Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis

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Research: Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism (*BMJ* 2012;345:e7498)

STUDY QUESTION

What is the efficacy and safety of antiplatelet agents and different oral anticoagulants in the long term secondary prevention of recurrent venous thromboembolism in patients at high risk of recurrence?

SUMMARY ANSWER

Vitamin K antagonists (VKA) (standard adjusted dose and low intensity), dabigatran, rivaroxaban, and apixaban reduced the risk of recurrent venous thromboembolism among patients needing long term secondary prevention for the disorder; acetylsalicylic acid (ASA) was associated with the lowest risk reduction.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

New oral anticoagulants and ASA have recently been evaluated for the long term secondary prevention of recurrent venous thromboembolism, offering a simplified approach to anticoagulation and a potentially better harm profile than VKA. All treatments reduced the recurrence of venous thromboembolism compared with placebo or observation.

Selection criteria for studies

We included clinical trials of patients with symptomatic venous thromboembolism receiving anticoagulant treatment (≥three months), who were randomly allocated to receive an antiplatelet agent, an oral anticoagulant, or placebo or observation. We did an electronic literature search of Medline, Embase, and the Cochrane Central Registry of Controlled Trials from the inception of the database to May 2013. Publications from potentially relevant journals were also searched by hand.

Primary outcomes(s)

Symptomatic recurrent venous thromboembolism and major bleeding episodes.

Main results and role of chance

We included 13 randomised trials in the network meta-analysis. All treatments reduced the absolute risk of recurrent venous thromboembolism; standard adjusted dose VKA (target international normalised ratio 2.0-3.0) showed the highest risk difference (odds ratio 0.07; 95% credible interval 0.03 to 0.15) and ASA showed the lowest risk difference (0.65; 0.39 to 1.03), compared with placebo or observation. Risk of major bleeding was higher with standard adjusted dose VKA (5.24; 1.78 to 18.25) compared with placebo or observation. Apixaban seemed to be associated with a reduction in major bleeding compared with standard adjusted dose VKA (0.03; 0.001 to 0.45) and was associated with the greatest risk reduction for major bleeding events among all treatments.

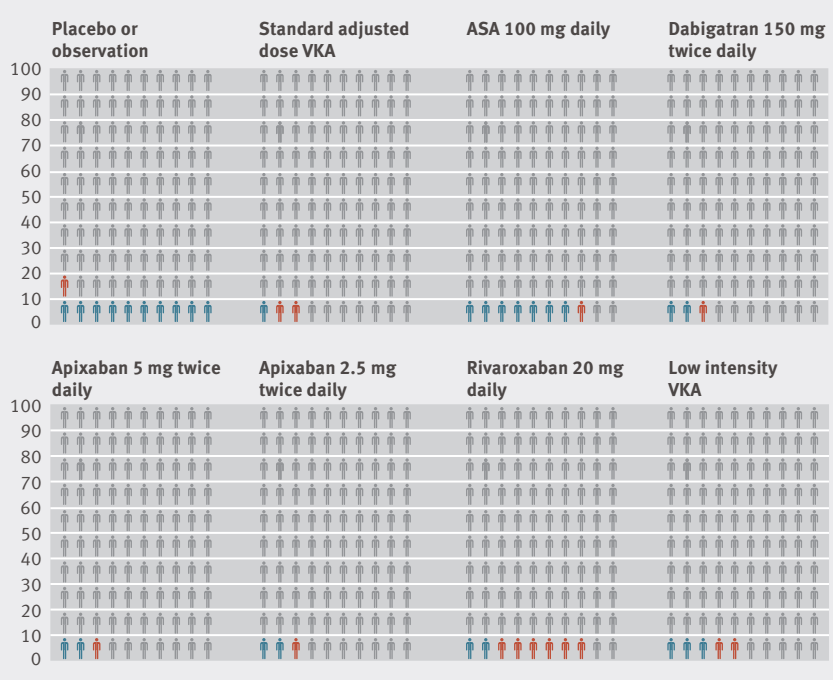
Bias, confounding, and other reasons for caution

Although ASA was associated with the lowest risk reduction, its use for secondary prevention of recurrent venous thromboembolism could be valuable in patients with arterial disease who are at low to moderate risk of recurrent venous thromboembolism. Detailed subgroup and individual patient level data were not available. Similarly, limited data were available for some anticoagulant agents included in the analysis. For example, only one study assessed rivaroxaban, and reported no major bleeding in the placebo arm during follow-up, resulting in uncertain effect estimates for major bleeding and rivaroxaban use.

Study funding/potential competing interests:

MC is a recipient of a New Investigator Award from the Heart and Stroke Foundation of Canada and holds a T2 research chair in cancer and thrombosis from the University of Ottawa. CC is a recipient of a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research and has received funding from Canadian Network and Centre for Trials Internationally (CANNeCTIN). MAR is the recipient of a Career Scientist Award from the Heart and Stroke Foundation of Ontario. PSW is a recipient of a Canada research chair in venous thromboembolism.

Absolute risks of recurrent VTE (blue) and major bleeding episodes (red)



Preventing sexual abusers of children from reoffending: systematic review of medical and psychological interventions

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STUDY QUESTION

What interventions work for sexual abusers of children and for those at risk of carrying out such abuse?

SUMMARY ANSWER

Research is inconclusive concerning the effectiveness of psychological and medical interventions for adults who have sexually abused children, and of interventions for children with sexual behaviour problems. For adolescent sexual offenders, there is limited evidence from only one randomised controlled trial that multisystemic therapy reduces the risk of further sexual offences.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous systematic reviews found weak evidence for effects of medical and psychological interventions in reducing the risk of reoffence in identified sexual offenders against adults. This study examined interventions intended to reduce the risk of future sexual offending against children, and similarly found the research insufficient for strong conclusions.

Selection criteria for studies

We conducted a systematic review with GRADE methods of interventions designed to prevent offending and reoffending among known sexual abusers of children and interventions for people at risk of committing such offences. Only studies with low or moderate risk of bias were used for conclusions. We considered both randomised controlled trials and prospective, controlled observational studies. All individual oriented psychological, educational, and pharmacological interventions for adults, adolescents, and children were considered.

Primary outcomes

Arrests, convictions, breaches of conditions, and offenders' self reported sexual abuse of children after one year or more.

Main results and role of chance

From 167 full text articles selected for full review, 22 were deemed eligible and only eight met minimal quality (three randomised controlled trials; five observational studies). We found weak evidence that multisystemic therapy—a community based programme based on social learning, social ecological theory, and systematic family therapy—reduced sexual reoffending among adolescent perpetrators (one randomised controlled trial, relative risk 0.18, 95% confidence interval 0.04 to 0.73). The scientific evidence was insufficient to draw conclusions concerning cognitive behavioural therapy for adult perpetrators, adolescent perpetrators, and children with sexual behaviour problems. No studies that met minimal quality thresholds were available for pharmacological treatments or selective prevention for individuals at risk.

The lack of evidence is troubling given that treatment programmes for sexual abusers of children are widely implemented in correctional and forensic mental health settings. Furthermore, most European countries have committed to providing effective treatment for adults and young people at risk for sexually abusing children through the 2007 Convention on the Protection of Children against Sexual Exploitation and Sexual Abuse. This EU convention also creates an obligation to evaluate such treatment programmes, which should motivate new high quality studies needed to advance knowledge on this topic of high social concern.

Bias, confounding, and other reasons for caution

The evaluation of bias and the research synthesis were conducted with only one method. Different methods of rating study quality could result in different conclusions.

Study funding

The Swedish Government Department of Social Affairs commissioned the systematic review and funded some of the work.

Quality of scientific evidence for interventions intended to reduce the risk of future sexual offences against children

Population	Intervention	Quality of scientific evidence
Adult sexual abusers of children	Cognitive behavioural therapy	Insufficient (one randomised controlled trial; four observational studies)
Adolescent sexual abusers	Multisystemic therapy	Weak (one randomised controlled trial)
Adolescent sexual abusers	Cognitive behavioural therapy	Insufficient (one observational study)
Children with sexual behaviour problems	Cognitive behavioural therapy	Insufficient (one randomised controlled trial)
Adults, adolescents, or children	Pharmacological	No studies meeting minimum standards
Adults or young people at risk of abusing but yet to do so (secondary or selective prevention)	Any psychological or pharmacological treatment for individuals	No studies meeting minimum standards

Transcutaneous electrical nerve stimulation as adjunct to primary care management for tennis elbow: pragmatic randomised controlled trial (TATE trial)

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Clinical review: The management of tennis elbow (*BMJ* 2011;342:d2687)

STUDY QUESTION

Can transcutaneous electrical nerve stimulation (TENS), as a patient controlled adjunct to primary care management for tennis elbow, provide superior pain relief to primary care management alone.

SUMMARY ANSWER

TENS conferred no additional clinical benefit over primary care management consisting of information and advice on analgesia and exercise for patients with tennis elbow, probably partly owing to poor adherence to treatment recommendations.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A need exists for safe, self administered interventions to provide pain relief for patients with tennis elbow. TENS as an adjunct to primary care management failed to show any additional pain relief compared with primary care management alone.

Design

This was a pragmatic, randomised controlled trial with two intervention groups: primary care management plus TENS and primary care management alone.

Participants and setting

We recruited 241 adults with a first or new clinical diagnosis of tennis elbow from 38 general practices in North Staffordshire.

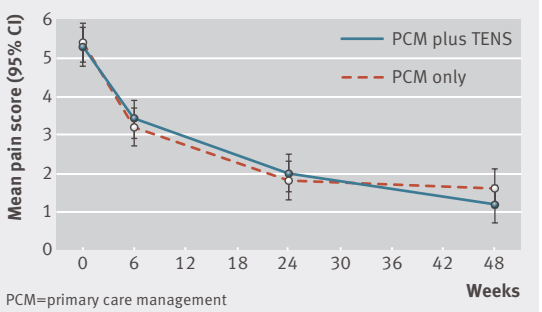
Primary outcome(s)

The primary outcome measure was self reported elbow pain intensity (0-10, numerical rating scale) at six weeks' follow-up, with long term assessments at six and 12 months.

Main results and the role of chance

By intention to treat analysis, we found no significant differences between the two groups for pain relief at any time point. A large (>25%) within group improvement in pain intensity occurred in both groups, with most improvement occurring in the first six weeks. Between group differences for mean change in pain intensity (positive values indicating differences in favour of primary care management plus TENS) were −0.33 (95% confidence interval −0.96 to 0.31; P=0.314) at six weeks, 0.20 (−0.81 to 0.42; P=0.526) at six months, and 0.45 (−0.15 to 1.06; P=0.139) at 12 months, adjusted for age, sex, and baseline pain score. We found no statistically significant differences between the groups for secondary outcomes, which included self reported global change in elbow problems, limitation in function, work absence, general health, and health beliefs and perceptions.

Course of pain intensity scores (0-10 numerical rating scale) during trial



PCM=primary care management
TENS=transcutaneous electrical nerve stimulation

Harms

No cases of harm were reported.

Bias, confounding, and other reasons for caution

A double blind design was not feasible given the type of study intervention, so we cannot comment on the efficacy of TENS. The trial did not investigate the effectiveness of TENS alone or the extent to which the observed improvements were the result of spontaneous recovery, as a no-treatment control group was not included. High levels of follow-up (86%) were achieved for the primary outcome at six weeks, but differential and higher non-response occurred in the primary care management group at six and 12 months. Both groups reported low adherence to treatment recommendations, which is likely to have contributed to the absence of an effect for both primary and secondary outcomes.

Generalisability to other populations

This is the largest trial to investigate primary care management of tennis elbow so far, and patients were recruited from a wide geographical area. Exclusion criteria were limited to reflect a broad population with tennis elbow. Our results show very similar patterns of clinically meaningful improvement in pain and function compared with findings from previous trials of primary care interventions. The results provide further evidence of the challenges of implementing effective self-management treatment strategies and changing patients' behaviour in primary care.

Study funding/potential competing interests

The study was funded by the National Institute for Health Research (NIHR) under the Research for Patient Benefit Programme. CDM is supported by an Arthritis Research UK clinician scientist award. EMH is an NIHR senior investigator.

Trial registration number

Current Controlled Trials ISRCTN87141084.

Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials

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STUDY QUESTION

In reports of trials published in major general medical journals, how complete are the descriptions of non-pharmacological interventions, what elements are the most commonly missing, and can the missing details be obtained from their authors?

SUMMARY ANSWER

Less than half (39%) of the interventions evaluated were adequately described, most commonly missing were details about intervention materials and procedures, and many missing details could be provided by contact with trial authors.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Incomplete descriptions of interventions render the interventions uninterpretable and unusable by clinicians, patients, and researchers. Missing information is a common problem in reports of non-pharmacological interventions, which can be partially remediated by contacting authors of trial reports for missing details.

Study selection and data sources

We included all reports of randomised trials of non-pharmacological interventions published in 2009 in one of the six leading general medical journals (*New England Journal of Medicine*, *JAMA*, *Lancet*, *Annals of Internal Medicine*, *PLOS Medicine*, *BMJ*). Two raters independently assessed the unabridged primary report, plus any references, appendices, or websites, by using an eight item checklist. We emailed questions about missing details to corresponding authors and then reassessed relevant items.

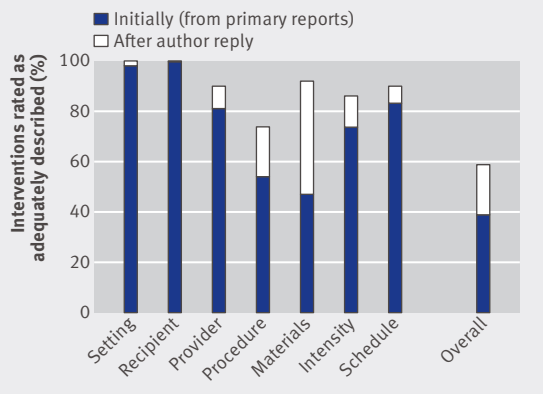
Design

This was an analysis of a consecutive sample of randomised trials of non-pharmacological interventions.

Main results

Of the 137 interventions, from 133 eligible trial reports, only 53 (39%) were adequately described. When we used authors' responses (63 responses from 88 contacted authors), this increased to 81 (59%). The most frequently missing item was "intervention materials" (47% complete), which also improved the most after response from authors (92% complete). Some authors (27/70) provided materials or further information; other authors (21/70) could not, with reasons including copyright or intellectual property concerns, not having the materials or intervention details, or not being aware of their importance. Although 46 (34%) interventions had further information or materials on a relevant website, many of these websites were not mentioned in the report, not freely accessible, or no longer functioning.

Percentage of interventions rated as adequately described, in primary report and after author reply, for each checklist item



Bias, confounding, and other reasons for caution

Of the authors we contacted, 28% did not respond, which limits the completeness of our verification of missing intervention details with authors. As our sample of reports was selected only from leading general medical journals, the findings may not be generalisable and our study may have underestimated the size of the problem.

Study funding/potential competing interests

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