CLINICAL SIGNPOST
COPD

Cardiac impact of inhaled therapy in the largest randomised placebo-controlled trial in COPD history: have we reached the SUMMIT?

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SUMMIT supports the efficiency and cardiovascular safety of LABA and ICS in COPD patients at cardiovascular risk http://ow.ly/p6Is300ffoc

Background

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide. Although COPD primarily affects the lungs, it has become clear that systemic effects of COPD significantly contribute to its severity and overall mortality. Due to its high prevalence in the older population, and smoking as a shared risk factor, cardiovascular disease (CVD) is of particular importance [1]. Indeed, more patients with COPD die from CVD than from COPD itself [2–5]. Research indicates a number of mechanisms that explain this relationship, including systemic inflammation, physical inactivity, neurohumoural activation, arrhythmias, endothelial dysfunction and a greater fall in pleural pressure during inspiration [6]. Thus, bronchodilation might positively impact on CVD. In line with that reasoning, endothelial function and blood pressure were improved after lung volume reduction surgery in patients with severe COPD [7]. Furthermore, retrospective data from the National Emphysema Treatment Trial suggest that long-acting β_2-agonists (LABA) reduce mortality [8]. There are also data suggesting that inhaled corticosteroids (ICS) may have a beneficial effect on the risk of cardiovascular events in COPD, possibly by decreasing systemic inflammation [9].

Besides the well-characterised positive effects of inhaled therapy, safety issues remain. Both LABA and long-acting muscarinic antagonists (LAMA), as well as fixed combinations of both, and the combination of ICS and LABA, seem to be safe when used in the appropriate dose in patients with stable CVD [10, 11]. However, the cardiac safety of LABA and LAMA is less evident when used in COPD patients with uncontrolled, substantial or acute CVD [10]. Therefore, the Study to Understand Mortality and Morbidity in COPD (SUMMIT), focusing on COPD patients with increased cardiovascular risk, was well positioned to inform us of the cardiovascular safety and effects of ICS and LABA.

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Design and endpoints

SUMMIT is a placebo-controlled, double-blind, randomised, parallel-group, multicentre trial [6]. COPD patients with moderate airflow limitation (⩾50% and ⩽70% predicted forced expiratory volume in 1 s (FEV_1)) and a history of CVD or increased risk of CVD were randomised 1:1:1:1 to one of four double-blind treatment groups: placebo, fluticasone furoate (FF), vilanterol (VI), or a combination of FF and VI [6]. This was an endpoint-driven study designed to have 90% power to detect a 30% reduction in all-cause mortality with FF/VI compared to placebo [6]. Clinical events were adjudicated meticulously by an endpoint committee. With >16 000 patients included, the primary endpoint, all-cause mortality, showed a 12% relative reduction with FF/VI compared to placebo, which was not statistically significant (p=0.137) [12]. The predefined secondary endpoints were 1) the effect of FF/VI compared with placebo on the rate of decline in FEV_1, and 2) the effect of FF/VI compared with placebo on a cardiovascular composite endpoint comprised of on-treatment cardiovascular death, myocardial infarction, stroke, unstable angina and transient ischaemic attack [6].

Combination therapy reduced the secondary endpoint, rate of FEV_1 decline, by 8 mL per year compared with placebo (p=0.019) [12]. When analysing the monotherapy arms, this effect was related to the inhaled corticosteroid use rather than the β_2-agonist use (table 1). For the other secondary endpoint, the risk of cardiovascular events was not significantly different between FF/VI and placebo (p=0.478) [12]. It must be kept in mind, however, that these were secondary endpoints and the primary endpoint was negative, thus making inferences problematic.

Other prespecified endpoints demonstrated an improvement compared to placebo in the rate of moderate and severe exacerbations (table 1). There was no difference between the treatment groups in pneumonia and other adverse events. Analysis of subgroups such as patients with atrial fibrillation or a myocardial infarction are ongoing and are likely to be available in subsequent publications.

Comments

The SUMMIT trial is the largest COPD randomised, placebo-controlled trial ever. The study investigators report a negative finding, albeit that the direction of effect was as anticipated. SUMMIT was designed to have 90% power to detect a 30% reduction in the risk of all-cause mortality on FF/VI compared with placebo [6]. This assumption might have been too optimistic. ClinicalTrials.gov and other resources [6] do not inform us about previous studies that led to this assumption. Two preceding large studies [4, 13] with mortality signals included patients with more severe COPD and less cardiovascular risk, making inferences for SUMMIT challenging.

Physicians are often hesitant to treat airway obstruction with inhaled LABA in patients with CVD [14]. The currently presented data of the large and meticulously controlled SUMMIT trial in a moderately dyspnoeic COPD population at increased cardiovascular risk do not indicate major signals for cardiac safety. These important and timely data should reassure physicians on the use of LABA in moderate COPD patients at cardiovascular risk in general. However, questions on subgroups such as patients with atrial fibrillation or recent myocardial infarction remain, and this clinical relevant information is be eagerly awaited.

By their systemic effects, concurrent use of LABA and LAMA, *i.e.* dual bronchodilation, might potentially increase cardiovascular effects [10]. Recent phase III studies of dual bronchodilators (some of them using Holter data) did not exhibit conclusive safety signals [10, 15, 16]. However, these trials were smaller than SUMMIT and have not investigated a cohort with increased cardiovascular risk. SUMMIT did not permit tiotropium at baseline but following severe exacerbation, tiotropium could be added. Therefore, SUMMIT

TABLE 1 Main results of the SUMMIT trial

	Placebo	FF	VI	FF/VI	p-value[#]
Mortality	275 (6.7%)	251 (6.1%)	265 (6.4%)	246 (6.0%)	0.137
FEV_1 decline mL·year^{-1} mean±SE	46±2.5	38±2.4	47±2.4	38±2.4	0.019
Cardiovascular endpoint[¶]	173 (4.2%)	161 (3.9%)	180 (4.4%)	174 (4.2%)	0.478
Moderate and severe exacerbations per year	0.35	0.31	0.31	0.25	<0.0001
Severe exacerbations per year	0.07	0.06	0.06	0.05	0.0004
Pneumonia cases per 100 person-years	3.8	4.2	2.8	3.9	>0.05

SUMMIT: Study to Understand Mortality and Morbidity in COPD; FF: fluticasone furoate; VI: vilanterol; FEV_1: forced expiratory volume in 1 s. [#]: FF/VI compared to placebo; [¶]: on-treatment cardiovascular death, myocardial infarction, stroke, unstable angina and transient ischaemic attack.

TABLE 2 Comparison between the three largest randomised placebo-controlled trials in chronic obstructive pulmonary disease (COPD) history: SUMMIT, TORCH and UPLIFT

	SUMMIT	TORCH	UPLIFT
First author [ref.], year	Vestbo [12], 2016	Calverley [4], 2007	Tashkin [23], 2008
Duration years	Median 1.8	3	4
Subjects	16 485 ITT (16 568 total)	6112 (6184 in *post hoc* analysis)	5993 (5994 in *post hoc* analysis)
Inclusion criteria	COPD II Age 40–80 years ⩾10 pack-years FEV_1/FVC <70%, and post-BD FEV_1 ⩾50 and ⩽70% pred mMRC ⩾2 History or increased risk of cardiovascular disease[#]	COPD II–III Age 40–80 years ⩾10 pack-years FEV_1/FVC ⩽70% and pre-BD FEV_1 <60% pred with poor reversibility Able to use inhaler and relief medication correctly Women unable to conceive	COPD Age ⩾40 years ⩾10 pack-years FEV_1/FVC ⩽70% at visits 1 and 2, and post-BD FEV_1 ⩽70% pred Able to use inhaler and perform acceptable PFTs Maintained on stable respiratory medications
Exclusion criteria	Asthma or current other respiratory disorders Positive chest radiography LVRS Lung transplant α_1-antitrypsin deficiency LTOT LTOC Exacerbation during run-in period	Asthma or current other respiratory disorders Positive chest radiography in the last 6 months LVRS Lung transplant α_1-antitrypsin deficiency LTOT LTOC Recent other investigational drugs Drug (component) hypersensitivity Exacerbation during run-in period	Asthma or other respiratory disorders Pulmonary resection LVRS Lung transplant LTOT Drug (component) hypersensitivity Recent other investigational drugs Oral corticosteroid use at unstable doses or ⩾10 $mg \cdot day^{-1}$ Exacerbation before or during run-in period Women able to conceive, pregnant or nursing
Specific disease exclusion criteria	Current severe heart failure (NYHA class IV, ejection fraction <30%) ICD End-stage chronic renal disease Conditions other than vascular disease or COPD likely to cause death within 3 years or study incompletion	Serious, uncontrolled disease or psychological disorders likely to interfere results or to cause death within 3 years Alcohol, drug or solvent abuse	Significant diseases likely to interfere results or participants' participation History of myocardial infarction (within last 6 months) Cardiac arrhythmia or heart failure hospitalisation (in the last year) Renal impairment Malignancy NAG Symptomatic BPH or PBNO Alcohol or abuse (within the last year)

Continued

TABLE 2 Continued

	SUMMIT	TORCH	UPLIFT
Comparator	Placebo (all prior use of ICS and LABA/LAMA discontinued)	Placebo (SABA/SAMA, theophyllines, smoking cessation therapy, intermittent oxygen therapy and short courses of oral corticosteroids permitted)	Placebo (use of all respiratory medications except inhaled anticholinergic drugs permitted)
Drug of investigation	Vilanterol 25 µg plus fluticasone furoate 100 µg	Salmeterol xinafoate 50 µg plus fluticasone propionate 500 µg	Tiotropium 18 µg
Third arm	Vilanterol 25 µg	Salmeterol xinafoate 50 µg	
Fourth arm	Fluticasone furoate100 µg	Fluticasone propionate 500 µg	
Device	Novel dry-powder inhaler	All Diskus/Accuhaler	HandiHaler, twice daily
Primary endpoint	All-cause mortality (negative)	All-cause mortality (negative)	Rate of decline in trough and 90-min post-BD FEV_1 (negative)
Cardiac/mortality endpoint	All-cause mortality (p=0.137) and composite cardiovascular endpoint (p=0.478) were not significantly decreased for combination therapy compared to placebo	All-cause mortality was numerically lower for combination therapy or salmeterol compared to placebo Mortality in fluticasone group was numerically higher *Post hoc* analysis: salmeterol alone or in combination did not increase the risk of cardiovascular events	Cardiac AEs lower in tiotropium treated except for angina and cardiac failure Mortality lower in tiotropium group (14.4%) *versus* placebo (16.3%) *Post hoc* analysis: decreased cardiac mortality in tiotropium treated

SUMMIT: Study to Understand Mortality and Morbidity in COPD; TORCH: Towards a Revolution in COPD Health; UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium; ITT: intention to treat; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BD: bronchodilator; mMRC: modified Medical Research Council dyspnoea score; PFT: pulmonary function test; LVRS: lung volume reduction surgery; LTOT: long-term oxygen therapy; LTOC: long-term oral corticosteroid therapy; NYHA: New York Heart Association; ICD: implantable cardioverter defibrillator; NAG: narrow-angle glaucoma; BPH: benign prostatic hyperplasia; PBNO: primary bladder-neck obstruction; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists; SABA: short-acting β_2-agonists; SAMA: short-acting muscarinic antagonists; AE: adverse event. #: established coronary artery disease, established peripheral vascular disease, previous stroke, previous myocardial infarction or diabetes mellitus with target organ disease, or if ⩾60 years of age and receiving medication for two or more of hypercholesterolaemia, hypertension, diabetes mellitus or peripheral vascular disease.

provides only limited data on dual bronchodilation and thus is unable to comment on safety issues of LABA plus LAMA.

The improvement in FEV_1 and the reduction of moderate and severe exacerbations with FF, VI and FF/VI confirms effects that were seen in previous studies, such as TORCH (Towards a Revolution in COPD Health) and a meta-analysis [4, 16]. Besides, the effect of FF/VI on FEV_1 was smaller than in trials evaluating dual bronchodilation [10, 15, 16]. Effects on quality of life were not reported.

SUMMIT is the largest study showing a reduction in the rate of FEV_1 decline in a predefined analysis. As discussed above, secondary endpoints in a study with a negative primary endpoint have to be interpreted with caution. Nevertheless, clinically, it is reasonable to assume that the two endpoints are independent of each other since a small effect on the rate of FEV_1 decline (8mL per year) will not impact mortality. However, it is questionable whether this small difference observed over a relatively short time period (median study exposure 1.8 years) has clinical relevance, especially since recent trials show clinically relevant effects of dual bronchodilation compared to salmeterol plus fluticasone [17]. Further studies might define subgroups where ICS affect disease progression, such as in COPD patients with blood eosinophilia or a Th2 gene expression profile [18–20]. Unfortunately, blood eosinophils were not routinely evaluated in SUMMIT.

Compared to placebo, the combination treatment had no significant effect on the incidence of pneumonia in SUMMIT [12]. This is in contrast with previous studies and a meta-analysis [21, 22]. This contrast might be explained by the different patient characteristics or different inclusion and exclusion criteria (table 2). Lung function was less compromised (higher FEV_1) and CVD more common in SUMMIT participants than in previous large COPD cohorts (table 2) [24, 25]. The relatively low dose of the ICS may also have been beneficial because the pneumonia risk is dose dependent [24]. In line with ICS meta-analyses, the phase III COPD studies using FF/VI showed increased pneumonia rates with increasing FF dose [21, 24]. Finally, the relatively short mean follow-up might also have contributed to the observed pneumonia rates in SUMMIT [12, 24].

Was the therapy used in SUMMIT the optimal inhaled treatment? A recent trial available only as press release shows a reduction in exacerbations with the dual bronchodilator indacaterol/glycopyrronium as compared to the LABA/ICS salmeterol/fluticasone [17]. The press release does not clarify whether this finding is driven by the reduction of severe, moderate or mild (mainly lung function driven) exacerbations, but it would be interesting to know what the effects of dual bronchodilation in a SUMMIT-like population are. However, given that inhaled therapy in COPD improves convincing clinical endpoints such as lung function, exacerbations, exercise capacity and quality of life, another large placebo-controlled bronchodilator study with mortality as the primary endpoint is unlikely to be performed for ethical and financial reasons [4, 23]. In this regard, it appears that we have reached the summit.

Similar to previous COPD trials, 47% of the SUMMIT patients were active smokers [12]. Smoking cessation is the most effective way to reduce pulmonary as well as cardiovascular morbidity and mortality, and thus remains of principal importance in COPD treatment [26].

Conclusion

SUMMIT clearly supports the efficiency and cardiovascular safety of LABA and ICS in COPD patients at cardiovascular risk. Subsequent subgroup analysis is likely to provide further important information. Nevertheless, diagnosing and targeting underlying CVD might be a more effective way to address mortality in COPD. Accordingly, β-blockade and angiotensin receptor blockade targeting neurohumoural activation, as is present in COPD, shows promise [3, 27].

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