GP Research Review™

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In this issue:

Cardiology Research Review™

Reducing risk in coronary artery disease. Are Australian patients in general practice achieving targets? The Coronary Artery Disease in general practice study (CADENCE)

Authors: Driscoll A et al

Summary: This Australian study investigated general practitioners' perception and management of risk factors in patients with chronic stable angina in primary care. 2031 consecutive stable angina patients were recruited by 207 GPs who documented their risk factors and reported if they were optimally controlled. Based upon national guidelines, recommended targets were achieved in 60% of patients for blood pressure, 24% for body mass index, 23% for waist circumference, 17% for lipid profiles and 54% of diabetics for haemoglobin A1c. However, GPs perceived risk factors to be 'optimally controlled' in 86% of patients for blood pressure, 44% for weight, 70% for lipids and 60% for haemoglobin A1c. In conclusion, cardiovascular risk factor control was frequently suboptimal in primary care despite being perceived by the GPs to be satisfactory.

Comment: Aggressive risk factor modification is important in patients with established vascular disease to try and prevent progression and events. This Australian study suggests that we overestimate our attainment of targets, and that there is significant room for improvement, particularly for control of blood pressure, diabetes and lipids, where there are effective treatments that are far less dependent on patient lifestyle factors than BMI and waist circumference.

Reference: Internal Med J 2013;43(5):526-531
http://onlinelibrary.wiley.com/doi/10.1111/j.1445-5994.2012.02929.x/abstract

Comparison of bleeding complications and one-year survival of low molecular weight heparin versus unfractioned heparin for acute myocardial infarction in elderly patients. The FAST-MI registry

Authors: Puymirat E et al

Summary: This study compared the use of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) in the management of acute MI in elderly patients (≥75 years). 963 consecutive patients with acute MI admitted to an intensive care unit <48h from symptom onset were included. The impact of LMWH on bleeding, the need for blood transfusion and 1-year survival was assessed. Major bleeding (2.4% vs 6.1%; p=0.004) and blood transfusions (4.6% vs 9.7%; p=0.002) were less frequent with LMWH than with UFH, even after multivariate adjustment. One-year survival, and stroke and reinfarction-free survival, were also significantly better with LMWH (odds ratios 0.66 and 0.71, respectively). In conclusion, use of LMWH is associated with less bleeding, less need for transfusion, and better survival than UFH in elderly patients admitted for acute MI.

Comment: In Australia, enoxaparin has largely replaced unfractionated heparin as the anticoagulant of choice in the management of ACS, with similar or better short and long term outcomes and less bleeding. It is reassuring to see that these benefits are maintained in elderly patients with ACS, so that Clexane can be used with confidence in this group of patients in whom this condition is not uncommon.

Reference: Int J Cardiol 2013;166(1):106-110
http://tinyurl.com/jvogfrc

Cardiology Research Review™

Vernakalant: conversion of atrial fibrillation in patients with ischemic heart disease

Authors: Torp-Pedersen C et al

Summary: This study investigated the efficacy and safety of intravenous vernakalant for the conversion of AF to sinus rhythm in patients with a history of ischaemic heart disease (IHD). The efficacy analysis included patients with recent onset AF, while the safety analysis included all patients with AF or atrial flutter who were exposed to the drug. 1052 patients were included in the analysis (274 with a history of IHD and 778 without IHD). Conversion of AF to sinus rhythm was not affected by IHD: in patients with recent onset AF the placebo-adjusted conversion rate with vernakalant was 45.7% in patients with IHD and 47.3% in patients without IHD. The rate of treatment-emergent serious adverse events and discontinuations did not differ between IHD and non-IHD groups in the 24 hours after treatment. No cases of torsades de pointes, ventricular fibrillation, or death were reported in patients with IHD.

Comment: Vernakalant is an atrial specific IV anti-arrhythmic that has been shown to revert up to 50% of patients with recent onset AF (<7 days). This study shows that it is as effective in patients with IHD as those without but unfortunately this drug is unavailable in Australia, and there are no longer plans to apply for registration here.

Reference: Int J Cardiol 2013;166(1):147-151
http://tinyurl.com/kguhh2a

High-sensitivity cardiac troponin T levels and secondary events in outpatients with coronary heart disease from the Heart and Soul Study

Authors: Beatty A et al

Summary: This study determined the association between high-sensitivity cardiac troponin T (hsTnT) levels and structural and functional measures of heart disease in patients with CHD. 984 patients with CHD had serum hsTnT levels measured and underwent exercise treadmill testing with stress echocardiography before being followed up for a median of 8.2 years. Higher hsTnT levels at baseline were associated with greater inducible ischaemia and worse left ventricular ejection fraction, left atrial function, diastolic function, left ventricular mass, and treadmill exercise capacity. 32.2% of patients had a cardiovascular event during follow-up. After adjustment for confounding factors, each doubling in hsTnT level was associated with a 37% increase in cardiovascular events (hazard ratio, 1.37; p=0.001). In conclusion, higher hsTnT levels were independently predictive of secondary events in outpatients with stable CHD.

Comment: Chronic elevation of hsTnT in patients after a primary cardiac event has been associated with a greater risk of secondary events but the strength and magnitude of the association has not been well documented. This study shows that an elevated hsTnT is associated with cardiac structural and functional abnormalities and quantifies the risk of secondary events in this population, but before it should be routinely included as a marker for increased risk, a confirmatory study showing incremental value should be done.

Reference: JAMA Intern Med 2013;173(9):763-769
http://archinte.jamanetwork.com/article.aspx?articleid=1675872

Abbreviations used in this Cardiology Update

LMWH = low molecular weight heparin
UFH = unfractionated heparin
IHD = ischaemic heart disease
hsTnT = high sensitivity cardiac troponin

Independent commentary by Associate Professor John Amerena, Cardiologist and Director of the Geelong Cardiology Research Unit.

The efficacy and safety of ezetimibe/simvastatin combination compared with intensified lipid-lowering treatment strategies in diabetic subjects with and without metabolic syndrome

Authors: Jimenez JG et al

Summary: This *post hoc* analysis of data from a 6-week study of patients with CV disease, diabetes, an LDL cholesterol level 70–160 mg/dL and with (n=617) or without (n=191) metabolic syndrome assessed the consistency of effect associated with switching from baseline simvastatin 20mg or atorvastatin 10mg to ezetimibe/simvastatin 10/20mg compared with doubling the baseline statin dose or switching to rosuvastatin 10mg. Participants with and without metabolic syndrome had greater mean percent changes in LDL cholesterol level after switching to ezetimibe/simvastatin compared with doubling the baseline statin dose (–22.49% vs. –9.64% and –25.14% vs. –4.75%, respectively); the respective mean percent changes associated with switching to rosuvastatin were –19.20% and –19.75%. Compared with doubling the baseline statin dose, switching to ezetimibe/simvastatin also reduced total cholesterol and apolipoprotein B levels in participants with and without metabolic syndrome; HDL cholesterol and apolipoprotein A1 levels were not significantly affected. The safety profiles were similar across the groups.

Comment: A major therapeutic question is the stepwise process of increasing medications when targets are not being achieved – to increase dose or change medication? This was a small, short duration study in patients with diabetes and CV disease. The initial study group were on simvastatin 20mg or atorvastatin 10mg, and after a run-in period were changed to ezetimibe/simvastatin, doubling of the statin itself or change to the more potent drug, rosuvastatin. The study actually focused on the metabolic syndrome status of the patients and the efficacy of statins. Metabolic syndrome status did not affect the response to the lipid-lowering agents. Adding ezetimibe or rosuvastatin had very appreciable favourable effects on LDL cholesterol levels, which were considerably greater than simply doubling the dose of the run-in statin. This is a somewhat interesting study in terms of the efficacy of ezetimibe; however, of course, long-term CV outcomes are the endpoint of real interest.

Reference: Diabetes Obes Metab 2013;15(6):513–22
http://onlinelibrary.wiley.com/doi/10.1111/dom.12059/abstract

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor gemigliptin compared with sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone

Authors: Rhee EJ et al, Gemigliptin Study 006 Group

Summary: Asian patients with type 2 diabetes inadequately controlled with metformin (n=425) were randomly allocated to receive add-on gemigliptin 50mg once daily or 25mg twice daily or sitagliptin 100mg once daily for 24 weeks. Noninferiority was seen between gemigliptin 50mg once daily and sitagliptin for reduction in Hb_{A1c} (–0.77% and –0.8%, respectively) and among all three arms for the proportions of participants achieving Hb_{A1c} <7% (48.87–54.07%). Gemigliptin therapy also resulted in significant decreases in fasting plasma glucose level, postprandial glucose level and glucose AUC_{0-2h}, and increases in glucagon-like peptide-1 level and β-cell sensitivity to glucose. Adverse events were comparable between gemigliptin and sitagliptin.

Comment: Gemigliptin was originally developed as LC15-0444 by LG Life Sciences who were joined by Double-Crane Pharmaceutical Company in 2010 to market the drug in Asia with the cute name of Zemiglo. So as a new dipeptidyl peptidase-4 inhibitor, it was compared against sitagliptin, the original Merck product, which was approved by the US FDA in 2006. The study was conducted in 425 Asian patients with type 2 diabetes inadequately controlled by metformin. The target population is obviously of considerable relevance in Australia. Over the 24-week period of the study, Hb_{A1c} fell from an initial value of around 8% and plateaued at about 7.2%, with no sign of tolerance or rebound, and approximately equal responses to gemigliptin and sitagliptin. Adverse effects were about the same for both drugs, but at the somewhat high rate of 50%, although the majority of these resolved. The study reinforces the efficacy of dipeptidyl peptidase-4 inhibitors and provides alternative molecules potentially for different patients.

Reference: Diabetes Obes Metab 2013;15(6):523–30
http://onlinelibrary.wiley.com/doi/10.1111/dom.12060/abstract

Neck circumference as a simple tool for identifying the metabolic syndrome and insulin resistance

Authors: Stabe C et al

Summary: This research explored the clinical significance of neck circumference to metabolic syndrome and insulin resistance in 301 men and 752 women with BMI 18.5–40.0 kg/m^2 (mean age 39.4 years), including 306 (34% male) with type 2 diabetes. In both men and women, neck circumference was significantly positively correlated with a number of anthropometric measurements and metabolic syndrome risk factors, including waist circumference, BMI, visceral fat, triglyceride level, fasting glucose level, fasting insulin level and homeostatic model assessment of insulin resistance, and significantly negatively associated with HDL cholesterol level and moderately negatively associated with insulin sensitivity. Neck circumference was associated with the largest AUC for insulin resistance in women ($p<0.001$) and a large AUC for metabolic syndrome in both sexes.

Comment: This was a study of a novel anthropomorphic measurement, being neck circumference, and its association with metabolic syndrome and diabetes. Although there has been a focus on abdominal fat and its pro-inflammatory role, there is also evidence for an impact of upper bodyfat. In passing, epicardial fat verges on the toxic, so basically fat and perhaps ectopic fat is a particularly sinister biochemical reservoir. Neck circumference correlated 50% with visceral fat and similarly 50% with waist circumference. The (negative) correlation with insulin sensitivity was modest in magnitude, but highly statistically significant. It is possible in our diverse community that measurements of neck circumference might be more culturally accessible and acceptable, yet still yield useful medical information.

Reference: Clin Endocrinol 2013;78(6):874–81
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2012.04487.x/abstract

Depression, obesity, and smoking were independently associated with inadequate glycemic control in patients with type 1 diabetes

Authors: Melin EO et al

Summary: The associations between inadequate glycaemic control of diabetes and psychological, anthropometric and lifestyle variables were explored in 292 adults with type 1 diabetes. Independent predictors of Hb_{A1c} >8.6% included self-reported depression (adjusted odds ratio 4.8; 19.8 for women), obesity (4.3; 7.0 for women) and smoking (3.0; 4.2 for men). Associations between Hb_{A1c}>8.6% and alexithymia, antidepressant medication and physical inactivity were evident only on bivariate analysis. Associations were also seen between self-reported depression and alexithymia, self-rated anxiety, physical inactivity and absence of abdominal obesity.

Comment: This Scandinavian study investigated interactions between mental health or state of well-being and glycaemic status in subjects with type 1 diabetes. The burden of having and managing type 1 diabetes on a never-ending basis is enough to cause a serious mental impact, but there are also factors such as high circulating cytokines that may implicate a causative association. The study involved 300 patients with type 1 diabetes, with assessments using self-reporting instruments and biochemical measurements. Depression was associated with Hb_{A1c} >8.6%, and the association was as strong as for obesity and smoking. Clearly, psychological aspects as well as the usual factors should be addressed in getting type 1 diabetes patients to Hb_{A1c} goals.

Reference: Eur J Endocrinol 2013;168(6):861–9
http://www.eje-online.org/content/168/6/861.abstract

Abbreviations used in this Diabetes Update

AUC = area under the receiver operating characteristic curve
BMI = body mass index
CV = cardiovascular
HbA1c = glycosylated haemoglobin

Independent commentary by Professor Peter Little, Head of Pharmacy and Leader, Diabetes Complications Group, Health Innovations Research Institute at RMIT University, Bundoora, Victoria. Peter is a past national President of Diabetes Australia.

Allergy Research Review™

Poor air quality in classrooms related to asthma and rhinitis in primary schoolchildren of the French 6 Cities Study

Authors: Hermelingmeier KE et al

Summary: To investigate indoor air quality and asthma/allergies of schoolchildren this study assessed 401 randomly chosen classrooms in 108 primary schools attended by 6590 children. Assessment included skin prick testing for common allergens and screening for exercise-induced asthma. The authors reported approximately 30% of children were highly exposed to poor air quality in classrooms. Past year rhinoconjunctivitis was significantly associated with high levels of formaldehyde and there was an increase in the prevalence of past year asthma in classrooms with high levels of acrolein, nitrogen dioxide and fine particles with aerodynamic diameter ≤2.5 µm.

Comment: At first glance this study appears as solid evidence that childhood exposure within an urban, developed and modern society is a major contributing factor to atopic and airway diseases. There is certainly evidence from experimental and epidemiological data to support the relationship of the pollutants assessed here and allergic disease. It is not unsurprising to see the relationship with the particulate, aldehyde and acrolein exposure high in those with allergic asthma and rhinitis. The study, however, also demonstrates a protective effect of formaldehyde and acrolein for asthma in the non-allergic and thus one should not be too quick to assume that this 5 day air sampling and thorough clinical assessment is the ultimate link. Nonetheless disturbing and perhaps the only reassurance for our children is that most French schools are not mechanically ventilated compared to the air conditioned classrooms of Australia.

Reference: Thorax 2012 Aug;67(8):682-8
http://tinyurl.com/l47x5el

Abbreviations used in this Allergy Update

HDM SIT = house dust mite specific immunotherapy

SNI –= saline nasal irrigation

AR = allergic rhinitis

Repeated low-dose intradermal allergen injection suppresses allergen-induced cutaneous late responses

Authors: Rotiroti G et al

Summary: To investigate the effect of low-dose intradermal grass pollen administration on cutaneous reactivity to allergen, 30 adults sensitised to grass and tree pollens were randomised into 3 treatment groups: 6 fortnightly intradermal injections of grass pollen extract; 2 intradermal injections separated by 10 weeks; or a single intradermal injection at 10 weeks. Following treatment the participants were assessed for cutaneous early and late responses after double-blind intradermal injection with grass and birch pollen. The team observed significantly smaller cutaneous late responses to grass pollen in the treatment group that received 6 fortnightly intradermal grass pollen injections compared to the control groups that received 2 injections separated by 10 weeks ($P < .01$) or a single injection ($P < .001$). Early responses were equivalent in all groups. The team also observed induction of grass pollen-specific IgG antibodies in the treatment group.

Comment: This is an impressive study from Steve Durham's group. The 90%+ inhibition of delayed or late phase responses to allergen after low dose exposure is convincing as it was both allergen specific and assessed on the patient's arm and back with similar responses. The IgG induction confirms the systemic response. Such data is evidence for the influence of dermal/epidermal dendritic cells on inducing such a tolerogenic response. In comparison, the same group's work on sublingual and 20,000 fold increased doses only produced a 40% reduction in late phase responses. The speculation raised by such data suggests the potential for a low dose intradermal route (cf subcutaneous) with patches rather than injections and the complete falsity of 'home made' sublingual treatments.

Reference: J Allergy Clin Immunol 2012;130(4):918-24
http://tinyurl.com/lwferah

Independent commentary by A/Prof. Richard J Harvey, a dedicated rhinologist (nose, sinus, allergy and endoscopic sinus and skull base surgery) at St Vincent's Hospital in Sydney. He is the Head of Rhinology & Skull Base Surgery at the Applied Medical Research Center of UNSW and is A/Professor at both the University of NSW and Macquarie University.

Rheumatology Research Review™

Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis

Authors: Heijstek MW et al

Summary: This study investigated whether measles-mumps-rubella (MMR) booster vaccination affects disease activity in patients with juvenile idiopathic arthritis (JIA). The trial included 137 patients with JIA aged 4–9 years who were recruited from 5 academic hospitals in the Netherlands between May 2008 and July 2011. Patients were randomised to receive MMR booster vaccination (n=68) or no vaccination (controls; n=69). Disease activity was measured by the Juvenile Arthritis Disease Activity Score (JADAS-27), ranging from 0 (no activity) to 57 (high activity). Disease activity during the 12-month follow-up did not differ between 63 revaccinated patients (JADAS-27, 2.8) and 68 controls (JADAS-27, 2.4). At 12 months, seroprotection rates were higher in revaccinated patients than in controls (measles, 100% vs 92%; mumps, 97% vs 81%; and rubella, 100% vs 94%, respectively), as were antibody concentrations against measles (1.63 vs 0.78 IU/mL; p=0.03), mumps (168 vs 104 RU/mL; p=0.03), and rubella (69 vs 45 IU/mL; p=0.01).

Comment: Trust the Dutch to get their act organised. Does vaccination make arthritis worse and does therapy stop humoral response? The answer to the first question is a clear no for JIA but the second remains opaque in this study, although it is becoming clearer in adult RA. We should vaccinate prior to putting them on nearly any therapy.

Reference: JAMA 2013;309(23):2449-56
http://tinyurl.com/mh4uqdo

Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the Abatacept Clinical Trial Program

Authors: Weinblatt ME et al

Summary: This analysis of pooled data from 8 clinical trials of intravenous (IV) abatacept in rheumatoid arthritis (RA) assessed safety events over short-term (duration ≤12 months) and cumulative (short-term plus long-term extensions) abatacept treatment periods. The short-term periods involved 3173 IV abatacept-treated patients with 2331 patient-years of exposure; the cumulative period comprised 4149 IV abatacept-treated patients with 12,132 patient-years of exposure. Incidence rates per 100 patient-years for serious infections were low and consistent over time (3.68 for abatacept vs 2.60 for placebo during the short-term, and 2.87 for abatacept during the cumulative period). Hospitalised infections were generally similar to external RA patient cohorts and were consistent over time. Incidence rates of malignancies were similar for abatacept- and placebo-treated patients during the short-term period (0.73 vs 0.59) and remained low during the abatacept cumulative period (0.73). Standardised incidence ratios of some tissue-specific malignancies (e.g., colorectal and breast) in the cumulative period tended to be lower, while others (lymphoma and lung) tended to be higher, compared with the general population; however, incidence rates were comparable with RA cohorts. Autoimmune events were rare and infusion reactions uncommon.

Comment: I think the jury would probably conclude that abatacept has a lower risk of infection and this data supports that with a rate only slightly higher than placebo (plus methotrexate). The cancer data and autoimmunity are also very reassuring.

Reference: J Rheumatol 2013;40(6):787-97
http://jrheum.org/content/40/6/787.abstract

Abbreviations used in this Rhematology Update

MMR = measles-mumps-rubella
JIA = juvenile idiopathic arthritis
JADAS = juvenile arthritis disease activity score
RA = rheumatoid arthritis
IV = intravenous

Independent commentary by Professor Graeme Jones, Professor of Rheumatology and Epidemiology and Head of the Musculoskeletal Unit at the Menzies Research Institute as well as Head of the Department of Rheumatology at Royal Hobart Hospital. He is also the Medical Director of the Arthritis Foundation of Australia.

