IMICAMS

系统评价及其流程

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Systematic Reviews

- A systematic review summarises the results of available carefully designed healthcare studies (controlled trials) and provides a high level of evidence on the effectiveness of healthcare interventions. Judgments may be made about the evidence and inform recommendations for healthcare.

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Key characteristics of a systematic review

- a clearly stated set of objectives with pre-defined eligibility criteria for studies
- an explicit, reproducible methodology
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies

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系统评价流程

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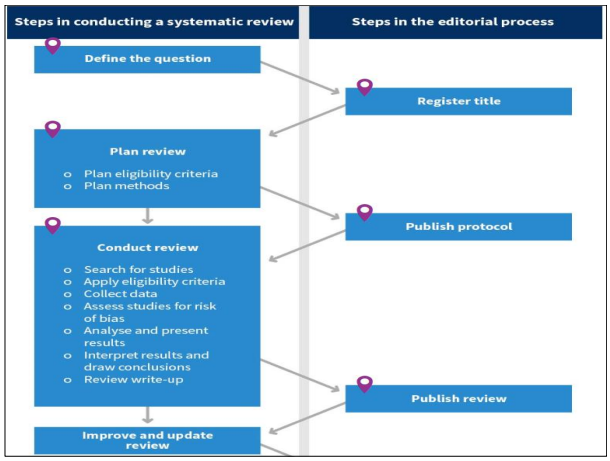
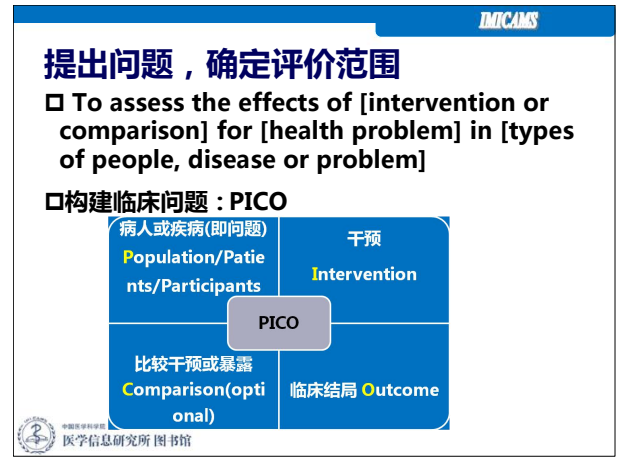

Steps in conducting a systematic review
Steps in the editorial process
Define the question
Register title
Plan review
Plan eligibility criteria
Plan methods
Publish protocol
Conduct review
Search for studies
Apply eligibility criteria
Collect data
Assess studies for risk of bias
Analyse and present results
Interpret results and draw conclusions
Review write-up
Publish review
Improve and update review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提出问题，确定评价范围
To assess the effects of [intervention or comparison] for [health problem] in [types of people, disease or problem]
构建临床问题：PICO
病人或疾病(即问题) Population/Patients/Participants
干预 Intervention
PICO
比较干预或暴露 Comparison(optional)
临床结局 Outcome
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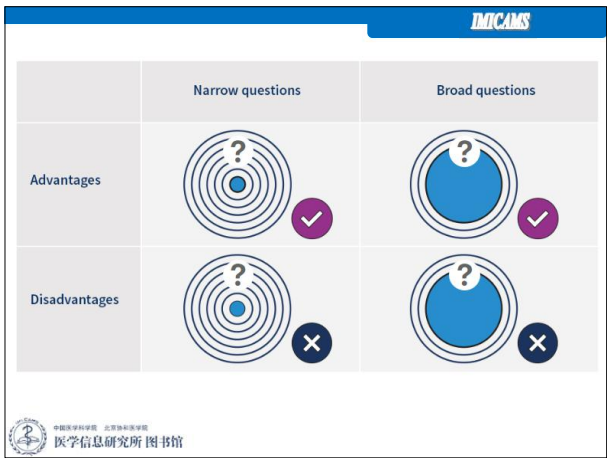
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Narrow questions
Broad questions
Advantages
Disadvantages
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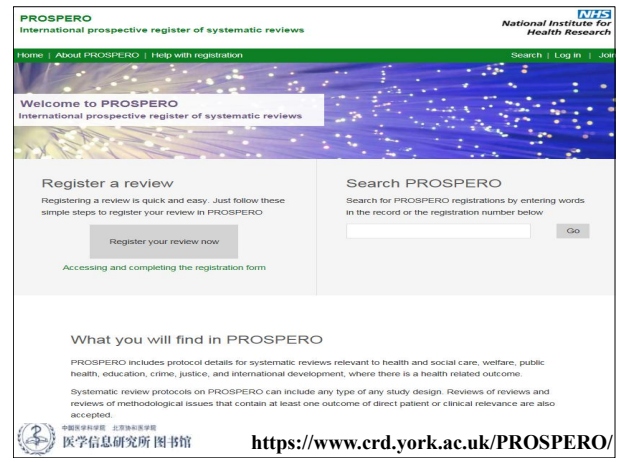
PROSPERO
International prospective register of systematic reviews
NHS National Institute for Health Research
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Welcome to PROSPERO
International prospective register of systematic reviews
Register a review
Registering a review is quick and easy. Just follow these simple steps to register your review in PROSPERO
Register your review now
Accessing and completing the registration form
Search PROSPERO
Search for PROSPERO registrations by entering words in the record or the registration number below
Go
What you will find in PROSPERO
PROSPERO includes protocol details for systematic reviews relevant to health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome.
Systematic review protocols on PROSPERO can include any type of any study design. Reviews of reviews and reviews of methodological issues that contain at least one outcome of direct patient or clinical relevance are also accepted.
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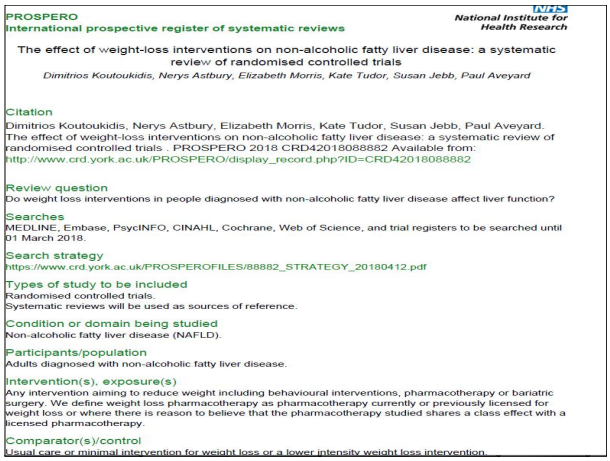
https://www.crd.york.ac.uk/PROSPERO/



PROSPERO
International prospective register of systematic reviews

NIHR National Institute for Health Research

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

Dimitrios Koutoukidis, Nerys Astbury, Elizabeth Morris, Kate Tudor, Susan Jebb, Paul Aveyard

Citation

Dimitrios Koutoukidis, Nerys Astbury, Elizabeth Morris, Kate Tudor, Susan Jebb, Paul Aveyard. The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials . PROSPERO 2018 CRD42018088882 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018088882

Review question

Do weight loss interventions in people diagnosed with non-alcoholic fatty liver disease affect liver function?

Searches

MEDLINE, Embase, PsycINFO, CINAHL, Cochrane, Web of Science, and trial registers to be searched until 01 March 2018.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/88882_STRATEGY_20180412.pdf

Types of study to be included

Randomised controlled trials.
Systematic reviews will be used as sources of reference.

Condition or domain being studied

Non-alcoholic fatty liver disease (NAFLD).

Participants/population

Adults diagnosed with non-alcoholic fatty liver disease.

Intervention(s), exposure(s)

Any intervention aiming to reduce weight including behavioural interventions, pharmacotherapy or bariatric surgery. We define weight loss pharmacotherapy as pharmacotherapy currently or previously licensed for weight loss or where there is reason to believe that the pharmacotherapy studied shares a class effect with a licensed pharmacotherapy.

Comparator(s)/control

Usual care or minimal intervention for weight loss or a lower intensity weight loss intervention.

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确定纳入排除标准

□纳入标准

- ➢①研究类型：双盲或单盲的平行随机对照研究
- ➢②研究对象：择期手术后成人患者
- ➢③干预措施
  - 研究组：ω-3脂肪乳剂（鱼油）+PN
  - 对照组: PN
- ➢④结局指标：感染并发症发生率等及“成本-效果”分析

□排除标准

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Searching for studies

- □ Review authors should work closely from the start with the Trials Search Co-ordinator (TSC) of their Cochrane Review Group (CRG).
- □ Studies (not reports of studies) are included in Cochrane reviews but identifying reports of studies is currently the most convenient approach to identifying the majority of studies and obtaining information about them and their results.
- □ Trials registers and trials results registersare an increasingly important source of information.
- □ The Cochrane Central Register of Controlled Trials (CENTRAL)MEDLINE and EMBASE (if access is available to either the review author or TSC) should be searched for all Cochrane reviews, either directly or via the CRG’s Specialized Register.
- □ Searches should seekhigh sensitivity, which may result in relativelylow precision.
- □ Too many different search concepts should be avoided, but a wide variety of search terms should be combined withOR within each concept.
- □ Both free-text and subject headings should be used (for exampleMedical Subject Headings (MeSH)and EMTREE).
- □ Existing highly sensitive search strategies (filters)to identify randomized trials should be used, such as the newly revised Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE (but do not apply these filters in CENTRAL).

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检索文献

□数据库

- ➢PubMed、EMBASE、Cochrane Library、Web of Science
- ➢中国生物医学文献数据库、万方、CNKI、维普
- ➢……

□其它

- ➢临床试验注册信息
- ➢手工检索期刊及参考文献回溯
- ➢会议摘要与会议论文
- ➢……

47 zabicipril$.tw.
48 zofenopril$.tw.
49 or/6-48
50 hypertension/
51 hypertens$.tw.
52 exp blood pressure/
53 (blood pressure or bloodpressure).mp.
54 or/50-53
55 randomized controlled trial.pt.
56 controlled clinical trial.pt.
57 randomi?ed.ab.
58 placebo.ab.
59 clinical trials as topic/
60 randomly.ab.
61 trial.ti.
62 or/55-61
63 animals/ not (humans/ and animals/)
64 62 not 63
65 5 and 49 and 54 and 64

49. ((high or increased or elevated) adj2 blood pressure).tw.
50. exp Hyperlipidemias/
51. hyperlipid*.tw.
52. hyperlip?emia*.tw.
53. hypercholesterol*.tw.
54. hypercholester?emia*.tw.
55. hyperlipoprotein?emia*.tw.
56. hypertriglyceri?emia*.tw.
57. exp Arteriosclerosis/
58. exp Cholesterol/
59. cholesterol.tw.
60. "coronary risk factor* ".tw.
61. Blood Pressure/
62. blood pressure.tw.
63. or/22-62
64. 21 and 63
65. randomized controlled trial.pt.
66. controlled clinical trial.pt.
67. randomized.ab.
68. placebo.ab.
69. drug therapy.fs.
70. randomly.ab.
71. trial.ab.
72. groups.ab.
73. 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. exp animals/ not humans.sh.
75. 73 not 74
76. 64 and 75

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术后认知功能障碍（postoperative cognitive dysfunction，POCD）是心脏和非心脏手术后一种常见的并发症，其特征是注意、感知、学习、记忆、语言、执行、抽象思维等认知功能轻度损害，可持续数天、数月至数年[1]。POCD 更易发生于老年人，与年龄、手术、麻醉、感染、创伤及患者的受教育程度、合并基础疾病等多个危险因素有关，但目前年龄是其唯一明确的危险因素[2]。目前关于 POCD 的发病机制尚不明确，包括基因学说、胆碱能系统学说、神经递质学说、神经炎症学说等，其中中枢神经炎症反应的作用越来越受到关注[3]。右美托咪定是一种高选择性跨膜 G 蛋白偶联的 α2 肾上腺素能受体激动剂，有研究表明右美托咪定可以抑制炎症反应，降低老年患者 POCD 的风险。但不同研究的样本量较小，研究质量参差不齐，结论不一致。因此本研究旨在采用 Meta 分析方法评价右美托咪定对老年患者早期 POCD 及炎症因子的影响。

1 资料与方法

1.1 纳入与排除标准

1.1.1 研究类型 随机对照试验（randomized controlled trial，RCT）。

1.1.2 研究对象 年龄≥65 岁的择期非心脏、神经外科手术患者。

1.1.3 干预措施 试验组患者术前、术中或术后使用右美托咪定，对照组采用生理盐水或其他安慰剂。

1.1.4 结局指标 术后第 1、3、7 天认知功能障碍发生率；手术结束时、术后 1 h、术后 24 h 血清炎性因子 TNF-α 水平；手术结束时、术后 1 h、术后 24 h 血清炎性因子 IL-6 水平；术后 24 h 血清炎性因子 CRP 水平。

1.1.5 排除标准 ① 非中、英文文献；② 重复发表的文献；③ 相关结局数据缺失且与作者联系无法获取者；④ 患者处于 ASA 分级＞Ⅲ级，合并中枢神经系统疾病，服用镇静或抗抑郁药，语言听力障碍等情况。

1.2 文献检索策略

计算机检索 PubMed、EMbase、The Cochrane Library、CBM、CNKI、WanFang Data 和 VIP 数据库，搜集所有公开发表的关于右美托咪定对老年患者 POCD 影响的 RCT，检索时限均为建库截至 2017 年 4 月，同时追溯纳入研究的参考文献，以补充获取相关文献。检索采取主题词和自由词相结合的方式。英文检索词包括：dexmedetomidine、dex、postoperative cognitive dysfunction、POCD、TNF-α、IL-6、CRP；中文检索词包括：右美托咪定、右美、术后认知功能障碍、TNF-α、IL-6、CRP。以 PubMed 为例，其检索策略见框 1。

1.3 文献筛选与资料提取

由 2 名评价员独立筛选文献、提取资料，如遇分歧则讨论或交由第三名评价员裁定[4]。文献筛选时首先阅读文题和摘要，在排除明显不相关的文献后，进一步阅读全文，以确定最终是否纳入。资料提取内容主要包括：① 纳入研究的基本信息，包括研究题目、第一作者、发表杂志及时间等；② 研究对象的基线特征，包括各组的样本数、患者的年龄、性别和疾病状况等。③ 干预措施的具体细节、随访时间等；④ 偏倚风险评价的关键要素；⑤ 所关注的结局指标和结果测量数据。

1.4 纳入研究的偏倚风险评价

由 2 名评价员采用 Cochrane 手册推荐的 RCT 偏倚风险评估标准[4]评价纳入 RCT 的偏倚风险。如遇分歧，通过讨论或由第三名评价员裁决。

框 1 PubMed 检索策略

#1 dexmedetomidine
#2 dex
#3 #1 OR #2
#4 postoperative cognitive dysfunction
#5 POCD
#6 #4 OR #5
#7 TNF-α
#8 IL-6
#9 CRP
#10 #7 OR #8 OR #9
#11 #3 AND #6 AND #10

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筛选文献，提取数据

- 根据纳入排除标准筛选文献
- 提取数据
  - 制作数据提取表格
  - 由两名研究者独立进行资料提取，完成后进行交叉核对，如有分歧，通过双方讨论或请第三位研究者协助解决

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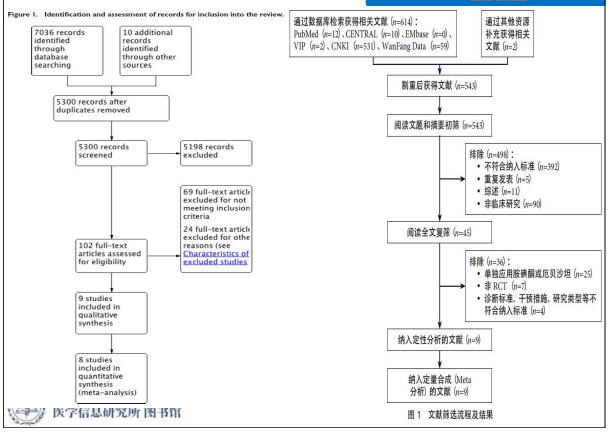

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图 1 文献筛选流程及结果

Data extraction

- Data from eligible studies were abstracted independently by 2 investigators.
- Discrepancies were resolved by discussion with a third investigator and by referencing the original report.

Table Study characteristics

Study, publication year	Country	Prevalence of prehypertension, %	Population-attributable risk, %	Sample size (% women)	Age, y, average (range or SD)	Follow-up, y	Stroke events for primary analysis	Study quality
ARIC, 2006[12]	United States	37	13	8,960 (55)[a]	53 (45–64)	11.6	All stroke	Good
China National, 2009[13]	China	35	20	158,666 (51)	56 (≥40)	7.8	All stroke	Good

	Location	Year of baseline data collection	Study duration (years)	n (% women)	Age range (years)	Number with diabetes (% women)	Ascertainment of diabetes	Number of strokes (% women)	Fatal or non-fatal strokes included	Maximum adjustment available
APCSC (Australia and New Zealand)[14]	Australia and New Zealand (nine cohorts)	1989–96	7	99 624 (45%)	20–104	4784 (31%)	Self-report or medical assessment	1671 (41%)	Both	Age, SBP, smoking, BMI, total cholesterol
APCSC (Asia)[14]	Asia (27 cohorts)	1961–93	7	436 832 (33%)	20–107	17 763 (23%)	Self-report or medical assessment	2872 (31%)	Both	Age, SBP, smoking, BMI, total cholesterol

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Data extraction(suggested)

- Study, publication year(Author, year)
- Location
- Prevalence/ incidence of hypertension,
- Population attributable risk%
- Number of strokes(% female), incidence, prevalence
- Sample size (% female)
- Age mean(range or SD) stratify
- Duration or follow-up(Years_time period)
- Stroke subtype , mortality, recurrence
- Diagonostic criteria(hypertension and stroke), Data source
- Study quality
- Covariance
- OR, RR, CI

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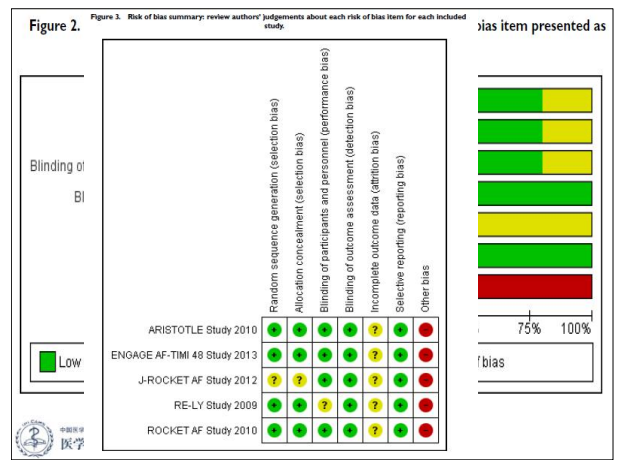
偏倚风险评价

域（Domain）	描述内容
随机序列产生（选择偏倚）	尽可能详细地描述分配序列的生成方法
分配隐藏（选择偏倚）	尽可能详细地描述隐藏随机分配序列的方法，并陈述分配干预措施之前始终充分隐藏了分配序列的可信度
对参加研究的患者、研究人员的设盲（实施偏倚）	对参加研究的患者和主要研究人员设盲使其不知道干预措施的分配方案的所有方法，并提供可提示盲法设置是否有效的所有信息
对评估结局人员采用盲法（测量偏倚）	针对每个主要结局或每类结局，对评估结局人员设盲使其不知道干预措施的分配方案的所有方法，并提供可提示盲法设置是否有效的所有信息
结局数据的完整性（失访偏倚）	针对每个主要结局或每类结局，描述每个主要结局的相关结局数据的完整性，包括数据分析中失访和排除的情况。陈述是否报告了失访和排除的病例数据，报告的失访/排除病例数（与随机化参加研究的患者总数相比）、失访/排除的原因及系统评价作者在分析中是否重新纳入
选择性报告结局	陈述如何评价选择性报告结局的可能性及评价结果
其它偏倚来源	陈述上述六个方面未涉及的其它重要偏倚来源。若系统评价方案预先设定了某特殊问题/亚项，应对每个问题/亚项做出相应的回答



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分析数据，提出结果

- 合并效应量
  - 分类变量的Meta分析: 相对危险度(Risk ratio, RR), 比值比(Odds ratio, OR), 危险差(Risk difference, RD)
  - 连续性变量的Meta分析: 加权均数差(Mean difference, MD), 标准经均数差(Standardized mean difference, SMD)
- 异质性检验

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解释结果，得出结论

- 总结归纳分析结果
- 评估报告偏倚
- 描述分析的局限性
- 基于分析，得出结论
- 提出今后研究方向建议

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谢　谢!

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

Search strategy

Medline

	Searches
1	Non-alcoholic Fatty Liver Disease/
2	*Fatty Liver/
3	((nonalcoholic or non-alcoholic) adj5 (fatty liver or steatohepatitis)).ti,ab.
4	(fatty liver or steatohepatitis).ti.
5	(nafld or nash).ti,ab.
6	1 or 2 or 3 or 4 or 5
7	Weight Loss/
8	Weight Reduction Programs/
9	diet therapy/ or caloric restriction/ or diet, reducing/
10	exp Obesity/dh [Diet Therapy]
11	(weight adj3 (loss or lose or lost or losing or chang* or reduc* or manag*)).ti,ab.
12	((energy or calori*) adj2 (reduc* or restrict)).ti,ab.
13	((weight or overweight or obes*) adj5 (program* or service? or intervention?)).ti,ab.
14	exp Anti-Obesity Agents/
15	exp Obesity/dt, th [Drug Therapy, Therapy]
16	((weight or overweight or obes*) adj3 (therap* or treat* or drug? or agent?)).ti,ab.
17	exp OBESITY/su [Surgery]
18	exp Bariatric Surgery/
19	((weight loss or bariatric or obes*) adj5 surg*).ti,ab. or bariatric*.ti.
20	(((gastric or jejunoileal) adj3 (band* or bypass* or balloon* or diver*)) or gastrectom* or gastroplast* or ((biliopancreatic or bilio-pancreatic) adj2 diver*)).ti,ab.
21	obesity management/ or bariatrics/
22	((obes* or overweight) adj3 manage*).ti,ab.
23	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	randomized controlled trial.pt.
25	controlled clinical trial.pt.
26	randomized.ab.
27	placebo.ab.
28	drug therapy.fs.
29	randomly.ab.
30	trial.ab.
31	groups.ab.
32	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33	exp animals/ not humans.sh.
34	32 not 33
35	6 and 23 and 34

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

Embase

	Searches
1	nonalcoholic fatty liver/
2	*Fatty Liver/
3	((nonalcoholic or non-alcoholic) adj5 (fatty liver or steatohepatitis)).ti,ab.
4	(fatty liver or steatohepatitis).ti.
5	(nafld or nash).ti,ab.
6	1 or 2 or 3 or 4 or 5
7	weight reduction/
8	weight loss program/
9	diet therapy/ or exp diet restriction/ or low calory diet/ or low fat diet/
10	exp Obesity/dm
11	(weight adj3 (loss or lose or lost or losing or chang* or reduc* or manag*)).ti,ab.
12	((energy or calori*) adj2 (reduc* or restrict)).ti,ab.
13	((weight or overweight or obes*) adj5 (program* or service? or intervention?)).ti,ab.
14	exp antiobesity agent/
15	exp Obesity/dt, th
16	((weight or overweight or obes*) adj3 (therap* or treat* or drug? or agent?)).ti,ab.
17	exp OBESITY/su
18	exp Bariatric Surgery/
19	((weight loss or bariatric or obes*) adj5 surg*).ti,ab. or bariatric*.ti.
20	(((gastric or jejunoileal) adj3 (band* or bypass* or balloon* or diver*)) or gastrectom* or gastroplast* or ((biliopancreatic or bilio-pancreatic) adj2 diver*)).ti,ab.
21	obesity management/ or bariatrics/
22	((obes* or overweight) adj3 manage*).ti,ab.
23	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	6 and 23
25	randomized controlled trial/
26	single blind procedure/ or double blind procedure/
27	crossover procedure/
28	random*.tw.
29	(random or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.
30	25 or 26 or 27 or 28 or 29
31	(exp animals/ or nonhuman/) not human/
32	30 not 31
33	24 and 32

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

PsycINFO

	Searches
1	((nonalcoholic or non-alcoholic) adj5 (fatty liver or steatohepatitis)).ti,ab.
2	(fatty liver or steatohepatitis).ti.
3	(nafld or nash).ti,ab.
4	1 or 2 or 3
5	weight loss/ or weight control/
6	(weight adj3 (loss or lose or lost or losing or chang* or reduc* or manag*)).ti,ab.
7	((energy or calori*) adj2 (reduc* or restrict)).ti,ab.
8	((weight or overweight or obes*) adj5 (program* or service? or intervention?)).ti,ab.
9	((weight or overweight or obes*) adj3 (therap* or treat* or drug? or agent?)).ti,ab.
10	bariatric surgery/
11	((weight loss or bariatric or obes*) adj5 surg*).ti,ab. or bariatric*.ti.
12	(((gastric or jejunoileal) adj3 (band* or bypass* or balloon* or diver*)) or gastrectom* or gastroplast* or ((biliopancreatic or bilio-pancreatic) adj2 diver*)).ti,ab.
13	((obes* or overweight) adj3 manage*).ti,ab.
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	4 and 14
16	random*.ti,ab,hw,id.
17	trial*.ti,ab,hw,id.
18	controlled stud*.ti,ab,hw,id.
19	placebo*.ti,ab,hw,id.
20	((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id.
21	(cross over or crossover or factorial* or latin square).ti,ab,hw,id.
22	(assign* or allocat* or volunteer*).ti,ab,hw,id.
23	treatment effectiveness evaluation/
24	mental health program evaluation/
25	exp experimental design/
26	(clinical trial or treatment outcome).md.
27	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	15 and 27

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

Cinahl

#	Query
S14	S3 AND S12 Limiters - Clinical Queries: Therapy - Best Balance
S13	S3 AND S12
S12	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11	(MH "Obesity+/DH/DT/SU/TH")
S10	TI (((weight loss or bariatric or obes*) N5 surg*)) OR AB (((weight loss or bariatric or obes*) N5 surg*)) OR TI bariatric* OR TI ((((gastric or jejunoileal) N3 (band* or bypass* or balloon* or diver*)) or gastrectom* or gastroplast* or ((biliopancreatic or bilio-pancreatic) N2 diver*))) OR AB ((((gastric or jejunoileal) N3 (band* or bypass* or balloon* or diver*)) or gastrectom* or gastroplast* or ((biliopancreatic or bilio-pancreatic) N2 diver*)))
S9	(MH "Bariatric Surgery+")
S8	TI (((weight or overweight or obes*) N3 (therap* or treat* or drug? or agent?))) AND AB (((weight or overweight or obes*) N3 (therap* or treat* or drug? or agent?)))
S7	(MH "Antiobesity Agents+")
S6	TI ((weight N3 (loss or lose or lost or losing or chang* or reduc* or manag*))) OR AB ((weight N3 (loss or lose or lost or losing or chang* or reduc* or manag*))) OR TI (((energy or calori*) N2 (reduc* or restrict))) OR AB (((energy or calori*) N2 (reduc* or restrict))) OR TI (((weight or overweight or obes*) N5 (program* or service? or intervention?))) OR AB (((weight or overweight or obes*) N5 (program* or service? or intervention?)))
S5	(MH "Diet, Reducing") OR (MH "Diet Therapy")
S4	(MH "Weight Loss") OR (MH "Weight Reduction Programs")
S3	S1 OR S2
S2	TI ("fatty liver" or steatohepatitis) OR AB (((nonalcoholic or non-alcoholic) N5 ("fatty liver" or steatohepatitis))) OR TI (nafld or nash) OR AB (nafld or nash)
S1	(MM "Fatty Liver") OR (MH "Nonalcoholic Fatty Liver Disease")

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

Cochrane

ID	Search
#1	MeSH descriptor: [Non-alcoholic Fatty Liver Disease] explode all trees
#2	((nonalcoholic or non-alcoholic) near (fatty liver or steatohepatitis)):ti,ab,kw or fatty liver or steatohepatitis:ti or nafld or nash:ti,ab,kw (Word variations have been searched)
#3	#1 or #2
#4	weight or obes* or overweight or bariatric*:ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Weight Loss] this term only
#6	MeSH descriptor: [Weight Reduction Programs] explode all trees
#7	MeSH descriptor: [Diet Therapy] this term only
#8	MeSH descriptor: [Diet, Reducing] explode all trees
#9	MeSH descriptor: [Caloric Restriction] explode all trees
#10	(weight near/3 (loss or lose or lost or losing or chang* or reduc* or manag*)):ti,ab,kw or ((energy or calori*) near/2 (reduc* or restrict)):ti,ab,kw or ((weight or overweight or obes*) near (program* or service? or intervention?)):ti,ab,kw (Word variations have been searched)
#11	MeSH descriptor: [Anti-Obesity Agents] explode all trees
#12	((weight or overweight or obes*) near/3 (therap* or treat* or drug? or agent?)):ti,ab,kw (Word variations have been searched)
#13	MeSH descriptor: [Bariatric Surgery] explode all trees
#14	bariatric*:ti or ((weight loss or bariatric or obes*) near surg*):ti,ab,kw or (((gastric or jejunoileal) near/3 (band* or bypass* or balloon* or diver*)) or gastrectom* or gastroplast* or ((biliopancreatic or bilio-pancreatic) near/2 diver*)):ti,ab,kw or ((obes* or overweight) near/3 manage*):ti,ab,kw (Word variations have been searched)
#15	MeSH descriptor: [Obesity] explode all trees
#16	MeSH descriptor: [Obesity Management] explode all trees
#17	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18	#3 and #17

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

WoS

Set	Save search history and/or create an alertOpen a saved search history
# 9	#8 AND #7
# 8	TOPIC: ((random* or blind* or allocat* or assign* or trial* or crossover* or cross-over*))
# 7	#6 AND #1
# 6	#5 OR #4 OR #3 OR #2
# 5	TOPIC: (((obes* or overweight) NEAR/3 manage*))
# 4	TOPIC: (((weight loss or bariatric or obes*) NEAR5 surg*)) OR TOPIC: (bariatric*) OR TOPIC: ((((gastric or jejunoileal) NEAR/3 (band* or bypass* or balloon* or diver*)) or gastrectom* or gastroplast* or ((biliopancreatic or bilio-pancreatic) NEAR/2 diver*)))
# 3	TOPIC: (((weight or overweight or obes*) NEAR/3 (therap* or treat* or drug? or agent?)))
# 2	TOPIC: ((weight NEAR/3 (loss or lose or lost or losing or chang* or reduc* or manag*))) OR TOPIC: (((energy or calori*) NEAR/2 (reduc* or restrict))) OR TOPIC: (((weight or overweight or obes*) NEAR/5 (program* or service? or intervention?)))
# 1	TOPIC: (((nonalcoholic or non-alcoholic) NEAR/5 ("fatty liver" or steatohepatitis))) OR TITLE: ("fatty liver" or steatohepatitis) OR TOPIC: (nafld OR nash)

Trial Registers

ClinicalTrials.gov
Other terms=(obesity OR obesity OR weight OR overweight OR bariatric OR bariatrics) AND Condition=("nonalcoholic fatty liver" OR "non alcoholic fatty liver" OR "nonalcoholic steatohepatitis" OR "non-alcoholic steatohepatitis" OR nafld OR nash)
WHO ICTRP
nonalcoholic fatty liver AND obese OR non alcoholic fatty liver AND obese OR nonalcoholic steatohepatitis AND obese OR non-alcoholic steatohepatitis AND obese OR nafld AND obese OR nash AND obese nonalcoholic fatty liver AND obesity OR non alcoholic fatty liver AND obesity OR nonalcoholic steatohepatitis AND obesity OR non-alcoholic steatohepatitis AND obesity OR nafld AND obesity OR nash AND obesity nonalcoholic fatty liver AND overweight OR non alcoholic fatty liver AND overweight OR nonalcoholic steatohepatitis AND overweight OR non-alcoholic steatohepatitis AND overweight OR nafld AND overweight OR nash AND overweight nonalcoholic fatty liver AND weight OR non alcoholic fatty liver AND weight OR nonalcoholic steatohepatitis AND weight OR non-alcoholic steatohepatitis AND weight OR nafld AND weight OR nash AND weight nonalcoholic fatty liver AND bariatric OR non alcoholic fatty liver AND bariatric OR nonalcoholic steatohepatitis AND bariatric OR non-alcoholic steatohepatitis AND bariatric OR nafld AND bariatric OR nash AND bariatric nonalcoholic fatty liver AND bariatrics OR non alcoholic fatty liver AND bariatrics OR nonalcoholic steatohepatitis AND bariatrics OR non-alcoholic steatohepatitis AND bariatrics OR nafld AND bariatrics OR nash AND bariatrics

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Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome (Review)

Bala MM, Celinska-Lowenhoff M, Szot W, Padjas A, Kaczmarczyk M, Swierz MJ, Undas A

Bala MM, Celinska-Lowenhoff M, Szot W, Padjas A, Kaczmarczyk M, Swierz MJ, Undas A.
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[Intervention Review]

Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

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ABSTRACT

Background

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial or venous thrombosis (or both) and/or pregnancy morbidity in association with the presence of antiphospholipid antibodies. The prevalence is estimated at 40 to 50 cases per 100,000 people. The most common sites of thrombosis are cerebral arteries and deep veins of the lower limbs. People with a definite APS diagnosis have an increased lifetime risk of recurrent thrombotic events.

Objectives

To assess the effects of antiplatelet or anticoagulant agents, or both, for the secondary prevention of recurrent thrombosis, particularly ischemic stroke, in people with antiphospholipid syndrome.

Search methods

We searched the Cochrane Stroke Group Trials Register (February 2017), CENTRAL (last search February 2017), MEDLINE (from 1948 to February 2017), Embase (from 1980 to February 2017), and several ongoing trials registers. We also checked the reference lists of included studies, systematic reviews, and practice guidelines, and we contacted experts in the field.

Selection criteria

We included randomized controlled trials (RCTs) that evaluated any anticoagulant or antiplatelet agent, or both, in the secondary prevention of thrombosis in people diagnosed with APS according to the criteria valid when the study took place. We did not include studies specifically addressing women with obstetrical APS.

Data collection and analysis

Pairs of review authors independently selected studies for inclusion, extracted data, and assessed the risk of bias for the included studies. We resolved any discrepancies through discussion or by consulting a third review author and, in addition, one review author checked all the extracted data.

Main results

We included five studies involving 419 randomized participants with APS. Only one study was at low risk of bias in all domains. One study was at low risk of bias in all domains for objective outcomes but not for quality of life (measured using the EQ-5D-5L questionnaire). We judged the other three studies to be at unclear or high risk of bias in three or more domains.

The duration of intervention ranged from 180 days to a mean of 3.9 years. One study compared rivaroxaban (a novel oral anticoagulant: NOAC) with standard warfarin treatment and reported no thrombotic or major bleeding events, but it was not powered to detect such differences (low-quality evidence). Investigators reported similar rates of clinically relevant non-major bleeding (risk ratio (RR) 1.45, 95% confidence interval (CI) 0.25 to 8.33; moderate-quality evidence) and minor bleeding (RR 1.21, 95% CI 0.51 to 2.83) for participants receiving rivaroxaban and the standard vitamin K antagonists (VKA). This study also reported some small benefit with rivaroxaban over the standard VKA treatment in terms of quality of life health state measured at 180 days with the EQ-5D-5L 100 mm visual analogue scale (mean difference (MD) 7 mm, 95% CI 2.01 to 11.99; low-quality evidence) but not measured as health utility (MD 0.04, 95% CI −0.02 to 0.10 [on a scale from 0 to 1]).

Two studies compared high dose VKA (warfarin) with moderate/standard intensity VKA and found no differences in the rates of any thrombotic events (RR 2.22, 95% CI 0.79 to 6.23) or major bleeding (RR 0.74, 95% CI 0.24 to 2.25) between the groups (low-quality evidence). Minor bleeding analyzed using the RR and any bleeding using the hazard ratio (HR) were more frequent in participants receiving high-intensity warfarin treatment compared to the standard-intensity therapy (RR 2.55, 95% CI 1.07 to 6.07; and HR 2.03, 95% CI 1.12 to 3.68; low-quality evidence).

In one study, it was not possible to estimate the RR for stroke with a combination of VKA plus antiplatelet agent compared to a single antiplatelet agent, while for major bleeding, a single event occurred in the single antiplatelet agent group. In one study, comparing combined VKA plus antiplatelet agent with dual antiplatelet therapy, the RR of the risk of stroke over three years of observation was 5.00 (95% CI 0.26 to 98.0). In a single small study, the RR for stroke during one year of observation with a dual antiplatelet therapy compared to single antiplatelet drug was 0.14 (95% CI 0.01 to 2.60).

Authors' conclusions

There is not enough evidence for or against NOACs or for high-intensity VKA compared to the standard VKA therapy in the secondary prevention of thrombosis in people with APS. There is some evidence of harm for high-intensity VKA regarding minor and any bleeding. The evidence was also not sufficient to show benefit or harm for VKA plus antiplatelet agent or dual antiplatelet therapy compared to a single antiplatelet drug. Future studies should be adequately powered, with proper adherence to treatment, in order to evaluate the effects of anticoagulants, antiplatelets, or both, for secondary thrombosis prevention in APS. We have identified five ongoing trials mainly using NOACs in APS, so increasing experimental efforts are likely to yield additional evidence of clinical relevance in the near future.

PLAIN LANGUAGE SUMMARY

Anticoagulant drugs and/or antiplatelet drugs for reducing the risk of blood clots and strokes in susceptible individuals

Review question

This review aimed to find out which type of treatment works best for preventing future stroke and other blood clotting (thrombotic) events, in people with antiphospholipid syndrome (APS).

Background

APS is a disease where the immune system produces antibodies directed against the proteins attached to their own cells. The presence of such antibodies may increase the risk of developing blood clots (thrombosis) in the blood vessels, or causing pregnancy-related complications (such as recurrent miscarriage, death of a baby in womb, premature birth, poor growth of the baby, or serious illness in a pregnant women). Blood clots in the arteries can cause strokes, resulting in brain damage or reversible nerve symptoms. Blood

clots in veins are associated with pain and limb swelling, and if they move they can block blood flow to the lungs. Two types of drugs are commonly used to prevent blood clots in people with APS: anticoagulants and antiplatelets. Anticoagulants prevent blood clot formation by interfering with the activity of proteins involved in blood clotting (clotting factors); while antiplatelets, usually aspirin, prevent platelets from sticking together and impair clot formation. Treatment with some anticoagulants (such as warfarin) requires regular blood tests to ensure their adequate action, and a balanced diet in terms of vitamin K intake, mainly in green leafy vegetables.

Study characteristics

The evidence is current to February 2017. We looked for studies that randomly allocated people with APS to different treatments, including anticoagulants, antiplatelets, or both. We identified five studies involving 419 participants. The average age of the participants was between 41 and 50 years, and the studies included people with previous stroke or previous blood clots in large veins or arteries. Studies took place in eight different countries and had a variety of funding sources. One trial compared a novel anticoagulant (rivaroxaban) with the standard anticoagulant (warfarin). Two studies compared a high dose versus standard dose of warfarin , and two studies compared combinations of antiplatelets, anticoagulants, or both. Interventions lasted from 180 days to an average of 3.9 years (SD 2.0).

Key results

In one study with an anticoagulant (rivaroxaban), participants had no episodes of blood clotting, and there was no difference in the risk of bleeding (moderate-quality evidence). In the two studies comparing higher and lower doses of anticoagulant (warfarin), similar proportions of participants had blood clotting and major bleeding problems (low-quality evidence), but the higher dose warfarin group had a greater risk of minor bleeding problems and any bleeding problems (low-quality evidence). The two studies comparing combinations of antiplatelets and anticoagulants were both small, not well reported, and their results were inconclusive (very low-quality evidence).

Quality of the evidence

One study was well designed, and we judged it to be at low risk of bias; we judged a second study to be at low risk of bias for the main results. We considered all other studies to be at unclear or high risk of bias because of concerns about their methods or reporting of results. All the results were imprecise and did not clearly indicate benefit or harm.

Authors' conclusions

We did not find enough evidence in our review to judge the benefit or harm of using anticoagulant (rivaroxaban) versus anticoagulant (warfarin) for preventing blood clots or stroke in people with APS. Treatment with high doses of the anticoagulant warfarin was associated with a higher risk of minor and any bleeding than treatment with standard doses, but we found no difference in terms of benefit. There was not enough evidence to show benefit or harm of any combination of anticoagulants and/or antiplatelets. Five ongoing studies will likely provide additional evidence in the near future.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Anticoagulant drugs: VKA high dose versus standard VKA therapy

Patient or population: people with antiphospholipid syndrome and a history of stroke or thromboembolic events
Setting: specialist centres
Intervention: anticoagulant drugs VKA high dose
Comparison: standard VKA therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk				
	Risk with standard VKA therapy	Risk difference with VKA high dose			
Any thromboembolic event Follow-up: mean 2.7 years (SD not reported) and 3.4 years (SD 1.2)	Study population 44 per 1000	54 more per 1000 (9 fewer to 231 more)	RR 2.22 (0.79 to 6.23)	223 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Major bleeding Follow-up: mean 2.7 years (SD not reported) and 3.4 years (SD 1.2)	Study population 62 per 1000	16 fewer per 1000 (47 fewer to 77 more)	RR 0.74 (0.24 to 2.25)	223 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Death (any cause)[c] Follow-up: mean 2.7 years (SD not reported) and 3.4 years (SD 1.2)	Study population 18 per 1000	9 more per 1000 (13 fewer to 138 more)	RR 1.53 (0.27 to 8.79)	223 (2 RCTs)	⊕⊕◯◯ Low[a,b]
Stroke[c] Follow-up: mean 2.7 years (SD not reported) and 3.4 years (SD 1.2)	Study population		RR 1.37 (0.26 to 7.12)	223 (2 RCTs)	⊕⊕◯◯ Low[a,b]

	18 per 1000	7 more per 1000 (13 fewer to 108 more)			
Any bleeding[d] Follow-up: mean 2.7 years (SD not reported) and 3.4 years (SD 1.2)	Study population		RR 1.56 (0.93 to 2.62) HR 2.03 (1.12 to 3.68)	223 (2 RCTs)	⊕⊕◯◯ Low[a,b]
	168 per 1000	94 more per 1000 (12 fewer to 272 more)			
Adverse events Follow-up: mean 2.7 years (SD not reported) and 3.4 years (SD 1.2)	See footnote[e]				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RR**: risk ratio; **SD**: standard deviation; **VKA**: vitamin K antagonists.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect,
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different,
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Unclear risk of bias due to incomplete outcome reporting and selective outcome reporting; seriously underpowered study, terminated early due to poor recruitment.
[b] Low number of events and wide confidence interval.
[c] Death and stroke are shown in the table, although other types of thromboembolic events were considered as outcomes.
[d] Our review has an outcome 'any bleeding that does not meet criteria for major bleeding', however both studies reported any bleeding and one of them minor bleeding, therefore we decided to keep it in the 'Summary of findings' table for the information on harm; when analyzed by RR it was not significant, but when the time to event was taken into account there was a difference between treatment groups.
[e] Only one of the two included studies reported adverse events other than bleeding as outcomes and leading to treatment withdrawal (WAPS); these were essential thrombocythemia in one participant and headache in one participant, but the study did not indicate the group in which those participants were included.

BACKGROUND

Description of the condition

Antiphospholipid syndrome (APS) is an autoimmune condition where the presence of antiphospholipid (aPL) antibodies is associated with recurrent thrombosis (both arterial and venous), pregnancy morbidity, or both. The pathogenesis of APS involves the activation of monocytes, platelets, endothelial cells and complements, which induce thrombosis (Chighizola 2015; Giannakopoulos 2007; Giannakopoulos 2013). Primary APS is diagnosed in 53.1% of cases, while 36.2% of cases are secondary APS (associated with other autoimmune diseases, especially with systemic lupus erythematosus, or SLE) (Cervera 2002). In the general population, estimates of the prevalence of aPL antibodies range from 1% to 5% of otherwise healthy people in Petri 2000 to up to 10% in George 2009. The prevalence is higher in people with rheumatoid arthritis (16%) or SLE (30% to 40%) (George 2009). According to the APS ACTION group data (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking), aPL prevalence in people with thrombotic events was 6% in women with pregnancy morbidity and 13% in people with stroke (Andreoli 2013).

The prevalence of APS is estimated at 40 to 50 cases per 100,000 people, and the incidence is about five new cases per 100,000 people per year (Gomez-Puerta 2014). The estimated association between aPL positivity and annual risk of thrombosis in people with no previous thrombosis is 0% to 4% (Erkan 2007), while in people with SLE the annual risk for thrombotic events is 2.5% to 3.8%. However, 4% to 21% of people with thrombosis are positive for aPL antibodies (Lim 2006).

The diagnosis of APS is presently based on the 2006 modified classification criteria, which include relatively specific and the most common clinical and laboratory findings: that is, vascular thrombosis, pregnancy morbidity, or both, with the presence of lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL) and/or anti-beta$_2$ glycoprotein-I antibodies (anti-β_2GPI) in plasma in medium to high titers. Antibodies must be detected at least twice in a 12-week period. To confirm the diagnosis of APS, one clinical and one laboratory criterion must be fulfilled (Miyakis 2006). The previous classification criteria for APS, established in Sapporo in 1999, did not include anti-β_2GPI antibodies and set the minimum time between two measurements at six weeks (Wilson 1999).

Associated with thrombosis, aPL antibodies are a heterogeneous group of antibodies found in people with APS. The presence of LA in plasma is the strongest risk factor for both venous and arterial thrombosis (Galli 2003).

Thrombosis in APS may affect both venous and arterial vessels, with the most common sites being deep veins of the lower limbs and cerebral arteries (Keeling 2012). In people diagnosed with APS, about 13% have had a stroke and 7% a transient ischemic attack (TIA) (Panichpisal 2012), whereas aPL antibodies were found in about 20% of people under 50 years of age diagnosed with stroke (Bushnell 2000). Experts believe that the simultaneous presence of all three types of antibodies (LA, aCL and anti-β_2GPI), the so called 'triple-antibody positivity', is associated with a significantly higher thrombotic risk than the combination of two antibodies ('double-antibody positivity') or the presence of just one type of antibody ('single-antibody positivity') (Iwaniec 2016; Pengo 2011; Pengo 2015). In a large cohort of unselected APS cases, the most frequently occurring clinical manifestations of APS were deep vein thrombosis, thrombocytopenia, livedo reticularis, and stroke, followed by pulmonary embolism, pregnancy loss, and TIA (Cervera 2002; Cervera 2009). TIA is defined as a condition with similar symptoms to a stroke, usually caused by a clot. However, the main difference between a stroke and TIA is that with TIA the blockage of the vessel is temporary. TIA symptoms occur rapidly and usually last for fewer than five minutes; all symptoms should resolve within 24 hours (Chatzikonstantinou 2013). When a TIA is over, it usually causes no permanent injury to the brain. There is also a more recent definition -a tissue-based definition adopted by the American Heart Association and American Stroke Association (AHA/ASA) -according to which TIA is a transient, short-lasting episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton 2009). Other clinical manifestations comprise heart valve disease, preeclampsia or eclampsia, premature birth, pulmonary hypertension, and leg ulcers (Ruiz-Irastorza 2010). The most severe form of APS is catastrophic APS (CAPS), which occurs in less than 1% of people with APS and has a mortality rate of 30% (Cervera 2010). Some studies have reported that people with arterial thrombosis are at higher risk of developing recurrence than those with venous thrombosis (Chighizola 2015). In a large European cohort study in which most participants had index venous thrombosis, recurrent arterial thromboses were the most common events (Cervera 2009). However, another study in people at high risk did not show that recurrent events depend on the index event (Chighizola 2015; Pengo 2010).

In a large cohort of unselected APS cases, the five-year survival rate in people with APS was approximately 90% to 94% (Cervera 2002; Cervera 2009). The median age at disease diagnosis was 31 years, and most people were diagnosed between the age of 15 and 50 years. Taking into account the clinical manifestations of the disease, which include cerebrovascular events (13% of people with stroke and 7% of people with TIA) and the young age of disease diagnosis onset, APS may exert a strong impact with high socioeconomic costs (Chighizola 2015).

Several studies have linked increased risk for thrombosis in people with aPL antibodies with the presence of cardiovascular risk factors such as hypercholesterolemia, smoking, and hypertension (Erkan 2007; Matyja-Bednarczyk 2014; Saraiva 2015). Therefore, careful assessment of the cardiovascular risk factors present in people with aPL is advised (Chighizola 2015).

Description of the intervention

Secondary thromboprophylaxis consists of antiplatelets (most commonly aspirin), anticoagulants (most commonly vitamin K antagonists (VKA): warfarin or acenocoumarol), or both (Espinosa 2015). People may receive aspirin or warfarin with the target international normalized ratio (INR) of 2.0 to 3.0, or heparin when VKAs are contraindicated. Novel oral anticoagulants (rivaroxaban, dabigatran, or apixaban) and antiplatelets (clopidogrel or prasugrel) can also be used alone or with aspirin. Where there are thrombotic complications at INR of 2.0 to 3.0, clinicians may modify the therapy to a higher target INR, combine two drugs, or, in high-risk patients, even prescribe triple antithrombotic therapy (one anticoagulant such as warfarin plus two antiplatelet agents, like aspirin and clopidogrel). However, this is associated with a higher risk of hemorrhage or major bleeding (Nalli 2014). Selecting the appropriate intensity of anticoagulation to balance the risk of recurrent thrombosis and the risk of bleeding in APS is a real challenge for clinicians. Retrospective studies have suggested a high-intensity anticoagulation with warfarin (INR set > 3) to prevent recurrent thrombosis in people with APS (Lim 2006). However, randomized trials suggested adopting moderate-intensity anticoagulation with an INR targeted at 2.5 (range 2.0 to 3.0) as the best choice available for secondary thrombosis prevention in people with APS (Crowther 2003; Finazzi 2005).

An important issue is also the value of the INR at the time of recurrent thrombosis-studies have reported that in people who received VKA, most of the recurrent thrombotic events occurred in those with an INR below 3, while people in high-intensity anticoagulation groups were below an INR range for over 40% of time, which may have biased the results (Chighizola 2015; Ruiz-Irastorza 2011). This advice of moderate-intensity anticoagulation applied mainly to people with APS and venous thromboembolism; therefore, clinicians should exercise caution when adapting it to arterial thrombotic events, which are less frequent (Finazzi 2005; Ruiz-Irastorza 2011). It would be important to look at these two anticoagulant regimens as separate interventions. There are also studies suggesting that hydroxychloroquine can have an antithrombotic effect due to its antiplatelet properties (Erkan 2014; Ruiz-Irastorza 2011).

Intake of foods rich in vitamin K as well as drugs or other substances that may enhance or inhibit the metabolism of the anticoagulant agent used, can influence the effectiveness and safety of VKA (Chighizola 2014). VKA treatment often requires lifestyle modification and regular dose adjustment based on measured INR values, with monitoring for bleeding. These measures are necessary because they help to assure treatment effectiveness and safety. However, they may have a deep impact on the quality of life of the patient, since they would require regular attendance at a healthcare facility: they can be time-consuming, may incur additional costs, and may interfere with daily activity to an extent that they are a burden for some patients (Hasan 2015).

How the intervention might work

Aspirin is an antiplatelet agent, inhibiting cyclooxygenase 1 (COX-1) in platelets, which in turn inhibits the production of thromboxane A2 (TXA2) (Warner 2011). Clopidogrel is also an antiplatelet drug, but it works by inhibiting P2Y receptors and impairs the activation of the glycoprotein (GP) IIb/III complex by fibrinogen (Wijeyeratne 2011). The mechanism of action of oral anticoagulant agents such as warfarin or acenocoumarol is antagonising vitamin K and thus inhibiting the production of coagulation factors II, VII, IX, X, and C and S proteins (Ageno 2012). Heparin binds to antithrombin and then makes a complex with an activated factor X, inactivating it, which leads to the inhibition of blood coagulation (Hirsh 2001). Non-vitamin K antagonist oral anticoagulants (NOACs) are the direct inhibitors of either factor IIa (thrombin) or factor Xa (Weitz 2016). Dabigatran etexilate strongly and reversibly inhibits thrombin and thus restrains the conversion of fibrinogen into fibrin, while rivaroxaban and apixaban directly inhibit active factor Xa (both free and thrombus-bound), which breaks the coagulation cascade (Ageno 2012).

The thrombotic risk in people with APS is high. Therefore, treatment guidelines currently recommend providing people with an APS diagnosis and thrombosis with life-long anticoagulants, antiplatelet therapy, or both, to prevent future arterial or venous thrombotic events (Ruiz-Irastorza 2011). However, these treatments increase the risk of bleeding, especially in people receiving the combination therapy (Nalli 2014), and they can also be associated with other adverse events (Raschi 2016).

Why it is important to do this review

No Cochrane Review has addressed the prevention of recurrent thrombosis in people with diagnosed APS. One Cochrane Review addressed preventing recurrent miscarriage in women with antiphospholipid antibodies or lupus anticoagulant (Empson 2005). A protocol registered by Cochrane Vascular considered using antiplatelet or anticoagulant agents to prevent recurrent peripheral vascular thrombosis in such patients (Islam 2016), and another review registered with the Cochrane Pregnancy and Childbirth Group is addressing the use of aspirin, heparin, or both for preventing recurrent miscarriage in women with APS. A separate Cochrane Review focuses on primary prevention of thrombosis in people with antiphospholipid antibodies since they are different from those already diagnosed with APS (Bala 2017). However, none of these reviews address the issue of prevention of other types of thrombosis, such as stroke, in people with APS. Several randomized trials have examined the efficacy of using antiplatelet (aspirin) or anticoagulant agents (such as warfarin) in people diagnosed with APS. Clinical trials using NOACs in such patients are ongoing (Woller 2016). Therefore, it is important to summarize the effects of those therapies in people with APS.

OBJECTIVES

To assess the effects of antiplatelet or anticoagulant agents, or both, for the secondary prevention of recurrent thrombosis, particularly ischemic stroke, in people with antiphospholipid syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) comparing participants allocated to one of two or more different treatment regimens.

Types of participants

People with antiphospholipid syndrome (APS) diagnosed according to the criteria valid when the study was carried out, such as the Sapporo or Sydney criteria (Miyakis 2006; Wilson 1999). We did not include studies specifically addressing women with recurrent miscarriages, as a separate Cochrane Review covers this topic (Empson 2005).

Types of interventions

We included trials comparing any antiplatelet agents, any anticoagulant agents, or their combination in any dose and mode of delivery versus no intervention/ placebo or another antiplatelet/ anticoagulant regimen.

Types of outcome measures

Primary outcomes

- Any thromboembolic event, including death or any arterial or venous thrombosis
- Major bleeding

We defined major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria, as clinically overt bleeding with a confirmed decrease in the hemoglobin level of at least 2 g/dL or transfusion-due to the occurrence of clinical symptoms-of at least 2 units of packed red cells, occurring at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial, retroperitoneal), or resulting in death (Schulman 2005). This definition does not consider any time restrictions.

Secondary outcomes

- Each type of thromboembolic event analyzed separately (i.e. death from all causes, stroke, TIA, venous thromboembolism, etc.)
- Quality of life measured with a validated questionnaire
- Any bleeding that does not meet the criteria for major bleeding
- Adverse event other than bleeding

We analyzed thromboembolic events as defined by the authors of the primary studies, especially with regard to TIA; this definition was originally time-based (Advisory Council 1975), but updates later based it on tissues (Easton 2009). If possible, we planned to take this into account in subgroup analysis.
We assessed all outcomes at the end of follow-up.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for trials in all languages and arranged for the translation or extraction of data of relevant articles where necessary.

Electronic searches

We searched the Cochrane Stroke Group trials register (last searched 27 February 2017) and the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) (searched 27 February 2017) (Appendix 1).
- MEDLINE Ovid (from 1948 to 27 February 2017) (Appendix 2).
- Embase (from 1980 to 27 February 2017) (Appendix 3).

We developed the MEDLINE search strategy (Appendix 2) and adapted it for the other databases (Appendix 1; Appendix 3). We also searched the following ongoing trials registers (Appendix 4).

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 23 January 2017).
- Stroke Trials Registry (www.strokecenter.org/trials; searched 23 January 2017).
- European Trials Register (www.clinicaltrialsregister.eu; searched 23 January 2017).
- ISRCTN Registry (www.isrctn.com; searched 23 January 2017).
- The World Health Organization (WHO) International Trials Registry Platform (www.who.int/ictrp/en; searched 23 January 2017).

Searching other resources

We checked reference lists of all included studies, systematic reviews, and practice guidelines relevant to the topic of the review. We contacted experts in the field: Pier L Meroni (Milan), Munther A Khamashta (London), Philip G de Groot (Utrecht), Phillippe de Moerloose (Geneva), and Vittorio Pengo (Italy) to inquire about additional studies and manufacturers of the original drugs, such as Bayer, Boehringer Ingelheim, Bristol-Meyers-Squibb/Pfizer, and Daiichi Sankyo with regard to additional studies.

Data collection and analysis

Selection of studies

We used Covidence in the process of study selection. It allows importing search results, independent screening by two review authors, comparing the results, and extracting the data. Pairs of review authors (MMB, MC-L, WS, AP, MK, MJS, and trainee reviewers named in the Acknowledgements) independently screened titles and abstracts of the references obtained as a result of our searching activities and excluded obviously irrelevant reports. We retrieved the full-text articles for the remaining references, and pairs of review authors (MMB, MC-L, WS, AP, MK, MJS and trainee reviewers) independently screened them and identified studies for inclusion, as well as identifying and recording reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third review author (AU, MMB, WS, MC-L). We collated multiple reports of the same study so that each study, not each reference, was the unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram (Moher 2009).

Data extraction and management

We planned to use Covidence for data extraction, but the forms available in Covidence were not flexible enough to fit our extraction purposes; therefore, we decided to use Microsoft Excel 2013 spreadsheets. We extracted data on study settings, time frame and methods, population inclusion and exclusion criteria as well as population characteristics, details of interventions and co-interventions, and details of outcomes and their definitions. Pairs of review authors (MMB, MC-L, WS, AP, MK, MJS) independently extracted data from the included studies. We compared the extracted results and resolved any discrepancies by discussion. One review author (MMB) additionally checked all the data extracted.

Assessment of risk of bias in included studies

Pairs of review authors (MMB, MC-L, WS, AP, MK, MJS) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (MMB, MC-L, WS). We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded the risk of bias for each domain as high, low, or unclear and provided information from the study report together with a justification for our judgment in the 'Risk of bias' tables. We judged trials as being at low risk of bias if they were at low risk of bias in all of the domains; we judged other cases as being at high risk of bias.

Measures of treatment effect

For binary outcomes we calculated the risk ratio (RR) with 95% confidence intervals (CIs); for continuous outcomes (quality of life) we planned to calculate the mean difference (MD) or standardized mean difference (SMD) (when different scales were used) with 95% CI. Since only one study reported quality of life data, we presented the results as MDs with 95% CIs. For survival outcomes, such as hazard ratio (HR) for death, we used a generic inverse variance method for the meta-analysis. In all analyses we planned to calculate pooled estimates using the random-effects model (Der Simonian 1986), and we planned to conduct sensitivity analyses using the fixed-effect model meta-analyses (Greenland 1985; Mantel 1959). Since single studies were included in many comparisons, we showed the results on the forest plot using the fixed-effect model. As we detected no heterogeneity in analyses where there was more than one study we decided not to pursue the sensitivity analyses with the fixed-effect model.

Unit of analysis issues

Regarding unit of analysis issues, we planned to follow the advice of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We anticipated that in most trials the unit of analysis would be individual participants. However, if there were cluster-randomized trials the unit of analysis would be the cluster. For cross-over trials we would include the first phase only in the analysis. We did not include any cluster-randomized trials or cross-over trials in the review.

Dealing with missing data

If data were missing, we attempted to contact the study authors to request them. If unsuccessful, for the data assumed to be missing at random we planned to analyze the data as reported, and we

planned to conduct sensitivity analyses. For the data assumed to be missing in a systematic way, we planned to assume that all missing participants were treatment failures. We planned to conduct sensitivity analyses on missing data to test this approach.

Assessment of heterogeneity

We used the I^2 statistic and Q test to measure heterogeneity among the trials in each analysis (Higgins 2011).

Assessment of reporting biases

We planned to analyze reporting bias using funnel plots for all primary outcomes if there were a sufficient number of studies. However, due to low number of studies for each comparison and outcome, we did not produce funnel plots.

Data synthesis

Where we considered studies to be clinically, methodologically, and statistically similar, we conducted a meta-analysis by pooling the appropriate data using Review Manager 5 (RevMan 5) (RevMan 2014). For binary outcome data we calculated RRs or HRs (if such data were available); for continuous outcomes (quality of life) we used MDs. If necessary, we used the methods described by Parmar 1998 and Thierney 2007 to calculate data relevant to pool HRs from the data available in the study (hazard rates, log rank P values, events, ratios, curve data, follow-up information) using a spreadsheet in Microsoft Office Excel 2003.
If pooling was not possible we planned to summarize the results narratively, using text, figures, and tables.

Subgroup analysis and investigation of heterogeneity

If possible, we planned to explore heterogeneity by subgroup analyses taking into account the type of drug (anticoagulant, antiplatelet, combination); dose of the active treatment; APS diagnostic criteria; single-, double- and triple-antibody positivity; lupus anticoagulant positivity versus other antibodies; time-based versus tissue-based definition of TIA; presence versus absence of traditional cardiovascular risk factors; type of index event (arterial versus venous); and INR value at thrombotic event.
We did not detect significant heterogeneity in any of the comparisons; however, we report results separately for different comparisons. We did not attempt any subgroup analyses because of the limited number of studies included in the review.

Sensitivity analysis

We planned to conduct sensitivity analyses for missing data using worst-best, best-best, best-worst and worst-worst case scenarios. In addition, we planned to conduct sensitivity analyses according to low and high risk of bias and the amount of missing data (trials with no missing data versus trials with missing data).

'Summary of findings' table

We summarized the evidence in three 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3), using GRADEpro (GRADEpro). In the development process we followed the GRADE approach as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to include the following outcomes in our 'Summary of findings' tables: any thromboembolic event, major bleeding, each type of thromboembolic event analyzed separately, quality of life, any bleeding that does not meet the criteria for major bleeding, and adverse events other than bleeding. However, due to the limitations in the number of outcomes reported, we only included stroke and death for 'each type of thromboembolic event analyzed separately'.

RESULTS

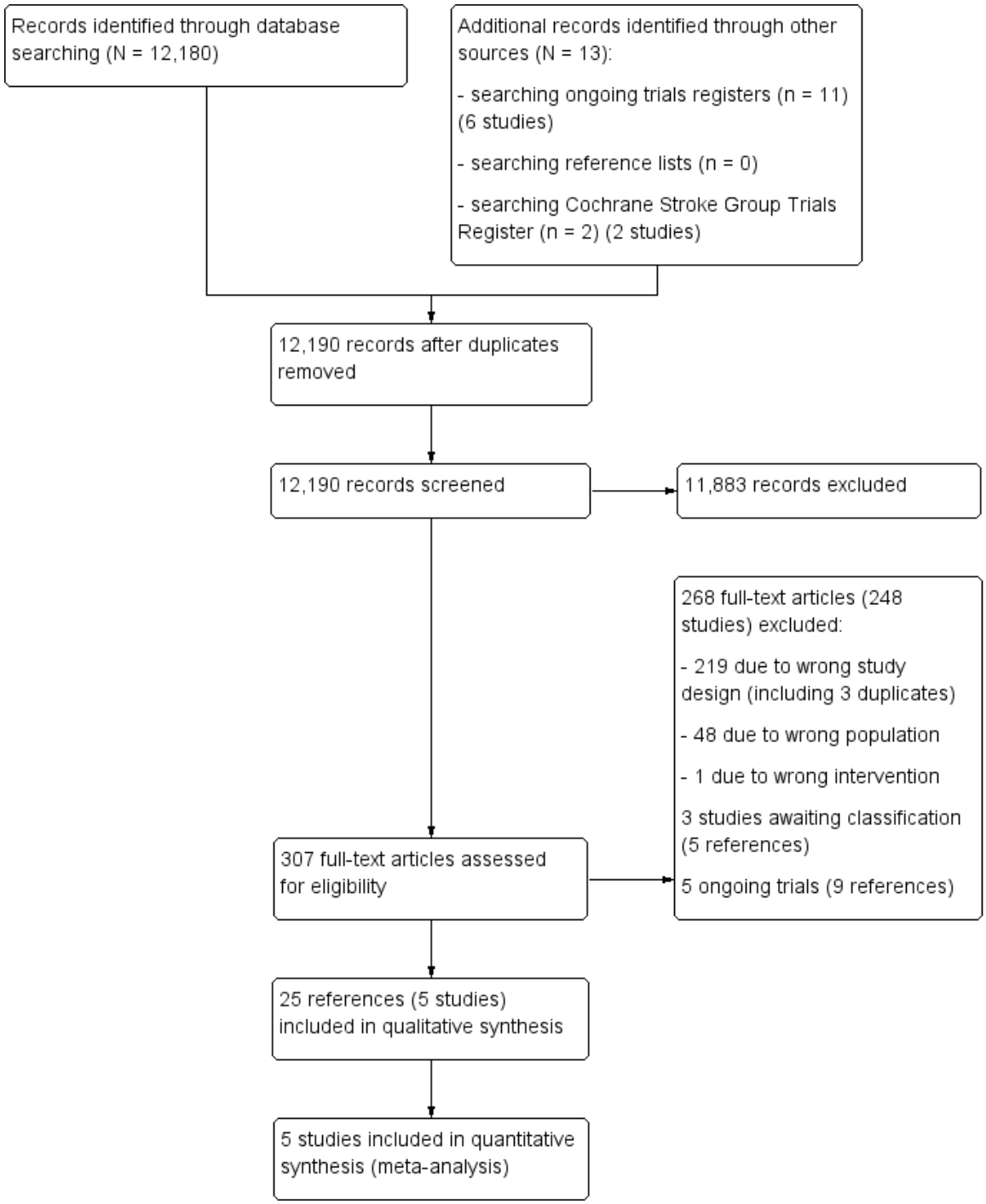
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

We carried out our searches in February 2017 and identified 12,190 unique records (Figure 1). Of those records, we retrieved 307 and checked the full text. We disregarded 248 studies published in 268 reports because the study design (n = 219), population (n = 48), or intervention (n = 1) did not meet inclusion criteria.

Figure 1. Study flow diagram.



We included five studies, reported in 25 records (Crowther 2003; Okuma 2010; RAPS; WAPS; Yamazaki 2009). In addition, we identified five ongoing trials reported in nine journal publications and clinical trial registries (2010-019764-36; ASTRO-APS; JASPRES; NCT02926170; TRAPS). We identified three additional studies, but we have not been able to finally classify them as included or excluded because we need additional information from the authors (Kondratyeva 2010; Okuma 2014; Yamazaki 2007).

Included studies

Authors described the five included studies as randomized controlled trials (RCTs). One was a non-inferiority trial (RAPS), two were described as double blind (Crowther 2003; Okuma 2014), one was open label but with blinded endpoint adjudication (WAPS), and one study was published only in conference abstracts (Yamazaki 2009). We present detailed information on each study in Characteristics of included studies.

Participants

All of the studies included people with diagnosed APS; in total 419 participants were randomized and 413 participants were analyzed for the outcomes relevant for this review.

The mean age of the participants was 41 to 50 years. The criteria for inclusion of studies differed: Okuma 2010 specified and cited criteria for participants' diagnosis; in Crowther 2003 and RAPS the information provided in the article followed the criteria published in Miyakis 2006; WAPS used criteria published in Wilson 1999; and Yamazaki 2009 did not report specific inclusion criteria. Okuma 2010 and Yamazaki 2009 only included people with previous stroke, while in RAPS a previous arterial event was an exclusion criterion, as was recurrent venous thromboembolism (VTE) while on warfarin with INR in the therapeutic range 2.0 to 3.0. Crowther 2003 and WAPS included people with both previous arterial and VTE.

Four studies reported the prevalence of systemic lupus erythematosus (SLE) in study participants, which ranged from 13% to 35% (Crowther 2003; Okuma 2010; RAPS; WAPS).

Crowther 2003, RAPS, and WAPS reported details about antibodies present. Lupus anticoagulant was the only type of antibody detected for 26% of participants in WAPS, 43% in Crowther 2003, and 46% in RAPS. Anticardiolipin antibodies were the sole type of antibody for 3% of participants in RAPS, 18% in WAPS, and for 39% of participants in Crowther 2003. Both types of antibodies were present for 18% of participants in Crowther 2003 and 56% of the participants in WAPS. RAPS also reported the percentage of participants with beta$_2$glycoprotein I antibodies only (4%) and more than one type of antibodies, both without (30%) and including triple positivity (16%).

Okuma 2010 reported cardiovascular risk factors: 59.6% of participants had a history of hypertension, 20.2% had diabetes, 20.2% had hyperlipidemia, and 10.1% had atrial fibrillation.

Location

Okuma 2010 and Yamazaki 2009 took place in Japan, Crowther 2003 in Canada, RAPS in the UK, and WAPS in Italy, Norway, Poland, Argentina, Czech Republic and Slovak Republic.

Setting

Crowther 2003, RAPS, and WAPS took place in specialist centres or clinics, Okuma 2010 in neurology department of university hospitals, and Yamazaki 2009 did not specify the setting.

Interventions

Two studies compared treatment with two intensities of warfarin: Crowther 2003 assessed high-intensity warfarin with a target INR of 3.1 to 4.0 and an average value of 3.3 versus a moderate (standard) intensity with a target INR of 2.0 to 3.0 and an average value of 2.3, and WAPS evaluated warfarin with a target of 3.5 and mean of 3.2 (range 3.0 to 4.5) versus standard antithrombotic therapy. Standard antithrombotic therapy included warfarin at target 2.5 (range 2.0 to 3.0; mean 2.5) in participants with previous VTE, cardioembolic cerebral or peripheral ischemia, atrial fibrillation or rheumatic valve disease (95% of participants), or aspirin 100 mg/d in participants with non-embolic arterial thrombosis (5% of participants). In addition, in Crowther 2003 14% of participants in the high-intensity group and 10% participants in the moderate-intensity group received aspirin, while in WAPS 7% of participants in the high-intensity group and 5% of participants in the standard-therapy group received anticoagulation and aspirin according to the criteria of the treating physician. In Crowther 2003, participants in the high-intensity group were within the target INR for 40% of the time and below it for 43% of the time (but 86% of the time between 2.0 and 3.1), while in the moderate-intensity groups those values were 71% and 19%.

RAPS compared a standard-intensity warfarin treatment (mean INR 2.5) versus a non-vitamin K oral antagonist (NOAC): rivaroxaban 20 mg/d. The mean INR in the warfarin group was 2.7, and the mean time in therapeutic range at day 180 was 55%.

Okuma 2010 and Yamazaki 2009 compared a single antiplatelet agent with combinations of antiplatelet and anticoagulant agents (VKA) or dual antiplatelet therapy. They included a comparison of aspirin 100 mg/d with a combination of aspirin and anticoagulant agents (a non-specified vitamin K antagonist) with a target INR of 2.0 to 3.0 (Okuma 2010), or a three-arm comparison

of aspirin 100 mg/d, aspirin 100 mg/d plus cilostazol 200 mg/d, and aspirin 100 mg/d plus warfarin (with a target INR 2.0 to 2.5) (Yamazaki 2009). The mean INR in the combined treatment group in Okuma 2010 was 2.4, while Yamazaki 2009 did not report these data.

The duration of intervention varied among the studies and ranged from 180 days to a mean of 3.9 years (SD 2.0). Only one study reported an additional 30 days follow-up without intervention (RAPS). In Yamazaki 2009, one of the arms was stopped for "humanitarian" considerations (strokes revealed on MRI in three participants taking aspirin only).

Outcomes

The primary outcome in Okuma 2010 and Yamazaki 2009 was recurrent stroke; in Crowther 2003 recurrent thrombosis was the primary outcome. WAPS reported two co-primary outcomes: vascular death or major thrombosis (arterial or venous) and vascular death or major thrombosis or major hemorrhage. The primary outcome in RAPS was a surrogate outcome: percent change in endogenous thrombin potential from randomization to day 42 of study, plus reported thromboembolism (VTE or any other thrombotic events) up to day 210 as a secondary outcome. In four trials, safety outcomes included major, minor, or any bleeding (Crowther 2003; Okuma 2010; RAPS; WAPS).

Authors did not specify the secondary outcomes in Crowther 2003, Okuma 2010, or Yamazaki 2009. The secondary outcomes for efficacy in RAPS included other coagulation measures and quality of life (measured using the EQ-5D-5L questionnaire). The secondary endpoints in WAPS included combinations of different thrombotic events. Two trials specifically reported adverse events as outcomes (RAPS; WAPS).

Excluded studies

We excluded one study; see Characteristics of excluded studies.

Risk of bias in included studies

We presented details for each study in the Characteristics of included studies table. Figure 2 shows the overall risk of bias in each domain for studies in this review; Figure 3 shows risk of bias by trial.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

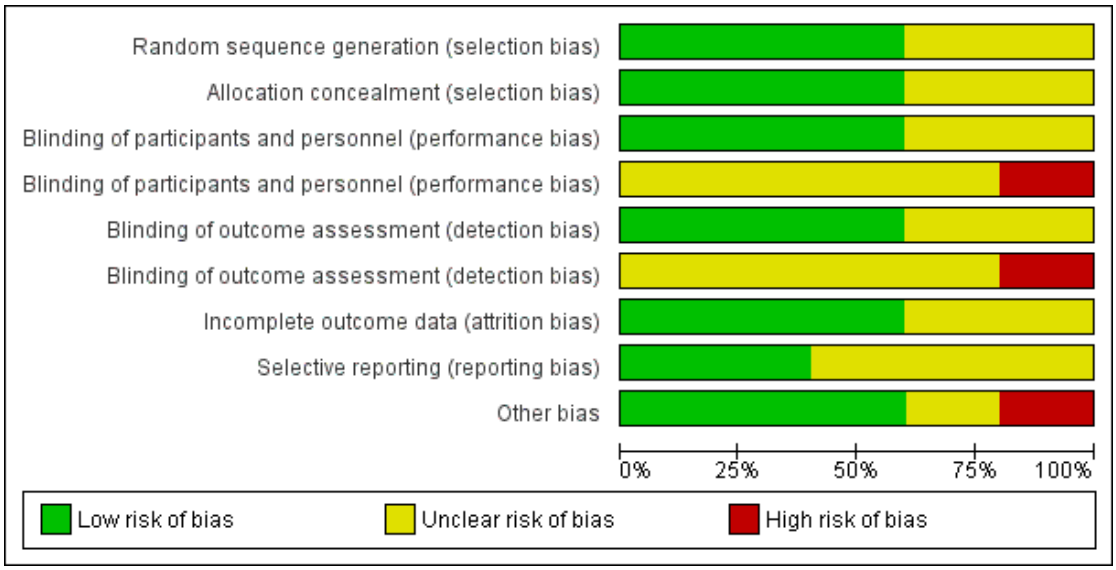
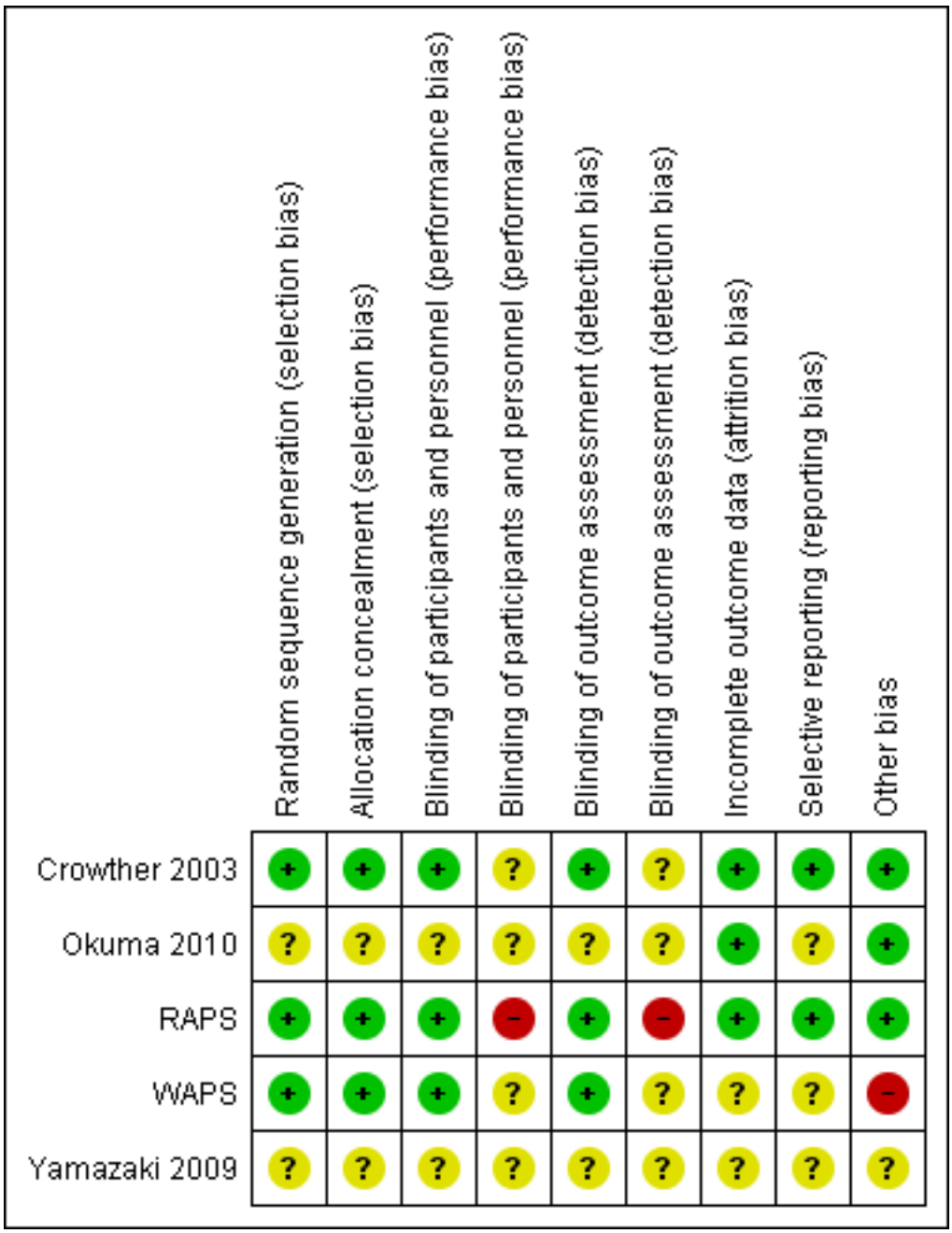


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Four of the included studies were published as full articles, and one consisted of several conference abstracts, hence data extracted from this study were very limited (Yamazaki 2009).
Only one study was at low risk of bias in all domains (Crowther 2003), and one was at low risk of bias in all domains for one group of outcomes (RAPS).

Allocation

In two of the included studies the risk of bias in random sequence generation and allocation concealment domains was unclear as no detailed information was provided (Okuma 2010; Yamazaki 2009).
The three other studies presented clear information, and therefore we judged them to be at low risk of bias in these domains (Crowther 2003; RAPS; WAPS). They all used central randomization: sequence generation was by means of a random numbers table (Crowther 2003), random permuted blocks of various length with stratification by centre and patient type (RAPS), and a program based on the biased-coin algorithm (WAPS).

Blinding

We assessed blinding of participants, personnel and outcome assessors for two groups of outcomes: objective outcomes, for example stroke, bleeding, and mortality; and subjective outcomes, such as quality of life.
Yamazaki 2009 did not provide any information about blinding, so the risk of bias in this study was unclear. Okuma 2010, although described as double blind, did not provide clear information about blinding; it also did not provide clear information about outcome definition or verification, so we judged the risk of bias as unclear. Crowther 2003 explicitly stated that the trial was double blind and that the participants, treating physicians, auxiliary personnel, and a panel of outcomes assessors were all unaware of the treatment assignments, so we considered the risk of bias to be low. RAPS and WAPS did not blind the participants and personnel. In our judgement, due to the objective definition or verification of outcomes in both studies, the lack of blinding likely did not influence objective outcomes, so we judged them to be at low risk of bias for those outcomes, but the lack of blinding could influence subjective outcomes, such as quality of life in RAPS, so we judged it to be at a high risk of bias for this outcome. WAPS explicitly stated that outcome assessors were blinded, so we judged the risk of bias to be low.

Incomplete outcome data

We assessed Crowther 2003, Okuma 2010, and RAPS to be at low risk of bias for incomplete outcome data, as there were either no or low amounts of missing data, the trials applied the intention-to-treat (ITT) principle, missing data were balanced between the groups, or the reasons for missing data were reported and were unlikely to be related to study outcomes. Although WAPS reported results per all randomized participants, it did not follow up 6/109 participants (information confirmed with the authors; it is not clear from which group), and although the number of participants in the analysis equaled the number of participants randomized, it is not clear how the participants who were not followed up were included in the analysis. In Yamazaki 2009, there was insufficient information available, so we judged the risk of bias as unclear.

Selective reporting

We assessed the risk of bias for selective reporting in Crowther 2003 and RAPS as low. RAPS provided the protocol and reported outcomes as specified in protocol. We did not identify the protocol for Crowther 2003, but the description in the Methods section stating pre-specified outcome and reporting for all those outcomes convincingly indicated a low risk of bias.
We obtained a protocol for WAPS, but there were several discrepancies between the outcomes listed there and in the study publication, so we judged the risk of bias to be unclear.
We did not identify the protocol for Okuma 2010, and the primary outcomes were partially reported as indicated in the Methods section, but the numbers of events were not reported, so we judged the risk of bias to be unclear.
We did not identify the protocol for Yamazaki 2009, and the information provided was insufficient to judge the risk of bias.

Other potential sources of bias

We did not identify any source of potential bias in three studies (Crowther 2003; Okuma 2010; RAPS). In one study there was little information overall, and the risk in this domain was unclear (Yamazaki 2009). WAPS was seriously underpowered: the planned sample size was 500 participants per arm, while the number of participants recruited to the study was 109 in total. The study was terminated early due to poor recruitment. Therefore, we judged that this poor recruitment could have introduced bias, and we assessed risk of bias as high.

Effects of interventions

See: **Summary of findings for the main comparison** Anticoagulant drugs: VKA high dose versus standard VKA therapy; **Summary of findings 2** Novel oral anticoagulant (NOAC) versus standard VKA therapy; **Summary of findings 3** VKA plus antiplatelet agents (VKA + AP)versus single antiplatelet agent

We summarized the effects of interventions in four separate comparison groups.

1. Anticoagulant drugs in two un-pooled subgroups: NOAC (rivaroxaban) or high dose VKA versus standard VKA treatment.
2. Anticoagulant (VKA) plus antiplatelet agent versus a single antiplatelet.
3. Anticoagulant (VKA) plus antiplatelet agent versus dual antiplatelet therapy.
4. Dual antiplatelet therapy versus a single antiplatelet treatment.

If possible, we reported the results for each outcome for those comparisons. In the first comparison group we presented the results for NOAC versus standard VKA and for high dose VKA versus standard VKA in separate subgroups. We also summarized the results in separate 'Summary of findings' tables for each comparison (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

For many comparisons and outcomes, we included only single studies, or there were no differences regarding risk of bias, so we planned to carry out sensitivity analysis regarding risk of bias if sufficient information became available. With respect to missing data, RAPS excluded participants' data from the analysis only in the control group but not in the experimental group, so we tested worst- and best-case scenarios for the missing data of participants in the control group. WAPS did not provide information about the treatment arm of participants who were not followed up, therefore we could not attempt any sensitivity analysis.

Any thromboembolic event

Anticoagulant drugs

Three studies reported on this outcome.

NOAC versus standard VKA therapy

RAPS did not report any events of recurrent VTE or other thrombotic event at 210 days of follow-up; it was also not powered to detect differences in the occurrence of clinical events (Analysis 1.1). We observed no change in the results in the sensitivity analysis (Table 1).

VKA high dose versus standard VKA therapy

Two studies compared the effects of high and standard doses of warfarin: Crowther 2003 assessed the recurrence of any thrombosis, and WAPS, vascular death or major thrombosis. Together, they reported a total of 11 versus 5 events during a mean of 2.7 years (SD not reported) and a mean of 3.4 years (SD 1.2) of follow-up respectively, but the pooled difference was not significant, and the confidence interval was wide (RR 2.22, 95% CI 0.79 to 6.23) (Analysis 1.1). Results did not change when we pooled the log hazard ratio, calculated on the basis of data reported in the studies (Analysis 1.2).

Crowther 2003 reported INR values in the two participants with thrombotic events in the moderate intensity group (INR 1.6 and INR 2.8), while the INR values were 3.1, 1.0, 0.9, 1.9, and 3.9 in five out of six participants with events in the high-intensity group (one participant discontinued treatment).

Other comparisons

The studies included under other comparisons reported results only for stroke (Okuma 2010; Yamazaki 2009): see below.

Major bleeding

Anticoagulant drugs

Three studies reported on this outcome.

NOAC versus standard VKA therapy

RAPS did not report any events of major bleeding at 210 days of follow-up (Analysis 1.3).

We observed no change in the results in the sensitivity analysis (Table 1).

VKA high dose versus standard VKA therapy

Two studies comparing high and standard warfarin dose examined major bleeding (Crowther 2003; WAPS), reporting five versus seven cases in total during a mean of 2.7 years (SD not reported) and a mean of 3.4 years (SD 1.2) of follow-up, respectively.The difference was not significant (RR 0.74, 95% CI 0.24 to 2.25) (Analysis 1.3). Results did not change when we pooled the log hazard ratio calculated on the basis of data provided in the studies (Analysis 1.4).

VKA plus antiplatelet versus single antiplatelet agent

Yamazaki 2009 did not provide any information regarding occurrence of major bleeding in participants included in the study, while Okuma 2010 reported a single case of minor cerebral hemorrhage (which we defined as major bleeding) in the single antiplatelet group at a mean of 3.9 years (SD 2.0) of follow-up (Analysis 2.2).

Other comparisons

The study included under other comparisons did not report results for major bleeding (Yamazaki 2009).

Each type of thromboembolic event analyzed separately (i.e. death, stroke, TIA, venous thromboembolism, etc.)

Death from all causes

Anticoagulant drugs

Three studies reported on this outcome.

NOAC versus standard VKA therapy

RAPS reported one death due to non-Hodgkin's lymphoma in a participant taking warfarin during 210 days of follow-up (Analysis 1.5).

VKA high dose versus standard VKA therapy

Two studies comparing high and standard warfarin dose reported either no death during a mean of 2.7 years (SD not reported) of follow-up (Crowther 2003), or three versus two deaths during a mean of 3.4 years (SD 1.2) years of follow-up (WAPS) (Analysis 1.5).

No other comparisons reported data for this outcome.

Stroke

Anticoagulant drugs

Three studies reported on this outcome.

NOAC versus standard VKA therapy

RAPS did not report any events in the NOAC (rivaroxaban) or warfarin standard dose groups at 210 days of follow-up, but the trial was not powered to detect differences in the occurrence of clinical events (Analysis 1.6).

VKA high dose versus standard VKA therapy

Two studies assessed the effect of high-dose versus standard-dose warfarin (Crowther 2003; WAPS). The number of events was low (three versus two events) during a mean of 2.7 years (SD not reported) and a mean of 3.4 years (SD 1.2) of follow-up, respectively. We observed no significant difference between treatment groups, and the confidence interval was wide (RR 1.37, 95% CI 0.26 to 7.12) (Analysis 1.6).

VKA plus antiplatelet versus single antiplatelet agent

Although two studies comparing anticoagulant plus antiplatelet agents versus a single antiplatelet drug (aspirin) reported stroke as an outcome (Okuma 2010; Yamazaki 2009), only one small study (reported only in conference abstracts) provided results that could be shown on a forest plot (Yamazaki 2009). It did not show significant differences between the treatment groups at one-year follow-up, but the aspirin group was discontinued for "humanitarian" reasons, as all three events took place in this group, while no events occurred in the combined treatment group (Analysis 2.1). Okuma 2010 reported significant differences in the cumulative incidence of stroke in 3.9 years mean follow-up (SD 2.0) in favor of the combination group (log-rank test, P = 0.026) but did not report the numbers of participants with an event or hazard ratio.

VKA plus antiplatelet versus dual antiplatelet therapy

Only Yamazaki 2009 (reported in conference abstracts) provided results that could be shown on a forest plot. It did not show significant differences between the treatment groups at three years follow-up (RR 5.0, 95% CI 0.26 to 98.0) (Analysis 3.1), but there were only two events in the VKA plus antiplatelet group and no events in the dual antiplatelet group, so confidence intervals were wide.

Dual antiplatelet therapy versus single antiplatelet agent

Only Yamazaki 2009 provided results that could be shown on a forest plot but did not show a significant difference between treatment groups at one-year follow-up. However, the aspirin group was discontinued for "humanitarian" reasons, as all three events occurred in this group, while there were no events in the combined treatment group (RR 0.14, 95% CI 0.01 to 2.60) (Analysis 4.1).

Transient ischemic attack

Anticoagulant drugs

Three studies reported on this outcome.

NOAC versus standard VKA therapy

RAPS did not report any events at 210 days of follow-up; however, it was not powered to detect differences in the occurrence of clinical events (Analysis 1.7).

VKA high dose versus standard VKA therapy

Crowther 2003 reported no TIA events over a mean of 2.7 years (SD not reported) of follow-up, while in WAPS the number of events was low in both the high- and moderate-intensity warfarin groups (two versus one event) during a mean of 3.4 years (SD 1.2) of follow-up. We observed no significant difference between treatment groups, and the confidence interval was wide (Analysis 1.7). RAPS and WAPS both used the TIA definition based on the time of symptoms occurrence.
No other comparisons reported data on this outcome.

Venous thromboembolism

Anticoagulant drugs therapy

Three studies reported on this outcome.

NOAC versus standard VKA therapy

RAPS did not report any events at 210 days of follow-up, but it was not powered to detect differences in the occurrence of clinical events (Analysis 1.8).

VKA high dose versus standard VKA therapy

In two studies comparing the effect of high-dose versus standard-dose warfarin, the number of events was low (six versus one event) during a mean of 2.7 years (SD not reported) and a mean of 3.4 years (SD 1.2) of follow-up, respectively (Crowther 2003; WAPS). We observed no significant difference between treatment groups, and the confidence interval was wide (Analysis 1.8).
No other comparisons reported data on this outcome.

Myocardial infarction

Anticoagulant drugs

Three studies reported on this outcome.

NOAC versus standard VKA therapy

Similar to other endpoints, RAPS did not report any events at 210 days of follow-up (Analysis 1.9).

VKA high dose versus standard VKA therapy

From two studies comparing high-dose warfarin with standard-dose warfarin, WAPS did not report any event at a mean of 3.4 years (SD 1.2) of follow-up, while Crowther 2003 reported a single event in each of the treatment groups (Analysis 1.9) during a mean of 2.7 years (SD not reported) of follow-up.
No other comparisons reported data on this outcome.

Other thrombotic events

Anticoagulant drugs

Two studies reported on this outcome.

NOAC versus standard VKA therapy

RAPS reported no cases of microvascular thrombosis at 210 days of follow-up (Analysis 1.10).

VKA high dose versus standard VKA therapy

WAPS reported a single case of superficial thrombophlebitis in the high-intensity group over a mean of 3.4 years (SD 1.2) of follow-up (Analysis 1.10).
No other comparisons reported data on this outcome.

Quality of life measured with a validated questionnaire

Anticoagulant drugs

Only one study reported on this outcome.

NOAC versus standard VKA therapy

RAPS, using the EQ-5D-5L questionnaire, reported the results at day 180 in terms of health utility without any significant differences between rivaroxaban and standard-dose warfarin (MD 0.04, 95% CI -0.02 to 0.10 [on a scale from 0 to 1]) (Analysis 1.11); the health state visual analogue scale showed a small significant difference in favor of rivaroxaban (MD 7 mm, 95% CI 2.01 to 11.99) (Analysis 1.11).
No other comparisons reported data on this outcome.

Any bleeding that does not meet the criteria for major bleeding

Anticoagulant drugs

Three studies examined the risk of any bleeding events other than major bleeding and reported on them in different configurations.

NOAC versus standard VKA therapy

RAPS reported no significant differences between rivaroxaban and standard-dose warfarin regarding clinically relevant bleeding at 210 days of follow-up (RR 1.45, 95% CI 0.25 to 8.33) (Analysis 1.12). It also reported on minor bleeding but did not find any significant differences between the treatment groups at 210 days of follow-up (RR 1.21, 95% CI 0.51 to 2.83) (Analysis 1.13). As four participants from the warfarin group were excluded from the analysis reported for this outcome (and all separate thrombotic outcomes) in the RAPS study, we did a sensitivity analysis to test if including these participants would change results: there was no change (Table 1).

VKA high dose versus standard VKA therapy

In WAPS the occurrence of minor bleeding was more frequent in the high-dose warfarin group compared with the standard-dose warfarin group during a mean of 3.4 years (SD 1.2) of follow-up (RR 2.55, 95% CI 1.07 to 6.07) (Analysis 1.13). The authors of the WAPS study also reported minor bleeding as a hazard ratio, showing a higher rate of those events with a higher dose (HR 2.92, 95% CI 1.13 to 7.52).

Two studies comparing high- and standard-dose warfarin reported on any bleeding during a mean of 2.7 years (SD not reported) and a mean of 3.4 years (SD 1.2) of follow-up, respectively (Crowther 2003; WAPS). We detected no significant difference between the treatment groups when we pooled the results using a risk ratio (RR 1.56, 95% CI 0.93 to 2.62) (Analysis 1.14). However, when we pooled log hazard ratios, calculated using the data reported in the published studies, the difference became significant (HR 2.03, 95% CI 1.12 to 3.68), indicating a higher risk of any bleeding in the higher-dose warfarin group (Analysis 1.15).

Anticoagulant (VKA) plus antiplatelet versus single antiplatelet agent

Yamazaki 2009 did not provide any information regarding the occurrence of any bleeding in participants included in the study, while Okuma 2010 reported a single case of subcutaneous hemorrhage (which we defined as minor bleeding) in the combined treatment group and no cases of gastrointestinal bleeding (no definition or classification provided) (Analysis 2.2).

No other comparisons reported data on this outcome.

Adverse events other than bleeding

Anticoagulant drugs

Two studies reported adverse events other than bleeding as outcomes (RAPS; WAPS).

NOAC versus standard VKA therapy

RAPS reported the occurrence of serious adverse events in four participants receiving rivaroxaban and four participants receiving warfarin. In the rivaroxaban group, investigators judged two of those events to be unrelated to the study drug: one was a previous intracranial hemorrhage, incidentally detected on brain imaging without any new or recurrent symptoms, and the other was a grade 1 event (grade 2 abdominal pain, vomiting, arthralgia and myalgia). Additionally, two events were judged unlikely to be related to the study drug (grade 4 intestinal perforation; grade 2 suspected deep vein thrombosis on the basis of a Doppler scan judged to be related to previous femoral vein deep vein thrombosis and without any new thrombosis). In the warfarin group, investigators judged three events to be unrelated to the study drug (grade 3 asthma exacerbation; grade 4 sepsis; high grade non-Hodgkin's lymphoma stage IV B, which resulted in death), and they classified one event as a grade 3 serious adverse reaction, probably related to warfarin (hemorrhoidal hemorrhage).

VKA high dose versus standard VKA therapy

WAPS reported on any adverse events leading to treatment withdrawal and reported two withdrawals associated with reported events, such as essential thrombocythemia in one participant and headache in one participant, but authors did not indicate the group in which those participants were included.

No other comparisons reported data on this outcome.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Novel oral anticoagulant (NOAC) versus standard VKA therapy

Patient or population: people with antiphospholipid syndrome and a history of stroke or thromboembolic events
Setting: specialist centres
Intervention: novel oral anticoagulants (NOAC)
Comparison: standard VKA therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk					
	Standard VKA therapy	Risk difference with NOAC				
Any thromboembolic Follow-up: 210 days	Study population		Not estimable	115 (1 RCT)	⊕⊕◯◯ Low[a]	Single study not powered to show differences in clinical events
	0 per 1000	0 per 1000 (0 to 0)				
Major bleeding Follow-up: 210 days	Study population		Not estimable	115 (1 RCT)	⊕⊕◯◯ Low[a]	Single study not powered to show differences in clinical events
	0 per 1000	0 per 1000 (0 to 0)				
Death (any cause)[b] Follow-up: 210 days	Study population		RR 0.34 (0.01 to 8.15)	115 (1 RCT)	⊕⊕◯◯ Low[c]	Single study not powered to show differences in clinical events
	17 per 1000	11 fewer per 1000 (17 fewer to 123 more)				
Stroke[b] Follow-up: 210 days	Study population		Not estimable	115 (1 RCT)	⊕⊕◯◯ Low[a]	Single study not powered to show differences in clinical events
	0 per 1000	0 per 1000 (0 to 0)				

Quality of life - Health state[d] (100 mm VAS) Follow-up: 180 days	The mean quality of life at day 180 was 73	MD 7 higher (2.01 higher to 11.99 higher)	-	112 (1 RCT)	⊕⊕◯◯ Low[e,f]	Single study not powered to show differences in clinical events
Clinically relevant non-major bleeding Follow-up: 210 days	Study population		RR 1.45 (0.25 to 8.33)	112 (1 RCT)	⊕⊕⊕◯ Moderate[g]	Single study not powered to show differences in clinical events
	36 per 1000	16 more per 1000 (27 fewer to 267 more)				
Adverse events Follow-up: 210 days	See footnote[h]					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio; **VKA**: vitamin K antagonists.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]No events in experimental or control group, non-estimable.
[b]Death and stroke are shown in the table, although other types of thromboembolic events were considered as outcomes.
[c]No events in experimental group, single event in control group, very wide confidence interval.
[d]This outcome reported as health utility and health state separately; health utility judged as low quality of evidence and showed no significant difference.
[e]No blinding of patient, personnel, or outcome assessors.
[f]Wide confidence interval.
[g]Low number of events and wide confidence interval.
[h]Serious adverse events reported in 4 participants in each group. In the rivaroxaban group 2 were judged to be unrelated to the study drug (previous grade 1 intracranial hemorrhage incidentally detected on brain imaging without any new or recurrent symptoms; grade 2 abdominal pain, vomiting, arthralgia and myalgia) and 2 were judged unlikely to be related to the study drug (grade 4 intestinal perforation; grade 2 suspected deep vein thrombosis on the basis of Doppler scan judged to be related to previous femoral vein deep vein thrombosis and without any new thrombosis). In the warfarin group 3 events were judged not to be related to study drug (grade 3 asthma exacerbation; grade 4 sepsis; high-grade non-Hodgkin's lymphoma stage

IV B which resulted in death) and 1 event was classified as grade 3 serious adverse reaction probably related to warfarin (hemorrhoidal hemorrhage).

VKA plus antiplatelet agents (VKA + AP) versus single antiplatelet agent

Patient or population: people with antiphospholipid syndrome, with previous stroke
Setting: Japan, 1 centre or unknown number of centres
Intervention: combination of VKA and antiplatelet agent (VKA + AP)
Comparison: single antiplatelet drug (AP1)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with single antiplatelet drug	Risk with VKA + AP				
Stroke Follow-up: 1 year	Study population		RR 0.14 (0.01 to 2.6)	40 (1 RCT)	⊕◯◯◯ Very low[a,b]	1 small study published only as conference abstracts; single antiplatelet drug group discontinued after 1 year for humanitarian considerations
	150 per 1000	129 fewer per 1000 (from 149 fewer to 240 more)				
Major bleeding (minor cerebral hemorrhage) Follow-up: mean 3.9 years (SD 2.0)	Study population		RR 0.40 (0.02 to 8.78)	20 (1 RCT)	⊕◯◯◯ Very low[b,c]	-
	91 per 1000	55 fewer per 1000 (89 fewer to 707 more)				
Any bleeding that does not meet criteria for major bleeding - GI bleeding (no definition) Follow-up: mean 3.9 years (SD 2.0)	Study population		-	-	-	-
	0 per 1000	0 per 1000 (0 to 0)	Not estimable	20 (1 RCT)	⊕◯◯◯ Very low[c,d]	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **RR**: Risk ratio; **OR**: Odds ratio; **SD**: standard deviation; **VKA**: vitamin K antagonists

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Insufficient information regarding all aspects of study design, no clear sequence generation, allocation concealment, blinding, completeness of outcome data and selective outcome reporting.

[b] Low number of events and only in control group; non-estimable.

[c] Insufficient information regarding randomization, concealment, blinding, selective outcome reporting.

[d] Non-estimable due to no events in experimental and control group.

DISCUSSION

Summary of main results

We identified one study comparing NOAC (rivaroxaban) with standard warfarin treatment, but it was not powered to detect differences in the rates of thrombotic or major bleeding events and reported no events and no significant differences for clinically relevant, non-major or minor bleeding events (quality of evidence was low to moderate). Therefore, we could draw no meaningful conclusions regarding benefit or harm for either of the treatments groups.

We identified two studies comparing high-intensity anticoagulation with moderate- (standard) intensity anticoagulation in the secondary prevention of recurrent thrombosis in people with antiphospholipid syndrome and found that the differences in the rates of thrombotic events or major bleeding between treatment groups were not statistically significant, but there was some evidence of an increased risk of minor and any bleeding in the high-intensity group (low-quality evidence). However, one of those studies was underpowered and in the other one the rate of thrombosis was lower than expected.

We identified two small, poorly reported studies at high risk of bias comparing a combination of antiplatelet and anticoagulant (VKA) agents with a single antiplatelet agent, but the trials did not provide any conclusive evidence regarding benefits or harms of those drugs in the secondary prevention of stroke in people with antiphospholipid syndrome (very low-quality evidence).

We identified only one small, poorly reported study at high risk of bias comparing antiplatelet plus anticoagulant (VKA) agents versus dual antiplatelet therapy. It did not provide any conclusive results regarding the effects of those drugs in people with antiphospholipid syndrome (very low-quality evidence).

We also identified only one small, poorly reported trial at high risk of bias comparing dual antiplatelet therapy and a single antiplatelet agent. The study did not provide any conclusive results regarding the effects of those drugs in people with antiphospholipid syndrome (very low-quality evidence).

Overall completeness and applicability of evidence

There were no thrombotic events reported for NOAC compared with standard VKA treatment. The number of thrombotic events reported for high-dose VKA compared with standard-dose VKA was low (16 events in 223 participants). The evidence for antiplatelet agents or a combination of antiplatelet and anticoagulant agents was even poorer, with very small and poorly reported studies. The completeness of data therefore is a concern in this review with regard to the effects of antiplatelets, anticoagulants, or both, as studies did not report the data required for meta-analysis in the assessment of either benefit or harm. In addition, we have not been able to finally assess three additional studies due to unclear reporting of methods or data.

All five included studies reported including people with antiphospholipid syndrome, but qualifying clinical events differed between the studies. The study comparing NOAC to the standard VKA therapy included only people with previous venous thromboembolism while taking no or sub-therapeutic doses of anticoagulation treatment and without VTE while on warfarin at INR 2.0 to 3.0, so the results may not be applicable to people with a previous arterial event related to APS and with the recurrent event despite standard anticoagulation. Although both studies, which compared high-intensity VKA with moderate-intensity anticoagulants, included people with both arterial and venous thrombosis, most participants had prior venous thrombosis (69% to 75%). Therefore, those results may not be fully applicable to people with previous arterial thrombosis.

Similarly, two studies comparing the use of anticoagulant plus antiplatelet agents versus a single antiplatelet agent or dual antiplatelet therapy included only people with previous stroke; therefore results may not be applicable to people with previous venous thromboembolism.

The proportions of participants with each type of antibody and participants positive for two or three types of antibodies differed between studies. This would seem to increase the generalizability of evidence in this review, but due to low number of studies we could not explore the influence of those factors on the effects of studied interventions.

Additional ongoing studies of NOACs compared with standard anticoagulants may add to the body of evidence and help to provide better-quality evidence on the benefits and harms of using NOACs in secondary prevention of thrombotic events in people with antiphospholipid syndrome.

Quality of the evidence

We analyzed data from five trials involving 419 participants with antiphospholipid syndrome. All five trials took place over the previous 14 years. We judged only one study to be at low risk of bias in all domains (Crowther 2003), while another was at low risk of bias in all domains for one group of outcomes (RAPS). We judged the other three studies to be at unclear risk of selection bias, performance bias, detection bias, attrition bias, and/or reporting bias, or at high risk of other bias. We did not detect important heterogeneity between the results of the studies. However, all of the analyses provided imprecise results with wide confidence intervals. We could not assess publication bias due to the low number of studies.

We judged the quality of evidence to be low to moderate for the outcomes in the comparison of NOACs versus standard anticoagulants and low for the outcomes in the comparison of high-inten-

sity and standard-intensity anticoagulants, while for all outcomes in other comparisons we considered the evidence to be very low.

Potential biases in the review process

In our comprehensive searches, supplemented by seeking additional information from experts, unpublished sources, and manufacturers, we attempted to identify all RCTs of potential relevance to the review. We did not apply any limitations to our searches, and for studies published in a language in which none of the review authors was fluent we sought help. In fact, when we compared the number of studies identified in other recent reviews, meta-analyses, or practice guidelines, our review identified more studies (published, ongoing, awaiting classification) than previous publications (Alegria 2010; Da Silva 2015; Danowski 2013; Dufrost 2016; Erkan 2014; Keeling 2012; Kim 2016; Ruiz-Irastorza 2011).
Due to very low number of studies in each comparison we did not produce funnel plots.

Agreements and disagreements with other studies or reviews

We identified three recent reviews that covered topics similar to our review.
Da Silva 2015 compared high- and moderate-intensity warfarin treatment on the basis of two studies that were also included in our review (Crowther 2003; WAPS), concluding that moderate-intensity anticoagulation is more suitable for people with antiphospholipid syndrome. However, they based their conclusion on the findings of higher rates of thrombotic events in the high-intensity group, which was probably an error as the number of events on the forest plot does not match the number of events reported by the study, and on a higher risk of minor bleeding on the basis of pooled results for both studies, while in fact Crowther 2003 did not report minor bleeding events.
Dufrost 2016 examined effects of NOACs in antiphospholipid syndrome and, in addition to RAPS (which we also identified), this review included case reports and case series. They concluded that NOACs should be used with caution in people with antiphospholipid syndrome and called for additional RCTs with clinical primary endpoints.
Kim 2016 focused on the intensity of warfarin anticoagulation in people with antiphospholipid syndrome and included several retrospective studies and two RCTs that we also included. That review concluded that more evidence is required with larger sample sizes and better adherence to treatment.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence identified in this systematic review was not sufficient to draw any conclusion on the benefit or harm of using NOAC agents versus standard VKA anticoagulation, antiplatelet plus VKA agents versus single or dual antiplatelet therapy, or dual versus single antiplatelet therapy, for the secondary prevention of recurrent thrombosis in people with antiphospholipid syndrome.

Likewise, there was insufficient evidence to draw any conclusion on the benefits of using high-intensity versus standard-intensity VKA, although there was some evidence of harm (increased risk of minor and any bleeding) associated with high-intensity VKA.

Implications for research

Future research should be adequately powered and ensure proper adherence to treatment to assess the effects of the intervention on clinically important outcomes in people with antiphospholipid syndrome (APS), enabling meaningful conclusions regarding the effects of antiplatelet and anticoagulant agents and their intensity. There is a special need to evaluate the efficacy and safety of other NOAC agents (i.e. dabigatran, apixaban, edoxaban) versus standard care for treating APS.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Crowther 2003

Methods	**Study type**: double-blinded parallel RCT **Location**: Canada, tertiary care rheumatology and thromboembolism clinics **Number of centres**: 13 **Time frame of the study**: February 1998 to May 2001 **Follow-up**: mean 2.7 years (SD not provided)
Participants	**Inclusion criteria**: people with arterial/venous thrombosis, objectively confirmed; and either a positive test for antiphospholipid antibodies on 2 occasions ≥ 3 months apart defined as lupus anticoagulant (according to the definition by the International Society on Thrombosis and Haemostasis), a moderate/high titre of IgG anticardiolipin antibody, or both **Exclusion criteria**: anticardiolipin antibodies only in IgM class; clinically significant bleeding predisposition (e.g. refractory thrombocytopenia: platelet count < 50,000/mm ^{3}); an episode of intracranial hemorrhage, stroke, or gastrointestinal bleeding within the previous 3 months; a contraindication to warfarin; a history of recurrent thrombosis during warfarin treatment with target INR ≥ 2.0; pregnancy/planned pregnancy during the study; a geographic location that would make follow-up impossible **Total number of participants**: 114 participants randomized, 114 analyzed: 56 in intervention (high intensity) group, 58 in control (moderate intensity) group **Characteristics**: Age (mean): high-intensity group: 43 years (range 20 to 80); moderate-intensity group: 41 years (range 21 to 81) Sex: high-intensity group: 27 (48%) women; moderate-intensity group: 41 (72%) women; baseline difference Systemic lupus erythematosus: 14% Previous events: history of venous thrombosis: 75%; thromboembolism within the last 6 months: 32% Cardiovascular risk factors: NR Antibodies present: lupus anticoagulant only: 43%; anticardiolipin antibodies only: 39%; lupus anticoagulant and anticardiolipin antibodies: 18%
Interventions	**Treatment groups**: • high-intensity warfarin treatment with targeted INR of 3.1 to 4.0; average follow-up 2.6 years • moderate-intensity warfarin treatment with targeted INR of 2.0 to 3.0; average follow-up 2.7 years Average INR values in high-intensity group: 3.3; in moderate-intensity group, 2.3 % of time when INR • above the target: high: 17%; moderate: 11% • within the target: high: 40%; moderate: 71% • below the target: high: 43%; moderate: 19% In the high-intensity group, INR was between 2.0 and 3.1 for 86% of time when below target **Descriptions of treatments and concomitant treatment**: 8 participants (14%) in high-

	intensity group and 6 participants (10%) in moderate-intensity group received aspirin during study
Outcomes	**Primary outcomes** • for treatment efficacy - recurrent trombosis (stroke, transient ischemic attack, myocardial infarction, peripheral arterial thrombosis, cerebral vein thrombosis, deep vein thrombosis, or pulmonary embolism) - objective diagnostic tests, confirmed by blinded adjudication • for treatment safety - bleeding (major or any) - explicit definition not provided; objective diagnostic tests, confirmed by blinded adjudication **Secondary outcomes**: not reported
Notes	**Funding**: Canadian Institutes for Health Research; warfarin used in the study was provided by DuPont Pharma Originally planned sample size was 90 participants, with minimum follow-up of 2 years. After blinded interim analysis due to lower than expected number of events, the Steering Committee extended enrolment and reduced the duration of follow-up; the last participants included to 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table: blocks of 2, 4, and 6
Allocation concealment (selection bias)	Low risk	Telephone calls to study co-ordinating centre
Blinding of participants and personnel (performance bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Low risk	Thrombosis and bleeding: double-blind; explicit statement that participants, treating physicians, other study personnel unaware of the treatment assignments
Blinding of participants and personnel (performance bias) Quality of life	Unclear risk	-
Blinding of outcome assessment (detection bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Low risk	Thrombosis and bleeding: explicit statement that adjudicators were unaware of the treatment assignment
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	-

Crowther 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Discontinuations, withdrawals and missing data: Intervention: 21/56 discontinued (11 withdrew consent; 5 suspected thrombotic events; 3 major hemorrhage; 1 pregnant; 1 thrombocytopenia); 4/56 censored Control: 13/58 discontinued (7 withdrew consent; 5 suspected thrombotic event; 1 major hemorrhage): 2/58 censored ITT: all participants included in the analysis; reasons for missing data reported, unlikely to be related to study outcomes
Selective reporting (reporting bias)	Low risk	No protocol available, but all thrombotic and bleeding outcomes pre-specified and reported as stated in Methods section of published study
Other bias	Low risk	None identified

Okuma 2010

Methods	**Study type**: double-blinded parallel RCT **Location**: Japan, Departments of Neurology of University Hospitals **Number of centres**: NR **Time frame of the study**: October 2002 to November 2004 **Follow-up**: mean 3.9 years (SD 2.0)
Participants	**Inclusion criteria**: participants with history of Ischemic stroke; antiphospholipid antibodies on 2 or more occasions $\geq$ 6 weeks apart: positive IgG beta$_2$ glycoprotein I (β_2-GPI)-dependent anticardiolipin antibody and/or lupus anticoagulant present **Exclusion criteria**: NR **Total number of participants**: 20 participants randomized, 20 analyzed: 11 in single AP group (AP), 9 in AP + VKA group **Characteristics**: Mean age: AP: 47 years; AP + VKA: 49 years Sex: 50% women Systemic lupus erythematosus: 35% Previous events: stroke: 100% Cardiovascular risk factors: hypertension 59.6%, diabetes mellitus 20.2%, atrial fibrillation 10.1%, hyperlipidemia 20.2% Antibodies present: NR
Interventions	**Treatment groups**: • single antiplatelet therapy (100 mg aspirin) • combination of antiplatelet and anticoagulant treatment (target INR 2 to 3); mean INR 2.4 (SD 0.3) **Descriptions of treatments and concomitant treatment**: no concomitant treatment

Okuma 2010 (*Continued*)

	reported
Outcomes	**Primary outcomes**: recurrent episode of stroke - no definition or method of verification provided **Secondary outcomes**: hemorrhagic complications (e.g. cerebral hemorrhage, gastrointestinal bleeding, subcutaneous hemorrhage)-no definitions or method of verification provided
Notes	**Funding**: NR No details of sample size calculations provided; several attempts to contact the authors for additional information unsuccessful

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge; the authors stated that randomization was done using "a randomly generated score"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of participants and personnel (performance bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Unclear risk	Stroke and hemorrhage: described as double-blind, but blinding unclear; no information about definition or objective outcome verification so influence of lack of blinding not clear
Blinding of participants and personnel (performance bias) Quality of life	Unclear risk	-
Blinding of outcome assessment (detection bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Unclear risk	Stroke and hemorrhage: described as double-blind, but blinding unclear; no information about definition of objective outcome verification so influence of lack of blinding not clear
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	-
Incomplete outcome data (attrition bias) All outcomes	Low risk	No discontinuations or withdrawals reported; all outcome data included
Selective reporting (reporting bias)	Unclear risk	No protocol available, primary outcomes partially reported as indicated in Methods section of published study, but the numbers

Okuma 2010 (*Continued*)

		of events not reported
Other bias	Low risk	None identified

RAPS

Methods	**Study type**: unblinded phase II/III non-inferiority RCT **Location**: UK, specialist hematology and rheumatology clinics **Number of centres**: 2 **Time frame of the study**: June 2013 to November 2014 **Follow-up**: 210 days
Participants	**Inclusion criteria**: thrombotic APS according to Sapporo criteria with positive antiphospholipid antibodies (lupus anticoagulant, IgG or IgM anticardiolipin or anti-β_2-GPI antibodies above 99th percentile) on $\geq$ 2 occasions $\geq$ 12 weeks apart; $\geq$ 1 episode of VTE during sub-therapeutic (INR < 2.0) anticoagulant treatment or no treatment; on standard-intensity warfarin (target INR 2.5) for $\geq$ 3 months since the last VTE; contraception in women (unless sterilized or postmenopausal) **Exclusion criteria**: previous arterial thrombotic events due to APS; recurrent VTE on warfarin at target INR 2 to 3; age < 18 years; pregnancy or lactation; severe renal impairment (creatinine clearance using Cockcroft and Gault formula $\leq$ 29 mL/min); alanine aminotransferase > 2 upper limit of normal; cirrhosis of Child-Pugh class B or C; thrombocytopenia (< 75 × 10^9 /L); non-adherence to warfarin regimen according to clinical judgment; receiving drugs: azole antifungals, protease inhibitors for HIV, strong CYP3A4 inducers, dronedarone; refusal to provide information to a family doctor or other health-care professional responsible for anticoagulation care about study participation **Total number of participants**: 116 participants randomized: 57 in the rivaroxaban group and 50 in the warfarin group; 110 analyzed for the primary outcome (thrombin potential endogenous); for outcomes analyzed in this review: 57 in the rivaroxaban group, 58 for efficacy, and 55 or 58 for safety in the warfarin group **Characteristics**: no baseline differences reported Mean age: rivaroxaban 47 years (SD 17); warfarin 50 years (SD 14) BMI: rivaroxaban 28 (SD 6); warfarin 30 (SD 6) INR: rivaroxaban 2.8 (95% CI 2.6 to 2.9); warfarin 2.7 (95% CI 2.5 to 3.0) Sex: 72% women Systemic lupus erythematosus: 19% Previous events: deep vein thrombosis or pulmonary embolism 100% Cardiovascular risk factors: NR Antibodies present: lupus anticoagulant only: 46%; anticardiolipin antibodies only: 3%; β_2-GPI antibodies only: 4%; more than 1 type of antibodies without triple positive: 30%; more than 1 type of antibodies including triple positive: 16%
Interventions	**Treatment groups**: • rivaroxaban • warfarin at target INR 2.5; at day 42; INR 2.7 (95% CI 2.6 to 2.9) Participants received interventions for 180 days Mean INR in warfarin group: 2.7 (95% CI 2.6 to 2.9). Mean time in therapeutic range 55% (SD 23)

RAPS (*Continued*)

	Descriptions of treatments and concomitant treatment: concomitant treatment not reported
Outcomes	**Primary outcomes** Change (percentage) in endogenous thrombin potential from randomization to day 42 of study **Secondary outcomes** Thromboembolism up to day 210 (in the protocol 180 days)-VTE only or VTE and any other thrombotic events-verification by objective diagnostic methods Percentage change up to day 42: thrombin generation curve (lag-time, time to peak, peak thrombin concentration); markers of in vivo coagulation (prothrombin fragment 1.2, thrombin-antithrombin complex, D-dimer) Serious adverse events (SAEs) to day 210 - reviewed by external independent staff Bleeding events to day 210 - blinded review of bleeding events Quality of Life (QoL) at day 180 - measured using the EQ-5D-5L questionnaire
Notes	**Funding**: Arthritis Research UK; Comprehensive Clinical Trials Unit at UCL; LUPUS UK, Bayer; National Institute for Health Research Biomedical Research Centre

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random permuted blocks of various length, stratified
Allocation concealment (selection bias)	Low risk	Central
Blinding of participants and personnel (performance bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Low risk	For thromboembolism and laboratory coagulation measures, SAE, bleeding - due to objective definition or verification of outcomes, lack of blinding will likely not influence outcomes
Blinding of participants and personnel (performance bias) Quality of life	High risk	For quality of life, lack of blinding likely introduces bias
Blinding of outcome assessment (detection bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Low risk	For thromboembolism and laboratory coagulation measures: SAE - due to objective definition/verification of outcomes lack of blinding will likely not influence outcomes Bleeding - blinded verification of outcomes
Blinding of outcome assessment (detection bias) Quality of life	High risk	For quality of life, lack of blinding likely introduces bias

RAPS (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Discontinuations, withdrawals and missing data: Intervention: 1/57 with missing data - did not attend 180-day visit, included in analyses of thrombotic and bleeding event, excluded from quality of life analyses Control: 4/59 with missing data (1 withdrew consent and no follow-up data obtained; 1 withdrew consent after day 42 but returned for 180-day visit; 1 died after day 180; 1 lost to follow-up after day 42); 1 excluded from analysis of thrombotic events; 4 excluded from analysis of bleeding events at day 210; 3 to 4 excluded from analyses of quality of life data Small amount of missing data; missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; modified ITT analysis including all randomized participants with assessable data
Selective reporting (reporting bias)	Low risk	All reported as in protocol
Other bias	Low risk	None identified

WAPS

Methods	**Study type**: unblinded parallel RCT **Location**: hematological centres in Italy, Norway, Poland, Argentina, Czech Republic, and Slovak Republic **Number of centres**: 26 **Time frame of the study**: NR **Follow-up**: median 3.6 years (IQR 2.7 to 4.5); mean high-intensity group 3.5 (SD 1.2); standard management group 3.3 (SD 1.2); mean for both groups 3.4 (SD 1.2)
Participants	**Inclusion criteria**: people with antiphospholipid syndrome diagnosed within previous 5 years (all had confirmed history of major arterial or venous thrombosis) for whom clinicians were uncertain regarding benefit/risk balance of high-dose warfarin **Exclusion criteria**: age < 18; recurrent thrombosis during anticoagulant prophylaxis in past; active bleeding or hemorrhagic disorders contraindicating oral anticoagulant therapy; pregnancy; co-morbidities precluding oral anticoagulants or any serious illness with a life expectancy < 3 years; inability to give informed consent or to attend regular follow-up visits; evident benefit of high-dose warfarin (e.g. recurrent thrombosis despite treatment with low-dose warfarin); platelets < 50 x 10^9 /L; hypothrombinemia/LA hemorrhagic syndrome; acute viral and HIV infection **Total number of participants**: 109 participants randomized, although 6 participants were not followed: 109 analyzed: 54 in high-intensity group, 55 in standard-management group

WAPS (*Continued*)

	Characteristics: Mean age: high-intensity warfarin group: 41.1 years (SD 12.1); standard-management group: 41.0 years (SD 12.3) Sex: 62% women Systemic lupus erythematosus: 13% Previous events: prior arterial thrombosis: 40%, prior venous thrombosis: 69% Cardiovascular risk factors: NR Antibodies present: lupus anticoagulant only: 26%, anticardiolipin antibodies only: 18%, lupus anticoagulant and anticardiolipin antibodies: 56% Data regarding antiphospholipid antibodies reported for 52/54 participants in the high-intensity group and 52/55 participants in the standard management group as other participants had borderline values for antibodies (information from the authors)
Interventions	**Treatment groups**: 1. high-intensity warfarin treatment with INR range 3.0 to 4.5, target 3.5 2. standard management, which included: i) warfarin at doses adjusted to an INR 2.0 to 3.0, target 2.5 (in participants with history of VTE, cardioembolic cerebral or peripheral ischemias, AF or rheumatic valve disease) (52 participants), or ii) low-dose aspirin 100 mg/d (participants with non-embolic arterial thrombosis) (3 participants) Mean INR during follow up 3.2 (SD 0.6) in high-intensity group and 2.5 (SD 0.3) in standard group **Descriptions of treatments and concomitant treatment**: 4 participants (7.4%) in the high-intensity warfarin group and 3 participants (5.5%) in standard-management group were given anticoagulation + aspirin according to the decision of treating physician
Outcomes	There was some discrepancy between the outcomes listed in the protocol and reported in the study Methods and Results **Primary outcomes**: Vascular death or major thrombosis (non-fatal major arterial and venous thrombotic events, i.e. myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, transient Ischemic attack) (not listed in the protocol, reported) Vascular death or major thrombosis or major hemorrhage (fatal, intracranial, retroperitoneal, necessary blood transfusion or surgery) (listed in the protocol and reported) **Secondary outcomes**: all-cause mortality (listed in the protocol and reported); total thrombotic events (major thrombosis and superficial thrombophlebitis) (listed in the protocol, reported); minor thrombotic events (superficial thrombophlebitis) (listed in the protocol and reported); major thrombotic events (MI, stroke, TIA, PE, DVT) (listed in the protocol and not reported as separate outcome); fatal and non-fatal cerebrovascular and cardiac events (not listed in the protocol, listed as outcome in Methods section, not reported); events contributing to primary outcomes separately (listed in the protocol and reported); fatal and non-fatal major hemorrhage (listed and reported); minor hemorrhage (listed and reported); total hemorrhage (not listed in the protocol, reported); any adverse event leading to treatment withdrawal For all outcomes clear definitions provided and all verified by objective diagnostic methods

Notes	**Funding**: NR Originally planned sample size was 500 participants per arm. Following interim analysis for safety after 3 years the trial was stopped for futility, as recruitment was poorer than expected and transmission of data from centres was delayed Additional information on study design and results obtained from Dr Finazzi

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A program based on the biased-coin algorithm
Allocation concealment (selection bias)	Low risk	Central randomization
Blinding of participants and personnel (performance bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Low risk	Thrombotic events and bleeding: no blinding, due to objective diagnostic verification or definition lack of blinding will likely not influence the outcome
Blinding of participants and personnel (performance bias) Quality of life	Unclear risk	-
Blinding of outcome assessment (detection bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Low risk	All outcomes: blinded endpoint adjudication by external committee blinded to participants' treatment assignment. Each event was validated independently by two evaluators, and disagreement between the evaluators was assessed by the chairman of the study
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	-
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Discontinuations, withdrawals and missing data: Intervention: 5/54 discontinued, but followed and included in the analyses Control: 4/55 discontinued, but followed and included in the analyses The authors reported following the ITT principle; however, according to the information from the author 6 participants were not followed; not clear from which group, the number of participants in the analysis equals the number of participants random-

WAPS (*Continued*)

		ized, not clear how the participants not followed were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol available; discrepancies between the outcomes listed in the protocol and in the study, all important outcomes reported
Other bias	High risk	Originally planned sample size was 500 patients per arm. Following interim analysis for safety after 3 years the trial was stopped for futility, as recruitment was poorer than expected and transmission of data from centres was delayed

Yamazaki 2009

Methods	**Study type**: parallel RCT **Location**: Japan **Number of centres**: 1 **Time frame of the study**: NR **Follow-up**: 3 years **Funding**: Ministry of Health, Japan
Participants	**Inclusion criteria**: people with APS and history of stroke **Exclusion criteria**: NR **Total number of participants**: 60 participants randomized, 60 analyzed: 20 in aspirin alone group; 20 in aspirin + cilostazol group; 20 in aspirin + warfarin group **Characteristics**: Age: NR Sex: NR Systemic lupus erythematosus: NR Previous events: NR Cardiovascular risk factors: NR Antibodies present: NR
Interventions	**Treatment groups**: • 100 mg/d aspirin alone group • 100 mg/d aspirin + cilostazol 100 mg twice daily • 100 mg/d aspirin + warfarin (INR 2.0 to 2.5) group **Descriptions of treatments and concomitant treatment**: NR
Outcomes	**Primary outcomes**: recurrence of stroke based on brain MRI **Secondary outcomes**: NR
Notes	All 3 groups were planned to be followed up for 3 years; however; group treated with 100 mg/d aspirin alone was discontinued after a year for "humanitarian" reasons; several attempts to contact the authors for additional information were unsuccessful

Yamazaki 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details apart from "patients were randomly treated"
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) Quality of life	Unclear risk	-
Blinding of outcome assessment (detection bias) For thromboembolism and laboratory coagulation measures, SAE, bleeding	Unclear risk	Insufficient information provided
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	-
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to judge if all outcome data reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided
Other bias	Unclear risk	Insufficient information provided

AC: anticoagulant; **AF**: atrial fibrillation; **AP**: antiplatelet; **APS**: antiphospholipid syndrome; **BMI**: body mass index; **CI**: confidence interval; **DVT**: deep vein thrombosis; **INR**: international normalized ratio; **ITT**: intention-to-treat; **LA**: lupus anticoagulant; **MI**: myocardial infarction; **MRI**: magnetic resonance imaging; **NR**: not reported; **PE**: pulmonary embolism; **RCT**: randomized controlled trial; **SAE**: serious adverse events; **SD**: standard deviation; **TIA**: transient ischemic attack; **VKA**: vitamin K antagonists; **VTE**: venous thromboembolism.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cuadrado 2009	Wrong patient population - mixed population - all with antibodies, most patients not fulfilling APS criteria (66%) , 34% meeting obstetric APS criteria, no separate results for those 2 groups

APS: antiphospholipid syndrome.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kondratyeva 2010

Methods	**Study type**: open parallel RCT; no blinding **Location**: Russia, specialist centre **Number of centres**: 1 **Time frame of the study**: 2003 to June 2008 **Follow-up**: in warfarin group follow-up information provided for randomized and non-randomized participants together (51.6 months), in combined treatment group 58.4 months
Participants	**Inclusion criteria**: people with diagnosis of APS **Exclusion criteria**: severe renal or hepatic insufficiency, severe bleeding in the last 3 months, planning pregnancy in the next year **Total number of participants**: 72 randomized and analyzed: 39 into warfarin group and 33 into aspirin and warfarin group **Characteristics**: in combined group (not provided for all randomized participants (characteristics provided for 1 of the groups for combined participants randomized and not randomized): Mean age: 40.5 years (SD 11.9) Women: 76% Systemic lupus erythematosus: 51.5% Previous events: VTE 78.8%; arterial thrombosis 54.5%
Interventions	**Treatment groups**: • warfarin dose not specified • warfarin and aspirin with doses not specified **Descriptions of treatments and concomitant treatment**: NR
Outcomes	**Outcomes**: recurrence of thrombosis,TIA, hemorrhage major and minor; instrumental verification for thrombotic events reported, but not clear what was meant by that
Notes	**Funding**: NR The study included additional cohort of participants who were not randomized but received 1 of the treatments, and results in the publication were provided for randomized and non-randomized participants together. However, we were able to obtain additional information from a study author regarding the results for the randomized participants only In the final publication, no information on APS criteria used for diagnosis; in the interim publication most included participants met the 1999 criteria for APS, other participants had suspected APS, 11 participants were excluded from

	the study, but not clear if before or after randomization

Okuma 2014

Methods	**Study type**: not clear, information that the study examined prevalence of antiphospholipid antibodies in people 1 month after stroke and that participants were randomly assigned to 2 groups, possible that it is an RCT **Location**: Japan **Number of centres**: 1 **Time frame of the study**: NR **Follow-up**: NR
Participants	**Inclusion criteria**: antiphospholipid antibodies; history of ischemic stroke **Exclusion criteria**: NR **Total number of participants**: 250 participants **Characteristics**: NR
Interventions	**Treatment groups**: • single antiplatelet therapy • combination of antiplatelet and anticoagulation therapy **Descriptions of treatments and concomitant treatment**: NR
Outcomes	**Primary outcome**: recurrence of stroke **Secondary outcomes**: incidences of: anti-s2-glycoprotein I (anti-s2-GPI) antibodies, IgG anticardiolipin (IgG aCL) , lupus anticoagulant, phosphatidylserine dependent anti-prothrombin antibody (PS-PT), antiphosphatidyl serine antibody (PS), and antiphosphatidyl inositol antibody (PI)
Notes	**Funding**: NR Trying to contact the study authors regarding details of the study methods and results

Yamazaki 2007

Methods	**Study type**: RCT **Location**: Japan **Number of centres**: 1 **Time frame of the study**: NR **Follow-up**: NR
Participants	**Inclusion criteria**: APS; cerebral infarction in history **Exclusion criteria**: NR **Total number of participants**: 30 participants randomized, 30 analyzed: 10 in low-dose aspirin alone group; 10 in aspirin + cilostazol group; 10 in aspirin + warfarin group **Characteristics**: NR
Interventions	**Treatment groups**: • low dose aspirin alone group • aspirin + cilostazol group • (aspirin + warfarin group **Descriptions of treatments and concomitant treatment**: concomitant treatment not reported

Yamazaki 2007 (*Continued*)

Outcomes	**Primary outcome**: change in plasma derived microparticle levels **Secondary outcomes**: worsening of lacunar infarctions in MRI
Notes	**Funding**: NR Possible that it is the same study as Yamazaki 2009, but waiting for confirmation from the study authors

APS: antiphospholipid syndrome; **MRI**: magnetic resonance imaging; **NR**: not reported; **RCT**: randomized controlled trial; **SD**: standard deviation; **TIA**: transient ischemic attack; **VTE**: venous thromboembolism.

Characteristics of ongoing studies *[ordered by study ID]*

2010-019764-36

Trial name or title	Rivaroxaban versus acenocumarol en la profilaxis secundaria del sindrome antifosfolipido: un estudio multicentrico, prospectivo y randomizado
Methods	**Study type**: open-label, non-inferiority, parallel RCT **Location**: Spain **Number of centres**: NR **Time frame of the study**: NR **Follow-up**: NR
Participants	**Inclusion criteria**: age 18-64 years; diagnosed with definite APS according to Sydney criteria; an episode of venous of arterial thrombosis; obtaining informed consent; (ability to adhere to the study visits scheme and to the requirements of the study; women who are not pregnant and are not willing to get pregnant during the study **Exclusion criteria**: refuse to give consent to study; age < 18 years; women of childbearing potential who do not use contraception, pregnant or lactating or those who plan to become pregnant during the study; a history of hypersensitivity to any of drugs used in the study; cerebral or GI bleeding within 6 months prior to the study; neurosurgery within 4 weeks prior to inclusion or other surgery in the last 10 days; active peptic ulcer; PLT < 30 x 10^9 /L; ALT or AST 120 UI/mL (> 3 x ULN); active malignancy (excluding CIN or dermatological neoplasia); GFR < 30 mL/min or symptoms of kidney disease; any condition that could cause interruption in the study; severe uncontrolled arterial hypertension (180/110 mmHg) or systolic BP > 180 mmHg, or diastolic BP > 110 mmHg; less than 6 months since last thrombotic event; active bleeding or increased risk of bleeding that contraindicates treatment with LMWH or VKA; the presence of any other contraindication to study drugs and warfarin; using NSAIDs with half-life of 17 hours, or CYP3A4 inhibitors or CYP3A4 inducers; HIV/HBV/HCV infection; Child-Pugh B liver disease with coagulopathy or Child-Pugh C **Total number of participants**: planned sample size 218 participants
Interventions	**Treatment groups**: • rivaroxaban 10 mg • acenocoumarol 4 mg, dose adjusted to INR 2.0 to 3.0 or 2.5 to 3.5 in participants with recurrent thromboembolic events despite anticoagulation treatment **Descriptions of treatments and concomitant treatment**: concomitant treatment not reported

2010-019764-36 (*Continued*)

Outcomes	**Primary outcomes**: efficacy outcome: thrombotic ischemic vascular event during study period; deep vein thrombosis, pulmonary thromboembolism, acute myocardial infarction, other vascular event confirmed objectively **Safety outcome**: major bleeding during study period **Secondary outcomes**: drug side effects, minor bleeding, any cause mortality, immunological parameters
Starting date	-
Contact information	Josep Ordi-Ros
Notes	**Funding**: NR EudraCT 2010-019764-36

ASTRO-APS

Trial name or title	Apixaban for the secondary prevention of thrombosis among patients with antiphospholipid syndrome: study rationale and design (ASTRO-APS)
Methods	**Study type**: phase 4 prospective, randomized, open-label blinded event pilot study **Location**: USA **Number of centres**: NR **Time frame of the study**: February 2015 to December 2019 **Follow-up**: 13 months
Participants	**Inclusion criteria**: age ≥ 18 years; a clinical diagnosis of the APS and receiving anticoagulation (warfarin with target INR 2.5, 3.0 or 3.5 or another anticoagulant and willing to be randomized to study interventions); at least 6 months of anticoagulation for the indication of thrombosis completed, no acute neurologic symptoms associated with thrombosis, CVA, or TIA for a minimum of 6 months; consent to contact the participant's anticoagulation provider for the information on INRs, dosing and any adverse events; negative pregnancy test within 24 hours prior to the start of study drug; no breastfeeding; women of childbearing potential - contraception for the duration of treatment; males who are sexually active with women of childbearing potential must agree to follow instructions for method(s) of contraception for treatment and a total of 93 days post-treatment completion (azoospermic males and women of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements. Pregnancy test still needed); agreement to undergo brain MRI **Exclusion criteria**: another indication for long-term anticoagulation not approved by FDA for apixaban; a life expectancy of less than 1 year; not able to attend follow-up appointments; participating in another trial within the last 30 days or in a conflicting clinical trial; concomitant dual antiplatelet therapy; taking aspirin of dose > 165 mg/d; hemoglobin < 8 mg/dL; PLT < 50,000/mL; serum creatinine level of > 2.5 mg/dL (221 μmol/L) or CrCl < 25 mL/min; ALT or AST > 2 times the upper limit of the normal range; total bilirubin more than 1.5 x ULN; active cancer and treatment for it within the last 3 months; receiving a CYP3A4 inhibitor and P-gp inhibitor; receiving a CYP3A4 and P-gp inducer; intend to become pregnant or breast feed within the next year; allergy to apixaban, rivaroxaban, or edoxaban; history of thrombosis while receiving warfarin at a target INR of 2 to 3 and assigned a higher target INR by the treating clinician; active pathological bleeding; a history of arterial thromboembolism; requires clopidogrel, ticagrelor, prasugrel, or another P2Y12 inhibitor; a history of catastrophic APS (CAPS); radiographic evidence of prior arterial thrombosis on MRI **Total number of participants**: estimated 200 participants

ASTRO-APS (*Continued*)

Interventions	**Treatment groups**: • apixaban 2.5 mg, twice daily • warfarin at target INR of ≥ 2.0 as prescribed before study **Descriptions of treatments and concomitant treatment**: concomitant treatment not reported
Outcomes	**Primary outcomes**: rate of thrombosis (arterial and/or venous) and vascular death, major bleeding and clinically relevant non-major bleeding **Secondary outcomes**: rate of the net clinical benefit outcome of thrombosis and bleeding, patient accrual regarding definite APS criteria; patient satisfaction using Anti-Clot Treatment Scale
Starting date	February 2015
Contact information	Scott Woller Intermountain Medical Center University of Utah School of Medicine, Eccles Outpatient Care Center 5169S Cottonwood St Suite #307, Murray, UT 84107, USA. Email: scott.woller@imail.org
Notes	**Funding**: grant paid to the Intermountain Medical Center, Murray UT, by Bristol-Meyers-Squibb NCT02295475

JASPRES

Trial name or title	Japan antiphospholipid syndrome-stroke prevention study
Methods	**Study type**: open-label, parallel RCT, phase 4 **Location**: Japan **Number of centres**: NR **Time frame of the study**: 2006 to 2009 **Follow-up**: 2 years
Participants	**Inclusion criteria**: age ≥ 20 years;APS diagnosed according to Sapporo criteria; cerebral infarct in history **Exclusion criteria**: pregnant women or planned pregnancy; patients with contradictions to warfarin or antiplatelet drugs; patients required to take warfarin; severe hepatic, renal or cardiac failure **Total number of participants**: planned sample size 100 participants
Interventions	**Treatment groups**: • warfarin aimed at INR 2.0 for 2 years • cilostazol 200 mg/d for 2 years or ticlopidine 100 to 200 mg/d for 2 years **Descriptions of treatments and concomitant treatment**: NR
Outcomes	**Primary outcome**: Cerebral Infarct Score in MRI **Secondary outcomes**: NR
Starting date	1 January 2006

JASPRES (*Continued*)

Contact information	Tatsuya Atsumi, Hokkaido University Hospital Medicine II; N14 W5, Kita-ku, Sapporo; 011-706-5915; at3tat@med.hokudai.ac.jp
Notes	**Funding**: Health and Labour Sciences Research Grants C000000342

NCT02926170

Trial name or title	Rivaroxaban versus acenocumarol for secondary thromboprophylaxis in patients with antiphospholipid syndrome: a randomized, prospective, phase III study Analysis of stratification prognostic factors
Methods	**Study type**: open-label, parallel non-inferiority RCT, phase 3 **Location**: NR **Number of centres**: NR **Time frame of the study**: March 2013 to February 2018 **Follow-up**: 36 months
Participants	**Inclusion criteria**: diagnosed thrombotic APS; previous treatment with acenocoumarol for a minimum period of 6 months; positivity for lupus anticoagulant and/or anti-cardiolipin or anti-β_2GPI antibodies IgG or IgM $\geq$ 40 **Exclusion criteria**: major hemorrhage (cerebral or gastrointestinal) within the previous 6 months; neurosurgery within the previous 4 weeks; any surgery within the previous 10 days; active peptic ulcus; ALT or GPT > 120 UI/mL non-lupus related in the previous 30 days; platelets < 30 x 10^9 in the previous 30 days; recently diagnosed malignancy; any criteria listed in the summary of the product characteristics (SPC); renal disease with a creatinine clearance < 30 mL/min or with a known uncontrolled renal disease; concomitant administration of drugs that could interfere with CYP3A4 **Total number of patients**: 190 participants randomized 1:1
Interventions	**Treatment groups**: • rivaroxaban (20 mg/d; participants with creatine clearance 30-49 L/min will receive 15 mg/d) • acenocoumarol aimed at INR 2.0 to 3.0 or 2.5 to 3.5 in those with recurrent thrombotic episodes **Descriptions of treatments and concomitant treatment**: concomitant treatment not reported
Outcomes	**Primary outcomes**: a new thrombotic event (arterial or venous), confirmed by appropriate imaging studies; major bleeding **Secondary outcomes**: incidence of treatment-emergent adverse events: all adverse events; serious adverse events (SAE); all bleeding events; overall causes of death; death due to thrombotic events: time to the first thrombotic event; type of thrombotic events (arterial or venous); evaluation of a prognostic biomarker panel: measurement of D-dimer, P-selectine and Von-Willebrand factor
Starting date	March 2013
Contact information	Josefina Cortes, MD, PhD, Vall d'Hebron Research Institute
Notes	**Funding**: NR NCT02926170

TRAPS

Trial name or title	Trial on rivaroxaban in antiphospholipid syndrome (TRAPS) trial
Methods	**Study type**: non-inferiority, phase 3, parallel, open-label RCT **Location**: Italy **Number of centres**: approximately 40 **Time frame of the study**: December 2014 to December 2018 **Follow-up**: up to 4 years
Participants	**Inclusion criteria**: signed consent form; age 18-75 years; positive for 3 types of antiphospholipid antibodies; history of thrombosis with or without pregnancy morbidity (Miyaki criteria) **Exclusion criteria**: rivaroxaban-related severe hyperreactivity; creatinine clearance < 30 mL/min; current pregnancy or breastfeeding; concomitant treatment with other anticoagulants; taking p-glycoprotein and CYP3A4 inhibitors; procedure or conditions associated with hemorrhage: major surgical procedure/trauma up to 30 days before the study; clinically significant GI bleeding within 6 months before randomization; history of intracranial, intraocular, spinal or atraumatic intra-articular bleeding; chronic hemorrhagic disorder; intracranial neoplasm, arteriovenous malformation or aneurysm; scheduled invasive procedure with possibility of uncontrolled bleeding; systolic blood pressure 180 mmHg or higher; liver cirrhosis or ALT > 3 upper normal value **Total number of participants**: planned sample size 536 participants
Interventions	**Treatment groups**: • rivaroxaban 20 mg daily, or 15 mg daily if CrCl = 30-50 mL/min • warfarin at target INR 2.0 to 3.0 **Descriptions of treatments and concomitant treatment**: concomitant treatment excludes from the study
Outcomes	**Primary outcome**: acute thrombosis, major bleeding or death; **Secondary outcome**: (efficacy) single type of thromboembolic event, all-cause mortality; (safety) major/minor bleeding
Starting date	December 2014
Contact information	Vittorio Pengo Clinical Cardiology, Thrombosis Centre, University of Padova School of Medicine Via Giustiniani 2 35128 Padua, Italy Email: vittorio.pengo@unipd.it
Notes	**Funding**: none NCT02157272

ALT: alanine aminotransferase; **AST**: aspartate aminotransferase; **APS**: antiphospholipid syndrome; **BP**: blood pressure; **CIN**: cervical intra-epithelial neoplasia; **CrCl**: creatine clearance; **CVA**: cerebrovascular accident; **FDA**: Food and Drug Administration; **GFR**: glomerular filtration rate;**GI**: gastrointestinal; **HBV/HCV**: hepatitis B/C virus; **GPT**: glutamic-pyruvic acid transaminase; **INR**: international normalized ratio;**LMWH**: low-molecular-weight heparin;**MRI**: magnetic resonance imaging;**NR**: not reported; **NSAIDS**: non-steroidal anti-inflammatory drugs; **PLT**: platelet; **RCT**: randomized controlled trial; **TIA**: transient ischemic attack; **ULN**: upper limit of normal; **VKA**: vitamin K antagonists.

DATA AND ANALYSES

Comparison 1. Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any thromboembolic event at the longest follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 NOAC	1	115	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.79, 6.23]
2 Any thromboembolic event at the longest follow-up	2		Hazard Ratio (Random, 95% CI)	2.17 [0.74, 6.31]
2.1 Warfarin high-dose	2		Hazard Ratio (Random, 95% CI)	2.17 [0.74, 6.31]
3 Major bleeding at the longest follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 NOAC	1	115	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.24, 2.25]
4 Major bleeding at the longest follow-up	2		Hazard Ratio (Random, 95% CI)	0.83 [0.25, 2.72]
4.1 High-dose warfarin	2		Hazard Ratio (Random, 95% CI)	0.83 [0.25, 2.72]
5 Mortality (any cause) at the longest follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 NOAC	1	115	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.15]
5.2 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.27, 8.79]
6 Stroke at the longest follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 NOAC	1	115	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.26, 7.12]
7 TIA at the longest follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 NOAC	1	115	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.19, 21.81]
8 VTE at the longest follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 NOAC	1	115	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	4.44 [0.77, 25.72]
9 Myocardial infarction at the longest follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 NOAC	1	115	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.07, 16.16]
10 Other thrombotic events at the longest follow-up	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 NOAC (microvascular thrombosis)	1	115	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 High-dose warfarin (superficial thrombophlebitis)	1	109	Risk Ratio (M-H, Random, 95% CI)	3.05 [0.13, 73.37]
11 Quality of life at day 180	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Health utility	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Health state	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Clinically relevant non-major bleeding at 210 days	1	112	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.25, 8.33]
12.1 NOAC	1	112	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.25, 8.33]

13 Minor bleeding at the longest follow-up	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 NOAC	1	112	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.51, 2.83]
13.2 High-dose warfarin	1	109	Risk Ratio (M-H, Random, 95% CI)	2.55 [1.07, 6.07]
14 Any bleeding at the longest follow-up	2	223	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.93, 2.62]
14.1 High-dose warfarin	2	223	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.93, 2.62]
15 Any bleeding at the longest follow-up	2		Hazard Ratio (Random, 95% CI)	2.03 [1.12, 3.68]
15.1 High-dose warfarin	2		Hazard Ratio (Random, 95% CI)	2.03 [1.12, 3.68]

Comparison 2. VKA plus antiplatelet agent vs single antiplatelet agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke at 1-year follow-up	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.60]
2 Bleeding outcomes at a mean of 3.9 years	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.18, 7.95]
2.1 Major bleeding (minor cerebral hemorrhage)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.02, 8.78]
2.2 GI bleeding (no definition)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Minor bleeding (subcutaneous hemorrhage)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.60 [0.16, 79.01]

Comparison 3. VKA plus antiplatelet agent vs dual antiplatelet therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke at 3 years	1	40	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 98.00]

Comparison 4. Dual antiplatelet therapy vs single antiplatelet agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke at 1 year	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.60]

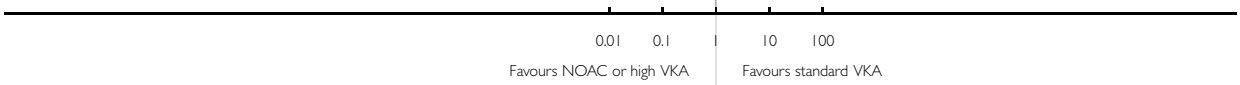
Analysis 1.1. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 1 Any thromboembolic event at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 1 Any thromboembolic event at the longest follow-up

Study or subgroup	NOAC or VKA high dose n/N	standard VKA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 NOAC					
RAPS	0/57	0/58			Not estimable
Subtotal (95% CI)	**57**	**58**			**Not estimable**
Total events: 0 (NOAC or VKA high dose), 0 (standard VKA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-dose warfarin					
Crowther 2003	6/56	2/58		44.0 %	3.11 [0.65, 14.75]
WAPS	5/54	3/55		56.0 %	1.70 [0.43, 6.76]
Subtotal (95% CI)	**110**	**113**		**100.0 %**	**2.22 [0.79, 6.23]**
Total events: 11 (NOAC or VKA high dose), 5 (standard VKA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.33$, df = 1 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.51 (P = 0.13)					
Test for subgroup differences: Not applicable					

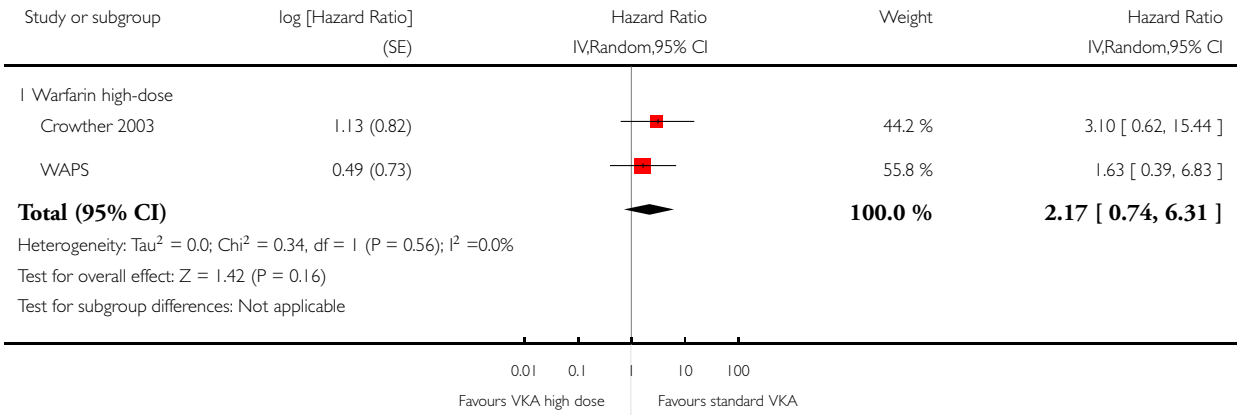


Analysis 1.2. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 2 Any thromboembolic event at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 2 Any thromboembolic event at the longest follow-up



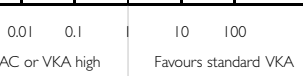
Analysis 1.3. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 3 Major bleeding at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 3 Major bleeding at the longest follow-up

Study or subgroup	NOAC or VKA high dose n/N	standard VKA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 NOAC					
RAPS	0/57	0/58			Not estimable
Subtotal (95% CI)	**57**	**58**			**Not estimable**
Total events: 0 (NOAC or VKA high dose), 0 (standard VKA)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-dose warfarin					
Crowther 2003	3/56	4/58		59.2 %	0.78 [0.18, 3.32]
WAPS	2/54	3/55		40.8 %	0.68 [0.12, 3.90]
Subtotal (95% CI)	**110**	**113**		**100.0 %**	**0.74 [0.24, 2.25]**
Total events: 5 (NOAC or VKA high dose), 7 (standard VKA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.54 (P = 0.59)					
Test for subgroup differences: Not applicable					

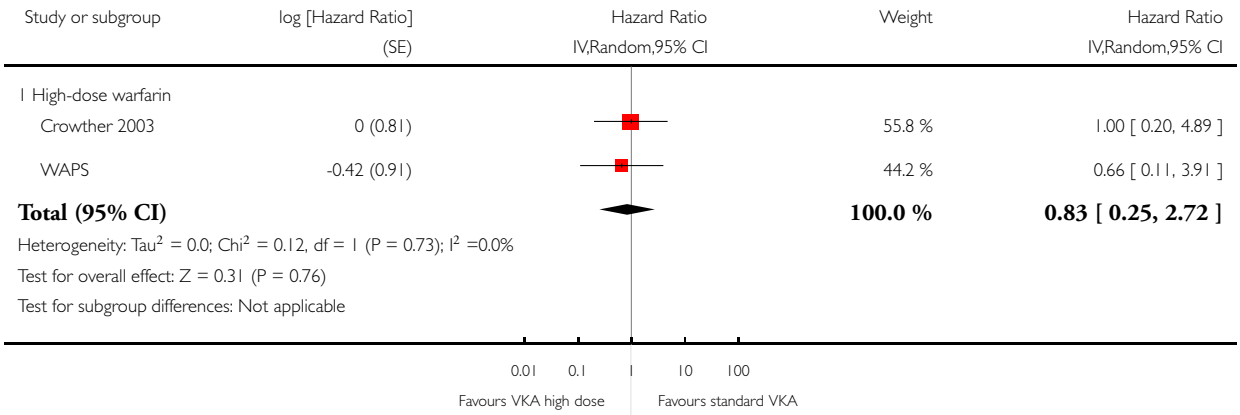


Analysis 1.4. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 4 Major bleeding at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 4 Major bleeding at the longest follow-up

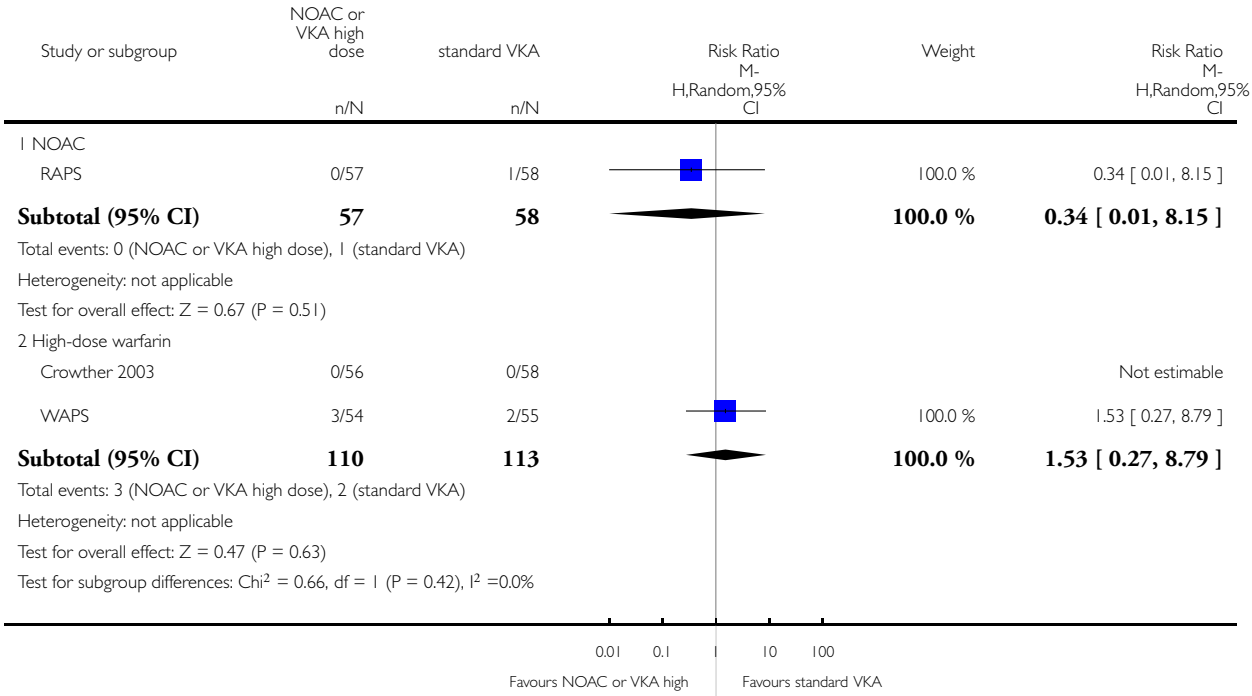


Analysis 1.5. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 5 Mortality (any cause) at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 5 Mortality (any cause) at the longest follow-up

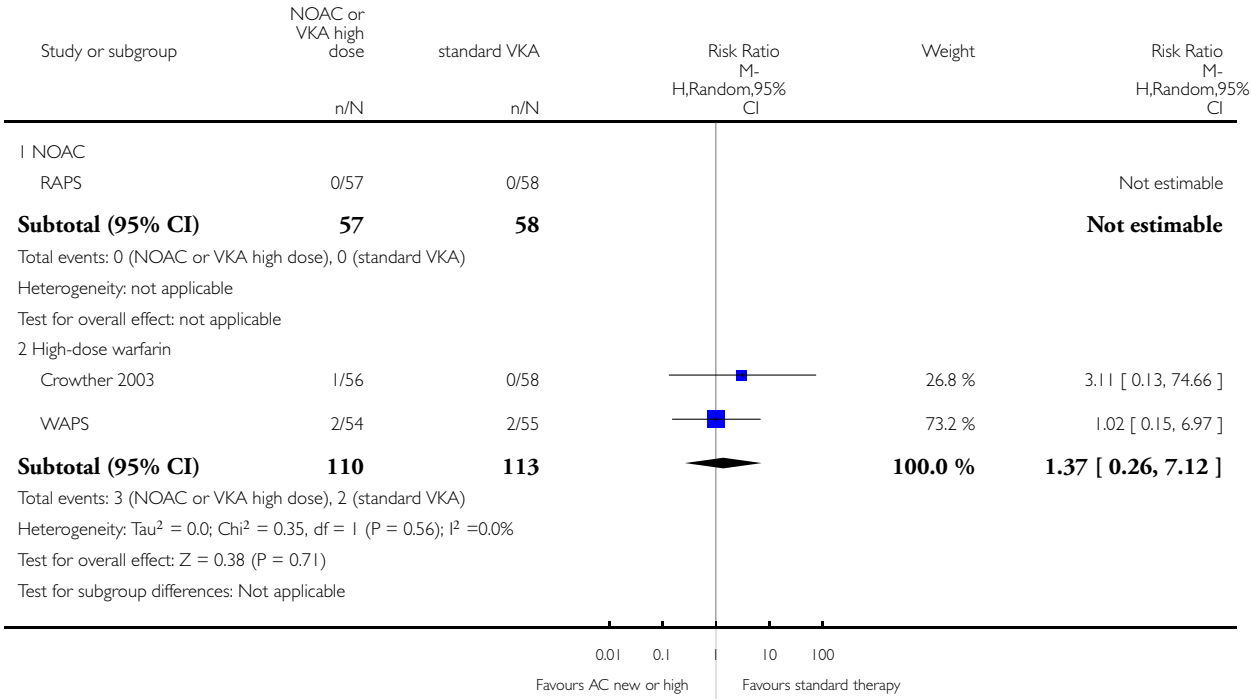


Analysis 1.6. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 6 Stroke at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 6 Stroke at the longest follow-up

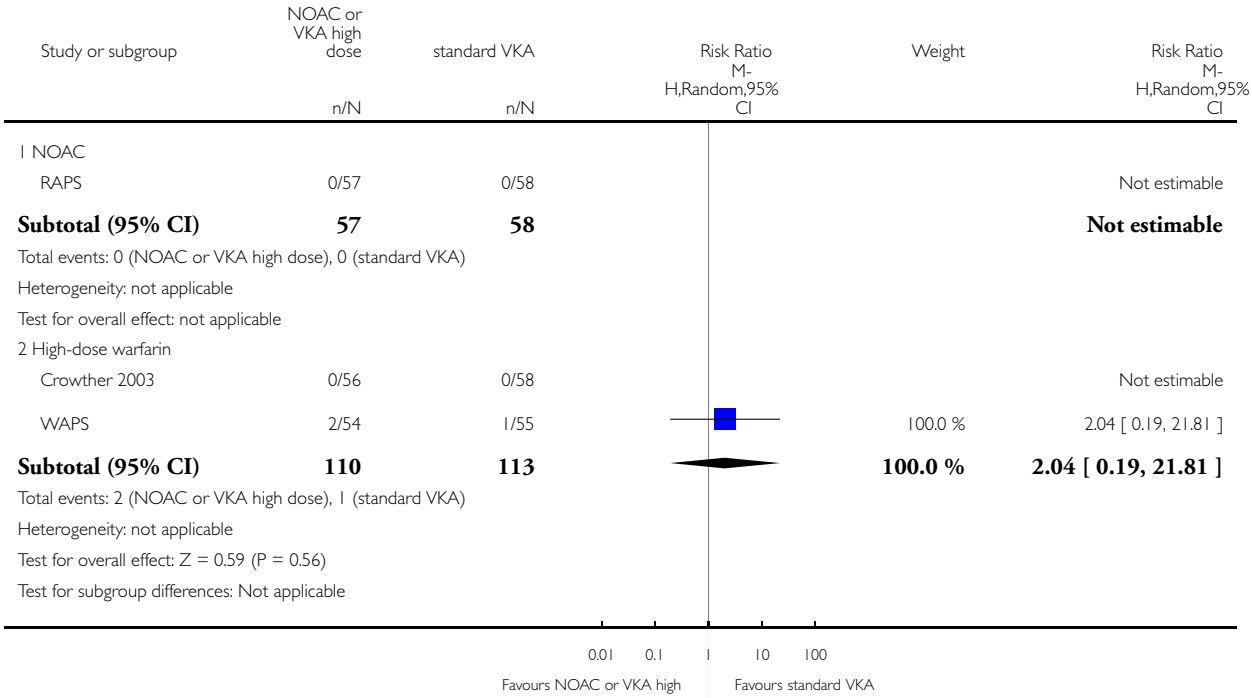


Analysis 1.7. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 7 TIA at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 7 TIA at the longest follow-up

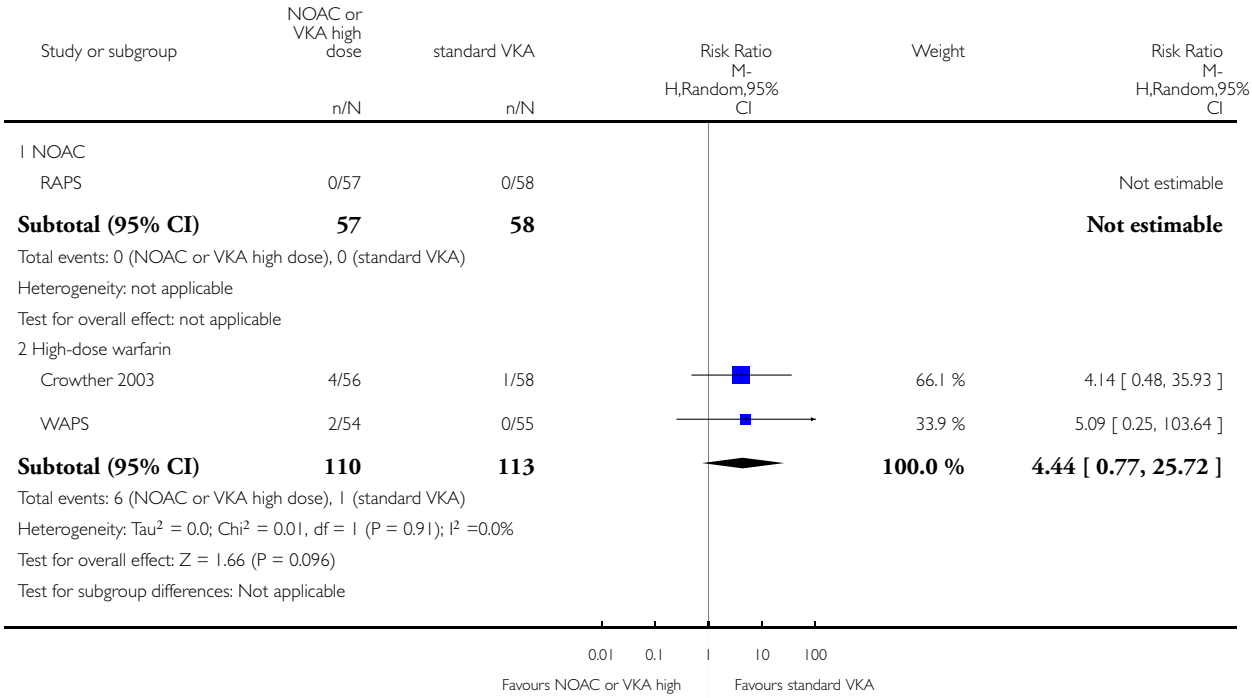


Analysis 1.8. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 8 VTE at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 8 VTE at the longest follow-up

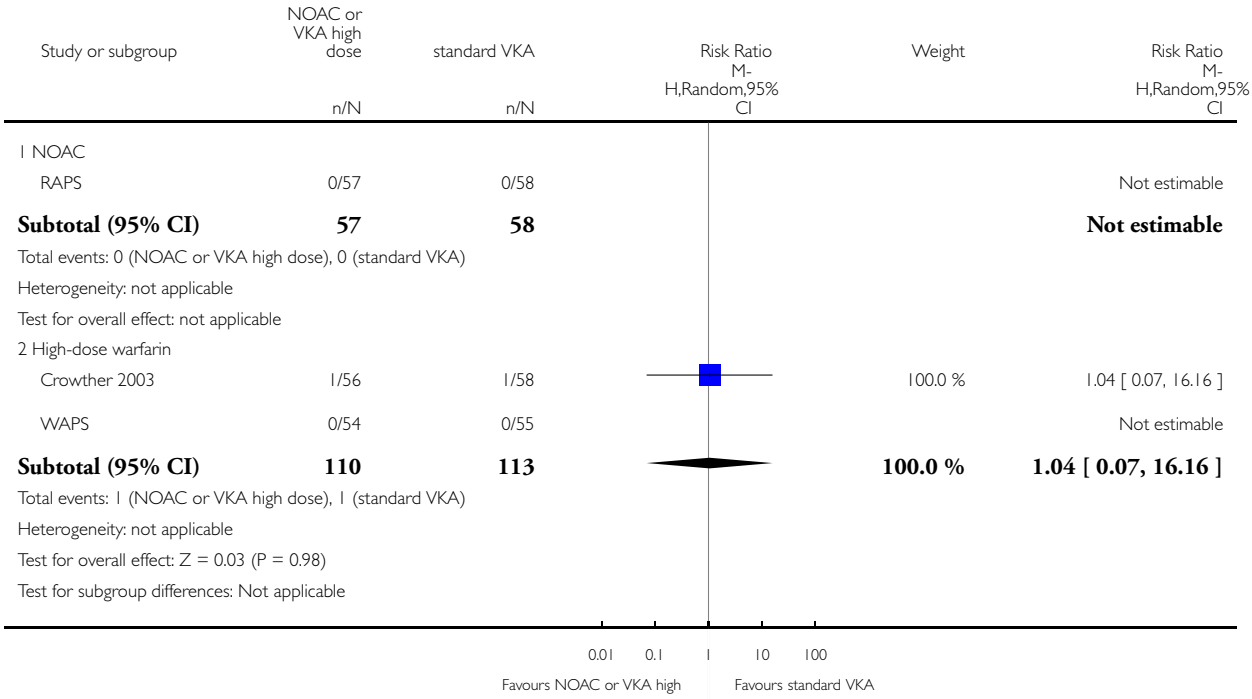


Analysis 1.9. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 9 Myocardial infarction at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 9 Myocardial infarction at the longest follow-up

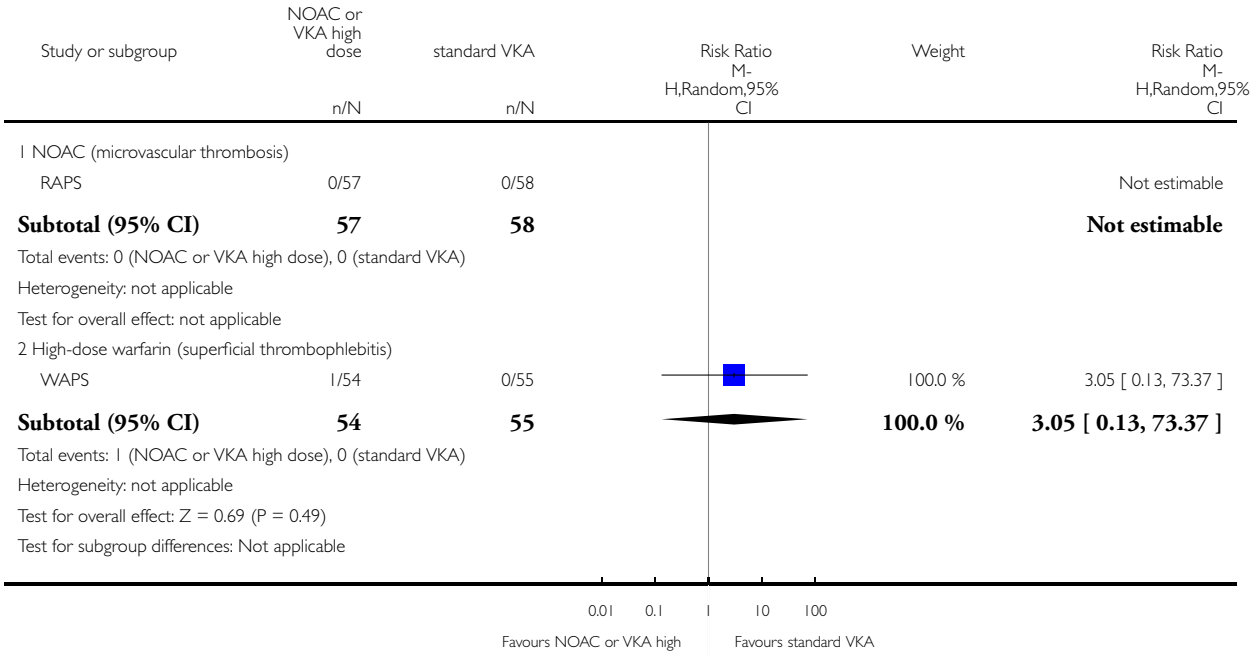


Analysis 1.10. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 10 Other thrombotic events at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 10 Other thrombotic events at the longest follow-up



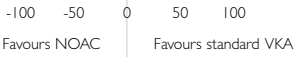
Analysis 1.11. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 11 Quality of life at day 180.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 11 Quality of life at day 180

Study or subgroup	NOAC N	Mean(SD)	standard VKA N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Health utility						
RAPS	56	0.82 (0.15)	55	0.78 (0.15)		0.04 [-0.02, 0.10]
2 Health state						
RAPS	56	80 (13.47)	56	73 (13.47)		7.00 [2.01, 11.99]



Analysis 1.12. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 12 Clinically relevant non-major bleeding at 210 days.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 12 Clinically relevant non-major bleeding at 210 days

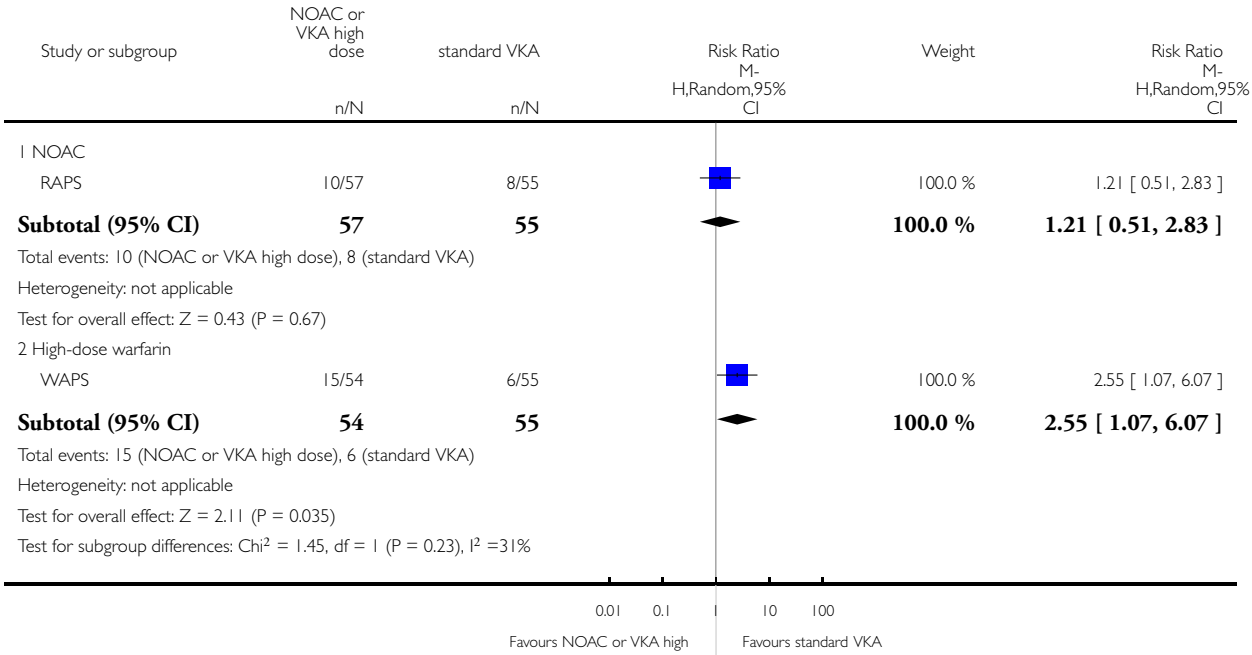
Study or subgroup	NOAC n/N	standard VKA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 NOAC					
RAPS	3/57	2/55		100.0 %	1.45 [0.25, 8.33]
Total (95% CI)	**57**	**55**		**100.0 %**	**1.45 [0.25, 8.33]**
Total events: 3 (NOAC), 2 (standard VKA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.41 (P = 0.68)					
Test for subgroup differences: Not applicable					

Analysis 1.13. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 13 Minor bleeding at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 13 Minor bleeding at the longest follow-up

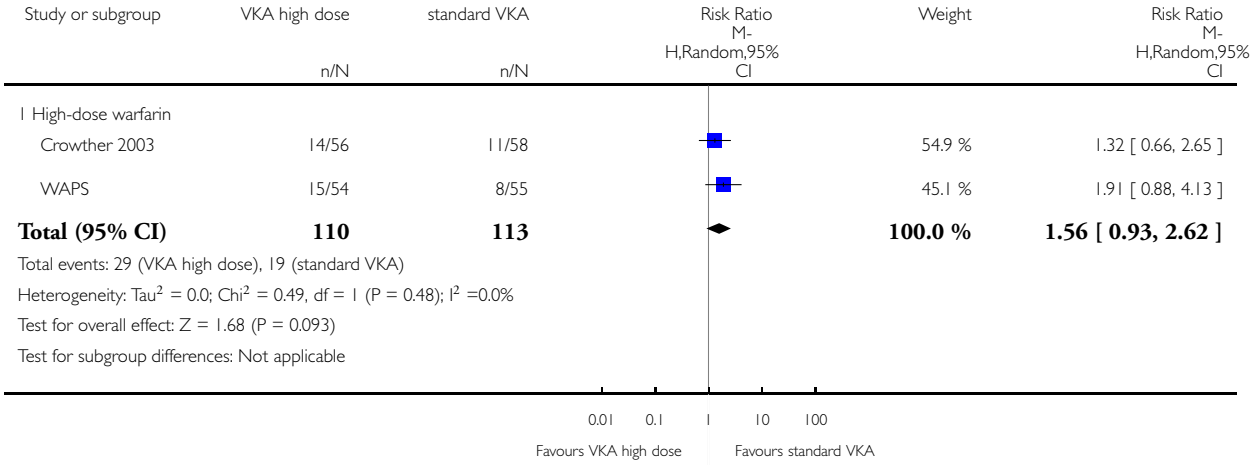


Analysis 1.14. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 14 Any bleeding at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 14 Any bleeding at the longest follow-up

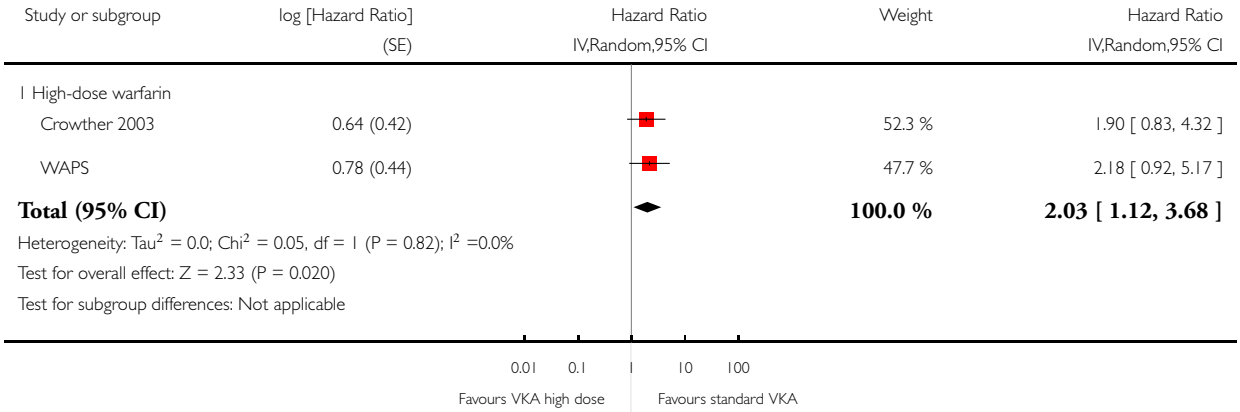


Analysis 1.15. Comparison 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy, Outcome 15 Any bleeding at the longest follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 1 Anticoagulant drugs (NOAC) or high-dose VKA vs standard VKA therapy

Outcome: 15 Any bleeding at the longest follow-up

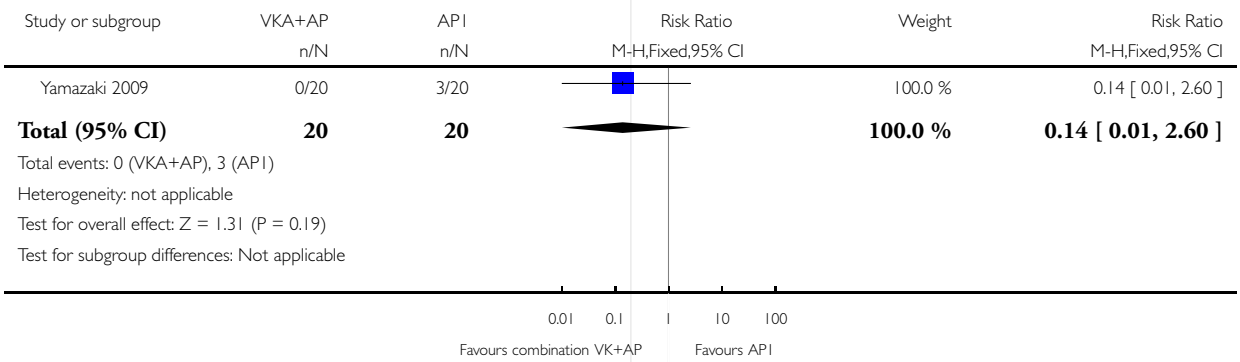


Analysis 2.1. Comparison 2 VKA plus antiplatelet agent vs single antiplatelet agent, Outcome 1 Stroke at 1-year follow-up.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 2 VKA plus antiplatelet agent vs single antiplatelet agent

Outcome: 1 Stroke at 1-year follow-up

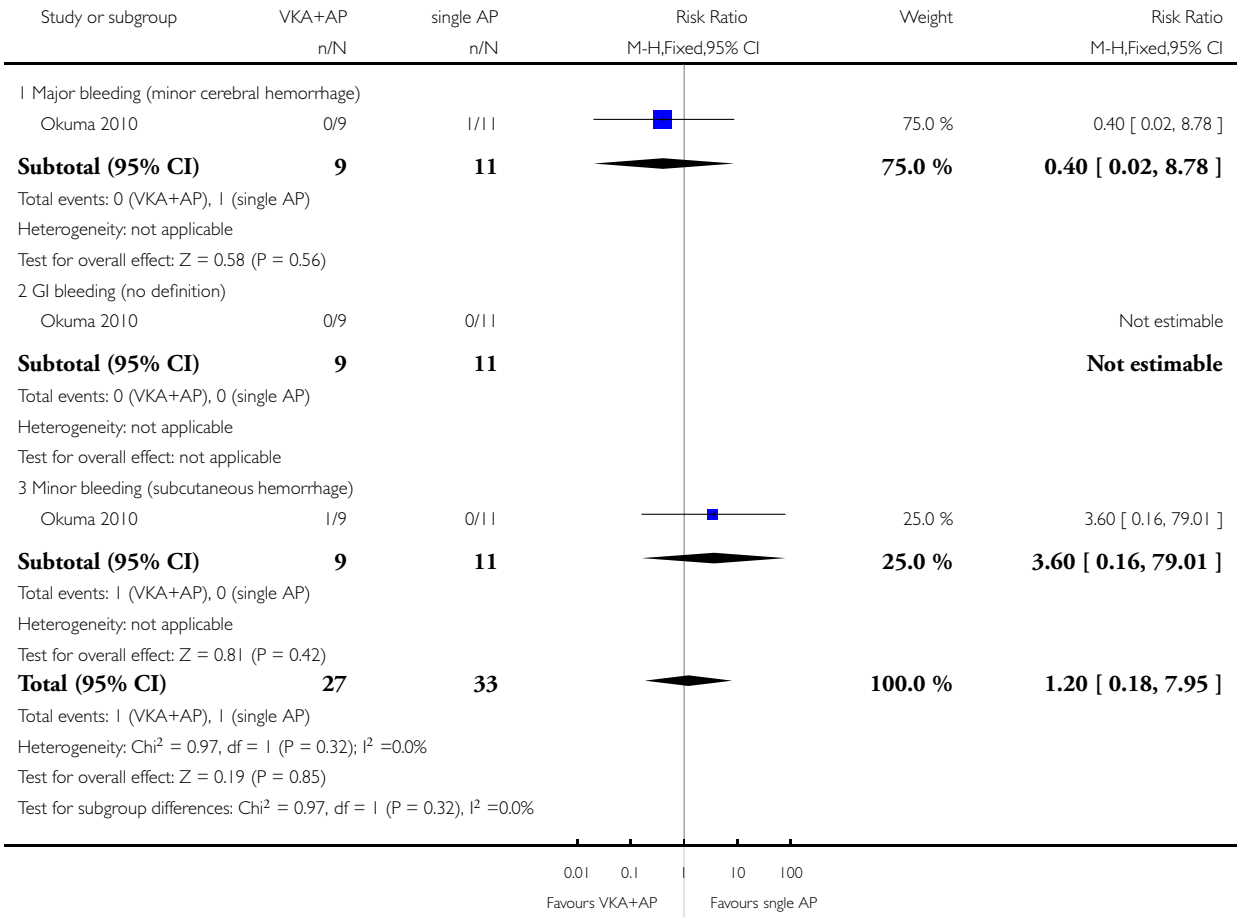


Analysis 2.2. Comparison 2 VKA plus antiplatelet agent vs single antiplatelet agent, Outcome 2 Bleeding outcomes at a mean of 3.9 years.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 2 VKA plus antiplatelet agent vs single antiplatelet agent

Outcome: 2 Bleeding outcomes at a mean of 3.9 years

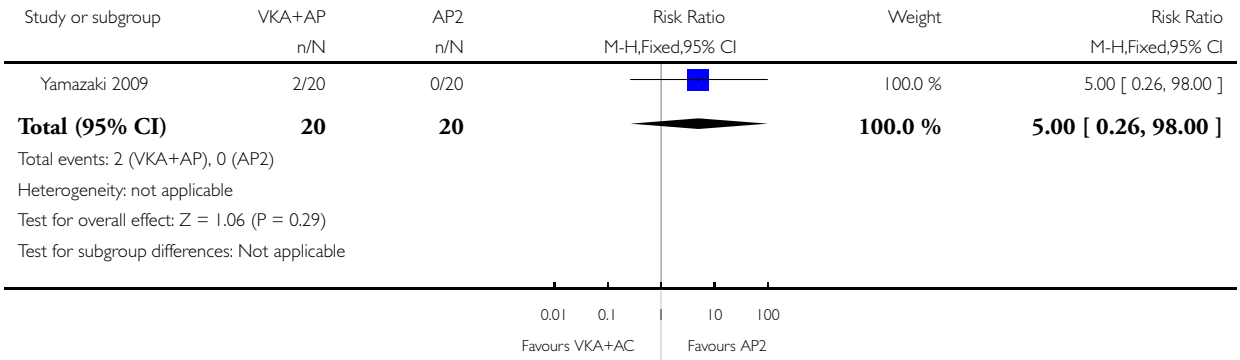


Analysis 3.1. Comparison 3 VKA plus antiplatelet agent vs dual antiplatelet therapy, Outcome 1 Stroke at 3 years.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 3 VKA plus antiplatelet agent vs dual antiplatelet therapy

Outcome: 1 Stroke at 3 years

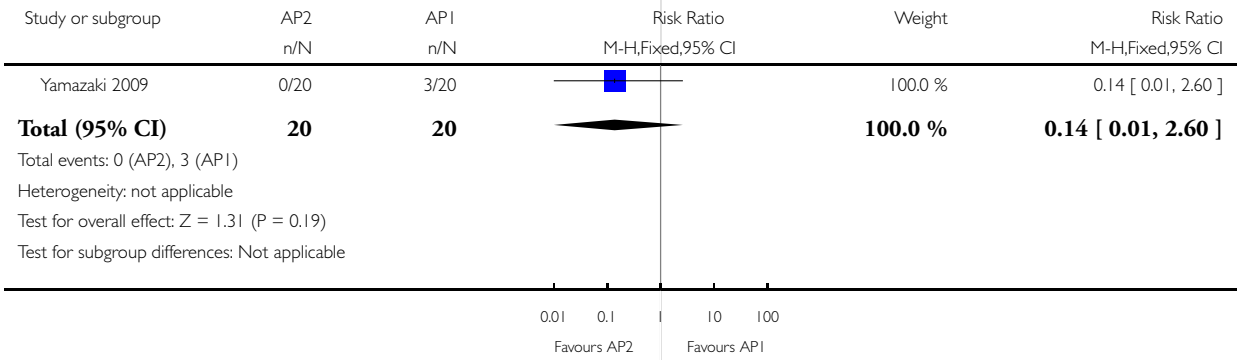


Analysis 4.1. Comparison 4 Dual antiplatelet therapy vs single antiplatelet agent, Outcome 1 Stroke at 1 year.

Review: Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome

Comparison: 4 Dual antiplatelet therapy vs single antiplatelet agent

Outcome: 1 Stroke at 1 year



ADDITIONAL TABLES

Table 1. Sensitivity analysis missing data RAPS study

Rivaroxaban versus warfarin in standard-dose: sensitivity analysis for participants excluded from analyses at 210 days						
Outcome (excluded 1 participant from warfarin group)	**Best case (warfarin participant had worst possible outcome)**			**Worst case (warfarin participant had best possible outcome)**		
	Rivaroxaban	**Warfarin**	**Best case**	**Rivaroxaban**	**Warfarin**	**Worst case**
Any thromboembolic event (including stroke, TIA, VTE, myocardial infarction, other thromboembolic events)	0/57	1/59	0.34 (0.01 to 8.29)	0/57	0/59	Non-estimable (no events)
Death	0/57	2/59	0.21 (0.01 to 4.22)	0/57	1/59	0.34 (0.01 to 8.29)
Outcome (excluded 4 patients from warfarin group)	**Best case**			**Worst case**		
Major bleeding	0/57	4/59	0.11 (0.01 to 2.09)	0/57	0/59	Non-estimable (no events)
Clinically relevant non-major bleeding	0/57	6/59	0.52 (0.14 to 1.97)	0/57	2/59	1.55 (0.27 to 8.95)
Minor bleeding	10/57	12/59	0.86 (0.40 to 1.84)	10/57	8/59	1.29 (0.55 to 3.04)

TIA: transient ischemic attack; **VTE**: venous thromboembolism.

APPENDICES

Appendix 1. Appendix: CENTRAL search strategy

ID Search Hits
#1 MeSH descriptor: [Anticoagulants] this term only
#2 MeSH descriptor: [Blood Coagulation Factors] explode all trees
#3 MeSH descriptor: [Blood Coagulation] this term only
#4 (anticoagul* or antithromb*):ti,ab,kw (Word variations have been searched)
#5 MeSH descriptor: [Warfarin] 3 tree(s) exploded
#6 MeSH descriptor: [4-Hydroxycoumarins] explode all trees
#7 MeSH descriptor: [Coumarins] this term only
#8 MeSH descriptor: [Phenindione] 3 tree(s) exploded
#9 (warfarin* or coumadin* or coumarin* or cumarin* or phenprocoum* or phenprocum* or dicoumar* or dicumar* or acenocoumar* or acenocumar* or fluindione or phenindione or clorindione or diphenadione or ethyl biscoumacetate):ti,ab,kw (Word variations have been searched)
#10 (Vitamin K antagonist* or VKA or VKAs or antivitamin K):ti,ab,kw (Word variations have been searched)
#11 MeSH descriptor: [Antithrombins] explode all trees
#12 MeSH descriptor: [Thrombin] explode all trees
#13 ((direct* near thrombin near inhib*) or DTI*1):ti,ab,kw (Word variations have been searched)
#14 (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin* or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil):ti,ab,kw (Word variations have been searched)
#15 MeSH descriptor: [Factor Xa] explode all trees
#16 ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) near/5 inhib*):ti,ab,kw (Word variations have been searched)
#17 (activated near/5 (factor X or factor 10) near/5 inhib*):ti,ab,kw (Word variations have been searched)
#18 xabans:ti,ab,kw (Word variations have been searched)
#19 (antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717 or darexaban or edoxaban or SSR126517E or fidexaban or idrabiotaparinux or letaxaban or tanogitran or taxexaban):ti,ab,kw (Word variations have been searched)
#20 MeSH descriptor: [Heparin] explode all trees
#21 (heparin* or lmwh* or enoxaparin* or glycosaminoglycan* or nadroparin* or mesoglycan* or tedelparin* or certoparin or tinzaparin or parnaparin or dalteparin or reviparin or fraxiparin* or danaparoid or lomoparan or org 10172 or mesoglycan or pentosan polysul* or sp54 or sp-54 or cy222 or cy-222 or cy216 or cy-216 or dermatan sul* or heparan sul*):ti,ab,kw (Word variations have been searched)
#22 {or #1-#21}
#23 MeSH descriptor: [Platelet Aggregation Inhibitors] this term only
#24 MeSH descriptor: [Cyclooxygenase Inhibitors] explode all trees
#25 MeSH descriptor: [Thienopyridines] explode all trees
#26 MeSH descriptor: [Phosphodiesterase Inhibitors] explode all trees
#27 MeSH descriptor: [Thromboxane A2] explode all trees
#28 MeSH descriptor: [Purinergic P2Y Receptor Antagonists] this term only
#29 MeSH descriptor: [Platelet Activation] explode all trees
#30 MeSH descriptor: [Blood Platelets] explode all trees and with qualifier(s): [Drug effects - DE]
#31 (antiplatelet* or anti-platelet* or antithrombocytic or anti-thrombocytic):ti,ab,kw (Word variations have been searched)
#32 ((platelet* or thrombocyte*) near/5 (inhibit* or antagonist* or antiaggreg* or anti-aggreg*&)):ti,ab,kw (Word variations have been searched)
#33 (cyclooxygenase inhibitor* or thienopyridine* or phosphodiesterase inhibitor*):ti,ab,kw (Word variations have been searched)
#34 (thromboxane A2 near/3 (inhib* or antag*)):ti,ab,kw (Word variations have been searched)
#35 (aspirin* or acetyl salicylic acid* or acetyl?salicylic acid*):ti,ab,kw (Word variations have been searched)
#36 (ARC1779 or AZD6140 or alprostadil or asasantin or carnitine or cilostazol or clopidogrel or cloricromene or cv4151 or cv-4151 or defibrotide or dilazep or dipyridamol* or disintegrin* or ditazol or E5880 or E5510 or epoprostenol* or fluribrofen or fut-175 or iloprost* or indobufen or isbogrel or kbt3022 or kbt-3022 or ketanserin* or ketoprofen or ketorolac or levamisol* or ligustrazine* or

tromethamine* or milrinone* or mopidamol* or naudicelle or nimesulide or ozagrel* or oky046 or oky-046 or oky-1581 or phthalzinol or picotamide or policosanol or prasugrel or procainamide or sarpogrelate or satigrel or sulphinpyrazone or sulfinpyrazone or suloctadil or terutroban or ticagrelor or ticlopidine or trapidil or triflusal or vorapaxar):ti,ab,kw (Word variations have been searched)
#37 {or #23-#36}
#38 #22 or 37
#39 MeSH descriptor: [Antiphospholipid Syndrome] this term only
#40 MeSH descriptor: [Phospholipids] explode all trees
#41 MeSH descriptor: [Phospholipids] explode all trees
#42 MeSH descriptor: [Cardiolipins] this term only
#43 MeSH descriptor: [Antibodies, Antiphospholipid] explode all trees
#44 ((antiphospholipid or anti-phospholipid or phospholipid or anti-cardiolipin or anticardiolipin or cardiolipin or beta 2-glycoprotein I) near/5 (auto* or antibod* or syndrome or inhibit$)):ti,ab,kw (Word variations have been searched)
#45 (APS or APLS or aCLIN):ti,ab,kw (Word variations have been searched)
#46 (lupus near/5 (coagulant* or inhibit* or antibod*)):ti,ab,kw (Word variations have been searched)
#47 Ashersons syndrome:ti,ab,kw (Word variations have been searched)
#48 Hughes syndrome:ti,ab,kw (Word variations have been searched)
#49 MeSH descriptor: [beta 2-Glycoprotein I] explode all trees
#50 MeSH descriptor: [Glycoproteins] this term only
#51 "beta 2-glycoprotein I":ti,ab,kw (Word variations have been searched)
#52 {or #39-#51}
#53 #38 and #52

Appendix 2. Appendix: MEDLINE search strategy

1. exp anticoagulants/
2. exp Blood coagulation factors/ai, de or exp Blood coagulation/ai, de
3. (anticoagul$ or antithromb$).tw.
4. Warfarin/ or 4-hydroxycoumarins/ or acenocoumarol/ or coumarins/ or dicumarol/ or ethyl biscoumacetate/ or phenindione/ or phenprocoumon/
5. exp Vitamin K/ai
6. (warfarin$ or coumadin$ or coumarin$ or cumarin$ or phenprocoum$ or phenprocum$ or dicoumar$ or dicumar$ or acenocoumar$ or acenocumar$ or fluindione or phenindione or clorindione or diphenadione or ethyl biscoumacetate).tw,nm.
7. (Vitamin K antagonist$ or VKA or VKAs or antivitamin K).tw.
8. exp antithrombins/ or hirudin therapy/ or thrombin/ai
9. ((direct$ adj5 thrombin adj5 inhib$) or DTI$1).tw.
10. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw,nm.
11. factor Xa/
12. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5 inhib$).tw.
13. (activated adj5 (factor X or factor 10) adj5 inhib$).tw.
14. xabans.tw.
15. (antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717 or darexaban or edoxaban or SSR126517E or fidexaban or idrabiotaparinux or letaxaban or tanogitran or taxexaban).tw,nm.
16. heparin/ or exp heparin, low-molecular-weight/ or heparinoids/
17. (heparin$ or lmwh$ or enoxaparin$ or glycosaminoglycan$ or nadroparin$ or mesoglycan$ or tedelparin$ or certoparin or tinzaparin or parnaparin or dalteparin or reviparin or fraxiparin$ or danaparoid or lomoparan or org 10172 or mesoglycan or pentosan polysul$ or sp54 or sp-54 or cy222 or cy-222 or cy216 or cy-216 or dermatan sul$ or heparan sul$).tw,nm.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp Platelet aggregation inhibitors/

20. exp Cyclooxygenase Inhibitors/ or exp Thienopyridines/ or exp Phosphodiesterase Inhibitors/ or Thromboxane A2/ai or exp Purinergic P2Y Receptor Antagonists/
21. exp Platelet activation/de
22. exp Blood Platelets/de
23. (antiplatelet$ or anti-platelet$ or antithrombocytic or anti-thrombocytic).tw.
24. ((platelet$ or thrombocyte$) adj5 (inhibit$ or antagonist$ or antiaggreg$ or anti-aggreg$)).tw.
25. (cyclooxygenase inhibitor$ or thienopyridine$ or phosphodiesterase inhibitor$).tw.
26. (thromboxane A2 adj3 (inhib$ or antag$)).tw.
27. (aspirin$ or acetyl salicylic acid$ or acetyl?salicylic acid$).tw,nm.
28. (ARC1779 or AZD6140 or alprostadil or asasantin or carnitine or cilostazol or clopidogrel or cloricromene or cv4151 or cv-4151 or defibrotide or dilazep or dipyridamol$ or disintegrin$ or ditazol or E5880 or E5510 or epoprostenol$ or fluribrofen or fut-175 or iloprost$ or indobufen or isbogrel or kbt3022 or kbt-3022 or ketanserin$ or ketoprofen or ketorolac or levamisol$ or ligustrazine$ or tromethamine$ or milrinone$ or mopidamol$ or naudicelle or nimesulide or ozagrel$ or oky046 or oky-046 or oky-1581 or phthalzinol or picotamide or policosanol or prasugrel or procainamide or sarpogrelate or satigrel or sulphinpyrazone or sulfinpyrazone or suloctadil or terutroban or ticagrelor or ticlopidine or trapidil or triflusal or vorapaxar).tw,nm.
29. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. Antiphospholipid Syndrome/
31. Phospholipids/
32. Cardiolipins/
33. antibodies, antiphospholipid/ or antibodies, anticardiolipin/ or lupus coagulation inhibitor/
34. ((antiphospholipid or anti-phospholipid or phospholipid or anti-cardiolipin or anticardiolipin or cardiolipin or beta 2-glycoprotein I) adj5 (auto$ or antibod$ or syndrome or inhibit$)).tw.
35. (APS or APLS or aCLIN).tw.
36. (lupus adj5 (coagulant$ or inhibit$ or antibod$)).tw.
37. Ashersons syndrome.tw.
38. Hughes syndrome.tw.
39. beta 2-Glycoprotein I/ or Glycoproteins/
40. beta 2-Glycoprotein I.tw.
41. 30 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 18 or 29
43. 41 and 42
44. Randomized Controlled Trials as Topic/
45. Random Allocation/
46. Controlled Clinical Trials as Topic/
47. control groups/
48. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
49. double-blind method/
50. single-blind method/
51. Placebos/
52. placebo effect/
53. Drug Evaluation/
54. Research Design/
55. randomized controlled trial.pt.
56. controlled clinical trial.pt.
57. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
58. (random$ or RCT or RCTs).tw.
59. (controlled adj5 (trial$ or stud$)).tw.
60. (clinical$ adj5 trial$).tw.
61. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
62. (quasi-random$ or quasi random$ or pseudo-random$ or pseud or random$).tw.
63. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
64. placebo$.tw.

65. controls.tw.
66. exp animals/ not humans.sh.
67. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
68. 67 not 66
69. 43 and 67
70. 43 and 68

Appendix 3. Appendix: Embase search strategy

1. exp anticoagulant agent/ or exp anticoagulant therapy/
2. exp blood clotting/
3. exp blood clotting factor/
4. (anticoagul$ or antithromb$).tw.
5. exp coumarin derivative/
6. (warfarin$ or coumadin$ or coumarin$ or cumarin$ or phenprocoum$ or phenprocum$ or dicoumar$ or dicumar$ or acenocoumar$ or acenocumar$ or fluindione or phenindione or clorindione or diphenadione or ethyl biscoumacetate).tw.
7. exp vitamin K group/
8. (Vitamin K antagonist$ or VKA or VKAs or antivitamin K).tw.
9. ((direct$ adj5 thrombin adj5 inhib$) or DTI$1).tw.
10. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw.
11. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5 inhib$).tw.
12. (antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717 or darexaban or edoxaban or SSR126517E or fidexaban or idrabiotaparinux or letaxaban or tanogitran or taxexaban).tw.
13. xabans.tw.
14. (heparin$ or lmwh$ or enoxaparin$ or glycosaminoglycan$ or nadroparin$ or mesoglycan$ or tedelparin$ or certoparin or tinzaparin or parnaparin or dalteparin or reviparin or fraxiparin$ or danaparoid or lomoparan or org 10172 or mesoglycan or pentosan polysul$ or sp54 or sp-54 or cy222 or cy-222 or cy216 or cy-216 or dermatan sul$ or heparan sul$).tw.
15. or/1-14
16. exp antithrombocytic agent/
17. exp thrombocyte aggregation/
18. exp thrombocyte aggregation inhibition/
19. thienopyridine derivative/
20. exp prostaglandin synthase inhibitor/ or thienopyridine derivative/ or exp phosphodiesterase inhibitor/ or thromboxane A2/ or purinergic P2Y receptor antagonist/
21. thrombocyte activation/
22. exp thrombocyte/
23. (antiplatelet$ or anti-platelet$ or antithrombocytic or anti-thrombocytic).tw.
24. ((platelet$ or thrombocyte$) adj5 (inhibit$ or antagonist$ or antiaggreg$ or anti-aggreg$)).tw.
25. (cyclooxygenase inhibitor$ or thienopyridine$ or phosphodiesterase inhibitor$).tw.
26. (thromboxane A2 adj3 (inhib$ or antag$)).tw.
27. (aspirin$ or acetyl salicylic acid$ or acetyl?salicylic acid$).tw.
28. (ARC1779 or AZD6140 or alprostadil or asasantin or carnitine or cilostazol or clopidogrel or cloricromene or cv4151 or cv-4151 or defibrotide or dilazep or dipyridamol$ or disintegrin$ or ditazol or E5880 or E5510 or epoprostenol$ or fluribrofen or fut-175 or iloprost$ or indobufen or isbogrel or kbt3022 or kbt-3022 or ketanserin$ or ketoprofen or ketorolac or levamisol$ or ligustrazine$ or tromethamine$ or milrinone$ or mopidamol$ or naudicelle or nimesulide or ozagrel$ or oky046 or oky-046 or oky-1581 or phthalzinol or picotamide or policosanol or prasugrel or procainamide or sarpogrelate or satigrel or sulphinpyrazone or sulfinpyrazone or suloctadil or terutroban or ticagrelor or ticlopidine or trapidil or triflusal or vorapaxar).tw.
29. or/16-28
30. antiphospholipid syndrome/

31. phospholipid/ or exp phospholipid antibody/
32. cardiolipin/ or exp cardiolipin antibody/
33. lupus anticoagulant/
34. ((antiphospholipid or anti-phospholipid or phospholipid or anti-cardiolipin or anticardiolipin or cardiolipin or beta 2-glycoprotein I) adj5 (auto$ or antibod$ or syndrome or inhibit$)).tw.
35. (APS or APLS or aCLIN).tw.
36. (lupus adj5 (coagulant$ or inhibit$ or antibod$)).tw.
37. (Ashersons syndrome or hughes syndrome).tw.
38. glycoprotein/ or beta2 glycoprotein 1/ or exp beta2 glycoprotein 1 antibody/
39. or/30-38
40. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/
41. Randomization/
42. Controlled clinical trial/ or "controlled clinical trial (topic)"/
43. control group/ or controlled study/
44. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
45. Crossover Procedure/
46. Double Blind Procedure/
47. Single Blind Procedure/ or triple blind procedure/
48. placebo/ or placebo effect/
49. (random$ or RCT or RCTs).tw.
50. (controlled adj5 (trial$ or stud$)).tw.
51. (clinical$ adj5 trial$).tw.
52. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
53. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
54. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
55. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
56. (cross-over or cross over or crossover).tw.
57. (placebo$ or sham).tw.
58. trial.ti.
59. (assign$ or allocat$).tw.
60. controls.tw.
61. or/40-60
62. 15 or 29
63. 39 and 61 and 62
64. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
65. 63 not 64

Appendix 4. Appendix: Trials registries search strategies

ClinicalTrials.gov (www.clinicaltrials.gov)

Antiphospholipid AND Syndrome AND EXACT "Interventional" [STUDY-TYPES]
Hughes AND Syndrome AND EXACT "Interventional" [STUDY-TYPES]
Asherson AND Syndrome AND EXACT "Interventional" [STUDY-TYPES]
Antiphospholipid Syndrome AND anticoagulant
Antiphospholipid syndrome AND antiplatelet
Antiphospholipid Syndrome AND warfarin
Antiphospholipid Syndrome AND apixaban
Antiphospholipid Syndrome AND dabigatran

Antiphospholipid Syndrome AND rivaroxaban
Antiphospholipid Syndrome AND heparin
Antiphospholipid Syndrome AND RCT
Antiphospholipid AND intervention
Antiphospholipid AND anticoagulant
Antiphospholipid AND antiplatelet
Antiphospholipid AND warfarin
Antiphospholipid AND apixaban
Antiphospholipid AND dabigatran
Antiphospholipid AND rivaroxaban
Antiphospholipid AND heparin
Antiphospholipid AND RCT

Stroke Trials Registry (www.strokecenter.org/trials).

Antiphospholipid syndrome
antiphosphoipid antibody
Hughes syndrome
Asherson syndrome

European Trials Register (www.clinicaltrialsregister.eu).

Antiphospholipid AND Syndrome
Hughes AND Syndrome
Asherson AND Syndrome
Antiphospholipid AND Antibody
Antiphospholipid Syndrome AND anticoagulant
Antiphospholipid syndrome AND intervention
Antiphospholipid syndrome AND antiplatelet
Antiphospholipid Syndrome AND warfarin
Antiphospholipid Syndrome AND apixaban
Antiphospholipid Syndrome AND dabigatran
Antiphospholipid Syndrome AND rivaroxaban
Antiphospholipid Syndrome AND heparin
Antiphospholipid Syndrome AND RCT

4) ISRCTN Registry (http://www.isrctn.com/).

filter 'condition': Antiphospholipid syndrome
filter 'condition': Hughes syndrome
filter 'condition': Asherson syndrome

The World Health Organization (WHO) International Trials Registry Platform

Antiphospholipid AND Syndrome
Hughes AND Syndrome
Asherson AND Syndrome
Antiphospholipid Syndrome AND anticoagulant
Antiphospholipid syndrome AND intervention
Antiphospholipid syndrome AND antiplatelet
Antiphospholipid Syndrome AND warfarin
Antiphospholipid Syndrome AND apixaban
Antiphospholipid Syndrome AND dabigatran
Antiphospholipid Syndrome AND rivaroxaban
Antiphospholipid Syndrome AND heparin

Antiphospholipid Syndrome AND RCT
Antiphospholipid AND intervention
Antiphospholipid AND anticoagulant
Antiphospholipid AND antiplatelet
Antiphospholipid AND warfarin
Antiphospholipid AND apixaban
Antiphospholipid AND dabigatran
Antiphospholipid AND rivaroxaban
Antiphospholipid AND heparin
Antiphospholipid AND RCT

CONTRIBUTIONS OF AUTHORS

MMB, MCL, and AU developed the concept of the study, and MMB, AP, and WS developed the search strategy. MMB, MCL, WS, AP, MK, and MJS participated in title and abstract screening, full-text screening, and data extraction. MMB and MC-L participated in data analyses; MMB, MC-L, WS, and AU participated in data interpretation. All authors contributed to the preparation of the review text and have agreed upon this final version.

DECLARATIONS OF INTEREST

Malgorzata M Bala: receives honoraria as a freelancer from a company doing health technology assessments and systematic reviews for various clients; she is not aware of any direct conflict of interest.

Magdalena Celinska-Lowenhoff: none known.

Wojciech Szot: participates in clinical trials not related to the topic of this review.

Agnieszka Padjas: none known.

Mateusz Kaczmarczyk: none known.

Mateusz Swierz: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes in people responsible for the conduct of the review: additional help from two other authors and trainee reviewers in title and abstract screening, full-text screening, data extraction and risk of bias assessment, consulting as third review authors.

Use of Microsoft Excel spreadsheet instead of Covidence for data extraction due to insufficient flexibility of Covidence data extraction tables.

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review of randomised controlled trials

Dimitrios Koutoukidis, Nerys Astbury, Elizabeth Morris, Kate Tudor, Susan Jebb, Paul Aveyard

Citation

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Review question

Do weight loss interventions in people diagnosed with non-alcoholic fatty liver disease affect liver function?

Searches

MEDLINE, Embase, PsycINFO, CINAHL, Cochrane, Web of Science, and trial registers to be searched until 01 March 2018.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/88882_STRATEGY_20180412.pdf

Types of study to be included

Randomised controlled trials.
Systematic reviews will be used as sources of reference.

Condition or domain being studied

Non-alcoholic fatty liver disease (NAFLD).

Participants/population

Adults diagnosed with non-alcoholic fatty liver disease.

Intervention(s), exposure(s)

Any intervention aiming to reduce weight including behavioural interventions, pharmacotherapy or bariatric surgery. We define weight loss pharmacotherapy as pharmacotherapy currently or previously licensed for weight loss or where there is reason to believe that the pharmacotherapy studied shares a class effect with a licensed pharmacotherapy.

Comparator(s)/control

Usual care or minimal intervention for weight loss or a lower intensity weight loss intervention.

Context

Primary outcome(s)

Any index of liver disease, including (but not limited to):
• Steatosis (liver fat) based on any assessment method (histology or radiology)
• Liver enzymes (ALT, AST, ALP, GGT, ELF, NAFLD fibrosis score, FIB-4 Index)
• Liver histology (NAS, inflammation, fibrosis, liver cell injury)
• Other non-invasive markers of fibrosis.

Timing and effect measures
Studies will be included only if they report both weight and liver fat at 12 months follow-up.

Secondary outcome(s)

Mediating variables
• Weight
• Insulin resistance.

Timing and effect measures
We will include trials of interventions without restriction on the length of intervention or the length of follow-up of participants.

Data extraction (selection and coding)

An experienced librarian will create and run the search strategy. Two reseachers will independently select the studies for review. Using a pre-defined data extraction form, they will also independently extract the following data:
• Publication details: Author, title, date of publication, journal, DOI
• Study characteristics: Country, setting, inclusion/exclusion criteria
• Participants' baseline characteristics: age, sex, co-morbidities, weight, BMI
• Intervention characteristics: materials, procedures, intervention provider, mode of delivery, type of location, duration and intensity of intervention, intervention tailoring
• Nature of control group intervention, if any
• Outcomes: data on the above outcomes, length and timings of follow-up, number of participants followed-up at each time point.
The researchers will resolve any ambiguities by discussion or referral to a third reviewer as appropriate.

Risk of bias (quality) assessment

Two reviewers will independently evaluate the risk of bias using the Cochrane risk of bias tool. Risk of bias will be assessed as high, low, or uncertain based on random sequence generation, allocation concealment, blinding of outcome assessment, and attrition, and other bias. Weight loss trials often have substantial attrition. High risk of attrition bias will be defined as <50% of the sample being followed up at the last time point or at 6 months (whichever is earlier) or where attrition rates differ between trial arms (>20% difference). If a meta-analysis is considered appropriate, we will run a sensitivity analysis testing if effect sizes differ when excluding studies at high or unclear risk of bias. We will assess possible publication bias with a funnel plot, if sufficient studies are available.

Strategy for data synthesis

Data will be synthesized narratively and we are likely to conduct a meta-analysis of each of the primary outcomes using appropriate statistical software. We will decide a priori whether to use random or fixed effects models based on the similarity of the study populations and outcomes that we pool. The pooled estimates will be presented as mean differences with 95% confidence intervals (CI) for continuous outcomes and as risk ratios with 95% CI for dichotomous outcomes. Standardised mean differences will be used when the same outcome is measured with different methodology. Statistical heterogeneity will be assessed with the I^2 statistic. We will interpret the data in light of changes in mediating variables. For example, studies where interventions for weight loss do not succeed in producing weight loss may also not lead to a difference in outcome indices of liver disease.

We will record the analytic method of dealing with missing data in each study. We will use the data as analysed in the published studies, acknowledging that variation in methods of dealing with missing data exists.

Analysis of subgroups or subsets

If appropriate, we will conduct separate analyses for one intervention versus another and for one intervention versus a minimal intervention.

We also plan to conduct a subgroup analysis to explore the effect of different types of interventions (diet, diet and exercise, exercise, pharmacotherapy, surgery).

Contact details for further information

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Organisational affiliation of the review

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https://www.phc.ox.ac.uk/research/health-behaviours

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Conflicts of interest

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(there is not an English language summary)

Country

England

Stage of review

Review_Ongoing

Subject index terms status

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Subject index terms

Humans; Liver Diseases, Alcoholic; Non-alcoholic Fatty Liver Disease; Weight Loss

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Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

17 April 2018