

Cardiology Research Review

Making Education Easy

Issue 21 – 2009

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Welcome to the May edition of NZ Cardiology Research

Review, with summaries and editorial comment for newly published research from a wide spectrum of the cardiology world. Colleagues' interpretations of study results will of course vary and readers' comments are always welcome – important new insights will certainly be passed on in future issues.

Kind regards,

Dr Stewart Mann

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TIPS on how a polypill might work

Authors: The Indian Polycap Study (TIPS) Group

Summary: This multicentre, double-blind study investigated the efficacy of a polypill (Polycap) in subjects without cardiovascular disease. 2053 participants aged 45–80 years were randomised to receive the Polycap daily (containing hydrochlorothiazide 12.5mg, atenolol 50mg, ramipril 5mg, simvastatin 20mg and aspirin 100mg), or 1 of 8 other treatments (monotherapies or various combinations of these same agents). BP reductions seen with Polycap were similar to those seen in groups receiving 3 BP-lowering drugs. Polycap reduced LDL cholesterol levels less than simvastatin alone (0.70 vs 0.83 mmol/L; $p = 0.04$), but both treatments were more effective than those without simvastatin ($p < 0.0001$). Heart rate reductions with Polycap and other groups using atenolol were similar, and greater than those in groups without atenolol ($p < 0.0001$). The reductions in 11-dehydrothromboxane B2 with Polycap were similar to those seen with 3 BP-lowering drugs plus aspirin, and aspirin alone. Polycap tolerability was similar to that of other treatments. In conclusion, the Polycap could be used to reduce multiple risk factors and cardiovascular risk.

Comment: Wald and Law first propounded the Polypill concept in 2003. The idea was greeted by a mixture of enthusiasm, scepticism and hostility but many agreed that some research should be done. It has taken a long time for this to start but at last one publication has arrived which shows the concept has legs – even if the only outcome measures so far are reduction in physiological parameters and risk factors. It seems that the whole might be a little less than the sum of its parts but so are the side effects. Wider research is necessary to see if longer-term outcomes can be improved, especially if the concept is to be offered to those at moderate risk levels. The concept may prove attractive already, especially to those with high cardiovascular risk currently asked to take a number of separate products.

Reference: *Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. The Lancet 2009;373(9672):1341-1351*

[http://dx.doi.org/10.1016/S0140-6736\(09\)60611-5](http://dx.doi.org/10.1016/S0140-6736(09)60611-5)

Acute heart failure? Just RELAX!

Authors: Teerlink JR et al

Summary: This double-blind dose-finding study investigated the effects of relaxin on dyspnoea and other clinical outcomes in patients with acute heart failure. 234 patients were recruited from 54 sites in 8 countries and enrolled within 16 hours of presentation. Patients were randomised to standard care plus a 48-h IV infusion of placebo or relaxin 10–250 µg/kg per day. Likert scale assessments showed that dyspnoea improved with relaxin 30 µg/kg compared with placebo (40% vs 23% of patients had moderate or marked improvement at 6h, 12h and 24h; $p = 0.044$). This was confirmed by VAS through day 14 ($p = 0.053$). Length of stay was shorter in relaxin than placebo recipients (10.2 vs 12.0 days), and the rate of cardiovascular death or readmission due to heart or renal failure at day 60 was lower (2.6% vs 17.2%; $p = 0.053$). In conclusion, relaxin had favourable effects on dyspnoea and other clinical outcomes in patients with acute heart failure.

Comment: Acute presentations of patients with heart failure are more commonly associated with high rather than low blood pressure. We are of course familiar with the role of overstimulation of pressor hormones (renin-angiotensin-aldosterone system and catecholamines) in this condition and many treatments are targeted at blocking these mechanisms or directly at reducing afterload. Most trials in heart failure treatment focus on the chronic situation and on systolic dysfunction. This trial of a 48-hour infusion of a vasodilating natural human polypeptide at the time of an acute presentation with many of the subjects having preserved systolic function, showed favourable effects. These were seen despite liberal use of nitrates or nitroprusside, especially in the placebo group.

Reference: *Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. The Lancet 2009;373(9673):1429-1439*

[http://dx.doi.org/10.1016/S0140-6736\(09\)60622-X](http://dx.doi.org/10.1016/S0140-6736(09)60622-X)

Statins good for reduction of venous thromboembolism

Authors: Glynn RJ et al

Summary: This analysis of JUPITER data investigated the effects of rosuvastatin on the risk of venous thromboembolism. 17,802 initially healthy volunteers with an LDL cholesterol level <3.4 mmol/L and a high sensitivity C-reactive protein (hsCRP) level ≥ 2 mg/L were randomised to receive rosuvastatin 20 mg/day or placebo for up to 5 (median 1.9) years. During follow-up, 34 rosuvastatin vs 60 placebo recipients developed symptomatic venous thromboembolism, representing rates of 0.18 and 0.32 events per 100 person-years of follow-up in the respective groups (hazard ratio 0.57; 95% CI 0.37–0.86; $p = 0.007$). The rates of pulmonary embolism were 0.09 vs 0.12 events per 100 person-years of follow-up in the respective groups (hazard ratio 0.77; 95% CI 0.41–1.45; $p = 0.42$), and the rates of deep-vein thrombosis only were 0.09 and 0.20, respectively (hazard ratio, 0.45; $p = 0.004$). In conclusion, rosuvastatin reduced the occurrence of symptomatic venous thromboembolism in healthy volunteers.

Comment: Two more papers from the Jupiter trial this month. This analysis showed that rates of symptomatic venous thromboembolism were reduced in the treatment (rosuvastatin) group to a similar extent as coronary events (i.e. about 40% relative risk reduction). As it showed for the main results, absolute risk reductions were very small (in this case 0.0014% for each year of treatment – NNT >71,000). However, it is interesting that a powerful statin can reduce venous thromboembolic events as this has not been shown consistently before.

Reference: A randomized trial of rosuvastatin in the prevention of venous thromboembolism. NEJM 2009; 360(18):1851-1861

<http://content.nejm.org/cgi/content/abstract/360/18/1851>

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Perhaps reduction of CRP has merit after all

Authors: Ridker PM et al in behalf of the Jupiter Trial Study Group

Summary: This study investigated the cardiovascular benefits of lowering hsCRP and LDL cholesterol levels. 15,548 initially healthy men and women participating in the JUPITER trial were randomised to receive rosuvastatin 20 mg/day or placebo for up to 5 (median 1.9) years. Prespecified endpoints were non-fatal MI or stroke, admission for unstable angina, arterial revascularisation and cardiovascular death. Compared with placebo, rosuvastatin recipients who achieved LDL cholesterol <1.8 mmol/L had a 55% reduction in vascular events ($p < 0.0001$), and those who achieved hsCRP <2 mg/L had a 62% reduction ($p < 0.0001$). Rosuvastatin recipients who achieved LDL cholesterol <1.8 mmol/L and hsCRP <1 mg/L had a 79% reduction in vascular events. Achieved hsCRP levels were predictive of event rates regardless of the lipid endpoint used. In conclusion, for people wanting pharmacological prophylaxis, reductions in LDL cholesterol and hsCRP levels are indicative of successful treatment with rosuvastatin.

Comment: Other papers reported in this review previously have cast doubt on the idea that CRP acts as a risk factor – rather than just a risk marker that tracks with other risk factors. Since we have no intervention yet that lowers CRP without affecting other factors (such as LDL cholesterol) it is difficult to prove or disprove the hypothesis. However, this retrospective analysis of the results of the Jupiter trial suggests that reduction of CRP has independent importance in correlating with outcome events, may be a slightly more important predictor than LDL cholesterol, and reduction of both is summative. Prospective evidence is needed however to substantiate proof of concept.

Reference: Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. The Lancet 2009; 373(9670):1175-1182

[http://dx.doi.org/10.1016/S0140-6736\(09\)60447-5](http://dx.doi.org/10.1016/S0140-6736(09)60447-5)

White is OK but red not so good (when it comes to meat)

Authors: Sinha R et al

Summary: This study examined the relationships between dietary red meat, white meat and processed meat intake and mortality. More than 500,000 people aged 50–71 years had their meat intake estimated from a food frequency questionnaire at baseline and were then followed for 10 years. 47,976 males and 23,276 females died during follow-up. Compared with the lowest quintile, men and women in the highest quintile of red meat intake (hazard ratios 1.31 for men and 1.36 for women) and processed meat intake (hazard ratios 1.16 and 1.25) were at increased risk for overall mortality. Cancer mortality risk and cardiovascular disease risk were also elevated in men and women in the highest vs lowest quintile of red meat and processed meat intake. White meat intake was inversely associated with total mortality and cancer mortality for both men and women. In conclusion, dietary intake of red and processed meat was associated with increased total mortality cancer mortality, and cardiovascular disease mortality.

Comment: This cross-sectional epidemiological study of older people and their diets found that those consuming higher quantities of red or processed meats had higher risks for total, cancer and cardiovascular mortality although hazard ratios between highest vs lowest quintiles were only modestly elevated (mainly 1.1-1.2). Women seemed to have the highest ratios. Consumption of white meats appeared to have an opposite trend. So, down with the beef, lamb and sausages, up with the chicken (and don't forget the fish and vegetables).

Reference: Meat intake and mortality: a prospective study of over half a million people. Arch Intern Med. 2009;169(6):562-571

<http://archinte.ama-assn.org/cgi/content/abstract/169/6/562>

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Take a LITTLE wine for thy health's sake

Authors: Brugger-Andersen T et al for the OPTIMAAL Study Group

Summary: This study investigated the impact of alcohol consumption on prognosis in patients with coronary artery disease. 5477 patients who had heart failure and/or LV dysfunction after MI were stratified according to their average alcohol consumption prior to the index infarction: non-users, moderate users (1–7 drinks per week) or heavy users (>7 drinks per week). 946 patients died during the 2.7-year follow-up period. After adjustment for age and smoking status, moderate users were found to have a 24% lower risk of all-cause death ($p < 0.001$), 26% lower risk of cardiovascular death ($p < 0.000$) and 8% lower risk for hospitalisation ($p = 0.030$) than non-users, but mortality did not differ between non-users and heavy users. In conclusion, there was a strong positive association between moderate alcohol use and survival in patients with complicated MI, but heavy drinkers and non-drinkers had a poorer prognosis.

Comment: Richard Peto recently helped with a study of mortality and morbidity in relation to alcohol consumption in Siberia. Such was the level of consumption generally that the cut-off for his control (low-alcohol) group was those drinking less than one bottle of vodka a week. By contrast, this analysis from the OPTIMAAL trial had a cut-off for “high-alcohol” consumption of >7 drinks in the week prior to an index myocardial infarction which could be a worry to many. Apparently consumption of that “extreme” level wiped out the mortality advantage conferred by “moderate” consumption (1-7 weekly drinks) compared with complete abstinence. Now that's a worry.

Reference: *Moderate alcohol consumption is associated with reduced long-term cardiovascular risk in patients following a complicated acute myocardial infarction. Int J Card 2009; 133(2):229-232*

<http://dx.doi.org/10.1016/j.ijcard.2007.12.046>

Snake oil for hypertension, anyone?

Authors: Siebers R et al

Summary: This study evaluated the advice given by health food stores and pharmacies for patients with suspected hypertension. An individual approached 26 health food stores and 26 pharmacies for advice on a hypothetical problem of hypertension. 25 out of 26 health food stores failed to refer the individual to a medical practitioner, instead recommending and selling a wide variety of unproven compounds. In conclusion, there needs to be a formal training programme for health food store staff, and better regulation of the use of complementary and alternative medicines in NZ.

Comment: The idea of consuming products for health reasons that have no scientifically proven benefit does not enter my belief system (in contrast to what I might want to believe about wine consumption!). I do like a little garlic with some foods but wouldn't dream of dosing myself as an alternative for proven medication for an important condition. This New Zealand study shows just how misleading the alternative medicine industry can be when unproven nostrums are recommended for a treatable risk factor. The results speak for themselves – at least to anyone with basic medical knowledge. I wonder how the some politicians who need to persuade us of the science behind climate change so vigorously support such an evidence-free industry and expect us to have confidence in their integrity.

Reference: *High blood pressure advice given by natural health food stores. J NZ Med Ass 2009; 122(1293)*

<http://www.nzma.org.nz/journal/abstract.php?id=3566>

*Independent commentary by Dr Stewart Mann,
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at the University of Otago, Wellington*

Some evidence for the benefit of 12-month clopidogrel therapy after DES

Authors: Butler MJ et al on behalf of the Melbourne Interventional Group

Summary: This study examined the impact of clopidogrel treatment duration on outcome in patients receiving a drug-eluting stent (DES). Data for 2,980 patients in the Melbourne Interventional Group registry who underwent PCI and were followed for at least 12 months were evaluated. Patients treated with a DES with a longer planned duration of clopidogrel (≥ 12 months) had lower 12-month mortality than those with a shorter (≤ 6 months) planned duration (2.8% vs 5.3%, $p = 0.012$) but other endpoints were similar between the 2 groups. 12-month mortality in patients receiving a bare-metal stent was unrelated to clopidogrel duration. Kaplan-Meier analysis showed improved cumulative survival with longer planned clopidogrel use. DES patients who stopped clopidogrel treatment prematurely had increased rates of 12-month mortality ($p < 0.0001$) and major adverse cardiac events ($p = 0.005$). In conclusion, longer (≥ 12 months) planned duration of clopidogrel treatment resulted in reduced 12-month mortality in patients treated with DES.

Comment: This Australian study had slightly odd methodology but was one way of examining the conundrum of for how long patients should take clopidogrel after PCI in the absence of prospective trials. Of the outcomes assessed only 12-month mortality for those receiving a drug-eluting stent appeared to be reduced by a planned full 12-month period of clopidogrel therapy – other indices of cardiovascular disease were similar and duration had no effect on outcomes for bare-metal stents. Those who stopped taking clopidogrel ‘prematurely’ did have a much higher mortality although reasons for stopping may have included non-coronary life-threatening disease or poor compliance, both of which would confer a poorer survival.

Reference: *The effect of intended duration of clopidogrel use on early and late mortality and major adverse cardiac events in patients with drug-eluting stents. AHJ 2009; 157(5):899-907*

<http://dx.doi.org/10.1016/j.ahj.2009.02.018>

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Getting closer to optimal aspirin dosing

Authors: Steinhubl SR et al on behalf of the CHARISMA Investigators

Summary: This study retrospectively analysed data from a primary prevention trial to assess the effects of different aspirin dosages on cardiovascular events in patients with cardiovascular disease who were also taking clopidogrel. 15,595 outpatients were randomised to receive placebo or clopidogrel 75 mg/day in a double-blind manner, then had aspirin added (<100 mg/day, n = 7180; 100 mg/day, n = 4961, >100 mg/day, n = 3454) for a median 28 months. The primary efficacy endpoint was a composite of MI, stroke or cardiovascular death and the safety endpoint was severe or life-threatening bleeding. The hazard of the primary efficacy endpoint was found to be independent of dose, as was the incidence of the safety endpoint. In patients taking clopidogrel as well as aspirin, daily aspirin doses >100mg were associated with nonsignificant reductions in efficacy and increases in harm. In conclusion, aspirin dosages \geq 100 mg/day had no clear benefit in patients taking aspirin only, and may be potentially harmful in patients also taking clopidogrel.

Comment: Like the other study of clopidogrel reviewed this month, this retrospective cohort analysis of the CHARISMA trial did not use a prospective or randomised protocol to assess the question at hand so results are tentative. Despite the large number of patients (over 15,500), results of the comparisons of aspirin dose used were at best marginally significant. Doses of aspirin less than 100mg/day seemed adequate although it is not clear if these were enteric-coated which may reduce therapeutic effect at such dosage levels. Higher doses were associated with hazard when combined with clopidogrel.

Reference: *Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding.* *Ann Int Med* 2009; 150(6):379-386

<http://www.annals.org/cgi/content/abstract/150/6/379>

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Better survival after cardiac arrest induced hypoxic brain injury – how cool is that?

Authors: Wolff B et al

Summary: This study investigated the impact of the time interval between cardiac arrest and treatment with mild therapeutic hypothermia (MTH) on neurological outcome. 49 consecutive patients successfully resuscitated from cardiac arrest were enrolled and were treated with MTH (body core temperature between 32.0 and 34.0 °C, target temperature 33.0 °C) over 24 h using a closed-loop endovascular system. 28 patients were discharged with a good neurological outcome (no/mild cerebral disability). Multivariate stepwise regression showed time to target temperature (TTT) was an independent predictor for good outcome (odds ratio for every hour TTT: 0.69; 95% CI 0.51–0.98). Age, BMI, asystole as presenting rhythm, and thrombolysis during resuscitation were also independent predictors for good outcome. In conclusion, early achievement of MTH by endovascular cooling after cardiac arrest improves neurologic outcome.

Comment: We lately seem to have had an epidemic of individuals successfully resuscitated from community cardiac arrest, many of whom appear to do well from both cardiac and cerebral points of view. This necessarily small and retrospective study underwrites the practice – already fully introduced in intensive care units – of cooling such victims for a period and demonstrates that instituting the cooling as early as possible has advantages.

Reference: *Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest.* *Int J Card* 2009;133(2):223-228

<http://dx.doi.org/10.1016/j.ijcard.2007.12.039>

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