# **Review Article**

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# Cardiovascular safety of new inhaled medications for asthma and chronic obstructive pulmonary disease: a critical review from pharmacist perspective

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#### **ABSTRACT**

Individuals with chronic respiratory disorder often have cardiovascular comorbidities and are more vulnerable to adverse effects from medication. Inhaler medications are effective in managing many respiratory diseases, but some have concern about its potential cardiovascular effect from long-term therapy and inappropriate use of these drugs. In the past few years, new members of inhaled long-acting beta-2 agonists and anticholinergics have become available. Based on the published data we reviewed, the adverse cardiovascular effects of these drugs are relatively low, and largely comparable to existing agents. However, most of the studies have very strict selection criteria for subjects, with limited study periods. Therefore, some level of concern remains with the clinical use of these agents, often in patients with substantial cardiovascular or other comorbidities, and are likely to use these drug for very long periods. Perhaps the monitoring of therapeutic efficacy and toxicity by laboratory methods needs to be further explored.

Keywords: Cardiovascular complications, Laboratory monitoring, Respiratory medicine

# INTRODUCTION

The respiratory and cardiovascular systems are closely connected, and are both influenced by the autonomic nerve system. Respiratory disorders are among the common risk factors contributing to the development of cardiovascular diseases (CVD), and effective management of respiratory disorders can reduce complications and mortality from CVD.

However, many medications used for respiratory diseases exhibit extra-pulmonary effects that can adversely affect cardiovascular function.

Advances in drug development and design have significantly reduced the cardiovascular effect of these drugs, including improved receptor selectivity, direct pulmonary drug delivery, reduced bioavailability, and improved elimination of the absorbed drug. In the past few years some new medications were marketed, including two long-acting beta-2 agonists (LABA; indacaterol, vilanterol); and three long acting anticholinergics (LAAC; glycopyrronium, umeclidinium, aclidinium). 1,2

These new agents are indicated as sole therapy or as part of combination therapy, mainly for the treatment of chronic obstructive pulmonary disease (COPD).

However, COPD patients often have cardiovascular comorbidities, and are therefore usually more vulnerable to the extra-pulmonary effect from respiratory drugs. This critical review presents a pharmacist's perspective of the cardiovascular adverse effects (AE) of respiratory

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drugs, especially on new members of (a) inhaled longacting beta-2 agonists and (b) inhaled long-acting anticholinergic respiratory drugs.

# Cardiovascular adverse effects of respiratory drugs

# Beta-2 agonists

Beta-2 agonists are bronchodilators that are commonly used for asthma and COPD, which selectively bind to beta-2 receptors primarily found at the airways. Non-selective beta-agonists (e.g. isoprenaline) will activate beta-1 receptors at the cardiovascular system, contributing to higher mortality. However, studies found that even highly selective beta-2 agonists can affect the heart.

Inhaled beta-2 agonists are generally categorised into short-acting (SABA) and long-acting (LABA).<sup>3-5</sup> Although highly selective, they are known to be associated with extra-pulmonary effects such as tremor, palpitations, headache, hyperglycaemia, and decreased serum potassium levels, as well as potentially contributing to ischemia and heart failure (HF).<sup>6,8-14</sup> It is believed that these effects are related to systemic absorption of the drug.<sup>15</sup> In addition, we also observed tissue specific distribution of beta-2 agonists, whereby the active (R)-salbutamol appeared to accumulate greater in the cardiac tissue.<sup>16</sup>

Furthermore, beta-1 and beta-2-receptors were found adjusting quickly to demand. Continuous exposure to beta-2 agonists can cause down-regulation of the receptors, but its effect on the development of CVD is still unclear. The Studies found that this can lead to diminished response to beta-2 agonists and increased risk of asthma-related deaths, particularly among individuals with genetic risk factor such as Arg16 genotype on the ADRB2 gene. Furthermore, some data suggests that genetic variations at the beta-1 receptor (ADRB1) are related to a higher risk of HF and cardiovascular events, particularly in individuals with long-term exposure to accumulated doses of beta-2 agonist. 21,22

# Short acting beta-2 agonists (SABA)

One of the most common AE from SABA use is increasing heart rate (HR) and arrhythmia.  $^{8,23,24}$  Increased HR is an independent risk factor for cardiomyopathy, myocardial infarction (MI), cardiovascular mortality, and atrial fibrillation (AF).  $^{24}$  It is estimated that every 15 bpm increase in HR is associated with an increased risk of AF by 15%.  $^{24}$ 

The study by Kallergis EM et al has found significant changes in cardiac electrophysiologic properties with SABA use.<sup>23</sup> When SABA was used for subjects with cardiovascular and other comorbidities, some studies reported increased risk of arrhythmia.<sup>24,25</sup> A study investigated 70 critically ill adults that reported 5

incidences of ventricular arrhythmia within recommended doses of SABA, without observing significant increases in HR. <sup>24</sup> In addition, a large cohort study has concluded that the use of beta-2 agonists (both SABA and LABA) was associated with a modest increased risk of arrhythmia, including AF, atrial flutter, and fatal arrhythmias. <sup>25</sup> However, these findings were not consistent, for example, a study observed increased HR without significant changes in QTc in asthmatic children given repeated doses of salbutamol. <sup>8</sup>

SABA use was also found associated with increased incidences of HF. A nested, case-control study involving over 13,000 cases found that SABA use was associated with higher risks of hospital admission due to worsening of HF among subjects who were previously diagnosed with congestive HF.<sup>17</sup> It was suggested that HF can cause beta-1 receptor down-regulation, but the density of beta-2 receptors in myocardial tissue remains unchanged or even increases. Regular use of beta-2 agonists causes desensitisation and down-regulation of cardiac beta-2 receptors, which leads to worsening of disease.<sup>17,18,23</sup> In contrast, individuals without HF would have normal beta-1 receptors, hence beta-2 receptors have a minor role in setting the HR and contractility.<sup>17</sup>

In addition, SABA use was also associated with other cardiovascular AEs. This includes reports of increased incidences in MI, angina, stroke, and transient ischemic attack, as well as other extra-pulmonary effects even at relatively low doses.<sup>26,27</sup>

However, some of these incidences of cardiovascular AE were believed to be clinically insignificant and remain controversial. 8,23,24,27 In addition, most studies had significant limitations, such as the use of self-reported records or lack of controlled groups. Given that SABA treatment is essential and proven effective in relieving symptoms during acute asthma and COPD, the balance of risks and benefits greatly support its use over potential risks of relatively minor AE. However, regular use and over reliance on SABA for relieving symptoms is not recommended, especially among individuals with existing CVD. 28,29

# Long acting beta-2 agonists

The second generation of LABAs (Salmeterol, eformoterol/formeterol) has been commonly used for controlling symptoms of asthma and COPD. 9,30 Large numbers of studies demonstrated their efficacy in reducing symptom frequency and severity. 3,9,29,31 However, the use of LABAs has ongoing safety concerns, since the first generation agent (e.g. fenoterol) was found associated with increased asthma mortality. A long-term study in 2006 has also identified increased asthma related death with the use of salmeterol. 9,31,32 Consequently, LABA is only recommended for use in combination with corticosteroids, especially among asthma patients. 3,5,9,18,26,29,31,33 In addition, ongoing concerns

about the safety and its use in children has prompted the FDA to require more safety studies from drug companies, including 5 double blinded (DB) randomised controlled trial (RCT) by 2017. 34,35

Within the last few years, studies examined the utilisation of inhaled corticosteroids (ICS)+LABAs (salmeterol and efomoterol) in adult asthma patients and observed no significant increase in cardiovascular AEs, including electrocardiogram (ECG) changes, vital signs, and laboratory variables. The reported AEs were considered relatively minor in clinical consequences, and showed no difference between the two LABAs. 5,26,37 However, the use of SABAs was permitted in many studies, and it may mask the true effect of LABAs. 38-41 Some studies also suggested that ICSs can contribute to dose-dependent reduction of cardiotoxicity from LABAs. 5,29,38,42,43 Increased efficacy is believed to be a result of molecular interaction, where ICSs activate the beta2-receptor gene. In turn, LABAs modulate phosphorylation of glucocorticosteroid receptors, priming them for steroiddependent activation. 44,45

Despite no significant differences in overall cardiac AE, a placebo-controlled study that examined the use of salmeterol has observed that African American subjects appear to have increased asthma-related deaths or life-threatening events. The frequency of these events was relatively low (<1%), and suspected to be associated with genetic variation in beta-receptors. In addition, a studies also observed a non-statistically significant trend in the incidence of macrovascular AE, or even reported increased incidence of asthma exacerbation from LABA use in young children. 26,46

In contrast to the treatment of asthma, utilisation of LABAs in COPD is less specific about the co-administration of ICSs. Studies utilising Holter monitoring have observed non-statistically significant trends of increased cardiovascular AEs among LABA-treated subjects (e.g. accelerations of idioventricular rhythms, tachycardia, ventricular extrasystoles). <sup>11,47</sup> In addition, Campbell et al. observed that more than 90% of all subjects experienced at least one episode of supraventricular premature beat in either group. <sup>47</sup> Surprisingly, the study by Hanrahan JP et al observed an overall reduced HR among subjects, and suggested it may be due to overall improvement in COPD. <sup>11</sup>

However, the study observed higher withdrawal rates due to cardiovascular AEs among the LABA treatment group (3.8% vs. 1.7%). Despite the large sample size, a study by Vogelmeier C et al did not report any incidences of cardiac AEs, whereby there was no mention of ECG use or vital signs assessment. <sup>48</sup>

The evidence to date suggested that the use of LABA is relatively safe and effective for asthma and COPD patients.<sup>3,9,29,31</sup> But, few studies have included subjects with both asthma and COPD co-morbidity, or subjects

with significant CVD co-morbidities. In addition, most studies examining COPD patients had limited follow up periods. More recently, very long-acting beta-2 agonists (VLABA) have been developed.<sup>49</sup> Indacaterol was the first VLABA to be approved in 2009, and further VLABAs were developed afterwards, including indacaterol, vilanterol, olodaterol and carmoterol, with indacaterol and vilanterol being registered medications in Australia.<sup>15,49,50</sup> The once a day administration can potentially improve compliance and subsequent symptom control. <sup>15,49,51</sup>

## Indacaterol (maleate, OAB149)

Indacaterol is a fast-acting and long-duration LABA, which has 20-fold greater affinity to beta-2 than beta-1 receptors. <sup>15</sup> It is available as a single ingredient product (150 mcg and 300 mcg) or a combination product with glycopyrronium (QVA149; 110/50 mcg), to be administered via the Breezhaler® inhaler device. <sup>15,52</sup> Studies have found that after a once daily inhaled dose, indacaterol had a bioavailability of 43.2% (75% pulmonary and 25% intestinal absorption), C<sub>max</sub> at 15-30 minutes, half-life of 40-52 hours, and achievesd steady state concentration after 12 to 14 days. <sup>15,52</sup>

A number of clinical trials have demonstrated the efficacy of indacaterol in improving forced expiratory volume in 1<sup>st</sup> second (FEV1) in COPD patients when compared with placebo or other LABAs. <sup>15,40,49,51,53,54</sup> Additionally, regular daily dosing was not found associated with loss in efficacy or potential beta-2 adrenoceptor down-regulation. <sup>55</sup> A 12-week trial has demonstrated that indacaterol is non-inferior to tiotropium. <sup>15</sup> Furthermore, patients reported immediate symptom relief due to the fast onset of action, which can contribute to better compliance. <sup>40</sup>

Cough was a common AE observed in up to 30% of subjects, but most studies demonstrated no statistically significant increase in cardiovascular AEs among study subjects. 15,40,41,51,53-55 However, manufacturer's warnings of systemic effects included: increased HR, blood pressure (BP), and ECG changes, including flattening of T wave, QTc prolongation and ST segment depression. 15

Although only a small fraction of subjects were involved, incidences of cardiac AEs were reported in some of the studies. Korn et al. reported higher incidences of serious cardiac AEs from the indacaterol group compared to the salmeterol group (6 versus 2 subjects). 40

The incidence of tachycardia and tremor were found to be infrequent (2%), whereas the incidence of QTc prolongation was observed in up to 3.3% (vs. 2.0% in placebo group) of subjects, but they were not deemed to be clinically significant (<500 ms). The study by Kerwin EM et al observed no difference in pulse and QTc intervals, but reported significant lowering in diastolic BP among subjects from the 300 mcg indacaterol group. The study by the subjects from the 300 mcg indacaterol group.

Increases in blood glucose were also observed during clinical trials. However, only the study by Dahl et al. reported statistically significant differences between indacaterol 600 mcg (5.86 mmol/L) and the placebo (5.61

mmol/L) after 52 weeks of therapy.<sup>51</sup> Additionally, the study by Kinoshita observed high incidences of subject's self-recorded non-cardiovascular AEs, being the main reason for subject discontinuation from the study.<sup>41</sup>

Table 1: List of studies that examine cardiovascular safety of inhaled long acting beta-2 agonist where significant cardiovascular AE were observed.

Reference	Agent	Study design	Sample	Duration	Cardio- respiratory	Cardiovascular AE	Notes
Appleton <sup>26</sup>	SABA (Salbutamol, Terbutaline); LABA (Salmeterol, Eformoterol)	Longitudinal cohort	3812 asthma subjects; Age>18 year	~3.5years (follow-up)	comorbidity Excluded (except COPD)	SABA is significantly associated with cardiovascular AE; LABA not significantly increases cardiovascular AE; LABA with ICS shows no link to significant AE	No controlled group; No conflict of interest declaired
Campbell <sup>47</sup>	Eformoterol	Prospective, placebo controlled DB-RCT, with parallel- group	204 COPD subjects; Age≥40 year	8 weeks	excluded	Non-clinical meaningful increase in ventricular premature beats; No statistical different in change in QT interval	Funded and supported by Novartis and East Hanover
Dahl <sup>51</sup>	Indaceterol, eformoterol	DB, double- dummy, parallel group study	1,732 COPD patients; Age≥40 year	1 year	Excluded	LABA had minimal influence on QTc interval and systemic events; One single events of atrial tachycardia and QT interval of >60 ms	Funded by Novartis
Donohue <sup>39</sup>	Umeclidinium/ Vilanterol (125/25mcg)	Placebo- controlled DB-RCT	563 COPD patients; Age≥40 year	52 weeks	Excluded	LAMA monotherapy was associated with atrial arrhythmias, whereas combination therapy was similar to placebo; No significant change in HR, QTc or PR interval; Discontinuation was higher in drug groups	Funded by GSK
Feldman <sup>55</sup>	Indacaterol	DB-RCT	416 COPD patients; Age≥40 year	12 weeks	Excluded	AE are similar to placebo; Small changes in potassium levels; Non-significant trends of increased QTc interval in small number of subjects	Supported by Novartis
Kerwin <sup>54</sup>	Indacaterol (75 mcg)	Placebo- controlled DB-RCT	641 COPD patients; Age≥40 year	12 weeks	Excluded	Very well tolerated; Increase infrequent reports of tachycardia and tremor	Supported by several pharmaceutical manufacturers
Kinoshita <sup>41</sup>	Indacaterol	Multicentre, placebo controlled DB-RCT	347 COPD patients; Age≥40 year	12 weeks	Excluded asthma	300 mcg of indacaterol reduces diastolic BP; No significant difference in serum potassium levels, HR, BP, QTc interval; No serious AE reported	Employees of Novartis helped in the preparation of the manuscript
Korn <sup>40</sup>	Indacaterol, Salmeterol	Multicentre, randomised, parallel- group, DB, double- dummy	1123 COPD patients; Age≥40 year	12 weeks	Excluded	Indacaterol showed more serious AE, mostly cardiac disorders; AE were similar across groups;	Funded by Novartis
Nelson <sup>32</sup>	Salmeterol	Multicentre, placebo controlled	26,355; Age > 12 year	28 weeks (terminatio n during	N/A	Small but statistically significant increase in asthma-related deaths and	Termination by GSK

		DB-RCT with parallel- group.		enrolment)		life-threatening events, especially in African American subjects	
Warnier <sup>13</sup>	Beta2- mimetics (not specified)	Ongoing longitudinal, primary care-based, cross- sectional study	158 asthma and 6303 non-asthma subjects; Age>18 year	Up to 2 years per patient in the 7 year study period	Included	Asthma subjects had an increased risk of cardiovascular AE (arrhythmias), but nonasthma subjects had no increased risk	Funded by several agencies and pharmaceutica l manufacturers
Wilchesky <sup>25</sup>	LABA (eformoterol, salmeterol); SABA (salbutamol, fenoterol, isoproterenol, orciprenaclin, pirbuterol, procaterol, terbutaline)	Population- based, retrospective cohort, nested case-control	76,661 patients; Age ≥ 67 year	6.7 years (follow- up)	Included	SABA: significantly increases risk of AF/flutter; LABA/SABA: Modest increase in arrhythmias	Supported by several pharmaceuti cal companies, but not involved in design or conduct of study

Although varying cardiovascular effects were identified, studies so far suggest that the use of indacaterol was relatively safe and effective. Besides of limitations and conflict of interest, these studies only evaluated the short-term safety of the medication and excluded subjects with high risk of CVD. Nevertheless, due to potential effects to the cardiovascular system, indacaterol should be used with caution in patients with CVDs until further safety information is available.

#### Vilanterol

Vilanterol is a highly selective VLABA, with greater beta-2 selectivity than salbutamol, eformoterol and indacaterol. Vilanterol is available via the Ellipta® inhaler device at a dose of 25 mcg daily. It is only available as a combination product, either with an ICS (fluticasone) or with a LAAC (umeclidinium). Studies have found that vilanterol has low bioavailability, where only 27% of vilanterol was absorbed when given as a combination product with umeclidinium. After a once daily inhaled dose,  $C_{\rm max}$  was reached after 5-15 minutes, half-life was 11 hours, and steady state developed after 6 days.

The Vilanterol/fluticasone combination was found to be effective in reducing asthma exacerbations by 24% compared to fluticasone alone, whereas the once a day dosing was believed to be able to improve compliance and disease control. 42,44

The vilanterol/umeclidinium combination product also showed improved lung function among COPD patients.<sup>58</sup> At the time of review, all studies we identified investigated the use of vilanterol in combination with either ICS or LAAC. In general, the use of vilanterol was not found associated with an increased risk of cardiac events, including arrhythmias, cardiac ischemia, hypertension, cardiac failure, QTc prolongation and ECG

changes. 42,58,59 Incidences of cardiovascular AE were very low across treatment groups (<1-2%) and the placebo group (2%). The most commonly experienced cardiovascular AE were ventricular extrasystoles, ventricular tachycardia and AF. 42 A non-statistical significant trend of QTc prolongation was seen in vilanterol groups (3-6%) compared to placebo controlled groups (2%). 42

Among studies that investigate vilanterol/umeclidinium combination therapy, increased HR was observed in the treatment group (by 4.8 bpm). A study by Donohue JF et al also observed some differences among subjects discontinued from the study, where abnormalities in ECG or Holter monitoring was twice as high in treatment than placebo groups. 39

However, a study by Hanania NA et al found that vilanterol monotherapy was not associated with significant changes in QTc interval or vital signs among COPD patients, even with increased doses. <sup>59</sup> However, limitations of these studies make it not possible to distinguish between the effect of vilanterol and SABA use (allowed as when required dosing) and its association with disease severity. In addition, the limited number of clinical trials currently available, strict selection criteria, short duration of follow up and other conflict of interests prevents us from making meaningful conclusions on the long-term safety of vilanterol, which is intended to be used in a wide range of patients with multiple comorbidities.

# Inhaled anticholinergics

Drugs with anticholinergic properties are well known to exhibit cardiovascular AEs, such as increasing HR, affecting heart rhythm, and increasing BP and cardiac output. In addition, other aspects of anticholinergic effects (e.g. sedation, drowsiness, memory impairment) will also inadvertently affect patients with CVDs. The significance of these effects largely depends on the dose, duration, and selectivity of the drugs, as well as the patient's vulnerability. A recently cohort study has found that long-term use of medication with anticholinergic

burden was associated with a significant increase in CVD events and mortality. <sup>61,62</sup> Inhaled anticholinergics such as ipratropium and tiotropium have quaternary nitrogen structures, which reduce systemic absorption.

Table 2: List of studies that examine cardiovascular safety of inhaled long acting beta-2 agonist where significant cardiovascular AE were not observed.

References	Agent	Study design	Sample	Duration	Cardio- respiratory comorbidity	Cardiovascular AE	Notes
Donohue <sup>60</sup>	Umeclidinium / Vilanterol (62.5/25mcg)	Multicentre, placebo controlled, DB-RCT	1532 COPD patients; Age≥40 year	24 weeks	Excluded	No clinical relevant changes compared to placebo (ECG, vital signs, BP, HR, QTc interval)	Funded by GSK
Hanania <sup>59</sup>	Vilanterol (3-50 mcg)	Phase IIb, multicentre, placebo-controlled, DB-RCTp	605 COPD patients; Age40-80 year	28 days	Excluded	AE were similar or lower compared to placebo group; QTc interval and vital signs were similar compared to placebo	Funded by GSK
Jenkins <sup>37</sup>	Eformoterol with budesonide	DB, double- dummy, randomised	489 asthma subjects; Age≥12 year	24 weeks	N/A	Well tolerated; AE, ECG, vital signs and laboratory variables were similar to placebo	Funded by AstraZeneca
Kornmann <sup>53</sup>	Indacaterol, salmeterol	DB, placebo- controlled	1,002 COPD patients; Age≥40 year	26 weeks	Asthma excluded	cardiovascular AE were similar across groups Potassium levels were higher in indacaterol and salmeterol group compared to placebo	Funded by Novartis
Nathan <sup>36</sup>	Eformoterol +/- Fluticasone	Mulitcentre, DB, parallel-group	475 asthma patients; Age>12 year	12 weeks	Excluded	No significant difference to placebo or fluticasone; AE were mild to moderate and no hospitalisations	Several drug companies
Vogelmeier <sup>38</sup>	Eformoterol	Randomised, partially DB (eformoterol and placebo)	847 COPD patients; Age ≥ 40 yr	6 months	Excluded	No cardiovascular AE reported; No significant difference in AE to tiotropium or placebo	Sponsored by several companies, including AstraZeneca and Boehringer Ingelheim
Vogelmeier <sup>48</sup>	Salmeterol	Randomised, DB, double-dummy, parallel-group	7384 COPD patients; Age≥40 year	1 year	Not specified	No cardiovascular AE reported; No significant difference in AE to tiotropium or placebo	Sponsored by several companies, including AstraZeneca and GSK

In addition, the selectivity to muscarinic receptors (especially M3- receptor) helps limit extra-pulmonary AEs. However, a recent study has found that 55% of patients who reported cardiovascular AEs of anticholinergic drugs were using inhaled agents, as well as other extra-pulmonary AE such as urinary retention. <sup>63,64</sup> Nevertheless, the latest report from FDA (in 2010) has concluded that tiotropium use was not related

to increased risks of stroke or heart attack; in contrast, the overall rate of cardiovascular mortality was found to be lower in the tiotropium group than placebo. 65

Inhaled anticholinergics are commonly used for patient with COPD, and demonstrated benefits in reducing incidences of exacerbations and improving symptom control.<sup>66</sup> Therefore, it is reasonable to suggest that

appropriate use of these agents can have cardiovascular benefits, but do not induce remission. Hence, patients were likely to use these agents for long periods of time; usually much longer than those examined in clinical trials. Thus, many questions about its long-term safety still remained unanswered. In addition, many COPD patients have cardiovascular comorbidities, and will likely experience greater negative effects from inhaled anticholinergic use. <sup>66-68</sup>

## Short-acting anticholinergic

Short-acting anticholinergics (e.g. ipratropium) have been used for both asthma and COPD patients for the past decades, but it is not a first line recommended agent to either condition. A Cochrane review in 2013 identified that COPD patients who use ipratropium had higher rates of severe AEs and higher hospitalisation, compared to patients receiving tiotropium. However, the review only identified two eligible studies, and the mortality rate was not found to be significantly different.<sup>69</sup>

A few recent studies have found that ipratropium use was associated with clinically important cardiovascular AEs. A case-control cohort study involving over 15,000 COPD patients reported increased risk of stroke (OR 2.02 and 2.97) among patients who used ipratropium within the past 6 months and within the past 30 days respectively, irrespective of the accumulated dose of ipratropium. Another study linked the exposure of ipratropium with up to a 40% increased risk of cardiovascular events, including HF, acute coronary syndrome and arrhythmia. However, this risk was not associated with patients whose last exposure to ipratropium was more than 6 months ago. <sup>71</sup>

In addition, the Lung Health Study has identified an increase of 5-year cardiovascular mortality (but not overall mortality) among patients using ipratropium compared to subjects being treated with a placebo. 72 The trend of (non-statistically significant) increased incidences of arrhythmia due to ipratropium use was also observed in a large cohort study involving over 75,000 COPD patients from Canada, and among patients with congestive HF.<sup>25,73</sup> Generally, current data is mostly derived from observational studies, and the safety of short-acting inhaled anticholinergies among patients with cardiovascular comorbidity remains unclear. Until more evidence is available, it has been suggested that for patients without considerable underlying risk factors, the clinical significance of cardiovascular effects from ipratropium was relatively low.<sup>25</sup>

# Long-acting anticholinergics (LAAC), or long-acting muscarinic antagonists (LAMA)

Inhaled LAACs, such as tiotropium, is an established primary treatment option for patients with COPD. Unlike short-acting agents, inhaled LAACs are mostly utilised in the treatment of COPD. Despite general concern about

extra-pulmonary anticholinergic effects, studies have demonstrated cardiovascular benefits with the use of LAACs. 68 In the last few years, glycopyrronium, achidinium, and umeclidinium are available as the new inhaled LAACs indicated for the treatment of COPD. Although most studies indicated similar short-term efficacy to tiotropium, its efficacy and safety for long-term use among a wide range of patient was largely unknown.

## **Tiotropium**

Tiotropium delivered by the Handihaler® device has been commonly used for COPD control. The safety and efficacy of long-term tiotropium use has been examined in a few studies, mostly directly through the UPLIFT trial. The UPLIFT trial found that after 4-year of treatment, mortality rate among subjects treated with tiotropium is 16% lower than the placebo controlled subjects.

The tiotropium group also showed reduced cardiovascular mortality, and a very low incidence of stroke and MI, which were not statistically significant.<sup>74</sup> The findings from most of the other studies are largely consistent, and in-line with the 2010 FDA report.65 However, the UPLIFT trial has observed a relatively low mortality rate (~1.1%) among all subjects, whereas data from recent studies raised some concerns about long-term use of inhaled LAACs among patients with pre-existing disorder.62,74 arrhythmia or cardiac epidemiological study utilising UK Healthcare System Database has found that patients who are newly prescribed with tiotropium (compared to LABAs) were associated with higher rates of stroke (OR 1.49), angina (OR 1.38), and MI (OR 1.26).

However, the overall mortality rate was found to be lower (OR 0.7). Recent reviews including over 50,000 subjects from 42 RCT have found that the difference in mortality between tiotropium (delivered in HandiHaler®) and LABA (+/-ICS) were not consistent among studies. Additionally, the use of ICSs could significantly affect outcome findings among subjects with asthma comorbidity.

Besides HandiHaler®, a new Respimat® SoftMist® inhaler was developed for administering tiotropium. A dose of 5 mcg tiotropium via SoftMist® inhaler demonstrated to be non-inferior to 18 mcg via HandiHaler® in improving lung function. The use of the SoftMist® device was associated with increased overall mortality compared to subjects using placebo, LABA, or tiotropium via HandiHaler® (OR 1.51–1.63), and even higher cardiovascular mortality (OR 1.81).

The reason for increased mortality is not yet fully understood, but it is likely to be associated with greater systemic bioavailability, which was found to be dose dependent. On the other hand, a study by Wu YK et al

has shown that 5 mcg via SoftMist® inhaler is not associated with significant change of HR variation after 3 months of therapy, compared to 18 mcg via Handihaler®. Although study findings were not consistent, the safety of higher dose tiotropium via

SoftMist® inhaler is a concern until more data is available. However, these findings should not affect the well-documented long-term safety on the use of tiotropium via Handihaler®.

Table 3: List of studies that examine the cardiovascular safety of inhaled anticholinergics, where cardiovascular AEs were observed.

Reference	Agent	Study design	Sample	Duration	Cardio- respiratory comorbidity	Cardio-respiratory AE	Notes
D'Urzo <sup>89</sup>	Glycopyrronium	Placebo controlle d DB- RCT	822 COPD subjects; Mean age: 64	26 weeks	Excluded	No statistical difference in cardiovascular AE, Reported 3 AF and 2 HF	Sponsor by Novartis
Dahl <sup>92</sup>	Glycopyrronium + indacaterol	Multicen tre, placebo control, DB-RCT	339 COPD subjects; Mean age: 63	52 weeks	Excluded	No statistical difference in cardiovascular AE, Trial registry recorded 7 incidence of cardiac adverse events	Sponsor and writing support by Novartis
Donohue <sup>58</sup>	Umeclidinium, vilanterol, umeclidinium + vilanterol	Placebo- controlle d DB- RCT	1532 COPD subjects; Mean age: 63	24 weeks	Excluded	Serious adverse events are higher in all treatment groups than placebo controlled (6-8% vs 3%); Including 9 fetal events (3 in each treatment groups); Trial registry recorded 10 cases of serious cardiac adverse events from umeclidinium groups (compared to 1 case in placebo controlled)	Sponsor by GSK
Jones <sup>102</sup>	Aclidinium	Placebo control, DB-RCT	828 COPD subjects; Mean age: 62	24 weeks	Excluded	No statistical significant difference in AE between the groups, Trial registry recorded 7 incidences of serious cardiac events (compared to 1 case in placebo controlled)	Sponsor by Almirall
Kelleher <sup>110</sup>	Umeclidinium	Placebo controlle d, DB-4- way crossove r study	16 healthy male subjects; Age 21-58 yr	Single dose PK study	N/A	Modest increase in HR and QTc interval	Supraclinic al dose, GSK conducted trial
Kelleher <sup>109</sup>	Umeclidinium, umeclidinium + vilanterol	Placebo and moxiflox acin- controlle d, crossove r study	103 non- smoking health subjects; Age 19-63 yr	10-day PK study	N/A	AEs are more common in treatment subjects, No significant change in HR, QTc intervals, or other ECG changes	Supraclinic al dose, GSK conducted trial
Kerwin <sup>90</sup>	Glycopyrronium, tiotropium	Placebo controlle d, semi open label study	1066 COPD subjects; Mean age: 64	52 weeks	Excluded	No statistical difference in cardiovascular AE, Reported 4 AF in glycopyrronium group	Sponsor and writing support by Novartis
Singh <sup>104</sup>	Aclidinium + formoterol	Multicen tre, placebo control, DB- RCT, Phase III trial	1729 COPD subjects; Mean age: 63	24 weeks	Excluded	No statistical significant difference in AE between the groups, 4 mortality recorded (3 in aclidinium group) and no result is yet recorded in trial registry	Sponsor and conducted by Almirall

# Glycopyrronium (NVA237)

Glycopyrronium is a new LAAC marketed for the treatment of COPD, delivered via Breezhaler® device in 50 mcg once daily dosing. Its bioavailability was approximately 55%, with most absorption via the lungs, and a long plasma half-life (52-57 hours). 83

A study of 255 moderate-severe COPD patients has found that cardiovascular AEs of glycopyrronium did not show a dose-dependent relationship. A relatively large number of studies have been conducted to examine the use of glycopyrronium in COPD, and initial studies demonstrated therapeutic effects and AEs comparable to tiotropium. However, some studies have reported higher cardiovascular events among glycopyrronium treated subjects than tiotropium or placebo groups.

The rate of AEs observed in short-duration clinical trials is about 5%, and not significantly different to placebo controls. 87,88 A series of GLOW trials has investigated the use of glycopyrronium in extended duration of up to 52 weeks, either as monotherapy or in combination with LABAs. Most studies have found low incidences of extra-pulmonary effects among subjects without significant cardiovascular co-morbidity. However, GLOW 1 trail reported 3 cases of serious AF and 2 cases of congestive HF among glycopyrronium treated subjects; GLOW 2 trial observed high withdrawal rates (76% subjects completed the 52-week study), and reported 4 cases of AF, as well as transient ischemic attack and syncope among glycopyrronium groups, but no difference in mortality.<sup>89,90</sup> Despite similar AEs, the GLOW 7 trial observed a non-statistically significant but higher trend of mortality rate in the 26-weeks study.

The study also observed 5 cases of severe cardiovascular effects, and higher incidences of QTc prolongation (>450msec: 5.6% vs 1.9%; OR increase >30-60 msec from baseline: 5.9% vs 5.2%), but no reports of severe QTc prolongation (>500 msec). A study examined the combination of glycopyrronium+indacaterol observed 5 mortalities among 339 subjects (4 in treatment and 1 in the placebo group) during a 52-week study period, without clinical relevance in ECG or vital sign changes. In addition, the Clinical Trial Registry (NCT01120717) has reported non-statistically significant trends of higher incidences in serious AEs, including 7 incidences of cardiac specific AEs.

#### Aclidinium

Aclidinium bromide is a new LAMA indicated for treatment of COPD with the recommended dose of 375 mcg (322 mcg of aclidinium) twice daily via Genuair® device, or equivalent dose of 400 mcg twice daily via a metered dose inhaler device. Aclidinium exhibits linear time-dependent pharmacokinetics, where studies found that more than 10% of inhaled dose was absorbed into systemic circulation. After an inhaled dose, the drug was

detected in plasma samples within 10-15 minutes, and had a half-life of 1-3 hours. Aclidinium is highly metabolised, but the physiological activities of aclidinium metabolites are largely unknown. <sup>93,94</sup>

Short-duration studies have demonstrated the efficacy of aclidinium in improving respiratory functions (mostly measured by FEV1) among COPD subjects, which is comparable to tiotropium. Most of these studies have reported increased extra-pulmonary effects, but no significant difference in severe AEs was observed. 95-99 A study by Beeh KM et al has observed higher incidence of AEs in the aclidinium group than the placebo (44.1% vs 30.6%), but no mention of cardiovascular effects. [100] Both ACCORD COPD I and ACCORD COPD II trials found no significant increase in clinically important systemic and cardiovascular effects after 12-weeks therapy, and reported low incidences of systemic anticholinergic AEs (<2% of all AEs). ACCORD COPD II trial also determined that no dose-dependent relationship with AE was observed.

Although not statistically significant, the extension study of ACCORD COPD I trial found that approximately 5% of subjects experienced adverse cardiac events during the 52-week study period. According to the report on Clinical Trial Registry (NCT00970268, D'Urzo A et al), the majority of serious cardiac AEs were recorded among subjects assigned to the higher dose of aclidinium. Similarly, a non-statistically significant trend of cardiac AEs was also observed in a 24-weeks clinical study (NCT01001494; Jones PW et al). However, Gelb AF et al. has found the incidences of AEs did not appear to be significantly different between two treatment doses, with only 2% of subjects experiencing cardiac AEs.

One clinical study involving subjects with some cardiovascular comorbidities (ACLIFORM-COPD trial) has found no conclusive evidence of significant safety concerns from aclidinium use (in combination with formoterol). The study found that incidences of severe AEs were <5%, and a potential systemic anticholinergic effect of <3%. Although 4 deaths were recorded in the treatment groups, the study did not report any significant change in ECG pattern.

### Umeclidinium (GSK573719)

Umeclidinium is a new high affinity LAMA that is designed for COPD, with a recommended dose of 62.5 mcg daily via Ellipta® inhaler. After a single inhaled dose, it had an estimated bioavailability of 13%, peak plasma concentration was observed at approximately 5 minutes then disappeared rapidly within 4-5 hours. <sup>105</sup>

Among short-term studies, umeclidinium has demonstrated efficacy in improving lung function (mainly via FEV1) and was generally well tolerated among COPD subjects. This included a study investigating supraclinical dose of 5-10x the dose

currently recommended for clinical use. 107 Longer duration clinical trials have found that the use of

umeclidinium was not associated with a significant increase in cardiac AEs.  $^{58,108}\,$ 

Table 4: List of studies that examine the cardiovascular safety of inhaled anticholinergics, where cardiovascular AEs were not observed.

Reference	Agent	Study design	Sample	Duration	Cardio- respiratory comorbidity		Notes
Beier <sup>98</sup>	Aclidinium, tiotropium	Phase IIIb, placebo controlled, DB- RCT	485 COPD subjects; Mean age: 62	6 weeks	Excluded	No serios cardiovascular AEs are reported	Sponsor by Almirall
Celli <sup>74</sup>	Tiotropium	Multicentre, placebo controlled, DB- RCT	5993 COPD patients; Mean age: 65	4 years	Not specified	Lower mortality rate is observed with tiotropium group	No conflict of interest declared
Decramer <sup>108</sup>	Umeclidinium, umeclidinium + vilanterol, tiotropium,	Multicentre, BD-RCT, parallel controlled 1. UMEC/VI vs VI vs. TIO (NCT01316900)  2. UMEC/VI vs UMEC vs TIO (NCT01316913)	846 COPD subjects; Mean age 63 872 COPD subjects; Mean age: 65	24 weeks	Excluded	Although incidence of adverse event is higher in UMCEC treatment arms compared to TIO, serious AE are lower in UMEC/VI than TIO or VI group. All serious cardiac AE reported in VI arm only No statistical significant in AE incident among all groups, but incidence is relatively high (>30% of participants). Serious AE is slightly higher in UMEC groups compared to TIO (6-11% vs 4%), including all CV AE reported during the study period.	Sponser by GSK
Gelb <sup>103</sup>	Aclidinium	DB- parallel groups study	605 COPD subjects; Mean age 64	52 weeks	Excluded	No statistical significant difference in AE between the groups	No controlled group, Sponsor by Almirall
Kerwin <sup>96</sup>	Aclidinium	Multicentre, placebo control, DB-Phase III trial	561 COPD subjects; Mean age:94	12 weeks	Excluded	No statistical significant difference in AE between the groups	Sponsor by Almirall
Rennard <sup>97</sup>	Aclidinium	Placebo controlled DB- RCT	544 COPD subjects; Mean age:63	12 week	Excluded	Non statistical significant increase in tachycardia, and other systemic anticholinergic effects	Sponsor by Almirall
Trivedi <sup>106</sup>	Umeclidinium	Placebo controlled DB- RCT	246 COPD subjects; Mean age: 63	12 weeks	Excluded	No statistical significant different in adverse event between groups	Sponser by GSK
Van de Maele <sup>84</sup>	Glycopyrronium, indacaterol, glycopyrronium + indacetrol	Placebo controlled, BD- RCT, with parallel group	257 COPD subjects; Mean age: 64	14 days	Excluded	No significant difference in HR or QTc interval	Supported by Novartis, Employees of Novartis helped in the preparation of the manuscript
Wang <sup>91</sup>	Glycopyrronium	Multicentre, placebo controlled DB- RCT	460 COPD subjects; Mean age: 65	26 weeks	Excluded	No statistical difference in cardiovascular AE, Higher trend of mortality	Sponsor by Novartis, Employees of Novartis helped in the preparation of the manuscript

However, Donohue JF et al observed that the use of umeclidinium (+/- vilanterol) was associated with non-statistically significant trends of serious AE, including 9 fatal incidents among 1252 subjects. Other vital observations such as ECG monitoring were not found to be significantly different.<sup>58</sup> In addition, reports in the Clinical Trial Registry identified a non-statistically significant higher incidence of cardiac AEs compared to tiotropium (NCT01316913; Decramer M et al), and placebo (NCT01387230; Trivedi R et al).

Study by Kelleher D et al observed an increase in QTc interval among healthy subjects treated with very high dose of umeclidinium (in combination with vilanterol). <sup>109</sup> This was also seen in subjects commencing verapamil in the study by Mehta R et al However, the study observed an approximate 10 msec increase in QTc interval with no subject experiencing clinically important QTc prolongation (>500 msec, or >60 msec from baseline), and suggested it is unlikely to contribute towards significant adverse clinical outcomes. <sup>105</sup>

# Biochemistry monitoring of therapeutic efficacy and toxicity

Most of the studies identified in this review have very strict selection criteria for subjects, and had limited study periods. Despite the relative low risk of cardiovascular AEs being reported, some level of concerns remain with the clinical use of these agent, especially among patients with substantial cardiovascular and other comorbidities who are likely to use these drugs for very long time period. Biochemistry test, such as serum potassium levels and glucose levels, are known to be associated with some of the cardiovascular AEs. However, most studies showed no change in potassium levels during beta-2 agonist treatment, whereas other studies observed small changes but no mention of its relationship with cardiovascular events. 51,53-55 An earlier semi-open label study has reported a decrease in serum potassium levels in ~5% of subjects treated with LABAs, but no statistically significant difference was observed in laboratory values, ECG and vital signs.<sup>38</sup> In addition, one study has found that serum potassium and glucose levels were slightly increased without reaching significance, and incidences of other AEs were lower in the treatment group.<sup>59</sup>

Although these agents were administered via an inhaler device, small amounts of the drug were absorbed systematically, and it is believed that high plasma levels can contribute to greater extra-pulmonary effects. <sup>9,18</sup> In addition, the systemic bioavailability of drugs largely depends on the pharmacokinetic properties, inhaler device used, as well as technique. For example, Harvey et al identified that ipratropium can exacerbate myocardial injury if it is administered after the onset of acute myocardial ischemia. The degree of exacerbated myocardial injury is found to be similar to atropine. In the study, a significant increase in myocardial injury was

observed at an ipratropium concentration from 1x10-9 M (approximately 412ng/L). However, most studies identified in this review did not examine the systemic concentration of these drugs. Besides, our previous study did not find a linear relationship between plasma salbutamol concentration and the accumulated dose administered, nor did we observe a linear relationship with clinically important AEs, such as effect on QTc interval or serum potassium levels. 112 A similar relationship was also observed during high-dose pharmacokinetic studies of umeclidinium. In addition, most of these agents were extensively metabolised after being systemically absorbed, but cardiovascular AEs of these metabolites were not well studied. For example, Vilanterol has a high first-pass metabolism, mainly by CYP3A4 and as a substrate for the P-glycoprotein transporter, where its primary metabolites have weak beta-agonist activity.<sup>57</sup>

In addition, co-administration with verapamil, a P-glycoprotein transporter and CYP3A4 inhibitor, was found to increase plasma level of umeclidinium by about 40% in a high-dose pharmacokinetic study. 105 However, the plasma level of umeclidinium was not found to be significantly increased among subjects with reduced CYP2D6 activities (poor metaboliser) despite previous indications that the drug was metabolised by CYP2D6 enzymes. 113

#### **CONCLUSION**

In summary, most studies have shown that new LABAs and LAACs were non-inferior to existing agents for the treatment of asthma or COPD. However, studies have not demonstrated a superior safety profile. Additionally, most studies only examined the safety of these agents for a relatively short period, and often excluded subjects with significant cardiovascular and respiratory comorbidities. This is not comparable to real life utilizations of the agents, as many COPD patients have multiple comorbidities and will be likely using these drugs for a long period of time. Therefore, more studies are needed to examine the long-term safety of these agents in a more inclusive clinical scenario.

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