

# Cardiology

## Risk factors identified for atrioventricular block

Atrioventricular (AV) block is one of the commonest reasons for pacemaker implantation. The cause of AV block is most often attributed to idiopathic fibrosis of the conduction system. Researchers have now looked closer for any identifiable or modifiable risk factors for AV block. A population based cohort study investigated the incidence of AV block in 6,100 participants. Of these, 8.6% had ECG evidence of conduction disease and 1% had been hospitalised with AV block. Analysis revealed that for every 10mmHg increase in systolic blood pressure there was an associated 22% increased risk of AVN block. Another independent risk factor identified was impaired fasting glucose levels – also found to produce a 22% increased risk of AV block per 20mg/dL rise in fasting glucose levels. These factors remained statistically significant after adjustment for coronary events. The study estimate that 47% and 11% of AV blocks may have been avoided if all participants exhibited ideal blood pressures and normal fasting glucose levels, respectively. Atrioventricular block may be avoided if blood pressure and glucose targets are achieved.

Kerola T, Eranti A, Aro AL, et al. Risk Factors Associated With Atrioventricular Block. *JAMA Netw Open*.2019;2(5):e194176. doi:10.1001/jamanetworkopen.2019.4176

## Antibiotic envelope for implantable cardiac devices

An estimated 1.5 million patients worldwide receive cardiac implantable electronic devices (CIEDs) each year. Despite best surgical practice and the use of various antibiotic prophylaxis strategies, infections associated with their placement remains a rare but major complication. A trial has assessed the safety and efficacy of absorbable, antibiotic-eluting envelopes that encase the devices and if their use as an adjunct can reduce incidence of infection following CIED implantation. Participants due to receive a CIED were randomly assigned to receive the envelope (n=3495) or not (n=3488) and all participants were given standard-of-care infection prophylaxis and followed up for 12

months. The envelope group had a 40% lower incidence of major CIED infections than the standard-of-care alone group. The use of an antibacterial envelope for CIEDs resulted in a significantly lower incidence of major infections than the standard-of-care, without a higher incidence of complications. The authors support the use of an antibiotic-eluting envelope as an adjunct for cardiac implantable electronic devices.

Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial Envelope to Prevent Cardiac Implantable Device Infection. *NEJM* 2019; 380:1895-1905

## Atrial fibrillation ablation and quality of life

Catheter ablation as a means to manage the rhythm control for symptomatic atrial fibrillation is a well-established and successful treatment. Researchers have set out to investigate if catheter ablation is not only symptom improving but if it also improves quality of life versus medical antiarrhythmic drug therapy alone. Participants with paroxysmal or persistent symptomatic atrial fibrillation were randomised to receive pulmonary vein isolation ablation (n=79) or medical therapy with an untested (for the individual) antiarrhythmic drug (n=76). Quality of life was assessed via a health survey given at baseline and at 12 months. Those treated with ablation had significantly improved quality of life survey scores versus the drug therapy alone cohort. The study findings also re-confirmed the significant superiority of ablation in improving the burden of atrial fibrillation versus antiarrhythmic drugs. This study has shown that catheter ablation is an efficacious means of improving disease burden and quality of life in those with atrial fibrillation.

Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA*.2019;321(11):1059–1068. doi:10.1001/jama.2019.0335

## Egg consumption under watch again

The discussion surrounding dietary cholesterol consumption has been controversial for many years. Traditionally, consumption has been viewed negatively for its apparent association with poor cardiovascular health. However, several years ago

health statements were made that seemingly vindicated dietary cholesterol and egg consumption from their association with cardiovascular disease, and sugar consumption had taken over as the main food evil. As a result, advice on dietary inclusion had changed to reflect this. Now to complicate things further, a study has once again found a link between egg consumption and poor cardiovascular health. Self-reported diet data were pooled from nearly 30,000 adults across 6 prospective cohort studies. For each additional 300mg of dietary cholesterol consumed per day, or each additional half egg eaten per day, there was a significantly increased risk of incident cardiovascular disease and all-cause mortality. Among adults in the United States, intake of dietary cholesterol or eggs was associated with cardiovascular disease.

Zhong VW, Van Horn L, Cornelis MC, et al. Associations of Dietary Cholesterol or Egg Consumption With Incident Cardiovascular Disease and Mortality. *JAMA*. 2019;321(11):1081–1095. doi:10.1001/jama.2019.1572

## Task sharing strategies for hypertension

Cardiovascular disease disproportionately burdens low- and middle-income countries. Exacerbating this, there are fewer resources available to help and this is becoming a problem as non-communicable disease become increasingly prevalent. Hypertension is an important risk factor for cardiovascular disease, and importantly, it is modifiable. A meta-analysis has assessed if a task sharing strategy for managing hypertension is efficacious. Task sharing involves the movement of primary care duties to non-physicians who take over some aspects of management, a potentially cost-saving strategy. This research included 31 studies in its meta-analysis where task sharing across different groups of healthcare workers was found to reduce systolic blood pressure. Mean differences were -5.34mmHg with nurses, -8.12mmHg with pharmacists, -4.67mmHg with dietitians, -3.67mmHg with community health workers and -4.85mmHg reduction is systolic blood pressure overall. Task sharing interventions may be an effective strategy in reducing blood pressure in low- and middle-income countries.

Anand TN, Joseph LM, Geetha AV, et al. Task sharing with non-physician health-care

workers for management of blood pressure in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Global Health* 2019; 7(6), pp. e761-e771.

## Obs & Gyn

### Impact of vaccine on cervical cancer

A retrospective cohort study has looked at the efficacy of the bivalent human papillomavirus (HPV) vaccination in Scotland. The study analysed cervical screening results from girls aged 20, born between 1995 and 1996, who had been part of the vaccination programme at aged 12-13. Results were compared with screening results from girls aged 20, born in 1988, who had not received the HPV vaccine. Analysis revealed that routine vaccination with the bivalent HPV vaccine had been associated with a 79% and 89% reduction in cervical intraepithelial neoplasia (CIN) grade 1 and CIN grade 3, respectively, compared with those who had not received the vaccine. The study also revealed that a younger age at immunisation harnessed greater vaccine efficacy. Additionally, there was evidence of herd immunity among unvaccinated women. The authors argue that these findings should act as encouragement to implement HPV vaccine programmes in countries not already doing so, and especially in countries where cervical screening programmes do not exist.

Palmer T, Wallace L, Pollock K, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. *BMJ* 2019; 365 :l1161

### Pre-eclampsia and chronic kidney disease

Pre-eclampsia is a potentially dangerous condition that can complicate pregnancies but usually resolves soon after delivery. However, there may be long term complications and we know from existing literature that pre-eclampsia may be associated with development of chronic kidney disease but results from studies have been highly variable. A study based in Denmark has assessed rates of kidney disease between women with and without a history of pre-eclampsia in pregnancies reaching at least 20 weeks' gestation. Overall, women with history of pre-eclampsia were at higher risk of developing chronic

renal conditions, even after adjusting for cardiovascular disease and hypertension. Chronic, glomerular and hypertensive kidney disease was most strongly associated with pre-eclampsia. The association was particularly strong for early pre-term pre-eclampsia (<34 weeks). By contrast, pre-eclampsia was only modestly associated with acute renal conditions. Chronic renal condition associations were most often found within 5 years of last pregnancy. The Authors urge further research to determine which women are at risk of long term problems and what follow up would be appropriate for these women.

Kristensen JH, Basit S, Wohlfahrt J, et al. Pre-eclampsia and risk of later kidney disease: nationwide cohort study. *BMJ* 2019; 365 :l1516

### Breast cancer in transgender women

Breast cancer is the commonest malignancy in females - in men it is rare and the pattern of breast cancer type is different. It is important to consider the effects that hormonal therapy may have on the development of breast cancer in those who take it - a common practice for transgender women (assigned male at birth) as a means of gender affirming therapy. New research has looked at the incidence and patterns of breast cancer within the transgender populations to assess if hormonal therapies alter the risk of breast cancer in transgender women. The study indeed found an increased risk of breast cancer in transgender women compared to cisgender men (assigned male at birth and remain male). There was a lower risk of breast cancer in transgender men compared to cisgender women. In transgender women the pattern of breast cancer was typically more 'female' with ductal, oestrogen, progesterone and human epidermal growth factor 2 positive cancers. The authors suggest that standard breast cancer screening programmes may be sufficient for inclusion of transgender people using hormonal treatments.

de Blok CJM, Wiepjes CM, et al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands. *BMJ* 2019; 365 :l1652

### Progesterone and early pregnancy bleeding

Miscarriage affects one in five pregnancies and is most common in the first twelve weeks. Bleeding in

early pregnancy is often associated with pregnancy loss. Progesterone is considered a 'pro-pregnancy' hormone as its endogenous production is essential for the maintenance of pregnancy. Some studies have suggested that exogenous progesterone therapy may improve pregnancy outcomes in women with bleeding in early pregnancy. A randomised, double-blind, placebo-controlled trial has added to this conversation. Women with vaginal bleeding in early pregnancy were randomised to receive vaginal suppositories containing either 400mg of progesterone (n=2079) or placebo (n=2074) twice daily from time of bleeding to 16 weeks' gestation. There was no significant difference in outcome of pregnancy found between the two groups, with 75% live births after 34 weeks' gestation in the progesterone group and 72% in the placebo group. Neither was there any difference in adverse events between the groups. Progesterone did not improve outcomes for women with early pregnancy bleeding.

Coomarasamy A, Devall AJ, Versha C, et al. A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy. *NEJM* 2019; 380:1815-1824

### Systematic lymphadenectomy in ovarian cancer

A randomised trial has investigated if there is any benefit from systematically removing pelvic and paraaortic lymph nodes during operations in women undergoing surgery for advanced ovarian cancer. Participants with macroscopic complete resection of cancer with normal nodes before and during surgery were intraoperatively randomly assigned to undergo lymphadenectomy (n=323) or not (n=324). There were no significant differences found in median overall survival between groups - with a survival of 69.2 months with no lymphadenectomy and 65.5 months with lymphadenectomy. Median progression-free survival was the same in both groups (25 months). However, serious post-operative complications were significantly more frequent in the lymphadenectomy group with 12% requiring repeat laparotomy versus 6%. In this study, patients with macroscopically complete resection of advanced ovarian cancer and clinically negative lymph nodes did not benefit from lymphadenectomy - which was actually found to have

higher complication rates than no lymphadenectomy.

Harter P, Sehouli J, Lorusso D, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. *NEJM* 2019; 380:822-832

## Paediatrics

### Outcomes with normal Apgar scores

The Apgar score is a well established screening tool used to assess the health status of new-borns at 1, 5, and 10 minutes of life - with a maximum score of 10 indicating good health. Scores of 7 and above are considered normal and those below 7 are associated with neonatal morbidity. A population based cohort study has now looked at outcomes of infants scoring within the normal range and born without malformation at-term in Sweden. Infants selected had Apgar scores of  $\geq 7$  at 1, 5, and 10 minutes. Outcomes of infants scoring 7, 8 or 9 were compared with those scoring 10 at the specified time points. Infants with lower-end normal scores were associated with higher rates of neonatal infection, mortality, and asphyxia related complications versus infants scoring 10. There were also worse outcomes seen in infants scoring 10 at five minutes falling to 9 or below at ten minutes, versus those scoring 10 steadily. The study concludes that it is optimal for infants to score 10 at each time point.

Razaz N, Cnattingius S, Joseph KS. Association between Apgar scores of 7 to 9 and neonatal mortality and morbidity: population based cohort study of term infants in Sweden. *BMJ* 2019; 365:l1656

### Repeat prenatal corticosteroids in preterm labour

Preterm infants are at risk of respiratory distress and long term neurological consequences. Maternal corticosteroids are given to women who are expected to undergo preterm labour to help mature the lungs of infants and reduce adverse outcome associated with preterm birth. In women who are deemed at risk of preterm birth and given corticosteroids, but who do not progress to delivery, the benefit of additional corticosteroids remain unclear. Researchers have pooled data from eleven trials to assess the outcomes of mothers and infants at risk of preterm birth who have been given multiple doses of corticosteroids. The study found that repeat prenatal corticoste-

roids given to women at ongoing risk of preterm birth reduced risk of infants needing respiratory support. However, body size measurements were lower in infants exposed to repeat prenatal doses. The authors suggest significant clinical benefit may be provided with the least effect on infant growth when repeat doses are limited to a maximum of three doses with the total dose of corticosteroids not exceeding 48mg.

Crowther CA, Middleton PF, Voysey M, et al. (2019) Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: An individual participant data meta-analysis. *PLoS Med* 16(4): e1002771.

### Breastfeeding protective against pollution

There is independent evidence for association between both breastfeeding and ambient air pollution on the respiratory health of children. A study has now investigated if breastfeeding might mitigate the effect that ambient air pollution has on child respiratory health. The study involved over 6,700 Chinese children, aged 7-14 years. Breastfeeding was considered when given for longer than 3 months via self-report from mothers. Lung function was assessed with spirometers and considered impaired when forced vital capacity was less than 85%, forced expiratory volume in one second was less than 85%, and peak expiratory flow less than 75%. Of the participants included, 70% were breastfed in infancy. By ages 7-14, exposure to higher concentration of air pollution was associated with higher rates of lung function impairment in the children who had not been breastfed. These findings support the notion of a protective effect of breastfeeding on respiratory health in breastfed children exposed to air pollution.

Zhang C, Guo Y, Xiao X, et al. Association of Breastfeeding and Air Pollution Exposure With Lung Function in Chinese Children. *JAMA Netw Open*. 2019;2(5):e194186. doi:10.1001/jamanetworkopen.2019.4186

### Prenatal exposure to benzodiazepines

The use of benzodiazepines and z-hypnotics in pregnancy is controversial and there is unclear evidence on the long term sequelae for children exposed to these drugs whilst in utero. A study has set out to quantify any association of motor, communication, and attention-deficit/hyperactivity disorder (ADHD) outcomes in children exposed to these

drug groups in utero. Mother-child dyads (n=36,086 children, 0.8% of which had exposure in utero) were followed up throughout pregnancy until the child reached 5 years old. The researchers found moderate association between drug exposure in late pregnancy and greater gross motor and communication deficits in children born to women with depressive and anxiety disorders. These impairments were not considered clinically relevant. There was no increased risk for ADHD symptoms or fine motor impairments. The study has ongoing follow-up in teenagers which may be able to shed some more light on outcomes of children with prenatal exposure to benzodiazepines and z-hypnotics.

Lupattelli A, Chambers CD, Bandoli G, Association of Maternal Use of Benzodiazepines and Z-Hypnotics During Pregnancy With Motor and Communication Skills and Attention-Deficit/Hyperactivity Disorder Symptoms in Preschoolers. *JAMA Netw Open*. 2019;2(4):e191435.

### Alternative for second-line cessation of status epilepticus

Convulsive status epilepticus is one of the commonest paediatric emergencies worldwide. In the UK, following benzodiazepines as first-line management, phenytoin is the recommended standard second-line intravenous anticonvulsant given to help terminate status. However, existing data suggests that phenytoin has a relatively poor safety profile. A study has now compared the use of levetiracetam as a second line treatment with phenytoin. This randomised open-label clinical trial was performed across 30 emergency departments in the UK and included participants aged 6 months to 18 years. The study found convulsive status was terminated in 70% of children given levetiracetam versus 64% given phenytoin second line. There was no significant difference between time taken for cessation of status between groups. Whilst levetiracetam was not significantly superior to phenytoin, these results, combined with existing data on its relatively better safety profile, suggest levetiracetam could be an appropriate alternative for use as a second-line anticonvulsant in paediatric status epilepticus.

Lyttle M, Rainford N, Gamble C, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (ECLIPSE): a multicentre, open-label, randomised trial. *The Lancet* 2019; 393:2125-2134

## Misc

### Extended venous thromboembolism prophylaxis

Hospital stay for medical illness increases risk of venous thromboembolism (VTE). Thromboprophylaxis may be given until discharge to combat this. However, the risk of VTE remains increased in the period after discharge from hospital. In some cases patients are given extended-duration thromboprophylaxis (EDT) to carry on for a short period following discharge but there are increased financial costs and risks associated with bleeding events. A meta-analysis has now assessed the safety and efficacy of EDT on post-discharge risk of VTE. Across 5 randomised controlled trials, including over 40,000 patients, EDT of 4-6 weeks post-discharge was compared with VTE results from control cohorts. The use of EDT for 4-6 weeks post-discharge was found to significantly reduce the burden of VTE. However, this was considered at the expense of major or fatal bleeding events, also significantly associated with EDT. Whilst the number needed to treat with EDT for VTE was stronger than the number needed to harm via fatal bleeding events, the researchers urge further investigation into defining risks and benefits of extended VTE prophylaxis.

Bajaj NS, Vaduganathan M, Qamar A, et al. (2019) Extended prophylaxis for venous thromboembolism after hospitalization for medical illness: A trial sequential and cumulative meta-analysis. *PLoS Med* 16(4): e1002797.

### Purposeful life and mortality

There is a growing body of literature suggesting that a strong sense of purpose in life leads to both physical and mental health benefits. A study has now investigated the link between feelings of a purposeful life and mortality. Researchers have assessed if there is any association via the United States Health and Retirement Study which includes data from nearly 7,000 participants aged 50 and older. Feelings of life purpose were assessed using a 7-item questionnaire and participants were followed up for all-cause and specific-cause mortality. Higher scores in the questionnaire indicated greater purpose in life. Analysis revealed that stronger purpose in life was associated with decreased mortality. Specific-cause mortality associations were also

found with heart, circulatory and blood conditions. The authors urge that future research should focus on evaluating the effect of life purpose enhancing interventions on health outcomes and mortality and in addition further research should be sought to understand any biological mechanisms at play.

Alimujiang A, Wiensch A, Boss J, et al. Association Between Life Purpose and Mortality Among US Adults Older Than 50 Years. *JAMA Netw Open*. 2019;2(5):e194270. doi:10.1001/jamanetworkopen.2019.4270

### Vaccination to reduce anogenital cancer

The human papillomavirus genotype 16 (HPV16) is linked with the development of anal cancer in the population of men who have sex with men (MSM). In the Netherlands, the prevalence of anal cancer among MSM is similar to the rate of cervical cancer among adult women. There are worldwide anti-HPV vaccination programmes for young girls, ideally given before start of sexual activity. Boys and men, however, are often not invited for vaccination. This is true in the Netherlands where a research group has compiled a computer model to assess the potential efficacy of introducing the HPV vaccine to the male population. The models predicted that targeted vaccination given to at-risk MSM groups could reduce anogenital HPV16 infection by 30%. The benefit was estimated to be even greater when given in a sex-neutral manner to 12 year old boys at the same time as their female counterparts, reducing infection by up to 75%. This study supports inclusion of boys and men in HPV vaccination programmes.

Bogaards JA, Mooij SH, Xiridou M, Schim van der Loeff MF (2019) Potential effectiveness of prophylactic HPV immunization for men who have sex with men in the Netherlands: A multi-model approach. *PLoS Med* 16(3): e1002756.

### β-blockers for compensated liver cirrhosis

Decompensated liver cirrhosis carries a high level of morbidity and mortality. This stage of the disease is characterised by ascites, encephalopathy and bleeding associated with portal hypertension. A landmark study has found that through long term use of β-blockers the progression from compensated to decompensated cirrhosis in patients with clinically significant portal hypertension (CSPH =  $\geq 10$ mmHg portal pressure gradient) can be reduced. This double-blind randomised controlled trial was set across eight

hospitals in Spain. Participants with compensated cirrhosis and CSPH were either given non-selective β-blockers (propranolol or carvedilol) (n=100) or placebo (n=101) and followed up for 37 months. Those given β-blockers had a significantly reduced incidence of decompensation or death versus the placebo control group (16% versus 27%, respectively). These results were linked with a significantly reduced incidence of ascites. In this landmark study, β-blockers were found to increase decompensation-free survival in patients with compensated cirrhosis and CSPH, potentially through mediating the development of ascites. The authors suggest routine assessment of CSPH in this patient group.

Villanueva C, Albillos A, Genesca J, et al. β-blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet* 2019; 393:1597:1608.

### Mindfulness-based cognitive training for surgeons

The job of a physician can be stressful and adequate coping mechanisms are required to prevent burnout and the more severe personal consequences seen in physician burnout, including suicide. A pilot study has investigated if mindfulness-based meditation can improve stress, wellbeing and performance amongst surgeons. Participants were postgraduate year 1 surgical residents (n=21) at the University of California, San Francisco. Weekly 2-hour mindfulness-based stress reduction classes were given to the participants who were also required to take up an additional 20 minutes of daily home practice over an 8-week period. Psychological wellbeing was assessed via an online survey, executive function was assessed via tasks testing 6 cognitive domains, and motor skills were evaluated with two laparoscopic skills tasks. The results from this pilot survey showed higher mindfulness, lower stress, better executive function scores, and faster motor skills in the residents following the 8 week course. The findings from this study support the use of mindfulness based practices to help improve cognitive coping strategies in physicians.

Lebares CC, Guvva EV, Oлару M, et al. Efficacy of Mindfulness-Based Cognitive Training in Surgery: Additional Analysis of the Mindful Surgeon Pilot Randomized Clinical Trial. *JAMA Netw Open*. 2019;2(5):e194108. doi:10.1001/jamanetworkopen.2019.4108