

Quantifying risk of embolism with different COCP formulations

A large observational cohort study has found that use of combined oral contraceptive pills (COCP) containing levonorgestrel with 20 µg of oestrogen was associated with the lowest risk of pulmonary embolism (PE) and arterial thromboembolic events.

The French healthcare system collects data on drugs prescribed, demographic factors, and hospital admission diagnoses. Using this data for a 27-month period, from July 2010 to September 2012, the authors identified 4.9 million women who had

been prescribed a COCP, yielding 5.4 million women years of use.

Overall 3,253 serious events were recorded in COCP users; 1,800 PE, 1,046 ischaemic strokes (CVA), and 407 myocardial infarctions (MI). The absolute risk rates were 33, 19 and 7 per 100,000 women years of COCP use respectively.

More than half (56.7%) of the events occurred among the 26.1% of users who were over 35 years of age.

After controlling for progestogen type and available demographic data (age and socioeconomic status, hypertension and diabetes) users of 20 µg pills had a lower event risk compared with 30-40 µg pills. Adjusted relative risk (RR) for:

- PE, RR 0.75 (95% CI: 0.67-0.85)
- CVA, RR 0.82 (95% CI: 0.70-0.96)
- MI, RR 0.56 (95% CI: 0.39-0.79)

After controlling for oestrogen dose and available demographic data, a lower event risk was found for

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Advertisement Feature

The London Diabetes Centre — first of its kind, joined-up thinking in diabetes care



Dr Ralph Abraham explains how the new identity for London Medical's diabetes practice is a culmination of a vision nurtured over 25 years.



The London Diabetes Centre
Joined-up thinking about
your health and wellbeing

On October 15, the diabetes practice of London Medical marked a major milestone in our 25-year history by commencing operations as The London Diabetes Centre. This marks the achievement of my original vision when I started this practice in 1991 — to found a clinic where people with diabetes, which is complex and requires different specialists and treatments for individual patients, will get better expertise and support at every level, every time, in the course of the disease they live with, for many years.

The conviction that we treat the whole person — not just the disease — remained the touchstone of our success and reputation over the next quarter-century. Today, we are widely regarded not only as the most experienced diabetes team in the UK private sector, but also a global centre of excellence. Almost 20,000 people with every type of diabetes have come to seek our expertise that ranges from preventative to tertiary.

What does our 'whole person' approach look like?

By consciously designing a one-stop shop where the patient is able to access a complete range of specialists required to treat diabetes, take all tests, and find the pumps, insulins, medications, advice and supplies they need in one integrated set-up, in one location. This experience of complete care

was new to patients when we first started, not to mention the ongoing monitoring, patient support and education services that we took to a whole new level.

How are we integrated?

By remaining an integral part of London Medical, thus providing on-site access to expertise in a wider range of specialities and facilities. This is not only necessary but absolutely crucial for the quality management of diabetes where complications implicate every system in the human body. Arteries. The heart. Blood pressure. The liver. Sleep apnoea. Nerves. Eyes. Kidneys. Feet. Skin. Diabetes care involves different systems as glucose and the circulation connects them all. With cardiologists, endocrinologists, ophthalmologists, diabetes nurse specialists, nutritionists, podiatrists, orthotic specialists, neurologists, dermatologists... we cover the field with our deep interconnectivity. This is unique in London, everyone in one place.

As The London Diabetes Centre, we are committed to continually bringing the most advanced treatments and technologies to our patients — from the young who are diagnosed with needing insulin injections, to adults with advanced arterial disease which puts them at risk of heart attack and stroke. Equally, we look forward to continuing to work with the GP community in helping all who live with diabetes live life to the fullest.

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levonorgestrel formulations compared with those containing desogestrel or gestodene. Compared with levonorgestrel RR of PE with desogestrel or gestodene formulations was 2.16 (95% CI: 1.93-2.41) and 1.63 (95% CI: 1.34-1.97) respectively.

Cohort observational studies such as this can only show associations, but given the large number of women observed the results do carry some weight. This is despite the lack of data on BMI and smoking for example. Nevertheless, PE appeared to be the most common of the three serious events observed and was associated with both higher oestrogen and third generation COCPs. CVA and MI were very uncommon in this cohort but an association with higher oestrogen dose COCPs was shown.

I took several messages away from this study. COCPs appear to be remarkably safe with very low absolute numbers of venous and arterial thromboembolic events.

Levonorgestrel containing formulations may be a slightly safer option than the newer progestogen formulations in terms of PE. When prescribing COCPs to over 35 year olds, I will use a 20 µg formulation unless there is a compelling reason not to.

DR CHRIS BARCLAY

Weill A, Dalichampt M, Raguideau F et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ* 2016;353:i2002

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*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 FEV₁ of 0.137 L for SPIOLTO® vs. 0.058 L for tiotropium 5 µg [$p < 0.0001$]).³ 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.³ As measured by the Mahler Transitional Dyspnoea Index (TDI) focal score at 24 weeks. Pooled analysis of the pivotal phase III TONADO 1 and 2 replicate studies.³ An increase in Mahler TDI score indicates an improvement in breathlessness.² Mahler TDI focal score increased by 1.983 units with SPIOLTO® compared to baseline, 1.627 units with Spiriva® compared to baseline and 0.356 units with SPIOLTO® compared to Spiriva® (22% improvement vs Spiriva®; $p < 0.05$).³

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. Pitcaim G et al. *J Aerosol Med* 2005;18:264–272.
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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 ≤ 50 ml/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 beta₂-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. Cardiosensitive 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 beta₂-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 ($\geq 1/100$ to $< 1/10$): Dry mouth. Uncommon ($\geq 1/1,000$ 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

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Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). (UK only)

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