Cardiology

Liraglutide for heart failure

Currently, there are no heart failure (HF) therapies that target the abnormal cardiac metabolic derangements that are seen in patients with HF and reduced left ventricular ejection fraction (LVEF). Early studies on such patients using glucagon-like peptide 1 (GLP-1) agonists have shown promising cardio-protective effects, regardless of type 2 diabetes status.

A phase 2, double-blind, placebo-controlled randomised trial was conducted to establish if the GLP-1 agonist liraglutide could improve clinical stability in patients with advanced HF and reduced LVEF (≤40%). Primary outcomes included time to associated re-hospitalisation and time to death, higher values for each indicating better clinical stability. Patients who had been hospitalised with an acute HF episode within the previous 14 days (n=300) were randomised.

There were no significant effects on primary outcomes between the placebo and liraglutide groups. For liraglutide vs placebo, death was 12% vs 11%, and rehospitalisation was 41% vs 34%.

This study does not support the use of liraglutide in this setting.

Margulies KB, Hernandez AF, Redfield MM, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2016; 316: 500–508.

Ticagrelor versus aspirin in stroke

In the first 90 days following a stroke the risk of recurrent ischaemic events is high. Even with aspirin this risk is 10–15%. Ticagrelor is an antiplatelet agent that inhibits the P2Y12 receptor on platelets.

A multi-centre double-blind, controlled trial compared the the effectiveness of ticagrelor versus aspirin in reducing risk of recurrent ischaemic events. The SOCRATES trial included over 13 000 patients across 33 countries. Patients who had a non-severe ischaemic stroke or transient ischaemic attack were randomly assigned either ticagrelor or aspirin 24 hours after symptom onset for 90 days. The endpoints measured included time to occurrence of stroke, myocardial infarction or death within the 90-day period. The primary endpoint was reached by 6.7% of patients treated with ticagrelor vs. 7.5% with aspirin.

There was no evidence of a higher risk of major or intracranial haemorrhage with ticagrelor, but there were more instances of dyspnoea and minor bleeding.

Ticagrelor was not found to be superior to aspirin in reducing recurrence of ischaemic events.

Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *NEJM* 2016; 375: 35–43.

Cardiac ablation for secondary tachycardia

Implantable cardioverter-defibrillators (ICDs) are sometimes placed in an individual following a myocardial infarction (MI), significantly reducing the risk of death caused by tachycardia which is usually resultant from post-MI scarring.

The VANISH randomised multicentre trial compared the effect of ICD and baseline antiarrhythmic drugs (AAD) plus catheter ablation (n=132) with ICD plus escalating AAD (n=127). The primary outcomes were death, three or more documented tachycardia episodes (within 24h), or appropriate ICD shock.

During a mean follow-up of 28 months, primary outcomes occurred in 59% of patients in the ablation group and 68% of those in the escalated-therapy group.

In the VANISH trial, ischaemic cardiomyopathy patients with an ICD experienced a significantly lower rate of the primary outcomes assessed, including death, when treated with cardiac ablation compared to those treated with escalating antiarrhythmic drugs.

Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *NEJM* 2016; 375: 111–121.

Respiratory

Ventilation methods in immunocompromised patients

For immunocompromised patients with acute respiratory failure high-flow nasal cannula oxygen therapy is increasingly being used as an alternative to standard oxygen. The use of another alternative method, non-invasive ventilation, is controversial.

One study set out to compare the outcomes of patients receiving treatment with these different ventilation methods in a post-hoc subgroup analysis on patients from a multicentre, randomised controlled trial. The primary outcome was the number of patients who, within 28 days post-randomisation, required endotracheal intubation.

A total of 82 immunocompromised patients with acute respiratory failure were included in the analysis and treated with standard oxygen (n=30), high-flow nasal cannula oxygen alone (n=26) or high-flow nasal cannula oxygen associated with non-invasive ventilation(n=26). By the 28-day mark 65% of patients in the non-invasive treatment setting required intubation. The results for the standard oxygen and high-flow cannula alone were lower with 43% and 31% respectively.

In immunocompromised patients requiring treatment for respiratory failure, non-invasive ventilation methods might be associated with an increased risk of intubation.

Frat J-P, Ragot S, Girault C, et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. *Lancet Resp* 2016; 4: 646–652.

Fracking and asthma exacerbation

The controversial unconventional natural gas development (UNGD), often referred to as 'fracking', is known for its environmental impacts. Asthma exacerbations are often linked to environmental influences but the effects of UNGD on respiratory health have yet to be investigated. A nested case control study set out to evaluate any associations between UNGD and asthma exacerbations.

Data were extracted from patient records from the Geisinger Clinic, Pennsylvania, and examined for asthma exacerbations in mild, moderate and severe events. The day prior to the index date of each patient's asthma event was evaluated for nearby UNGD activity. It is important to note that many events in UNGD may have plausible associations with respiratory outcomes including increased truck traffic and sleep disruption and that 'fracking' is only one phase in the UNGD process.

The analysis found that there was a statistical association between areas that unconventional natural gas development was occurring in and increased risk of mild, moderate and severe asthma exacerbations.

Rasmussen SG, Ogburn EL, McCormack M, et al. Association between unconventional natural gas development in the Marcellus shale and asthma exacerbations. *JAMA Intern Med* 2016; DOI: 10.1001/jamainternmed.2016.2436.

Indacaterol–glycopyrronium regime for COPD

For patients with chronic obstructive pulmonary disease (COPD) and high

risk of exacerbation the recommended first-line treatment is either a long-acting beta-agonist (LABA) combined with an inhaled glucocorticoid or a long acting muscarinic antagonist (LAMA).

One study set out to investigate the effectiveness of a LABA-LAMA regime compared to a LAMA-glucocorticoid setting. In a randomised double-blind trial, COPD patients with a high risk of exacerbation were given either the LABA indacaterol combined with the LAMA glycopyrronium (n=1680) or the LABA Salmeterol plus an inhaled glucocorticoid fluticasone (n=1682). The primary outcome was annual rate of COPD exacerbation events.

The LABA-LAMA regime showed superiority in reducing exacerbation rate by 11% compared to the LABA-glucocorticoid group (rate of 3.59 vs 4.03). There was also a longer time to first exacerbation (71 days vs 51 days) and longer time to moderate or severe events in the LABA-LAMA group.

For COPD patients with a recent history of exacerbations a regime of combined LABA-LAMA indacaterol-glycopyrronium was superior in preventing exacerbations compared to LABA-glucocorticoid.

Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. *NEJM* 2016; 374: 2222–2234.

Paediatrics

Breastfeeding and infant antibiotic exposure

Long-term benefits of breastfeeding include decreased frequency of infection and childhood obesity risk – an effect likely due to the influence on an infant's microbiota and weight development.

One retrospective cohort study investigated if early-life antibiotic-use negated these benefits.

Later-life antibiotic use and BMI z scores were two parameters used to measure infection frequency and weight development in a cohort of 226 healthy children (2-6yo, 54% male) in northern Finland.

Of these, 113 children had no antibiotic exposure during feeding and each month they were breastfed for decreased the mean number of post-weaning antibiotic courses by 5% and the mean BMI z score by 0.08 units. To compare, the early-life antibiotic exposure group (n=113) had less of a benefit with an estimated 4% decrease in post-weaning antibiotic courses and there was no beneficial effect seen on the BMI z score.

Antibiotic exposure in a child during breastfeeding may weaken the beneficial effects on health and weight that are seen in the long-term in children who have been breastfed.

Korpela K, Salonen A, Virta LJ, et al. Association of early-life antibiotic use and protective effects of breastfeeding: role of the intestinal microbiota. *JAMA Pediatrics* 2016; 170: 750–757.

C. difficile-associated reactive arthritis

Clostridium difficile infection (CDI) has an increasing prevalence in children. Most recognised for its gastrointestinal manifestations, CDI is also associated with an inflammatory reactive arthritis, a morbid yet poorly understood condition.

A nested case-control study aimed to better understand the incidence and characteristics of this CDI-associated manifestation.

Information was collated from electronic paediatric health records from three hospital networks.

Evaluation of paediatric CDI records revealed that around 2% of children with CDI were affected by CDI-associated reactive arthritis. Diagnosis of this complication was occasionally misattributed to septic arthritis and only 35% of cases were correctly diagnosed by health care professionals. The majority of affected children were seen in an emergency or acute setting, demonstrating the morbidity of this manifestation.

Better recognition of *Clostridium difficile* infection-associated reactive arthritis is required as the incidence of CDI increases.

Horton DB, Strom BL, Putt ME, et al. Epidemiology of clostridium difficile Infection–associated reactive arthritis in children: an underdiagnosed, potentially morbid condition. *JAMA Pediatrics* 2016; DOI: 10.1001/jamapediatrics.2016.0217.

Delayed parenteral nutrition intervention

Macronutrient deficiency is common for critically ill children in an intensive care unit (ICU) as oral feeding is often not possible and this may lead to an increased risk of new infection. The preferred intervention is parenteral nutrition via nasogastric tube but there is debate about when best to initiate this and adult trials have already questioned the benefit of early intervention.

A randomised multicentre trial investigated the difference in benefit of providing parenteral nutrition at an early interval, 24 hours after ICU admission (n=723), and later at 8 days post-admission (n=717).

Both groups experienced similar mortality but rates of new infection were lower in the late nutrition cohort (10.7% vs 18.5%). The mean ICU stay was around six days in the the late cohort vs nine days in the early cohort and the late cohort also experienced a shorter duration of necessary mechanical ventilator support.

Delaying parenteral nutrition for critically ill children in ICU for 1 week may be clinically superior than providing parenteral nutritional intervention early.

Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *NEJM* 2016; 374: 1111–1122.

Obs & Gyn

Obstetric outcomes with cervical treatment

Treatment for local cervical intraepithelial neoplasia (CIN) is correlated with an increased risk in preterm birth among other undesirable obstetric outcomes.

A meta-analysis searching over 70 studies assessed the effect of local treatment for CIN on the risk of these outcomes.

Of around six million identified participants, 65 082 had CIN treatment prior to pregnancy. This group had a significantly increased risk (10.7% vs 5.4%) of overall preterm births (<37 weeks) and extreme (<28–30 weeks) preterm births (1.0% vs 0.3%).

Differences in risk were also observed among the treatment types, with techniques that involved removing or ablating more tissue associated with worse outcomes. Furthermore, pregnant women with untreated CIN had an overall increased risk compared to the general population (5.9% vs 5.6%).

There is an increased baseline risk for women with CIN of pre-term births that is further increased by pre-pregnancy treatment for CIN.

Kyrgiou M, Athanasiou A, Paraskevaidi M, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ* 2016; 354: i3633.

Dengue and adverse foetal outcomes

Currently there is little known about the possible adverse foetal effects that infection during pregnancy with the mosquito-borne disease dengue may have.

A systematic review and meta-analysis investigated the risk that dengue may pose on foetal outcomes including miscarriage, preterm birth and low birthweight.

In total 16 studies between 1994-2014 from 10 countries were eligible for inclusion in the systematic review and eight were eligible for inclusion in the meta-analyses, these included 292 women exposed to dengue in pregnancy.

The most common adverse outcomes were pre-term birth and low birth-weight. The results showed a large variation, even between studies from the same country. For example, Malaysia saw a prevalence of preterm births between 3.1–26.6%. The prevalence of miscarriage associated with gestational dengue infection ranged between 3.8% in Sri Lanka and 16% in India.

This study suggests an association between symptomatic infection with dengue during pregnancy and a possible increased risk of adverse foetal outcomes.

Paixão E, Teixeira M, Costa M, et al. Dengue during pregnancy and adverse fetal outcomes: a systematic review and meta-analysis. *Lancet Infect Dis* 2016; 16: 857–865.

Plant-based therapies for the menopause

The use of complementary therapies to help manage menopausal symptoms is widespread. An average of 40% of women in Western countries use such therapies in an attempt to alleviate symptoms associated with the menopause.

A systematic review and meta-analysis set out to determine the association of plant based therapies with alleviation of menopausal symptoms including hot flushes, night sweats and vaginal dryness. Data were taken from 62 studies that used a randomised trial setting to assess plant-based therapies with a total of 6653 women included.

Phytoestrogens were associated with decreased hot flushes and vaginal dryness but no effect was seen for night sweats. Intervention with dietary and supplementary soy isoflavones also correlated with improved hot flushes and vaginal dryness.

The meta-analysis conducted suggests there may be a positive association with the use of phytoestrogen supplements and a modest reduction in some menopausal symptoms.

Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. *JAMA* 2016; 315: 2554–2563.

Infection

Tenofovir for maternal hepatitis B transmission

Antivirals have shown success in reducing the symptom burden in patients with chronic hepatitis B virus (HBV) but total eradication is not common and initial prevention of transmission remains the main strategy for control. To investigate prevention of mother-to-child transmission a recent study looked at the effect that the antiviral tenofovir disoproxil fumarate (TDF) had on mother-to-child transmission rates.

In this multicentre, open-label, randomised trial 200 HBV positive expectant mothers were randomly assigned, in a 1:1 ratio, to receive normal care or to receive TDF from 30–32 weeks of gestation until week four postpartum with follow up until week 28. The primary outcomes were rates of transmission and birth defects.

The results showed a significantly lower rate of mother-to-child transmission in the TDF cohort with transmission in only 5% of infants (vs 18%). Birth defect rates and safety profiles were similar in both groups.

TDF given to HBV-positive expectant mothers in their third trimester may reduce the risk of mother-to-child transmission.

Pan CQ, Duan Z, Dai E, Zhang S, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *NEJM* 2016; 37: 2324–2334.

Seven-year efficacy of RTS,S/AS01

The malaria candidate vaccine, RTS,S/AS01, is undergoing evaluation to see if it should be included in routine vaccination schedules.

A seven-year follow-up of children who had been randomly assigned three doses of either the vaccine or a control at 5–17 months of age was conducted to investigate the primary endpoint of clinical malaria occurrence.

For the children assigned the vaccine there were 1002 cases of clinical malaria in 223 children and 992 cases in the 224 children assigned the control.

The candidate vaccine did initially provide some protection in the first year with a 35.9% efficacy but this waned over time and in its fourth year efficacy was close to zero with a negative efficacy during the fifth year in children with a higher-than-average exposure to malaria parasites.

RTS,S/AS01 given in a three-dose program was initially protective against clinical malaria, but this was offset by rebound in later years for children in areas with higher-than-average exposure to malaria parasites.

Olotu A, Fegan G, Wambua J, et al. Seven-year efficacy of RTS,S/AS01 malaria vaccine among young African children. *NEJM* 2016; 374: 2519–2529.

Sertraline for cryptococcal meningitis

There is a crucial need for an effective and accessible antifungal drug to combat the high mortality seen in adults with cryptococcal meningitis.

An open-label dose-finding study investigated the effect of added sertraline on HIV-infected individuals presenting with cryptococcal meningitis.

Participants were randomly assigned to receive escalating doses of sertraline combined with standard amphotericin therapy. The primary outcome was two-week cerebrospinal fluid (CSF) clearance rate of Cryptococcus. Participants received sertraline in 200 mg (n=48), 300 mg (n=36), or 400 mg (n=28) daily doses for two weeks followed by consolidation therapy with 200 mg/day for eight weeks with an initial further 60 participants receiving 200 mg daily to test for safety. Across the sertraline doses CSF clearance averaged a rate of –0·37 colony forming units per mL per day, a higher clearance than seen in historical trials on patients receiving amphotericin and fluconazole.

Sertraline, when added to standard therapy for cryptococcal meningitis, might improve CSF fungal clearance.

Rhein J, Morawski BM, Hullsiek KH, et al. Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis: an open-label dose-ranging study. *Lancet Infect Dis* 2016; 16: 809–18.