

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
bronchspirometry.mp. OR
bronchspirometry/ 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
bronchspirometry.mp. OR

bronchspirometry/ 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
bronchspirometry.mp. OR
bronchspirometry/ 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 <i>or</i> Control (usual care, O2)	Yes	No	Unclear
Subjects with COPD (any GOLD Stage) (i.e irreversible airway obstruction, NOT asthma and NOT α -1 antitrypsin deficiency, or were the outcomes in the group with COPD reported separately?)	Yes	No	Unclear
Age of subjects > 19 years of age	Yes	No	Unclear
Minimum of 50 subjects per arm	Yes	No	Unclear
Study duration \geq 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

UNIQUE IDENTIFIER # _____

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 subgroups)			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 %				

UNIQUE IDENTIFIER # _____

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 <i>(write in)</i>			Placebo/control <i>(write in)</i>
	I	II	III	
Current smoker				
Ex-smoker				
Never smoked				

Notes:

INTERVENTION

		Drug name	Dosing regimen <i>(describe)</i>
Intervention	I		
	II		
	III		
<u>Placebo / Control</u>			

Notes:

Study duration (months): Mean _____ **Median** _____

Range: _____ **months**

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 <i>(write in in subgroups)</i>			Placebo/control <i>(write in)</i>
	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

CLINICAL OUTCOMES

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

	Intervention <i>(write in in subgroups)</i>			Placebo/control <i>(write in)</i>
	<u>I</u>	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 <i>(describe)</i>				

FORCED AIR EXPIRATORY VOLUME (FEV1)

	Intervention <i>(write in subgroups)</i>			Placebo/control <i>(write in)</i>
	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				

CLINICAL SYMPTOMS

	Intervention <i>(write in subgroups)</i>			Placebo/control <i>(write in)</i>
	I	II	III	
Dyspnea n/N and %	Baseline: Followup:	Baseline: Followup:	Baseline: Followup:	Baseline: Follow-up:
Cough	Baseline: Follow-up:	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 <i>or</i> 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		Placebo/control	
<i>(write in)</i>		<i>(write in)</i>	
# 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		Placebo/control	
<i>(write in)</i>		<i>(write in)</i>	
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 <i>(write in)</i>		Placebo / control <i>(write in)</i>	
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 <i>(describe)</i>
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		Placebo/control	
<i>(write in)</i>		<i>(write in)</i>	
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 <i>(describe)</i>		Other <i>(describe)</i>	
Other <i>(describe)</i>		Other <i>(describe)</i>	
Other <i>(describe)</i>		Other <i>(describe)</i>	

FORCED AIR EXPIRATORY VOLUME (FEV1)

Intervention		Placebo / control	
<i>(write in)</i>		<i>(write in)</i>	
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		Placebo / control	
<i>(write in)</i>		<i>(write in)</i>	
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		Placebo/control	
<i>(write in)</i>		<i>(write in)</i>	
# 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		Placebo/control	
<i>(write in)</i>		<i>(write in)</i>	
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 (i.e., irreversible airway obstruction, NOT asthma and NOT α -1 antitrypsin deficiency, or were the outcomes in the group with COPD reported separately?	Yes	No	Unclear
FEV1/FVC measured with spirometry	Yes	No	Unclear

TYPE OF STUDY

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

 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 ≥ 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 <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	
Duration, pack years		Duration, pack years	
Other <i>(write in)</i>		Other <i>(write in)</i>	

Notes:

FEV1/FVC

COPD subjects <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
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 (mild)		FEV1/FVC <0.70 and FEV1 ≥ 80% predicted (mild)	
GOLD, stage 0 Cough, FEV1/FVC >0.70		GOLD, stage 0 Cough, FEV1/FVC >0.70	

COPD subjects <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
GOLD, stage 1 FEV1/FVC <0.70, FEV1 \geq 80% pred		GOLD, stage 1 FEV1/FVC <0.70, FEV1 \geq 80% pred	
GOLD, stage 2 FEV1/FVC <0.70, FEV1 \geq 30% and < 80% pred		GOLD, stage 2 FEV1/FVC <0.70, FEV1 \geq 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 <i>(write in)</i>		Other <i>(write in)</i>	

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 <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	
Duration, pack years		Duration, pack years	
Other <i>(write in)</i>		Other <i>(write in)</i>	

Notes:

FEV1/FVC

COPD subjects <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
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 (mild)		FEV1/FVC <0.70 and FEV1 ≥ 80% predicted (mild)	
GOLD, stage 0 Cough, FEV1/FVC >0.70		GOLD, stage 0 Cough, FEV1/FVC >0.70	

COPD subjects <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
GOLD, stage 1 FEV1/FVC <0.70, FEV1 \geq 80% pred		GOLD, stage 1 FEV1/FVC <0.70, FEV1 \geq 80% pred	
GOLD, stage 2 FEV1/FVC <0.70, FEV1 \geq 30% and < 80% pred		GOLD, stage 2 FEV1/FVC <0.70, FEV1 \geq 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 <i>(write in)</i>		Other <i>(write in)</i>	

Notes:

Subgroup 2 _____

COPD		COPD	
<i>(write in)</i> _____		<i>(write in)</i> _____	
# Subjects:		# Subjects:	
Mean age		Mean age	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
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 <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
Current smoker		Current smoker	
Ex-smoker		Ex-smoker	
Never smoked		Never smoked	
Duration, pack years		Duration, pack years	
Other <i>(write in)</i>		Other <i>(write in)</i>	

Notes:

FEV1/FVC

COPD subjects <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
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 (mild)		FEV1/FVC <0.70 and FEV1 ≥ 80% predicted (mild)	
GOLD, stage 0* Cough, FEV1/FVC >0.70		GOLD, stage 0 Cough, FEV1/FVC >0.70	

COPD subjects <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
GOLD, stage 1 FEV1/FVC <0.70, FEV1 \geq 80% pred		GOLD, stage 1 FEV1/FVC <0.70, FEV1 \geq 80% pred	
GOLD, stage 2 FEV1/FVC <0.70, FEV1 \geq 30% and < 80% pred		GOLD, stage 2 FEV1/FVC <0.70, FEV1 \geq 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 <i>(write in)</i>		Other <i>(write in)</i>	

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 <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
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 <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
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 <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
Age, years <i>(write in)</i>		Age, years <i>(write in)</i>	
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 <i>(write in)</i>		No COPD / Control <i>(write in)</i>	

QUALITY OF LIFE

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

COPD subjects <i>(write in)</i>		No COPD / Control <i>(write in)</i>	
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

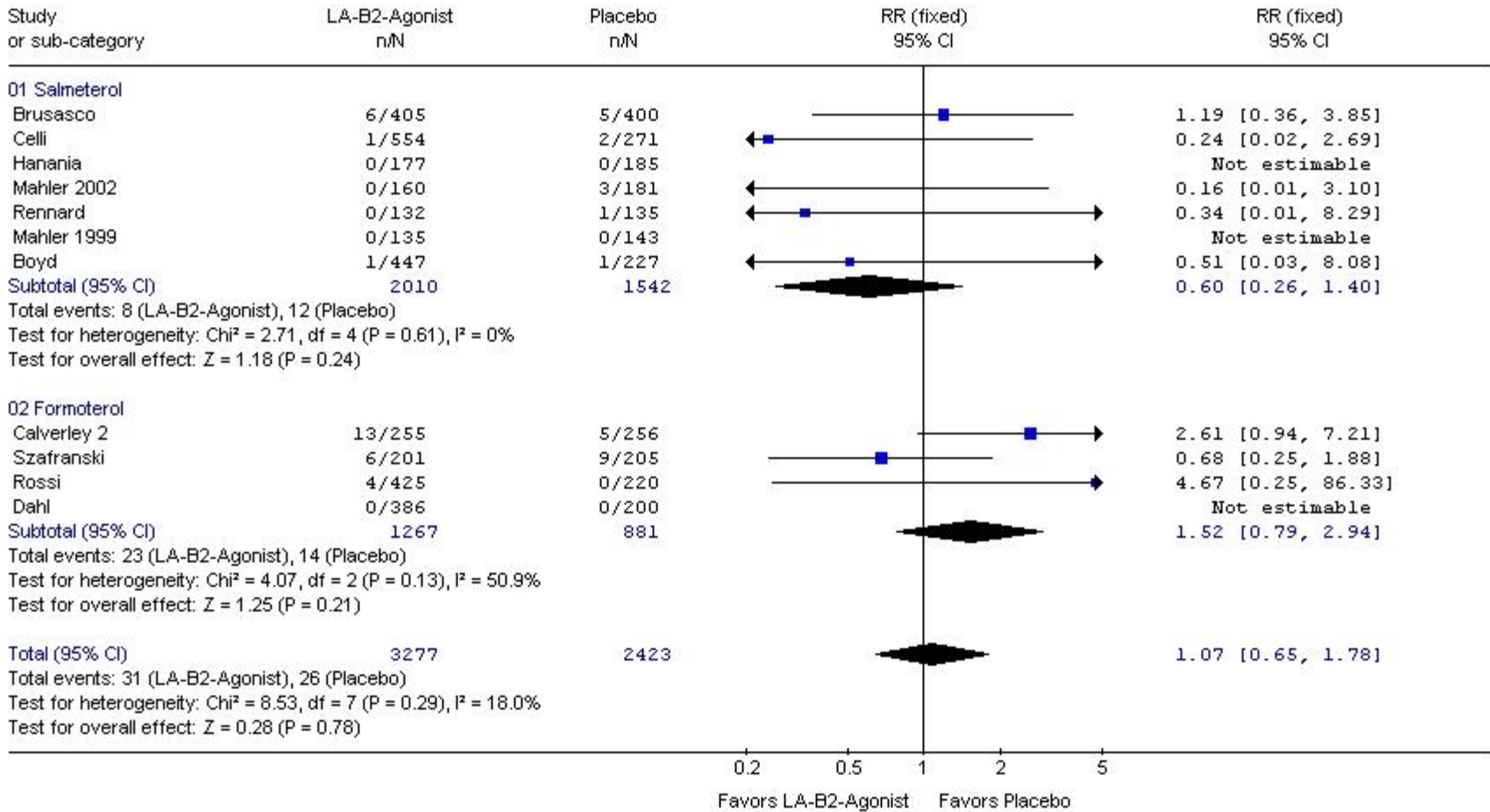
** Chronic Respiratory Questionnaire

For SUBGROUPS - photocopy Outcomes pages and attach

Appendix D
Evidence Tables
and Figures

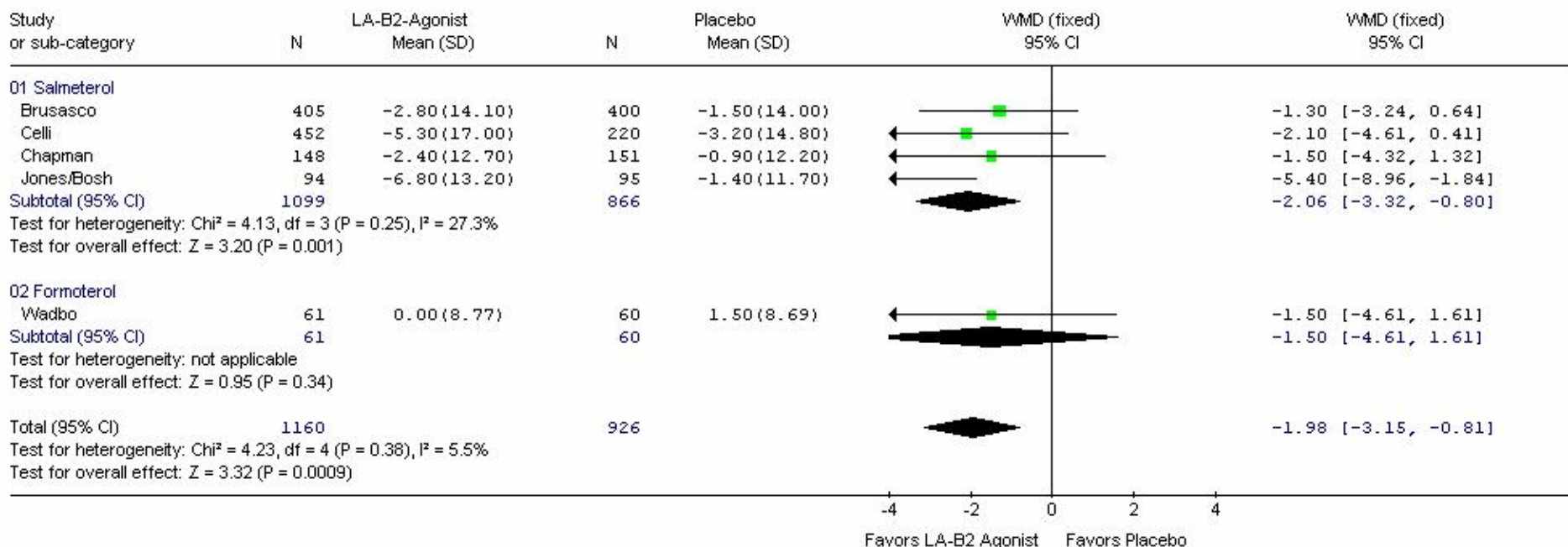
Evidence Figure 1

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



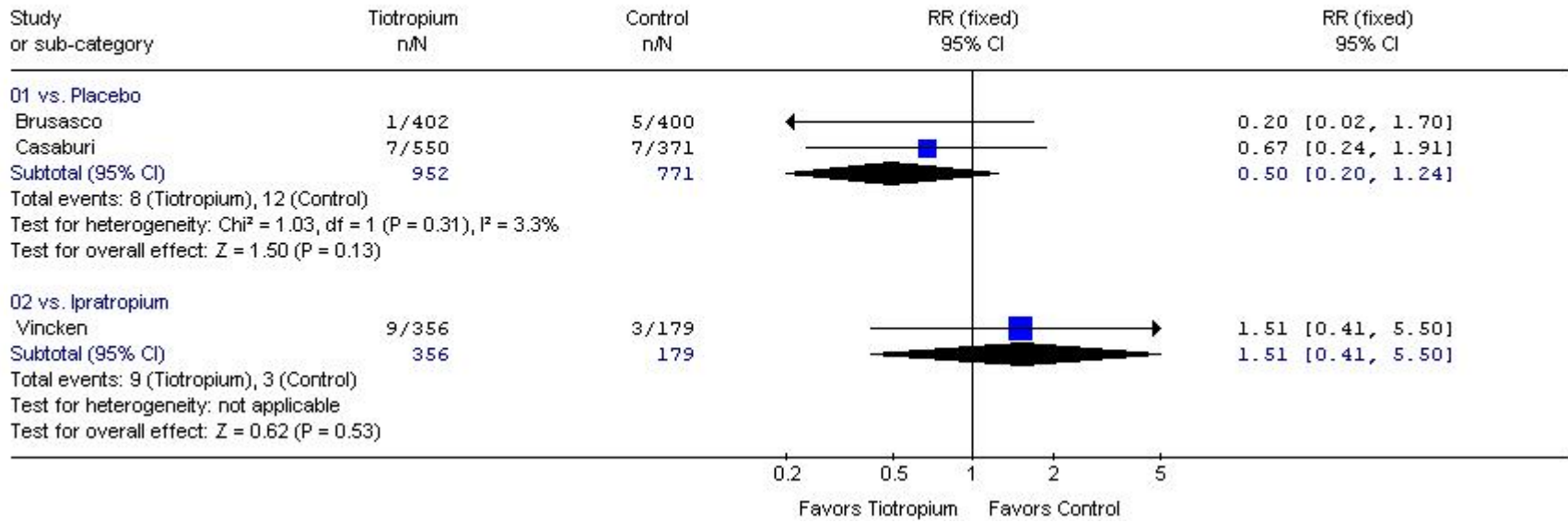
Evidence Figure 2.

Review: Interventions for COPD using Spirometry
 Comparison: 01 Long-Acting B2-Agonists vs. Placebo
 Outcome: 03 St George Respiratory Questionnaire: Change per group



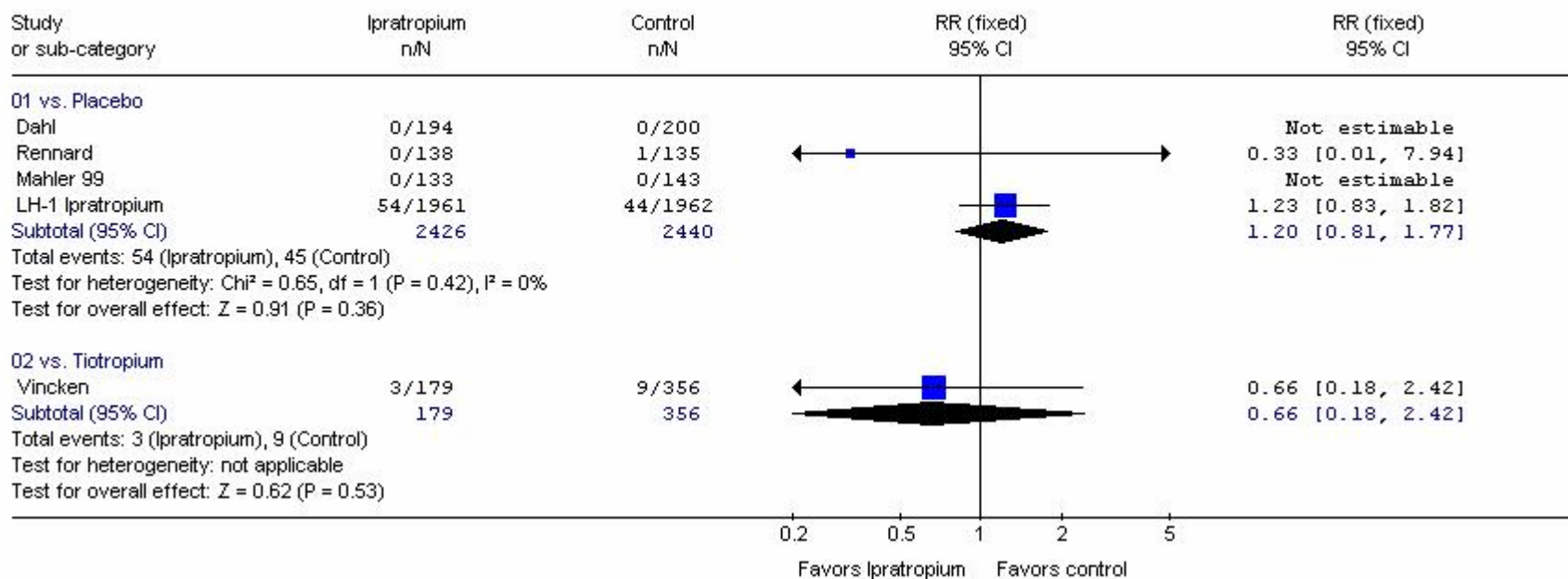
Evidence Figure 3.

Review: Inhaled Therapies for the Management of COPD
 Comparison: 02 Tiotropium vs. Placebo or Ipratropium
 Outcome: 02 Mortality



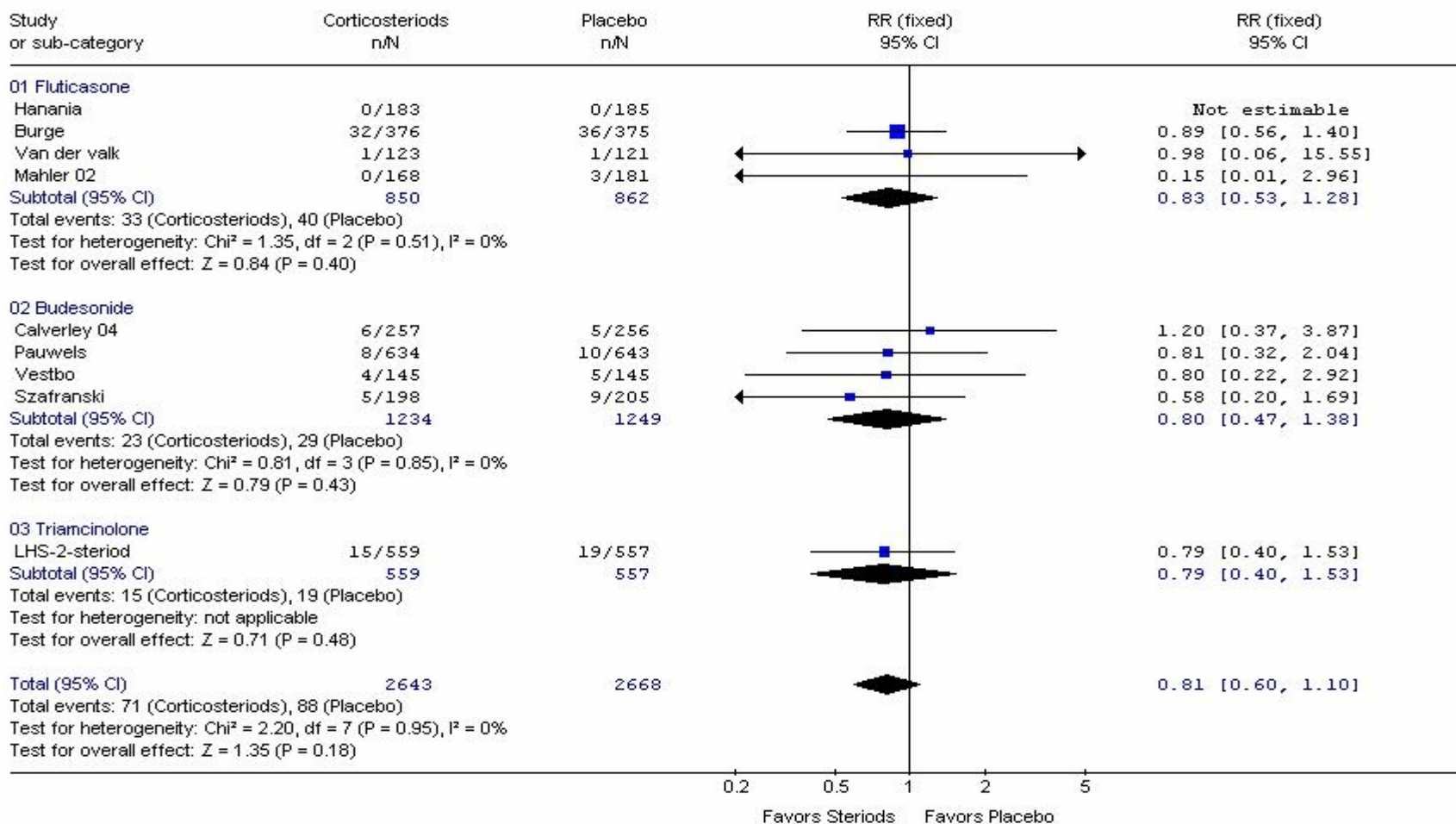
Evidence Figure 4.

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



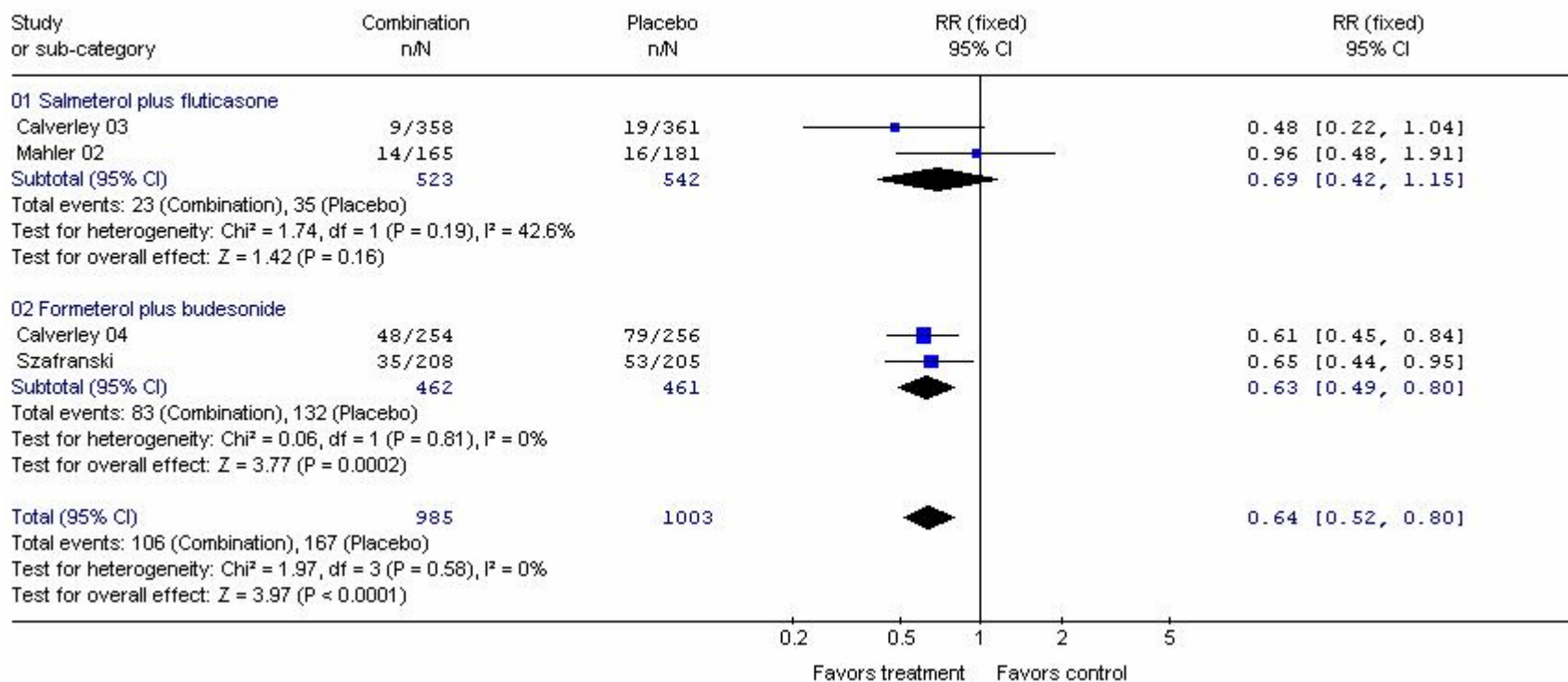
Evidence Figure 5.

Review: Interventions for COPD using Spirometry
 Comparison: 04 Inhaled Corticosteroids vs. Placebo
 Outcome: 02 Mortality



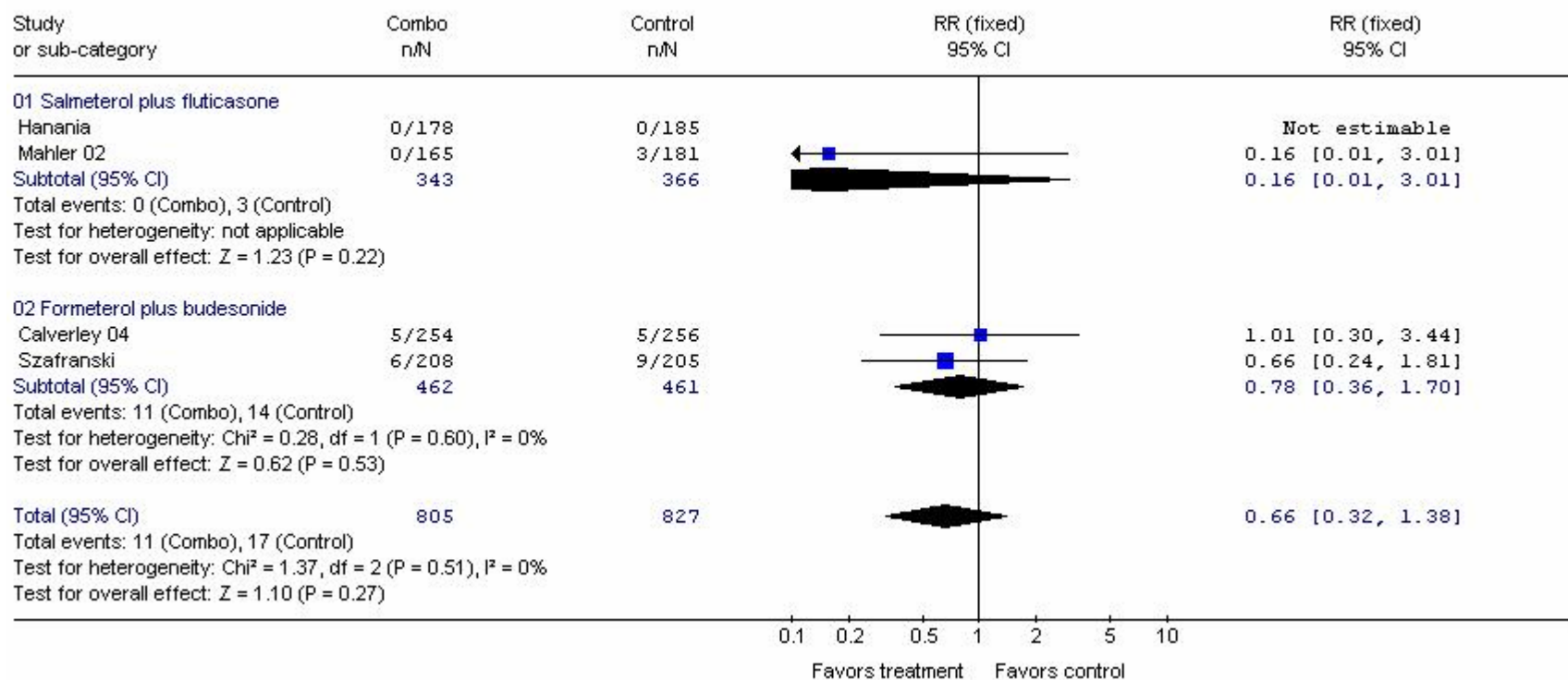
Evidence Figure 6.

Review: Interventions for COPD using Spirometry
 Comparison: 08 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Placebo
 Outcome: 01 Exacerbations



Evidence Figure 7.

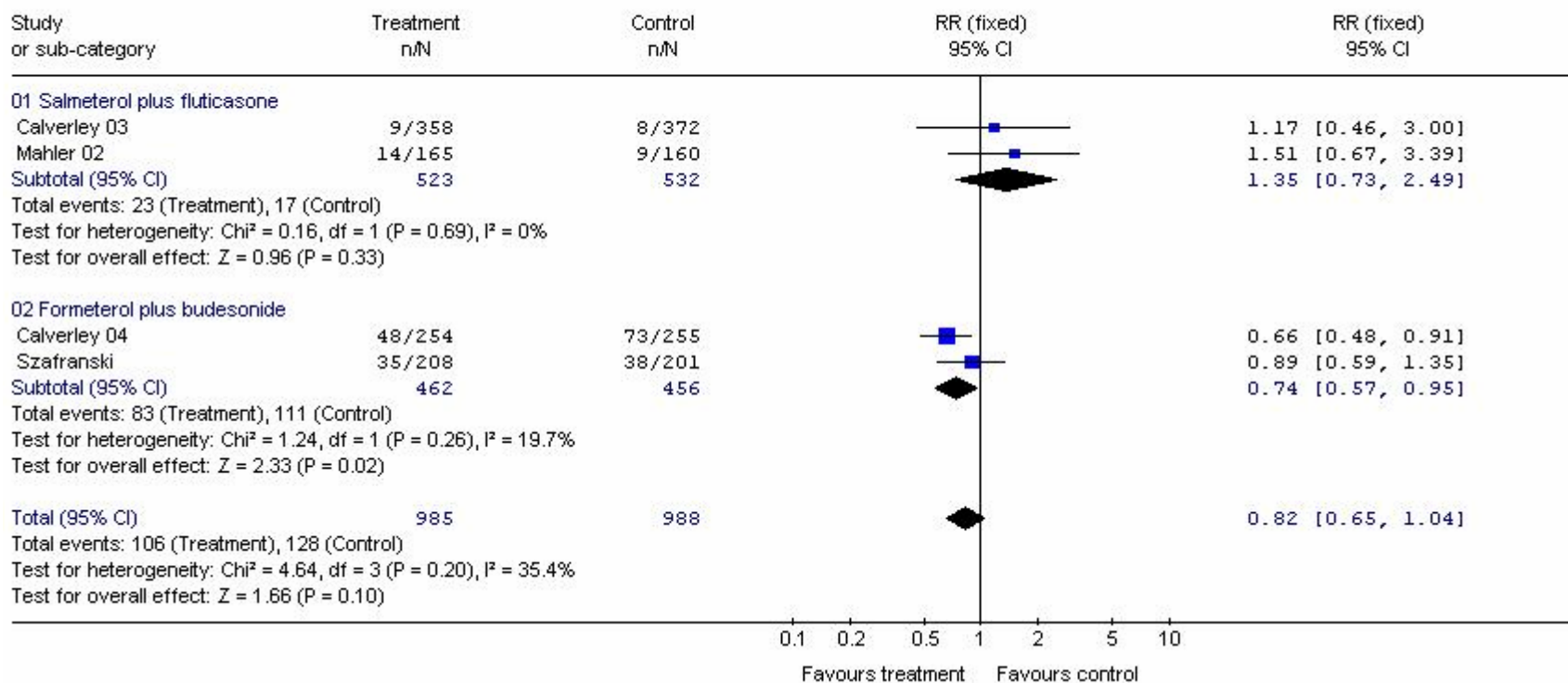
Review: Interventions for COPD using Spirometry
 Comparison: 08 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Placebo
 Outcome: 02 Mortality



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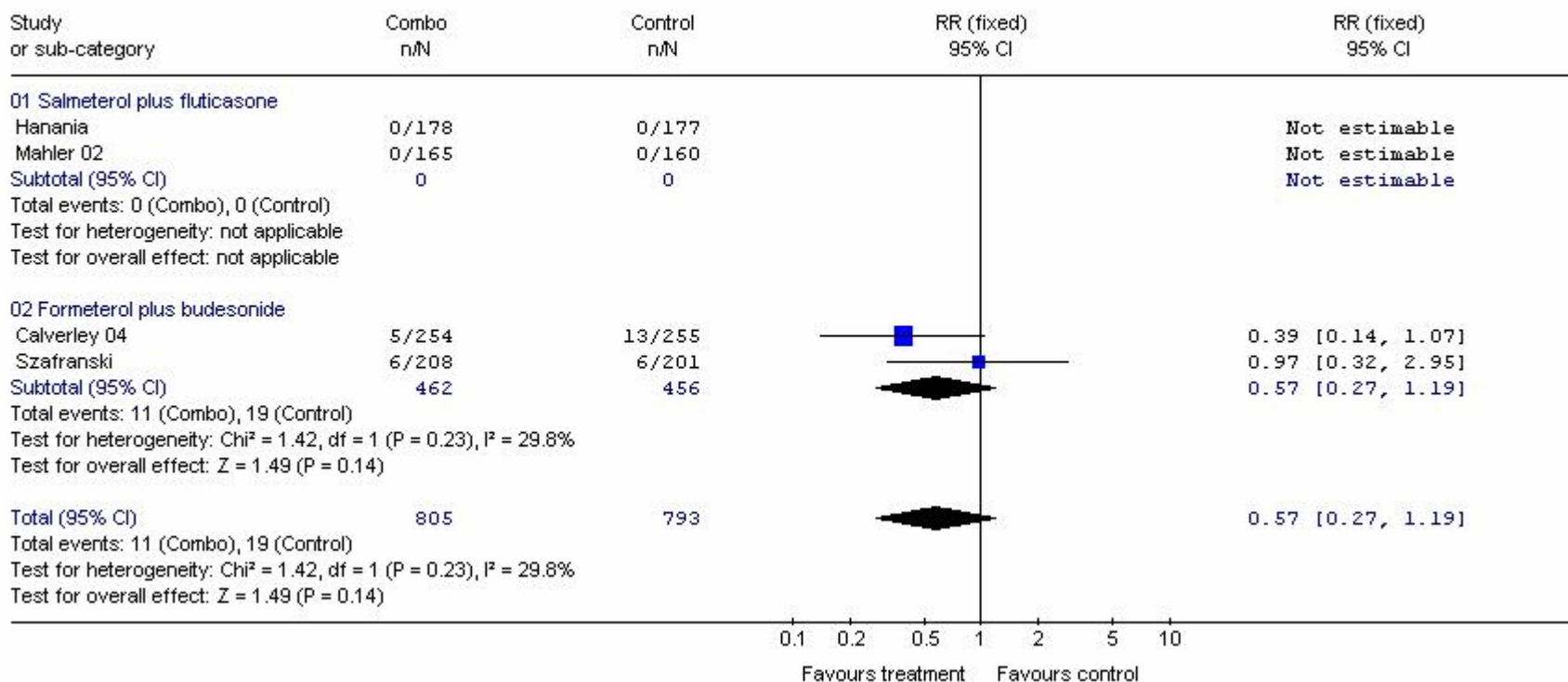
Evidence Figure 8.

Review: Interventions for COPD using Spirometry
 Comparison: 09 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Long-Acting B2-Agonists
 Outcome: 01 Exacerbations



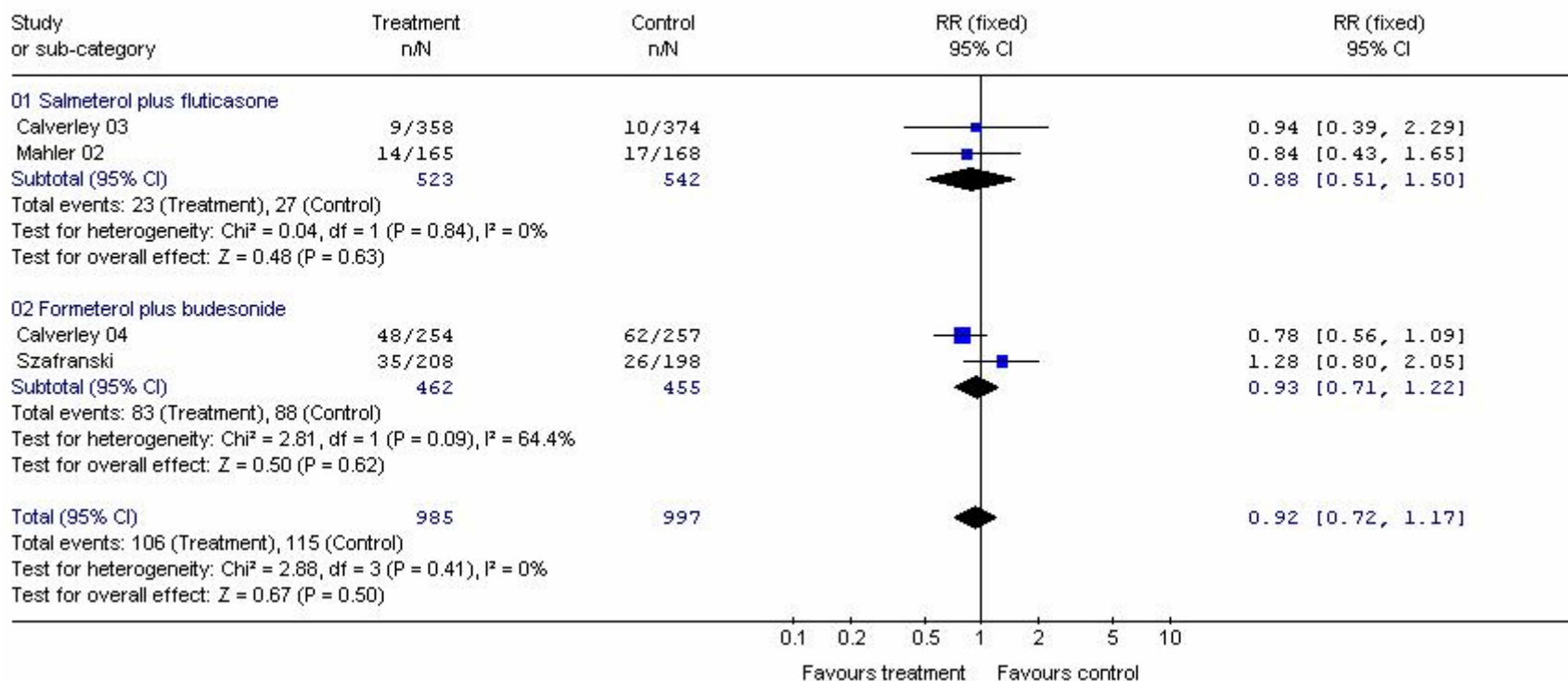
Evidence Figure 9.

Review: Interventions for COPD using Spirometry
 Comparison: 09 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Long-Acting B2-Agonists
 Outcome: 02 Mortality



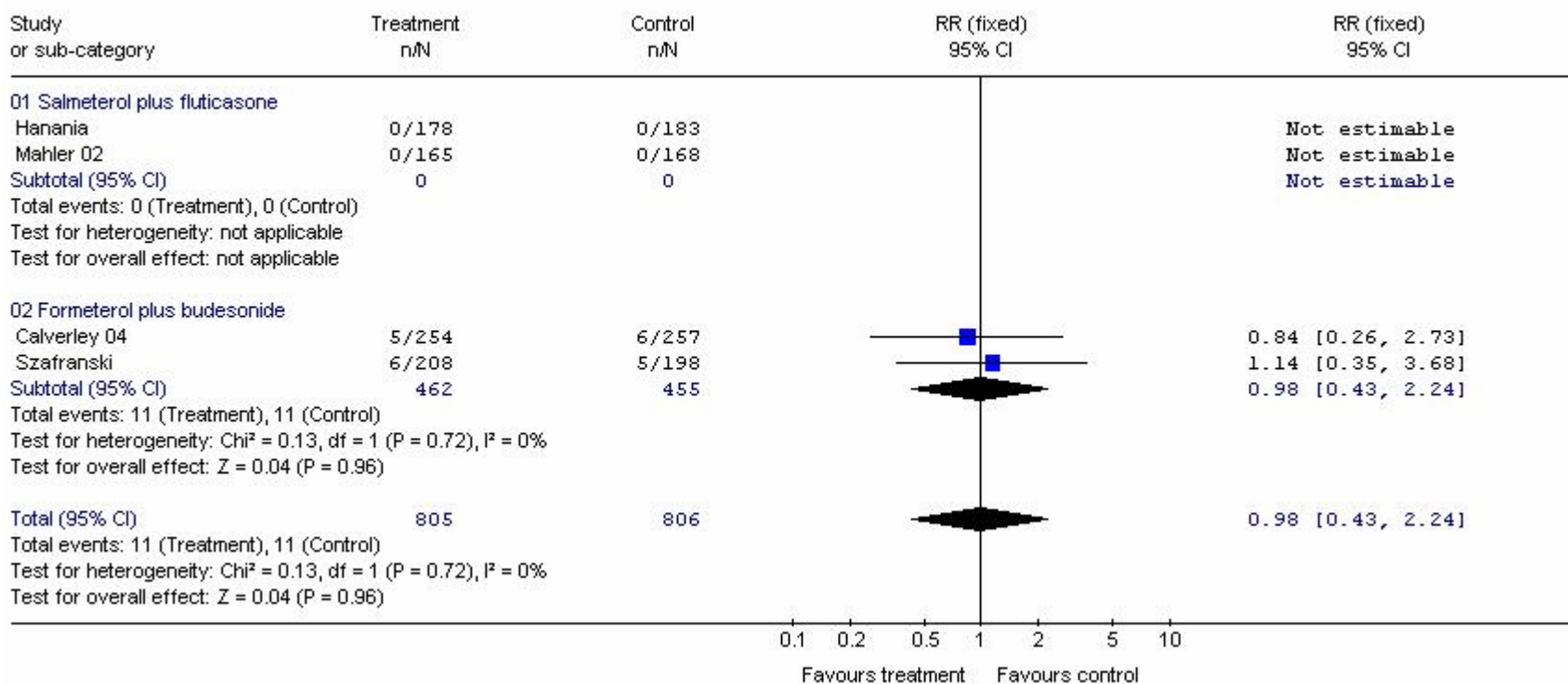
Evidence Figure 10.

Review: Interventions for COPD using Spirometry
 Comparison: 10 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Corticosteroids
 Outcome: 01 Exacerbations



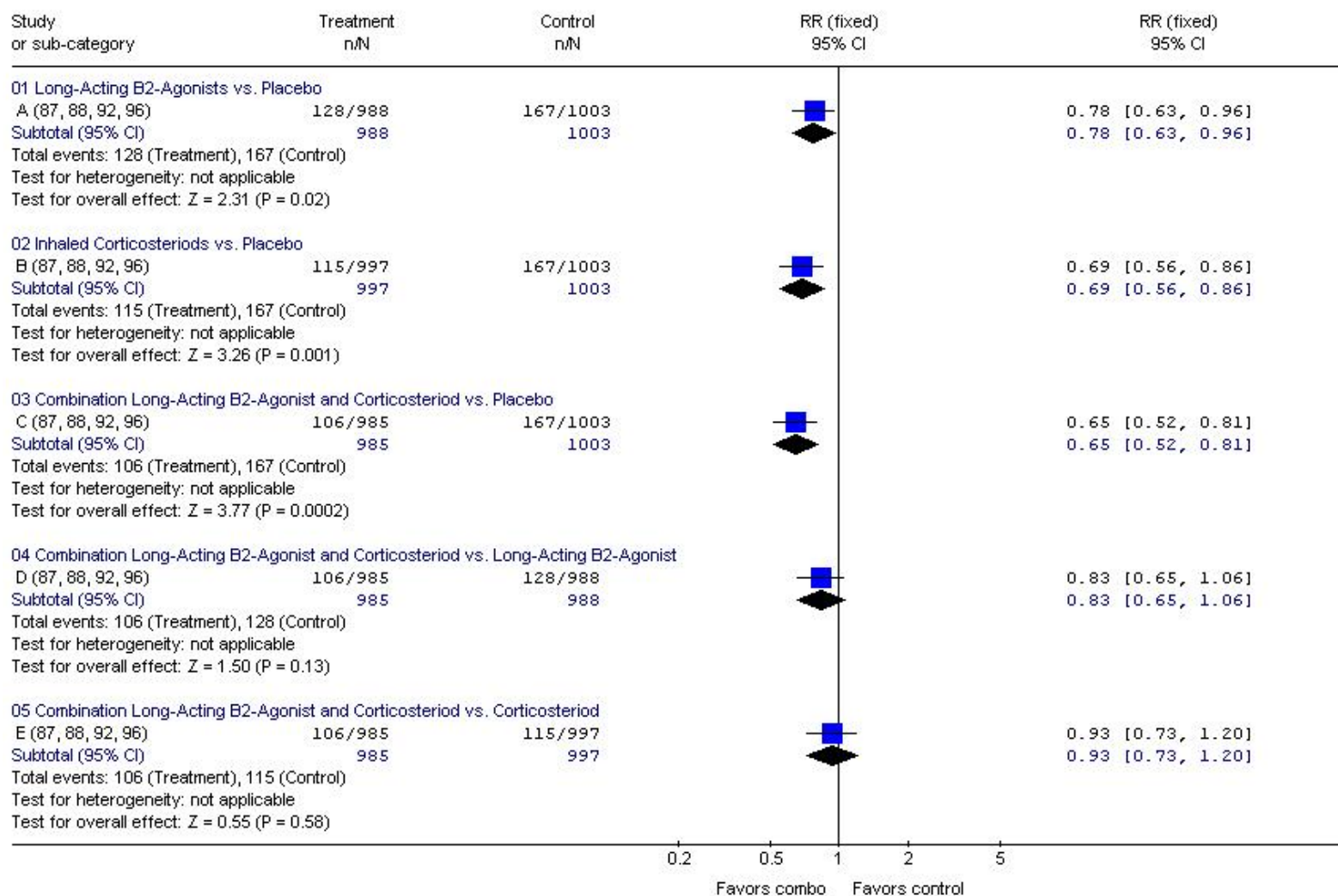
Evidence Figure 11.

Review: Interventions for COPD using Spirometry
 Comparison: 10 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Corticosteroids
 Outcome: 02 Mortality



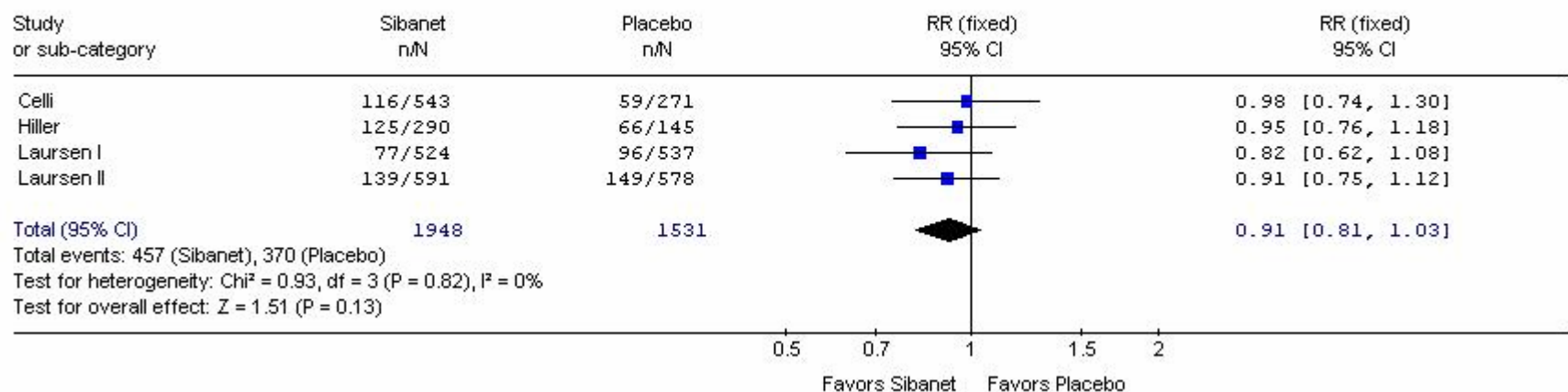
Evidence Figure 12.

Review: Combination Long-Acting B2-Agonists and Corticosteroid Analyses
 Comparison: 01 Long-Acting B2-Agonists, Corticosteroids and Combination vs. Control
 Outcome: 01 Exacerbations



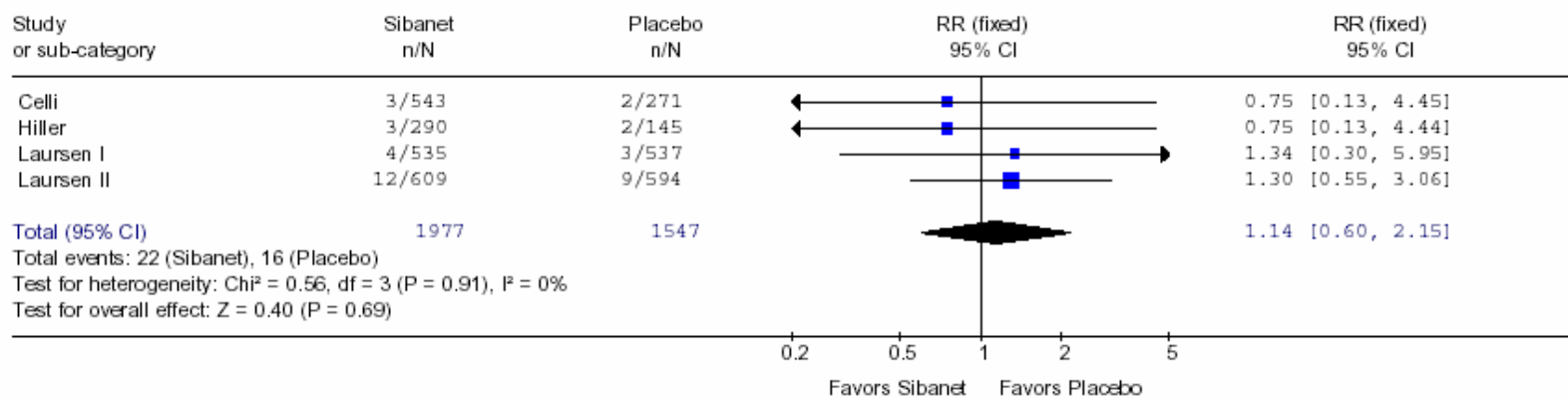
Evidence Figure 13.

Review: Interventions for COPD using Spirometry
 Comparison: 05 Sibanet vs. Placebo
 Outcome: 01 Exacerbations



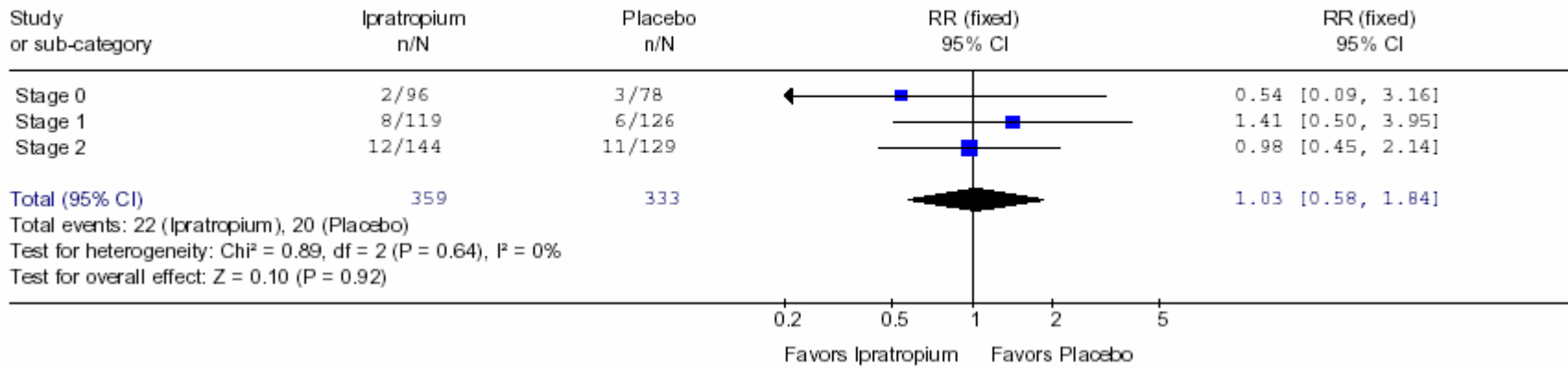
Evidence Figure 14.

Review: Interventions for COPD using Spirometry
 Comparison: 05 Sibanet vs. Placebo
 Outcome: 02 Mortality



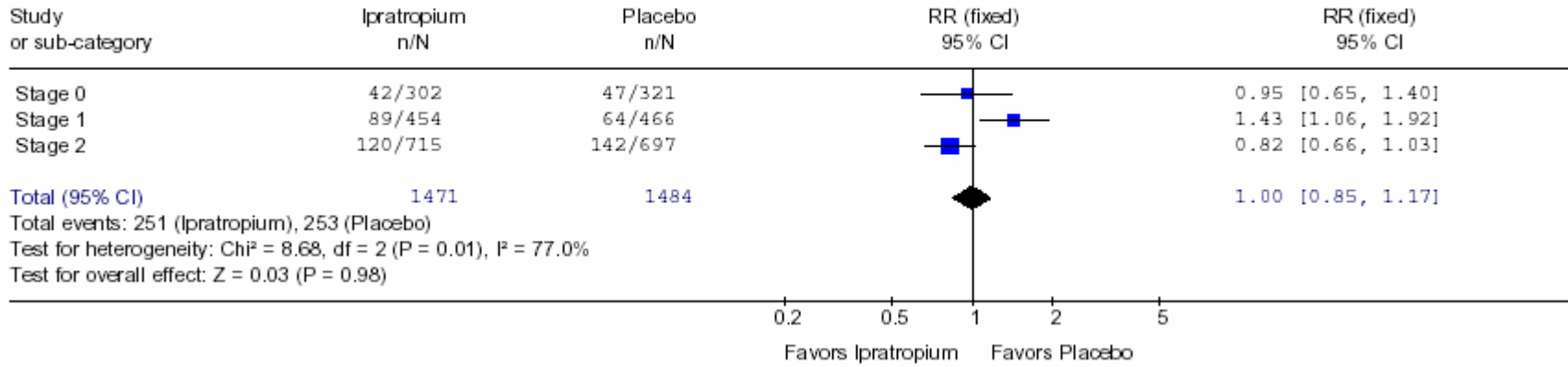
Evidence Figure 15.

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



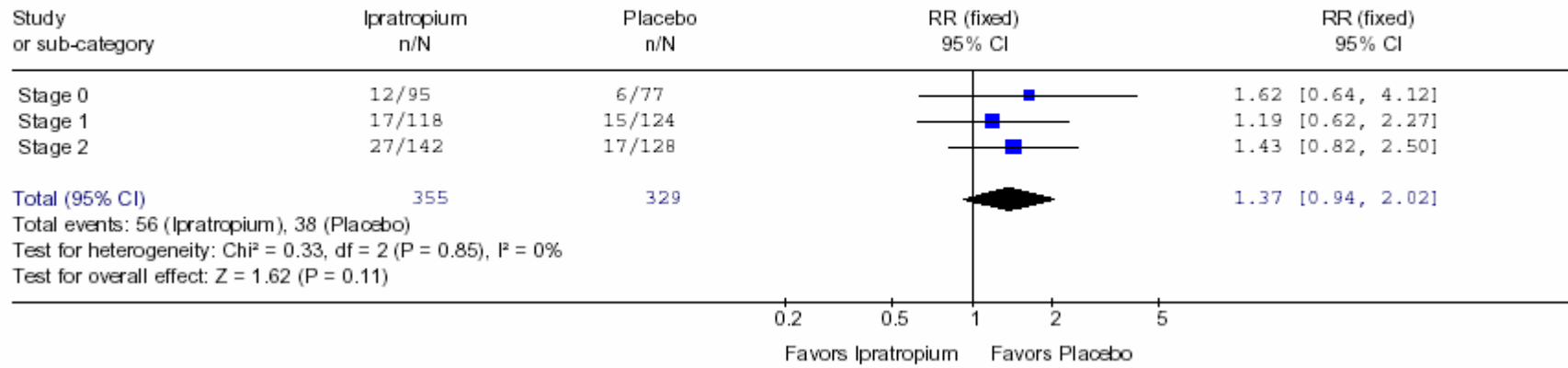
Evidence Figure 16.

Review: LH-1 Relative Risks
 Comparison: 01 Ipratropium versus Placebo
 Outcome: 02 Cough and sputum at year 3: Subjects with any symptom at baseline



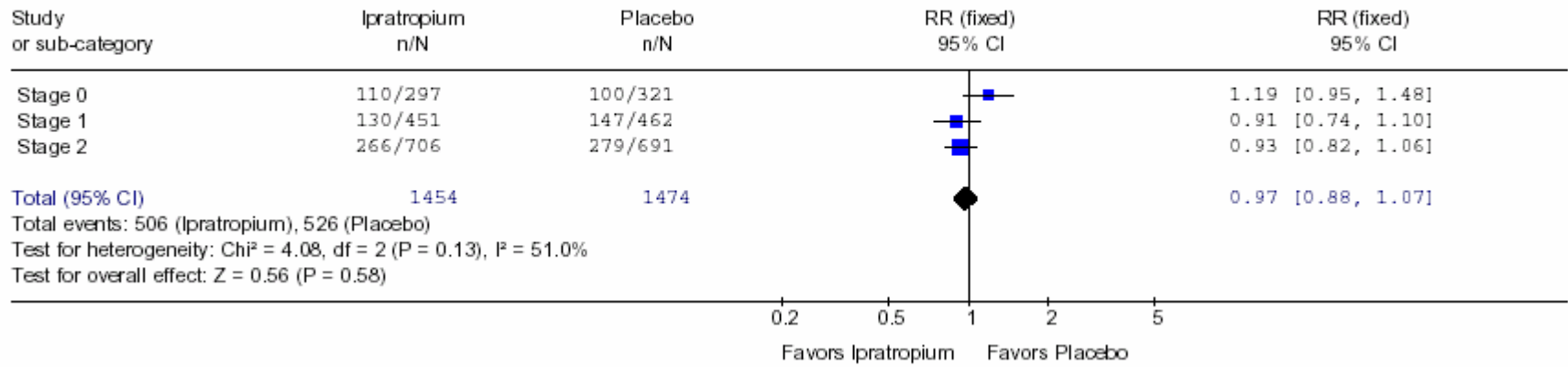
Evidence Figure 17.

Review: LH-1 Relative Risks
 Comparison: 01 Ipratropium versus Placebo
 Outcome: 03 Dyspnea at year 3: Subjects with no symptoms at baseline



Evidence Figure 18.

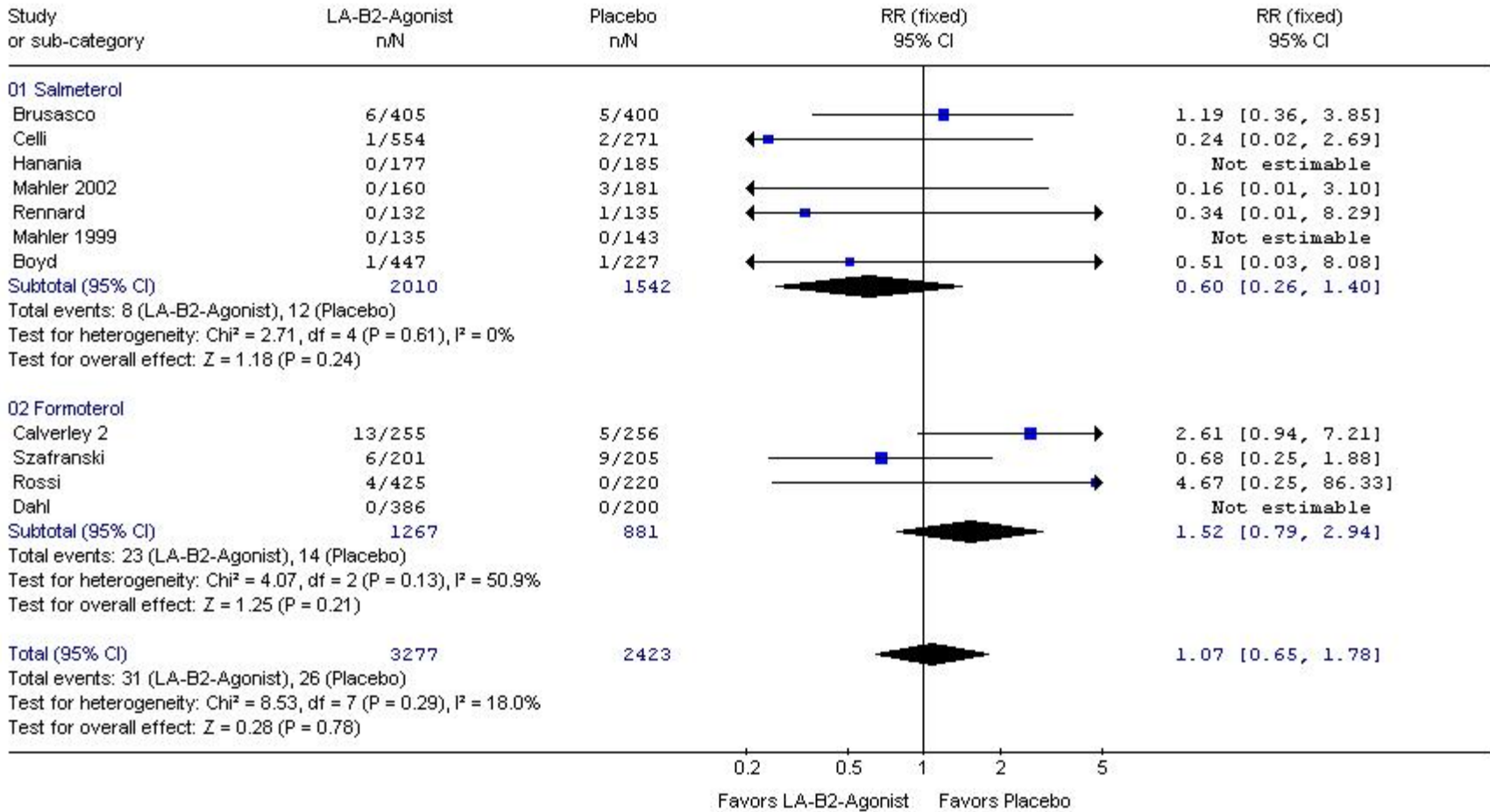
Review: LH-1 Relative Risks
 Comparison: 01 Ipratropium versus Placebo
 Outcome: 04 Dyspnea at year 3: Subjects with any symptom at baseline



Appendix D
Evidence Tables
and Figures

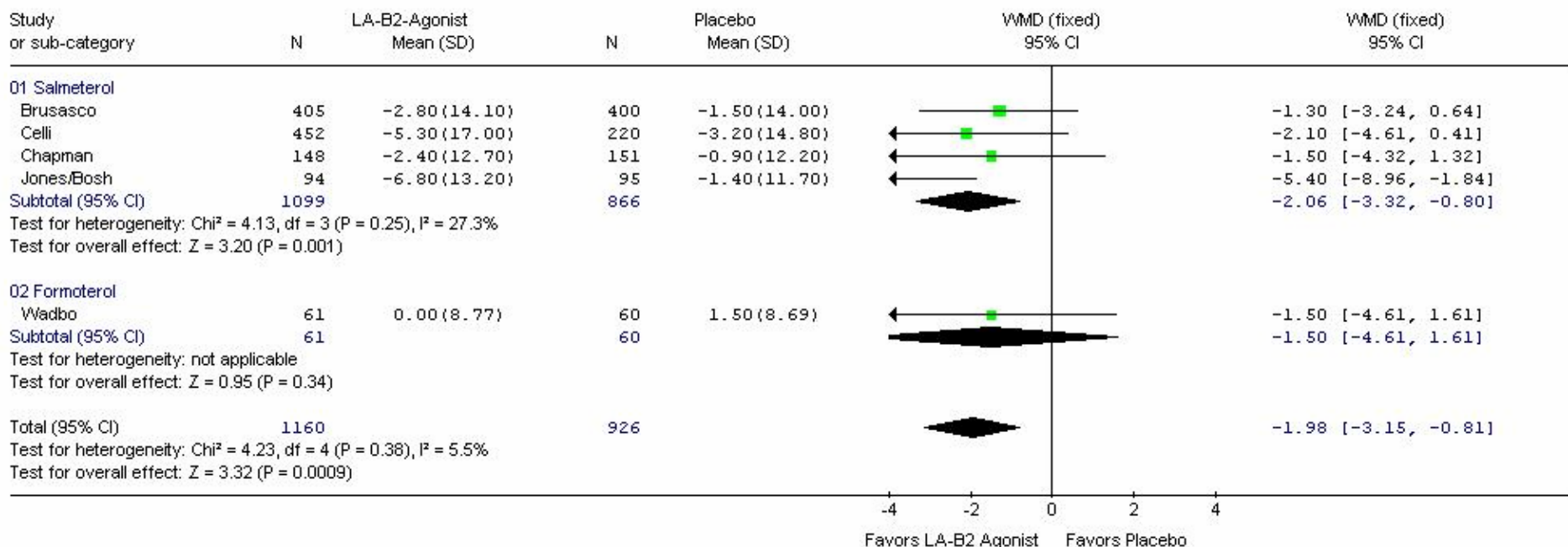
Evidence Figure 1

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



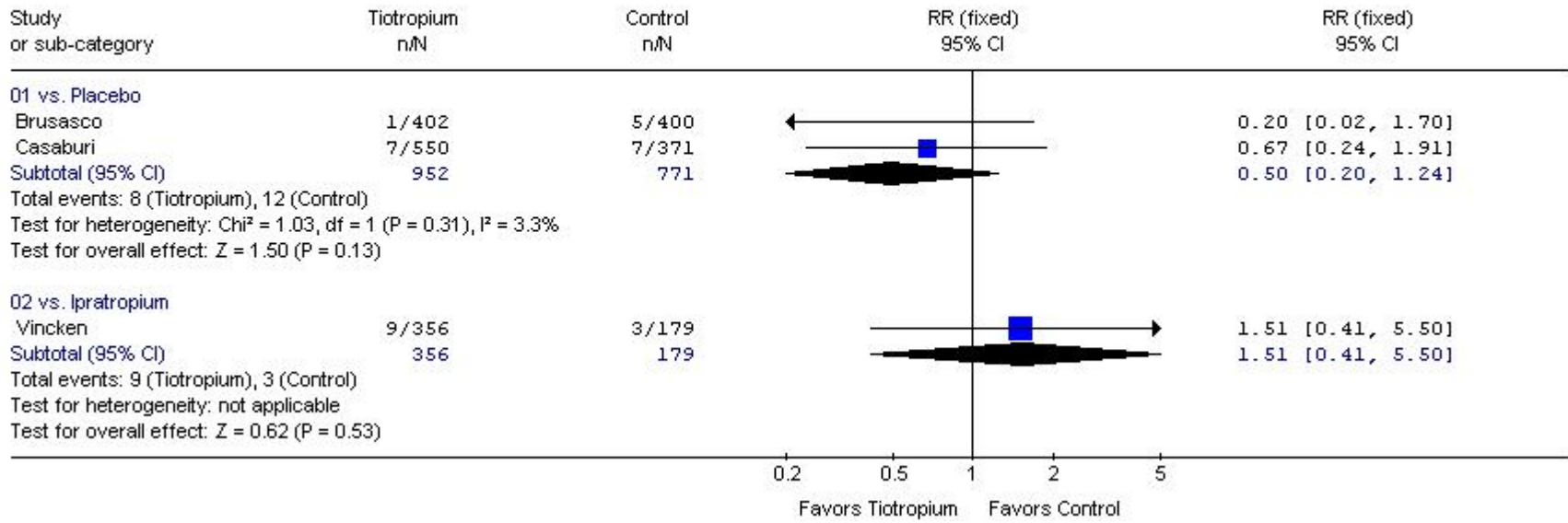
Evidence Figure 2.

Review: Interventions for COPD using Spirometry
 Comparison: 01 Long-Acting B2-Agonists vs. Placebo
 Outcome: 03 St George Respiratory Questionnaire: Change per group



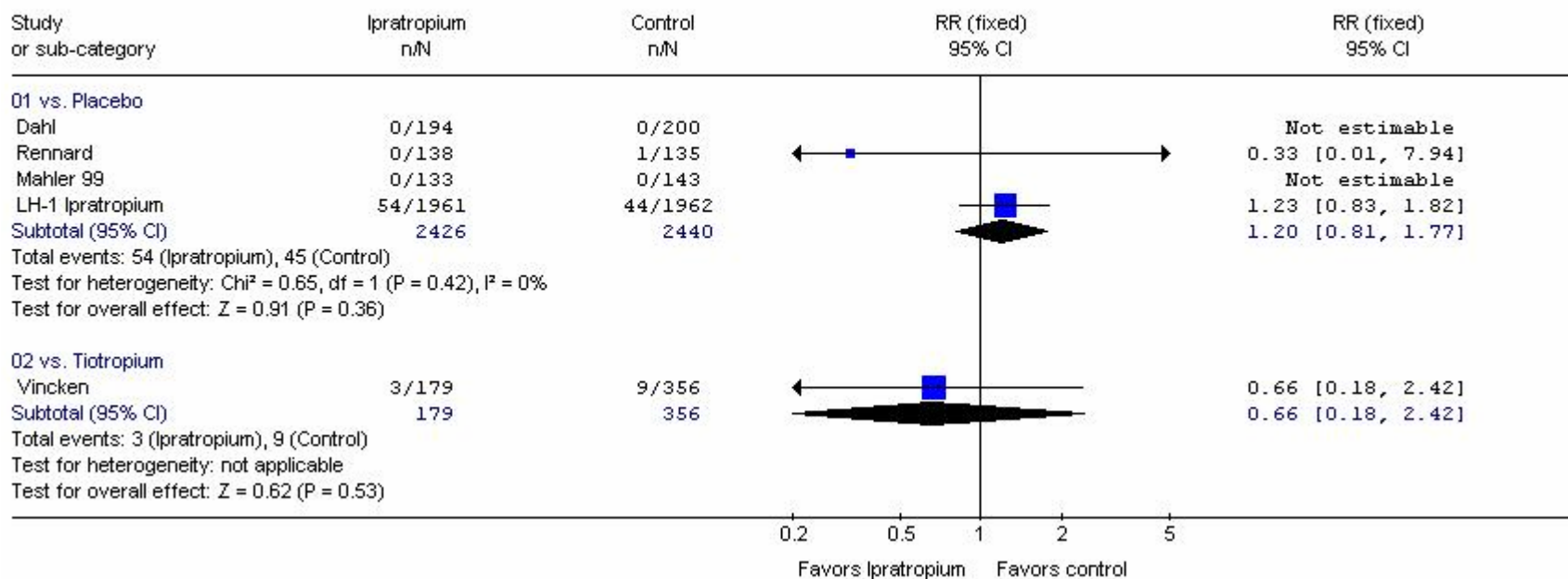
Evidence Figure 3.

Review: Inhaled Therapies for the Management of COPD
 Comparison: 02 Tiotropium vs. Placebo or Ipratropium
 Outcome: 02 Mortality



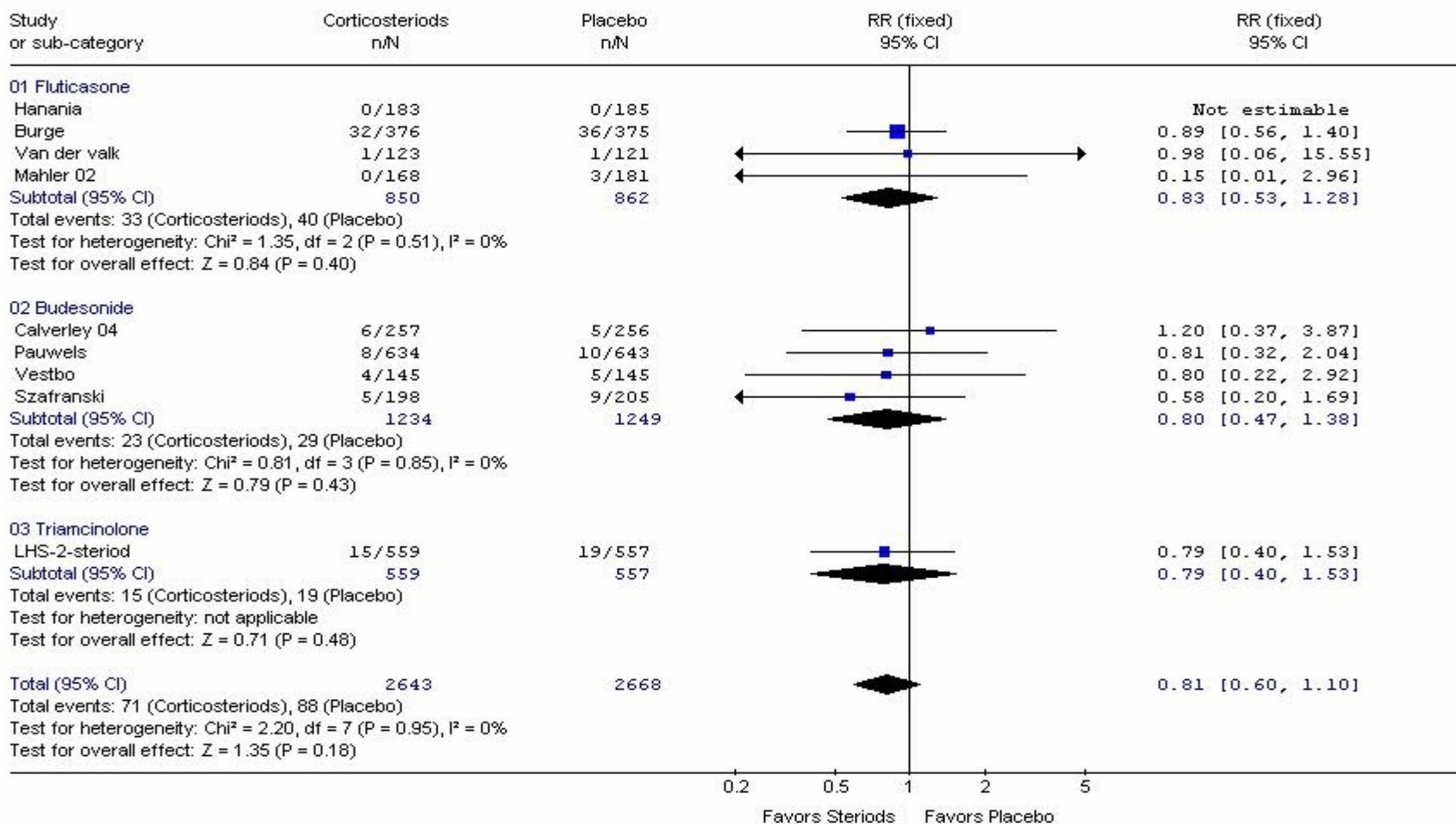
Evidence Figure 4.

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



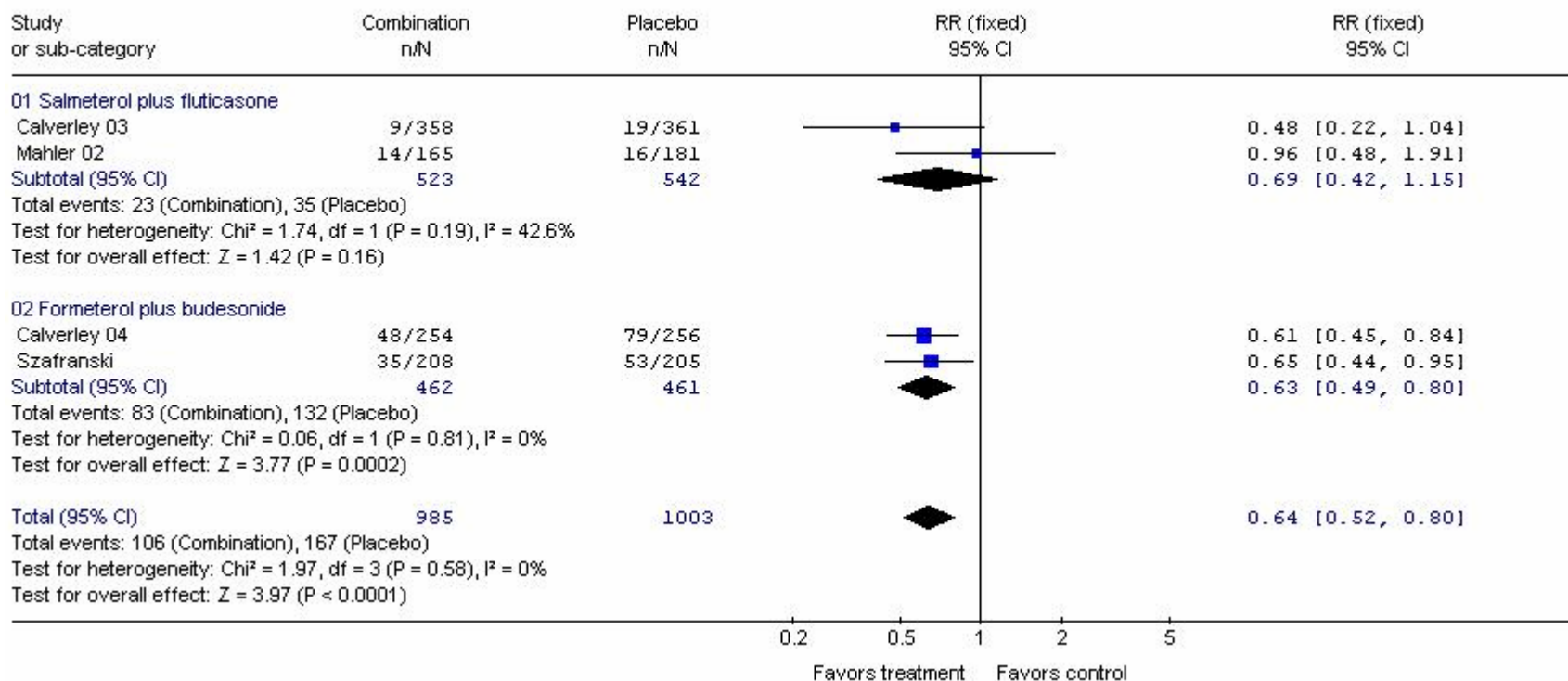
Evidence Figure 5.

Review: Interventions for COPD using Spirometry
 Comparison: 04 Inhaled Corticosteroids vs. Placebo
 Outcome: 02 Mortality



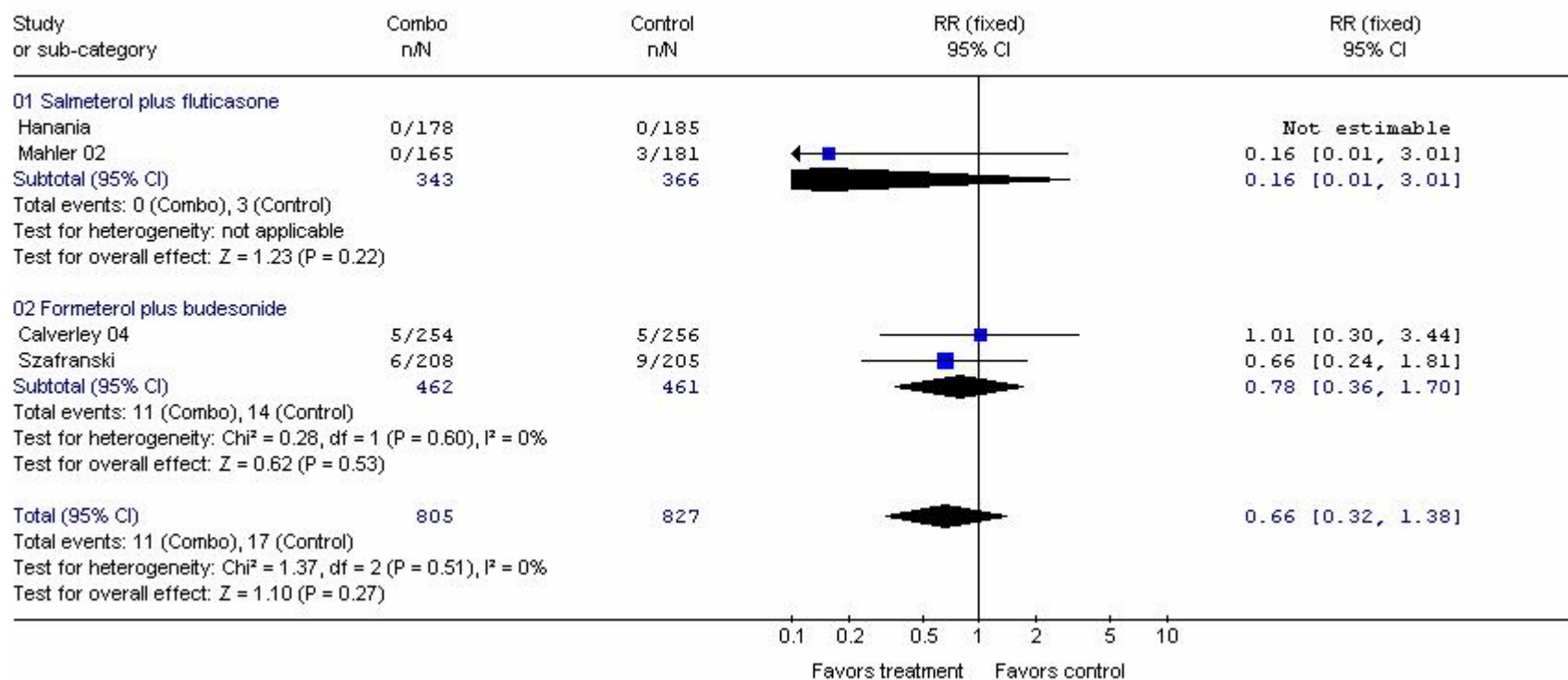
Evidence Figure 6.

Review: Interventions for COPD using Spirometry
 Comparison: 08 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Placebo
 Outcome: 01 Exacerbations



Evidence Figure 7.

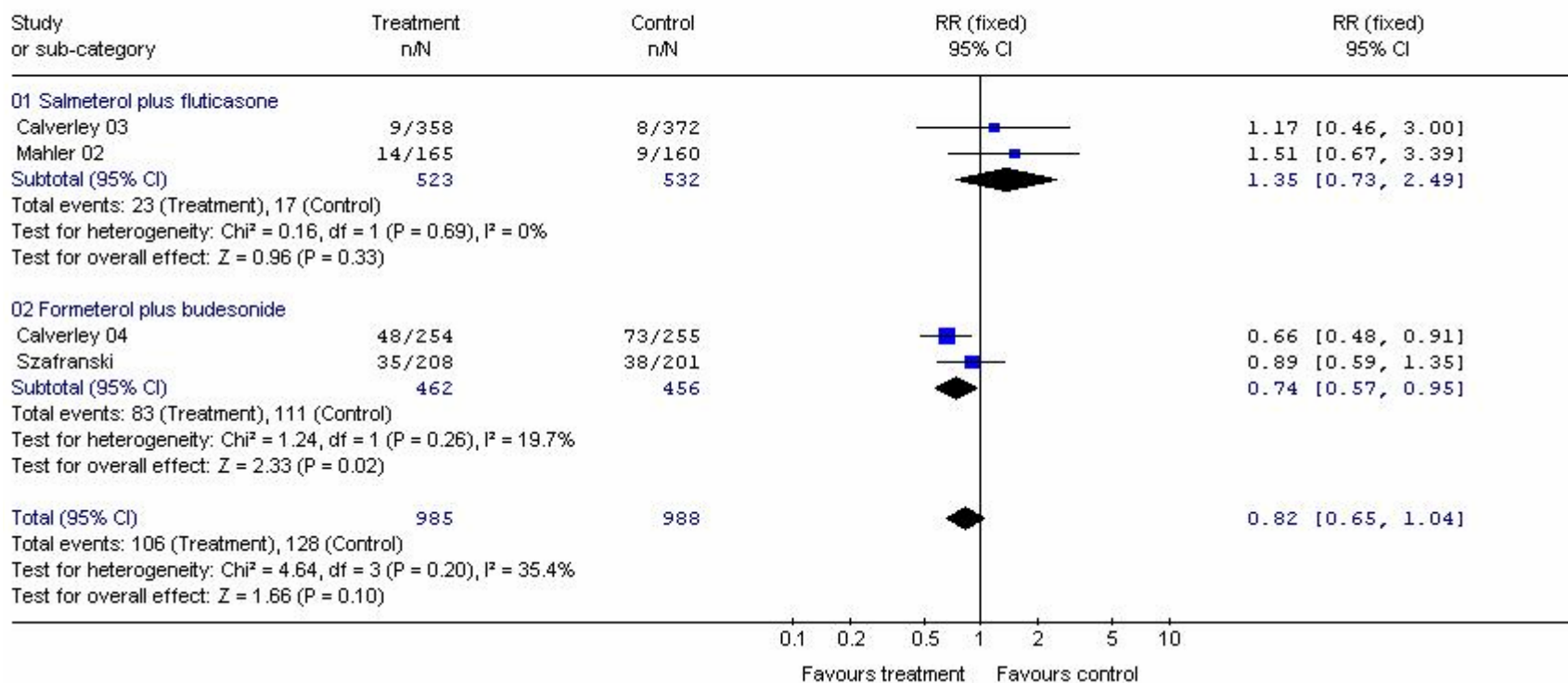
Review: Interventions for COPD using Spirometry
 Comparison: 08 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Placebo
 Outcome: 02 Mortality



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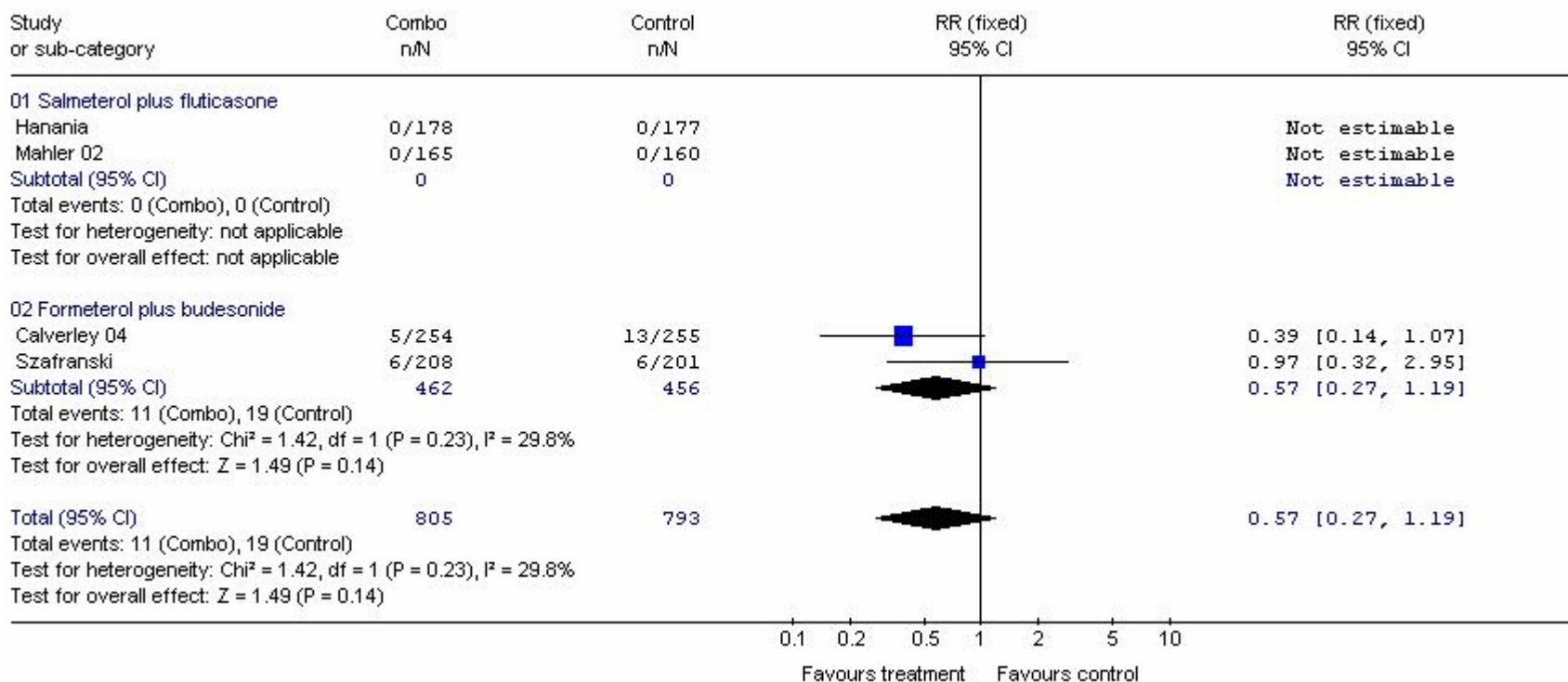
Evidence Figure 8.

Review: Interventions for COPD using Spirometry
 Comparison: 09 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Long-Acting B2-Agonists
 Outcome: 01 Exacerbations



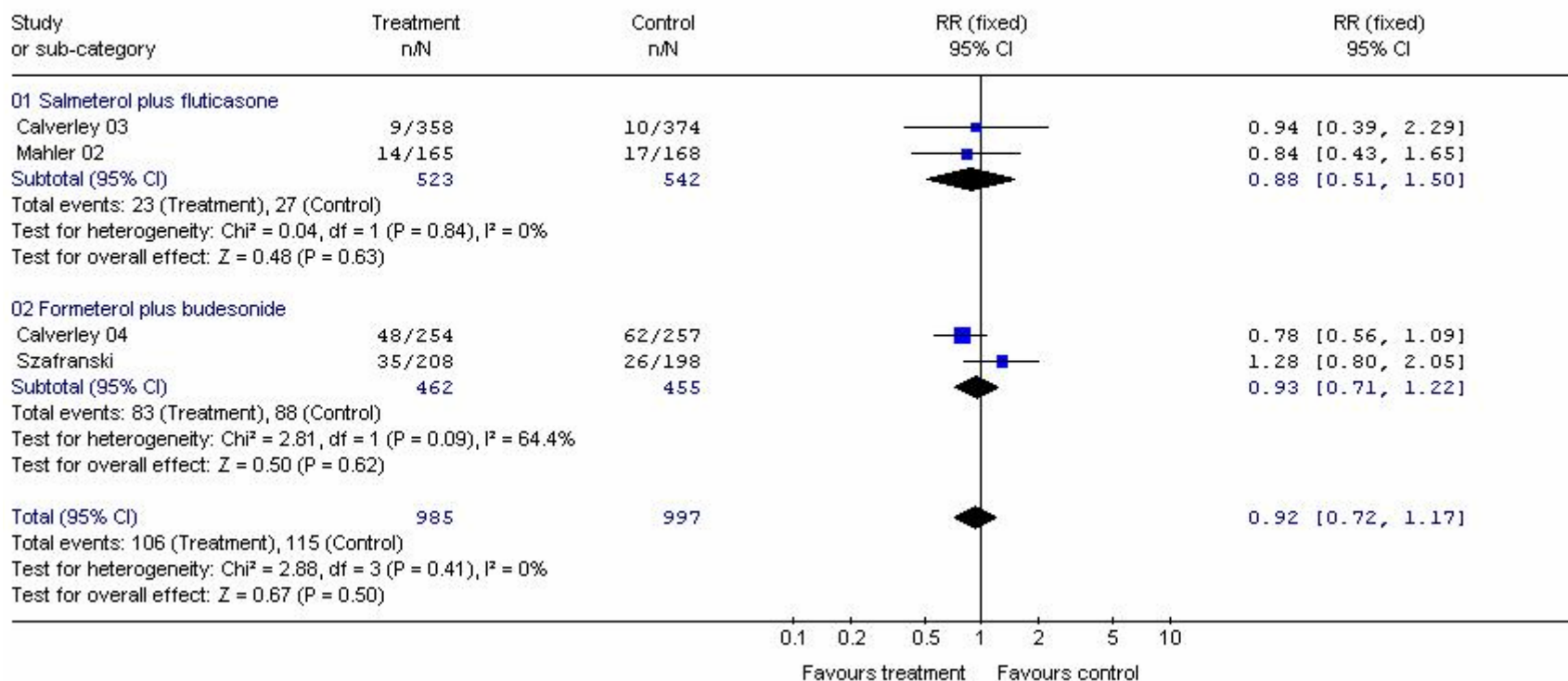
Evidence Figure 9.

Review: Interventions for COPD using Spirometry
 Comparison: 09 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Long-Acting B2-Agonists
 Outcome: 02 Mortality



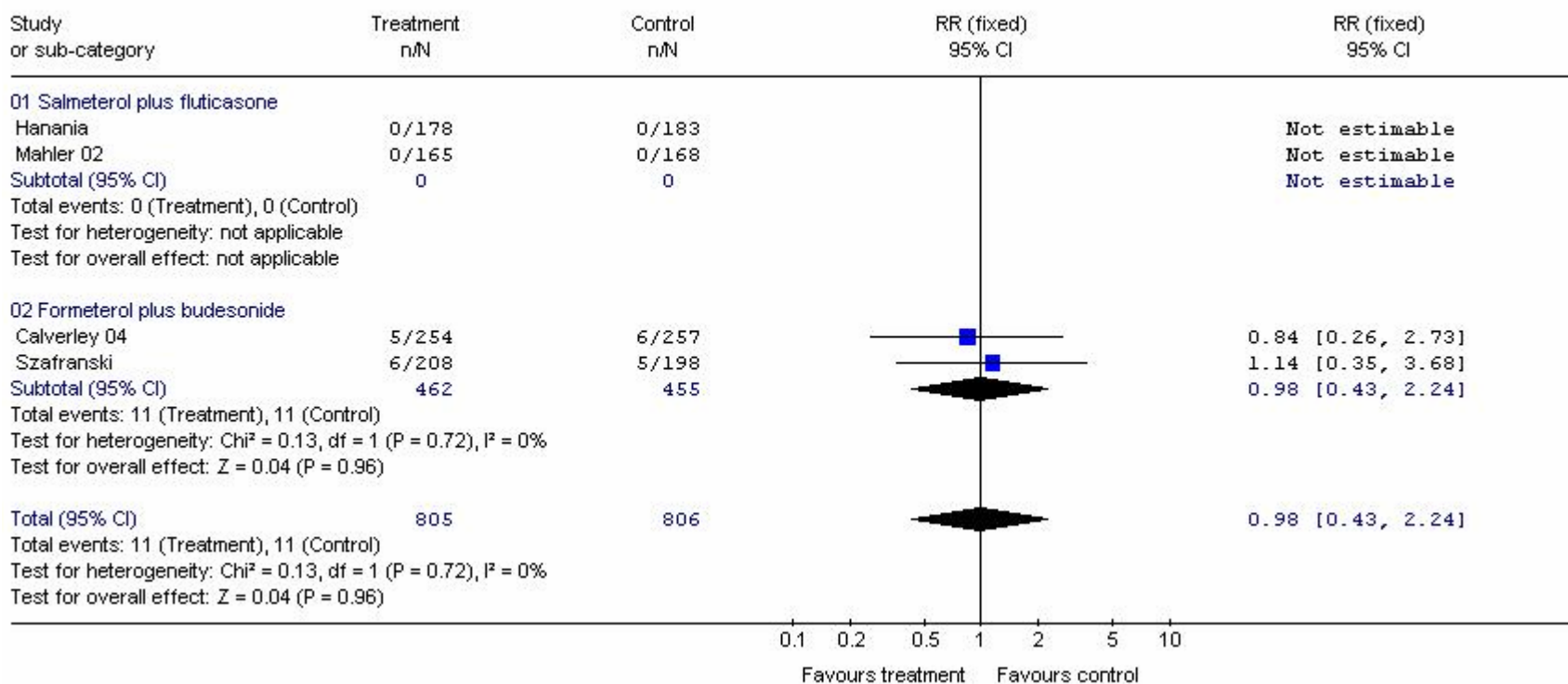
Evidence Figure 10.

Review: Interventions for COPD using Spirometry
 Comparison: 10 Combination of Long-Acting B2-Agonists and Corticosteroids vs. Corticosteroids
 Outcome: 01 Exacerbations



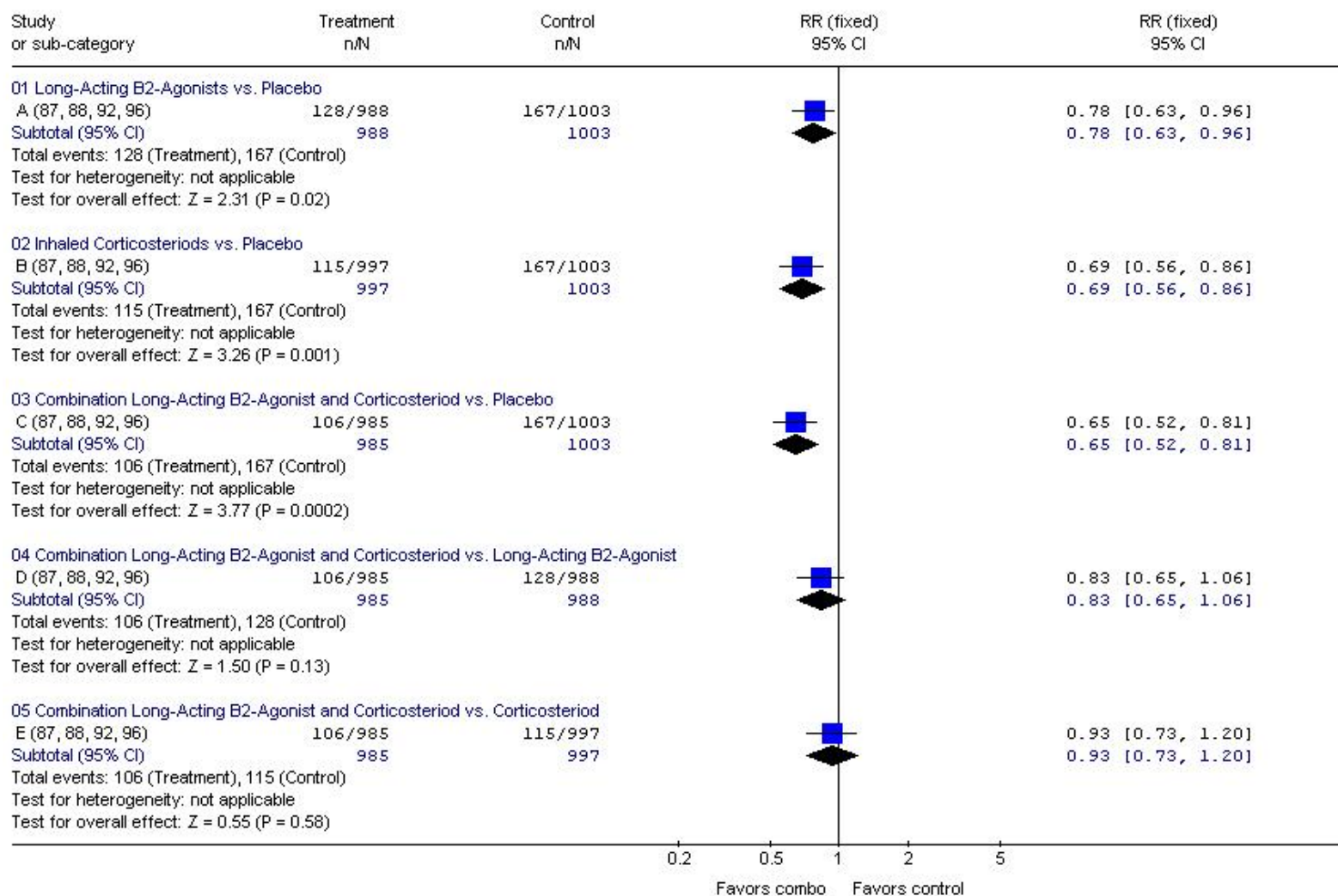
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 Outcome: 02 Mortality



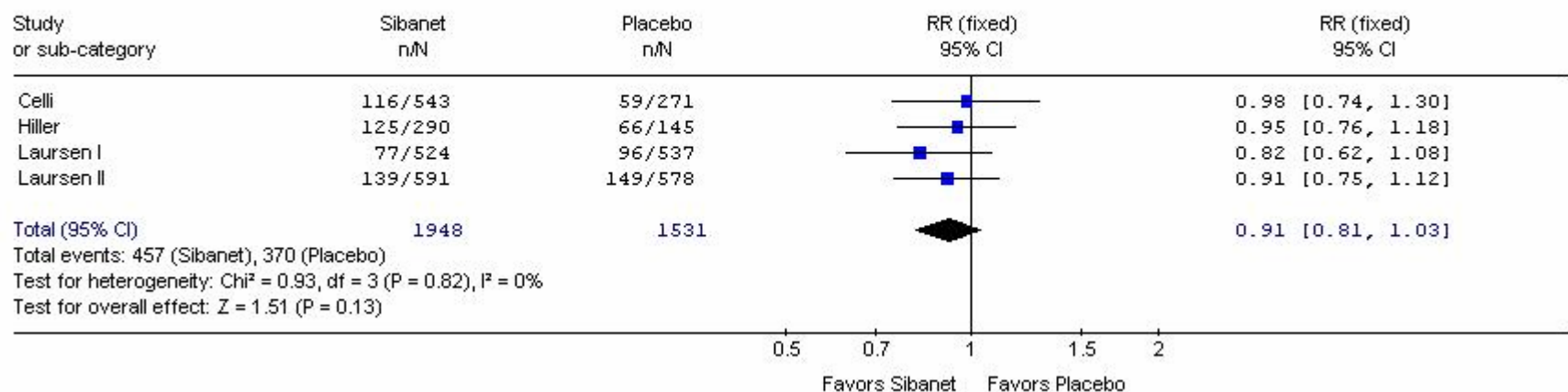
Evidence Figure 12.

Review: Combination Long-Acting B2-Agonists and Corticosteroid Analyses
 Comparison: 01 Long-Acting B2-Agonists, Corticosteroids and Combination vs. Control
 Outcome: 01 Exacerbations



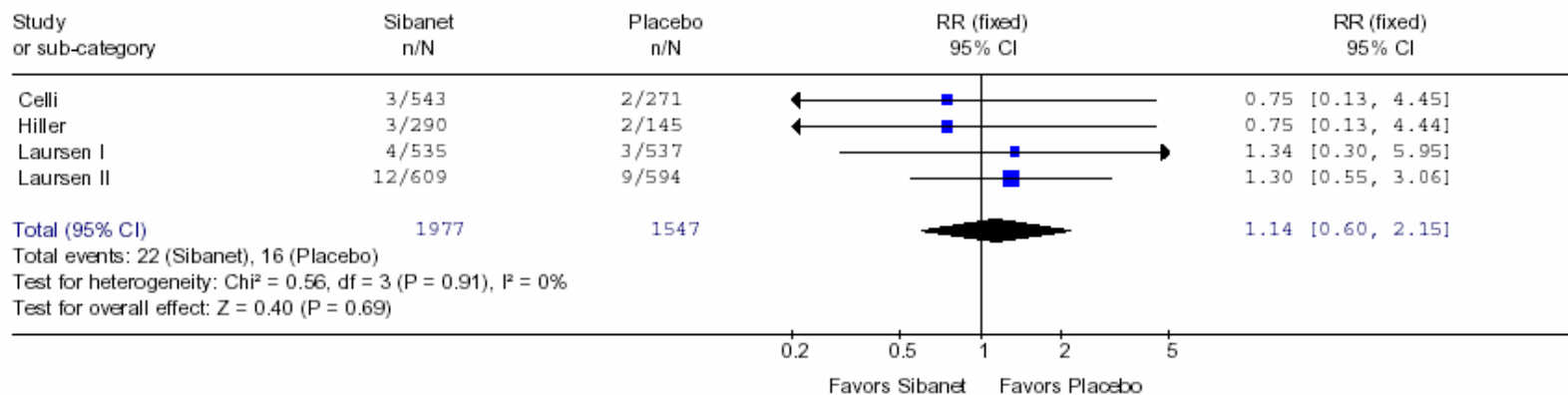
Evidence Figure 13.

Review: Interventions for COPD using Spirometry
 Comparison: 05 Sibanet vs. Placebo
 Outcome: 01 Exacerbations



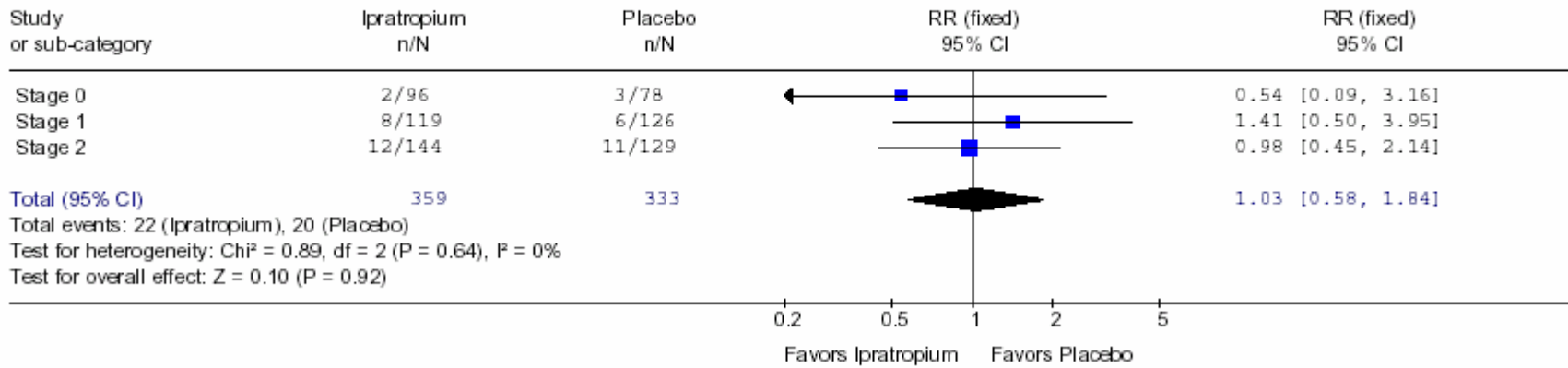
Evidence Figure 14.

Review: Interventions for COPD using Spirometry
 Comparison: 05 Sibanet vs. Placebo
 Outcome: 02 Mortality



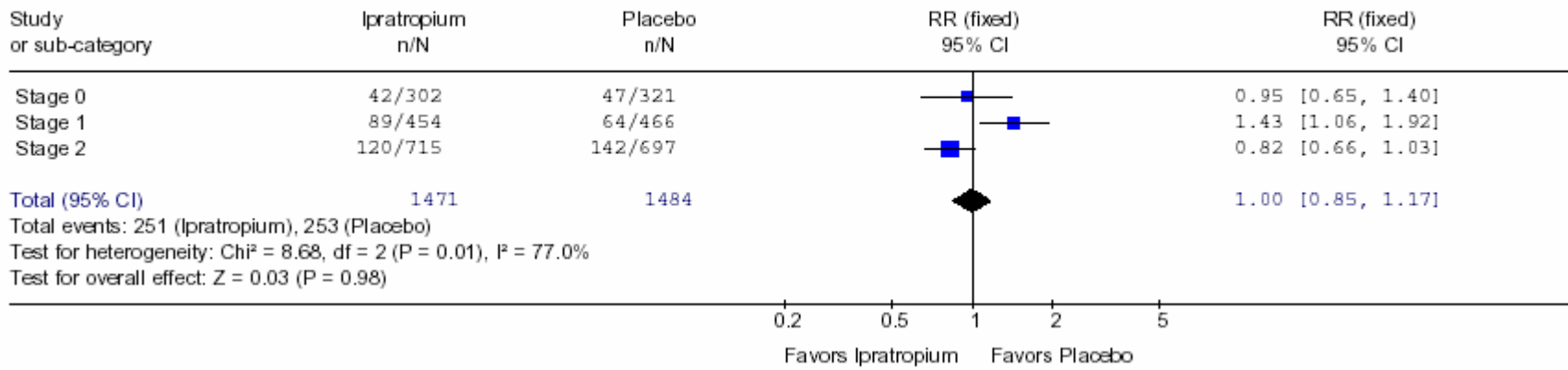
Evidence Figure 15.

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



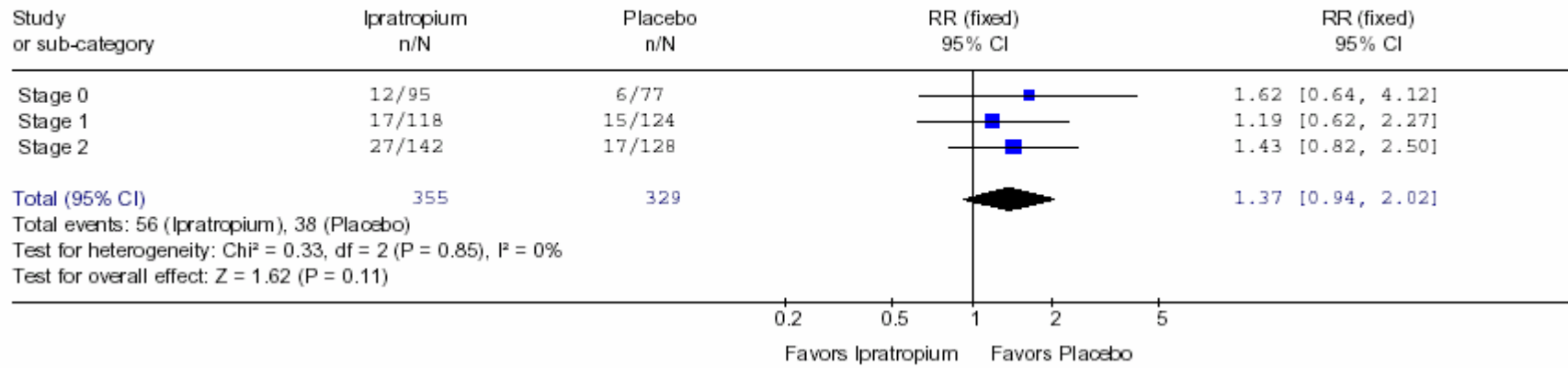
Evidence Figure 16.

Review: LH-1 Relative Risks
 Comparison: 01 Ipratropium versus Placebo
 Outcome: 02 Cough and sputum at year 3: Subjects with any symptom at baseline



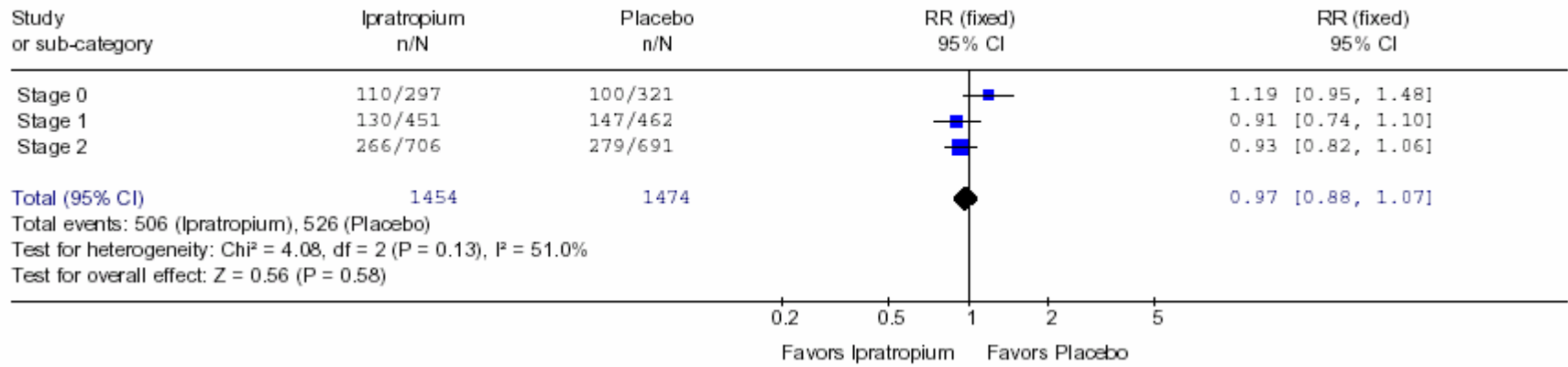
Evidence Figure 17.

Review: LH-1 Relative Risks
 Comparison: 01 Ipratropium versus Placebo
 Outcome: 03 Dyspnea at year 3: Subjects with no symptoms at baseline



Evidence Figure 18.

Review: LH-1 Relative Risks
 Comparison: 01 Ipratropium versus Placebo
 Outcome: 04 Dyspnea at year 3: Subjects with any symptom at baseline



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) Subjects had "any respiratory symptom," defined as cough, sputum, or wheeze)
Female	71.9 (2,182 / 3,034)	16.1 (see notes)	6.2 (188 / 3,034)	4.6 (140 / 3,034)	1.2 (36 / 3,034)	
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. 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	
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 Norwegians¹⁵⁴						
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 III¹⁵⁰						
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 I¹⁵⁶						
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 III¹⁵⁰					
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 β 2 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 steroids = 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 \geq 10 pack-years 3) FEV ₁ /FVC ratio \leq 70% 4) FEV ₁ 50% of the predicted normal 5) \geq 1 COPD exacerbation requiring a course of oral corticosteroids 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 \leq 65% of predicted normal and \leq 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 50ug, 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) Sildenafil 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 \geq 15 pack-years 3) FEV ₁ /FVC ratio \leq 65% 4) FEV ₁ 20-70% of the predicted normal 5) FEV ₁ reversibility to 400 ug salbutamol of \leq 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 β_2 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 $\leq 70\%$ 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.
Szafrański 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 $\leq 70\%$ 6) FEV ₁ $\leq 50\%$ 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 β_2 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 β_2 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 β_2 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, O ₂) 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 β_2 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 \leq 65% of predicted and $>$ 0.70 L, with an FEV ₁ /FVC ratio of \leq 70% at initial screening (or FEV ₁ \geq 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 <i>via</i> 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) \geq 35 years of age 2) \geq 10 pack-year history of smoking 3) a diagnosis of COPD as defined by ATS 4) a baseline FEV ₁ \leq 65% of the predicted normal value and $>$ 0.70 L (or, if $<$ 0.70 L, \geq 40% of predicted normal value) 5) an FEV ₁ /FVC ratio of \leq 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 β 2 agonists for COPD using spirometry (continued)

Study (Reference)	Study Duration	Intervention(s), Dose Per Day; Control(s)	Baseline FEV₁ (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 \leq 70% of predicted normal and a FEV ₁ /FVC ratio of \leq 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 \geq 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, O ₂) 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 <i>via</i> 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 FEV ₁ /FVC ≤70% with an FEV ₁ 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 FEV ₁ ≤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
Calverley et al, 2003 ⁸⁸				<i>See Long-Acting β₂ Agonists for details</i>
Calverley et al, 2003 ⁸⁷				<i>See Long-Acting β₂ Agonists for details</i>
Hanania et al, 2003 ⁹¹				<i>See Long-Acting β₂ Agonists for details</i>
Szafranski et al, 2003 ⁹²				<i>See Long-Acting β₂ Agonists for details</i>
Mahler et al, 2002 ⁹⁶				<i>See Long-Acting β₂ Agonists for details</i>
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., sarcoidosis) 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 prebronchodilator FEV ₁ 5) FEV ₁ reversibility after 10 days of treatment with oral prednisolone 37.5 mg daily of less than 15% of prebronchodilator 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) Sibanadet 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 \geq 15 pack-years 3) FEV ₁ /FVC ratio \leq 65% 4) FEV ₁ 20-70% of the predicted normal 5) FEV ₁ reversibility to 400 ug salbutamol of \leq 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) Sibanadet 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 \leq 70% 4) FEV ₁ 20-70% of the predicted normal range.
Laursen et al, 2003 ¹¹⁹	3 months	1) Sibanadet 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 \geq 2 years) 2) smoking history of at least 15 pack-years 3) pre- and post-bronchodilator FEV ₁ /FVC \leq 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) Sibanadet 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 \geq 2 years) 2) smoking history of at least 15 pack-years 3) pre- and post-bronchodilator FEV ₁ /FVC \leq 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 bronchodilation 4) PaO ₂ 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 FEV₁ (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 \leq 60% 8) reversibility of FEV ₁ postinhalation of 80 ug of ipratropium bromide via metered dose inhalator with aerochamber \leq 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 FEV₁ (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 FEV₁ (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) PaCO ₂ of >50 torr 5) PaO ₂ 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 β 2 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 (14.5)	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 %		Change per group
	1) Salmeterol 50 ug b.i.d. (n=554)	95/554 (17.1)	74/553 (13.4)	1/554 (<1)	-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			Not reported		<i>Chronic Respiratory Disease Questionnaire</i> ; Treatment difference vs. pbo
	1) Salmeterol 50 ug b.i.d. (n=177)	Not reported	Not reported	0/177	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			"Deterioration of COPD"; n/N %		Not reported
	1) Formoterol 4.5 ug b.i.d. (n=171)	Not reported	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			Not reported		Change per group
	1) Salmeterol 50 ug b.i.d. (n=201)	52/201 (26)	Not reported	Not reported	-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			Not reported		Change per group
	1) Salmeterol 50 ug b.i.d. (n=213)	82/213 (38.5)	Not reported	3/213 (1.4)	-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 β_2 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	<i>Chronic Respiratory Disease Questionnaire</i> ; 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) -6.1 (p=0.009 vs. pbo) -1.9
	2) Formoterol 24 ug b.i.d.(n=214)	31/214 (14.5)	5/214 (2.3)	1/214 (<1)	
	3) placebo (n=220)	39/220 (17.7)	20/220 (9.1)	0/220	
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) 1.5% (95%CI -0.8 to 3.7)
	2) placebo (n=60)	23/60 (38.3)	6/60 (10.0)	Not reported	
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) -3.3 (-5.8 to -0.8) (est.) (p=0.009)
	2) Formoterol 24 ug b.i.d. (n=192)	37/192 (19.3)	2/192 (1)	0/192	
	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	<i>Chronic Respiratory Disease Questionnaire</i> ; Change per group 10.3 (p=0.078 vs. pbo) 6.8
	2) placebo (n=135)	41/135 (30.4)	20/135 (14.8)	1/135	
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	
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	<i>Chronic Respiratory Disease Questionnaire</i> 7.1 (1.4) (p=0.007 vs. pbo) 2.1 (1.3)
	2) placebo (n=143)	47/143 (32.9)	21/143 (14.7)	0/143	

Evidence Table 14. Outcomes of studies of long-acting β 2 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) -2.3 (11.6) -1.4 (11.7)
	2) Salmeterol 100 ug b.i.d. (n=94)	Not reported	Not reported	Not reported R	
	3) placebo (n=95)	Not reported	Not reported	Not reported	
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 β 2 agonists

Studies	N	Duration	Long-Acting β 2 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%
Szafanski, 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 β 2 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 β 2 agonists (continued)

Studies	N	Duration	Long-Acting β 2 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%
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Studies	N	Duration	Long-Acting β 2 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 n/N %	Mortality: n/N (%)	St George's Respiratory Questionnaire
Celli et al., 2003 ⁹⁰	1) Sibanadet 500 ug t.i.d. (n=543)	116/543 (21.4)	Deterioration of COPD; n/N % 89/543 (16.4)	3/543 (<1)	Treatment difference vs. pbo; Change per group -4.2 (0.8 SE)
	2) placebo (n=271)	59/271 (21.9)	51/268 (19)	2/271 (<1)	
Hiller et al., 2003 ¹¹⁸	1) Sibanadet 500 ug t.i.d. (n=290)	125/290 (43.1)	Deterioration of COPD; n/N % 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	1) Sibanadet (n=535)	77/524 (14.7) (ITT population)	Deterioration of COPD; n/N % 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	1) Sibanadet (n=609)	139/591 (23.5) (ITT population)	Deterioration of COPD; n/N % 128/609 (21)	12/609 (2.0)	Change per group -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 β 2 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	1.3; 43%
Laursen, 2003 ¹¹⁹ Study 2	1203	6.5 months	-3.3	-2.3	Not applicable	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	Experimental maintenance intervention (n=87); Control (standard care) (n=85)	Not reported Not reported	10/87 (11.5) 10/85 (11.8)	Chronic Respiratory Disease Questionnaire; Score at 12 months 96.0 (21.3) / n=74 95.9 (21.1) / n=64
Brooks et al., 2002 ¹²²	Enhanced followup (n=50) Control (conventional followup) (n=59)	35 episodes 33 episodes	Not reported Not reported	No significant changes between groups
Finnerty et al., 2001 ¹²³	Rehabilitation (6-week outpatient-based program) (n=50); Control (n=50)	Not reported Not reported	Not reported Not reported	Treatment difference vs. control; 6-month score for each group -8.1 (95% CI -14.9 to -1.4); 50.6 (2.5 SE), n=24, p<0.02 vs. control 57.1 (3.0 SE), n=25
Griffiths et al., 2000 ¹²⁴	Rehabilitation (6-week multidisciplinary program) (n=99) Control (n=101)	Number of patients admitted to hospital 40 (p=0.98 vs. control) 41	6/99 (6.1) 12/101 (11.9)	Treatment difference vs. control; 12-month score for each group -4.8 (95 %CI -8.4 to -1.2), p=0.010; 61.5 (17.5), n=93 69 (13.3), n=89
Ringbaek et al., 2000 ¹²⁵	Rehabilitation (8 week program) (n=24) Control (n=21)	Discontinuations due to exacerbation of COPD; n/N % 3/24 (12.5) 0/21	Not reported Not reported	Treatment difference vs. control 0.1 (95% CI -9.8 to 10)
Engstrom et al., 1999 ¹²⁶	Rehabilitation (physiotherapy program) (n=26) Control (n=24)	Deterioration of COPD; n/N % 4/26 (15.4) non-compliers to treatment 3/24 (12.5)	0/26 0/24	Change per group 0.3 (2.2) ITT pop. / -0.2 (1.9) on treatment (n=20) 2.1 (2.9)
Wedzicha et al., 1998 ¹²⁷ (Moderate)	Rehabilitation (exercise training and education for 8 weeks) (n=33) Control (education) (n=33)	Not reported Not reported	0/33 1/33	Treatment difference vs. control; change per group -5.4 (95% CI -10.7 to 0.02); -2 (95% CI -6 to 3) 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	Self-management (n=96)	Acute exacerbations (episode) of COPD 299	COPD hospitalizations; n/N % 31/96 (32.3)	5/96 (5.2)	Treatment difference vs. pbo; 12-month change -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	Self-management (n=127)	Not reported	Not reported	3/127 (2.4)	Treatment difference vs. pbo -0.6 (-2.8 to 1.7)
	Control (n=121)	Not reported	Not reported	3/121 (2.5)	
Hermiz et al., 2002 ³⁹	Enhanced followup (n=84)	Not reported	Not reported	9/84 (10.7)	Treatment difference vs. pbo 1.32 (-2.97 to 5.62)
	Control (n=93)	Not reported	Not reported	10/93 (10.8)	
Weinberger et al., 2002 ¹⁶¹	Pharmaceutical care program group (n=185)	Not reported	Breathing-related hospital or ED visit (%) 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	Education (n=31)	Not reported	COPD hospitalizations; n/N % 0/31	Not reported	Means (SD) at followup 40.0 (16) 43.1 (21) p-value = 0.54
	Control (n=31)	Not reported	2/31 (6.5)	Not reported	
Watson et al., 1997 ¹⁶³	Self-management (use of Action Plan & booklet) (n=29)	Not reported	Visits to GP or PN; n/N (%) 3/29 (10.3)	0/29	Means (SD) at followup 39 (17) significant improvement than base [43(15)] 39 (16)
	Control (usual care) (n=27)	Not reported	2/27 (7.4)	0/27	
Weinberger et al., 1996 ¹⁶⁴	Primary care intervention (n=295)	Not reported	Number of readmissions per month; mean (SD) 0.19 (0.3)	According to total study group 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	Education/enhanced followup (n=73)	Not reported	Number (%) of admissions to hospital 12 (18)	3/73 (4.1)	Sickness Impact Profile; mean change (95% CI) 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	Enhanced followup (group visited by respiratory health worker) (n=42)	Not reported	Respiratory illness hospitalizations; n/N % 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