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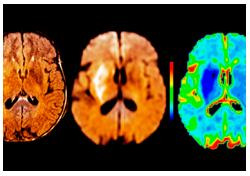
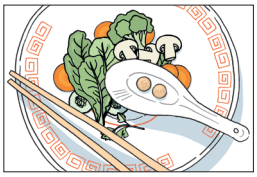


Tenecteplase after recanalisation in patients with stroke p 77



Dapaglifozin and calorie restriction for diabetes remission p 78

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ORIGINAL RESEARCH Multicentre randomised controlled trial

Intra-arterial tenecteplase after successful endovascular recanalisation in patients with acute posterior circulation arterial occlusion (ATTENTION-IA)

Hu W, Tao C, Wang L, et al

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Find this at doi: 10.1136/bmj-2024-080489

Study question Does intra-arterial tenecteplase administered after successful endovascular recanalisation improve 90 day functional outcomes in patients with acute posterior circulation arterial occlusion?

Methods This prospective, randomised, blinded endpoint clinical trial was conducted in 31 hospitals in China. A total of 208 patients with successful recanalisation (grade 2b50-3 on the extended thrombolysis in cerebral infarction scale) of an occlusion in the V4 segment of the vertebral artery; proximal, middle, or distal section of the basilar artery; or P1 segment of the posterior cerebral artery were enrolled. Patients were randomised to either intra-arterial tenecteplase (0.0625 mg/kg, maximum dose 6.25 mg) administered proximal to the residual thrombus (if still present) or distal to the origin of the main pontine perforator branches over 15 seconds, or endovascular treatment only (control group). The primary outcome was functional independence (modified Rankin scale score 0 or 1) at 90 days after randomisation. Safety outcomes included symptomatic intracranial haemorrhage within 36 hours and 90 day mortality. All efficacy and safety analyses were conducted by intention to treat and adjusted for age, pre-stroke modified Rankin scale score, time from onset of moderate to severe stroke (National Institutes of Health stroke scale score ≥6) to randomisation, hypertension, and baseline stroke severity.

Study answer and limitations At 90 days, 36 patients (34.6%) in the tenecteplase group and 27 (26.0%) in the control group had a modified Rankin scale score of 0 or 1 (adjusted risk ratio 1.36, 95% confidence interval (CI) 0.92 to 2.02; P=0.12). All cause mortality within 90 days was similar between the tenecteplase and control groups: 29 (27.9%) versus 28 (26.9%), adjusted risk ratio 1.13, 0.73 to 1.74. Symptomatic intracranial haemorrhage within 36 hours occurred in eight patients (8.3%) in the tenecteplase group and three (3.1%) in the control group (adjusted risk ratio 3.09, 0.78 to 12.20). Weaknesses included the exclusive enrolment of Chinese patients, which limited generalisability to western populations, and the open label design.

What this study adds In patients with acute ischaemic stroke due to acute posterior large or proximal vessel occlusion, intra-arterial tenecteplase administered after successful recanalisation was not associated with a statistically significant reduction in combined disability and mortality at 90 days.

Funding, competing interests, and data sharing Funded by the Fundamental Research Funds for the Central Universities. No competing interests declared. Data sharing is available on request.

Study registration ClinicalTrials.gov NCT05684172.

Dapaglifozin and calorie restriction for diabetes remission

ORIGINAL RESEARCH Multicentre, double blind, randomised, placebo controlled trial

Dapagliflozin plus calorie restriction for remission of type 2 diabetes

Liu Y, Chen Y, Ma J, et al

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Find this at doi: 10.1136/bmj-2024-081820

Study question Is the combined regimen of dapagliflozin and calorie restriction a practicable method to achieve remission of type 2 diabetes?

Methods This multicentre, double blind, randomised, placebo controlled trial enrolled 328 patients with type 2 diabetes aged 20-70 years, with body mass index >25 and duration of diabetes less than six years in 16 centres in mainland China from June 2020 to January 2023. Participants were assigned in a one-to-one ratio to calorie restriction with dapagliflozin 10 mg/day or placebo. The primary outcome was the incidence of remission of diabetes (defined as glycated haemoglobin <6.5% and fasting plasma glucose <126 mg/dL in the absence of all antidiabetic drugs for at least two months) over 12 months.

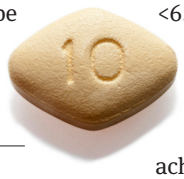
Effects of dapagliflozin compared with placebo on diabetes remission and metabolic risk factors. Values are means (SD) unless stated otherwise

	Dapagliflozin (n=165)	Placebo (n=163)	Intervention effect (95% CI)*	P value
Primary outcome				
No (%) in diabetes remission	73 (44)	46 (28)	1.56 (1.17 to 2.09)	0.002
Secondary outcomes				
Change in body weight, kg	−5.0 (4.5)	−3.2 (3.8)	−1.3 (−1.9 to −0.7)	<0.001
Change in waist circumference, cm	−5.6 (5.7)	−4.9 (5.9)	−0.5 (−1.2 to 0.1)	0.11
Change in fat mass, %	−2.1 (2.8)	−1.4 (3.4)	−0.5 (−0.9 to 0)	0.05
Change in lean mass, %	2.1 (3.2)	1.2 (4.2)	0.2 (−0.3 to 0.8)	0.42
Change in systolic blood pressure, mm Hg	−4.0 (12.3)	−3.6 (13.1)	−1.9 (−3.0 to −0.7)	0.002
Change in diastolic blood pressure, mm Hg	−1.4 (8.7)	−1.3 (8.8)	−0.3 (−1.2 to 0.6)	0.47
Change in fasting plasma glucose, mg/dL	−23.4 (25.0)	−13.8 (29.1)	−9.2 (−11.8 to −6.7)	<0.001
Change in HbA_{1c}, %	−1.0 (1.0)	−0.8 (0.9)	−0.2 (−0.3 to −0.1)	0.003
Median (IQR) change in HOMA-IR	−1.8 (−3.7-−0.2)	−0.6 (−2.0-0.6)	−0.8 (−1.1 to −0.4)	<0.001
Median (IQR) change in HOMA-β, %	4.0 (−16.8-25.0)	2.8 (−12.7-20.8)	−0.7 (−6.3 to 5.0)	0.82
Change in total cholesterol, mg/dL	5.1 (35.4)	−1.0 (34.1)	2.1 (−1.5 to 5.6)	0.26
Change in low density lipoprotein cholesterol, mg/dL	0.9 (29.4)	−2.7 (31.7)	2.1 (−1.0 to 5.2)	0.19
Change in high density lipoprotein cholesterol, mg/dL	4.8 (6.9)	2.3 (6.2)	1.3 (0.4 to 2.2)	0.003
Change in triglycerides, mg/dL	−17.3 (−62.0-7.1)	−4.4 (−35.4-20.4)	−16.4 (−31.3 to −1.6)	0.03

CI=confidence interval; HbA_{1c}=glycated haemoglobin; HOMA-IR=homoeostasis model assessment of insulin resistance; HOMA-β=homoeostasis model assessment of β cell function; IQR=interquartile range; SD=standard deviation.
*Risk ratio (95% CI) for primary outcome. Estimated mean difference (95% CI) for secondary outcomes; that is, effect of dapagliflozin minus that of placebo, from mixed effects linear regression model with metformin treatment as stratification factor, study centre as random effect, and baseline value, treatment group, time, and their interaction as fixed effects. Changes in each group are defined as values measured when diabetes remission was determined (2 months after either dapagliflozin or placebo was stopped) minus those measured at baseline; in participants who discontinued trial in advance or did not meet drug stopping criteria, changes are reported as values measured at final visit minus those measured at baseline.

COMMENTARY Combined strategy is effective but questions remain

The view that the hyperglycaemia associated with type 2 diabetes is inexorably progressive was challenged by the publication of the DiRECT study in 2018.[1 2] Through a mean weight loss of 10 kg achieved by a period of total diet replacement (often referred to as the "soups and shakes" diet), 46% of participants achieved remission of type 2 diabetes at 12 months. The longer term sustainability of the remission achieved is less clear, with 36% still in remission at two years in the DiRECT study but only 13% at five years with continued support.[3 4] The English NHS Type 2 Diabetes Path to Remission Programme provides access to similar interventions in the real world for people within six years of diagnosis of type 2 diabetes and body mass index >27 (appropriately adjusted according to ethnicity), with 12 month remission rates of approximately 30%.[5] Around 35 000 people have now been referred into the national programme.



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The linked study by Liu and colleagues (doi:10.1136/bmj-2024-081820) investigated the combined effect of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor dapagliflozin with calorie restriction on remission of type 2 diabetes over 12 months.[6] They used a moderate calorie restriction (reduction by 500-750 kcal/day) for participants in both arms, which they argue is more practical and acceptable than the more restrictive total diet replacement approach adopted in DiRECT. Remission of type 2 diabetes was defined as glycated haemoglobin (HbA_{1c}) <6.5% and fasting glucose of <7.0 mmol/L in the absence of any glucose lowering medication for at least two months.

Remission of type 2 diabetes was achieved in 44% of participants in the calorie restriction plus dapagliflozin group over a 12 month period (median 9 months) compared with 28% in those on calorie restriction alone (risk ratio 1.56, 95% confidence interval 1.17 to 2.09). Changes in body weight were modest (−5.0 kg in the combined group versus −3.2 kg in the calorie restriction alone group). Two serious adverse events (admission to hospital for urinary tract infections) were reported in the dapagliflozin group, with mild and moderate adverse events being similar across the two groups.

Putting findings in context

The study highlights important considerations around the remission levels in both study groups. In the calorie restriction plus dapagliflozin arm, despite a mean body weight loss of only 5 kg, remission levels were comparable to those observed at 12 months in the DiRECT trial, in which a 10 kg mean weight loss was achieved.[2] In the calorie restriction alone arm, despite a mean weight loss of only 3.2 kg, remission levels were also impressive and comparable to those seen in the real

Study answer and limitations The incidence of diabetes remission was higher in the dapagliflozin group (73/165; 44%) than in the placebo group (46/163; 28%) (risk ratio 1.56, 95% confidence interval 1.17 to 2.09) over 12 months, meeting the predefined primary endpoint. Changes in body weight, body fat, systolic blood pressure, and metabolic risk factors were also significantly greater in the dapagliflozin group than in the placebo group. No significant differences were seen between the two groups in the occurrence of adverse events. The findings cannot be generalised to patients with type 2 diabetes of more than six years' duration or to populations of other races or ethnic groups.

What this study adds The combined regimen of dapagliflozin and regular calorie restriction provides an alternative and practical strategy to achieve remission for patients with early type 2 diabetes.

Funding, competing interests, and data sharing
This study was funded by the grants from the National Nature Science Foundation of China, National Nature Science Foundation of China for Distinguished Young Scholars, and AstraZeneca. The authors have no competing interests to declare. Data from this study can be requested from the corresponding author.

Study registration ClinicalTrials.gov NCT04004793.

A challenge is long term sustainability of remission related to maintenance of weight loss

world in the NHS Type 2 Diabetes Path to Remission Programme with a much greater calorie restriction (just over 800 kcal/day) and mean weight loss of 9.4 kg. Could participants' baseline characteristics have influenced these results? Early evaluation of the NHS Type 2 Diabetes Path to Remission Programme shows that shorter duration of type 2 diabetes and lower baseline HbA_{1c} are independent predictors of higher remission rates.[5] Liu and colleagues report a short median duration of diabetes of 0.3 years and 0.2 years in the dapagliflozin and placebo arms, respectively.[6] This is a notably shorter duration than in both the DIADEM-I and DiRECT trials in addition to the Path to Remission Programme, the last two of which also reported slightly higher baseline HbA_{1c} values.[2-7] Metformin was taken by approximately half of the participants in each study arm and continued for at least four months, in contrast to the DiRECT trial in which this was stopped on initiation of total diet replacement.

The marked increase in type 2 diabetes remission levels with the addition of dapagliflozin to moderate calorie restriction is notable, showing the efficacy of this combination strategy. Mechanistically, SGLT-2 inhibitor driven glycosuria results in a more selective energy deficit that mimics the effects of dietary calorie restriction on energy metabolism, possibly permitting less dietary calorie restriction for a similar effect size.[8]

What we still don't know

Total diet replacement interventions for remission of type 2 diabetes have been successfully implemented at a population level for eligible and willing people with recent onset of type 2 diabetes.[5] A challenge is long term sustainability of remission related to maintenance of weight loss,[9] and a combination strategy may be attractive in the new era of obesity pharmacotherapy.[10] Aside from the potent glycosuric effects of SGLT-2 inhibitors, newer incretin mimetics achieve potent weight loss and high levels of normoglycaemia.[11 12]

Should such glucose lowering drugs be discontinued at the point of remission, and is the loss of cardiovascular or renal protection offset by the delay in type 2 diabetes? Can specific drug mechanisms be harnessed for a more individualised approach to remission of type 2 diabetes? Despite the low adverse event rate highlighted in this study, the drug safety profile in a combined strategy also needs to be evaluated. The optimal balance of lifestyle components needs to be considered; achieving remission through less intense calorie restriction may prove more inclusive at the population level and may also serve to reduce interventional unit cost. Despite these uncertainties, SGLT-2 inhibitors are now co-first line drugs (with metformin) for many patients with type 2 diabetes.[13] The study by Liu and colleagues supports more research into combined approaches to achieving successful and sustainable remission of type 2 diabetes.[6]

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r40

Individualised care for cervical precancer

ORIGINAL RESEARCH Register based nationwide cohort study

Short term complications of conisation and long term effects on fertility related outcomes in Denmark

Aagaard M, á Rogvi J, Modin F, et al

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Find this at doi: 10.1136/bmj-2023-078140

Study question Does conisation affect rates of infertility treatment or infertility diagnoses, and are numbers of reported short term complications of conisation accurate at a population level?

Methods This retrospective cohort study used routinely collected data from several Danish registers. The study population comprised women living in Denmark who had at least one cervical biopsy in hospital or in the primary care sector from 2006 to the end of 2018. The conisation cohort included 48 048 conisations on women aged 23-65 who had undergone the procedure within 120 days of a cervical biopsy. The biopsy cohort comprised 48 048 biopsies on women who had undergone a cervical biopsy but not conisation and were matched by age and time of procedure. Short term outcomes investigated were infection, bleeding, and gynaecological operations within 30 days of conisation. Long term fertility related outcomes were analysed using incidence rate ratios from Cox regression models.

Study answer and limitations Bleeding, infection, and gynaecological operations were registered for 2.81% (n=1351), 0.48% (n=231), and 3.95% (n=1897) of all conisations within 30 days of the procedure, respectively. These frequencies are higher than previous studies with comparable outcome definitions. Women in the conisation cohort had increased risk of stenosis (incidence rate ratio 14.81, 95% confidence interval 7.55 to 29.05, 0.41% *v* 0.03% (n=176 *v* 12)) and cervical dilatation (2.68, 2.41 to 2.97, 4.01% *v* 1.58% (n=1735 *v* 668)) compared with women in the biopsy cohort. No significant differences were observed for the other outcomes when adjusting for baseline covariates (such as age and region of residence). Cervical suturing after bleeding was associated with a substantial increase in the risk of stenosis and cervical dilatation. Results for women treated with cervical suturing after conisation were based on few events in a small subgroup, and are therefore associated with major uncertainty.

What this study adds Conisation does not increase rates of infertility treatment, regardless of whether women subsequently give birth, and it does not increase rates of infertility diagnoses. Short term complications after conisation that require hospital assessment are not infrequent.

Funding, competing interests, and data sharing
Funded by the Lundbeck Foundation and supported by The Centre of General Practice, Faculty of Health and Medical Sciences (University of Copenhagen). No competing interests declared. Data available through Danish public registers.

Long term outcomes in conisation cohort compared with biopsy cohort (Denmark, 2006-18)

Outcomes	Incidence (%)	Incidence rate (95% CI)	IRR unadjusted (95% CI)	P value	IRR adjusted* (95% CI)	P value
Stenosis						
Conisation cohort	176 (0.41)	0.67 (0.58 to 0.78)	14.81 (7.55 to 29.05)	<0.001	12.57 (6.33 to 24.96)	<0.001
With cervical sutures†	—‡	14.2 (1.72 to 51.30)	269.29 (67.44 to 1075.3)	<0.001	372.66 (115.47 to 1202.7)	<0.001
Biopsy cohort	12 (0.03)	0.04 (0.02 to 0.08)	—	—	—	—
Cervix dilatation						
Conisation cohort	1735 (4.01)	6.86 (6.54 to 7.19)	2.68 (2.41 to 2.97)	<0.001	2.83 (2.56 to 3.14)	<0.001
With cervical sutures†	—‡	14.64 (1.77 to 52.88)	5.48 (1.33 to 22.59)	0.02	6.15 (1.44 to 26.23)	0.01
Biopsy cohort	668 (1.58)	2.53 (2.35 to 2.73)	—	—	—	—
Fertility consultation						
Conisation cohort	2451 (5.66)	9.69 (9.31 to 10.08)	0.90 (0.85 to 0.95)	0.001	0.96 (0.91 to 1.02)	0.18
With cervical sutures†	—‡	13.42 (1.63 to 48.48)	1.23 (0.29 to 5.12)	0.78	2.75 (0.64 to 11.79)	0.17
Biopsy cohort	2762 (6.55)	10.79 (10.39 to 11.20)	—	—	—	—
Fertility treatment						
Conisation cohort	1337 (3.09)	5.21 (4.94 to 5.50)	0.92 (0.85 to 1.00)	0.05	0.98 (0.90 to 1.06)	0.66
With cervical sutures†	—‡	6.60 (0.17 to 36.75)	1.17 (0.16 to 8.45)	0.88	2.81 (0.36 to 22.27)	0.33
Biopsy cohort	1474 (3.50)	5.66 (5.38 to 5.96)	—	—	—	—
Infertility diagnosis						
Conisation cohort	623 (1.44)	2.40 (2.22 to 2.60)	1.02 (0.91 to 1.15)	0.75	1.01 (0.90 to1.13)	0.85
With cervical sutures†	0 (0.00)	0	—	—	—	—
Biopsy cohort	621 (1.47)	2.35 (2.22 to 2.60)	—	—	—	—
All cause death						
Conisation cohort	301 (0.70)	1.15 (1.02 to 1.28)	1.02 (0.87 to 1.20)	0.80	0.95 (0.81 to 1.12)	0.53
With cervical sutures†	0 (0.0)	0	—	—	—	—
Biopsy cohort	300 (0.71)	1.12 (1.00 to 1.26)	—	—	—	—

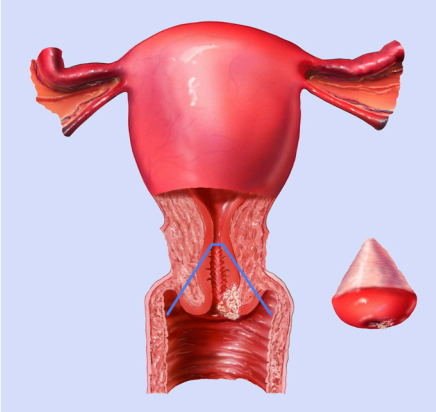
Data are incidence rate per 1000 women years and incidence rate ratios (IRRs) with 95% confidence intervals (CIs).
*Adjusted for the following covariates at baseline: age, marital status, equivalent disposable annual income, educational attainment level, country of origin, region of residence, occupational status, number of children in household, and Charlson comorbidity index.
†Occurrence of outcomes for conisations treated with cervical sutures for bleeding within 30 days of conisation.
‡Cumulative incidence is not reported when outcomes occur fewer than five times owing to regulations.

COMMENTARY Decision to treat surgically should be weighed against the rate of complications

The introduction of organised cervical screening programmes has enabled the early diagnosis and treatment of cervical intraepithelial neoplasia (CIN), reducing the incidence of invasive cervical cancer and mortality from the disease.[1] However, surgical treatments for CIN that excise a cone shaped part of the cervix are not without complications. In a large linked study from Denmark (doi:10.1136/bmj-2023-078140), Aagaard and colleagues obtained data from nationwide registries and investigated short and long term complication rates after conisation for CIN.[2] The authors compared the outcomes for more than 48 000 women who underwent conisation with a matched population who had colposcopically directed biopsy alone.

The authors explored long term outcomes that included cervical stenosis, fertility related consultations or treatment, infertility diagnosis, and death. The adjusted incidence rate ratio of cervical stenosis for treated women compared with untreated women was 12.6. This risk increased with age and increasing number of conisations. The use of cervical sutures to control intraoperative or postoperative bleeding increased the adjusted incidence rate ratio of cervical stenosis to 372.7, although there was uncertainty as shown by the large confidence intervals, probably because of the limited number of women who had this complication. This increased risk could be attributed to the suturing technique, which causes the cervical crater lips to converge.

Cervical stenosis has been thought to inhibit sperm penetration and conception, but this large population based study found no effect of treatment on subsequent need for fertility consultation or treatment. Although data were more inconclusive for the small cohort of treated women who had cervical sutures or several conisations, overall findings were in agreement with previous meta-analyses that reported an increase in second trimester miscarriage and preterm birth but no impact on fertility or first trimester miscarriage.[4-6] The association between untreated CIN and fertility is less well understood.



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Fertility is unlikely to be affected after the procedure

Clinical implications and complications

Although cervical stenosis does not appear to have an impact on future fertility, it could have other clinical implications. Stenosis might impair the collection of adequate cytology samples in women with high risk human papillomavirus after treatment, and affect the accuracy of colposcopic assessment owing to incomplete visualisation of the transformation zone. Therefore, cervical stenosis might adversely affect the accuracy of follow-up in women known to be at high risk of future invasive cervical cancer for at least 20 years after treatment compared with the general population.[7-9]

The authors reported an overall 6.3% risk of at least one short term complication within 30 days, which included bleeding, infection, and subsequent gynaecological operations. This risk was four and a half times higher than having a biopsy alone. The rate was greater among women with two or more previous conisations (17.0%), followed by those with one previous conisation (9.8%), or those with no previous conisation (6.0%). Complication rates were also higher among older women, which could reflect the need for deeper excisions owing to higher rates of type 3 transformation zones in this group.

The high rate of treatment complications should be considered when making treatment decisions. Clinicians should carefully consider the need for treatment, taking into account the patient's age, fertility wishes, and disease characteristics. Low grade CIN (CIN1) should be managed conservatively in young women because this reflects a state of viral replication with no true carcinogenic potential in most patients.[10] When considering treatment for high grade CIN (CIN2 or CIN3), at the moment, all women with CIN3, regardless of age, must inevitably be treated. However, the high spontaneous regression rates of CIN2 of up to 60% in women younger than 30 should be balanced against the long term cumulative risk of invasion.[11 12]

Balancing benefits and harms

When making a decision to treat, every effort should be made to balance clearance that will minimise the need for further excisions, while preserving healthy cervical tissue. Increasing length of excision increases reproductive morbidity,[5] and this might explain why this study reported that women who had undergone several previous conisations were more likely to have fertility treatment. Although the treatment technique is not specified in this study owing to lack of registry data, it is known that more radical excisions like cold knife conisations remove more tissue and have higher complication rates than less radical excisions such as large loop excisions of the transformation zone.[13] Treatments should be tailored to each woman's characteristics and lesion, and only be performed under colposcopic guidance to balance oncological and reproductive outcomes, and other complications discussed in this study. This process can only be achieved with continuous, high quality training.[14]

A major limitation of this study was the lack of data on treatment technique and the length and volume of the tissue excised.

To conclude, this study adds to our knowledge about the complications after conisation, and overall confirms that fertility is unlikely to be affected after the procedure, although the impact on fertility from cervical sutures and several excisions might be higher. However, given the data presented on the risk of other complications including cervical stenosis, this study highlights the importance of carefully considering the need for local surgical treatment in the context of the individual patient, her history, lesion, and reproductive wishes.

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Relative efficacy of prehabilitation interventions and their components

McIsaac DI, Kidd G, Gillis C, et al

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Find this at doi: 10.1136/bmj-2024-081164

Study question What prehabilitation components, or combinations of components, are most likely to improve complication rates, length of stay, health related quality of life, or physical recovery after surgery?

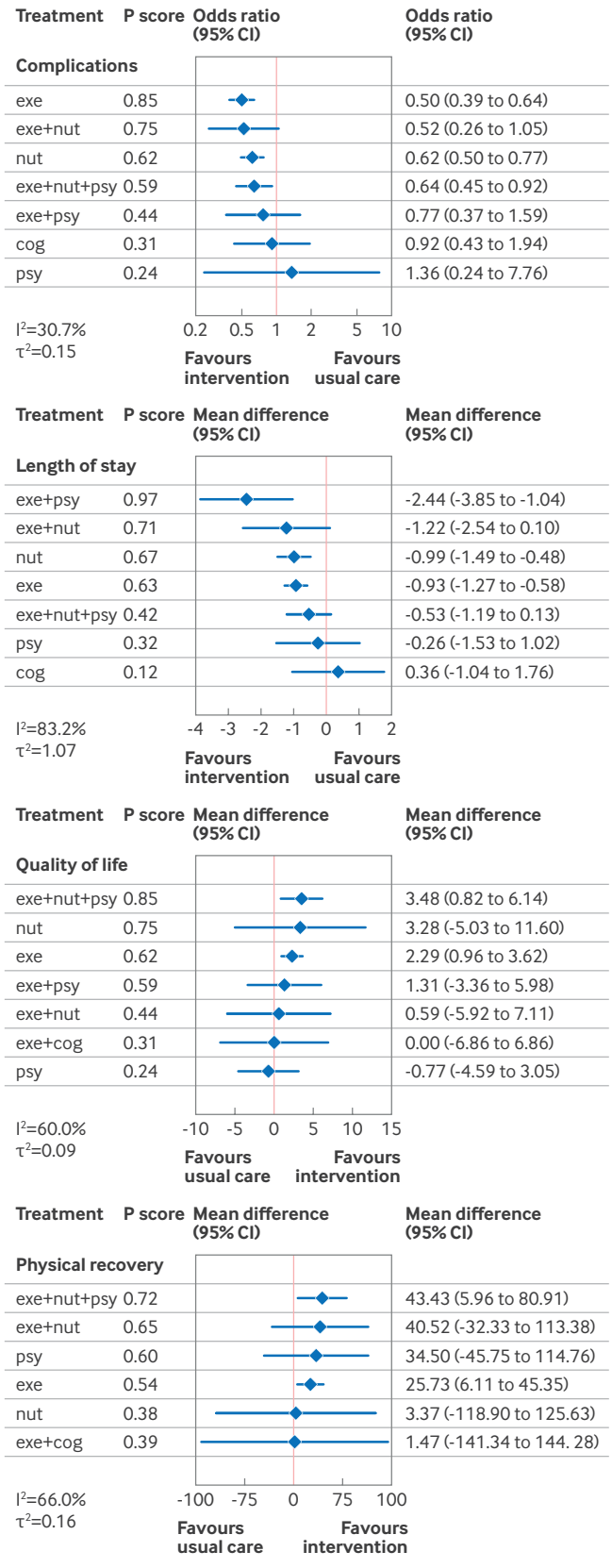
Methods A systematic review with network meta-analysis (to compare treatments) and component network meta-analysis (to compare individual components) was conducted and informed by partnership with patients, clinicians, researchers, and health system leaders. Medline, Embase, PsycINFO, CINAHL, Cochrane Library, and Web of Science were searched on 1 March 2022, and updated on 25 October 2023. Randomised controlled trials of adults preparing for major surgery were identified in which patients were allocated to prehabilitation interventions or usual care and where critical outcomes were reported. Random effects network meta-analysis and component network meta-analysis were used to generate summary effect estimates. Certainty in findings was assessed using the Confidence in Network Meta-Analysis (CINeMA) approach.

SPL

Study answer and limitations 186 unique randomised controlled trials with 15 684 participants were included. Prehabilitation interventions based on isolated exercise (odds ratio 0.50 (95% confidence interval (CI) 0.39 to 0.64)), or exercise in combination with other components, were most likely to improve complication rates, length of stay, health related quality of life and physical recovery. Nutrition was also a promising component (−0.99 days of stay (−1.49 to −0.48)). Certainty of these results, however, was primarily low to very low due to trial level bias and imprecision.

What this study adds Exercise prehabilitation, nutritional prehabilitation, and multicomponent interventions that included exercise may benefit adult patients before surgery.

Funding, competing interests, and data sharing Canadian Institutes of Health Research supported this research. The authors had no other financial relationships with any organisations that might have an interest in the submitted work in the previous three years; CG has received honorariums from Abbott Nutrition, Nestle Nutrition, and Fresenius Kabi for lectures unrelated to this work; no other authors have relationships or activities that could appear to have influenced the submitted work. Study data are available from the primary author on request.



Treatment effects obtained from treatment level network meta-analysis for all outcomes (active interventions *v* usual care; postoperative complications, length of stay in hospital, quality of life, physical recovery). P score measures of treatment ranking are also provided (range 0-1, where values nearer 1 indicate preferred interventions). cog=cognitive; exe=exercise; nut=nutrition; psy=psychosocial; UC=usual care