The Big Four Bulletin
29 August 2018 No. 601

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BMJ

The BMJ has produced no new content this week.

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JAMA: Journal of the American Medical Association (28 August 2018, Vol. 320, No. 8)

Effect of a Strategy of Initial Laryngeal Tube Insertion vs Endotracheal Intubation on 72-Hour Survival in Adults With Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial
Henry E. Wang, Robert H. Schmicker, Mohamud R. Daya, et al
JAMA. 2018; 320 (8): 769-778.
https://jamanetwork.com/journals/jama/fullarticle/2698491

Abstract
Importance Emergency medical services (EMS) commonly perform endotracheal intubation (ETI) or insertion of supraglottic airways, such as the laryngeal tube (LT), on patients with out-of-hospital cardiac arrest (OHCA). The optimal method for OHCA advanced airway management is unknown.
Objective To compare the effectiveness of a strategy of initial LT insertion vs initial ETI in adults with OHCA.
Design, Setting, and Participants Multicenter pragmatic cluster-crossover clinical trial involving EMS agencies from the Resuscitation Outcomes Consortium. The trial included 3004 adults with OHCA and anticipated need for advanced airway management who were enrolled from December 1, 2015, to November 4, 2017. The final date of follow-up was November 10, 2017.
Interventions Twenty-seven EMS agencies were randomized in 13 clusters to initial airway management strategy with LT (n = 1505 patients) or ETI (n = 1499 patients), with crossover to the alternate strategy at 3- to 5-month intervals.
Main Outcomes and Measures The primary outcome was 72-hour survival. Secondary outcomes included return of spontaneous circulation, survival to hospital discharge, favorable neurological status at hospital discharge (Modified Rankin Scale score ≤3), and key adverse events.

Results Among 3004 enrolled patients (median [interquartile range] age, 64 [53-76] years, 1829 [60.9%] men), 3000 were included in the primary analysis. Rates of initial airway success were 90.3% with LT and 51.6% with ETI. Seventy-two hour survival was 18.3% in the LT group vs 15.4% in the ETI group (adjusted difference, 2.9% [95% CI, 0.2%-5.6% ;[*P* .(04. = Secondary outcomes in the LT group vs ETI group were return of spontaneous circulation (27.9% vs 24.3%; adjusted difference, 3.6% [95% CI, 0.3%-6.8% ;[*P* ;(03. = hospital survival (10.8% vs 8.1%; adjusted difference, 2.7% [95% CI, 0.6%-4.8% ;[*P* ;(01. = and favorable neurological status at discharge (7.1% vs 5.0%; adjusted difference, 2.1% [95% CI, 0.3%-3.8% ;[*P* .(02. = There were no significant differences in oropharyngeal or hypopharyngeal injury (0.2% vs 0.3%), airway swelling (1.1% vs 1.0%), or pneumonia or pneumonitis (26.1% vs 22.3%.(

Conclusions and Relevance Among adults with OHCA, a strategy of initial LT insertion was associated with significantly greater 72-hour survival compared with a strategy of initial ETI. These findings suggest that LT insertion may be considered as an initial airway management strategy in patients with OHCA, but limitations of the pragmatic design, practice setting, and ETI performance characteristics suggest that further research is warranted.

Effect of a Strategy of a Supraglottic Airway Device vs Tracheal Intubation During Out-of-Hospital Cardiac Arrest on Functional Outcome: The AIRWAYS-2 Randomized Clinical Trial

Jonathan R. Benger, Kim Kirby, Sarah Black, et al

JAMA. 2018; 320 (8): 779-791.
https://jamanetwork.com/journals/jama/article-abstract/2698493

Abstract

Importance The optimal approach to airway management during out-of-hospital cardiac arrest is unknown.

Objective To determine whether a supraglottic airway device (SGA) is superior to tracheal intubation (TI) as the initial advanced airway management strategy in adults with nontraumatic out-of-hospital cardiac arrest.

Design, Setting, and Participants Multicenter, cluster randomized clinical trial of paramedics from 4 ambulance services in England responding to emergencies for approximately 21 million people. Patients aged 18 years or older who had a nontraumatic out-of-hospital cardiac arrest and were treated by a participating paramedic were enrolled automatically under a waiver of consent between June 2015 and August 2017; follow-up ended in February 2018.

Interventions Paramedics were randomized 1:1 to use TI (764 paramedics) or SGA (759 paramedics) as their initial advanced airway management strategy.

Main Outcomes and Measures The primary outcome was modified Rankin Scale score at hospital discharge or 30 days after out-of-hospital cardiac arrest, whichever occurred sooner. Modified Rankin Scale score was divided into 2 ranges: 0-3 (good outcome) or 4-6 (poor outcome; 6 = death). Secondary outcomes included ventilation success, regurgitation, and aspiration.

Results A total of 9296 patients (4886 in the SGA group and 4410 in the TI group) were enrolled (median age, 73 years; 3373 were women [36.3%]), and the modified Rankin Scale score was known for 9289 patients. In the SGA group, 311 of 4882 patients (6.4%) had a good outcome (modified Rankin Scale score range, 0-3) vs 300 of 4407 patients (6.8%) in the TI group (adjusted risk difference [RD], −0.6% [95% CI, −1.6% to 0.4%]). Initial ventilation was successful in 4255 of 4868 patients (87.4%) in the SGA group

compared with 3473 of 4397 patients (79.0%) in the TI group (adjusted RD, 8.3% [95% CI, 6.3% to 10.2%]). However, patients randomized to receive TI were less likely to receive advanced airway management (3419 of 4404 patients [77.6%] vs 4161 of 4883 patients [85.2%] in the SGA group). Two of the secondary outcomes (regurgitation and aspiration) were not significantly different between groups (regurgitation: 1268 of 4865 patients [26.1%] in the SGA group vs 1072 of 4372 patients [24.5%] in the TI group; adjusted RD, 1.4% [95% CI, −0.6% to 3.4%]; aspiration: 729 of 4824 patients [15.1%] vs 647 of 4337 patients [14.9%], respectively; adjusted RD, 0.1% [95% CI, −1.5% to 1.8%]).

Conclusions and Relevance Among patients with out-of-hospital cardiac arrest, randomization to a strategy of advanced airway management with a supraglottic airway device compared with tracheal intubation did not result in a favorable functional outcome at 30 days.

Global Mortality From Firearms, 1990-2016

The Global Burden of Disease 2016 Injury Collaborators

JAMA. 2018; 320 (8): 792-814.
https://jamanetwork.com/journals/jama/fullarticle/2698492

Abstract

Importance Understanding global variation in firearm mortality rates could guide prevention policies and interventions.

Objective To estimate mortality due to firearm injury deaths from 1990 to 2016 in 195 countries and territories.

Design, Setting, and Participants This study used deidentified aggregated data including 13 812 location-years of vital registration data to generate estimates of levels and rates of death by age-sex-year-location. The proportion of suicides in which a firearm was the lethal means was combined with an estimate of per capita gun ownership in a revised proxy measure used to evaluate the relationship between availability or access to firearms and firearm injury deaths.

Exposures Firearm ownership and access.

Main Outcomes and Measure Cause-specific deaths by age, sex, location, and year.

Results Worldwide, it was estimated that 251 000 (95% uncertainty interval [UI], 195 000-276 000) people died from firearm injuries in 2016, with 6 countries (Brazil, United States, Mexico, Colombia, Venezuela, and Guatemala) accounting for 50.5% (95% UI, 42.2%-54.8%) of those deaths. In 1990, there were an estimated 209 000 (95% UI, 172 000 to 235 000) deaths from firearm injuries. Globally, the majority of firearm injury deaths in 2016 were homicides (64.0% [95% UI, 54.2%-68.0%]; absolute value, 161 000 deaths [95% UI, 107 000-182 000]); additionally, 27% were firearm suicide deaths (67 500 [95% UI, 55 400-84 100]) and 9% were unintentional firearm deaths (23 000 [95% UI, 18 200-24 800]). From 1990 to 2016, there was no significant decrease in the estimated global age-standardized firearm homicide rate (−0.2% [95% UI, −0.8% to 0.2%]). Firearm suicide rates decreased globally at an annualized rate of 1.6% (95% UI, 1.1-2.0), but in 124 of 195 countries and territories included in this study, these levels were either constant or significant increases were estimated. There was an annualized decrease of 0.9% (95% UI, 0.5%-1.3%) in the global rate of age-standardized firearm deaths from 1990 to 2016. Aggregate firearm injury deaths in 2016 were highest among persons aged 20 to 24 years (for men, an estimated 34 700 deaths [95% UI, 24 900-39 700] and for women, an estimated 3580 deaths [95% UI, 2810-4210]). Estimates of the number of firearms by country were associated with higher rates of firearm suicide) P ;001. > R (0.21 = ^{2}and homicide) P ;001. > R.(0.35 = ^{2}

Conclusions and Relevance This study estimated between 195 000 and 276 000 firearm injury deaths globally in 2016, the majority of which were firearm homicides. Despite an overall decrease in rates of firearm injury death since 1990, there was variation among countries and across demographic subgroups.

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The Lancet (25 August 2018, Vol. 392, No. 10148)

Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: A randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial

Patrick M O'Neil, Andreas L Birkenfeld, Barbara McGowan, et al.

The Lancet: Volume 392, ISSUE 10148, P637-649, August 25, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31773-2/fulltext

Summary

Background

Obesity is a major public health issue, and new pharmaceuticals for weight management are needed. Therefore, we evaluated the efficacy and safety of the glucagon-like peptide-1 (GLP-1) analogue semaglutide in comparison with liraglutide and a placebo in promoting weight loss.

Methods

We did a randomised, double-blind, placebo and active controlled, multicentre, dose-ranging, phase 2 trial. The study was done in eight countries involving 71 clinical sites. Eligible participants were adults (≥18 years) without diabetes and with a body-mass index (BMI) of 30 kg/m ^{2} or more. We randomly assigned participants (6:1) to each active treatment group (ie, semaglutide [0·05 mg, 0·1 mg, 0·2 mg, 0·3 mg, or 0·4 mg; initiated at 0·05 mg per day and incrementally escalated every 4 weeks] or liraglutide [3·0 mg; initiated at 0·6 mg per day and escalated by 0·6 mg per week]) or matching placebo group (equal injection volume and escalation schedule to active treatment group) using a block size of 56. All treatment doses were delivered once-daily via subcutaneous injections. Participants and investigators were masked to the assigned study treatment but not the target dose. The primary endpoint was percentage weight loss at week 52. The primary analysis was done using intention-to-treat ANCOVA estimation with missing data derived from the placebo pool. This study is registered with ClinicalTrials.gov, number NCT02453711.

Findings

Between Oct 1, 2015, and Feb 11, 2016, 957 individuals were randomly assigned (102–103 participants per active treatment group and 136 in the pooled placebo group). Mean baseline characteristics included age 47 years, bodyweight 111·5 kg, and BMI 39·3 kg/m ^{2}. Bodyweight data were available for 891 (93%) of 957 participants at week 52. Estimated mean weight loss was −2·3% for the placebo group versus −6·0% (0·05 mg), −8·6% (0·1 mg), −11·6% (0·2 mg), −11·2% (0·3 mg), and −13·8% (0·4 mg) for the semaglutide groups. All semaglutide groups versus placebo were significant (unadjusted p≤0·0010), and remained significant after adjustment for multiple testing (p≤0·0055). Mean bodyweight reductions for 0·2 mg or more of semaglutide versus liraglutide were all significant (−13·8% to −11·2% *vs* −7·8%). Estimated weight loss of 10% or more occurred in 10% of participants receiving placebo compared with 37–65% receiving 0·1 mg or more of semaglutide (p<0·0001 *vs* placebo). All semaglutide doses were generally well

tolerated, with no new safety concerns. The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, as seen previously with GLP-1 receptor agonists.

Interpretation

In combination with dietary and physical activity counselling, semaglutide was well tolerated over 52 weeks and showed clinically relevant weight loss compared with placebo at all doses.

Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): Results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials

Kenneth B Gordon, Bruce Strober, Mark Lebwohl, et al.

The Lancet: Volume 392, ISSUE 10148, P650-661, August 25, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31713-6/fulltext

Summary

Background

Risankizumab is a humanised IgG1 monoclonal antibody that binds to the p19 subunit of interleukin-23, inhibiting this key cytokine and its role in psoriatic inflammation. We aimed to assess the efficacy and safety of risankizumab compared with placebo or ustekinumab in patients with moderate-to-severe chronic plaque psoriasis.

Methods

UltIMMa-1 and UltIMMa-2 were replicate phase 3, randomised, double-blind, placebo-controlled and active comparator-controlled trials done at 139 sites in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Japan, Mexico, Poland, Portugal, South Korea, Spain, and the USA. Eligible patients were 18 years or older, with moderate-to-severe chronic plaque psoriasis. In each study, patients were stratified by weight and previous exposure to tumour necrosis factor inhibitor and randomly assigned (3:1:1) by use of interactive response technology to receive 150 mg risankizumab, 45 mg or 90 mg ustekinumab (weight-based per label), or placebo. Following the 16-week double-blind treatment period (part A), patients initially assigned to placebo switched to 150 mg risankizumab at week 16; other patients continued their originally randomised treatment (part B, double-blind, weeks 16–52). Study drug was administered subcutaneously at weeks 0 and 4 during part A and at weeks 16, 28, and 40 during part B. Co-primary endpoints were proportions of patients achieving a 90% improvement in the Psoriasis Area Severity Index (PASI 90) and a static Physician's Global Assessment (sPGA) score of 0 or 1 at week 16 (non-responder imputation). All efficacy analyses were done in the intention-to-treat population. These trials are registered with ClinicalTrials.gov, numbers NCT02684370 (UltIMMa-1) and NCT02684357 (UltIMMa-2), and have been completed.

Findings

Between Feb 24, 2016, and Aug 31, 2016, 506 patients in UltIMMa-1 were randomly assigned to receive 150 mg risankizumab (n=304), 45 mg or 90 mg ustekinumab (n=100), or placebo (n=102). Between March 1, 2016, and Aug 30, 2016, 491 patients in UltIMMa-2 were randomly assigned to receive 150 mg risankizumab (n=294), 45 mg or 90 mg ustekinumab (n=99), or placebo (n=98). Co-primary endpoints were met for both studies. At week 16 of UltIMMa-1, PASI 90 was achieved by 229 (75·3%) patients receiving risankizumab versus five (4·9%) receiving placebo (placebo-adjusted difference 70·3% [95% CI 64·0–76·7]) and 42 (42·0%) receiving ustekinumab (ustekinumab-adjusted difference 33·5% [22·7–44·3]; p<0·0001 *vs* placebo and ustekinumab). At week 16 of UltIMMa-2, PASI 90 was achieved by 220 (74·8%) patients receiving risankizumab versus

two (2·0%) receiving placebo (placebo-adjusted difference 72·5% [95% CI 66·8–78·2]) and 47 (47·5%) receiving ustekinumab (ustekinumab-adjusted difference 27·6% [16·7–38·5]; p<0·0001 *vs* placebo and ustekinumab). In UltIMMa-1, sPGA 0 or 1 at week 16 was achieved by 267 (87·8%) patients receiving risankizumab versus eight (7·8%) receiving placebo (placebo-adjusted difference 79·9% [95% CI 73·5–86·3]) and 63 (63·0%) receiving ustekinumab (ustekinumab-adjusted difference 25·1% [15·2–35·0]; p<0·0001 *vs* placebo and ustekinumab). In UltIMMa-2, 246 (83·7%) patients receiving risankizumab versus five (5·1%) receiving placebo (placebo-adjusted difference 78·5% [95% CI 72·4–84·5]) and 61 (61·6%) receiving ustekinumab achieved sPGA 0 or 1 at week 16 (ustekinumab-adjusted difference 22·3% [12·0–32·5]; p<0·0001 *vs* placebo and ustekinumab). The frequency of treatment-emergent adverse events in UltIMMa-1 and UltIMMa-2 was similar across risankizumab (part A: 151 [49·7%] of 304 and 134 [45·6%] of 294; part B: 182 [61·3%] of 297 and 162 [55·7%] of 291), placebo (part A: 52 [51·0%] of 102 and 45 [45·9%] of 98), ustekinumab (part A: 50 [50·0%] of 100 and 53 [53·5%] of 99; part B: 66 [66·7%] of 99 and 70 [74·5%] of 94), and placebo to risankizumab (part B: 65 [67·0%] of 97 and 61 [64·9%] of 94) treatment groups throughout the study duration.

Interpretation

Risankizumab showed superior efficacy to both placebo and ustekinumab in the treatment of moderate-to-severe plaque psoriasis. Treatment-emergent adverse event profiles were similar across treatment groups and there were no unexpected safety findings.

Intravenous remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour (RESPITE): An open-label, multicentre, randomised controlled trial

Matthew J A Wilson, Christine MacArthur, Catherine A Hewitt, et al. on behalf of the RESPITE Trial Collaborative Group

The Lancet: Volume 392, ISSUE 10148, P662-672, August 25, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31613-1/fulltext

Summary

Background

About a third of women receiving pethidine for labour pain subsequently require an epidural, which provides effective pain relief but increases the risk of instrumental vaginal delivery. Remifentanil patient-controlled analgesia (PCA) in labour is an alternative to pethidine, but is not widely used. We aimed to evaluate epidural analgesia progression among women using remifentanil PCA compared with pethidine.

Methods

We did an open-label, multicentre, randomised controlled trial in 14 UK maternity units. We included women aged 16 years or older, beyond 37 weeks' gestation, in labour with a singleton cephalic presentation, and who requested opioid pain relief. We randomly assigned eligible participants (1:1) to either the intravenous remifentanil PCA group (40 μg bolus on demand with a 2 min lockout) or the intramuscular pethidine group (100 mg every 4 h, up to 400 mg in 24 h), using a web-based or telephone randomisation service with a minimisation algorithm for parity, maternal age, ethnicity, and mode of labour onset. Because of the differences in routes of drug administration, study participants and health-care providers were not masked to the group allocation. The primary outcome was the proportion of women who received epidural analgesia after enrolment for pain relief in labour. Primary analyses were unadjusted and analysed by the intention-to-treat principle. This study is registered with the ISRCTN registry, number ISRCTN29654603.

Findings

Between May 13, 2014, and Sept 2, 2016, 201 women were randomly assigned to the remifentanil PCA group and 200 to the pethidine group. One participant in the pethidine group withdrew consent, leaving 199 for analyses. The proportions of epidural conversion were 19% (39 of 201) in the remifentanil PCA group and 41% (81 of 199) in the pethidine group (risk ratio 0·48, 95% CI 0·34–0·66; p<0·0001). There were no serious adverse events or drug reactions directly attributable to either analgesic during the study.

Interpretation

Intravenous remifentanil PCA halved the proportion of epidural conversions compared with intramuscular pethidine. This finding challenges routine pethidine use as standard of care in labour.

Vulnerability to snakebite envenoming: A global mapping of hotspots

Joshua Longbottom, Freya M Shearer, Maria Devine, et al.

The Lancet: Volume 392, ISSUE 10148, P673-684, August 25, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31224-8/fulltext

Summary

Background

Snakebite envenoming is a frequently overlooked cause of mortality and morbidity. Data for snake ecology and existing snakebite interventions are scarce, limiting accurate burden estimation initiatives. Low global awareness stunts new interventions, adequate health resources, and available health care. Therefore, we aimed to synthesise currently available data to identify the most vulnerable populations at risk of snakebite, and where additional data to manage this global problem are needed.

Methods

We assembled a list of snake species using WHO guidelines. Where relevant, we obtained expert opinion range (EOR) maps from WHO or the Clinical Toxinology Resources. We also obtained occurrence data for each snake species from a variety of websites, such as VertNet and iNaturalist, using the spocc R package (version 0.7.0). We removed duplicate occurrence data and categorised snakes into three groups: group A (no available EOR map or species occurrence records), group B (EOR map but <5 species occurrence records), and group C (EOR map and ≥5 species occurrence records). For group C species, we did a multivariate environmental similarity analysis using the 2008 WHO EOR maps and newly available evidence. Using these data and the EOR maps, we produced contemporary range maps for medically important venomous snake species at a 5 × 5 km resolution. We subsequently triangulated these data with three health system metrics (antivenom availability, accessibility to urban centres, and the Healthcare Access and Quality [HAQ] Index) to identify the populations most vulnerable to snakebite morbidity and mortality.

Findings

We provide a map showing the ranges of 278 snake species globally. Although about 6·85 billion people worldwide live within range of areas inhabited by snakes, about 146·70 million live within remote areas lacking quality health-care provisioning. Comparing opposite ends of the HAQ Index, 272·91 million individuals (65·25%) of the population within the lowest decile are at risk of exposure to any snake for which no effective therapy exists compared with 519·46 million individuals (27·79%) within the highest HAQ Index decile, showing a disproportionate coverage in reported antivenom availability. Antivenoms were available for 119 (43%) of 278 snake species evaluated by WHO, while globally 750·19 million (10·95%) of those living within snake ranges live more than 1 h from population centres. In total, we identify about 92·66 million people living within these

vulnerable geographies, including many sub-Saharan countries, Indonesia, and other parts of southeast Asia.

Interpretation

Identifying exact populations vulnerable to the most severe outcomes of snakebite envenoming at a subnational level is important for prioritising new data collection and collation, reinforcing envenoming treatment, existing health-care systems, and deploying currently available and future interventions. These maps can guide future research efforts on snakebite envenoming from both ecological and public health perspectives and better target future estimates of the burden of this neglected tropical disease.

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The New England Journal of Medicine (23 August 2018, Vol. 379, No. 8)

A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest

Gavin D. Perkins, Chen Ji, Charles D. Deakin, et al. for the PARAMEDIC2 Collaborators

N Engl J Med 2018; 379: 711-721 August 23, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1806842

Abstract

Background

Concern about the use of epinephrine as a treatment for out-of-hospital cardiac arrest led the International Liaison Committee on Resuscitation to call for a placebo-controlled trial to determine whether the use of epinephrine is safe and effective in such patients.

Methods

In a randomized, double-blind trial involving 8014 patients with out-of-hospital cardiac arrest in the United Kingdom, paramedics at five National Health Service ambulance services administered either parenteral epinephrine (4015 patients) or saline placebo (3999 patients), along with standard care. The primary outcome was the rate of survival at 30 days. Secondary outcomes included the rate of survival until hospital discharge with a favorable neurologic outcome, as indicated by a score of 3 or less on the modified Rankin scale (which ranges from 0 [no symptoms] to 6 [death]).

Results

At 30 days, 130 patients (3.2%) in the epinephrine group and 94 (2.4%) in the placebo group were alive (unadjusted odds ratio for survival, 1.39; 95% confidence interval [CI], 1.06 to 1.82; P=0.02). There was no evidence of a significant difference in the proportion of patients who survived until hospital discharge with a favorable neurologic outcome (87 of 4007 patients [2.2%] vs. 74 of 3994 patients [1.9%]; unadjusted odds ratio, 1.18; 95% CI, 0.86 to 1.61). At the time of hospital discharge, severe neurologic impairment (a score of 4 or 5 on the modified Rankin scale) had occurred in more of the survivors in the epinephrine group than in the placebo group (39 of 126 patients [31.0%] vs. 16 of 90 patients [17.8%]).

Conclusions

In adults with out-of-hospital cardiac arrest, the use of epinephrine resulted in a significantly higher rate of 30-day survival than the use of placebo, but there was no significant between-group difference in the rate of a favorable neurologic outcome because more survivors had severe neurologic impairment in the epinephrine group.

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, Peter A. Forsyth, Alain Algazi, et al.
N Engl J Med 2018; 379: 722-730 August 23, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1805453

Abstract
Background
Brain metastases are a common cause of disabling neurologic complications and death in patients with metastatic melanoma. Previous studies of nivolumab combined with ipilimumab in metastatic melanoma have excluded patients with untreated brain metastases. We evaluated the efficacy and safety of nivolumab plus ipilimumab in patients with melanoma who had untreated brain metastases.
Methods
In this open-label, multicenter, phase 2 study, patients with metastatic melanoma and at least one measurable, nonirradiated brain metastasis (tumor diameter, 0.5 to 3 cm) and no neurologic symptoms received nivolumab (1 mg per kilogram of body weight) plus ipilimumab (3 mg per kilogram) every 3 weeks for up to four doses, followed by nivolumab (3 mg per kilogram) every 2 weeks until progression or unacceptable toxic effects. The primary end point was the rate of intracranial clinical benefit, defined as the percentage of patients who had stable disease for at least 6 months, complete response, or partial response.
Results
Among 94 patients with a median follow-up of 14.0 months, the rate of intracranial clinical benefit was 57% (95% confidence interval [CI], 47 to 68); the rate of complete response was 26%, the rate of partial response was 30%, and the rate of stable disease for at least 6 months was 2%. The rate of extracranial clinical benefit was 56% (95% CI, 46 to 67). Treatment-related grade 3 or 4 adverse events were reported in 55% of patients, including events involving the central nervous system in 7%. One patient died from immune-related myocarditis. The safety profile of the regimen was similar to that reported in patients with melanoma who do not have brain metastases.
Conclusions
Nivolumab combined with ipilimumab had clinically meaningful intracranial efficacy, concordant with extracranial activity, in patients with melanoma who had untreated brain metastases.

Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery
Loïc Sentilhes, Norbert Winer, Elie Azria, et al. for the Groupe de Recherche en Obstétrique et Gynécologie
N Engl J Med 2018; 379: 731-742 August 23, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1800942

Abstract
Background
The use of tranexamic acid reduces mortality due to postpartum hemorrhage. We investigated whether the prophylactic administration of tranexamic acid in addition to prophylactic oxytocin in women with vaginal delivery would decrease the incidence of postpartum hemorrhage.
Methods
In a multicenter, double-blind, randomized, controlled trial, we randomly assigned women in labor who had a planned vaginal delivery of a singleton live fetus at 35 or more weeks of gestation to receive 1 g of tranexamic acid or placebo, administered intravenously, in

addition to prophylactic oxytocin after delivery. The primary outcome was postpartum hemorrhage, defined as blood loss of at least 500 ml, measured with a collector bag.

Results

Of the 4079 women who underwent randomization, 3891 had a vaginal delivery. The primary outcome occurred in 156 of 1921 women (8.1%) in the tranexamic acid group and in 188 of 1918 (9.8%) in the placebo group (relative risk, 0.83; 95% confidence interval [CI], 0.68 to 1.01; P=0.07). Women in the tranexamic acid group had a lower rate of provider-assessed clinically significant postpartum hemorrhage than those in the placebo group (7.8% vs. 10.4%; relative risk, 0.74; 95% CI, 0.61 to 0.91; P=0.004; P=0.04 after adjustment for multiple comparisons post hoc) and also received additional uterotonic agents less often (7.2% vs. 9.7%; relative risk, 0.75; 95% CI, 0.61 to 0.92; P=0.006; adjusted P=0.04). Other secondary outcomes did not differ significantly between the two groups. The incidence of thromboembolic events in the 3 months after delivery did not differ significantly between the tranexamic acid group and the placebo group (0.1% and 0.2%, respectively; relative risk, 0.25; 95% CI, 0.03 to 2.24).

Conclusions

Among women with vaginal delivery who received prophylactic oxytocin, the use of tranexamic acid did not result in a rate of postpartum hemorrhage of at least 500 ml that was significantly lower than the rate with placebo.

Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth

Mariana Widmer, Gilda Piaggio, Thi M.H. Nguyen, et al. for the WHO CHAMPION Trial Group

N Engl J Med 2018; 379: 743-752 August 23, 2018
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Abstract

Background

Postpartum hemorrhage is the most common cause of maternal death. Oxytocin is the standard therapy for the prevention of postpartum hemorrhage, but it requires cold storage, which is not available in many countries. In a large trial, we compared a novel formulation of heat-stable carbetocin with oxytocin.

Methods

We enrolled women across 23 sites in 10 countries in a randomized, double-blind, noninferiority trial comparing intramuscular injections of heat-stable carbetocin (at a dose of 100 µg) with oxytocin (at a dose of 10 IU) administered immediately after vaginal birth. Both drugs were kept in cold storage (2 to 8°C) to maintain double-blinding. There were two primary outcomes: the proportion of women with blood loss of at least 500 ml or the use of additional uterotonic agents, and the proportion of women with blood loss of at least 1000 ml. The noninferiority margins for the relative risks of these outcomes were 1.16 and 1.23, respectively.

Results

A total of 29,645 women underwent randomization. The frequency of blood loss of at least 500 ml or the use of additional uterotonic agents was 14.5% in the carbetocin group and 14.4% in the oxytocin group (relative risk, 1.01; 95% confidence interval [CI], 0.95 to 1.06), a finding that was consistent with noninferiority. The frequency of blood loss of at least 1000 ml was 1.51% in the carbetocin group and 1.45% in the oxytocin group (relative risk, 1.04; 95% CI, 0.87 to 1.25), with the confidence interval crossing the margin of noninferiority. The use of additional uterotonic agents, interventions to stop bleeding, and adverse effects did not differ significantly between the two groups.

Conclusions
Heat-stable carbetocin was noninferior to oxytocin for the prevention of blood loss of at least 500 ml or the use of additional uterotonic agents. Noninferiority was not shown for the outcome of blood loss of at least 1000 ml; low event rates for this outcome reduced the power of the trial.

Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation
Jennifer K. Litton, Hope S. Rugo, Johannes Ettl, et al.
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Abstract
Background
The poly(adenosine diphosphate–ribose) inhibitor talazoparib has shown antitumor activity in patients with advanced breast cancer and germline mutations in BRCA1 and BRCA2 (BRCA1/2).
Methods
We conducted a randomized, open-label, phase 3 trial in which patients with advanced breast cancer and a germline BRCA1/2 mutation were assigned, in a 2:1 ratio, to receive talazoparib (1 mg once daily) or standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles). The primary end point was progression-free survival, which was assessed by blinded independent central review.
Results
Of the 431 patients who underwent randomization, 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy. Median progression-free survival was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months vs. 5.6 months; hazard ratio for disease progression or death, 0.54; 95% confidence interval [CI], 0.41 to 0.71; P<0.001). The interim median hazard ratio for death was 0.76 (95% CI, 0.55 to 1.06; P=0.11 [57% of projected events]). The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% vs. 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; P<0.001). Hematologic grade 3–4 adverse events (primarily anemia) occurred in 55% of the patients who received talazoparib and in 38% of the patients who received standard therapy; nonhematologic grade 3 adverse events occurred in 32% and 38% of the patients, respectively. Patient-reported outcomes favored talazoparib; significant overall improvements and significant delays in the time to clinically meaningful deterioration according to both the global health status–quality-of-life and breast symptoms scales were observed.
Conclusions
Among patients with advanced breast cancer and a germline BRCA1/2 mutation, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to progression-free survival. Patient-reported outcomes were superior with talazoparib.

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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/
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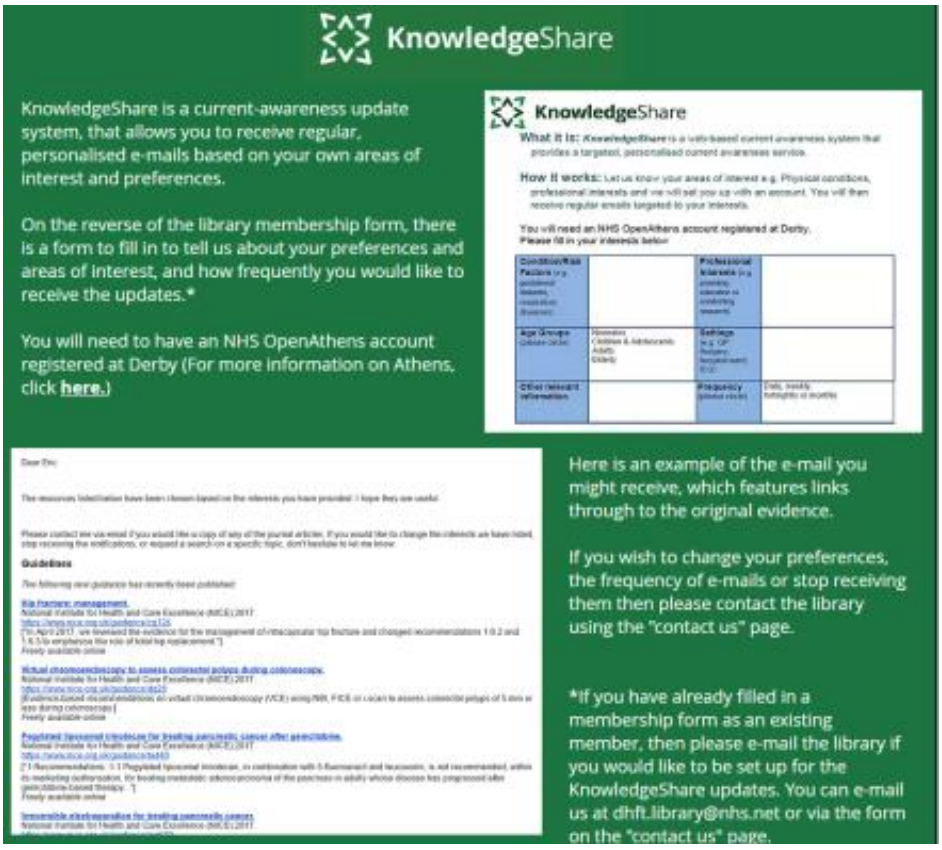

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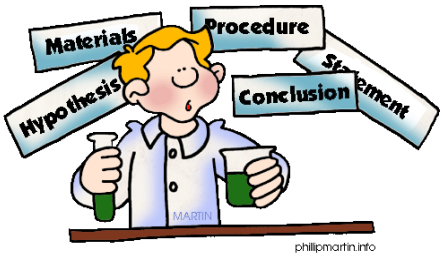

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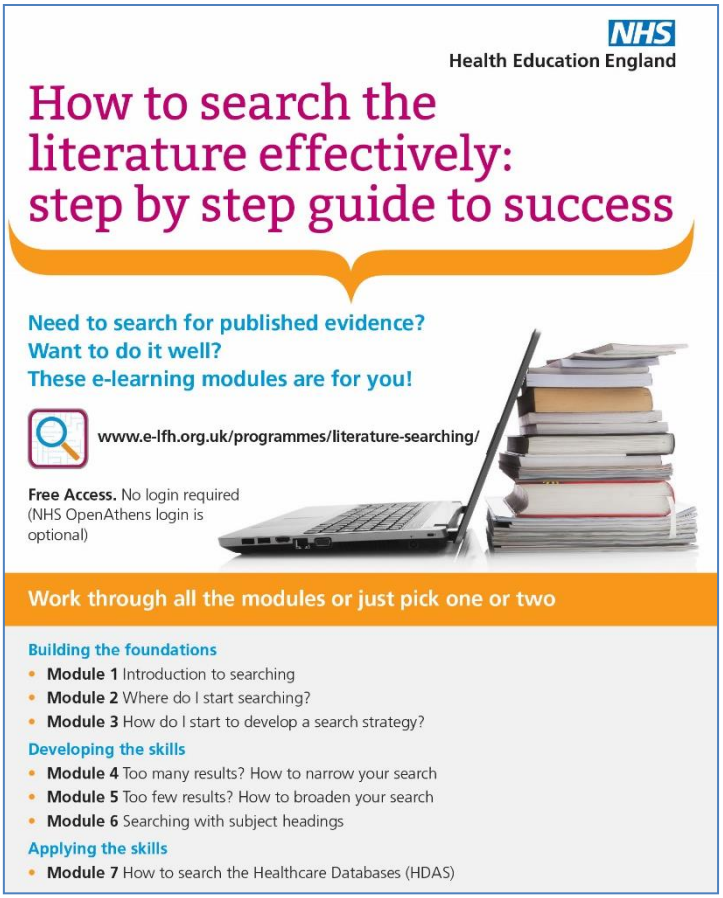

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