

Abstracts

80th (Autumn) Meeting of Ulster Society of Internal Medicine, Friday 17th October 2008

Sir Samuel Irwin Lecture Theatre,
Royal Victoria Hospital, Belfast.



PROGRAMME:

Chairman: Dr Kate Ritchie

2.00pm Papers

3.00pm Invited Abstract: 'Update on Management of type 2 Diabetes'.
Prof. Patrick Bell, Royal Victoria Hospital.

3.30pm Afternoon Tea

3.50pm Papers

4.30pm Presentation of prize for best abstract

4:50pm Guest lecture: 'Occupational lung disease in the 21st century'. Dr Chris Stenton, Consultant Respiratory Physician, Newcastle-Upon-Tyne.

PAPERS

EPITHELIAL TO MESENCHYMAL TRANSITION IN SKIN – POSSIBLE IMPLICATIONS FOR SCLERODERMA

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Fibrogenic growth factors can force epithelial cells of the lung, kidney and liver to undergo transition to a mesenchymal phenotype – a process known as epithelial to mesenchymal transition (EMT)¹. EMT contributes to fibrosis in these organs, and can be inhibited/reversed in animal models². EMT has not been shown in fibrotic skin disorders. We hypothesised that EMT is a mechanism of dermal fibrosis and may mediate fibrosis in scleroderma and other skin lesions.

Human keratinocytes (HaCaT cells) were stimulated with TGFβ and TNFα (which occur in fibrotic skin). Cells lysates were probed by western blot for epithelial (E-cadherin) and mesenchymal (vimentin) markers. Supernatants were analysed for matrix metalloproteinases (MMP-2/-9), enzymes associated with the invasive, motile phenotype integral to EMT and CXCL8, a chemokine secreted in high quantities by activated fibroblasts. Keratinocytes stimulated with TGFβ and TNF became spindle-shaped, with loss of cell-cell contact. There was a switch from epithelial to mesenchymal proteome: vimentin expression increased 3.4 fold, E-cadherin fell by 60% (p=0.02*). MMP-2 increased from 121±44 to 1174±86 relative gelatinolytic units (RGU), p<0.001*, and MMP-9 from 24 to 805±80 RGU, p<0.001*. CXCL8 increased from 671 to 1562pg/ml, p=0.0005*. (* t test TGFβ +TNFα vs. control)

Keratinocytes stimulated with TGFβ+TNFα (present in cutaneous scleroderma) undergo changes consistent with EMT. These novel data suggest EMT is a possible mechanism of skin fibrosis. Targeting EMT *in vivo* by inhibiting downstream regulators of TGFβ and TNFα signalling may be a novel approach to limit progression of dermal fibrosis in scleroderma / other diseases.

REFERENCES:

1. Kim KK, Kugler MC, Wolters PJ, Robillard L, Galvez MG, Brumwell AN, et al. Alveolar epithelial cell mesenchymal transition develops *in vivo* during pulmonary fibrosis and is regulated by the extracellular matrix. *PNAS* 2006;103(35):13180-5.
2. Zeisberg M, Hanai J, Sugimoto H, Mammoto T, Charytan D, Strutz F, et al. BMP-7 counteracts TGF-beta1-induced epithelial-to-mesenchymal transition and reverses chronic renal injury. *Nat Med* 2003;9(7):964-8.

THE USE OF IMPLANTABLE CARDIOVERTER DEFIBRILLATORS IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY; EXPERIENCE OF A TERTIARY REFERRAL CENTRE IN NORTHERN IRELAND.

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Hypertrophic Cardiomyopathy (HCM) is the most common cause of sudden cardiac death (SCD) in young people¹. The implantable cardioverter-defibrillator (ICD) has been shown to be a safe and effective therapeutic intervention in patients with HCM, both for primary and secondary prevention of SCD. We reviewed ICD data of patients with HCM to determine the indications for, efficacy, safety and complications of the device.

Out of 828 patients currently being reviewed in ICD clinic, Royal Victoria Hospital, Belfast 28 patients (4%) had HCM as primary diagnosis. Twenty four (85%) ICDs were inserted for primary prevention and 4 (15%) for secondary prevention of SCD. Pre ICD insertion the following risk factors for SCD were identified; 13 (46%) had a family history of SCD, 6 (21%) had a history of syncope, 5 (17%) had nonsustained ventricular tachycardia, 4 (14%) had ventricular tachycardia, 4 (14%) had frequent ventricular premature complex, 2 (7%) had atrial fibrillation and 2 (7%) had supraventricular tachycardia on holter monitor prior ICD insertion, 2 (7%) had an inappropriate blood pressure response to exercise and 2 (7%) had a raised left ventricular outflow tract velocity. The mean septal diameter was 22±6mm. The mean age of ICD insertion was 49.6±17years. During a mean follow up period of 32months, 9 appropriate shocks were delivered in 6 patients (21%) and 3 inappropriate shocks were delivered in 3 (10%) patients. Four patients who had appropriate shock delivered were on oral amiodarone and one patient on sotalol. Complications identified included one patients requiring ICD box replacement and one patient required lead replacement due to insulation defect of the leads.

The high rate of appropriate ICD shocks in our study is similar to published data². Risk assessment for SCD should be performed in every HCM patient and ICD should be considered in high risk patients.

REFERENCES:

1. Maron BJ, Spirito P. Implantable Defibrillators and Prevention of Sudden Death in Hypertrophic Cardiomyopathy, *J Cardiovasc Electrophysiol* 2008 [Epub ahead of print].
2. Maron BJ, Spirito P, Shen WK *et al.* Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy; *JAMA* 2007;298(4):405-12.

BISPHOSPHONATE PRESCRIBING GUIDELINES – IS EVERYONE A LOSER?

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Osteoporotic fractures are 3 to 4 times more likely in persons with chronic kidney disease (CKD). Early menopause, previous exposure to steroids and increased risk of falls are all contributory factors^{1,2}. National Institute of Clinical Excellence (NICE) guidelines on the treatment of osteoporosis do not extend to the CKD population³ and current manufacturer guidelines do not recommend the use of bisphosphonates (BPs) in those patients with an eGFR < 30ml/min⁴. We aimed to assess compliance with prescribing guidelines and to determine if BPs are underutilized across the entire spectrum of CKD.

Data was collected from a computerised data base of six-hundred and thirty seven patients with CKD currently attending our renal unit. Six point three percent (40/637) of the CKD population were prescribed a BP, 50% (20/40) of whom had an eGFR < 30ml/min. Four point four percent (28/637) had a documented diagnosis of osteoporosis (OP) or OP related fracture. However, of those with eGFR > 30 ml/min and thus eligible for BP therapy, only one third (3/9) were actually prescribed a BP. Nine point four percent (60/637) of the total population were receiving long term steroid therapy but only 50% (15/28) of those with eGFR >30 ml/min, and thus eligible, were prescribed a BP.

This study demonstrates non-adherence to bisphosphonate prescribing guidelines in persons with an eGFR <30 ml/min. However, and perhaps more importantly, we have highlighted an underutilisation of BP therapy in those with eGFR >30 ml/min. BPs have established efficacy in the treatment of OP and OP related fracture in the general population.^{1,2} The underutilisation of BPs in CKD observed in this study, endorsed by both national and manufacturers' guidelines, may be explained in part by the absence of supportive data in CKD, theoretical concerns of inducing low bone turnover states, and previous reports of acute tubular necrosis with intravenous preparations.^{1,2}

This study generates the following questions: Should we be extrapolating data from the general population, should we extrapolate the data and adjust the dosage, or should we wait for randomised controlled trials on BPs in CKD. As previous authors have suggested, extrapolation of data with dose adjustment seems the most practical and safe approach for the short term.

REFERENCES:

1. Hamilton DV. Osteoporosis in women undergoing chronic dialysis. *Br J Renal Med* 2007;**12**(2):19-21.
2. Miller PD. Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. *Curr Osteoporosis Rep* 2005;**2**:5-12. 3. National Institute for Health and Clinical Excellence. <http://www.nice.org.uk/> 4. British National Formulary. <http://www.bnf.org/bnf/>

IS HYPERFILTRATION ASSOCIATED WITH THE FUTURE RISK OF DEVELOPING DIABETIC NEPHROPATHY? A META-ANALYSIS

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Aims: Glomerular hyperfiltration is well established as a phenomenon occurring early in type 1 and type 2 diabetes, however, there is no consistent answer regarding whether hyperfiltration predicts the later development of nephropathy. We performed a systematic review and meta-analysis of observational studies that compared the risk of developing diabetic nephropathy in patients with and without glomerular hyperfiltration.

Methods: A systematic review and meta - analysis was carried out. Cohort studies in type 1 and 2 diabetic participants were included if they contained data on the development of incipient or overt nephropathy with baseline measurement of glomerular filtration rate (GFR) and presence or absence of hyperfiltration.

Results: Eleven cohort studies following 830 patients were included. After a study median follow up of 7.9 years, 124 patients had developed nephropathy. Using a random effects model, the pooled odds of progression to a minimum of microalbuminuria in individuals with hyperfiltration was 2.54 (95% CI 1.25-5.17) times that of individuals with normofiltration. There was moderate heterogeneity (Heterogeneity test $p = 0.07$, $I^2 = 42\%$) and some evidence of funnel plot asymmetry, possibly due to publication bias. The pooled weighted mean difference in baseline GFR was 13.4 ml/min/1.73m² (95% CI 5.4-21.3) greater in the group progressing to nephropathy compared to those not progressing (Heterogeneity test $p < 0.01$).

Conclusions: In published studies, individuals with glomerular hyperfiltration were at increased risk of progression to diabetic nephropathy using study level data. Further larger studies are required to explore this relationship and the role of potential confounding variables.

AUDIT OF SECONDARY PREVENTION OF OSTEOPOROSIS IN POST-MENOPAUSAL FEMALES TREATED IN A DISTRICT GENERAL HOSPITAL

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Background: Osteoporosis may lead to significant morbidity and disability through an increased susceptibility to fracture. Post-menopausal females are a high-risk group accounting for 74% of neck of femur fractures in our unit. Appropriate treatment may reduce the risk of re-fracture in this group.

Aim: To compare current practice to guidelines contained in the National Institute for Clinical Excellence (NICE) Technology Appraisal 87.

Methods: A sample group of 100 patients was identified retrospectively using emergency department records. Female patients over 55 years of age with diagnosis of a classical osteoporotic fracture were included.

Results: 62% were aged 75 or greater. 62% sustained a fracture of neck of femur, 29% a wrist fracture and 9% a vertebral fracture. 8% underwent a DEXA scan. In the under 75 group 30 patients (of an eligible 38 (79%)) did not receive a DEXA scan. Treatment was consistent with the NICE guidelines in 41% of patients. Most (33 (80%)) were aged 75 or over and 8 (20%) were aged under 75. In the under 75 age group, treatment was commenced in 17 of 38 patients (45%). In 9 patients (24%) treatment was commenced without performing a DEXA scan. 47% of those aged 75 or over and 79% of those in the under-75 age group did not receive treatment according to NICE guidelines.

Conclusions: DEXA scanning is under-utilised, contributing to significant inconsistent treatment decisions. Adherence to the NICE guidelines is higher in the 75 and over age group, however in a significant proportion treatment is sub-optimal.

Chronic kidney disease associated with mortality in Northern Ireland

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Introduction: We sought to investigate if the increased mortality shown to be associated with chronic kidney disease (CKD) in the US population¹ is also present in Northern Ireland (NI).

Methods: All creatinine results in Northern Ireland between 1st Jan 2001 - 31st Dec 2002 were collected. Estimated glomerular filtration rates (eGFR) were then calculated using the 4 variable modified diet in renal disease (MDRD) equation. A patient level database was created and mortality follow up was provided from the Registrar Generals office up to 31st Dec 2006.

Results: 2,065,694 creatinine results from 585,566 patients were collected. Mean (Standard Deviation) duration of follow up was 3.3 (2.2) yrs. During survival follow up there were 60,209 deaths. Using eGFR as time varying covariate within a Cox proportional hazards model the following association between CKD and mortality was demonstrated.

Adjusted† hazard ratios (CI 95%) for death from any cause	
Estimated GFR	Death from any cause
> 60 ml/min/1.73m ²	1.00 (Reference)
45 - 59 ml/min/1.73m ²	1.01 (0.99-1.03)
30 - 44 ml/min/1.73m ²	1.45 (1.41-1.48)
15 - 29 ml/min/1.73m ²	2.19 (2.11-2.27)
< 15 ml/min/1.73m ²	3.45 (3.23-3.68)
†Adjusted for Age and Sex	

Conclusions: This study demonstrates a graded association between CKD and mortality in the tested NI population. The risk of death rose sharply when an estimated GFR of < 45 ml/min/1.73m² was recorded. Having previously calculated the prevalence of CKD (eGFR < 60 ml/min/1.73m²) in NI as 3.69%; this further work clearly indicates the clinical and public health importance of CKD.

REFERENCES:

1. Go, AS, Chertow GM, Fan D, *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Eng J Med* 2000;**351**:1296-1305.
2. Quinn MP, Rainey A, Cairns KJ, *et al.* The practical implications of using standardized estimation equations in calculating the prevalence of chronic kidney disease. *Nephrol Dialysis Transplant* 2000;**23**(2):542-548.

FATAL TRANSMISSION OF TUBERCULOSIS IN AN ACUTE MEDICAL ADMISSION UNIT (AMAU).

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A 33 year old male was admitted from the local Psychiatric unit with apparent pneumonia. A chronic schizophrenic and heavy smoker, he had spent some 15 years in institutional care in various facilities. He was treated with high flow humidified oxygen and nebulised bronchodilators. 48 hours later he was found to be sputum smear positive for AAFB.

He was isolated and the Infection Control Team mobilised. He turned out to have a fully sensitive M.TB organism and responded well to treatment. BTS TB guidelines were followed and all staff and patients in the same ward bay as the patient were informed and letters sent to all GPs.

One patient contact had oesophageal carcinoma and was a chronic alcoholic. He developed post operative pleural effusion (TB culture positive) some 6 months post exposure. A second contact (also alcoholic) was investigated as possible lung cancer some 30 months after exposure and was Smear positive for AAFB. Both patients died on treatment for their TB.

All 3 TB isolates were identical. The index case is alive and well. This highlights the danger of even short delays in diagnosis and appropriate isolation of TB patients. It also highlights the use of RFLP/genotyping in case series and evaluation.