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BMJ (10 February 2018, Vol. 360, No. 8140)

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study
Elisabetta Patorno, Allison B Goldfine, Sebastian Schneeweiss, et al.
BMJ 2018; 360 :k119 (Published 06 February 2018)
http://www.bmj.com/content/360/bmj.k119

Abstract
Objective To evaluate the cardiovascular safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus, in direct comparisons with DPP-4 inhibitors (DPP-4i), GLP-1 receptor agonists (GLP-1RA), or sulfonylureas, as used in routine practice.
Design Population based retrospective cohort study.
Setting Nationwide sample of patients with type 2 diabetes from a large de-identified US commercial healthcare database (Optum Clinformatics Datamart).
Participants Three pairwise 1:1 propensity score matched cohorts of patients with type 2 diabetes 18 years and older who initiated canagliflozin or a comparator non-gliflozin antidiabetic agent (i.e. a DPP-4i, a GLP-1RA, or a sulfonylurea) between April 2013 and September 2015.
Main outcome measures The primary outcomes were heart failure admission to hospital and a composite cardiovascular endpoint (comprised of being admitted to hospital for acute myocardial infarction, ischemic stroke, or hemorrhagic stroke). Hazard ratios and 95% confidence intervals were estimated in each propensity score matched cohort controlling for more than 100 baseline characteristics.
Results During a 30 month period, the hazard ratio for heart failure admission to hospital associated with canagliflozin was 0.70 (95% confidence interval 0.54 to 0.92) versus a DPP-4i (n=17 667 pairs), 0.61 (0.47 to 0.78) versus a GLP-1RA (20 539), and 0.51 (0.38 to 0.67) versus a sulfonylurea (17 354). The hazard ratio for the composite cardiovascular endpoint associated with canagliflozin was 0.89 (0.68 to 1.17) versus a DPP-4i, 1.03 (0.79 to 1.35) versus a GLP-1RA, and 0.86 (0.65 to 1.13) versus a sulfonylurea. Results were

similar in sensitivity analyses further adjusting for baseline hemoglobin A1c levels and in subgroups of patients with and without prior cardiovascular disease or heart failure.
Conclusions In this large cohort study, canagliflozin was associated with a lower risk of heart failure admission to hospital and with a similar risk of myocardial infarction or stroke in direct comparisons with three different classes of non-gliflozin diabetes treatment alternatives as used in routine care.

Effectiveness of a childhood obesity prevention programme delivered through schools, targeting 6 and 7 year olds: cluster randomised controlled trial (WAVES study)

Peymane Adab, Miranda J Pallan, Emma R Lancashire, et al.
BMJ 2018; 360 :k211 (Published 07 February 2018)
http://www.bmj.com/content/360/bmj.k211

Abstract
Objective To assess the effectiveness of a school and family based healthy lifestyle programme (WAVES intervention) compared with usual practice, in preventing childhood obesity.
Design Cluster randomised controlled trial.
Setting UK primary schools from the West Midlands.
Participants 200 schools were randomly selected from all state run primary schools within 35 miles of the study centre (n=980), oversampling those with high minority ethnic populations. These schools were randomly ordered and sequentially invited to participate. 144 eligible schools were approached to achieve the target recruitment of 54 schools. After baseline measurements 1467 year 1 pupils aged 5 and 6 years (control: 28 schools, 778 pupils) were randomised, using a blocked balancing algorithm. 53 schools remained in the trial and data on 1287 (87.7%) and 1169 (79.7%) pupils were available at first follow-up (15 month) and second follow-up (30 month), respectively.
Interventions The 12 month intervention encouraged healthy eating and physical activity, including a daily additional 30 minute school time physical activity opportunity, a six week interactive skill based programme in conjunction with Aston Villa football club, signposting of local family physical activity opportunities through mail-outs every six months, and termly school led family workshops on healthy cooking skills.
Main outcome measures The protocol defined primary outcomes, assessed blind to allocation, were between arm difference in body mass index (BMI) z score at 15 and 30 months. Secondary outcomes were further anthropometric, dietary, physical activity, and psychological measurements, and difference in BMI z score at 39 months in a subset.
Results Data for primary outcome analyses were: baseline, 54 schools: 1392 pupils (732 controls); first follow-up (15 months post-baseline), 53 schools: 1249 pupils (675 controls); second follow-up (30 months post-baseline), 53 schools: 1145 pupils (621 controls). The mean BMI z score was non-significantly lower in the intervention arm compared with the control arm at 15 months (mean difference −0.075 (95% confidence interval −0.183 to 0.033, P=0.18) in the baseline adjusted models. At 30 months the mean difference was −0.027 (−0.137 to 0.083, P=0.63). There was no statistically significant difference between groups for other anthropometric, dietary, physical activity, or psychological measurements (including assessment of harm).
Conclusions The primary analyses suggest that this experiential focused intervention had no statistically significant effect on BMI z score or on preventing childhood obesity. Schools are unlikely to impact on the childhood obesity epidemic by incorporating such interventions without wider support across multiple sectors and environments.

Trial registration Current Controlled Trials ISRCTN97000586.

Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy: population based cohort study in Sweden
Martina Persson, Neda Razaz, Kristina Tedroff, et al.
BMJ 2018; 360 :k207 (Published 08 February 2018)
http://www.bmj.com/content/360/bmj.k207

Abstract
Objective To investigate associations between Apgar score at five and 10 minutes across the entire range of score values (from 0 to 10) and risks of childhood cerebral palsy or epilepsy, and to analyse the effect of changes in Apgar scores from five to 10 minutes after birth in infants born ≥37 completed weeks.
Design, setting, and participants Population based cohort study in Sweden, including 1 213 470 non-malformed live singleton infants, born at term between 1999 and 2012. Data on maternal and pregnancy characteristics and diagnoses of cerebral palsy and epilepsy were obtained by individual record linkages of nationwide Swedish registries.
Exposures Apgar scores at five and 10 minutes.
Main outcome measure Cerebral palsy and epilepsy diagnosed up to 16 years of age. Adjusted hazard ratios were calculated, along with 95% confidence intervals.
Results 1221 (0.1%) children were diagnosed as having cerebral palsy and 3975 (0.3%) as having epilepsy. Compared with children with an Apgar score of 10 at five minutes, the adjusted hazard ratio for cerebral palsy increased steadily with decreasing Apgar score: from 1.9 (95% confidence interval 1.6 to 2.2) for an Apgar score of 9 to 277.7 (154.4 to 499.5) for an Apgar score of 0. Similar and even stronger associations were obtained between Apgar scores at 10 minutes and cerebral palsy. Associations between Apgar scores and epilepsy were less pronounced, but increased hazard ratios were noted in infants with a five minute Apgar score of 7 or less and a 10 minute Apgar score of 8 or less. Compared with infants with an Apgar of 9-10 at both five and 10 minutes, hazard ratios of cerebral palsy and epilepsy were higher among infants with a five minute Apgar score of 7-8 and a 10 minute Apgar score of 9-10.
Conclusion Risks of cerebral palsy and epilepsy are inversely associated with five minute and 10 minute Apgar scores across the entire range of Apgar scores.

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JAMA: Journal of the American Medical Association (13 February 2018, Vol. 319, No. 6)

Effect of the Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk Emergency Department Patients: The PROPER Randomized Clinical Trial
Yonathan Freund, Marine Cachanado, Adeline Aubry, et al.
JAMA. 2018;319(6):559-566. doi:10.1001/jama.2017.21904
https://jamanetwork.com/journals/jama/fullarticle/2672630

Abstract

Importance The safety of the pulmonary embolism rule-out criteria (PERC), an 8-item block of clinical criteria aimed at ruling out pulmonary embolism (PE), has not been assessed in a randomized clinical trial.
Objective To prospectively validate the safety of a PERC-based strategy to rule out PE.
Design, Setting, and Patients A crossover cluster–randomized clinical noninferiority trial in 14 emergency departments in France. Patients with a low gestalt clinical probability of PE were included from August 2015 to September 2016, and followed up until December 2016.
Interventions Each center was randomized for the sequence of intervention periods. In the PERC period, the diagnosis of PE was excluded with no further testing if all 8 items of the PERC rule were negative.
Main Outcomes and Measures The primary end point was the occurrence of a thromboembolic event during the 3-month follow-up period that was not initially diagnosed. The noninferiority margin was set at 1.5%. Secondary end points included the rate of computed tomographic pulmonary angiography (CTPA), median length of stay in the emergency department, and rate of hospital admission.
Results Among 1916 patients who were cluster-randomized (mean age 44 years, 980 [51%] women), 962 were assigned to the PERC group and 954 were assigned to the control group. A total of 1749 patients completed the trial. A PE was diagnosed at initial presentation in 26 patients in the control group (2.7%) vs 14 (1.5%) in the PERC group (difference, 1.3% [95% CI, −0.1% to 2.7% ;[P .(052. = One PE (0.1%) was diagnosed during follow-up in the PERC group vs none in the control group (difference, 0.1% [95% CI, −∞ to 0.8%]). The proportion of patients undergoing CTPA in the PERC group vs control group was 13% vs 23% (difference, −10% [95% CI, −13% to −6% ;[P .(001. > In the PERC group, rates were significantly reduced for the median length of emergency department stay (mean reduction, 36 minutes [95% CI, 4 to 68]) and hospital admission (difference, 3.3% [95% CI, 0.1% to 6.6%.([
Conclusions and Relevance Among very low-risk patients with suspected PE, randomization to a PERC strategy vs conventional strategy did not result in an inferior rate of thromboembolic events over 3 months. These findings support the safety of PERC for very low-risk patients presenting to the emergency department.
Trial Registration clinicaltrials.gov Identifier :NCT02375919

Effect of a Quality Improvement Intervention on Clinical Outcomes in Patients in India With Acute Myocardial Infarction: The ACS QUIK Randomized Clinical Trial
Mark D. Huffman, Padinhare P. Mohanan, Raji Devarajan, et al.
JAMA. 2018;319(6):567-578. doi:10.1001/jama.2017.21906
https://jamanetwork.com/journals/jama/article-abstract/2672631

Abstract:
Importance Wide heterogeneity exists in acute myocardial infarction treatment and outcomes in India.
Objective To evaluate the effect of a locally adapted quality improvement tool kit on clinical outcomes and process measures in Kerala, a southern Indian state.
Design, Setting, and Participants Cluster randomized, stepped-wedge clinical trial conducted between November 10, 2014, and November 9, 2016, in 63 hospitals in Kerala, India, with a last date of follow-up of December 31, 2016. During 5 predefined steps over the study period, hospitals were randomly selected to move in a 1-way crossover from the control group to the intervention group. Consecutively presenting patients with acute myocardial infarction were offered participation.

Interventions Hospitals provided either usual care (control group; n = 10 066 participants [step 0: n = 2915; step 1: n = 2649; step 2: n = 2251; step 3: n = 1422; step 4; n = 829; step 5: n = 0]) or care using a quality improvement tool kit (intervention group; n = 11 308 participants [step 0: n = 0; step 1: n = 662; step 2: n = 1265; step 3: n = 2432; step 4: n = 3214; step 5: n = 3735]) that consisted of audit and feedback, checklists, patient education materials, and linkage to emergency cardiovascular care and quality improvement training.
Main Outcomes and Measures The primary outcome was the composite of all-cause death, reinfarction, stroke, or major bleeding using standardized definitions at 30 days. Secondary outcomes included the primary outcome's individual components, 30-day cardiovascular death, medication use, and tobacco cessation counseling. Mixed-effects logistic regression models were used to account for clustering and temporal trends.
Results Among 21 374 eligible randomized participants (mean age, 60.6 [SD, 12.0] years; n = 16 183 men [76%] ; n = 13 689 [64%] with ST-segment elevation myocardial infarction), 21 079 (99%) completed the trial. The primary composite outcome was observed in 5.3% of the intervention participants and 6.4% of the control participants. The observed difference in 30-day major adverse cardiovascular event rates between the groups was not statistically significant after adjustment (adjusted risk difference, −0.09% [95% CI, −1.32% to 1.14%]; adjusted odds ratio, 0.98 [95% CI, 0.80-1.21]). The intervention group had a higher rate of medication use including reperfusion but no effect on tobacco cessation counseling. There were no unexpected adverse events reported.
Conclusions and Relevance Among patients with acute myocardial infarction in Kerala, India, use of a quality improvement intervention compared with usual care did not decrease a composite of 30-day major adverse cardiovascular events. Further research is needed to understand the lack of efficacy.
Trial Registration clinicaltrials.gov Identifier: NCT02256657

Association of the Affordable Care Act Dependent Coverage Provision With Prenatal Care Use and Birth Outcomes

Jamie R. Daw, Benjamin D. Sommers,
JAMA. 2018;319(6):579-587. doi:10.1001/jama.2018.0030
https://jamanetwork.com/journals/jama/article-abstract/2672632

Abstract
Importance The effect of the Affordable Care Act (ACA) dependent coverage provision on pregnancy-related health care and health outcomes is unknown.
Objective To determine whether the dependent coverage provision was associated with changes in payment for birth, prenatal care, and birth outcomes.
Design, Setting, and Participants Retrospective cohort study, using a differences-in-differences analysis of individual-level birth certificate data comparing live births among US women aged 24 to 25 years (exposure group) and women aged 27 to 28 years (control group) before (2009) and after (2011-2013) enactment of the dependent coverage provision. Results were stratified by marital status.
Main Exposures The dependent coverage provision of the ACA, which allowed young adults to stay on their parent's health insurance until age 26 years.
Main Outcomes and Measures Primary outcomes were payment source for birth, early prenatal care (first visit in first trimester), and adequate prenatal care (a first trimester visit and 80% of expected visits). Secondary outcomes were cesarean delivery, premature birth, low birth weight, and infant neonatal intensive care unit (NICU) admission.

Results The study population included 1 379 005 births among women aged 24-25 years (exposure group; 299 024 in 2009; 1 079 981 in 2011-2013), and 1 551 192 births among women aged 27-28 years (control group; 325 564 in 2009; 1 225 628 in 2011-2013). From 2011-2013, compared with 2009, private insurance payment for births increased in the exposure group (36.9% to 35.9% [difference, −1.0%]) compared with the control group (52.4% to 51.1% [difference, −1.3%]), adjusted difference-in-differences, 1.9 percentage points (95% CI, 1.6 to 2.1). Medicaid payment decreased in the exposure group (51.6% to 53.6% [difference, 2.0%]) compared with the control group (37.4% to 39.4% [difference, 1.9%]), adjusted difference-in-differences, −1.4 percentage points (95% CI, −1.7 to −1.2). Self-payment for births decreased in the exposure group (5.2% to 4.3% [difference, −0.9%]) compared with the control group (4.9% to 4.3% [difference, −0.5%]), adjusted difference-in-differences, −0.3 percentage points (95% CI, −0.4 to −0.1). Early prenatal care increased from 70% to 71.6% (difference, 1.6%) in the exposure group and from 75.7% to 76.8% (difference, 0.6%) in the control group (adjusted difference-in-differences, 0.6 percentage points [95% CI, 0.3 to 0.8]). Adequate prenatal care increased from 73.5% to 74.8% (difference, 1.3%) in the exposure group and from 77.5% to 78.8% (difference, 1.3%) in the control group (adjusted difference-in-differences, 0.4 percentage points [95% CI, 0.2 to 0.6]). Preterm birth decreased from 9.4% to 9.1% in the exposure group (difference, −0.3%) and from 9.1% to 8.9% in the control group (difference, −0.2%) (adjusted difference-in-differences, −0.2 percentage points (95% CI, −0.3 to −0.03). Overall, there were no significant changes in low birth weight, NICU admission, or cesarean delivery. In stratified analyses, changes in payment for birth, prenatal care, and preterm birth were concentrated among unmarried women.
Conclusions and Relevance In this study of nearly 3 million births among women aged 24 to 25 years vs those aged 27 to 28 years, the Affordable Care Act dependent coverage provision was associated with increased private insurance payment for birth, increased use of prenatal care, and modest reduction in preterm births, but was not associated with changes in cesarean delivery rates, low birth weight, or NICU admission.

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The Lancet (10 February 2018, Vol. 391, No. 10120)

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial
Michael EJ Lean, Wilma S Leslie, Alison C Barnes, et al.
The Lancet Volume 391, No. 10120, p541–551, 10 February 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)33102-1/fulltext

Summary
Background
Type 2 diabetes is a chronic disorder that requires lifelong treatment. We aimed to assess whether intensive weight management within routine primary care would achieve remission of type 2 diabetes.
Methods
We did this open-label, cluster-randomised trial (DiRECT) at 49 primary care practices in Scotland and the Tyneside region of England. Practices were randomly assigned (1:1), via a computer-generated list, to provide either a weight management programme (intervention) or best-practice care by guidelines (control), with stratification for study site (Tyneside or Scotland) and practice list size (>5700 or ≤5700). Participants, carers, and

research assistants who collected outcome data were aware of group allocation; however, allocation was concealed from the study statistician. We recruited individuals aged 20–65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body-mass index of 27–45 kg/m^2, and were not receiving insulin. The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance. Co-primary outcomes were weight loss of 15 kg or more, and remission of diabetes, defined as glycated haemoglobin (HbA_{1c}) of less than 6·5% (<48 mmol/mol) after at least 2 months off all antidiabetic medications, from baseline to 12 months. These outcomes were analysed hierarchically. This trial is registered with the ISRCTN registry, number 03267836.

Findings

Between July 25, 2014, and Aug 5, 2017, we recruited 306 individuals from 49 intervention (n=23) and control (n=26) general practices; 149 participants per group comprised the intention-to-treat population. At 12 months, we recorded weight loss of 15 kg or more in 36 (24%) participants in the intervention group and no participants in the control group (p<0·0001). Diabetes remission was achieved in 68 (46%) participants in the intervention group and six (4%) participants in the control group (odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001). Remission varied with weight loss in the whole study population, with achievement in none of 76 participants who gained weight, six (7%) of 89 participants who maintained 0–5 kg weight loss, 19 (34%) of 56 participants with 5–10 kg loss, 16 (57%) of 28 participants with 10–15 kg loss, and 31 (86%) of 36 participants who lost 15 kg or more. Mean bodyweight fell by 10·0 kg (SD 8·0) in the intervention group and 1·0 kg (3·7) in the control group (adjusted difference −8·8 kg, 95% CI −10·3 to −7·3; p<0·0001). Quality of life, as measured by the EuroQol 5 Dimensions visual analogue scale, improved by 7·2 points (SD 21·3) in the intervention group, and decreased by 2·9 points (15·5) in the control group (adjusted difference 6·4 points, 95% CI 2·5–10·3; p=0·0012). Nine serious adverse events were reported by seven (4%) of 157 participants in the intervention group and two were reported by two (1%) participants in the control group. Two serious adverse events (biliary colic and abdominal pain), occurring in the same participant, were deemed potentially related to the intervention. No serious adverse events led to withdrawal from the study.

Interpretation

Our findings show that, at 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care.

Funding

Diabetes UK.

Safety, tolerability, and immunogenicity of two Zika virus DNA vaccine candidates in healthy adults: randomised, open-label, phase 1 clinical trials

Martin R Gaudinski, Katherine V Houser, Kaitlyn M Morabito et al.

The Lancet Volume 391, No. 10120, p552–562, 10 February 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)33105-7/fulltext

Summary

Background

The Zika virus epidemic and associated congenital infections have prompted rapid vaccine development. We assessed two new DNA vaccines expressing premembrane and envelope Zika virus structural proteins.

Methods
We did two phase 1, randomised, open-label trials involving healthy adult volunteers. The VRC 319 trial, done in three centres, assessed plasmid VRC5288 (Zika virus and Japanese encephalitis virus chimera), and the VRC 320, done in one centre, assessed plasmid VRC5283 (wild-type Zika virus). Eligible participants were aged 18–35 years in VRC19 and 18–50 years in VRC 320. Participants were randomly assigned 1:1 by a computer-generated randomisation schedule prepared by the study statistician. All participants received intramuscular injection of 4 mg vaccine. In VRC 319 participants were assigned to receive vaccinations via needle and syringe at 0 and 8 weeks, 0 and 12 weeks, 0, 4, and 8 weeks, or 0, 4, and 20 weeks. In VRC 320 participants were assigned to receive vaccinations at 0, 4, and 8 weeks via single-dose needle and syringe injection in one deltoid or split-dose needle and syringe or needle-free injection with the Stratis device (Pharmajet, Golden, CO, USA) in each deltoid. Both trials followed up volunteers for 24 months for the primary endpoint of safety, assessed as local and systemic reactogenicity in the 7 days after each vaccination and all adverse events in the 28 days after each vaccination. The secondary endpoint in both trials was immunogenicity 4 weeks after last vaccination. These trials are registered with ClinicalTrials.gov, numbers NCT02840487 and NCT02996461.
Findings
VRC 319 enrolled 80 participants (20 in each group), and VRC 320 enrolled 45 participants (15 in each group). One participant in VRC 319 and two in VRC 320 withdrew after one dose of vaccine, but were included in the safety analyses. Both vaccines were safe and well tolerated. All local and systemic symptoms were mild to moderate. In both studies, pain and tenderness at the injection site was the most frequent local symptoms (37 [46%] of 80 participants in VRC 319 and 36 [80%] of 45 in VRC 320) and malaise and headache were the most frequent systemic symptoms (22 [27%] and 18 [22%], respectively, in VRC 319 and 17 [38%] and 15 [33%], respectively, in VRC 320). For VRC5283, 14 of 14 (100%) participants who received split-dose vaccinations by needle-free injection had detectable positive antibody responses, and the geometric mean titre of 304 was the highest across all groups in both trials.
Interpretation
VRC5283 was well tolerated and has advanced to phase 2 efficacy testing.
Funding
Intramural Research Program of the Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Preliminary aggregate safety and immunogenicity results from three trials of a purified inactivated Zika virus vaccine candidate: phase 1, randomised, double-blind, placebo-controlled clinical trials

Kayvon Modjarrad, Leyi Lin, Sarah L George, et al.
The Lancet Volume 391, No. 10120, p563–571, 10 February 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)33106-9/fulltext

Summary
Background
A safe, effective, and rapidly scalable vaccine against Zika virus infection is needed. We developed a purified formalin-inactivated Zika virus vaccine (ZPIV) candidate that showed protection in mice and non-human primates against viraemia after Zika virus challenge. Here we present the preliminary results in human beings.

Methods
We did three phase 1, placebo-controlled, double-blind trials of ZPIV with aluminium hydroxide adjuvant. In all three studies, healthy adults were randomly assigned by a computer-generated list to receive 5 µg ZPIV or saline placebo, in a ratio of 4:1 at Walter Reed Army Institute of Research, Silver Spring, MD, USA, or of 5:1 at Saint Louis University, Saint Louis, MO, USA, and Beth Israel Deaconess Medical Center, Boston, MA, USA. Vaccinations were given intramuscularly on days 1 and 29. The primary objective was safety and immunogenicity of the ZPIV candidate. We recorded adverse events and Zika virus envelope microneutralisation titres up to day 57. These trials are registered at ClinicalTrials.gov, numbers NCT02963909, NCT02952833, and NCT02937233.
Findings
We enrolled 68 participants between Nov 7, 2016, and Jan 25, 2017. One was excluded and 67 participants received two injections of Zika vaccine (n=55) or placebo (n=12). The vaccine caused only mild to moderate adverse events. The most frequent local effects were pain (n=40 [60%]) or tenderness (n=32 [47%]) at the injection site, and the most frequent systemic reactogenic events were fatigue (29 [43%]), headache (26 [39%]), and malaise (15 [22%]). By day 57, 52 (92%) of vaccine recipients had seroconverted (microneutralisation titre ≥1:10), with peak geometric mean titres seen at day 43 and exceeding protective thresholds seen in animal studies.
Interpretation
The ZPIV candidate was well tolerated and elicited robust neutralising antibody titres in healthy adults.
Funding
Departments of the Army and Defense and National Institute of Allergy and Infectious Diseases.

Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals

Nathalie Conrad, Andrew Judge, Jenny Tran et al.

The Lancet, Volume 391, No. 10120, p572–580, 10 February 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32520-5/fulltext

Summary
Background
Large-scale and contemporary population-based studies of heart failure incidence are needed to inform resource planning and research prioritisation but current evidence is scarce. We aimed to assess temporal trends in incidence and prevalence of heart failure in a large general population cohort from the UK, between 2002 and 2014.
Methods
For this population-based study, we used linked primary and secondary electronic health records of 4 million individuals from the Clinical Practice Research Datalink (CPRD), a cohort that is representative of the UK population in terms of age and sex. Eligible patients were aged 16 years and older, had contributed data between Jan 1, 2002, and Dec 31, 2014, had an acceptable record according to CPRD quality control, were approved for CPRD and Hospital Episodes Statistics linkage, and were registered with their general practice for at least 12 months. For patients with incident heart failure, we extracted the most recent measurement of baseline characteristics (within 2 years of diagnosis) from electronic health records, as well as information about comorbidities, socioeconomic status, ethnicity, and region. We calculated standardised rates by applying direct age and

sex standardisation to the 2013 European Standard Population, and we inferred crude rates by applying year-specific, age-specific, and sex-specific incidence to UK census mid-year population estimates. We assumed no heart failure for patients aged 15 years or younger and report total incidence and prevalence for all ages (>0 years).

Findings

From 2002 to 2014, heart failure incidence (standardised by age and sex) decreased, similarly for men and women, by 7% (from 358 to 332 per 100 000 person-years; adjusted incidence ratio 0·93, 95% CI 0·91–0·94). However, the estimated absolute number of individuals with newly diagnosed heart failure in the UK increased by 12% (from 170 727 in 2002 to 190 798 in 2014), largely due to an increase in population size and age. The estimated absolute number of prevalent heart failure cases in the UK increased even more, by 23% (from 750 127 to 920 616). Over the study period, patient age and multi-morbidity at first presentation of heart failure increased (mean age 76·5 years [SD 12·0] to 77·0 years [12·9], adjusted difference 0·79 years, 95% CI 0·37–1·20; mean number of comorbidities 3·4 [SD 1·9] *vs* 5·4 [2·5]; adjusted difference 2·0, 95% CI 1·9–2·1). Socioeconomically deprived individuals were more likely to develop heart failure than were affluent individuals (incidence rate ratio 1·61, 95% CI 1·58–1·64), and did so earlier in life than those from the most affluent group (adjusted difference −3·51 years, 95% CI −3·77 to −3·25). From 2002 to 2014, the socioeconomic gradient in age at first presentation with heart failure widened. Socioeconomically deprived individuals also had more comorbidities, despite their younger age.

Interpretation

Despite a moderate decline in standardised incidence of heart failure, the burden of heart failure in the UK is increasing, and is now similar to the four most common causes of cancer combined. The observed socioeconomic disparities in disease incidence and age at onset within the same nation point to a potentially preventable nature of heart failure that still needs to be tackled.

Funding

British Heart Foundation and National Institute for Health Research.

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The New England Journal of Medicine (8 February 2018, Vol. 378, No. 6)

Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

Murray A. Raskind, Elaine R. Peskind, Bruce Chow, et al.

N Engl J Med 2018; 378:507-517. February 8, 2018. DOI: 10.1056/NEJMoa1507598
http://www.nejm.org/doi/full/10.1056/NEJMoa1507598

Abstract

Background

In randomized trials, prazosin, an α1-adrenoreceptor antagonist, has been effective in alleviating nightmares associated with post-traumatic stress disorder (PTSD) in military veterans.

Methods

We recruited veterans from 13 Department of Veterans Affairs medical centers who had chronic PTSD and reported frequent nightmares. Participants were randomly assigned to receive prazosin or placebo for 26 weeks; the drug or placebo was administered in escalating divided doses over the course of 5 weeks to a daily maximum of 20 mg in men and 12 mg in women. After week 10, participants continued to receive prazosin or placebo in a double-blind fashion for an additional 16 weeks. The three primary outcome measures

were the change in score from baseline to 10 weeks on the Clinician-Administered PTSD Scale (CAPS) item B2 (“recurrent distressing dreams”; scores range from 0 to 8, with higher scores indicating more frequent and more distressing dreams); the change in score from baseline to 10 weeks on the Pittsburgh Sleep Quality Index (PSQI; scores range from 0 to 21, with higher scores indicating worse sleep quality); and the Clinical Global Impression of Change (CGIC) score at 10 weeks (scores range from 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change).

Results

A total of 304 participants underwent randomization; 152 were assigned to prazosin, and 152 to placebo. At 10 weeks, there were no significant differences between the prazosin group and the placebo group in the mean change from baseline in the CAPS item B2 score (between-group difference, 0.2; 95% confidence interval [CI], −0.3 to 0.8; P=0.38), in the mean change in PSQI score (between-group difference, 0.1; 95% CI, −0.9 to 1.1; P=0.80), or in the CGIC score (between-group difference, 0; 95% CI, −0.3 to 0.3; P=0.96). There were no significant differences in these measures at 26 weeks (a secondary outcome) or in other secondary outcomes. At 10 weeks, the mean difference between the prazosin group and the placebo group in the change from baseline in supine systolic blood pressure was a decrease of 6.7 mm Hg. The adverse event of new or worsening suicidal ideation occurred in 8% of the participants assigned to prazosin versus 15% of those assigned to placebo.

Conclusions

In this trial involving military veterans who had chronic PTSD, prazosin did not alleviate distressing dreams or improve sleep quality. (Funded by the Department of Veterans Affairs Cooperative Studies Program; PACT ClinicalTrials.gov number, NCT00532493.)

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma

María-Victoria Mateos, Meletios A. Dimopoulos, Michele Cavo, et al.

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http://www.nejm.org/doi/full/10.1056/NEJMoa1714678

Abstract

Background

The combination of bortezomib, melphalan, and prednisone is a standard treatment for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation. Daratumumab has shown efficacy in combination with standard-of-care regimens in patients with relapsed or refractory multiple myeloma.

Methods

In this phase 3 trial, we randomly assigned 706 patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation to receive nine cycles of bortezomib, melphalan, and prednisone either alone (control group) or with daratumumab (daratumumab group) until disease progression. The primary end point was progression-free survival.

Results

At a median follow-up of 16.5 months in a prespecified interim analysis, the 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group (P<0.001), and the rate of complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001). In the daratumumab group,

22.3% of the patients were negative for minimal residual disease (at a threshold of 1 tumor cell per 105 white cells), as compared with 6.2% of those in the control group (P<0.001). The most common adverse events of grade 3 or 4 were hematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively. Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients.

Conclusions

Among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab. The daratumumab-containing regimen was associated with more grade 3 or 4 infections. (Funded by Janssen Research and Development; ALCYONE ClinicalTrials.gov number, NCT02195479.)

Mogamulizumab (Anti-CCR4) in HTLV-1–Associated Myelopathy

Tomoo Sato, Ariella L.G. Coler-Reilly, Naoko Yagishita, et al.

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http://www.nejm.org/doi/full/10.1056/NEJMoa1704827

Abstract

Background

Human T-lymphotropic virus type 1 (HTLV-1) causes the debilitating neuroinflammatory disease HTLV-1–associated myelopathy–tropical spastic paraparesis (HAM–TSP) as well as adult T-cell leukemia–lymphoma (ATLL). In patients with HAM–TSP, HTLV-1 infects mainly CCR4+ T cells and induces functional changes, ultimately causing chronic spinal cord inflammation. We evaluated mogamulizumab, a humanized anti-CCR4 monoclonal antibody that targets infected cells, in patients with HAM–TSP.

Methods

In this uncontrolled, phase 1–2a study, we assessed the safety, pharmacokinetics, and efficacy of mogamulizumab in patients with glucocorticoid-refractory HAM–TSP. In the phase 1 dose-escalation study, 21 patients received a single infusion of mogamulizumab (at doses of 0.003 mg per kilogram of body weight, 0.01 mg per kilogram, 0.03 mg per kilogram, 0.1 mg per kilogram, or 0.3 mg per kilogram) and were observed for 85 days. Of those patients, 19 continued on to the phase 2a study and received infusions, over a period of 24 weeks, of 0.003 mg per kilogram, 0.01 mg per kilogram, or 0.03 mg per kilogram at 8-week intervals or infusions of 0.1 mg per kilogram or 0.3 mg per kilogram at 12-week intervals.

Results

The side effects of mogamulizumab did not limit administration up to the maximum dose (0.3 mg per kilogram). The most frequent side effects were grade 1 or 2 rash (in 48% of the patients) and lymphopenia and leukopenia (each in 33%). The dose-dependent reduction in the proviral load in peripheral-blood mononuclear cells (decrease by day 15 of 64.9%; 95% confidence interval [CI], 51.7 to 78.1) and inflammatory markers in cerebrospinal fluid (decrease by day 29 of 37.3% [95% CI, 24.8 to 49.8] in the CXCL10 level and of 21.0% [95% CI, 10.7 to 31.4] in the neopterin level) was maintained with additional infusions throughout the phase 2a study. A reduction in spasticity was noted in 79% of the patients and a decrease in motor disability in 32%.

Conclusions
Mogamulizumab decreased the number of HTLV-1–infected cells and the levels of inflammatory markers. Rash was the chief side effect. The effect of mogamulizumab on clinical HAM–TSP needs to be clarified in future studies. (Funded by the Japan Agency for Medical Research and Development and the Ministry of Health, Labor, and Welfare; UMIN trial number, UMIN000012655.)

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
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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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Friday 16th 1:00pm — 2:00pm Library IT Room

Critical Appraisal (Qualitative Study paper) – *please book in advance*
Tuesday 20th 2:00pm — 3:30pm Library Seminar Room 1

- **MARCH**

Undertaking RCT Research: study design basics and critical appraisal
Tuesday 6th 2:30pm — 4:00pm Library Seminar Room 1

Reflective Writing (for NMC Revalidation) – *please book in advance*
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Using Evidence-Based Databases – *please book in advance*
Thursday 15th 12:00pm — 1:00pm Library IT Room

Critical Appraisal (Cohort Study paper) – *please book in advance*
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