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BMJ (6 October 2018, Vol. 363, No. 8170)

Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): Randomised, multicentre, non-inferiority trial
Elvin Kedhi, Enrico Fabris, Martin van der Ent, et al.
BMJ 2018; 363 (Published 02 October 2018)
https://www.bmj.com/content/363/bmj.k3793

Abstract
Objective To show that limiting dual antiplatelet therapy (DAPT) to six months in patients with event-free ST-elevation myocardial infarction (STEMI) results in a non-inferior clinical outcome versus DAPT for 12 months.
Design Prospective, randomised, multicentre, non-inferiority trial.
Setting Patients with STEMI treated with primary percutaneous coronary intervention (PCI) and second generation zotarolimus-eluting stent.
Participants Patients with STEMI aged 18 to 85 that underwent a primary PCI with the implantation of second generation drug-eluting stents were enrolled in the trial. Patients that were event-free at six months after primary PCI were randomised at this time point.

Interventions Patients that were taking DAPT and were event-free at six months were randomised 1:1 to single antiplatelet therapy (SAPT) (ie, aspirin only) or to DAPT for an additional six months. All patients that were randomised were then followed for another 18 months (ie, 24 months after the primary PCI).
Main outcome measures The primary endpoint was a composite of all cause mortality, any myocardial infarction, any revascularisation, stroke, and thrombolysis in myocardial infarction major bleeding at 18 months after randomisation.
Results A total of 1100 patients were enrolled in the trial between 19 December 2011 and 30 June 2015. 870 were randomised: 432 to SAPT versus 438 to DAPT. The primary endpoint occurred in 4.8% of patients receiving SAPT versus 6.6% of patients receiving DAPT (hazard ratio 0.73, 95% confidence interval 0.41 to 1.27, P=0.26). Non-inferiority was met (P=0.004 for non-inferiority), as the upper 95% confidence interval of 1.27 was smaller than the prespecified non-inferiority margin of 1.66.
Conclusions DAPT to six months was non-inferior to DAPT for 12 months in patients with event-free STEMI at six months after primary PCI with second generation drug-eluting stents.

Collaboration between academics and industry in clinical trials: Cross sectional study of publications and survey of lead academic authors

Kristine Rasmussen, Lisa Bero, Rita Redberg, et al.
BMJ 2018; 363 (Published 03 October 2018)
https://www.bmj.com/content/363/bmj.k3654

Abstract
Objectives To determine the role of academic authors, funders, and contract research organisations in industry funded trials of vaccines, drugs, and devices and to determine lead academic authors' experiences with industry funder collaborations.
Design Cross sectional analysis of trial publications and survey of lead academic authors.
Eligibility criteria for selecting studies The most recent 200 phase III and IV trials of vaccines, drugs, and devices with full industry funding, at least one academic author, published in one of the top seven high impact general medical journals (*New England Journal of Medicine*, *Lancet*, *JAMA*, *BMJ*, *Annals of Internal Medicine*, *JAMA Internal Medicine*, and *PLoS Medicine*).
Results Employees of industry funders co-authored 173 (87%) of publications; 183 (92%) trials reported involvement of funders in design, and 167 (84%) reported involvement of academic authors. Data analysis involved the funder in 146 (73%) trials and the academic authors in 79 (40%). Trial reporting involved the funder in 173 (87%) trials and academic authors in 197 (99%). Contract research organisations were involved in the reporting of 123 (62%) trials.
Eighty (40%) of 200 lead academic authors responded to the survey. Twenty nine (33%) of the 80 responders reported that academics had final say on the design. Ten responders described involvement of an unnamed funder and/or contract research organisation employee in the data analysis and/or reporting. Most academic authors found the collaboration with industry funder beneficial, but 3 (4%) experienced delay in publication due to the industry funder and 9 (11%) reported disagreements with the industry funder, mostly concerning trial design and reporting.
Conclusions Industry employees and academic authors are involved in the design, conduct, and reporting of most industry funded trials in high impact journals. However, data analysis is often conducted without academic involvement. Academics view the collaboration as beneficial, but some report loss of academic freedom.

Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: Meta-analysis

Xian Shen, Bin Zhao

BMJ 2018; 362 (Published 10 September 2018)
https://www.bmj.com/content/362/bmj.k3529

Abstract

Objective To evaluate the relative efficacy of programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors versus conventional drugs in patients with cancer that were PD-L1 positive and PD-L1 negative.

Design Meta-analysis of randomised controlled trials.

Data sources PubMed, Embase, Cochrane database, and conference abstracts presented at the American Society of Clinical Oncology and European Society of Medical Oncology up to March 2018.

Review methods Studies of PD-1 or PD-L1 inhibitors (avelumab, atezolizumab, durvalumab, nivolumab, and pembrolizumab) that had available hazard ratios for death based on PD-L1 positivity or negativity were included. The threshold for PD-L1 positivity or negativity was that PD-L1 stained cell accounted for 1% of tumour cells, or tumour and immune cells, assayed by immunohistochemistry staining methods.

Results 4174 patients with advanced or metastatic cancers from eight randomised controlled trials were included in this study. Compared with conventional agents, PD-1 or PD-L1 inhibitors were associated with significantly prolonged overall survival in both patients that were PD-L1 positive (n=2254, hazard ratio 0.66, 95% confidence interval 0.59 to 0.74) and PD-L1 negative (1920, 0.80, 0.71 to 0.90). However, the efficacies of PD-1 or PD-L1 blockade treatment in patients that were PD-L1 positive and PD-L1 negative were significantly different (P=0.02 for interaction). Additionally, in both patients that were PD-L1 positive and PD-L1 negative, the long term clinical benefits from PD-1 or PD-L1 blockade were observed consistently across interventional agent, cancer histotype, method of randomisation stratification, type of immunohistochemical scoring system, drug target, type of control group, and median follow-up time.

Conclusions PD-1 or PD-L1 blockade therapy is a preferable treatment option over conventional therapy for both patients that are PD-L1 positive and PD-L1 negative. This finding suggests that PD-L1 expression status alone is insufficient in determining which patients should be offered PD-1 or PD-L1 blockade therapy.

Evaluation of the causal effects between subjective wellbeing and cardiometabolic health: Mendelian randomisation study

Robyn E Wootton, Rebecca B Lawn, Louise A C Millard, et al.

BMJ 2018; 362 (Published 25 September 2018)
https://www.bmj.com/content/362/bmj.k3788

Abstract

Objectives To investigate whether the association between subjective wellbeing (subjective happiness and life satisfaction) and cardiometabolic health is causal.

Design Two sample, bidirectional mendelian randomisation study.

Setting Genetic data taken from various cohorts comprised of the general population (mostly individuals of European ancestry, plus a small proportion of other ancestries); follow-up analysis included individuals from the United Kingdom.
Participants Summary data were used from previous genome wide association studies (number of participants ranging from 83 198 to 339 224), which investigated traits related to cardiovascular or metabolic health, had the largest sample sizes, and consisted of the most similar populations while minimising sample overlap. A follow-up analysis included 337 112 individuals from the UK Biobank (54% female (n=181 363), mean age 56.87 years (standard deviation 8.00) at recruitment).
Main outcome measures Subjective wellbeing and 11 measures of cardiometabolic health (coronary artery disease; myocardial infarction; total, high density lipoprotein, and low density lipoprotein cholesterol; diastolic and systolic blood pressure; body fat; waist to hip ratio; waist circumference; and body mass index).
Results Evidence of a causal effect of body mass index on subjective wellbeing was seen; each 1 kg/m^2 increase in body mass index caused a −0.045 (95% confidence interval −0.084 to −0.006, P=0.02) standard deviation reduction in subjective wellbeing. Follow-up analysis of this association in an independent sample from the UK Biobank provided strong evidence of an effect of body mass index on satisfaction with health (β=−0.035 unit decrease in health satisfaction (95% confidence interval −0.043 to −0.027) per standard deviation increase in body mass index, P<0.001). No clear evidence of a causal effect was seen between subjective wellbeing and the other cardiometabolic health measures, in either direction.
Conclusions These results suggest that a higher body mass index is associated with a lower subjective wellbeing. A follow-up analysis confirmed this finding, suggesting that the effect in middle aged people could be driven by satisfaction with health. Body mass index is a modifiable determinant, and therefore, this study provides further motivation to tackle the obesity epidemic because of the knock-on effects of higher body mass index on subjective wellbeing.

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JAMA: Journal of the American Medical Association (9 October 2018, Vol. 320, No. 14)

Effect of Immediate vs Delayed Pushing on Rates of Spontaneous Vaginal Delivery Among Nulliparous Women Receiving Neuraxial Analgesia: A Randomized Clinical Trial

Alison G. Cahill, Sindhu K. Srinivas, Alan T. N. Tita, et al.
JAMA. 2018; 320 (14): 1444-1454.
https://jamanetwork.com/journals/jama/article-abstract/2706136

Abstract
Importance It is unclear whether the timing of second stage pushing efforts affects spontaneous vaginal delivery rates and reduces morbidities.
Objective To evaluate whether immediate or delayed pushing results in higher rates of spontaneous vaginal delivery and lower rates of maternal and neonatal morbidities.
Design, Setting, and Participants Pragmatic randomized clinical trial of nulliparous women at or beyond 37 weeks' gestation admitted for spontaneous or induced labor with neuraxial analgesia between May 2014 and December 2017 at 6 US medical centers. The interim analysis suggested futility for the primary outcome and recruitment was terminated with 2414 of 3184 planned participants. Follow-up ended January 4, 2018.

Interventions Randomization occurred when participants reached complete cervical dilation. Immediate group participants (n = 1200) began pushing immediately. Delayed group participants (n = 1204) were instructed to wait 60 minutes.
Main Outcomes and Measures The primary outcome was spontaneous vaginal delivery. Secondary outcomes included total duration of the second stage, duration of active pushing, operative vaginal delivery, cesarean delivery, postpartum hemorrhage, chorioamnionitis, endometritis, perineal lacerations (≥second degree), and a composite outcome of neonatal morbidity that included neonatal death and 9 other adverse outcomes.
Results Among 2414 women randomized (mean age, 26.5 years), 2404 (99.6%) completed the trial. The rate of spontaneous vaginal delivery was 85.9% in the immediate group vs 86.5% in the delayed group, and was not significantly different (absolute difference, −0.6% [95% CI, −3.4% to 2.1%]; relative risk, 0.99 [95% CI, 0.96 to 1.03]). There was no significant difference in 5 of the 9 prespecified secondary outcomes reported, including the composite outcome of neonatal morbidity (7.3% for the immediate group vs 8.9% for the delayed group; between-group difference, −1.6% [95% CI, −3.8% to 0.5%]) and perineal lacerations (45.9% vs 46.4%, respectively; between-group difference, −0.4% [95% CI, −4.4% to 3.6%]). The immediate group had significantly shorter mean duration of the second stage compared with the delayed group (102.4 vs 134.2 minutes, respectively; mean difference, −31.8 minutes [95% CI, −36.7 to −26.9], *P* < .001), despite a significantly longer mean duration of active pushing (83.7 vs 74.5 minutes; mean difference, 9.2 minutes [95% CI, 5.8 to 12.6], *P* < .001), lower rates of chorioamnionitis (6.7% vs 9.1%; between-group difference, −2.5% [95% CI, −4.6% to −0.3%], *P* = .005), and fewer postpartum hemorrhages (2.3% vs 4.0%; between-group difference, −1.7% [95% CI, −3.1% to −0.4%], *P* = .03).
Conclusions and Relevance Among nulliparous women receiving neuraxial anesthesia, the timing of second stage pushing efforts did not affect the rate of spontaneous vaginal delivery. These findings may help inform decisions about the preferred timing of second stage pushing efforts, when considered with other maternal and neonatal outcomes.

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, Sean M. Bagshaw, Massimo Antonelli, et al. for the EUPHRATES Trial Investigators

JAMA. 2018; 320 (14): 1455-1463.
https://jamanetwork.com/journals/jama/article-abstract/2706139

Abstract

Importance Polymyxin B hemoperfusion reduces blood endotoxin levels in sepsis. Endotoxin activity can be measured in blood with a rapid assay. Treating patients with septic shock and elevated endotoxin activity using polymyxin B hemoperfusion may improve clinical outcomes.
Objective To test whether adding polymyxin B hemoperfusion to conventional medical therapy improves survival compared with conventional therapy alone among patients with septic shock and high endotoxin activity.
Design, Setting, and Participants Multicenter, randomized clinical trial involving 450 adult critically ill patients with septic shock and an endotoxin activity assay level of 0.60 or higher enrolled between September 2010 and June 2016 at 55 tertiary hospitals in North America. Last follow-up was June 2017.

Interventions Two polymyxin B hemoperfusion treatments (90-120 minutes) plus standard therapy completed within 24 hours of enrollment (n = 224 patients) or sham hemoperfusion plus standard therapy (n = 226 patients).
Main Outcomes and Measures The primary outcome was mortality at 28 days among all patients randomized (all participants) and among patients randomized with a multiple organ dysfunction score (MODS) of more than 9.
Results Among 450 eligible enrolled patients (mean age, 59.8 years; 177 [39.3%] women; mean APACHE II score 29.4 [range, 0-71 with higher scores indicating greater severity), 449 (99.8%) completed the study. Polymyxin B hemoperfusion was not associated with a significant difference in mortality at 28 days among all participants (treatment group, 84 of 223 [37.7%] vs sham group 78 of 226 [34.5%]; risk difference [RD], 3.2%; 95% CI, −5.7% to 12.0%; relative risk [RR], 1.09; 95% CI, 0.85-1.39; *P* = .49) or in the population with a MODS of more than 9 (treatment group, 65 of 146 [44.5%] vs sham, 65 of 148 [43.9%]; RD, 0.6%; 95% CI, −10.8% to 11.9%; RR, 1.01; 95% CI, 0.78-1.31; *P* = .92). Overall, 264 serious adverse events were reported (65.1% treatment group vs 57.3% sham group). The most frequent serious adverse events were worsening of sepsis (10.8% treatment group vs 9.1% sham group) and worsening of septic shock (6.6% treatment group vs 7.7% sham group).
Conclusions and Relevance Among patients with septic shock and high endotoxin activity, polymyxin B hemoperfusion treatment plus conventional medical therapy compared with sham treatment plus conventional medical therapy did not reduce mortality at 28 days.

Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration

C. Mary Healy, Marcia A. Rench, Laurie S. Swaim, et al.
JAMA. 2018; 320 (14): 1464-1470.
https://jamanetwork.com/journals/jama/article-abstract/2706137

Abstract
Importance Immunization with tetanus, diphtheria, and acellular pertussis (Tdap) vaccine is recommended in the United States during weeks 27 through 36 of pregnancy to prevent life-threatening infant pertussis. The optimal gestation for immunization to maximize concentrations of neonatal pertussis toxin antibodies is unknown.
Objective To determine pertussis toxin antibody concentrations in cord blood from neonates born to women immunized and unimmunized with Tdap vaccine in pregnancy and optimal gestational age for immunization to maximize concentrations of neonatal antibodies.
Design, Setting, and Participants Prospective, observational, cohort study of term neonates in Houston, Texas (December 2013-March 2014).
Exposures Tdap immunization during weeks 27 through 36 of pregnancy or no Tdap immunization.
Main Outcomes and Measures Primary outcome was geometric mean concentrations (GMCs) of pertussis toxin antibodies in cord blood of Tdap-exposed and Tdap-unexposed neonates and proportions of Tdap-exposed and Tdap-unexposed neonates with pertussis toxin antibody concentrations of 15 IU/mL or higher, 30 IU/mL or higher, and 40 IU/mL or higher, cutoffs representing quantifiable antibodies or levels that may be protective until the infant immunization series begins. Secondary outcome was the optimal gestation for immunization to achieve maximum pertussis toxin antibodies.

Results Six hundred twenty-six pregnancies (mean maternal age, 29.7 years; 41% white, 27% Hispanic, 26% black, 5% Asian, 1% other; mean gestation, 39.4 weeks) were included. Three hundred twelve women received Tdap vaccine at a mean gestation of 31.2 weeks (range, 27.3-36.4); 314 were unimmunized. GMC of neonatal cord pertussis toxin antibodies from the Tdap-exposed group was 47.3 IU/mL (95% CI, 42.1-53.2) compared with 12.9 IU/mL (95% CI, 11.7-14.3) in the Tdap-unexposed group, for a GMC ratio of 3.6 (95% CI, 3.1-4.2; $P < .001$). More Tdap-exposed than Tdap-unexposed neonates had pertussis toxin antibody concentrations of 15 IU/mL or higher (86% vs 37%; difference, 49% [95% CI, 42%-55%]), 30 IU/mL or higher (72% vs 17%; difference, 55% [95% CI, 49%-61%]), and 40 IU/mL or higher (59% vs 12%; difference, 47% [95% CI, 41%-54%]); $P < .001$ for each analysis. GMCs of pertussis toxin antibodies were highest when Tdap vaccine was administered during weeks 27 through 30 and declined thereafter, reaching a peak at week 30 (57.3 IU/mL [95% CI, 44.0-74.6]).
Conclusions and Relevance Immunization with Tdap vaccine during the third trimester of pregnancy, compared with no immunization, was associated with higher neonatal concentrations of pertussis toxin antibodies. Immunization early in the third trimester was associated with the highest concentrations.

Trends in the Incidence and Recurrence of Inpatient-Treated Spontaneous Pneumothorax, 1968-2016

Rob J. Hallifax, Raph Goldacre, Martin J. Landray, et al.

JAMA. 2018; 320 (14): 1471-1480.
https://jamanetwork.com/journals/jama/article-abstract/2706138

Abstract

Importance Spontaneous pneumothorax is a common disease known to have an unusual epidemiological profile, but there are limited contemporary population-based data.
Objective To estimate the incidence of hospital admissions for spontaneous pneumothorax, its recurrence and trends over time using large, longstanding hospitalization data sets in England.
Design, Setting, and Participants A population-based epidemiological study was conducted using an English national data set and an English regional data set, each spanning 1968 to 2016, and including 170 929 hospital admission records of patients 15 years and older. Final date of the study period was December 31, 2016.
Exposures Calendar year (for incidence) and readmission to hospital for spontaneous pneumothorax (for recurrence).
Main Outcomes and Measures Primary outcomes were rates of hospital admissions for spontaneous pneumothorax and recurrence, defined as a subsequent hospital readmission with spontaneous pneumothorax. Record-linkage was used to identify multiple admissions per person and comorbidity. Risk factors for recurrence over 5 years of follow-up were assessed using cumulative time-to-failure analysis and Cox proportional hazards regression.
Results From 1968 to 2016, there were 170 929 hospital admissions for spontaneous pneumothorax (median age, 44 years [IQR, 26-88]; 73.0% male). In 2016, there were 14.1 spontaneous pneumothorax admissions per 100 000 population 15 years and older (95% CI, 13.7-14.4), a significant increase compared with earlier years, up from 9.1 (95% CI, 8.1-10.1) in 1968. The population-based rate per 100 000 population 15 years and older was higher for males (20.8 [95% CI, 20.2-21.4]) than for females (7.6 [95% CI, 7.2-7.9]). Of patients with spontaneous pneumothorax, 60.8% (95% CI, 59.5%-62.0%) had chronic lung disease. Record-linkage analysis demonstrated that the overall increase in

admissions over time could be due in part to an increase in repeat admissions, but there were also significant increases in the annual rate of first-known spontaneous pneumothorax admissions in some population subgroups, for example in women 65 years and older (annual percentage change from 1968 to 2016, 4.08 [95% CI, 3.33-4.82], *P* < .001). The probability of recurrence within 5 years was similar by sex (25.5% [95% CI, 25.1%-25.9%] for males vs 26.0% [95% CI, 25.3%-26.7%] for females), but there was variation by age group and presence of chronic lung disease. For example, the probability of readmission within 5 years among males aged 15 to 34 years with chronic lung disease was 39.2% (95% CI, 37.7%-40.7%) compared with 19.6% (95% CI, 18.2%-21.1%) in men 65 years and older without chronic lung disease.

Conclusions and Relevance This study provides contemporary information regarding the trends in incidence and recurrence of inpatient-treated spontaneous pneumothorax.

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The Lancet (6 October 2018, Vol. 392, No. 10154)

Amoxicillin–clavulanate versus azithromycin for respiratory exacerbations in children with bronchiectasis (BEST-2): A multicentre, double-blind, non-inferiority, randomised controlled trial

Vikas Goyal, Keith Grimwood, Catherine A Byrnes, et al.

The Lancet: Volume 392, ISSUE 10154, P1197-1206, October 06, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31723-9/fulltext

Summary

Background

Although amoxicillin–clavulanate is the recommended first-line empirical oral antibiotic treatment for non-severe exacerbations in children with bronchiectasis, azithromycin is also often prescribed for its convenient once-daily dosing. No randomised controlled trials involving acute exacerbations in children with bronchiectasis have been published to our knowledge. We hypothesised that azithromycin is non-inferior to amoxicillin-clavulanate for resolving exacerbations in children with bronchiectasis.

Methods

We did this parallel-group, double-dummy, double-blind, non-inferiority randomised controlled trial in three Australian and one New Zealand hospital between April, 2012, and August, 2016. We enrolled children aged 1–19 years with radiographically proven bronchiectasis unrelated to cystic fibrosis. At the start of an exacerbation, children were randomly assigned to oral suspensions of either amoxicillin–clavulanate (22·5 mg/kg, twice daily) and placebo or azithromycin (5 mg/kg per day) and placebo for 21 days. We used permuted block randomisation (stratified by age, site, and cause) with concealed allocation. The primary outcome was resolution of exacerbation (defined as a return to baseline) by 21 days in the per-protocol population, with a non-inferiority margin of −20%. We assessed several secondary outcomes including duration of exacerbation, time to next exacerbation, laboratory, respiratory, and quality-of-life measurements, and microbiology. This trial was registered with the Australian/New Zealand Registry (ACTRN12612000010897).

Findings

We screened 604 children and enrolled 236. 179 children had an exacerbation and were assigned to treatment: 97 to amoxicillin–clavulanate, 82 to azithromycin). By day 21, 61 (84%) of 73 exacerbations had resolved in the azithromycin group versus 73 (84%) of 87

in the amoxicillin–clavulanate group. The risk difference showed non-inferiority (−0·3%, 95% CI −11·8 to 11·1). Exacerbations were significantly shorter in the amoxicillin–clavulanate group than in the azithromycin group (median 10 days [IQR 6–15] *vs* 14 days [8–16]; p=0·014). Adverse events were attributed to the trial medication in 17 (21%) of 82 children in the azithromycin group versus 23 (24%) of 97 in the amoxicillin–clavulanate group (relative risk 0·9, 95% CI 0·5 to 1·5).

Interpretation

By 21 days of treatment, azithromycin is non-inferior to amoxicillin–clavulanate for resolving exacerbations in children with non-severe bronchiectasis. In some patients, such as those with penicillin hypersensitivity or those likely to have poor adherence, azithromycin provides another option for treating exacerbations, but must be balanced with risk of treatment failure (within a 20% margin), longer exacerbation duration, and the risk of inducing macrolide resistance.

Single dose moxidectin versus ivermectin for Onchocerca volvulus infection in Ghana, Liberia, and the Democratic Republic of the Congo: A randomised, controlled, double-blind phase 3 trial

Nicholas O Opoku, Didier K Bakajika, Eric M Kanza, et al.

The Lancet: Volume 392, ISSUE 10154, P1207-1216, October 06, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32844-1/fulltext

Summary

Background

The morbidity and socioeconomic effects of onchocerciasis, a parasitic disease that is primarily endemic in sub-Saharan Africa, have motivated large morbidity and transmission control programmes. Annual community-directed ivermectin treatment has substantially reduced prevalence. Elimination requires intensified efforts, including more efficacious treatments. We compared parasitological efficacy and safety of moxidectin and ivermectin.

Methods

This double-blind, parallel group, superiority trial was done in four sites in Ghana, Liberia, and the Democratic Republic of the Congo. We enrolled participants (aged ≥12 years) with at least 10 *Onchocerca volvulus* microfilariae per mg skin who were not co-infected with *Loa loa* or lymphatic filariasis microfilaraemic. Participants were randomly allocated, stratified by sex and level of infection, to receive a single oral dose of 8 mg moxidectin or 150 μg/kg ivermectin as overencapsulated oral tablets. The primary efficacy outcome was skin microfilariae density 12 months post treatment. We used a mixed-effects model to test the hypothesis that the primary efficacy outcome in the moxidectin group was 50% or less than that in the ivermectin group. The primary efficacy analysis population were all participants who received the study drug and completed 12-month follow-up (modified intention to treat). This study is registered with ClinicalTrials.gov, number NCT00790998.

Findings

Between April 22, 2009, and Jan 23, 2011, we enrolled and allocated 998 participants to moxidectin and 501 participants to ivermectin. 978 received moxidectin and 494 ivermectin, of which 947 and 480 were included in primary efficacy outcome analyses. At 12 months, skin microfilarial density (microfilariae per mg of skin) was lower in the moxidectin group (adjusted geometric mean 0·6 [95% CI 0·3–1·0]) than in the ivermectin group (4·5 [3·5–5·9]; difference 3·9 [3·2–4·9], p<0·0001; treatment difference 86%). Mazzotti (ie, efficacy-related) reactions occurred in 967 (99%) of 978 moxidectin-treated participants and in 478 (97%) of 494 ivermectin-treated participants, including ocular reactions (moxidectin 113 [12%] participants and ivermectin 47 [10%] participants),

laboratory reactions (788 [81%] and 415 [84%]), and clinical reactions (944 [97%] and 446 [90%]). No serious adverse events were considered to be related to treatment.

Interpretation

Skin microfilarial loads (ie, parasite transmission reservoir) are lower after moxidectin treatment than after ivermectin treatment. Moxidectin would therefore be expected to reduce parasite transmission between treatment rounds more than ivermectin could, thus accelerating progress towards elimination.

Measuring human capital: A systematic analysis of 195 countries and territories, 1990–2016

Stephen S Lim, Rachel L Updike, Alexander S Kaldjian, et al.
The Lancet: Volume 392, ISSUE 10154, P1217-1234, October 06, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31941-X/fulltext

Summary

Background

Human capital is recognised as the level of education and health in a population and is considered an important determinant of economic growth. The World Bank has called for measurement and annual reporting of human capital to track and motivate investments in health and education and enhance productivity. We aim to provide a new comprehensive measure of human capital across countries globally.

Methods

We generated a period measure of expected human capital, defined for each birth cohort as the expected years lived from age 20 to 64 years and adjusted for educational attainment, learning or education quality, and functional health status using rates specific to each time period, age, and sex for 195 countries from 1990 to 2016. We estimated educational attainment using 2522 censuses and household surveys; we based learning estimates on 1894 tests among school-aged children; and we based functional health status on the prevalence of seven health conditions, which were taken from the Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016). Mortality rates specific to location, age, and sex were also taken from GBD 2016.

Findings

In 2016, Finland had the highest level of expected human capital of 28·4 health, education, and learning-adjusted expected years lived between age 20 and 64 years (95% uncertainty interval 27·5–29·2); Niger had the lowest expected human capital of less than 1·6 years (0·98–2·6). In 2016, 44 countries had already achieved more than 20 years of expected human capital; 68 countries had expected human capital of less than 10 years. Of 195 countries, the ten most populous countries in 2016 for expected human capital were ranked: China at 44, India at 158, USA at 27, Indonesia at 131, Brazil at 71, Pakistan at 164, Nigeria at 171, Bangladesh at 161, Russia at 49, and Mexico at 104. Assessment of change in expected human capital from 1990 to 2016 shows marked variation from less than 2 years of progress in 18 countries to more than 5 years of progress in 35 countries. Larger improvements in expected human capital appear to be associated with faster economic growth. The top quartile of countries in terms of absolute change in human capital from 1990 to 2016 had a median annualised growth in gross domestic product of 2·60% (IQR 1·85–3·69) compared with 1·45% (0·18–2·19) for countries in the bottom quartile.

Interpretation

Countries vary widely in the rate of human capital formation. Monitoring the production of human capital can facilitate a mechanism to hold governments and donors accountable for investments in health and education.

Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt–chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in allcomers with coronary artery disease (BIONYX): An international, single-blind, randomised non-inferiority trial

Clemens von Birgelen, Paolo Zocca, Rosaly A Buiten, et al.
The Lancet: Volume 392, ISSUE 10154, P1235-1245, October 06, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32001-4/fulltext

Summary

Background

During the past decade, many patients had zotarolimus-eluting stents implanted, which had circular shape cobalt–chromium struts with limited radiographic visibility. The Resolute Onyx stent was developed to improve visibility while reducing strut thickness, which was achieved by using a novel composite wire with a dense platinum–iridium core and an outer cobalt–chromium layer. We did the first randomised clinical trial to assess the safety and efficacy of this often-used stent compared with the Orsiro stent, which consists of ultrathin cobalt–chromium struts.

Methods

We did an investigator-initiated, assessor-blinded and patient-blinded, randomised non-inferiority trial in an allcomers population at seven independently monitored centres in Belgium, Israel, and the Netherlands. Eligible participants were aged 18 years or older and required percutaneous coronary intervention with drug-eluting stents. After guide wire passage with or without predilation, members of the catheterisation laboratory team used web-based computer-generated allocation sequences to randomly assign patients (1:1) to either the Resolute Onyx or the Orsiro stent. Randomisation was stratified by sex and diabetes status. Patients and assessors were masked to allocated stents, but treating clinicians were not. The primary endpoint was target vessel failure at 1 year, a composite of cardiac death, target-vessel-related myocardial infarction, and target vessel revascularisation, and was assessed by intention to treat (non-inferiority margin 2·5%) on the basis of outcomes adjudicated by an independent event committee. This trial is registered with ClinicalTrials.gov, number NCT02508714.

Findings

Between Oct 7, 2015, and Dec 23, 2016, 2516 patients were enrolled, 2488 of whom were included in the intention-to-treat analysis (28 withdrawals or screening failures). 1243 participants were assigned to the Resolute Onyx group, and 1245 to the Orsiro group. Overall, 1765 (70·9%) participants presented with acute coronary syndromes and 1275 (51·2%) had myocardial infarctions. 1-year follow-up was available for 2478 (99·6%) patients. The primary endpoint was met by 55 (4·5%) patients in the Resolute Onyx group and 58 (4·7%) in the Orsiro group. Non-inferiority of Resolute Onyx to Orsiro was thus established (absolute risk difference −0·2% [95% CI −1·9 to 1·4]; upper limit of the one-sided 95% CI 1·1%; $p_{non\text{-}inferiority}$=0·0005). Definite or probable stent thrombosis occurred in one (0·1%) participant in the Resolute Onyx group and nine (0·7%) in the Orsiro group (hazard ratio 0·11 [95% CI 0·01–0·87]; p=0·0112).

Interpretation

The Resolute Onyx stent was non-inferior to Orsiro for a combined safety and efficacy endpoint at 1-year follow-up in allcomers. The low event rate in both groups suggests that

both stents are safe, and the very low rate of stent thrombosis in the Resolute Onyx group warrants further clinical investigation.

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The New England Journal of Medicine (4 October 2018, Vol. 379, No. 14)

Acceleration of BMI in Early Childhood and Risk of Sustained Obesity
Mandy Geserick, Mandy Vogel, Ruth Gausche, et al.
N Engl J Med 2018; 379: 1303-1312 October 4, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1803527

Abstract
Background
The dynamics of body-mass index (BMI) in children from birth to adolescence are unclear, and whether susceptibility for the development of sustained obesity occurs at a specific age in children is important to determine.
Methods
To assess the age at onset of obesity, we performed prospective and retrospective analyses of the course of BMI over time in a population-based sample of 51,505 children for whom sequential anthropometric data were available during childhood (0 to 14 years of age) and adolescence (15 to 18 years of age). In addition, we assessed the dynamics of annual BMI increments, defined as the change in BMI standard-deviation score per year, during childhood in 34,196 children.
Results
In retrospective analyses, we found that most of the adolescents with normal weight had always had a normal weight throughout childhood. Approximately half (53%) of the obese adolescents had been overweight or obese from 5 years of age onward, and the BMI standard-deviation score further increased with age. In prospective analyses, we found that almost 90% of the children who were obese at 3 years of age were overweight or obese in adolescence. Among the adolescents who were obese, the greatest acceleration in annual BMI increments had occurred between 2 and 6 years of age, with a further rise in BMI percentile thereafter. High acceleration in annual BMI increments during the preschool years (but not during the school years) was associated with a risk of overweight or obesity in adolescence that was 1.4 times as high as the risk among children who had had stable BMI. The rate of overweight or obesity in adolescence was higher among children who had been large for gestational age at birth (43.7%) than among those who had been at an appropriate weight for gestational age (28.4%) or small for gestational age (27.2%), which corresponded to a risk of adolescent obesity that was 1.55 times as high among those who had been large for gestational age as among the other groups.
Conclusions
Among obese adolescents, the most rapid weight gain had occurred between 2 and 6 years of age; most children who were obese at that age were obese in adolescence.

Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis
Kim Papp, Kenneth Gordon, Diamant Thaçi, et al.
N Engl J Med 2018; 379: 1313-1321 October 4, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1806382

Abstract
Background
Tyrosine kinase 2 (TYK2) signaling pathways, which mediate cytokine signaling, are implicated in the pathophysiology of psoriasis. Selective inhibitors of TYK2 may be effective in treating psoriasis.
Methods
We conducted a phase 2, double-blind trial of a TYK2 inhibitor, BMS-986165, in adults with moderate-to-severe psoriasis, excluding patients with a previous lack of response to agents targeting cytokine signaling through the same tyrosine kinase pathway. Patients were randomly assigned to receive the drug orally at a dose of 3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily, or 12 mg daily or to receive placebo. The primary end point was a 75% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12 (higher scores indicate greater severity of psoriasis).
Results
A total of 267 patients received at least one dose in an intervention group of the trial. At week 12, the percentage of patients with a 75% or greater reduction in the PASI score was 7% (3 of 45 patients) with placebo, 9% (4 of 44 patients) with 3 mg of BMS-986165 every other day (P=0.49 vs. placebo), 39% (17 of 44 patients) with 3 mg daily (P<0.001 vs. placebo), 69% (31 of 45 patients) with 3 mg twice daily (P<0.001 vs. placebo), 67% (30 of 45 patients) with 6 mg twice daily (P<0.001 vs. placebo), and 75% (33 of 44 patients) with 12 mg daily (P<0.001 vs. placebo). There were three serious adverse events in patients receiving the active drug, as well as one case of malignant melanoma 96 days after the start of treatment.
Conclusions
Selective inhibition of TYK2 with the oral agent BMS-986165 at doses of 3 mg daily and higher resulted in greater clearing of psoriasis than did placebo over a period of 12 weeks. Larger and longer-duration trials of this drug are required to determine its safety and durability of effect in patients with psoriasis.

Candida auris Outbreak and Its Control in an Intensive Care Setting
David W. Eyre, Anna E. Sheppard, Hilary Madder, et al.
N Engl J Med 2018; 379:1322-1331 October 4, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1714373

Abstract
Background
Candida auris is an emerging and multidrug-resistant pathogen. Here we report the epidemiology of a hospital outbreak of C. auris colonization and infection.
Methods
After identification of a cluster of C. auris infections in the neurosciences intensive care unit (ICU) of the Oxford University Hospitals, United Kingdom, we instituted an intensive patient and environmental screening program and package of interventions. Multivariable logistic regression was used to identify predictors of C. auris colonization and infection. Isolates from patients and from the environment were analyzed by whole-genome sequencing.
Results
A total of 70 patients were identified as being colonized or infected with C. auris between February 2, 2015, and August 31, 2017; of these patients, 66 (94%) had been admitted to the neurosciences ICU before diagnosis. Invasive C. auris infections developed in 7 patients. When length of stay in the neurosciences ICU and patient vital signs and

laboratory results were controlled for, the predictors of C. auris colonization or infection included the use of reusable skin-surface axillary temperature probes (multivariable odds ratio, 6.80; 95% confidence interval [CI], 2.96 to 15.63; P<0.001) and systemic fluconazole exposure (multivariable odds ratio, 10.34; 95% CI, 1.64 to 65.18; P=0.01). C. auris was rarely detected in the general environment. However, it was detected in isolates from reusable equipment, including multiple axillary skin-surface temperature probes. Despite a bundle of infection-control interventions, the incidence of new cases was reduced only after removal of the temperature probes. All outbreak sequences formed a single genetic cluster within the C. auris South African clade. The sequenced isolates from reusable equipment were genetically related to isolates from the patients.

Conclusions

The transmission of C. auris in this hospital outbreak was found to be linked to reusable axillary temperature probes, indicating that this emerging pathogen can persist in the environment and be transmitted in health care settings.

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

Faiez Zannad, Stefan D. Anker, William M. Byra, et al. for the COMMANDER HF Investigators

N Engl J Med 2018; 379: 1332-1342 October 4, 2018

https://www.nejm.org/doi/full/10.1056/NEJMoa1808848

Abstract

Background

Heart failure is associated with activation of thrombin-related pathways, which predicts a poor prognosis. We hypothesized that treatment with rivaroxaban, a factor Xa inhibitor, could reduce thrombin generation and improve outcomes for patients with worsening chronic heart failure and underlying coronary artery disease.

Methods

In this double-blind, randomized trial, 5022 patients who had chronic heart failure, a left ventricular ejection fraction of 40% or less, coronary artery disease, and elevated plasma concentrations of natriuretic peptides and who did not have atrial fibrillation were randomly assigned to receive rivaroxaban at a dose of 2.5 mg twice daily or placebo in addition to standard care after treatment for an episode of worsening heart failure. The primary efficacy outcome was the composite of death from any cause, myocardial infarction, or stroke. The principal safety outcome was fatal bleeding or bleeding into a critical space with a potential for causing permanent disability.

Results

Over a median follow-up period of 21.1 months, the primary end point occurred in 626 (25.0%) of 2507 patients assigned to rivaroxaban and in 658 (26.2%) of 2515 patients assigned to placebo (hazard ratio, 0.94; 95% confidence interval [CI], 0.84 to 1.05; P=0.27). No significant difference in all-cause mortality was noted between the rivaroxaban group and the placebo group (21.8% and 22.1%, respectively; hazard ratio, 0.98; 95% CI, 0.87 to 1.10). The principal safety outcome occurred in 18 patients who took rivaroxaban and in 23 who took placebo (hazard ratio, 0.80; 95% CI, 0.43 to 1.49; P=0.48).

Conclusions

Rivaroxaban at a dose of 2.5 mg twice daily was not associated with a significantly lower rate of death, myocardial infarction, or stroke than placebo among patients with worsening chronic heart failure, reduced left ventricular ejection fraction, coronary artery disease, and no atrial fibrillation.

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Sources

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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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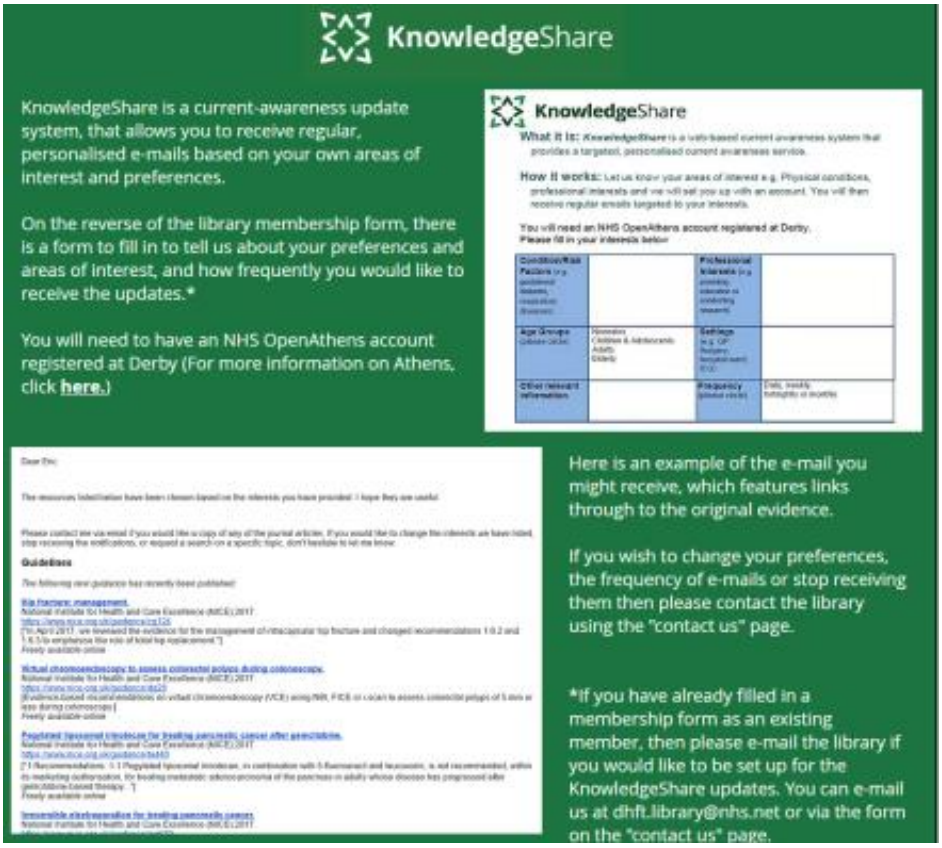

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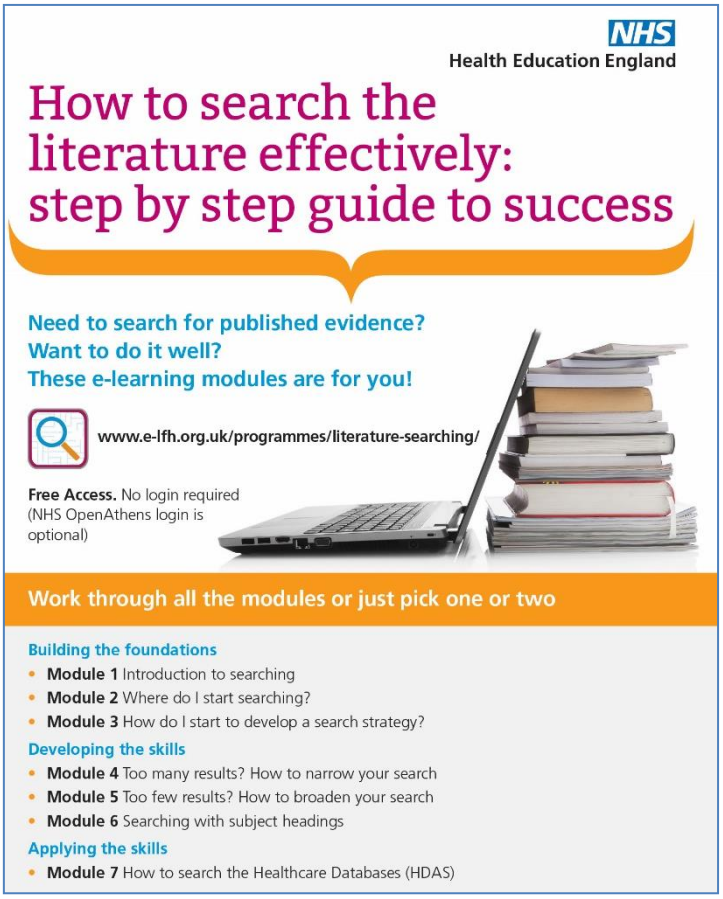

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