

Limited generalisability of UPLIFT findings to clinical practice

ABSTRACT

Background The findings of the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study may be poorly generalisable to tiotropium use in clinical practice.

Methods An audit of 226 patients admitted to Wellington Hospital with a chronic obstructive pulmonary disease exacerbation determined the proportion of patients prescribed tiotropium on discharge that would have been ineligible for inclusion in the UPLIFT study.

Results Among 100 patients prescribed tiotropium, 38/100; 38% (95% CI 28.5% to 48.3%) would have been ineligible for UPLIFT at the time of the hospital discharge due to recent cardiovascular comorbidity or moderate to severe renal impairment.

Conclusions The UPLIFT findings have limited generalisability to over a third of patients prescribed tiotropium following a hospital admission with a chronic obstructive pulmonary disease exacerbation in New Zealand.

The initial clinical research programme of the inhaled anticholinergic agents ipratropium bromide and tiotropium in chronic obstructive pulmonary disease (COPD) suggested their use may increase the risk of serious cardiovascular events and mortality.¹ ² These concerns were allayed with publication of the large, postregistration study Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) which reported no increased risk of mortality or myocardial infarction with tiotropium HandiHaler.³ However, the UPLIFT findings may be poorly generalisable to patients with COPD, due to the exclusion of potential research participants with recent cardiac comorbidity or renal impairment.^{2,3}

To determine the generalisability of the UPLIFT findings, we undertook an audit of patients admitted to hospital with an exacerbation of COPD. Discharge coding was used to search for all non-elective admissions to Wellington Hospital with a primary diagnostic code of COPD (International Classification of Diseases, 10th Revision code J44.x). Admissions were examined in chronological order from 1 January 2011 until 100 patients prescribed tiotropium on discharge were included. If a patient had multiple admissions, the first admission with COPD was examined. In New Zealand tiotropium is only available in the HandiHaler 18 µg per actuation preparation.

Data were collected from electronic records, including: tiotropium prescribing, cardiovascular comorbidities, renal function and medications. Comorbidities were further categorised by the cardiovascular and renal exclusion criteria used in postregistration tiotropium HandiHaler studies including the UPLIFT trial:

- ▶ cardiac arrhythmias that were deemed unstable or life-threatening, or required intervention or change in drug therapy within the last year
 - ▶ myocardial infarction that occurred within the last 6 months
 - ▶ heart failure (New York Heart Association Class III or IV) that required hospital inpatient management within the last year
 - ▶ moderate to severe renal impairment, which for the audit was defined as a discharge estimated glomerular filtration rate <60 ml/min/1.73 m²
- There were 247 admissions between 1 January 2011 and 31 August 2011.

There were 21 patients excluded because either they did not survive the admission, the discharge diagnosis was not COPD or there were inadequate discharge notes.

There were 100 patients prescribed tiotropium on discharge, of whom 14, 14% (95% CI 7.9% to 22.4%) were also prescribed ipratropium bromide. Of patients prescribed tiotropium on discharge, 38/100, 38% (95% CI 28.5% to 48.3%) would have been ineligible for inclusion in the UPLIFT study because of recent cardiovascular or renal comorbidity (table 1). There were 10/100 patients in whom tiotropium was started during the index hospital admission; 5 of these patients would have been ineligible for inclusion in UPLIFT. Information on eligibility at the time of first tiotropium prescription was not available for the 90 patients prescribed tiotropium prior to hospital admission. The incidence of comorbidities was similar in patients not prescribed tiotropium, reflecting the common occurrence of

Table 1 Cardiovascular and renal comorbidity and medications prescribed in patients with COPD, according to prescription of tiotropium on discharge

	Tiotropium N (% of 100)	Not on tiotropium N (% of 126)
Comorbidity		
Arrhythmias	25 (25)	30 (24)
Atrial fibrillation	19 (19)	27 (21)
Supraventricular tachycardia	6 (6)	1 (1)
Ventricular tachycardia	3 (3)	2 (2)
Myocardial infarction	15 (15)	16 (13)
Heart failure	29 (29)	35 (28)
Renal impairment in the last 1 year	46 (46)	65* (52)
Patients with at least one of the above comorbidities	60 (60)	64 (51)
UPLIFT criteria		
Unstable arrhythmias in the last 1 year	14 (14)	14 (11)
Myocardial infarction in the last 6 months	2 (2)	1 (1)
Heart failure requiring admission in the last 1 year	11 (11)	16 (13)
Moderate to severe renal impairment on discharge	28 (28)	50* (40)
Patients with at least one UPLIFT exclusion criterion	38 (38)	49 (39)
Concurrent medications (%)		
Inhaled short acting antimuscarinic	14 (14)	71 (56)
Inhaled LABA	80 (80)	63 (50)
ICS	88 (88)	89 (71)
Combined LABA/ICS	61 (61)	40 (32)
β blocker	6 (6)	11 (9)
Anticoagulant	38 (38)	56 (44)
ACE-i/Angiotensin II receptor blocker	24 (24)	36 (29)
Loop diuretic	40 (40)	32 (25)
Statin	14 (14)	38 (30)
Digoxin	5 (5)	13 (10)
Calcium channel blocker	13 (13)	19 (15)
Amiodarone	1 (1)	3 (2)
Nitrate	8 (8)	9 (7)

*Total number=124 as two patients in the non-tiotropium group had no renal function measured during admission. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long acting β agonist; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

cardiovascular and renal comorbidities in patients admitted with an exacerbation of COPD, and suggesting their presence did not influence its prescription.

In summary, 38% of patients prescribed tiotropium would not have been eligible for inclusion in the UPLIFT study at the time of hospital discharge due to recent cardiovascular or renal comorbidity. The tiotropium HandiHaler datasheet does not give details of the limited evidence-base for tiotropium HandiHaler in patients with COPD with these comorbidities⁴ and this is likely to underlie the observed prescription patterns.

We conclude that the UPLIFT findings have limited generalisability to over a third of patients prescribed tiotropium following a hospital admission with a COPD exacerbation in New Zealand.

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