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BMJ (28 April 2018, Vol. 361, No. 8150)

Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: Cohort study based on longitudinal data from the Framingham Heart Study

Laila Staerk, Biqi Wang, Sarah R Preis, et al.
BMJ 2018; 361 (Published 26 April 2018)
https://www.bmj.com/content/361/bmj.k1453

Abstract
Objective To examine the association between risk factor burdens—categorized as optimal, borderline, or elevated—and the lifetime risk of atrial fibrillation.
Design Community based cohort study.
Setting Longitudinal data from the Framingham Heart Study.
Participants Individuals free of atrial fibrillation at index ages 55, 65, and 75 years were assessed. Smoking, alcohol consumption, body mass index, blood pressure, diabetes, and history of heart failure or myocardial infarction were assessed as being optimal (that is, all risk factors were optimal), borderline (presence of borderline risk factors and absence of any elevated risk factor), or elevated (presence of at least one elevated risk factor) at index age.
Main outcome measure Lifetime risk of atrial fibrillation at index age up to 95 years, accounting for the competing risk of death.
Results At index age 55 years, the study sample comprised 5338 participants (2531 (47.4%) men). In this group, 247 (4.6%) had an optimal risk profile, 1415 (26.5%) had a borderline risk profile, and 3676 (68.9%) an elevated risk profile. The prevalence of elevated risk factors increased gradually when the index ages rose. For index age of 55 years, the lifetime risk of atrial fibrillation was 37.0% (95% confidence interval 34.3% to 39.6%). The lifetime risk of atrial fibrillation was 23.4% (12.8% to 34.5%) with an optimal risk profile, 33.4% (27.9% to 38.9%) with a borderline risk profile, and 38.4% (35.5% to 41.4%) with an elevated risk profile. Overall, participants with at least one elevated risk factor were associated with at least 37.8% lifetime risk of atrial fibrillation. The gradient in lifetime risk across risk factor burden was similar at index ages 65 and 75 years.
Conclusions Regardless of index ages at 55, 65, or 75 years, an optimal risk factor profile was associated with a lifetime risk of atrial fibrillation of about one in five; this risk rose to more than one in three a third in individuals with at least one elevated risk factor.

Age and sex of surgeons and mortality of older surgical patients: Observational study

Yusuke Tsugawa, Anupam B Jena, Ruth L Newhouse, et al.

BMJ 2018; 361 (Published 25 April 2018)
https://www.bmj.com/content/361/bmj.k1343

Abstract

Objective To investigate whether patients' mortality differs according to the age and sex of surgeons.

Design Observational study.

Setting US acute care hospitals.

Participants 100% of Medicare fee-for-service beneficiaries aged 65-99 years who underwent one of 20 major non-elective surgeries between 2011 and 2014.

Main outcome measure Operative mortality rate of patients, defined as death during hospital admission or within 30 days of the operative procedure, after adjustment for patients' and surgeons' characteristics and indicator variables for hospitals.

Results 892 187 patients who were treated by 45 826 surgeons were included. Patients' mortality was lower for older surgeons than for younger surgeons: the adjusted operative mortality rates were 6.6% (95% confidence interval 6.5% to 6.7%), 6.5% (6.4% to 6.6%), 6.4% (6.3% to 6.5%), and 6.3% (6.2% to 6.5%) for surgeons aged under 40 years, 40-49 years, 50-59 years, and 60 years or over, respectively (P for trend=0.001). There was no evidence that adjusted operative mortality differed between patients treated by female versus male surgeons (adjusted mortality 6.3% for female surgeons versus 6.5% for male surgeons; adjusted odds ratio 0.97, 95% confidence interval 0.93 to 1.01). After stratification by sex of surgeon, patients' mortality declined with age of surgeon for both male and female surgeons (except for female surgeons aged 60 or older); female surgeons in their 50s had the lowest operative mortality.

Conclusion Using national data on Medicare beneficiaries in the US, this study found that patients treated by older surgeons had lower mortality than patients treated by younger surgeons. There was no evidence that operative mortality differed between male and female surgeons.

Anticholinergic drugs and risk of dementia: Case-control study

Kathryn Richardson, Chris Fox, Ian Maidment, et al.

BMJ 2018; 361 (Published 25 April 2018)
https://www.bmj.com/content/361/bmj.k1315

Abstract

Objectives To estimate the association between the duration and level of exposure to different classes of anticholinergic drugs and subsequent incident dementia.

Design Case-control study.

Setting General practices in the UK contributing to the Clinical Practice Research Datalink.

Participants 40 770 patients aged 65-99 with a diagnosis of dementia between April 2006 and July 2015, and 283 933 controls without dementia.

Interventions Daily defined doses of anticholinergic drugs coded using the Anticholinergic Cognitive Burden (ACB) scale, in total and grouped by subclass, prescribed 4-20 years before a diagnosis of dementia.

Main outcome measures Odds ratios for incident dementia, adjusted for a range of demographic and health related covariates.

Results 14 453 (35%) cases and 86 403 (30%) controls were prescribed at least one anticholinergic drug with an ACB score of 3 (definite anticholinergic activity) during the exposure period. The adjusted odds ratio for any anticholinergic drug with an ACB score of 3 was 1.11 (95% confidence interval 1.08 to 1.14). Dementia was associated with an increasing average ACB score. When considered by drug class, gastrointestinal drugs with an ACB score of 3 were not distinctively linked to dementia. The risk of dementia increased with greater exposure for antidepressant, urological, and antiparkinson drugs with an ACB score of 3. This result was also observed for exposure 15-20 years before a diagnosis.
Conclusions A robust association between some classes of anticholinergic drugs and future dementia incidence was observed. This could be caused by a class specific effect, or by drugs being used for very early symptoms of dementia. Future research should examine anticholinergic drug classes as opposed to anticholinergic effects intrinsically or summing scales for anticholinergic exposure.

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JAMA: Journal of the American Medical Association (1 May 2018, Vol. 319, No. 17)

Effect of Glyburide vs Subcutaneous Insulin on Perinatal Complications among Women with Gestational Diabetes: A Randomized Clinical Trial

Marie-Victoire Sénat, Helene Affres, Alexandra Letourneau, et al. for the Groupe de Recherche en Obstétrique et Gynécologie (GROG)

JAMA. 2018; 319 (17): 1773-1780.
https://jamanetwork.com/journals/jama/fullarticle/2679942

Abstract
Importance Randomized trials have not focused on neonatal complications of glyburide for women with gestational diabetes.
Objective To compare oral glyburide vs subcutaneous insulin in prevention of perinatal complications in newborns of women with gestational diabetes.
Design, Settings, and Participants The Insulin Daonil trial (INDAO), a multicenter noninferiority randomized trial conducted between May 2012 and November 2016 (end of participant follow-up) in 13 tertiary care university hospitals in France including 914 women with singleton pregnancies and gestational diabetes diagnosed between 24 and 34 weeks of gestation.
Intervention Women who required pharmacologic treatment after 10 days of dietary intervention were randomly assigned to receive glyburide (n=460) or insulin (n=454). The starting dosage for glyburide was 2.5 mg orally once per day and could be increased if necessary 4 days later by 2.5 mg and thereafter by 5 mg every 4 days in 2 morning and evening doses, up to a maximum of 20 mg/d. The starting dosage for insulin was 4 IU to 20 IU given subcutaneously 1 to 4 times per day as necessary and increased according to self-measured blood glucose concentrations.
Main Outcomes and Measures The primary outcome was a composite criterion including macrosomia, neonatal hypoglycemia, and hyperbilirubinemia. The noninferiority margin was set at 7% based on a 1-sided 97.5% confidence interval.
Results Among the 914 patients who were randomized (mean age, 32.8 [SD, 5.2] years), 98% completed the trial. In a per-protocol analysis, 367 and 442 women and their neonates were analyzed in the glyburide and insulin groups, respectively. The frequency of the primary outcome was 27.6% in the glyburide group and 23.4% in the insulin group, a difference of 4.2% (1-sided 97.5% CI, −∞ to 10.5% ;*P*.(19.=

Conclusion and Relevance This study of women with gestational diabetes failed to show that use of glyburide compared with subcutaneous insulin does not result in a greater frequency of perinatal complications. These findings do not justify the use of glyburide as a first-line treatment.

Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial

Angela Huttner, Anna Kowalczyk, Adi Turjeman, et al.
JAMA. 2018; 319 (17): 1781-1789.
https://jamanetwork.com/journals/jama/article-abstract/2679131

Abstract

Importance The use of nitrofurantoin and fosfomycin has increased since guidelines began recommending them as first-line therapy for lower urinary tract infection (UTI).

Objective To compare the clinical and microbiologic efficacy of nitrofurantoin and fosfomycin in women with uncomplicated cystitis.

Design, Setting, and Participants Multinational, open-label, analyst-blinded, randomized clinical trial including 513 nonpregnant women aged 18 years and older with symptoms of lower UTI (dysuria, urgency, frequency, or suprapubic tenderness), a positive urine dipstick result (with detection of nitrites or leukocyte esterase), and no known colonization or previous infection with uropathogens resistant to the study antibiotics. Recruitment took place from October 2013 through April 2017 at hospital units and outpatient clinics in Geneva, Switzerland; Lodz, Poland; and Petah-Tiqva, Israel.

Interventions Participants were randomized in a 1:1 ratio to oral nitrofurantoin, 100 mg 3 times a day for 5 days (n = 255), or a single 3-g dose of oral fosfomycin (n = 258). They returned 14 and 28 days after therapy completion for clinical evaluation and urine culture collection.

Main Outcomes and Measures The primary outcome was clinical response in the 28 days following therapy completion, defined as clinical resolution (complete resolution of symptoms and signs of UTI without prior failure), failure (need for additional or change in antibiotic treatment due to UTI or discontinuation due to lack of efficacy), or indeterminate (persistence of symptoms without objective evidence of infection). Secondary outcomes included bacteriologic response and incidence of adverse events.

Results Among 513 patients who were randomized (median age, 44 years [interquartile range, 31-64]), 475 (93%) completed the trial and 377 (73%) had a confirmed positive baseline culture. Clinical resolution through day 28 was achieved in 171 of 244 patients (70%) receiving nitrofurantoin vs 139 of 241 patients (58%) receiving fosfomycin (difference, 12% [95% CI, 4%-21%]; *P* = .004). Microbiologic resolution occurred in 129 of 175 (74%) vs 103 of 163 (63%), respectively (difference, 11% [95% CI, 1%-20%]; *P* = .04). Adverse events were few and primarily gastrointestinal; the most common were nausea and diarrhea (7/248 [3%] and 3/248 [1%] in the nitrofurantoin group vs 5/247 [2%] and 5/247 [1%] in the fosfomycin group, respectively).

Conclusions and Relevance Among women with uncomplicated UTI, 5-day nitrofurantoin, compared with single-dose fosfomycin, resulted in a significantly greater likelihood of clinical and microbiologic resolution at 28 days after therapy completion.

Effect of Atropine with Propofol vs Atropine with Atracurium and Sufentanil on Oxygen Desaturation in Neonates Requiring Nonemergency Intubation: A Randomized Clinical Trial

Xavier Durrmeyer, MD, PhD1,2; Sophie Breinig, MD3; Olivier Claris, MD, PhD4; et al.

JAMA. 2018; 319 (17): 1790-1801.
https://jamanetwork.com/journals/jama/article-abstract/2679941

Abstract

Importance Propofol or a combination of a synthetic opioid and muscle relaxant are both recommended for premedication before neonatal intubation but have yet to be compared.

Objective To compare prolonged desaturation during neonatal nasotracheal intubation after premedication with atropine-propofol vs atropine-atracurium-sufentanil treatment.

Design, Setting, and Participants Multicenter, double-blind, randomized clinical trial (2012-2016) in 6 NICUs in France that included 173 neonates requiring nonemergency intubation. The study was interrupted due to expired study kits and lack of funding.

Interventions Eighty-nine participants were randomly assigned to the atropine-propofol group and 82 to the atropine-atracurium-sufentanil group before nasotracheal intubation.

Main Outcomes and Measures The primary outcome was prolonged desaturation (Spo_2 <80% lasting > 60 seconds), using intention-to-treat analysis using mixed models. Secondary outcomes assessed the characteristics of the procedure and its tolerance.

Results Of 173 neonates randomized (mean gestational age, 30.6 weeks; mean birth weight, 1502 g; 71 girls), 171 (99%) completed the trial. Of 89 infants, 53 (59.6%) in the atropine-propofol group vs 54 of 82 (65.9%) in the atropine-atracurium-sufentanil group achieved the primary outcome (adjusted RD, −6.4; 95% CI, −21.0 to 8.1; $P = .38$). The atropine-propofol group had a longer mean procedure duration than did the atropine-atracurium-sufentanil group (adjusted RD, 1.7 minutes; 95% CI, 0.1-3.3 minutes; $P = .04$); a less frequent excellent quality of sedation rate, 51.7% (45 of 87) vs 92.6% (75 of 81; $P < .001$); a shorter median time to respiratory recovery, 14 minutes (IQR, 8-34 minutes) vs 33 minutes (IQR, 15-56 minutes; $P = .002$), and shorter median time to limb movement recovery, 18 minutes (IQR, 10-43 minutes) vs 36 minutes (IQR, 19-65 minutes; $P = .003$). In the 60 minutes after inclusion, Spo_2 was preserved significantly better in the atropine-propofol group (time × treatment interaction $P = .02$). Of the atropine-propofol group 20.6% had head ultrasound scans that showed worsening intracranial hemorrhaging (any or increased intraventricular hemorrhage) in the 7 days after randomization vs 17.6% in the atropine-atracurium-sufentanil group (adjusted RD, 1.2; 95% CI, −13.1 to 15.5, $P = .87$). Severe adverse events occurred in 11% of the atropine-propofol group and in 20% of the atropine-atracurium-sufentanil group.

Conclusions and Relevance Among neonates undergoing nonemergency nasotracheal intubation, the frequency of prolonged desaturation did not differ significantly between atropine used with propofol or atropine used with atracurium and sufentanil. However, the study may have been underpowered to detect a clinically important difference, and further research may be warranted.

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The Lancet (28 April 2018, Vol. 391, No. 10131)

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): A randomised non-inferiority trial

Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, et al.
The Lancet: Volume 391, No. 10131, p1683–1692, 28 April 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30295-2/fulltext

Summary

Background

Treatment-resistant major depressive disorder is common; repetitive transcranial magnetic stimulation (rTMS) by use of high-frequency (10 Hz) left-side dorsolateral prefrontal cortex stimulation is an evidence-based treatment for this disorder. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS that can be delivered in 3 min, versus 37·5 min for a standard 10 Hz treatment session. We aimed to establish the clinical effectiveness, safety, and tolerability of iTBS compared with standard 10 Hz rTMS in adults with treatment-resistant depression.

Methods

In this randomised, multicentre, non-inferiority clinical trial, we recruited patients who were referred to specialty neurostimulation centres based at three Canadian university hospitals (Centre for Addiction and Mental Health and Toronto Western Hospital, Toronto, ON, and University of British Columbia Hospital, Vancouver, BC). Participants were aged 18–65 years, were diagnosed with a current treatment-resistant major depressive episode or could not tolerate at least two antidepressants in the current episode, were receiving stable antidepressant medication doses for at least 4 weeks before baseline, and had an HRSD-17 score of at least 18. Participants were randomly allocated (1:1) to treatment groups (10 Hz rTMS or iTBS) by use of a random permuted block method, with stratification by site and number of adequate trials in which the antidepressants were unsuccessful. Treatment was delivered open-label but investigators and outcome assessors were masked to treatment groups. Participants were treated with 10 Hz rTMS or iTBS to the left dorsolateral prefrontal cortex, administered on 5 days a week for 4–6 weeks. The primary outcome measure was change in 17-item Hamilton Rating Scale for Depression (HRSD-17) score, with a non-inferiority margin of 2·25 points. For the primary outcome measure, we did a per-protocol analysis of all participants who were randomly allocated to groups and who attained the primary completion point of 4 weeks. This trial is registered with ClinicalTrials.gov, number NCT01887782.

Findings

Between Sept 3, 2013, and Oct 3, 2016, we randomly allocated 205 participants to receive 10 Hz rTMS and 209 participants to receive iTBS. 192 (94%) participants in the 10 Hz rTMS group and 193 (92%) in the iTBS group were assessed for the primary outcome after 4–6 weeks of treatment. HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and from 23·6 (4·3) to 13·4 (7·9) in the iTBS group (adjusted difference 0·01, lower 95% CI −1·16; p=0·0011), which indicated non-inferiority of iTBS. Self-rated intensity of pain associated with treatment was greater in the iTBS group than in the 10 Hz rTMS group (mean score on verbal analogue scale 3·8 [SD 2·0] *vs* 3·4 [2·0] out of 10; p=0·011). Dropout rates did not differ between groups (10 Hz rTMS: 13 [6%] of 205 participants; iTBS: 16 [8%] of 209 participants); p=0·6004). The most common treatment-related adverse event was headache in both groups (10 Hz rTMS: 131 [64%] of 204; iTBS: 136 [65%] of 208).

Interpretation

In patients with treatment-resistant depression, iTBS was non-inferior to 10 Hz rTMS for the treatment of depression. Both treatments had low numbers of dropouts and similar side-effects, safety, and tolerability profiles. By use of iTBS, the number of patients treated per day with current rTMS devices can be increased several times without compromising clinical effectiveness.

Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): A systematic review and meta-analysis

Derek K Chu, Lisa H-Y Kim, Paul J Young, et al.

The Lancet: Volume 391, No. 10131, p1693–1705, 28 April 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30479-3/fulltext

Summary

Background

Supplemental oxygen is often administered liberally to acutely ill adults, but the credibility of the evidence for this practice is unclear. We systematically reviewed the efficacy and safety of liberal versus conservative oxygen therapy in acutely ill adults.

Methods

In the Improving Oxygen Therapy in Acute-illness (IOTA) systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, HealthSTAR, LILACS, PapersFirst, and the WHO International Clinical Trials Registry from inception to Oct 25, 2017, for randomised controlled trials comparing liberal and conservative oxygen therapy in acutely ill adults (aged ≥18 years). Studies limited to patients with chronic respiratory diseases or psychiatric disease, patients on extracorporeal life support, or patients treated with hyperbaric oxygen therapy or elective surgery were excluded. We screened studies and extracted summary estimates independently and in duplicate. We also extracted individual patient-level data from survival curves. The main outcomes were mortality (in-hospital, at 30 days, and at longest follow-up) and morbidity (disability at longest follow-up, risk of hospital-acquired pneumonia, any hospital-acquired infection, and length of hospital stay) assessed by random-effects meta-analyses. We assessed quality of evidence using the grading of recommendations assessment, development, and evaluation approach. This study is registered with PROSPERO, number CRD42017065697.

Findings

25 randomised controlled trials enrolled 16 037 patients with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery. Compared with a conservative oxygen strategy, a liberal oxygen strategy (median baseline saturation of peripheral oxygen [SpO_2] across trials, 96% [range 94–99%, IQR 96–98]) increased mortality in-hospital (relative risk [RR] 1·21, 95% CI 1·03–1·43, I^2=0%, high quality), at 30 days (RR 1·14, 95% CI 1·01–1·29, I^2=0%, high quality), and at longest follow-up (RR 1·10, 95% CI 1·00–1·20, I^2=0%, high quality). Morbidity outcomes were similar between groups. Findings were robust to trial sequential, subgroup, and sensitivity analyses.

Interpretation

In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO_2 range of 94–96%. These results support the conservative administration of oxygen therapy.

Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): A national cross-sectional study

Chen Wang, Jianying Xu, Lan Yang, et al. for the China Pulmonary Health Study Group

The Lancet: Volume 391, No. 10131, p1706–1717, 28 April 2018

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30841-9/fulltext

Summary

Background

Although exposure to cigarette smoking and air pollution is common, the current prevalence of chronic obstructive pulmonary disease (COPD) is unknown in the Chinese adult population. We conducted the China Pulmonary Health (CPH) study to assess the prevalence and risk factors of COPD in China.

Methods

The CPH study is a cross-sectional study in a nationally representative sample of adults aged 20 years or older from ten provinces, autonomous regions, and municipalities in mainland China. All participants underwent a post-bronchodilator pulmonary function test. COPD was diagnosed according to 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.

Findings

Between June, 2012, and May, 2015, 57 779 individuals were invited to participate, of whom 50 991 (21 446 men and 29 545 women) had reliable post-bronchodilator results and were included in the final analysis. The overall prevalence of spirometry-defined COPD was 8·6% (95% CI 7·5–9·9), accounting for 99·9 (95% CI 76·3–135·7) million people with COPD in China. Prevalence was higher in men (11·9%, 95% CI 10·2–13·8) than in women (5·4%, 4·6–6·2; p<0·0001 for sex difference) and in people aged 40 years or older (13·7%, 12·1–15·5) than in those aged 20–39 years (2·1%, 1·4–3·2; p<0·0001 for age difference). Only 12·0% (95% CI 8·1–17·4) of people with COPD reported a previous pulmonary function test. Risk factors for COPD included smoking exposure of 20 pack-years or more (odds ratio [OR] 1·95, 95% CI 1·53–2·47), exposure to annual mean particulate matter with a diameter less than 2·5 μm of 50–74 μg/m^3 (1·85, 1·23–2·77) or 75 μg/m^3 or higher (2·00, 1·36–2·92), underweight (body-mass index <18·5 kg/m^2; 1·43, 1·03–1·97), sometimes childhood chronic cough (1·48, 1·14–1·93) or frequent cough (2·57, 2·01–3·29), and parental history of respiratory diseases (1·40, 1·23–1·60). A lower risk of COPD was associated with middle or high school education (OR 0·76, 95% CI 0·64–0·90) and college or higher education (0·47, 0·33–0·66).

Interpretation

Spirometry-defined COPD is highly prevalent in the Chinese adult population. Cigarette smoking, ambient air pollution, underweight, childhood chronic cough, parental history of respiratory diseases, and low education are major risk factors for COPD. Prevention and early detection of COPD using spirometry should be a public health priority in China to reduce COPD-related morbidity and mortality.

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The New England Journal of Medicine (26 April 2018, Vol. 378, No. 17)

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

Bruce C.V. Campbell, Peter J. Mitchell, Leonid Churilov, et al. for the EXTEND-IA TNK Investigators

N Engl J Med 2018; 378:1573-1582 April 26, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1716405

Abstract

Background

Intravenous infusion of alteplase is used for thrombolysis before endovascular thrombectomy for ischemic stroke. Tenecteplase, which is more fibrin-specific and has longer activity than alteplase, is given as a bolus and may increase the incidence of vascular reperfusion.

Methods

We randomly assigned patients with ischemic stroke who had occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible to undergo thrombectomy to receive tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or alteplase (at a dose of 0.9 mg per kilogram; maximum dose, 90 mg) within 4.5 hours after symptom onset. The primary outcome was reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. Noninferiority of tenecteplase was tested, followed by superiority. Secondary outcomes included the modified Rankin scale score (on a scale from 0 [no neurologic deficit] to 6 [death]) at 90 days. Safety outcomes were death and symptomatic intracerebral hemorrhage.

Results

Of 202 patients enrolled, 101 were assigned to receive tenecteplase and 101 to receive alteplase. The primary outcome occurred in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (incidence difference, 12 percentage points; 95% confidence interval [CI], 2 to 21; incidence ratio, 2.2; 95% CI, 1.1 to 4.4; P=0.002 for noninferiority; P=0.03 for superiority). Tenecteplase resulted in a better 90-day functional outcome than alteplase (median modified Rankin scale score, 2 vs. 3; common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). Symptomatic intracerebral hemorrhage occurred in 1% of the patients in each group.

Conclusions

Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset.

Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa

Jeremy D. Keenan, Robin L. Bailey, Sheila K. West, et al. for the MORDOR Study Group

N Engl J Med 2018; 378:1583-1592 April 26, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1715474

Abstract

Background

We hypothesized that mass distribution of a broad-spectrum antibiotic agent to preschool children would reduce mortality in areas of sub-Saharan Africa that are currently far from meeting the Sustainable Development Goals of the United Nations.

Methods

In this cluster-randomized trial, we assigned communities in Malawi, Niger, and Tanzania to four twice-yearly mass distributions of either oral azithromycin (approximately 20 mg per kilogram of body weight) or placebo. Children 1 to 59 months of age were identified in twice-yearly censuses and were offered participation in the trial. Vital status was determined at subsequent censuses. The primary outcome was aggregate all-cause mortality; country-specific rates were assessed in prespecified subgroup analyses.

Results

A total of 1533 communities underwent randomization, 190,238 children were identified in the census at baseline, and 323,302 person-years were monitored. The mean (±SD) azithromycin and placebo coverage over the four twice-yearly distributions was

90.4±10.4%. The overall annual mortality rate was 14.6 deaths per 1000 person-years in communities that received azithromycin (9.1 in Malawi, 22.5 in Niger, and 5.4 in Tanzania) and 16.5 deaths per 1000 person-years in communities that received placebo (9.6 in Malawi, 27.5 in Niger, and 5.5 in Tanzania). Mortality was 13.5% lower overall (95% confidence interval [CI], 6.7 to 19.8) in communities that received azithromycin than in communities that received placebo (P<0.001); the rate was 5.7% lower in Malawi (95% CI, −9.7 to 18.9), 18.1% lower in Niger (95% CI, 10.0 to 25.5), and 3.4% lower in Tanzania (95% CI, −21.2 to 23.0). Children in the age group of 1 to 5 months had the greatest effect from azithromycin (24.9% lower mortality than that with placebo; 95% CI, 10.6 to 37.0). Serious adverse events occurring within a week after administration of the trial drug or placebo were uncommon, and the rate did not differ significantly between the groups. Evaluation of selection for antibiotic resistance is ongoing.

Conclusions

Among postneonatal, preschool children in sub-Saharan Africa, childhood mortality was lower in communities randomly assigned to mass distribution of azithromycin than in those assigned to placebo, with the largest effect seen in Niger. Any implementation of a policy of mass distribution would need to strongly consider the potential effect of such a strategy on antibiotic resistance.

Birth Outcomes for Pregnant Women with HIV Using Tenofovir–Emtricitabine

Kathryn Rough, George R. Seage, Paige L. Williams, et al.

N Engl J Med 2018; 378:1593-1603 April 26, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1701666

Abstract

Background

In a previous trial of antiretroviral therapy (ART) involving pregnant women with human immunodeficiency virus (HIV) infection, those randomly assigned to receive tenofovir, emtricitabine, and ritonavir-boosted lopinavir (TDF–FTC–LPV/r) had infants at greater risk for very premature birth and death within 14 days after delivery than those assigned to receive zidovudine, lamivudine, and ritonavir-boosted lopinavir (ZDV–3TC–LPV/r).

Methods

Using data from two U.S.-based cohort studies, we compared the risk of adverse birth outcomes among infants with in utero exposure to ZDV–3TC–LPV/r, TDF–FTC–LPV/r, or TDF–FTC with ritonavir-boosted atazanavir (ATV/r). We evaluated the risk of preterm birth (<37 completed weeks of gestation), very preterm birth (<34 completed weeks), low birth weight (<2500 g), and very low birth weight (<1500 g). Risk ratios with 95% confidence intervals were estimated with the use of modified Poisson models to adjust for confounding.

Results

There were 4646 birth outcomes. Few infants or fetuses were exposed to TDF–FTC–LPV/r (128 [2.8%]) as the initial ART regimen during gestation, in contrast with TDF–FTC–ATV/r (539 [11.6%]) and ZDV–3TC–LPV/r (954 [20.5%]). As compared with women receiving ZDV–3TC–LPV/r, women receiving TDF–FTC–LPV/r had a similar risk of preterm birth (risk ratio, 0.90; 95% confidence interval [CI], 0.60 to 1.33) and low birth weight (risk ratio, 1.13; 95% CI, 0.78 to 1.64). As compared to women receiving TDF–FTC–ATV/r, women receiving TDF–FTC–LPV/r had a similar or slightly higher risk of preterm birth (risk ratio, 1.14; 95% CI, 0.75 to 1.72) and low birth weight (risk ratio, 1.45; 95% CI, 0.96 to 2.17). There were no significant differences between regimens in the risk of very preterm birth or very low birth weight.

Conclusions
The risk of adverse birth outcomes was not higher with TDF–FTC–LPV/r than with ZDV–3TC–LPV/r or TDF–FTC–ATV/r among HIV-infected women and their infants in the United States, although power was limited for some comparisons.

Brief Report
Prenatal Correction of X-Linked Hypohidrotic Ectodermal Dysplasia
Holm Schneider, Florian Faschingbauer, Sonia Schuepbach-Mallepell, et al.
N Engl J Med 2018; 378:1604-1610 April 26, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1714322

Abstract
Genetic deficiency of ectodysplasin A (EDA) causes X-linked hypohidrotic ectodermal dysplasia (XLHED), in which the development of sweat glands is irreversibly impaired, an condition that can lead to life-threatening hyperthermia. We observed normal development of mouse fetuses with *Eda* mutations after they had been exposed in utero to a recombinant protein that includes the receptor-binding domain of EDA. We administered this protein intraamniotically to two affected human twins at gestational weeks 26 and 31 and to a single affected human fetus at gestational week 26; the infants, born in week 33 (twins) and week 39 (singleton), were able to sweat normally, and XLHED-related illness had not developed by 14 to 22 months of age.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
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/
If you have not already registered for an NHS Athens Account, please register at: NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username and password. Once registered, your account can be accessed from any device with online access.	https://openathens.nice.org.uk/

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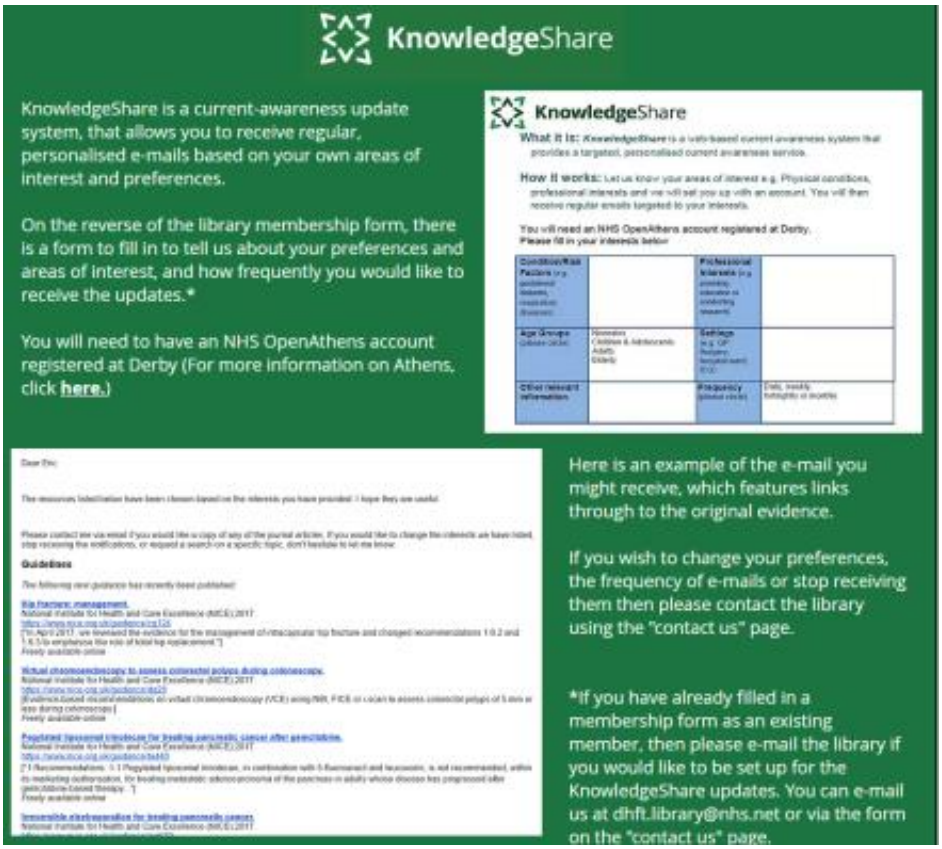

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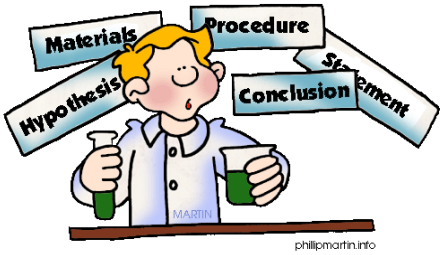

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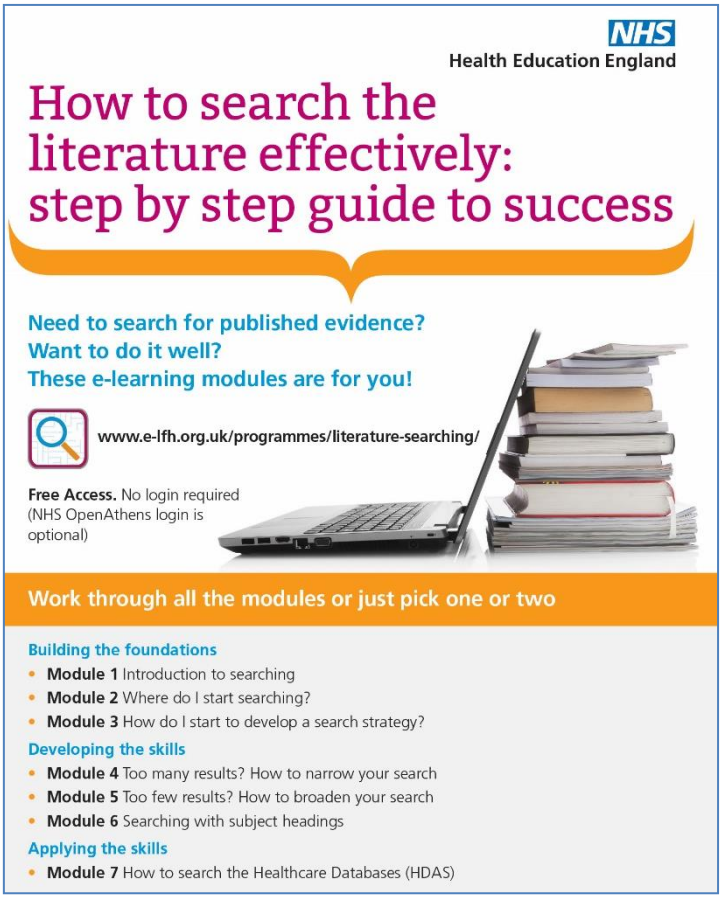

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