RESEARCH

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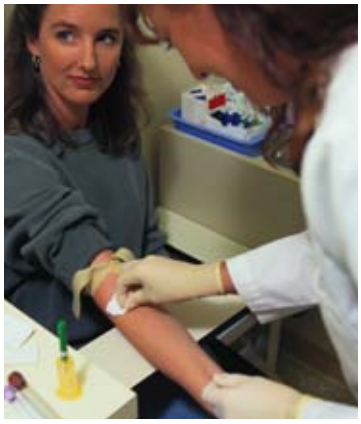

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Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism
According to this meta-analysis of nine studies including 16 701 patients, the new oral anticoagulants have a similar risk of recurrence of acute venous thromboembolism and all cause mortality as vitamin K antagonists, although rivaroxaban is associated with a reduced risk of bleeding. Large randomized controlled trials are needed, powered to directly compare new oral anticoagulants and assess the superiority of any one of these drugs over another, say the authors.

Uncertainties in baseline risk estimates and confidence in treatment effects
The GRADE system provides a framework for evaluating how risk of bias, publication bias, imprecision, inconsistency, and indirectness may reduce confidence in estimates of relative effects of interventions on outcomes. However, GRADE and all other systems for rating confidence in effect estimates do not fully address uncertainty in baseline risk and its impact on confidence in absolute estimates of treatment effect. In this article in our Research Methods and Reporting series, the authors examine factors that may reduce confidence in estimates of baseline risk and thus estimates of absolute treatment benefit.

WHAT OUR READERS ARE SAYING

Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation
According to this indirect treatment analysis of phase III clinical trials of stroke prevention in atrial fibrillation published on 5 November [http://www.bmj.com/content/345/bmj.e7097], apixaban, rivaroxaban, and dabigatran have broadly similar effects on the main endpoints for secondary prevention, although the endpoints of haemorrhagic stroke, vascular death, major bleeding, and intracranial bleeding were less common with dabigatran 110 mg twice daily than with rivaroxaban. For primary prevention, the three drugs showed some differences in efficacy and bleeding. The authors point out that these results are hypothesis generating and should be confirmed in a head to head randomised trial.

SATURN STILLS/SPL

Here's what two rapid respondents said:
"There are clear protocols in place for reversal of warfarin and there is a wealth of clinical experience in the management of warfarin related complications. This is not the case with the new oral anticoagulants and herein lies the danger . . . Mechanisms must be put in place to ensure that both those prescribing them and those who deal with their complications are well informed with regard to limitations in terms of monitoring and reversal."

"I believe that the conclusion about primary prevention can not be drawn from the analysis . . . If there is important heterogeneity between the populations of the trials and the reason for focusing on the secondary prevention subgroups is to allow more homogeneity, the logical consequence is that the complementary subgroups (primary prevention) are even more heterogeneous than the whole trial populations. Comparisons between those subgroups are seriously biased. And if 57 tests have been performed in each subgroup the probability that some of the results reach statistical significance only by chance is quite high."

General health checks in adults for reducing morbidity and mortality from disease: Cochrane systematic review and meta-analysis

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EDITORIAL by MacAuley

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STUDY QUESTION

What are the benefits and harms of general health checks in terms of outcomes relevant to patients?

SUMMARY ANSWER

General health checks did not reduce morbidity or mortality, neither overall nor for cardiovascular or cancer causes, although they increased the number of new diagnoses. Important harmful outcomes were often not studied or reported.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

General health checks are widely assumed to be effective in reducing morbidity and mortality from disease, but these benefits have not been demonstrated. Our results suggest that general health checks in adults do not reduce morbidity or mortality from disease. In the absence of benefits, the increased number of diagnoses with health checks suggests overdiagnosis and overtreatment.

Selection criteria for studies

Randomised trials comparing health checks with no health checks in adult populations unselected for disease or risk factors. Health checks were defined as screening general populations for more than one disease or risk factor in more than one organ system. We did not include geriatric trials.

Primary outcomes

Total mortality and cause-specific mortality

Main results and role of chance

We identified 16 trials, 14 of which had available outcome data (182 880 participants). Nine trials provided data on total mortality (11 940 deaths), and comparison of health checks versus no health checks gave a risk ratio of 0.99 (95% confidence interval 0.95 to 1.03). Eight trials provided data on cardiovascular mortality (4567 deaths), with a risk ratio of 1.03 (0.91 to 1.17), and eight provided data on cancer mortality (3663 deaths), with a risk ratio of 1.01 (0.92 to 1.12). Subgroup and sensitivity analyses did not alter these findings.

Bias, confounding, and other reasons for caution

For our primary outcomes, most trials were probably reliable in terms of comparability of groups and outcome ascertainment. For other outcomes, lack of blinding and missing outcome data were major issues. The main limitations are the old age of the trials, the sparse reporting of harms, and the differences between the trials, including differences among the types of health checks used. A possible explanation for the apparent lack of effect is that opportunistic screening by general practitioners may have eroded the potential for a benefit from systematic health checks. Another possible explanation is that people at highest risk of disease tend not to accept invitations for health checks.

Study funding/potential competing interests

Funding was from the Nordic Cochrane Centre and a grant from Trygfonden (non-profit foundation).

Effects of general health checks on mortality

	Trial data					
Outcome	No of trials	No of people	No of deaths	Median (range) follow-up (years)	Risk ratio (95% CI)	Heterogeneity (I^2)
Total mortality	9	155 899	11 940	9 (4–22)	0.99 (0.95 to 1.03)	0%
Cardiovascular mortality	8	152 435	4567	10.4 (4–22)	1.03 (0.91 to 1.17)	64%
Cancer mortality	8	139 290	3663	10.4 (4–22)	1.01 (0.92 to 1.12)	33%

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Effect of intensive structured care on individual blood pressure targets in primary care: multicentre randomised controlled trial

On behalf of the VIPER-BP study investigators

EDITORIAL by Clark and McManus

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STUDY QUESTION

Is intensive, structured care to optimise blood pressure control based on individual risk targets more effective than usual care for those with persistent hypertension?

SUMMARY ANSWER

The intervention was associated with an 8.8% improvement in achieving individualised blood pressure control (36.2% *v* 27.4%). However, achieving risk based blood pressure targets and applying intensified management remains challenging.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Systematic reviews suggest that better blood pressure control can be attained with a more intensive and structured approach to managing hypertension in primary care. This strategy increased the proportion of participants achieving individual risk based blood pressure targets compared with usual care. However, achieving stringent blood pressure targets is challenging, and more intensive management requires greater modification of treatment (7.9% *v* 1.9%) owing to adverse events.

Design

Blinded randomisation by computer generated group assignment stratified according to nominated blood pressure target (three strata) and block randomisation. After a 28 day run-in treatment phase, participants not at their individual blood pressure target were randomised to usual care or to the intervention. The intervention comprised computer assisted clinical profiling and risk target setting (all participants) with intensified follow-up and stepwise drug treatment titration (initial angiotensin receptor blocker monotherapy or two forms of combination therapy).

Participants and setting

2185 participants (mean age 59 (SD) 12 years) from 119 general practice clinics throughout Australia. Of these, 416 (19.0%) achieved their individual blood pressure target during the 28 day run-in period. Subsequently, 1562 participants (blood pressure 150 (SD)17/88 (SD 11 mm Hg) were randomised to usual care (n=524) or intervention (n=1038) groups.

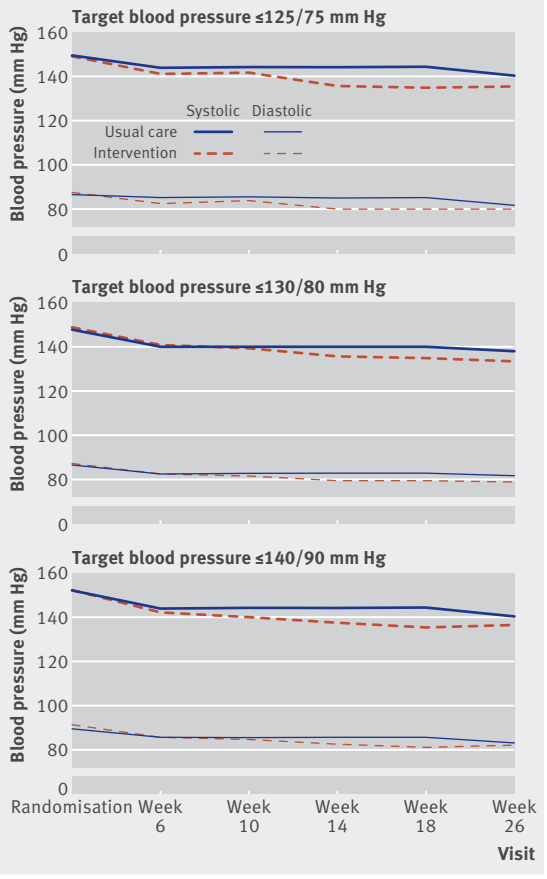
Primary outcome

Individual blood pressure target achieved at 26 weeks.

Main results and the role of chance

Overall, 8.8% more participants in the intervention group achieved the primary endpoint (358/988 (36.2%) intervention *v* 138/504 (27.4%) control participants): adjusted relative risk 1.28 (95% confidence interval 1.10 to 1.49), P=0.0013. There was a 9.5% absolute difference in favour of the intervention group in reaching the classic blood pressure target of ≤140/90 mm Hg (627/988 (63.5%) intervention *v* 272/504 (54.0%) control): adjusted relative risk 1.18 (1.07 to 1.29), P<0.001. The intervention group achieved a mean adjusted reduction in blood pressure of 13.2 (95% confidence interval −12.3 to −14.2)/7.7 (−7.1 to −8.3) mm Hg *v* 10.1 (−11.3 to −8.8)/5.5 (−4.7 to −6.2) mm Hg in the control group (P<0.001).

Change in systolic and diastolic blood pressure according to individual blood pressure target at randomisation (n=1492)



Harms

Improved blood pressure control was counterbalanced by an increase in treatment related adverse events and subsequent need for modification of treatment: 82 (7.9%) intervention *v* 10 (1.9%) control participants.

Generalisability to other populations

Derived from a large, pragmatic effectiveness trial, these data are highly relevant to the large number of people with persistent hypertension in primary care.

Study funding/potential competing interests The Baker IDI Heart and Diabetes Institute designed and carried out the study with support from Novartis Pharmaceuticals.

Muscular strength in male adolescents and premature death: cohort study of one million participants

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bmj.com
Research: Association between muscular strength and mortality in men (*BMJ* 2008;337:a439)

STUDY QUESTION Is muscular strength in adolescence associated with all cause and cause specific premature mortality (<55 years)?

SUMMARY ANSWER Low muscular strength in adolescents is an emerging risk factor for major causes of death in young adulthood and middle age, with an effect size for all cause mortality equivalent to that of well established risk factors.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Muscular strength in adulthood is associated with mortality and morbidity. Muscular strength in adolescence was associated with a 20-35% lower risk of premature mortality due to any cause, cardiovascular disease, or suicide, independently of body mass index or blood pressure.

Participants and setting
We followed 1 142 599 Swedish male adolescents aged 16-19 years over a period of 24 years.

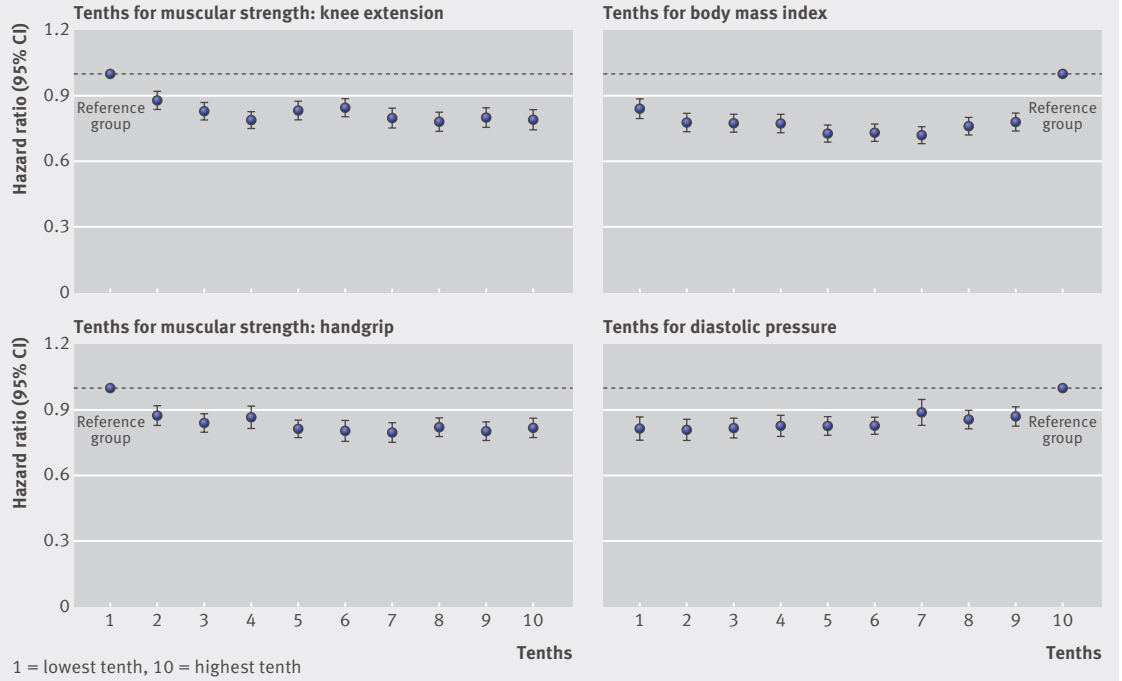
Design, size, and duration
This is a prospective cohort study based on several Swedish national registries, including the Swedish Military Service Registry. Baseline examination included knee extension, handgrip, and elbow flexion strength tests, as well as measures of blood pressure and body mass index. We used Cox regression to estimate hazard ratios for mortality according to muscular strength categories (tenths).

Main results and the role of chance
During a median follow-up period of 24 years, 26 145 participants died. Suicide was a more frequent cause of death in young adulthood (22.3%) than was cardiovascular disease (7.8%) or cancer (14.9%). High muscular strength in adolescence, as assessed by knee extension and handgrip tests, was associated with a 20-35% lower risk of premature mortality due to any cause or cardiovascular disease, independently of body mass index or blood pressure; we found no association with mortality due to cancer. We found a similar effect size on all cause mortality for body mass index and blood pressure. Stronger adolescents had a 20-30% lower risk of death from suicide and were 15-65% less likely to have any psychiatric diagnosis (such as schizophrenia and mood disorders). All cause mortality rates per 100 000 person years ranged between 122.3 and 86.9 for the weakest and strongest adolescents.

Bias, confounding, and other reasons for caution
Sampling bias is unlikely in this study, as almost the whole population targeted participated in this study. We took into account basic potential confounders, as well as classic risk factors and socioeconomic factors.

Study funding/potential competing interests
The study was funded by the Swedish Research Council. FBO was supported by grants from the Spanish Ministry of Science and Innovation.

Relation of muscular strength, body mass index, and blood pressure with all cause premature death (n=1 142 599)



1 = lowest tenth, 10 = highest tenth
Models were adjusted for birth cohort, conscription age, and conscription office

Sharing of clinical trial data among trialists: a cross sectional survey

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EDITORIAL by Godlee and Groves

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STUDY QUESTION What are clinical trialists' opinions and experiences of sharing of clinical trial data with investigators who are not directly collaborating with the research team?

SUMMARY ANSWER Respondents strongly supported the principle of sharing clinical trial data, indicating a willingness to share data but also raising several practical concerns.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Data sharing policies are increasingly promoted to improve access to clinical trial data, but little is known about support for these policies among clinical trialists. About three quarters of corresponding authors of recently published trials in high impact general medical journals who responded to our survey supported initiatives for sharing clinical trial data, expressing a willingness to share data but also raising practical concerns related to appropriate data use, investigator or funder interests, and protection of research subjects.

Design, participants, and setting

Cross sectional, web based survey of clinical trialists who were corresponding authors of clinical trials published in 2010 or 2011 in one of six general medical journals with the highest impact factor in 2011.

Primary outcome(s)

Support for and prevalence of data sharing through data repositories and in response to individual requests for data, concerns with data sharing through repositories, and reasons for granting or denying requests.

Main results and the role of chance

Of 683 potential respondents, 317 (46%) completed the survey. In principle, 236 (74%) thought that sharing de-identified data through data repositories should be required, and 229 (72%) thought that investigators should be required to share de-identified data in response to individual requests. In practice, only 56 (18%) indicated that they were required by the trial funder to deposit the data in a repository; of these 32 (57%) had done so. One hundred and forty nine respondents (47%) had received an individual request to share their clinical trial data; of these, 115 (77%) had granted at least one request and 56 (38%) had denied at least one. Respondents' most common concerns about data sharing were related to appropriate data use, investigator or funder interests, and protection of research subjects (figure).

Bias, confounding, and other reasons for caution

Fewer than half of potential participants completed our survey, meaning that our findings could overestimate support for and willingness to engage in data sharing in the clinical trial community, and limiting the external validity of our findings. Furthermore, even among survey respondents, our findings may have been biased by social desirability, as respondents might have been less likely to report beliefs and behaviours that could be negatively perceived by others.

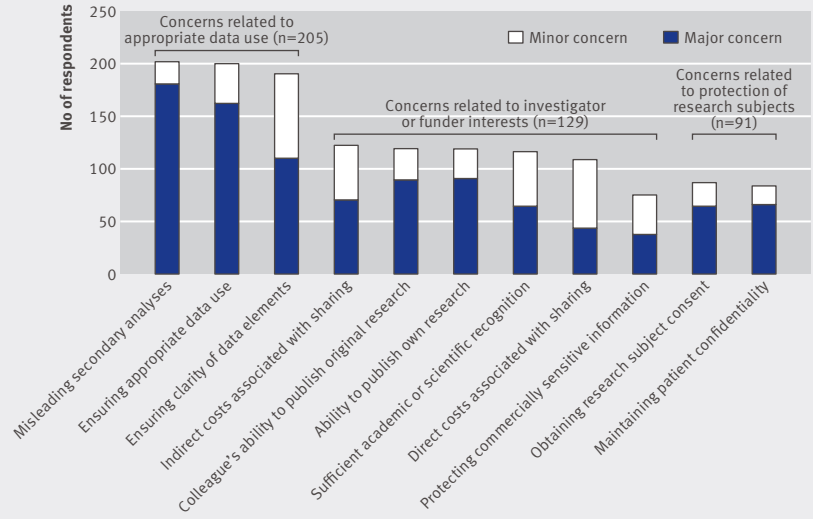
Generalisability to other populations

Our study was limited to corresponding authors of clinical trials published in the highest impact general medical journals. Our findings may not be applicable to the entire clinical trial research community, although these high impact studies are likely to address important clinical questions that can potentially affect clinical decision making.

Study funding/potential competing interests

This study was not supported by any external grants or funds. The authors have received support from a Yale University School of Medicine Medical Student Research Fellowship (VR), the Centers of Medicare and Medicaid Services (HMK and JSR), a National Heart Lung Blood Institute Cardiovascular Outcomes Center Award (HMK), Medtronic (HMK, JSR, and CPG), and the National Institute on Aging and the American Federation for Aging Research (JSR); and provide advisory or monitoring roles for UnitedHealthcare (HMK), FAIR Health (CPG and JSR), and Genzyme/Sanofi (SJ) (see full article for details).

Major and minor concerns with data sharing among 317 survey respondents, grouped by overarching concern*



*Sample number for each overarching category indicates the number of respondents who initially selected that category and were then given the opportunity to select more detailed concerns from among multiple choice responses

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Editorial: Clinical trial data for all drugs in current use (*BMJ* 2012;345:e7304)

Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials

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- Visit the BMJ Group's cardiology portal at bmj.com/specialties/cardiovascular-medicine
- Clinical review: Venous thromboembolism (*BMJ* 2006;332:215)

STUDY QUESTION For patients with acute venous thromboembolism, how do the novel oral anticoagulants compare with traditional treatment with vitamin K antagonists for the prevention of recurrence of acute venous thromboembolism, major bleeding, and all cause mortality?

SUMMARY ANSWER No differences were found between different novel oral anticoagulants and vitamin K antagonists for recurrence of acute venous thromboembolism, major bleeding, or all cause mortality, with the exception of rivaroxaban (a factor Xa inhibitor), which was associated with a reduced risk of major bleeding. An indirect comparison between rivaroxaban and dabigatran did not show significant differences between the two agents.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Novel oral anticoagulants have been proposed as "non-inferior" alternatives to vitamin K antagonists in the treatment of acute venous thromboembolism, although there are wide confidence intervals around the point estimate in each individual study. This meta-analysis showed that these novel oral anticoagulants are associated with similar risk of recurrence of acute venous thromboembolism, major bleeding, and all cause mortality, with narrower confidence intervals.

Selection criteria for studies

We searched Medline, Embase, and the Cochrane Library. To be eligible for inclusion, studies had to include patients with symptomatic acute venous thromboembolism objectively diagnosed with standard imaging techniques; the intervention had to be treatment with a novel oral anticoagulant with or without initial heparin treatment; the comparison had to be treatment with vitamin K antagonists, always with initial heparin treatment; the outcome had to be recurrent acute venous thromboembolism, bleeding, all cause mortality; and the study had to be a randomised controlled trial.

Primary outcomes

Recurrence of acute venous thromboembolism, major bleeding, and all cause mortality.

Main results and the role of chance

Of the 1782 identified studies, nine met our inclusion criteria, involving 16 701 patients evaluated for efficacy and 16 611 for safety. The novel oral anticoagulants with trial data were rivaroxaban, apixaban, dabigatran, and ximelagatran. For recurrent acute venous thromboembolism and for all cause mortality, there were no significant differences in events rates between any of the anticoagulants and conventional treatment. Rivaroxaban reduced the risk of major bleeding compared with conventional treatment. The adjusted indirect comparison between rivaroxaban and dabigatran did not show superiority of either drug over the others for major bleeding or the other endpoints.

Bias, confounding, and other reasons for caution

Studies were all randomised controlled trials. Most trials were not double blind, though the assessment of outcomes was done by a blinded adjudication committee in most studies. Of the nine studies, we assessed the risk of bias as low in four studies and unclear in five studies. In three of the five studies graded as having unclear potential for bias this was due to only a single domain, with all other domains classified as low potential for bias. There were no direct comparisons between different novel oral anticoagulants. Duration of study and protocol varied between studies, and there are limited data to support decision making in specific populations (such as oncology patients, elderly patients).

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Outcome of treatment with novel oral anticoagulants (rivaroxaban and dabigatran only) compared with vitamin K antagonists	
Endpoint and treatment	**RR* (95% CI)**
Recurrence of acute venous thromboembolism	
Rivaroxaban	0.85 (0.55 to 1.31)
Dabigatran	1.09 (0.76 to 1.57)
Major bleeding	
Rivaroxaban	0.57 (0.39 to 0.84)
Dabigatran	0.76 (0.49 to 1.18)
All cause mortality	
Rivaroxaban	0.96 (0.72 to 1.27)
Dabigatran	1.00 (0.67 to 1.50)

* Relative risk <1.0 favours novel oral anticoagulants, >1.0 favours vitamin K antagonists.