

# Predictors of response to tiotropium versus salmeterol in asthmatic adults

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**Background:** Tiotropium has activity as an asthma controller. However, predictors of a positive response to tiotropium have not been described.

**Objective:** We sought to describe individual and differential responses of asthmatic patients to salmeterol and tiotropium when added to an inhaled corticosteroid, as well as predictors of a positive clinical response.

**Methods:** Data from the double-blind, 3-way, crossover National Heart, Lung, and Blood Institute's Asthma Clinical Research Network's Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (ClinicalTrials.gov number, NCT00565266) trial were analyzed for individual and differential treatment responses to salmeterol and tiotropium and predictors of a positive response to the end points FEV<sub>1</sub>, morning peak expiratory flow (PEF), and asthma control days (ACDs).

**Results:** Although approximately equal numbers of patients showed a differential response to salmeterol and tiotropium in terms of morning PEF (n = 90 and 78, respectively) and ACDs (n = 49 and 53, respectively), more showed a differential response to tiotropium for FEV<sub>1</sub> (n = 104) than salmeterol (n = 62). An acute response to a short-acting bronchodilator, especially albuterol, predicted a positive clinical response to tiotropium for FEV<sub>1</sub> (odds ratio, 4.08; 95% CI, 2.00-8.31; P < .001) and morning PEF (odds ratio, 2.12; 95% CI, 1.12-4.01; P = 0.021), as did a decreased FEV<sub>1</sub>/forced vital capacity ratio (FEV<sub>1</sub> response increased 0.39% of baseline for every 1% decrease in FEV<sub>1</sub>/forced vital capacity ratio). Higher cholinergic tone was also a predictor, whereas ethnicity, sex, atopy, IgE level, sputum eosinophil count, fraction of exhaled nitric oxide, asthma duration, and body mass index were not.

**Conclusion:** Although these results require confirmation, predictors of a positive clinical response to tiotropium include a positive response to albuterol and airway obstruction, factors that could help identify appropriate patients for this therapy. (J Allergy Clin Immunol 2013;132:1068-74.)

**Key words:** Asthma, tiotropium, salmeterol, responder analysis, predictor of response

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## Abbreviations used

ACD:	Asthma control day
ACRN:	Asthma Clinical Research Network
FVC:	Forced vital capacity
HFA:	Hydrofluoroalkane
ICS:	Inhaled corticosteroid
LABA:	Long-acting $\beta$ -agonist
LAMA:	Long-acting muscarinic antagonist
NHLBI:	National Heart, Lung, and Blood Institute
OR:	Odds ratio
PEF:	Peak expiratory flow
TALC:	Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (ClinicalTrials.gov number, NCT00565266) trial

Multiple conflicting strategies have been proposed in attempting to obtain the best outcomes for patients with chronic diseases, including asthma. Although much of the past several decades has been devoted to developing standardized treatment guidelines and attempting to improve physician and patient adherence,<sup>1,2</sup> more recent efforts have been devoted to identifying the best treatment approaches for specific patients and subgroups of patients (ie, "personalizing" treatment approaches).<sup>3</sup> Such attempts have used a variety of strategies, including the use of biomarkers, patient-specific and physiologic "predictors," and genetic/genomic approaches.<sup>3-5</sup>

Although investigators have explored predictors of response to a variety of drugs used to treat asthmatic patients, including short-acting bronchodilators and leukotriene modifiers,<sup>6-9</sup> more attention has been devoted to identifying variables that can be used to predict the response to glucocorticoids, particularly inhaled corticosteroids (ICSs).<sup>7-10</sup> These experiences have both provided valuable insights and approaches to move this area of investigation forward.<sup>11</sup>

Within this framework, less information has been published concerning predictors of response of subjects to treatment with long-acting bronchodilators, such as long-acting  $\beta$ -agonists (LABAs) and long-acting anticholinergic agents (long-acting muscarinic antagonists [LAMAs]). In addition, no data are available describing the intrasubject response of asthmatic patients treated with both a LABA (salmeterol) and a LAMA

(tiotropium bromide). This report describes the response of add-on therapy with the LABA salmeterol or the LAMA tiotropium

bromide in individual patients with asthma treated with an ICS in the National Heart, Lung, and Blood Institute (NHLBI)'s Asthma

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From the National Heart, Lung and Blood Institute's Asthma Clinical Research Network and its Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) trial.

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Clinical Research Network (ACRN) Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) trial ([ClinicalTrials.gov](http://ClinicalTrials.gov) number, NCT00565266).<sup>12</sup> In addition to individual patient responses, differential responses to the 2 drugs and predictors of a positive clinical response for the outcomes of morning peak expiratory flow (PEF), FEV<sub>1</sub>, and asthma control days (ACDs; ie, days with no asthma symptoms and no need for rescue albuterol use for symptoms [excluding premedication for exercise]) are described.

## METHODS

### TALC trial design

The TALC trial was a double-blind, 3-way crossover trial that randomized patients whose symptoms were inadequately controlled on a low dose of ICS alone (80 µg of beclomethasone hydrofluoroalkane [HFA] twice daily) to treatment with double the dose of ICS alone (160 µg of beclomethasone HFA twice daily), single-dose ICS (80 µg of beclomethasone HFA twice daily) plus salmeterol (50 µg twice daily), and single-dose ICS (80 µg of beclomethasone HFA twice daily) plus tiotropium (18 µg every morning through a Handihaler; Boehringer Ingelheim, Ridgefield, Conn).<sup>12</sup> Each treatment period lasted 14 weeks, with 2-week baseline run-in/run-out periods in which patients were treated with single-dose ICSs before each of the 3 treatment periods.

Inclusion criteria included a history of asthma, which was confirmed either based on bronchodilator reversibility testing ( $\geq 12\%$  improvement in FEV<sub>1</sub> and  $\geq 200$ -mL improvement after 4 puffs, 90 µg each, of albuterol) or bronchial hyperresponsiveness to methacholine (PC<sub>20</sub> FEV<sub>1</sub> for methacholine of  $\leq 8$  mg/mL for patients not taking an ICS or  $\leq 16$  mg/mL for patients taking an ICS); 174 qualified on the basis of methacholine hyperresponsiveness and 36 on the basis of the albuterol reversal requirements, although many of the patients who qualified on the basis of methacholine hyperresponsiveness would also have qualified based on the albuterol reversal requirement had both tests been performed for everyone.

### Response analyses and statistical approaches

Potential predictors of response to tiotropium and salmeterol were evaluated. Although this work should be considered exploratory, prespecified hypotheses for predictors of a positive response included the following: (1) increased cholinergic tone (lower resting heart rate) would predict a better response to tiotropium, and (2) positive response to short-acting bronchodilator ( $\geq 12\%$  and  $\geq 200$ -mL increase in FEV<sub>1</sub>) would predict a positive response to a long-acting bronchodilator of the same class (ie, a positive response to albuterol would predict a positive clinical response to salmeterol and a positive response to ipratropium would predict a positive clinical response to tiotropium).

Morning PEF and ACD data were collected daily, and therefore 2-week averages before the beginning and end of a treatment were used to characterize the drug response. Responses to morning PEF, prebronchodilator FEV<sub>1</sub> (at the end of the dosing interval for all drugs), and ACDs (days with no asthma symptoms and no rescue albuterol use) were defined as both continuous and categorical variables. A lung function response was defined as a relative change between the end and the beginning of a treatment in morning PEF and FEV<sub>1</sub>. A 7.5% change was used as a cutoff to create the categorical response variables similar to a previous NHLBI Childhood Asthma Research and Education Network clinical trial.<sup>7</sup> For the average patient in the TALC trial, a 7.5% improvement in morning PEF would translate to approximately 28 L/min and a 7.5% improvement in FEV<sub>1</sub> would translate to approximately 173 mL. The ACD response was defined as an absolute change between the end and beginning of a treatment, and a 0.1 change was used as a cutoff. A 0.1 change in ACDs translates to 36.5 days on an annualized basis.

A 2-dimensional response was defined as a positive response to either lung function or ACDs and having had no asthma exacerbation while receiving that treatment, providing a binary response. Only patients with complete data for all treatment periods were included in these analyses (n = 166 for FEV<sub>1</sub> and ACDs, n = 168 for morning PEF, and n = 160 for 2-dimensional response; figures provide numbers for the various outcomes listed).

The set of potential predictors included demographic and asthma characteristics, pulmonary function, and biomarkers. Several biomarkers were logarithmically transformed because of skewed distributions. Bronchodilator reversibility variables were dichotomized based on a 12% or greater and 200-mL or greater increase over baseline in FEV<sub>1</sub>. Other continuous predictors that are normally distributed were dichotomized based on their mean values. Predictors that were not normally distributed were dichotomized based on the mean of the logarithmically transformed values. SAS software, version 9.2 (SAS Institute, Cary, NC), was used for both univariate and multivariate analyses. The categorical responses were examined through PROC LOGISTIC for both categorical and continuous predictors. The continuous responses were examined through PROC MIXED for categorical predictors and for continuous predictors through PROC REG for univariate and PROC GLMSELECT for multivariate approaches. Stepwise selection processes were applied for multivariate analyses. TIBCO Spotfire SPLUS, version 8.1, for Windows software (TIBCO Spotfire, Somerville, Mass) was used for graphic displays of the results. A 2-sided *P* value of less than .05 was considered statistically significant.

## RESULTS

### NHLBI's ACRN TALC trial results

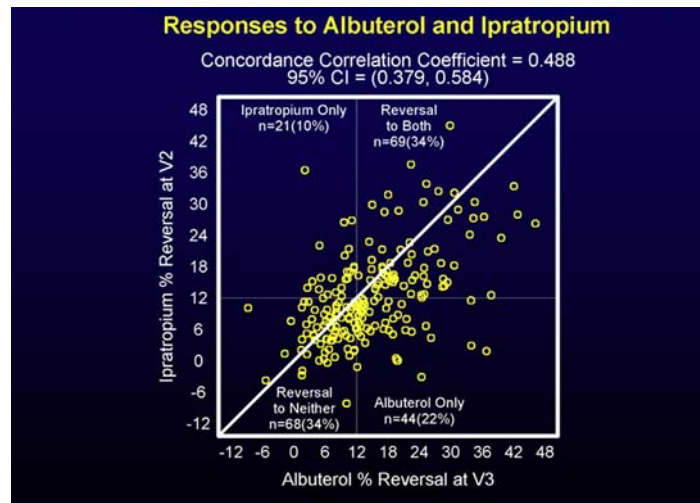
Two hundred ten patients were randomized in the trial (32.9% male and 87.5% atopic), with an average age of  $42.2 \pm 12.3$  (mean  $\pm$  SD) years, an average duration of asthma of  $26.1 \pm 14.1$  years, and an FEV<sub>1</sub> of  $2.31 \pm 0.77$  L ( $71.5\% \pm 14.9\%$  of predicted value). The use of tiotropium resulted in a superior primary outcome compared with a doubling of the ICS dose, as assessed by measuring morning PEF, with a mean difference of 25.8 L/min ( $P < .001$ ), and superiority in most secondary outcomes, including evening PEF, with a difference of 35.3 L/min ( $P < .001$ ); the proportion of ACDs, with a difference of 0.079 ( $P = .01$ ); FEV<sub>1</sub> before bronchodilation, with a difference of 0.10 L ( $P = .004$ ); and daily symptom scores, with a difference of  $-0.11$  points ( $P < .001$ ). The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and increased the prebronchodilator FEV<sub>1</sub> more than salmeterol, with a difference of 0.11 L ( $P = .003$ ).<sup>12</sup>

Although the average reversibility after 4 puffs of bronchodilator was similar for albuterol ( $14.9\% \pm 9.8\%$ ) and ipratropium ( $12.4\% \pm 9.5\%$ ), tests were performed on different days), individual patient responses to these agents showed marked variability. As shown in Fig 1, of the 202 patients who had acceptable data, 22% reversed ( $\geq 12\%$  improvement in FEV<sub>1</sub>) to albuterol alone, 10% to ipratropium alone, 34% to both agents, and 34% to neither. Note that the additional criterion requiring a 200-mL or greater improvement in FEV<sub>1</sub> cannot be incorporated in the definition of reversibility when examining it on a continuous scale, as presented in the figures. When using reversibility as a dichotomous predictor variable, this additional criterion is incorporated (Table I). When a 200-mL or greater improvement is incorporated in the definition, 6 fewer subjects reverse to albuterol and 2 fewer subjects reverse to ipratropium (one of these subjects did not have tiotropium clinical response data available).

### Individual and differential responses to tiotropium and salmeterol

Fig 2 and Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org) show individual and differential responses of patients to both tiotropium and salmeterol for the end points of





**FIG 1.** Acute responses (defined as FEV<sub>1</sub> percentage change) of patients in the TALC trial to 4 puffs of albuterol and 4 puffs of ipratropium administered on different days after bronchodilator drug withholding.

morning PEF, FEV<sub>1</sub> (at the end of the dosing interval for all drugs), and ACDs. For the end point of morning PEF, 20% of patients had a positive response ( $\geq 7.5\%$  improvement) to tiotropium alone, salmeterol alone, and both medications, whereas 40% had a positive response to neither (Fig 2, A). Not surprisingly, an approximately equal number of patients had a differential response to tiotropium (78 patients) and salmeterol (90 patients; see Fig E1, A). For the end point of FEV<sub>1</sub>, positive responses ( $\geq 7.5\%$  improvement) were noted for tiotropium alone in 26% patients, salmeterol alone for 14% of patients, and both medications for 9% of patients, with 51% showing a response to neither medication (Fig 2, B). In this case the differential response favored tiotropium (104 patients) when compared with salmeterol (62 patients; see Fig E1, B). Finally, for the end point of ACDs, a positive response (0.1 proportion increase in ACDs) was noted for tiotropium alone in 13% of patients, salmeterol alone in 16% of patients, both medications in 29% of patients, and neither medication in 43% of patients (Fig 2, C), whereas differential responses were again approximately equal for tiotropium (53 patients) and salmeterol (49 patients; see Fig E1, C).

### Prespecified predictors of a positive response to tiotropium and salmeterol

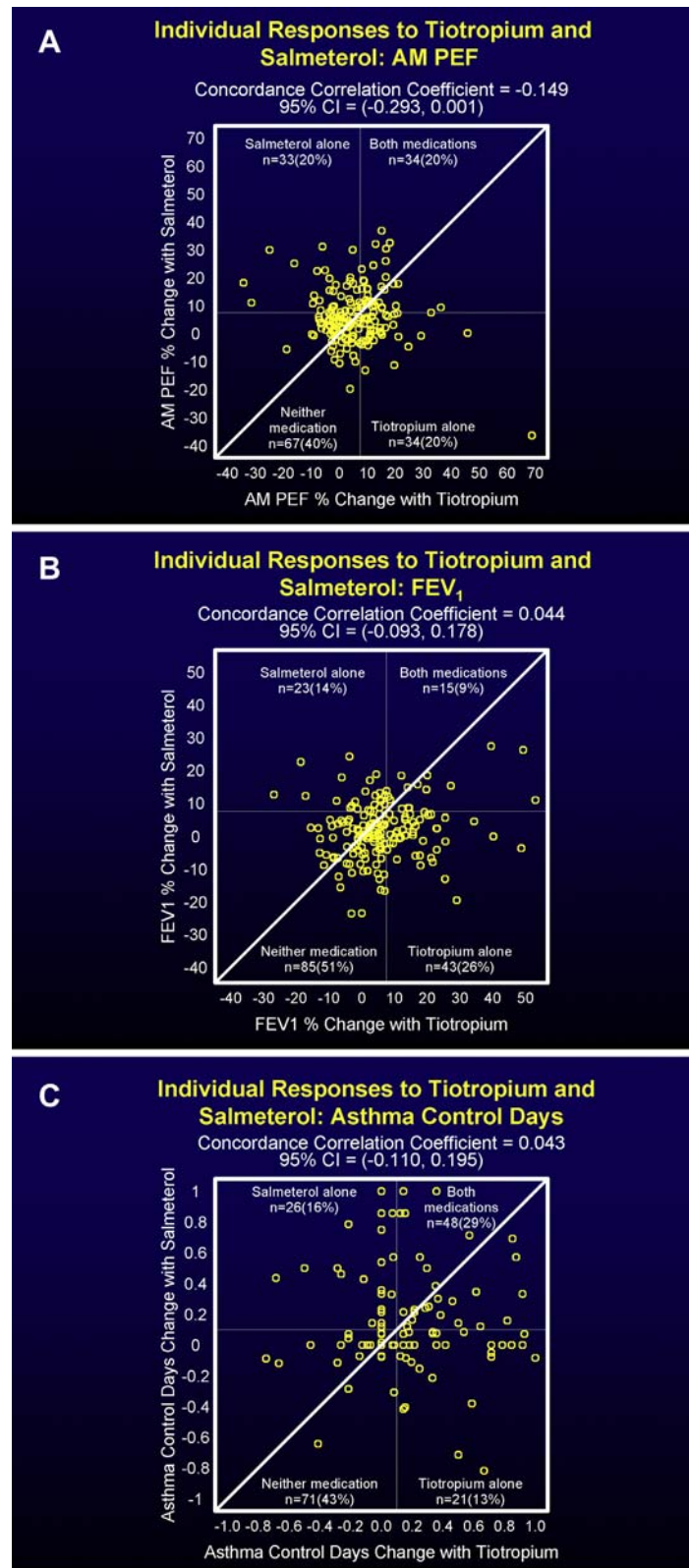
**Higher cholinergic tone predicting response to tiotropium.** Increased cholinergic tone was inferred from a lower resting heart rate. When comparing patients with a 25th percentile or lower resting heart rate with patients with a 75th percentile or greater resting heart rate, significant odds ratios (ORs) for a positive response to tiotropium were noted for ACDs (OR, 3.0; 95% CI, 1.13-7.94;  $P = .027$ ) and a 2-dimensional response (OR, 4.17; 95% CI, 1.52-11.43;  $P = .006$ ).

**Acute response to short-acting bronchodilator predicting response to long-acting bronchodilator.** Fig 3 shows the relationship between the acute FEV<sub>1</sub> response to 4 puffs of the short-acting bronchodilators albuterol (Fig 3, A) and ipratropium (Fig 3, B) and the analogous long-acting bronchodilators salmeterol (Fig 3, A) and tiotropium (Fig 3, B) during the TALC trial. An acute response to albuterol ( $\geq 12\%$

improvement in FEV<sub>1</sub>) was associated with a positive response to salmeterol (7.5% improvement in FEV<sub>1</sub> during the trial) in 28% of patients (Fig 3, A). (Sixteen percent of the total population both reversed and had a treatment response.) An acute response to ipratropium ( $\geq 12\%$  improvement in FEV<sub>1</sub>) was associated with a positive response to tiotropium (7.5% improvement in FEV<sub>1</sub> during the trial) in 46% of patients (Fig 3, B). (Twenty percent of the total population both reversed and had a treatment response.) The ORs, 95% CIs, and  $P$  values for the ability of a positive response to a short-acting bronchodilator ( $\geq 12\%$  and  $\geq 200$ -mL improvement in FEV<sub>1</sub>) to predict a positive clinical response in the clinical trial for the 3 major clinical outcomes of FEV<sub>1</sub>, morning PEF, and ACDs are shown in Table I. A positive response to albuterol predicted a positive response to salmeterol only in terms of morning PEF (OR, 2.81; 95% CI, 1.46-5.40;  $P = .002$ ), whereas a positive response to ipratropium predicted a positive response to tiotropium in terms of both FEV<sub>1</sub> (OR, 3.01; 95% CI, 1.52-5.94;  $P = .002$ ) and morning PEF (OR, 2.07; 95% CI, 1.09-3.92;  $P = .026$ ). Interestingly, the acute response to albuterol was a better predictor of a positive response to tiotropium than the acute response to ipratropium: FEV<sub>1</sub> (OR, 4.08; 95% CI, 2.00-8.31;  $P < .001$ ) and morning PEF (OR, 2.12; 95% CI, 1.12-4.01;  $P = .021$ ). Two-dimensional responses were only noted for albuterol, which predicted positive responses to both salmeterol (OR, 3.40; 95% CI, 1.67-6.95;  $P < .001$ ) and tiotropium (OR, 2.40; 95% CI, 1.23-4.69;  $P = .01$ ). For no outcome measure did the acute response to ipratropium predict a positive response to salmeterol (Table I).

### Additional exploratory predictors of a positive response to tiotropium

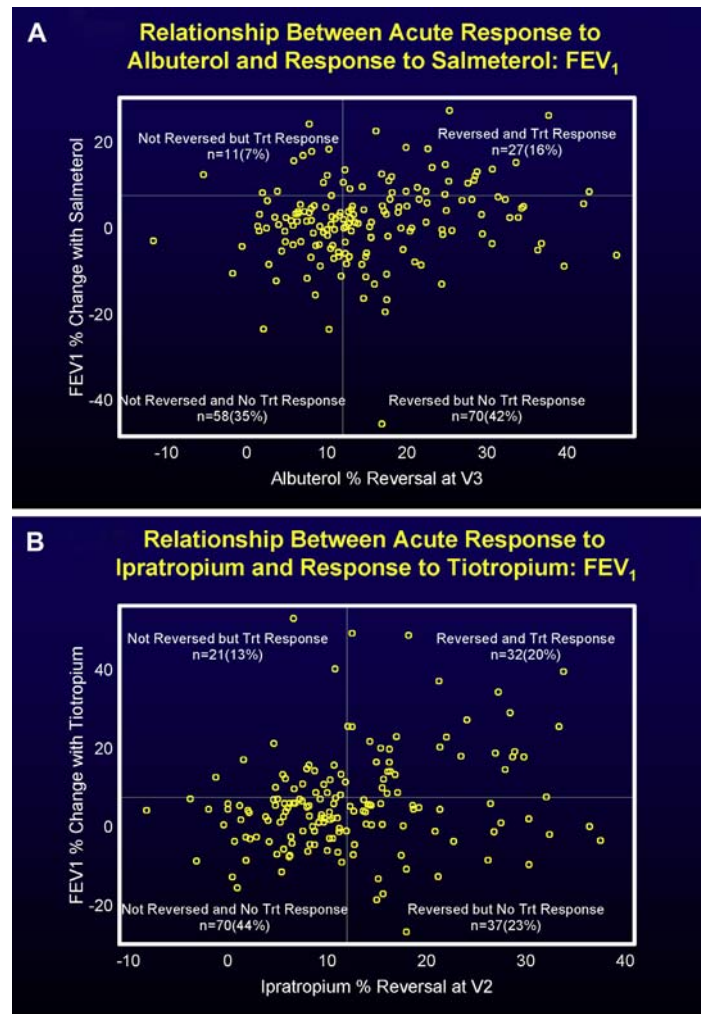
A lower FEV<sub>1</sub>/forced vital capacity (FVC) ratio predicted a positive clinical response to tiotropium in terms of both FEV<sub>1</sub> (OR, 3.10; 95% CI, 1.59-6.07;  $P < .001$ ) and morning PEF (OR, 2.32; 95% CI, 1.24-4.37;  $P = .009$ ). When analyzed as a continuous variable, the FEV<sub>1</sub> response increased by 0.39% of baseline for every 1% decrease in FEV<sub>1</sub>/FVC ratio. Finally, younger patients ( $< 42$  years old) responded better to tiotropium clinically in terms of ACDs (OR, 2.64; 95% CI, 1.40-4.99;



**FIG 2.** Individual patient responses to salmeterol and tiotropium in terms of morning PEF (**A**), FEV<sub>1</sub> (**B**), and ACDs (**C**).

$P = .003$ ) than older patients ( $\geq 42$  years old). Exploratory predictors not associated with a positive clinical response to tiotropium included ethnicity, sex, atopy ( $\geq 1$  positive skin test

result), IgE level (natural logarithm), sputum eosinophil count, fraction of exhaled nitric oxide (natural logarithm), asthma duration, and body mass index.



**FIG 3.** Relationship between the acute response (defined as FEV<sub>1</sub> percentage change) to a short-acting bronchodilator and the clinical effect of a long-acting bronchodilator. **A**, Acute response to 4 puffs of albuterol and clinical response to salmeterol in terms of FEV<sub>1</sub>. **B**, Acute response to 4 puffs of ipratropium and clinical response to tiotropium in terms of FEV<sub>1</sub>. *Trt*, Treatment.

**DISCUSSION**

Tiotropium has now been shown to have activity as an asthma controller when added to ICSs in several well-designed clinical trials.<sup>12-15</sup> This report describes individual response, differential response, and predictors of response of individual patients to both salmeterol and tiotropium when added to an ICS. The crossover design of the trial permitted an evaluation of the response of both drugs in every patient who completed the

treatment periods in which salmeterol and tiotropium were assigned. Three different outcomes were examined, which could be considered to represent different aspects of the treatment response. The FEV<sub>1</sub> at the end of the drug-dosing interval could be considered a time of maximum vulnerability for patients. In the TALC trial similar results were obtained for both morning and evening PEF; therefore morning PEF could be considered to represent lung function through the day and night. ACDs are

**TABLE I.** ORs for the ability of an acute response to a short-acting bronchodilator (12% and 200-mL improvement in FEV<sub>1</sub>) to predict a clinical response to a long-acting bronchodilator (7.5% improvement in FEV<sub>1</sub>, 7.5% improvement in morning PEF, and 0.1 proportional increase in ACDs)

	Acute albuterol to predict clinical salmeterol		Acute ipratropium to predict clinical tiotropium		Acute albuterol to predict clinical tiotropium		Acute ipratropium to predict clinical salmeterol	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
FEV <sub>1</sub>	1.56 (0.74-3.29)	.24	3.01 (1.52-5.94)	.002	4.08 (2.00-8.31)	<.001	1.49 (0.72-3.10)	.29
Morning PEF	2.81 (1.46-5.40)	.002	2.07 (1.09-3.92)	.026	2.12 (1.12-4.01)	.021	1.67 (0.89-3.16)	.11
ACDs	1.42 (0.77-2.65)	.27	1.07 (0.57-2.02)	.82	1.27 (0.68-2.37)	.46	0.90 (0.48-1.68)	.73
2D response	3.40 (1.67-6.95)	<.001	1.76 (0.88-3.51)	.11	2.40 (1.23-4.69)	.01	1.28 (0.63-2.61)	.50

2D response, Two-dimensional response in FEV<sub>1</sub>, morning PEF, or ACDs and no asthma exacerbation.

a patient-centric outcome of great importance to both patients and physicians and are weakly related to lung function.

Several important observations have been made in this report. First, large numbers of patients responded either to salmeterol or tiotropium, but not to both agents, suggesting that at the time of drug administration, different mechanisms were operating to produce airway constriction and symptoms in these 2 groups of patients. This observation is consistent with the data presented by Kerstjens et al,<sup>15</sup> who reported that when a group of patients with asthma whose symptoms were inadequately controlled with a combination ICS/LABA were started on tiotropium, they demonstrated an increase in their mean FEV<sub>1</sub> and a decrease in asthma exacerbations. Second, patients with more cholinergic tone, as well as younger patients, displayed a better response to tiotropium in selected outcomes. Third, although the response to a short-acting bronchodilator did predict a positive response to a long-acting bronchodilator-controller of the same class, albuterol response better predicted a response to tiotropium than did ipratropium. Albuterol appeared to be a better predictor of a response to tiotropium than ipratropium because it was a more effective bronchodilator in this population (ie, 44% of the study population had a positive response to ipratropium, whereas 56% of the population showed a positive response to albuterol). Finally, increased airway obstruction, as reflected in a decreased FEV<sub>1</sub>/FVC ratio, also predicted a positive response to tiotropium. Ethnicity, sex, atopy, IgE level, sputum eosinophil count, fraction of exhaled nitric oxide, asthma duration, and body mass index did not predict a clinical response.

Definitive recommendations concerning how to translate these findings into clinical practice cannot be made on the basis of these observations alone. Clearly, the findings need to be replicated in an independent study. However, if the findings were replicated, we could suggest that if a patient with asthma still has suboptimal asthma control after a trial of ICSs alone (ie, has asthma symptoms or rescue  $\beta$ -agonist use most days of the week and/or  $\geq 2$  awakenings per week for asthma and/or compromised lung function [FEV<sub>1</sub>  $\leq 70\%$  of predicted value]), he or she should undergo spirometry before and after administration of 4 puffs of albuterol. Patients with airway obstruction, as demonstrated by a reduced FEV<sub>1</sub>/FVC ratio, a positive response to albuterol, or both, should be good candidates for treatment with tiotropium as an add-on therapy. Whether this strategy should be reserved for patients in whom combination ICS-LABA therapy “fails” or whether physicians and patients should have the option of adding either tiotropium or a LABA to an ICS when monotherapy does not produce adequate asthma control awaits further investigation.

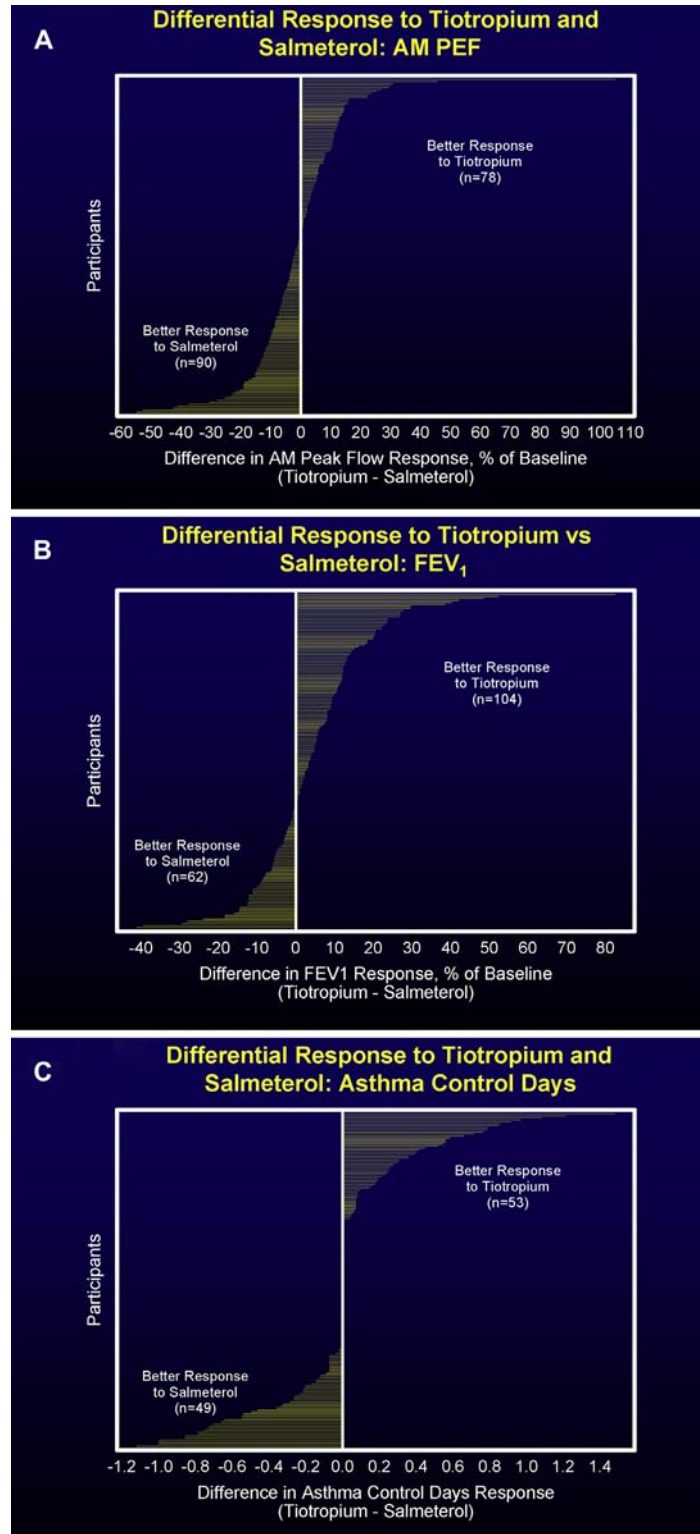
We thank our colleagues at TEVA for their gift of beclomethasone dipropionate-HFA, which was used in this trial. We also thank all of the patients who took part in the TALC and BASALT trials, as well as the outstanding work of our study coordinators, who made this work possible.

**Clinical implications: Personalized therapy for asthma requires identification of factors associated with positive responses. Predictors of positive responses to tiotropium and salmeterol add-on therapy were identified in the NHLBI's ACRN TALC trial.**

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**FIG E1.** Differential patient responses to salmeterol and tiotropium in terms of morning PEF (A), FEV<sub>1</sub> (B), and ACDs (C).