Cardiovascular disease

Moderate exercise lowers risk of atrial fibrillation in older women

A moderate amount of physical activity appears to reduce the risk of atrial fibrillation (AF) significantly in middle-aged and elderly women, according to a study published in *Heart*.

Information about physical activity was obtained from 36,513 women, aged 49-83 (median 60) years in the Swedish Mammography Cohort who had completed a questionnaire at study entry. Participants reported their time spent on leisure-time exercise and on walking or cycling throughout their lifetime (at study entry, and at 30 and 50 years of age).

Walking/cycling for transportation was considered to be low to moderate intensity physical activity, while leisure-time exercise was considered to be moderate to high intensity physical activity.

The authors used the Swedish National Inpatient Register to determine whether participants were diagnosed with AF. Results were adjusted for potential confounders.

Overall, 2,915 cases of AF were diagnosed during a median follow-up period of 12 years.

The risk of AF decreased with increasing levels of physical activity at study entry:

- Leisure-time exercise ≥ 4 hr/week compared with < 1 hr/week, RR 0.85 (95% CI: 0.75-0.95)
- Walking/cycling for ≥ 40 min/day compared with almost never walking or cycling, RR 0.81 (95% CI: 0.72-0.92).

AF is the most common arrhythmia »

*In the 52-week trials, SPIOLTO® administered once daily in the morning provided clear improvement in lung function within 5 minutes after the first dose compared to tiotropium 5 µg (mean increase in FEV_1 of 0.137 L for SPIOLTO® vs. 0.058 L for tiotropium 5 µg [p<0.0001]).[1] †SPIOLTO® resulted in statistically significant improvements in SGRQ total scores and responder rates vs. both monotherapies (p<0.05) after 24 weeks. Response defined as a ≥4 change in SGRQ score. Pooled analysis of the pivotal phase III TONADO™ 1 and 2 studies.[1] ‡After 24 weeks, SPIOLTO® Respimat® significantly improved mean TDI focal score compared to tiotropium 5 µg. More patients treated with SPIOLTO® Respimat® had a clinically meaningful improvement in TDI focal score (MCID, defined as a value of at least 1 unit) compared to tiotropium 5 µg (54.9% vs. 50.6%, p=0.0546).[1]

References:
1. SPIOLTO® Respimat® Summary of Product Characteristics. **2.** Beeh K-M *et al. Pulm Pharmacol Ther* 2015;32:53–59. **3.** Buhl R *et al. Eur Resp* J 2015;45:969–979. **4.** Boehringer Ingelheim. Data on file TOL15 02(c). **5.** SPIRIVA® Respimat® Summary of Product Characteristics. **6.** SPIRIVA® HandiHaler® Summary of Product Characteristics. **7.** Dalby R, Spallek M, Voshaar T. *Int J Pharm* 2004;283:1–9. **8.** Pitcairn G *et al. J Aerosol Med* 2005;18:264–272. **9.** Hochrainer D *et al. J Aerosol Med* 2005;18:273–282.

SPIOLTO® RESPIMAT® (tiotropium/olodaterol)
Inhalation solution containing 2.5 microgram tiotropium (as bromide monohydrate) and 2.5 microgram olodaterol (as hydrochloride) per puff. **Action:** Inhalation solution containing a long acting muscarinic receptor antagonist, tiotropium, and a long acting beta2-adrenergic agonist, olodaterol. **Indication:** Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **Dose and Administration:** Adults only aged 18 years or over: 5 microgram tiotropium and 5 microgram of olodaterol given as two puffs from the Respimat inhaler once daily, at the same time of the day. **Contraindications:** Hypersensitivity to tiotropium or olodaterol or any of the excipients; benzalkonium chloride, disodium edetate, purified water, 1M hydrochloric acid (for pH adjustment); atropine or its derivatives e.g. ipratropium or oxitropium. **Warnings and Precautions:** Not for use in asthma or for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. Inhaled medicines may cause inhalation-induced paradoxical bronchospasm. Caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. Patients should be cautioned to avoid getting the spray into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using Spiolto Respimat and consult a specialist immediately. In patients with moderate to severe renal impairment (creatinine clearance ≤ 50ml/min) use only if the expected benefit outweighs the potential risk. Caution in patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalised for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (> 100 beats per minute) as these patients were excluded from the clinical trials. In some patients, like other beta-adrenergic agonists, olodaterol may produce a clinically significant cardiovascular effect as measured by increases in pulse rate, blood pressure and/or symptoms. Caution in patients with: cardiovascular disorders, especially ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, and aneurysm; convulsive disorders or thyrotoxicosis; known or suspected prolongation of the QT interval (e.g. QT>0.44 s); patients unusually responsive to sympathomimetic amines; in some patients beta2-agonists may produce significant hypokalaemia; increases in plasma glucose after inhalation of high doses. Caution in planned operations with halogenated hydrocarbon anaesthetics due to increased susceptibility of adverse cardiac effects. Should not be used in conjunction with any other long-acting $beta_2$-adrenergic agonists. Immediate hypersensitivity reactions may occur after administration. Should not be used more frequently than once daily. **Interactions:** Although no formal drug interaction studies have been performed, inhaled Spiolto Respimat has been used concomitantly with other COPD medicinal products, including short acting sympathomimetic bronchodilators and inhaled corticosteroids without clinical evidence of drug interactions. The co-administration of the component tiotropium with other anticholinergic containing drugs has not been studied and therefore is not recommended. Concomitant administration of other adrenergic agents (alone or as part of combination therapy) may potentiate the undesirable effects of Spiolto Respimat. Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalaemic effect of adrenergic agonists. Beta-adrenergic blockers may weaken or antagonise the effect of olodaterol. Cardioselective beta-blockers could be considered, although they should be administered with caution. MAO inhibitors, tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of Spiolto Respimat on the cardiovascular system. **Fertility, pregnancy and lactation:** There is a very limited amount of data from the use of tiotropium in pregnant women. For olodaterol no clinical data on exposed pregnancies are available. As a precautionary measure, avoid the use of Spiolto Respimat during pregnancy. Like other $beta_2$-adrenergic agonists, olodaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. It is not known whether tiotropium and/or olodaterol pass into human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Spiolto Respimat should be made taking into account the benefit of breast-feeding to the child and the benefit of therapy for the woman. Clinical data on fertility are not available for tiotropium or olodaterol or the combination of both components. **Effects on ability to drive and use machines:** No studies have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery. **Undesirable effects:** Common (≥ 1/100 to < 1/10): Dry mouth. Uncommon (≥ 1/1,000 to <1/100): Dizziness, insomnia, headache, atrial fibrillation, palpitations, tachycardia, hypertension, cough, constipation. Serious undesirable effects include anaphylactic reaction and consistent with anticholinergic effects: glaucoma, constipation, intestinal obstruction including ileus paralytic and urinary retention. An increase in anticholinergic effects may occur with increasing age. The occurrence of undesirable effects related to beta-adrenergic agonist class should be taken into consideration such as, arrhythmia, myocardial ischaemia, angina pectoris, hypotension, tremor, nervousness, muscle spasms, fatigue, malaise, hypokalaemia, hyperglycaemia and metabolic acidosis. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** Single pack: 1 Respimat inhaler and 1 cartridge providing 60 puffs (30 medicinal doses) £32.50 **Legal category:** POM **MA numbers:** PL 14598/0101 **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** June 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 Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). (UK only)**

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that we encounter in primary care. It is associated with increased morbidity and mortality.

The association between exercise and AF is somewhat dichotomous and there may be a U-shaped relationship between the intensity of exercise and AF risk, see p19. In men, long-term regular intense sporting activity particularly of the endurance variety can increase the risk of developing AF. However, in older men moderate physical activity seems to decrease the risk.

This study addressed an area that is relatively light on evidence at present; the association between AF and exercise in middle-aged and elderly women.

This was a large prospective study with complete follow up. However, the authors acknowledge that it relied on self-reporting of physical activity and the intensity of exercise was not measured.

The authors concluded that moderate physical activity was sufficient to reduce risk of AF in middle-aged and older women significantly.

These findings provide further support for encouraging regular exercise in our patients.

DR PETER SAVILL

● **Drca N, Wolk A, Jensen-Urstad M et al. Physical activity is associated with a reduced risk of atrial fibrillation in middle-aged and elderly women. *Heart* 2015;101:1627-1630 doi:10.1136/heartjnl-2014-307145**

See also Playing it safe:exercise and cardiovascular health, p15

Diabetes

Is high intensity intermittent exercise beneficial in type 2 diabetes?

Recent research from Newcastle University suggests that high intensity intermittent exercise is associated with improved cardiac structure and reduced liver fat in type 2 diabetes patients.

In this prospective randomised controlled trial, 28 patients with type 2 diabetes were allocated randomly to high intensity intermittent training (HIIT) or standard care. Baseline investigations included cardiac structure, glycaemic control, liver and visceral fat and blood parameters. The two groups were well matched in terms of their baseline characteristics. Eleven patients in the control group, mean age 59 ± 9 years, and 12 from the intervention arm, mean age 61 ± 9 years, completed the study.

The HIIT group performed 36 cycle ergometry sessions over 12 weeks i.e. three sessions per week at a gym on non-consecutive days. Patients had to perform at least 32 (89%) of the sessions to be included in the final analysis. The exercise intensity was measured between 6 and 20 on the Borg Rating of Perceived Exertion. After a five-minute warm up in which the participants progressed from RPE of 9 to 13 ('very light' to 'somewhat hard'), there were five intervals reaching RPE 16/17 ('very hard'), before a three-minute recovery period.

The length of the intensive intervals was initially two minutes, and this was extended by ten seconds every week, so that week 12 consisted of 3 min 50s intervals. Initially supervised, the sessions were then self-administered using an iPod, and adherence checked with an exercise diary and phone calls.

Cardiac MRI, cardiac spectroscopy and liver and visceral fat MRIs were undertaken, in addition to measurement of blood parameters. The results of the scans were interpreted by doctors unaware of which arm the patient had been allocated to.

Compared with controls the HIIT group showed improved cardiac structure, systolic function, early diastolic filling rates and peak torsion. The HIIT group also showed a significant 39% reduction in liver fat ($P < 0.05$).

HIIT had no effect on fasting glucose or fasting insulin levels. The intervention group showed a modest reduction in HbA_{1c} (7.1% ± 1.0% to 6.8% ± 0.9%) compared with the control group (7.2% ± 0.5% to 7.4% ± 0.7%). The reduction in liver fat correlated with the HbA_{1c} changes.

Changes in left ventricular structure are identifiable in diabetes patients before the development of overt cardiac disease. HIIT has been shown to elicit a strong cardiovascular response, and the authors set out to investigate whether this translated into measurable changes in patients.

The authors say that HIIT should be considered to reduce cardiometabolic risk in patients with type 2 diabetes. I would support this but sound a note of caution about the paper.

The study was small, and the effects on glycaemic control did not achieve statistical significance. There was no intervention arm for continuous moderate exercise, so it is unclear whether this would have any benefits compared with the control group.

The study was recruited from volunteers responding to advertisements in local newspapers and from diabetes community groups and a large number of patients failed the selection criteria (201 out of 256 originally assessed for eligibility).

The HIIT would need to be continued, and adherence to the regimen over the longer term would also be important for benefits to be sustained.

Although there are questions to be answered, any increase in activity will benefit patients, and HIIT is a popular exercise regimen at the moment.

DR MATTHEW LOCKYER

● **Cassidy S, Thoma C, Hallsworth K et al (2015). High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia.* doi:10.1007/s00125-015-3741-2**

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