Lessons From Large Clinical Trials in Managing COPD Patients

KOAH Hastalarının Klinik Takibinden Elde Edilen Dersler

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ABSTRACT

Large, multicenter, randomized controlled trials in COPD have recently been completed. The largest of these studies are "Towards a Revolution in COPD Health" (TORCH) and "Understanding Potential Long-Term Impacts on Function with Tiotropium" (UPLIFT®). These studies make considerable contributions to understanding the natural history of COPD. The objective of this article is to review the data from these different trials in order to find what can be learnt of the management of COPD. The long-term improvements in lung function, health-related quality of life, and possibly survival from the use of long-acting bronchodilators in these trials suggest an influence on the progression of the disease.

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Key words: Bronchodilators, lung function, FEV_1, fluticasone, inhaled corticosteroids, long-acting beta agonists, long-acting anticholinergics, mortality, salmeterol, tiotropium

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ÖZET

Kronik obstrüktif akciğer hastalığında yürütülen çok merkezli ve randomize kontrollü çalışmalar yakın zamanda tamamlanmıştır. Bu çalışmalardan en büyük olanları TORCH ve UPLIFT® dir. Bu çalışmalar KOAH' ın doğal seyrinin anlaşılmasını sağlayan önemli katkılar sağlamaktadır. Bu yazıda KOAH tanı ve tedavisine katkısı olabilecek birçok farklı çalışmanın sonuçlarının değerlendirilmesi amaçlandı. Bütün bu çalışmalarda, uzun etkili bronkodilatörlerin kullanımının, solunum fonksiyonlarını, sağlıkla ilişkili yaşam kalitesini ve büyük olasılıkla sağ kalımı etkileyerek hastalık seyri üzerinde olumlu etkiler gösterdiğini desteklemektedir.

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Anahtar sözcükler: Bronkodilatörler, akciğer fonksiyonu, FEV_1, flutikazon, inhale kortikosteroidler, uzun etkili beta agonistler, uzun etkili antikolinerjikler, mortalite, salmeterol, tiotropium

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Burden of COPD

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, and represents a substantial economic and social burden worldwide. Global prevalence of COPD in the general population has been reported to be between 7.5% and 10% [1-3], and is predominantly associated with smoking. In a meta-analysis of 67 population-based studies (representing >111,000 cases of COPD from 28 countries), the prevalence of COPD was significantly higher among smokers (15.4%) and ex-smokers (10.7%) than people who had never smoked (4.3%) [2]. Prevalence of COPD was the subject of a prospective study in Turkey and reported in the BOLD study. The Adana study demonstrated a COPD prevalence of 12 %, most of these patient had not previously been diagnosed or received any treatment [1].

The burden of morbidity and mortality due to COPD is predicted to increase [4]. COPD is the fourth leading cause of mortality in the US and Europe [5], and approximately 2.7 million deaths worldwide were attributable to COPD in 2000 [4]. Age-adjusted mortality due to COPD doubled between 1970 and 2002 in the US [6], and total deaths from COPD are projected to increase by more than 30% in the next 10 years [7], with notable increases predicted in women [4].

It is not surprising that the economic costs attributed to COPD are substantial. For example, mean annual direct costs of COPD under usual clinical practice in Spain were calculated in a prospective study to be 1876 US$ per patient in 2003 (nearer 3000US$ for severe COPD) [8], which is approximately twice the equivalent cost reported for asthma [9]. In the UK, direct costs were estimated to equate to approximately 1900US$ per per-

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son per year in 1996, whilst in the US in the late 1990s, the annual cost of COPD was estimated to be 23.9 billion US$, equating to approximately 1500US$ per patient per year [10].

Rationale for large clinical studies: TORCH and UPLIFT®

A post hoc analysis of randomized controlled trials reported that the long-acting anticholinergic drug, tiotropium, may reduce the rate of decline in FEV_1 in COPD patients [11]. In addition, two retrospective analyses suggested that use of ICS, either as monotherapy or in combination with a long-acting $ß_2$-agonist (LABA), may reduce all-cause mortality in patients with COPD [12-13]. Longer-term trials were required to further investigate these effects: specifically an effect of LABA/ICS on all-cause mortality and of tiotropium on the rate of decline in FEV_1.

The "Towards a Revolution in COPD Health" (TORCH) trial was a 3-year, double-blind, parallel-group, placebo-controlled study of 6184 COPD patients randomized to salmeterol and fluticasone propionate, either as monotherapy or in combination. The primary outcome was all-cause mortality over 3 years [14], with a post hoc analysis on the rate of decline in FEV_1 [15].

The "Understanding Potential Long-term Impacts on Function and Tiotropium" (UPLIFT®) trial was a 4-year, randomized, double-blind, placebo-controlled, parallel-group study involving 5993 patients with moderate-to-severe COPD randomized to receive either tiotropium or placebo. These patients continued to receive their otherwise usual bronchodilator therapy. The primary outcome of the UPLIFT® study was rate of decline in FEV_1 over 4 years [16].

Summary of key findings from TORCH and UPLIFT®

TORCH

TORCH did not achieve a significant decrease in mortality among patients treated with LABA–ICS combination therapy versus short-acting bronchodilators (placebo) (hazard ratio [HR] 0.825, 95% confidence interval [CI], 0.681–1.002; p = 0.052) [17]. However, active treatments significantly reduced the annual rate of exacerbations compared with placebo ($p < 0.001$) and exacerbations requiring hospital admission were reduced with the combination therapy and salmeterol alone compared with placebo ($p \leq 0.03$). The combination therapy also improved average HRQL compared with placebo and monotherapies over the 3-year trial period. Adverse event data from TORCH indicated an increased incidence of pneumonia among patients receiving ICS treatment, both as a combination treatment and as monotherapy.

Sustained increase in lung function was observed in all active groups compared with placebo (short active bronchodilators group) [17]. A post hoc analysis (stated as being planned before unblinding) on rate of decline in postbronchodilator FEV_1 showed an effect on the active treatment groups compared with placebo [15]. The rate of FEV_1 decline was 55 ml/year in the placebo (short-acting bronchodilators) group. In comparison, the rates of decline in the active treatment groups were significantly less ($p \leq 0.03$) at 39 ml/year for combined therapy and 42 ml/year for ICS and LABA monotherapy. The rates of decline were similar between the active treatment groups, with no significant benefit of the combination over the individual components.

UPLIFT®

UPLIFT® reported on moderate to severe COPD patients who received the usual treatment (including LABA, ICS alone or in combination), and were randomized to tiotropium or placebo (control). These data did not show significant differences in the rate of decline in lung function or HRQL score between the tiotropium and control groups, but achieved a sustained increase in lung function and HRQL over 4 years ($p < 0.001$) [18]. The rate of postbronchodilator FEV_1 decline was 40 ml/year for tiotropium and 42 ml/year for the control group. At the end of the 4-year treatment period, the tiotropium group had not yet reached the level of impaired HRQL documented at baseline. Further, statistical significant increase in the proportion of patients achieving the reported minimal clinically significant difference of at least 4 units ($p < 0.001$) occurred in the tiotropium group compared with the control group.

UPLIFT® demonstrated a significant reduction in the risk of having an exacerbation and an exacerbation leading to a hospitalization in the tiotropium group. Survival was significantly increased while patients received tiotropium and when including the follow-up of prematurely discontinued patients for the protocol-defined treatment period. Additionally, overall cardiac and respiratory morbidity was reduced.

Comparison of designs

As expected for trials with different primary objectives, considerable differences exist between the TORCH and UPLIFT® trial designs and entry criteria (Table 1). Aside from the different primary and secondary outcomes and treatment durations, a key difference is the medications that were permitted during the trials, other than the study drugs [14,16]. TORCH patients in the placebo (maintenance with short-acting bronchodilators) group did not receive appropriate maintenance treatment according to the GOLD guidelines [19], which should include long-acting bronchodilators. This treatment group cannot, therefore, be considered as "standard" or "usual" care. Indeed, in part due to the positive outcomes of TORCH, this type of long-term, inappropriately-treated "placebo" comparison would no longer be considered ethical.

The UPLIFT® study permitted use of ICS, LABA, and their combination, but excluded inhaled anticholinergics. No restrictions were imposed for medications prescribed to treat exacerbations. Hence, UPLIFT® closely represented "usual" COPD care as underlying therapy, other than inhaled anticholinergics, regardless of whether

Table 1. Study designs

	UPLIFT®	TORCH
Duration (years)	4	3
Number of randomized patients	5993	6112
Primary endpoint	Decline in lung function	All-cause mortality
Secondary endpoints	• Decline in SGRQ score • Exacerbations • Mortality	• Exacerbations • SGRQ score
Run-in phase	• Continue therapy and adaptation (except inhaled anticholinergics)	• Withdrawal (ie, ICS, LABA and tiotropium)
Nonpermitted respiratory medications	• Other inhaled anticholinergics	• Other ICS • Other LABA • Long-term use of oral corticosteroids • Tiotropium (unavailable at onset of trial, excluded throughout)
Frequency of control visits	• General: 3 months (+ first month) • Lung function: 6 months (+ first month) • SGRQ: 6 months	• General: 3 months • Lung function: 6 months • SGRQ: 6 months
Reversibility test	• 80 µg ipratropium bromide plus 400 µg salbutamol • No exclusion due to reversibility	• 400 µg salbutamol • Exclusion of patients with >10% reversibility
Quality assurance of spirometry	• Standardized equipment • External quality assurance • External, blinded reading	• Office-based spirometry • No additional quality assurance
Evaluation of mortality	• Vital status to 4 years • Vital status to 4+ years • Lower respiratory-related mortality • Cardiac-related mortality • On-treatment mortality • Primary COD determined by independent committee	• Vital status to 3 years • COPD-related mortality to 3 years • On-treatment mortality • Primary COD and relationship with COPD determined by independent committee • Two interim safety analyses
Definition of exacerbation	• An increase in, or new onset of, more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid	• A symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these
Inclusion criteria	• Outpatient with clinical diagnosis of COPD • Age ≥40 years • Smoking history ≥10 pack-years • Postbronchodilatora FEV_1 ≤70% predictedb • Postbronchodilatora FEV_1/FVC ≤70%	• Diagnosis of COPD • Age 40–80 years • Smoking history ≥10 pack-years • Prebronchodilator FEV_1 ≤60% predictedb • Prebronchodilator FEV_1/FVC ≤70% • Postbronchodilatorc FEV_1 increase <10% of predicted valueb
Exclusion critera	• Asthma or a coexisting illness that could preclude participation in the study or interfere with the study results • Use of oxygen therapy for >12 hours/day • Respiratory infection or exacerbation of COPD within 4 weeks of screening or during the run-in period • Recent history of myocardial infaction or heart failure • History of thoractomy with pulmonary resection	• Asthma or a coexisting illness that could preclude participation in the study or interfere with the study results • Use of oxygen therapy for >12 hours/day • Respiratory infection or exacerbation of COPD within 4 weeks of screening or during the run-in period • Recent history of myocardial infaction or heart failure • History of thoractomy with pulmonary resection

Notes: After supervised administration of 80 µg ipratropium (four actuations) followed by 400 µg salbutamol (four actuatations) 60 minutes later and the test was 30 minutes after the salbutamol dose (test 90 minutes after ipratropium); bEuropean Community for Coal and Steel (ECCS) criteria; c400 µg salbutamol.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β2-agonists; SGRQ, St George's Respiratory Questionnaire; COD, cause of death. (Reproduced with permission from reference 58)

patients were randomized to receive tiotropium or placebo. At baseline, 60% of patients in UPLIFT were being treated with ICS or LABA (either alone or in combination) and evidence suggests that more patients may have been prescribed these drugs during the trial [18]. Hence, many patients in the control group in UPLIFT® could have been receiving similar medication to that of the active groups in TORCH.

Comparison of patients

Demographic characteristics were similar between the two study populations. In both trials, the mean age of patients was 65 years and 75% of patients were male, which is typical of the demographics of treated patients with COPD. Mean body mass index (BMI) for both studies was also similar (25 and 26 for TORCH and UPLIFT®, respectively). Mean duration of COPD was approximately 10 years in the UPLIFT® study; however, similar statistics were not provided for the TORCH trial.

Mean prebronchodilator FEV_1 was similar between the two trials (approximately 1.1 litres). Mean baseline postbronchodilator FEV_1 (absolute and percent predicted) was higher in UPLIFT® (around 47% of predicted) than in TORCH (around 44% of predicted). In contrast, the mean baseline FEV_1/forced vital capacity (FVC) was lower in UPLIFT® (around 43% of predicted) compared with TORCH (around 48% of predicted). However, these differences between the trials may in part be due to the different short-acting bronchodilator regimen used (see above), which makes comparisons difficult.

Comparison of the TORCH and UPLIFT® decline in lung function

Rate of decline in FEV_1

The data from the post-hoc analysis of TORCH suggest that all three active groups reduce the rate of decline in postbronchodilator FEV_1 [15]. Adjusted rates of decline in FEV_1 were –42±3 ml/year for salmeterol alone and fluticasone propionate alone, –39±3 ml/year for salmeterol/fluticasone combination, and –55±3 ml/year for placebo (short-acting bronchodilators) (Figure 1). No significant differences exist between the combination and individual drugs alone. In an editorial, Suissa suggested that the patients who withdrew from the study could have had the lowest FEV_1 values at the beginning of the study and therefore, the "regression to the mean" could have exaggerated the rate of decline since these were the patients with the slowest decline in FEV_1 [20].

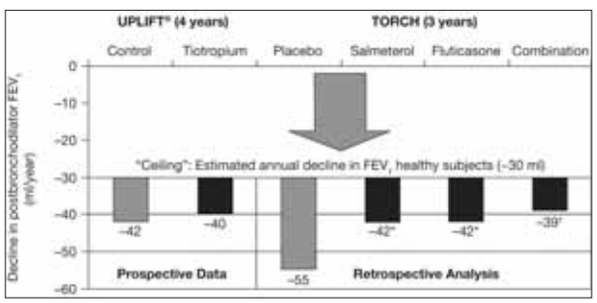

Figure 1. Change in rate of decline in FEV_1 in UPLIFT® and TORCH, including ceiling effect (possible rate of decline in healthy individuals). Data from the individual trials have been placed on the same axes for illustrative purposes only and do not represent directly comparable data between the trials. (Reproduced with permission from reference 58)
Abbreviations: FEV_1, forced expiratory volume in 1 second.
Notes: *p = 0.003 vs placebo; †p < 0.001 vs placebo.

The effect of ICS on the rate of decline in FEV_1 were reported from two meta-analyses of randomized placebo-controlled trials ≥1 year in length [21-22]. The majority of the same trials were included in both meta-analyses, but these studies reported different results. As the rate of FEV_1 decline was a tertiary endpoint in TORCH, it is sensible to view the data from this trial as hypothesis generating only; they continue to propose the hypothesis that FEV_1 decline in COPD can be reduced by pharmacotherapy.

Additional support for this hypothesis comes from a post hoc, retrospective analysis of two 1-year trials with tiotropium. These double blind, placebo-controlled, randomized trials comparing tiotropium (total N=971) with placebo showed promising improvement in the rate of decline of FEV_1. The mean decline in trough (premedication) FEV_1 was 46 ml/year lower between days 8 and 344 (p=0.005) and 40 ml/year lower between days 50 and 344 (p=0.036) versus short-acting bronchodilators (placebo) [11]. These data, along with the TORCH post-hoc data, suggest that FEV_1 decline can be reduced by effective treatment with maintenance long-acting bronchodilator therapy alone.

UPLIFT® showed no difference between tiotropium and the control group in terms of rate of decline in FEV_1 (calculated from day 30 until end of study) for both components of the primary outcome: differences were 2 ml/year when measured postbronchodilator (–40±1 vs –42±1 ml/year; p=0.21; Figure 1) and 0 ml/year when measured prebronchodilator (–30±1 ml/year for each group; p=0.95) [18].

Consideration of the UPLIFT® and TORCH data together, and in the context of other studies, may indicate an important insight into the decline in FEV_1. The rate of decline observed in the control arm of UPLIFT® (–42 ml/year) is similar to that for the active monotherapy groups in TORCH (–42 ml/year). The active group in UPLIFT® produced a similar rate of decline to the TORCH salmeterol/fluticasone combination group (–40 vs –39 ml/year). As the TORCH investigators indicated, the TORCH placebo group was similar to the placebo groups (use of short acting bronchodilators only) reported in previous trials [23-30]. However, the UPLIFT® control group included patients treated with LABA and ICS (72%, 74%, and 46% received LABA, ICS, or LABA/ICS combination, respectively), and could therefore be considered a more "active" control group than the TORCH placebo. It is possible that tiotropium was unable to further reduce this decline due to a ceiling effect (ie, medications can only reduce the rate of decline to a certain amount since there is a basal rate of decline in FEV_1 in normal individuals) (Figure 1).

Table 2. Mean (SE) rate of decline (ml/year) in postbrochodilator FEV_1 by subgroup

	UPLIFT®				TORCH[40]	
	Control	Tiotropium	Difference	p value	All patients	p value
Age (years)				**0.57[a]**		**< 0.001[b]**
<55	54 (4)	47 (3)	–6 (5)	0.21	51.7 (4.3)	
≥55, <65	48 (2)	45 (2)	–3 (3)	0.29	51.3 (2.6)	
≥65, <75	35 (2)	36 (2)	1 (3)	0.84	39.5 (2.4)	
≥75	35 (4)	29 (4)	–6 (6)	0.35	36.7 (4.7)	
Smoking status				**0.90[a]**		**< 0.001[b]**
Former	38 (2)	36 (2)	–2 (2)	0.34	36.6 (2.1)	
Current	52 (3)	50 (2)	–4 (4)	0.45	55.0 (2.3)	
Region[c]				**0.81[a]**		**< 0.001[b]**
Asiac	31 (6)	26 (5)	–5 (8)	0.54	30.7 (4.2)	
Eastern Europe	43 (3)	45 (3)	2 (4)	0.61	38.2 (3.3)	
Latin America	44 (5)	42 (5)	–2 (7)	0.82	n/a	
US	39 (3)	35 (3)	–4 (4)	0.34	49.4 (3.4)	
Western Europe	45 (2)	41 (2)	–4 (3)	0.22	50.9 (2.8)	
Other	n/a	n/a	n/a	n/a	48.4 (4.2)	
Gender				**0.63[a]**		**= 0.027[b]**
Male	43 (1)	41 (1)	–2 (2)	0.38	46.6 (1.8)	
Female	39 (3)	35 (3)	–4 (4)	0.29	38.5 (3.2)	
GOLD Stage				**0.08[a]**		**n/p**
I/II	49 (2)	43 (2)	–6 (3)	0.02	n/p	
III	38 (2)	39 (2)	0 (3)	0.87	n/p	
IV	23 (5)	32 (5)	9 (7)	0.24	n/p	
BMI[d]				**0.77[a]**		**< 0.001[b]**
<20	55 (4)	53 (4)	–1 (6)	0.85	51.1 (4.4)	
≥20, <25	49 (2)	44 (2)	–5 (3)	0.12	50.2 (2.5)	
≥25, <30[d]	37 (2)	36 (2)	–2 (3)	0.59	42.1 (2.9)	
≥30[d]	34 (3)	34 (3)	0 (4)	0.98	35.1 (3.2)	
Concomitant medication						
LABA				**0.57[a]**		**n/p**
Yes	44 (2)	40 (2)	–4 (3)	0.22	n/p	
No	41 (2)	39 (2)	–2 (2)	0.54	n/p	
ICS				**0.68[a]**		**n/p**
Yes	45 (2)	42 (2)	–3 (3)	0.27	n/p	
No	40 (2)	38 (2)	–2 (2)	0.47	n/p	
LABA + ICS				**0.71[a]**		**n/p**
Yes	43 (2)	42 (2)	–2 (3)	0.52	n/p	
No	41 (2)	38 (2)	–3 (3)	0.26	n/p	
Anticholinergics				**0.69[a]**		**n/p**
Yes	42 (2)	39 (2)	–3 (3)	0.22	n/p	
No	42 (2)	41 (2)	–2 (3)	0.60	n/p	

Notes: [a]Subgroup by treatment interaction; [b]Effect of covariate on slopes of all patients pooled regardless of study drug group; [c]Geographical descriptions differed trials. Pacific countries were combined with Asia in TORCH; [d]BMI = weight (kg)/[height (m)]^2. 29 was the cut-off for TORCH.
Abbreviations: n/a, not applicable; n/p, not published; GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI, body mass index; ICS, inhaled corticosteroids; LABA, long-acting $ß_2$-agonists. (Reproduced with permission from reference 58)

The UPLIFT® authors suggest some preliminary evidence to support the above hypothesis of a ceiling effect. Subgroup analysis of the 1554 patients not receiving ICS or LABA at baseline showed a significantly lower postbronchodilator rate of decline in FEV_1 for tiotropium versus control (40±3 vs 47±3 ml/year; p= 0.046) [18]. However, this needs further investigation, since interpretation is currently difficult. As such, the greater effect seen in TORCH compared with UPLIFT® may be driven by the less active treatment received by the placebo group in the TORCH study versus the control group in the UPLIFT® study. Therefore, results from TORCH and UPLIFT® suggest that all treatments, including maintenance therapy with long-acting bronchodilators, can reduce the rate of decline in FEV_1, with the impact on this decline being dependent on the type of agent or combination of agents received.

Subgroup analyses of UPLIFT® and TORCH also provide us with some insight into patient characteristics that may affect the rate of FEV_1 decline (Table 2). There are some consistencies in the results seen in the studies. For instance, seemingly contrary to previous models of decline in lung function in COPD [31], decline is more rapid in younger patients (aged <55 years) than older patients. BMI was associated with the rate of FEV_1 decline, with a higher BMI seemingly being beneficial in both trials. Low BMI and fat-free mass are known independent predictors of disease severity and mortality [32-33], however, this association with the rate of FEV_1 decline is a novel finding. Although the rate of FEV_1 decline appears to be more rapid in men than women, percentage changes in rate of decline in FEV_1 were similar between the sexes, suggesting that this may be associated with airway size rather than a true difference in rate of disease progression. Geographical region was also associated with the rate of decline; however, with the exception of a lower rate of decline in Asia, this was not consistent between the studies and, therefore, could also be an artefact of airway size. In UPLIFT®, the rate of FEV_1 decline was more rapid in the earlier stages of COPD (GOLD stage II vs stages III and IV). Importantly, there is some suggestion that tiotropium may positively affect the rate of decline in these earlier stage patients (p=0.02), although further supportive evidence is required to confirm this observation.

Comparison of exacerbation data

Exacerbations are part of the natural course of COPD and are responsible for the morbidity and mortality of this disease [34-37]. Exacerbations are associated with reduced quality of life [38-40] and increased mortality [41]. They are also the main driver of costs in COPD [42]. Unsurprisingly, therefore, reducing exacerbations is a key goal of COPD treatment [19].

There is inconsistency in how exacerbations are defined and analyzed, which makes it difficult to compare data on exacerbations between trials [43]. In UPLIFT®, an exacerbation was defined as "an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days, requiring treatment with an antibiotic and/or systemic (oral, intramuscular or intravenous) steroid" [16]. Exacerbations were categorized as mild (treated at home without seeing a healthcare provider), moderate (visit with healthcare provider, at home or as outpatient), or severe (requiring hospitalization for >24 hours). In TORCH, exacerbations were defined as symptomatic deterioration requiring treatment with systemic corticosteroids and/or antibiotics (moderate exacerbation) or hospitalization (severe exacerbation) [14,17].

In UPLIFT®, compared with controls, tiotropium significantly delayed time-to-first exacerbation (16.7 vs 12.5 months) and time-to-first hospitalization for exacerbations (lower risk of hospitalization; HR, 0.86 [95% CI, 0.78–0.95]; p=0.002) (Table 3) [18]. Exacerbations requiring hospitalization were infrequent (0.15 vs 0.16 per patient-year), which may explain why any difference between tiotropium and placebo groups was not statistically significant (p=0.34). Tiotropium also reduced the

Table 3. The most frequently occurring adverse events categorized by ranges of incidence rate per year

Incidence rate per range (actual)	UPLIFT® (4 years)		TORCH (3 years)[15]			
	Control	Tiotropium	Placebo	Salmeterol	Fluticasone	Combination
≥0.10	COPD ex (0.46)	COPD ex (0.38)	COPD ex (0.92) Upper RTI(0.10)	COPD ex (0.76)	COPD ex (0.78) Nasopharyngitis(0.10)	COPD ex (0.67) Upper RTI (0.11) Nasopharyngitis (0.10)
0.08–0.09	-	-	Nasopharyngitis (0.09) Headache (0.08)	Nasopharyngitis (0.09) Upper RTI (0.08)	Upper RTI (0.09)	Nasopharyngitis (0.09)
0.06–0.07	-	-	-	Headache (0.06)	Pneumonia (0.07) Headache (0.06)	Pneumonia (0.07)
0.04–0.05	Dyspnea (0.05) Pneumonia (0.05) Nasopharyngitis (0.04) Upper RTI (0.04)	Pneumonia (0.05) Nasopharyngitis (0.04) Dyspnoea (0.04)	Bronchitis (0.05) Pneumonia (0.04) Back pain (0.04)	Bronchitis (0.05) Pneumonia (0.04) Back pain (0.04)	Bronchitis (0.05) Back pain (0.04) Sinusitis (0.04) Cough (0.04)	Bronchitis (0.05) Headache (0.05) Back pain (0.04) Sinusitis (0.04)

Abbreviations: COPD ex, chronic obstructive pulmonary disease exacerbations; RTI, respiratory tract infection. (Reproduced with permission from reference 58)

mean number of exacerbations by 14% (rate per patient-year, 0.73 vs 0.85; HR, 0.86 [95% CI, 0.81–0.91]; p < 0.001), and reduced the number of days with exacerbations (13.64 vs 12.11; HR, 0.89 [95% CI, 0.83–0.95]; p=0.001) compared with controls. These results were consistent with those from other shorter duration studies in which tiotropium has been shown to reduce the number of exacerbations by 20–50% [44,48], number of exacerbation days by 31–50% [45,47,48], number of hospitalizations due to exacerbations by 20–30% [49] and time-to-first exacerbation [44,45,47]. Compared with short-acting bronchodilators, associated healthcare resource utlilization was also consistently reduced with tiotropium in these earlier studies [45,47,49].

Rates of moderate or severe exacerbations per patient-year were reduced in all active groups in the TORCH study (0.85, 0.93, 0.97, and 1.13 for combination, fluticasone only, salmeterol only, and placebo groups, respectively; p<0.001 vs placebo); significantly lower rates were also seen with the combination group vs salmeterol (p=0.002) and fluticasone (p=0.02) monotherapy groups [17]. Both the combination and salmeterol groups reduced, by the same magnitude, the rate of exacerbations requiring hospitalization versus placebo (0.16 and 0.16 vs 0.19 per patient-year; p=0.03 and p=0.02, respectively) [17]. These data confirm those from a previous 1-year study in which salmeterol/fluticasone combination and the single agents have reduced the frequency of exacerbations by 25% and 19–20%, respectively [5].

It is possible to draw some comparisons between the UPLIFT® and TORCH studies. There were significant improvements in multiple measures of exacerbations with the active groups in both trials. In terms of rates of exacerbations per patient-year, these were slightly lower with tiotropium compared with the active treatment groups in TORCH (0.73 vs 0.85–0.97). Similar to the results for lung function decline, the exacerbation rate (0.85 per patient-year) in the placebo group in UPLIFT® was closer to the rates seen in the active treatment groups in TORCH than the TORCH placebo group (exacerbation rate of 1.13 per patient-year). Again, the fact that the UPLIFT® placebo group included patients treated with LABA and ICS, and the postulated "ceiling effect" described above, may explain why there was a relatively low rate of exacerbation in this group compared with the TORCH placebo group and, therefore, why the extent of the improvement beyond this (14%) with tiotropium was lower than the 25% improvement seen in TORCH (Figure 2). This may also suggest a benefit from a triple combination of tiotropium, LABA and ICS.

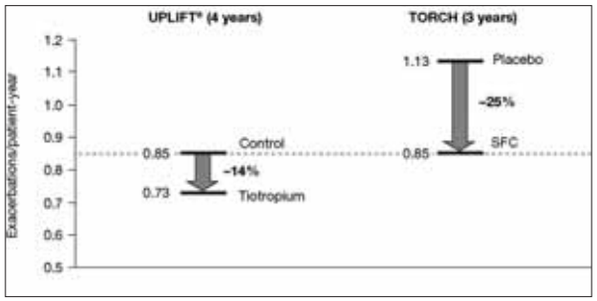

Figure 2. Change in exacerbation rates by the active treatment groups in UPLIFT® and TORCH. Data from the individual trials have been placed on the same axes for illustrative purposes only and do not represent directly comparable data between the trials. (Reproduced with permission from reference 58)

Comparison of mortality data

A key goal of COPD therapy is to reduce mortality [19]. In UPLIFT®, mortality data have been reported for two intent-to-treat 4-year "vital status" analyses for which at least 45 months follow-up was available, including patients who had discontinued, and for patients "on treatment" [18]. These analyses were a) from days 1–1440 (planned 4 years of study treatment), b) the protocol-defined on-treatment period of 1470 days (1440 days planned treatment plus 30 days follow-up), and c) the first to actual last day of treatment plus 30 days follow-up. The difference in 4-year all-cause mortality between the tiotropium and placebo groups was not statistically significant for the protocol-defined 1470-day vital status analysis (p=0.09); a significant difference between groups was observed, however, according to both the 1440-day analysis and the on-treatment analysis. A possible reason for the difference between the 1470-day and the other analyses is that data were received on only 75% of patients for the former compared with, for example, 95% of patients for the 1440-day analysis. A recent meta-analysis of safety with tiotropium has addressed a composite variable of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke [51]. The results of this meta-analysis is discussed later in the safety and tolerability section.

In TORCH, mortality data was on an intent-to-treat basis and was analyzed from day 1 to the end of the treatment period (3 years). Unlike UPLIFT®, the follow-up period (15 days in TORCH; 30 days in UPLIFT®) was not included. There was no statistically significant difference in the 3-year all-cause mortality rate between the salmeterol/fluticasone combination group and the placebo group (p=0.052). A slightly higher mortality rate was observed in the salmeterol-only arm (13.5%) than the combination arm (difference not significant vs combination arm [12.6%] or placebo [15.2%]). In the fluticasone-only arm, the mortality rate (16%) was actually higher numerically than placebo and significantly higher than in the combination arm (p=0.007).

Although the UPLIFT® and TORCH studies are not directly comparable, Figure 3 provides a comparison similar to Figure 1. The results of UPLIFT® showed that a long-acting bronchodilator (tiotropium) appeared to have an impact on mortality. Consistent with this, after factorial analysis, some authors suggested that the effect on mortality observed in the combination arm in TORCH is entirely due to the long-acting bronchodilator, ie, the LABA (salmeterol) [20,52]. Indeed, a higher mortality rate was seen in the fluticasone-only arm compared

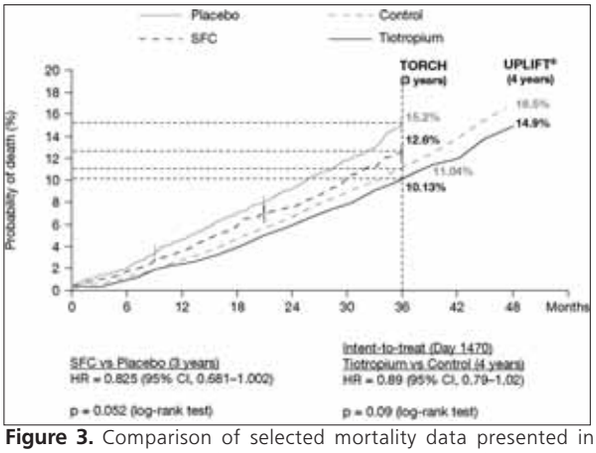

Figure 3. Comparison of selected mortality data presented in the TORCH and UPLIFT® primary publications [15,18]. Data from the individual trials have been placed on the same axes for illustrative purposes only and do not represent directly comparable data between the trials. (Reproduced with permission from reference 58)

Abbreviations: CI, confidence interval; HR, hazard ratio; SFC, salmeterol and fluticasone in combination.

with the combination arm and with placebo (difference vs placebo was not significant). The role of ICS in long-term treatment in COPD is still under debate [53,54]. Overall, the results from UPLIFT® and TORCH suggest that both tiotropium and the salmeterol/fluticasone combination may reduce the risk of mortality.

Comparison of safety and tolerability data

The proportions of patients experiencing adverse events (AEs) were similar between UPLIFT® and TORCH (ranges across groups and trials were 89–93%, 40–52%, and 18–25% for AEs, serious AEs [SAEs], and events leading to withdrawal, respectively) [17,18]. Side effects were generally those expected from the class of drugs used. In UPLIFT®, tiotropium reduced the rate of cardiac (including congestive heart failure and myocardial infarction) and lower respiratory (including respiratory failure and dyspnea) SAEs compared with controls ($p < 0.05$); there was no significant difference in the incidence of stroke between tiotropium and control. This finding contrasts with the suggestion from a recent meta-analysis that anticholinergics are associated with an increase in risk of cardiovascular events [51],51 although the results of UPLIFT® are consistent with a pooled analysis of patient-level data from 19 other trials with tiotropium. The most frequently occurring AE in all groups of both trials was COPD exacerbations (Table 3). Fluticasone-containing treatment was associated with an increased probability of having pneumonia in TORCH. Incidences of pneumonia were 19.6%, 18.3%, 13.3%, and 12.3% in the combination, fluticasone-only, salmeterol-only, and placebo arms, respectively, with significant differences between the combination and fluticasone-only arms versus placebo ($p < 0.001$) and combination versus salmeterol-only arms ($p < 0.001$). There were no significant ocular or bone-related safety signals observed with active TORCH treatments. In UPLIFT®, dry mouth and constipation were observed, two side effects that are consistent with the known safety profile for tiotropium.

Overall, the results from UPLIFT® confirm the favorable safety profile with tiotropium [55]. No strong safety signals were seen with salmeterol monotherapy in TORCH; the increased risk of pneumonia with fluticasone-containing regimens mirrors previous studies [56, 57].

CONCLUSIONS

Large clinical trials in COPD have revealed the impact of long-term bronchodilators in the treatment of COPD. Long-acting bronchodilators in the form of tiotropium and salmeterol (in combination with fluticasone propionate) can actually improve lung function and may delay progression of COPD, thus positively affecting disease prognosis. Mortality may also be reduced. Despite international and national guidelines recommending long-acting bronchodilators for COPD, these agents are currently under-prescribed. UPLIFT® and TORCH results support an urgent change in prescribing practices.

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