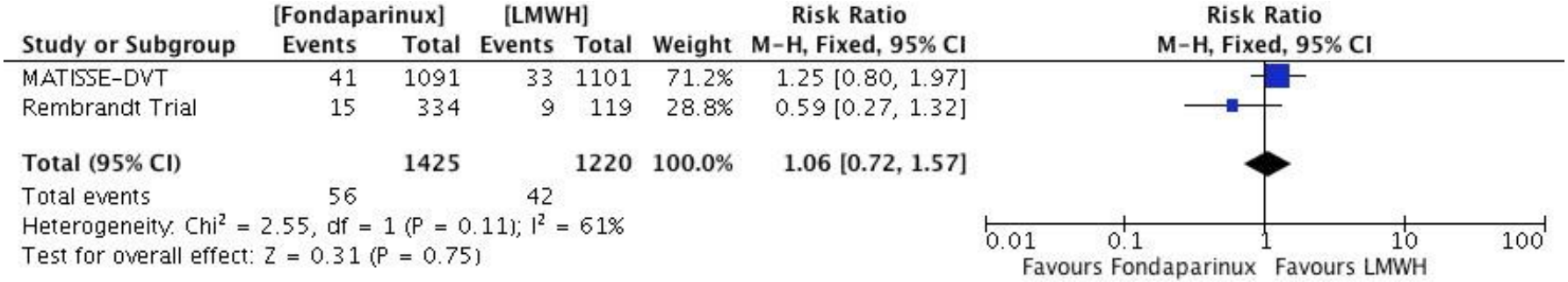
Forest plot of comparison: 1 Fondaparinux versus LMWH, outcome: 1.2 Bleeding [Initial Treatment].

Figure 6 (Analysis 1.3)



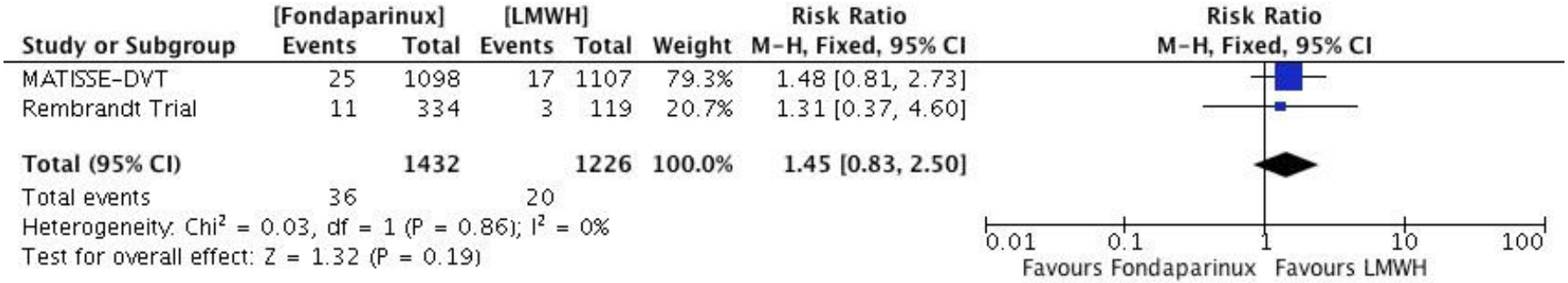
Forest plot of comparison: 1 Fondaparinux versus LMWH, outcome: 1.3 Major bleeding [Initial Treatment].

Figure 7 (Analysis 1.7)



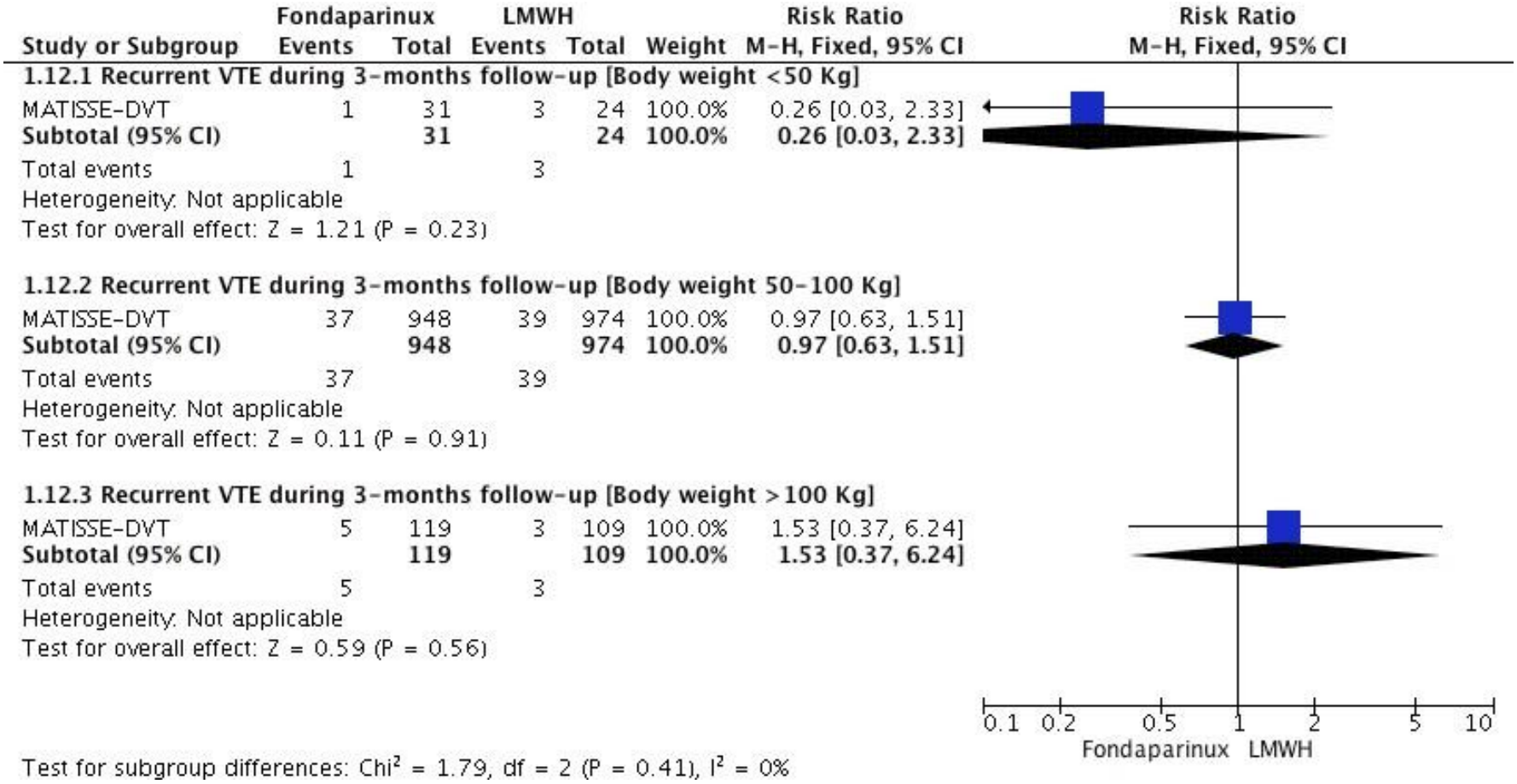
Forest plot of comparison: 1 Fondaparinux versus LMWH, outcome: 1.7 All-cause mortality during 3-months follow-up.

Figure 8 (Analysis 1.9)



Forest plot of comparison: 1 Fondaparinux versus LMWH, outcome: 1.9 Pulmonary embolism during 3-months follow-up.

Figure 9 (Analysis 1.12)



Forest plot of comparison: 1 Fondaparinux versus LMWH, outcome: 1.12 Recurrent VTE during 3-months follow-up [Body weight].

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Internal sources

- No sources of support provided

External sources

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Appendices

1 CENTRAL search strategy

#1 MeSH descriptor: [Thrombosis] this term only		1304
#2	MeSH descriptor: [Thromboembolism] this term only	1067
#3	MeSH descriptor: [Venous Thromboembolism] this term only	454
#4	MeSH descriptor: [Venous Thrombosis] explode all trees	2326
#5 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw		16405
#6 MeSH descriptor: [Pulmonary Embolism] explode all trees		936
#7 PE or DVT or VTE:ti,ab,kw		3909
#8 ((vein* or ven*) near thromb*):ti,ab,kw		6681
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8		19453
#10 MeSH descriptor: [Anticoagulants] this term only		3859
#11MeSH descriptor: [Polysaccharides] this term only and with qualifier(s): [Therapeutic use - TU]		169
#12 fondapar* or Arixtra		337
#13 Sanorg-34006 or Sanorg34006		7
#14 SSR-126517* or SSR126517*		9
#15 pentasac* in Trials		42
#16 MeSH descriptor: [Factor X] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI]		236
#17 Factor X* near/4 (antag* or inhib* or block*)		3817
#18 FX* near/4 (antag* or inhib* or block*)		56
#19 Factor 10* near/4 (antag* or inhib* or block*)		10839
#20 *arinux		376
#21 ORG31540*		19
#22 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21		15001
#23 #9 and #22 in Trials (Word variations have been searched)		2279