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Evaluation qualitative et quantitative du phénomène de réplification des méta-analyses : Illustration avec les anticoagulants oraux directs dans le traitement des thromboses

Céline Chapelle

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N° d'ordre NNT : 2023STET045

THÈSE DE DOCTORAT
DE L'UNIVERSITÉ JEAN MONNET SAINT-ÉTIENNE
Membre de l'Université de LYON

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Spécialité de doctorat : Recherche clinique

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Céline CHAPELLE

**ÉVALUATION QUALITATIVE ET QUANTITATIVE DU PHÉNOMÈNE
DE RÉPLICATION DES MÉTA-ANALYSES
ILLUSTRATION AVEC LES ANTICOAGULANTS ORAUX DIRECTS DANS LE
TRAITEMENT DES THROMBOSES**

Devant le jury composé de :

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Co-directeur de thèse

Avant-propos

Cette thèse a été préparée au sein du laboratoire INSERM U1059 SAINBIOSE (Santé Ingénierie BIOlogie Saint-Étienne), dans l'équipe Dysfonctions Vasculaires et de l'Hémostase (DVH) dirigée par le Pr Patrick Mismetti puis le Pr Stéphane Avril.

Ce travail a été réalisé sous la direction du Pr Silvy Laporte, responsable du Service de Pharmacologie Clinique du CHU de Saint-Étienne et co-directrice de l'équipe DVH. Il a été co-dirigé par le Dr Edouard Ollier (UMR INSERM 1059). Cette thèse s'est déroulée pendant 3 ans (2020-2023).

Ce travail a été réalisé en parallèle de mon travail de biostatisticienne à temps plein au sein du Service de Pharmacologie Clinique du CHU de Saint-Étienne.

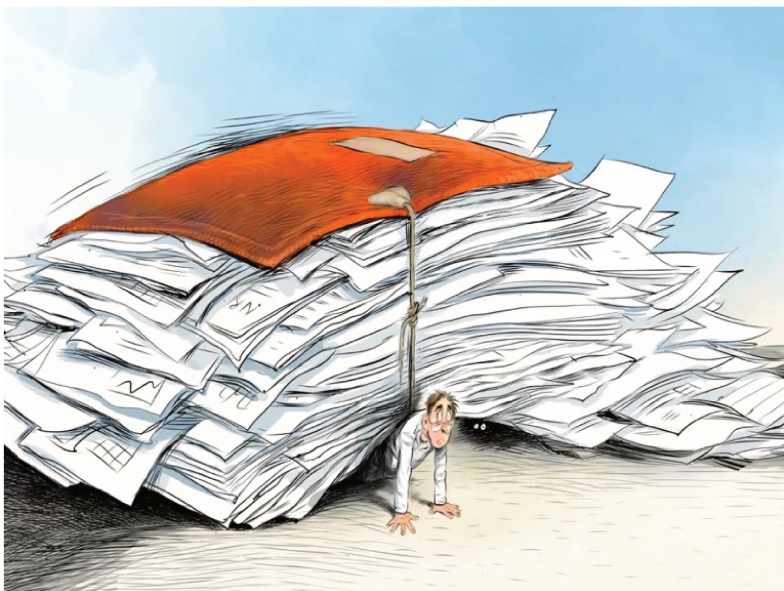


Illustration de David Parkins

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Liste des publications scientifiques

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Abréviations

ANR	Agence Nationale de la Recherche
AOD	Anticoagulants Oraux Directs
DVH	Dysfonctions Vasculaires et de l'Hémostase
EPICLIN.....	Conférence francophone d'EPIdémiologie CLINique
ETEVE.....	Événements ThromboEmboliques veineux
F-CRIN.....	French Clinical Research Infrastructure Network
HBPM.....	Héparines de Bas Poids Moléculaires
HR	Hazard Ratio
MTEV.....	Maladie ThromboEmbolique Veineuse
OR	Odds Ratio
RECaP	Réseau national de Recherche en Epidémiologie Clinique et en Santé Publique
RoB.....	Risk of Bias
ROBIS	Risk of Bias in Systematic reviews
RR.....	Risque Relatif
SAINBIOSE	SANté Ingénierie BIOlogie Saint-Étienne
SIGAPS	Système d'Interrogation, de Gestion et d'Analyse des Publications Scientifiques
SIS	Sciences Ingénierie Santé
VoE.....	Vibration of effects
PICO.....	Population, Intervention, Comparateur, Outcome

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1. Introduction

1.1. Publication scientifique

1.1.1. La communication scientifique comme devoir du chercheur

La communication scientifique se fait aujourd'hui principalement sous deux formes : écrite et orale. L'écrit scientifique se matérialise par des publications d'articles ou de livres alors que la communication orale scientifique se pratique essentiellement lors de conférences scientifiques en présence d'experts du domaine. Le point commun de ces deux formes est qu'elles sont soumises à une évaluation préalable par les pairs.

La communication scientifique fait partie intégrante du « devoir » du chercheur, à savoir faire avancer l'état de la connaissance et partager ses découvertes. Celle-ci est indispensable aux chercheurs pour la diffusion des résultats de leurs travaux de recherche et permettre l'avancée de la recherche. La publication d'articles scientifiques permet aux chercheurs de mettre en valeur leurs travaux et leur expertise, et d'obtenir la reconnaissance de leurs pairs dans un ou plusieurs domaines de recherche. Une publication de la recherche attire ainsi l'attention sur les chercheurs et leurs institutions, le nombre de publications d'un chercheur étant fréquemment utilisé comme mesure de son niveau de compétence, entraînant une grande pression pour publier.

1.1.2. « Publish or perish »

Apparue dans les années 1930, l'expression « publish or perish » (publier ou périr) prend tout son sens dans les années 1980 avec l'instauration de mesures purement quantitatives de la « productivité » du chercheur par son nombre de publications (Figure 1). Cette expression a alors pour but de dénoncer la pression exercée sur les chercheurs à travers l'obligation,

notamment pour avancer dans sa carrière, de publier les résultats de ses travaux de recherche dans des revues scientifiques. Publier est un enjeu majeur pour les chercheurs au cours de leurs carrières pour 1) faire connaître leurs travaux ; 2) être reconnus par leurs pairs et les experts du domaine ; 3) obtenir des financements ; 4) progresser dans leur carrière.

En France, les chercheurs en médecine sont principalement « notés » en fonction de leur production scientifique via les points SIGAPS. Ces points (de 1 à 32) sont attribués aux auteurs d'un article après la publication, et dépendent de la qualité de la revue dans laquelle ils publient et de leur rang parmi les auteurs. Ces points sont ensuite transformés en une somme d'argent perçue pendant 4 ans par l'établissement de santé auquel les auteurs sont rattachés. En 2020, la valeur du point SIGAPS était d'environ 750€. Mais cette « rémunération », même indirecte, ne pousse-t-elle pas trop souvent les chercheurs à publier beaucoup en terme quantitatif, de façon plus rapide, à tout prix, quelle que soit la qualité de la recherche ? Les publications d'opinion d'experts peuvent être privilégiées au détriment des publications de travaux originaux et envahissent la littérature sans apporter de connaissance nouvelle.

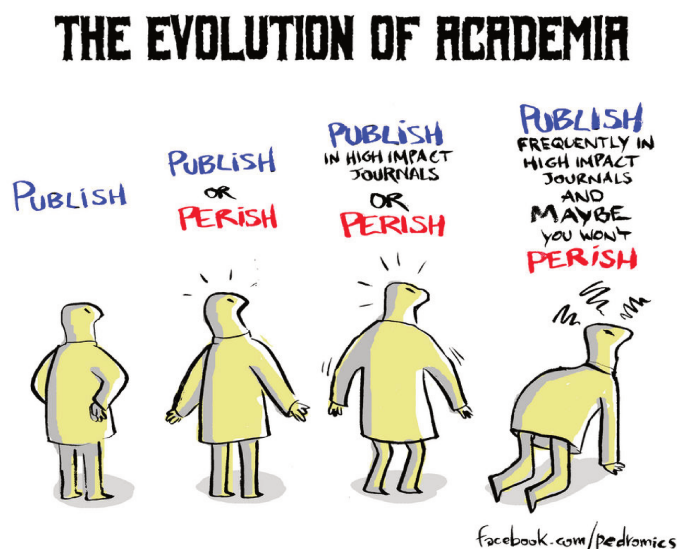


Figure 1. Illustration de l'adage « Publish or Perish ». Par Pedro Veliça (alias Pedromics).

1.2. Envahissement et conséquences de la production de masse

1.2.1. Envahissement des publications scientifiques

Depuis de nombreuses années, le développement de nombreuses molécules et stratégies a généré une forte augmentation du nombre d'essais thérapeutiques et d'études observationnelles. Le nombre de publications scientifiques ne cesse d'augmenter tous les ans. En effet, si nous ne nous intéressons qu'aux articles publiés et référencés dans PubMed quel que soit le domaine médical, on est passé de plus de 532,000 sur l'année 2000 à un peu plus de 942,000 en 2010, soit une augmentation de 77%. Et ce nombre ne cesse d'augmenter puisque sur l'année 2020, le nombre de publications référencées dans PubMed s'élevait à 1,638,000, pour atteindre au total plus de 35 millions d'articles référencés dans ce seul outil (Figure 2).

Même si le nombre important de publications scientifiques montre que la recherche est florissante, cette multiplication d'articles scientifiques pose questions notamment en termes d'intérêt scientifique et d'intégrité. À la lecture d'un article scientifique rapportant les résultats d'un essai clinique ou d'une étude observationnelle, il est important de se poser les questions suivantes : l'étude publiée apporte-t-elle de nouvelles connaissances à la science ? Est-elle fiable ? La recherche a-t-elle été menée de manière transparente, juste et objective ? L'ensemble des acteurs de la recherche ont-ils été respectés de manière égale ? Ces questions sont fondamentales car les essais de mauvaise qualité méthodologique n'apportent finalement pas de réponse fiable et représentent un gaspillage de ressources de recherche (2–4). Cette course à la publication peut entraîner une propagation rapide d'informations pas toujours exactes (on parle d'infodémie) et une production de masse d'essais de mauvaise qualité méthodologique. Dans cette masse d'information, il n'est pas toujours facile de trouver et sélectionner les résultats utiles issus d'études fiables et pertinentes qui sont noyés parmi de nombreux autres sans intérêt.

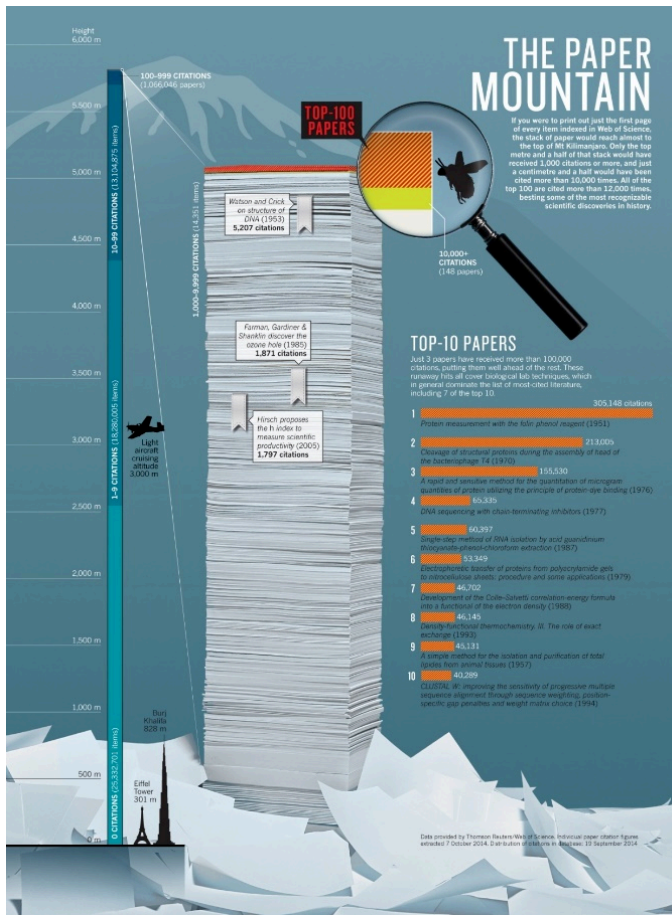


Figure 2. Illustration de Kyle Bean. Issue de la publication de Van Noorden et al. (5).

Ainsi, depuis une quinzaine d'années, des pratiques contraires à un certain nombre de principes de base émergent, notamment la multiplication des publications sur un même sujet de recherche, plagiats ou encore fraudes (6). En psychologie par exemple, il n'est pas rare de trouver de multiples présentations traitant du même sujet mais qui sont présentées sous des titres différents dont les noms des auteurs ont été inversés, ou de multiples publications traitant du même sujet qui n'apportent rien de nouveau à la science (7). L'épidémie de COVID-19 n'a pas échappé à ce « rush à la publication » avec pas moins de 200,000 articles en lien avec la COVID-19 publiés depuis le début de la pandémie. Néanmoins, plus d'une centaine d'articles ont été rétractés après avoir été publiés dans des revues scientifiques pour causes, entre autres, de plagiat ou de données douteuses (8). Malgré tout, certaines de ces publications continuent

d'être citées. De la même façon, un chercheur chinois aurait publié pas moins de 284 publications en 2020 et 2021 sur la COVID-19, publications qui seraient sans grand intérêt (9). Ces dérives, observées dans de nombreux domaines, sont probablement liées à la pression du « publish or perish » et entraînent une multiplication des publications scientifiques.

1.2.2. Conséquences de la production de masse

Alors que la recherche scientifique devrait suivre un raisonnement hypothético-déductif (générer une hypothèse, concevoir l'étude et la réaliser, collecter les données puis les analyser, et tester l'hypothèse, interpréter les résultats, communiquer puis reformuler une nouvelle question si besoin), on observe aujourd'hui une distorsion de la connaissance scientifique (10,11). Ces distorsions peuvent survenir à chaque niveau du raisonnement hypothético-déductif.

1/ Lors de la génération d'une hypothèse

Pour générer une hypothèse, il faut se baser sur l'ensemble de la littérature. Si une hypothèse a déjà été bien documentée dans la littérature, notamment avec des revues systématiques et méta-analyses, il n'y aura pas d'intérêt scientifique à tester de nouveau cette hypothèse.

2/ Lors de la conception de l'étude

Pour concevoir une étude, il faut calculer un nombre de sujets nécessaires pour répondre à la question posée. Dans le cas d'un événement rare, il faudra beaucoup de sujets pour pouvoir mettre en évidence une différence. Néanmoins, si l'étude est trop petite, on peut manquer de puissance et ne pas arriver à mettre en évidence la différence que l'on veut montrer.

3/ Lors de la réalisation de l'étude

Lors de la réalisation de l'étude, il peut y avoir une insuffisance des contrôles qualité entraînant une mauvaise qualité des données. Cette insuffisance des contrôles qualité sont identifiables dans les publications, avec par exemple une homogénéité des distributions des variables quantitatives ou encore des erreurs de saisie (12–15). Au final, ces essais de mauvaise qualité méthodologique n'apportent pas de réponse fiable, représentent un gaspillage des ressources de recherche (16) et risque de faire adopter à tort des traitements n'apportant pas le bénéfice prétendu. Ces essais de mauvaise qualité méthodologique sont dangereux et non éthiques (2,17–19).

4/ Lors de l'analyse des données

Lors de l'analyse des données, on va retrouver des dérives en lien avec la génération de l'hypothèse et la conception de l'étude.

Souvent face à l'échec de mise en évidence de l'hypothèse initiale, les chercheurs sont tentés d'aller poser des questions nouvelles dans la base de données et de refaire des tests statistiques.

Il s'agit de p-hacking.

Le p-hacking est un terme utilisé pour décrire les techniques utilisées pour augmenter les chances de trouver un résultat statistiquement significatif, notamment une adaptation de l'analyse en cours de réalisation en fonction des résultats qu'elle produit (20–23). L'adaptation de l'analyse peut concerner la méthode statistique mise en œuvre (par exemple le choix de la méthode ou des covariables), mais aussi le jeu de données (par exemple exclusion de patients avec des données extrêmes). Dans tous les cas, le p-hacking entraîne des résultats faux positifs (24–26) (Figure 3).

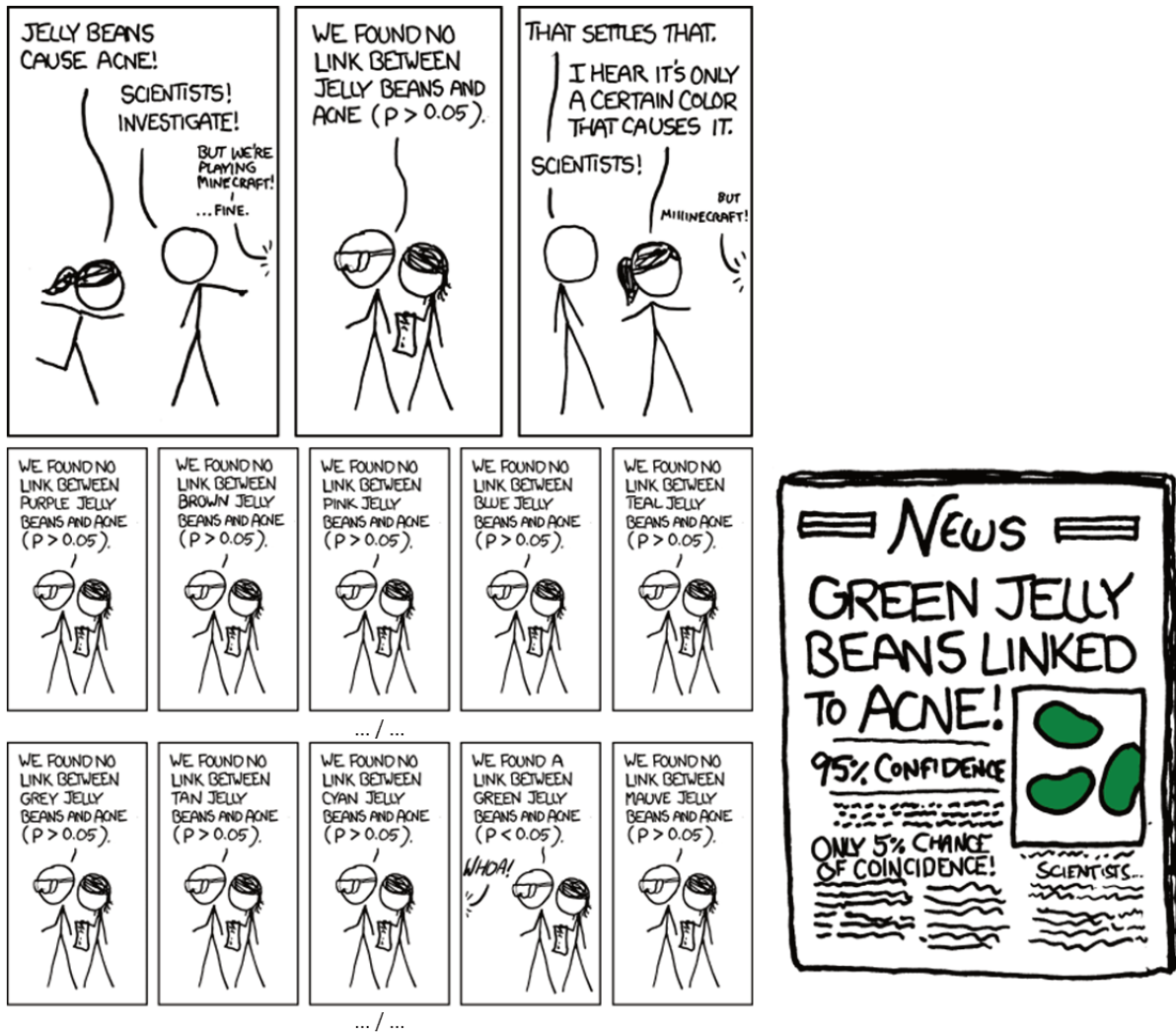


Figure 3. Extrait d'une illustration d'un exemple de p-hacking. Cette figure est tirée et adaptée de xkcd webcomic, sous licence CC-BY-NC 2.5 (27).

Ce phénomène de p-hacking est souvent illustré par le concept de vibration des effets (VoE en anglais). Ce concept de vibration des effets décrit la mesure dans laquelle une association estimée peut varier en fonction des approches analytiques utilisées (28). Il peut arriver que cette variation des résultats entraîne des résultats opposés alors même qu'ils sont obtenus à partir des mêmes données (connu sous le nom de « effet Janus »).

Avec le p-hacking, on peut parfois trouver des résultats statistiquement significatifs que l'on cherche à expliquer. Mais quand on cherche à expliquer des résultats que l'on a trouvés alors qu'on ne les cherchait pas, on fait du harking (Hypothesizing After the Results are Known). Le harking est un terme qui désigne le fait de choisir ses hypothèses en fonction des résultats obtenus (29). Cette pratique consiste à effectuer de nombreux tests à partir des données recueillies et à formuler a posteriori des hypothèses correspondant aux résultats significatifs dans l'échantillon. Comme le p-hacking, le harking entraîne des résultats faux positifs. Cette pratique a été observée par exemple en psychiatrie où un lien a été trouvé entre les tentatives de suicide et les moments de pleine lune (30–32).

La fraude scientifique est également une pratique émergente (33). Elle se présente sous trois formes : falsification des données, fabrication de celles-ci et plagiat.

La falsification (ou manipulation) des données consiste à altérer volontairement les données pour les rendre plus conformes aux hypothèses que l'on privilégie. Cette notion de falsification comprend : « La manipulation, la modification ou l'omission de données, de documents originaux, de méthodes ou de résultats, y compris les graphiques et les images, sans le mentionner, ce qui fausse les résultats ou les conclusions ». Par exemple, changer de critère de jugement au cours d'une étude, déclarer que l'essai est en double aveugle alors qu'il ne l'est pas, ou encore donner une conclusion non conforme aux données présentées.

La fabrication (ou fabulation) des données et résultats consiste à créer un essai sans aucune donnée réelle. C'est ce qu'on appelle les études « zombies ». Les résultats scientifiques de ces essais sont faux, biaisés, et peuvent fausser les autres recherches.

Enfin, le plagiat « consiste principalement en une appropriation frauduleuse de textes ou de résultats d'autrui. » (Rapport COMETS). Il se présente sous 4 formes : copie ou « vol » de textes (copie intégrale, paraphrase, patchwork, plagiat de traductions...), appropriation des

résultats de quelqu'un d'autre, vol d'idées et/ou de données, auto-plagiat (appelé aussi « salami slicing » qui consiste à découper un travail en plusieurs parties pour faire plusieurs articles, avec recopie de parties rédigées par soi-même).

Au-delà du gaspillage économique, les conséquences de la fraude peuvent être potentiellement graves sur la santé humaine. En effet, il n'est pas rare que des patients aient reçu un traitement sur la base d'études cliniques ultérieurement rétractées pour pratiques frauduleuses. C'est le cas par exemple de l'Ivermectine dans la COVID-19. Ce traitement, qui est à la base un antiparasitaire utilisé chez les animaux, a été présenté comme un nouveau traitement « miracle » contre la COVID-19 sur la base d'essais randomisés frauduleux. Un premier article en préprint (34) a finalement été rétracté pour risque potentiel de fabrication de données, plagiat et manquement à l'éthique (35). Une autre étude pose question sur la randomisation mise en œuvre (36). Aussi, les résultats des méta-analyses incluant ces essais frauduleux ne sont pas fiables et sont faux (37), notamment quand l'essai frauduleux représente plus de 10% de l'effet global (38,39).

5/ Lors de l'interprétation des résultats

Lors de l'interprétation des résultats, on peut être amené à sur-interpréter ou interpréter de manière erronée les résultats obtenus dans le but de véhiculer un message positif. Cette pratique se nomme « spin des conclusions » ou enjolivement des conclusions, et consiste à transformer un résultat négatif (essai non concluant) en conclusion positive (en faveur de l'intérêt du nouveau traitement) (40–52). Les conséquences des spins sont très graves. En effet, si le lecteur ne s'attarde par exemple que sur la conclusion de l'abstract, on peut lui faire croire que le nouveau traitement a un intérêt clinique alors qu'en réalité celui-ci n'est pas démontré.

6/ Lors de la communication des résultats

La dernière étape du raisonnement est de communiquer les résultats et de les publier. Pourtant, tous les résultats ne sont pas publiés. Il existe plusieurs dérives sur cette communication des résultats qui affectent soit la façon dont sont rapportés les résultats dans la publication de l'étude, soit l'étude entière.

Parmi les dérives qui affectent la façon dont sont rapportés les résultats, on peut distinguer le « selective reporting » et ce qui a été nommé l'effet chrysalide. Le « selective reporting » consiste à faire une publication sélective des analyses notamment en fonction de leur positivité (53–55). L'effet chrysalide ou embellissement des données, consiste à rapporter les résultats d'une étude sous une forme ne correspondant pas exactement à la réalité afin de les rendre plus favorables ou plus attractifs et à métamorphoser des résultats médiocres en beaux articles (56). L'embellissement des données peut être réalisée de manière involontaire mais aussi volontaire, la limite avec la fraude est difficile à déterminer et est floue (Figure 4) (57).

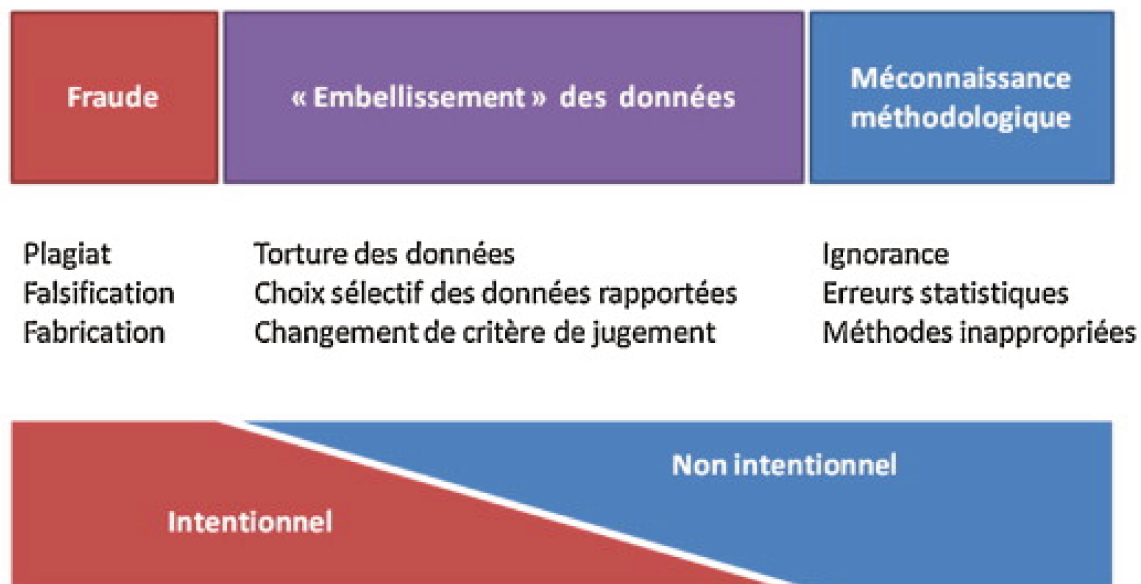


Figure 4. De l'embellissement des données à la fraude : un continuum à limites floues.

D'après Seror et al. (57).

La dérive qui affecte l'étude entière s'appelle le biais de publication. Celui-ci survient lorsque les travaux sont non publiés, la possibilité de publier ou non un essai étant dépendante de son résultat. En effet, les études dont les résultats sont statistiquement significatifs ont généralement plus de chances d'être publiées que les études ne montrant pas de différence significative (58). Ce biais, qui est toujours décrit dans les méta-analyses, peut fausser les conclusions si seuls les résultats publiés sont inclus dans la méta-analyse (59,60) et risque de surestimer l'effet traitement (61,62).

La détection du biais de publication est graphique, via funnel plot, représentant pour chaque études les estimations ponctuelles de l'effet traitement en fonction de la précision de l'estimation, c'est-à-dire la taille de l'étude (63–65). En l'absence de biais de publications, les estimations de l'effet traitement se répartissent de façon homogène (symétrique) autour de la valeur commune. Lorsque la répartition des estimations n'est plus homogène autour de cette valeur centrale et devient asymétrique, on peut suspecter la présence d'un possible biais de publication (Figure 5).

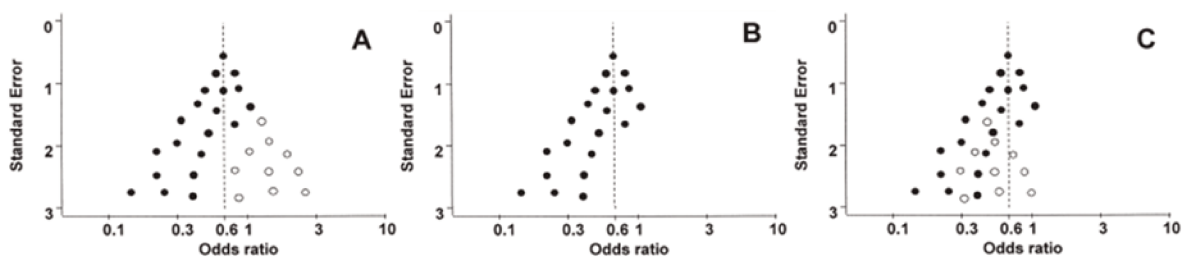


Figure 5. Exemple de funnel plot. (A) symétrique en l'absence de biais de publication (les cercles vides correspondent aux « petites » études ne montrant pas d'effets statistiquement significatifs) ; (B) asymétrique en présence d'un biais de publication (les « petites » études ne montrant pas d'effets statistiquement significatifs sont manquantes) ; (C) asymétrique en présence d'un biais dû à la faible qualité méthodologique des « petites » études (les cercles

vides indiquent les « petites » études de qualité insuffisante dont les résultats sont biaisés en faveur d'effets plus importants). (D'après Sterne et al. (66)).

Ces nombreuses distorsions entraînent un détournement de la médecine fondée sur les preuves (67,68) mais aussi une crise de la reproductibilité (en anglais, « replication crisis ») (69–71). La recherche scientifique se doit d'être reproductible, il est essentiel de pouvoir répliquer les méthodes, les résultats des études et inférences (conclusions). En effet, compte tenu des aléas d'échantillonnage, le risque de trouver un résultat faux positif ne peut pas être écarté. La réalisation d'une autre étude similaire pour confirmer un résultat précédemment publié est donc une bonne chose. Pourtant, on parle aujourd'hui de crise de la reproductibilité car de nombreux résultats publiés sont difficiles, voire impossibles à reproduire.

1.3. La méta-analyse comme solution pour gérer la prolifération des preuves ?

Cette multiplication du nombre de publications peut également s'expliquer par la nécessité de valider ou invalider des résultats trouvés précédemment mais complique le travail de synthèse de ces résultats. Afin de répondre aux besoins grandissants des acteurs de santé, médecins prescripteurs ou responsables de politique de santé publique, d'avoir des données synthétiques permettant de prendre des décisions en se basant sur une somme de connaissances en constante augmentation, les méthodes méta-analytiques ont été développées.

1.3.1. Principes de la méta-analyse

La méta-analyse est une démarche systématique qui permet de combiner les résultats de plusieurs essais cliniques répondant à une question thérapeutique donnée en suivant une méthodologie rigoureuse pour en faire une synthèse de la littérature reproductible et quantifiée (72). Cette synthèse permet de gagner en puissance statistique et en précision dans l'estimation de la taille de l'effet mais aussi de réconcilier des résultats apparemment discordants. Pour synthétiser les résultats des études d'une façon précise et fiable, la méta-analyse doit suivre une démarche argumentée et reproductible avec une approche là-aussi hypothético-déductive, qui se base sur trois grands principes : 1) exhaustivité des essais analysés, 2) sélection rigoureuse et argumentée des études et 3) quantification de l'effet étudié.

1/ Exhaustivité des essais analysés

La méta-analyse se doit d'être aussi exhaustive que possible. Pour cela, elle s'appuie sur une recherche exhaustive de tous les essais publiés ou non, favorables ou non au traitement étudié, significatifs ou non. Elle permet ainsi de combiner quantitativement les résultats de toutes les études abordant une même question de recherche.

Néanmoins, l'existence de travaux non publiés rend l'exhaustivité difficile à atteindre. En effet, les essais montrant des résultats statistiquement significatifs favorables pour un traitement ont souvent plus de chance d'être publiés que des essais ne montrant pas de différences significatives ou présentant des résultats non favorables. Ce phénomène, qui consiste à la possibilité de publier ou non l'essai en fonction de son résultat, est appelé biais de publication. Pour éviter ce biais et garantir l'exhaustivité, il est nécessaire de prendre en considération toutes les études éligibles, publiées ou non. Il faut pour cela réaliser la recherche des études à partir de l'ensemble des sources d'information disponibles : les bases de données bibliographiques informatisées (Medline, Embase...), registres d'essais (Cochrane, clinicaltrial.gov), et résumés

des principaux congrès du domaine. En addition, une recherche à partir des références des articles retenus permet de détecter des travaux parfois plus anciens publiés au moment où l'enregistrement bibliographique n'était pas aussi performant qu'aujourd'hui. L'industrie pharmaceutique peut également être interrogée pour repérer des éventuels essais qui ne seraient pas publiés.

2/ Sélection rigoureuse et argumentée des études

Compte tenu du nombre très élevé et croissant d'articles scientifiques, la méta-analyse implique de plus en plus une sélection importante et argumentée des études. Pour cela, les auteurs doivent clairement définir les critères d'inclusion et d'exclusion permettant de retenir ou non une étude pour l'analyse et fournir la liste des études non prises en considération avec les raisons d'exclusion.

3/ Quantification de l'effet étudié

La méta-analyse permet d'estimer la taille de l'effet étudié à l'aide de calculs statistiques en se basant sur l'hypothèse d'un effet commun : chaque étude est un échantillon produisant une estimation de l'effet traitement, le pool de ces études et la combinaison des effets traitements obtenus dans chacune des études, permet d'approcher l'effet théorique attendu. Le regroupement des données de plusieurs essais devrait améliorer la précision mais également la fiabilité de l'effet étudié.

1.3.2. Intérêts et limites de la méta-analyse

La méta-analyse est souvent réalisée pour tenter de répondre à une question qui prête à controverse avec des études à la limite de la significativité statistique ou qui donnent des résultats discordants.

L'intérêt des méta-analyses a évolué et elle permet aujourd'hui de :

- répondre à une question qui n'était pas initialement posée par les études ;
- expliquer la variabilité des résultats entre les études ;
- tester et augmenter la généralisation d'un résultat sur un spectre plus large de patients.

Compte tenu de la stricte sélection des patients inclus dans les essais, le regroupement de plusieurs essais incluant des patients ayant des caractéristiques différentes permet d'approcher le « patient moyen tout venant ». L'estimation issue de la méta-analyse est ainsi généralement plus proche de l'effet qui est observé dans la vraie vie en pratique courante ;

- réaliser des analyses en sous-groupes et vérifier ainsi la cohérence du résultat chez tous les sous-groupes de patients.

Mais l'utilisation et l'interprétation des méta-analyses doivent se faire avec précaution. La principale critique faite à la méta-analyse est de mélanger des choses non comparables. En effet, une méta-analyse peut combiner des études qui ont été faites avec des objectifs différents, populations différentes et méthodes différentes. Il est ainsi essentiel de rendre compte le mieux possible de l'hétérogénéité entre les études et ainsi tester des hypothèses qui n'auraient pas été testées dans chaque étude prise individuellement. Une autre critique faite à la méta-analyse est qu'elle n'est pas toujours exhaustive. Il est pour cela primordial de bien définir l'objectif et les critères de sélection des essais dans la méta-analyse. Par exemple, si la méta-analyse n'inclut que les essais significatifs, celle-ci ne sera pas exhaustive et pas fiable (biais de publication).

Enfin, les biais des essais inclus dans la méta-analyse sont la première source de biais en méta-analyse, un certain nombre de biais pouvant faire conclure à tort à une différence. En effet, si les essais méta-analysés ne sont pas de bonne qualité et présentent eux-mêmes des biais, le résultat de la méta-analyse sera également biaisé et l'interprétation des résultats pourra être erronée. Cela représente un danger notamment lorsqu'on souhaite méta-analyser par exemple des études observationnelles qui sont déjà soumises à de nombreux biais. Il faut ainsi être vigilant dans la sélection des essais afin de garantir une qualité méthodologique de la méta-analyse satisfaisante.

1.3.3. Flambée des publications de méta-analyses

La méta-analyse d'essais randomisés apporte le plus haut niveau de preuve pour démontrer l'efficacité d'un traitement (Figure 6). Cette synthèse est devenue une pratique courante en recherche clinique.

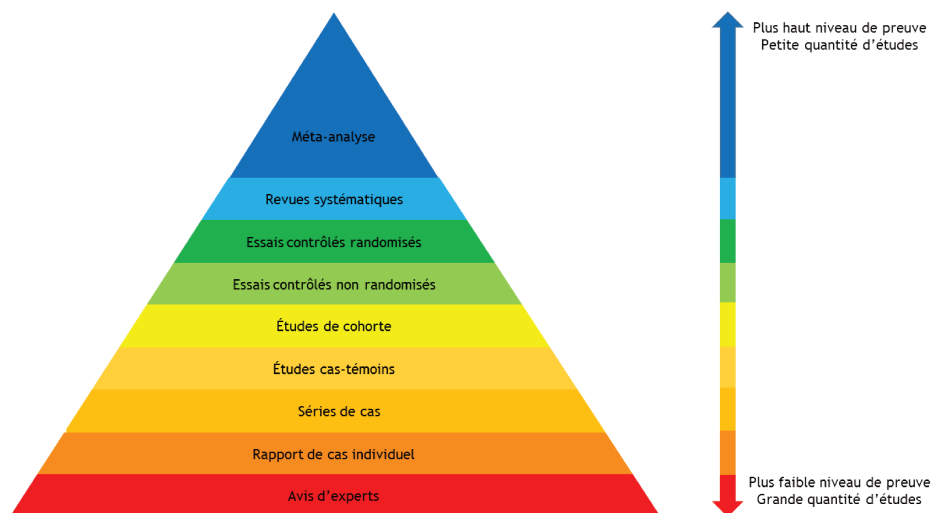


Figure 6. Illustration des niveaux de preuve des études.

Ce type de recherche n'a pas échappé à la flambée des publications, le nombre de publications de méta-analyses ayant explosé depuis les années 2000 passant de moins de 1,500 publications sur l'année 2000 à plus de 30,000 en 2020 sur PubMed. En 2022, pas moins de 300,000 méta-

analyses sont référencées dans PubMed (Figure 7). Le nombre de méta-analyses sur données publiées a augmenté de façon spectaculaire en raison de la facilité d'obtention des données agrégées et du développement de logiciels statistiques gratuits et faciles à utiliser. Aujourd'hui, la réalisation et la publication des méta-analyses sont accessibles à tout chercheur et pas seulement qu'à des experts statisticiens.

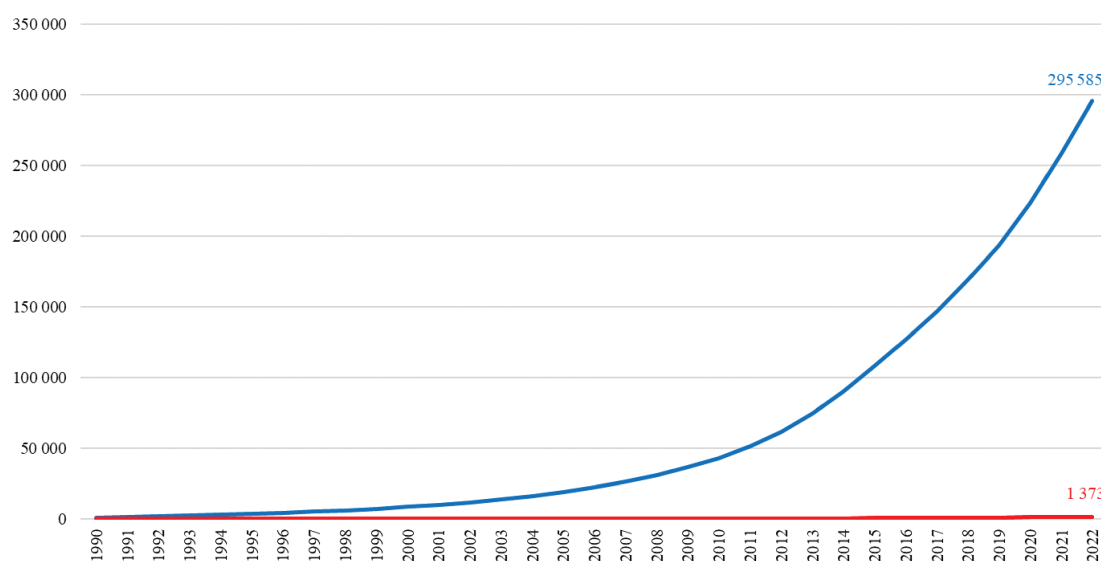


Figure 7. Évolution du nombre de méta-analyses référencées dans PubMed entre 1990 et 2022. *Bleue : méta-analyses sur données résumées. Équation de recherche PubMed : ((meta-analysis[Title/Abstract]) OR (Meta-Analysis[Publication Type]) OR (network meta-analysis[Title/Abstract]) OR (indirect comparison*[Title/Abstract]) OR (pooled-analysis[Title/Abstract])) NOT ("individual patient data meta analysis"[Title/Abstract]) NOT ("ipd meta analysis"[Title/Abstract])). Rouge : méta-analyses sur données individuelles. Équation de recherche PubMed : ("individual patient data meta analysis"[Title/Abstract]) OR ("ipd meta analysis"[Title/Abstract])).*

Au final, comme pour les essais, la publication des méta-analyses a atteint des proportions épidémiques. La plupart des méta-analyses seraient ainsi inutiles, trompeuses et/ou

contradictoires (11), et deux méta-analyses sur trois comporteraient au moins une autre méta-analyse se chevauchant et couvrant les mêmes comparaisons, indications et résultats (73,74).

1.3.4. Réplication des méta-analyses

Comme nous l'avons vu précédemment, la réplication d'une étude antérieure peut être positive lorsque l'objectif de la réplication est de confirmer un résultat précédemment publié, afin de vérifier la reproductibilité. Par exemple, chez les patients atteints de cancer, un effet prometteur inattendu des héparines de bas poids moléculaires (HBPM) sur la survie des patients avait été observé dans les premiers essais. Ces premiers résultats positifs étaient issus de sous-groupes post hoc mais n'ont pas été retrouvés dans les études suivantes. Nous avons conduit la méta-analyse cumulative et avons montré une amélioration significative de la survie avec les HBPM sur les premières études, avec à partir de 2005 une régression progressive des résultats vers l'absence d'effet antitumoral des HBPM (Figure 8) (75).

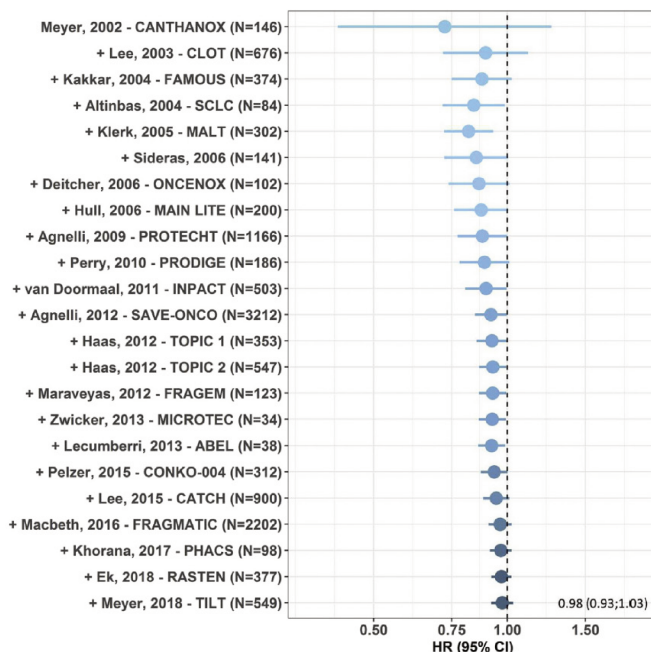


Figure 8. Méta-analyse cumulative. Issue de la publication Laporte et al. (75).

L'objectif de la réplication d'une méta-analyse est différent de celui de la réplication d'une étude antérieure. En effet, il n'y a aucune raison de trouver un résultat différent de celui de la méta-analyse initiale, celle-ci devant être reproductible. En réalité, la réplication peut être :

- Une actualisation de la méta-analyse précédente afin d'inclure les données des nouveaux essais ;
- Une tentative d'amélioration de la qualité méthodologique (par exemple en ne sélectionnant que les études en double aveugle) ou d'enrichissement des données (par exemple en intégrant un nouveau critère d'évaluation non publié dans les méta-analyses précédentes) ;
- Une redondance pure et simple.

Les méta-analyses étant faciles à faire et plus rapides à conduire qu'un essai randomisé, elles sont de plus en plus nombreuses, répliquées, voire redondantes, dans de nombreux domaines (74,76) : supplémentation en Vitamine D et fractures (77) ou chutes (78), acide tranexamique et saignement chirurgical (79), arthrose du genou (80), rupture du tendon d'Achille (81), maladie coronarienne (82,83), multiples domaines (84), fibrillation auriculaire (85), santé environnementale et professionnelle (86), épidémiologie génétique (87), traitements systémiques du psoriasis (88), et plus récemment sur le COVID-19 (89). Néanmoins, la sur-publication de méta-analyses dans un même domaine et sur les mêmes études augmente le risque de trouver des résultats discordants notamment en fonction du choix méthodologique et des méthodes utilisées pour combiner les effets du traitement ce qui peut paradoxalement prêter à confusion sur l'interprétation des résultats. Au final, la réplication serait acceptable seulement si elle produisait des méta-analyses moins biaisées.

Puljak et al. ont proposé des solutions potentielles pour limiter la redondance, comme par exemple l'enregistrement prospectif et obligatoire des revues systématiques avec une meilleure prévention de la duplication au moment de l'enregistrement, le rejet par les éditeurs et reviewers des revues dupliquées/redondantes et inadéquates, l'élimination des revues zombies (revues enregistrées abandonnées), ou encore le développement des revues systématiques vivantes (en anglais « living meta-analysis ») (90).

2. Méta-recherche

La méta-recherche consiste à étudier les problématiques méthodologiques survenant après la recherche et développer des solutions méthodologiques et techniques pour répondre à ces problématiques (Figure 9). La méta-recherche permet ainsi de comprendre comment sont exploités les résultats de la recherche clinique et ainsi de mettre en évidence l'importance du phénomène de distorsion de la réalité par les pratiques de recherche et de publications actuelles (méta-épidémiologie).

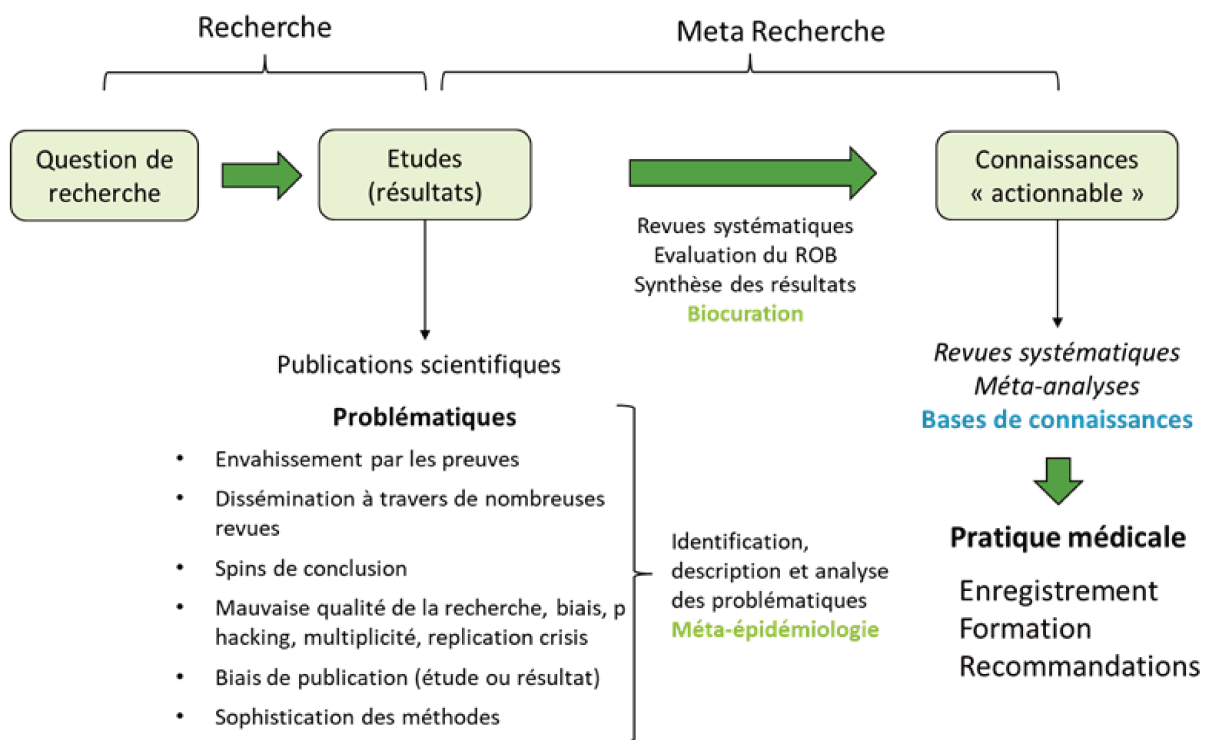


Figure 9. Illustration de la méta-recherche. D'après <https://shupt.univ-lyon1.fr/meta-recherche/>.

La méta-épidémiologie est basée sur deux concepts : la méta-analyse et l'épidémiologie. En reprenant l'approche méta-analytique, les études méta-épidémiologiques permettent de comparer un effet traitement entre des essais avec et sans une particularité méthodologique dans des échantillons de méta-analyses, et d'étudier son influence sur l'effet traitement. Il est

possible par exemple d'évaluer l'impact du design des études sur les résultats en réalisant une méta-analyse stratifiée sur le design des études (91,92) ou encore sur les caractéristiques des essais (93,94). Il est possible, via les études méta-épidémiologiques, de détecter et quantifier les biais. Au final, le but de l'approche méta-épidémiologique est d'améliorer la méthodologie des essais cliniques et la qualité des protocoles de recherche clinique.

L'objectif de cette thèse est d'utiliser cette approche méta-épidémiologique pour caractériser le phénomène de réplication des méta-analyses. L'ensemble de la thèse a porté sur la thématique de recherche du Laboratoire SAINBIOSE (SANTé Ingénierie BIOlogie Saint-Étienne), équipe Dysfonctions Vasculaires et de l'Hémostase (DVH) en s'appuyant sur l'exemple des anticoagulants oraux directs (AOD) dans le traitement de la maladie thromboembolique veineuse (MTEV). Le phénomène de réplication des méta-analyses a été abordé sous trois angles :

1. Illustration, mise en évidence sur un domaine/sujet précis
2. Analyse qualitative du phénomène de réplication et de la qualité méthodologique
3. Développement d'un outil statistique pour l'analyse quantitative des résultats issus du phénomène de réplication.

Dans le premier travail, nous avons illustré ce phénomène sur les méta-analyses réalisées dans un même domaine et répondant à la même question PICO (Population, Intervention, Comparateur, Outcome/événement d'intérêt). Pour ce premier travail, nous nous sommes intéressés aux méta-analyses ayant comparé les AOD vs HBPM dans le traitement aigu de la MTEV dans un contexte de cancer. Nous avons ensuite décrit ce phénomène de réplication des méta-analyses en élargissant le domaine à l'ensemble des patients traités par AOD pour un événement thromboembolique veineux (ETEVE) quel que soit le comparateur utilisé. Et enfin, à

partir de la caractérisation de la réplication des méta-analyses faite précédemment, nous avons mesuré l'impact de cette réplication sur la reproductibilité des résultats des méta-analyses.

3. Illustration du phénomène de répliation des méta-analyses répondant à la même question PICO

Contexte. Les méta-analyses sont largement utilisées pour renforcer les preuves disponibles et obtenir des estimations plus précises de l'effet du traitement que n'importe quel essai individuel. En voulant préparer les mises à jour des recommandations françaises pour le traitement des thromboses associées au cancer, nous avons recherché une méta-analyse dans la littérature ayant fait la synthèse des 4 essais randomisés pivots conduits avec cette question PICO spécifique : chez les patients atteints de thrombose et cancer, les AOD sont-ils plus efficaces et aussi sûrs que les HBPM en termes de risque de récidence thromboembolique et de risque hémorragique ? Cette démarche a mis en évidence une répliation massive des méta-analyses à partir de seulement 4 études. Pour dénoncer ce phénomène, nous avons réalisé une revue systématique exhaustive des méta-analyses existantes publiées pour cette même question PICO et choisi un nom adapté au contexte de l'époque : une épidémie de méta-analyses.

Ce travail a été publié dans **Journal of Thrombosis and Haemostasis (article complet en Annexe 1)**, impact factor 16.0 (2021). Ce travail a également été présenté sous forme de communication affichée lors de la journée de la Recherche de l'École Doctorale SIS le 9 juin 2022 (poster en Annexe 2).


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BRIEF REPORT

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An epidemic of redundant meta-analyses

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Méthodes. Une revue systématique de la littérature a été réalisée afin d'identifier les méta-analyses publiées entre le 1er janvier 2018 et le 6 octobre 2020 et évaluant les AOD vs HBPM chez les patients atteints de thrombose et cancer. Les résultats des méta-analyses ont été présentés graphiquement à l'aide d'un forest plot représentant la taille de l'effet (exprimé par le RR) et son intervalle de confiance à 95%. Un RR égal à 1 indiquait l'absence de différence entre les traitements, un RR < 1 indiquait que les AOD étaient plus efficaces que les HBPM et un RR > 1 indiquait que les HBPM étaient plus efficaces que les AOD.

Principaux résultats. Au total, 20 méta-analyses ont été identifiées et incluses dans la revue. Parmi elles, 5 combinaient les résultats de 2 essais randomisés, 4 méta-analyses combinaient les résultats de 3 essais randomisés et 11 combinaient les résultats des 4 essais randomisés. Ce travail a permis de mettre en évidence que globalement au sein de chaque catégorie de méta-analyses (incluant 2, 3 ou 4 essais randomisés), les résultats d'efficacité et de sécurité étaient similaires (Figure 10).

Conclusion. Dans ce travail, la réplique des méta-analyses était de la redondance avec un ratio de 20 méta-analyses pour 4 essais randomisés. Véritable enthousiasme scientifique ? Pression du « publier ou périr » ? Dans tous les cas, au-delà du risque potentiel de trouver des résultats discordants, leur multiplication peut être source de confusion, les praticiens ne bénéficiant plus d'une réponse rapide et synthétique, et peut paraître disproportionnée lorsque le nombre de méta-analyses publiées dépasse le nombre d'études originales. La duplication des méta-analyses soulève donc surtout des questions scientifiques, éthiques et économiques.

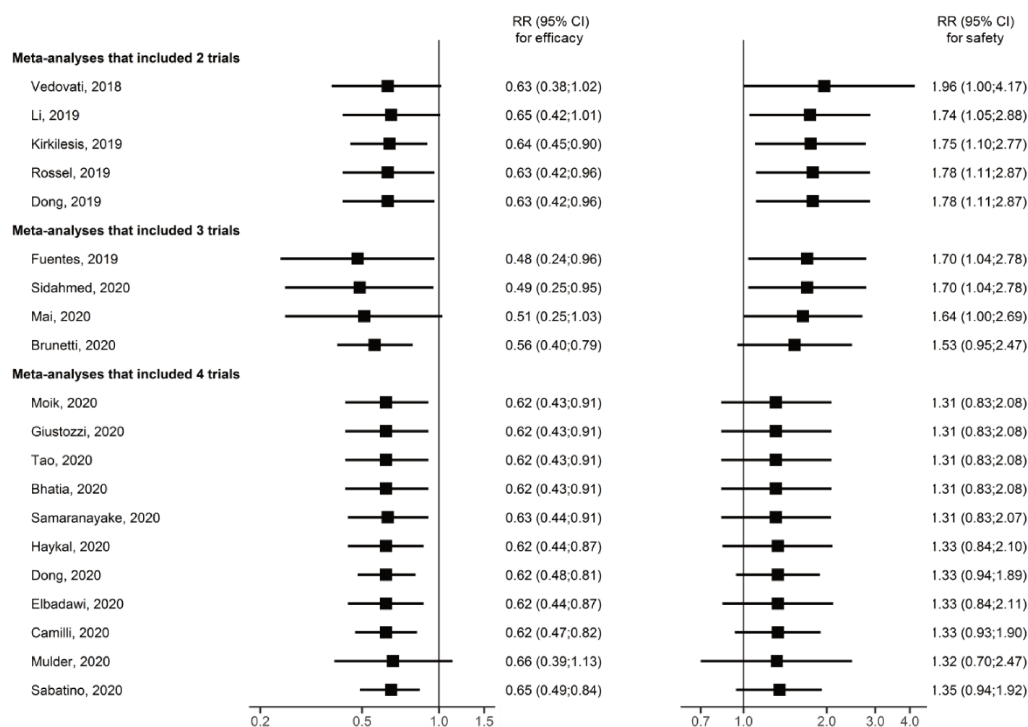





Figure 10. Estimation de l'effet traitement en fonction du nombre d'essais randomisés inclus dans les méta-analyses pour les résultats d'efficacité (récidives thromboemboliques) et de sécurité (hémorragies majeures).

Lors de la mise à jour des recommandations françaises, nous avons fait le choix de nous référer aux résultats de la première méta-analyse enregistrée publiée et de l'originalité (au sens de nouveauté) mais peut-être pas celui de la méta-analyse ayant la meilleure qualité méthodologique. Nous nous sommes ainsi retrouvés face à trois méta-analyses enregistrées publiées quasiment toutes en même temps que nous n'avons pas pu départager. Notre curiosité face à ce phénomène de redondance nous a permis de voir que certaines méta-analyses étaient contemporaines, la redondance était ainsi involontaire et difficile à éviter, mais parfois cette redondance était volontaire avec des publications à l'identique plus d'un an après la première. Il nous semblait important de décrire comment le phénomène de réplification survenait mais aussi de le caractériser en termes de biais et qualité méthodologique.

4. Caractérisation du phénomène de réplication des méta-analyses

Contexte. Différents arguments sont évoqués pour justifier la réplication d'une méta-analyse. Que cette réplication soit plus ou moins volontaire serait finalement une problématique minime, voire acceptable si la réplication servait à produire des méta-analyses de meilleure qualité. Nous nous sommes intéressés à ce phénomène de réplication et ses caractéristiques en termes de biais et qualité méthodologique des méta-analyses. Pour étudier ce phénomène de réplication, nous sommes restés dans le même domaine de la thrombose et avons réalisé une synthèse des méta-analyses existantes évaluant l'efficacité et/ou la sécurité des AOD pour le traitement des ETEV quel que soit le comparateur utilisé.

Ce travail a été publié dans **Journal of Clinical Epidemiology** (article complet en Annexe 3), impact factor 7.2 (2022). Ce travail a également été présenté sous forme de communication affichée lors du congrès EPICLIN à Nancy du 10 au 12 mai 2023 (poster en Annexe 4).

 ELSEVIER	 Check for updates	 Journal of Clinical Epidemiology
<small>Journal of Clinical Epidemiology 162 (2023) 98–106</small>		
ORIGINAL ARTICLE		
Replication of systematic reviews: is it to the benefit or detriment of methodological quality?		
Céline Chapelle ^{a,*} , Edouard Ollier ^a , Paul Bonjean ^b , Clara Locher ^c , Paul Jacques Zufferey ^d , Michel Cucherat ^e , Silvy Laporte ^a		

Méthodes. Ce travail a été enregistré dans PROSPERO (CRD42022316273). Une recherche exhaustive de la littérature a été réalisée afin d'identifier les méta-analyses publiées évaluant les AOD dans le traitement aigu ou prolongé de la MTEV (y compris dans un contexte de cancer). Dans un premier temps, les méta-analyses ont été classées en fonction de la question PICO (Population, Intervention, Comparison and Outcome) puis réparties en 3 catégories selon la classification proposée par Tugwell et al. (95) : originale, réplique conceptuelle et réplique excessive (duplication). Le risque de biais des méta-analyses a été évalué à l'aide de l'outil ROBIS (Risk of Bias in Systematic Reviews) (96). Les méta-analyses ont été classées à risque de biais faible, incertain ou élevé.

Résultats. Au total, 144 méta-analyses ont été identifiées et incluses dans la revue. Parmi elles, 26 (18.1%) étaient des originales, 87 (60.4%) des répliques conceptuelles et 31 (21.5%) des répliques excessives. Globalement, 99 (68.7%) méta-analyses ont été évaluées à risque de biais élevé, 39 (27.1%) à risque de biais faible et 6 (4.2%) à risque de biais incertain. Comparées aux méta-analyses originales, la qualité méthodologique globale des répliques n'était pas améliorée. La comparaison entre les répliques conceptuelles et les méta-analyses originales n'a révélé aucune différence en termes de qualité méthodologique : OR = 1.09 (IC 95% 0.38-2.85) (Figure 11A). La comparaison entre les répliques excessives et les méta-analyses originales suggère une meilleure qualité méthodologique bien que la différence ne soit pas statistiquement significative : OR = 0.77 (IC 95% 0.24-2.42) (Figure 11B). Les répliques excessives semblent avoir une meilleure qualité méthodologique que les répliques conceptuelles bien que la différence ne soit pas statistiquement significative : OR = 0.71 (IC 95% 0.29-1.78) (Figure 11C).

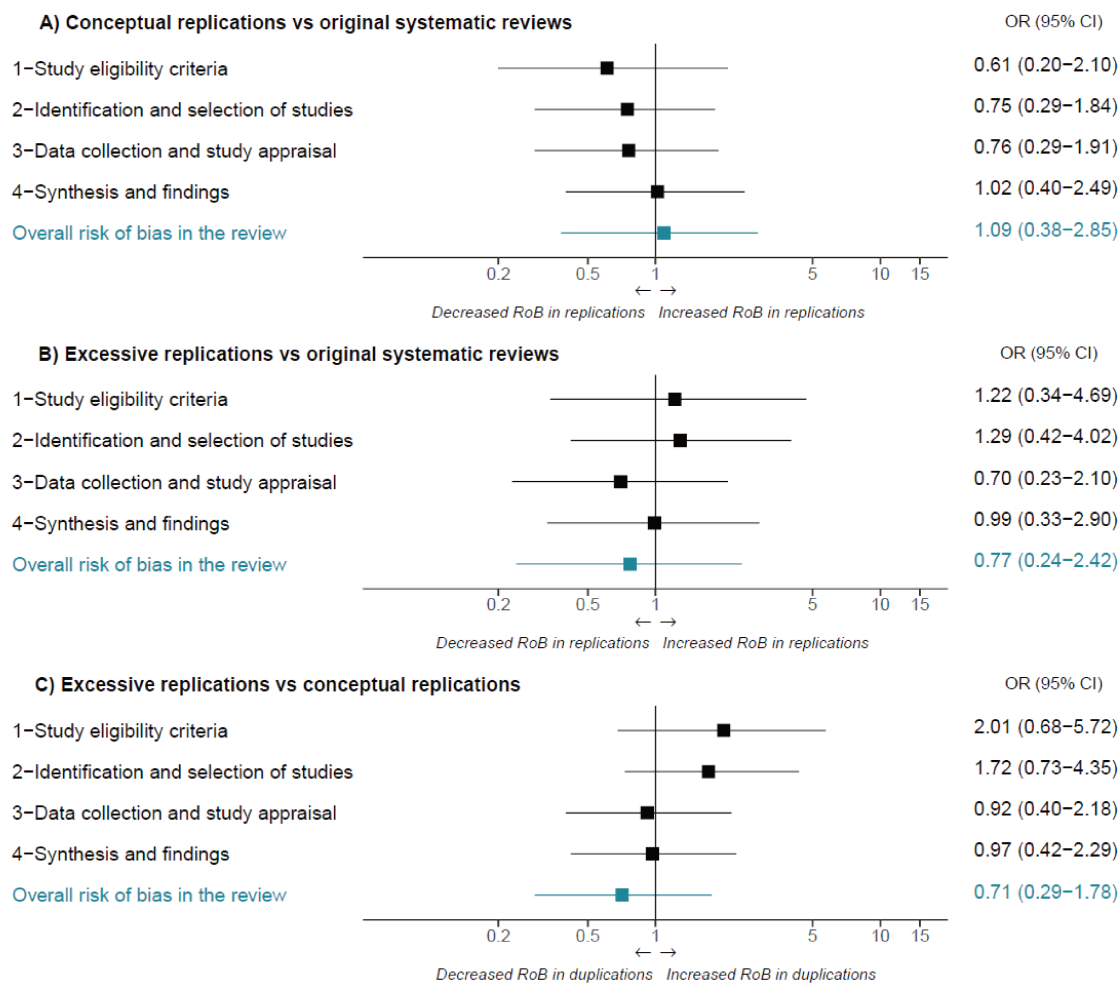


Figure 11. Comparaison du risque de biais pour chaque domaine de l'outil ROBIS. A) entre les réplifications conceptuelles et les méta-analyses originales (la référence est originales) ; B) entre les réplifications excessives et les méta-analyses originales (la référence est originales) ; C) entre les réplifications excessives et les réplifications conceptuelles (la référence est réplifications conceptuelles). Un OR < 1 indique un risque de biais plus faible par rapport à la référence, un OR de 1 indique l'absence de différence, et un OR > 1 indique un risque de biais plus élevé par rapport à la référence. 95% IC : intervalle de confiance à 95 % ; OR : odds ratio ; RoB : risque de biais.

Conclusion. La production massive de revues systématiques a entraîné un gaspillage considérable sous la forme de publications excessives (redondantes) et de qualité méthodologique médiocre. Alors que nous nous attendions à observer une amélioration de la qualité méthodologique dans les méta-analyses répliquées (répondant à la même question PICO), nous avons pu observer que, dans ce domaine, leur qualité méthodologique n'était finalement pas améliorée. Si ce n'est pas pour améliorer sa qualité méthodologique, l'intérêt scientifique d'une répllication est discutable. De plus, les variations méthodologiques entre les méta-analyses pourraient conduire à une variation des résultats. L'estimation du niveau de variabilité des résultats entre les différentes méta-analyses étudiant un même résultat (outcome) et incluant les mêmes études permettrait de caractériser leur reproductibilité. Il n'existe pas à notre connaissance de travaux ayant analysé de manière quantitative cette reproductibilité.

5. Impact de la réplication des méta-analyses sur la reproductibilité des résultats

Contexte. Comme nous l'avons observé précédemment, la réplication d'une méta-analyse peut être positive dans le cas d'une actualisation d'un travail précédent mais négative notamment en cas de redondance. Aussi, les résultats de méta-analyses ayant les mêmes événements d'intérêts et les mêmes études incluses peuvent varier selon les populations d'intérêt ou la méthodologie statistique utilisée. Ce phénomène de "vibration des effets", naturellement observé à partir de travaux de recherche multiples par la réplication des résultats des méta-analyses, n'a jamais été analysé quantitativement. Une analyse quantitative des résultats est nécessaire pour : 1) décomposer la variabilité totale observée et quantifier l'ampleur de la variabilité générée par le processus de réplication et 2) identifier les variables qui pourraient expliquer cette variabilité. Cette analyse est essentielle pour analyser la distorsion (ou l'amélioration) des estimations de l'effet traitement créées par le phénomène de réplication et pour mieux caractériser la robustesse des estimations de l'effet traitement.

Ce travail a été effectué à partir de la synthèse des méta-analyses réalisée dans le travail précédent et a été publié dans **Research Synthesis Methods (article complet en Annexe 5)**, impact factor 9.8 (2022).

A framework to characterise the reproducibility of meta-analysis results with its application to direct oral anticoagulants in the acute treatment of venous thromboembolism

Céline Chapelle¹  | Gwénaél Le Teuff² | Paul Jacques Zufferey³ |
Silvy Laporte¹ | Edouard Ollier¹ 

Méthodes. Pour chaque méta-analyse, l'estimation ponctuelle globale de l'effet traitement, (estimée par le RR, l'OR ou le HR selon les méta-analyses) ainsi que sa précision (estimée par l'erreur standard et calculée à partir de l'intervalle de confiance à 95% de l'estimation globale) ont été collectées pour les résultats d'efficacité (récidive thromboembolique) et de sécurité (hémorragie majeure). Les résultats ont été regroupés par groupe de réplification comprenant le résultat de la méta-analyse originale et les résultats de toutes les méta-analyses ultérieures répliquées (évaluant le même résultat, la même indication de traitement et la même comparaison). Afin de décomposer la variabilité totale observée en variabilité inter et intra groupes de réplification, un modèle à effets aléatoires nichés à 2 niveaux a été utilisé prenant en compte la méta-analyse au sein des groupes de réplification. Ce modèle permet de décomposer la variabilité totale en 3 quantités : variabilité entre groupes de réplification, variabilité au sein des groupes de réplification, et variabilité au sein de la méta-analyse (variabilité résiduelle). Un coefficient de corrélation intra-groupe de réplification a été calculé afin de quantifier la reproductibilité des résultats des méta-analyses au sein des groupes de réplification. Pour étudier l'influence des caractéristiques de la méta-analyse sur la reproductibilité des résultats, nous avons ajouté au modèle précédent, une méta-régression incluant des covariables afin de

modéliser à la fois les paramètres moyens et la variance résiduelle de l'effet traitement global et de son incertitude.

Résultats. Au sein des groupes de réplication, la reproductibilité de l'estimation de l'effet traitement global des résultats d'efficacité était bonne. Concernant les résultats de sécurité, la reproductibilité était bonne dans les analyses princeps et modérée dans les analyses secondaires. La reproductibilité de l'erreur standard de l'estimation de l'effet traitement global au sein des groupes de réplication était bonne dans les analyses princeps et modérée dans les analyses secondaires, pour les résultats d'efficacité comme pour les résultats de sécurité. Au sein des groupes de réplication, l'effet moyen du traitement et la variabilité résiduelle étaient plus élevés dans les résultats de sécurité que dans les résultats d'efficacité (Figure 11). Aussi, l'incertitude de l'effet du traitement et la variabilité résiduelle de l'effet du traitement augmentaient en fonction des méthodes méta-analytiques utilisées, en particulier dans les méta-analyses en réseau, celles qui utilisent une approche bayésienne ou un modèle à effets aléatoires pour combiner les résultats (Figure 12).

Conclusion. Le modèle proposé a permis de quantifier la reproductibilité des résultats des méta-analyses et de caractériser les déterminants influençant la variabilité du processus de réplication. Au sein des groupes de réplication, la reproductibilité des méta-analyses était globalement bonne lorsque l'on considère l'estimation globale de l'effet traitement et modérée lorsque l'on considère les erreurs standard de l'estimation globale de l'effet traitement. La variabilité du processus de réplication dépendait notamment des méthodes méta-analytiques utilisées, de la réplication et des méta-analyses n'ayant pas d'auteurs en commun avec les autres. Cette variabilité des résultats peut entraîner une confusion sur l'interprétation des résultats.

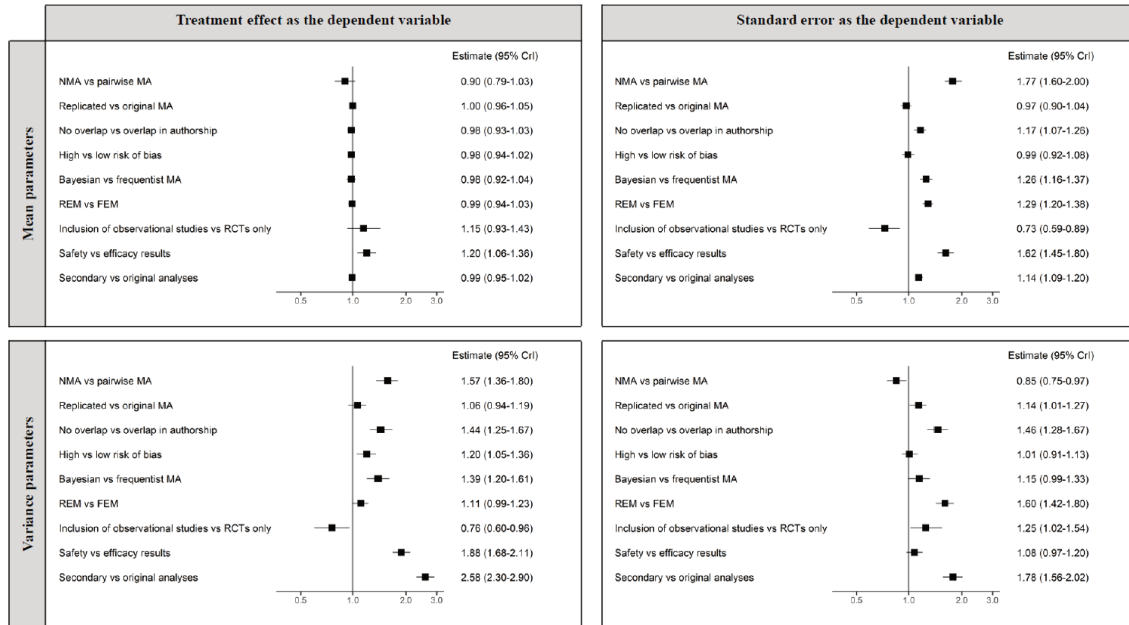


Figure 12. Reproductibilité des résultats d'efficacité (récidive thromboembolique) et de sécurité (hémorragie majeure) au sein des groupes de répliation. Haut : sur la variation moyenne de l'estimation de l'effet traitement (gauche) et de son incertitude (droite). **Bas :** sur la décomposition de la variabilité au sein de la méta-analyse (variabilité résiduelle) de l'estimation de l'effet traitement (gauche) et de son incertitude (droite). 95% CrI: 95% credible interval; FEM: fixed-effect model; MA: meta-analysis; NMA: network meta-analysis; REM: random-effects model; RCTs: randomised controlled trials.

6. Discussion générale

6.1. Constats et limites

Ce travail de thèse a débuté par la constatation d'une réplification massive du nombre de méta-analyses répondants à la même question PICO, dans le domaine de l'évaluation des AOD dans la thrombose associée au cancer. Nous avons pu constater qu'il s'agissait principalement de redondance. La publication que nous avons faite de ce constat n'a pas été très efficace (article 1), puisque 9 autres méta-analyses incluant les mêmes 4 essais randomisés ont encore été publiées depuis.

Face à ce phénomène de réplification, parfois involontaire, parfois évitable, nous avons voulu caractériser ce phénomène en termes de réduction des biais, notre idée étant qu'une réplification pour améliorer la qualité méthodologique de la méta-analyse originale serait plutôt positive. Plus de 80% des méta-analyses publiées dans le domaine des AOD pour le traitement de la MTEV étaient associées à de la réplification, dont plus d'un quart était clairement de la redondance (article 2). Malheureusement, quel que soit le type de réplification, la qualité méthodologique était globalement médiocre mais pas améliorée. De ce fait, l'intérêt scientifique de la réplification des méta-analyses, et surtout des redondances, est discutable. De plus, au sein de ces réplifications, des variations méthodologiques entre les méta-analyses peuvent conduire à une variation des résultats (vibration des effets), apportant un peu plus de confusion dans leur interprétation (article 3). À l'aide d'un modèle à effets aléatoires nichés à 2 niveaux, nous avons pu montrer qu'au sein des groupes de réplification, l'estimation globale de l'effet traitement avait plutôt une bonne reproductibilité mais que la reproductibilité des erreurs standards était plutôt modérée. Nous avons également mis en avant que la variabilité des résultats dépendait des méthodes méta-analytiques utilisées et de la réplification.

Au final, nous avons constaté que, dans ce domaine des AOD pour le traitement de la MTEV, la réplication des méta-analyses est importante, n'apporte pas d'amélioration de la qualité méthodologique et entraîne une variabilité des résultats, notamment de l'incertitude des résultats.

Avant de généraliser la caractérisation de la réplication et les conséquences en termes de vibration des résultats, il serait intéressant d'étendre ces analyses à d'autres domaines afin d'évaluer au mieux ce phénomène de réplication. Toutefois, il faudrait trouver ou proposer un autre outil que la ROBIS tool, ou éventuellement le simplifier, pour évaluer la qualité méthodologique des méta-analyses. En effet, l'utilisation de cet outil est complexe et très chronophage, ce qui peut s'avérer problématique notamment dans le cas d'une revue de grande envergure. Pour évaluer le risque de biais d'une méta-analyse, nous avons mis entre 30 minutes et 45 minutes par méta-analyse en tenant compte d'une lecture attentive de l'article. De plus, même si cet outil est une aide pour classer une méta-analyse en risque de biais faible ou élevé, le choix final du classement reste très subjectif.

Nous avons proposé une évaluation quantitative du phénomène de réplication dans un domaine. Il serait très intéressant de croiser nos résultats avec une étude qualitative pour connaître les motivations des chercheurs à publier une méta-analyse redondante. Cela permettrait de voir l'écart entre ce que nous avons appelé une redondance pour une course à la publication, et ce que les chercheurs pensent réellement. Quoi qu'il en soit, pour éviter les répliques inutiles, qu'elles soient volontaires ou involontaires, il faut avant tout comprendre les motivations des chercheurs à publier une méta-analyse et leur façon de procéder avant de se lancer dans une méta-analyse, notamment concernant le dépistage des précédentes publications.

6.2. De la pression à la réplication

Publier est important pour une carrière universitaire et pour le renouvellement des équipes de recherche, pouvant conduire à une compétition avec le syndrome du "publier ou périr" qui en découle. La rentabilité d'un chercheur, ou d'une équipe, et sa visibilité dépendent (trop) de sa capacité à beaucoup publier, rapidement et à tout prix. Pour cela, la période entre le début du travail de recherche et la rédaction d'une publication doit être la plus courte possible. Alors que le délai entre la mise en place d'un essai clinique et sa publication prend généralement plusieurs années, la réalisation de revues systématiques et de méta-analyses se compte en mois plutôt qu'en année, et est un moyen de répondre dans des délais plus courts à la pression exercée. De plus, la facilité d'obtention des données agrégées et le développement de logiciels statistiques gratuits et faciles à utiliser rendent la réalisation et la publication des méta-analyses accessible à tout chercheur et non qu'à des experts statisticiens. Cette course à la publication liée à la pression du « publier ou périr » a ainsi entraîné une forte augmentation du nombre de publications de méta-analyses, pouvant ainsi conduire malheureusement au non-respect des bonnes pratiques scientifiques et à des dérives menaçant même l'outil dans son utilité en termes de santé publique (97). Parmi ces dérives, le phénomène de réplication des méta-analyses, notamment de la redondance des méta-analyses, est de plus en plus dénoncé depuis une dizaine d'années dans de nombreux domaines (74,76–89). Pour savoir si la réplication d'une méta-analyse est utile, il est essentiel de comprendre comment distinguer les différents types de réplication.

6.3. Distinguer les réplifications inutiles

La notion de reproductibilité désigne la capacité à reproduire les résultats et les conclusions d'une expérience aléatoire. La méta-analyse étant un outil de synthèse reproductible, sa réplification dans les mêmes conditions en termes de population, interventions comparées, études incluses et méthodes statistiques utilisées pour combiner les effets du traitement, va générer des résultats et conclusions identiques à ceux de la méta-analyse initiale. Ainsi, répliquer une méta-analyse pour vérifier sa reproductibilité n'a aucun substrat scientifique, mais peut avoir un fondement autre. En 2016, Ioannidis a montré que seules 3% des revues systématiques sont à la fois bien faites et cliniquement utiles et que 27% sont redondantes et non nécessaires (11), remettant en question l'utilité des revues systématiques et des méta-analyses (98). Face à cet échec, il convient aux chercheurs de justifier la nécessité de la réplification, afin d'identifier les différents types de réplification et de justifier (ou non) leur place dans la création de connaissance nouvelle.

En effet, les arguments scientifiques en faveur de la réplification des méta-analyses ne sont pas toujours bien exposés dans les publications, laissant penser que les auteurs ne se rendent pas compte qu'ils font de la réplification. La réplification serait ainsi involontaire ? Oui c'est possible, par exemple en cas de publication concomitante par des équipes différentes au même moment du calendrier. On peut laisser le bénéfice du doute aux auteurs pensant apporter de nouveaux résultats, sans avoir connaissance d'un même projet en cours, notamment parce que le protocole n'est pas publié. Dans le cas contraire, la publication d'une réplification est clairement volontaire et représente un gaspillage de ressources. Il existe finalement 2 types de réplifications : la réplification directe (ou excessive) et la réplification conceptuelle.

La réplification directe est une réplification intentionnelle pour vérifier les résultats de la question de recherche initiale. Elle s'apparente à de la redondance. Ce type de réplification n'a aucun intérêt scientifique et représente un gaspillage de ressources scientifiques. Elle pourrait

éventuellement être intéressante si elle permettait d'améliorer la qualité méthodologique des méta-analyses. Dans notre illustration avec les AOD dans le traitement de la MTEV, nous avons constaté que plus de 20% des méta-analyses représentaient de la réplication excessive, et ainsi de la redondance, sans bénéfice sur la qualité méthodologique.

La réplication conceptuelle vise à élargir ou à restreindre la question de recherche tout en conservant la même question PICO et les mêmes objectifs que la méta-analyse originale. Ce type de réplication a globalement un intérêt scientifique puisqu'elle va produire de la connaissance nouvelle. C'est notamment le cas lorsqu'il s'agit de mettre à jour la méta-analyse originale avec les données d'une ou plusieurs nouvelle(s) étude(s) randomisée(s), lorsque les chercheurs souhaitent se concentrer sur un comparateur ou une intervention, mettre en évidence des sous-groupes de patients ou s'intéresser à d'autres critères d'évaluations. Attention néanmoins au prétexte de mises à jour de méta-analyses pour inclure des études à méthodologie dégradée. La question de la validité des méta-analyses se pose lorsque des études non randomisées sont incluses dans la méta-analyse, car les études observationnelles pour l'évaluation de thérapeutique sont à haut risque de biais. En incluant des études biaisées, les résultats de la méta-analyse seront également biaisés, ce qui remet en question la qualité méthodologique de la méta-analyse. Concernant ce type de réplication, la question de l'intégrité scientifique se pose également lorsqu'un même auteur publie plusieurs papiers incluant les mêmes études et change seulement le sous-groupe de patients ou l'intervention ou le critère d'évaluation. Par exemple, dans notre illustration avec les AOD dans le traitement de la MTEV, un auteur a publié pas moins de 5 articles la même année ayant la même question PIC en changeant seulement le critère d'évaluation.

Finalement, la réplication des méta-analyses a entraîné un envahissement non nécessaire des publications, créant ainsi de la confusion pour les lecteurs. La variabilité des résultats et de son

incertitude, engendrées par la réplication des méta-analyses et par les choix méthodologiques faits, entraînent encore un peu plus de confusion. En effet, la diversité des méthodes pour réaliser une méta-analyse (par paire, en réseau, fréquentiste, bayésienne, pool du nombre d'événements ou des hazard ratios, modèle à effets fixes ou aléatoires) peut donner des résultats discordants. Ces résultats contradictoires et pas évident à interpréter, seront confus pour le lecteur et peuvent entraîner une perte de crédibilité et de confiance envers les chercheurs (99).

6.4. Solutions pour éviter l'envahissement des publications de méta-analyses redondantes

Afin d'éviter la réplication inutile et ainsi l'envahissement des publications de méta-analyses, plusieurs solutions existent.

En 2020, Tugwell et al. ont développé une checklist de quatre questions pour aider les chercheurs à décider s'il convient ou non de reproduire des revues systématiques et méta-analyses (95). L'idée est bonne mais malheureusement l'utilisation de cette checklist présente des inconvénients. En effet, l'application de la checklist nécessite du temps et des experts à la fois en méthodologie des revues systématiques et du domaine. De plus, l'utilisation de cette checklist dépend de la capacité des chercheurs à reconnaître la valeur de la réplication d'une revue systématique et à distinguer la réplication intéressante de la réplication inutile. Ce n'est pas cette checklist qui va éviter la réplication inutile.

L'enregistrement préalable des protocoles permet de lutter contre la réplication inutile mais aussi d'éviter toute approche inductive et de déclarer l'objectif de la recherche une fois les résultats obtenus. Depuis 2015, l'enregistrement des protocoles des méta-analyses est fortement recommandé (mais pas obligatoire) et de plus en plus demandé par les revues pour pouvoir

publier. L'enregistrement préalable des protocoles devrait être obligatoire mais serait valable à condition que l'ensemble des protagonistes jouent le jeu : les auteurs des publications qui doivent s'assurer de l'originalité de leur travail avant de commencer, mais aussi les éditeurs et reviewers qui devraient systématiquement rechercher dans les bases de données bibliographiques l'existence d'une réplique et ne pas accepter des publications qui seraient considérées comme de la réplique inutile. Bien évidemment, l'enregistrement n'implique pas un processus d'évaluation prospective s'il ne précède la publication que de quelques semaines comme c'est parfois le cas dans les déclarations des revues systématiques. Aujourd'hui, ce n'est plus seulement l'enregistrement qui est important mais aussi la date de cet enregistrement.

La **science ouverte** (« open science ») apparaît comme le mouvement émergent actuel qui prône à rendre la recherche scientifique et les résultats qu'elle produit (y compris les résultats négatifs) universellement accessibles. En 2021, l'Organisation des Nations Unies pour l'éducation, la science et la culture (UNESCO) a publié des recommandations sur une science ouverte et en propose une définition commune : « la science ouverte s'entend comme un concept inclusif qui englobe différents mouvements et pratiques visant à rendre les connaissances scientifiques multilingues, librement accessibles à tous et réutilisables par tous, à renforcer la collaboration scientifique et le partage des informations au profit de la science et de la société, ainsi qu'à ouvrir les processus de création, d'évaluation et de diffusion des connaissances scientifiques aux acteurs de la société au-delà de la communauté scientifique traditionnelle ». Parmi les principes de la science ouverte, on retrouve notamment l'ouverture de la connaissance scientifique, définie comme la diffusion sans entrave :

- de toutes les publications scientifiques gratuitement (Open Access) ;
- des données brutes (Open Research Data) ;
- des codes sources des logiciels de traitement des données (Open Source) ;

- des noms et rapports des reviewers des publications scientifiques (Open Peer Review) ;
- d'une évaluation rigoureuse des articles après leur publication (Open Post Publication Peer Review) ;
- de toutes les ressources éducatives (Open Educational Ressources).

La science ouverte est un des grands chantiers du moment. Même si elle ne permettrait pas de limiter complètement les redondances de méta-analyses, notamment celles qui sont involontaires, elle pourrait éviter la réplication inutile et devrait être obligatoire pour toutes les méta-analyses publiées. En effet, il faudrait que les auteurs de méta-analyses, rapportent explicitement les critères d'éligibilité ainsi que l'ensemble des restrictions qui vont permettre d'inclure ou non une étude dans la synthèse, les méthodes utilisées pour la recherche des études ainsi que leurs équations de recherche dans l'ensemble des bases de données, les méthodes utilisées pour combiner les effets du traitement et la prise en compte de l'hétérogénéité, ainsi qu'une description complète de toutes les analyses en sous-groupes ou de sensibilité réalisées. Néanmoins, les revues limitant le nombre de mots des publications, les méthodes ne peuvent pas être fournies entièrement, ce qui contraint les auteurs à se focaliser sur les parties qu'ils jugent comme importantes. Aussi, de plus en plus de revues imposent de suivre des recommandations de présentation des méta-analyses (« reporting guidelines »).

Les « **reporting guidelines** » sont des outils d'aide à la rédaction des publications. Ces outils contiennent une liste minimale d'informations nécessaires dans la publication pour s'assurer que celle-ci soit, entre autres, compréhensible par les lecteurs ou répliquable par les chercheurs. En effet, une méta-analyse bien décrite est plus utile car elle permet aux éditeurs, reviewers et lecteurs de comprendre ce qui a été fait et comment ça a été fait.

Ces « reporting guidelines » dépendent du type d'étude. Parmi les plus connues :

- CONSORT : pour les essais randomisés
- STROBE : pour les études observationnelles
- PRISMA ou QUOROM : pour les revues systématiques
- PRISMA-P : pour les protocoles.

Ces recommandations sont impératives pour garantir l'éthique et la validité de la recherche. Mais pour que ça fonctionne, il faudrait que toutes les revues qui publient des méta-analyses imposent les mêmes guidelines.

Une autre solution serait de ne **pas valoriser les méta-analyses** dans les titres et travaux des chercheurs. Mais c'est certainement un peu trop radical et bien dommage car les méta-analyses originales sont une vraie création de connaissance et recherche. Avant d'en arriver là, on pourrait orienter la publication des méta-analyses dans des revues spécialistes, utilisant un reporting guideline identique ou imposer un reporting guideline pour toutes les revues qui souhaitent publier des méta-analyses. C'est un peu le système de la Cochrane mais l'outil est lourd, non mis à jour régulièrement, non enrichi régulièrement et pourrait conduire à un monopole pour ce type de publication.

La **publication systématique d'une mise à jour de la méta-analyse** en même temps que la publication d'un nouvel essai randomisé permettrait de devancer les autres chercheurs et limiterait la réplique inutile puisque la méta-analyse serait déjà réalisée. Au moment de la publication de notre exemple de redondance des méta-analyses évaluant les AOD dans le traitement des thromboses et cancer, 11 méta-analyses combinaient les résultats des 4 essais randomisés existants et 9 autres méta-analyses ont été publiées depuis ce travail, soit un total de 20 méta-analyses pour répondre à la même question de recherche. Lors de la publication du

cinquième essai randomisé du domaine (étude CASTA DIVA), les auteurs ont de ce fait décidé de publier avec l'essai lui-même la mise à jour de la méta-analyse incluant du coup 5 essais (100). Au final, après une recherche dans PubMed, aucune réplique de cette méta-analyse n'a été retrouvée. Cette technique semblerait être efficace pour éviter la réplique inutile et la redondance.

Les « **living meta-analyses** » (méta-analyses vivantes) pourraient également être une solution pour éviter la réplique inutile. Cette approche émergente permet la mise à jour régulière et dynamique des méta-analyses en intégrant de nouvelles données pertinentes au fur et à mesure de leur disponibilité sur des plateformes en ligne. La seule difficulté de cette méthode est qu'elle nécessite de disposer en permanence de ressources et main-d'œuvre pour effectuer la veille continue, la saisie des nouvelles données et l'analyse. Cela nécessite un engagement important de la part du ou des chercheurs impliqués dans ce travail afin de garantir que la revue systématique reste à jour et pertinente. Néanmoins, cette solution est certainement la meilleure des solutions proposées pour éviter la réplique inutile.

Globalement, l'émergence de procédures de régulation pourrait permettre de lutter contre la redondance et améliorer la reproductibilité et la transparence de la recherche scientifique. La condition pour que cela fonctionne est que l'ensemble des acteurs de la recherche restent vigilants. Tout d'abord, avant de se lancer dans un travail de revue systématique et méta-analyse, qui est souvent long et fastidieux, les auteurs devraient vraiment se poser la question de son utilité et vérifier que ce travail n'a pas déjà été publié (revue de la littérature dans les bases de données bibliographiques) ou n'est pas en cours de réalisation (vérification des protocoles en cours ou terminé dans les bases d'enregistrement des protocoles des revues systématiques). A la réception d'un article, les éditeurs, éditeurs associés et reviewers devraient

vérifier dans les bases de données bibliographiques si un travail similaire n'est pas déjà publié. Malheureusement ce n'est pas fait par manque de temps et d'experts mais pourtant les revues systématiques dupliquées/redondantes devraient être systématiquement rejetées, voire retirées après publication. Certains penseront que réaliser une recherche bibliographique pour prendre seulement connaissance de l'existant est trop long et représente une perte de temps. Mais c'est faux ! Cette recherche bibliographique est, dans tous les cas, nécessaire pour écrire le rationnel de la revue systématique et ainsi justifier de la réalisation de celle-ci. Cette démarche éviterait la réplication inutile et l'envahissement des publications. De plus, le développement de l'intelligence artificielle pourrait permettre de réaliser très rapidement un tour d'horizon des publications répondant à une même question PICO. La publication d'une revue systématique sans création de connaissance est un manquement à l'intégrité scientifique, une demande de rétractation devrait être systématiquement demandée.

La réponse pour freiner cette course à la publication ne serait-elle pas simplement de ne plus quantifier la productivité du chercheur seulement par son nombre de publications mais de prendre en compte également la qualité de son travail (par exemple, accès libre aux données et aux codes, enregistrement préalable du protocole, respect des « reporting guidelines », impact factor de la revue) ? Les pistes sont finalement nombreuses...

6.5. Conclusion

Une course à la publication semble être engagée depuis de nombreuses années entraînant de nombreuses dérives et une distorsion de la connaissance scientifique. Pour freiner cette course à la publication et faire de la « bonne science », la responsabilité individuelle (juridique et morale) et collective des chercheurs doit être placée au cœur des principes de l'éthique de la recherche. Mais il faudrait certainement commencer par réduire l'importance des citations et des publications comme outil de financement et d'embauche des chercheurs. En 1994, le Pr Douglas Altman disait : *“We need less research, better research, and research done for the right reasons. Abandoning using a number of publications as a measure of ability would be a start.”* (101). Presque 30 ans plus tard, cet adage n'a jamais été autant d'actualité.



The scandal of poor medical research

BMJ

We need less research,
better research,
and research done
for the right reasons

Doug Altman (1948-2018)

LONDON, SATURDAY 29 JANUARY 1994

7. Perspectives

Dans le cadre de mon travail de biostatisticienne au sein du Service de Pharmacologie Clinique du CHU de Saint-Étienne, je vais pouvoir continuer ces travaux de méta-recherche. Ces futurs travaux seront réalisés en collaboration avec les membres du groupe méta-recherche du réseau national F-CRIN RECaP. Nous pourrions effectuer ce même travail de caractérisation de la réplication en élargissant le domaine clinique, mais il faudrait une fiche d'extraction plus facile. Cela pourrait faire l'objet d'un travail de Master 2.

Dans la poursuite de ce travail de thèse, nous avons commencé à travailler sur les réseaux de citations. Pour cela, nous nous intéressons aux études réalisées sur les AOD, quel que soit le type d'étude (essai randomisé, étude observationnelle, revue, méta-analyse, étude de cas...). Nous allons ainsi pouvoir construire et analyser le réseau des citations (« qui cite qui ») et ainsi caractériser les différents comportements de citations, notamment l'autocitation, dans ce domaine.

Nous avons également été sollicité pour participer à un projet financé par l'Agence Nationale de la Recherche (ANR) obtenu par le Pr Florian Naudet (Université de Rennes) autour de l'intégrité scientifique. Je vais être amenée à travailler sur un work-package sur les études « zombies », c'est-à-dire les études sans aucune donnée réelle. L'objectif de ce travail est de faire une revue systématique des essais frauduleux et de décrire leurs caractéristiques avec précision. Il sera ainsi possible d'évaluer comment les essais « zombies » se comportent dans les méta-analyses, en identifiant toutes les méta-analyses qui ont été réalisées avec des essais « zombies » et en développant des méthodes de méta-analyse qui pourraient être des signaux d'alerte.

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Annexes

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Annexe 1.

Article « An Epidemic of Redundant Meta-analyses. »

BRIEF REPORT

An epidemic of redundant meta-analyses

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Abstract

Background: Meta-analyses are widely used to strengthen available evidence and obtain more precise estimates of treatment effect than any individual trial. Paradoxically, multiplication of meta-analyses on the same topic can lead to confusion as practitioners no longer benefit from a rapid and synthetic response. This phenomenon may appear disproportionate when the number of published meta-analyses exceeds the number of original studies.

Objectives: To describe an example of redundant meta-analyses published in the same area with the same randomized clinical trials (RCTs).

Methods: A systematic review was performed to identify all published meta-analyses of original RCTs that compared direct oral anticoagulants with low molecular weight heparins in cancer patients with venous thromboembolism (VTE). Forest plots were used to represent the meta-analyses results for efficacy (VTE recurrence) and safety (major bleeding) endpoints. An authors' network was constructed to explore the links between the authors of the published meta-analyses.

Results: In the past 3 years, four original RCTs were the subject of 20 published meta-analyses by 142 authors: five, four, and 11 meta-analyses pooled the data of two, three, and four RCTs, respectively. The results of meta-analyses were similar regarding the risks of VTE recurrence and major bleeding. The 11 meta-analyses of four RCTs were published within 6 months of the publication of the last RCT.

Conclusions: The epidemic proportions of such redundant literature and authorship could be moderated by developing “living” meta-analyses and encouraging authors of new RCTs to update the corresponding meta-analysis in the same paper as their original research.

KEYWORDS

cancer, meta-analysis, randomized controlled trial, redundant publications, venous thromboembolism

Essentials

- Multiplication of meta-analyses on the same topic may be confusing for practitioners.
- We propose an example of redundant meta-analyses in the field of cancer-associated venous thromboembolism.
- Four randomized trials were the subject of no less than 20 published meta-analyses in the past 3 years.
- Such redundancies and rush to publication could be limited by developing 'living' meta-analyses.

1 | INTRODUCTION

Meta-analyses of randomized controlled trials (RCTs) are widely used in medicine to improve accuracy of treatment effect's estimates over individual trial results. Updating existing meta-analyses as soon as relevant new data emerge is therefore an important contribution to medical knowledge. However, results from meta-analyses of the same trials may differ depending on methodological choices. Multiplication of meta-analyses on the same topic can paradoxically lead to confusion by increasing the risk of conflicting results.¹ Such a phenomenon may reflect the topic characteristics (high priority or emerging question), the authors' enthusiasm to be the first to publish, and/or an avid search for the positive impact of these fast publications on both authors' and editors' citation scores. In any case, it becomes disproportionate when the number of published meta-analyses exceeds the number of original studies.

While preparing an update of the French guidelines for the treatment of cancer-associated venous thromboembolism (VTE), we found a flurry of meta-analyses on this subject. We decided to explore this phenomenon by performing a descriptive review of the existing meta-analyses that included the four published pivotal RCTs of direct oral anticoagulants (DOACs) versus low molecular weight heparins (LMWHs) in cancer patients with VTE.²⁻⁵

2 | MATERIALS AND METHODS

The four original RCTs included a pilot trial of 406 patients comparing rivaroxaban and dalteparin with recurrent VTE as primary endpoint,² a phase 3 noninferiority trial of 1050 patients comparing edoxaban and dalteparin with a combined (recurrent VTE plus major bleeding) primary endpoint,³ a phase 3 superiority trial of 300 patients comparing apixaban and dalteparin with major bleeding as primary endpoint,⁴ and one phase 3 noninferiority trial of apixaban versus dalteparin in 1170 patients, with recurrent VTE as primary endpoint.⁵

An exhaustive literature search, both manual and computer-assisted on electronic databases (PubMed, Cochrane Database,

and Google Scholar) using a predefined search strategy was performed with publication time limits between January 1, 2018 (first publication of RCTs of DOACs in cancer patients with VTE) to October 6, 2020. We constructed a search equation using the following relevant keywords: venous thromboembolism, deep venous thrombosis, pulmonary embolism, venous thrombosis, cancer, anticoagulants, dabigatran, apixaban, rivaroxaban, edoxaban, DOAC, meta-analysis. The search was not restricted to articles published in English.

Two reviewers independently assessed the meta-analyses for possible inclusion and extracted details on publication (authors, journal, year), number of studies and patients, statistical method, software used to pool data, and results on efficacy (recurrent VTE) and safety (major bleeding) endpoints.

The results of the meta-analyses were presented graphically by a forest plot, including the effect size expressed as the relative risk with the corresponding 95% confidence interval. A relative risk equal to 1 indicates no difference between the treatments, less than 1 indicates that DOACs are more effective than LMWHs, and greater than 1 indicates that LMWHs are more effective than DOACs. An authors' network was also constructed to explore the links between the authors of the published meta-analyses.

Graphs were performed using R statistical software, version 3.6.2, downloaded from www.r-project.org.

3 | RESULTS AND DISCUSSION

At the time the search was ended (October 6, 2020), 46 records were identified, of which 26 were discarded on title and abstract ($n = 24$) or full-text ($n = 2$). The 20 remaining meta-analyses were published in nonpredatory peer-reviewed journals: five studies pooled the data of two RCTs,⁶⁻¹⁰ four studies pooled the data of three RCTs,¹¹⁻¹⁴ and 11 studies pooled the data of four RCTs.¹⁵⁻²⁵ The main characteristics of the 20 meta-analyses are described in Table 1 and the results of the 20 meta-analyses for efficacy and safety endpoint are shown Figure 1. Within each category of meta-analysis (two, three, or 4 RCTs), the results were similar regarding the risks of VTE recurrence (differences in pooled relative

TABLE 1 Description of the 20 meta-analyses

Author, Year, Journal	Preregistered	No. patients	Method for Pooling	Model	Measure of Treatment Effect	Software	Differences Between Meta-analysis
Meta-analyses that included two randomized trials [2,3]							
Vedovati, 2018 ⁶ <i>Thromb Res</i>	No ^a	1430	NA	NA	RR	R	No details on statistical methods Extraction of HR
Li, 2019 ⁷ <i>Thromb Res</i>	CRD42017080898	1452	MH	D-L REM	RR	Review Manager	Extraction of no. events/patients
Kirkilesis, 2019 ⁸ <i>Eur J Vasc Endovasc Surg</i>	No	1452	MH	FEM	RR	Review Manager	Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE)
Rosset, 2019 ⁹ <i>PLoS One</i>	No ^a	1452	IV	D-L REM	RR	R	Extraction of HR
Dong, 2019 ¹⁰ <i>J Thromb Thrombolysis</i>	CRD42019122535	1452	IV	D-L REM	RR	STATA	Extraction of HR
Meta-analyses that included three randomized trials [2-4]							
Fuentes, 2019 ¹¹ <i>Mayo Clin Proc</i>	No ^a	1739	MH	D-L REM	OR	R	No details on statistical methods Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE)
Sidahmed, 2020 ¹² <i>Crit Rev Oncol Hematol</i>	CRD42019124874 ^a	1739	MH	D-L REM	OR	Review Manager + STATA	Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE)
Mai, 2020 ¹³ <i>J Thromb Thrombolysis</i>	CRD42019123504	1756	MH	D-L REM	RR	Review Manager	Extraction of no. events/patients Denominator as no. randomized patients (HOKUSAI-VTE and ADAM-VTE)
Brunetti, 2020 ¹⁴ <i>J Thromb Thrombolysis</i>	No	1739	MH	FEM	RR	Review Manager	Extraction of no. events/patients Discordance on no. events (ADAM-VTE)
Meta-analyses that included four randomized trials [2-5]							
Moik, 2020 ¹⁵ <i>Res Pract Thromb Haemost</i>	CRD42020177760	2894	MH	D-L REM	RR	STATA	Extraction of no. events/patients
Giustozzi, 2020 ¹⁶ <i>Thromb Haemost</i>	CRD42020175589	2894	MH	D-L REM	RR	Review Manager	Extraction of no. events/patients
Tao, 2020 ¹⁷ <i>Eur J Haematol</i>	No	2894	MH	D-L REM	RR	Review Manager	Extraction of no. events/patients
Bhatia, 2020 ¹⁸ <i>Am J Cardiol</i>	No	2894	MH	D-L REM	RR	STATA	Extraction of no. events/patients
Samaranayake, 2020 ¹⁹ <i>Intern Med J</i>	No ^a	2822	MH	D-L REM	RR	Review Manager	Extraction of no. events/patients Discordance on denominators of the randomized trial

(Continues)

TABLE 1 (Continued)

Author, Year, Journal	Preregistered	No. patients	Method for Pooling	Model	Measure of Treatment Effect	Software	Differences Between Meta-analysis
Haykal, 2020 ²⁰ <i>Thromb Res</i>	CRD42020179596	2907	MH	D-L REM	RR	Review Manager	Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE) Denominator as no. randomized patients (ADAM-VTE)
Dong, 2020 ²¹ <i>Ann Pharmacother</i>	CRD42019145284	2894	MH	FEM	RR	Review Manager	Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE)
Elbadawi, 2020 ²² <i>Eur Heart J Cardiovasc Pharmacother</i>	CRD42020180354	2894	IV	D-L REM	RR	Review Manager	Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE)
Camilli, 2020 ²³ <i>Crit Rev Oncol Hematol</i>	No	2894	IV	D-L REM	RR	R	Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE) Division by 2 of denominators from SELECT-D, ADAM-VTE and CARAVAGGIO
Mulder, 2020 ²⁴ <i>Blood</i>	Open Science Frame-work	2894	IV	K-H REM	RR	R	Extraction of no. events/patients Modification of the definition of recurrence of VTE with exclusion of Splanchnic vein thrombosis, cerebral vein thrombosis, and arterial thromboembolic events (SELECT-D and ADAM-VTE)
Sabatino, 2020 ²⁵ <i>JACC CardioOncology</i>	No	2907	IV	FEM	RR	Open Meta Analyst + Review Manager	Extraction of no. events/patients Events over 12 months (HOKUSAI-VTE) Denominator as no. randomized patients (ADAM-VTE)

Abbreviations: D-L, DerSimonian-Laird; FEM, fixed-effect model; HR, hazard ratio; IV, inverse-variance method; K-H, Knapp-Hartung; MH, Mantel-Haenszel method; NA, not available; OR, odds ratio; REM, random-effects model; RR, relative risk.

^aNetwork meta-analysis.

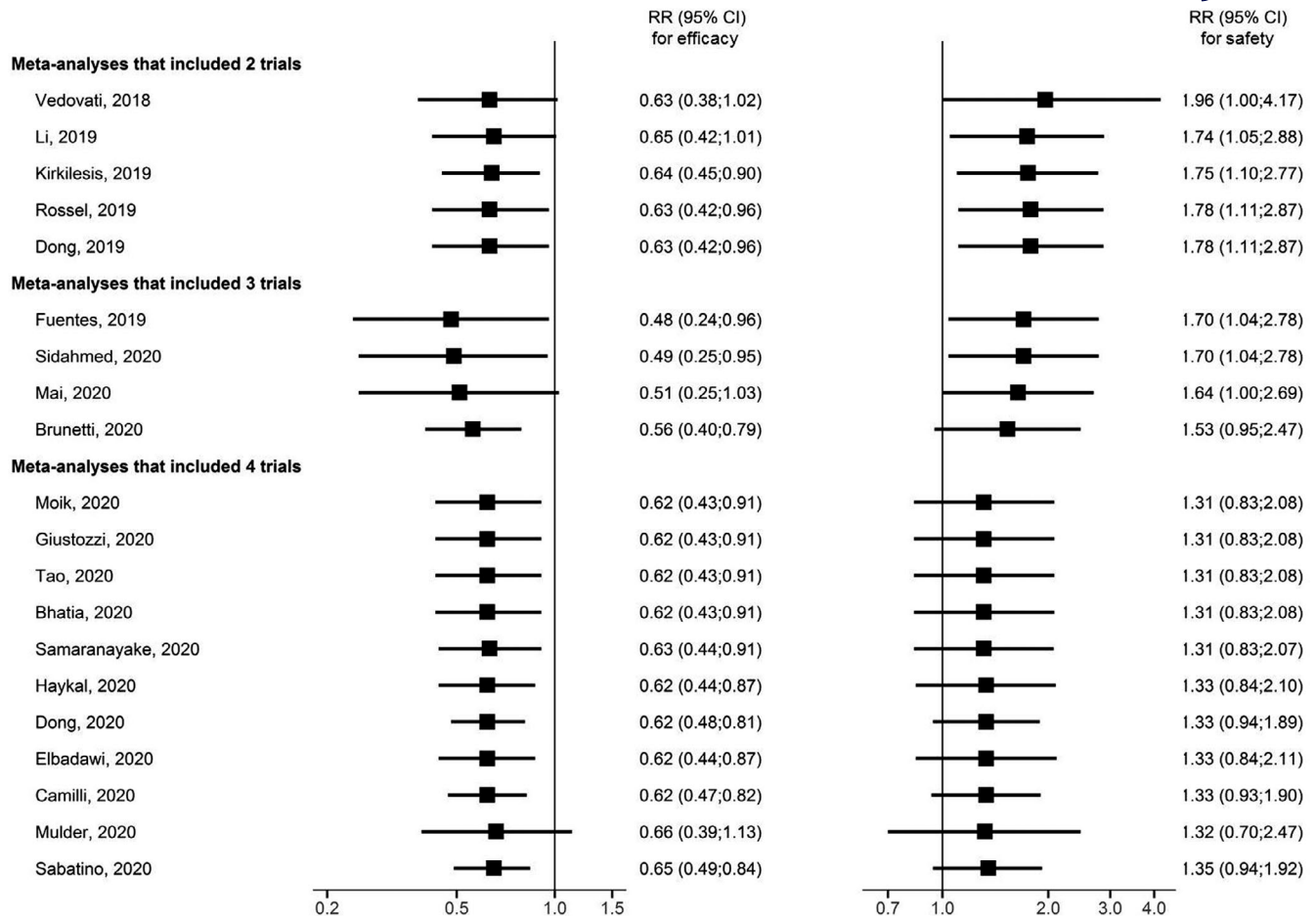


FIGURE 1 Treatment effect estimate by number of studies included in the meta-analyses for efficacy (recurrent venous thromboembolism) on the left and safety (major bleeding) on the right

risks ranging from 0 to 0.08) and major bleeding, except for one of the 11 meta-analysis of four RCTs²⁴ that did not confirm a statistically significant reduction of VTE recurrence risk with DOACs compared with LMWH (Figure 1). The small differences observed between the results of the meta-analyses can be attributed to minor methodological differences such as the method of data extraction (from the original number of events or from reported hazard ratios), the length of follow-up (up to 12 months in one RCT, 6 months in the other three RCTs), the choice of denominators, or the definition of the clinical events taken into account for the analysis (see details in Table 1).

Eleven meta-analyses were published within 6 months following the publication of the most recent RCT,⁵ with journal submission mostly within 2 weeks following the publication of the new trial (Figure 2). A total of 142 researchers authored the 20 meta-analyses. Seventeen researchers (12.0%) also authored one or two of the original RCTs, and eight researchers authored two meta-analyses with different teams (Figure 3).

Four RCTs were the subject of 20 published meta-analyses in the past 3 years. Fortunately, in the present example, the results of these meta-analyses were nearly identical. There is, however, one notable exception: unlike the 10 other meta-analyses of four RCTs, Mulder et al. did not take into account splanchnic, cerebral vein, and arterial (systemic) thrombotic events in their study.²⁴ As a result, these researchers could not confirm the important message that DOACs significantly reduce recurrent VTE rates in cancer patients with VTE. Deciding which meta-analyses are right or wrong is left to the appreciation of clinicians, provided that they are aware of all published meta-analyses, including the discrepant one, and able to interpret their results.

Beside the potential for discrepant results illustrated here, such multiplication of redundant meta-analyses raises scientific, ethical, and economic questions for both researchers and publishers. Does this ratio (20 meta-analyses/4 RCTs) reflect genuine scientific enthusiasm or a system driven by “publish or perish” pressure? The wide availability of free and easy-to-use statistical software may make it

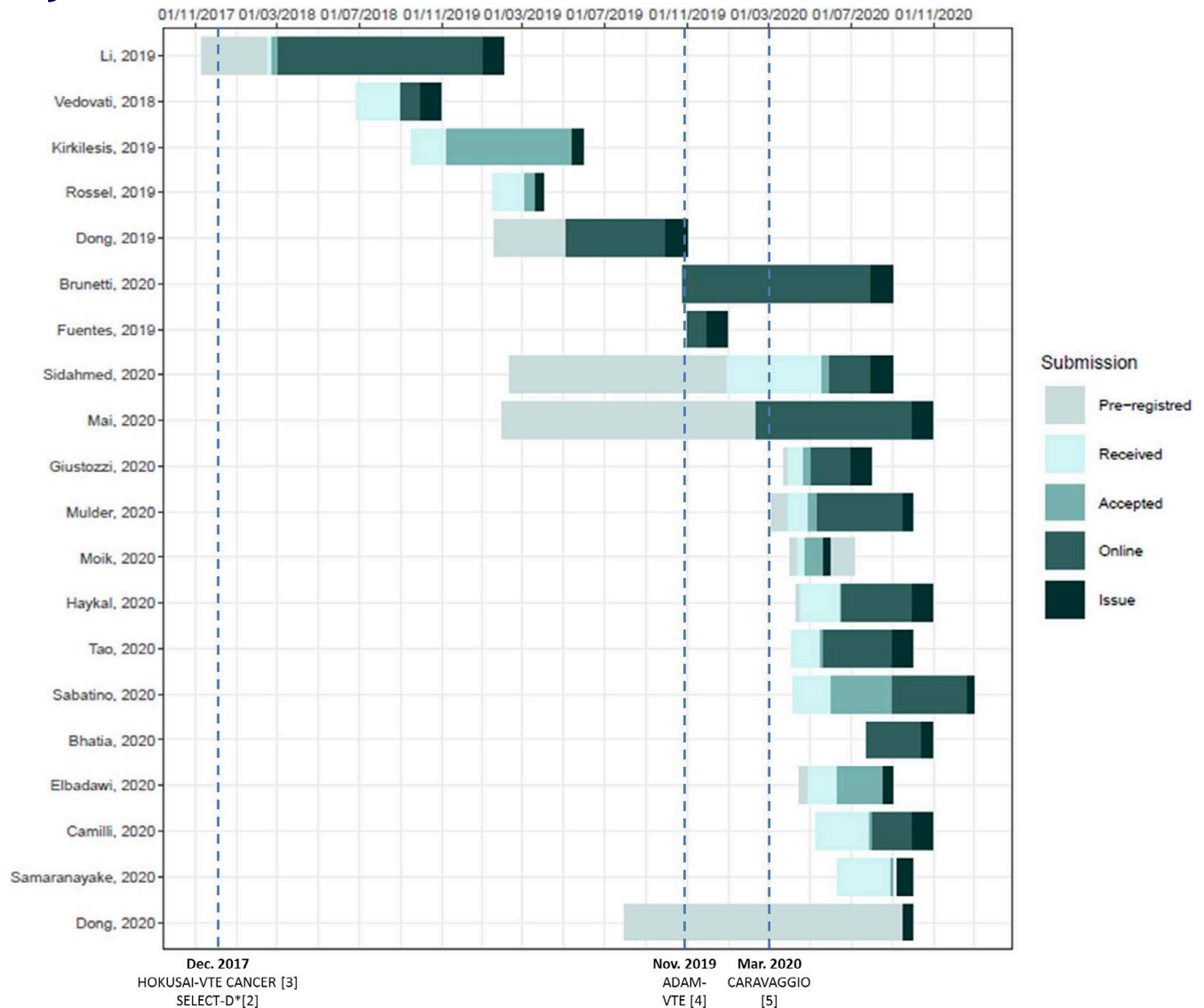


FIGURE 2 Calendar of publications for the four randomized controlled trials and 20 meta-analyses of direct oral anticoagulants versus low molecular weight heparins in cancer patients with venous thromboembolism. Dong, 2020: no information is given on the process of publication. *Congress presentation of results

tempting for any researcher, even with limited knowledge in statistical methods or the concerned medical field, to conduct and publish such low-cost research. Such appropriation of someone else's work may even appear morally illegitimate. On the other hand, a trialist is not a meta-analyst, and *vice versa*. Therefore, both specialties should be incited to associate their respective competences to produce meta-analyses that are both clinically relevant and scientifically irreproachable.²⁶

Proposals to moderate this rush to publication and authorship inflation could include using central sites that host "living" meta-analyses such as the Cochrane Library (<https://www.cochranelibrary.com/>) or recent real-time analyses of coronavirus disease 2019 treatments (<http://www.metaevidence.org/COVID19.aspx>, <https://covid-nma.com/>). Also, the authors of new RCTs should be

encouraged to update the corresponding meta-analysis in the same paper as their original research.²⁷ In the best of all possible worlds, both researchers and journals should collaborate to contain the waste of time and resources reflected in a production of redundant literature that has now reached "epidemic proportions."¹

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Contribution to concept and design: Silvy Laporte, Philippe Girard, Corinne Frere, Patrick Mismetti, Michel Cucherat. Analysis and/or interpretation of data: Céline Chapelle, Edouard Ollier, Silvy Laporte,

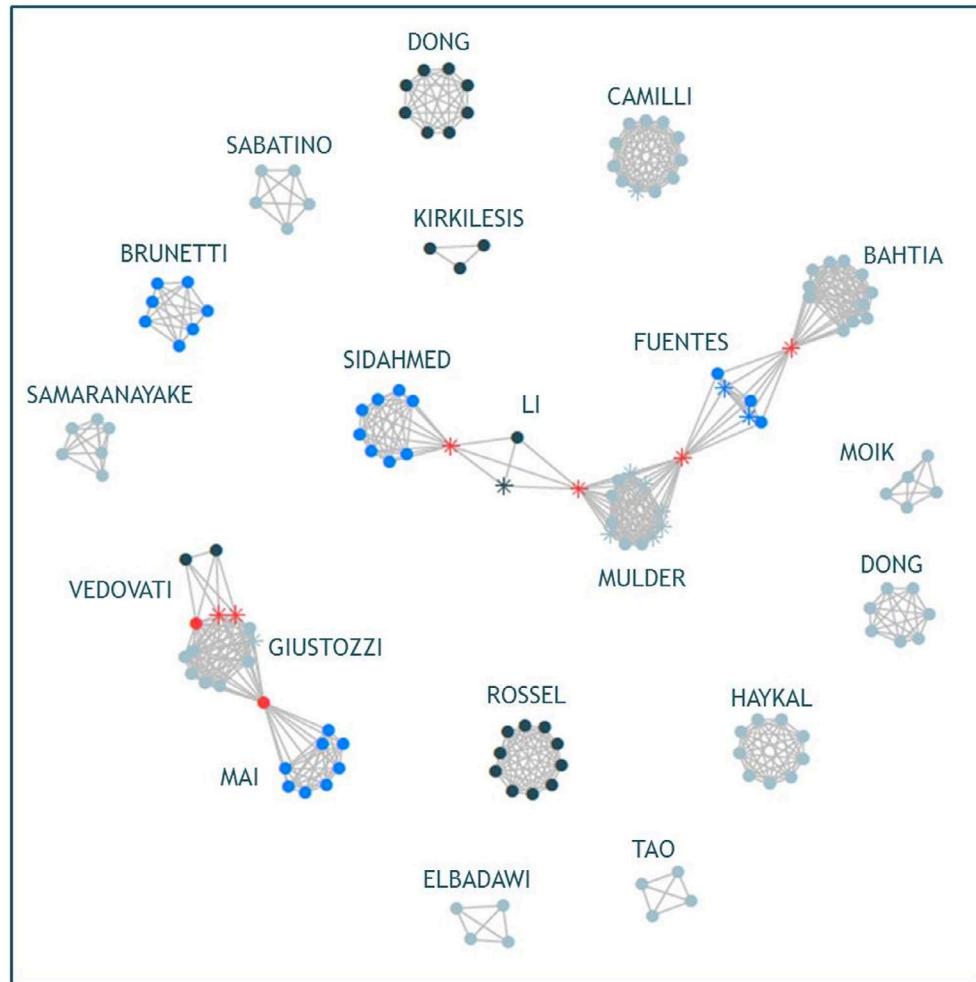


FIGURE 3 Authors' network publishing meta-analysis for 20 meta-analyses of direct oral anticoagulants versus low molecular weight heparins in cancer patients with venous thromboembolism. Each point represents an author of a meta-analysis and each star represents an author of both a randomized controlled trial and a meta-analysis. Dark points represent the authors of a meta-analysis of two trials. Blue points represent the authors of a meta-analysis of three trials. Light blue points represent the authors of a meta-analysis of four trials. Red points represent an author who participated in two different meta-analyses. Two authors are directly connected by an edge if they are both authors in the same meta-analysis. The first author's last name is associated with each meta-analysis

Michel Cucherat. Critical writing or revising the intellectual content: Céline Chapelle, Philippe Girard, Edouard Ollier, Silvy Laporte. Final approval of the version to be published: all authors.

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Annexe 2.

**Poster « Impacts positifs et négatifs de l’outil méta-analytique sur la
synthèse des connaissances scientifiques. »**

Impacts positifs et négatifs de l'outil méta-analytique sur la synthèse des connaissances scientifiques

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CONTEXTE

- **Méta-analyse : combiner des résultats de plusieurs essais pour en faire une synthèse reproductible et quantifiée**
 - Démarche systématique et rigoureuse
 - Intérêt : confirmer/infirmen un résultat ou réconcilier des résultats discordants
 - Largement utilisée pour améliorer la précision des estimations de l'effet du traitement
 - Considérée comme le **plus haut niveau de preuve** = référence en recherche clinique ⇒ « boom » des publications des méta-analyses (500/an en 2000 → 6000/an en 2020)
 - Importance de **mettre à jour** les méta-analyses existantes dès publication de nouvelles données
- **Mais impact des méta-analyses peut être négatif**
 - **Sur-publication des méta-analyses** sur le même sujet ⇒ pollution des articles scientifiques ⇒ risque de **résultats conflictuels** ⇒ **confusion** sur l'interprétation des résultats
 - Méta-analyse d'études biaisés ⇒ résultats biaisés

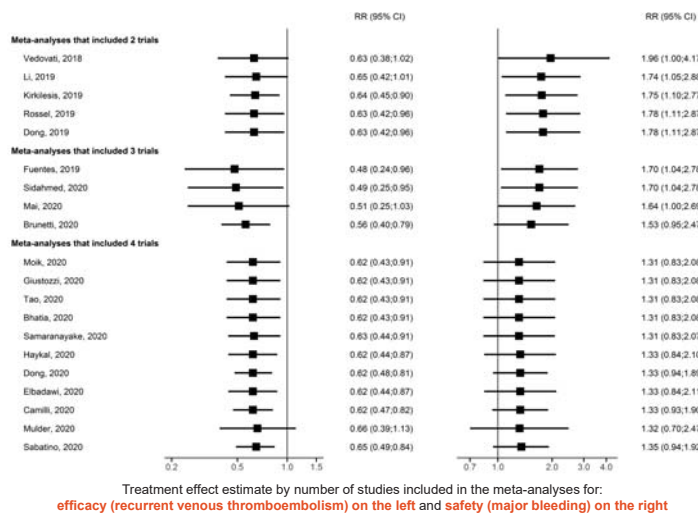
Réaliser une synthèse descriptive des méta-analyses existantes incluant les 4 essais pivots publiés (HOKUSAI-VTE cancer, SELECT-D, ADAM-VTE, CARAVAGGIO) évaluant les AODs vs HBPMs chez les patients atteints de cancer et thrombose

MÉTHODES

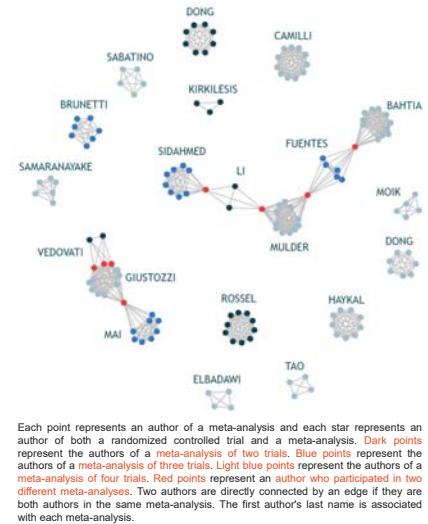
- **Méthodes classique de recherche et sélection des études**
 - Recherche exhaustive : Pubmed, Cochrane, Google Scholar
 - Équation de recherche avec mots clés et MeSH Terms
 - Entre le 1/1/2018 et le 6/10/2020
 - Sélection et extraction par 2 personnes
- **Résultats des méta-analyses représentés par forestplot**
- **4 essais randomisés publiés : HOKUSAI-VTE cancer (Raskob, 2018), SELECT-D (Young, 2018), ADAM-VTE (McBane, 2020), CARAVAGGIO (Agnelli, 2020)**
- **20 méta-analyses identifiées combinant les résultats de :**
 - 2 essais randomisés : N = 5
 - 3 essais randomisés : N = 4
 - 4 essais randomisés : N = 11

RÉSULTATS

Résultat principal : estimation de l'effet traitement



Réseau des auteurs



- **Publication** : Chapelle C, Ollier E, Girard P, Frere C, Mismetti P, Cucherat M, Laporte S. An epidemic of redundant meta-analyses. J Thromb Haemost. 2021 May;19(5):1299-1306

DISCUSSION

- Multiplication des **méta-analyses redondantes** : soulèvent des **questions scientifiques, éthiques et économiques**. Pression du « Publish or Perish » ?
- Proposition pour **modérer cette ruée à la publication** : méta-analyses vivantes, mise à jour de la méta-analyse dans la même publication que l'essai randomisé
- Importance de la **collaboration** entre chercheurs et revues

Annexe 3.

**Article « Replication of Systematic Reviews: Is It to the Benefit or
Detriment of Methodological Quality? »**

ORIGINAL ARTICLE

Replication of systematic reviews: is it to the benefit or detriment of methodological quality?

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Abstract

Objectives: To perform an overview of the overlap of systematic reviews (SRs) assessing direct oral anticoagulants and characterize these reviews in terms of bias and methodological quality (PROSPERO: CRD42022316273).

Study Design and Setting: A PubMed-indexed search was performed from inception to January 31, 2022 to identify SRs evaluating direct oral anticoagulants in patients treated for an acute venous thromboembolism. The risk of bias of these SRs was assessed according to the Risk Of Bias In Systematic reviews tool. Redundancy was defined as overlap in terms of the type of population considered, the interventions compared, and the studies included.

Results: A total of 144 SRs were evaluated, of which 26 (18.1%) were classified as original, 87 (60.4%) as conceptual replications, and 31 (21.5%) as excessive replications. The risk of bias was high in 19 (73.1%) of the original SRs, 65 (74.7%) of the conceptual replications, and 21 (67.7%) of the excessive replications. Compared to the original SRs, the overall methodological quality was not improved in either conceptual or excessive replications.

Conclusion: A large number of SRs was classified as replications; a fifth constituted excessive replications. The replications showed no improvement in overall methodological quality compared to the original SRs. © 2023 Elsevier Inc. All rights reserved.

Keywords: Systematic review; Bias; Methodological quality; Replication; Redundancy; Duplication

Data availability: Data will be made available on request.

Funding source: This research was not financed by any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Reproducible research statement: Study protocol: Registered in PROSPERO (registration no. CRD42022316273) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=316273). Statistical code and dataset: The analysis scripts and dataset may be requested from Céline Chapelle (E-mail address: celine.chapelle@chu-st-etienne.fr).

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1. Introduction

For many years now, a race to publish seems to have been underway. However, the increasing number of scientific articles published each year raises issues in terms of scientific integrity and value. Specifically, the notion of “publish or perish” [1] and the mass production of trials of poor methodological quality that ultimately fail to provide reliable results [2,3] and represent a waste of research resources [4–6] have become a harsh reality. In view of their high level of evidence, systematic reviews and meta-

What is new?**Key findings**

- More than 80% of the systematic reviews analyzed were replications and were considered as being of poor methodological quality; a fifth of these reviews constituted excessive replications, showing overlap of population types, interventions compared, and studies included.

What this adds to what was known?

- Methodological quality tended to improve in excessive replications compared to original systematic reviews or conceptual replications but the differences were not statistically significant.

What is the implication and what should change now?

- Systematic reviews replications of poor methodological quality represent a considerable waste of effort and resources.
- Authors, publishers, and reviewers should be vigilant and carefully scrutinize already existing reviews to avoid wasteful replication.

analyses have become a common feature of clinical research, and therefore do not escape this rush to publish [7,8]. In particular, meta-analyses of aggregate data (i.e., those based on effect estimates of studies reported in the literature) have dramatically increased due to the facility of obtaining aggregate data and the development of free and easy-to-use statistical software.

Meta-analytical methods were originally developed to quantitatively synthesize an abundance of published data and produce a readily comprehensible and concise overview of a therapeutic field to facilitate decision-making. However, the validity of meta-analyses depends mainly on the quality of their development and reporting. Many systematic reviews and meta-analyses are of poor quality, principally due to methodological weaknesses in their execution [7]. Given the mass of systematic reviews and meta-analyses published, it is difficult to distinguish the most reliable, relevant, and least biased results. This is especially true when these systematic reviews and meta-analyses are redundant or show contradictory results [7,9] and when their number exceeds that of individual studies [10,11]. Overlap, replication, and redundancy have already been observed in many fields of medical research [12–26]. Various arguments have been invoked to justify replication and redundancy, such as the wish to update an earlier systematic review and meta-analysis by including data from new high-quality trials not evaluated previously, reluctance to extrapolate the results obtained to all patients

in the absence of subgroup analyses, the need to assess an end point not evaluated in other systematic reviews and meta-analyses, or a change in endpoint definition. In fact, redundancy might be acceptable if its sole aim was to produce a less biased meta-analysis. Redundancy may also be unintentional, especially when similar systematic reviews and meta-analyses are accepted for publication by different journals during the same period, but this could be avoided by preregistration of systematic reviews. In addition, Tugwell et al. [27] developed a checklist and guidance to aid assessment of whether or not replication of systematic reviews would be useful. Up to now, this mechanism of replication has never been described, especially with regards to the links between the authors of such successive systematic reviews.

Our study aimed in particular to investigate replication and its characteristics in terms of the biases and methodological quality of the systematic reviews concerned. With this objective in mind, and to illustrate the phenomenon of replication, we chose the example of direct oral anticoagulants (DOACs) used for the acute treatment of venous thromboembolism (VTE), in view of the recent development of these medicinal products and the large number of systematic reviews published on this topic.

2. Materials and methods*2.1. Identification and selection of systematic reviews and data extraction*

The study protocol was prospectively registered in the International prospective register of systematic reviews (PROSPERO, <https://www.crd.york.ac.uk/PROSPERO>, registration number CRD42022316273).

We sought to identify all relevant published systematic reviews including randomized controlled trials or observational studies evaluating DOACs in relation to any comparator in patients treated for VTE during the acute and/or extended phase of anticoagulation, including patients receiving acute treatment for VTE in the context of cancer. A literature search was performed on PubMed from inception to January 31, 2022 using keywords and medical subject headings terms with no restrictions on language or publication period. Initially, the search was not restricted to the treatment of VTE to include systematic reviews addressing several indications. The full electronic search equation is presented in [Appendix Table 1](#).

One of the authors (C.C.) screened the titles and abstracts of publications for possible inclusion. Then, two of the authors (C.C. and P.B.) independently screened the full-text articles and discrepancies between reviewers being resolved by discussion. To be eligible, the systematic reviews had to meet the following criteria: (1) include randomized controlled trials or observational studies; (2) evaluate DOACs in relation to any comparator (active standard treatment: vitamin-K antagonists, aspirin, or low-

molecular-weight heparin; nonactive treatment: placebo or control; or other DOACs); and (3) include patients treated for an acute VTE during the acute or extended phase of anticoagulation. Pairwise (individual patient data or aggregated data) and network meta-analyses were included. Systematic reviews including only one study assessing DOACs in acute VTE patients were excluded. To characterize replication, only full-text articles were included in this review.

Data were independently extracted by two of the authors (C.C. and P.B.). In the event of discrepancies between reviewers, a consensus was reached by discussion. The following data were extracted from each systematic review: publication details (author names, year of publication, journal, free-access journal, and impact factor of the journal), details of the meta-analysis (pairwise or network design, statistical model, registration, number of studies included, names and designs of the studies included, treatments, and method used to assess the risk of bias of the included studies [tool used and use of this tool to assess the effect of bias on the results]), and citations of previous systematic reviews in the field. A systematic review was defined as having no overlap in authorship if it shared no common author with other systematic reviews. Two systematic reviews were considered as having an overlap in authorship if they shared at least one common author.

2.2. Description of the phenomenon of replication

Systematic reviews are first classified according to their Population, Intervention, Comparison, and Outcome question. Each systematic review is then assigned to one of three replication categories according to the definitions used by Tugwell et al. [27]: original, conceptual replication, or excessive replication. The original category comprises both original and updated systematic reviews, that is, both the original systematic reviews published on a particular topic and any updates published by the same team [28]. Conceptual replication corresponds to replication to broaden or narrow the research question, although maintaining the same objectives as the original systematic reviews, but (1) adding new randomized studies, (2) focusing on a comparator or an intervention, (3) highlighting patient subgroups, (4) investigating other outcomes, or (5) adding nonrandomized studies. Finally, excessive replication is defined as overlap in terms of the type of population, the interventions compared, and the studies included. If several systematic reviews are published at the same time, the first systematic review registered is considered as the original one. Two of the authors (C.C. and S.L.) assigned each systematic review to one of the three categories; discrepancies being resolved by discussion.

2.3. Quality assessment of the systematic reviews

Two authors (C.C. and P.B.) independently assessed the risk of bias of the systematic reviews according to the Risk

Of Bias In Systematic reviews (ROBIS) tool; discrepancies between reviewers being resolved by discussion. Using this tool, the assessment of the risk of bias of the systematic reviews was accomplished in two phases: (1) identification of concerns regarding the review process and (2) appraisal of the overall risk of bias [29]. Phase 1 covered four domains: study eligibility criteria, study identification and selection, data collection and study appraisal, and synthesis and findings. Each of the four domains was subjectively assessed as having a low, unclear, or high risk of bias, based on the questions specified in the tool. In the second phase, the overall risk of bias of the systematic reviews was assessed as low, unclear, or high, based on assessment of the four domains in phase 1.

2.4. Statistical analysis

The descriptive analysis was performed according to the category of replication (original, conceptual replication, or excessive replication) using numbers and percentages for qualitative data, and means with their standard deviation, as well as medians with interquartile range for quantitative data.

Network diagrams were used to visualize the links between authors of the systematic reviews. To visualize the number of replications of systematic reviews associated with the original systematic review, we used alluvial diagrams. To analyze whether the methodological quality of the systematic reviews differed between the original, conceptual replication, and excessive replication categories, a logistic regression analysis was performed, taking the replication category (original, conceptual replication, or excessive replication) as the covariate and the risk of bias in each domain and overall (high vs. low) as the dependent variable. The coefficient of the covariate was expressed as a ratio.

All analyses were performed using R statistical software (R Foundation for Statistical Computing). Network diagrams were plotted using *igraph* and *network* packages [30].

3. Results

3.1. Study selection

The search procedure identified 1,258 potentially eligible systematic reviews, of which 988 were excluded after a scan of their titles and abstracts (Appendix Figure 1). After assessment of the full texts, 91 additional references were excluded. Finally, 144 systematic reviews were included in the review (references listed in the Appendix).

3.2. Description of the systematic reviews included according to the category of replication

Among these 144 systematic reviews, 26 were classified as original, 87 as conceptual replications, and 31 as

excessive replications. For 19 (73.1%) of the 26 original systematic reviews, we identified at least one other systematic review showing overlap, that is, a conceptual replication, an excessive replication, or both (Fig. 1). Some original systematic reviews exhibited extensive overlap with up to 15 conceptual replications and 12 excessive replications.

The characteristics of the 144 systematic reviews included are summarized in Table 1 and fully described in Appendix Tables 2 and 3. Most of the systematic reviews had a pairwise design and had been performed in Europe and North America. Most conceptual replications (54.0%) were published in a free-access format compared to 42.3% and 45.2% of the original systematic reviews and excessive replications, respectively. A protocol of the systematic review had been registered in 46.1%, 27.6%, and 19.3% of the original reviews, conceptual replications, and excessive replications, respectively, mainly in the PROSPERO database. A quarter of the excessive replications indicated protocol registration within 10 days before submission of the systematic review for publication, compared to 2 months for original systematic reviews and 3 months for conceptual replications. Twenty (64.5%) excessive replications had assessed the risk of bias of the studies included, compared with more than 70% in the original systematic reviews and conceptual replications. No

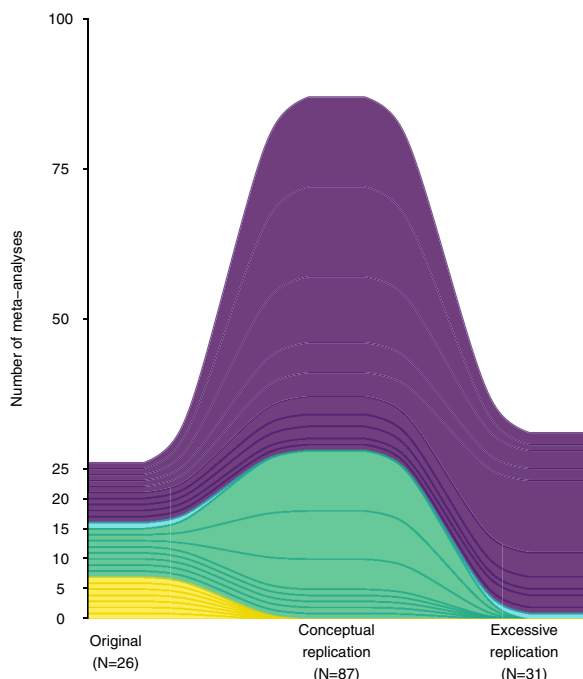


Fig. 1. Alluvial diagram of the number of replications associated with the corresponding original systematic review. Yellow: no associated conceptual or excessive replication; green: at least one conceptual and no excessive replication associated; blue: at least one excessive and no conceptual replication associated; purple: at least one conceptual and one excessive replication associated. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

overlap in authorship with other systematic reviews was observed in 14 (45.2%) of the 31 excessive replications, 35 (40.2%) of the 87 conceptual replications, and seven (26.9%) of the 26 original systematic reviews. Of the 734 authors of systematic reviews, 537 (73.2%) had published an original systematic review and/or a conceptual replication (Appendix Figure 2). The remaining 197 authors (26.8%) had published at least one excessive replication, of which 51 (25.9%) had also published at least one original systematic review or a conceptual replication.

Forty one (47.1%) of the 87 conceptual replications cited a previous systematic review, of which 17 included a justification for the replication and 27 cited another conceptual replication (Table 2). Twenty one (67.7%) of the 31 excessive replications cited a previous systematic review, of which 14 included a justification for the replication and 15 cited the original systematic review. Eight of the 31 excessive replications cited the systematic review they duplicated.

The reasons for conceptual replication were to add new randomized studies (26.4%), to highlight particular patient subgroups (20.7%), to investigate other outcomes (19.5%), to focus on a comparator or an intervention (17.2%), and to add nonrandomized studies (16.1%). The characteristics of the 87 conceptual replications are summarized in Appendix Table 4.

3.3. Risk of bias of the systematic reviews

Overall, the risk of bias was assessed as high in 99 (68.7%) systematic reviews and low in 39 (27.1%) systematic reviews (Table 1). A high risk of bias was observed in almost 70% of the original and conceptual replications but in 61.3% of the excessive replications. The high overall risk of bias of the systematic reviews was mainly due to the high risk of bias in domain 4 of the ROBIS tool regarding study synthesis and findings (Fig. 2, Appendix Table 5).

3.4. Comparison of risk of bias

Compared to original systematic reviews, the overall methodological quality was not improved in replications (Fig. 3).

Comparison of conceptual replications vs. original systematic reviews revealed no difference in either overall methodological quality (odds ratio 1.09, 95% confidence interval [0.38–2.85]) or the risk of bias in each domain (Fig. 3A). The risk of bias of the individual items within each domain is presented in Appendix Figure 3.

Comparison of excessive replications vs. original systematic reviews suggested a better overall methodological quality (odds ratio 0.77, 95% confidence interval [0.24–2.42]), although the difference was not statistically significant (Fig. 3B). The risk of bias of individual items within each of these domains is presented in Appendix Figure 4.

Table 1. Summary of the characteristics of the systematic reviews included according to the replication category

Characteristics of the Systematic Reviews	Original (N = 26)	Conceptual replication (N = 87)	Excessive replication (N = 31)
Type of meta-analysis			
Individual patient data meta-analysis	3 (11.5)	3 (3.4)	0 (0.0)
Pairwise meta-analysis	18 (69.2)	62 (71.3)	23 (74.2)
Network meta-analysis	5 (19.2)	22 (25.3)	8 (25.8)
Median (IQR) number of authors of the publication	6 (4–9)	6 (5–8)	6 (4–8)
Free-access publication	11 (42.3)	47 (54.0)	14 (45.2)
Journal not indexed for MEDLINE ^a	0 (0.0)	4 (4.6)	4 (12.9)
Median (IQR) impact factor of the journal	5.24 (3.06–7.66)	3.50 (2.77–5.72)	3.00 (2.32–5.33)
Geographic location of the first author			
Europe	10 (38.5)	34 (39.1)	16 (51.6)
North America	10 (38.5)	28 (32.2)	11 (35.5)
Asia	5 (19.2)	22 (25.3)	2 (6.4)
Other	1 (3.8)	3 (3.4)	2 (6.4)
Design of the included studies			
RCTs only	23 (88.5)	72 (82.8)	30 (96.8)
Observational studies only	0 (0.0)	3 (3.4)	1 (3.2)
RCTs and observational studies	3 (11.5)	12 (13.8)	0 (0.0)
Assessment of the risk of bias of the included studies			
Descriptive (table/figure)	20 (76.9)	65 (74.7)	20 (64.5)
Analysis according to risk of bias	16	52	16
Registration of the protocol	4	13	4
PROSPERO	12 (46.1)	24 (27.6)	6 (19.3)
Cochrane database	10	22	5
Open Science Framework	2	1	0
Open Science Framework	0	1	1
Median time (IQR) from registration to submission of the publication (mo)	2.6 (2.2–3.2)	5.8 (3.1–8.7)	0.4 (0.3–12.7)
No overlap in authorship	7 (26.9)	35 (40.2)	14 (45.2)
Risk of bias of the systematic reviews (ROBIS tool)			
Low	7 (26.9)	22 (25.3)	10 (32.3)
Unclear	1 (3.9)	3 (3.4)	2 (6.4)
High	18 (69.2)	62 (71.3)	19 (61.3)

Values are numbers (percentages) unless stated otherwise.

Abbreviations: IQR, interquartile range; RCT, randomized controlled trial.

^a At the time of the publication.

Table 2. Citations of the systematic reviews included according to the replication category

Characteristics of the Systematic Reviews	Conceptual replication (N = 87)	Excessive replication (N = 31)
Citations of previous systematic reviews	41 (47.1)	21 (67.7)
Inclusion of a justification	17	14
Citations of the original systematic review	10/41 (24.4)	15/21 (71.4)
Inclusion of a justification	2	9
Citations of a conceptual replication	27/41 (65.8)	10/21 (47.6)
Inclusion of a justification	13	7
Citations of an excessive replication	11/41 (26.8)	8/21 (38.1)
Inclusion of a justification	4	5

Values are numbers (percentages) unless stated otherwise.

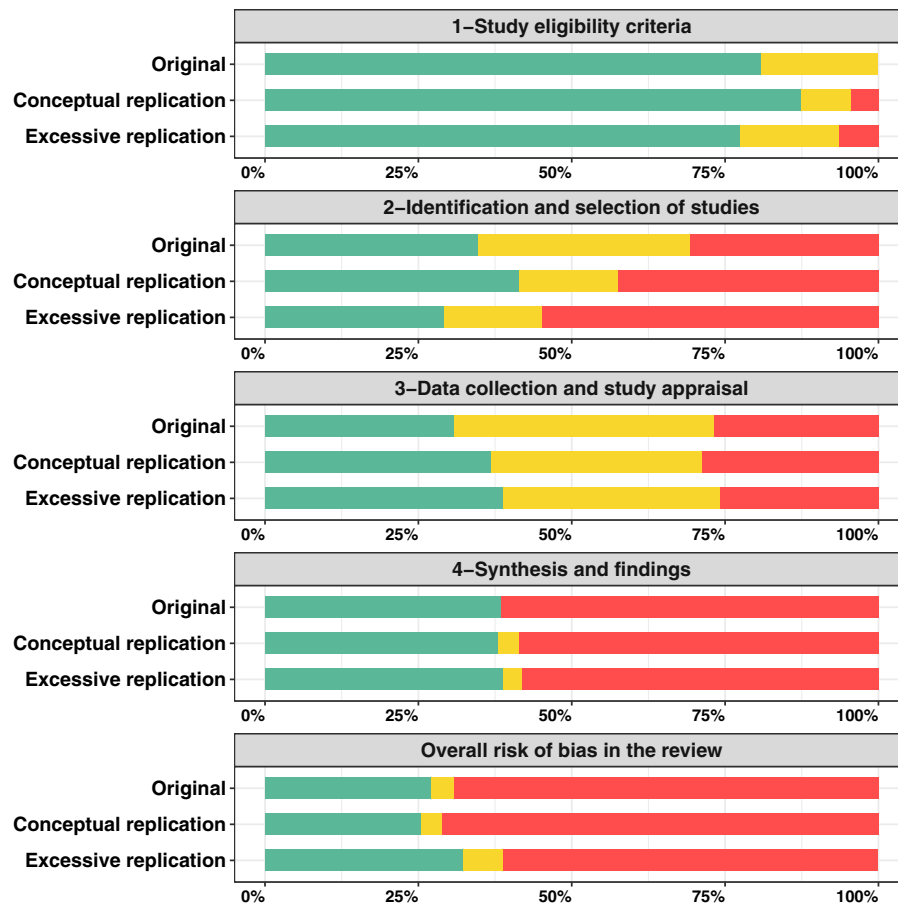


Fig. 2. Risk of bias of the systematic reviews for each ROBIS tool domain according to the replication category (original, conceptual replication, or excessive replication) presented as percentages across all systematic reviews included. Green: low risk of bias; orange: unclear risk of bias; red: high risk of bias. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Comparison of excessive replications vs. conceptual replications suggested a better overall methodological quality of excessive replication, although the difference was not statistically significant (Fig. 3C). The risk of bias of individual items within each domain is presented in Appendix Figure 5.

4. Discussion

This systematic overview included 144 systematic reviews evaluating DOACs vs. any comparator in patients treated for VTE, of which 87 (60.4%) were conceptual replications and 31 (21.5%) were excessive replications. Compared with other systematic reviews, excessive replications assessed the risk of bias of the included studies to a lesser extent and barely 20% registered the protocol of the systematic review (19.3%). However, excessive replications showed a trend toward a lower risk of bias than the other types of systematic review.

To the best of our knowledge, this is the first study analyzing replications among systematic reviews assessing DOACs in the acute treatment of VTE and evaluating the methodological quality of excessive replications compared

to original systematic reviews. Overlap of systematic reviews assessing DOACs has previously been evaluated only with regard to stroke prevention in atrial fibrillation [23]. In that context, the extent of overlap was substantial, possibly owing to the small number of trials compared to the number of systematic reviews. Several other studies have also observed overlap and redundancy of systematic reviews in many fields of medical research [10,13–22,24–26]. A quarter of the excessive replications included in the present review cited the systematic review they duplicated, indicating that these systematic reviews were performed despite awareness of other systematic reviews with a similar Population, Intervention, Comparison, and Outcome question, suggesting deliberate redundancy. The justifications for replication advanced by the authors of systematic reviews included, for example, the assessment of an outcome not previously evaluated or of the separate components of composite outcomes, the need for subgroup analyses, the availability of new data, or the inclusion of a larger number of studies and patients. Other nonvalid justifications were also advanced, such as to “have a clear presentation and summarization of the study and sensitivity analysis”. Ioannidis [7] and Siontis et al. [12] also noted that the authors of redundant systematic reviews and meta-analyses did not systematically cite previous systematic

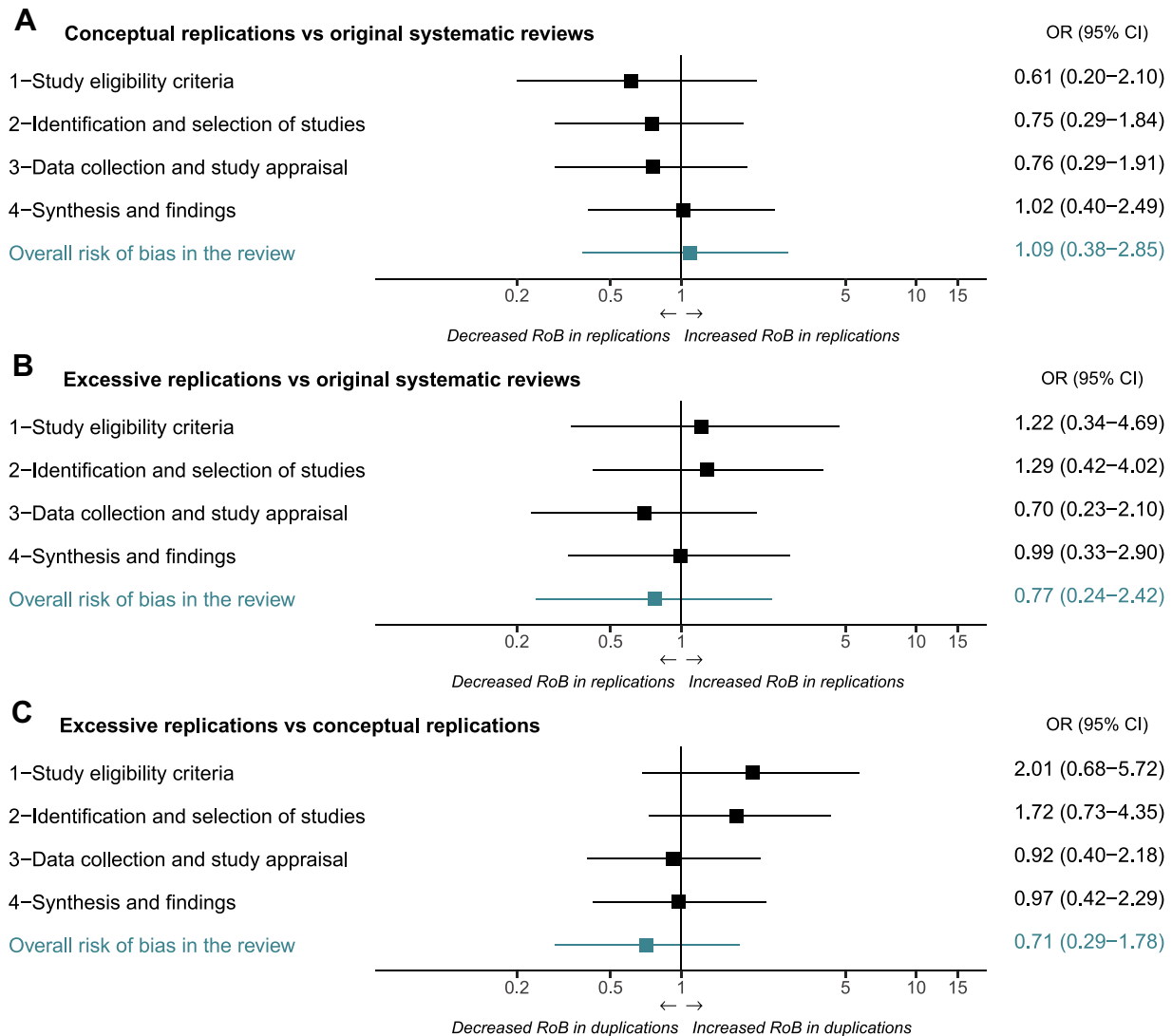


Fig. 3. Comparison of the risk of bias for each ROBIS tool domain between (A) conceptual replications and original systematic reviews (reference: original systematic reviews); (B) excessive replications and original systematic reviews (reference: original systematic reviews); (C) excessive replications and conceptual replications (reference: conceptual replications). An OR < 1 denotes a lower risk of bias compared to the reference, an OR of 1 denotes no difference, and an OR > 1 denotes a higher risk of bias compared to the reference. 95% CI, 95% confidence interval; OR, odds ratio; RoB, risk of bias. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

reviews and meta-analyses concerning the same topic. They found that only 3% of these prior meta-analyses “were cited by subsequent studies claiming to be replications addressing the same question.”

Based on the ROBIS quality assessment tool, more than 70% of the systematic reviews included in this overview were considered to be at high risk of bias. For this reason, despite the level of evidence of these systematic reviews and meta-analyses, they were not always synonymous with high-quality research. Even assuming that when a systematic review is replicated, the methodological quality might be improved, this was not the case and these replications retained a high overall risk of bias. Most of the systematic reviews evaluated were therefore of low methodological quality, replications decreasing their quality still further. The quality of systematic reviews needs to be improved

through prospective registration of the protocol, an exhaustive search strategy, reporting of the methods and results of additional analyses, and assessment of the potential impact of the risk of bias of the studies included in the meta-analysis of the results obtained. This conclusion is consistent with those of studies evaluating the methodological quality of systematic reviews and meta-analyses concerning many other clinical issues and finding this to be generally poor [26,31–41]. As we have seen, some authors registered their systematic reviews only a few weeks before publication, which does not comply with PROSPERO requirements and suggests retrospective rather than prospective registration. The prospective registration of a systematic review protocol has two objectives. The first is to avoid excessive replication and therefore redundancy. The second is to avoid any inductive approach and thus to

declare the research objective once the results have been obtained. Registration does not imply a prospective evaluation process if it precedes publication by only a few weeks. Nowadays, it is not only registration that is important but also the date of this registration.

The reporting of systematic reviews and meta-analyses should be further regulated and authors should follow the guidelines issued. In particular, the consistency of the publication with the protocol should be carefully assessed and reported to enable identification of any sources of bias and explanation of disparities between the results of different meta-analyses. Bolland and Gray reviewed meta-analyses evaluating the effects of vitamin D supplementation on bone fractures and found their results to be discordant owing to substantial disparities in trial selection, outcome definition, and statistical methodology [14]. Among the seven meta-analyses included in their review, only four included all eligible trials and two even included trials that did not meet their eligibility criteria. Finally, assessment of the quality of the methodology and results of redundant systematic reviews and meta-analyses is crucial to ensure that these do not convey misleading, inaccurate, or biased information.

Our overview has some limitations. First, we performed an umbrella review and restricted our search to a single database. Although the list of systematic reviews indexed by PubMed is comprehensive, we may have missed some additional published and unpublished systematic reviews. The extent of replication is therefore potentially even more than that we describe here. A second limitation is that we based our analysis of replication on the date of registration of the protocol whenever possible, but otherwise on the date of publication of the systematic reviews (online or in printed issues) without considering the delay in editorial and publication procedures. The third limitation concerns evaluation of the level of bias present within a systematic review. We chose to use the ROBIS tool which requires substantial reflection to complete, an issue that could become problematic in the context of a larger review. Furthermore, the assessment of each risk of bias domain requires careful analysis of the systematic review concerned to correctly rate the risk of bias, adding to the difficulty of using this tool. Finally, even when used by experienced methodologists, the ROBIS tool remains subjective.

5. Conclusion

The massive production of systematic reviews has led to a considerable waste in the form of excessive replicated publications of poor methodological quality. This waste could be avoidable in most cases if authors, publishers, and reviewers were sufficiently vigilant. Authors have a role to play before starting their review, first by systematically checking the evidence already existing or likely to be published soon and then, if a further systematic review and meta-analysis is considered necessary, by systematically registering its protocol, assuming

that excessive replication is not deliberate. In that case, publishers and reviewers should scrutinize the existing evidence to avoid wasteful excessive replication and should ensure that the recommendations of well-established guidelines for the reporting of systematic reviews and meta-analyses are fully respected to improve the publication quality.

CRedit authorship contribution statement

Céline Chapelle: Conceptualization, Methodology, Data curation, Formal analysis, Software, Writing – original draft, Writing – review & editing. **Edouard Ollier:** Conceptualization, Methodology, Formal analysis, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **Paul Bonjean:** Data curation, Writing – original draft, Writing – review & editing. **Clara Locher:** Conceptualization, Writing – original draft, Writing – review & editing. **Paul Jacques Zufferey:** Conceptualization, Writing – original draft, Writing – review & editing. **Michel Cucherat:** Conceptualization, Writing – original draft, Writing – review & editing. **Silvy Laporte:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Céline Chapelle, Edouard Ollier, Paul Bonjean, Clara Locher, and Paul Jacques Zufferey: none. Michel Cucherat has received personal fees from Bayer and BMS for consulting. Silvy Laporte has received personal fees from Bayer for consulting, personal fees continuing medical education lectures from Pfizer, and personal fees for continuing medical education lectures from Eli Lilly.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinepi.2023.08.012>.

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Replication of Systematic Reviews: Is It to the Benefit or Detriment of Methodological Quality?

Appendix

Appendix Table 1. Full electronic search equation used for systematic reviews identification in PubMed database up to January 31st, 2022.

1	((Factor Xa Inhibitors/therapeutic use[MeSH Terms]) OR (Factor Xa Inhibitors/adverse effects[MeSH Terms]) OR (direct thrombin inhibitors[MeSH Terms]) OR (thrombin inhibitors, direct[MeSH Terms]) OR (dabigatran[Title/Abstract]) OR (rivaroxaban[Title/Abstract]) OR (apixaban[Title/Abstract]) OR (edoxaban[Title/Abstract]) OR (argatroban[Title/Abstract]) OR (direct oral anticoagulant*[Title/Abstract]) OR (direct oral anti-coagulant*[Title/Abstract]) OR (DOAC*[Title/Abstract]) OR (DOA[Title/Abstract]) OR (DOAs[Title/Abstract]) OR (direct OAC*[Title/Abstract]) OR (anticoagulation strategies[Title]) OR (novel oral anticoagulant*[Title]) OR (non-vitamin K antagonist[Title/Abstract]) OR (non-vitamin-K-antagonist*[Title/Abstract]) OR (nonvitamin K oral anticoagulant*[Title/Abstract]) OR (direct oral anticoagulation*[Title/Abstract]) OR (new oral anticoagulant*[Title/Abstract]) OR (NOAC*[Title/Abstract]) OR (target-specific oral anticoagulant*[Title/Abstract]) OR (TSOAC*[Title/abstract]))
2	((meta-analysis[Title/Abstract]) OR (Meta-Analysis[Publication Type]) OR (network meta-analysis[Title/Abstract]) OR (indirect comparison*[Title/Abstract]) OR (pooled-analysis[Title/Abstract]))
3	(("2005/01/01"[Date - Publication] : "3000"[Date - Publication]))
4	“recommendations”[Title]
5	“design”[Title]
6	“protocol”[Title]
7	1 AND 2 AND 3 NOT 4 NOT 5 NOT 6

Appendix Table 2. Characteristics of the systematic reviews included in the overview. The table is ordered by clinical context (initial, extended, or both initial and extended VTE treatment, or initial VTE treatment in cancer patients), type of meta-analysis (pairwise or network), and date of online publication.

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal [§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Initial VTE treatment										
Prins MH, 2013 (1)	Thromb J	24053656	20/09/2013	The Netherlands	IPD MA	Yes	1.561	2 RCTs	No	None
van der Hulle T, 2014 (2)	J Thromb Haemost	24330006	13/12/2013	The Netherlands	MA	Yes	5.720	5 RCTs	No	Cochrane
van der Hulle T, 2014 (3)	J Thromb Haemost	24819040	19/06/2014	The Netherlands	MA	Yes	5.720	4 RCTs	No	Cochrane
Larsen TB, 2014 (4)	PLoS One	25479007	05/12/2014	Denmark	MA	Yes	3.234	4 RCTs	No	Cochrane
Schulman S, 2014 (5)	Circulation	24344086	16/12/2013	Canada	IPD MA	No	14.430	2 RCTs	No	None
Antoniazzi S, 2014 (6)	Eur J Intern Med	24629895	11/03/2014	France	MA	No	3.609	2 RCTs	No	None
Goldhaber SZ, 2016 (7)	Thromb Haemost	27411591	27/09/2016	USA	IPD MA	No	5.627	2 RCTs	No	None
Goldhaber SZ, 2017 (8)	Thromb Haemost	29202209	30/11/2017	USA	IPD MA	No	4.952	2 RCTs	No	None
Gómez-Outes A, 2014 (9)	Thromb Res	25037495	06/07/2014	Spain	MA	No	2.447	6 RCTs	No	Cochrane
van Es N, 2014 (10)	Blood	24963045	24/06/2014	The Netherlands	MA	No	10.452	6 RCTs	No	None
Loffredo L, 2015 (11)	Intern Emerg Med	25539954	25/12/2014	Italy	MA	No	2.340	7 RCTs	No	JADAD
Di Minno MN, 2015 (12)	Ann Med	25665582	09/02/2015	Italy	MA	Yes	3.763	6 RCTs	No	JADAD

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Mumoli N, 2015 (13)	Int J Cardiol	25863742	27/03/2015	Italy	MA	No	4.638	6 RCTs	No	None
Dentali F, 2015 (14)	Intern Emerg Med	25982918	16/05/2015	Italy	MA	No	2.340	6 RCTs	No	JADAD
Di Minno MND, 2017 (15)	Eur Respir J	28954772	27/09/2017	Italy	MA	Yes	12.242	6 RCTs	No	None
Yamashita Y, 2018 (16)	Thromb Res	29655001	10/04/2018	Japan	MA	No	3.266	6 RCTs	No	Cochrane
Makam RCP, 2018 (17)	PLoS One	29795629	24/05/2018	USA	MA	Yes	2.776	5 RCTs	No	Cochrane
Aryal MR, 2019 (18)	Blood Adv	31405948	13/08/2019	USA	MA	Yes	4.584	5 Obs.	No	NOS
Chaudhary R, 2020 (19)	J Am Geriatr Soc	32441334	22/05/2020	USA	MA	No	5.562	6 RCTs	No	Cochrane
Zhou B, 2021 (20)	Front Cardiovasc Med	34568446	08/09/2021	China	MA	Yes	6.050	4 RCTs	No	None
Vedovati MC, 2014 (21)	Int J Cardiol	25217215	30/08/2014	Italy	MA	No	4.000	5 RCTs	No	Cochrane
Sharma M, 2015 (22)	Circulation	25995317	20/05/2015	UK	MA	Yes	17.047	8 RCTs	Yes (11/02/2014)	Cochrane
Di Minno MN, 2015 (23)	Blood Transfus Cochrane Database Syst Rev	25545875	25/11/2014	Italy	MA	Yes	1.514	5 RCTs	No	None
Robertson L, 2015 (24)	Cochrane Database Syst Rev	26636644	04/12/2015	UK	MA	No	6.103	5 RCTs	Yes (09/03/2015)	Cochrane
Brekelmans MPA, 2018 (25)	TH Open	31249922	08/01/2018	The Netherlands	MA	Yes	Not indexed	5 RCTs	No	None
Robertson L, 2015 (26)	Cochrane Database Syst Rev	26123214	30/06/2015	UK	MA	No	6.103	11 RCTs	Yes (09/03/2015)	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Touma L, 2015 (27)	Am J Cardiol	25547937	02/12/2014	Canada	MA	No	3.154	2 RCTs	No	Cochrane
Raccah BH, 2016 (28)	Chest	26836922	18/01/2016	Israel	MA	No	6.147	4 RCTs	Yes (15/09/2014)	Cochrane
Chen HY, 2021 (29)	Clin Drug Investig	33709339	11/03/2021	Taiwan	MA	No	2.859	2 RCTs + 5 Obs.	Yes (06/02/2020)	Cochrane + NOS
Senoo K, 2017 (30)	J Cardiol	27502316	05/08/2016	Japan	MA	Yes	2.918	3 RCTs	No	Cochrane
Bleker SM, 2017 (31)	Thromb Haemost Res Pract	28816341	17/08/2017	The Netherlands	IPD MA	No	4.952	3 RCTs	No	None
Haas S, 2021 (32)	Thromb Haemost	33870028	20/03/2021	Germany	IPD MA	Yes	Not indexed	2 Obs.	No	None
Valeriani E, 2020 (33)	J Thromb Haemost	32202042	22/03/2020	Italy	MA	Yes	5.824	6 RCTs	Yes (28/01/2020)	Cochrane
Mai V, 2021 (34)	Pharmacol Res	33246169	25/11/2020	Canada	MA	No	7.658	7 RCTs + 14 Obs.	Yes (05/07/2020)	Cochrane + ROBINS-I
Elshafei MN, 2021 (35)	J Thromb Thrombolysis	32556939	18/06/2020	Qatar	MA	Yes	2.300	5 Obs.	No	NOS
Katel A, 2021 (36)	Cureus	34026385	20/04/2021	Nepal	MA	Yes	Not indexed	5 Obs.	No	NOS
Li R, 2020 (37)	Thromb Res	32977134	17/09/2020	China	MA	No	3.944	1 RCT + 6 Obs.	Yes (28/04/2020)	Cochrane + NIH
Karathanos C, 2021 (38)	J Vasc Surg Venous Lymphat Disord	33965611	06/05/2021	Greece	MA	No	2.859	2 RCTs + 6 Obs.	No	JADAD + NOS
Mainbourg S, 2021 (39)	Thromb Res	33161284	15/10/2020	France	MA	No	3.944	2 RCTs	Yes (28/04/2020)	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal [§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Fox BD, 2012 (40)	BMJ	23150473	13/11/2012	Canada	NMA	Yes	17.000	9 RCTs	No	Cochrane
Castellucci LA, 2014 (41)	JAMA	25226478	17/09/2014	Canada	NMA	No	35.289	6 RCTs	Yes (24/02/2014)	Cochrane
Kang N, 2014 (42)	Thromb Res	24713109	24/03/2014	USA	NMA	No	2.447	6 RCTs	No	Cochrane
Mantha S, 2015 (43)	J Thromb Thrombolysis	24989022	03/07/2014	USA	NMA	Yes	1.884	6 RCTs	No	Cochrane
Hirschl M, 2014 (44)	Vasa	25147012	21/08/2014	Austria	NMA	No	1.000	6 RCTs	No	Cochrane
Cohen AT, 2015 (45)	PLoS One	26716830	30/12/2015	UK	NMA	Yes	3.057	6 RCTs	No	NIH
Sadlon AH, 2016 (46)	Swiss Med Wkly Am J Cardiovasc Drugs	27683276	28/09/2016	Switzerland	NMA	Yes	1.654	4 RCTs	No	Cochrane
Wang Z, 2021 (47)	Am J Cardiovasc Drugs	33817758	04/04/2021	China	NMA	No	3.571	4 RCTs	Yes (17/01/2020)	Cochrane + NOS
Extended VTE treatment										
Sardar P, 2013 (48)	Drugs	23812923	28/06/2013	USA	MA	No	5.530	4 RCTs	No	Cochrane
Sindet-Pedersen C, 2015 (49)	Thromb Res	26277682	29/07/2015	Denmark	MA	No	2.320	4 RCTs	No	Cochrane
Marik PE, 2015 (50)	PLoS One	26587983	20/11/2015	USA	MA	Yes	3.057	3 RCTs	No	Cochrane
Caldeira D, 2016 (51)	Expert Opin Drug Saf	26958897	12/04/2016	Portugal	MA	No	3.439	3 RCTs	No	None
Ebraheem M, 2020 (52)	J Thromb Haemost	32510840	08/06/2020	Canada	MA	Yes	5.824	3 RCTs	Yes (04/12/2017)	Cochrane
Vasanthamohan L, 2018 (53)	J Thromb Haemost	29772108	17/05/2018	Canada	MA	Yes	4.662	2 RCTs	No	Cochrane
Mai V, 2019 (54)	Chest	31174635	04/06/2019	Canada	MA	No	8.308	4 RCTs	Yes (14/02/2018)	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal [§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Castellucci LA, 2013 (55)	BMJ	23996149	30/08/2013	Canada	NMA	Yes	16.378	4 RCTs	Yes (07/01/2013)	Cochrane
Alotaibi G, 2014 (56)	Int Angiol	25056161	01/08/2014	Canada	NMA	No	0.833	3 RCTs	No	Cochrane
Sobieraj DM, 2015 (57)	Thromb Res	25795564	04/03/2015	USA	NMA	No	2.320	4 RCTs	No	Cochrane
Cohen AT, 2016 (58)	PLoS One	27487187	03/08/2016	UK	NMA	Yes	2.806	4 RCTs	No	Checklist
Rollins BM, 2014 (59)	Clin Ther	25092394	02/08/2014	USA	NMA	No	3.030	5 RCTs	No	JADAD
Wang KL, 2019 (60)	Heart	30327391	16/10/2018	Taiwan	NMA	No	5.213	6 RCTs	Yes (15/05/2017)	Cochrane
Mai V, 2019 (61)	PLoS One	30933993	01/04/2019	Canada	NMA	Yes	2.740	6 RCTs	No	Cochrane
Djulgovic M, 2020 (62)	J Eval Clin Pract	31190408	12/06/2019	USA	NMA	No	2.431	4 RCTs	No	Cochrane
Initial and extended VTE treatment										
Mak KH, 2012 (63)	BMJ Open	23043126	06/10/2012	Singapore	MA	Yes	1.583	5 RCTs	No	JADAD
Holster IL, 2013 (64)	Gastroenterology	23470618	05/03/2013	The Netherlands	MA	Yes	13.926	7 RCTs	No	Cochrane
Chatterjee S, 2014 (65)	Mayo Clin Proc	24996233	01/07/2014	USA	MA	No	6.262	6 RCTs	No	Cochrane
Alotaibi GS, 2013 (66)	Thromb Res	23932014	26/07/2013	Canada	MA	No	2.427	8 RCTs	Yes (30/01/2013)	Cochrane + NOS
Bloom BJ, 2014 (67)	Am J Cardiol	24440332	24/12/2013	Canada	MA	No	3.276	3 RCTs	No	Cochrane
Sardar P, 2014 (68)	J Am Geriatr Soc	24786913	01/05/2014	USA	MA	No	3.060	5 RCTs	No	Cochrane
Kakkos SK, 2014 (69)	Eur J Vasc Endovasc Surg	24951377	18/06/2014	Greece	MA	Yes	7.069	10 RCTs	No	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Tornyos A, 2015 (70)	J Thromb Thrombolysis	25059624	25/07/2014	Hungary	MA	Yes	1.884	2 RCTs	No	Cochrane
Caldeira D, 2015 (71)	J Neurol	25119841	14/08/2014	Portugal	MA	Yes	3.408	6 RCTs	No	Cochrane
Chai-Adisaksopha C, 2014 (72)	Blood	25150296	22/08/2014	Canada	MA	No	10.452	7 RCTs	No	Cochrane
Gómez-Outes A, 2014 (73)	Vasc Health Risk Manag	25404858	07/11/2014	Spain	MA	Yes	Not indexed	10 RCTs	No	Cochrane
Gómez-Outes A, 2015 (74)	J Cardiovasc Pharmacol Ther	25802423	23/03/2015	Spain	MA	No	2.538	10 RCTs	No	Cochrane
Caldeira D, 2015 (75)	JAMA Ophthalmol	25950647	07/05/2015	Portugal	MA	Yes	4.340	6 RCTs	No	Cochrane
Caldeira D, 2015 (76)	Pharmacoevid Drug Saf	26009864	23/05/2015	Portugal	MA	No	2.908	2 RCTs	No	Cochrane
Caldeira D, 2015 (77)	Heart	26037103	02/06/2015	Portugal	MA	No	5.693	6 RCTs	No	Cochrane
Dentali F, 2015 (78)	Semin Thromb Hemost	26408921	26/09/2015	Italy	MA	No	3.505	10 RCTs	No	JADAD
Caldeira D, 2015 (79)	Aliment Pharmacol Ther	26434935	04/10/2015	Portugal	MA	Yes	6.320	9 RCTs	Yes (10/03/2015)	Cochrane
Chai-Adisaksopha C, 2015 (80)	J Thromb Haemost	26356595	05/10/2015	Canada	MA	Yes	5.565	8 RCTs	Yes (18/09/2014)	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Almutairi AR, 2017 (81)	Clin Ther	28668628	28/06/2017	USA	MA	No	3.185	7 RCTs + 1 Obs.	Yes (07/10/2015)	Cochrane + ACROBAT NRSI
Sun MT, 2017 (82)	JAMA Ophthalmol	28687831	06/07/2017	Australia	MA	Yes	6.669	7 RCTs	No	Cochrane
Sardar P, 2015 (83)	Int J Cardiol	25464465	13/11/2014	USA	MA	No	4.638	12 RCTs	No	Cochrane
Skaistis J, 2015 (84)	PLoS One	26383245	18/09/2015	USA	MA	Yes	3.057	10 RCTs	Yes (17/08/2014)	Cochrane
Miller CS, 2017 (85)	Clin Gastroenterol Hepatol	28458008	27/04/2017	Canada	MA	Yes	7.683	13 RCTs	No	JADAD + Cochrane
Gu ZC, 2018 (86)	Front Pharmacol	29692734	10/04/2018	China	MA	Yes	3.845	7 RCTs	No	Cochrane
Gómez-Outes A, 2018 (87)	Semin Thromb Hemost	29723893	03/05/2018	Spain	MA	No	3.401	7 RCTs	Yes (21/11/2016)	Cochrane
Wei AH, 2018 (88)	Int J Cardiol	29801762	18/05/2018	China	MA	No	3.471	4 RCTs	No	Cochrane + adapted risk of bias tool for observational
Elsebaie MAT, 2019 (89)	J Thromb Haemost	30690830	25/02/2019	Egypt	MA	Yes	4.157	8 RCTs	No	Cochrane
Huang HK, 2021 (90)	J Am Heart Assoc	33759542	24/03/2021	Taiwan	MA	Yes	4.605	9 RCTs	Yes (05/07/2020)	Cochrane + NOS
Zhuang Y, 2021 (91)	JRSM Open	34178359	13/06/2021	China	MA	Yes	Not indexed	7 RCTs	No	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal [§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Gu ZC, 2020 (92)	Clin Gastroenterol Hepatol	31195162	11/06/2019	China	MA	Yes	11.382	11 RCTs + 5 Obs.	Yes (08/08/2018)	Cochrane + NOS
Ha JT, 2019 (93)	Ann Intern Med	31307056	16/07/2019	Australia	MA	No	21.317	8 RCTs	Yes (04/12/2017)	Cochrane
Loke YK, 2014 (94)	Br J Clin Pharmacol	24617578	10/03/2014	UK	NMA	Yes	4.500	8 RCTs	No	Cochrane
Jugrin AV, 2016 (95)	J Med Econ	26390231	18/09/2015	Belgium	NMA	Yes	2.264	7 RCTs	No	None
Burr N, 2017 (96)	Lancet Gastroenterol Hepatol	28403994	16/11/2016	UK	NMA	No	12.856	9 RCTs	No	JADAD + NOS
Sterne JA, 2017 (97)	Health Technol Assess	28279251	01/03/2017	UK	NMA	Yes	4.513	13 RCTs	Yes (09/08/2013)	Cochrane
Wolfe Z, 2018 (98)	J Thromb Haemost	29723935	03/05/2018	USA	NMA	Yes	4.662	7 RCTs	No	Cochrane
Kupó P, 2020 (99)	Angiology	31533437	18/09/2019	Hungary	NMA	Yes	3.619	9 RCTs	Yes (06/08/2018)	Cochrane
Pompilio G, 2020 (100)	TH Open	32355907	28/04/2020	Italy	NMA	Yes	Not indexed	9 RCTs + 1 Obs.	No	Cochrane + NOS
Oh HJ, 2021 (101)	Medicine (Baltimore)	33726018	19/03/2021	Korea	NMA	Yes	1.644	11 RCTs	No	Cochrane
Chen J, 2022 (102)	Eur J Vasc Endovasc Surg	34973879	29/12/2021	China	NMA	No	7.069	10 RCTs	No	Cochrane
Initial VTE treatment in cancer patients										
Carrier M, 2014 (103)	Thromb Res	25457583	08/10/2014	Canada	MA	No	2.447	6 RCTs	Yes (24/04/2014)	Cochrane
Vedovati MC, 2015 (104)	Chest	25211264	11/11/2014	Italy	MA	No	5.940	6 RCTs	No	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Brunetti ND, 2017 (105)	Int J Cardiol	28062137	27/12/2016	Italy	MA	No	4.164	7 RCTs	No	JADAD
Xing J, 2018 (106)	Medicine (Baltimore)	30075504	01/08/2018	China	MA	Yes	1.870	1 RCT + 3 Obs.	No	NOS
Kahale LA, 2018 (107)	Cochrane Database Syst Rev	29920657	19/06/2018	Lebanon	MA	No	7.755	7 RCTs	Yes (02/11/2016)	Cochrane
Li A, 2019 (108)	Thromb Res	29506866	02/03/2018	USA	MA	Yes	2.869	2 RCTs + 11 Obs.	Yes (19/12/2017)	Cochrane + ROBINS-I
Dong Y, 2019 (109)	J Thromb Thrombolysis	31062143	06/05/2019	China	MA	Yes	2.054	2 RCTs + 9 Obs.	Yes (05/03/2019)	Cochrane + NOS
Kirkilelis GI, 2019 (110)	Eur J Vasc Endovasc Surg	31097186	13/05/2019	Greece	MA	Yes	5.328	8 RCTs	No	Cochrane
Wang Y, 2019 (111)	Front Pharmacol	31354488	10/07/2019	China	MA	Yes	4.225	6 RCTs + 3 Obs.	No	Cochrane + NOS
Yang M, 2019 (112)	J Cancer Res Ther	31939435	13/01/2020	China	MA	Yes	1.326	2 RCTs + 7 Obs.	Yes (04/09/2018)	JADAD + NOS
Al Yami MS, 2018 (113)	J Thromb Thrombolysis	29948754	12/06/2018	Saudi Arabia	MA	Yes	2.941	8 RCTs	No	Cochrane
Mai V, 2020 (114)	J Thromb Thrombolysis	32052314	12/02/2020	Canada	MA	Yes	2.300	3 RCTs	Yes (22/02/2019)	Cochrane
Brunetti ND, 2020 (115)	J Thromb Thrombolysis	31654194	25/10/2019	Italy	MA	Yes	2.300	3 RCTs	No	None
Mulder FI, 2020 (116)	Blood	32396939	12/05/2020	The Netherlands	MA	No	22.113	4 RCTs	Yes (05/03/2020)	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Giustozzi M, 2020 (117)	Thromb Haemost Res Pract	32365386	04/05/2020	Italy	MA	No	5.249	4 RCTs	Yes (28/04/2020)	Cochrane
Moik F, 2020 (118)	Thromb Haemost	32548553	21/05/2020	Austria	MA	Yes	Not indexed	4 RCTs	Yes (05/07/2020)	Cochrane
Haykal T, 2020 (119)	Thromb Res	32788122	18/06/2020	USA	MA	No	3.944	4 RCTs	No	Cochrane
Tao DL, 2020 (120)	Eur J Haematol	32441350	18/06/2020	USA	MA	No	2.997	4 RCTs	No	None
Sabatino J, 2020 (121)	JACC CardioOncol	34396250	06/07/2020	Italy	MA	Yes	6.250	4 RCTs	No	Cochrane
Bhatia K, 2020 (122)	Am J Cardiol	32807386	25/07/2020	USA	MA	No	2.778	4 RCTs	No	None
Camilli M, 2020 (123)	Crit Rev Oncol Hematol	32911455	02/08/2020	Italy	MA	No	6.312	4 RCTs	No	Cochrane
Elbadawi A, 2021 (124)	Eur Heart J Cardiovasc Pharmacother	32556105	18/08/2020	USA	MA	No	6.617	4 RCTs	Yes (05/07/2020)	Cochrane
Desai A, 2020 (125)	Ecancermedic alsience	33014133	25/08/2020	USA	MA	Yes	Not indexed	4 RCTs	No	None
Song X, 2021 (126)	Ann Transl Med	33569464	21/01/2021	China	MA	Yes	3.932	4 RCTs + 14 Obs.	No	ROBINS-I
Alsubaie NS, 2021 (127)	Thromb J	34717653	30/10/2021	Saudi Arabia	MA	Yes	2.062	4 RCTs	No	Cochrane
Hussain MR, 2022 (128)	Crit Rev Oncol Hematol	34838704	25/11/2021	USA	MA	No	6.312	4 RCTs + 11 Obs.	Yes (11/08/2020)	Cochrane + ROBINS-I
Murphy AC, 2022 (129)	Heart Lung Circ	34896013	09/12/2021	Australia	MA	No	2.975	4 RCTs	No	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Dong S, 2021 (130)	Ann Pharmacother	32938202	16/09/2020	China	MA	No	3.154	8 RCTs	Yes (12/12/2019)	Cochrane
Desai R, 2020 (131)	Sci Rep	33144679	03/11/2020	USA	MA	Yes	4.379	10 RCTs	No	Cochrane
Mohamed MFH, 2021 (132)	Clin Appl Thromb Hemost	33651658	01/01/2021	Qatar	MA	Yes	1.846	1 RCT + 16 Obs.	No	Cochrane + NOS
Liang B, 2021 (133)	Sci Prog	33913387	01/04/2021	China	MA	Yes	2.774	4 RCTs	Yes (23/10/2019)	None
Planquette B, 2022 (134)	Chest	34627853	08/10/2021	France	MA	No	9.410	5 RCTs	No	None
Posch F, 2015 (135)	Thromb Res	26210891	17/07/2015	Austria	NMA	No	2.320	4 RCTs	No	Cochrane
Vedovati MC, 2018 (136)	Thromb Res	30196195	01/09/2018	Italy	NMA	No	3.266	6 RCTs	No	Cochrane
Sobieraj DM, 2018 (137)	Clin Appl Thromb Hemost	30244595	24/09/2018	USA	NMA	Yes	1.846	6 RCTs	No	Cochrane
Rossel A, 2019 (138)	PLoS One	30897142	21/03/2019	Switzerland	NMA	Yes	2.740	7 RCTs	No	Cochrane
Fuentes HE, 2019 (139)	Mayo Clin Proc	31685262	02/11/2019	USA	NMA	No	6.942	3 RCTs	No	Cochrane
Ueyama H, 2021 (140)	J Thromb Thrombolysis	32458316	26/05/2020	USA	NMA	Yes	2.300	10 RCTs	No	Cochrane
Sidahmed S, 2020 (141)	Crit Rev Oncol Hematol	32540780	30/05/2020	USA	NMA	No	6.312	7 RCTs	Yes (11/03/2019)	Cochrane
Samaranayake CB, 2022 (142)	Intern Med J	32896977	08/09/2020	Australia	NMA	No	2.048	4 RCTs	No	Cochrane
Brandão GMS, 2022 (143)	Vascular	33794711	01/04/2021	Brazil	NMA	No	1.285	4 RCTs	Yes (31/03/2021)	Cochrane

First author, year*	Journal	PMID	Date of online publication	Country of first author	Type of MA	Free access publication	Impact factor of the journal[§]	Design and number of studies included in the MA	Registration (date)	Tool used to assess the RoB of the studies included in the SR
Riaz IB, 2022 (144)	Mayo Clin Proc	34172290	22/06/2021	USA	NMA	Yes	7.616	4 RCTs	Yes (16/05/2020)	Cochrane

* Year of publication in print. [§] At the time of publication

IPD = individual patient data; MA = meta-analysis; NMA = network meta-analysis; RoB = risk of bias; SR = systematic reviews; VTE = venous thromboembolism

Appendix Table 3. PICO question of the systematic reviews included in the overview.

The table is ordered by clinical context (initial, extended, or both initial and extended VTE treatment, or initial VTE treatment in cancer patients), type of meta-analysis (pairwise or network), date of online publication, and replication category.

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Initial VTE treatment					
Prins MH, 2013 (1)	VTE	Rivaroxaban	VKA	rVTE / CRB	Original
van der Hulle T, 2014 (2)	VTE	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
van der Hulle T, 2014 (3)	VTE	DOAC	VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Larsen TB, 2014 (4)	VTE	DOAC	VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Schulman S, 2014 (5)	VTE	Dabigatran	VKA	rVTE / MB	Original
Antoniazzi S, 2014 (6)	VTE or AF or orthopedic surgery	Dabigatran	LMWH or VKA	MB	Excessive replication
Goldhaber SZ, 2016 (7)	VTE	Dabigatran	VKA	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]
Goldhaber SZ, 2017 (8)	VTE + elderly or CKD	Dabigatran	VKA	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]
Gómez-Outes A, 2014 (9)	VTE	DOAC	Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
van Es N, 2014 (10)	VTE	DOAC	Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]
Loffredo L, 2015 (11)	VTE	DOAC	VKA	rVTE / MB	Excessive replication
Di Minno MN, 2015 (12)	VTE	DOAC	VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Mumoli N, 2015 (13)	VTE	DOAC	VKA	rVTE	Excessive replication
Dentali F, 2015 (14)	VTE	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]
Di Minno MND, 2017 (15)	VTE	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Yamashita Y, 2018 (16)	VTE	DOAC	Hep/VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Makam RCP, 2018 (17)	VTE or NVAf	DOAC	VKA or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [focus on comparator]
Aryal MR, 2019 (18)	VTE	Rivaroxaban and apixaban	-	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Chaudhary R, 2020 (19)	VTE + elderly	DOAC	VKA or Hep/VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Zhou B, 2021 (20)	VTE	DOAC	VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Vedovati MC, 2014 (21)	PE	DOAC	Hep/VKA	rVTE / CRB	Original
Sharma M, 2015 (22)	VTE or AF + elderly	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Di Minno MN, 2015 (23)	VTE	DOAC	VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Robertson L, 2015 (24)	PE	DOAC	VKA or Hep/VKA	rPE / MB	Original
Brekelmans MPA, 2018 (25)	PE	DOAC	Hep/VKA	rVTE	Excessive replication
Robertson L, 2015 (26)	DVT	DOAC	VKA or Hep/VKA	rVTE / MB	Original
Touma L, 2015 (27)	VTE or AF or orthopedic surgery	Apixaban	VKA or Hep/VKA	All-cause death / any bleed	Replication to broaden or narrow the research question [focus on intervention]
Raccach BH, 2016 (28)	VTE or AF + renal failure	DOAC	VKA or Hep/VKA	ICH	Original
Chen HY, 2021 (29)	VTE or AF + CKD and dialysis	DOAC	VKA	Stroke or SE or VTE / MB	Replication to broaden or narrow the research question [add NRS]
Senoo K, 2017 (30)	VTE + Japanese	DOAC	Hep/VKA	rVTE / any bleed	Original
Bleker SM, 2017 (31)	VTE	Factor-Xa	Hep/VKA	MB	Original
Haas S, 2021 (32)	VTE	Rivaroxaban	Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [focus on intervention]
Valeriani E, 2020 (33)	VTE	DOAC	VKA	rVTE / MB	Original
Mai V, 2021 (34)	Acute VTE + obese	DOAC	VKA	rVTE / MB	Original

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Elshafei MN, 2021 (35)	Acute VTE + obese	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Katel A, 2021 (36)	Acute VTE + obese	DOAC	VKA or Hep/VKA	rVTE / MB	Excessive replication
Li R, 2020 (37)	DVT	Rivaroxaban	VKA or Hep/VKA	PTS	Original
Karathanos C, 2021 (38)	DVT	Rivaroxaban	VKA	PTS	Replication to broaden or narrow the research question [add NRS]
Mainbourg S, 2021 (39)	VTE or AF or ACS or orthopedic surgery	DOAC	LMWH or VKA or Hep/VKA or placebo	Proximal DVT + PE / MB	Original
Fox BD, 2012 (40)	VTE	DOAC	Hep/VKA	rVTE / MB	Original
Castellucci LA, 2014 (41)	VTE	DOAC	Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Kang N, 2014 (42)	VTE	DOAC	Hep/VKA	All-cause death / MB	Excessive replication
Mantha S, 2015 (43)	VTE	DOAC	Hep/VKA	rVTE / MB	Excessive replication
Hirschl M, 2014 (44)	VTE	DOAC	VKA	rVTE / MB	Excessive replication
Cohen AT, 2015 (45)	VTE	DOAC	Hep/VKA	rVTE / MB	Excessive replication
Sadlon AH, 2016 (46)	VTE or AF + elderly	DOAC	VKA or Hep/VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Wang Z, 2021 (47)	VTE or AF + renal disease	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]
Extended VTE treatment					
Sardar P, 2013 (48)	VTE (extended)	DOAC	VKA or placebo	rVTE / MB	Original
Sindet-Pedersen C, 2015 (49)	VTE (extended)	DOAC	VKA or placebo	rVTE / MB	Excessive replication
Marik PE, 2015 (50)	VTE (extended)	DOAC	Placebo	rVTE / MB	Replication to broaden or narrow the research question [focus on comparator]
Caldeira D, 2016 (51)	VTE or AF or ACS	DOAC	VKA or aspirin or placebo	ACS	Replication to broaden or narrow the research question [investigate other outcomes]
Ebraheem M, 2020 (52)	VTE (extended)	DOAC	Placebo	rVTE / MB	Excessive replication
Vasanthamohan L, 2018 (53)	VTE (extended)	DOAC	Aspirin or placebo	rVTE / MB	Original
Mai V, 2019 (54)	VTE (extended)	DOAC	Aspirin or placebo	All-cause death / MB	Replication to broaden or narrow the research question [add new RCTs]
Castellucci LA, 2013 (55)	VTE (extended)	DOAC	VKA or placebo	rVTE / MB	Original

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Alotaibi G, 2014 (56)	VTE (extended)	DOAC	Placebo	rVTE / MB	Replication to broaden or narrow the research question [focus on comparator]
Sobieraj DM, 2015 (57)	VTE (extended)	DOAC	VKA or placebo	rVTE / CRB	Excessive replication
Cohen AT, 2016 (58)	VTE (extended)	DOAC	VKA or placebo	rVTE / MB	Excessive replication
Rollins BM, 2014 (59)	VTE (extended)	DOAC	VKA or placebo	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Wang KL, 2019 (60)	VTE (extended)	DOAC	VKA or aspirin or placebo	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Mai V, 2019 (61)	VTE (extended)	DOAC	VKA or aspirin or placebo	rVTE / MB	Replication to broaden or narrow the research question [focus on intervention]
Djulgovic M, 2020 (62)	VTE (extended)	DOAC	Aspirin or placebo	rVTE / MB	Replication to broaden or narrow the research question [focus on comparator]
Both initial and extended VTE treatment					
Mak KH, 2012 (63)	VTE or AF or ACS or orthopedic surgery	DOAC	LMWH or VKA or Hep/VKA or aspirin or placebo	Acute coronary events / MB	Original
Holster IL, 2013 (64)	VTE or AF or ACS or orthopedic surgery or medical	DOAC	LMWH or VKA or Hep/VKA or aspirin or placebo	GIB	Original
Chatterjee S, 2014 (65)	VTE or AF or ACS	DOAC	VKA or placebo	Discontinuation due to all causes	Replication to broaden or narrow the research question [investigate other outcomes]
Alotaibi GS, 2013 (66)	Acute VTE and extended	DOAC	VKA or Hep/VKA or placebo	rVTE / CRB	Replication to broaden or narrow the research question [add new RCTs]
Bloom BJ, 2014 (67)	VTE or AF	Dabigatran	VKA	All-cause death / CRB	Replication to broaden or narrow the research question [focus on intervention]
Sardar P, 2014 (68)	VTE or AF or medical + elderly	DOAC	LMWH or VKA or Hep/VKA or aspirin or placebo	rVTE / CRB	Original
Kakkos SK, 2014 (69)	Acute VTE and extended	DOAC	VKA or placebo	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Tornyos A, 2015 (70)	VTE or AF or ACS or orthopedic surgery or medical	Apixaban	LMWH or VKA or Hep/VKA or aspirin or placebo	MI	Replication to broaden or narrow the research question [investigate other outcomes]

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Caldeira D, 2015 (71)	VTE or AF or ACS or orthopedic surgery or medical	DOAC	LMWH or VKA or Hep/VKA or aspirin or placebo	ICH	Replication to broaden or narrow the research question [investigate other outcomes]
Chai-Adisaksopha C, 2014 (72)	VTE or AF	DOAC	VKA or Hep/VKA	MB	Replication to broaden or narrow the research question [focus on comparator]
Gómez-Outes A, 2014 (73)	Acute VTE and extended	DOAC	VKA or Hep/VKA or placebo	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Gómez-Outes A, 2015 (74)	Acute VTE and extended	DOAC	VKA or Hep/VKA or placebo	Fatal VTE / fatal bleed	Excessive replication
Caldeira D, 2015 (75)	VTE or AF or orthopedic surgery	DOAC	LMWH or VKA or aspirin or placebo	Intraocular bleeding	Replication to broaden or narrow the research question [investigate other outcomes]
Caldeira D, 2015 (76)	VTE or AF or orthopedic surgery	DOAC	LMWH or VKA	Renal failure	Replication to broaden or narrow the research question [investigate other outcomes]
Caldeira D, 2015 (77)	VTE or AF	DOAC	VKA or Hep/VKA	Fatal bleed	Replication to broaden or narrow the research question [focus on comparator]
Dentali F, 2015 (78)	VTE or AF	DOAC	VKA or placebo	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]
Caldeira D, 2015 (79)	VTE or AF or orthopedic surgery	DOAC	LMWH or VKA or Hep/VKA or aspirin or placebo	GIB	Replication to broaden or narrow the research question [investigate other outcomes]
Chai-Adisaksopha C, 2015 (80)	VTE or AF	DOAC	VKA or Hep/VKA	CV death / MB	Replication to broaden or narrow the research question [investigate other outcomes]
Almutairi AR, 2017 (81)	VTE or AF	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Sun MT, 2017 (82)	VTE or AF	DOAC	VKA or Hep/VKA	Intraocular bleeding	Replication to broaden or narrow the research question [investigate other outcomes]
Sardar P, 2015 (83)	VTE or AF or ACS or orthopedic surgery or medical	DOAC	LMWH or VKA or Hep/VKA or aspirin or placebo	MB	Replication to broaden or narrow the research question [add new RCTs]
Skaistis J, 2015 (84)	VTE or AF	DOAC	VKA	MB	Replication to broaden or narrow the research question [focus on comparator]
Miller CS, 2017 (85)	VTE or AF	DOAC	LMWH or VKA or Hep/VKA or	Major GIB	Replication to broaden or narrow the research question [investigate other outcomes]

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
			aspirin or placebo		
Gu ZC, 2018 (86)	VTE or AF	DOAC	VKA	Any fracture	Replication to broaden or narrow the research question [investigate other outcomes]
Gómez-Outes A, 2018 (87)	VTE	DOAC	VKA	All-cause death	Replication to broaden or narrow the research question [investigate other outcomes]
Wei AH, 2018 (88)	VTE or AF or ACS or orthopedic surgery	Dabigatran	LMWH or VKA or placebo	MI / -	Replication to broaden or narrow the research question [investigate other outcomes]
Elsebaie MAT, 2019 (89)	VTE + thrombophilia	DOAC	VKA or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [highlight patient subgroups]
Huang HK, 2021 (90)	VTE or AF	DOAC	VKA	Any fracture	Replication to broaden or narrow the research question [investigate other outcomes]
Zhuang Y, 2021 (91)	VTE	DOAC	VKA	rVTE / MB	Replication to broaden or narrow the research question [focus on comparator]
Gu ZC, 2020 (92)	AF or VTE or medical or PCI or CAD/PAD	DOAC	LMWH or VKA or Hep/VKA or aspirin	Major GIB	Original
Ha JT, 2019 (93)	VTE or AF or medical or CVD + CKD	DOAC	LMWH or VKA or aspirin or placebo	All-cause death / MB	Original
Loke YK, 2014 (94)	VTE or AF or ACS or orthopedic surgery	DOAC	LMWH or VKA or Hep/VKA or aspirin or placebo	MI	Original
Jugrin AV, 2016 (95)	Acute VTE and extended	Dabigatran or rivaroxaban	VKA	rVTE / CRB	Replication to broaden or narrow the research question [highlight patient subgroups]
Burr N, 2017 (96)	VTE or AF	DOAC	LMWH or VKA or Hep/VKA	Major GIB	Replication to broaden or narrow the research question [investigate other outcomes]
Sterne JA, 2017 (97)	VTE or AF or orthopedic surgery or medical	DOAC	LMWH or VKA or aspirin or placebo	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Wolfe Z, 2018 (98)	VTE or AF or orthopedic surgery or medical	DOAC	Control	ICH	Replication to broaden or narrow the research question [investigate other outcomes]
Kupó P, 2020 (99)	VTE or AF or ACS or PCI	DOAC	VKA or aspirin or placebo	MI / MB	Replication to broaden or narrow the research question [focus on comparator]

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Pompilio G, 2020 (100)	Acute VTE and extended	DOAC	VKA or Hep/VKA or aspirin or placebo	rVTE / CRB	Replication to broaden or narrow the research question [add NRS]
Oh HJ, 2021 (101)	VTE or AF or orthopedic surgery	DOAC	LMWH or VKA or aspirin or placebo or no treatment	Major GIB	Replication to broaden or narrow the research question [investigate other outcomes]
Chen J, 2022 (102)	VTE or medical or orthopedic surgery	DOAC	LMWH or VKA	MB	Replication to broaden or narrow the research question [focus on comparator]
Initial VTE treatment in cancer patients					
Carrier M, 2014 (103)	Cancer-associated thrombosis	DOAC	Hep/VKA	rVTE / MB	Original
Vedovati MC, 2015 (104)	Cancer-associated thrombosis	DOAC	Hep/VKA	rVTE / MB	Excessive replication
Brunetti ND, 2017 (105)	Cancer-associated thrombosis or medical + cancer	DOAC	VKA or LMWH	rVTE / CRB	Replication to broaden or narrow the research question [add new RCTs]
Xing J, 2018 (106)	Cancer-associated thrombosis	Rivaroxaban	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Kahale LA, 2018 (107)	Cancer-associated thrombosis	DOAC	LMWH or VKA or Hep/VKA	All-cause death / MB	Replication to broaden or narrow the research question [add new RCTs]
Li A, 2019 (108)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Dong Y, 2019 (109)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Kirkilesis GI, 2019 (110)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Excessive replication
Wang Y, 2019 (111)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Yang M, 2019 (112)	Cancer-associated thrombosis	Factor-Xa	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Al Yami MS, 2018 (113)	Cancer-associated thrombosis	DOAC	LMWH or VKA or Hep/VKA	rVTE / CRB	Replication to broaden or narrow the research question [add new RCTs]
Mai V, 2020 (114)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Original
Brunetti ND, 2020 (115)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Mulder FI, 2020 (116)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Giustozzi M, 2020 (117)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Moik F, 2020 (118)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Haykal T, 2020 (119)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Tao DL, 2020 (120)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Sabatino J, 2020 (121)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Bhatia K, 2020 (122)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Camilli M, 2020 (123)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Elbadawi A, 2021 (124)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Desai A, 2020 (125)	Cancer-associated thrombosis or Cancer	DOAC	LMWH or placebo	rVTE / MB	Excessive replication
Song X, 2021 (126)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Alsubaie NS, 2021 (127)	Cancer-associated thrombosis or medical or cancer	DOAC	LMWH or placebo	rVTE / MB	Excessive replication
Hussain MR, 2022 (128)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add NRS]
Murphy AC, 2022 (129)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Dong S, 2021 (130)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Desai R, 2020 (131)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Excessive replication
Mohamed MFH, 2021 (132)	Cancer-associated thrombosis	Rivaroxaban	LMWH	Net clinical benefit (rVTE and MB)	Replication to broaden or narrow the research question [add NRS]
Liang B, 2021 (133)	Cancer-associated thrombosis	Rivaroxaban	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [focus on intervention]
Planquette B, 2022 (134)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]

First author, year*	Population	Intervention	Comparator	Outcomes	Replication category
Posch F, 2015 (135)	Cancer-associated thrombosis	DOAC	Hep/VKA	rVTE / MB	Original
Vedovati MC, 2018 (136)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Sobieraj DM, 2018 (137)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Rossel A, 2019 (138)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Fuentes HE, 2019 (139)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Original
Ueyama H, 2021 (140)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Sidahmed S, 2020 (141)	Cancer-associated thrombosis	DOAC	LMWH or Hep/VKA	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Samaranayake CB, 2022 (142)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Replication to broaden or narrow the research question [add new RCTs]
Brandão GMS, 2022 (143)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication
Riaz IB, 2022 (144)	Cancer-associated thrombosis	DOAC	LMWH	rVTE / MB	Excessive replication

ACS: acute coronary syndrome; AF: atrial fibrillation; CAD: coronary artery disease; CVD: cardiovascular disease; CKD: chronic kidney disease; CRB: clinically relevant bleeding; DOAC: direct oral anticoagulant; DVT: deep-vein thrombosis; GIB: gastrointestinal bleeding; Hep: heparin; LMWH: low-molecular-weight heparin; MI: myocardial infarction; MB: major bleeding; NRS: non-randomised studies; NVAf: non-valvular atrial fibrillation; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; PE: pulmonary embolism; PTS: post-thrombotic syndrome RCTs: randomised controlled trials; rVTE: recurrent venous thromboembolism; SE: systemic embolism; VKA: vitamin-K antagonist; VTE = venous thromboembolism.

Appendix Table 4. Summary of the characteristics of the conceptual replications according to the reason for replication. Values are numbers (percentages) unless stated otherwise.

	Add new RCTs (N = 23)	Highlight patient subgroups (N = 18)	Investigate other outcomes (N = 17)	Focus on a comparator or intervention (N = 15)	Add NRS (N = 14)
Type of meta-analysis					
Individual patient data meta-analysis	0 (0.0)	2 (11.1)	0 (0.0)	1 (6.7)	0 (0.0)
Pairwise meta-analysis	13 (56.5)	13 (72.2)	14 (82.4)	9 (60.0)	13 (92.9)
Network meta-analysis	10 (43.5)	3 (16.7)	3 (17.6)	5 (33.3)	1 (7.1)
Median (IQR) number of authors of the publication	7 (5-10)	6 (5-7)	6 (5-7)	5 (3-10)	7 (7-8)
Free-access publication	8 (34.8)	10 (55.6)	11 (64.7)	8 (53.3)	10 (71.4)
Journal not indexed for MEDLINE*	0 (0.0)	1 (5.6)	0 (0.0)	2 (13.3)	1 (7.1)
Median (IQR) impact factor of the journal	4.51 (2.74-7.75)	3.76 (3.23-5.63)	4.34 (3.41-6.26)	3.06 (2.77-3.62)	2.86 (2.05-3.93)
Geographic location of the first author					
Europe	10 (43.5)	11 (61.1)	8 (47.1)	3 (20.0)	2 (14.3)
North America	8 (34.8)	3 (16.7)	4 (23.5)	9 (60.0)	4 (28.6)
Asia	4 (17.4)	3 (16.7)	4 (23.5)	3 (20.0)	8 (57.1)
Other	1 (4.3)	1 (5.6)	1 (5.9)	0 (0.0)	0 (0.0)
Design of the included studies					
RCTs only	23 (100.0)	18 (100.0)	17 (100.0)	14 (93.3)	0 (0.0)

	Add new RCTs (N = 23)	Highlight patient subgroups (N = 18)	Investigate other outcomes (N = 17)	Focus on a comparator or intervention (N = 15)	Add NRS (N = 14)
Observational studies only	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (14.3)
Both RCTs and observational studies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (85.7)
Assessment of the risk of bias of the included studies	21 (91.3)	8 (44.4)	13 (76.5)	12 (80.0)	11 (78.6)
Descriptive (table/figure)	14	7	9	11	11
Analysis according to risk of bias	7	1	4	1	0
Registration of the protocol	10 (43.5)	1 (5.6)	4 (23.5)	3 (20.0)	6 (42.9)
PROSPERO	8	1	4	3	6
Cochrane database	1	0	0	0	0
Open Science Framework	1	0	0	0	0
No overlap in authorship	8 (34.8)	5 (27.8)	6 (35.3)	7 (46.7)	9 (64.3)
Risk of bias of the systematic reviews (ROBIS tool)					
Low	8 (34.8)	3 (16.7)	5 (29.4)	3 (20.0)	3 (21.4)
Unclear	1 (4.3)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)
High	14 (60.9)	15 (83.3)	10 (58.8)	12 (80.0)	11 (78.6)

* At the time of the publication.

IQR = interquartile range; NRS = non-randomised studies; RCT = randomised controlled trial.

Appendix Table 5. Risk of bias for each systematic review included according to the ROBIS tool.

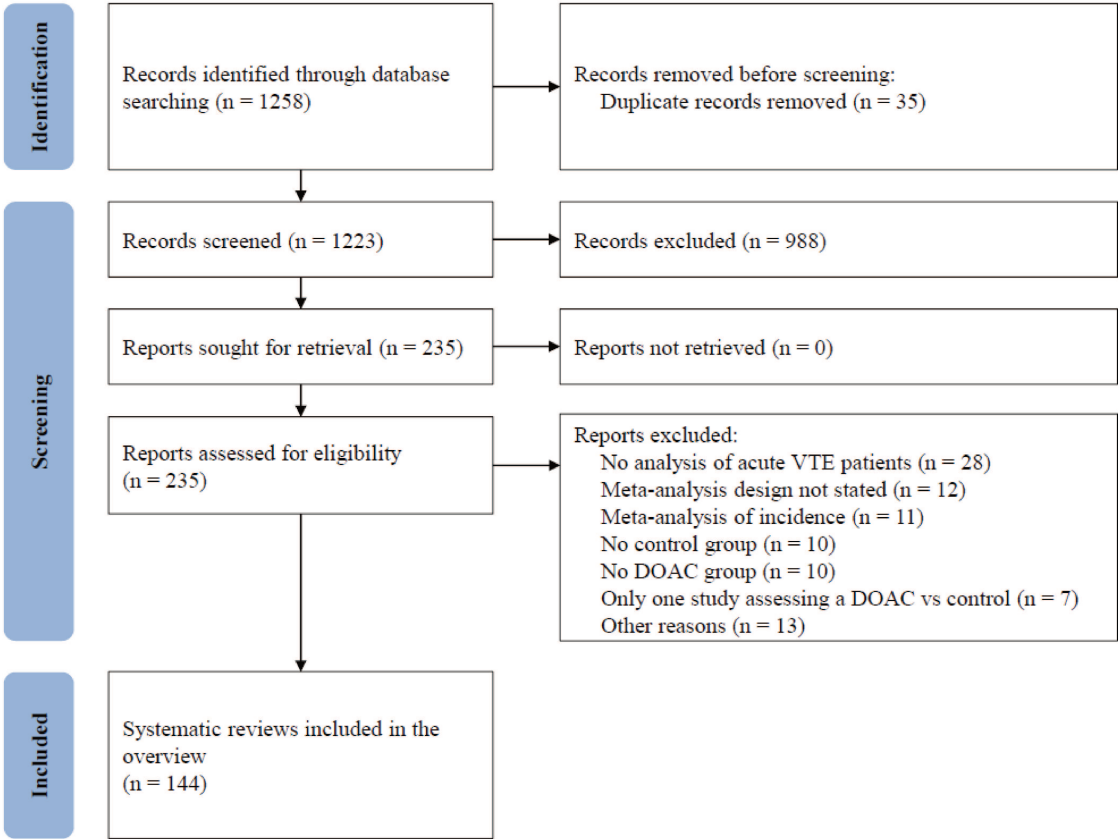
First author, year	Areas of potential bias in the review process				Overall judgment of the risk of bias in the review
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	
Prins MH, 2013 (1)	?	?	-	+	-
van der Hulle T, 2014 (2)	+	-	?	-	-
van der Hulle T, 2014 (3)	+	+	?	-	-
Larsen TB, 2014 (4)	+	+	?	-	-
Schulman S, 2014 (5)	?	?	-	+	-
Antoniazzi S, 2014 (6)	?	?	-	-	-
Goldhaber SZ, 2016 (7)	?	?	-	+	-
Goldhaber SZ, 2017 (8)	?	?	-	+	-
Gómez-Outes A, 2014 (9)	+	+	?	+	+
van Es N, 2014 (10)	+	?	-	-	-
Loffredo L, 2015 (11)	+	-	-	-	-
Di Minno MN, 2015 (12)	+	+	-	-	-
Mumoli N, 2015 (13)	?	-	-	-	-
Dentali F, 2015 (14)	+	+	-	+	+
Di Minno MND, 2017 (15)	?	?	-	-	-
Yamashita Y, 2018 (16)	+	+	-	-	-
Makam RCP, 2018 (17)	+	-	?	?	-
Aryal MR, 2019 (18)	+	-	+	-	-
Chaudhary R, 2020 (19)	+	-	-	+	-
Zhou B, 2021 (20)	+	?	-	-	-
Vedovati MC, 2014 (21)	+	-	-	-	-
Sharma M, 2015 (22)	+	+	+	-	-
Di Minno MN, 2015 (23)	+	-	-	-	-
Robertson L, 2015 (24)	+	+	+	+	+
Brekelmans MPA, 2018 (25)	?	-	-	-	-
Robertson L, 2015 (26)	+	+	+	+	+
Touma L, 2015 (27)	+	-	?	+	-
Raccach BH, 2016 (28)	+	?	?	+	+
Chen HY, 2021 (29)	+	+	+	-	-
Senoo K, 2017 (30)	+	-	?	-	-
Bleker SM, 2017 (31)	?	?	-	-	-
Haas S, 2021 (32)	?	?	-	-	-
Valeriani E, 2020 (33)	+	?	?	-	-
Mai V, 2021 (34)	+	+	+	+	+
Elshafei MN, 2021 (35)	+	+	?	+	+
Katel A, 2021 (36)	+	-	?	-	-

Li R, 2020 (37)	+	-	+	-	-
Karathanos C, 2021 (38)	+	-	-	-	-
Mainbourg S, 2021 (39)	+	-	?	-	?
Fox BD, 2012 (40)	+	+	?	-	-
Castellucci LA, 2014 (41)	+	+	-	-	-
Kang N, 2014 (42)	+	+	+	+	+
Mantha S, 2015 (43)	+	+	?	?	?
Hirschl M, 2014 (44)	+	-	+	-	-
Cohen AT, 2015 (45)	+	-	+	-	-
Sadlon AH, 2016 (46)	+	-	?	+	-
Wang Z, 2021 (47)	+	-	?	-	-
Sardar P, 2013 (48)	+	?	+	-	-
Sindet-Pedersen C, 2015 (49)	-	-	?	-	-
Marik PE, 2015 (50)	+	+	+	+	+
Caldeira D, 2016 (51)	?	?	-	?	?
Ebraheem M, 2020 (52)	+	+	+	+	+
Vasanthamohan L, 2018 (53)	+	+	?	+	+
Mai V, 2019 (54)	+	+	+	+	+
Castellucci LA, 2013 (55)	+	+	+	+	+
Alotaibi G, 2014 (56)	+	-	+	-	-
Sobieraj DM, 2015 (57)	+	+	+	+	+
Cohen AT, 2016 (58)	+	-	?	+	?
Rollins BM, 2014 (59)	+	-	+	-	-
Wang KL, 2019 (60)	+	?	+	-	-
Mai V, 2019 (61)	+	+	+	+	+
Djulbegovic M, 2020 (62)	+	-	+	-	-
Mak KH, 2012 (63)	?	-	-	-	-
Holster IL, 2013 (64)	+	-	?	-	-
Chatterjee S, 2014 (65)	+	-	?	+	-
Alotaibi GS, 2013 (66)	+	+	+	-	-
Bloom BJ, 2014 (67)	+	-	+	+	-
Sardar P, 2014 (68)	+	?	+	+	+
Kakkos SK, 2014 (69)	+	-	-	-	-
Tornyos A, 2015 (70)	+	?	?	+	+
Caldeira D, 2015 (71)	+	+	?	+	+
Chai-Adisaksopha C, 2014 (72)	+	+	+	+	+
Gómez-Outes A, 2014 (73)	+	?	?	-	-
Gómez-Outes A, 2015 (74)	+	-	?	+	+
Caldeira D, 2015 (75)	+	+	?	+	+
Caldeira D, 2015 (76)	-	-	?	-	-
Caldeira D, 2015 (77)	+	+	+	-	-
Dentali F, 2015 (78)	+	+	-	+	+
Caldeira D, 2015 (79)	+	+	?	-	-
Chai-Adisaksopha C, 2015 (80)	+	?	-	+	+

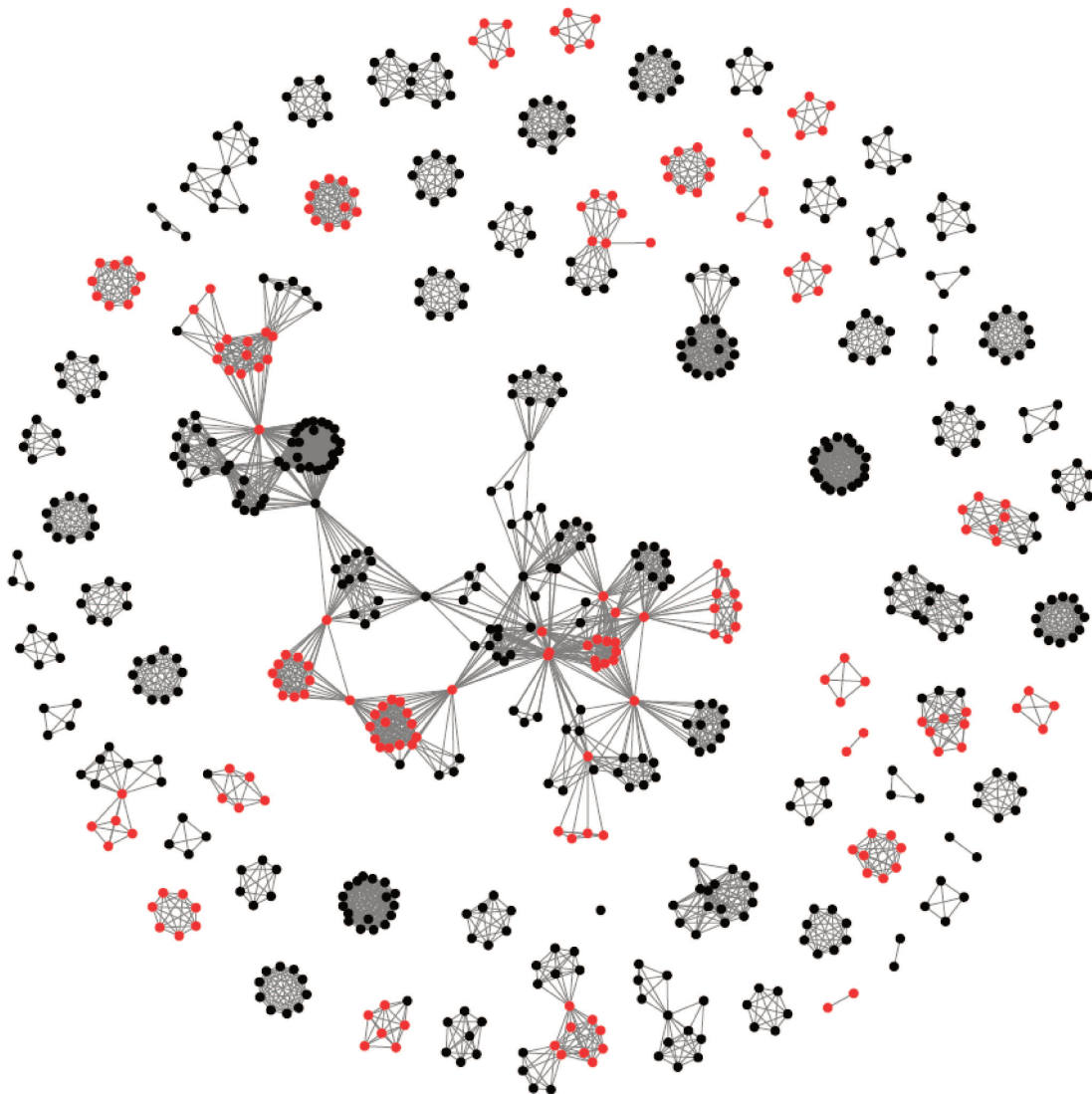
Almutairi AR, 2017 (81)	+	+	+	-	-
Sun MT, 2017 (82)	+	-	?	+	-
Sardar P, 2015 (83)	+	-	-	-	-
Skaistis J, 2015 (84)	+	-	?	-	-
Miller CS, 2017 (85)	+	+	-	-	-
Gu ZC, 2018 (86)	+	?	?	-	-
Gómez-Outes A, 2018 (87)	+	+	?	+	+
Wei AH, 2018 (88)	+	-	?	-	-
Elsebaie MAT, 2019 (89)	+	+	+	+	+
Huang HK, 2021 (90)	+	+	+	-	-
Zhuang Y, 2021 (91)	+	-	?	-	-
Gu ZC, 2020 (92)	+	-	?	-	-
Ha JT, 2019 (93)	+	+	+	-	-
Loke YK, 2014 (94)	+	?	-	-	-
Jugrin AV, 2016 (95)	-	-	-	-	-
Burr N, 2017 (96)	+	+	-	+	?
Sterne JA, 2017 (97)	+	+	+	-	-
Wolfe Z, 2018 (98)	+	-	?	+	-
Kupó P, 2020 (99)	+	-	?	+	-
Pompilio G, 2020 (100)	-	-	+	-	-
Oh HJ, 2021 (101)	+	-	-	-	-
Chen J, 2022 (102)	+	-	+	-	-
Carrier M, 2014 (103)	+	+	?	-	-
Vedovati MC, 2015 (104)	+	+	+	+	+
Brunetti ND, 2017 (105)	+	-	?	-	-
Xing J, 2018 (106)	?	-	-	-	-
Kahale LA, 2018 (107)	+	+	+	+	+
Li A, 2019 (108)	+	+	+	+	+
Dong Y, 2019 (109)	+	+	+	-	-
Kirkilesis GI, 2019 (110)	+	?	?	+	+
Wang Y, 2019 (111)	+	-	?	-	-
Yang M, 2019 (112)	+	-	-	-	-
Al Yami MS, 2018 (113)	+	-	?	-	-
Mai V, 2020 (114)	+	?	?	-	-
Brunetti ND, 2020 (115)	?	-	-	-	-
Mulder FI, 2020 (116)	+	+	+	+	+
Giustozzi M, 2020 (117)	+	+	+	-	-
Moik F, 2020 (118)	+	-	?	-	-
Haykal T, 2020 (119)	-	-	+	+	-
Tao DL, 2020 (120)	+	?	-	-	-
Sabatino J, 2020 (121)	+	-	+	-	-
Bhatia K, 2020 (122)	?	-	-	-	-
Camilli M, 2020 (123)	+	+	?	+	+
Elbadawi A, 2021 (124)	+	?	?	+	+

Desai A, 2020 (125)	+	-	-	-	-
Song X, 2021 (126)	+	-	-	-	-
Alsubaie NS, 2021 (127)	+	-	?	-	-
Hussain MR, 2022 (128)	+	-	+	-	-
Murphy AC, 2022 (129)	+	?	+	-	-
Dong S, 2021 (130)	+	-	+	+	-
Desai R, 2020 (131)	+	-	+	+	-
Mohamed MFH, 2021 (132)	+	+	?	+	+
Liang B, 2021 (133)	-	-	+	-	-
Planquette B, 2022 (134)	?	?	?	?	?
Posch F, 2015 (135)	+	+	-	-	-
Vedovati MC, 2018 (136)	+	+	+	+	+
Sobieraj DM, 2018 (137)	+	+	+	-	-
Rossel A, 2019 (138)	+	+	?	-	+
Fuentes HE, 2019 (139)	?	-	?	+	-
Ueyama H, 2021 (140)	+	-	+	-	-
Sidahmed S, 2020 (141)	+	?	+	+	+
Samaranayake CB, 2022 (142)	+	+	+	+	+
Brandão GMS, 2022 (143)	+	+	+	-	+
Riaz IB, 2022 (144)	+	+	?	+	+

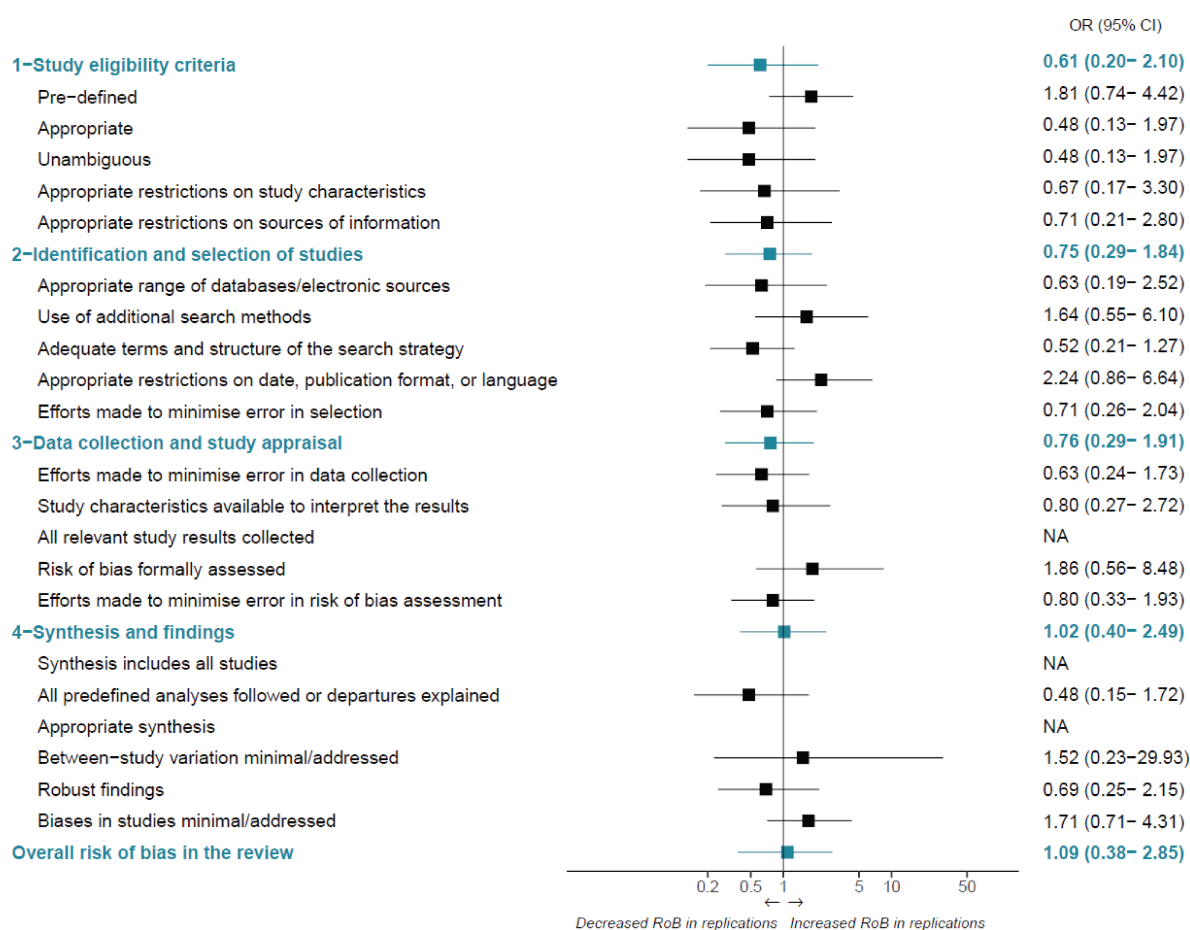
Appendix Figure 1. PRISMA flow diagram



Appendix Figure 2. Connections between authors according to the category of systematic review in which they participated (black: authors who participated in original systematic reviews or conceptual replications; red: authors who participated in at least one excessive replication). Each point (node) represents an author of a systematic review and each line (edges) represents the connections between two authors participating in the same systematic review, for a total of 734 nodes and 3293 edges.

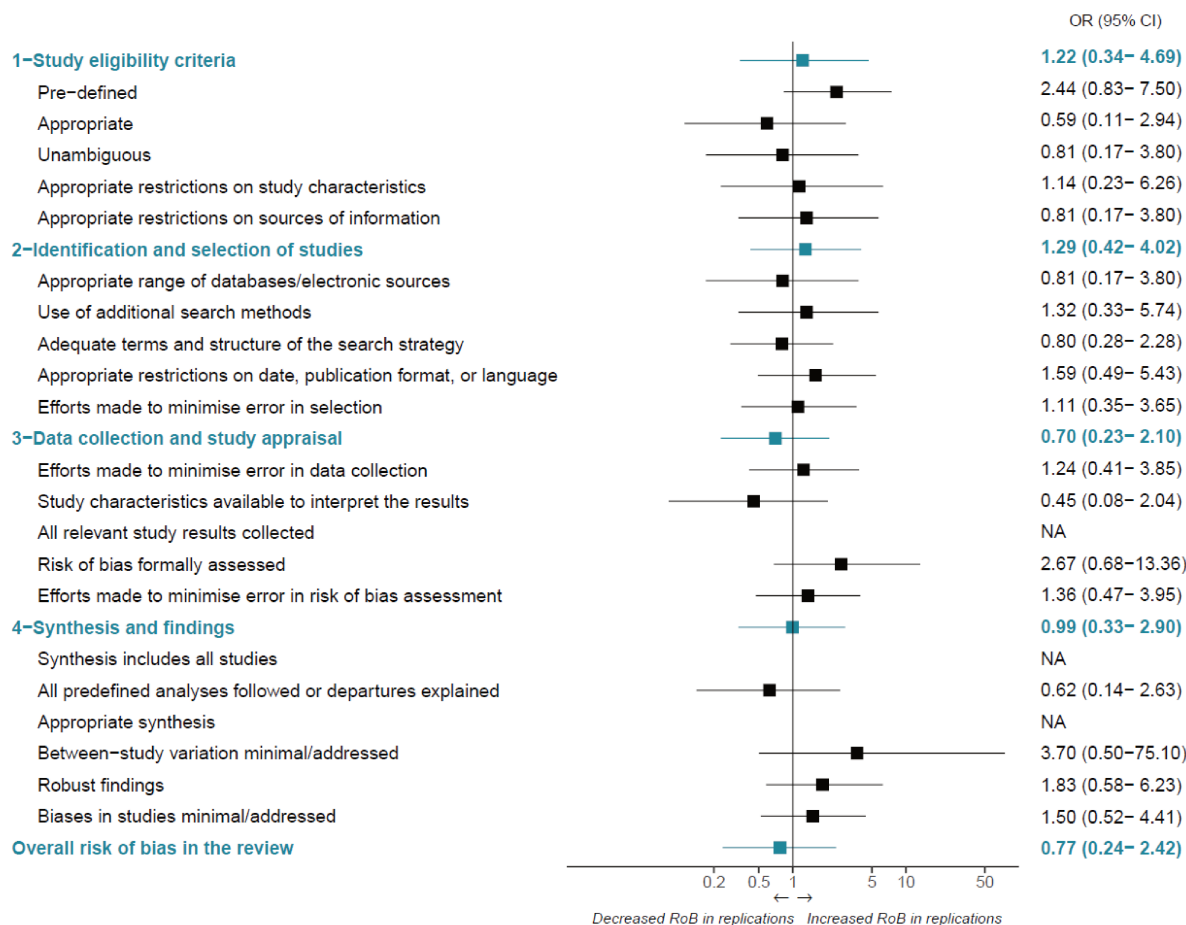


Appendix Figure 3. Comparison of the risk of bias within each ROBIS tool domain between conceptual replications and original systematic reviews (reference: original systematic reviews). An OR < 1 denotes a lower risk of bias in conceptual replications compared to original systematic reviews, an OR of 1 denotes no difference between conceptual replications and original systematic reviews, and an OR > 1 denotes a higher risk of bias in conceptual replications compared to original systematic reviews.



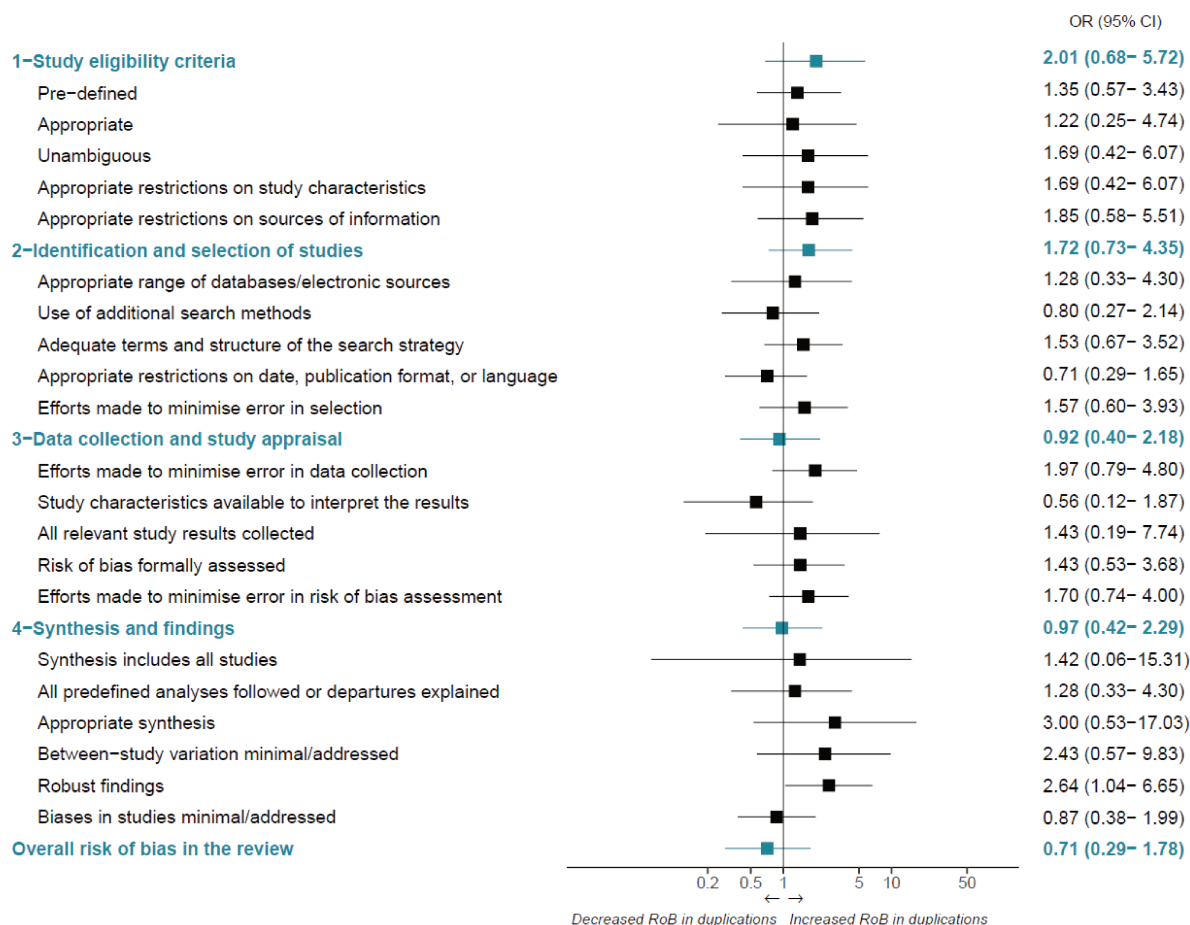
95% CI = 95% confidence interval; OR = odds ratio; RoB = risk of bias.

Appendix Figure 4. Comparison of the risk of bias within each ROBIS tool domain between excessive replications and original systematic reviews (reference: original systematic reviews). An OR < 1 denotes a lower risk of bias in excessive replications compared to original systematic reviews, an OR of 1 denotes no difference between excessive replications and original systematic reviews and an OR > 1 denotes a higher risk of bias in excessive replications compared to original systematic reviews.



95% CI = 95% confidence interval; OR = odds ratio; RoB = risk of bias.

Appendix Figure 5. Comparison of the risk of bias within each ROBIS tool domain between excessive replications (duplications) and conceptual replications (reference: conceptual replications). An OR < 1 denotes a lower risk of bias in excessive replications compared to conceptual replications, an OR of 1 denotes no difference between excessive and conceptual replications, and an OR > 1 denotes a higher risk of bias in excessive replications compared to conceptual replications.



95% CI = 95% confidence interval; OR = odds ratio; RoB = risk of bias.

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Annexe 4.

Poster « Prolifération des méta-analyses et qualité méthodologique, une association positive ? »

Prolifération des méta-analyses et qualité méthodologique, une association positive ?

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CONTEXTE

- **Multiplication** des publications de méta-analyses
- **Réplication** positive ou négative ? La plus récente est-elle :
 - Gain d'**exhaustivité** ?
 - Réduction du **risque de biais** méthodologique ?
 - **Envahissement** des publications ?
- **Objectifs**
 - Caractériser la **réplication** des méta-analyses en **termes de biais**
 - Évaluer l'**association** entre la **réplication** et la **qualité** méthodologique

MATÉRIELS ET MÉTHODES

- Enregistrement **PROSPERO** : CRD42022316273
- **Recherche exhaustive des méta-analyses** évaluant un AOD versus un comparateur chez les patients traités pour un événement thrombo-embolique veineux
- **Évaluation du risque de biais par ROBIS tool**
- **3 catégories de temporalité des méta-analyses**
 - **Initiale**
 - **Actualisation** : simple mise à jour d'une méta-analyse initiale ou d'une précédente mise à jour
 - **Redondance** : publication avec chevauchement en termes de type de populations, de comparaisons d'interventions et d'études incluses par rapport à une publication antérieure
- **Régression logistique** pour comparer la qualité méthodologique entre les catégories, avec :
 - **Covariable** : **temporalité** de la publication
 - **Variable dépendante** : **risque de biais** de la méta-analyse (élevé vs faible)

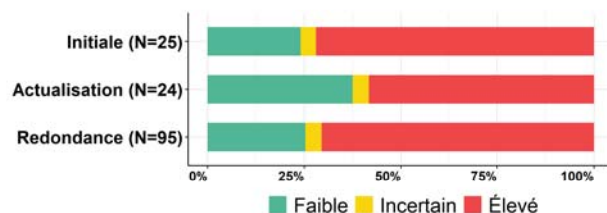
CONCLUSION

- **Actualisation = réplication positive** (qualité méthodologique améliorée)
- **Redondance** :
 - **Réplication négative** (pas de bénéfice méthodologique)
 - **Gaspillage** scientifique

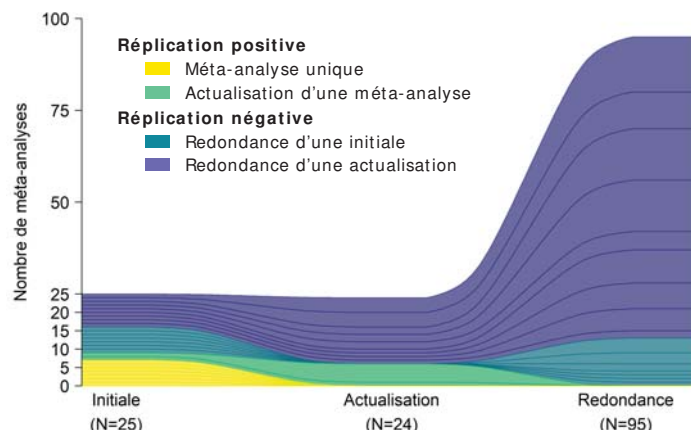


RÉSULTATS

- **144** méta-analyses, **68.7%** à risque élevé de biais

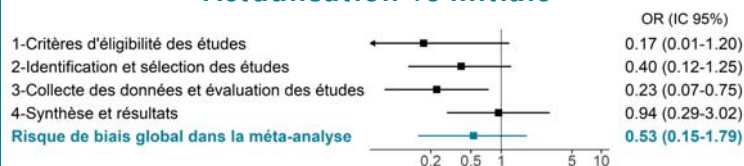


- **Illustration du phénomène de réplication**

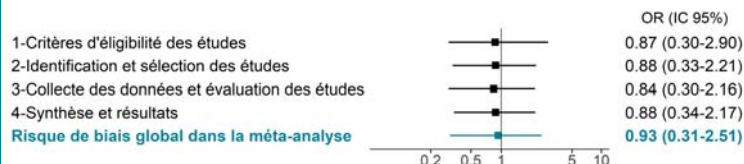


- **Comparaison de la qualité méthodologique des méta-analyses** (OR < 1 : diminution des biais)

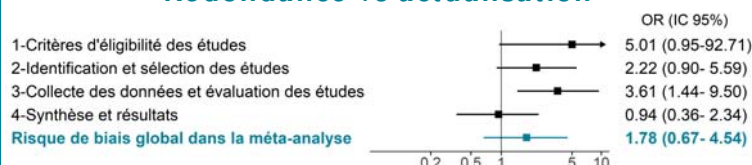
Actualisation vs initiale



Redondance vs initiale



Redondance vs actualisation



Annexe 5.

Article « A framework to characterise the reproducibility of meta-analysis results with its application to direct oral anticoagulants in the acute treatment of venous thromboembolism. »

A framework to characterise the reproducibility of meta-analysis results with its application to direct oral anticoagulants in the acute treatment of venous thromboembolism

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Abstract

The number of meta-analyses of aggregate data has dramatically increased due to the facility of obtaining data from publications and the development of free, easy-to-use, and specialised statistical software. Even when meta-analyses include the same studies, their results may vary owing to different methodological choices. Assessment of the replication of meta-analysis provides an example of the variation of effect 'naturally' observed between multiple research projects. Reproducibility of results has mostly been reported using graphical descriptive representations. A quantitative analysis of such results would enable (i) breakdown of the total observed variability with quantification of the variability generated by the replication process and (ii) identification of which variables account for this variability, such as methodological quality or the statistical analysis procedures used. These variables might explain systematic mean differences between results and dispersion of the results. To quantitatively characterise the reproducibility of meta-analysis results, a bivariate linear mixed-effects model was developed to simulate both mean results and their corresponding uncertainty. Results were assigned to several replication groups, those assessing the same studies, outcomes, treatment indication and comparisons classified in the same replication group. A nested random effect structure was used to break down the total variability within each replication group and between these groups to enable calculation of an intragroup correlation coefficient and quantification of reproducibility. Determinants of variability were investigated by modelling both mean and variance parameters using covariates. The proposed model was applied to the example of meta-analyses evaluating direct oral anticoagulants in the acute treatment of venous thromboembolism.

KEYWORDS

aggregate data, Bayesian analysis, bivariate mixed effect model, replication, reproducibility, vibration of effects

Highlights

What is already known

- Meta-analyses have recently proliferated to a massive extent, sometimes including the same studies and analysing the same outcomes, this phenomenon being designated result replication.
- Despite inclusion of the same studies, the results of meta-analyses may vary according to the methodological choices made.
- The reproducibility of meta-analysis results has mainly been explored using graphical descriptive representations with no quantitative analysis proposed.

What is new

- In this study, a bivariate linear mixed-effect model was developed to simulate both mean meta-analysis results and their standard errors.
- A nested random effect structure was used to break down the total variability within each replication group and between groups, each replication group containing results assessing the same studies, outcomes, treatment indication and comparisons. Reproducibility was then assessed using an intragroup correlation coefficient. Covariate effects were included to characterise the variation of both mean and variance model parameters.

1 | INTRODUCTION

The current race to publish has led to a substantial increase in scientific articles published each year and raises issues in terms of scientific integrity and value. Owing to their high level of evidence, meta-analyses have become common practice in clinical research, and are therefore not exempt from this rush to publish.^{1,2} In particular, the number of meta-analyses of aggregate data has dramatically increased owing to the ease of extracting data from publications and the development of free, user-friendly and dedicated statistical software. This phenomenon has resulted in the replication of meta-analyses, with several analyses having the same objectives and including the same studies. It is often described in the literature as redundancy and has already been observed in many fields of medical research.^{3–16}

Although investigating the same outcomes and including the same studies, these meta-analyses may differ in terms of the population of interest or the statistical methodology used, and these differences may influence their results. This phenomenon may be regarded as a ‘vibration of effects’ (VoE) and describes the extent to which the results of analyses could change according to the characteristics of the population included or the methodological choices made.¹⁷

The VoE phenomenon is classically investigated in a single research project by artificially producing multiple

meta-analyses from available studies.^{18,19} Assessment of the replication of meta-analysis results provides an example of VoE ‘naturally’ observed in multiple research projects. So far, the variability of meta-analysis results has mostly been reported using graphical descriptive representations,^{19–21} indicating the magnitude of effects (i.e., relative risk, RR) on the *x*-axis as a function of its level of significance (i.e., its *p*-value) on the *y*-axis. To the best of our knowledge, no quantitative analysis has been proposed up to now. The quantitative analysis of these results could enable breakdown of the total observed variability and subsequently quantification of the variability generated by the replication process. It could also allow identification of parameters likely to explain this variability, such as methodological quality or the statistical analysis procedures used. These parameters might explain systematic mean differences between meta-analysis results and/or dispersion (variance) of these results. Such quantitative analysis is thus essential to analyse the distortion (or improvement) in treatment effect estimates created by the phenomenon of replication and to better characterise the robustness of these estimates.

This paper aims to provide a general methodological framework for quantitative analysis of the reproducibility of meta-analysis results. The evaluation of direct oral anticoagulants (DOACs) in the acute treatment of venous thromboembolism (VTE) was chosen as an illustrative example of this approach.

2 | ILLUSTRATIVE EXAMPLE: META-ANALYSES OF DOACS IN THE TREATMENT OF ACUTE VTE

To illustrate the general methodological framework, we applied our approach to the example of meta-analyses evaluating DOACs in relation to any comparator in patients treated for VTE during the acute or extended phase of anticoagulation. The methods used for identification and selection of meta-analyses, data extraction and methodological quality assessment are described in Supplementary Table 1. For each meta-analysis, all treatment effect estimates concerning efficacy (recurrent VTE) and/or safety (major bleeding) outcomes were extracted. The estimated relative risk (RR) and the precision of the results defined by the standard error (SE) were then determined. The SE of the RR on a log scale was derived from the 95% confidence interval of RR ($CI_{95\%} = [RR_{LB}, RR_{UB}]$) using the following formula:

$$SE(\log RR) = \frac{\log(RR_{UB}) - \log(RR_{LB})}{2 \times 1.96},$$

The efficacy and safety results extracted were pooled in a single database to be jointly analysed and to provide more power for covariate analysis.

For each result, the following characteristics were also extracted: the type of meta-analysis (pairwise or network), the type of statistical model used (fixed or random-effect), the type of analysis (original analysis or secondary analyses, for example, results derived from subgroup or sensitivity analyses), the type of inference (frequentist or Bayesian), and the inclusion of non-randomised studies (yes or no).

The replication groups for meta-analysis results were then defined according to the types of population (treatment indication) and intervention compared. The results belonging to the same replication group therefore concerned the same studies, the same outcomes, the same treatment indications, and the same treatment comparisons. Each replication group therefore contained both the original results and those of all the subsequent meta-analyses that replicated it.

3 | GENERAL METHODOLOGICAL FRAMEWORK

The general methodological framework for evaluating the reproducibility of meta-analyses was composed of several parts: vibration of effects, variability breakdown, determinants of variability, reproducibility quantification

and vibration of effects simulation. Each of these parts is described below.

3.1 | Visualisation of the vibration of effects between and within replication groups

The vibration of effects (VoE) may be graphically visualised by representing the magnitude of effects (i.e., the RR) on the *x*-axis as a function of its level of significance (i.e., its *p*-value) on the *y*-axis. The *p*-value depends on both the effect size estimate and the precision of the estimation. Within the replication framework, the vibration may be represented in two formats: (1) as raw data, with each point representing a result observed in one meta-analysis, (2) as aggregated data of individual replication groups, with each point representing the median treatment effect of a particular replication group. The variability within each replication group was visualised by representing the range (minimum and maximum) of observed values for both RR and *p*-value within the replication group concerned.

3.2 | Variability breakdown

The data used to evaluate the reproducibility of the results of meta-analyses corresponded to several statistical results (*k*) from the meta-analyses (*j*) within a particular replication group (*i*) (See Section 2 for the definition of a replication group). The structure of the data is illustrated in Figure 1, with *I* replication groups. The *i*-th replication group contained J_i meta-analyses and the *j*-th meta-analysis of this group reported K_{ij} results (RR and SE) and associated covariates ($c = 1, \dots, C$).

First, a statistical result of one meta-analysis is a bidimensional quantity that is composed of an overall estimation of the treatment effect and its corresponding uncertainty, and these may be highly interdependent. To properly characterise such data, these two quantities need to be jointly analysed within the same model to take into account their interdependency. In the framework of meta-analysis results, reported values of treatment effect (RR) and its corresponding standard error (SE, representing the uncertainty of the estimation) were used and analysed within a bivariate model.

Second, the data structure needs to be defined in order to break down the total observed variability into variability between replication groups and variability within individual replication groups. For that purpose, a nested random effect structure must be defined due to the hierarchical nature of the data. In the illustrative

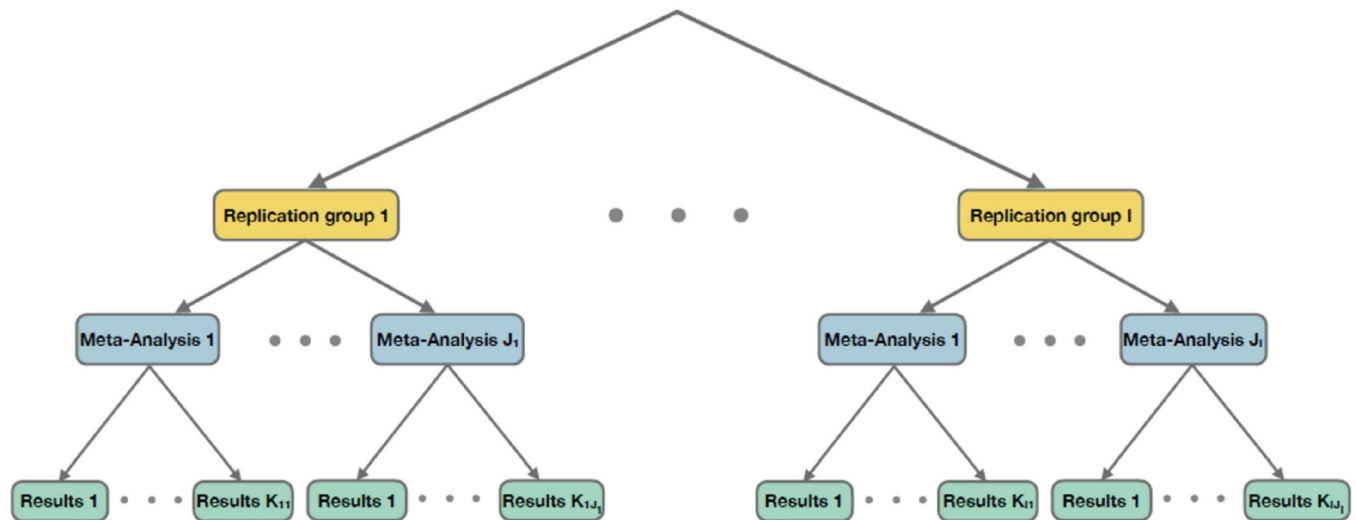


FIGURE 1 Schematic representation of the data structure of meta-analysis results representing i ($i = 1, \dots, I$) replication groups containing $j = 1, \dots, J_i$ meta-analyses which include $k = 1, \dots, K_{ij}$ results. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

example, a two-level nested structure was used to evaluate the meta-analyses within replication groups.

The following bivariate model with the nested random effect on the intercept was used:

with i, j and k denoting the k -th results of the j -th meta-analysis within the i -th replication group, respectively.

This model enables breakdown of the total variability into three components: (i) the variability between replica-

$$\begin{cases} \log(RR_{ijk}) = \beta_0^{RR} + u_i^{RR} + v_{ji}^{RR} + \varepsilon_{ijk}^{RR} \\ \log(SE_{ijk}) = \beta_0^{SE} + u_i^{SE} + v_{ji}^{SE} + \varepsilon_{ijk}^{SE} \end{cases}$$

$$\begin{pmatrix} u_i^{RR} \\ u_i^{SE} \end{pmatrix} \sim \mathcal{N}\left(0, \begin{bmatrix} \omega_{u,RR}^2 & \rho_u \omega_{u,RR} \omega_{u,SE} \\ \rho_u \omega_{u,RR} \omega_{u,SE} & \omega_{u,SE}^2 \end{bmatrix}\right), \begin{pmatrix} v_{ji}^{RR} \\ v_{ji}^{SE} \end{pmatrix} \sim \mathcal{N}\left(0, \begin{bmatrix} \omega_{v,RR}^2 & \rho_v \omega_{v,RR} \omega_{v,SE} \\ \rho_v \omega_{v,RR} \omega_{v,SE} & \omega_{v,SE}^2 \end{bmatrix}\right),$$

$$\begin{pmatrix} \varepsilon_{ijk}^{RR} \\ \varepsilon_{ijk}^{SE} \end{pmatrix} \sim \mathcal{N}\left(0, \begin{bmatrix} \sigma_{\varepsilon,RR}^2 & \rho_{\varepsilon} \sigma_{\varepsilon,RR} \sigma_{\varepsilon,SE} \\ \rho_{\varepsilon} \sigma_{\varepsilon,RR} \sigma_{\varepsilon,SE} & \sigma_{\varepsilon,SE}^2 \end{bmatrix}\right)$$

which may be summarised as follows:

$$\begin{pmatrix} \log RR_{ijk} \\ \log SE_{ijk} \end{pmatrix} \sim N\left(\begin{pmatrix} \beta_0^{RR} \\ \beta_0^{SE} \end{pmatrix}, \Sigma\right),$$

with

$$\Sigma = \begin{pmatrix} \omega_{u,RR}^2 + \omega_{v,RR}^2 + \sigma_{\varepsilon,RR}^2 & \rho_u \omega_{u,RR} \omega_{u,SE} + \rho_v \omega_{v,RR} \omega_{v,SE} + \rho_{\varepsilon} \sigma_{\varepsilon,RR} \sigma_{\varepsilon,SE} \\ \rho_u \omega_{u,RR} \omega_{u,SE} + \rho_v \omega_{v,RR} \omega_{v,SE} + \rho_{\varepsilon} \sigma_{\varepsilon,RR} \sigma_{\varepsilon,SE} & \omega_{u,SE}^2 + \omega_{v,SE}^2 + \sigma_{\varepsilon,SE}^2 \end{pmatrix},$$

tion groups (u_i), (ii) the variability within each replication group (v_{ji}) and (iii) the variability within each meta-analysis (residual variability, ε_{ijk}).

For each numerical outcome (RR or SE) of a meta-analysis, the parameter β_0 corresponds to the intercept. The parameters u_i and v_{ji} represent the random effect of the i -th replication group and the random effect of the

[Correction added on 07 December 2023, after first online publication: The above equation has been corrected in this version.]

j -th meta-analysis nested in the i -th replication group, respectively. The standard deviation ω_u quantifies the variability between replication groups, the standard deviation ω_v quantifying the variability between meta-analyses within each replication group. Finally, ε_{ijk} is the residual error (within meta-analysis variability) for the k -th result of the j -th meta-analysis within the i -th replication group with σ_ε^2 quantifying the within meta-analysis variability. The parameters ρ_u , ρ_v and ρ_ε represent the correlation of the random effects and the residual error between the two types of numerical outcomes (RR and SE).

3.3 | Determinants of variability

To investigate the effect of meta-analysis characteristics on result reproducibility, we extended the previous model to a meta-regression that included the covariates used for modelling both mean parameters and residual variance parameters of the overall treatment effect (RR) and its uncertainty (SE):

1. Investigation of the impact of C binary covariates on mean parameter value by including these covariates as predictors. The parameters β_c ($c = 1, \dots, C$) quantify the systematic difference in mean meta-analysis results between levels of the c -th covariate.

$$\begin{cases} \log(RR_{ijk}) = \beta_0^{RR} + u_i^{RR} + v_{ji}^{RR} + \sum_{c=1}^C \beta_c^{RR} \times X_{c_{ij}} + \varepsilon_{ijk}^{RR} \\ \log(SE_{ijk}) = \beta_0^{SE} + u_i^{SE} + v_{ji}^{SE} + \sum_{c=1}^C \beta_c^{SE} \times X_{c_{ij}} + \varepsilon_{ijk}^{SE} \end{cases}$$

2. Investigation of the impact of C binary covariates on within meta-analysis variability by stratifying residual variance on covariate levels. Residual variability was modelled using the following formula:

$$\begin{pmatrix} \varepsilon_{ijk}^{RR} \\ \varepsilon_{ijk}^{SE} \end{pmatrix} \sim \mathcal{N}\left(0, \begin{bmatrix} \sigma_{\varepsilon,RR}^2(X_{ij}) & \rho_\varepsilon \sigma_{\varepsilon,RR}(X_{ij}) \sigma_{\varepsilon,SE}(X_{ij}) \\ \rho_\varepsilon \sigma_{\varepsilon,RR}(X_{ij}) \sigma_{\varepsilon,SE}(X_{ij}) & \sigma_{\varepsilon,SE}^2(X_{ij}) \end{bmatrix}\right),$$

$$\sigma_{\varepsilon,RR}(X) = \sigma_{\varepsilon,RR} \times e^{\sum_{c=1}^C \gamma_c^{RR} \times X_{c_{ij}}} \text{ and } \sigma_{\varepsilon,SE}(X) = \sigma_{\varepsilon,SE} \times e^{\sum_{c=1}^C \gamma_c^{SE} \times X_{c_{ij}}}.$$

The parameters γ_c quantify systematic difference in terms of variability of meta-analysis results between levels of the c -th covariates.

The impact of covariates was expressed as the ratio of change from the reference value using the exponential of each coefficient (i.e., e^{β_c} and e^{γ_c}). The covariates assessed concerned: the nature of the results (efficacy vs. safety), the type of analysis (secondary vs. original analysis), the meta-

analysis design (network vs. pairwise), the temporality of the meta-analyses (replicated vs. original), the overlap in authorship (no [i.e., if a meta-analysis shared no common author with other meta-analyses] vs. yes), the risk of bias of the meta-analyses (high vs. low), the nature of the statistical analysis (Bayesian versus frequentist), the statistical model used to combine the results (random-effects model vs. fixed-effect model), the design of the studies included (inclusion of observational studies with or without randomised controlled trials (RCTs) vs. RCTs only). Using this model, two analyses were performed. The first analysis involved adjustment only on the nature of the result (safety vs. efficacy) and the type of analysis (secondary vs. original analysis) to quantify the reproducibility within replication groups. The second analysis involved adjustment on all the covariates described above to investigate factors that could potentially explain the differences between meta-analyses.

3.4 | Reproducibility quantification

The reproducibility of meta-analyses within replication groups could be quantified using the following intra-replication group correlation coefficient (IRGC):

$$IRGC(X) = \frac{\omega_u^2}{\omega_u^2 + \omega_v^2 + \sigma_\varepsilon^2(X)}.$$

The IRGC was calculated separately for RR and SE. This coefficient varies between 0 and 1. Values below 0.5 indicate poor reproducibility, between 0.5 and 0.75 moderate reproducibility, between 0.75 and 0.9 good reproducibility, any value above 0.9 indicating very good reproducibility.²² For RR, the IRGC is interpreted as the percentage of variability of the estimation of the treatment effect that is explained by the replication group, the closer the IRGC of the RR is to 1, the more reproducible the treatment effect within replication groups. For SE, the IRGC is interpreted as the percentage of variability of the precision of the estimation that is explained by the replication group, the closer the IRGC of the SE is to 1, the more reproducible the precision of the estimation within replication groups.

3.5 | Vibration of effect simulations

To visualise the impact of variability within replication groups and variability of the variation in overall treatment effect and its statistical significance, we conducted a simulation study for generating VoE plots from the bivariate normal mixed-effect model described previously. This generation was a two-step process.

The first step was to simulate RR and SE values for a dedicated replication group using the formula:

$$\begin{bmatrix} \log(RR_{sim}) \\ \log(SE_{sim}) \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \beta_0^{RR} + \sum_{c=1}^C \beta_c^{RR} \times X_c + u^{RR} \\ \beta_0^{SE} + \sum_{c=1}^C \beta_c^{SE} \times X_c + u^{SE} \end{bmatrix}, \begin{bmatrix} \omega_{v,RR}^2 + \sigma_{\epsilon,RR}^2(X) & \rho_v \omega_{v,RR} \omega_{v,SE} + \rho_\epsilon \sigma_{\epsilon,RR} \sigma_{\epsilon,SE} \\ \rho_v \omega_{v,RR} \omega_{v,SE} + \rho_\epsilon \sigma_{\epsilon,RR} \sigma_{\epsilon,SE} & \omega_{v,SE}^2 + \sigma_{\epsilon,SE}^2(X) \end{bmatrix} \right),$$

where u^{RR} and u^{SE} are random effects specific to the replication group studied. For the simulation, they were set at a value specific to the desired replication group.

The second step was to calculate a corresponding p-value based on the simulated values, using the following formula:

$$P_{sim} = 2 \times \left(1 - \Phi \left(\left| \frac{\log(RR_{sim})}{SE_{sim}} \right| \right) \right),$$

where Φ is the cumulative distribution function of the standard normal distribution $\mathcal{N}(0,1)$.

Simulated VoE could be then visualised using a heat map plotting the two-dimensional density of simulated p_{sim} on the y-axis and RR_{sim} values on the x-axis. The width of the area enclosed describes the variability of RR: the wider the area enclosed the more variable the treatment effect. The height of the area enclosed describes the variability of p_{sim} and thus the variability of result uncertainty.

All estimates and their 95% credible intervals (95% CrI) were based on a Bayesian inference method with prior distributions and performed using the rstan package²³ of R statistical software. The prior distribution of regression coefficients was a normal distribution $\mathcal{N}(0,4)$ and the prior distribution of variance components was half-normal. The number of chains was 2, the number of burn-in samples was 10,000 and the number of total MCMC iterations was 20,000. Diagnostic plots were used to assess convergence. The STAN code, both for univariate and multivariate model are provided in Supplementary Table 2.

4 | APPLICATION TO META-ANALYSES OF DOACS IN THE ACUTE TREATMENT OF VTE

4.1 | Description of the meta-analyses included

The search procedure identified 1258 potentially eligible meta-analyses, of which 144 were included in our review

(the list of references of the meta-analyses included is provided in the Supplementary files). Among these

144 meta-analyses, 119 assessed recurrent VTE and/or major bleeding outcomes, for a total of 857 results on recurrent VTE and 690 results on major bleeding. For efficacy, the results of the meta-analyses were split into 319 replication groups with a mean of 2.7 results per replication group (interquartile range from 1 to 3) and a maximum of 28 results for one replication group. For safety, the results of the meta-analyses were split into 295 replication groups with a mean of 2.4 results per replication group (interquartile range from 1 to 3) and a maximum of 23 results for one replication group. The median overlap between replication groups was 50.0% (interquartile range from 40.0% to 68.4%).

4.2 | Vibrations of effects of meta-analyses results

In the illustrative example of meta-analyses evaluating DOACs in the acute treatment of VTE, a median of 4 results (interquartile range from 1 to 9 both for efficacy and safety) per meta-analysis were available. VoE plots were stratified according to the nature of the outcomes (safety or efficacy), the type of comparator (DOACs or LMWH/VKA) and the type of results (original or secondary). A greater variability was observed concerning safety results compared to efficacy results (Figure 2 top panel for raw data and Figure 2 bottom panel for aggregated data) whatever the stratification factor (type of comparator or type of results).

With regard to raw data, when DOACs were compared to LMWH or VKA, the median treatment effect for recurrent VTE measured in the meta-analyses was 0.80 (interquartile range from 0.62 to 0.96 in favour of DOACs) and the median treatment effect for major bleeding was 0.83 (interquartile range from 0.55 to 1.33 in favour of LMWH and VKA) (Figure 2, top panel). When DOACs were compared to another DOAC, the median treatment effects for recurrent VTE and major bleeding were 1.03 (interquartile range from 0.86 to 1.25)

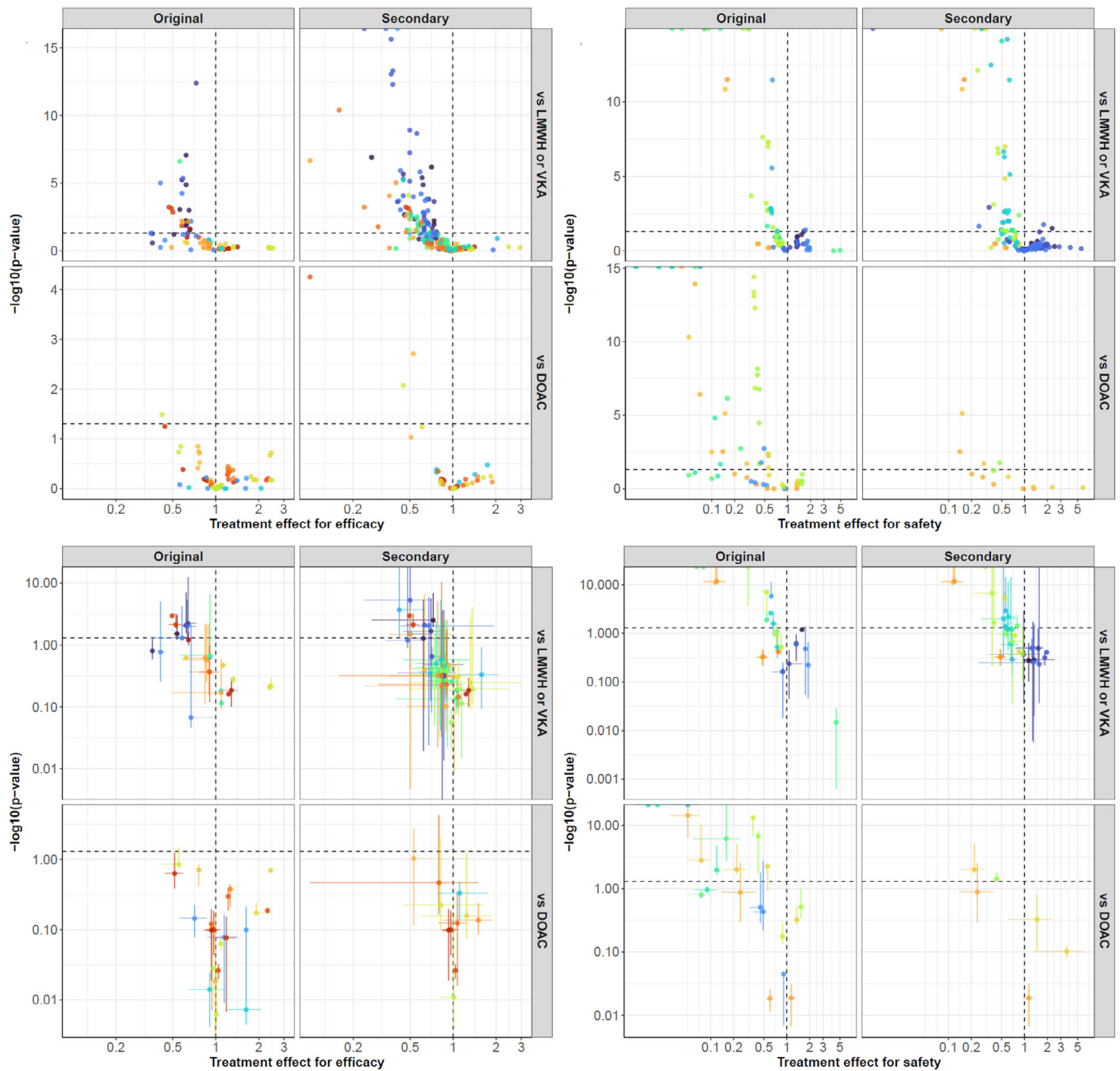


FIGURE 2 Vibration of efficacy results (recurrent venous thromboembolism) on the left and safety results (major bleeding) on the right according to the comparator. In the upper panels, each point represents a result observed in one meta-analysis. In the lower panels, each point represents aggregated data within replication groups, that is, the median of treatment effect within replication groups. The horizontal line represents the range (minimum and maximum) of the treatment effect observed within replication groups, the vertical line representing the range of the p-values within replication groups (on a log scale for the y-axis). The dashed vertical line represents the null effect of the relative risk (RR = 1), the dashed horizontal line representing the cut-off of statistical significance (p -value = 0.05). Original: original results in meta-analyses. Secondary: subgroup or sensitivity results in meta-analyses. DOAC: direct oral anticoagulant; LMWH: low-molecular-weight heparin; VKA: vitamin-K antagonist. [Colour figure can be viewed at wileyonlinelibrary.com]

and 0.40 (interquartile range from 0.14 to 0.89), respectively (Figure 2, top panel).

Concerning aggregate data, within the same replication group, when DOACs were compared to LMWH or VKA, the median average treatment effect for recurrent VTE within replication groups was 0.82 (interquartile

range from 0.66 to 0.97) and the median average treatment effect for major bleeding within replication groups was 0.72 (interquartile range from 0.54 to 1.23 (Figure 2, bottom panel)). When DOACs were compared to another DOAC, the median average treatment effect within replication groups was 1.02 (interquartile range from 0.93 to

TABLE 1 Analysis of the reproducibility of meta-analyses regarding efficacy (recurrent venous thromboembolism) and safety (major bleeding) results within replication groups.

Treatment effect	Recurrent VTE		Major bleeding	
	Original analysis	Secondary analysis	Original analysis	Secondary analysis
Variability—SD (95% CrI)				
Between replication groups ($\omega_{u,RR}$)		0.79 (0.74–0.83)		
Within replication groups ($\omega_{v,RR}$)		0.08 (0.05–0.11)		
Within meta-analysis ($\sigma_{e,RR}$)	0.14 (0.12–0.15)	0.37 (0.35–0.40)	0.24 (0.22–0.26)	0.64 (0.59–0.70)
IRGC (95% CrI)	0.96 (0.95–0.97)	0.81 (0.78–0.83)	0.91 (0.89–0.93)	0.60 (0.54–0.65)
Standard error	Recurrent VTE		Major bleeding	
	Original analysis	Secondary analysis	Original analysis	Secondary analysis
Variability—SD (95% CrI)				
Between replication groups ($\omega_{u,SE}$)		0.69 (0.64–0.75)		
Within replication groups ($\omega_{v,SE}$)		0.27 (0.22–0.32)		
Within meta-analysis ($\sigma_{e,SE}$)	0.30 (0.27–0.33)	0.44 (0.41–0.47)	0.28 (0.26–0.32)	0.42 (0.38–0.46)
IRGC (95% CrI)	0.75 (0.69–0.80)	0.64 (0.60–0.69)	0.76 (0.69–0.81)	0.66 (0.60–0.71)

Abbreviations: 95% CrI, 95% credible interval; IRGC, intra-replication group correlation coefficient; SD, standard deviation; VTE, venous thromboembolism.

1.23) for recurrent VTE and 0.39 (interquartile range from 0.11 to 0.89) for major bleeding (Figure 2, bottom panel).

4.3 | Breakdown of the variability

The proposed model (see Sections 3.2 and 3.3) was applied to meta-analyses evaluating DOACs with inclusion of the nature of the result (efficacy vs. safety) and the type of analysis (secondary vs. original analyses) as covariates to stratify the analysis and assess reproducibility with respect to these characteristics.

Regarding the treatment effect, the standard deviation for variability between replication groups ($\omega_{u,RR}$) and within replication groups ($\omega_{v,RR}$) was 0.79 (95% CrI, 0.74–0.83) and 0.08 (0.05–0.11), respectively (Table 1). For the efficacy outcome, the variability within meta-analyses was 0.14 (0.12–0.15) and 0.37 (0.35–0.40) in original and secondary analyses, respectively. This corresponded to an IRGC of 0.96 (0.95–0.97) and of 0.81 (0.78–0.83), respectively. For the safety outcome, the variability within meta-analyses was 0.24 (0.22–0.26) and 0.64 (0.59–0.70) in original and secondary analyses, respectively, corresponding to an IRGC of 0.91 (0.89–0.93) and of 0.60 (0.54–0.65), respectively. So very good reproducibility of the meta-analyses within replication groups was observed for the results of meta-analyses when considering the overall treatment effect estimated on efficacy for original analyses, good reproducibility for secondary analyses of efficacy and original analyses of safety, and moderate reproducibility for secondary analyses of safety.

Regarding reported standard errors of the treatment effect, the variability of the standard deviation between replication groups ($\omega_{u,SE}$) and within replication groups ($\omega_{v,SE}$) was 0.69 (95% CrI, 0.64–0.75) and 0.27 (0.22–0.32), respectively. For the efficacy outcome, the variability within meta-analyses was 0.30 (0.27–0.33) in original analyses and 0.44 (0.41–0.47) in secondary analyses. These values corresponded to an IRGC of 0.75 (0.69–0.80) and 0.64 (0.60–0.69), respectively. For the safety outcome, the variability within meta-analyses was 0.28 (0.26–0.32) for original analyses and 0.42 (0.38–0.46) for secondary analyses corresponding to an IRGC of 0.76 (0.69–0.81) and of 0.66 (0.60–0.71), respectively. These IRGC values indicate moderate reproducibility of the results of meta-analyses when considering the reported standard errors of the overall treatment effect estimation.

4.4 | Investigation of sources of variability of efficacy and safety results within replication groups

None of the covariates tested had an impact on the mean treatment effect (β_c^{RR}) except for safety results compared to efficacy results (ratio 1.20, 95% CrI [1.06–1.36]), Figure 3, top left panel). In terms of treatment effect uncertainty (Figure 3, top right panel), the safety results also had an impact on the treatment effect uncertainty (β_c^{SE}) compared to efficacy results (1.62 [1.45–1.80]), as well as on the results of secondary analyses compared to original analyses (1.14 [1.09–1.20]). The treatment effect uncertainty increased depending on the meta-analytical

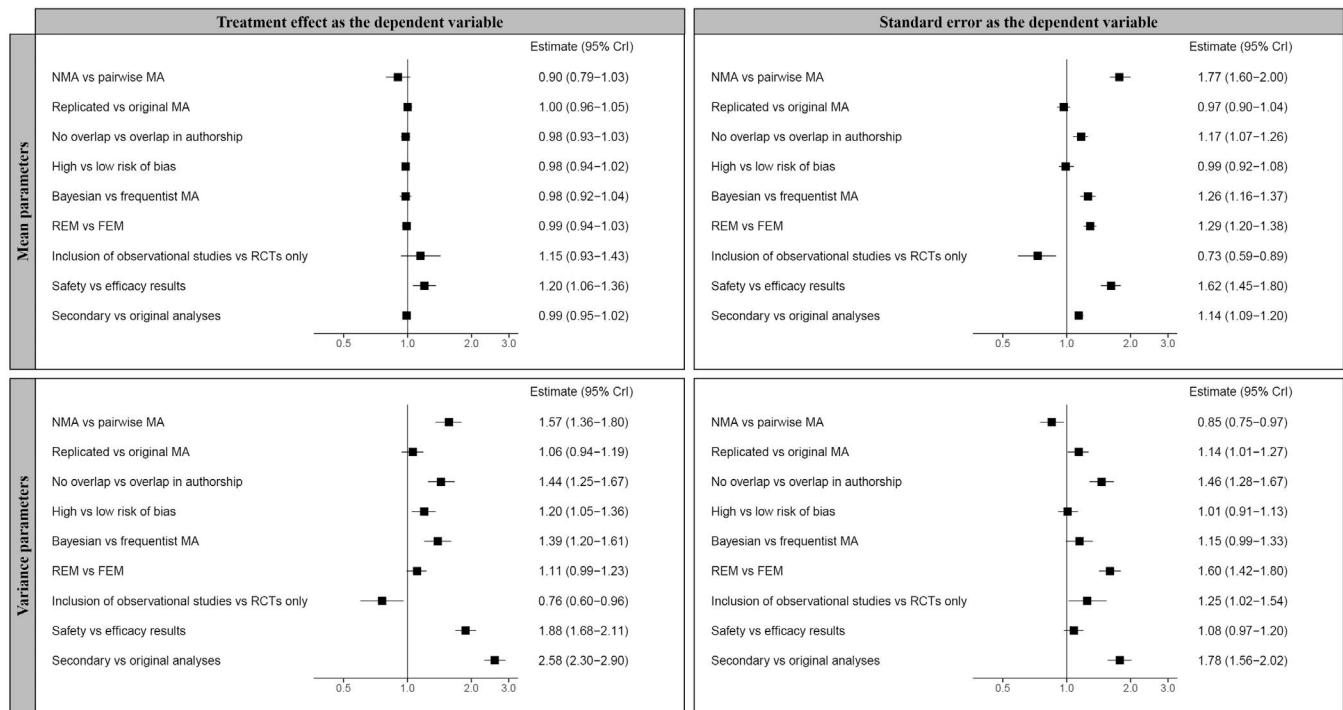


FIGURE 3 Reproducibility of efficacy (recurrent venous thromboembolism) and safety (major bleeding) results within replication groups with respect to the average variation of the treatment effect (top left) and its uncertainty (top right) and to the breakdown of the within-meta-analysis variability (residual variability) of the treatment effect (bottom left) and its uncertainty (bottom right). 95% CrI, 95% credible interval; FEM, fixed-effect model; MA, meta-analysis; NMA, network meta-analysis; REM: random-effects model; RCTs, randomised controlled trials.

methods used: by 77% in network meta-analyses compared to pairwise meta-analyses (1.77 [1.60–2.00]), by 29% in meta-analyses using a random-effects model to combine the results compared to a fixed-effect model (1.29 [1.20–1.38]), and by 26% in meta-analyses using a Bayesian approach compared to a frequentist approach (1.26 [1.16–1.37]). A 17% increase of uncertainty was observed in meta-analyses with no overlap in authorship compared to meta-analyses with overlap in authorship (1.17 [1.07–1.26]). Conversely, treatment effect uncertainty decreased by 27% in meta-analyses that included observational studies compared to meta-analyses that included only RCTs (0.73 [0.59–0.89]).

The impact of the covariates on the within meta-analysis variance (residual variability) is illustrated in Figure 3 (bottom panel). With respect to the treatment effect (γ_c^{RR}), the residual variability was increased by 158% in secondary analyses (2.58 [2.30–2.90]), and by 88% in safety results (1.88 [1.68–2.11]). [Correction added on 07 December 2023, after first online publication: The preceding sentence has been corrected in this version.] As regards the meta-analytical methods used, the residual variability was increased by 57% in network meta-analyses (1.57 [1.36–1.80]), and by 39% in meta-analyses using a Bayesian approach (1.39 [1.20–1.61]). A 44% and 20% increase in residual variability was observed in meta-

analyses with no overlap in authorship (1.44 [1.25–1.67]) and in meta-analyses with a high risk of bias (1.20 [1.05–1.36]). Conversely, residual variability decreased by 24% in meta-analyses that included observational studies compared to meta-analyses that included only RCTs (0.76 [0.60–0.96]). With respect to the standard error of the treatment effect (γ_c^{SE}), replicated meta-analyses, meta-analyses with no overlap in authorship, meta-analyses using a random-effects model to combine the results, meta-analyses that included observational studies, and secondary analyses were associated with an increase of the residual variability, whereas network meta-analyses were associated with a decrease in residual variability (0.85 [0.75–0.97]).

4.5 | Vibration of effect simulations

For the random effects u^{RR} and u^{SE} , posterior samples of each parameter shown to induce a treatment effect in a replication group were chosen from the model detailed in Section 4.4. The RR and SE values were simulated from the multivariate normal distribution described in Section 3.5. Covariates were set at specific values to represent classical scenarios of analysis. Two scenarios were simulated

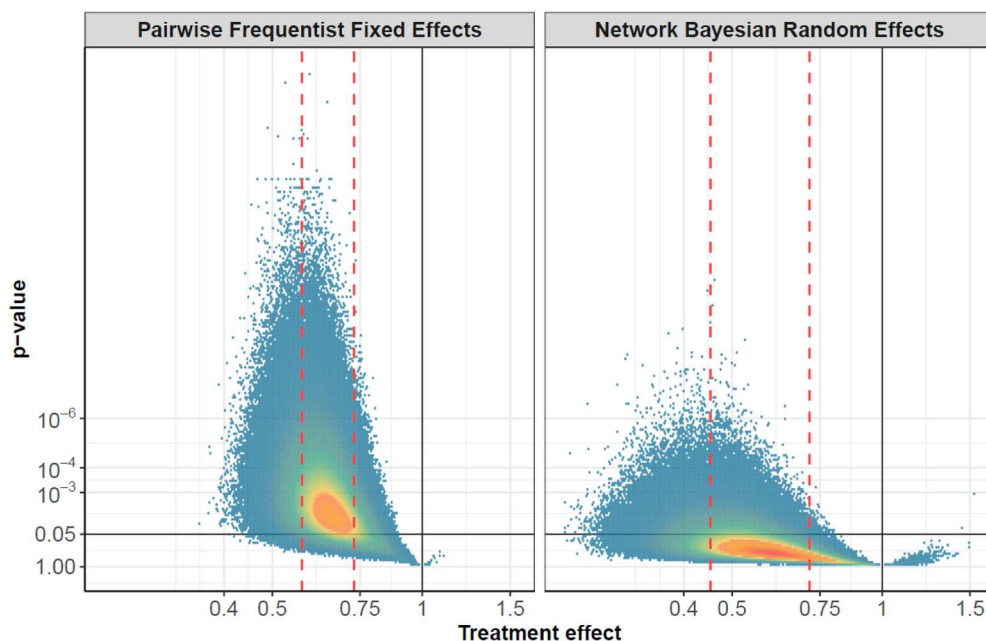


FIGURE 4 Predictive distribution of the vibration of effects using Monte Carlo simulations. Red dashed vertical lines represent the 10th and 90th percentiles of the treatment effect distribution. The continuous vertical line represents the null effect of the relative risk ($RR = 1$), the solid horizontal black line representing the cut-off of statistical significance ($p = 0.05$). [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

1. A pairwise meta-analysis with a fixed-effect model using a frequentist approach in an original meta-analysis with a low risk of bias
2. A network meta-analysis with a random-effects model using a Bayesian approach in an original meta-analysis with a low risk of bias.

For each scenario, 1000 values of RR and SE were sampled. The vibration of effect generated from the simulations is shown in Figure 4. This illustrates the variability in treatment effect estimates and its impact on statistical significance within a replication group in both simulation scenarios.

The effect size was in favour of DOACs both at the 10th percentile and the 90th percentile. In network meta-analyses using a Bayesian approach and a random-effects model, the 10th percentile was 0.45 and the 90th percentile was 0.71. Regarding pairwise meta-analyses using a frequentist approach and a fixed-effect model, the 10th percentile was 0.57 and the 90th percentile was 0.73. A greater variability in treatment effect estimates and a greater uncertainty of the estimation were observed in network meta-analyses using a Bayesian approach and a random-effects model compared to frequentist, pairwise meta-analyses. This resulted in getting more conservative results in network meta-analyses.

5 | DISCUSSION

This study is the first to propose a statistical framework for analysing the replication and reproducibility of meta-analyses. Meta-analysis results defined by the overall

effect size estimation (RR) and its uncertainty (SE), were jointly analysed using a bivariate, linear, mixed-effect model to investigate the inter-dependency between RR and SE values. Covariates were included into the model at two levels: (i) the mean effect and (ii) the residual variance (within meta-analysis variability). Analysis of RR values allowed detecting covariates associated with systematic differences among meta-analyses or accounting for a bias between meta-analyses differing in methodological quality. Analysis of SE values enabled identification of covariates influencing results dispersion. It was then possible to characterise the reproducibility by quantifying the intra-replication group correlation as a function of the methodological characteristics of the meta-analyses.

The proposed statistical model was applied to meta-analyses evaluating DOACs in the acute treatment of VTE. Reproducibility of the efficacy results within replication groups was very good in original analyses and good in secondary analyses, while reproducibility of safety results within replication groups was good in original analyses and moderate in secondary analyses. Within replication groups, both the mean treatment effect and the residual variability were increased in safety results compared to efficacy results. This could be explained by the lower number of events concerning safety outcomes compared to efficacy outcomes. We also found that the treatment effect uncertainty and the residual variability of the treatment effect were increased according to the meta-analytical methods used, particularly in network meta-analyses, in meta-analyses using a Bayesian approach, and in those using a random-effects model to combine the results. These findings were expected.

Indeed, whereas in standard pairwise meta-analyses, the distribution of effect modifiers can only vary from one study to another for a particular comparison (resulting in heterogeneity), in network meta-analyses, which include different trials comparing different interventions, the distribution of effect modifiers can vary from one study to another for a particular comparison but also between comparisons with potential inconsistency. Moreover, in the illustrative example evaluating DOACs in the acute treatment of VTE, the network of treatments was weakly connected, resulting in increased uncertainty. The increase in uncertainty is also explained by the use of a Bayesian approach, in which case the phenomenon is certainly driven by the frequent use of uninformative prior distributions.

In our statistical framework, we used a Bayesian inference method with prior distributions owing to the flexibility of the Bayesian approach. The disadvantage of this approach is the long computation time, from 30 min to more than 10 h, depending on the number of iterations, the number of chains and the number of cores if the computation is parallelised. The computation time would be faster using a frequentist approach, but to date there is no software solution available for estimating such models in frequentist mode. In the model proposed, dispersion of meta-analysis results was explained by introducing covariates in analysis of the standard deviation of the residual error (intra-meta-analysis variability). For meta-analysis specific covariates, another possibility would have been to include these in analyses of the standard deviation of the between meta-analysis random effect using the following formula:

$$\omega_{v,RR}(X) = \omega_{v,RR} \times e^{\sum_{c=1}^C \gamma_c^{RR} \times X_{cij}} \quad \text{and}$$

$$\omega_{v,SE}(X) = \omega_{v,SE} \times e^{\sum_{c=1}^C \gamma_c^{SE} \times X_{cij}} .$$

This would have allowed explanation of the variation of dispersion at the inter-meta-analysis level. In the example of meta-analyses evaluating DOACs, such covariate effects could not be accurately estimated due to the identifiability issue. This was certainly the consequence of a lack of between-meta-analyses data within individual replication groups. The accurate description of between-meta-analyses predictors of variability would necessitate a larger amount of data that be achieved by analysing the replication of meta-analyses for more than one drug and indication. Identifiability issues of between-group and within-group variances may also arise for datasets with too few replication groups or too few studies per

replication group. The estimation process would therefore give more weight to prior information. This situation might limit the number of covariates that could be included in the model. In this context, we advise introducing covariates into the model progressively in a step-wise manner in order to detect any over parameterization or convergence issues.

As pointed out by the reviewers, replication groups inherently have a certain overlap among the studies included in the meta-analyses. This overlap may induce a correlation between the random effects of two different replication groups. One of the limitations of the proposed approach is therefore that it cannot quantify the impact of this overlap on the correlation between the random effects of two different replication groups. One solution could be to include a correlation depending on the extent of overlap between two replication groups i and i' . This could be achieved using the following formula:

$$\text{cor}(u_i, u_{i'}) = \tanh(\rho_0 + \rho_1 \text{Overlap}_{ii'}).$$

The phenomenon of meta-analysis replication, often described as redundancy in the literature, has been already highlighted in various domains.^{5,6,8,16} Several arguments have been invoked to justify redundancy, such as: the wish to update the previous meta-analysis to include data from new high-quality trials, reluctance to extrapolate the results obtained to all patients in the absence of subgroup analyses, the need to assess an endpoint not evaluated in other meta-analyses or a change in endpoint definition or its assessment time. However, the term 'redundant' implicitly signifies that replication is unnecessary from a scientific point of view. However, this interpretation is somewhat limited because the phenomenon of meta-analysis replication could also be necessary, notably to improve imperfect meta-analyses in terms of conduct, methodology or results and thus methodological quality. In our illustrative example regarding meta-analyses evaluating DOACs in the acute treatment of VTE, the treatment effect uncertainty decreased by 12% in replicated meta-analyses compared to non-replicated meta-analyses, representing an improvement in the accuracy of the results.

Nevertheless, in order to answer this question about the usefulness of replication, we need to have a broader view of this phenomenon. Ideally, analyses should be applied more broadly and more generally to several domains or drugs simultaneously (for example, immunotherapy, vaccines, etc.). However, the covariates of interest are often time-consuming to extract or evaluate. For example, the methodological quality of the meta-analysis is an important covariate but the evaluation of the level

of bias within a systematic review using the ROBIS tool requires substantial reflection to complete, as the assessment of each risk of bias domain requires careful analysis of the meta-analysis in order to correctly rate the risk of bias. One solution to facilitate the process of extraction and reduce the time needed for its execution would be to use artificial intelligence to perform automatic extraction of covariates of interest from the text of the publication.

6 | CONCLUSION

The model proposed in our study allows quantification of the reproducibility of meta-analysis results and the identification of determinants influencing the variability of the replication process. The methods used to perform the meta-analyses, and replications, in particular those with no overlap in authorship, had an impact on treatment effect and its precision that could lead to confusion in interpretation of results.

AUTHOR CONTRIBUTIONS

Céline Chapelle: Conceptualization; methodology; project administration; data curation; formal analysis; software; writing – original draft; writing – review and editing. **Gwénaél Le Teuff:** Writing – review and editing. **Paul Jacques Zufferey:** Writing – review and editing. **Silvy Laporte:** Conceptualization; project administration; supervision; writing – review and editing. **Edouard Ollier:** Conceptualization; project administration; methodology; formal analysis; supervision; software; validation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REPRODUCIBLE RESEARCH STATEMENT

Study protocol: Registered in PROSPERO (registration no. CRD42022316273) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=316273). Statistical code and data set: The analysis scripts are available as supporting information and data set may be requested from Céline Chapelle (e-mail: celine.chapelle@chu-st-etienne.fr).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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A framework to characterise the reproducibility of meta-analysis results with its application to direct oral anticoagulants in the acute treatment of venous thromboembolism

Supplementary files

Supplementary Table 1. Methods used for identification and selection of meta-analyses, data extraction and methodological quality assessment.

Registration of the protocol	International prospective register of systematic reviews (PROSPERO), registration number CRD42022316273
Literature search	
Meta-analysis identification	Published meta-analyses including randomised controlled trials or observational studies evaluating DOACs in relation to any comparator in patients treated for VTE during the acute or the extended phase of anticoagulation, including patients receiving acute treatment for VTE in the context of cancer. The search was not restricted to the treatment of VTE in order to include meta-analyses addressing several indications.
Information sources	Literature search on PubMed from January 1 st , 2005 to January 31, 2022 using keywords and medical subject headings (MeSH) terms with no restriction on language or publication period.
Full electronic search equation	1 ((Factor Xa Inhibitors/therapeutic use[MeSH Terms]) OR (Factor Xa Inhibitors/adverse effects[MeSH Terms]) OR (direct thrombin inhibitors[MeSH Terms]) OR (thrombin inhibitors, direct[MeSH Terms]) OR (dabigatran[Title/Abstract]) OR (rivaroxaban[Title/Abstract]) OR (apixaban[Title/Abstract]) OR (edoxaban[Title/Abstract]) OR (argatroban[Title/Abstract]) OR (direct oral anticoagulant*[Title/Abstract]) OR (direct oral anti-coagulant*[Title/Abstract]) OR (DOAC*[Title/Abstract]) OR (DOA[Title/Abstract]) OR (DOAs[Title/Abstract]) OR (direct OAC*[Title/Abstract]) OR (anticoagulation strategies[Title]) OR (novel oral anticoagulant*[Title]) OR (non-vitamin K antagonist[Title/Abstract]) OR (non-vitamin-K-antagonist*[Title/Abstract]) OR (nonvitamin K oral anticoagulant*[Title/Abstract]) OR (direct oral anticoagulation*[Title/Abstract]) OR (new oral anticoagulant*[Title/Abstract]) OR (NOAC*[Title/Abstract]) OR (target-specific oral anticoagulant*[Title/Abstract]) OR (TSOAC*[Title/abstract]))
	2 ((meta-analysis[Title/Abstract]) OR (Meta-Analysis[Publication Type]) OR (network meta-analysis[Title/Abstract]) OR (indirect comparison*[Title/Abstract]) OR (pooled-analysis[Title/Abstract]))
	3 (("2005/01/01"[Date - Publication] : "3000"[Date - Publication]))
	4 "recommendations"[Title]
	5 "design"[Title]
	6 "protocol"[Title]
	7 1 AND 2 AND 3 NOT 4 NOT 5 NOT 6
	Meta-analysis selection
Selection process	One author screened titles and abstracts of publications for possible inclusion and then two authors independently screened the full-text articles retrieved, discrepancies between authors being resolved by discussion with a third author.

Eligibility criteria	<p>Pairwise (individual patient data or aggregated data) and network meta-analyses that: 1) included randomised controlled trials or observational studies; 2) evaluated DOACs in relation to any comparator (active standard treatment (vitamin-K antagonists, aspirin, or low-molecular-weight heparin), non-active treatment (placebo or control) or other DOACs); 3) included patients treated for an acute VTE during the acute or extended phase of anticoagulation.</p> <p>To characterise replication, only full-text articles were included.</p>
Exclusion criteria	Meta-analyses including only one study assessing DOACs in acute VTE patients.
Data extraction	
Data collection process	Two authors independently extracted the data, discrepancies being resolved by discussion.
Data items	<ul style="list-style-type: none"> - Publication details: <ul style="list-style-type: none"> • author names • year of publication • journal • free-access journal • impact factor of the journal - Details of the meta-analysis: <ul style="list-style-type: none"> • design (pairwise or network meta-analysis) • registration • number of studies included • names and designs of the studies included • treatments assessed • method used to assess the risk of bias of the included studies (tool employed and use of this tool to assess the effect of bias on the results) - Citation of previous meta-analyses in the field - All the results of the meta-analyses (original and secondary) for both efficacy (recurrent VTE) and safety (major bleeding) outcomes: <ul style="list-style-type: none"> • treatment effect (relative risk, odds ratio or hazard ratio) and its 95% confidence interval • p-value • I^2 of Higgins for heterogeneity between studies - Details of the analysis for all the results: <ul style="list-style-type: none"> • nature of the statistical analysis (frequentist or Bayesian) • statistical model used to combine the results (fixed-effect or random-effects model) • type of analysis (original or secondary results)
Definitions	<p>No overlap in authorship: if a meta-analysis shared no common author with other meta-analyses. Two meta-analyses were considered as having an overlap in authorship if they shared at least one common author.</p> <p>Original analysis: global result of the meta-analysis</p> <p>Secondary analysis: results from subgroups or sensitivity analyses</p>

Quality assessment	
Study risk of bias assessment	<p>Two persons independently assessed the risk of bias of the meta-analyses according to the Risk of Bias in Systematic Reviews (ROBIS) tool, discrepancies between reviewers being resolved by discussion.</p> <p>Assessment of the risk of bias of the meta-analyses was accomplished in three phases:</p> <ul style="list-style-type: none"> - 1) assessment of relevance (optional) - 2) identification of concerns regarding the review process - 3) appraisal of the overall risk of bias. <p>Phase 2 of the ROBIS tool covered four domains:</p> <ul style="list-style-type: none"> - study eligibility criteria - study identification and selection - data collection and study appraisal - synthesis and findings. <p>Each of these four domains was subjectively assessed as having a low, unclear or high risk of bias, based on the questions specified in the tool.</p> <p>In the last phase, the overall risk of bias of the meta-analyses was assessed as low, unclear or high, based on assessment of the four domains in phase 2.</p>

Supplementary Table 2. STAN code used for the variability breakdown (bivariate model) and to identify the determinants of variability

A. STAN code for the variability breakdown

```

code <- "
data {
  int<lower=1> N;
  matrix[2,N] dr;
  real COV1[N];
  real COV2[N];
  int<lower=1> J_U;
  int<lower=1, upper=J_U> subj_U[N];
  int<lower=1> J_V;
  int<lower=1, upper=J_V> subj_V[N];
}

parameters {
  real Beta0;
  real Beta_X1;
  real Beta_X2;

  real<lower=0> sigma_e;
  real sigma_e_X1;
  real sigma_e_X2;

  real Beta0_se;
  real Beta_X1_se;
  real Beta_X2_se;

  real<lower=0> sigma_e_se;
  real sigma_e_X1_se;
  real sigma_e_X2_se;

  vector<lower=0>[2] sigma_U;
  vector<lower=0>[2] sigma_V;
  corr_matrix[2] CORR_U;
  corr_matrix[2] CORR_V;
  corr_matrix[2] CORR_E;

  matrix[2,J_U] U;
  matrix[2,J_V] V;
}

transformed parameters {
  cov_matrix[2] Omega_U;
  cov_matrix[2] Omega_V;
  Omega_U = quad_form_diag(CORR_U, sigma_U);
  Omega_V = quad_form_diag(CORR_V, sigma_V);
}

```

```

model {
  real mu;
  real mu_se;
  vector[2] mu_V;
  vector[2] Sigma_E;
  matrix[2,2] Sigma_Mat;

  Beta0 ~ normal(0, 4);
  Beta_X1 ~ normal( 0, 4);
  Beta_X2 ~ normal( 0, 4);

  sigma_e ~ normal( 0, 4);
  sigma_e_X1 ~ normal( 0, 4);
  sigma_e_X2 ~ normal( 0, 4);

  Beta0_se ~ normal(0, 4);
  Beta_X1_se ~ normal( 0, 4);
  Beta_X2_se ~ normal( 0, 4);

  sigma_e_se ~ normal( 0, 4);
  sigma_e_X1_se ~ normal( 0, 4);
  sigma_e_X2_se ~ normal( 0, 4);

  CORR_U ~ lkj_corr(2);
  sigma_U ~ normal( 0, 4);

  CORR_V ~ lkj_corr(2);
  sigma_V ~ normal( 0, 4);

  for (i in 1:J_U){
    col(U,i) ~ multi_normal(rep_vector(0,2),Omega_U);
  }

  for (i in 1:J_V){
    col(V,i) ~ multi_normal(rep_vector(0,2),Omega_V);
  }

  for (i in 1:N){

    mu = ( Beta0 + U[1,subj_U[i]] + V[1,subj_V[i]] + Beta_X1*COV1[i] +
Beta_X2*COV2[i] );
    mu_se = ( Beta0_se + U[2,subj_U[i]] + V[2,subj_V[i]] + Beta_X1_se*COV1[i] +
Beta_X2_se*COV2[i] );

    mu_V[1] = mu;
    mu_V[2] = mu_se;

    Sigma_E[1]= sigma_e*exp( sigma_e_X1*COV1[i] + sigma_e_X2*COV2[i] ) ;
    Sigma_E[2]= sigma_e_se*exp( sigma_e_X1_se*COV1[i] + sigma_e_X2_se*COV2[i]
);
  }

```

```

Sigma_Mat = quad_form_diag(CORR_E, Sigma_E);

dr[,i] ~ multi_normal(mu_V, Sigma_Mat);
}
}
"

```

B. STAN code used to identify the determinants of variability

```

score <- "

data {
  int<lower=1> N;
  matrix[2,N] dr;
  real COV1[N];
  real COV2[N];
  real COV3[N];
  real COV4[N];
  real COV5[N];
  real COV6[N];
  real COV7[N];
  real COV8[N];
  real COV9[N];
  int<lower=1> J_U;
  int<lower=1, upper=J_U> subj_U[N];
  int<lower=1> J_V;
  int<lower=1, upper=J_V> subj_V[N];
}

parameters {
  real Beta0;
  real Beta_X1;
  real Beta_X2;
  real Beta_X3;
  real Beta_X4;
  real Beta_X5;
  real Beta_X6;
  real Beta_X7;
  real Beta_X8;
  real Beta_X9;

  real<lower=0> sigma_e;
  real sigma_e_X1;
  real sigma_e_X2;
  real sigma_e_X3;
  real sigma_e_X4;
  real sigma_e_X5;
  real sigma_e_X6;
  real sigma_e_X7;
  real sigma_e_X8;

```

```

real sigma_e_X9;

real Beta0_se;
real Beta_X1_se;
real Beta_X2_se;
real Beta_X3_se;
real Beta_X4_se;
real Beta_X5_se;
real Beta_X6_se;
real Beta_X7_se;
real Beta_X8_se;
real Beta_X9_se;

real<lower=0> sigma_e_se;
real sigma_e_X1_se;
real sigma_e_X2_se;
real sigma_e_X3_se;
real sigma_e_X4_se;
real sigma_e_X5_se;
real sigma_e_X6_se;
real sigma_e_X7_se;
real sigma_e_X8_se;
real sigma_e_X9_se;

vector<lower=0>[2] sigma_U;
vector<lower=0>[2] sigma_V;
corr_matrix[2] CORR_U;
corr_matrix[2] CORR_V;
corr_matrix[2] CORR_E;

matrix[2,J_U] U;
matrix[2,J_V] V;
}

transformed parameters {
  cov_matrix[2] Omega_U;
  cov_matrix[2] Omega_V;
  Omega_U = quad_form_diag(CORR_U, sigma_U);
  Omega_V = quad_form_diag(CORR_V, sigma_V);
}

model {
  real mu;
  real mu_se;
  vector[2] mu_V;
  vector[2] Sigma_E;
  matrix[2,2] Sigma_Mat;

  Beta0 ~ normal(0, 4);
  Beta_X1 ~ normal(0, 4);

```

```
Beta_X2 ~ normal( 0, 4);  
Beta_X3 ~ normal( 0, 4);  
Beta_X4 ~ normal( 0, 4);  
Beta_X5 ~ normal( 0, 4);  
Beta_X6 ~ normal( 0, 4);  
Beta_X7 ~ normal( 0, 4);  
Beta_X8 ~ normal( 0, 4);  
Beta_X9 ~ normal( 0, 4);
```

```
sigma_e ~ normal( 0, 4);  
sigma_e_X1 ~ normal( 0, 4);  
sigma_e_X2 ~ normal( 0, 4);  
sigma_e_X3 ~ normal( 0, 4);  
sigma_e_X4 ~ normal( 0, 4);  
sigma_e_X5 ~ normal( 0, 4);  
sigma_e_X6 ~ normal( 0, 4);  
sigma_e_X7 ~ normal( 0, 4);  
sigma_e_X8 ~ normal( 0, 4);  
sigma_e_X9 ~ normal( 0, 4);
```

```
Beta0_se ~ normal(0, 4);  
Beta_X1_se ~ normal( 0, 4);  
Beta_X2_se ~ normal( 0, 4);  
Beta_X3_se ~ normal( 0, 4);  
Beta_X4_se ~ normal( 0, 4);  
Beta_X5_se ~ normal( 0, 4);  
Beta_X6_se ~ normal( 0, 4);  
Beta_X7_se ~ normal( 0, 4);  
Beta_X8_se ~ normal( 0, 4);  
Beta_X9_se ~ normal( 0, 4);
```

```
sigma_e_se ~ normal( 0, 4);  
sigma_e_X1_se ~ normal( 0, 4);  
sigma_e_X2_se ~ normal( 0, 4);  
sigma_e_X3_se ~ normal( 0, 4);  
sigma_e_X4_se ~ normal( 0, 4);  
sigma_e_X5_se ~ normal( 0, 4);  
sigma_e_X6_se ~ normal( 0, 4);  
sigma_e_X7_se ~ normal( 0, 4);  
sigma_e_X8_se ~ normal( 0, 4);  
sigma_e_X9_se ~ normal( 0, 4);
```

```
CORR_U ~ lkj_corr(2);  
sigma_U ~ normal(0, 4);
```

```
CORR_V ~ lkj_corr(2);  
sigma_V ~ normal(0, 4);
```

```
for (i in 1:J_U){  
  col(U,i) ~ multi_normal(rep_vector(0,2),Omega_U);
```

```

}

for (i in 1:J_V){
  col(V,i) ~ multi_normal(rep_vector(0,2),Omega_V);
}

for (i in 1:N){

  mu = ( Beta0 + U[1,subj_U[i]] + V[1,subj_V[i]] + Beta_X1*COV1[i] +
Beta_X2*COV2[i] + Beta_X3*COV3[i] + Beta_X4*COV4[i] + Beta_X5*COV5[i] +
Beta_X6*COV6[i] + Beta_X7*COV7[i] + Beta_X8*COV8[i] + Beta_X9*COV9[i] );
  mu_se = ( Beta0_se + U[2,subj_U[i]] + V[2,subj_V[i]] + Beta_X1_se*COV1[i] +
Beta_X2_se*COV2[i] + Beta_X3_se*COV3[i] + Beta_X4_se*COV4[i] +
Beta_X5_se*COV5[i] + Beta_X6_se*COV6[i] + Beta_X7_se*COV7[i] +
Beta_X8_se*COV8[i] + Beta_X9_se*COV9[i] );

  mu_V[1] = mu;
  mu_V[2] = mu_se;

  Sigma_E[1]= sigma_e*exp( sigma_e_X1*COV1[i] + sigma_e_X2*COV2[i] +
sigma_e_X3*COV3[i] + sigma_e_X4*COV4[i] + sigma_e_X5*COV5[i] +
sigma_e_X6*COV6[i] + sigma_e_X7*COV7[i] + sigma_e_X8*COV8[i] +
sigma_e_X9*COV9[i] );
  Sigma_E[2]= sigma_e_se*exp( sigma_e_X1_se*COV1[i] + sigma_e_X2_se*COV2[i]
+ sigma_e_X3_se*COV3[i] + sigma_e_X4_se*COV4[i] + sigma_e_X5_se*COV5[i] +
sigma_e_X6_se*COV6[i] + sigma_e_X7_se*COV7[i] + sigma_e_X8_se*COV8[i] +
sigma_e_X9_se*COV9[i] );
  Sigma_Mat = quad_form_diag(CORR_E, Sigma_E);

  dr[,i] ~ multi_normal(mu_V, Sigma_Mat);
}
}
"

```

References of the meta-analyses included

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