Cardiovascular disease

Heart rate and age predict progression of atrial fibrillation

Heart rate is associated with progression of atrial fibrillation (AF) independent of rhythm, a large nationwide cohort study from the United States has found.

Data from the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) were analysed to determine incidence and predictors of AF progression.

Progression is defined either as a transition from a self-terminating to a non-self-terminating form (paroxysmal to persistent or permanent) or any transition to a more sustained form of AF (paroxysmal to persistent/permanent or persistent to permanent).

The authors also tested the discrimination and calibration of the HATCH score (hypertension, age, TIA/stroke, chronic obstructive pulmonary disease, heart failure) and CHA_2DS_2VASc score for identifying AF progression.

Of 6,235 patients with paroxysmal or persistent AF at baseline, 1,479 progressed, during a median follow-up of 18 months. Of these patients, 1,032 (70%) had paroxysmal AF at baseline and 447 (30%) had persistent AF.

The patients who progressed were older and had more comorbidities than patients who did not progress ($CHADS_2$ 2.3 ± 1.3 vs 2.1 ± 1.3; P < 0.0001).

At baseline, patients with AF progression were more often on a rate control as opposed to a rhythm control strategy (66 vs 56%; P < 0.0001) and had a higher heart rate (72 vs 68 bpm; P < 0.0001).

The strongest predictors of AF progression were:

- AF on the baseline ECG, OR 2.30 (95% CI: 1.95-2.73; P < 0.0001) and
- Age, OR 1.16 (95% CI: 1.09-1.24, P < 0.0001, per 10 year increase)

Patients with lower heart rate OR 0.84 (95% CI: 0.79-0.89, P < 0.0001, per 10 bpm decrease < 80 bpm) were less likely to progress. There was no significant interaction between rhythm on baseline ECG and heart rate.

The HATCH and CHA_2DS_2VASc scores had only modest discriminatory power for AF progression.

Paroxysms of AF tend to become longer in duration and more frequent over time with many patients progressing to permanent AF. Electrophysiological and structural remodelling promotes the maintenance and persistence of AF.

Predicting which patients are likely to progress from paroxysmal AF to more sustained forms can be difficult. The progression of AF has been shown to be associated with increased risk of hospitalisation and thromboembolic events.

In this study progression was strongly associated with heart rate and age. Within 18 months, almost a quarter of the patients with paroxysmal or persistent AF progressed to a more sustained form.

'While a rate or rhythm control strategy was not independently associated with AF progression, lower heart rate and/or stricter rate control may be of importance to prevent AF progression,' the authors conclude.

DR PETER SAVILL

● Holmqvist F, Kim S, Steinberg B et al. *Heart* 2015;101:894-899 doi:10.1136/heartjnl-2014-307043

Urology

Add-on therapy for overactive bladder shows promise

Mirabegron in combination with solifenacin significantly reduced overactive bladder (OAB) symptoms, in a small preliminary study from Japan.

A total of 223 patients (84% female), aged over 20, mean 65 years, with overactive bladder, currently being treated with either 2.5 mg or 5 mg of solifenacin, entered the treatment phase of the study. Mirabegron was given at 25 mg once daily for the first eight weeks of the 16-week open label study, and increased to 50 mg once daily if ineffective at eight weeks. Overall 130 patients increased their mirabegron dose at this time point.

Efficacy was assessed using the Overactive Bladder Symptom Score (OABSS). Overall, this score decreased significantly in patients taking combination therapy, with further improvement seen when increasing the dose of mirabegron. In all treatment groups the threshold for minimal clinically important change i.e. 3 points was exceeded (range -3.4 to -4.0).

Across all treatment groups, urinary frequency, nocturia episodes, urgency episodes and urgency incontinence episodes all decreased, see below, while the mean volume voided per micturition increased.

- Reduction in mean number of micturitions/24 hours ranged from -1.89 to -2.36
- Reduction in mean number of nocturia episodes/night ranged from -0.31 to -0.60
- Reduction in urgency episodes/24 hours ranged from -1.57 to -2.59 »

OCTASA 400mg MR Tablets (mesalazine) and OCTASA 800mg MR Tablets (mesalazine) – Prescribing Information. Please consult the Summaries of Product Characteristics (SmPCs) for full prescribing information. **Presentation:** Modified Release tablets containing 400mg mesalazine or 800mg mesalazine. **Indications:** *Ulcerative Colitis* – Treatment of mild to moderate acute exacerbations. Maintenance of remission. *Crohn's ileocolitis* – Maintenance of remission. **Dosage and administration:** *400mg tablets* – Adults: Acute disease: Six tablets a day in divided doses, with concomitant steroid therapy where indicated. Maintenance therapy: Three to six tablets a day in divided doses. *800mg tablets* – Adults: Mild Acute Disease: 3 tablets (2.4g) once daily or in divided doses. Moderate Acute Disease: 3 to 6 tablets (2.4g – 4.8g) daily. 2.4g may be taken once daily, higher doses should be taken in divided doses. Maintenance therapy: 2 to 3 tablets (1.6g to 2.4g) once daily or in divided doses. Not more than 3 tablets should be taken together. *400mg and 800mg tablets* – Tablets must be swallowed whole. *Elderly:* Normal adult dose may be used unless renal function is impaired. *Children:* Limited documentation of efficacy. Dose to be determined individually. Generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg. **Contra-indications:** Hypersensitivity to salicylates or any of the excipients, severe impairment of hepatic or renal function (GFR less than 20 ml/min), gastric or duodenal ulcer, haemorrhagic tendency. **Warnings and Precautions:** Blood tests (differential blood count; creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at discretion of treating physician. Follow-up tests are recommended 14 days after start of treatment, then a further two to three tests at intervals of 4 weeks. If findings are normal, carry out follow-up tests every 3 months. If additional symptoms occur, perform these tests immediately. Best avoided in patients with mild-moderate renal impairment; if necessary, use with extreme caution. Caution in patients with impaired hepatic function. If dehydration occurs, correct as soon as possible. Discontinue treatment if renal function deteriorates. Monitor patients with pulmonary disease, in particular asthma, very carefully. Discontinue immediately if acute intolerance reactions occur (e.g. abdominal cramps, acute abdominal pain, fever, severe headache and rash). Very rarely serious blood dyscrasia has been reported. Perform haematological investigations including a complete blood count especially if a patient develops signs and symptoms suggestive of blood dyscrasia during treatment, such as unexplained bleeding, haematoma, purpura, anaemia, persistent fever, or a sore throat. Stop treatment immediately if there is suspicion or evidence of blood dyscrasia and patients should seek immediate medical advice. Use with caution in the elderly subject to patients having normal renal function. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine. **Interactions:** Nephrotoxic agents (e.g. NSAIDs and azathioprine), digoxin, warfarin, azathioprine, 6-mercaptopurine or thioguanine. **Pregnancy and lactation:** Only to be used when the potential benefit outweighs the possible hazards. **Adverse reactions:** *Rarely:* Dizziness, headache myocarditis, pericarditis, abdominal pain, diarrhoea, flatulence, nausea, vomiting, bloating. *Very rarely:* Altered blood counts (aplastic anemia, granulocytosis, pancytopenia, neutropenia, leucopenia, thrombocytopenia), bone marrow depression, anaemia, peripheral neuropathy, vertigo, allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), eosinophilic pneumonia, pancreatitis, exacerbation of disease, changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis, hepatic function abnormal / abnormal liver function tests, alopecia, Stevens Johnson syndrome, erythema multiforme, bulbous skin reactions, urticaria, rash, myalgia, arthralgia, lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia, impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency, renal failure, which may be reversible on withdrawal, nephrotic syndrome, hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis, oligospermia (reversible). **Marketing Authorisation Numbers, Package Quantities and basic NHS price:** 400mg – PL36633/0002; packs of 90 tablets (£19.50) and 120 tablets (£26.00).800mg – PL36633/0001; packs of 90 tablets (£47.50) and 180 tablets (£95.00). **Legal category:** POM. **Marketing Authorisation Holder:** Tillotts Pharma UK Ltd, The Larbourne Suite, The Stables, Wellingore Hall, Wellingore, Lincolnshire, LN5 0HX, UK. Octasa is a trademark. ©2010 Tillotts Pharma UK Ltd. Further Information is available from the Marketing Authorisation Holder. Date of preparation of API: September 2014. UK/OC/0016/0215. Date of preparation: March 2015.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Tillotts Pharma UK Ltd. (address as above) Tel: 01522 813500.

www.tillotts.com

References: 1. MIMS. Accessed online, March 2015. 2. Data on file, Tillotts Pharma UK Limited. [Comparison of costs of Octasa® and Asacol® using NHS e-Pact data – November 2014]. 3. e-Pact data. NHS Business Services Authority. August 2014. 4. Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013. Available at http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/index.html accessed March 2015. 5. NICE clinical guideline 166. Ulcerative colitis. Management in adults, children and young people. June 2013. 6. NHS Electronic Drugs Tariff. Mesalazine prices. Available at http://www.ppa.org.uk/edt/March_2015/mindex.htm accessed March 2015.

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● Reduction in urinary incontinence episodes/24 hours ranged from -1.06 to -1.32

Overall, 23% of patients reported new side effects during the study (almost all of which were deemed mild or moderate). The most common side effect was constipation, seen in 5-9% of patients. Only one patient reported the new onset of dry mouth, and four discontinued treatment because of side effects.

This was an open label study with no placebo arm, over a relatively short time period of 16 weeks of treatment. So the results must therefore be interpreted with caution.

Mirabegron is a beta-3 adrenoceptor agonist which works by relaxing detrusor smooth muscle during bladder storage, and increasing bladder capacity, thus aiming to reduce urgency episodes and urinary frequency. It does not have the classic side effects associated with antimuscarinic therapy such as dry mouth. A technology appraisal by NICE in 2013 recommended use of mirabegron for patients where antimuscarinics are either contraindicated, not tolerated or ineffective.

Clearly, combination therapy represents a promising development in the medical treatment of the symptoms of overactive bladder. Formal, double blind, randomised controlled trials are shortly due to report and it will be interesting to see if these findings are replicated in a more rigorous trial setting.

More importantly, the results will need to be analysed to see if improvements in symptoms are clinically significant to patients in order to justify the addition of a further long-term therapy, and a significant increase in the cost of medical treatment.

DR JONATHAN REES

● **Yamaguchi O, Kakizaki H, Homma Y et al. Safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin: a post-marketing, open-label study in Japan (MILAI study). *BJU Int* 2015; doi:10.1111/bju.13068**

Diabetes

Subclinical LVD linked to poor outcomes in type 2 diabetes

Type 2 diabetes patients with subclinical left ventricular dysfunction (LVD) are at greater risk of death and hospitalisation, a prospective cohort study from Australia has shown.

A total of 230 asymptomatic patients with type 2 diabetes underwent echocardiography with the measurement of global longitudinal 2D strain to detect LVD. The cohort was followed for up to ten years. All the patients had normal LV ejection fraction (≥ 50%) and no evidence of coronary artery disease at recruitment to the study.

The primary endpoint was all-cause mortality and hospitalisation. Outcome data were obtained through centralised state-wide death and hospital admission registries.

At study entry, 104 patients (45%) of the cohort had evidence of LVD as detected by global longitudinal strain.

Over a median follow-up of 7.4 ± 2.6 years, 68 patients (30%) met the primary endpoint of death or hospitalisation; 37% of those with LVD and 24% of those with normal LV function.

Global longitudinal strain was independently associated with the primary endpoint (HR = 1.10; P = 0.04), as was systolic blood pressure (HR = 1.02; P < 0.001) and levels of glycosylated haemoglobin (HR = 1.28; P = 0.011). Patients with LVD had significantly worse outcomes than those without.

Diabetes mellitus is associated with both macro- and microvascular disease and this can lead to the development of heart failure.