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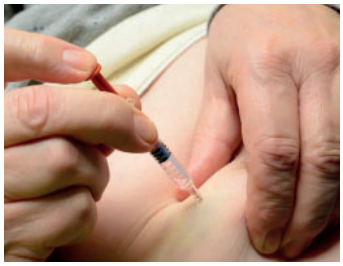

Effects of anticoagulation in non-cardiac surgery
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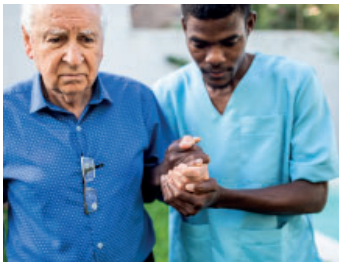
Use of non-antibiotic treatment as prophylaxis in recurrent UTI
p 396



Mortality and disability trends in adults older than 70 years
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ORIGINAL RESEARCH Systematic review and network meta-analysis

Benefits and harms of direct oral anticoagulation and low molecular weight heparin for thromboprophylaxis in patients undergoing non-cardiac surgery

Marcucci M, Etxeandia-Ikobaltzeta I, Yang S, et al

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Study question What are the benefits and harms of direct oral anticoagulation and low molecular weight heparin (LMWH) for prophylaxis of symptomatic venous thromboembolism in patients undergoing non-cardiac surgery?

Methods This study was conducted on 68 randomised controlled trials (51 orthopaedic) involving 45 445 adults undergoing non-cardiac surgery. Participants were randomly allocated to receive LMWH (at a standard prophylactic (low) dose or higher dose), direct oral anticoagulants, or no active treatment.

Study answer and limitations Standard prophylactic dose (odds ratio 0.33, 95% confidence interval 0.16 to 0.67, P=0.002) and high dose LMWH (0.19, 0.07 to 0.54, P=0.002) and direct oral anticoagulants (0.17, 0.07 to 0.41, P<0.001) were associated with a significant relative reduction in symptomatic venous thromboembolism of any extension (proximal or distal deep vein thrombosis, with or without pulmonary embolism (PE), or isolated PE) compared with no active treatment. Direct oral anticoagulants were more effective than prophylactic LMWH in symptomatic venous thromboembolism. Direct oral anticoagulants and LMWH were associated with a twofold to threefold increase in the odds of major bleeding compared with no active treatment (certainty of evidence, moderate to high), with absolute risk differences as high as 50 per 1000 in patients at high risk. No agent was effective in preventing PE. Overall, the findings were consistent for orthopaedic and non-orthopaedic surgery, and type of direct oral anticoagulant. The low methodological quality of some studies limited the certainty of estimates.

What this study adds The findings suggest that direct oral anticoagulants probably prevent symptomatic venous thromboembolism to a greater extent than prophylactic LMWH in non-cardiac surgery, and that direct oral anticoagulants and LMWH increase bleeding to a similar extent.

Systematic review registration PROSPERO CRD42018106181.

Funding, competing interests, and data sharing Supported by career awards and scholarships awarded to the leading investigators. No competing interests declared. No additional data available.

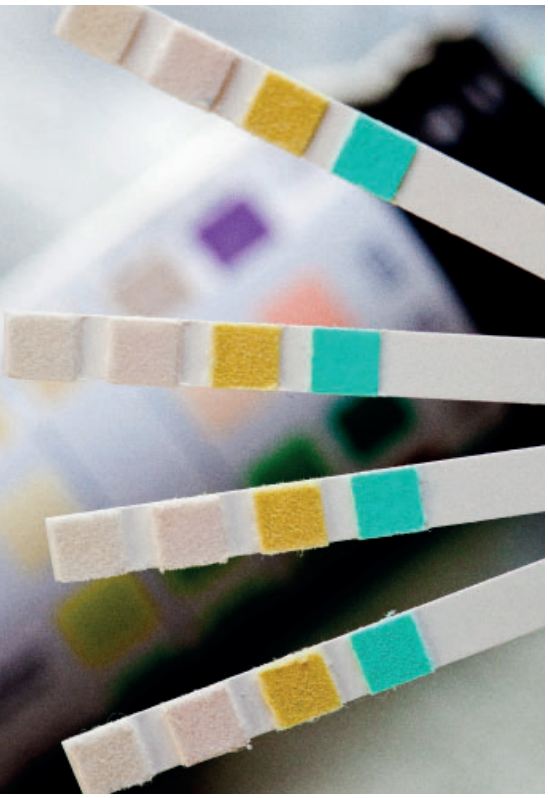
Network odds ratio (95% CI) and GRADE assessment of certainty of evidence, for treatment benefit and harm, with no active treatment as reference

Intervention	Symptomatic venous thromboembolism*	Major bleeding*
Low dose LMWH	0.33 (0.16 to 0.67)	2.04 (1.28 to 3.22)†
High dose LMWH	0.19 (0.07 to 0.54)	3.07 (1.39 to 6.77)
Direct oral anticoagulants	0.17 (0.07 to 0.41)	2.01 (1.08 to 3.73)

CI=confidence interval; LMWH=low molecular weight heparin; GRADE=grading of recommendations, assessment, development, and evaluation.
*Moderate to high certainty for all comparisons.
†Based on direct comparison.

Methenamine hippurate for recurrent UTIs

ORIGINAL RESEARCH Multicentre, open label, randomised, non-inferiority trial



GARO/PHANIE/ALAMY

Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women

Harding C, Mossop H, Homer T, et al

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Study question Is the non-antibiotic option of methenamine hippurate equivalent to the currently recommended treatment of daily low dose antibiotics in preventing episodes of urinary tract infection (UTI) in women with recurrent infections?

Methods This trial recruited participants from eight UK centres. Women aged ≥18 years with recurrent UTI, requiring prophylactic treatment, were randomly assigned (1:1) to receive antibiotic prophylaxis or methenamine hippurate for 12 months. Treatment allocation was not masked, and participants were allowed to switch between antibiotics or between treatment strategies; however, the need to adhere to the allocated intervention was emphasised. The primary outcome measure was the absolute difference in the incidence of symptomatic, antibiotic treated UTI during treatment. A patient and public involvement group predefined the non-inferiority margin as one UTI episode per person year. Analyses performed in a modified intention-to-treat population included all participants observed for at least six months, because these participants were assumed to provide a reliable estimate of UTI incidence.

Study answer and limitations 240 participants were randomised and the primary analysis included 205 (85%) participants (102 (85%) allocated to antibiotics, 103 (86%) allocated to methenamine hippurate). Incidence of antibiotic treated UTI during the treatment period was 0.89 episodes per person year was 0.89 and 1.38 episodes per person year in the antibiotic group and methenamine hippurate group, respectively (absolute difference 0.49 episodes (90% confidence interval 0.15 to 0.84)). Because this study was a non-inferiority trial with a difference between treatments less than the prespecified non-inferiority margin of one episode per person year, the authors reported that methenamine hippurate was no worse than antibiotics at preventing urinary tract infection. Patient partnership guided the non-inferiority margin chosen, along with the decision to use a clinical definition rather than a microbiological definition of urinary tract infection for the primary outcome.

Regardless of the prophylactic intervention taken, about half the women had a recurrent infection during the 12 months.

COMMENTARY New trial increases confidence in this non-antibiotic alternative

Over half of women have at least one urinary tract infection in their lifetime.[1] Recurrence (that is, at least three repeated infections per year or two infections in the preceding six months) occurs in about a quarter of women who have one episode.[2] Daily low dose antibiotics is the prophylactic intervention recommended by current guidelines.[3 4] Women with recurrent urinary tract infection describe frustration about the condition, its management, fears about frequent antibiotic use and consequences such as adverse events and resistance, and a desire for non-antibiotic alternative research.[5 6] Given the increasing global burden of antibiotic resistance,[7] strategies that minimise unnecessary antibiotic use are paramount at both individual and community level.

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Given the increasing global burden of antibiotic resistance, strategies that minimise unnecessary antibiotic use are paramount

Methenamine hippurate is a urinary antiseptic and non-antibiotic alternative. Systematic reviews[8 9] synthesising existing trials concluded that while methenamine hippurate might be effective, the evidence is inconclusive, and large, well conducted randomised trials are needed. In this issue, Harding and colleagues report a large trial (n=240) of women presenting with recurrent, uncomplicated urinary tract infection who were randomised to receive methenamine hippurate or low dose antibiotics for 12 months.[10]

The primary outcome was incidence of symptomatic urinary tract infection treated with antibiotics. Although self-reported, the diagnosis needed clinician confirmation, and clinicians recommended any antibiotic treatment.

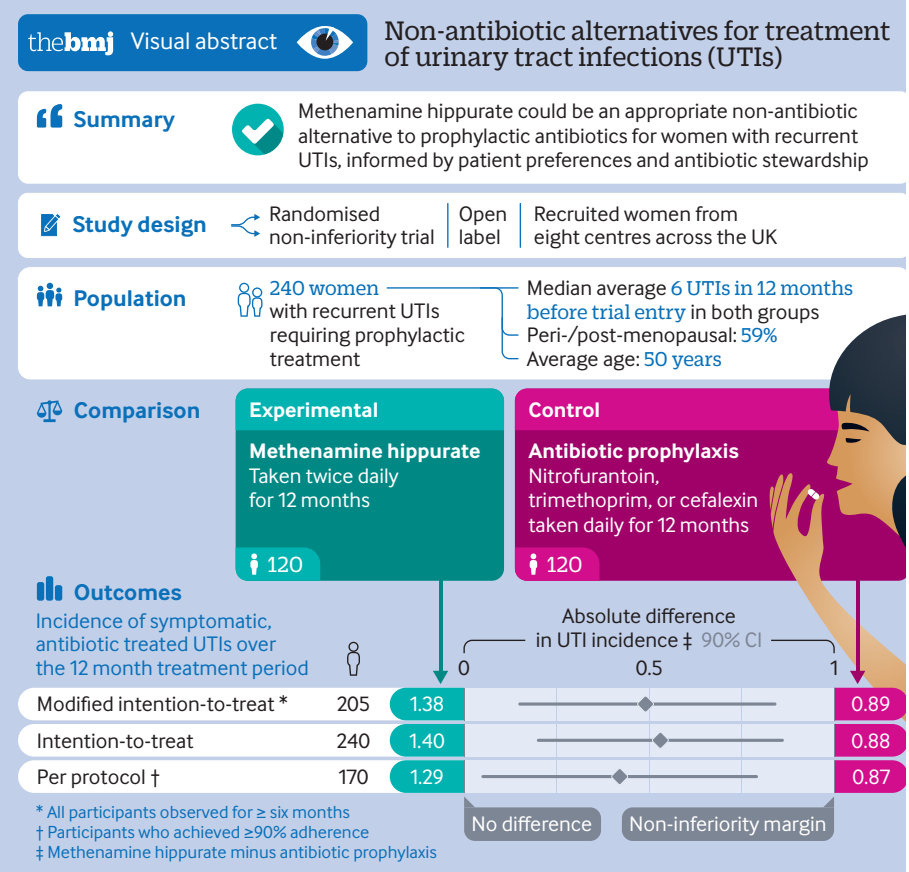
Over 12 months, the incidence of antibiotic treated urinary tract infection

(95% confidence interval 0.65 to 1.12) in the antibiotic group and 1.38 (1.05 to 1.72) in the methenamine hippurate group, with an absolute difference of 0.49 (90% confidence interval 0.15 to 0.84) confirming non-inferiority. Adverse reactions were reported by 34/142 (24%) and 35/127 (28%) participants receiving antibiotics and methenamine hippurate, respectively, and most reactions were mild. Study limitations included the lack of blinding and the lack of meaningful subanalyses according to the individual antibiotic.

What this study adds These findings suggest that non-antibiotic treatment with methenamine hippurate might be appropriate for women with a history of recurrent UTI episodes, informed by patient preferences and antibiotic stewardship initiatives.

Funding, competing interests, and data sharing
Funded by the National Institute for Health Research Health Technology Assessment Programme. No competing interests declared. Data sharing requests will be considered.

Trial registration ISRCTN70219762.



Balanced decisions

Balanced decisions require consideration of harms and treatment acceptability, as well as possible benefits. The number of adverse events and reactions was low and similar across the randomised groups, although the two serious adverse reactions were both in the antibiotic group and all four hospital admissions related to urinary tract infection and all six episodes of febrile infection occurred in the methenamine hippurate group. Long term safety data are lacking for methenamine hippurate. Treatment satisfaction was high and comparable between the groups, although women who took once daily antibiotic prophylaxis reported higher convenience scores than those taking twice daily methenamine hippurate.

One motivation to find effective non-antibiotic alternatives is to minimise antibiotic resistance, yet few methenamine hippurate trials have measured this outcome reliably. Harding and colleagues measured resistance in *Escherichia coli* isolated from perineal swabs as a secondary outcome. However, it was optional for participants to provide swabs every six months, with more missing data as the trial progressed. Only about half of participants provided an 18 month swab, introducing uncertainty. At six and 12 months, resistance rates to at least one antibiotic were higher in the antibiotic prophylaxis group than the methenamine hippurate group (72% *v* 56%, P=0.05), but at 18 months, the rate of multidrug resistance was higher in the methenamine hippurate group (20% *v* 5%, P=0.06).

Harding and colleagues conducted a non-blinded pragmatic trial, and appropriately acknowledge most caveats and limitations. For example, because several antibiotics were used (trimethoprim, nitrofurantoin, or cefalexin) and subgroup analyses were uninformative, how methenamine hippurate compares with different antibiotics remains unknown. Although the results need cautious interpretation, they align with others,[11] and this new research increases the confidence with which methenamine hippurate can be offered as an option to women needing prophylaxis against recurrent urinary tract infection.

Whether the non-inferiority margin (one episode of urinary tract infection) used in this trial was of the right magnitude to capture any clinically meaningful difference between treatments will likely inspire debate. However, we agree with the authors that decisions on preventive treatment for recurrent urinary tract infection are well suited to shared decision making,[12] where options are presented, the benefits and harms of each option are discussed, and each patient's values and preferences are considered before patients and clinicians decide together on the next steps. Harding and colleagues' trial will help to inform this important conversation.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.o533

Global, regional, and national burden of diseases and injuries for adults aged 70 years and older

GBD 2019 Ageing Collaborators

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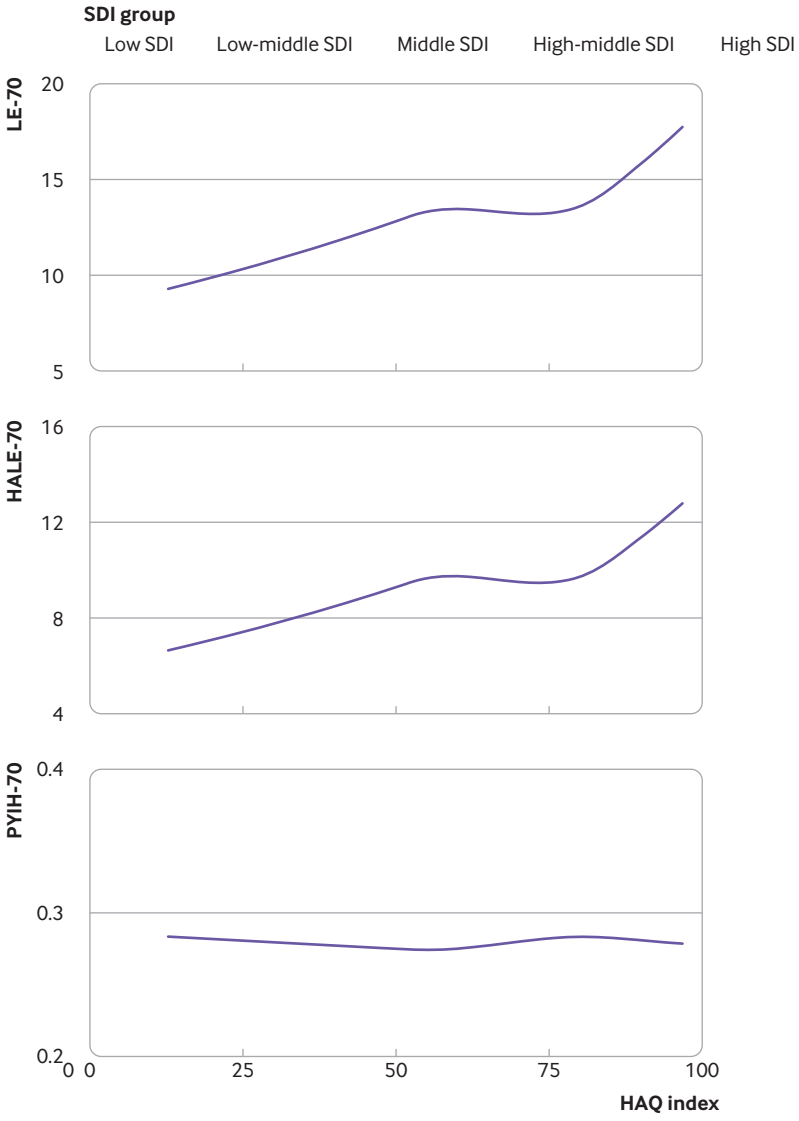
Find this at doi: 10.1136/bmj-2021-068208

Study question Using data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019), what are the mortality and disability trends for adults aged 70 and older, and are there patterns in causes of death, disability, and risk factors?

Methods Standardised GBD 2019 methods were used to analyse all cause mortality, cause specific mortality, and non-fatal disease burden by sex for adults aged 70 and older from 204 countries and territories between 1990 and 2019. Years of life lost, years lived with disability, disability adjusted life years, life expectancy at age 70 (LE-70), healthy life expectancy at age 70 (HALE-70), proportion of years in ill health at age 70 (PYIH-70), risk factors, and data coverage index were estimated.

Study answer and limitations Globally, the population of older adults has increased since 1990, and all cause death rates have decreased for men and women. However, mortality rates due to falls increased between 1990 and 2019. The probability of death among people aged 70-90 decreased, mainly because of reductions in non-communicable diseases. Globally, disability burden was largely driven by functional decline, vision and hearing loss, and painful conditions. LE-70 and HALE-70 showed continuous increases since 1990 globally, with certain regional disparities. Globally, higher LE-70 resulted in higher HALE-70 and slightly increased PYIH-70. Sociodemographic and healthcare access and quality indices were positively correlated with HALE-70 and LE-70. For high exposure risk factors, data coverage was moderate, while limited data were available for various dietary, environmental or occupational, and metabolic risks. Sources of uncertainty, lags in data availability, and variation in coding practices and other biases could not be fully quantified.

What this study adds Life expectancy at age 70 has continued to rise globally. Adults aged 70 and older living in high income countries and regions with better healthcare access and quality were found to experience the highest life expectancy and healthy life expectancy. Disability burden, however, remained constant.



Epidemiological transition in life expectancy at age 70 (LE-70), healthy life expectancy at age 70 (HALE-70), proportion of years spent in ill health at age 70 (PYIH-70) as a function of healthcare access and quality (HAQ) index for men and women, 2019. Dots represent countries and different colour coding represents sociodemographic index (SDI) group

Funding, competing interests, and data sharing Supported by the Bill & Melinda Gates Foundation and Center for Health Trends and Forecasts. No competing interests declared. GBD study data publicly available at healthdata.org