TITLE: Long-Acting Beta2-Agonists for Chronic Obstructive Pulmonary Disease: Safety and Harms

DATE: 19 November 2014

RESEARCH QUESTION

What is the evidence for the safety or harms of long-acting beta2-agonists for patients with chronic obstructive pulmonary disease (COPD), with regards to cardiac arrhythmia?

KEY FINDINGS

Twelve randomized controlled trials and five non-randomized studies were identified on the safety or harms of long-acting beta2-agonists for patients with chronic obstructive pulmonary disease, with regards to cardiac arrhythmia.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and November 7, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients with stable chronic obstructive pulmonary disease (COPD) or patients with both stable COPD and cardiac arrhythmia
Intervention	Long-acting beta2-agonists (e.g., formoterol, salmeterol, Symbicort, Dulera, Advair, Foradil, Oxis, Severent, Indacaterol)
Comparator	Any comparator, including each other
Outcomes	Safety: do they exacerbate a pre-existing arrhythmia? Harms: do they lead to an increased incidence of arrhythmia?
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies (safety only)

COPD = chronic obstructive pulmonary disease

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, and non-randomized studies.

Twelve randomized controlled trials and five non-randomized studies were identified on the safety or harms of long-acting beta2-agonists (LABAs) for patients with chronic obstructive pulmonary disease (COPD), with regards to cardiac arrhythmia. No health technology assessments or systematic reviews were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Twelve randomized controlled trials and five non-randomized studies were identified on the safety or harms of LABAs for patients with COPD, with regards to cardiac arrhythmia. Studies were included if they assessed patients for cardiac arrhythmias or if assessment included use of electrocardiography (ECG) or Holter monitor, despite not specifically mentioning cardiac arrhythmia in the abstract. Overall, the studies indicated that there was no increased harm regarding cardiac adverse events with the use of LABAs or LABAs combined with other drugs, compared with placebo or other monotherapy. No studies indicated if the patient population included those with pre-existing cardiac arrhythmia. Details on the included studies are provided in Table 2.

Table 2: Summary of Included Studies			
First author, year; Length of follow-up	**Study arms (LABA drugs indicated by italics)**	**Patient population; Number of patients (N)**	**Results**
Randomized Controlled Trials			
Donohue, 2014;[1] 52 weeks	• Umeclidinium 125 mcg + *vilanterol 25mcg* • Umeclidinium 125 mcg • Placebo	Patients with COPD; N = NR	Incidence of atrial arrhythmias with umeclidinium + vilanterol were similar to placebo
Donohue, 2013;[2] 24 weeks	• Umeclidinium 62.5mcg + *vilanterol 25 mcg*	Patients with COPD; N = 1,532	No clinically significant changes in

Table 2: Summary of Included Studies			
First author, year; Length of follow-up	**Study arms (LABA drugs indicated by italics)**	**Patient population; Number of patients (N)**	**Results**
	• Umeclidinium 62.5 mcg • *Vilanterol 25 mcg* • Placebo		electrocardiography were observed
Boscia, 2012;[3] Cross-over trial of 28 days each, with 2 week washout period between	• Fluticasone furoate 50 mcg + *vilanterol 25 mcg* • Fluticasone furoate 100 mcg + *vilanterol 25 mcg* • Fluticasone furoate 200 mcg + *vilanterol 25 mcg* • Placebo	Patients with COPD; mean age 58 years; 46% male; N = 54	No significant effects on ECG for all strengths compared with placebo
Hanania, 2012;[4] 28 days	• *Vilanterol 3 mcg* • *Vilanterol 6.25 mcg* • *Vilanterol 12.5 mcg* • *Vilanterol 25 mcg* • *Vilanterol 50 mcg* • Placebo	Patients with moderate to severe COPD; N = 602	No effects on pulse rate or QT intervals corrected for heart rate calculated by Fridericia formula, for all doses, compared with placebo
Lotvall, 2012;[5] 4 weeks	• Fluticasone furoate 400 mcg + *vilanterol 25 mcg* • Placebo	Patients with moderate to severe COPD; N = 60	No clinically relevant effects on vital signs or ECGs/Holter monitors compared with placebo
Chapman, 2011;[6] 52 weeks	• *Indacaterol 150 mcg* • *Indacaterol 300 mcg* • Placebo	Patients with COPD; N = 415	No clinically significant effects on ECGs (corrected QT interval) compared with placebo
Calverley, 2010;[7] 3 years	• *Salmeterol 50 mcg* + fluticasone propionate 500 mcg • *Salmeterol 50 mcg* • Fluticasone propionate 500mcg • Placebo	Patients with moderate to severe COPD; N = 6,184	Salmeterol alone or in combination did not increase the risk of cardiovascular events
Dahl, 2010;[8] 52 weeks	• *Indacaterol 300 mcg* • *Indacaterol 600 mcg* • *Formoterol 12 mcg* • Placebo	Patients with moderate to severe COPD; N = 1,732	Indacaterol had minimal impact on QTc interval
Donohue, 2010;[9] 26 weeks	• *Indacaterol 150 mcg* • *Indacaterol 300 mcg* • Tiotropium 18 mcg • Placebo	Patients with moderate to severe COPD; mean age 63 years; N = 1,683	Incidence of prolonged QTc interval was similar across treatments
Feldman, 2010;[10] 12 weeks	• *Indacaterol 150 mcg* • Placebo	Patients with moderate to severe COPD; mean age 63 years; N = 416	No patient had QTc > 500 msec.
Kato, 2010;[11] Single dose	• *Indacaterol 150 mcg* • *Indacaterol 300 mcg* • *Indacaterol 600 mcg*	Patients with moderate to severe COPD; mean age 67	No indacaterol dose showed clinically meaningful effect on

Table 2: Summary of Included Studies			
First author, year; Length of follow-up	**Study arms (LABA drugs indicated by italics)**	**Patient population; Number of patients (N)**	**Results**
	• Placebo	years; 92% male; N = 50	QTc interval compared with placebo
Van de Maele, 2010;[12] 14 days	• *Indacaterol 600 mcg* + glycopyrronium 100 mcg • *Indacaterol 300 mcg* + glycopyrronium 100 mcg • *Indacaterol 150 mcg* + glycopyrronium 100 mcg • *Indacaterol 300 mcg* • Placebo	Patients with moderate to severe COPD; mean age 64 years; 76% male; N = 255	No clinically relevant differences in QTc interval (Fridericia's) between groups; cardiovascular safety profile similar to placebo
Non-Randomized Studies			
Gershon, 2013;[13] Data from Ontario health care database covering 5.5 years	• *New use of LABAs* • New use of long-acting anticholinergic	Patients with COPD; age ≥ 60 years; N = 191,005	No significant difference in cardiovascular events between the 2 types of medications
Wilchesky, 2012;[14] Data from Saskatchewan health care database covering 13 years	• *New use of LABAs* • New use of ipratropium • Short-acting beta-agonists • Methylxanthines	Patients with COPD; age ≥ 55 years; N = 6,018	New use of LABAs may increase risk of cardiac arrhythmias, but results based on few cases
Wilchesky, 2012;[15] Data from Quebec health care database covering 13 years	• *New use of LABAs* • New use of ipratropium bromide • New use of short-acting beta-agonists • New use of methylxanthines	Patients with COPD; age ≥ 67 years; N = 76,661	New use of LABAs slightly increased the risk of cardiac arrhythmia
Pascoe, 2011;[16] Single dose	• *Indacaterol 400 mcg* • *Indacaterol 1,000 mcg* • *Indacaterol 2,000 mcg* • *Indacaterol 3,000 mcg*	Patients with mild to moderate COPD; ages 43-72 years; N = 16	No clinically significant ECG abnormalities occurred
Worth, 2011;[17] Clinical trial database comprised of studies ≥ 6 months duration	• *Indacaterol* • Other long-acting bronchodilators (*formoterol, salmeterol*, tiotropium) • Placebo	Patients with moderate to severe COPD; N = 4,635	Low incidence of notable QTc interval increases > 60 msec in all active treatments; Holter monitoring showed no clinically relevant effect of indacaterol compared with placebo on the development of arrhythmias

COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; LABA = long-acting beta2-agonist; mcg = microgram; msec = millisecond; N = total number of patients; QTc = corrected QT interval

REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses
No literature identified.

Randomized Controlled Trials

1. Donohue JF, Niewoehner D, Brooks J, O'Dell D, Church A. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. Respir Res [Internet]. 2014 [cited 2014 Nov 13];15:78. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113670
PubMed: PM25015176

2. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med. 2013 Oct;107(10):1538-46.
PubMed: PM23830094

3. Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. Clin Ther. 2012 Aug;34(8):1655-66.
PubMed: PM22789766

4. Hanania NA, Feldman G, Zachgo W, Shim JJ, Crim C, Sanford L, et al. The efficacy and safety of the novel long-acting beta2 agonist vilanterol in patients with COPD: a randomized placebo-controlled trial. Chest. 2012 Jul;142(1):119-27.
PubMed: PM22241764

5. Lotvall J, Bakke PS, Bjermer L, Steinshamn S, Scott-Wilson C, Crim C, et al. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. BMJ Open [Internet]. 2012 [cited 2014 Nov 13];2(1):e000370. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3263438
PubMed: PM22267687

6. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B, et al. Long-term safety and efficacy of indacaterol, a long-acting beta(2)-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest. 2011 Jul;140(1):68-75.
PubMed: PM21349928

7. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Cardiovascular events in patients with COPD: TORCH study results. Thorax. 2010 Aug;65(8):719-25.
PubMed: PM20685748

8. Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax. 2010 Jun;65(6):473-9.
PubMed: PM20522841

9. Donohue JF, Fogarty C, Lotvall J, Mahler DA, Worth H, Yorgancioglu A, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010 Jul 15;182(2):155-62.
PubMed: PM20463178

10. Feldman G, Siler T, Prasad N, Jack D, Piggott S, Owen R, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med [Internet]. 2010 [cited 2014 Nov 13];10:11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2848004
PubMed: PM20211002

11. Kato M, Makita H, Uemura K, Fukuchi Y, Hosoe M, Emery C, et al. Bronchodilator efficacy of single doses of indacaterol in Japanese patients with COPD: A randomised, double-blind, placebo-controlled trial. Allergol Int. 2010 Sep;59(3):285-93.
PubMed: PM20567133

12. Van de Maele B, Fabbri LM, Martin C, Horton R, Dolker M, Overend T. Cardiovascular safety of QVA149, a combination of Indacaterol and NVA237, in COPD patients. COPD. 2010 Dec;7(6):418-27.
PubMed: PM21166630

Non-Randomized Studies

13. Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, Upshur R, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med. 2013 Jul 8;173(13):1175-85.
PubMed: PM23689820

14. Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 1: Saskatchewan cohort study. Chest. 2012 Aug;142(2):298-304.
PubMed: PM22871755

15. Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort. Chest. 2012 Aug;142(2):305-11.
PubMed: PM22871756

16. Pascoe S, Reynolds C, Pleskow W, Perry S, Hmissi A, Kaiser G, et al. Safety, tolerability and pharmacokinetics of single escalating doses of indacaterol, a once-daily beta2-agonist bronchodilator, in subjects with COPD. Int J Clin Pharmacol Ther. 2011 Feb;49(2):153-61.
PubMed: PM21255532

17. Worth H, Chung KF, Felser JM, Hu H, Rueegg P. Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. Respir Med. 2011 Apr;105(4):571-9.
PubMed: PM21227674

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

APPENDIX – FURTHER INFORMATION:

Pooled Studies

Randomized Controlled Trials

18. Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. Lancet Respir Med. 2014 Jun;2(6):472-86.
PubMed: PM24835833

19. Bleecker ER, Siler T, Owen R, Kramer B. Bronchodilator efficacy and safety of indacaterol 150 mug once daily in patients with COPD: an analysis of pooled data. Int J Chron Obstruct Pulmon Dis [Internet]. 2011 [cited 2014 Nov 13];6:431-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186741
PubMed: PM22003288

Non-Randomized Studies

20. Wedzicha JA, Dahl R, Buhl R, Schubert-Tennigkeit A, Chen H, D'Andrea P, et al. Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients. Respir Med. 2014 Aug 4.
PubMed: PM25135743

Study Design Not Specified

21. Donohue JF, Singh D, Kornmann O, Lawrence D, Lassen C, Kramer B. Safety of indacaterol in the treatment of patients with COPD. Int J Chron Obstruct Pulmon Dis [Internet]. 2011 [cited 2014 Nov 13];6:477-92. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186746
PubMed: PM22003293

Review Articles

22. Decramer ML, Hanania NA, Lotvall JO, Yawn BP. The safety of long-acting beta2-agonists in the treatment of stable chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis [Internet]. 2013 [cited 2014 Nov 2013];8:53-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3558319
PubMed: PM23378756

23. Hanania NA. Evaluating the safety of COPD medications: an evidence-based review. Chest. 2013 Oct;144(4):1357-67.
PubMed: PM24081347

24. McKeage K. Indacaterol: a review of its use as maintenance therapy in patients with chronic obstructive pulmonary disease. Drugs. 2012 Mar 5;72(4):543-63. PubMed: PM22356291

25. Steiropoulos P, Papanas N, Nena E, Bouros D. Indacaterol: a new long-acting beta2-agonist in the management of chronic obstructive pulmonary disease. Expert Opin Pharmacother. 2012 May;13(7):1015-29. PubMed: PM22471750

26. Gross NJ, Donohue JF. Nebulized formoterol: a review of clinical efficacy and safety in COPD. Int J Chron Obstruct Pulmon Dis [Internet]. 2010 [cited 2014 Nov 13];5:223-32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921690 PubMed: PM20714376

27. Singh S, Loke YK. An overview of the benefits and drawbacks of inhaled corticosteroids in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis [Internet]. 2010 [cited 2014 Nov 13];5:189-95. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921686 PubMed: PM20714372