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Contents

BMJ (22 September 2018)

- Intramuscular versus intravenous oxytocin to prevent postpartum haemorrhage at vaginal delivery: Randomised controlled trial
- Association between maternal gluten intake and type 1 diabetes in offspring: National prospective cohort study in Denmark
- External validation of computed tomography decision rules for minor head injury: Prospective, multicentre cohort study in the Netherlands

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JAMA: The Journal of the American Medical Association (25 September 2018)

- Effect of Algorithm-Based Therapy vs Usual Care on Clinical Success and Serious Adverse Events in Patients with Staphylococcal Bacteremia: A Randomized Clinical Trial
- Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial
- Prevalence of Variant Reclassification Following Hereditary Cancer Genetic Testing

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The Lancet (22 September 2018)

- Alcohol use and burden for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016
- Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): A randomised, double-blind, placebo-controlled trial
- Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): A randomised, controlled, parallel-group, unmasked trial

- Brexanolone injection in post-partum depression: Two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

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The New England Journal of Medicine (20 September 2018)

- Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients
- Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness
- Variation in Childhood Diarrheal Morbidity and Mortality in Africa, 2000–2015

BMJ (22 September 2018, Vol. 362, No. 8168)

Intramuscular versus intravenous oxytocin to prevent postpartum haemorrhage at vaginal delivery: Randomised controlled trial
Nita Adnan, Rebecca Conlan-Trant, Ciara McCormick, et al.
BMJ 2018; 362 (Published 04 September 2018)
https://www.bmj.com/content/362/bmj.k3546

Abstract
Objective To determine whether intravenous oxytocin is more effective than intramuscular oxytocin at preventing postpartum haemorrhage at vaginal delivery.
Design Double blind placebo controlled randomised trial.
Setting University affiliated maternity unit in the Republic of Ireland.
Participants 1075 women aged 18 years or older, at term with a singleton pregnancy who were aiming for a vaginal delivery with an actively managed third stage of labour.
Interventions Women were allocated to an intravenous bolus of oxytocin (10 IU in 1 mL given slowly over one minute) and placebo intramuscular injection (1 mL 0.9% saline) or an intramuscular bolus of oxytocin (10 IU in 1 mL) and placebo intravenous injection (1 mL 0.9% saline given slowly over one minute) at vaginal delivery. Allocation was by a secure web based randomisation service with masking of participants and clinicians to the trial intervention.
Main outcome measures The primary outcome was postpartum haemorrhage (PPH, measured blood loss ≥500 mL). Secondary outcomes were severe PPH (measured blood loss ≥1000 mL), need for blood transfusion, admission to a high dependency unit, and side effects to oxytocin.
Results Between 4 January 2016 and 13 December 2017, 1075 women were randomised and 1035 (96.3%) included in the primary and secondary analyses (517 in the intravenous oxytocin group and 518 in the intramuscular oxytocin group). The incidence of PPH was not significantly lower in the intravenous group (18.8%, 97/517) compared with intramuscular group (23.2%, 120/518): adjusted odds ratio 0.75 (95% confidence interval 0.55 to 1.03). The incidence of severe PPH, however, was significantly lower in the intravenous group (4.6%, 24/517) compared with intramuscular group (8.1%, 42/518): 0.54 (0.32 to 0.91) as was the need for blood transfusion (1.5% *v* 4.4%, 0.31, 0.13 to 0.70) and admission to a high dependency unit (1.7% *v* 3.7%, 0.44, 0.20 to 0.98). The number needed to treat to prevent one case of severe PPH was 29 (95% confidence interval 16 to 201) and to prevent one case of blood transfusion was 35 (20 to 121). The incidence of

side effects to oxytocin was not increased in the intravenous group compared with intramuscular group (4.1% *v* 5.2%, 0.75, 0.42 to 1.35).
Conclusion Intravenous oxytocin for the third stage of labour results in less frequent severe PPH, blood transfusion, and admission to a high dependency unit than intramuscular oxytocin, and without excess side effects.

Association between maternal gluten intake and type 1 diabetes in offspring: National prospective cohort study in Denmark
Julie C Antvorskov, Thorhallur I Halldorsson, Knud Josefsen, et al.
BMJ 2018; 362 (Published 19 September 2018)
https://www.bmj.com/content/362/bmj.k3547

Abstract
Objective To examine the association between prenatal gluten exposure and offspring risk of type 1 diabetes in humans.
Design National prospective cohort study.
Setting National health information registries in Denmark.
Participants Pregnant Danish women enrolled into the Danish National Birth Cohort, between January 1996 and October 2002,
Main outcome measures Maternal gluten intake, based on maternal consumption of gluten containing foods, was reported in a 360 item food frequency questionnaire at week 25 of pregnancy. Information on type 1 diabetes occurrence in the participants' children, from 1 January 1996 to 31 May 2016, were obtained through registry linkage to the Danish Registry of Childhood and Adolescent Diabetes.
Results The study comprised 101 042 pregnancies in 91 745 women, of whom 70 188 filled out the food frequency questionnaire. After correcting for multiple pregnancies, pregnancies ending in abortions, stillbirths, lack of information regarding the pregnancy, and pregnancies with implausibly high or low energy intake, 67 565 pregnancies (63 529 women) were included. The average gluten intake was 13.0 g/day, ranging from less than 7 g/day to more than 20 g/day. The incidence of type 1 diabetes among children in the cohort was 0.37% (n=247) with a mean follow-up period of 15.6 years (standard deviation 1.4). Risk of type 1 diabetes in offspring increased proportionally with maternal gluten intake during pregnancy (adjusted hazard ratio 1.31 (95% confidence interval 1.001 to 1.72) per 10 g/day increase of gluten). Women with the highest gluten intake versus those with the lowest gluten intake (≥20 *v* <7 g/day) had double the risk of type 1 diabetes development in their offspring (adjusted hazard ratio 2.00 (95% confidence interval 1.02 to 4.00)).
Conclusions High gluten intake by mothers during pregnancy could increase the risk of their children developing type 1 diabetes. However, confirmation of these findings are warranted, preferably in an intervention setting.

External validation of computed tomography decision rules for minor head injury: Prospective, multicentre cohort study in the Netherlands
Kelly A Foks, Crispijn L van den Brand, Hester F Lingsma, et al.
BMJ 2018; 362 (Published 24 August 2018)
https://www.bmj.com/content/362/bmj.k3527

Abstract

Objective To externally validate four commonly used rules in computed tomography (CT) for minor head injury.
Design Prospective, multicentre cohort study.
Setting Three university and six non-university hospitals in the Netherlands.
Participants Consecutive adult patients aged 16 years and over who presented with minor head injury at the emergency department with a Glasgow coma scale score of 13-15 between March 2015 and December 2016.
Main outcome measures The primary outcome was any intracranial traumatic finding on CT; the secondary outcome was a potential neurosurgical lesion on CT, which was defined as an intracranial traumatic finding on CT that could lead to a neurosurgical intervention or death. The sensitivity, specificity, and clinical usefulness (defined as net proportional benefit, a weighted sum of true positive classifications) of the four CT decision rules. The rules included the CT in head injury patients (CHIP) rule, New Orleans criteria (NOC), Canadian CT head rule (CCHR), and National Institute for Health and Care Excellence (NICE) guideline for head injury.
Results For the primary analysis, only six centres that included patients with and without CT were selected. Of 4557 eligible patients who presented with minor head injury, 3742 (82%) received a CT scan; 384 (8%) had a intracranial traumatic finding on CT, and 74 (2%) had a potential neurosurgical lesion. The sensitivity for any intracranial traumatic finding on CT ranged from 73% (NICE) to 99% (NOC); specificity ranged from 4% (NOC) to 61% (NICE). Sensitivity for a potential neurosurgical lesion ranged between 85% (NICE) and 100% (NOC); specificity from 4% (NOC) to 59% (NICE). Clinical usefulness depended on thresholds for performing CT scanning: the NOC rule was preferable at a low threshold, the NICE rule was preferable at a higher threshold, whereas the CHIP rule was preferable for an intermediate threshold.
Conclusions Application of the CHIP, NOC, CCHR, or NICE decision rules can lead to a wide variation in CT scanning among patients with minor head injury, resulting in many unnecessary CT scans and some missed intracranial traumatic findings. Until an existing decision rule has been updated, any of the four rules can be used for patients presenting minor head injuries at the emergency department. Use of the CHIP rule is recommended because it leads to a substantial reduction in CT scans while missing few potential neurosurgical lesions.

Back to Contents

JAMA: Journal of the American Medical Association (25 September 2018, Vol. 320, No. 12)

Effect of Algorithm-Based Therapy vs Usual Care on Clinical Success and Serious Adverse Events in Patients with Staphylococcal Bacteremia: A Randomized Clinical Trial

Thomas L. Holland, Issam Raad, Helen W. Boucher, et al for the Staphylococcal Bacteremia Investigators
JAMA. 2018; 320 (12): 1249-1258.
https://jamanetwork.com/journals/jama/fullarticle/2703352

Abstract

Importance The appropriate duration of antibiotics for staphylococcal bacteremia is unknown.

Objective To test whether an algorithm that defines treatment duration for staphylococcal bacteremia vs standard of care provides noninferior efficacy without increasing severe adverse events.
Design, Setting, and Participants A randomized trial involving adults with staphylococcal bacteremia was conducted at 16 academic medical centers in the United States (n = 15) and Spain (n = 1) from April 2011 to March 2017. Patients were followed up for 42 days beyond end of therapy for those with *Staphylococcus aureus* and 28 days for those with coagulase-negative staphylococcal bacteremia. Eligible patients were 18 years or older and had 1 or more blood cultures positive for *S aureus* or coagulase-negative staphylococci. Patients were excluded if they had known or suspected complicated infection at the time of randomization.
Interventions Patients were randomized to algorithm-based therapy (n = 255) or usual practice (n = 254). Diagnostic evaluation, antibiotic selection, and duration of therapy were predefined for the algorithm group, whereas clinicians caring for patients in the usual practice group had unrestricted choice of antibiotics, duration, and other aspects of clinical care.
Main Outcomes and Measures Coprimary outcomes were (1) clinical success, as determined by a blinded adjudication committee and tested for noninferiority within a 15% margin; and (2) serious adverse event rates in the intention-to-treat population, tested for superiority. The prespecified secondary outcome measure, tested for superiority, was antibiotic days among per-protocol patients with simple or uncomplicated bacteremia.
Results Among the 509 patients randomized (mean age, 56.6 [SD, 16.8] years; 226 [44.4%] women), 480 (94.3%) completed the trial. Clinical success was documented in 209 of 255 patients assigned to algorithm-based therapy and 207 of 254 randomized to usual practice (82.0% vs 81.5%; difference, 0.5% [1-sided 97.5% CI, −6.2% to ∞]). Serious adverse events were reported in 32.5% of algorithm-based therapy patients and 28.3% of usual practice patients (difference, 4.2% [95% CI, −3.8% to 12.2%]). Among per-protocol patients with simple or uncomplicated bacteremia, mean duration of therapy was 4.4 days for algorithm-based therapy vs 6.2 days for usual practice (difference, −1.8 days [95% CI, −3.1 to −0.6.([
Conclusions and Relevance Among patients with staphylococcal bacteremia, the use of an algorithm to guide testing and treatment compared with usual care resulted in a noninferior rate of clinical success. Rates of serious adverse events were not significantly different, but interpretation is limited by wide confidence intervals. Further research is needed to assess the utility of the algorithm.

Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial

Paulina Salminen, Risto Tuominen, Hannu Paajanen, et al

JAMA. 2018; 320 (12): 1259-1265.
https://jamanetwork.com/journals/jama/article-abstract/2703354

Abstract
Importance Short-term results support antibiotics as an alternative to surgery for treating uncomplicated acute appendicitis, but long-term outcomes are not known.
Objective To determine the late recurrence rate of appendicitis after antibiotic therapy for the treatment of uncomplicated acute appendicitis.
Design, Setting, and Participants Five-year observational follow-up of patients in the Appendicitis Acuta (APPAC) multicenter randomized clinical trial comparing appendectomy with antibiotic therapy, in which 530 patients aged 18 to 60 years with

computed tomography–confirmed uncomplicated acute appendicitis were randomized to undergo an appendectomy (n = 273) or receive antibiotic therapy (n = 257). The initial trial was conducted from November 2009 to June 2012 in Finland; last follow-up was September 6, 2017. This current analysis focused on assessing the 5-year outcomes for the group of patients treated with antibiotics alone.

Interventions Open appendectomy vs antibiotic therapy with intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole.

Main Outcomes and Measures In this analysis, prespecified secondary end points reported at 5-year follow-up included late (after 1 year) appendicitis recurrence after antibiotic treatment, complications, length of hospital stay, and sick leave.

Results Of the 530 patients (201 women; 329 men) enrolled in the trial, 273 patients (median age, 35 years [IQR, 27-46]) were randomized to undergo appendectomy, and 257 (median age, 33 years, [IQR, 26-47]) were randomized to receive antibiotic therapy. In addition to 70 patients who initially received antibiotics but underwent appendectomy within the first year (27.3% [95% CI, 22.0%-33.2%]; 70/256), 30 additional antibiotic-treated patients (16.1% [95% CI, 11.2%-22.2%]; 30/186) underwent appendectomy between 1 and 5 years. The cumulative incidence of appendicitis recurrence was 34.0% (95% CI, 28.2%-40.1%; 87/256) at 2 years, 35.2% (95% CI, 29.3%-41.4%; 90/256) at 3 years, 37.1% (95% CI, 31.2%-43.3%; 95/256) at 4 years, and 39.1% (95% CI, 33.1%-45.3%; 100/256) at 5 years. Of the 85 patients in the antibiotic group who subsequently underwent appendectomy for recurrent appendicitis, 76 had uncomplicated appendicitis, 2 had complicated appendicitis, and 7 did not have appendicitis. At 5 years, the overall complication rate (surgical site infections, incisional hernias, abdominal pain, and obstructive symptoms) was 24.4% (95% CI, 19.2%-30.3%) (n = 60/246) in the appendectomy group and 6.5% (95% CI, 3.8%-10.4%) (n = 16/246) in antibiotic group ($P < .001$), which calculates to 17.9 percentage points (95% CI, 11.7-24.1) higher after surgery. There was no difference between groups for length of hospital stay, but there was a significant difference in sick leave (11 days more for the appendectomy group).

Conclusions and Relevance Among patients who were initially treated with antibiotics for uncomplicated acute appendicitis, the likelihood of late recurrence within 5 years was 39.1%. This long-term follow-up supports the feasibility of antibiotic treatment alone as an alternative to surgery for uncomplicated acute appendicitis.

Prevalence of Variant Reclassification Following Hereditary Cancer Genetic Testing

Jacqueline Mersch, Nichole Brown, Sara Pirzadeh-Miller, et al

JAMA. 2018; 320 (12): 1266-1274.
https://jamanetwork.com/journals/jama/article-abstract/2703350

Abstract

Importance Variant reclassification is an important component of hereditary cancer genetic testing; however, there are few published data quantifying the prevalence of reclassification.

Objective Retrospective cohort study of individuals who had genetic testing from 2006 through 2016 at a single commercial laboratory.

Design, Setting, and Participants A retrospective cohort of individuals who had genetic testing between 2006 and 2016 at a single commercial laboratory was assessed. Variants were classified as benign, likely benign, variant of uncertain significance, likely pathogenic, or pathogenic. Retrospective chart reviews were conducted for patients from the University of Texas Southwestern (UTSW) Medical Center.

Exposures Hereditary cancer genetic testing.

Main Outcomes and Measures Frequency of and time to amended reports; frequency and types of variant reclassification.
Results From 2006 through 2018, 1.45 million individuals (median [interquartile range] age at testing, 49 years [40.69-58.31 years], 95.6% women) had genetic testing, and 56.6% (n = 821 724) had a personal history of cancer. A total of 1.67 million initial tests were reported and 59 955 amended reports were issued due to variant reclassification. Overall, 6.4% (2868 of 44 777) of unique variants were reclassified. Reclassification to a different clinical category was rare among unique variants initially classified as pathogenic or likely pathogenic (0.7%, 61 of 9112) or benign or likely benign (0.2%, 15 of 8995). However, 7.7% (2048 of 26 670) of unique variants of uncertain significance were reclassified: 91.2% (1867 of 2048) were downgraded to benign or likely benign (median time to amended report, 1.17 years), 8.7% (178 of 2048) were upgraded to pathogenic or likely pathogenic variants (median time to amended report, 1.86 years). Because most variants were observed in more than 1 individual, 24.9% (46 890 of 184 327) of all reported variants of uncertain significance were reclassified.
Conclusions and Relevance Following hereditary cancer genetic testing at a single commercial laboratory, 24.9% of variants of uncertain significance were reclassified, which included both downgrades and upgrades. Further research is needed to assess generalizability of the findings for other laboratories, as well as the clinical consequences of the reclassification as a component of a genetic testing program.

Back to Contents

The Lancet (22 September 2018, Vol. 392, No. 10152)

Alcohol use and burden for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016

GBD 2016 Alcohol Collaborators

The Lancet: Volume 392, ISSUE 10152, P1015-1035, September 22, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31310-2/fulltext

Summary
Background
Alcohol use is a leading risk factor for death and disability, but its overall association with health remains complex given the possible protective effects of moderate alcohol consumption on some conditions. With our comprehensive approach to health accounting within the Global Burden of Diseases, Injuries, and Risk Factors Study 2016, we generated improved estimates of alcohol use and alcohol-attributable deaths and disability-adjusted life-years (DALYs) for 195 locations from 1990 to 2016, for both sexes and for 5-year age groups between the ages of 15 years and 95 years and older.
Methods
Using 694 data sources of individual and population-level alcohol consumption, along with 592 prospective and retrospective studies on the risk of alcohol use, we produced estimates of the prevalence of current drinking, abstention, the distribution of alcohol consumption among current drinkers in standard drinks daily (defined as 10 g of pure ethyl alcohol), and alcohol-attributable deaths and DALYs. We made several methodological improvements compared with previous estimates: first, we adjusted alcohol sales estimates to take into account tourist and unrecorded consumption; second, we did a new meta-analysis of relative risks for 23 health outcomes associated with alcohol use; and

third, we developed a new method to quantify the level of alcohol consumption that minimises the overall risk to individual health.

Findings

Globally, alcohol use was the seventh leading risk factor for both deaths and DALYs in 2016, accounting for 2·2% (95% uncertainty interval [UI] 1·5–3·0) of age-standardised female deaths and 6·8% (5·8–8·0) of age-standardised male deaths. Among the population aged 15–49 years, alcohol use was the leading risk factor globally in 2016, with 3·8% (95% UI 3·2–4·3) of female deaths and 12·2% (10·8–13·6) of male deaths attributable to alcohol use. For the population aged 15–49 years, female attributable DALYs were 2·3% (95% UI 2·0–2·6) and male attributable DALYs were 8·9% (7·8–9·9). The three leading causes of attributable deaths in this age group were tuberculosis (1·4% [95% UI 1·0–1·7] of total deaths), road injuries (1·2% [0·7–1·9]), and self-harm (1·1% [0·6–1·5]). For populations aged 50 years and older, cancers accounted for a large proportion of total alcohol-attributable deaths in 2016, constituting 27·1% (95% UI 21·2–33·3) of total alcohol-attributable female deaths and 18·9% (15·3–22·6) of male deaths. The level of alcohol consumption that minimised harm across health outcomes was zero (95% UI 0·0–0·8) standard drinks per week.

Interpretation

Alcohol use is a leading risk factor for global disease burden and causes substantial health loss. We found that the risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption, and the level of consumption that minimises health loss is zero. These results suggest that alcohol control policies might need to be revised worldwide, refocusing on efforts to lower overall population-level consumption.

Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): A randomised, double-blind, placebo-controlled trial

J Michael Gaziano, Carlos Brotons, Rosa Coppolecchia, et al

The Lancet: Volume 392, ISSUE 10152, P1036-1046, September 22, 2018

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31924-X/fulltext

Summary

Background

The use of aspirin in the primary prevention of cardiovascular events remains controversial. We aimed to assess the efficacy and safety of aspirin versus placebo in patients with a moderate estimated risk of a first cardiovascular event.

Methods

ARRIVE is a randomised, double-blind, placebo-controlled, multicentre study done in seven countries. Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate on the basis of the number of specific risk factors. We excluded patients at high risk of gastrointestinal bleeding or other bleeding, or diabetes. Patients were randomly assigned (1:1) with a computer-generated randomisation code to receive enteric-coated aspirin tablets (100 mg) or placebo tablets, once daily. Patients, investigators, and others involved in treatment or data analysis were masked to treatment allocation. The primary efficacy endpoint was a composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischaemic attack. Safety endpoints were haemorrhagic events and incidence of other adverse events, and were analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00501059.

Findings
Between July 5, 2007, and Nov 15, 2016, 12 546 patients were enrolled and randomly assigned to receive aspirin (n=6270) or placebo (n=6276) at 501 study sites. Median follow-up was 60 months. In the intention-to-treat analysis, the primary endpoint occurred in 269 (4·29%) patients in the aspirin group versus 281 (4·48%) patients in the placebo group (hazard ratio [HR] 0·96; 95% CI 0·81–1·13; p=0·6038). Gastrointestinal bleeding events (mostly mild) occurred in 61 (0·97%) patients in the aspirin group versus 29 (0·46%) in the placebo group (HR 2·11; 95% CI 1·36–3·28; p=0·0007). The overall incidence rate of serious adverse events was similar in both treatment groups (n=1266 [20·19%] in the aspirin group *vs* n=1311 [20·89%] in the placebo group. The overall incidence of adverse events was similar in both treatment groups (n=5142 [82·01%] *vs* n=5129 [81·72%] in the placebo group). The overall incidence of treatment-related adverse events was low (n=1050 [16·75%] *vs* n=850 [13·54%] in the placebo group; p<0·0001). There were 321 documented deaths in the intention-to-treat population (n=160 [2·55%] *vs* n=161 [2·57%] of 6276 patients in the placebo group).
Interpretation
The event rate was much lower than expected, which is probably reflective of contemporary risk management strategies, making the study more representative of a low-risk population. The role of aspirin in primary prevention among patients at moderate risk could therefore not be addressed. Nonetheless, the findings with respect to aspirin's effects are consistent with those observed in the previously published low-risk primary prevention studies.

Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): A randomised, controlled, parallel-group, unmasked trial
Friedrich Koehler, Kerstin Koehler, Oliver Deckwart, et al
The Lancet: Volume 392, ISSUE 10152, P1047-1057, September 22, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31880-4/fulltext

Summary
Background
Remote patient management in patients with heart failure might help to detect early signs and symptoms of cardiac decompensation, thus enabling a prompt initiation of the appropriate treatment and care before a full manifestation of a heart failure decompensation. We aimed to investigate the efficacy of our remote patient management intervention on mortality and morbidity in a well defined heart failure population.
Methods
The Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial was a prospective, randomised, controlled, parallel-group, unmasked (with randomisation concealment), multicentre trial with pragmatic elements introduced for data collection. The trial was done in Germany, and patients were recruited from hospitals and cardiology practices. Eligible patients had heart failure, were in New York Heart Association class II or III, had been admitted to hospital for heart failure within 12 months before randomisation, and had a left ventricular ejection fraction (LVEF) of 45% or lower (or if higher than 45%, oral diuretics were being prescribed). Patients with major depression were excluded. Patients were randomly assigned (1:1) using a secure web-based system to either remote patient management plus usual care or to usual care only and were followed up for a maximum of 393 days. The primary outcome was percentage of days lost due to unplanned cardiovascular hospital admissions or all-cause death, analysed in the full analysis set. Key secondary outcomes were all-cause and cardiovascular mortality. This

study is registered with ClinicalTrials.gov, number NCT01878630, and has now been completed.

Findings

Between Aug 13, 2013, and May 12, 2017, 1571 patients were randomly assigned to remote patient management (n=796) or usual care (n=775). Of these 1571 patients, 765 in the remote patient management group and 773 in the usual care group started their assigned care, and were included in the full analysis set. The percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause death was 4·88% (95% CI 4·55–5·23) in the remote patient management group and 6·64% (6·19–7·13) in the usual care group (ratio 0·80, 95% CI 0·65–1·00; p=0·0460). Patients assigned to remote patient management lost a mean of 17·8 days (95% CI 16·6–19·1) per year compared with 24·2 days (22·6–26·0) per year for patients assigned to usual care. The all-cause death rate was 7·86 (95% CI 6·14–10·10) per 100 person-years of follow-up in the remote patient management group compared with 11·34 (9·21–13·95) per 100 person-years of follow-up in the usual care group (hazard ratio [HR] 0·70, 95% CI 0·50–0·96; p=0·0280). Cardiovascular mortality was not significantly different between the two groups (HR 0·671, 95% CI 0·45–1·01; p=0·0560).

Interpretation

The TIM-HF2 trial suggests that a structured remote patient management intervention, when used in a well defined heart failure population, could reduce the percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality.

Brexanolone injection in post-partum depression: Two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

Samantha Meltzer-Brody, Helen Colquhoun, Robert Riesenberg, et al

The Lancet: Volume 392, ISSUE 10152, P1058-1070, September 22, 2018

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31551-4/fulltext

Summary

Background

Post-partum depression is associated with substantial morbidity, and improved pharmacological treatment options are urgently needed. We assessed brexanolone injection (formerly SAGE-547 injection), a positive allosteric modulator of γ-aminobutyric-acid type A ($GABA_A$) receptors, for the treatment of moderate to severe post-partum depression.

Methods

We did two double-blind, randomised, placebo-controlled, phase 3 trials, at 30 clinical research centres and specialised psychiatric units in the USA. Eligible women were aged 18–45 years, 6 months post partum or less at screening, with post-partum depression and a qualifying 17-item Hamilton Rating Scale for Depression (HAM-D) score (≥26 for study 1; 20–25 for study 2). Women with renal failure requiring dialysis, anaemia, known allergy to allopregnanolone or to progesterone, or medical history of schizophrenia, bipolar disorder, or schizoaffective disorder were excluded. Patients were randomly assigned (1:1:1) to receive a single intravenous injection of either brexanolone 90 μg/kg per h (BRX90), brexanolone 60 μg/kg per h (BRX60), or matching placebo for 60 h in study 1, or (1:1) BRX90 or matching placebo for 60 h in study 2. Patients, the study team, site staff, and the principal investigator were masked to treatment allocation. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 h, assessed in all patients who started infusion of study drug or placebo, had a valid HAM-D baseline assessment, and had at least one post-baseline HAM-D assessment. The safety

population included all randomised patients who started infusion of study drug or placebo. Patients were followed up until day 30. The trials have been completed and are registered with ClinicalTrials.gov, numbers NCT02942004 (study 1) and NCT02942017 (study 2).

Findings

Participants were enrolled between Aug 1, 2016, and Oct 19, 2017, in study 1, and between July 25, 2016, and Oct 11, 2017, in study 2. We screened 375 women simultaneously across both studies, of whom 138 were randomly assigned to receive either BRX90 (n=45), BRX60 (n=47), or placebo (n=46) in study 1, and 108 were randomly assigned to receive BRX90 (n=54) or placebo (n=54) in study 2. In study 1, at 60 h, the least-squares (LS) mean reduction in HAM-D total score from baseline was 19·5 points (SE 1·2) in the BRX60 group and 17·7 points (1·2) in the BRX90 group compared with 14·0 points (1·1) in the placebo group (difference −5·5 [95% CI −8·8 to −2·2], p=0·0013 for the BRX60 group; −3·7 [95% CI −6·9 to −0·5], p=0·0252 for the BRX90 group). In study 2, at 60 h, the LS mean reduction in HAM-D total score from baseline was 14·6 points (SE 0·8) in the BRX90 group compared with 12·1 points (SE 0·8) for the placebo group (difference −2·5 [95% CI −4·5 to −0·5], p=0·0160). In study 1, 19 patients in the BRX60 group and 22 patients in the BRX90 group had adverse events compared with 22 patients in the placebo group. In study 2, 25 patients in the BRX90 group had adverse events compared with 24 patients in the placebo group. The most common treatment-emergent adverse events in the brexanolone groups were headache (n=7 BRX60 group and n=6 BRX90 group *vs* n=7 placebo group for study 1; n=9 BRX90 group *vs* n=6 placebo group for study 2), dizziness (n=6 BRX60 group and n=6 BRX90 group *vs* n=1 placebo group for study 1; n=5 BRX90 group *vs* n=4 placebo group for study 2), and somnolence (n=7 BRX60 group and n=2 BRX90 group *vs* n=3 placebo group for study 1; n=4 BRX90 group *vs* n=2 placebo group for study 2). In study 1, one patient in the BRX60 group had two serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). In study 2, one patient in the BRX90 group had two serious adverse events (altered state of consciousness and syncope), which were considered to be treatment related.

Interpretation

Administration of brexanolone injection for post-partum depression resulted in significant and clinically meaningful reductions in HAM-D total score at 60 h compared with placebo, with rapid onset of action and durable treatment response during the study period. Our results suggest that brexanolone injection is a novel therapeutic drug for post-partum depression that has the potential to improve treatment options for women with this disorder.

Back to Contents

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Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients

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Abstract

Background

Lorcaserin, a selective serotonin 2C receptor agonist that modulates appetite, has proven efficacy for weight management in overweight or obese patients. The cardiovascular safety and efficacy of lorcaserin are undefined.

Methods
We randomly assigned 12,000 overweight or obese patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors to receive either lorcaserin (10 mg twice daily) or placebo. The primary safety outcome of major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke) was assessed at an interim analysis to exclude a noninferiority boundary of 1.4. If noninferiority was met, the primary cardiovascular efficacy outcome (a composite of major cardiovascular events, heart failure, hospitalization for unstable angina, or coronary revascularization [extended major cardiovascular events]) was assessed for superiority at the end of the trial.
Results
At 1 year, weight loss of at least 5% had occurred in 1986 of 5135 patients (38.7%) in the lorcaserin group and in 883 of 5083 (17.4%) in the placebo group (odds ratio, 3.01; 95% confidence interval [CI], 2.74 to 3.30; P<0.001). Patients in the lorcaserin group had slightly better values with respect to cardiac risk factors (including blood pressure, heart rate, glycemic control, and lipids) than those in the placebo group. During a median follow-up of 3.3 years, the rate of the primary safety outcome was 2.0% per year in the lorcaserin group and 2.1% per year in the placebo group (hazard ratio, 0.99; 95% CI, 0.85 to 1.14; P<0.001 for noninferiority); the rate of extended major cardiovascular events was 4.1% per year and 4.2% per year, respectively (hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.55). Adverse events of special interest were uncommon, and the rates were generally similar in the two groups, except for a higher number of patients with serious hypoglycemia in the lorcaserin group (13 vs. 4, P=0.04).
Conclusions
In a high-risk population of overweight or obese patients, lorcaserin facilitated sustained weight loss without a higher rate of major cardiovascular events than that with placebo.

Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness
Alex C. Spyropoulos, Walter Ageno, Gregory W. Albers, et al. for the MARINER Investigators
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Abstract
Background
Patients who are hospitalized for medical illness remain at risk for venous thromboembolism after discharge, but the role of extended thromboprophylaxis in the treatment of such patients is a subject of controversy.
Methods
In this randomized, double-blind trial, medically ill patients who were at increased risk for venous thromboembolism on the basis of a modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score of 4 or higher (scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism) or a score of 2 or 3 plus a plasma d-dimer level of more than twice the upper limit of the normal range (defined according to local laboratory criteria) were assigned at hospital discharge to either once-daily rivaroxaban at a dose of 10 mg (with the dose adjusted for renal insufficiency) or placebo for 45 days. The primary efficacy outcome was a composite of symptomatic venous thromboembolism or death due to venous thromboembolism. The principal safety outcome was major bleeding.
Results

Of the 12,024 patients who underwent randomization, 12,019 were included in the intention-to-treat analysis. The primary efficacy outcome occurred in 50 of 6007 patients (0.83%) who were given rivaroxaban and in 66 of 6012 patients (1.10%) who were given placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.52 to 1.09; P=0.14). The prespecified secondary outcome of symptomatic nonfatal venous thromboembolism occurred in 0.18% of patients in the rivaroxaban group and 0.42% of patients in the placebo group (hazard ratio, 0.44; 95% CI, 0.22 to 0.89). Major bleeding occurred in 17 of 5982 patients (0.28%) in the rivaroxaban group and in 9 of 5980 patients (0.15%) in the placebo group (hazard ratio, 1.88; 95% CI, 0.84 to 4.23).

Conclusions

Rivaroxaban, given to medical patients for 45 days after hospital discharge, was not associated with a significantly lower risk of symptomatic venous thromboembolism and death due to venous thromboembolism than placebo. The incidence of major bleeding was low.

Variation in Childhood Diarrheal Morbidity and Mortality in Africa, 2000–2015

Robert C. Reiner, Nicholas Graetz, Daniel C. Casey, et al.
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https://www.nejm.org/doi/full/10.1056/NEJMoa1716766

Abstract

Background

Diarrheal diseases are the third leading cause of disease and death in children younger than 5 years of age in Africa and were responsible for an estimated 30 million cases of severe diarrhea (95% credible interval, 27 million to 33 million) and 330,000 deaths (95% credible interval, 270,000 to 380,000) in 2015. The development of targeted approaches to address this burden has been hampered by a paucity of comprehensive, fine-scale estimates of diarrhea-related disease and death among and within countries.

Methods

We produced annual estimates of the prevalence and incidence of diarrhea and diarrhea-related mortality with high geographic detail (5 km^2) across Africa from 2000 through 2015. Estimates were created with the use of Bayesian geostatistical techniques and were calibrated to the results from the Global Burden of Diseases, Injuries, and Risk Factors Study 2016.

Results

The results revealed geographic inequality with regard to diarrhea risk in Africa. Of the estimated 330,000 childhood deaths that were attributable to diarrhea in 2015, more than 50% occurred in 55 of the 782 first-level administrative subdivisions (e.g., states). In 2015, mortality rates among first-level administrative subdivisions in Nigeria differed by up to a factor of 6. The case fatality rates were highly varied at the national level across Africa, with the highest values observed in Benin, Lesotho, Mali, Nigeria, and Sierra Leone.

Conclusions

Our findings showed concentrated areas of diarrheal disease and diarrhea-related death in countries that had a consistently high burden as well as in countries that had considerable national-level reductions in diarrhea burden.

Back to Contents

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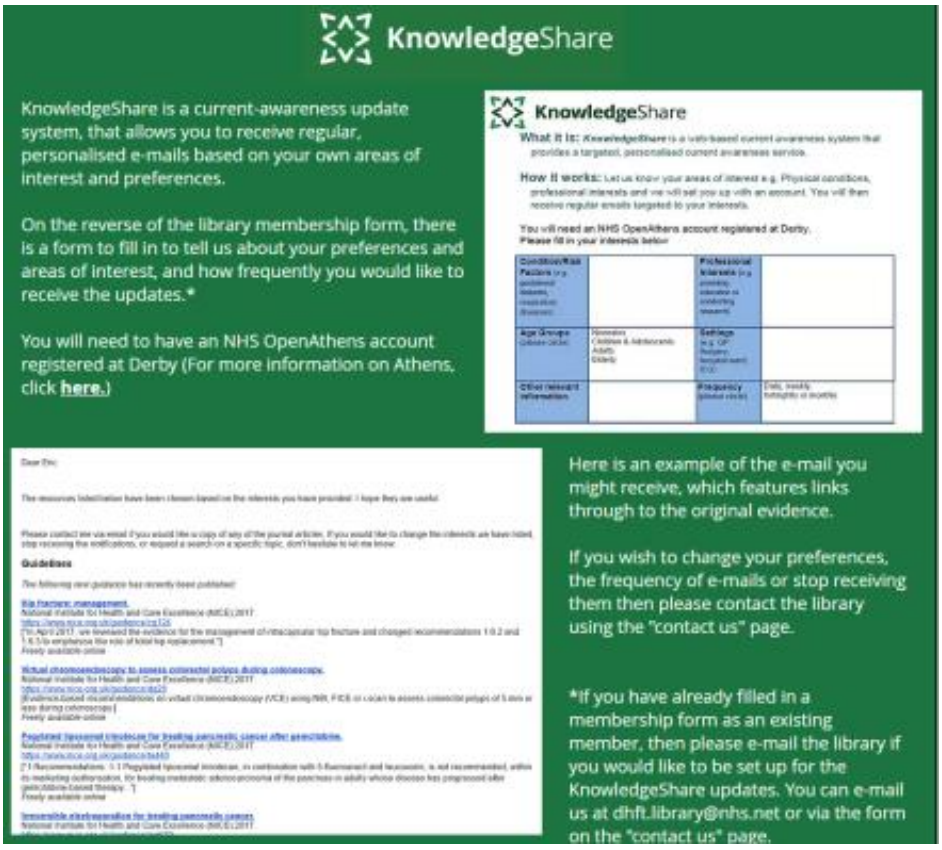

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