

ABSTRACT FROM CURRENT LITERATURE

Comprehensive comparative effectiveness and safety of first line antihypertensive drug classes: a systematic, multinational, large scale analysis

Suchard MA, Schuemie MJ, Krumholz HM, et al
Lancet 2019; 394:1816-26

Background: Uncertainty remains about the optimal monotherapy for hypertension, with current guidelines recommending any primary agent among the first line drug classes-thiazide or thiazide like diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and non-dihydropyridine calcium channel blockers, in the absence of comorbid indications. Randomised trials have not further refined this choice.

Methods: We developed a comprehensive framework for real world evidence that enables comparative effectiveness and safety evaluation across many drugs and outcomes from observational data encompassing millions of patients, while minimizing inherent bias. Using this framework, we did a systematic, large scale study under a new user cohort design to estimate the relative risks of three primary (acute myocardial infarction, hospitalization for heart failure, and stroke) and six secondary effectiveness and 46 safety outcomes comparing all first-line classes across a global network of six administrative claim and three electronic health record databases. The framework addressed residual confounding, publication bias, and p-hacking using large scale propensity adjustment, a large set of control outcomes, and full disclosure of hypotheses tested.

Findings: Using 4.9 million patients, we generated 22000 calibrated, propensity score adjusted hazard ratios (HRs) comparing all classes and outcomes across databases. Most estimates revealed no effectiveness differences between classes; however, thiazide or thiazide like diuretics showed better primary effectiveness than angiotensin converting enzyme inhibitors: acute myocardial infarction (HR 0.84, 95% CI 0.75-0.95), hospitalisation for heart failure (0.83, 0.74-0.95), and stroke (0.83, 0.74-0.95) risk while on initial treatment Safety profiles also favoured thiazide or thiazide like diuretics over angiotensin converting enzyme inhibitors. The non-dihydropyridine calcium channel blockers were significantly inferior to the other four classes.

Interpretation: This comprehensive framework introduces a new way of doing observational health care science at scale. The approach supports equivalence between drug classes for initiating monotherapy for hypertension- in

keeping with current guidelines, with the exception of thiazide or thiazide like diuretics superiority to angiotensin-converting enzyme inhibitors and the inferiority of non dihydropyridine calcium channel blockers.

Guselkumab versus secukinumab for the treatment of moderate to severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial

Reich K, Armstrong AW, Langley RG, et al
Lancet 2019; 394: 831-39

Background: Antibodies targeting interleukin (IL) 23 and IL-17A effectively treat moderate-to severe psoriasis. ECLIPSE is the first comparator study of an IL-23p19 inhibitor, guselkumab, versus an IL-17A inhibitor, secukinumab. The primary objective of this study was to show superiority of clinical response, at week 48 for guselkumab versus secukinumab.

Methods: In this phase 3, multicentre, double blind, randomised, comparator-controlled trial at 142 outpatient clinical sites in nine countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Poland, Spain, and the USA), eligible patients were aged 18 years or older, had moderate to severe plaque type psoriasis, and were candidates for phototherapy or systemic therapy. Eligible patients were randomly assigned with permuted block randomisation using an interactive web response system to receive either guselkumab (100 mg at weeks 0 and 4 then every 8 weeks) or secukinumab (300 mg at weeks 0, 1, 2, 3, and 4, and then every 4 weeks). The primary endpoint, the proportion of patients in the intention to treat population who achieved 90% reduction or more from baseline of Psoriasis Area and Severity Index (PASI 90 response) at week 48, and major secondary endpoints (the proportions of patients in the guselkumab group and in the secukinumab group who achieved a PASI 75 response at both weeks 12 and 48, a PASI 90 response at week 12, a PASI 75 response at week 12, a PASI 100 response at week 48, an Investigator's Global Assessment [IGA] score of 0 [cleared] at week 48, and an IGA score of 0 or 1 [minimal] at week 48 were to be tested in a fixed sequence to control type I error rate. Safety was evaluated in patients who received one or more doses of study drug from week 0 to 56. The study is registered with Clinical Trials gov, NCT03090100.

Findings: This study was done between April 27, 2017, and Sept 20, 2018. 1048 eligible patients were enrolled and , of these, 534 were assigned to receive guselkumab and 514 to receive

secukinumab. The proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group (451 [84%]) than in the secukinumab group (360 [70%]) $p < 0.0001$. Although non inferiority (margin of 10 percentage points) was established for the first major secondary endpoint (452 [85%]) of patients in the guselkumab group vs 412 [80%] of patient in the secukinumab group achieving a PASI 75 response at both weeks 12 and 48), superiority was not established ($p = 0.0616$). Consequently, formal statistical testing was not done for subsequent major secondary endpoints. Proportions of patients with adverse events infections, and serious adverse events were similar between the two treatments and, in general safety findings were consistent with trial observations.

Interpretation: Guselkumab showed superior long term efficacy based on PASI 90 at week 48 when compared with secukinumab for treating moderate to severe psoriasis. This finding could assist health care providers in their decision making process when selecting a biologic for treating moderate to severe psoriasis.

Penicillin V four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study

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BMJ 2019; 367: 15337*

Objective: To determine whether total exposure to penicillin V can be reduced while maintaining adequate clinical efficacy when treating pharyngotonsillitis caused by group A streptococci.

Design: Open label randomised controlled non inferiority study.

Setting: 17 primary healthcare centres in Sweden between September 2015 and February 2018.

Participants: Patients aged 6 years and over with pharyngotonsillitis caused by group A streptococci and three or four Centor criteria (fever $\geq 38.5^{\circ}\text{C}$, tender lymph nodes, coatings of the tonsils, and absence of cough).

Interventions: Penicillin V 800 mg four times daily for five days (total 16 g) compared With the current recommended dose of 1000 mg three times daily for 10 days (total 30 g).

Main Outcome Measures: Primary outcome was clinical cure five to seven days after the end of antibiotic treatment. The non inferiority margin was prespecified to 10 percentage points. Secondary outcomes were bacteriological eradication, time to relief of symptoms, frequency of relapses, complications and new tonsillitis, and patterns of adverse events.

Results: Patients (n=433) were randomly allocated to the five day (n=215) or 10 day (n=218) regimen.

Clinical cure in the per protocol population was 89.6% (n=181/202) in the five day group and 93.3% (n=182/195) in the 10 day group (95% confidence interval 9.7 to 2.2). Bacteriological eradication was 80.4% (n=156/194) in the five day group and 90.7% (n=165/182) in the 10 day group. Eight and seven patients had relapses, no patients and four patients had complications, and six and 13 patients had new tonsillitis in the five day and 10 day groups, respectively. Time to relief of symptoms was shorter in the five day group. Adverse events were mainly diarrhoea, nausea, and vulvovaginal disorders; the 10 day group had higher incidence and longer duration of adverse events.

Conclusions: Penicillin V four times daily for five days was non-inferior in clinical outcome to penicillin V three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci. The number of relapses and complications did not differ between the two intervention groups. Five day treatment with penicillin V four times daily might be an alternative to the currently recommended 10 day regimen.

Status of care for end stage kidney disease in countries and regions worldwide: international cross sectional survey

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BMJ 2019; 367: 15873*

Objective: To determine the global capacity (availability, accessibility, quality, and affordability) to deliver kidney replacement therapy (dialysis and transplantation) and conservative kidney management.

Design: International cross sectional survey.

Setting: International Society of Nephrology (ISN) survey of 182 countries from July to September 2018.

Participants: Key stakeholders identified by ISN's national and regional leaders.

Main Outcome Measures: Markers of national capacity to deliver core components of kidney replacement therapy and conservative kidney management.

Results: Responses were received from 160 (87.9%) of 182 countries, comprising 97.8% (7338.5 million of 7501.3 million) of the world's population. A wide variation was found in capacity and structures for kidney replacement therapy and conservative kidney management namely, funding mechanisms, health workforce, service delivery, and available technologies. Information on the prevalence of treated end stage kidney disease was available in 91 (42%) of 218 countries worldwide. Estimates varied more than 800 fold from 4 to 3392 per million population. Rwanda was the only low income country to report data on the prevalence of treated disease; 5 (<10%) of 53

African countries reported these data. Of 159 countries, 102 (64%) provided public funding for kidney replacement therapy. Sixty eight (43%) of 159 countries charged no fees at the point of care delivery and 34 (21%) made some charge. Haemodialysis was reported as available in 156 (100%) of 156 countries, peritoneal dialysis in 119 (76%) of 156 countries, and kidney transplantation in 114 (74%) of 155 countries. Dialysis and kidney transplantation were available to more than 50% of patients in only 108 (70%) and 45 (29%) of 154 countries that offered these services, respectively. Conservative kidney management was available in 124 (81%) of 154 countries. Worldwide, the median number of nephrologists was 9.96 per million population, which varied with income level.

Conclusions: These comprehensive data show the capacity of countries (including low income countries) to provide optimal care for patients with end stage kidney disease. They demonstrate substantial variability in the burden of such disease and capacity for kidney replacement therapy and conservative kidney management, which have implications for policy.

Childhood haemorrhagic stroke: a 7 year single centre experience

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Arch Dis Child 2019; 104: 1198-1202

Background: In recent years, there has been increasing research interest in improving diagnostic and management protocols in childhood arterial ischaemic stroke (AIS). However, childhood stroke comprises, in approximately equal parts, both arterial ischaemic, and haemorrhagic stroke (HS).

Objective: The aim of this study was to focus on the aetiology, clinical presentation, treatment and short-term outcome of children with spontaneous intracranial bleeding in a university hospital and elucidate differences to childhood AIS.

Design: We performed a retrospective analysis of electronic medical records of children (28 days-18 years) diagnosed with HS between 2010 and 2016.

Results: We included 25 children (male child, n=11) with a median age of 8 years 1 month. The most common clinical presentations were vomiting (48%), headache (40%) and altered level of consciousness (32%). In more than half of the patients, HS was caused by vascular malformations. Other risk factors were brain tumour, coagulopathy and miscellaneous severe underlying diseases. Aetiology remained unclear in one child. Therapy was neurosurgical in most children (68%). Two patients died, 5 patients needed further (rehabilitation) treatment and 18 children could be discharged home.

Conclusions: HS differs from AIS in aetiology (vascular malformations as number one risk

factor), number of risk factors ('mono-risk' disease), clinical presentation (vomiting, headache and altered level of consciousness) and (emergency) therapy.

Association between early life (prenatal and postnatal) antibiotic administration and coeliac disease: a systematic review

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Arch Dis Child 2019, 104: 1083-1089

Objective: Whether prenatal or postnatal exposure to antibiotics is associated with an increased risk of coeliac disease (CD) is unclear. We systematically reviewed studies on the association between early life antibiotic exposure and the risk of CD or CD autoimmunity.

Design: Systematic review of observational studies.

Data sources: The PubMed and Embase databases were searched up to December 2018, with no language restrictions. Additional references were obtained from reviewed articles. Eligibility criteria for selecting studies Cohort cross-sectional and case control studies that assessed the association between prenatal and/or postnatal antibiotic exposure and the odds of developing CD (as defined by authors of the original studies) or CD autoimmunity were eligible for inclusion.

Results: Six studies were included. In two large cohort studies that focused on prenatal antibiotic exposure, no association with the risk of CD was found (adjusted OR=1.16; 95% CI 0.94 to 1.43 and adjusted HR=1.33; 95% CI 0.69 to 2.56) in the Norwegian and Swedish cohorts, respectively. In three studies that evaluated the association of postnatal antibiotic exposure with the risk of CD, the results were contradictory, with only the Italian cohort study reporting a significant positive association (adjusted incidence rate ratio=1.24; 95% CI 1.07 to 1.43). A large, multicentre cohort study that evaluated the association between postnatal antibiotic exposure and CD autoimmunity in human leukocyte antigen (HLA) positive subjects found no association.

Conclusions: We found no evidence of an association between prenatal or postnatal antibiotic exposure and CD.

Nationwide study of appendicitis in children

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BJS 2019; 106: 1623-1631

Background: Paediatric surgical care is increasingly being centralized away from low volume centres, and prehospital delay is considered a risk factor for more complicated appendicitis. The aim of this study was to determine the incidence of paediatric appendicitis in Sweden, and to assess whether distance to the hospital was a risk factor for complicated disease.

Methods: A nationwide cohort study of all paediatric appendicitis cases in Sweden, 2001-2014, was undertaken, including incidence of disease in different population strata, with trends over time. The risk of complicated disease determined by regression methods, with travel time as the primary exposure and individual level socioeconomic determinants as independent variables.

Results: Some 38939 children with appendicitis were identified. Of these, 16.8 per cent had complicated disease, and the estimated risk of paediatric appendicitis by age 18 years was 2.5 per cent. Travel time to the treating hospital was not associated with complicated disease (adjusted odds ratio (OR) 1.00 (95 per cent ci. 0.96 to 1.05) per 30 min increase; $P=0.934$). Level of education ($P=0.177$) and family income ($P=0.120$) were not independently associated with increased risk of complicated disease. Parental unemployment (adjusted OR 1.17, 95 per cent ci. 1.05 to 1.32; $P=0.006$) and having parents born outside Sweden (1 parents born in Sweden: adjusted OR 1.12, 1.01 to 1.25; both parents born outside Sweden: adjusted OR 1.32, 1.18 to 1.47; $P < 0.001$) were associated with an increased risk of complicated appendicitis.

Conclusion: Every sixth child diagnosed with appendicitis in Sweden has a more complicated course of disease. Geographical distance to the surgical facility was not a risk factor for complicated appendicitis.

Human model of burn injury that quantifies the benefit of cooling as a first aid measure

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BJS 2019; 106: 1472-1479

Background: Burn injuries are a major cause of morbidity and mortality worldwide. Cooling is widely practised as a first aid measure, but the efficacy of cooling burns in human skin has not been demonstrated. A safe, consistent, ethically acceptable model of burning and cooling in live human skin in vivo was developed, and used to quantify the effects of cooling.

Methods: Novel apparatus was manufactured to create and cool burns in women who were anaesthetized for breast reconstruction surgery using a deep inferior epigastric artery perforator flap. Burns were excised between 1 and 3 h after creation, and analysed using histopathological assessment.

Results: All 25 women who were approached agreed to take part in the study. There were no adverse events. Increased duration of contact led to increased burn depth, with a contact time of 7.5 s at 70°C leading to a mid dermal burn. Burn

depth progressed over time following injury, but importantly this was modified by cooling the burn at 16°C for 20 min. On average, cooling salvaged 25.2 per cent of the dermal thickness.

Conclusion: This study demonstrated the favourable effects of cooling on human burns. Public health messaging should emphasize cooling as first aid for burns. This model will allow analysis of the molecular effects of cooling burns, and provide a platform for testing novel therapies aimed at reducing the impact of burn injury.

Comparison of the efficacy and safety of two advanced vessel sealing technologies in total laparoscopic hysterectomy

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J Obstet Gynaecol, Res 2019; 11: 2220-2227

Aim: Adequately powered, randomized controlled studies evaluating efficacy and safety of advanced bipolar energy devices in gynecologic laparoscopic surgery are very few. We aimed to compare the two most commonly used devices in total laparoscopic hysterectomy.

Methods: This randomized controlled trial was carried out in the department of obstetrics and gynecology in an education and research hospital. One hundred thirty two women who underwent total laparoscopic hysterectomy for benign indications were included. Women with age younger than 18 years, suspected malignancy, stage 3-4 endometriosis, and cervical/intraligamentary leiomyoma were excluded. Patients were randomized preoperatively to LigaSure or Articulating Enseal. One experienced surgeon performed all operations.

Results: LigaSure was used in 67 patients and Enseal was used in 65 patients. Primary outcomes of the study were operative time (time from start of sealing and transaction of the round ligament until completion of colpotomy) and total operative time (time from skin incision to skin closure). Secondary outcomes were intraoperative blood loss (blood lost during operative time period) and perioperative complications. Operative time was significantly shorter in LigaSure group ($P = 0.001$). Total operative time, intraoperative blood loss and perioperative complications were similar. When two groups were further classified according to uterine weight taking 300 g as cut off value, operative time was significantly shorter in LigaSure group in both subgroups ($P = 0.003$ and $P = 0.007$).

Conclusion: LigaSure use in total laparoscopic hysterectomy shortens operative time when compared with Enseal; without an apparent increase in intraoperative blood loss and perioperative complications. On the other side, total operative time remains unaffected.