Evidence Report

Contract No. 290-02-0009
Prepared by Minnesota Evidence-based Practice Center, Minneapolis, Minnesota

Use of Spirometry for Case Finding, Diagnosis, and Management of Chronic Obstructive Pulmonary Disease (COPD)

Appendixes

Appendix A
Technical Expert Panel Members

Technical Expert Panel Members and Areas of Expertise

TEP Member	Area of Expertise
John Connett, PhD University of Minnesota School of Public Health Minneapolis, Minnesota	Biostatistics
Anne Fuhlbrigge, MD Brigham and Women's Hospital Harvard Medical School Boston, Massachusetts	Epidemiology, COPD
Anne Marie Joseph, MD VA Medical Center Minneapolis, Minnesota	General medicine, smoking cessation
Michael Light, MD University of Miami School of Medicine Miami, Florida	Pediatrics, airways disease
Katherine Sherif, MD Center for Women's Health Drexel University College of Medicine Philadelphia, Pennsylvania	General medicine, disease prevention
Stuart W. Stoloff, MD Stuart W. Stoloff, MD, Ltd. Carson City, Nevada	Primary care, airways disease
Barbara Yawn Olmsted Medical Center Rochester, Minnesota	Pulmonary care, airways disease

Appendix B
Exact Search Strings

Search Strings for Use of Spirometry for Case Finding, Diagnosis, and Management of Chronic Obstructive Pulmonary Disease (COPD)

Question 1 (prevalence)

The literature search was done on MEDLINE (via OVID) using the following combination of MeSH headings, keywords, and publication types:

((copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ OR
chronic obstructive pulmonary disease.mp. OR
emphysema.mp. OR
emphysema/ OR
bronchitis.mp. OR
bronchitis/ OR
chronic bronchitis.mp. OR
bronchitis, chronic/ OR
airflow limitation.mp. OR
airway obstruction/)

AND

(diagnosis.mp. OR
diagnosis/ OR
epidemiology.mp. OR
epidemiology/ OR
community.mp. OR
residence characteristics/ OR
catchment.mp. OR
"catchment area (health)"/ OR
prevalence.mp. OR
prevalence/ OR
incidence.mp. OR
incidence/ OR
risk assessment.mp. OR
risk assessment/ OR
(high adj1 risk).ti,ab.)

AND

(spirometry.mp. or spirometry/ OR
bronchospirometry.mp. OR
bronchospirometry/ OR
respiratory function tests.mp. OR
respiratory function tests/)

AND

(cohort studies/ OR
case reports.pt. OR
case-control studies/))

OR

((exp pulmonary disease, chronic obstructive/ OR
copd.mp.)

AND

(exp spirometry/ OR
spiromet:.mp.)

AND

(exp pulmonary disease, chronic obstructive/ep OR
prevalen:.mp. OR
prevalence/))

Question 2 (smoking cessation)

The literature search was done on MEDLINE (via OVID) using the following combination of MeSH headings, keywords, and publication types:

((copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ OR
chronic obstructive pulmonary disease.mp. OR
emphysema.mp. OR
emphysema/ OR
bronchitis.mp. OR
bronchitis/ OR
chronic bronchitis.mp. OR
bronchitis, chronic/ OR
airflow limitation.mp. OR
airway obstruction/)

AND

(spirometry.mp. OR
spirometry/ OR
bronchospirometry.mp. OR

bronchospirometry/ OR
respiratory function tests.mp. OR
respiratory function tests/)

AND

(smoking/ OR
smoking cessation/ OR
smoking cessation therapy.mp. OR
smoking psychology.mp.)

AND

(randomized controlled trial.pt. OR
controlled clinical trial.pt. OR
case-control studies/))

OR

((exp spirometry/ OR
spiromet:.mp.)

AND

(smoking cessation/ OR
(smoking adj cessation).mp. OR
exp smoking/dh, dt, th))

Question 3 (Sin review update)

The literature search was done on MEDLINE (via OVID) using the following combination of MeSH headings, keywords, and publication types (search results were limited to controlled clinical trials, meta analyses or randomized controlled trials, and limited to references published from the years 2002 to 2004):

Combination of short-acting β-2 agonists and ipratropium bromide

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR

pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(Ipratropium/ AND
adrenergic β-agonists/)

Long-acting β-2 Agonists

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR
pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(adrenergic β-agonists/ OR
receptors, adrenergic, β -2/ OR
(adrenergic adj1 beta).ti,ab. OR
salmeterol.mp. OR
formoterol.mp.)

Long-acting Anticholinergics

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR

mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR
pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(cholinergic antagonists/ OR
tiotropium.mp. OR
scopolamine derivatives/)

Inhaled Corticosteroids

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR
pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(glucocorticosteroids.mp. OR
corticosteroids/ OR
beclomethasone.mp. OR
budesonide.mp. OR
fluticasone.mp. OR
triamcinolone.mp.)

Combination of Inhaled Corticosteroids and Long-Acting β-2 Agonists

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR
pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(glucocorticosteroids.mp. OR
corticosteroids/ OR
beclomethasone.mp. OR
budesonide.mp. OR
fluticasone.mp. OR
triamcinolone.mp.)

AND

(salmeterol.mp. OR
formoterol.mp.)

Non-invasive Mechanical Ventilation

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR
pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR

Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(nippv.mp. OR
nimv.mp. OR
bi-level.mp. OR
respiration, artificial/ OR
positive-pressure respiration/)

Pulmonary Rehabilitation

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR
pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(exercise tolerance/ OR
dyspnea/rh [Rehabilitation] OR
exercise therapy/)

Oxygen Therapy

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR

pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

oxygen inhalation therapy/

Disease Management

(obstructive.mp. OR
chronic obstructive.mp. OR
bronchitis.mp. OR
bronchitis/ OR
emphysema.mp. OR
mediastinal emphysema / OR
subcutaneous emphysema / OR
emphysema / OR
pulmonary emphysema / OR
airway obstruction.mp. OR
airway obstruction/ OR
copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ or
lung diseases, obstructive/)

AND

(self care/ OR
patient education/ OR
primary health care/)

Question 4 (prognosis)

The literature search was done on MEDLINE (via OVID) using the following combination of MeSH headings, keywords, and publication types:

((copd.mp. OR
Pulmonary Disease, Chronic Obstructive/ OR
chronic obstructive pulmonary disease.mp. OR
emphysema.mp. OR

emphysema/ OR
bronchitis.mp. OR
bronchitis/ OR
chronic bronchitis.mp. OR
bronchitis, chronic/ OR
airflow limitation.mp. OR
airway obstruction/)

AND

(spirometry.mp. OR
spirometry/ OR
bronchospirometry.mp. OR
bronchospirometry/ OR
respiratory function tests.mp. OR
respiratory function tests/)

AND

(prognosis/ OR
prognosis.mp.)

AND

(cohort studies/ OR
case reports.pt. OR
case-control studies/))

OR

((exp pulmonary disease, chronic obstructive/ OR
copd.mp.)

AND

(exp spirometry/ OR
spiromet:.mp.)

AND

(exp prognosis/ OR
prognos:.mp.))

Appendix C
Abstraction Forms

UNIQUE IDENTIFIER #_____

Interventions for COPD / Spirometry
Article Abstraction Form:

Author (first):_____

Journal:_____ Year Publication: _____

Country:_____ (where study performed)

Reviewer:_____

VERIFICATION/SELECTION OF STUDY ELIGIBILITY

Randomized	Yes	No	Unclear
Placebo ***or*** Control (usual care, O2)	Yes	No	Unclear
Subjects with COPD (any GOLD Stage)	Yes	No	Unclear
(i.e irreversible airway obstruction, NOT asthma and NOT α-1 antitrypsin deficiency, or were the outcomes in the group with COPD reported separately?			
Age of subjects > 19 years of age	Yes	No	Unclear
Minimum of 50 subjects per arm	Yes	No	Unclear
Study duration ≥ 3 months (exception pulmonary rehabilitation)	Yes	No	Unclear
Were subjects stable for at least 1 month prior to initiation of therapy	Yes	No	Unclear
Clinical outcomes of interest (death, respiratory death, hospitalizations – any reason or COPD exacerbations, physician visits – any reason or due to COPD, FEV1, FEV1/FVC ratio, SGRQ, CRQ QoL measures)	Yes	No	Unclear
***** Using Spirometry for measurement of PFT	Yes	No	Unclear

Stop if any of the above is "NO"

METHODS

Study Design and Conduct

Subject blinded	Yes	No	Unclear
Provider blinded	Yes	No	Unclear
Intention-to-treat analysis	Yes	No	Unclear
Crossover trial	Yes	No	Unclear

RANDOMIZATION ALLOCATION CONCEALMENT METHOD (circle one)

Clearly adequate: Centralized randomization by telephone, randomization scheme controlled by pharmacy, numbered or coded identical containers administered sequentially, on site computer system which can only be accessed after entering the characteristics of an enrolled participant, sequentially numbered sealed opaque envelopes.

Clearly Inadequate: Alternation (odd-even, etc..), date of birth, date of week

Unclear: Sealed envelopes but not sequentially numbered or opaque, other, list of random numbers read by someone entering patient into trial (open list) *or study noted to be random or "randomization" or "random allocation" but no details provided.*

PARTICIPANTS

Multi-center or single site (*circle one*) Total number of subjects eligible_____

Total # subjects enrolled _____ Subjects completed trial:_____

Setting: Community Primary Clinic Specialty Clinic Nursing Home
(*circle all that apply*) Other _____

	Intervention (or *write in subgoups*)			**Placebo/control** (*write in*)
	I	**II**	**III**	
# Subjects:				
Mean age				
Men: n / N and %				
Women: n / N and %				
Age < 65* n / N and %				
Age ≥ 65 n / N and %				
Race: white n / N and %				
Race: black n / N and %				
Race: Asian n / N and %				

Race: Hispanic n / N and %				
Race: Other n/N and %				
Asthma n/N and %				
Bronchitis n/N and %				
Emphysema n/N and %				

SMOKING HISTORY

	Intervention (*write in*)			**Placebo/control** (*write in*)
	I	**II**	**III**	
Current smoker				
Ex-smoker				
Never smoked				

Notes:

INTERVENTION

		Drug name	**Dosing regimen (*describe*)**
Intervention	**I**		
	II		
	III		
Placebo / Control			

Notes:

Study duration (months): Mean _____ Median _____

Range:_____ months

UNIQUE IDENTIFIER #_____

SUBJECTS RANDOMIZED / DROPOUTS / FOLLOWED

		Total Randomized	Lost to attrition	Due to side effects	# available for follow-up
Intervention	**I**				
	II				
	III				
	IV				
	V				
Placebo/Control					

Notes:

QUALITY OF LIFE

(provide SDs, SEs, p-values and confidence intervals when appropriate)

	Intervention (*write in in subgoups*)			**Placebo/control** (*write in*)
	I	**II**	**III**	
SGRQ*, baseline				
SGRQ*, end				
SGRQ*, mean change				
CRQ **, baseline				
CRQ, end**				
CRQ, mean change**				

**St George's Respiratory Questionnaire*
*** Chronic Respiratory Questionnaire*

UNIQUE IDENTIFIER #_____

CLINICAL OUTCOMES

(provide SDs, SEs, p-values and confidence intervals when appropriate)

	Intervention (*write in in subgoups*)			**Placebo/control** (*write in*)
	I	**II**	**III**	
Deaths, all causes				
Death, respiratory				
Total hospitalizations – any reason				
At least one hospitalization – any reason,				
Total hospitalizations – COPD exacerbations				
At least one hospitalization – COPD exacerbations				
Total physician visits – any reason				
At least one physician visit – any reason				
Total physician visits – due to COPD				
At least one physician visit – due to COPD				
Other (*describe*)				

FORCED AIR EXPIRATORY VOLUME (FEV1)

	Intervention (*write in subgoups*)			**Placebo/control** (*write in*)
	I	**II**	**III**	
FEV1, mean at baseline (+ SD/SE if provided**)**				
FEV1, mean at follow-up (+ SD/SE if provided**)**				
FEV1, mean change (if provided**)**				
FEV1, value < 80% > 79% predicted Stage 1:Mild				
FEV1 50%-79% Stage 2:Moderate				
FEV1 30-49% predicted: Stage 3 Severe				
FEV1 < 30% Stage 4 Very Severe				
Forced vital capacity ratio (FEV1/FVC), < 70%				
Other				

UNIQUE IDENTIFIER #_____

CLINICAL SYMPTOMS

	Intervention (*write in subgoups*)			**Placebo/control** (*write in*)
	I	**II**	**III**	
Dyspnea n/N and %	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:	Baseline: Follow-up:
Cough	Baseline: Follow-p:	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:
Sputum	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:
Wheeze	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:
Combined Clinical Symptoms	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:
Other	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:

*** If you need more of this form** _____
[*photocopy and attach additional sheets for more than 4 subgroups*]

Interventions for Smoking Cessation with the Addition of Spirometry
Article Abstraction Form:

Author (first):_____

Journal:_____ Year Publication: _____

Country:_____ (where study performed)

Reviewer:_____

VERIFICATION/SELECTION OF STUDY ELIGIBILITY

Randomized	Yes	No	Unclear
Placebo ***or*** Control	Yes	No	Unclear
Spirometry used	Yes	No	Unclear
Minimum of 50 subjects per arm	Yes	No	Unclear
Study duration $\geq$ 3 months	Yes	No	Unclear

Stop if any of the above is "NO"

METHODS

Study Design and Conduct

Subject blinded	Yes	No	Unclear
Provider blinded	Yes	No	Unclear
Intention-to-treat analysis	Yes	No	Unclear
Crossover trial	Yes	No	Unclear

RANDOMIZATION ALLOCATION CONCEALMENT METHOD (circle one)

Clearly adequate: Centralized randomization by telephone, randomization scheme controlled by pharmacy, numbered or coded identical containers administered sequentially, on-site computer system which can only be accessed after entering the characteristics of an enrolled participant, sequentially numbered sealed opaque envelopes.

Clearly Inadequate: Alternation (odd-even, etc..), date of birth, date of week

Unclear: Sealed envelopes but not sequentially numbered or opaque, other, list of random numbers read by someone entering patient into trial (open list) *or study noted to be random or "randomization" or "random allocation" but no details provided.*

PARTICIPANTS

Multicenter or single site (*circle one*)

Total number of subjects eligible_____

Total # subjects enrolled _____ Subjects completed trial:_____

Setting: Community Primary Clinic Specialty Clinic Nursing Home
(*circle all that apply*) Other _____

Intervention (*write in*)		**Placebo/control** (*write in*)	
# Subjects:		# Subjects:	
Mean age		Mean age	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Age < 65* n / N and %		Age ≥ 65 n / N and %	
Age ≥ 65 n / N and %		Age ≥ 65 n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	
Living status: alone n / N and %		Living status: alone n / N and %	
Living status: with smoker		Living status: with smoker	
Living status: with non smoker		Living status: with non smoker	
COPD: n / N and %		COPD: n / N and %	
Emphysema: n / N and %		Emphysema: n / N and %	
Other		Other	
Other		Other	

SMOKING HISTORY

(provide SDs, SEs, ranges, p-values and confidence intervals when appropriate)

Intervention (*write in*)		**Placebo/control** (*write in*)	
Mean # cigarettes Smoked/day		Mean # cigarettes Smoked/day	
Pack years		Pack years	
Mean age when starting smoking		Mean age when starting smoking	
Nicotine content > 1 mg/cig		Nicotine content > 1 mg/cig	
Nicotine content < 1 mg/cig		Nicotine content < 1 mg/cig	
Any prior attempt to quit		Any prior attempt to quit	
Prior attempts: none		Prior attempts: none	
Prior attempts: 1-2		Prior attempts: 1-2	
Prior attempts: ≥ 3		Prior attempts: ≥ 3	
Previous nicotine patch use		Previous nicotine patch use	
Previous nicotine gum use		Previous nicotine gum use	
Mean Fagerström score		Mean Fagerström score	
Other		Other	
Other		Other	
Other		Other	

Notes:

BASELINE LUNG FUNCTION

(provide SDs, SEs, ranges, p-values and confidence intervals when appropriate)

Intervention (*write in*)		**Placebo / control** (*write in*)	
FEV1, mean		**FEV1, mean**	
FEV1, value, % predicted		**FEV1, value, % predicted**	
Forced vital capacity ratio (FEV1/FVC),		**Forced vital capacity ratio (FEV1/FVC),**	
CO, ppb		**CO, ppb**	

INTERVENTION

	Intervention name: description	**Intervention frequency (*describe*)**
Intervention		
Placebo / Control		

Notes:

Mean study duration _____ months

Median study duration _____ months

Range:_____ months

SUBJECTS RANDOMIZED / DROPOUTS / FOLLOWED

	Total Randomized	Lost to attrition	Due to side effects	# available for follow-up
Intervention				
Placebo/Control				

Notes:

CESSATION

(provide SDs, SEs, p-values and confidence intervals when appropriate)

Intervention (*write in*)		**Placebo/control** (*write in*)	
Quit rate, last followup		**Quit rate, last followup**	
Made ≥ 1 attempt to quit or "ever quit"		**Made ≥ 1 attempt to quit or "ever quit"**	
CO-validated cessation		**CO-validated cessation**	
Other (*describe*)		**Other** (*describe*)	
Other (*describe*)		**Other** (*describe*)	
Other (*describe*)		**Other** (*describe*)	

FORCED AIR EXPIRATORY VOLUME (FEV1)

Intervention (*write in*)		**Placebo / control** (*write in*)	
FEV1, mean at baseline (+ SD/SE if provided**)**		**FEV1, mean at baseline** (+ SD/SE if provided**)**	
FEV1, mean at followup (+ SD/SE if provided**)**		**FEV1, mean at followup** (+ SD/SE if provided**)**	
FEV1, mean change (if provided**)**		**FEV1, mean change (**if provided**)**	
FEV1, value < 80% predicted		**FEV1, value < 80% predicted**	
Forced vital capacity ratio (FEV1/FVC), < 70%		**Forced vital capacity ratio (FEV1/FVC), < 70%**	
CO, ppb		**CO, ppb**	

QUALITY OF LIFE

(provide SDs, SEs, p-values and confidence intervals when appropriate)

Intervention (*write in*)		**Placebo / control** (*write in*)	
SGRQ*, mean change		**SGRQ*, mean change**	
CRQ, mean change**		**CRQ**, mean change**	

*St George's Respiratory Questionnaire
** Chronic Respiratory Questionnaire

For SUBGROUPS - *photocopy Outcomes pages and attach*

Subgroup _____

Intervention (*write in*)		**Placebo/control** (*write in*)	
# Subjects:		# Subjects:	
Mean age		Mean age	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Age < 65* n / N and %		Age ≥ 65 n / N and %	
Age ≥ 65 n / N and %		Age ≥ 65 n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	

SMOKING HISTORY

Intervention (*write in*)		**Placebo/control** (*write in*)	
Mean # cigarettes Smoked/day		Mean # cigarettes Smoked/day	
Pack years		Pack years	
Nicotine content > 1 mg/cig		Nicotine content > 1 mg/cig	
Nicotine content < 1 mg/cig		Nicotine content < 1 mg/cig	

Any prior attempt to quit		Any prior attempt to quit	
Prior attempts: none		Prior attempts: none	
Prior attempts: 1-2		Prior attempts: 1-2	
Prior attempts: ≥ 3		Prior attempts: ≥ 3	
Other		Other	
Other		Other	

Notes:

Subgroup 1_____

[*photocopy and attach additional sheets for more than 2 subgroups*]

	Total Randomized	Total Dropouts	Due to side effects	# available for follow-up
Intervention				
Placebo/Control				

Notes:

Prevalence COPD / Spirometry
Article Abstraction Form:

Author (first):_____

Journal:_____ Year Publication: _____

Country:_____ (where study performed)

Reviewer:_____

VERIFICATION/SELECTION OF STUDY ELIGIBILITY

Subjects with COPD Yes No Unclear
(i.e., irreversible airway obstruction, NOT asthma and NOT α-1 antitrypsin deficiency, or were the outcomes in the group with COPD reported separately?

FEV1/FVC measured with spirometry Yes No Unclear

TYPE OF STUDY

Source of data: (*circle*) Epidemiologic survey Cohort study Case/Control

Other (describe)_____

Prospective_____ Retrospective_____ Unclear_____

Subjects selected at random? Yes No Unclear

Control Group (i.e subjects with no COPD) Yes No Unclear

Multivariate analyses used? Yes No Unclear

SUBJECTS

Total number of subjects _____

COPD subjects _____ Control subjects _____

Setting: Community Primary Clinic Specialty Clinic Nursing Home
(*circle all that apply*)
Other (describe)_____

DEMOGRAPHICS

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
# Subjects:		# Subjects:	
Mean age		Mean age	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Age < 65* n / N and %		Age $\geq$ 65 n / N and %	
Age $\geq$ 65 n / N and %		Age $\geq$ 65 n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	

SMOKING HISTORY

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	
Duration, pack years		Duration, pack years	
Other (*write in*)		Other (*write in*)	

Notes:

FEV1/FVC

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Mean FEV1, L		Mean FEV1, L	
Mean FEV1, % of predicted		Mean FEV1, % of predicted	
FEV1 < 50% predicted		FEV1 < 50% predicted	
FEV1 50-70% predicted		FEV1 50-70% predicted	
FEV1 70%-80% predicted		FEV1 70%-80% predicted	
FEV1/FVC <0.70 and FEV1<50% predicted (severe)		FEV1/FVC <0.70 and FEV1<50% predicted (severe)	
FEV1/FVC <0.70 and FEV1≥50-<80% predicted (moderate)		FEV1/FVC <0.70 and FEV1≥50-<80% predicted (moderate)	
FEV1/FVC <0.70 and FEV1≥ 80% predicted (mold)		FEV1/FVC <0.70 and FEV1≥ 80% predicted (mold)	
GOLD, stage 0 Cough, FEV1/FVC >0.70		GOLD, stage 0 Cough, FEV1/FVC >0.70	

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
GOLD, stage 1 FEV1/FVC <0.70, FEV1 ≥ 80% pred		GOLD, stage 1 FEV1/FVC <0.70, FEV1 ≥ 80% pred	
GOLD, stage 2 FEV1/FVC <0.70, FEV1≥30% and < 80% pred		GOLD, stage 2 FEV1/FVC <0.70, FEV1≥30% and < 80% pred	
GOLD, stage 3 FEV1/FVC <0.70, FEV1< 30% pred		GOLD, stage 3 FEV1/FVC <0.70, FEV1< 30% pred	
Other (*write in*)		Other (*write in*)	

Notes:

COPD SUBGROUPS (Based on severity—mild, moderate, severe—or GOLD stage)

Subgroup 1 _____
[*photocopy and attach additional sheets for more than 3 subgroups*]

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
# Subjects:		# Subjects:	
Mean age		Mean age	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Age < 65* n / N and %		Age ≥ 65 n / N and %	
Age ≥ 65 n / N and %		Age ≥ 65 n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	

SMOKING HISTORY

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	
Duration, pack years		Duration, pack years	
Other (*write in*)		Other (*write in*)	

Notes:

FEV1/FVC

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Mean FEV1, L		Mean FEV1, L	
Mean FEV1, % of predicted		Mean FEV1, % of predicted	
FEV1 < 50% predicted		FEV1 < 50% predicted	
FEV1 50-70% predicted		FEV1 50-70% predicted	
FEV1 70%-80% predicted		FEV1 70%-80% predicted	
FEV1/FVC <0.70 and FEV1<50% predicted (severe)		FEV1/FVC <0.70 and FEV1<50% predicted (severe)	
FEV1/FVC <0.70 and FEV1≥50-<80% predicted (moderate)		FEV1/FVC <0.70 and FEV1≥50-<80% predicted (moderate)	
FEV1/FVC <0.70 and FEV1≥ 80% predicted (mold)		FEV1/FVC <0.70 and FEV1≥ 80% predicted (mold)	
GOLD, stage 0 Cough, FEV1/FVC >0.70		GOLD, stage 0 Cough, FEV1/FVC >0.70	

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
GOLD, stage 1 FEV1/FVC <0.70, FEV1 ≥ 80% pred		GOLD, stage 1 FEV1/FVC <0.70, FEV1 ≥ 80% pred	
GOLD, stage 2 FEV1/FVC <0.70, FEV1≥30% and < 80% pred		GOLD, stage 2 FEV1/FVC <0.70, FEV1≥30% and < 80% pred	
GOLD, stage 3 FEV1/FVC <0.70, FEV1< 30% pred		GOLD, stage 3 FEV1/FVC <0.70, FEV1< 30% pred	
Other (*write in*)		Other (*write in*)	

Notes:

Subgroup 2 _____

COPD (*write in*)_____		**COPD** (*write in*)_____	
# Subjects:		# Subjects:	
Mean age		Mean age	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Age < 65* n / N and %		Age ≥ 65 n / N and %	
Age ≥ 65 n / N and %		Age ≥ 65 n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	

SMOKING HISTORY

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	
Duration, pack years		Duration, pack years	
Other (*write in*)		Other (*write in*)	

Notes:

FEV1/FVC

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Mean FEV1, L		Mean FEV1, L	
Mean FEV1, % of predicted		Mean FEV1, % of predicted	
FEV1 < 50% predicted		FEV1 < 50% predicted	
FEV1 50-70% predicted		FEV1 50-70% predicted	
FEV1 70%-80% predicted		FEV1 70%-80% predicted	
FEV1/FVC <0.70 and FEV1<50% predicted (severe)		FEV1/FVC <0.70 and FEV1<50% predicted (severe)	
FEV1/FVC <0.70 and FEV1≥50-<80% predicted (moderate)		FEV1/FVC <0.70 and FEV1≥50-<80% predicted (moderate)	
FEV1/FVC <0.70 and FEV1≥ 80% predicted (mold)		FEV1/FVC <0.70 and FEV1≥ 80% predicted (mold)	
GOLD, stage 0* Cough, FEV1/FVC >0.70		GOLD, stage 0 Cough, FEV1/FVC >0.70	

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
GOLD, stage 1 FEV1/FVC <0.70, FEV1 ≥ 80% pred		GOLD, stage 1 FEV1/FVC <0.70, FEV1 ≥ 80% pred	
GOLD, stage 2 FEV1/FVC <0.70, FEV1≥30% and < 80% pred		GOLD, stage 2 FEV1/FVC <0.70, FEV1≥30% and < 80% pred	
GOLD, stage 3 FEV1/FVC <0.70, FEV1< 30% pred		GOLD, stage 3 FEV1/FVC <0.70, FEV1< 30% pred	
GOLD, stage 4			
Other (*write in*)		Other (*write in*)	

Notes:

*** GOLD, Stage 0 = at risk**
GOLD, Stage 1 = mild COPD
GOLD, Stage 2 = moderate COPD
GOLD, Stage 3 = severe COPD
GOLD, Stage 4 = very severe COPD

PREVALENCE (MILD COPD)

Write in definition_____

Time of followup_____

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	

PREVALENCE (MODERATE COPD)

Write in definition_____

Time of follow-up_____

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	
Other			

PREVALENCE (SEVERE COPD)

Write in definition_____

Time of followup_____

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Age, years (*write in*)		Age, years (*write in*)	
Men: n / N and %		Men: n / N and %	
Women: n / N and %		Women: n / N and %	
Race: white n / N and %		Race: white n / N and %	
Race: black n / N and %		Race: black n / N and %	
Race: Asian n / N and %		Race: Asian n / N and %	
Race: Other n / N and %		Race: Other n / N and %	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	

POSTIVE PREDICTIVE VALUE

COPD subjects (*write in*)		**No COPD / Control (*write in*)**	

QUALITY OF LIFE

(provide SDs, SEs, p-values and confidence intervals when appropriate)

COPD subjects (*write in*)		**No COPD / Control** (*write in*)	
SGRQ*, baseline		**SGRQ*, baseline**	
SGRQ*, end		**SGRQ*, end**	
SGRQ*, mean change		**SGRQ*, mean change**	
CRQ **, baseline		**CRQ**, baseline**	
CRQ, end**		**CRQ**, end**	
CRQ, mean change**		**CRQ**, mean change**	
SF-36-Physical functioning			
SF-36-			
SF-36-			

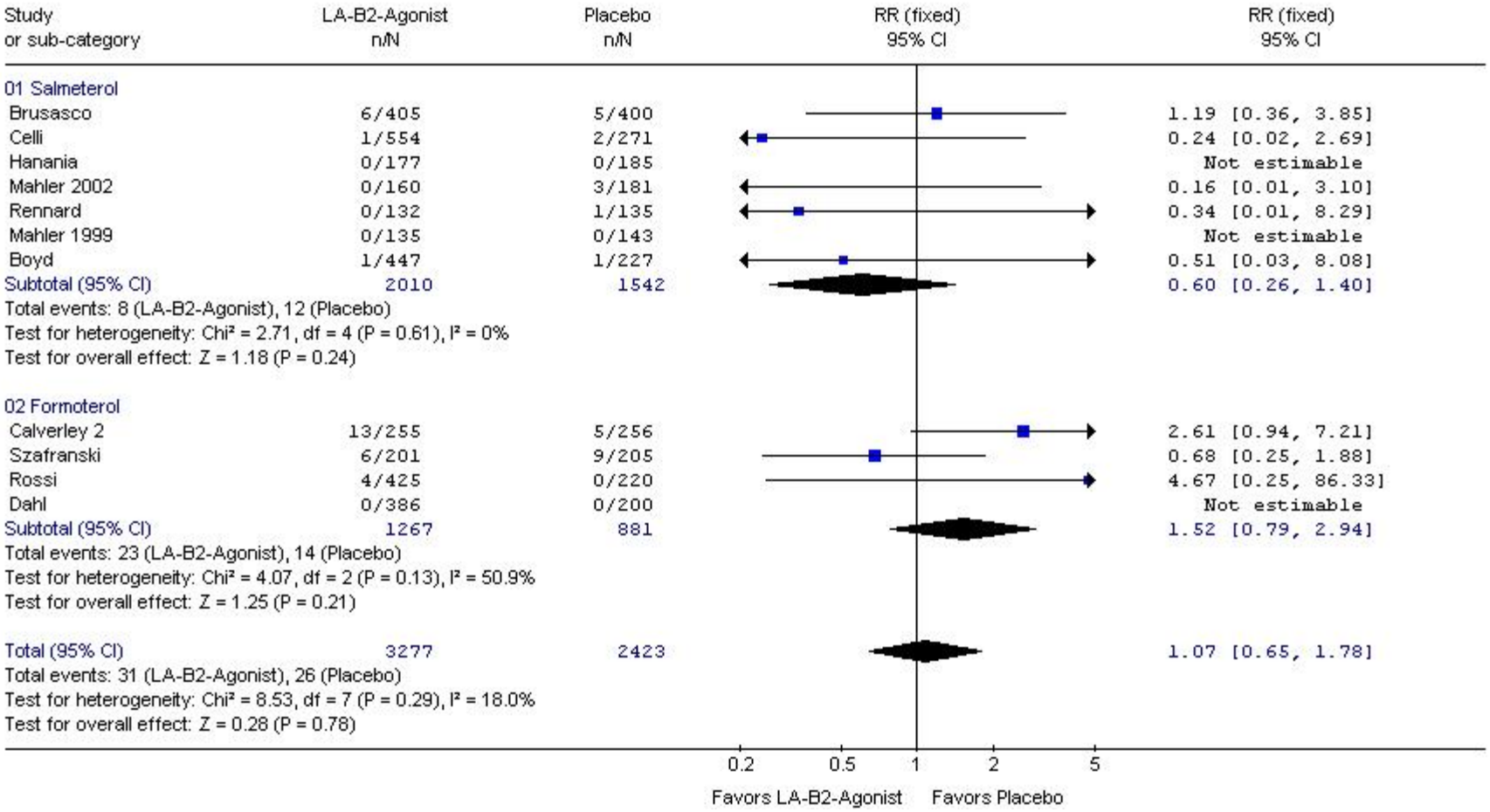
*St George's Respiratory Questionnaire
** Chronic Respiratory Questionnaire

For SUBGROUPS - *photocopy Outcomes pages and attach*

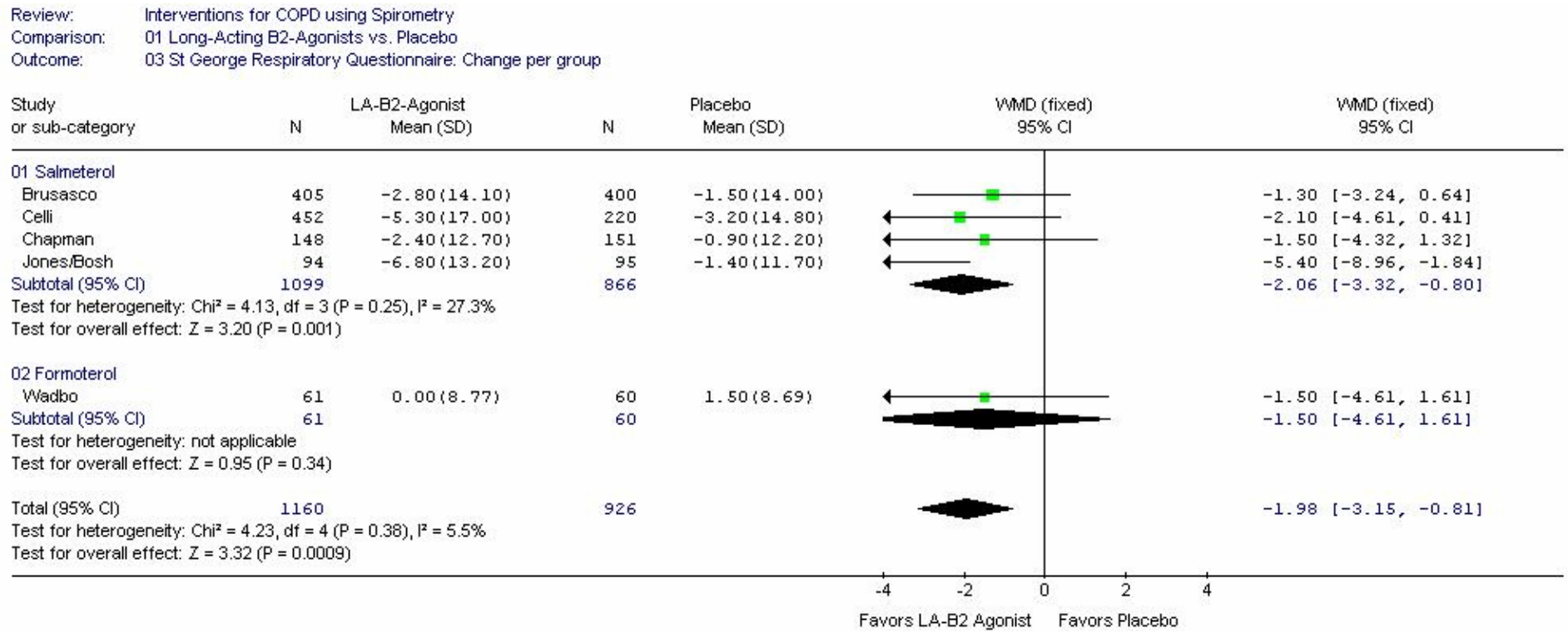
Appendix D
Evidence Tables and Figures

Evidence Figure 1

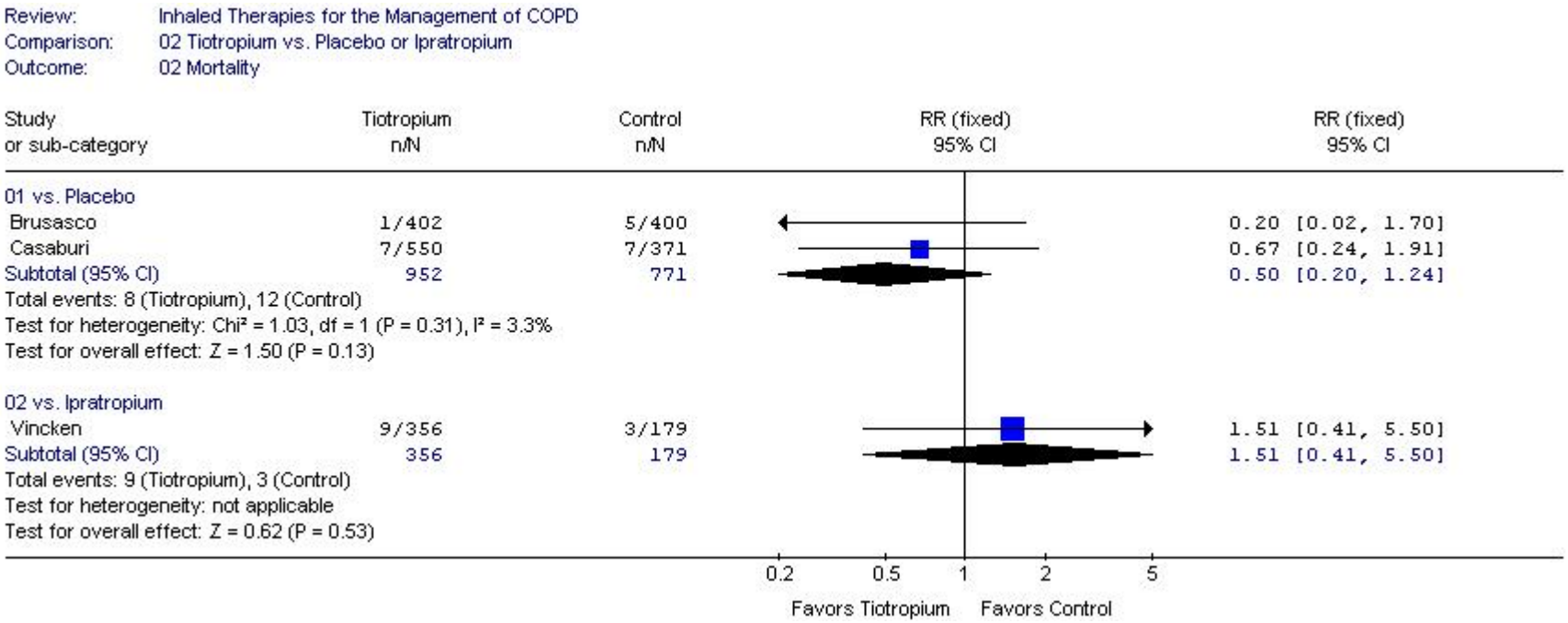
Review: Inhaled Therapies for the Management of COPD
Comparison: 01 Long-Acting B2-Agonists vs. Placebo
Outcome: 02 Mortality



Evidence Figure 2.

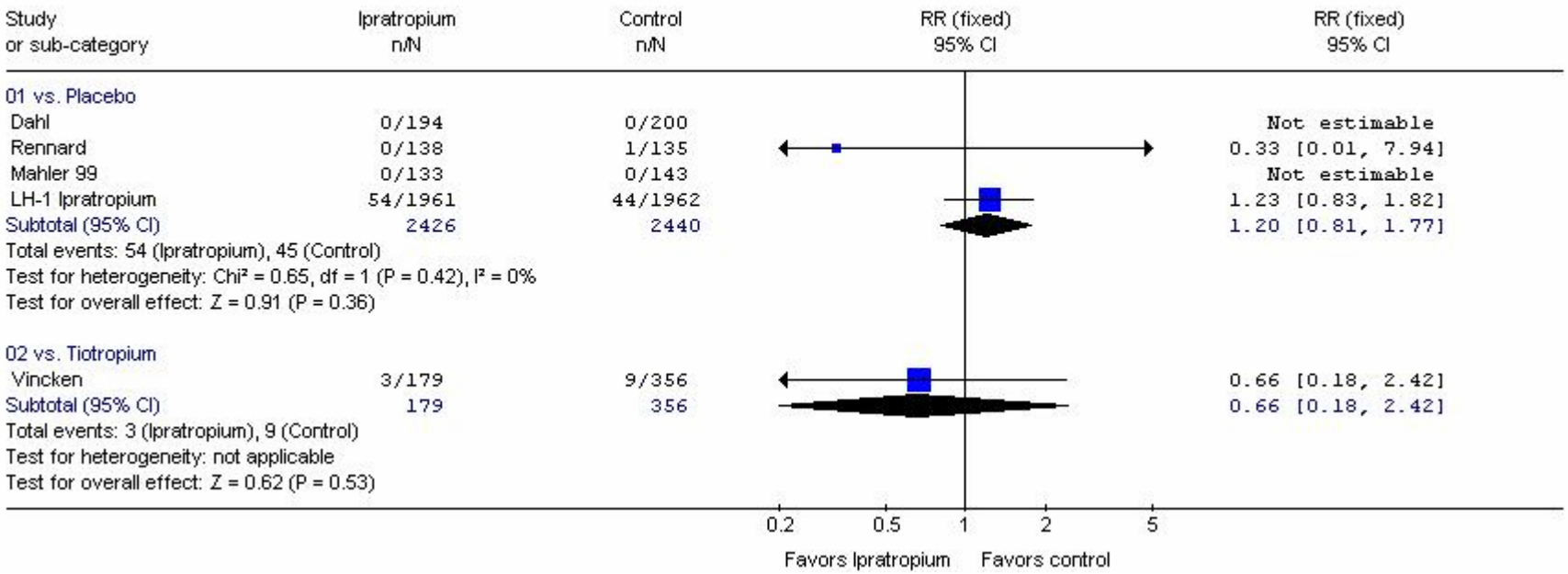


Evidence Figure 3.

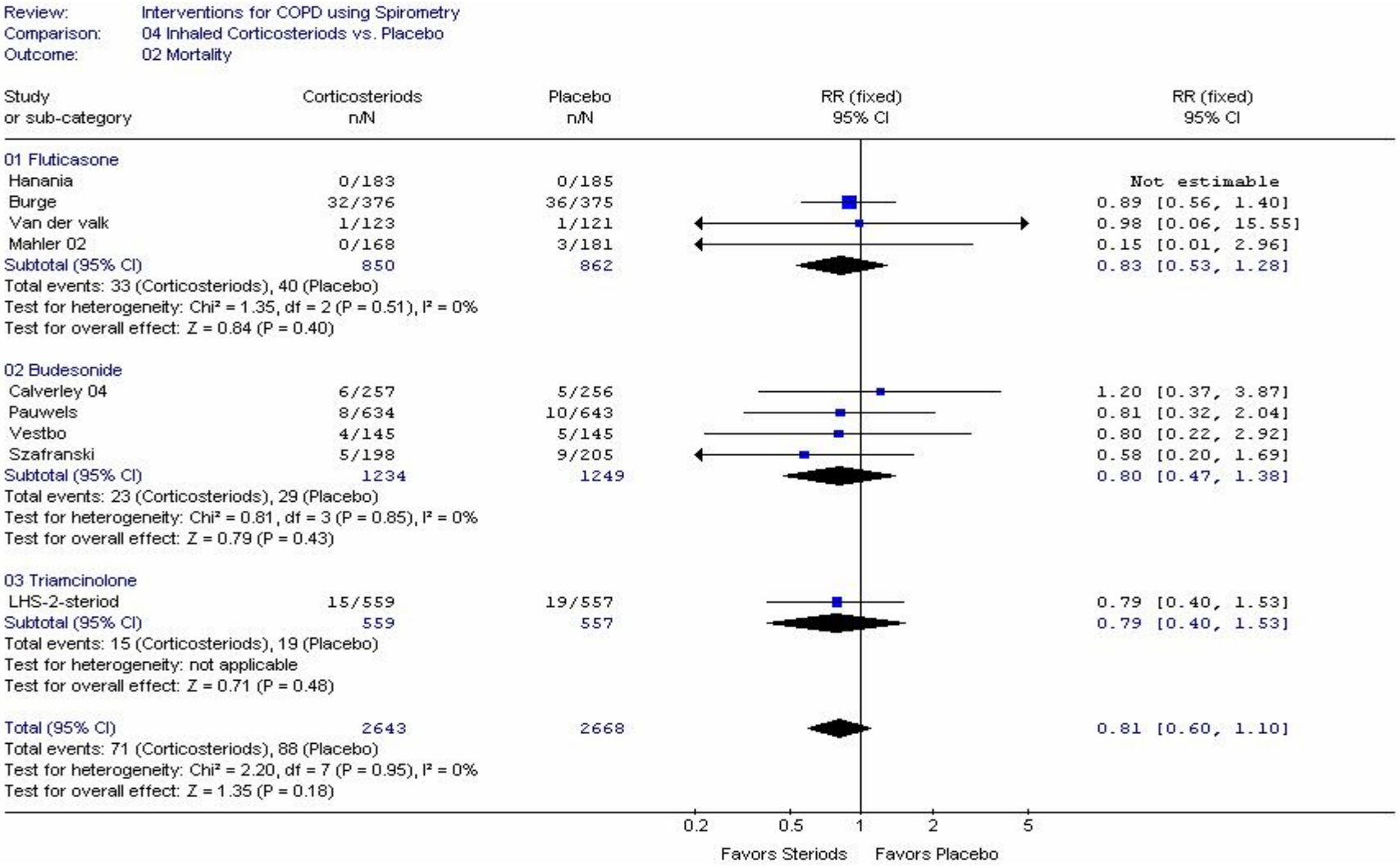


Evidence Figure 4.

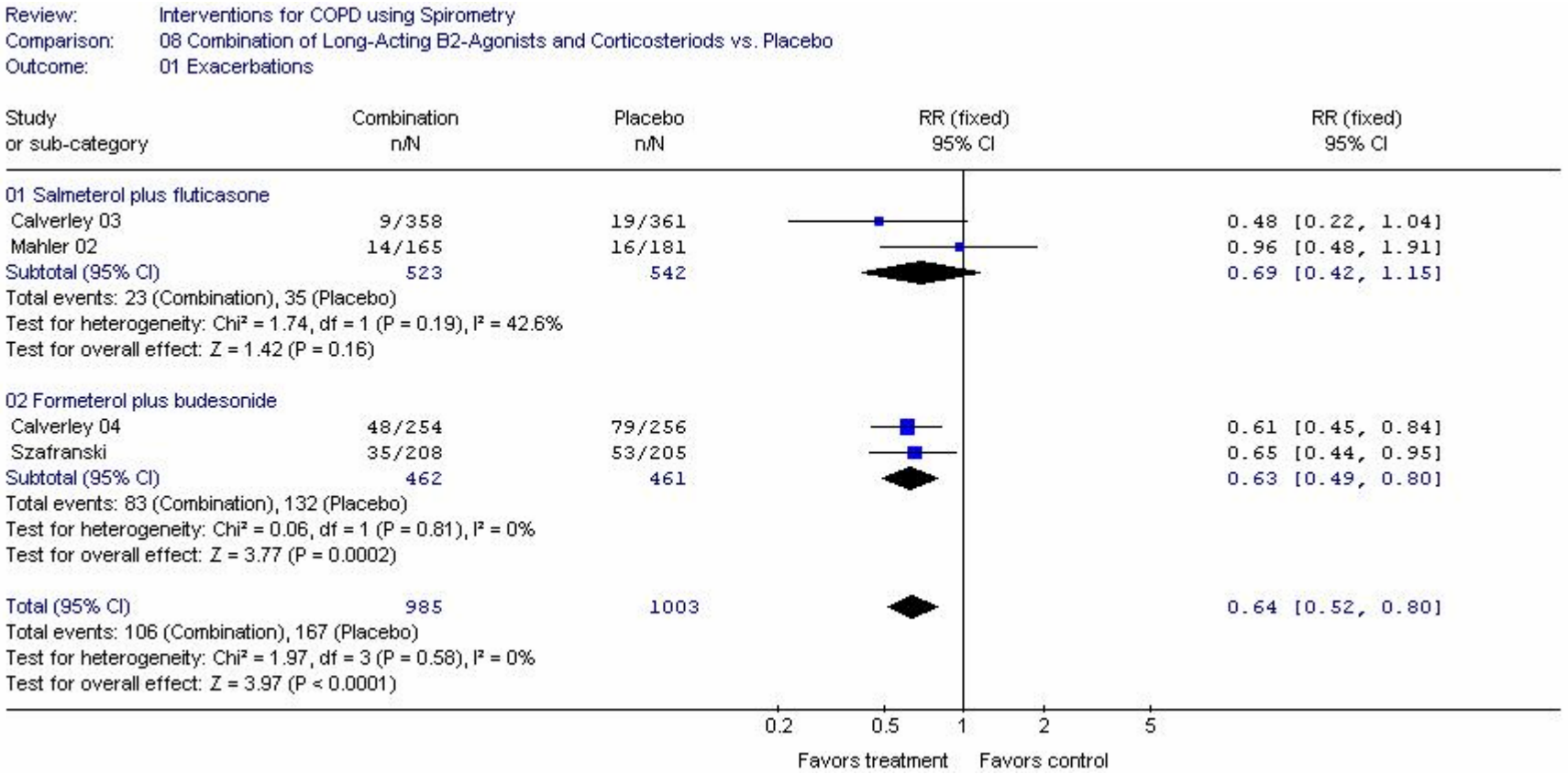
Review: Interventions for COPD using Spirometry
Comparison: 03 Ipratropium vs. Placebo or Tiotropium
Outcome: 02 Mortality



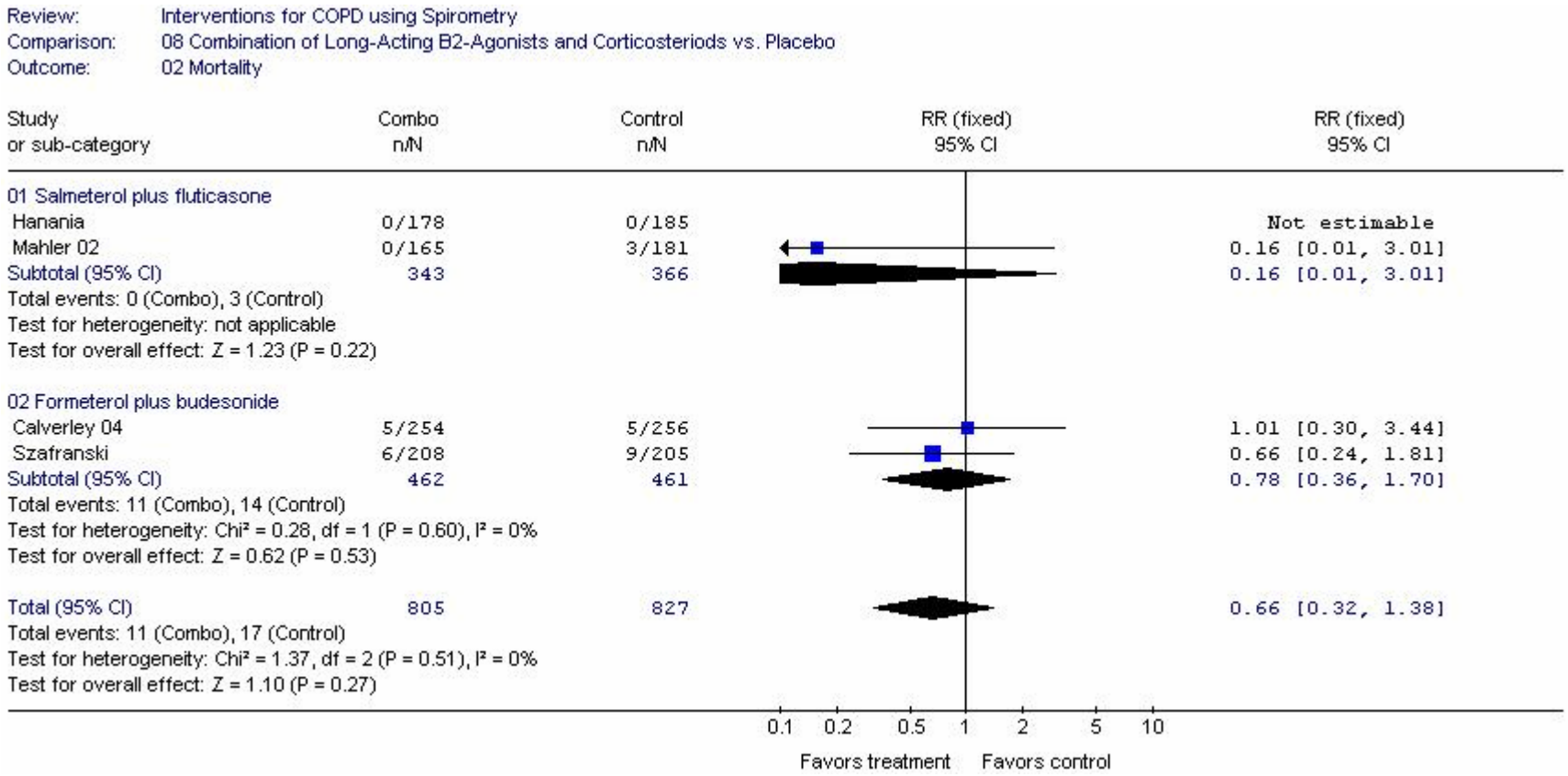
Evidence Figure 5.



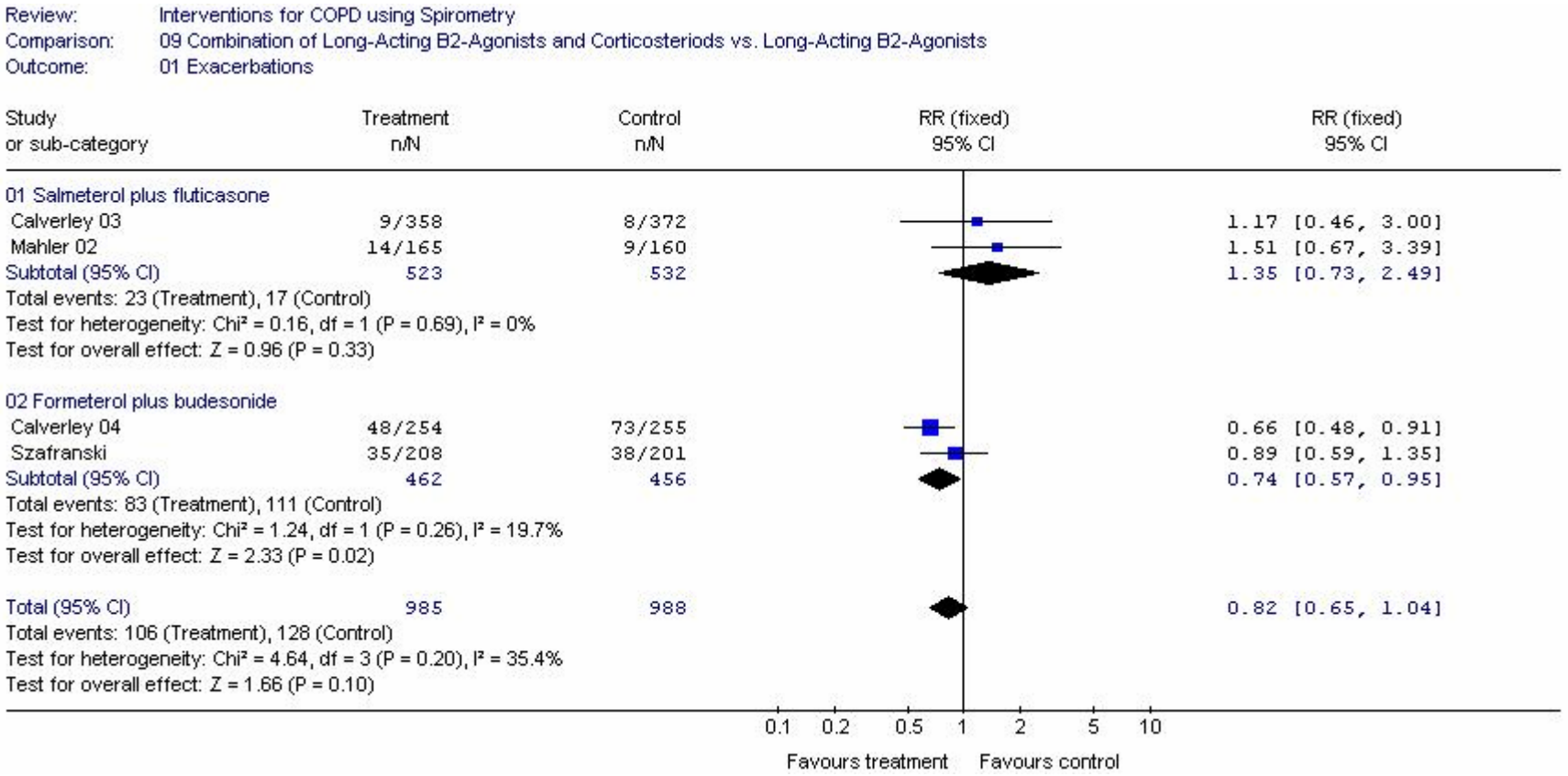
Evidence Figure 6.



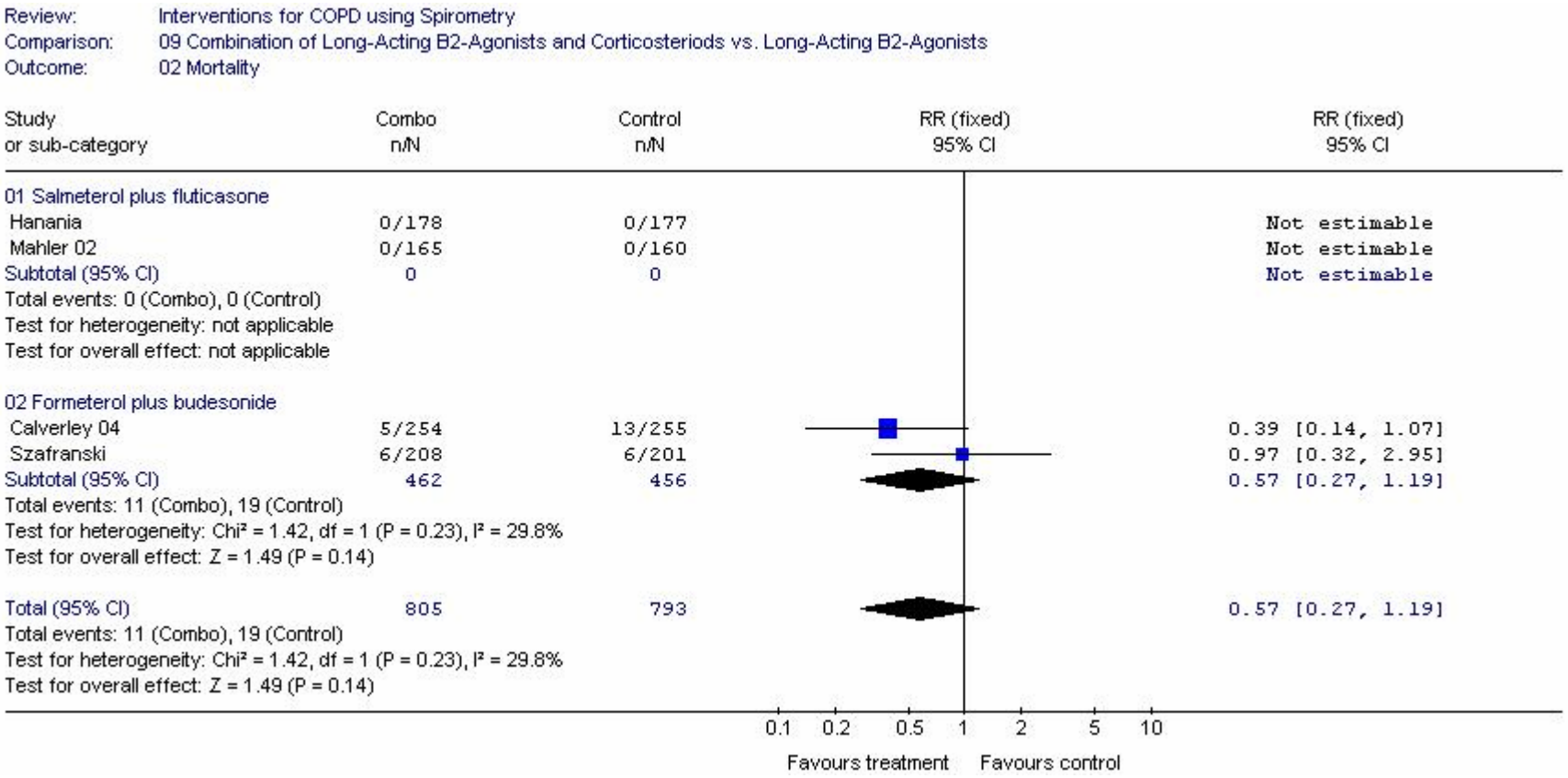
Evidence Figure 7.



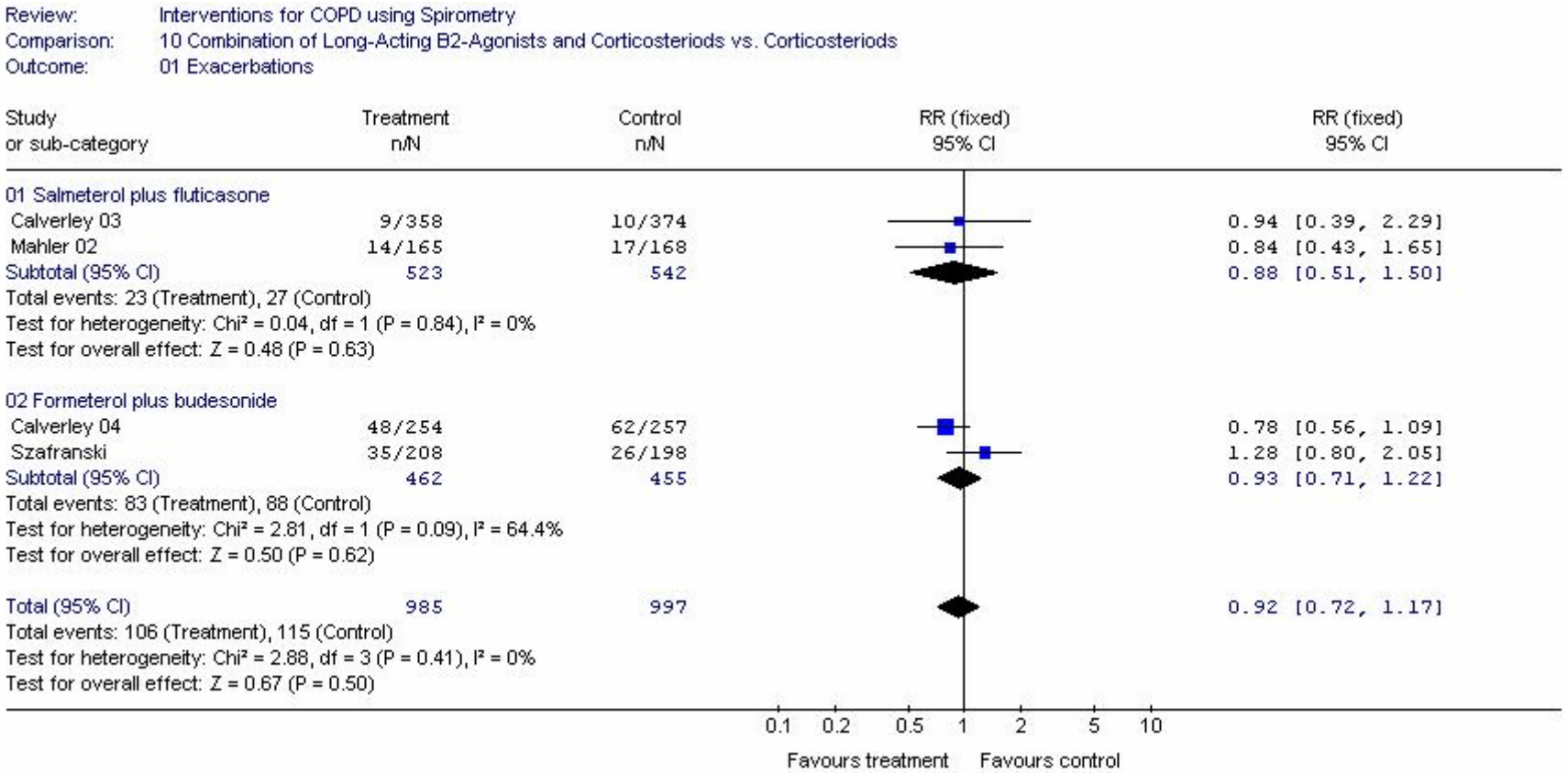
Evidence Figure 8.



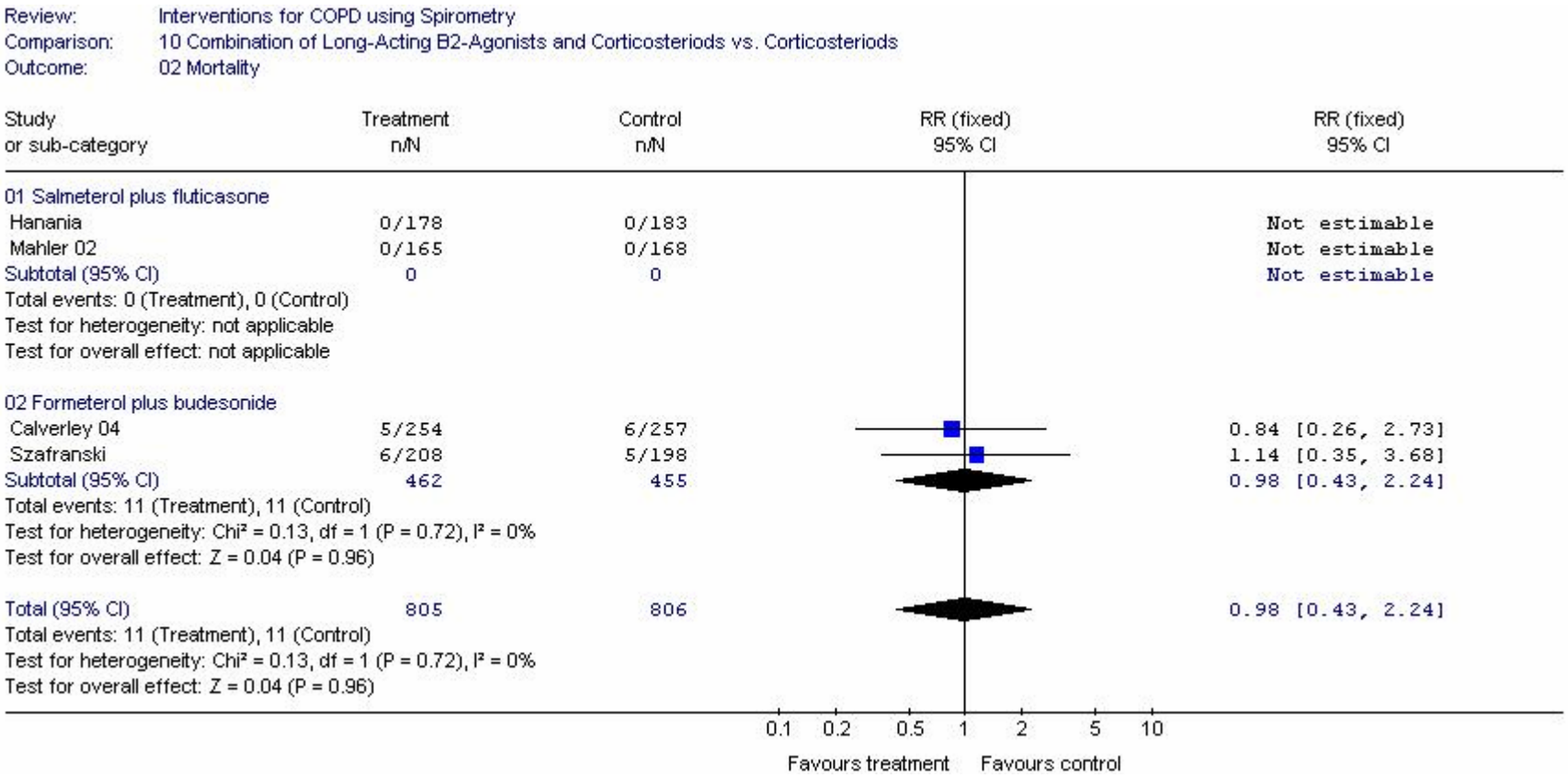
Evidence Figure 9.



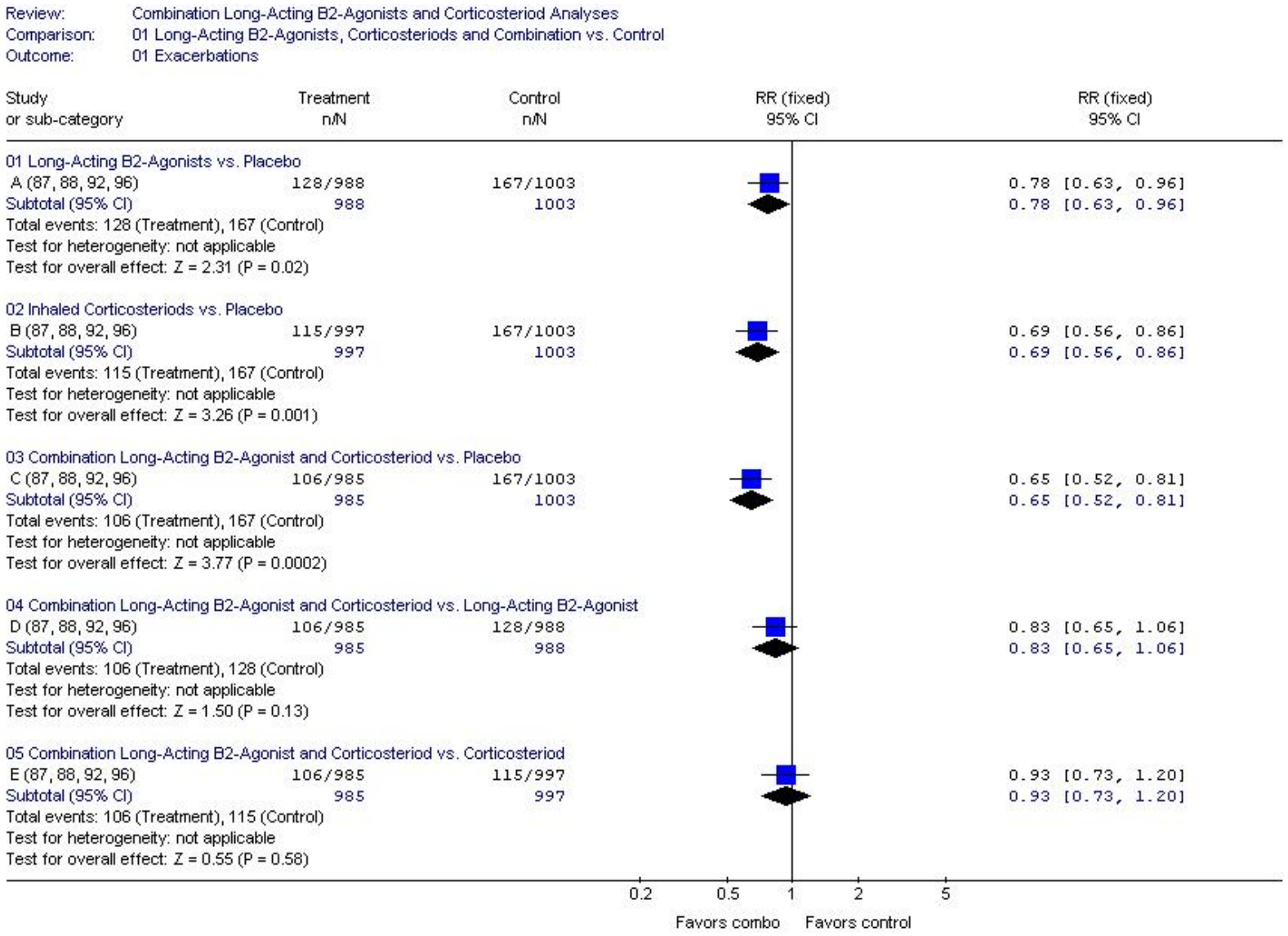
Evidence Figure 10.



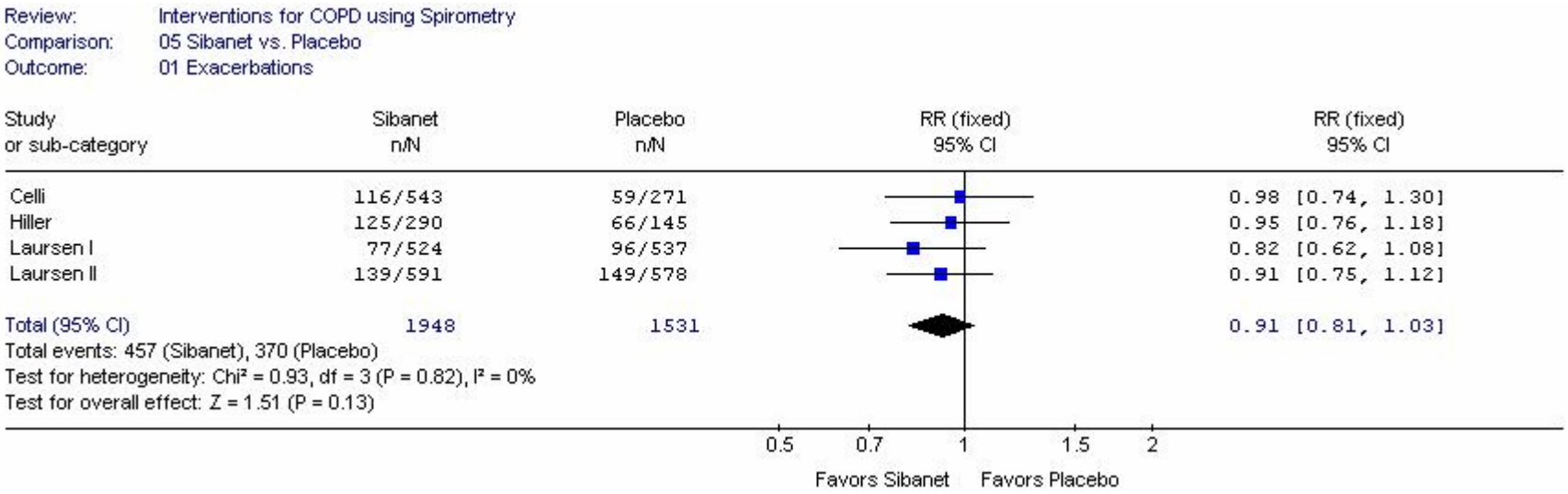
Evidence Figure 11.



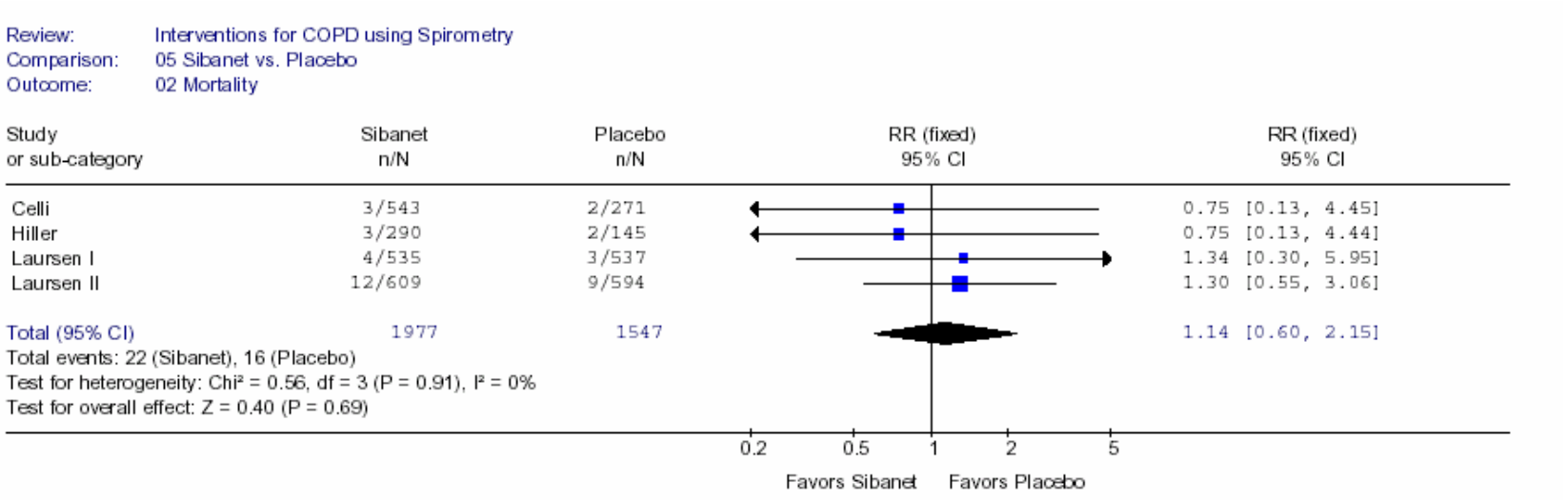
Evidence Figure 12.



Evidence Figure 13.

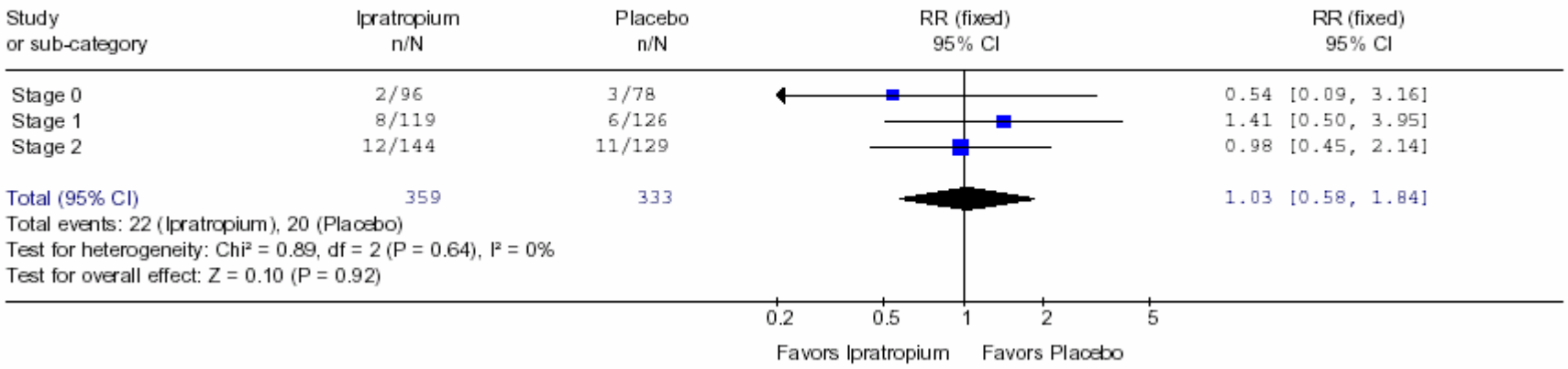


Evidence Figure 14.

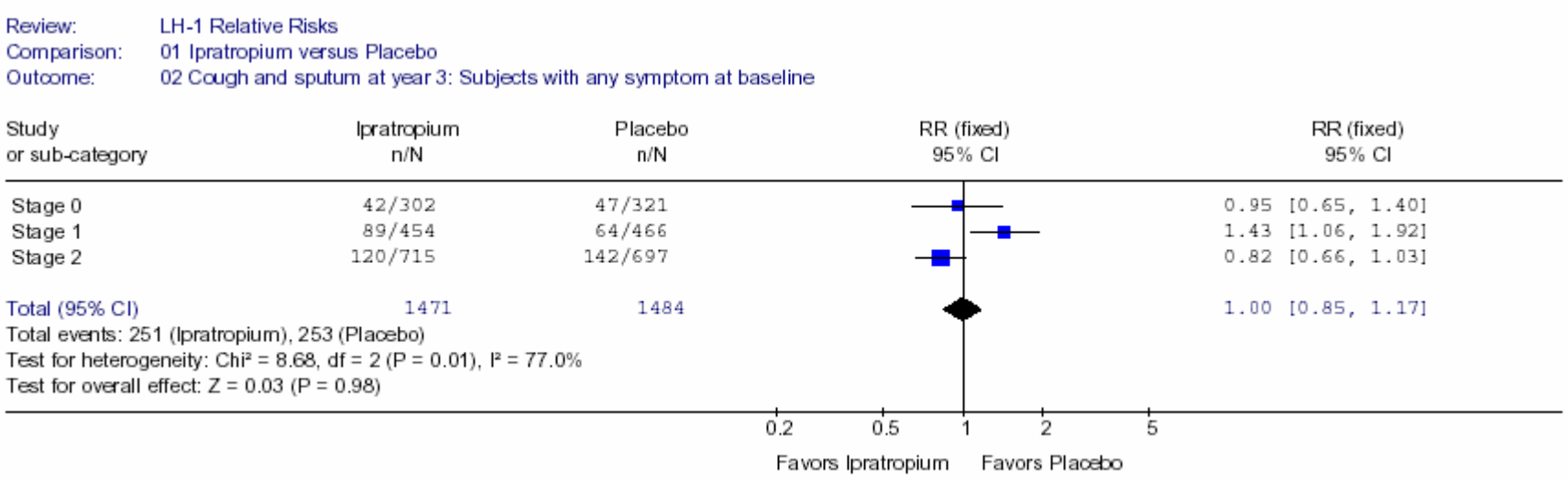


Evidence Figure 15.

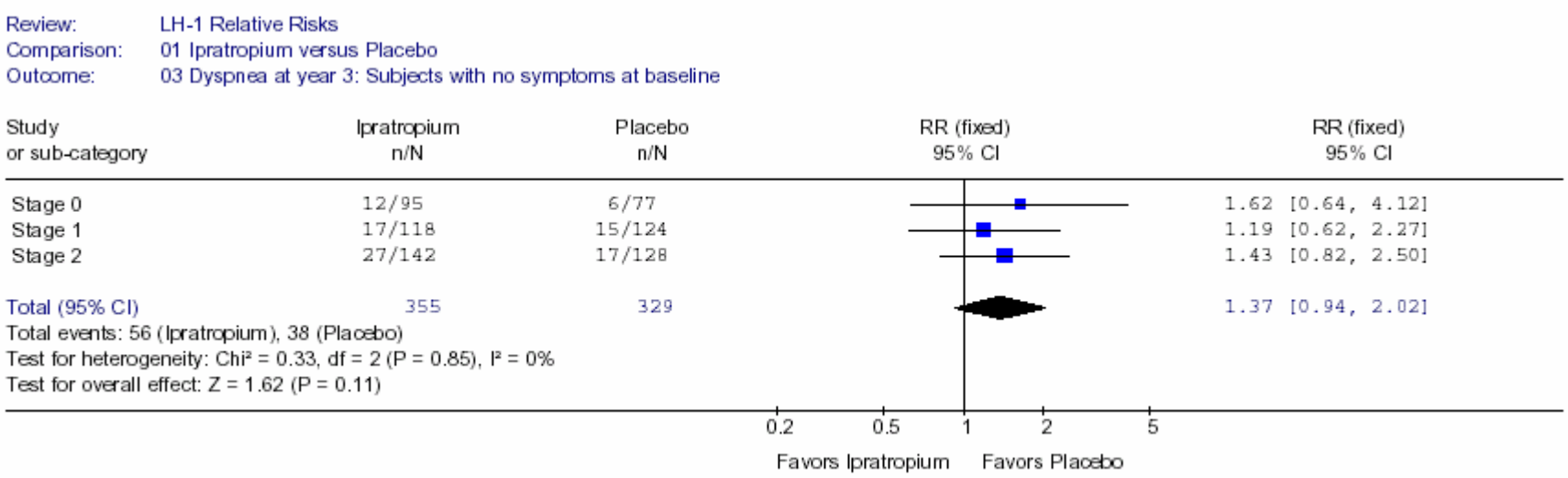
Review: LH-1 Relative Risks
Comparison: 01 Ipratropium versus Placebo
Outcome: 01 Cough and sputum at year 3: Subjects with no symptoms at baseline



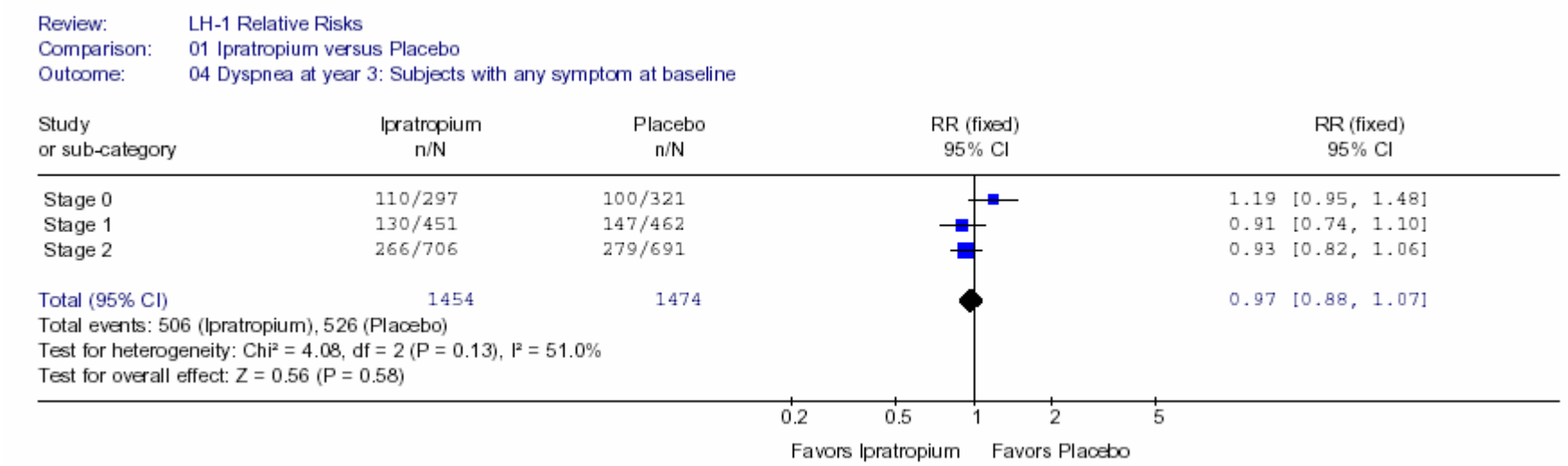
Evidence Figure 16.



Evidence Figure 17.



Evidence Figure 18.



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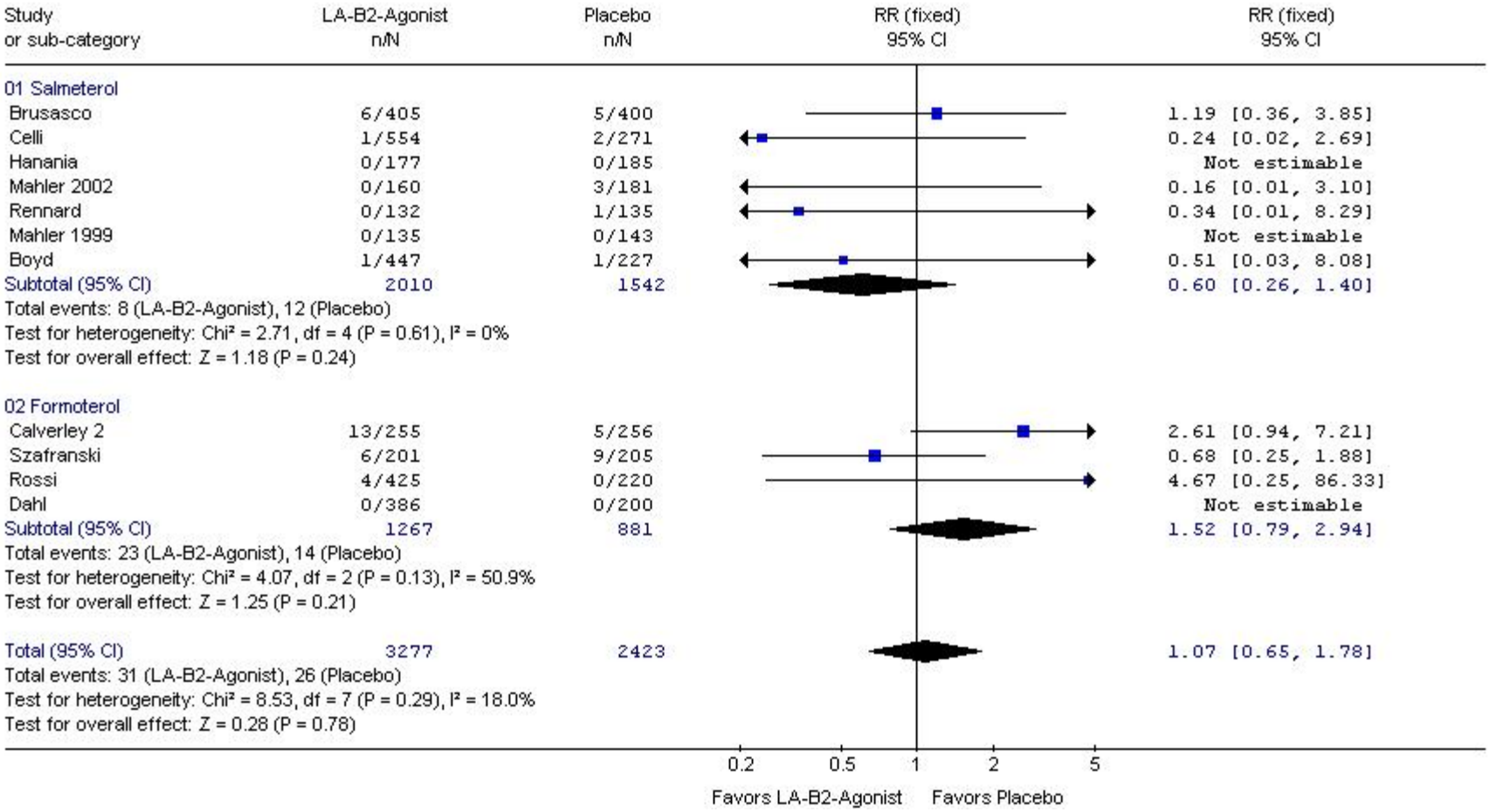
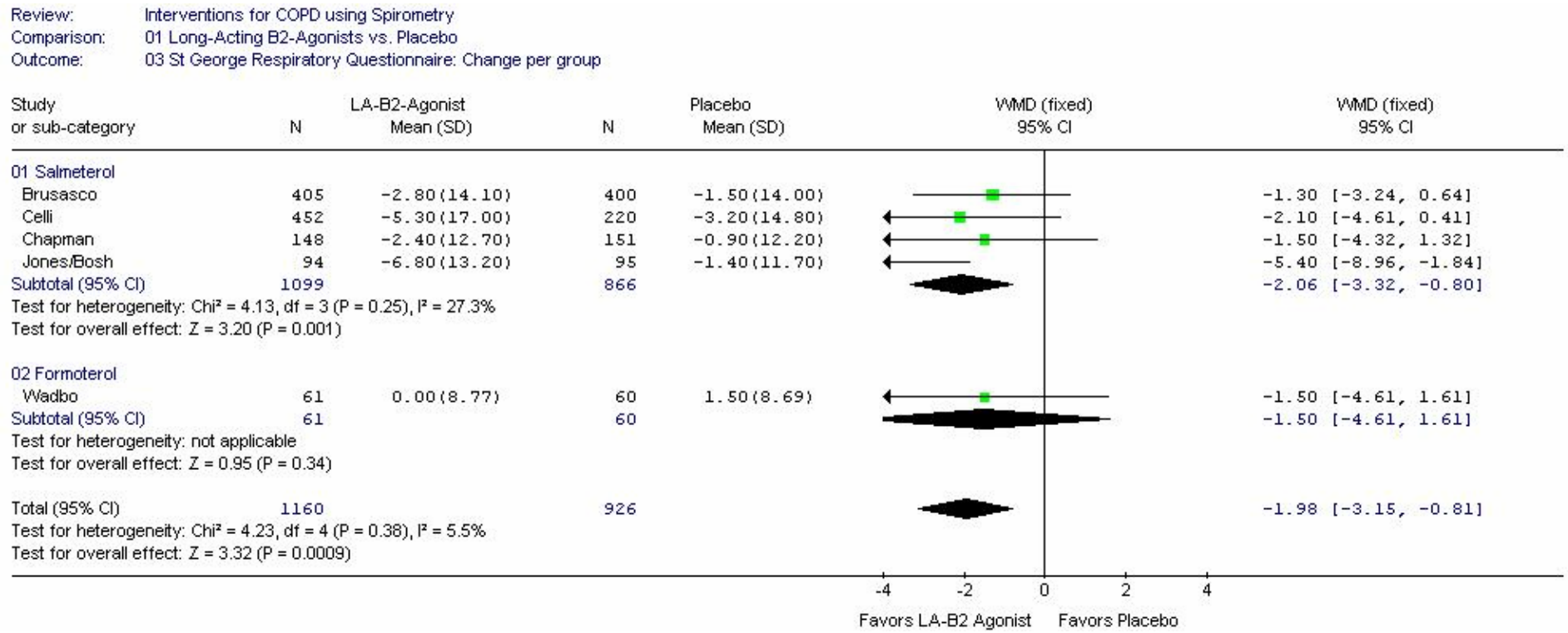
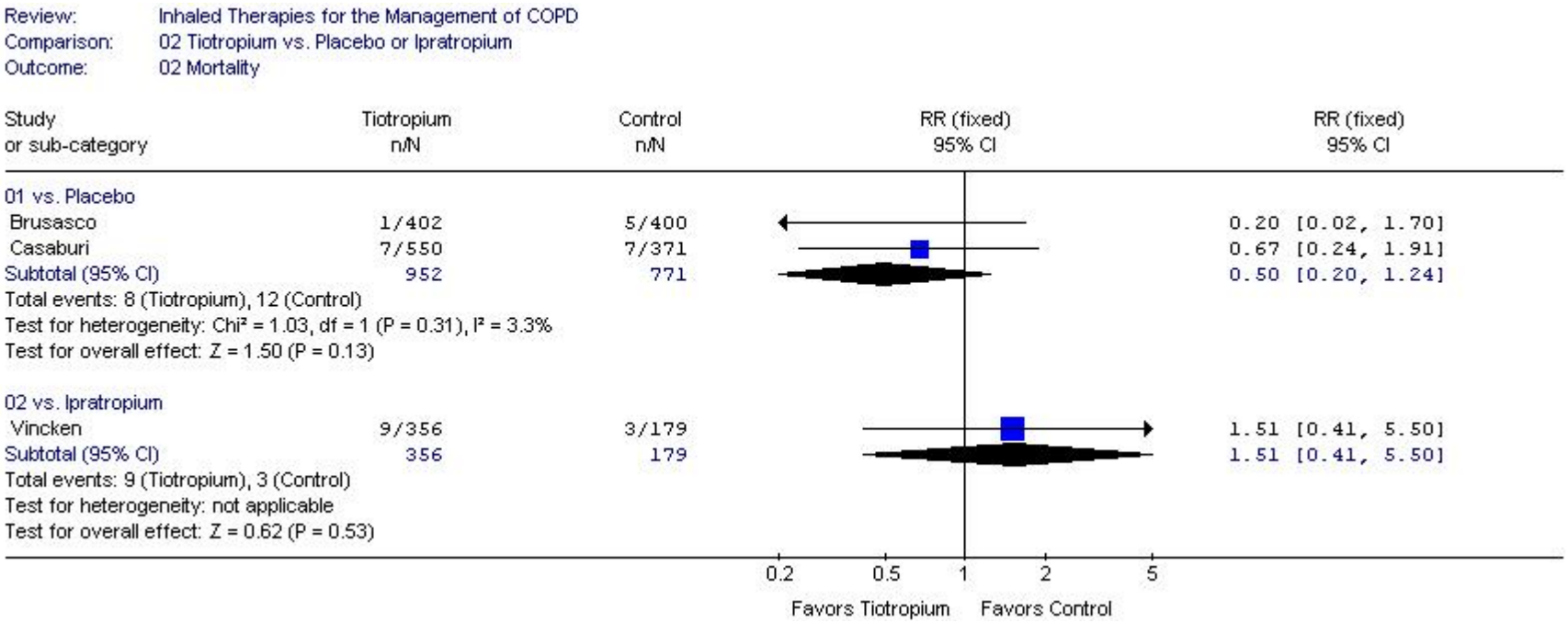
Comparison: 01 Long-Acting B2-Agonists vs. Placebo
Outcome: 02 Mortality



Evidence Figure 2.



Evidence Figure 3.



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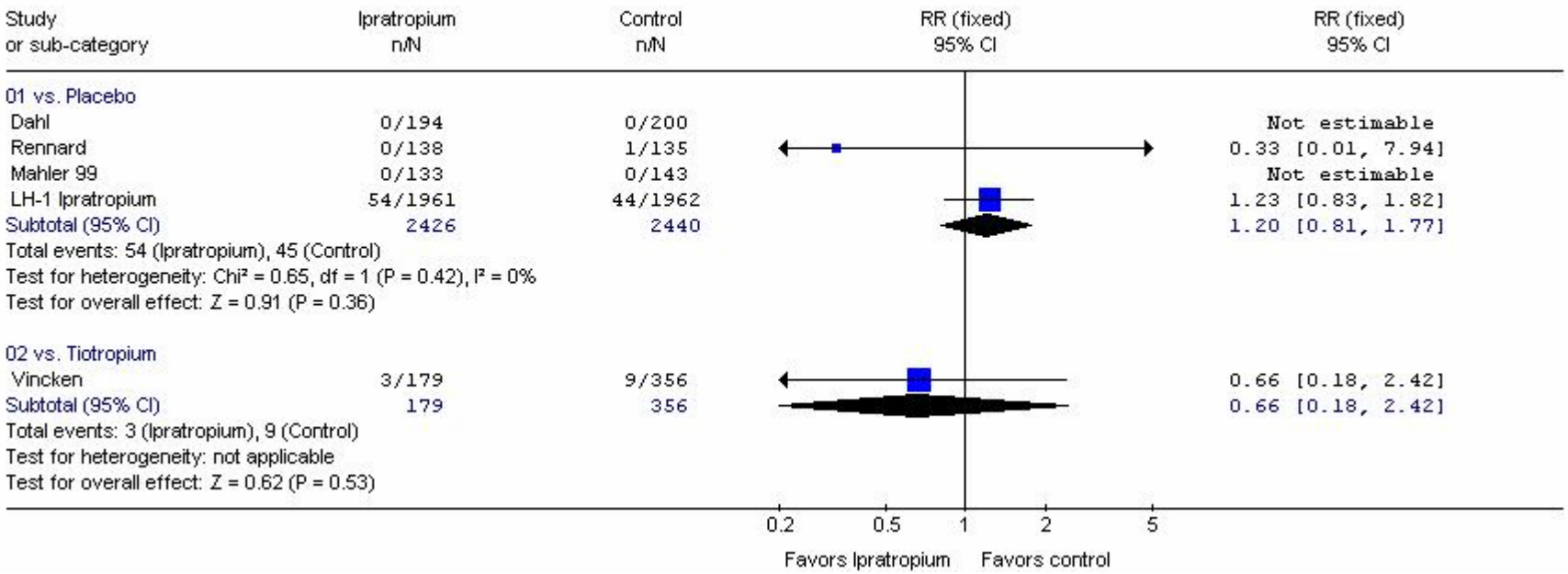
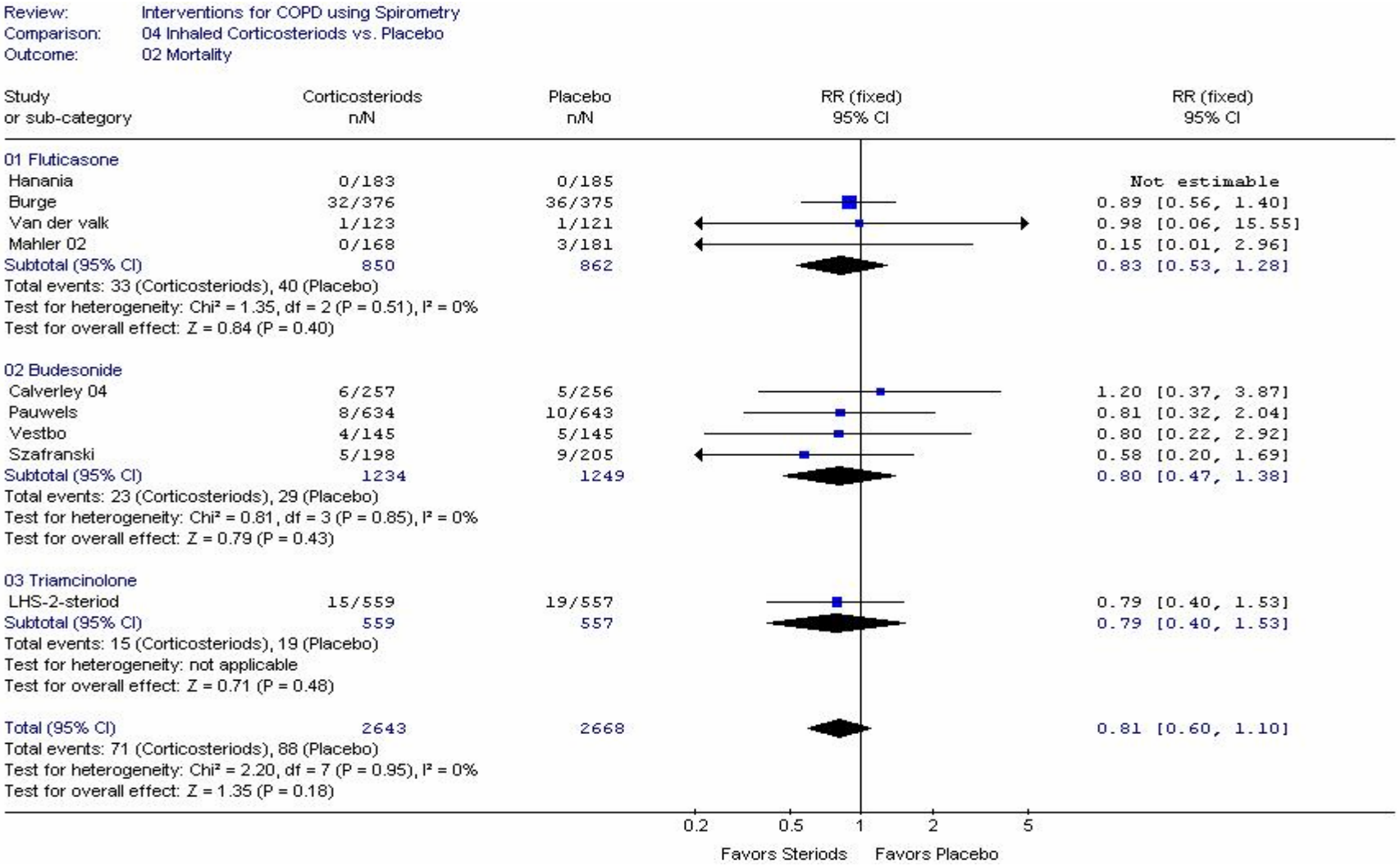
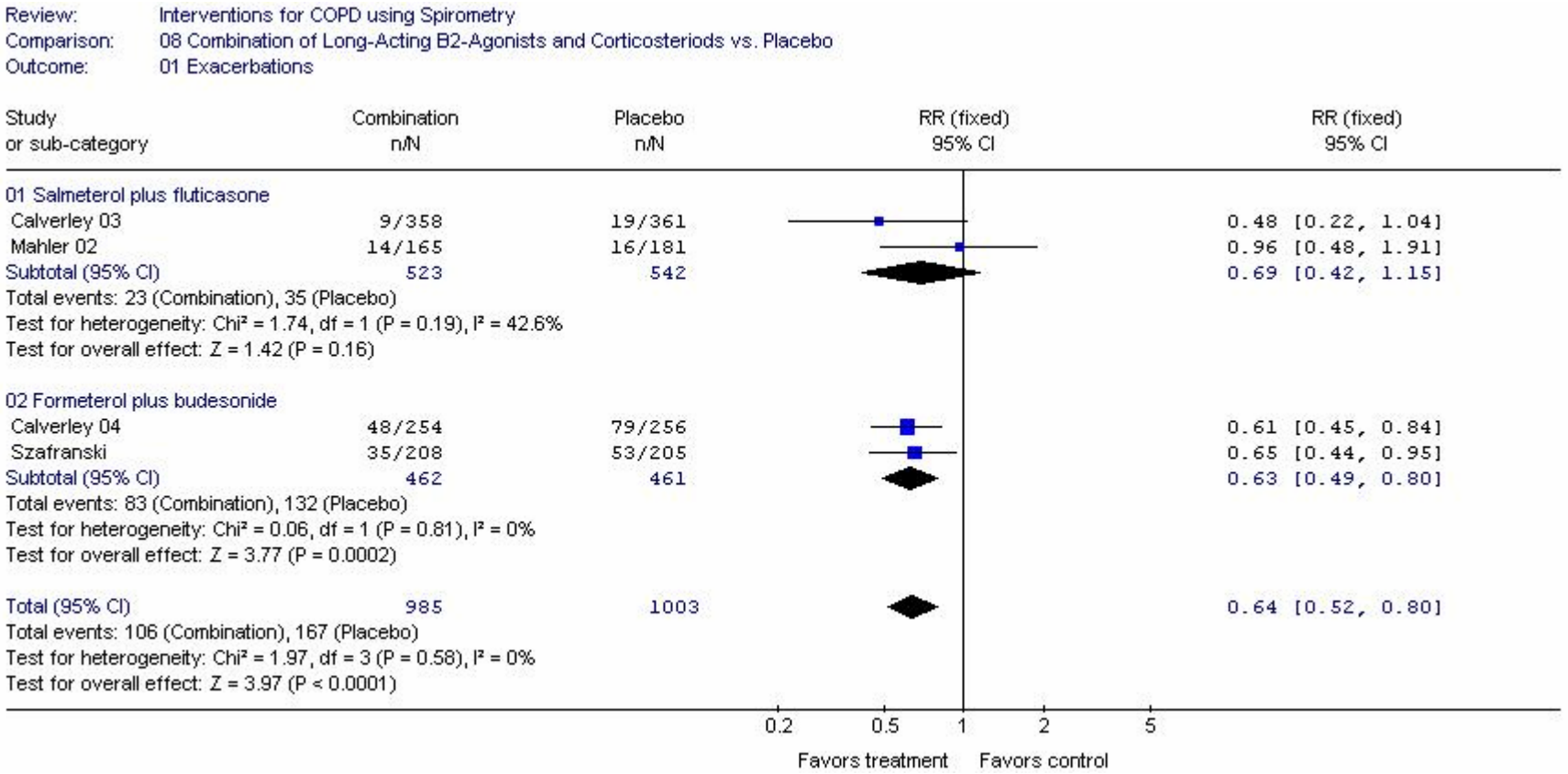


Evidence Figure 5.



Evidence Figure 6.



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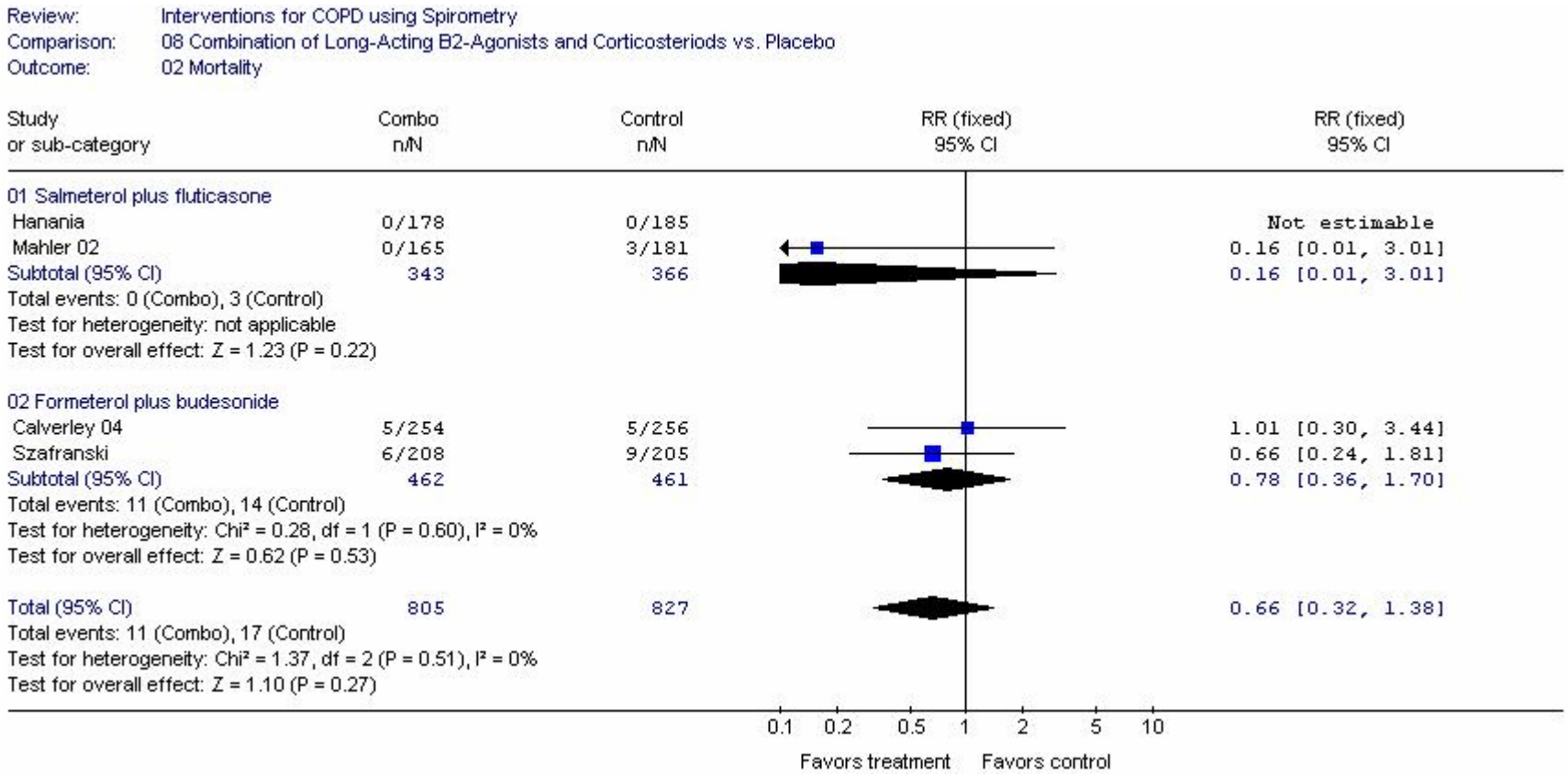

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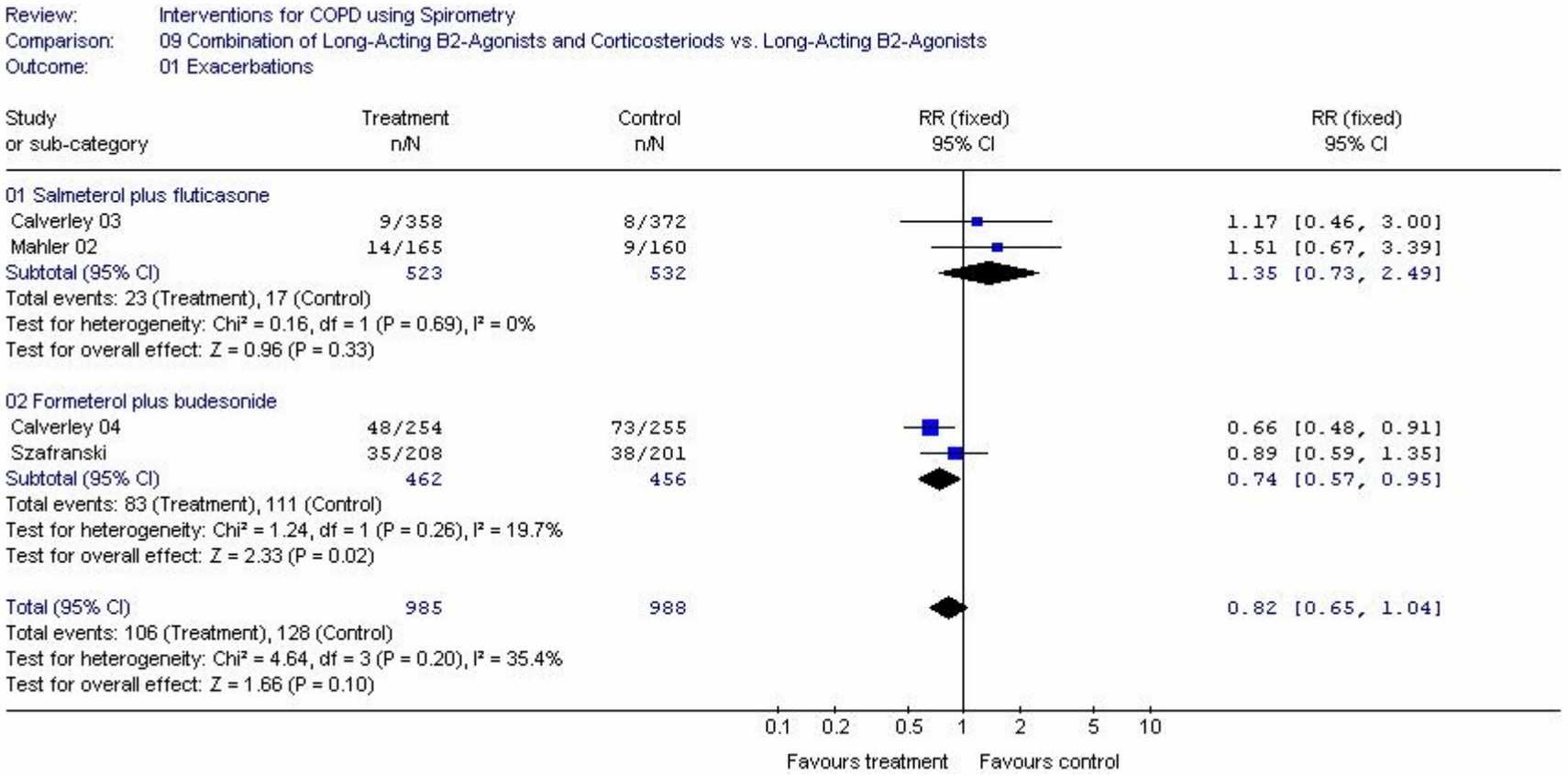

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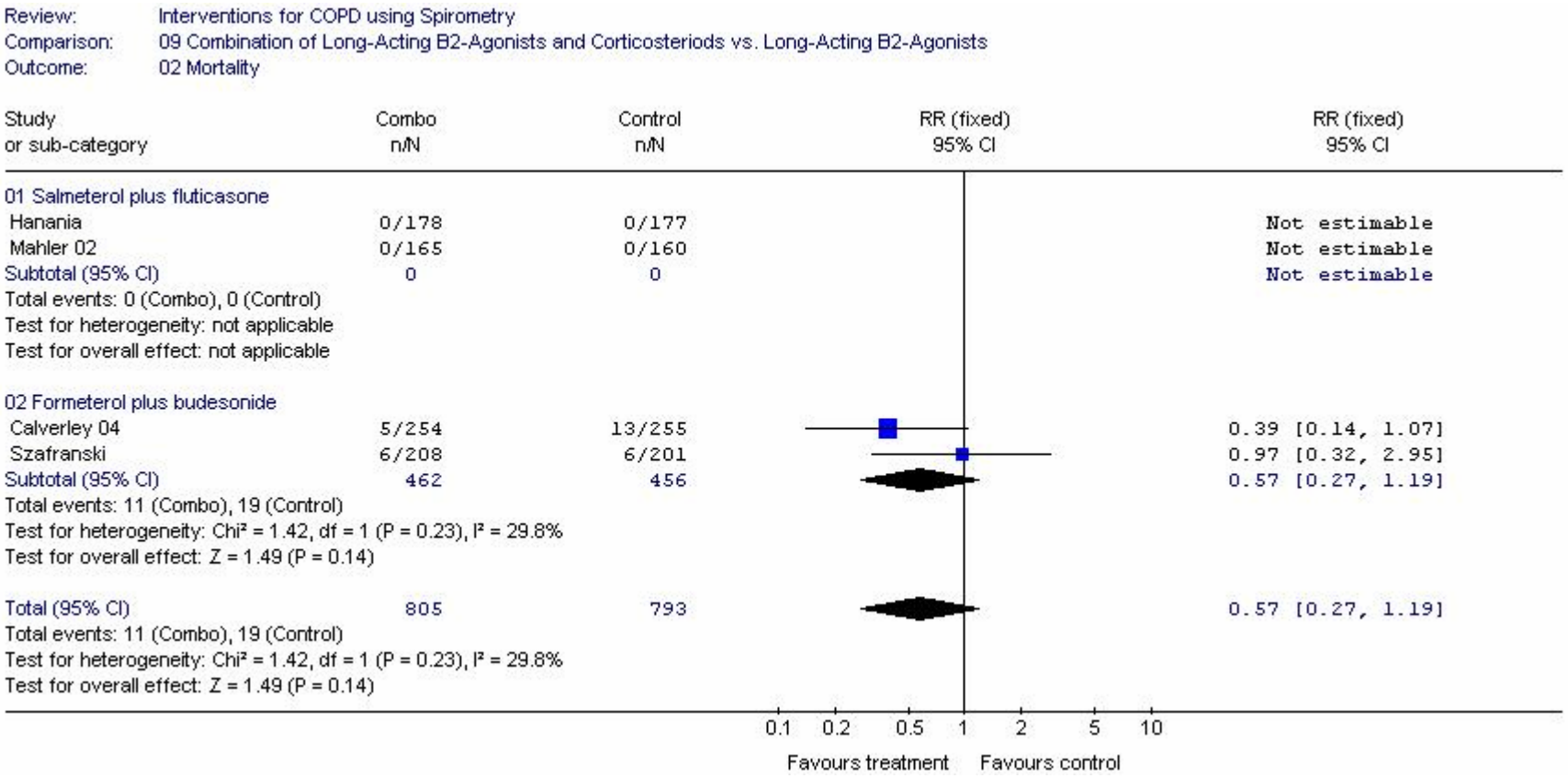

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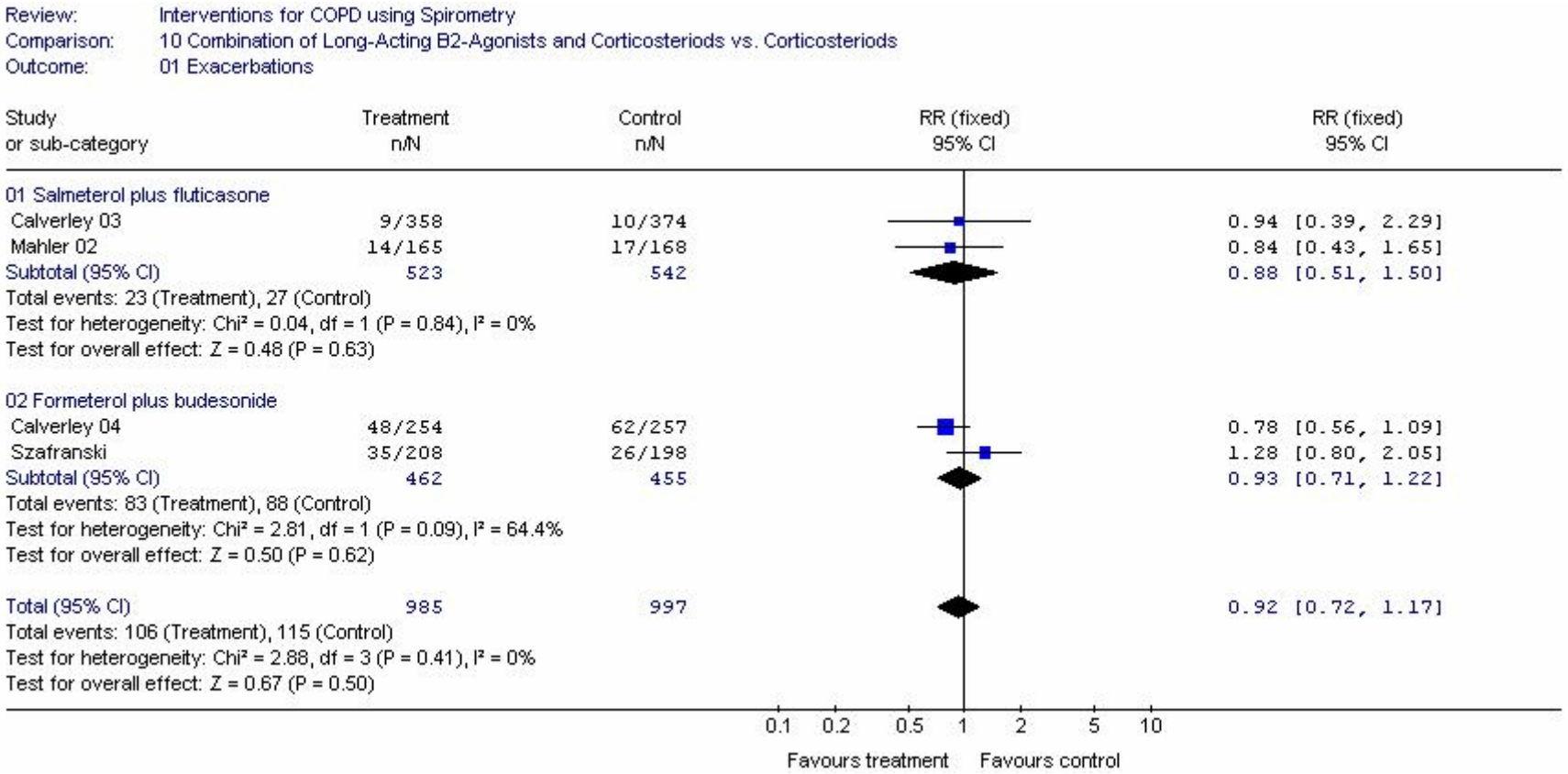
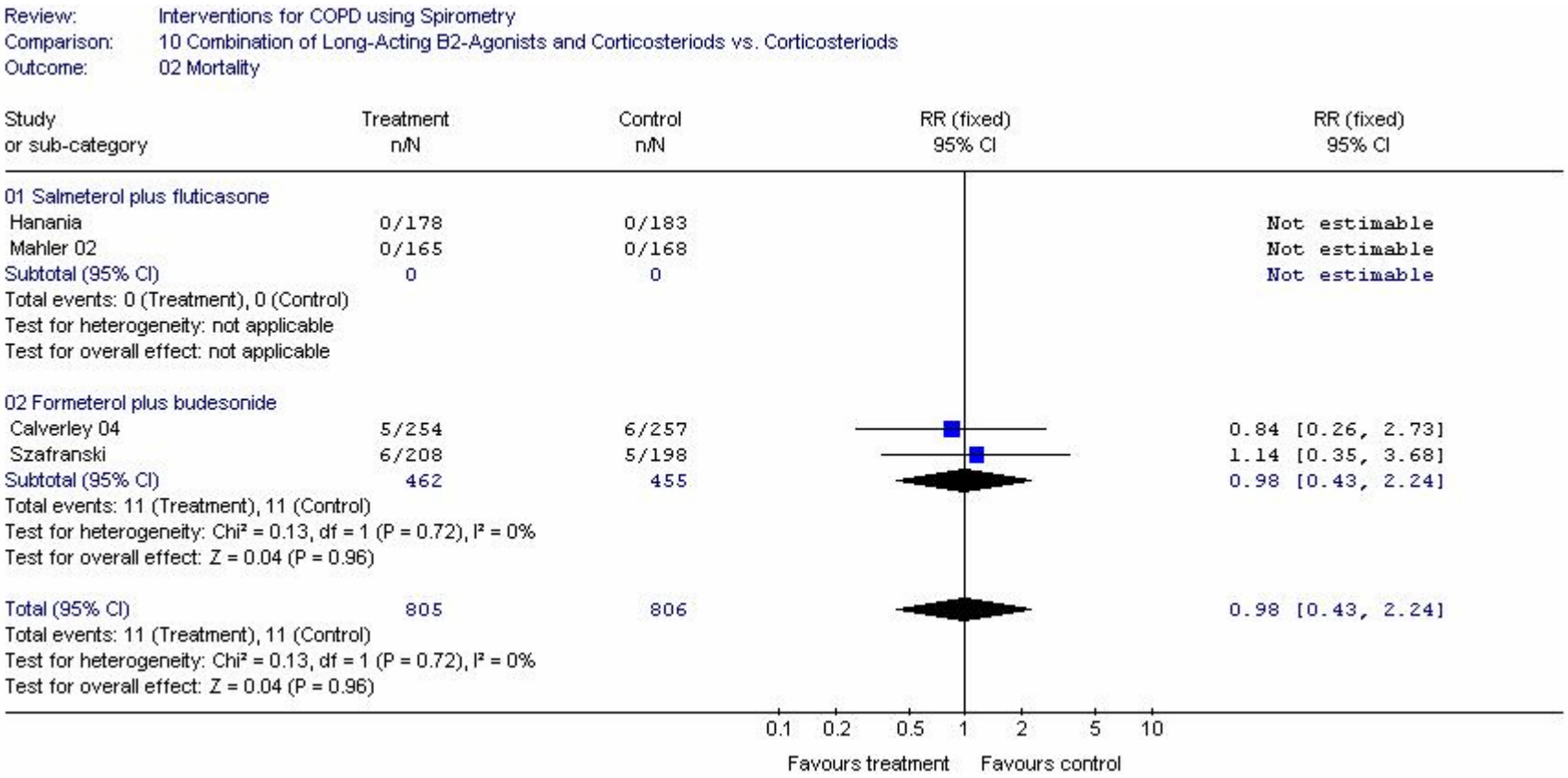
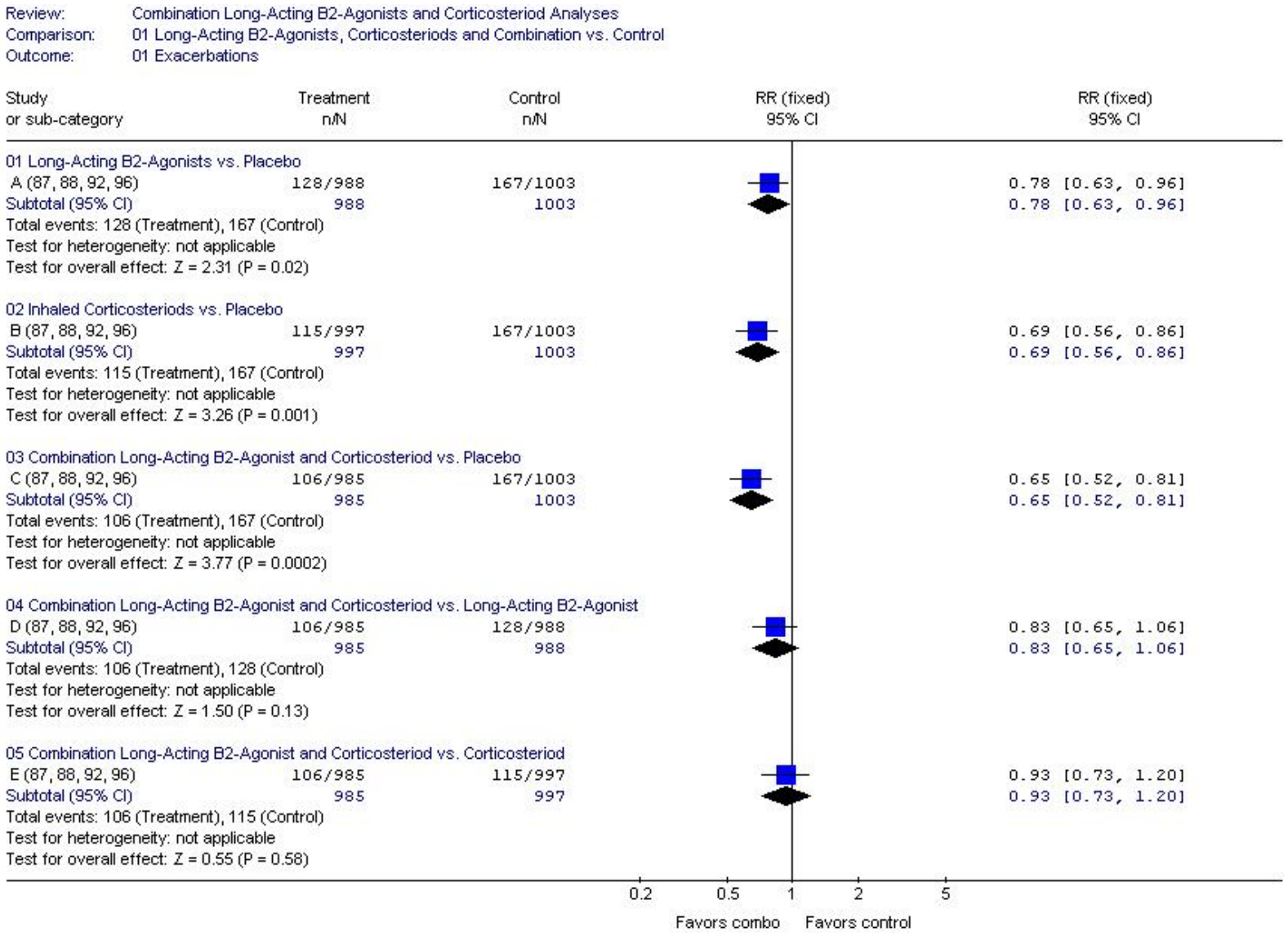


Evidence Figure 11.



Evidence Figure 12.



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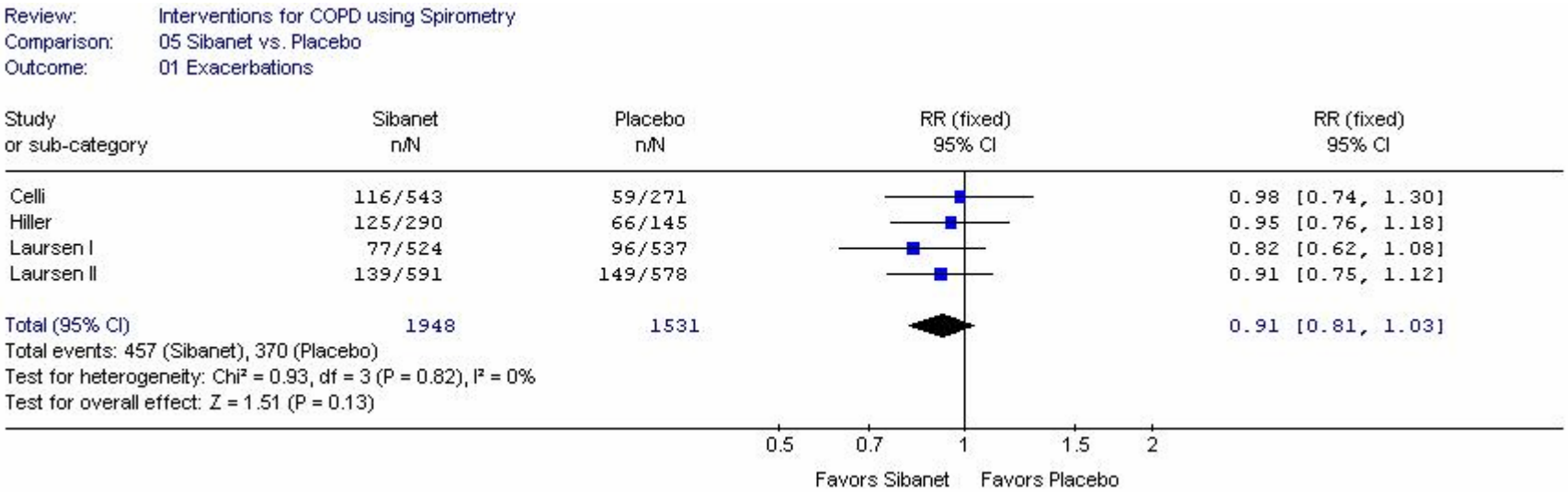
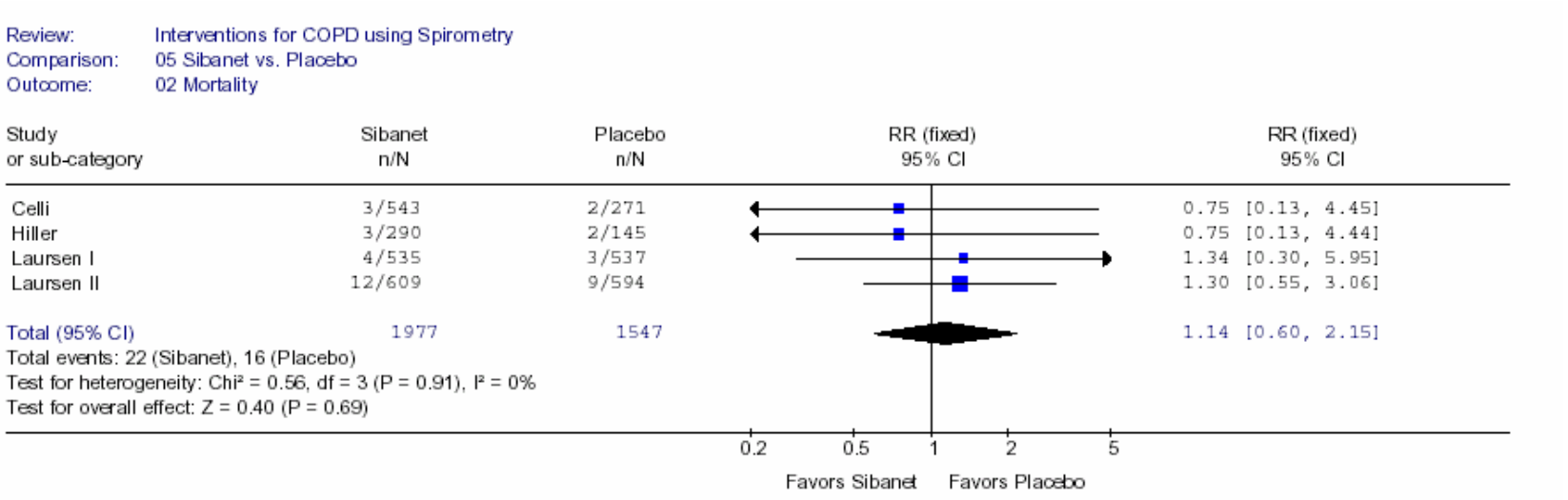


Evidence Figure 14.



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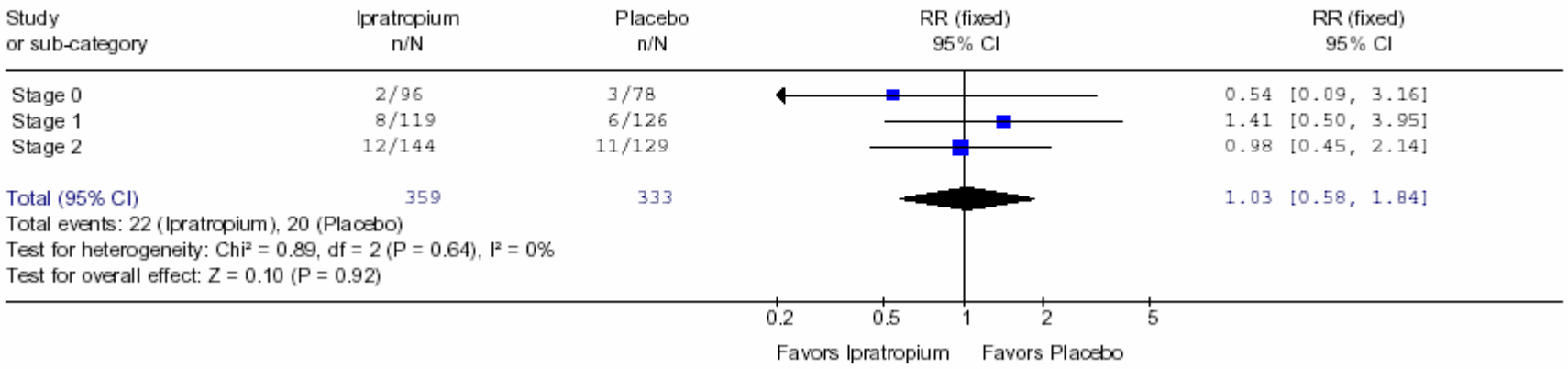
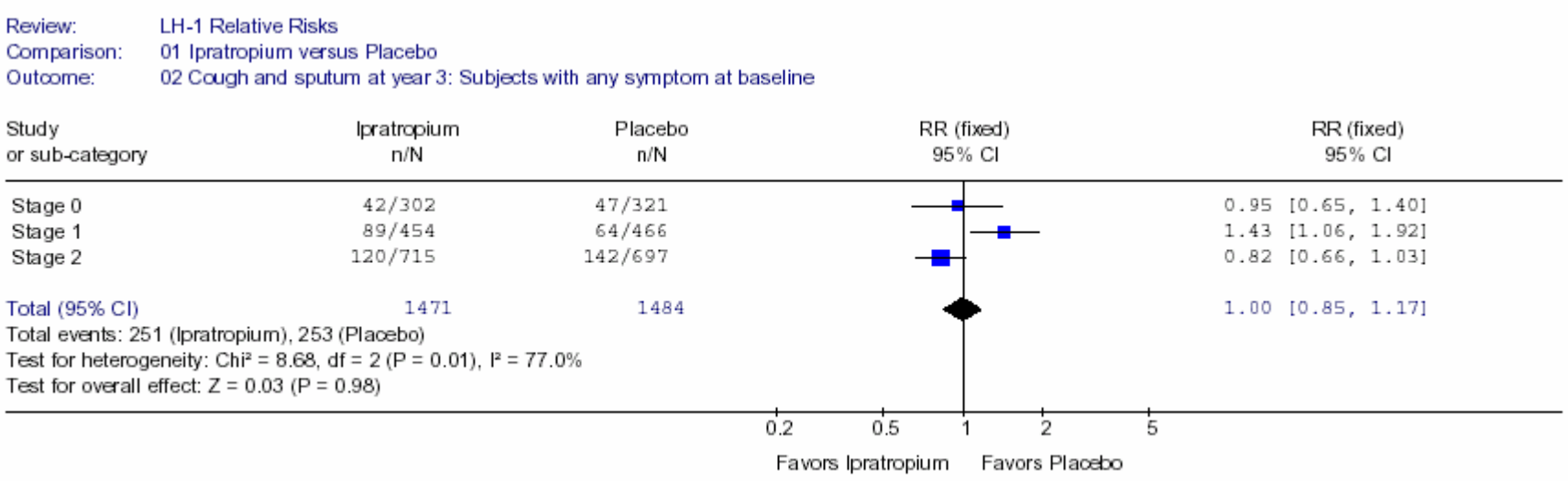
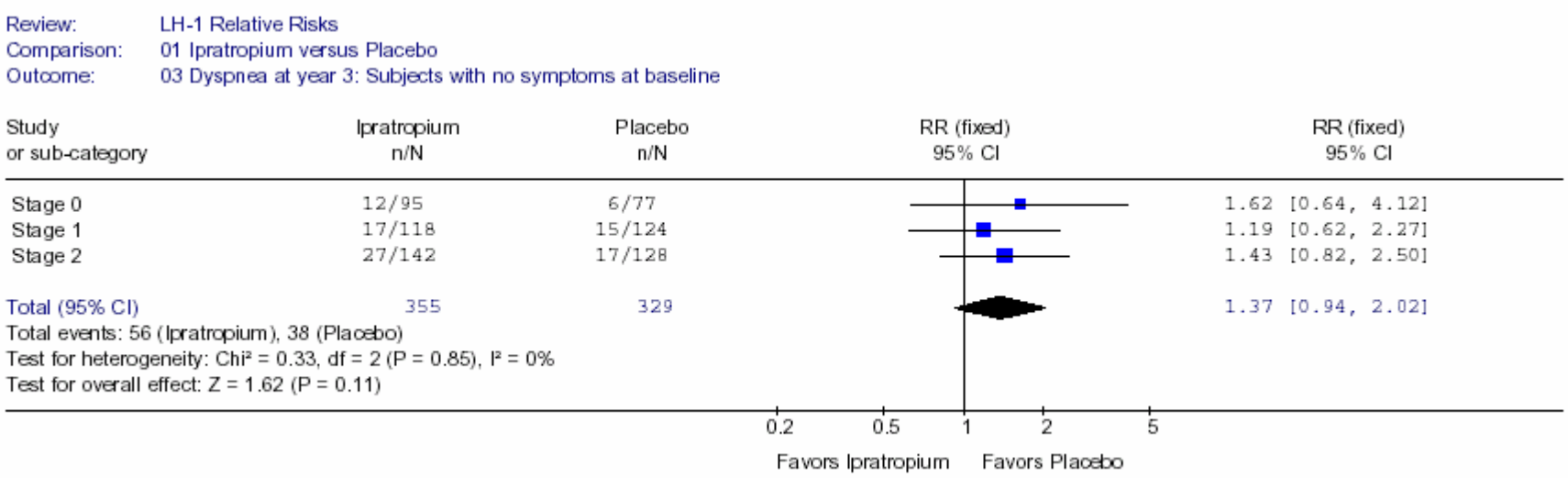


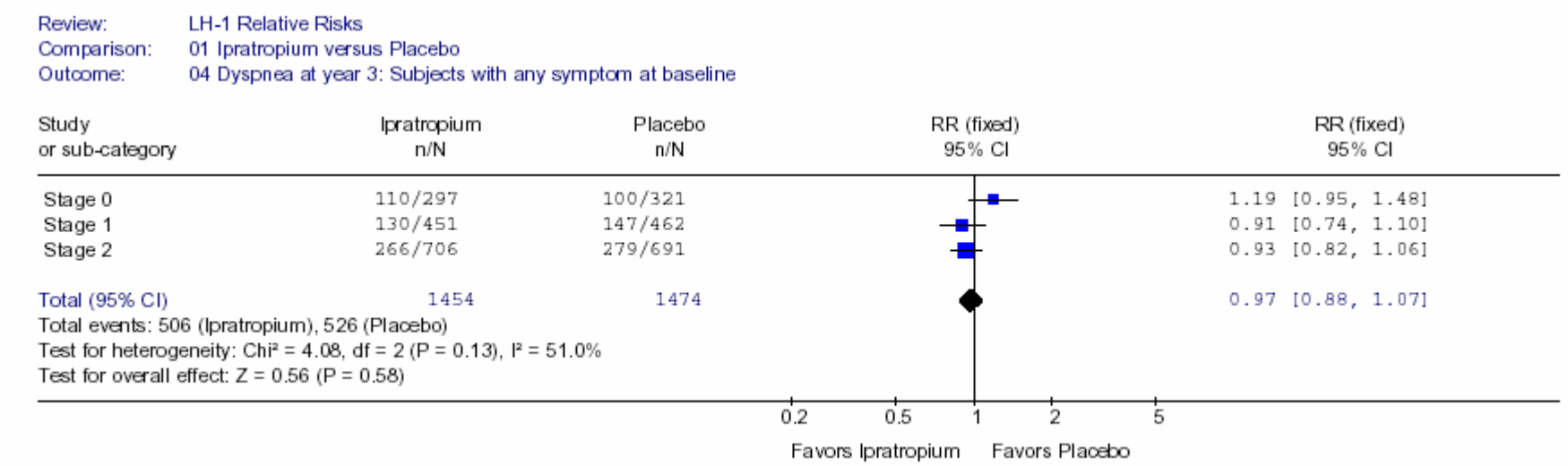
Evidence Figure 16.



Evidence Figure 17.



Evidence Figure 18.



Evidence Table 1. Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric categories for gender

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD > 3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% predicted) (n / N)	Notes
National Health and Nutrition Examination Survey-NHANES III[150]						
Male	Not reported	Not reported	9.1	7.4	Not reported	Estimated prevalence
Female	Not reported	Not reported	4.9	5.8	Not reported	
National Health and Nutrition Examination Survey-NHANES I[156]						
Male	61.9 (1,552 / 2,508)	16.1 (see notes)	9.8 (246 / 2,508)	10 (251 / 2,508)	2.2 (55 / 2,508)	Subjects had "any respiratory symptom," defined as cough, sputum, or wheeze)
Female	71.9 (2,182 / 3034)	16.1 (see notes)	6.2 (188 / 3,034)	4.6 (140 / 3,034)	1.2 (36 / 3,034)	Subjects had "any respiratory symptom," defined as cough, sputum, or wheeze)
European Community Respiratory Health Survey[157]						
Male	82.6 (6,145 / 7,441)	12.6 (940 / 7,441)	4.8 (356 / 7,441)	see note	see note	Stages GOLD1-IV were combined.
Female	86.6 (6,422 / 7,414)	10.9 (811 / 7,414)	2.4 (181 / 7,414)	see note	see note	Stages GOLD1-IV were combined.
Copenhagen City Heart Study[149]						
Male	74.7 (4,490 / 6,012)	7.1 (429 / 6,012)	6.7 (404 / 6,012)	11 (663 / 6,012)	<1 (26 / 6,012)	
Female	83.9 (5,951 / 7,096)	4.7 (337 / 7,096)	3.6 (259 / 7,096)	7.6 (542 / 7,096)	<1 (7 / 7,096)	
Mini-Finland Health Survey[151]						
Male	54 (1,740 / 3,255)*	Not reported	36 (1,163 / 3,255)	10 (314 / 3,255)	1 (38 / 3,255)	
Female	61 (2,275 / 3,753)*	Not reported	34 (1,286 / 3,753)	5 (184 / 3,753)	0.2 (8 / 3,753)	
Prevalence of COPD in Elderly Finns[152]						
Male	82.6 (252 / 305)*	Not reported	3.6 (11 / 305) (FEV_1 % predicted >80)	11.8 (36 / 305) (FEV_1 % predicted 40-79)	2 (6 / 305) (FEV_1 % predicted <40)	
Female	95.6 (435 / 455)*	Not reported	<1 (3 / 455) (FEV_1 % predicted >80)	2.9 (13 / 455) (FEV_1 % predicted 40-79)	<1 (4 / 455) (FEV_1 % predicted <40)	

Evidence Table 1. Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric categories for gender (continued)

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD > 3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% predicted) (n / N)	Notes
Prevalence of COPD in Norwegians[154]						
Male: age 18-44	96.4*	Not reported	1.3	2.3	0	
Male: age 45-73	88.3*	Not reported	2.4	8.6	0.6	
Female: age 18-44	97.9*	Not reported	1.2	0.7	0.1	
Female: age 45-73	90.8*	Not reported	0.9	8.1	0.2	

* Subjects may or may not be symptomatic and include "at risk"

Evidence Table 2. Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric categories for ethnicity

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD >3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)	Notes
National Health and Nutrition Examination Survey-NHANES III[150]						
White	Not reported	Not reported	7.1	6.7	NR	Estimated prevalence
Black	Not reported	Not reported	5	5.6	NR	
Other	Not reported	Not reported	8	5.3	NR	
National Health and Nutrition Examination Survey-NHANES I[156]						
White	67.6 (3310 / 4896)	16.4 (803 / 4896) (see notes)	7.5 (367 / 4,896)	6.9 (338 / 4,896)	1.6 (78 / 4,896)	Subjects had "any respiratory symptom," defined as cough, sputum, or wheeze)
Non-white	65.3 (422 / 646)	14 (90 / 646) (see notes)	10.5 (68 / 646)	8.4 (54 / 646)	1.8 (12 / 646)	

Evidence Table 3. Prevalence of COPD based upon American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric categories for age, gender, and ethnicity

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD >3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)
National Health and Nutrition Examination Survey-NHANES III[150]					
Black female, age 17-24	Not reported	Not reported	Not reported	1.1	0
Black female, age 25-44	Not reported	Not reported	Not reported	1.3	0.3
Black female, age 45-64	Not reported	Not reported	Not reported	6.5	1.6
Black female, age 65-74	Not reported	Not reported	Not reported	8.5	0
Black female, age 75-84	Not reported	Not reported	Not reported	6.7	3.6
Black female, age >85	Not reported	Not reported	Not reported	6.2	0
Black male, age 17-24	Not reported	Not reported	Not reported	2.7	0
Black male, age 25-44	Not reported	Not reported	Not reported	1.9	0
Black male, age 45-64	Not reported	Not reported	Not reported	10.8	2
Black male, age 65-74	Not reported	Not reported	Not reported	18.9	5.1
Black male, age 75-84	Not reported	Not reported	Not reported	30.1	5.1
Black male, age >85	Not reported	Not reported	Not reported	6.7	0
White female, age 17-24	Not reported	Not reported	Not reported	1	0
White female, age 25-44	Not reported	Not reported	Not reported	2.2	0.5
White female, age 45-64	Not reported	Not reported	Not reported	7.4	3.6
White female, age 65-74	Not reported	Not reported	Not reported	12.4	4
White female, age 75-84	Not reported	Not reported	Not reported	13.5	3.1
White female, age >85	Not reported	Not reported	Not reported	6.9	3.1
White male, age 17-24	Not reported	Not reported	Not reported	1.1	0
White male, age 25-44	Not reported	Not reported	Not reported	2.5	0.2
White male, age 45-64	Not reported	Not reported	Not reported	9.4	2.2
White male, age 65-74	Not reported	Not reported	Not reported	17.3	6.7
White male, age 75-84	Not reported	Not reported	Not reported	19.8	4.8
White male, age >85	Not reported	Not reported	Not reported	17.5	1

Evidence Table 4. Prevalence of spirometric categories: American Thoracic Society (ATS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) category criteria for smoking status

Variable / Country; Study	% Normal Spirometry and No Respiratory Symptoms (n / N)	% GOLD 0 or "At Risk" / Normal Spirometry + Symptoms of Cough, Sputum (n / N)	% GOLD 1 or Mild - FEV_1/FVC <70 and FEV_1 >80% Predicted) (n / N)	% ATS 1 or GOLD 2 or "Moderate" / FEV_1/FVC <70 and FEV_1 >50 to 80-85% Predicted) (n / N)	% ATS 2 or 3 or GOLD >3 or "Severe" / FEV_1/FVC <70 and FEV_1 <50% Predicted) (n / N)	Study, Population and Notes
National Health and Nutrition Examination Survey-NHANES I[150]						
Current smoker	56.9 (1,321 / 2,323)	21.3 (494 / 2,323) (see notes)	9.2 (213 / 2,323)	10.6 (247 / 2,323)	2.1 (48 / 2,323)	Subjects had "any respiratory symptom," defined as cough, sputum, or wheeze)
Previous smoker	66.1 (734 / 1,110)	15.8 (175 / 1,110) (see notes)	8.6 (96 / 1,110)	7.3 (81 / 1,110)	2.2 (24 / 1,110)	
Never smoker	79.3 (1,672 / 2,109)	10.6 (223 / 2,109) (see notes)	6.2 (130 / 2,109)	3 (64 / 2,109)	<1 (20 / 2,109)	
European Community Respiratory Health Survey[157]						
Current smoker	75.8 (4,135 / 5,455)	19.1 (1,044 / 5,455)	5.1 (276 / 5,455)	see note	see note	Stages GOLD1-IV were combined
Previous smoker	89 (2,727 / 3,065)	7.6 (233 / 3,065)	3.4 (105 / 3,065)	see note	see note	
Never smoker	92 (5,705 / 6,203)	7.6 (469 / 6,203)	<1 (29 / 6,203)	see note	see note	
Copenhagen City Heart Study[149]						
Current smoker	75.6 (6,265 / 8,255)	7.2 (597 / 8,255)	5.5 (457 / 8,255)	11.1 (916 / 8,255)	<1 (20 / 8,255)	
Previous smoker	83.4 (1,879 / 2,253)	4.4 (100/ 2,253)	4.7 (107 / 2,253)	6.9 (156 / 2,253)	<1 (11 / 2,253)	
Never smoker	88.3 (2,297 / 2,600)	2.7 (69 / 2,600)	3.8 (99 / 2,600)	5.1 (133 / 2,600)	<1 (2 / 2,600)	

Evidence Table 5. Losses to followup

Study	Group	Length of Followup (months)	N (# randomized)	Loss to Followup (n)	Loss to Followup (%)
Segnan et al., 1991[79]	All participants	12	923	120	13%
Risser et al., 1990[80]	Control	12	45	3	7%
	Intervention	12	45	9	20%
Sippel et al., 1999[81]	Control	9	102	19	18.6%
	Intervention	9	103	13	12.6%
Richmond et al., 1985[82]	Control	36	100	23	23%
	Intervention	36	100	15	15%
Rose et al., 1978[84]	Control	36	731	220	30%
	Intervention	36	714	258	36%
Humerfelt et al., 1998[83]	Control	12	1,310	109	8%
	Intervention	12	1,300	219	17%
Li et al., 1984*[85]	All participants	11	579	129	22%
	Total		**6,052**	**1,137**	**19%**

* In study by Li et al, the results of three participants were not included in the final results as it was uncertain which treatment had been received.

Evidence Table 6. Characteristics of studies of long-acting β2 agonists for COPD using spirometry

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects/Inclusion Criteria
Calverly et al, 2003[88]	1 year	1) Formoterol 4.5 ug b.i.d. (n=171) 2) Budesonide 200 ug, b.i.d. (n=257 3) Formoterol 4.5ug + Budesonide 160 ug, b.i.d. (n=254) 4) Placebo (n-256)	1) 1.00, 36% 2) 0.99, 36% 3) .98, 36% 4) 0.98, 36%	Worldwide 15 countries, 75% men and 25% women); mean age 64 (range 41-86); pack years = 39; Medication at enrollment: oral/inhaled steriods = 48%, short acting β agonists = 50%, long acting β agonists = 29%, xanthines 36%. 1) both genders at least 40 years old, with diagnosis of COPD (GOLD stage 3 and 4 with symptoms for more than 2 years) 2) current or ex-smokers with smoking history of ≥10 pack-years 3) FEV_1/FVC ratio ≤70% 4) FEV_1 50% of the predicted normal 5) ≥1 COPD exacerbation requiring a course of oral corticosteriods and/or antibiotics 2-12 months before first clinic visit.
Brusasco et al., 2003[89]	6 months	1) Tiotropium 18 ug q.d. (n=402) 2) Salmeterol 50 ug, b.i.d. (n=405) 3) placebo (n=400)	1) 1.12 (0.39), 39% 2) 1.07 (0.38), 38% 3) 1.09 (0.40), 39%	European, Canadian (18 countries) men and women (24%); mean age 64; pack years = 44. 1) relatively stable airway obstruction with FEV_1 ≤65% of predicted normal and ≤70% of FVC 2) over 40 years of age 3) with smoking history of >10 pack years.
Calverley et al., 2003[87]	1 year	1) Salmeterol 50 ug, b.i.d. (n=372) 2) Fluticasone 50*ug*, b.i.d.(n=374) 3) Salmeterol 50 ug + Fluticasone 500 ug, b.i.d. (n=358) 4) placebo (n=361)	1) 1.25 (0.45), 44% 2) 1.26 (0.45), 45% 3) 1.31 (0.53), 45% 4) 1.27 (0.47), 44%	European et al. (25 countries) men and women (28%); mean age 63; Current smokers = 51%, pack years = 43. 1) baseline FEV_1 before bronchodilation that was 25-70% of that predicted, an increase of less than 10% of predicted FEV_1 30 minutes after inhaling 400 ug salbutamol, and a prebronchodilator FEV_1/FVC ratio of 70% or less 2) at least 10 pack-years of smoking 3) of chronic bronchitis, at least one episode of acute COPD symptom exacerbation per year in the previous 3 years 4) at least one exacerbation in the year immediately before trial entry that required treatment with oral corticosteroids, antibiotics, or both.
Celli et al., 2003[90]	3 months	1) Sibenadet 500 ug, t.i.d. (n=543) 2) Salmeterol 50 ug, b.i.d. (n=554) 3) placebo (n=271)	1) 1.32 (0.48), 42% 2) 1.30 (0.46), 42% 3) 1.35 (0.50), 44%	Worldwide 15 countries (75% men and 25% women); Caucasian (96%), Black (1%), Oriental (2%), Others (1%); mean age 64 (range 35-80); pack years = 46; Medication at enrollment: oral/inhaled steroids = 54%, short acting β agonists = 55%, long acting β-agonists = 25%, xanthines 22%. 1) both genders ranging in age from 40 to 80 years, with diagnosis of COPD (with symptoms for more than 2 years) 2) current or ex-smokers with smoking history of ≥15 pack-years 3) FEV_1/FVC ratio ≤65% 4) FEV_1 20-70% of the predicted normal 5) FEV_1 reversibility to 400 ug salbutamol of ≤15% or <200 ml / Mean daily BCSS (Breathlessness, cough, and sputum scale) (1) 5.28, (2) 5.30.

Evidence Table 6. Characteristics of studies of long-acting β2 agonists for COPD using spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects/Inclusion Criteria
Hanania et al., 2003[91]	6 months	1) Salmeterol 50 ug, b.i.d. (n=177) 2) Fluticasone 250 ug, b.i.d. (n=183) 3) Salmeterol 50 ug + Fluticasone 250 ug b.i.d. (n=178) 4) placebo (n=185)	1) 1.25 (0.43), 42% 2) 1.31 (0.44), 42% 3) 1.25 (0.40), 41% 4) 1.29 (0.43), 42%	American men and women (37%), White (93%), Black (4%), Asian/other (3%); mean age 64 (range 40-87); Current smokers = 47%, (median) pack years = 57; Concurrent theophylline use = 11%; Emphysema 67%. 1) ≥40 years of age 2) current or former smokers with ≥20 pack-year history 3) diagnosis of COPD by ATS 4) baseline FEV_1/FVC ratio of ≤70% and baseline FEV_1 of <65% of predicted normal, but >0.70 L (or if ≤0.70 L, then >40% of predicted normal) 5) symptoms of chronic bronchitis and moderate dyspnea.
Szafranski et al., 2003[92]	1 year	1) Formoterol 4.5 ug b.i.d.(n=201) 2) Budesonide 200 ug, b.i.d. (n=198) 3) Formoterol 4.5 ug + Budesonide 160 ug, b.i.d. (n=208) 4) placebo (n=205)	1) 1.00; 36% 2) 1.01; 37% 3) 0.96; 36% 4) 0.98; 36%	Multinational (11 countries) men and women (21%); mean age 64 (range 40-92); Current smokers = 34%, pack years = 45; Previous use inhaled corticosteroids = 13%, short acting β agonists = 34%, long acting β agonists = 9%, xanthines 13%, combined inhaled β agonists/anticholinergic 11%. 1) adults with moderate-to-severe COPD (in line with GOLD guidelines for diagnosis, management and prevention of COPD) 2) outpatients aged ≥40 yrs 3) COPD symptoms for ≥2 years 4) ≥10 pack-years smoking history 5) FEV_1/FVC ≤70% 6) FEV_1 ≤50% predicted normal (stages IIB and III according to the GOLD classification) 7) total symptom score (including shortness of breath, cough, chest tightness, and night-time awakenings; each symptom scored 0-4) ≥2 per day during at least 7 days of the run-in period 8) documented use of short-acting inhaled bronchodilators for reliever medication; 9) ≥1 severe COPD exacerbation within 2-12 months before the first clinic visit.
Aalbers et al., 2002[93]	3 months	1) Formoterol 4.5 ug, b.i.d. (n=171) 2) Formoterol 9 ug, b.i.d. (n=166) 3) Formoterol 18 ug, b.i.d. (n=177) 4) placebo (n=173)	1) 1.44, 53% 2) 1.49, 54% 3) 1.51, 55% 4) 1.47, 54%	European (9 countries) men and women (32%); mean age 62 (range 49-79); Current smoker = 47%. 1) male and female aged 50-80 years, with clinical diagnosis of COPD 2) current or former smokers with smoking history of at least 10 pack-years 3) prebronchodilator FEV_1 > 0.7 L and 40-70% of predicted 4) FEV_1/FVC ratio <89% pred normal for females and <88% for males 5) total symptom score (night-time sleep disturbance, breathlessness, cough, and chest tightness; each symptom scored 0-4) had to be ≥2 on at least 7 days of run-in period / total symptom score 5.63 (sleep disturbance 1.74; breathlessness 2.56; cough 2.27; chest tightness 1.91).

Evidence Table 6. Characteristics of studies of long-acting β2 agonists for COPD using spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects/Inclusion Criteria
Chapman et al., 2002[94]	6 months	1) Salmeterol 50 ug, b.i.d. (n=201) 2) placebo (n=207)	1) 1.19, 44% 2) 1.28, 46%	European and Canadian (6 countries) men and women (36%); Current smokers = 43%; Previous use corticosteroids = 61%, theophylline = 21%. 1) men and women with COPD aged 40 years or older who were willing to give written, informed consent 2) taking anticholinergic agents (alone or as a combination product) for at least 4 weeks 3) history of smoking equivalent to at least 10 pack-years 4) sputum production on most days during at least three consecutive months for two consecutive years 5) baseline (visits 1, 2, or 3) FEV_1 85% or less of predicted 6) baseline FEV_1/FVC 70% or less of predicted 7) FEV_1 reversibility 5% to 15% of predicted, either by measurement 15 minutes after inhalation of salbutamol at baseline or documented evidence of such reversibility after inhalation of a β2 agonist within previous 12 months 8) symptoms (daytime symptom scores 0-5; night-time symptom scores 0-4) on at least seven out of previous 14 day and night periods of run-in phase.
Donohue et al., 2002[95]	6 months	1) Salmeterol 50 ug, b.i.d. (n=213) 2) Tiotropium 18 ug q.d. (n=209) 3) placebo (n=201)	1) 1.07 (0.37) 2) 1.11 (0.39) 3) 1.06 (0.36)	European, American, and South African (12 countries) men and women (25%); mean age 65; pack years = 47; Previous use β agonists = 66%, theophylline = 21%, anticholinergics = 53%, steroids = 72%. 1) relatively stable airway obstruction with $FEV_1 \leq 60\%$ of predicted normal and $FEV_1 \leq 70\%$ of FVC 2) at least 40 years of age 3) with smoking history of >10 pack-years.
Mahler et al., 2002[96]	6 months	1) Salmeterol 50 ug, b.i.d. (n=160) 2) Fluticasone 500 ug, b.i.d. (n=168) 3) Salmeterol 50 ug + Fluticasone 500 ug b.i.d. (n=165) 4) placebo (n=181)	1) 1.24, 40% 2) 1.23, 41% 3) 1.27, 41% 4) 1.32, 41%	American men and women (34%), White (93%), Black (5%), Asian/other (2%); mean age 63 (range 40-90); Current smokers = 48%, (median) pack years = 56; Inhaled steroids use = 25%; Emphysema 76%. 1) 40 years of age or older 2) current or former smokers with 20 pack-year or more history 3) diagnosis of COPD 4) baseline FEV_1/FVC of 70% or less and baseline FEV_1 of less than 65% of predicted but more than 0.70 L 5) daily cough productive of sputum for 3 months of the year for 2 consecutive years and dyspnea.

Evidence Table 6. Characteristics of studies of long-acting β2 agonists for COPD using spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects/Inclusion Criteria
Rossi et al., 2002[97]	1 year	1) Formoterol 12 ug, b.i.d.(n=211) 2) Formoterol 24 ug, b.i.d. (n=214) 3) Oral slow-release theophylline 200/300 mg, b.i.d. (n=209) 4) placebo (n=220)	1) 1.36, 47% 2) 1.39, 47% 3) 1.33, 46% 4) 1.40, 49%	European (13 countries) men and women (17%); mean age 63 (range 34-88). 1) male or female outpatients aged ≥40 years, with diagnosis of COPD, who were either current or ex-smokers of >10 pack-years according to ATS guidelines 2) FEV_1 <70% of the predicted value and ≥0.75 L, with an FEV_1/vital capacity ratio of <88% of that predicted in men and <89% of that predicted in women 3) daytime and/or night-time symptoms (ability to perform usual daily activities, breathlessness over the previous 24 hours, waking at night due to respiratory symptoms, breathlessness on rising, cough, and sputum production; each symptom scored 0-3) were to be present on at least 4 of last 7 days of run-in period.
Wadbo et al., 2002[98]	3 months	1) Formoterol 18 ug b.i.d. (n=61) 2) Ipratropium bromide 80 ug, t.i.d. (n=62) 3) placebo (n=60)	1) 33% 2) 34% 3) 33%	Swedish men and women (47%); mean age 64 (range 47-74); Current smokers = 28%. 1) male and female outpatients, aged 40-75 years, current or former smokers with history of >10 pack-years and with a diagnosis of COPD by the European Respiratory Society 2) history of reduced exercise capacity due to dyspnea on exertion 3) FEV_1 <60% of predicted normal value and a quotient FEV_1/FVC <70% 4) the reversibility had to be <12% of predicted normal value, 45 minutes after inhalation of 120 ug ipratropium bromide via pressurized metered dose inhaler or 27 ug formoterol via Turbuhaler given on two separate occasions 1-3 days apart; 5) oxygen tension in arterial blood (Pa, O2) at rest the second enrolment needed to be >7.3 kPa.
Dahl et al., 2001[99]	3 months	1) Formoterol 12 ug b.i.d. (n=194) 2) Formoterol 24 ug b.i.d. (n=192) 3) Ipratropium bromide 40 ug, t.i.d. (n=194) 4) placebo (n=200)	1) 1.33 (0.45), 46% 2) 1.31 (0.43), 45% 3) 1.29 (0.46), 45% 4) 1.29 (0.41), 44%	European and North American (11 countries) men and women (25%); mean age 64; Current smokers = 47%, (mean) pack years = 43. 1) male or female outpatients aged ≥40 years, with diagnosis of COPD according to ATS guidelines, who were either current or ex-smokers of >10 pack-years and gave written informed consent 2) FEV_1 <70% of predicted and >0.75 L, with the ratio FEV_1/vital capacity of <88% of that predicted in men and <89% of that predicted in women 3) daytime and/or nighttime symptoms (ability to perform usual daily activities, breathlessness over the previous 24 hours, waking at night due to respiratory symptoms, breathlessness on rising, cough, and sputum production; each symptom scored 0-3) were to be present on at least 4 of last 7 days of run-in period.

Evidence Table 6. Characteristics of studies of long-acting β2 agonists for COPD using spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects/Inclusion Criteria
Rennard et al., 2001[100]	3 months	1) Salmeterol 42 ug, b.i.d. (n=132) 2) Ipratropium 36 ug, t.i.d. (n=138) 3) placebo (n=135)	1) 1.22 2) 1.28 3) 1.30	American men and women (37%), White (94%), Black (5%), Hispanic (1%); mean age 63. 1) at least 35 years of age 2) FEV_1 ≤65% of predicted and >0.70 L, with an FEV_1/FVC ratio of ≤70% at initial screening (or FEV_1 ≥40% of predicted and <0.70 L) 3) responsiveness to both inhaled albuterol and ipratropium assessed at entry 4) score at least 1 on the Modified Medical Research Council five-point dyspnea scale (0-4).
van Noord et al., 2000[101]	3 months	1) Salmeterol 50 ug, b.i.d. (n=47) 2) Salmeterol 50 ug (b.i.d.) + Ipratropium bromide 40 ug (q.i.d.) (n=47) 3) placebo (n=50)	1) 1.20 (0.40), 42% 2) 1.20 (0.40 3) 1.20 (0.40, 41%	Dutch men and women (13%); mean age 64; Current smokers = 55%; Previous use β agonists = 100%, methylxanthines = 13%, anticholinergics = 43%, corticosteroids = 85%, mucolytics = 32%. 1) current or exsmokers with a smoking history equivalent to 10 pack-years with COPD according to ATS criteria 2) aged 40-75 years 3) no change in medication for COPD in the preceding 6 weeks and no major changes in smoking habits during the last 6 months 4) FEV_1 75% of predicted value after inhalation of 200 ug salbutamol *via* metered dose inhaler (MDI).
Mahler et al., 1999[102]	3 months	1) Salmeterol 42 ug, b.i.d. (n=135) 2) Ipratropium 36 ug, q.i.d. (n=133) 3) placebo (n=143)	1) 42% 2) 37% 3) 41%	American men and women (26%), White (91%), Black (7%), Hispanic (1%), Asian/Other (1%); mean age 63; Smoking (63 pack-years); Chronic bronchitis 24%, emphysema 47%, both 29%. 1) ≥35 years of age 2) ≥10 pack-year history of smoking 3) a diagnosis of COPD as defined by ATS 4) a baseline FEV_1 ≤65% of the predicted normal value and >0.70 L (or, if <0.70 L, ≥40% of predicted normal value) 5) an FEV_1/FVC ratio of ≤70%; 6) a baseline severity of breathlessness of grade 1 or higher on the modified Medical Research Council dyspnea scale.
Jones and Bosh, 1997[46]	4 months	1) Salmeterol 50 ug, b.i.d. (n=94) 2) Salmeterol 100 ug, b.i.d. (n=94) 3) placebo (n=95)	1) 1.40 (0.50), 47% 2) 1.40 (0.50), 45% 3) 1.30 (0.50), 45%	Worldwide (17 countries) men and women (14%); mean age 63; Previous use inhaled/oral steroids = 86%, methylxanthines 45%. 1) ranging in age from 40 to 70 years 2) a baseline FEV_1 of less than 70% predicted normal (values greater than 0.6L) after withholding bronchodilator therapy for at least the previous 4 hours 3) FEV_1/FVC ratio less than 60% 4) less than 15% reversibility of FEV_1 following salbutamol 400 ug by metered-dose inhaler or salbutamol 800 ug by breath-actuated device 5) daytime symptom scores of 2 or more, for at least 4 days of the last week of run-in period using symptom scoring scheme (0-5).

Evidence Table 6. Characteristics of studies of long-acting β2 agonists for COPD using spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects/Inclusion Criteria
Boyd et al., 1997[103]	4 months	1) Salmeterol 50 ug, b.i.d. (n=229) 2) Salmeterol 100 ug, b.i.d. (n=218) 3) placebo (n=227)	1) 1.31 (0.51) 2) 1.23 (0.47) 3) 1.31 (0.53)	European (18 countries) men and women (21%); mean age 62 (range 39-75); Current smokers = 43%; Previous use inhaled/oral corticosteroids = 64%, methylxanthines = 41%, anticholinergics = 19%, β agonists = 4%. 1) current or previous smokers aged 40-75 years, who had coughed up sputum on most days during at least three consecutive months in two consecutive years 2) at or between Visits 1, 2, and 3, a measurement of FEV_1 of ≤70% of predicted normal and a FEV_1/FVC ratio of ≤60% 3) at Visits 1, 2, and 3 (or documented in the previous 12 months), an increase in FEV1 of 5-15%, 15 minutes after inhalation of 400 or 800 ug of salbutamol from a metered-dose inhaler or Diskhaler™ inhaler, or 5 mg salbutamol nebulized for 3 minutes at 8 L min-1 from a nebulizer 4) daytime symptom score (scored 0-5; modified Medical Research Council dyspnea scale) of ≥2 on at least 4 of the 7 days prior to randomization.
Pooled summary	Range 3 months – 1 year	**Total No. = 13,013**	Range 0.96 – 1.51; 33% - 55%	

Evidence Table 7. Characteristics of studies of tiotropium for COPD using spirometry

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion criteria
Brusasco et al., 2003[89]	6 months	1) Tiotropium 18 ug q.d. (n=402) 2) Salmeterol 50 ug b.i.d. (n=405) 3) placebo (n=400)	1) 1.12 (0.39), 39% 2) 1.07 (0.38) 3) 1.09 (0.40), 39%	European, Canadian (18 countries) men and women (24%); mean age 64; pack years = 44. 1) relatively stable airway obstruction with FEV_1 ≤ 65% of predicted normal and ≤ 70% of FVC 2) over 40 years of age 3) with smoking history of >10 pack years.
Casaburi et al., 2002[104]	1 year	1) Tiotropium 18 ug q.d. (n=550) 2) placebo (n=371)	1) 1.04 (0.41), 39% 2) 1.00 (0.44), 38%	American and English men and women (35%); mean age 65; pack years = 61; Previous use β agonists = 99%, theophylline = 24%, anticholinergics = 56%, steroids = 49%. 1) outpatients of either sex who were ≥40-years-old with clinical diagnosis of COPD by ATS 2) at least 10 pack-year smoking history 3) clinically stable airway obstruction 4) FEV_1 of ≤65% of predicted normal value and ≤70% of FVC. COPD symptom scores (wheezing, shortness of breath, coughing, and chest tightness).
Donohue et al., 2002[95]	6 months	1) Tiotropium 18 ug q.d. (n=209) 2) Salmeterol 50 ug b.i.d. (n=213) 3) placebo (n=201)	1) 1.11 (0.39) 2) 1.07 (0.37) 3) 1.06 (0.36)	European, American, and South African (12 countries) men and women (25%); mean age 65; pack years = 47; Previous use β agonists = 66%, theophylline = 21%, anticholinergics = 53%, steroids = 72%. 1) relatively stable airway obstruction with FEV_1 ≤ 60% of predicted normal and FEV_1 ≤ 70% of FVC 2) at least 40 years of age 3) with smoking history of >10 pack-years.
Vincken et al., 2002[105]	1 year	1) Tiotropium 18 ug q.d. (n=356) 2) Ipratropium bromide 40 ug q.i.d. (n=179)	1) 1.25 (0.43), 42% 2) 1.18 (0.37), 39%	Dutch/Belgian men and women (15%); mean age 64 (range 47-74); pack years = 34; Previous use inhaled/oral β agonists = 81%, theophylline = 16%, anticholinergics = 61%, inhaled/oral steroids = 90%. 1) clinical diagnosis of COPD 2) FEV_1 of ≤ 65% of the predicted normal value and ≤ 70% of FVC 3) ≥ 40 years of age 4) smoking history of ≥10 pack-years. respiratory symptom (cough, sputum, dyspnea, or wheeze).
van Noord et al., 2000[106]	3.3 months	1) Tiotropium 18 ug q.d. (n=191) 2) Ipratropium 40 ug q.i.d. (n=97)	1) 1.24 (0.41), 42% 2) 1.19 (0.35), 40%	Dutch men and women (16%); mean age 64; pack years = 34; Previous use inhaled β agonists = 69%, theophylline = 14%, anticholinergics = 55%, inhaled/oral steroids = 86%. 1) clinical diagnosis of COPD according to the ATS criteria 2) stable airways obstruction with FEV_1 of < 65% predicted and a ratio of FEV_1 to FVC of < 70% 3) age at least 40 years 4) current or previous smokers (≥ 10 pack-years)
Pooled summary	Range 3.3 months - 1 year	Total No. = 3,574	Range 1.04 - 1.25; 38% - 42%	

Evidence Table 8. Characteristics of studies of ipratropium for COPD using spirometry

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Vincken et al., 2002[105]	1 year	1) Ipratropium bromide 40 ug q.i.d. (n=179) 2) Tiotropium 18 ug q.d. (n=356)	1) 1.18 (0.37), 39% 2) 1.25 (0.43), 42%	Dutch/Belgian men and women (15%); mean age 64 (range 47-74); pack years = 34; Previous use inhaled/oral β agonists = 81%, theophylline = 16%, anticholinergics = 61%, inhaled/oral steroids = 90%. 1) clinical diagnosis of COPD 2) FEV_1 of ≤65% of the predicted normal value and ≤70% of FVC 3) ≥40 years of age 4) smoking history of ≥10 pack-years. respiratory symptom (cough, sputum, dyspnea, or wheeze).
Wadbo et al., 2002[98]	3 months	1) Ipratropium bromide 80 ug t.i.d. (n=62) 2) Formoterol 18 ug b.i.d. (n=61) 3) placebo (n=60)	1) 34% 2) 33% 3) 33%	Swedish men and women (47%); mean age 64 (range 47-74); Current smokers = 28%. 1) male and female outpatients, aged 40-75 years, current or former smokers with history of >10 pack-years and with a diagnosis of COPD by the European Respiratory Society 2) history of reduced exercise capacity due to dyspnea on exertion 3) FEV_1 <60% of predicted normal value and a quotient FEV_1/FVC < 70% 4) the reversibility had to be <12% of predicted normal value, 45 minutes after inhalation of 120 ug ipratropium bromide via pressurized metered dose inhaler or 27 ug formoterol via Turbuhaler given on two separate occasions 1-3 days apart 5) oxygen tension in arterial blood (Pa, O2) at rest the second enrolment needed to be > 7.3 kPa.
Dahl et al., 2001[99]	3 months	1) Ipratropium bromide 40 ug t.i.d. (n=194) 2) Formoterol 12 ug b.i.d. (n=194) 3) Formoterol 24 ug b.i.d. (n=192) 4) placebo (n=200)	1) 1.29 (0.46), 45% 2) 1.33 (0.45), 46% 3) 1.31 (0.43), 45% 4) 1.29 (0.41), 44%	European and North American (11 countries) men and women (25%); mean age 64; Current smokers = 47%, (mean) pack years = 43. 1) male or female outpatients aged ≥40 years, with diagnosis of COPD according to ATS guidelines, who were either current or ex-smokers of >10 pack-years and gave written informed consent 2) FEV_1 <70% of predicted and >0.75 L, with the ratio FEV_1/vital capacity of < 88% of that predicted in men and <89% of that predicted in women 3) daytime and/or nighttime symptoms (ability to perform usual daily activities, breathlessness over the previous 24 hours, waking at night due to respiratory symptoms, breathlessness on rising, cough, and sputum production; each symptom scored 0-3) were to be present on at least 4 of last 7 days of run-in period.

Evidence Table 8. Characteristics of studies of ipratropium for COPD using spirometry (continued)

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Rennard et al., 2001[100]	3 months	1) Ipratropium 36 ug t.i.d. (n=138) 2) Salmeterol 42 ug b.i.d. (n=132) 3) placebo (n=135)	1) 1.28 2) 1.22 3) 1.30	American men and women (37%), White (94%), Black (5%), Hispanic (1%); mean age 63. 1) at least 35 years of age 2) FEV_1 ≤ 65% of predicted and >0.70 L, with an FEV_1/FVC ratio of ≤70% at initial screening (or FEV_1 ≥ 40% of predicted and < 0.70 L) 3) responsiveness to both inhaled albuterol and ipratropium assessed at entry 4) score at least 1 on the Modified Medical Research Council five-point dyspnea scale (0-4).
van Noord et al., 2000[106]	3.3 months	1) Ipratropium 40 ug q.i.d. (n=97) 2) Tiotropium 18 ug q.d. (n=191)	1) 1.19 (0.35); 40% 2) 1.24 (0.41); 42%	Dutch men and women (16%); mean age 64; pack years = 34; Previous use inhaled β agonists = 69%, theophylline = 14%, anticholinergics = 55%, inhaled/oral steroids = 86%. 1) clinical diagnosis of COPD according to the ATS criteria 2) stable airways obstruction with FEV_1 of <65% predicted and a ratio of FEV_1 to FVC of <70% 3) age at least 40 years 4) current or previous smokers (≥10 pack-years).
van Noord et al., 2000[101]	3 months	1) Ipratropium bromide 40 ug (q.i.d.) + Salmeterol 50 ug (b.i.d.) (n=47) 2) Salmeterol 50 ug b.i.d. (n=47) 3) placebo (n=50)	1) 1.20 (0.40); 41% 2) 1.20 (0.40); 42% 3) 1.20 (0.40, 41%	Dutch men and women (13%); mean age 64; Current smokers = 55%; Previous use β agonists = 100%, methylxanthines = 13%, anticholinergics = 43%, corticosteroids = 85%, mucolytics = 32%. 1) current or exsmokers with a smoking history equivalent to 10 pack-years with COPD according to ATS criteria 2) ages 40-75 years 3) no change in medication for COPD in the preceding 6 weeks and no major changes in smoking habits during the last 6 months 4) FEV_1 ≤75% of predicted value after inhalation of 200 ug salbutamol *via* metered dose inhaler (MDI).
Mahler et al., 1999[102]	3 months	1) Ipratropium 36 ug q.i.d. (n=133) 2) Salmeterol 42 ug b.i.d. (n=135) 3) placebo (n=143)	1) 37% 2) 42% 3) 41%	American men and women (26%); White (91%), Black (7%), Hispanic (1%), Asian/Other (1%); mean age 63; Smoking (63 pack-years); Chronic bronchitis 24%, emphysema 47%, both 29%. 1) ≥35 years of age 2) ≥10 pack-year history of smoking 3) a diagnosis of COPD as defined by ATS 4) a baseline FEV_1 ≤ 65% of the predicted normal value and >0.70 L (or, if <0.70 L, ≥40% of predicted normal value) 5) an FEV_1/FVC ratio of ≤70% 6) a baseline severity of breathlessness of grade 1 or higher on the modified Medical Research Council dyspnea scale

Evidence Table 8. Characteristics of studies of ipratropium for COPD using spirometry (continued)

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
COMBIVENT Inhalation Study Group, 1997[109]	3 months (85 days)	1) Ipratropium bromide 0.5 mg q.i.d. (n=214) 2) Albuterol sulfate 3.0 mg q.i.d. (n=216) 3) Combination (IB 0.5 mg + Albuterol 3.0mg), q.i.d. (n=222)	1) 0.91 2) 0.91, 34% 3) 0.92, 35%	American men and women (35%); White (93%), Black (6%), Other (1%); mean age 65 (41-86). 1) diagnosis of COPD who were at least 40 years old 2) smoking history of at least 10 pack-years 3) stable airway obstruction with FEV_1 ≤65% predicted normal and ≤70% of FVC 4) taking at least two prescribed therapeutic agents for control of their COPD symptoms for at least 3 months before participation in the trial.
LUNG HEALTH STUDY Anthonisen et al., 1994[19]	5 years	1) Ipratropium bromide t.i.d. plus smoking intervention (n=1961) 2) smoking intervention and placebo (n=1962) 3) Usual Care (no intervention) (n=1964)		American men and women smokers, aged 35 to 60 years (mean 48), with were thought to be at high risk for COPD (spirometric signs of early COPD, defined as FEV1/FVC ≤70% with an FEV1 between 55 to 90%. 1) Smoking defined as ≥10 cigarettes on at least 1 day during last 30 days preceding 1st screening visit
COMBIVENT Inhalation Aerosol Study Group, 1994[108]	3 months (85 days)	1) Ipratropium 21 ug t.i.d. (n=179) 2) Albuterol 100 ug t.i.d. (n=173) 3) Combination (IB 21 ug + Albuterol 120 ug), t.i.d. (n=182)	1) 1.00, 37% 2) 0.99, 37% 3) 1.00, 37%	American men and women (35%); White (94%), Black (5%), Other (1%); mean age 63 (40-88); Previous use inhaled β agonists = 93%, oral β agonists = 11%, theophylline = 81%, anticholinergics = 43%, inhaled/oral steroids = 41%. 1) diagnosis of COPD who were at least 40 years of age 2) relatively stable, moderately severe airway obstruction with FEV_1 ≤65% of predicted normal and FEV1 ≤70% of FVC 3) smoking history of more than 10 pack-years 4) regularly using at least two prescribed therapeutic agents for control of their COPD symptoms during the 3-month period immediately preceding consideration for entry into this trial.
Pooled summary	Range 3 months (85 days) - 1 year	Total No. = 9,819	Range 0.91 - 1.33 33% - 46%	

Evidence Table 9. Characteristics of studies of inhaled corticosteroids for COPD using spirometry

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion criteria
Calverly et al, 2003[88]				*See Long-Acting β2 Agonists for details*
Calverley et al, 2003[87]				*See Long-Acting β2 Agonists for details*
Hanania et al, 2003[91]				*See Long-Acting β2 Agonists for details*
Szafranski et al, 2003[92]				*See Long-Acting β2 Agonists for details*
Mahler et al, 2002[96]				*See Long-Acting β2 Agonists for details*
van der Valk et al, 2002[86]	6 months	1) Fluticasone 500 ug b.i.d. (n=123) 2) placebo (n=121)	1) Post 1.78 (0.53) 2) Post 1.69 (0.53), 56%	Dutch men and women (16%), mean age 64 years. Current smokers = 28%, pack years = 38; Mean number of exacerbations previous year = 1.3; Previous use corticosteroids = 83%, β agonists = 56%. 1) clinical diagnosis of stable COPD by ATS criteria 2) no history of asthma 3) no exacerbation in the month before enrollment 4) current or former smoker 5) age between 40 and 75 years 6) baseline prebronchodilator FEV_1 value of 25 to 80% of predicted 7) prebronchodilator ratio FEV_1 inspirator vital capacity (IVC) value of 60% or less 8) reversibility of FEV_1 postinhalation of 80 ug if ipratropium bromide via a metered dose inhalator with Aerochamber 12% of predicted value or less 9) thin layer chromatography greater than the thin layer chromatography predicted minus 1.64 SD 10) no maintenance treatment of oral steroids or antibiotics 11) no medical condition with low survival or serious psychiatric morbidity (e.g., cardiac insufficiency, alcoholism) 12) absence of any other active lung disease (e.g., sarcodosis) 13) use of medication such as nasal corticosteroids, theophyllines, chronic use of acetylcysteine, and all other bronchodilators was allowed.
Burge et al., 2000[111]	3 years	1) Fluticasone 500 ug b.i.d. (n=376) 2) placebo (n=375)	1) 1.25 (0.44), 50% 2) 1.23 (0.47), 50%	English men and women (25%); mean age 64 years; Current smokers = 38%, pack years = 44; Previous use inhaled corticosteroids = 54%. 1) current or former smokers aged 40-75 years with non-asthmatic COPD 2) baseline FEV_1 after bronchodilator was at least 0.8 litres but less than 85% of predicted normal, and the ratio of FEV_1 to forced vital capacity was less than 70% 3) previous use of inhaled and oral corticosteroids was permitted.

Evidence Table 9. Characteristics of studies of inhaled corticosteroids for COPD using spirometry (continued)

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion criteria
LHS Research Group, 2000[114]	4.5 years	1) Triamcinolone 600 ug b.i.d. (n=559) 2) placebo (n=557)	1) 2.16 (0.62), 65% 2) 2.10 (0.64), 63%	North American men and women (37%), White (95%), Nonwhite (5%); mean age 56; Current smokers = 90%; Chronic bronchitis 11%, Asthma 9%, Emphysema 8%. 1) previously Lung Health Study participants 2) 40 to 69 years of age with airflow obstruction 3) a ratio of FEV_1 to FVC of less than 0.70 and a value for FEV_1 of 30 to 90% of the predicted value 4) current smokers or quit within the previous two years. Daily cough and phlegm ≥3 months/year 35%, Daily cough or phlegm ≥3 months/ year 58%, Dyspnea while walking up a slight hill or hurrying 28%, wheezing apart from a cold 31%.
Pauwels et al., 1999[115]	3 years	1) Budesonide 400 ug b.i.d. (n=634) 2) placebo (n=643)	1) 2.53 (0.64), 77% 2) 2.54 (0.64), 77%	European (9 countries) men and women (27%); mean age 52 years; pack-years = 39; Previous use β agonists = 38%. 1) 30 to 65 years of age if currently smoking at least 5 cigarettes per day and smoked cigarettes for at least 10 years or a smoking history of at least 5 pack-years 2) FEV_1 after the use of bronchodilator - between 50% and 100% of the predicted normal value, and ratio of prebronchodilator FEV_1 to slow vital capacity less than 70% 3) increase in FEV_1 after inhalation of 1 mg of terbutaline from a dry-power inhaler - less than 10% of the predicted normal value 4) change in FEV_1 between the end of the first 3-month period of the run-in phase and the end of the second - less than 15%.
Vestbo et al., 1999[112]	3 years	1) Budesonide (800 ug, 400 ug b.i.d.) for 6 mo and (400 ug, b.i.d.) for 30 mo (n=145) 2) placebo (n=145)	1) Post 2.36 (0.79), 86% 2) Post 2.39 (0.86), 87%	Denmark men and women (40%); mean age 59 years; Current smokers = 77%. 1) CCHS participants 2) age 30-70 years 3) FEV_1/FVC ratio 0.7 or less 4) FEV_1 reversibility after inhalation of 1.0 mg terbutaline from Turbuhaler of less than 15% of prebronchdilator FEV_1 5) FEV_1 reversibility after 10 days of treatment with oral prednisolone 37.5 mg daily of less than 15% of prebronchdilator FEV_1 6) informed consent. Chronic mucus hypersecretion 35%, wheeze with dyspnea 22%.
Weir et al., 1999[117]	2 years	1) Beclomethasone dipropionate (750 ug for less than 50 kg) and (1000 ug for greater than 50 kg), b.i.d., (n=49) 2) placebo (n=49)	1) 1.07, 40% 2) 1.13, 41%	English men and women (26%); mean age 67 years; Current smokers = 39%, pack years = 55 1) clinical diagnosis with COPD 2) adult onset airflow obstruction with FEV_1 < 70% predicted and FEV_1/FVC <65%.

Evidence Table 9. Characteristics of studies of inhaled corticosteroids for COPD using spirometry (continued)

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion criteria
Bourbeau et al., 1998[116]	6 months	1) Budesonide 800 ug b.i.d, (n=39) 2) placebo (n=40)	1) 0.91 (0.33), 36% 2) 0.95 (0.30), 37%	Canadian men and women (22%); mean age 66 years; Current smokers = 39%, pack years = 51 1) age 40 years old or older 2) smokers or ex-smokers 3) no history of allergic asthma during childhood or as an adult 4) absence of exacerbation in respiratory symptoms during the two months prior study 5) pre-bronchodilator FEV_1 less than 65% of predicted and FEV_1/FVC less than 0.65 6) post-bronchodilator FEV_1 less than 80% 7) regular treatment with at least one bronchodilator 8) no inhaled corticosteroids in the previous month or oral corticosteroids in the previous two months 9) absence of any other active lung disease 10) absence of diabetes, active peptic ulcer disease, uncontrolled high blood pressure, or congestive heart failure 11) absence of disease other than COPD that might interfere with quality of life (dyspnea, fatigue, emotion, and mastery).
Paggiaro et al., 1998[113]	6 months	1) Fluticasone propionate 500 mg b.i.d. (n=142) 2) placebo (n=139)	1) 1.60 (0.58), 59% 2) 1.52 (0.62), 55%	European (13 countries), New Zealand, and South African men and women (23%); mean age 63 years (range 49-75); Current smokers = 49%; Previous use β agonists = 38%, methylxanthines = 34%, anticholinergics = 16%. 1) ages between 50 and 75 years with COPD by European Respiratory Society Consensus Statement 2) if current or ex-smokers, with a history of smoking equivalent to at least 10 pack-years and chronic bronchitis 3) history of at least one exacerbation each year for the previous 3 years that required a visit to their doctor or hospital, a high expectation, according to the investigator, of experiencing an exacerbation during the 6-month treatment period, a regular productive cough, a predicted FEV_1 of 35-90%, a ratio of FEV_1 to forced vital capacity of 70% or less, and reversibility in FEV_1 of less than 15% after inhalation of 400 ug or 800 ug salbutamol via a metered-dose inhaler or Diskhaler, respectively 4) a reversibility in FEV_1 of more than 15% but a volume change of less than 200 mL
Pooled summary	Range 6 months - 4.5 years	Total No. = 4,136	Range 0.91 - 2.53; 36% - 77% or 86% (post)	

Evidence Table 10. Characteristics of studies of sibanet (D2-receptor/β agonist) for COPD using spirometry

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion criteria
Celli et al., 2003[90]	3 months	1) Sibenadet 500 ug t.i.d. (n=543) 2) Salmeterol 50 ug b.i.d. (n=554) 3) placebo (n=271)	1) 1.32 (0.48), 42% 2) 1.30 (0.46), 42% 3) 1.35 (0.50), 44%	Worldwide 15 countries, 75% men and 25% women; Caucasian (96%), Black (1%), Oriental (2%), Others (1%); mean age 64 (range 35-80); pack years = 46; Medication at enrollment: oral/inhaled steroids = 54%, short acting β agonists = 55%, long acting β agonists = 25%, xanthines 22%. 1) both genders ranging in age from 40 to 80 years, with diagnosis of COPD (with symptoms for more than 2 years) 2) current or ex-smokers with smoking history of ≥15 pack-years 3) FEV_1/FVC ratio ≤65% 4) FEV_1 20-70% of the predicted normal 5) FEV_1 reversibility to 400 ug salbutamol of ≤15% or <200 ml. Mean daily BCSS (Breathlessness, cough, and sputum scale) (1) 5.28, (2) 5.30.
Hiller et al., 2003[118]	13 months	1) Sibenadet 500 ug t.i.d. (n=290) 2) placebo (n=145)	1) 1.25 (0.53), 41% 2) 1.25 (0.49), 41%	American men and women (43%), mean age 64 (range 41-80). Current smoker = 41%, pack years = 60; Medication at enrollment: corticosteroids = 38%; β agonists = 26%; Combined β agonist/anticholinergic 22%. 1) male and female patients with stable, uncomplicated COPD (with symptoms for at least 2 years) 2) ages 40-80 years with a smoking history of at least 15 pack-years 3) FEV_1/FVC ratio of ≤70% 4) FEV_1 20-70% of the predicted normal range.
Laursen et al, 2003[119]	3 months	1) Sibenadet 500 ug t.i.d.(n=524) 2) placebo (n=526)	1) 1.20 (0.36), 39% 2) 1.1 (0.46), 40%	European (3 countries) men and women (27%), mean age 65 (range 40-80); Current smoker = 46%, pack years = 51. 1) male and female patients, ages 40-80 years, with stable COPD, symptoms for ≥2 years) 2) smoking history of at least 15 pack-years 3) pre- and post-bronchodilator FEV_1/FVC ≤ 65% 4) pre- and post-bronchodilator FEV_1 20-70% of the predicted normal range. Mean daily BCSS (Breathlessness, cough and sputum scale) 5.11.
Laursen et al, 2003[119]	6.5 months	1) Sibenadet 500 ug t.i.d. (n=591) 2) placebo (n=578)	1) 1.40 (0.49), 41% 2) 1.20 (0.46), 40%	European (3 countries) men and women (26%), mean age 63 (range 40-79); Current smoker = 53%, pack years = 39. 1) male and female patients, ages 40-80 years, with stable COPD, symptoms for ≥2 years) 2) smoking history of at least 15 pack-years 3) pre- and post-bronchodilator FEV_1/FVC ≤ 65% 4) pre- and post-bronchodilator FEV_1 20-70% of the predicted normal range. Mean daily BCSS (Breathlessness, cough and sputum scale) 5.21.
Pooled summary	Range: 3 months - 13 months	Total No. = 4,022	Range 1.20 - 1.40; 39% - 42%	

Evidence Table 11. Characteristics of studies of pulmonary rehabilitation (program) for COPD using spirometry

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Ries et al., 2003[121]	2 years	Experimental maintenance intervention (n=87); control (standard care) (n=85)	1.07 (0.43); 45%	American men and women (46%); mean age 67 years. More details document wasn't supplied (referred to online supplement)
Brooks et al., 2002[122]	1 year	Enhanced followup (n=50); control (conventional followup) (n=59)	0.71 (0.04); 32%	Canadian men and women (41%); mean age 68 years. 1) severe stable COPD (FEV_1 <40% predicted, FEV_1/FVC < 0.70) 2) completion of inpatient or outpatient rehabilitation 3) nonsmoker for a minimum of 6 months 4) aged 49-85 years
Finnerty et al., 2001[123]	6 months	Rehabilitation (6-week outpatient-based program) (n=50); control (n=50)	0.99 (0.36); 41%	English men and women (32%); mean age 70 years; Current smokers = 12%. 1) long-standing airways disease, classified as COPD (known to the respiratory team at the hospital) 2) had their therapy optimized, the role of oral or inhaled steroids and nebulized bronchodilator therapy 3) assessed as to their ability to comply with requirements of program, specifically time and travel commitments involved
Griffiths et al., 2000[124]	1 year	Rehabilitation (6-week multidisciplinary program) (n=99); control (n=101)	0.91 (0.38); 40%	English men and women (40%); mean age 68 years; pack years = 45. 1) clinical diagnosis with chronic obstructive bronchitis, emphysema, or chronic poorly reversible asthma or bronchiectasis 2) FEV_1, measured at a time of clinical stability, less than 60% of predicted with less than 20% reversibility in response to inhaled β agonists 3) no change in symptoms or medication for 2 months before entry 4) additional, non-obstructive but disabling pulmonary disease, who matched the spirometric criteria
Ringbaek et al., 2000[125]	8 weeks	Rehabilitation (8 week program) (n=24); control (n=21)	50%	Denmark men and women (84%); mean age 63 years; Current smokers = 51%; Previous use oral/inhaled steroid 89%. 1) stable COPD with FEV_1/FVC ratio <70%, FEV_1 >0.6 2) age <75 years 3) oxygen saturation without oxygen supply >90%

Evidence Table 11. Characteristics of studies of pulmonary rehabilitation (program) for COPD using spirometry (continued)

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Engstrom et al., 1999[126]	1 year	Rehabilitation (physiotherapy program) (n=26); control (n=24)	31%	Swedish men and women (48%); mean age 66 years; Current smokers = 20%, pack-years = 38. 1) diagnosis of COPD (chronic obstructive disease; developing after at least 10 pack years of smoking; debut of symptoms after 40 years of age; dyspnea mainly elicited by exercise or infections; no history of clinically significant allergy) 2) age 45-75 years 3) FEV_1 of <50% pred. after bonchdilation 4) PaO2 of >8 kPa 5) stable clinical condition
Wedzicha et al., 1998[127] (Moderate)	8 weeks	Rehabilitation (exercise training and education for 8 weeks) (n=33); control (education) (n=33)	0.95 (0.32); 37%	English men and women (49%); mean age 67 years (44-81). 1) history of COPD 2) FEV_1 <70% predicted, with <15% reversibility to inhaled salbutamol 400 ug 3) exercise capacity that was limited by dyspnea 4) clinical stability for at least 3 weeks prior to recruitment, with no exacerbation over this period 5) medical treatment was optimized prior to entry and was not changed during the rehabilitation programs
Wedzicha et al., 1998[127] (Severe)	8 weeks	Rehabilitation (exercise training and education for 8 weeks) (n=30); control (education) (n=30)	0.87 (0.41); 38%	English men and women (49%); mean age 67 years (44-81). 1) history of COPD 2) FEV_1 <70% predicted, with <15% reversibility to inhaled salbutamol 400 ug 3) exercise capacity that was limited by dyspnea 4) clinical stability for at least 3 weeks prior to recruitment, with no exacerbation over this period 5) medical treatment was optimized prior to entry and was not changed during the rehabilitation programs
Pooled summary	Range 8 weeks - 2 years	Total No. = 693	Range 0.71 - 1.07; 31% - 50%	

Evidence Table 12. Characteristics of studies of disease management, education, and followup studies for COPD with/without spirometry

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Bourbean et al., 2003[159]	1 year	Self-management (n=96) Placebo (n=95)	Post 1.00 (0.33)	Canadian men and women (45%); mean age 69 years; Current smokers = 26%; Previous use β agonists = 96%, methylxanthines = 29%, anticholinergics = 63%, steroids = 85%. 1) stable COPD (respiratory symptoms and medication unchanged for at least 4 weeks before enrollment) 2) at least 50 years of age 3) current or previous smoker (at least 10 pack-years) 4) FEV_1 after the use of bronchodilator between 25% and 70% of the predicted normal value and FEV_1/FVC ratio less than 70% 5) no previous diagnosis of asthma, left congestive heart failure, terminal disease, dementia, or uncontrolled psychiatric illness 6) no participation in respiratory rehabilitation program in the past year 7) no long-term care facility stays Dyspnea 48%
Monninkhof et al., 2003[160]	1 year	Self-management education + fitness program (n=127) Control (n=121)	Post 1.71 (0.56); 56%	Dutch men and women (32%); mean age 65 years; Current smokers = 22%; Previous use long acting β agonists = 37%, inhaled corticosteroids = 52%. 1) clinical diagnosis of stable COPD by STS criteria 2) no history of asthma 3) no exacerbation in the month prior to enrollment 4) current or former smoker 5) ages 40-75 years 6) baseline prebronchodilator FEV_1 25-80% predicted 7) prebronchodilator ratio FEV_1/inspiratory vital capacity ≤60% 8) reversibility of FEV_1 postinhalation of 80 ug of ipratropium bromide via metered dose inhalator with aerochamber ≤12% predicted 9) TLC greater than TLC predicted - (1.64xSD) 10) no maintenance treatment of oral steroids or antibiotics 11) no medical condition with low survival or serious psychiatric morbidity 12) absence of any other active lung disease (e.g. sarcoidosis)
Hermiz et al., 2002[39]	3 months	Education/enhanced followup (home visits by nurse) (n=84) Control (standard care) (n=93)	No spirometry	Australian men and women (53%); mean age 67 years. 1) ages 30-80 years who attended or admitted hospitals (emergency departments) with COPD (identified from their records and invited to participate in the study) 2) provided with written consent about the study

Evidence Table 12. Characteristics of studies of disease management, education, and followup studies for COPD with/without spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Weinberger et al., 2002[161]	1 year	Pharmaceutical care program group (n=185) Peak flows meter monitoring control group (n=130) Usual care control (n=138)	No spirometry	American men and women (66%); mean age 62 years; White 87%; Current smokers 38%; Previous use sympathomimetics = 60%, methylxanthines = 16%, inhaled/systemic corticosteroids = 58%. 1) filled a prescription for methylxanthines, inhaled corticosteroids, inhaled or oral sympathomimetics, et al. during the preceding 4 months 2) reported having COPD as active problems 3) 18 years or older 4) received 70% or more of their medications from a single study drugstore 5) reported no significant impairment in vision, hearing, or speech that precluded participation 6) did not reside in an institution (e.g., nursing home) 7) provided written informed consent
Gallefoss and Bakke, 2000[162]	1 year	Education (n=31) Control (n=31)	59%	Norway men and women (50%); mean age 58 years; Current smokers = 55%. 1) COPD between 18 and 70 years of age, not suffering from any other serious disease 2) FEV_1 ≥40% and ≤80% of predicted 3) 32% patients were reversible to ipratropium bromide 80 ug and/or salbutamol
Watson et al., 1997[163]	6 months	Self-management (use of Action Plan & booklet) (n=29) Control (usual care) (n=27)	37%	New Zealand men and women (46%); mean age 68 years; Current smokers = 29%. 1) COPD as major functionally limiting disease (defined according to ATS criteria) 2) smoking history of greater than 10 pack-years 3) FEV_1 less than 65% of predicted 4) ratio of FEV_1/FVC less than 70% 5) current use of bronchodilator therapy
Weinberger et al., 1996[164]	6 months	Primary care intervention (n=295) Control (n=288)	No spirometry	American men and women (2%); mean age 63 years; White (non-Hispanic) 65%, Black (non-Hispanic) 27%, Other 8%. 1) patients hospitalized in the General Medicine Service 2) diagnosis of COPD that documented in medical record at or before time of index admission (because they are prevalent among veterans, because patients with this disease are commonly readmitted, and because hospital readmissions to treat this disease might be reduced if primary care physicians provided intervention to outpatients

Evidence Table 12. Characteristics of studies of disease management, education, and followup studies for COPD with/without spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Littlejohns et al., 1991[165]	1 year	Education/enhanced followup (n=73) Control (n=79)	45%	English men and women (35%); mean age 63 years; Current smokers = 25%. 1) ages 30-75 years 2) no other major disease 3) prebronchodilator FEV_1 less than 60% predicted 4) stable state as judged by the patient and physician with no change or perceived need for change in medication for at least six weeks before recruitment 5) informed written consent (Most days) cough 48%, produce sputum 38%, short of breath 67%, wheeze 25%
Cockcroft et al., 1987[166]	8 months	Enhanced followup (group visited by respiratory health worker) (n=42) Control (n=33)	0.78 (0.31)	English men and women (32%); mean age 70 years (46-84); Current smokers = 27%. 1) patients suffered from chronic respiratory disability caused mainly by COPD 2) patients who had been admitted to hospital at least twice during the previous 3 years and new patients who had been seen within the past year
Pooled summary	Range 3 months - 1 year	Total No. = 1,997	Range 0.78 - post 1.71; 37% - 59%	

Evidence Table 13. Characteristics of studies of non invasive mechanical ventilation for COPD using spirometry

Study	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV_1 (L); % Predicted of Normal	Description of Subjects / Inclusion Criteria
Jolliet et al., 2003[167]	2 years	Noninvasive pressure support ventilation (He/O_2) (n=59) Control (Air/O_2) (n=64)	0.73 (0.36)	Switzerland / Belgian men and women (42%); mean age 70 years. At least two of these criteria 1) worsening dyspnea during the last 10 days 2) respiratory rate of >25 breaths/minute 3) arterial pH <7.35 4) PaCO2 of >50 torr 5) PaO2 of <50 torr Dyspnea (Borg scale) points 4.7
Ambrosino et al., 2002[168]	6 months	Noninvasive positive pressure ventilation (n=63) Control (n=34)	30%	Italian men and women (29%); mean age 68 years. Patients known to be affected with COPD, according to ATS criteria, or with high probability of the disease based on their clinical history, physical examination, chest radiography, and, when available, previous pulmonary function test
Pooled summary	Range 6 months - 2 years	Total No. = 220	Range 0.73; 30%	

Evidence Table 14. Outcomes of studies of long-acting β2 agonists for COPD using spirometry

Study	Intervention	Exacerbations: Total Subjects with >1 Episode n/N (%)	Exacerbations - Other/ Hospitalizations Due to COPD/ or Other	Mortality: n/N (%)	St George's Respiratory Questionnaire
Brusasco et al., 2003[89]			Use of oral steroid bursts in management of COPD; n/N %		Change per group
	1) Salmeterol 50 ug (n=405)	142/405 (35)	56/405 (13.8)	6/405 (1.5)	2.8 (0.7)
	2) placebo (n=400)	156/400 (39)	58/400 (400)	5/400 (1.3)	1.5 (0.7)
Calverley et al., 2003[87]			Mean rate per patient/year		Treatment difference vs. combination therapy
	1) Salmeterol 50 ug b.i.d. (n=372)	8/372 (2.2)	1.04	Not reported	-1.1 (-2.2 to 0.1) (p=0.071)
	placebo (n=361)	19/361 (5.3)	1.3	Not reported	-2.2 (-3.3 to -1.0) (p=0.0003)
Celli et al., 2003[90]			"Deterioration of COPD"; n/N %		
	1) Salmeterol 50 ug b.i.d. (n=554)	95/554 (17.1)	74/553 (13.4)	1/554 (<1)	Change per group -5.3 (0.8)
	2) placebo (n=271)	59/271 (21.9)	51/268 (19)	2/271 (<1)	-3.2 (1.1)
Hanania et al., 2003[91]	1) Salmeterol 50 ug b.i.d. (n=177)	Not reported	Not reported	0/177	*Chronic Respiratory Disease Questionnaire;* Treatment difference vs. pbo 2.0 (ns vs. pbo)
	2) placebo (n=185)	Not reported	Not reported	0/185	
Szafranski et al, 2003[92]			Mean exacerbation rates/year		Change per group
	1) Formoterol 4.5 ug b.i.d.(n=201)	Not reported	1.84	6/201 (3)	-3.6
	2) placebo (n=205)	Not reported	1.87	9/205 (4.4)	-0.03
Aalbers et al., 2002[93]	1) Formoterol 4.5 ug b.i.d. (n=171)	Not reported	"Deterioration of COPD"; n/N % 7/171 (4.1)	Not reported	Not reported
	2) Formoterol 9 ug b.i.d. (n=169)	Not reported	12/169 (7.1)	Not reported	Not reported
	3) Formoterol 18 ug b.i.d. (n=178)	Not reported	18/178 (10.1)	Not reported	Not reported
	4) placebo (n=173)	Not reported	16/173 (9.2)	Not reported	Not reported
Chapman et al., 2002[94]	1) Salmeterol 50 ug b.i.d. (n=201)	52/201 (26)	Not reported	Not reported	Change per group -2.4 (12.7) (p=0.3 vs. pbo)
	2) placebo (n=207)	68/207 (33)	Not reported	Not reported	-0.9 (12.2)
Donohue et al, 2002[95]	1) Salmeterol 50 ug b.i.d. (n=213)	82/213 (38.5)	Not reported	3/213 (1.4)	Change per group -3.54 (p=0.39 vs. pbo)
	2) placebo (n=201)	92/201 (45.8)	Not reported	4/201 (2)	-2.43

Evidence Table 14. Outcomes of studies of long-acting β2 agonists for COPD using spirometry (continued)

Study	Intervention	Exacerbations: Total Subjects with >1 Episode n/N (%)	Exacerbations - Other/ Hospitalizations Due to COPD/ or Other	Mortality: n/N (%)	St George's Respiratory Questionnaire
Mahler et al., 2002[96]	1) Salmeterol 50 ug b.i.d. (n=160)	Not reported	Discontinuations due to exacerbations; n/N % 9/160 (5.6)	0/160	*Chronic Respiratory Disease Questionnaire;* Treatment difference vs. pbo 3.8 (ns vs. pbo)
	2) placebo (n=181)	Not reported	16/181 (8.8)	3/181 (1.7)	
Rossi et al., 2002[97]	1) Formoterol 12 ug b.i.d.(n=211)	34/211 (16.1)	COPD hospitalizations (severe exacerbations) 10/211 (4.7)	3/211 (1.4)	Change per group -5.3 (p=0.030 vs. pbo)
	2) Formoterol 24 ug b.i.d.(n=214)	31/214 (14.5)	5/214 (2.3)	1/214 (<1)	-6.1 (p=0.009 vs. pbo)
	3) placebo (n=220)	39/220 17.7)	20/220 (9.1)	0/220	-1.9
Wadbo et al., 2002[98]	1) Formoterol 18 ug b.i.d. (n=61)	"Adverse Events related to COPD" 23/61 (37.7)	"Deterioration of COPD leading to withdrawal"; n/N % 3/61 (4.9)	Not reported	Change per group (in %) 0.0% (95%CI -2.2 to 2.2)
	2) placebo (n=60)	23/60 (38.3)	6/60 (10.0)	Not reported	1.5% (95%CI -0.8 to 3.7)
Dahl et al., 2001[99]	1) Formoterol 12 ug b.i.d. (n=194)	"COPD Adverse Events" - includes exacerbations 25/194 (12.9)	COPD hospitalizations; n/N % 2/194 (1)	0/194	Treatment difference vs. pbo -5.06 (p<0.001)
	2) Formoterol 24 ug b.i.d. (n=192)	37/192 (19.3)	2/192 (1)	0/192	-3.3 (-5.8 to -0.8) (est.) (p=0.009)
	3) placebo (n=200)	37/200 (18.5)	4/200 (2)	0/200	
Rennard et al., 2001[100]	1) Salmeterol 42 ug, b.i.d. (n=132)	38/132 (28.8)	First exacerbation during week 1; n/N % 6/132 (4.6)	0/132	*Chronic Respiratory Disease Questionnaire*; Change per group 10.3 (p=0.078 vs. pbo)
	2) placebo (n=135)	41/135 (30.4)	20/135 (14.8)	1/135	6.8
van Noord et al., 2000[101]	1) Salmeterol 50 ug, b.i.d. (n=47)	11/47 (23)	Discontinuations due to exacerbations; n/N % 3/47 (6.4)	Not reported	Not reported
	2) placebo (n=50)	18/50 (36)	4/50 (8.0)	Not reported	Not reported
Mahler et al., 1999[102]	1) Salmeterol 42 ug b.i.d. (n=135)	28/135 (20.7)	First exacerbation during week 1; n/N % 7/135 (5.2)	0/135	*Chronic Respiratory Disease Questionnaire* 7.1 (1.4) (p=0.007 vs. pbo)
	2) placebo (n=143)	47/143 (32.9)	21/143 (14.7)	0/143	2.1 (1.3)

Evidence Table 14. Outcomes of studies of long-acting β2 agonists for COPD using spirometry (continued)

Study	Intervention	Exacerbations: Total Subjects with >1 Episode n/N (%)	Exacerbations - Other/ Hospitalizations Due to COPD/ or Other	Mortality: n/N (%)	St George's Respiratory Questionnaire
Jones and Bosh 1997[46]	1) Salmeterol 50 ug b.i.d. (n=94)	Not reported	Not reported	Not reported	Change per group -6.8 (13.2) (p<0.001 vs. pbo)
	2) Salmeterol 100 ug b.i.d. (n=94)	Not reported	Not reported	Not reported R	-2.3 (11.6)
	3) placebo (n=95)	Not reported	Not reported	Not reported	-1.4 (11.7)
Boyd et al., 1997[103]	1) Salmeterol 50 ug b.i.d. (n=229)	47/229 (21)	Not reported	1/229 (<1)	Not reported
	2) Salmeterol 100 ug (n=218)	54/218 (25)	Not reported	0/218	Not reported
	3) placebo (n=227)	59/227 (26)	Not reported	1/227 (<1)	Not reported

Evidence Table 15. Summary of outcomes for interventions for COPD using spirometry - long-acting β2 agonists

Studies	N	Duration	Long-Acting β2 Agonists Events, %	Placebo Events, %	ARR % [95%CI]	Relative Risk [95%CI]	Baseline Spirometry Range (FEV_1; %) Predicted
Exacerbations: Salmeterol							
Brusasco, 2003[89]	805	6 months	35.1	39	-4 [-11 to 3]	0.90 [0.75 to 1.08]	1.1; 38%
Calverley, 2003[87]	733	1 year	2.2	5.3	-3 [-6 to 0]	0.41 [0.18 to 0.92]	1.3; 45%
Celli, 2003[90]	825	3 months	17.1	21.8	-5 [-10 to 1]	0.79 [0.59 to 1.05]	1.3; 42%
Chapman, 2002[94]	408	6 months	25.9	32.9	-7 [-16 to 2]	0.79 [0.58 to 1.07]	1.2; 45%
Rennard, 2001[100]	267	3 months	28.8	30.4	-2 [-13 to 9]	0.95 [0.65 to 1.37]	1.3
Mahler, 2002[96]	341	6 months	5.6	8.8	-3 [-9 to 2]	0.64 [0.29 to 1.40]	1.3; 41%
van Noord, 2000[101]	97	3 months	23.4	36	-13 [-31 to 5]	0.65 [0.34 to 1.23]	1.1; 40%
Mahler, 1999[102]	278	3 months	20.7	32.9	-12 [-22 to -2]	0.63 [0.42 to 0.95]	41%
Boyd, 1997[103]	674	4 months	22.6	26	-3 [-10 to 4]	0.87 [0.66 to 1.15]	1.3
Overall	**4428**	3 months - 1 year	**19.7**	**24.5**	**-5 [-7 to -2]**	**0.81 [0.73 to 0.90]**	**1.1-1.3; 38-45%**
Exacerbations: Formeterol							
Calverley, 2003[88]	511	1 year	28.6	30.9	-2 [-10 to 6]	0.93 [0.71 to 1.21]	1.0; 36%
Aalbers, 2002[93]	691	3 months	7.1	9.2	-2 [-7 to 3]	0.77 [0.44 to 1.35]	1.5; 54%
Rossi, 2002[97]	645	1 year	27.5	34.1	-7 [-14 to 1]	0.81 [0.64 to 1.03]	1.4; 47%
Wadbo, 2002[98]	121	3 months	37.7	38.3	-1 [-18 to 17]	0.49 [0.13 to 1.88]	33%
Dahl, 2001[99]	586	3 months	16.1	18.5	-2 [-9 to 4]	0.87 [0.60 to 1.26]	1.3; 45%
Szafranski, 2003[92]	406	1 year	18.9	25.9	-7 [-15 to 1]	0.73 [0.51 to 1.06]	1.0; 36%
Overall	**2960**	**3 months - 1 year**	**19.0**	**25.4**	**-4 [-7 to -1]**	**0.79 [0.67 to 0.94]**	**1.0-1.5; 33-54%**
OVERALL	**7388**	**3 months - 1 year**	**19.4**	**24.8**	**-4 [-6 to -2]**	**0.82 [0.76 to 0.90]**	**1.1-1.5; 33-54%**

Studies	N	Duration	Long-Acting β2 Agonists Events, %	Tiotropium Events, %	ARR	Relative Risk (95%CI	Baseline Spirometry Range FEV_1; %) predicted
Exacerbations: Salmeterol vs. Tiotropium							
Brusasco, 2003[89]	807	6 months	35.1	32.1	3 [-4 to 9]	1.09 (0.90 to 1.33)	1.1; 39%
Mortality: Salmeterol							
Brusasco, 2003[89]	805	6 months	1.5	1.3	0 [-1 to 2]	1.19 [0.36 to 3.85]	1.1; 38%
Celli, 2003[90]	825	3 months	0.18	0.73	-1 [-2 to 1]	0.24 [0.02 to 2.69]	1.3; 42%
Hanania, 2003[91]	362	6 months	0	0	0 [-1 to 1]	Not estimable	1.3; 42%
Mahler, 2002[96]	341	6 months	0	1.7	-2 [-4 to 1]	0.16 [0.01 to 3.10]	1.3; 41%
Rennard, 2001[100]	267	3 months	0	0.74	-1 [-3 to 1]	0.34 [0.01 to 8.29]	1.3
Mahler, 1999[102]	278	3 months	0	0	0 [-1 to 1]	Not estimable	41%
Boyd, 1997[103]	674	4 months	0.22	0.44	0 [-1 to 1]	0.51 [0.03 to 8.08]	1.3
Overall	**3552**	**3 months - 6 months**	**0.39**	**0.77**	**0 [-1 to 1]**	**0.57 [0.27 to 1.22]**	**1.1-1.4; 38-42%**

Evidence Table 15. Summary of outcomes for interventions for COPD using spirometry - long-acting β2 agonists (continued)

Studies	N	Duration	Long-Acting β2 Agonists Events, %	Tiotropium Events, %	ARR	Relative Risk (95%CI	Baseline Spirometry Range FEV_1; %) predicted
Mortality: Formoterol							
Calverley 2003[88]	511	1 year	5.1	2	3. [0 to 6]	2.61 [0.94 to 7.21]	1.0: 36%
Szafranski, 2003[92]	406	1 year	3	4.4	-1 [-5 to 2]	0.68 [0.25 to 1.88]	1.0; 36%
Rossi, 2002[97]	645	1 year	0.94	0	1 [0 to 2]	4.67 [0.25 to 86.33]	1.4; 48%
Dahl, 2001[99]	586	3 months	0	0	0 [-1 to 1]	Not estimable	1.3; 45%
Overall	**2148**	**3 months - 1 year**	**1.8**	**0.6**	**1 [0 to 2]**	**1.52 [0.79 to 2.94]**	**1.0-1.4; 36-48%**
OVERALL	**5700**	**3 months - 1 year**	**0.96**	**1.1**	**0 [0 to 1]**	**1.00 [0.62 to 1.62]**	**1.0-1.4; 36-48%**
Mortality: Salmeterol vs. Tiotropium							
Brusasco, 2003[89]	807	6 months	1.5	0.0025	1.5	5.96 (0.72 to 49.25)	1.1; 39%

Studies	N	Duration	Long-Acting β2 Agonists: Mean Change	Placebo: Change		Weighted Mean Difference (95%CI)	Baseline Spirometry Range (FEV_1; %) Predicted
St George's Respiratory Questionnaire - Mean units of change: Salmeterol							
Brusasco, 2003[89]	805	6 months	-2.8	-1.5	Not applicable	-1.30 [-3.24 to 0.64]	1.1; 38%
Celli, 2003[90]	825	3 months	-5.3	-3.2	Not applicable	-2.10 [-4.61 to 0.41]	1.3; 42%
Chapman, 2002[94]	408	6 months	-2.4	-0.9	Not applicable	-1.50 [-4.32 to 1.32]	1.2; 45%
Jones, 1997[46]	283	4 months	-6.8	-1.4	Not applicable	-5.40 [-8.96 to -1.84]	1.40; 46%
Overall	**2321**	**3 months - 6 months**				**-2.06 [-3.32 to -0.80]**	**1.1-1.40; 38-46%**
St George's Respiratory Questionnaire - Mean units of change: Formoterol							
Calverley 2003[88]	511	1 year	Not reported	Not reported	Not applicable	-4.1	1.0: 36%
Dahl, 2001[99] 12ug	388	3 months	Not reported	Not reported	Not applicable	-5.1 [-7.6 to -2.6]	1.3; 45%
Dahl, 2001[99] 24ug	392	3 months	Not reported	Not reported	Not applicable	-3.4 [-5.9 to -0.9]	1.3; 45%
Wadbo, 2002[98]	121	3 months	0	1.5	Not applicable	-1.5 [-4.61 to 1.61]	33%
Overall	**1412**	**3 months**					
OVERALL	**3733**	**3 months - 6 months**				**-1.98 [-3.15 to -0.81]**	**1.1-1.40; 33-46%**

Evidence Table 16. Outcomes of studies of sibanet for COPD using spirometry

Study	Intervention	Exacerbations: Total Subjects With >1 Episode n/N (%)	Exacerbations - Other/ Hospitalizations Due to COPD / or Other	Mortality: n/N (%)	St George's Respiratory Questionnaire
Celli et al., 2003[90]			Deterioration of COPD; n/N %		Treatment difference vs. pbo; Change per group
	1) Sibenadet 500 ug t.i.d. (n=543)	116/543 (21.4)	89/543 (16.4)	3/543 (<1)	-4.2 (0.8 SE)
	2) placebo (n=271)	59/271 (21.9)	51/268 (19)	2/271 (<1)	-3.2 (1.1 SE)
Hiller et al., 2003[118]			Deterioration of COPD; n/N %		
	1) Sibenadet 500 ug t.i.d. (n=290)	125/290 (43.1)	73/290 (25.2); 12 discontinued the study	3/290 (1.0)	"No notable differences between the treatment groups"
	2) placebo (n=145)	66/145 (45.5)	39/145 (26.9); 3 discontinued the study	2/145 (1.4)	
Laursen et al., 2003[119]			Deterioration of COPD; n/N %		
	1) Sibenadet (n=535)	77/524 (14.7) (ITT population)	56/535 (10.5)	4/535 (<1)	"No statistically significant differences were seen" between the treatment groups
	2) placebo (n=537)	94/526 (17.9) (ITT population)	64/537 (11.9)	3/537 (<1)	
Laursen et al., 2003[119]			Deterioration of COPD; n/N %		Change per group
	1) Sibenadet (n=609)	139/591 (23.5)) (ITT population)	128/609 (21)	12/609 (2.0)	-3.25 (p ns vs. pbo)
	2) placebo (n=594)	149/578 (25.8) (ITT population)	115/594 (19.4)	9/594 (1.5)	-2.33

Evidence Table 17. Summary of outcomes for interventions for COPD using spirometry – sibanet

Studies	N	Duration	Sibanet Events, %	Placebo Events, %	ARR % [95% CI]	Relative Risk [95% CI]	Baseline Spirometry Range (FEV_1; %) Predicted
Exacerbations							
Celli, 2003[90]	814	3 months	21.4	21.8	0 [-6 to 6]	0.98 [0.74 to 1.30]	1.3; 43%
Hiller, 2003[118]	435	1 year	43.1	45.5	-2 [-12 to 7]	0.95 [0.76 to 1.18]	1.3; 41%
Laursen, 2003[119] Study 1	1061	3 months	14.7	17.9	-3 [-8 to 1]	0.82 [0.62 to 1.08]	1.1*; 39%
Laursen, 2003[119] Study 2	1169	6.5 months	23.5	25.8	-2 [-7 to 3]	0.91 [0.75 to 1.12]	1.3**; 40%
OVERALL	**3479**	**3 months - 1 year**	**23.5**	**24.2**	**-2 [-5 to 1]**	**0.91 [0.81 to 1.03]**	**1.1-1.4; 39-43%**
Mortality							
Celli, 2003[90]	814	3 months	0.55	0.74	0 [-1 to 1]	0.75 [0.13 to 4.45]	1.3; 43%
Hiller, 2003[118]	435	1 year	1	1.4	0 [-3 to 2]	0.75 [0.13 to 4.44]	1.3; 41%
Laursen, 2003[119] Study 1	1072	3 months	0.75	0.56	0 [-1 to 1]	1.34 [0.30 to 5.95]	1.1*; 39%
Laursen, 2003[119] Study 2	1203	6.5 months	2	1.5	0 [-1 to 2]	1.30 [0.55 to 3.06]	1.3**; 40%
OVERALL	**3524**	**3 months - 1 year**	**1.1**	**1**	**0 [-1 to 1]**	**1.14 [0.60 to 2.15]**	**1.1-1.4; 39-43%**

Studies	N	Duration	Long-Acting β2 Agonists: Mean Change	Placebo: Change		Weighted Mean Difference (95%CI)	Baseline Spirometry Range (FEV_1; %) Predicted
St George's Respiratory Questionnaire - Mean units of change							
Celli, 2003[90]	814	3 months	-4.2	-3.2	Not applicable	-1.00 [-3.51 to 1.51]	1.3; 43%
Laursen, 2003[119] Study 2	1203	6.5 months	-3.3	-2.3	Not applicable	-1	1.3**; 40%

* For 130 subjects assessed on day 1 only
** For 152 subjects assessed on day 1 only

Evidence Table 18. Outcomes of studies of pulmonary rehabilitation (program) for COPD using spirometry

Study	Intervention	Exacerbations -Other/ Hospitalizations Due to COPD / or Other	Mortality: n/N (%)	St. George's Respiratory Questionnaire
Ries et al., 2003[121]				Chronic Respiratory Disease Questionnaire; Score at 12 months
	Experimental maintenance intervention (n=87);	Not reported	10/87 (11.5)	96.0 (21.3) / n=74
	Control (standard care) (n=85)	Not reported	10/85 (11.8)	95.9 (21.1) / n=64
Brooks et al., 2002[122]	Enhanced followup (n=50)	35 episodes	Not reported	No significant changes between groups
	Control (conventional followup) (n=59)	33 episodes	Not reported	
Finnerty et al., 2001[123]				Treatment difference vs. control; 6-month score for each group
	Rehabilitation (6-week outpatient-based program) (n=50);	Not reported	Not reported	-8.1 (95% CI -14.9 to -1.4); 50.6 (2.5 SE), n=24, p<0.02 vs. control
	Control (n=50)	Not reported	Not reported	57.1 (3.0 SE), n=25
Griffiths et al., 2000[124]		Number of patients admitted to hospital		Treatment difference vs. control; 12-month score for each group
	Rehabilitation (6-week multidisciplinary program) (n=99)	40 (p=0.98 vs. control)	6/99 (6.1)	-4.8 (95 %CI -8.4 to -1.2), p=0.010; 61.5 (17.5), n=93
	Control (n=101)	41	12/101 (11.9)	69 (13.3), n=89
Ringbaek et al., 2000[125]		Discontinuations due to exacerbation of COPD; n/N %		Treatment difference vs. control
	Rehabilitation (8 week program) (n=24)	3/24 (12.5)	Not reported	0.1 (95% CI -9.8 to 10)
	Control (n=21)	0/21	Not reported	
Engstrom et al., 1999[126]		Deterioration of COPD; n/N %		Change per group
	Rehabilitation (physiotherapy program) (n=26)	4/26 (15.4) non-compliers to treatment	0/26	0.3 (2.2) ITT pop. / -0.2 (1.9) on treatment (n=20)
	Control (n=24)	3/24 (12.5)	0/24	2.1 (2.9)
Wedzicha et al., 1998[127]				Treatment difference vs. control; change per group
(Moderate)	Rehabilitation (exercise training and education for 8 weeks) (n=33)	Not reported	0/33	-5.4 (95% CI -10.7 to 0.02); -2 (95% CI -6 to 3)
	Control (education) (n=33)	Not reported	1/33	4 (95% CI 1 to 7)

Evidence Table 18. Outcomes of studies of pulmonary rehabilitation (program) for COPD using spirometry (continued)

Study	Intervention	Exacerbations -Other/ Hospitalizations Due to COPD / or Other	Mortality: n/N (%)	St. George's Respiratory Questionnaire
Wedzicha et al., 1998[127] (Severe)	Rehabilitation (exercise training and education for 8 weeks) (n=30)	Not reported	0/30	0.93 (95% CI -3.9 to 5.8); 3 (95% CI -2 to 7)
	Control (education) (n=30)	Not reported	1/30	2 (95% CI -1 to 5)

Evidence Table 19. Outcomes of studies of disease management, education, and followup studies for COPD with/without spirometry

Study	Intervention	Exacerbations: Total Subjects With >1 Episode n/N (%)	Exacerbations – Other / Hospitalizations due to COPD / or Other	Mortality: n/N (%)	St George's Respiratory Questionnaire; Change in Points (p vs. Control)
Bourbean et al., 2003[159]		Acute exacerbations (episode) of COPD	COPD hospitalizations; n/N %		Treatment difference vs. pbo; 12-month change
	Self-management (n=96)	299	31/96 (32.3)	5/96 (5.2)	-2.0 (-5.9 to 1.8)
	Usual care (placebo) (n=95)	362	48/95 (50.5)	9/95 (9.5)	
Monninkhof et al., 2003[160]					Treatment difference vs. pbo
	Self-management (n=127)	Not reported	Not reported	3/127 (2.4)	-0.6 (-2.8 to 1.7)
	Control (n=121)	Not reported	Not reported	3/121 (2.5)	
Hermiz et al., 2002[39]					Treatment difference vs. pbo
	Enhanced followup (n=84)	Not reported	Not reported	9/84 (10.7)	1.32 (-2.97 to 5.62)
	Control (n=93)	Not reported	Not reported	10/93 (10.8)	
Weinberger et al., 2002[161]			Breathing-related hospital or ED visit (%)		
	Pharmaceutical care program group (n=185)	Not reported	22.9	Not reported	Not reported
	Peak flows meter monitoring control group (n=130)	Not reported	23.9	Not reported	Not reported
	Usual care control (n=138)	Not reported	23.2	Not reported	Not reported
Gallefoss and Bakke, 2000[162]			COPD hospitalizations; n/N %		Means (SD) at followup
	Education (n=31)	Not reported	0/31	Not reported	40.0 (16)
	Control (n=31)	Not reported	2/31 (6.5)	Not reported	43.1 (21) p-value = 0.54
			Visits to GP or PN; n/N (%)		Means (SD) at followup
Watson et al., 1997[163]	Self-management (use of Action Plan & booklet) (n=29)	Not reported	3/29 (10.3)	0/29	39 (17) significant improvement than base [43(15)]
	Control (usual care) (n=27)	Not reported	2/27 (7.4)	0/27	39 (16)
Weinberger et al., 1996[164]			Number of readmissions per month; mean (SD)	According to total study group	
	Primary care intervention (n=295)	Not reported	0.19 (0.3)	59/695 (8.5)	Not reported
	Control (n=288)	Not reported	0.14 (0.2) p=0.005	47/701 (6.7)	Not reported

Evidence Table 19. Outcomes of studies of disease management, education, and followup studies for COPD with/without spirometry (continued)

Study	Intervention	Exacerbations: Total Subjects With >1 Episode n/N (%)	Exacerbations – Other / Hospitalizations due to COPD / or Other	Mortality: n/N (%)	St George's Respiratory Questionnaire; Change in Points (p vs. Control)
Littlejohns et al., 1991[165]			Number (%) of admissions to hospital		Sickness Impact Profile; mean change (95% CI)
	Education/enhanced followup (n=73)	Not reported	12 (18)	3/73 (4.1)	0.63 (-1.60 to 2.87)
	Control (n=79)	Not reported	14 (21) p=0.80	9/79 (11.4)	-0.4 (-1.85 to 1.05) p=0.46
Cockcroft et al, 1987[166]			Respiratory illness hospitalizations; n/N %		
	Enhanced followup (group visited by respiratory health worker) (n=42)	Not reported	22/42 (52.4)	5/42 (11.9)	Not reported
	Control (n=33)	Not reported	11/33 (33.3)	7/33 (21.2)	Not reported

Evidence Table 20. Prevalence of symptoms in LH-1 subjects at 3 years by baseline spirometry according to treatment assignment

Baseline Spirometry	Dyspnea (%)			Cough and Sputum (%)			Respiratory Hospitalizations (mean)*		
	Ipratropium	Placebo	Usual Care	Ipratropium	Placebo	Usual Care	Ipratropium	Placebo	Usual Care
Stage 0 and Normal	31.1	26.6	34	11	12.5	22	0.32	0.27	0.40
Stage 1	25.8	27.6	32.5	16.9	11.8	26	0.29	0.37	0.67
Stage 2	34.5	36.1	38	15.3	18.5	27.8	0.71	0.58	0.73
Totals	31	31.2	35.5	14.9	15	26	0.48	0.45	0.64

There are only 3 patients in Stage 3 and not represented here

*Per 100 patient years