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BMJ (7 July 2018, Vol. 362, No. 8160)

Periconception glycaemic control in women with type 1 diabetes and risk of major birth defects: Population based cohort study in Sweden
Jonas F Ludvigsson, Martin Neovius, Jonas Söderling, et al.
BMJ 2018; 362 (Published 05 July 2018)
https://www.bmj.com/content/362/bmj.k2638

Abstract
Objective To examine the association between maternal type 1 diabetes and the risk of major birth defects according to levels of glycated haemoglobin (HbA1C) within three months before or after estimated conception.
Design Population based historical cohort study using nationwide health registers.
Setting Sweden, 2003-15.
Participants 2458 singleton liveborn infants of mothers with type 1 diabetes and a glycated haemoglobin measurement within three months before or after estimated conception and 1 159 865 infants of mothers without diabetes.
Main outcome measures Major cardiac and non-cardiac birth defects according to glycated haemoglobin levels.
Results 122 cases of major cardiac defects were observed among 2458 infants of mothers with type 1 diabetes. Compared with 15 cases of major cardiac defects per 1000 infants of mothers without diabetes, the rates among infants of mothers with type 1 diabetes were 33 per 1000 for a glycated haemoglobin level of <6.5% (adjusted risk ratio 2.17, 95% confidence interval 1.37 to 3.42), 49 per 1000 for 6.5% to <7.8% (3.17, 2.45 to

4.11), 44 per 1000 for 7.8% to <9.1% (2.79, 1.90 to 4.12), and 101 per 1000 for ≥9.1% (6.23, 4.32 to 9.00). The corresponding adjusted risk differences were 17 (5 to 36), 32 (21 to 46), 26 (13 to 46), and 77 (49 to 118) cases of major cardiac defects per 1000 infants, respectively. 50 cases of major non-cardiac defects were observed among infants of mothers with type 1 diabetes. Compared with 18 cases of major non-cardiac defects per 1000 infants of mothers without diabetes, the rates among infants of mothers with type 1 diabetes were 22 per 1000 for a glycated haemoglobin level of <6.5% (adjusted risk ratio 1.18, 0.68 to 2.07), 19 per 1000 for 6.5% to <7.8% (1.01, 0.66 to 1.54), 17 per 1000 for 7.8% to <9.1% (0.89, 0.46 to 1.69), and 32 per 1000 for ≥9.1% (1.68, 0.85 to 3.33).
Conclusion Among liveborn infants of mothers with type 1 diabetes, increasingly worse glycaemic control in the three months before or after estimated conception was associated with a progressively increased risk of major cardiac defects. Even with glycated haemoglobin within target levels recommended by guidelines (<6.5%), the risk of major cardiac defects was increased more than twofold. The risk of major non-cardiac defects was not statistically significantly increased at any of the four glycated haemoglobin levels examined; the study had limited statistical power for this outcome and was based on live births only.

Association between maternal adherence to healthy lifestyle practices and risk of obesity in offspring: Results from two prospective cohort studies of mother-child pairs in the United States

Klodian Dhana, Jess Haines, Gang Liu, et al.
BMJ 2018; 362 (Published 04 July 2018)
https://www.bmj.com/content/362/bmj.k2486

Abstract
Objective To examine the association between an overall maternal healthy lifestyle (characterized by a healthy body mass index, high quality diet, regular exercise, no smoking, and light to moderate alcohol intake) and the risk of developing obesity in offspring.
Design Prospective cohort studies of mother-child pairs.
Setting Nurses' Health Study II (NHSII) and Growing Up Today Study (GUTS) in the United States.
Participants 24 289 GUTS participants aged 9-14 years at baseline who were free of obesity and born to 16 945 NHSII women.
Main outcome measure Obesity in childhood and adolescence, defined by age and sex specific cutoff points from the International Obesity Task Force. Risk of offspring obesity was evaluated by multivariable log-binomial regression models with generalized estimating equations and an exchangeable correlation structure.
Results 1282 (5.3%) offspring became obese during a median of five years of follow-up. Risk of incident obesity was lower among offspring whose mothers maintained a healthy body mass index of 18.5-24.9 (relative risk 0.44, 95% confidence interval 0.39 to 0.50), engaged in at least 150 min/week of moderate/vigorous physical activities (0.79, 0.69 to 0.91), did not smoke (0.69, 0.56 to 0.86), and consumed alcohol in moderation (1.0-14.9 g/day; 0.88, 0.79 to 0.99), compared with the rest. Maternal high quality diet (top 40% of the Alternate Healthy Eating Index 2010 diet score) was not significantly associated with the risk of obesity in offspring (0.97, 0.83 to 1.12). When all healthy lifestyle factors were considered simultaneously, offspring of women who adhered to all five low risk lifestyle factors had a 75% lower risk of obesity than offspring of mothers who did not adhere to any low risk factor (0.25, 0.14 to 0.47). This association was similar across sex and age

groups and persisted in subgroups of children with various risk profiles defined by factors such as pregnancy complications, birth weight, gestational age, and gestational weight gain. Children's lifestyle did not significantly account for the association between maternal lifestyle and offspring obesity risk, but when both mothers and offspring adhered to a healthy lifestyle, the risk of developing obesity fell further (0.18, 0.09 to 0.37).
Conclusion Our study indicates that adherence to a healthy lifestyle in mothers during their offspring's childhood and adolescence is associated with a substantially reduced risk of obesity in the children. These findings highlight the potential benefits of implementing family or parental based multifactorial interventions to curb the risk of childhood obesity.

Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: Prospective US cohort study

Dong Hoon Lee, NaNa Keum, visiting scientist, Frank B Hu, et al.
BMJ 2018; 362 (Published 03 July 2018)
https://www.bmj.com/content/362/bmj.k2575

Abstract
Objective To investigate the association of predicted lean body mass, fat mass, and body mass index (BMI) with all cause and cause specific mortality in men.
Design Prospective cohort study.
Setting Health professionals in the United States
Participants 38 006 men (aged 40-75 years) from the Health Professionals Follow-up Study, followed up for death (1987-2012).
Main outcome measures All cause and cause specific mortality.
Results Using validated anthropometric prediction equations previously developed from the National Health and Nutrition Examination Survey, lean body mass and fat mass were estimated for all participants. During a mean of 21.4 years of follow-up, 12 356 deaths were identified. A J shaped association was consistently observed between BMI and all cause mortality. Multivariable adjusted Cox models including predicted fat mass and lean body mass showed a strong positive monotonic association between predicted fat mass and all cause mortality. Compared with those in the lowest fifth of predicted fat mass, men in the highest fifth had a hazard ratio of 1.35 (95% confidence interval 1.26 to 1.46) for mortality from all causes. In contrast, a U shaped association was found between predicted lean body mass and all cause mortality. Compared with those in the lowest fifth of predicted lean body mass, men in the second to fourth fifths had 8-10% lower risk of mortality from all causes. In the restricted cubic spline models, the risk of all cause mortality was relatively flat until 21 kg of predicted fat mass and increased rapidly afterwards, with a hazard ratio of 1.22 (1.18 to 1.26) per standard deviation. For predicted lean body mass, a large reduction of the risk was seen within the lower range until 56 kg, with a hazard ratio of 0.87 (0.82 to 0.92) per standard deviation, which increased thereafter (P for non-linearity <0.001). For cause specific mortality, men in the highest fifth of predicted fat mass had hazard ratios of 1.67 (1.47 to 1.89) for cardiovascular disease, 1.24 (1.09 to 1.43) for cancer, and 1.26 (0.97 to 1.64) for respiratory disease. On the other hand, a U shaped association was found between predicted lean body mass and mortality from cardiovascular disease and cancer. However, a strong inverse association existed between predicted lean body mass and mortality from respiratory disease (P for trend <0.001).
Conclusions The shape of the association between BMI and mortality was determined by the relation between two body components (lean body mass and fat mass) and mortality.

This finding suggests that the “obesity paradox” controversy may be largely explained by low lean body mass, rather than low fat mass, in the lower range of BMI.

Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: Cohort study in primary care
Yana Vinogradova, Carol Coupland, Trevor Hill, et al.
BMJ 2018; 362 (Published 04 July 2018)
https://www.bmj.com/content/362/bmj.k2505

Abstract
Objective To investigate the associations between direct oral anticoagulants (DOACs) and risks of bleeding, ischaemic stroke, venous thromboembolism, and all cause mortality compared with warfarin.
Design Prospective open cohort study.
Setting UK general practices contributing to QResearch or Clinical Practice Research Datalink.
Participants 132 231 warfarin, 7744 dabigatran, 37 863 rivaroxaban, and 18 223 apixaban users without anticoagulant prescriptions for 12 months before study entry, subgrouped into 103 270 patients with atrial fibrillation and 92 791 without atrial fibrillation between 2011 and 2016.
Main outcome measures Major bleeding leading to hospital admission or death. Specific sites of bleeding and all cause mortality were also studied.
Results In patients with atrial fibrillation, compared with warfarin, apixaban was associated with a decreased risk of major bleeding (adjusted hazard ratio 0.66, 95% confidence interval 0.54 to 0.79) and intracranial bleeding (0.40, 0.25 to 0.64); dabigatran was associated with a decreased risk of intracranial bleeding (0.45, 0.26 to 0.77). An increased risk of all cause mortality was observed in patients taking rivaroxaban (1.19, 1.09 to 1.29) or on lower doses of apixaban (1.27, 1.12 to 1.45). In patients without atrial fibrillation, compared with warfarin, apixaban was associated with a decreased risk of major bleeding (0.60, 0.46 to 0.79), any gastrointestinal bleeding (0.55, 0.37 to 0.83), and upper gastrointestinal bleeding (0.55, 0.36 to 0.83); rivaroxaban was associated with a decreased risk of intracranial bleeding (0.54, 0.35 to 0.82). Increased risk of all cause mortality was observed in patients taking rivaroxaban (1.51, 1.38 to 1.66) and those on lower doses of apixaban (1.34, 1.13 to 1.58).
Conclusions Overall, apixaban was found to be the safest drug, with reduced risks of major, intracranial, and gastrointestinal bleeding compared with warfarin. Rivaroxaban and low dose apixaban were, however, associated with increased risks of all cause mortality compared with warfarin.

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JAMA: Journal of the American Medical Association (10 July 2018, Vol. 320, No. 2)

Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial
Steven R. Steinhubl, Jill Waalen, Alison M. Edwards, et al
JAMA. 2018; 320 (2): 146-155.
https://jamanetwork.com/journals/jama/article-abstract/2687353

Abstract

Importance Opportunistic screening for atrial fibrillation (AF) is recommended, and improved methods of early identification could allow for the initiation of appropriate therapies to prevent the adverse health outcomes associated with AF.
Objective To determine the effect of a self-applied wearable electrocardiogram (ECG) patch in detecting AF and the clinical consequences associated with such a detection strategy.
Design, Setting, and Participants A direct-to-participant randomized clinical trial and prospective matched observational cohort study were conducted among members of a large national health plan. Recruitment began November 17, 2015, and was completed on October 4, 2016, and 1-year claims-based follow-up concluded in January 2018. For the clinical trial, 2659 individuals were randomized to active home-based monitoring to start immediately or delayed by 4 months. For the observational study, 2 deidentified age-, sex- and CHA_2DS_2-VASc–matched controls were selected for each actively monitored individual.
Interventions The actively monitored cohort wore a self-applied continuous ECG monitoring patch at home during routine activities for up to 4 weeks, initiated either immediately after enrolling (n = 1364) or delayed for 4 months after enrollment (n = 1291).
Main Outcomes and Measures The primary end point was the incidence of a new diagnosis of AF at 4 months among those randomized to immediate monitoring vs delayed monitoring. A secondary end point was new AF diagnosis at 1 year in the combined actively monitored groups vs matched observational controls. Other outcomes included new prescriptions for anticoagulants and health care utilization (outpatient cardiology visits, primary care visits, or AF-related emergency department visits and hospitalizations) at 1 year.
Results The randomized groups included 2659 participants (mean [SD] age, 72.4 [7.3] years; 38.6% women), of whom 1738 (65.4%) completed active monitoring. The observational study comprised 5214 (mean [SD] age, 73.7 [7.0] years; 40.5% women; median CHA_2DS_2-VASc score, 3.0), including 1738 actively monitored individuals from the randomized trial and 3476 matched controls. In the randomized study, new AF was identified by 4 months in 3.9% (53/1366) of the immediate group vs 0.9% (12/1293) in the delayed group (absolute difference, 3.0% [95% CI, 1.8%-4.1%]). At 1 year, AF was newly diagnosed in 109 monitored (6.7 per 100 person-years) and 81 unmonitored (2.6 per 100 person-years; difference, 4.1 [95% CI, 3.9-4.2]) individuals. Active monitoring was associated with increased initiation of anticoagulants (5.7 vs 3.7 per 100 person-years; difference, 2.0 [95% CI, 1.9-2.2]), outpatient cardiology visits (33.5 vs 26.0 per 100 person-years; difference, 7.5 [95% CI, 7.2-7.9), and primary care visits (83.5 vs 82.6 per 100 person-years; difference, 0.9 [95% CI, 0.4-1.5]). There was no difference in AF-related emergency department visits and hospitalizations (1.3 vs 1.4 per 100 person-years; difference, 0.1 [95% CI, −0.1 to 0]).
Conclusions and Relevance Among individuals at high risk for AF, immediate monitoring with a home-based wearable ECG sensor patch, compared with delayed monitoring, resulted in a higher rate of AF diagnosis after 4 months. Monitored individuals, compared with nonmonitored controls, had higher rates of AF diagnosis, greater initiation of anticoagulants, but also increased health care resource utilization at 1 year.

Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial

Pooja Khatri, Dawn O. Kleindorfer, Thomas Devlin, et al for the PRISMS Investigators
JAMA. 2018; 320 (2): 156-166.

https://jamanetwork.com/journals/jama/article-abstract/2687354

Abstract

Importance More than half of patients with acute ischemic stroke have minor neurologic deficits (National Institutes of Health Stroke Scale [NIHSS] score of 0-5) at presentation. Although prior major trials of alteplase included patients with low NIHSS scores, few without clearly disabling deficits were enrolled.

Objective To evaluate the efficacy and safety of alteplase in patients with NIHSS scores of 0 to 5 whose deficits are not clearly disabling.

Design, Setting, and Participants The PRISMS trial was designed as a 948-patient, phase 3b, double-blind, double-placebo, multicenter randomized clinical trial of alteplase compared with aspirin for emergent stroke at 75 stroke hospital networks in the United States. Patients with acute ischemic stroke whose deficits were scored as 0 to 5 on the NIHSS and judged not clearly disabling and in whom study treatment could be initiated within 3 hours of onset were eligible and enrolled from May 30, 2014, to December 20, 2016, with final follow-up on March 22, 2017.

Interventions Participants were randomized to receive intravenous alteplase at the standard dose (0.9 mg/kg) with oral placebo (n = 156) or oral aspirin, 325 mg, with intravenous placebo (n = 157).

Main Outcomes and Measures The primary outcome was the difference in favorable functional outcome, defined as a modified Rankin Scale score of 0 or 1 at 90 days via Cochran-Mantel-Haenszel test stratified by pretreatment NIHSS score, age, and time from onset to treatment. Because of early termination of the trial, prior to unblinding or interim analyses, the plan was revised to examine the risk difference of the primary outcome by a linear model adjusted for the same factors. The primary safety end point was symptomatic intracranial hemorrhage (sICH) within 36 hours of intravenous study treatment.

Results Among 313 patients enrolled at 53 stroke networks (mean age, 62 [SD, 13] years; 144 [46%] women; median NIHSS score, 2 [interquartile range {IQR}, 1-3]; median time to treatment, 2.7 hours [IQR, 2.1-2.9]), 281 (89.8%) completed the trial. At 90 days, 122 patients (78.2%) in the alteplase group vs 128 (81.5%) in the aspirin group achieved a favorable outcome (adjusted risk difference, −1.1%; 95% CI, −9.4% to 7.3%). Five alteplase-treated patients (3.2%) vs 0 aspirin-treated patients had sICH (risk difference, 3.3%; 95% CI, 0.8%-7.4%).

Conclusions and Relevance Among patients with minor nondisabling acute ischemic stroke, treatment with alteplase vs aspirin did not increase the likelihood of favorable functional outcome at 90 days. However, the very early study termination precludes any definitive conclusions, and additional research may be warranted.

Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial

Dawn L. Hershman, Joseph M. Unger, Heather Greenlee, et al

JAMA. 2018; 320 (2): 167-176.
https://jamanetwork.com/journals/jama/article-abstract/2687355

Abstract

Importance Musculoskeletal symptoms are the most common adverse effects of aromatase inhibitors and often result in therapy discontinuation. Small studies suggest that acupuncture may decrease aromatase inhibitor–related joint symptoms.

Objective To determine the effect of acupuncture in reducing aromatase inhibitor–related joint pain.
Design, Setting, and Patients Randomized clinical trial conducted at 11 academic centers and clinical sites in the United States from March 2012 to February 2017 (final date of follow-up, September 5, 2017). Eligible patients were postmenopausal women with early-stage breast cancer who were taking an aromatase inhibitor and scored at least 3 on the Brief Pain Inventory Worst Pain (BPI-WP) item (score range, 0-10; higher scores indicate greater pain).
Interventions Patients were randomized 2:1:1 to the true acupuncture (n = 110), sham acupuncture (n = 59), or waitlist control (n = 57) group. True acupuncture and sham acupuncture protocols consisted of 12 acupuncture sessions over 6 weeks (2 sessions per week), followed by 1 session per week for 6 weeks. The waitlist control group did not receive any intervention. All participants were offered 10 acupuncture sessions to be used between weeks 24 and 52.
Main Outcomes and Measures The primary end point was the 6-week BPI-WP score. Mean 6-week BPI-WP scores were compared by study group using linear regression, adjusted for baseline pain and stratification factors (clinically meaningful difference specified as 2 points).
Results Among 226 randomized patients (mean [SD] age, 60.7 [8.6] years; 88% white; mean [SD] baseline BPI-WP score, 6.6 [1.5]), 206 (91.1%) completed the trial. From baseline to 6 weeks, the mean observed BPI-WP score decreased by 2.05 points (reduced pain) in the true acupuncture group, by 1.07 points in the sham acupuncture group, and by 0.99 points in the waitlist control group. The adjusted difference for true acupuncture vs sham acupuncture was 0.92 points (95% CI, 0.20-1.65; *P* = .01) and for true acupuncture vs waitlist control was 0.96 points (95% CI, 0.24-1.67; *P* = .01). Patients in the true acupuncture group experienced more grade 1 bruising compared with patients in the sham acupuncture group (47% vs 25%; *P* = .01).
Conclusions and Relevance Among postmenopausal women with early-stage breast cancer and aromatase inhibitor–related arthralgias, true acupuncture compared with sham acupuncture or with waitlist control resulted in a statistically significant reduction in joint pain at 6 weeks, although the observed improvement was of uncertain clinical importance.

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The Lancet (7 July 2018, Vol. 392, No. 10141)

Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): A multicentre, open-label, randomised controlled, phase 3 trial

Samir Jaber, Catherine Paugam, Emmanuel Futier, et al. for the BICAR-ICU Study Group
The Lancet: Volume 392, No. 10141, p31–40, 7 July 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31080-8/fulltext

Summary
Background
Acute acidaemia is frequently observed during critical illness. Sodium bicarbonate infusion for the treatment of severe metabolic acidaemia is a possible treatment option but remains controversial, as no studies to date have examined its effect on clinical outcomes. Therefore, we aimed to evaluate whether sodium bicarbonate infusion would improve these outcomes in critically ill patients.

Methods
We did a multicentre, open-label, randomised controlled, phase 3 trial. Local investigators screened eligible patients from 26 intensive care units (ICUs) in France. We included adult patients (aged ≥18 years) who were admitted within 48 h to the ICU with severe acidaemia (pH ≤7·20, $PaCO_2$ ≤45 mm Hg, and sodium bicarbonate concentration ≤20 mmol/L) and with a total Sequential Organ Failure Assessment score of 4 or more or an arterial lactate concentration of 2 mmol/L or more. We randomly assigned patients (1:1), by stratified randomisation with minimisation via a restricted web platform, to receive either no sodium bicarbonate (control group) or 4·2% of intravenous sodium bicarbonate infusion (bicarbonate group) to maintain the arterial pH above 7·30. Our protocol recommended that the volume of each infusion should be within the range of 125–250 mL in 30 min, with a maximum of 1000 mL within 24 h after inclusion. Randomisation criteria were stratified among three prespecified strata: age, sepsis status, and the Acute Kidney Injury Network (AKIN) score. The primary outcome was a composite of death from any cause by day 28 and the presence of at least one organ failure at day 7. All analyses were done on data from the intention-to-treat population, which included all patients who underwent randomisation. This study is registered with ClinicalTrials.gov, number NCT02476253.
Findings
Between May 5, 2015, and May 7, 2017, we enrolled 389 patients into the intention-to-treat analysis in the overall population (194 in the control group and 195 in the bicarbonate group). The primary outcome occurred in 138 (71%) of 194 patients in the control group and 128 (66%) of 195 in the bicarbonate group (absolute difference estimate −5·5%, 95% CI −15·2 to 4·2; p=0·24). The Kaplan-Meier method estimate of the probability of survival at day 28 between the control group and bicarbonate group was not significant (46% [95% CI 40–54] *vs* 55% [49–63]; p=0·09. In the prespecified AKIN stratum of patients with a score of 2 or 3, the Kaplan-Meier method estimate of survival by day 28 between the control group and bicarbonate group was significant (63% [95% CI 52–72] *vs* 46% [35–55]; p=0·0283). Metabolic alkalosis, hypernatraemia, and hypocalcaemia were observed more frequently in the bicarbonate group than in the control group, with no life-threatening complications reported.
Interpretation
In patients with severe metabolic acidaemia, sodium bicarbonate had no effect on the primary composite outcome. However, sodium bicarbonate decreased the primary composite outcome and day 28 mortality in the a-priori defined stratum of patients with acute kidney injury.

Management of multimorbidity using a patient-centred care model: A pragmatic cluster-randomised trial of the 3D approach
Chris Salisbury, Mei-See Man, Peter Bower, et al.
The Lancet: Volume 392, No. 10141, p41–50, 7 July 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31308-4/fulltext

Summary
Background
The management of people with multiple chronic conditions challenges health-care systems designed around single conditions. There is international consensus that care for multimorbidity should be patient-centred, focus on quality of life, and promote self-management towards agreed goals. However, there is little evidence about the effectiveness of this approach. Our hypothesis was that the patient-centred, so-called 3D approach (based on dimensions of health, depression, and drugs) for patients with

multimorbidity would improve their health-related quality of life, which is the ultimate aim of the 3D intervention.

Methods

We did this pragmatic cluster-randomised trial in general practices in England and Scotland. Practices were randomly allocated to continue usual care (17 practices) or to provide 6-monthly comprehensive 3D reviews, incorporating patient-centred strategies that reflected international consensus on best care (16 practices). Randomisation was computer-generated, stratified by area, and minimised by practice deprivation and list size. Adults with three or more chronic conditions were recruited. The primary outcome was quality of life (assessed with EQ-5D-5L) after 15 months' follow-up. Participants were not masked to group assignment, but analysis of outcomes was blinded. We analysed the primary outcome in the intention-to-treat population, with missing data being multiply imputed. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN06180958.

Findings

Between May 20, 2015, and Dec 31, 2015, we recruited 1546 patients from 33 practices and randomly assigned them to receive the intervention (n=797) or usual care (n=749). In our intention-to-treat analysis, there was no difference between trial groups in the primary outcome of quality of life (adjusted difference in mean EQ-5D-5L 0·00, 95% CI −0·02 to 0·02; p=0·93). 78 patients died, and the deaths were not considered as related to the intervention.

Interpretation

To our knowledge, this trial is the largest investigation of the international consensus about optimal management of multimorbidity. The 3D intervention did not improve patients' quality of life.

Personalised perioperative care by e-health after intermediate-grade abdominal surgery: A multicentre, single-blind, randomised, placebo-controlled trial

Eva van der Meij, Johannes R Anema, Wouter K G Leclercq, et al.

The Lancet: Volume 392, No. 10141, p51–59, 7 July 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31113-9/fulltext

Summary

Background

Instructing and guiding patients after surgery is essential for successful recovery. However, the time that health-care professionals can spend with their patients postoperatively has been reduced because of efficiency-driven, shortened hospital stays. We evaluated the effect of a personalised e-health-care programme on return to normal activities after surgery.

Methods

A multicentre, single-blind, randomised controlled trial was done at seven teaching hospitals in the Netherlands. Patients aged 18–75 years who were scheduled for laparoscopic cholecystectomy, inguinal hernia surgery, or laparoscopic adnexal surgery for a benign indication were recruited. An independent researcher randomly allocated participants to either the intervention or control group using computer-based randomisation lists, with stratification by sex, type of surgery, and hospital. Participants in the intervention group had access to a perioperative, personalised, e-health-care programme, which managed recovery expectations and provided postoperative guidance tailored to the patient. The control group received usual care and access to a placebo website containing standard general recovery advice. Participants were unaware of the study hypothesis and

were asked to complete questionnaires at five timepoints during the 6-month period after surgery. The primary outcome was time between surgery and return to normal activities, measured using personalised patient-reported outcome measures. Intention-to-treat and per-protocol analyses were done. This trial is registered in the Netherlands National Trial Register, number NTR4699.

Findings

Between Aug 24, 2015, and Aug 12, 2016, 344 participants were enrolled and randomly allocated to either the intervention (n=173) or control (n=171) group. 14 participants (4%) were lost to follow-up, with 330 participants included in the primary outcome analysis. Median time until return to normal activities was 21 days (95% CI 17–25) in the intervention group and 26 days (20–32) in the control group (hazard ratio 1·38, 95% CI 1·09–1·73; p=0·007). Complications did not differ between groups.

Interpretation

A personalised e-health intervention after abdominal surgery speeds up the return to normal activities compared with usual care. Implementation of this e-health programme is recommended in patients undergoing intermediate-grade abdominal, gynaecological, or general surgical procedures.

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The New England Journal of Medicine (5 July 2018, Vol. 379, No. 1)

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

David Adams, Alejandra Gonzalez-Duarte, William D. O'Riordan, et al.

N Engl J Med 2018; 379: 11-21 July 5, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1716153

Abstract

Background

Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

Methods

In this phase 3 trial, we randomly assigned patients with hereditary transthyretin amyloidosis with polyneuropathy, in a 2:1 ratio, to receive intravenous patisiran (0.3 mg per kilogram of body weight) or placebo once every 3 weeks. The primary end point was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7; range, 0 to 304, with higher scores indicating more impairment) at 18 months. Other assessments included the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (range, −4 to 136, with higher scores indicating worse quality of life), 10-m walk test (with gait speed measured in meters per second), and modified body-mass index (modified BMI, defined as [weight in kilograms divided by square of height in meters]×albumin level in grams per liter; lower values indicated worse nutritional status).

Results

A total of 225 patients underwent randomization (148 to the patisiran group and 77 to the placebo group). The mean (±SD) mNIS+7 at baseline was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group; the least-squares mean (±SE) change from baseline was −6.0±1.7 versus 28.0±2.6 (difference, −34.0 points; P<0.001) at 18 months. The mean (±SD) baseline Norfolk QOL-DN score was 59.6±28.2 in the patisiran group and 55.5±24.3 in the placebo group; the least-squares mean (±SE) change from baseline was −6.7±1.8 versus 14.4±2.7 (difference, −21.1 points; P<0.001) at 18 months. Patisiran also showed an effect on gait speed and modified BMI. At 18 months, the least-squares mean change

from baseline in gait speed was 0.08±0.02 m per second with patisiran versus −0.24±0.04 m per second with placebo (difference, 0.31 m per second; P<0.001), and the least-squares mean change from baseline in the modified BMI was −3.7±9.6 versus −119.4±14.5 (difference, 115.7; P<0.001). Approximately 20% of the patients who received patisiran and 10% of those who received placebo had mild or moderate infusion-related reactions; the overall incidence and types of adverse events were similar in the two groups.

Conclusions

In this trial, patisiran improved multiple clinical manifestations of hereditary transthyretin amyloidosis.

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

Merrill D. Benson, Márcia Waddington-Cruz, John L. Berk, et al.

N Engl J Med 2018; 379: 22-31 July 5, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1716793

Abstract

Background

Hereditary transthyretin amyloidosis is caused by pathogenic single-nucleotide variants in the gene encoding transthyretin (TTR) that induce transthyretin misfolding and systemic deposition of amyloid. Progressive amyloid accumulation leads to multiorgan dysfunction and death. Inotersen, a 2′-O-methoxyethyl–modified antisense oligonucleotide, inhibits hepatic production of transthyretin.

Methods

We conducted an international, randomized, double-blind, placebo-controlled, 15-month, phase 3 trial of inotersen in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy. Patients were randomly assigned, in a 2:1 ratio, to receive weekly subcutaneous injections of inotersen (300 mg) or placebo. The primary end points were the change in the modified Neuropathy Impairment Score+7 (mNIS+7; range, −22.3 to 346.3, with higher scores indicating poorer function; minimal clinically meaningful change, 2 points) and the change in the score on the patient-reported Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) questionnaire (range, −4 to 136, with higher scores indicating poorer quality of life). A decrease in scores indicated improvement.

Results

A total of 172 patients (112 in the inotersen group and 60 in the placebo group) received at least one dose of a trial regimen, and 139 (81%) completed the intervention period. Both primary efficacy assessments favored inotersen: the difference in the least-squares mean change from baseline to week 66 between the two groups (inotersen minus placebo) was −19.7 points (95% confidence interval [CI], −26.4 to −13.0; P<0.001) for the mNIS+7 and −11.7 points (95% CI, −18.3 to −5.1; P<0.001) for the Norfolk QOL-DN score. These improvements were independent of disease stage, mutation type, or the presence of cardiomyopathy. There were five deaths in the inotersen group and none in the placebo group. The most frequent serious adverse events in the inotersen group were glomerulonephritis (in 3 patients [3%]) and thrombocytopenia (in 3 patients [3%]), with one death associated with one of the cases of grade 4 thrombocytopenia. Thereafter, all patients received enhanced monitoring.

Conclusions

Inotersen improved the course of neurologic disease and quality of life in patients with hereditary transthyretin amyloidosis. Thrombocytopenia and glomerulonephritis were managed with enhanced monitoring.

Platelet Counts during Pregnancy
Jessica A. Reese, Jennifer D. Peck, David R. Deschamps, et al.
N Engl J Med 2018; 379: 32-43 July 5, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1802897

Abstract
Background
Platelet counts of less than 150,000 per cubic millimeter during uncomplicated pregnancies are described as gestational thrombocytopenia if no alternative cause is identified. Platelet counts may be even lower in women with pregnancy-related complications. However, the occurrence and severity of thrombocytopenia throughout pregnancy are not defined.
Methods
We evaluated platelet counts throughout pregnancy in women who delivered at Oklahoma University Medical Center between 2011 and 2014. These platelet counts were compared with those of nonpregnant women who were included in the National Health and Nutrition Examination Survey from 1999 through 2012.
Results
Among the 15,723 deliveries that occurred during the study period, 7351 women had sufficient data for our analyses. Of these women, 4568 had uncomplicated pregnancies, 2586 had pregnancy-related complications, and 197 had preexisting disorders associated with thrombocytopenia. Among the women who had uncomplicated pregnancies, the mean platelet count in the first trimester (mean gestation, 8.7 weeks) was 251,000 per cubic millimeter, which was lower than the mean platelet count in the 8885 nonpregnant women (273,000 per cubic millimeter) (P<0.001). At the time of delivery, 9.9% of the women with uncomplicated pregnancies had a platelet count below 150,000 per cubic millimeter. During the course of the uncomplicated pregnancies and deliveries, only 45 women (1.0%) had a platelet count below 100,000 per cubic millimeter. Among the 12 women with uncomplicated pregnancies who had a platelet count below 80,000 per cubic millimeter, only 5 (0.1%, among whom the range of platelet counts was 62,000 to 78,000 per cubic millimeter; median, 65,000) were identified by medical record review as having no alternative cause for the thrombocytopenia. Platelet counts of less than 150,000 per cubic millimeter at the time of delivery were more common among women who had pregnancy-related complications than among women who had uncomplicated pregnancies (11.9% vs. 9.9%, P=0.01). Throughout their pregnancies and deliveries, 59 women (2.3%) with pregnancy-related complications had a platelet count below 100,000 per cubic millimeter, and 31 (1.2%) had a platelet count below 80,000 per cubic millimeter.
Conclusions
Mean platelet counts decreased during pregnancy in all the women, beginning in the first trimester. In women who have a platelet count of less than 100,000 per cubic millimeter, a cause other than pregnancy or its complications should be considered.

Oral Tecovirimat for the Treatment of Smallpox
Douglas W. Grosenbach, Kady Honeychurch, Eric A. Rose, et al.
N Engl J Med 2018; 379: 44-53 July 5, 2018

https://www.nejm.org/doi/full/10.1056/NEJMoa1705688

Abstract

Background

Smallpox was declared eradicated in 1980, but variola virus (VARV), which causes smallpox, still exists. There is no known effective treatment for smallpox; therefore, tecovirimat is being developed as an oral smallpox therapy. Because clinical trials in a context of natural disease are not possible, an alternative developmental path to evaluate efficacy and safety was needed.

Methods

We investigated the efficacy of tecovirimat in nonhuman primate (monkeypox) and rabbit (rabbitpox) models in accordance with the Food and Drug Administration (FDA) Animal Efficacy Rule, which was interpreted for smallpox therapeutics by an expert advisory committee. We also conducted a placebo-controlled pharmacokinetic and safety trial involving 449 adult volunteers.

Results

The minimum dose of tecovirimat required in order to achieve more than 90% survival in the monkeypox model was 10 mg per kilogram of body weight for 14 days, and a dose of 40 mg per kilogram for 14 days was similarly efficacious in the rabbitpox model. Although the effective dose per kilogram was higher in rabbits, exposure was lower, with a mean steady-state maximum, minimum, and average (mean) concentration (Cmax, Cmin, and Cavg, respectively) of 374, 25, and 138 ng per milliliter, respectively, in rabbits and 1444, 169, and 598 ng per milliliter in nonhuman primates, as well as an area under the concentration–time curve over 24 hours (AUC0-24hr) of 3318 ng×hours per milliliter in rabbits and 14,352 ng×hours per milliliter in nonhuman primates. These findings suggested that the nonhuman primate was the more conservative model for the estimation of the required drug exposure in humans. A dose of 600 mg twice daily for 14 days was selected for testing in humans and provided exposures in excess of those in nonhuman primates (mean steady-state Cmax, Cmin, and Cavg of 2209, 690, and 1270 ng per milliliter and AUC0-24hr of 30,632 ng×hours per milliliter). No pattern of troubling adverse events was observed.

Conclusions

On the basis of its efficacy in two animal models and pharmacokinetic and safety data in humans, tecovirimat is being advanced as a therapy for smallpox in accordance with the FDA Animal Rule.

Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma

Ghassan K. Abou-Alfa, Tim Meyer, Ann-Lii Cheng, et al.

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https://www.nejm.org/doi/full/10.1056/NEJMoa1717002

Abstract

Background

Cabozantinib inhibits tyrosine kinases, including vascular endothelial growth factor receptors 1, 2, and 3, MET, and AXL, which are implicated in the progression of hepatocellular carcinoma and the development of resistance to sorafenib, the standard initial treatment for advanced disease. This randomized, double-blind, phase 3 trial evaluated cabozantinib as compared with placebo in previously treated patients with advanced hepatocellular carcinoma.

Methods

A total of 707 patients were randomly assigned in a 2:1 ratio to receive cabozantinib (60 mg once daily) or matching placebo. Eligible patients had received previous treatment with sorafenib, had disease progression after at least one systemic treatment for hepatocellular carcinoma, and may have received up to two previous systemic regimens for advanced hepatocellular carcinoma. The primary end point was overall survival. Secondary end points were progression-free survival and the objective response rate.

Results

At the second planned interim analysis, the trial showed significantly longer overall survival with cabozantinib than with placebo. Median overall survival was 10.2 months with cabozantinib and 8.0 months with placebo (hazard ratio for death, 0.76; 95% confidence interval [CI], 0.63 to 0.92; P=0.005). Median progression-free survival was 5.2 months with cabozantinib and 1.9 months with placebo (hazard ratio for disease progression or death, 0.44; 95% CI, 0.36 to 0.52; P<0.001), and the objective response rates were 4% and less than 1%, respectively (P=0.009). Grade 3 or 4 adverse events occurred in 68% of patients in the cabozantinib group and in 36% in the placebo group. The most common high-grade events were palmar–plantar erythrodysesthesia (17% with cabozantinib vs. 0% with placebo), hypertension (16% vs. 2%), increased aspartate aminotransferase level (12% vs. 7%), fatigue (10% vs. 4%), and diarrhea (10% vs. 2%).

Conclusions

Among patients with previously treated advanced hepatocellular carcinoma, treatment with cabozantinib resulted in longer overall survival and progression-free survival than placebo. The rate of high-grade adverse events in the cabozantinib group was approximately twice that observed in the placebo group.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
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The Lancet	www.thelancet.com
The New England Journal of Medicine	http://content.nejm.org/
The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled.	https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases or http://www.openathens.net/
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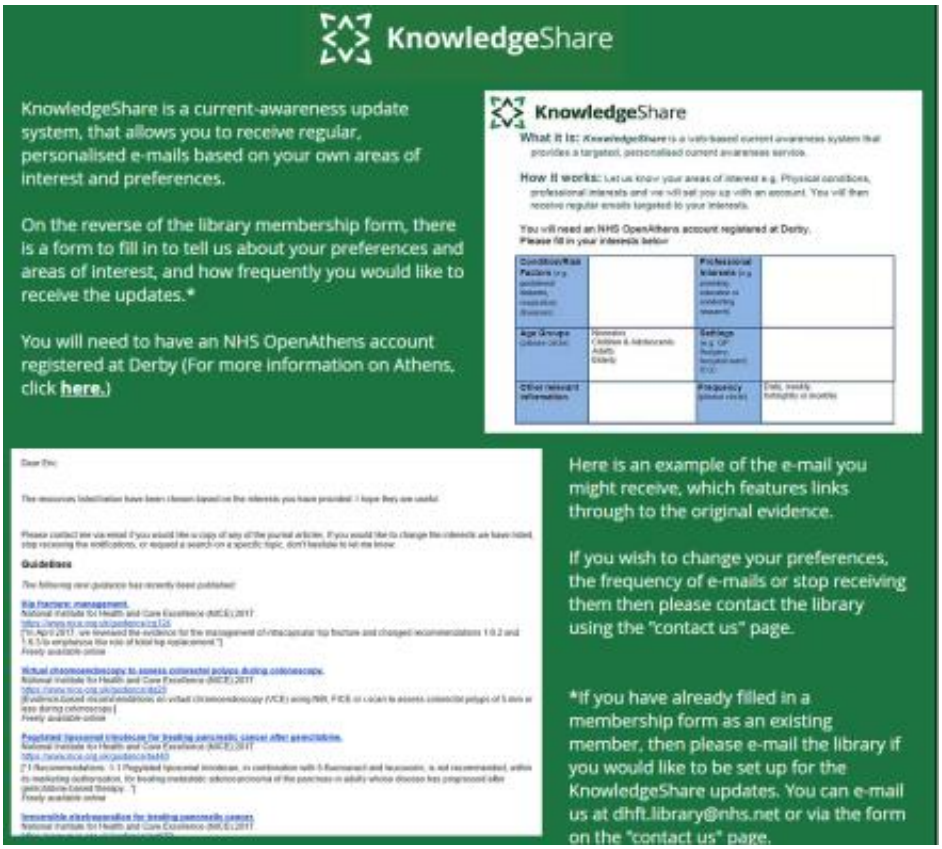

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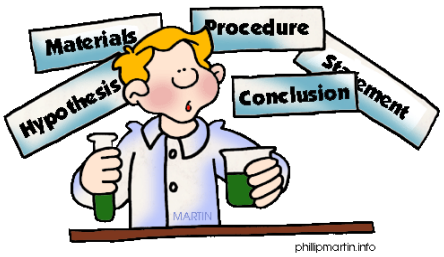

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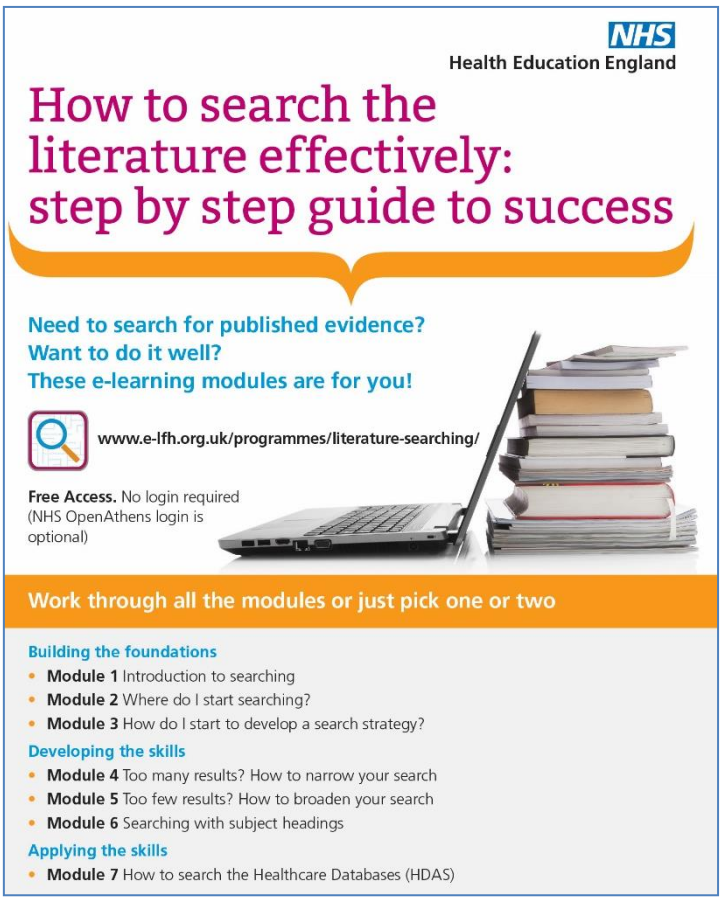

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