Cardiovascular

Safety and efficacy of digoxin

In the past, digoxin has been routinely used to treat heart failure and atrial fibrillation. However, since a study reported an increase in mortality rates associated with digoxin use, the prescribing of it has declined.

A recent systematic review of over 70 observational studies and randomised trials aimed to clarify this finding. Researchers assessed whether digoxin increased all-cause mortality or adverse clinical outcomes compared with placebo.

The meta-analysis had a combined total of over 4 million patient-years of follow up. Although the results from pooled observational studies showed an increased risk of death with digoxin (risk ratio, 1.6), the more robust data from randomised trials showed there was no difference in all-cause mortality between digoxin and placebo. Further analysis showed digoxin led to a small but significant reduction in hospital admission (risk ratio, 0.92).

Digoxin is associated with a neutral effect on mortality and a lower rate of admissions to hospital.

Ziff J, Lane A, Samra M, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015, 351, h4451.

Cancer screening following venous thromboembolism

Unprovoked venous thromboembolism (VTE) may be the earliest sign of cancer in around 10% of affected patients. Clinicians will often investigate these cases to detect an occult cancer, but the variation in practice is great. A recent randomised trial assessed the efficacy of two screening strategies at detecting occult cancers.

The trial randomised 850 patients to receive either limited occult cancer screening (blood testing, chest radiography, and breast, cervical, or prostate cancer screening) or limited screening plus computed tomography (CT) scanning. Researches aimed to quantify the number of cancers that screening did not detect and were subsequently diagnosed within 12 months.

Following screening, 14 of the 431 (3.2%) patients in the limited-screening group and 19 of the 423 (4.5%) patients in the CT group had an occult cancer diagnosed. Four occult cancers (29%) were missed by the limited screening, whereas five (26%) were missed by the CT screening – a non-significant difference.

For patients with unprovoked VTE, routine screening plus CT scans did not increase the detection of occult cancers.

Carrier M, Lazo-Langner A, Shivakumar, et al. Screening for occult cancer in unprovoked venous thromboembolism. *NEJM* 2015; 373: 697–704.

Antidote for dabigatran reversal

Dabigatran is an effective alternative to warfarin, but in the case of acute haemorrhage no antidote exists to reverse its anticoagulation action. Now a monoclonal antibody, idarucizumab, has been developed and may be able to reverse dabigatran's action. A phase one trial to test idarucizumab's safety and efficacy has been reported.

In total, 47 healthy adult volunteers were assigned in a 3:1 ratio to receive idarucizumab or placebo. All participants were prescribed seven doses of dabigatran (220 mg) over 4 days. To reverse the dabigatran-induced anticoagulation, intravenous idarucizumab (1–4 g, or 5 g plus 2.5 g after 5 min) was infused. Researchers monitored adverse reactions, and they also measured the reversal of thrombin time, clotting time, activated partial thromboplastin time, and thrombin time.

Drug-related adverse events occurred in seven participants and were all mild (infusion site erythema, epistaxis, haematuria, and haematoma). Idarucizumab immediately and completely reversed dabigatran-induced anticoagulation in a dose-dependent manner.

Idarucizumab caused an immediate, complete, and sustained reversal of dabigatran-induced anticoagulation without significant safety concerns.

Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet* 2015; 386: 680–690.

Infectious Disease

New cholera vaccine

Cholera is a major public health problem across many low-income countries, including much of Africa. A cholera vaccine has been available for purchase by UN organisations for 15 years, but its use in low-income countries has been limited, in part due to high costs. Now a newer and cheaper two-dose, oral cholera vaccine has been produced. To test its efficacy a study has been conducted in Bangladesh where cholera is endemic.

Researchers randomised over 250 000 people in poor urban population clusters to receive either no intervention, vaccination only, or vaccination plus behavioural change (education on safe drinking water and hand-washing). The primary outcome measured protected effectiveness against severe cholera 2 years after vaccination.

The coverage of the interventions among the groups ranged from 65–66%. The overall protectiveness was 37% in the vaccination group and 45% in the vaccination plus education group. Although the protection between the two groups was non-significant, both offered significantly more protection than the non-intervention group.

This new cholera vaccine reduced the burden of severe cholera.

Qadri F, Ali M, Chowdhury F, et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. *Lancet* 2015; 386: 1362–1371.

Ebola post-exposure prophylaxis

Accidental exposure to the Ebola virus for healthcare workers is a real and serious problem. There is an urgent need for a consensus regarding the risk assessment of Ebola virus transmission after exposure and to investigate the use and efficacy of post-exposure prophylaxis (PEP).

A hospital in London has devised a risk assessment and management algorithm for healthcare workers potentially exposed to the Ebola virus in west Africa. It also developed PEP using antiviral agents including favipiravir, tenofovir disoproxil fumarate, emtricitabine, raltegravir, and monoclonal antibodies. Participants were followed for 42 days after potential exposure.

Of the eight healthcare workers exposed to the Ebola virus, four were classified as having had low-risk exposures and were managed by watchful waiting. The remaining four individuals had intermediate (n=2), or maximum (n=2) risk exposures and were given PEP. None of the eight healthcare workers developed Ebola virus disease.

A standardised risk assessment algorithm should be adopted and guidelines developed to study the safety and efficacy of PEP.

Jacobs M, Aarons E, Bhagani S, et al. Post-exposure prophylaxis against Ebola virus disease with experimental antiviral agents: a case-series of healthcare workers. *Lancet Infectious Diseases* 2015; 15: 1300-1304.

Rapid, point-of-care testing for Ebola

Currently, a diagnosis of Ebola virus disease must be made in the laboratory using real-time RT-PCR which is time

consuming and complex. A point-of-care rapid diagnostic test kit, Corgenix ReEBOV Antigen Rapid, has now been developed. It requires little training and can use blood from fingerstick or venepuncture.

To test the accuracy of ReEBOV, a study has compared the diagnostic results from the gold-standard laboratory RT-PCR testing with ReEBOV among 28 patients with suspected Ebola and tested at point-of-care. For further comparison, 284 samples held in a reference laboratory were also tested.

In point-of-care testing, all 28 patients who tested positive for Ebola using RT-PCR were also positive using ReEBOV (sensitivity 100%). Further, 71 of 77 patients with negative RT-PCR tests were also negative by the ReEBOV (specificity 92%). The laboratory tests reproduced the same sensitivity and specificity as obtained with the point-of-care testing.

The ReEBOV rapid diagnostic test had 100% sensitivity and 92% specificity.

Broadhurst J, Kelly D, Miller A, et al. ReEBOV Antigen Rapid Test kit for point-of-care and laboratory-based testing for Ebola virus disease: a field validation study. *Lancet* 2015; 386: 867–874.

Neurology

Efficacy of antidepressants in adolescents

An influential trial published in 2001 investigating the efficacy and harms of antidepressants in adolescents provided evidence for their positive efficacy. However, some of the conclusions drawn from the study are feared to be 'at odds with the data'. Therefore, the primary data for this trial have now been re-analysed.

The initial study's objective was to compare the safety and efficacy of paroxetine and imipramine with placebo in the treatment of unipolar depression among 275 adolescents. The endpoint measured the proportion of responders with a 50% reduction in the Hamilton depression scale questionnaire score.

Re-analysis revealed that the efficacy of paroxetine and imipramine was not statistically or clinically significantly different from a placebo. Further, there were significantly increased risks of suicidal ideation and suicidal behaviour.

Contrary to the initial trial's findings, re-examination of the data showed neither paroxetine nor high-dose imipramine was efficacious for major depression in adolescents.

Noury L, Nardo M, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015; 351: h4320.

Intravenous versus oral steroids for multiple sclerosis relapses

Multiple sclerosis (MS) is characterised by an inflammatory process in the central nervous system and is associated with relapses. When relapses occur, treatment with high-dose intravenous corticosteroids has proven effective. However, it remains unknown whether oral corticosteroids which are cheaper, simpler and less invasive have equal efficacy.

To assess this, a non-inferiority, randomised trial recruited adults with relapsing-remitting MS who had suffered a recent relapse. Each patient was then randomised to receive either oral or intravenous methylprednisolone, 1000 mg, once daily for 3 days. The primary endpoint measured the proportion of patients who reported improved function by day 28.

Of the 82 patients assigned to the oral group, 66 (81%) achieved the primary outcome, compared with 72 of 90 patients (80%) in the intravenous group, yielding a non-significant treatment difference. Rates of adverse events were similar between the groups.

Oral administration of methylprednisolone was not inferior to intravenous administration for relapses of MS.

Le Page E, Veillard D, Laplaud D, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. *Lancet* 2015; 386: 974–981.

Recurrent intracranial haemorrhage and blood pressure

Intracerebral haemorrhage (ICH) is the most severe form of stroke and survivors are at high risk of recurrent ICH. The control of elevated blood pressure (BP) is the cornerstone of secondary prevention. However, there is limited evidence to show a reduction in BP reduces the incidence of recurrence.

A longitudinal study investigated this further by following over 1100 ICH survivors to monitor their BP and record recurrent ICHs. The authors classified recurrent ICH as either lobar (cortex and white matter) or nonlobar (thalami, basal ganglia, or brainstem).

Results revealed the event rate for lobar ICH was 84 per 1000 person-years among patients with inadequate BP control compared with 49 per 1000 person-years among patients with adequate BP control. The nonlobar ICH event rate was 52 per 1000 person-years with inadequate BP control and this was almost halved in patients with adequate BP control.

Inadequate BP control after an ICH was associated with a higher risk of recurrence.

Biffi A, Anderson D, Battey K, et al. Association between blood pressure control and risk of recurrent intracerebral haemorrhage. *JAMA* 2015; 314: 904–912.

Obstetrics

Antidepressants and persistent pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn (PPHN) is a serious condition resulting in high morbidity and mortality. In 2006 a public health notice warned of an increased risk of PPHN associated with late pregnancy exposure to selective serotonin reuptake inhibitors (SSRIs).

A new study has investigated the risk of PPHN associated with exposure to different antidepressant medications in late pregnancy (90 days before delivery). The researchers conducted a cohort study using data from over 3 million pregnant women across the USA.

A total of 130 000 (3.4%) of the cohort were taking antidepressants in late pregnancy, the majority of whom were prescribed SSRIs. Overall, the rate of infants diagnosed with PPHN and not exposed to antidepressants was 21 per 10 000 births, compared with 32 per 10 000 infants exposed to SSRIs and 29 per 10 000 for non-SSRIs.

There is an increased risk of PPHN associated with maternal use of SSRIs in late pregnancy, however the absolute risk remains small.

Huybrechts F, Bateman T, Palmsten K, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA* 2015; 313: 2142–2151.

Iron supplementation in pregnancy

Anaemia affects most African women during pregnancy and is most commonly due to iron deficiency. By taking iron supplements the risk of anaemia is reduced and is therefore recommended for all women in pregnancy. However, some studies have also suggested that iron supplementation in children can increase the rates of infectious diseases including malaria.

Therefore, a Kenyan trial has assessed the effect of antenatal iron supplementation on both maternal Plasmodium

infection risk and neonatal outcomes. It randomly assigned pregnant women to receive either 60 mg of ferrous fumerate daily (n=237) or placebo (n=233) until 1 month postpartum.

Results showed there was no significant difference in maternal Plasmodium infection risk between the two groups (52% in iron group, 52% in placebo group). However, average birthweight was significantly higher in the iron group (3202 g) compared with the placebo group (3053 g). Iron supplementation also significantly increased maternal mean haemoglobin.

Administration of daily iron supplementation during pregnancy did not alter maternal Plasmodium infection risk.

Mwangi M, Roth J, Smit M, et al. Effect of daily antenatal iron supplementation on Plasmodium infection in Kenyan women: a randomized clinical trial. *JAMA* 2015; 314: 1009–1020.

Predicting postnatal depression

Perinatal depression is a neglected global health priority. It affects 10–15% of women in high-income countries and has a greater burden on low-income countries. However, it is unclear to what extent women diagnosed with perinatal depression have a history of mental health problems prior to conception.

An Australian cohort study has now published research investigating this question. Authors analysed data from biannual mental health status questionnaires from almost 400 pregnant women that spanned from late childhood to after the delivery.

A total of 253 (66%) participants in the cohort had a previous history of a mental health problems. Of these, 117 had pregnancies, and perinatal depressive symptoms were reported in 57 (34%) of these pregnancies. In contrast, 8% of the 201 pregnancies with no preconception history of mental health problems reported perinatal depressive symptoms (odds ratio, 8.36).

Perinatal depressive symptoms are mostly preceded by mental health problems that begin before pregnancy.

Patton C, Romaniuk H, Spry E, et al. Prediction of perinatal depression from adolescence and before conception (VIHCS): 20-year prospective cohort study. *Lancet* 2015; 386: 875–883.

Paediatrics

Time to adrenaline injection in cardiac arrest

Cardiac arrest causing a non-shockable rhythm among children results in a mortality of 25–40%. Adrenaline (epinephrine) is recommended for the management of this paediatric emergency. Although evidence shows that a delay to the first adrenaline dose in an adult cardiac arrest is associated with decreased survival, it is unknown whether this remains true for children.

Therefore, paediatric cardiac arrest data were reviewed from across the USA. All children (<18 years) with a non-shockable rhythm and treated with adrenaline were included. The time to adrenaline administration and the survival to hospital discharge were analysed.

Of the 1558 children suffering cardiac arrest, 487 (31%) survived. The median time to adrenaline administration was 1 minute. A longer time to adrenaline administration was associated with a lower risk of survival to discharge, and decreased chance of a favourable neurological outcome.

A delay in administration of adrenaline to children in cardiac arrest was associated with a decreased survival.

Andersen W, Berg M, Saindon Z, et al. American Heart Association get with the guidelines–resuscitation investigators. Time to epinephrine and survival after paediatric in-hospital cardiac arrest. *JAMA* 2015; 314: 802–810.

Oxygen therapy for severe pneumonia

Developed countries widely use continuous positive airway pressure (CPAP) for children with severe pneumonia which yields favourable outcomes. However, CPAP requires expensive equipment that is often not available in many developing countries. Bubble CPAP (using tubing submerged in water to deliver oxygen) may be a viable and low-cost alternative for low-resource setting.

A recent trial in Bangladesh assessed whether oxygen therapy could be successfully delivered through bubble CPAP for children with severe pneumonia and hypoxaemia. The outcome measured treatment failure (death, mechanical ventilation, intubation, or clinical failure in the CPAP group) compared with oxygen therapy delivered through high- or low-flow nasal cannulas.

Of the 79 children assigned to the bubble CPAP group, only 5 (6%) had treatment failure. A total of 16 (24%) out of 67 who received low-flow oxygen and 10 (13%) of the 79 children who received high-flow oxygen had treatment failure. Significantly fewer children died in the bubble CPAP group than in the high- and low-flow groups.

Bubble CPAP improved the outcomes in children with very severe pneumonia and hypoxaemia.

Chisti J, Salam A, Smith H, et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. *Lancet* 2015; 386: 1057–1065.

Oxygen saturation targets for bronchiolitis

The most common lower respiratory tract infection of early life is viral bronchiolitis. Part of the management includes giving supplementary oxygen. However, the optimal oxygen saturation target to provide the best outcome is disputed.

Therefore, a recent trial assessed whether a target saturation of 90% or higher for oxygen supplementation resulted in equivalent outcomes to a normotoxic (94% or higher) target among infants with bronchiolitis. A total of 615 infants (aged 6 to 52 weeks) diagnosed with viral bronchiolitis were randomised to have either 90% (standard group) or 94% (modified group) target saturations. The primary outcome measured time to resolution of cough.

The median time to cough resolution was 15 days for each group. There were 35 serious adverse events recorded in the standard group compared with 25 in the modified group.

Management of infants with bronchiolitis to an oxygen saturation target of 90% or higher is as safe and effective as one of 94% or higher.

Cunningham S, Rodriguez A, Adams T, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet* 2015; 386: 1041–1048.

Intermittent hypoxaemia and bradycardia in preterm infants

Extremely preterm infants (<28 weeks gestation) experience intermittent hypoxaemia and bradycardia for many weeks after birth. The consequences of these episodes remain undetermined but there may be a link between hypoxaemia or bradycardia and late death or disability. A recent study investigated this hypothesis.

Researchers monitored each of the 1019 infants (gestational age 23–27 weeks) for episodes of hypoxaemia (oxygen saturations <80%) or bradycardia (pulse <80/min) for 10 seconds or longer. The primary outcome was a composite of death, motor impairment, cognitive or language delay, hearing loss, or blindness at 18 months of age.

The primary outcome was present in 414 infants (42.6%). Hypoxaemic episodes were associated with an increased risk of late death or disability

in 56.5% of those infants in the highest decile of hypoxaemic exposure and 37% of those in the lowest decile. Intermittent bradycardia did not add to the risk of an adverse outcome.

Prolonged hypoxaemic episodes in preterm infants were related to adverse 18-month outcomes.

Poets F, Roberts S, Schmidt B, et al. Canadian Oxygen Trial Investigators, 2015. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *JAMA* 2015; 314: 595–603.

Public Health

Sweet drinks and type 2 diabetes

It is now thought that the consumption of sugary and artificially sweetened drinks is likely to increase the likelihood of developing type 2 diabetes and obesity. However, few prospective studies have been conducted on this subject.

Therefore, a systematic review and meta-analysis was performed. The objective was to examine the relationship between consumption of sugar-sweetened drinks, artificially sweetened drinks, and fruit juice with the development of type 2 diabetes. The researchers also adjusted for adiposity.

A total of over 10 million person-years of data analysed from 17 cohort studies. Results demonstrated a higher consumption of sugar-sweetened drinks was associated with 13% greater incidence of type 2 diabetes per one serving/day, even after adjustment for adiposity. For artificially sweetened beverages the incidence rose by 8% per one serving/day. There was no risk increase for fruit juice.

Habitual consumption of sugar-sweetened drinks was associated with a greater incidence of type 2 diabetes, and was independent of adiposity.

Imamura F, O'Connor L, Ye Z, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ* 2015; 351: h3576.

The consequences of banning trans fats

Trans fats are a type of unsaturated fatty acid. Although sometimes produced naturally, they are mostly found in processed foods to prolong shelf-life. However, trans fats increase the risk of mortality from coronary heart disease (CHD), especially among lower socio-economic groups where consumption of trans fats is highest. A recent study published in the BMJ examined the impact of different policies to ban or reduce trans fat consumption on deaths from CHD in England.

A total ban on trans fatty acids in processed foods might prevent or postpone 7200 deaths (2.6%) from CHD from 2015–20 and reduce inequality of mortality from CHD by 15%. Policies to improve labelling or remove trans fats from restaurants would be half as effective. A total ban would have the greatest net cost savings of about £264 million (US$415 million).

Regulatory policy to eliminate trans fatty acids from processed foods in England may reduce deaths from CHD and promote health equality.

Allen K, Pearson-Stuttard J, Hooton W, et al. Potential of trans fats policies to reduce socioeconomic inequalities in mortality from coronary heart disease in England: cost effectiveness modelling study. *BMJ* 2015; 351: 4583.

Interventions promoting hand hygiene

Hand hygiene among healthcare workers is possibly the most effective measure to reduce healthcare-associated infections, but compliance remains poor in many hospitals. In 2005, the World Health Organization (WHO) launched a campaign (WHO-5) to improve hand hygiene in healthcare settings by promoting five interventions. They included: system change, training and education, feedback and observation, reminders, and a hospital safety climate.

To quantify the efficacy of the campaign a systematic review and meta-analysis was conducted. There were considerable data to suggest that WHO-5 improved compliance significantly (odds ratio, 1.35) but could be further improved by goal setting, reward incentives, and accountability. The costs of interventions ranged from US$225-4600 per 100 bed days.

Promotion of the WHO-5 campaign is effective at increasing hand hygiene compliance among healthcare workers.

Luangasanatip N, Hongsuwan M, Limmathurotsaku D, et al. Comparative efficacy of interventions to promote hand hygiene in hospital: systematic review and network meta-analysis. *BMJ* 2015; 351: h3728.

Surgery

Hypothermia to increase kidney-graft function

After kidney transplantation, up to 50% of recipients experience delayed graft function (defined as the requirement for dialysis within 1 week of transplantation). Recently, a randomised trial has investigated whether mild hypothermia in organ donors before organ recovery reduced the rate of delayed graft function.

A total of 370 organ donors were enrolled into the study. They were then randomly assigned to either one of two targeted temperature ranges: 34–35°C (hypothermia) or 36.5–37.5°C (normothermia). The primary outcome was delayed graft function in the kidney recipients.

The study was terminated early due to overwhelming efficacy of hypothermia. Delayed graft function developed in 79 of the 285 kidney recipients in the hypothermia group (28%) compared with 112 out of 287 recipients in the normothermia group (39%). This yielded a significant odds ratio of 0.62.

Mild hypothermia in organ donors significantly reduced the rate of delayed graft function among recipients.

Niemann U, Feiner J, Swain S, et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. *NEJM* 2015; 373: 405–414.

Medical therapy for ureteric colic

Ureteric colic is caused by the smooth muscle contractions in the ureter in response to kidney stones. Most kidney stones will pass spontaneously within 4 weeks so ureteric colic is often managed conservatively. However, smooth muscle relaxant drugs such as tamsulosin and nifedipine may aid stone expulsion.

To test this hypothesis, a UK trial recruited over 1100 adults with confirmed ureteric colic. Participants were assigned to receive either tamsulosin (400 µg, (n=378), nifedipine (30 mg, (n=379), or placebo (n=379) to be taken daily for 4 weeks. The primary outcome measured the proportion of participants who did not need further intervention for stone clearance.

A total of 81% of the participants in the tamsulosin group satisfied the primary outcome compared with 80% in both the nifedipine and placebo groups – an insignificant difference.

Tamsulosin 400 µg and nifedipine 30 mg were not effective at decreasing the need for further interventions for kidney stone clearance.

Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet* 2015; 386: 341–349.

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