

ICS is not associated with risk of pneumonia in asthma

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- Pathophysiology of pneumonia in asthma patients
- Non-ICS vs ICS
 - RCT: START trial
 - Meta-analysis
 - Prospective/retrospective study
- Dose dependence
 - RCT: FAST trial, SMART, RCT of FF
 - Retrospective study
- Limitation of study suggesting increased pneumonia risk of ICS

Title and Abstract: cortic* or steroid*[TI]
AND inhale*[TI] AND Asthm*[TI] AND
pneumoni* [TW]

(N=37)

Excluded (n=26)

- No pneumonia (n=2)
- No adults (n=10)
- Before 2002 (n=2)
- COVID-19 (n=3)
- NTM/TB (n=3)
- No human (n=2)
- COPD (n=2)
- No full text/review (n=2)

Associated with Increased pneumonia

- RCT (n=0)
- Meta-analysis (n=0)
- retrospective (n=4)

Don't
know
(n=1)

Not associated with increased pneumonia

- RCT (n=2)
- Meta-analysis (n=1)/systematic review(n=1)
- Prospective (n=1)
- retrospective (n=2)

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Pneumonia in asthma patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Asthma as a Risk Factor for Invasive Pneumococcal Disease

Thomas R. Talbot, M.D., M.P.H., Tina V. Hartert, M.D., M.P.H., Ed Mitchel, M.S.,
Natasha B. Halasa, M.D., M.P.H., Patrick G. Arbogast, Ph.D.,
Katherine A. Poehling, M.D., M.P.H., William Schaffner, M.D., Allen S. Craig, M.D.,
and Marie R. Griffin, M.D., M.P.H.

Asthma

- :1 hospitalization or ER visit with asthma code
- : >2 clinic visit with asthma code
- : >2 of SABA prescription
- : >1 of ICS/LABA/LTRA/Cromolyn

High risk asthma

- : >1 hospitalization or ER visit/oral steroid/>3 SABA

Low risk asthma

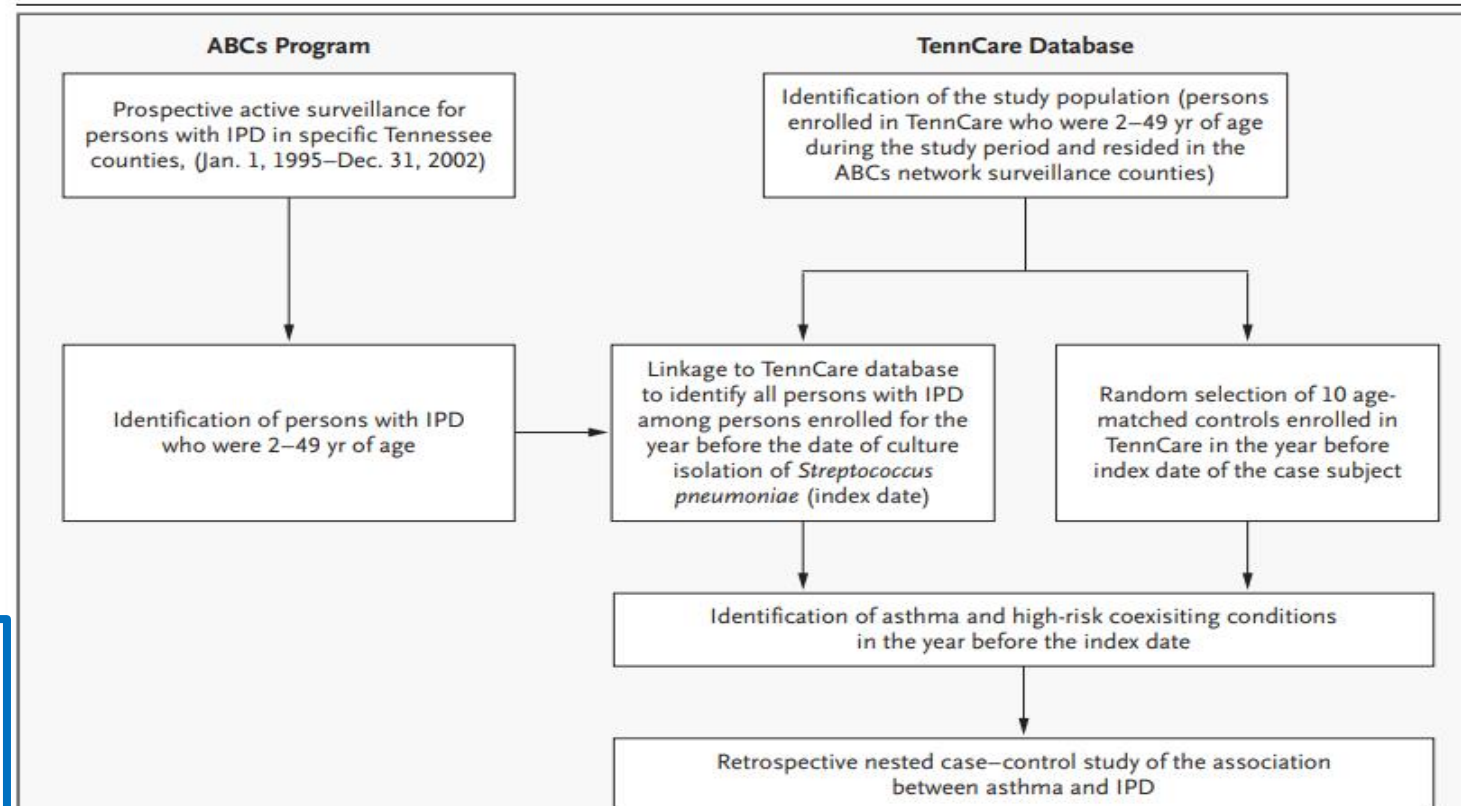


Figure 1. Diagram of the Nested Case–Control Study.

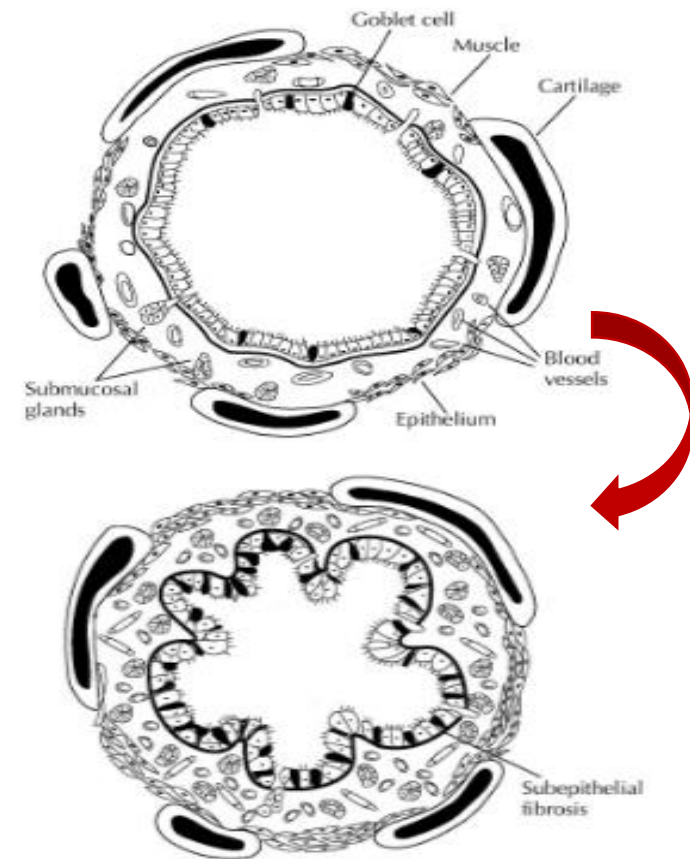
From January 1995 through August 1999, the Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance (ABCs) network encompassed five urban counties in Tennessee. In August 1999, the network was expanded to include six additional counties. TennCare denotes the Tennessee Medicaid program, and IPD invasive pneumococcal disease.

Asthma is risk factor for invasive pneumococcal disease

Table 2. Association between the Presence of Asthma and the Risk of Invasive Pneumococcal Disease.

Variable	Case Subjects (N=635)	Controls (N=6350)	Adjusted Odds Ratio for Invasive Pneumococcal Disease (95% CI)*
	<i>no./total no. (%)</i>		
Any asthma	114/635 (18.0)	516/6350 (8.1)	2.4 (1.9–3.1)
High-risk asthma	95/635 (15.0)	383/6350 (6.0)	2.6 (2.0–3.5)
Low-risk asthma	19/635 (3.0)	133/6350 (2.1)	1.7 (0.99–3.0)
Coexisting conditions that confer a high risk of invasive pneumococcal disease†			
Absent	51/347 (14.7)	410/5542 (7.4)	2.4 (1.7–3.4)
Present	63/288 (21.9)	106/808 (13.1)	2.3 (1.3–4.1)
Age‡			
2–4 yr	26/122 (21.3)	116/1220 (9.5)	2.3 (1.4–4.0)
5–17 yr	11/62 (17.7)	34/620 (5.5)	4.0 (1.5–10.7)
18–49 yr	77/451 (17.1)	366/4510 (8.1)	2.4 (1.8–3.3)

Airway remodeling
Decreased bacterial clearance



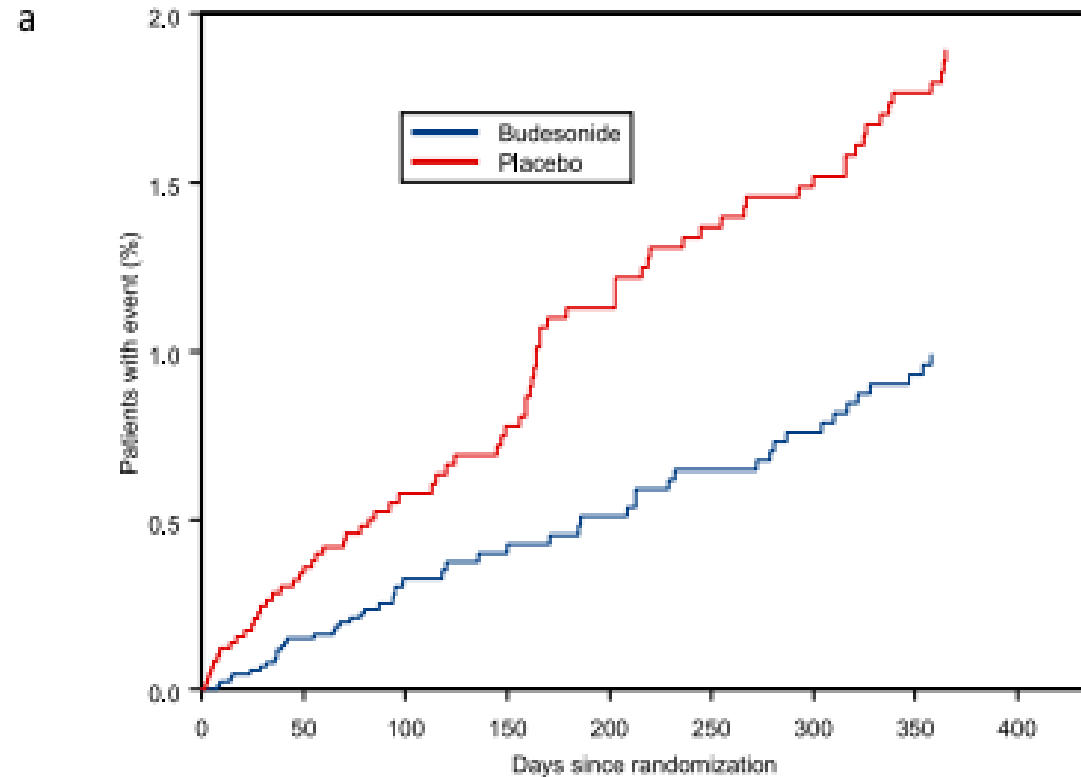
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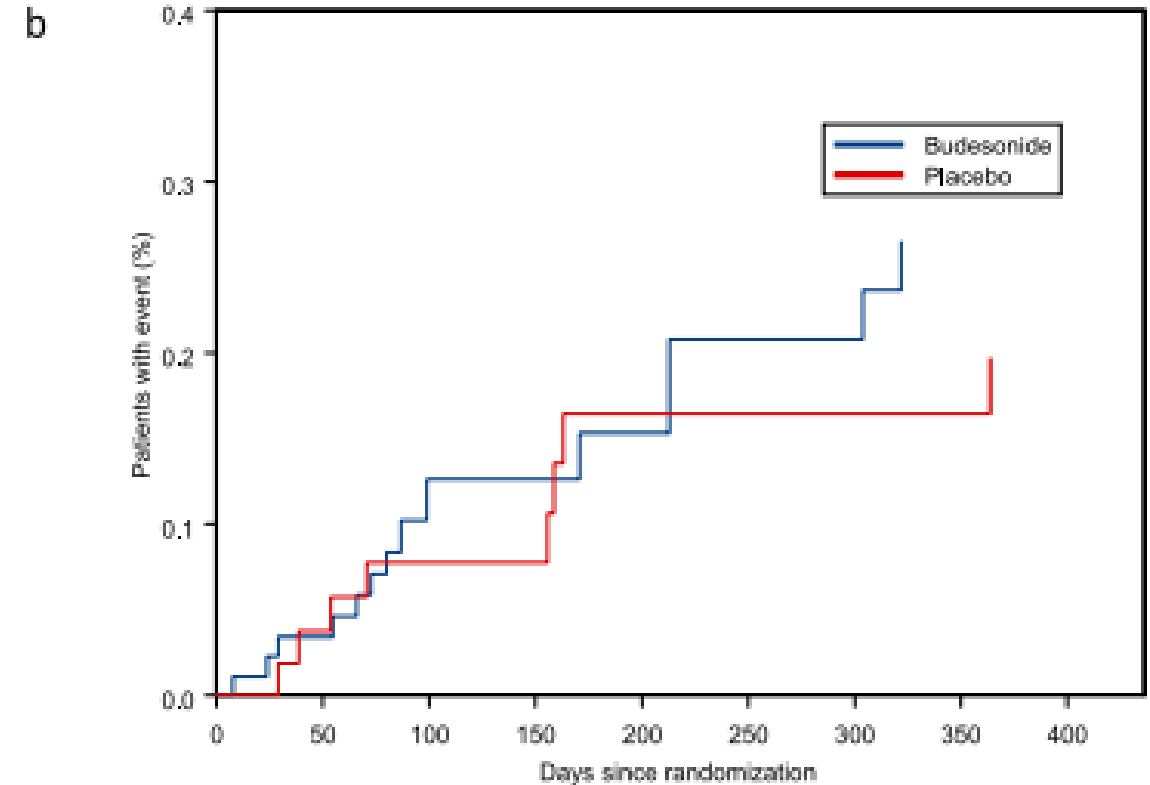
START trial

- The Steroid Treatment As Regular Therapy

P: >4 years old, asthma
I: Budesonide(B) or Budesonide/Formoterol (n=9,067)
C: Placebo (n=5,926)
O: pneumonia within 1 years



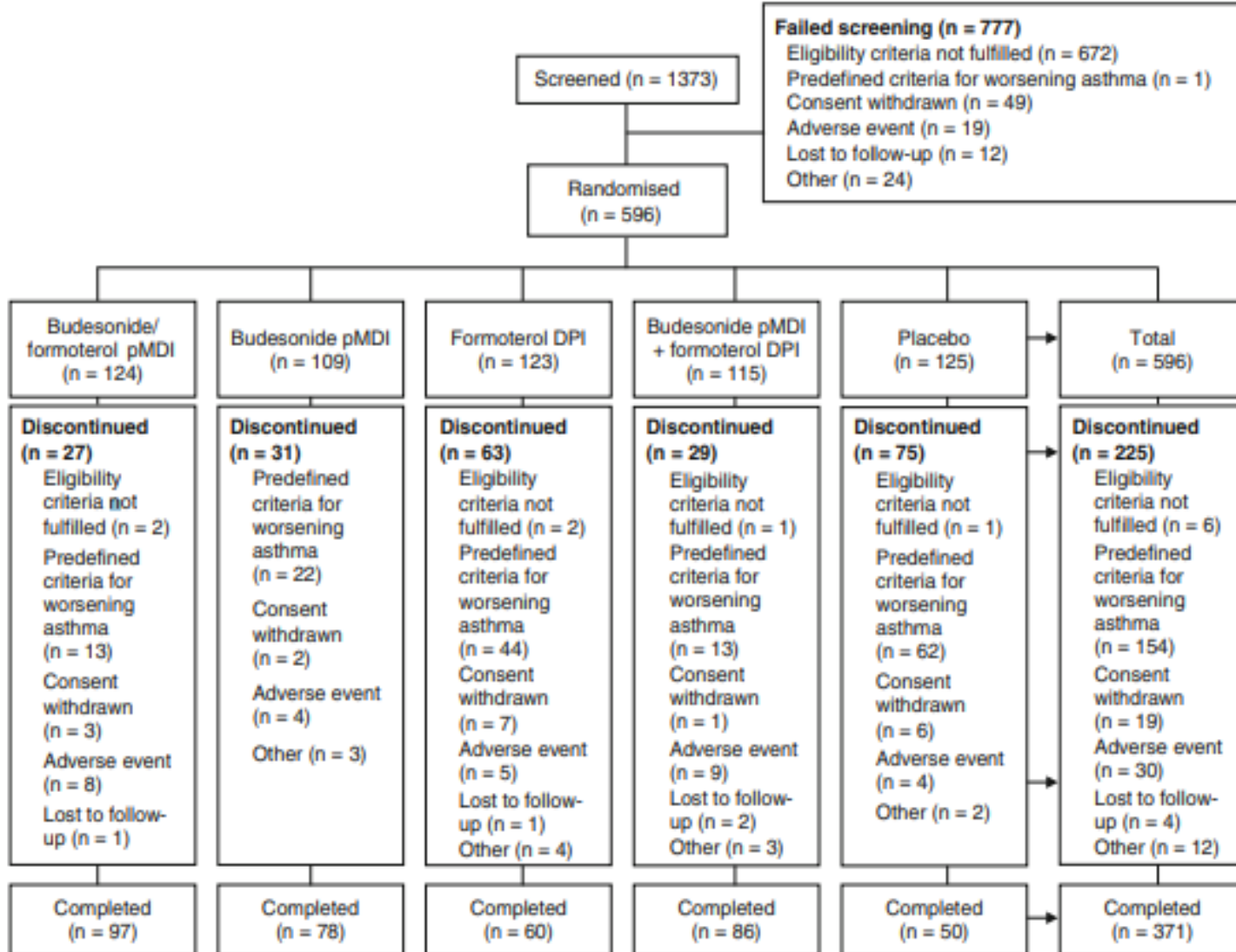
N at risk at day	90	180	270	360
Placebo:	3818	3357	3259	3099
Budesonide:	4889	3681	3559	3280



N at risk at day	90	180	270	360
Placebo:	3818	3357	3259	3099
Budesonide:	4889	3681	3559	3280

RCT of budesonide

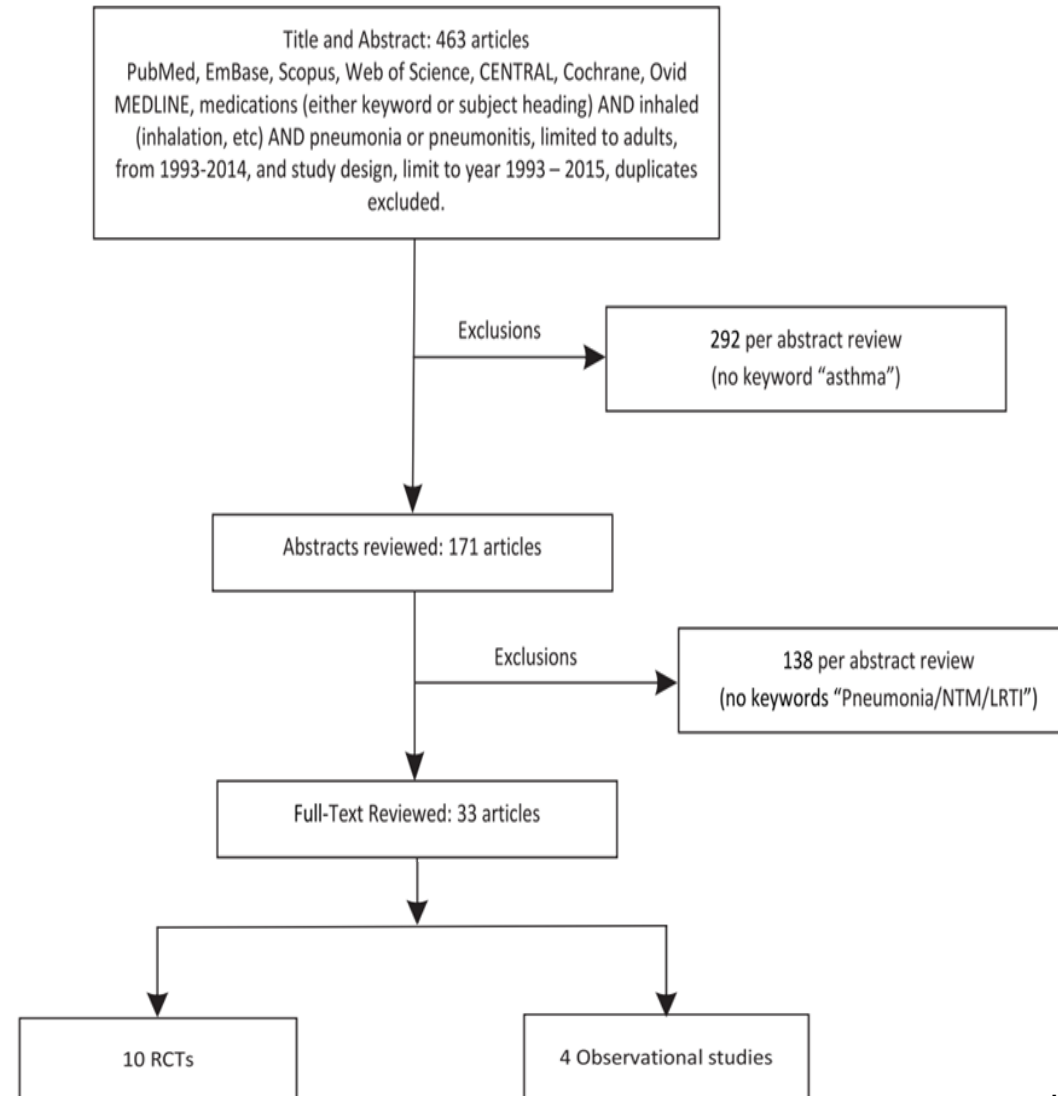
P: Aged ≥ 12 years with moderate to severe asthma w ICS at least 4w (FEV1 45-85%)
I: BF MDI 160ug BID/B160u BID/F 4.5ug bid/B MDI&F DPI (n=471)
C: Placebo (n=125)
O: mean change from baseline FEV1 at week 12w, safety



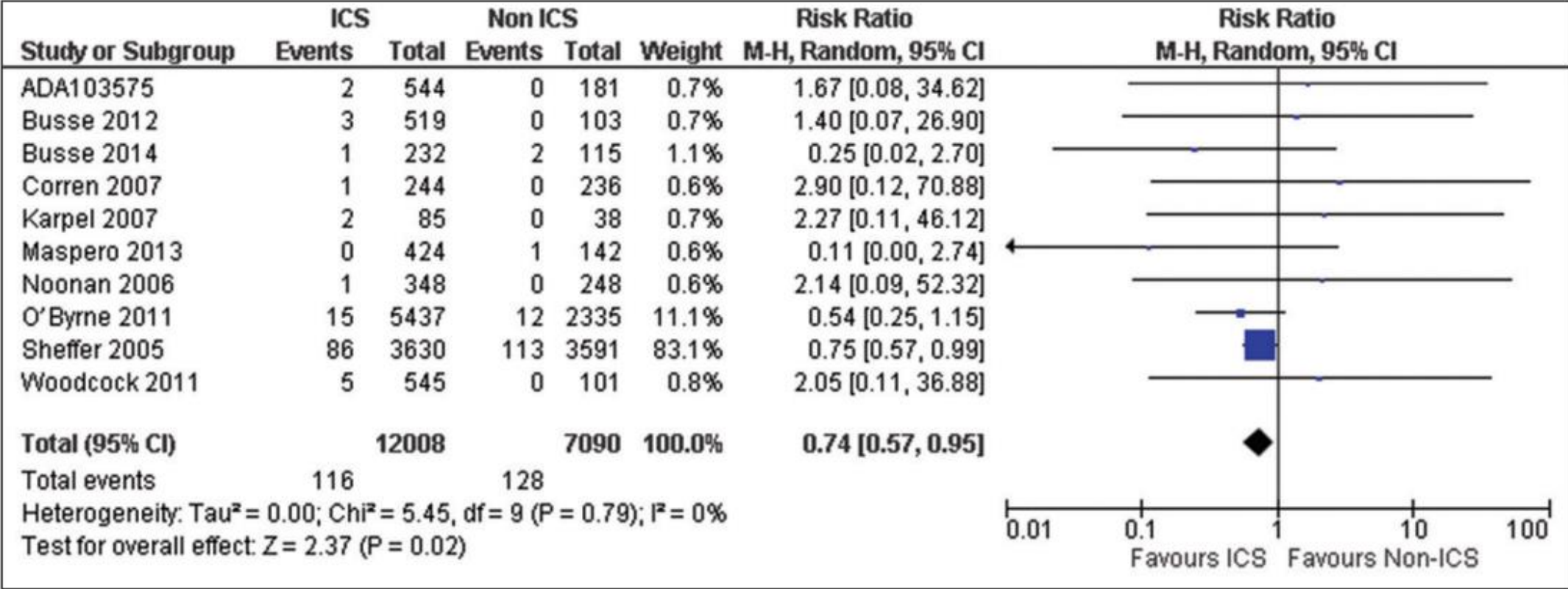
Drug related adverse event (discontinuation) (n=11)

BF MDI: 3 (T-wave inversion, AF, hoarseness)
 B MDI+F DPI: 5 (URI 1, other)
 B MDI: 1 (abdomen)
 F DPI : 1 (asthma)
 Placebo: 1 (asthma)

Meta-analysis



Meta-analysis of RCT



Literature review

Open Access Review Article

DOI: 10.7759/cureus.8717

Inhaled Corticosteroids as an Associated Risk Factor for Asthmatic Pneumonia: A Literature Review

Zin Mar Htun ¹, Israa Aldawudi ², Prakash C. Katwal ¹, Srood Jirjees ³, Safeera Khan ¹

1. Internal Medicine, California Institute of Behavioral Neurosciences and Psychology, Fairfield, USA 2. Radiology, California Institute of Behavioral Neurosciences and Psychology, Fairfield, USA 3. Neurology, California Institute of Behavioral Neurosciences and Psychology, Fairfield, USA

Observational study

Source	Age group	No. of patients	COPD excluded	Study type	Result	95% CI
Kim et al. [12]	>15 years	831,613	No; LAMA users included	Asthma ICS/asthma non-ICS	OR: 1.38	1.36-1.41
Ekbom et al. [13]	20-44 years	7,284	No; asthma self-reported diagnosis	Hospitalization/no-hospitalization	HR: 3.35	1.97-5.02
McKeever et al. [14]	18-80 years	43,169	Yes	Pneumonia/no pneumonia	OR: 1.24	1.5-1.79

Source	Age group	No. of patients	COPD excluded	Study duration	Study type	Result
Sheffer et al. [18]	5-66 years	7,221	Yes	3 years	Budesonide versus placebo	No difference (2.4% in the budesonide group versus 3.1% in the placebo group)
Woodcock et al. [19]	≥12 years	646	Yes	8 weeks	Five different groups of fluticasone furoate dosing versus placebo	Similar incidence to placebo in upper respiratory infection and respiratory tract infection; pneumonia not reported
Noonan et al. [20]	≥12 years	596	Yes	12 weeks	Four different groups of budesonide and/or formoterol dosing and formulation versus placebo	Pneumonia not reported
O'Byrne et al. [21]	Varies				Meta-analysis of RCT (26 trials and 60 trials)	No increased risk of pneumonia

1,234	Yes; asthma and COPD reported separately	Asthma ICS/asthma non-ICS	OR: 1.07 for asthma	0.61-1.87
62	Yes	Asthma ICS/asthma non-ICS	OR: 1.4 for COPD	0.95-2.09
2,662	Yes; asthma and COPD reported separately	Pneumonia/pneumonia (case-control)	No difference	
			OR: 1.1 for asthma	0.4-3.00
			OR: 3.26 for COPD	1.07-9.98

← RCT

Prospective study (USA)

ORIGINAL ARTICLE



Prehospital Use of Inhaled Corticosteroids and Point Prevalence of Pneumonia at the Time of Hospital Admission: Secondary Analysis of a Multicenter Cohort Study

Emir Festic, MD; Vikas Bansal, MBBS, MPH; Ognjen Gajic, MD, MS; and Augustine S. Lee, MD; on behalf of the United States Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG-LIPS)

Multi-centered prospective cohort

- P:** admitted to the hospital
-March 1st and August 31st 2009
-5,584 patients from 20 centers
- I:** ICS user
- C:** non-ICS user
- O:** pneumonia prevalence (1,234, 22%)

TABLE 2. Adjusted Prevalence of Pneumonia in the Whole Cohort and the Diagnostic Subgroups

Group	ICS group	Non-ICS group	OR (95% CI)	P value
Whole cohort	495	5089	1.20 (0.93-1.53)	.162
COPD	226	363	1.40 (0.95-2.09)	.093
Asthma	151	289	1.07 (0.61-1.87)	.81
Non-COPD/asthma	156	4473	1.32 (0.88-1.97)	.179

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid.

Univariate analysis

- ICS user (45%) vs non-ICS user (20%)
 - Among asthma, 66% (ICS) vs 34% (No), $p < 0.001$
- After adjustment** (demographic, comorbidities, medication) **OR 1.07 (0.61-1.87)**

Retrospective study (Canada)

ORIGINAL RESEARCH

Effectiveness and Safety of Inhaled Corticosteroids in Older Individuals with Chronic Obstructive Pulmonary Disease and/or Asthma

A Population Study

Tetyana Kendzerska^{1,2}, Shawn D. Aaron¹, Teresa To^{3,4,5}, Chris Licskai⁶, Matthew Stanbrook^{3,7}, Nicholas T. Vozoris⁷, Mary-Ellen Hogan⁸, Wan C. Tan⁹, Jean Bourbeau¹⁰, and Andrea S. Gershon^{3,4,7,11}; for the Canadian Respiratory Research Network

P: >66 years old, Canada, COPD or asthma, 2003-2014
 Provincial health administrative data (retrospective cohort)
 -> 87,690 asthma and 150,590 COPD
I: ICS exposure
O: hospitalization for OLD, pneumonia
Methods: propensity score matching

Outcomes	Individuals with Asthma Hazard Ratio (95% Confidence Interval), P Value			Individuals with Chronic Obstructive Pulmonary Disease Hazard Ratio (95% Confidence Interval), P Value		
	Number	History of Chronic Obstructive Pulmonary Disease		All 150,593	History of Asthma	
		All 87,690	Yes 23,799		No 63,891	Yes 37,319
Primary Outcomes						
Obstructive lung disease hospitalization	0.88 (0.85-0.92) <0.0001	0.95 (0.89-1.00), 0.07	0.84 (0.79-0.88) <0.0001	1.00 (0.98-1.02) 0.81	0.88 (0.84-0.92) <0.0001	1.06 (1.03-1.08) <0.0001
Pneumonia hospitalization	0.89 (0.86-0.93) <0.0001	0.90 (0.84-0.96) 0.001	0.89 (0.85-0.94) <0.0001	0.99 (0.96-1.01) 0.25	0.90 (0.86-0.95) <0.0001	1.03 (1.00-1.06) 0.03
Secondary Outcomes						
All-cause mortality	0.88 (0.86-0.91) <0.0001	0.91 (0.87-0.96) <0.001	0.87 (0.84-0.90) <0.0001	0.92 (0.91-0.94) <0.0001	0.90 (0.87-0.93) <0.0001	0.95 (0.93-0.96) <0.0001
Cardiovascular disease hospitalization	0.91 (0.88-0.94) <0.0001	0.96 (0.91-1.02) 0.22	0.89 (0.85-0.92) <0.0001	0.98 (0.96-1.00) 0.07	0.94 (0.90-0.98) <0.01	1.01 (0.98-1.04) 0.48
Cataract surgery	0.95 (0.89-1.03) 0.23	0.97 (0.85-1.11) 0.64	0.95 (0.87-1.04) 0.28	0.93 (0.88-0.98) <0.01	0.96 (0.86-1.06) 0.39	0.93 (0.87-0.99) 0.02
Hospitalization for fractures related to osteoporosis	1.00 (0.97-1.04) 0.85	0.98 (0.92-1.05) 0.59	1.01 (0.97-1.05) 0.61	1.00 (0.97-1.02) 0.76	0.94 (0.89-0.99) 0.02	1.02 (0.99-1.06) 0.18
Incident diabetes†	1.01 (0.97-1.06) 0.58	1.00 (0.91-1.10), 0.97	1.02 (0.96-1.08) 0.50	1.02 (0.98-1.07) 0.30	1.00 (0.93-1.08) 0.99	1.03 (0.98-1.08) 0.21

New user
 -to exclude prevalent user bias
 -preceding 1-year ICS-free period

In older asthma patients with ICS
 -> Greater benefit without COPD

Public health intervention targeting severe asthma reduce hospitalization (Brazil)

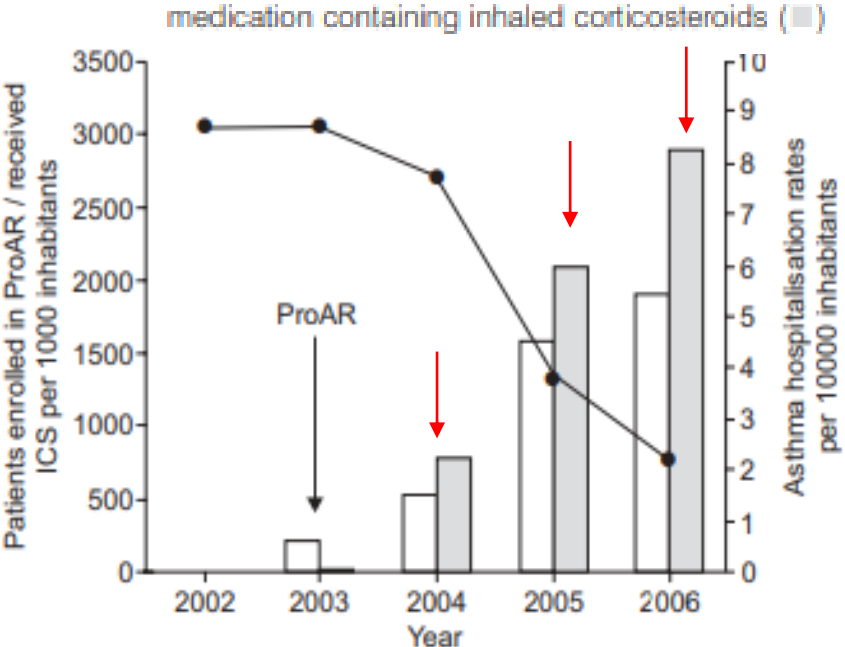
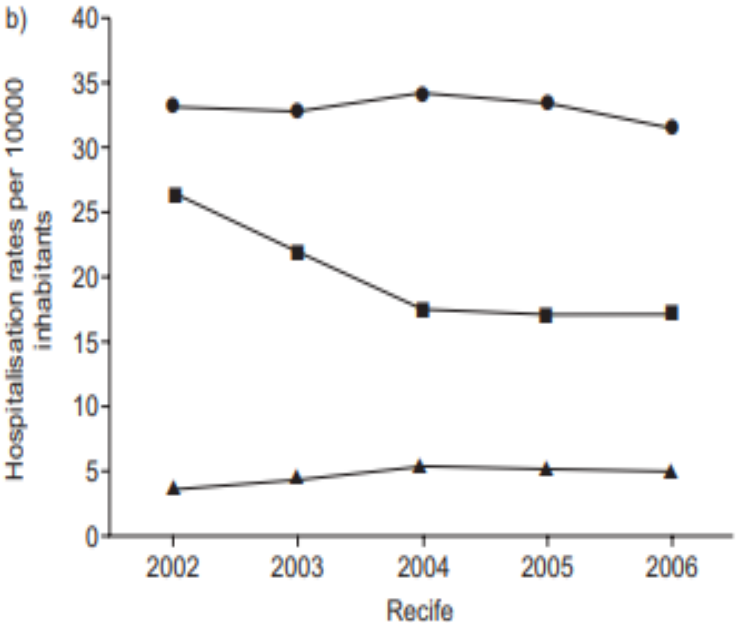
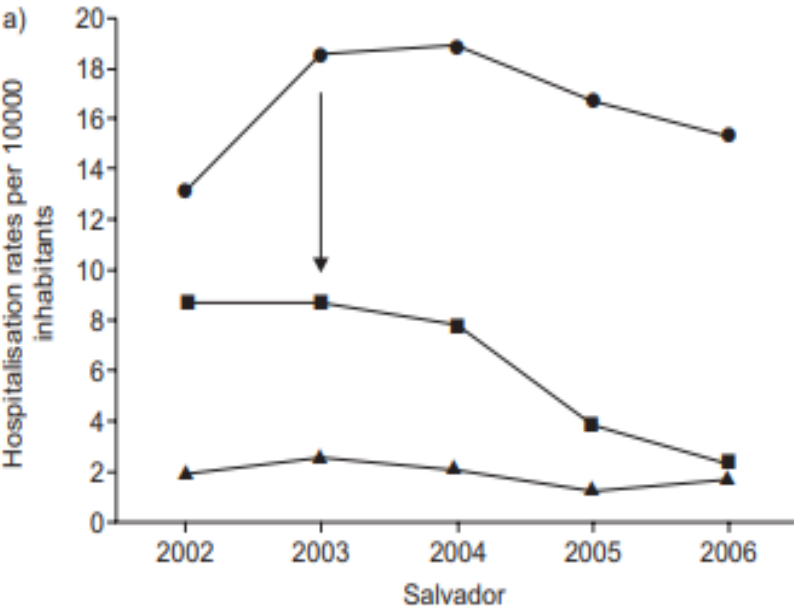
Eur Respir J 2010; 35: 515-521
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Rapid reduction in hospitalisations after an intervention to manage severe asthma

C. Souza-Machado^{*,#}, A. Souza-Machado^{*,†}, R. Franco^{*,‡}, E.V. Ponte[#], M.L. Barreto[§], L.C. Rodrigues^{||}, J. Bousquet^{**,##} and A.A. Cruz[#]



P: Asthma who had hospitalization 1998 to 2006
I: Programme for Control of Asthma in Bahia (ProAR) leads an initiative in Salvador City (Brazil)
C: Asthma from Recife
O: rate of asthma hospitalization, pneumonia, MI



Retrospective study (Japan)

Table 1. Characteristics of Patients at Admission

	with ICS (n=37)	without ICS (n=25)	p
ICS (equivalent doses of BDP) ($\mu\text{g}/\text{d}$)	777.9 \pm 315.6	0.0 \pm 0.0	
Sex	Male 18, Female 19	Male 10, Female 15	
Age (y)	53.2 \pm 17.2	56.4 \pm 21.6	NS
Serum albumin (mg/dl)	4.00 \pm 0.35	3.81 \pm 0.49	NS

P: asthma patients with hospitalization for CAP, 1989-2001
I: ICS user (oral steroid user excluded) (n=37)
C: non ICS user (n=25)
O: clinical characteristics of pneumonia

Table 3. Clinical Characteristics of Pneumonia in Study Subjects

	with ICS (n=37)	without ICS (n=25)	p
Body temperature ($^{\circ}\text{C}$)	37.8 \pm 1.0	37.6 \pm 1.1	NS
WBC (/ μl)	11,530 \pm 4,187	10,156 \pm 4,124	NS
ESR (mm/h)	52.9 \pm 33.1	63.0 \pm 33.9	NS
CRP (mg/dl)	12.2 \pm 7.5	12.2 \pm 9.0	NS
Resolution period (d)	10.8 \pm 4.0	11.0 \pm 4.0	NS

Table 4. Frequency of Pathogens Detected in Sputum, Blood or Pleural Effusions

Organism	Percent of episodes (%)	
	with ICS (n=37)	without ICS (n=25)
<i>Streptococcus pneumoniae</i>	32.4	32.0
<i>Haemophilus influenzae</i>	5.4	8.0
<i>Staphylococcus aureus</i>	0.0	4.0
<i>Klebsiella pneumoniae</i>	5.4	4.0
unknown	56.8	52.0

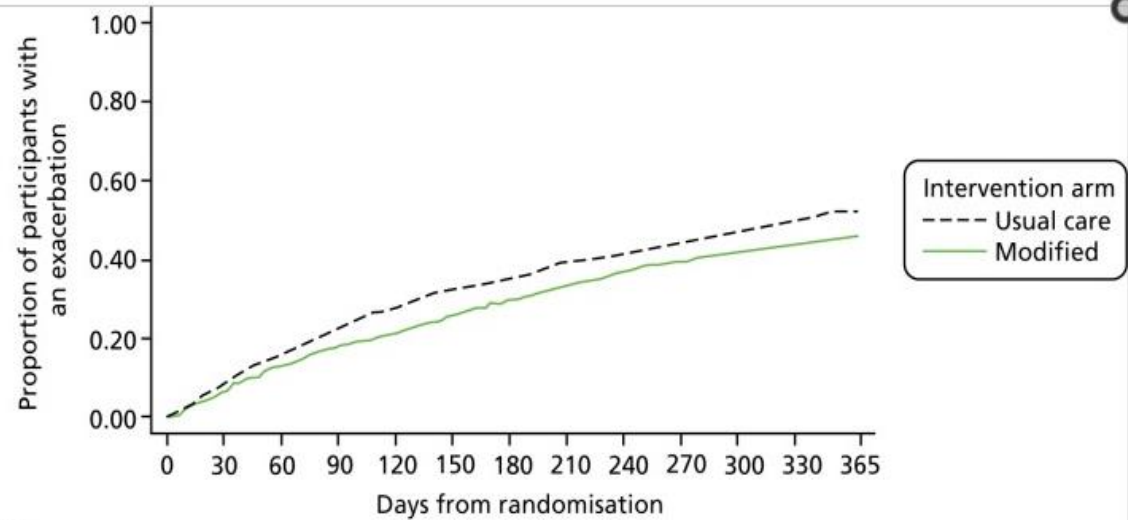
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FAST trial

Fourfold Asthma Study

P: >16 years old, ICS treated asthma with >1 AE Hx
I: Quadrupling of ICS at AE (n=933)
C: Usual care at AE (n=938)
O: Time to AE, adverse events



Number at risk	0	30	60	90	120	150	180	210	240	270	300	330	365
Treatment = usual care	938	791	671	592	521	463	349						
Treatment = modified	933	806	727	644	558	508	366						

Serious events (Pneumonia/lower respiratory infection):
 4/3 (usual) vs 5/0 (modified)

Cumulative dose of corticosteroid	Intervention arm, 12-month visit completed	
	Usual care (N= 700)	Modified (N= 679)
Total dose of inhaled corticosteroids (mg)		
Mean (SD)	328.5 (211.8)	385.2 (265.5)
Median (25th, 75th centiles)	292 (146, 365)	304 (178.4, 444.5)
Min., max.	36.5, 1414	29.2, 1592
Total dose of systemic corticosteroids (mg)		
Mean (SD)	151.3 (256.9)	120.9 (220.8)
Median (25th, 75th centiles)	0 (0, 210)	0 (0, 200)
Min., max.	0, 2120	0, 1770
Total dose of systemic corticosteroids (mg) in participants who took systemic corticosteroids		
n	306	247
Mean (SD)	346.1 (289.3)	332.3 (252.6)
Median (25th, 75th centiles)	240 (150, 400)	210 (180, 400)
Min., max.	25, 2120	15, 1770

Mild asthma

ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D., Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D., Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B., Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci., and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

Table 2. Medication Outcomes.*

Outcome	Albuterol Group (N=223)	Budesonide Maintenance Group (N=225)	Budesonide–Formoterol Group (N=220)
Glucocorticoid use			
No. of inhaled glucocorticoid-containing actuations per day			
Mean	NA	1.11±0.56	0.53±0.54
Median (IQR)	NA	1.23 (0.66–1.57)	0.37 (0.15–0.73)
Range	NA	0–2.01	0–3.95
Daily budesonide dose — μg			
Mean	NA	222±113	107±109
Median (IQR)	NA	247 (132–314)	73 (31–146)
Range†	NA	0–402	0–790
Oral glucocorticoid use, prednisone — mg	17.4±59.8	14.5±51.0	7.5±40.2

Table 3. Adverse Events.

Event	Albuterol Group (N=226)	Budesonide Maintenance Group (N=227)	Budesonide–Formoterol Group (N=222)
Any adverse event	185 (81.9)	190 (83.7)	174 (78.4)
Adverse events that occurred in ≥2% of patients in any group			
Upper respiratory tract infection	75 (33.2)	75 (33.0)	71 (32.0)
Nasopharyngitis	46 (20.4)	35 (15.4)	47 (21.2)
Asthma	46 (20.4)	26 (11.5)	17 (7.7)
Influenza	17 (7.5)	25 (11.0)	20 (9.0)
Lower respiratory tract infection	20 (8.8)	18 (7.9)	14 (6.3)
Headache	15 (6.6)	14 (6.2)	9 (4.1)
Cough	12 (5.3)	14 (6.2)	10 (4.5)
Respiratory tract infection	7 (3.1)	11 (4.8)	10 (4.5)
Seasonal allergy	12 (5.3)	8 (3.5)	7 (3.2)
Sinusitis	7 (3.1)	10 (4.4)	9 (4.1)
Back pain	9 (4.0)	7 (3.1)	7 (3.2)
Oropharyngeal pain	10 (4.4)	7 (3.1)	5 (2.3)
Ligament sprain	7 (3.1)	6 (2.6)	8 (3.6)
Gastroenteritis	8 (3.5)	8 (3.5)	4 (1.8)
Anxiety	7 (3.1)	6 (2.6)	6 (2.7)
Viral upper respiratory tract infection	5 (2.2)	8 (3.5)	6 (2.7)
Toothache	4 (1.8)	9 (4.0)	1 (0.5)
Migraine	7 (3.1)	2 (0.9)	5 (2.3)

Mild-moderate asthma



CHEST

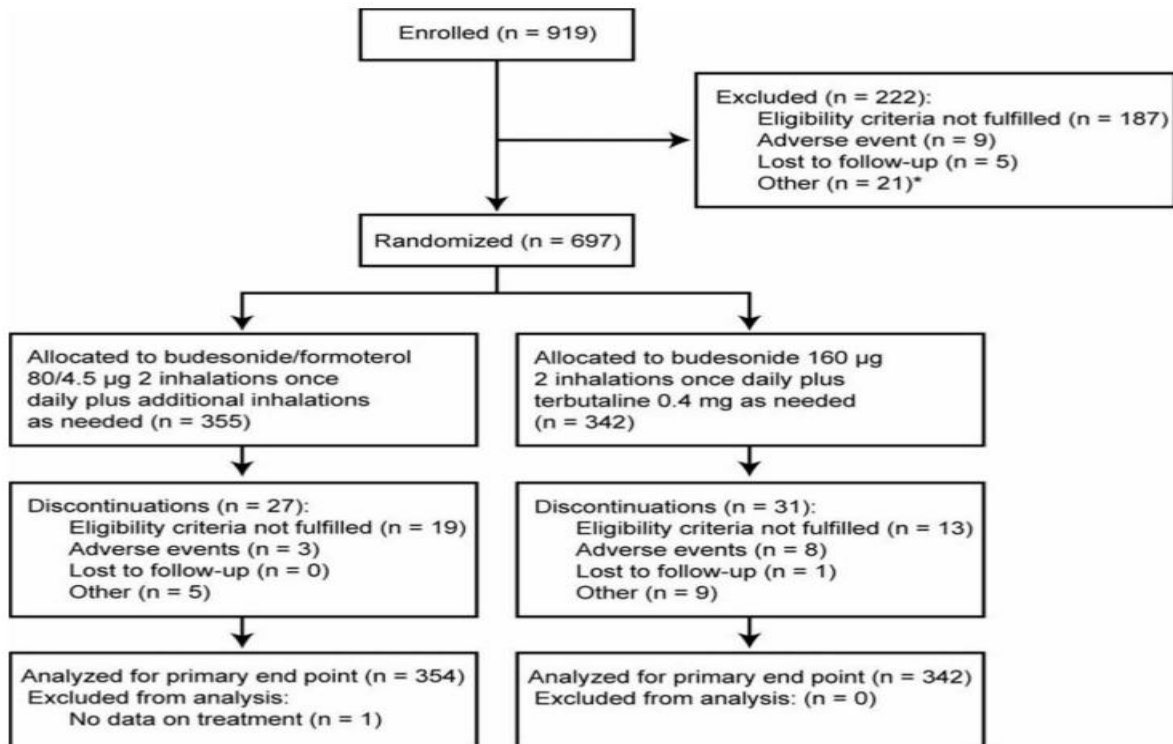
Original Research

ASTHMA

Budesonide/Formoterol in a Single Inhaler for Maintenance and Relief in Mild-to-Moderate Asthma*

A Randomized, Double-Blind Trial

Klaus F. Rabe, MD, PhD; Emilio Pizzichini, MD, PhD; Björn Stållberg, MD; Santiago Romero, MD; Ana M. Balanzat, MD; Tito Atienza, MD; Per Arve Lier, MD; and Carin Jorup, MD



P: >12-80years, asthma patients with ICS at least 3m
I: BF (80/4.5ug)+as needed (n=355)
C: B (160ug)+terbutaline (n=352)
O: Morning peak expiratory flow, safety profile

Adverse Events	Budesonide/Formoterol, 80 µg/4.5 µg, Two Inhalations qd (n = 354), No. (%)	Budesonide, 160 µg, Two Inhalations qd (n = 342), No.(%)
Palpitation*	0 (0)	3 (1)
Tremor*	0 (0)	3 (1)
Tachycardia*	3 (1)	0 (0)
Dysphonia†	3 (1)	1 (< 0.5)
Candidiasis†	0 (0)	2 (1)

Mean daily ICS dose (µg)

RCT of FF

P: Aged ≥ 12 years with asthma, FEV1 50-80%

Nov 2006- Aug 2007

I: FF 200mcg OD/AM&PM&BD and 400mg OD/AM&PM (n=545)

C: Placebo (n=101)

O: mean change from baseline FEV1 at week 8, safety

Table 3 Most common on-treatment AEs ($\geq 3\%$ incidence in any treatment group) (ITT population)

	Placebo (n = 101)	FF dose				
		200 mcg OD/AM (n = 105)	200 mcg OD/PM (n = 103)	400 mcg OD/AM (n = 111)	400 mcg OD/PM (n = 113)	200 mcg BD (n = 113)
Any AE, n (%)	28 (28)	36 (34)	32 (31)	43 (39)	35 (31)	38 (34)
Headache	6 (6)	8 (8)	7 (7)	10 (9)	7 (6)	9 (8)
Nasopharyngitis	4 (4)	8 (8)	8 (8)	3 (3)	7 (6)	6 (5)
★ Bronchitis	2 (2)	1 (< 1)	3 (3)	4 (4)	4 (4)	0
Pharyngolaryngeal pain	1 (< 1)	2 (2)	3 (3)	2 (2)	1 (< 1)	3 (3)
★ Upper respiratory tract infection	2 (2)	3 (3)	2 (2)	2 (2)	1 (< 1)	1 (< 1)
Dysphonia	0	1 (< 1)	1 (< 1)	1 (< 1)	2 (2)	3 (3)
Rhinitis	0	4 (4)	1 (< 1)	0	1 (< 1)	2 (2)
Rhinitis allergic	1 (< 1)	2 (2)	3 (3)	0	0	1 (< 1)
Dizziness	0	3 (3)	0	2 (2)	1 (< 1)	0
★ Influenza	2 (2)	0	1 (< 1)	3 (3)	0	0
Pharyngitis	4 (4)	2 (2)	0	0	0	0
★ Respiratory tract infection	0	1 (< 1)	0	3 (3)	1 (< 1)	0

AE = adverse event; AM = morning dosing; BD = twice daily; OD = once daily; PM = evening dosing

Retrospective study (Japan)

P: asthma patients with hospitalization for CAP, 1989-2001
Provincial health administrative data (retrospective cohort)
-> 87,690 asthma and 150,590 COPD
I: ICS user (oral steroid user excluded) (n=37)
C: non ICS user (n=25)
O: clinical characteristics of pneumonia

Table 5. Clinical Characteristics of Pneumonia in ICS Subjects

	<800 µg/day (n=8)	800 µg/day (n=18)	>800 µg/day (n=11)	p
Body temperature (°C)	37.9±0.8	37.8±1.3	37.4±0.6	NS
WBC (/µl)	11,390±3,458	12,088±4,652	11,066±4,547	NS
ESR (mm/h)	65.4±26.5	49.9±39.8	39.0±20.7	NS
CRP (mg/dl)	13.0±7.1	12.8±7.7	9.1±9.8	NS
★ Resolution period (d)	10.5±4.1	11.1±4.1	11.0±5.0	NS

- Turn over to Pf. Kim

Index

- Pathophysiology of pneumonia in asthma patients
- Non-ICS vs ICS
 - RCT: START trial
 - Meta-analysis
 - Prospective/retrospective study
- Dose dependence
 - RCT: FAST trial, SMART, RCT of FF
 - Retrospective study
- **Limitation of study suggesting increased pneumonia risk of ICS**

Limitation of study showing contrast results

- Retrospective study, health care database
 - Selection bias
 - Confounding factor (age, exclusion of COPD)

Retrospective, health care data (UK)



CHEST

Original Research

ASTHMA

6,857 asthma vs 36,312 sex and age matched In health care data

Inhaled Corticosteroids and the Risk of Pneumonia in People With Asthma

A Case-Control Study

Table 4—Analysis

Limitation

(n = 43,095)

ICS Use in the Past 90 d	adjusted OR ^b	95% CI
No steroids	1.00	...
Beclomethasone low dose ≤ 200 μg	1.12	0.94-1.33
Beclomethasone high dose > 200 μg	1.33	0.76-2.32
Budesonide low dose ≤ 200 μg	1.14	0.86-1.49
Budesonide high dose > 200 μg	1.19	0.66-2.16
Fluticasone low dose ≤ 250 μg	1.33	1.04-1.68
Fluticasone high dose > 250 μg	2.06	1.57-2.69

1. Definition: pneumonia or lower respiratory tract infection

2. Adjust: smoking status, comorbidity, influenza vaccination, Reliver inhaler, oral steroid, socioeconomic status

3. Pneumonia or LTRI: cause or results?

4. Type of ICS, different dose response?

Retrospective, health care data (Canada)

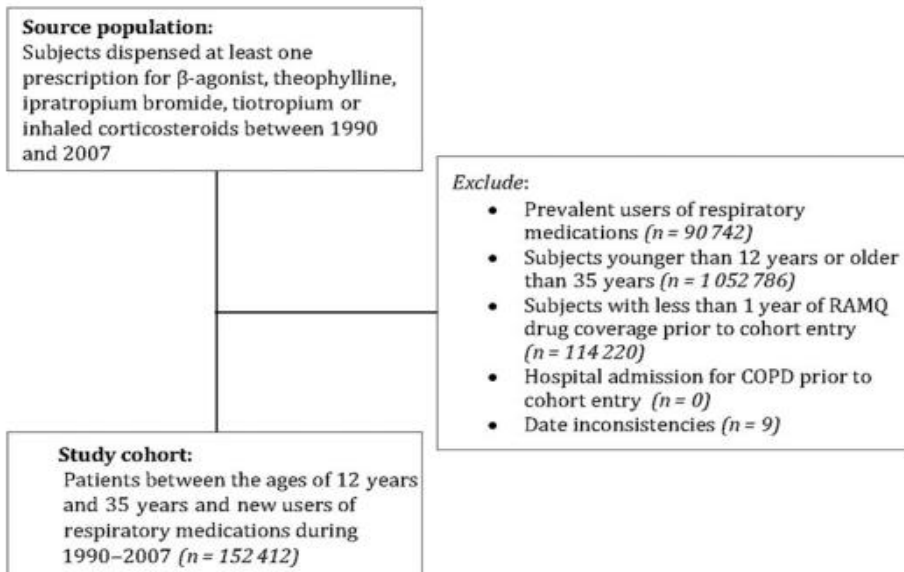
Pneumonia risk in asthma patients using inhaled corticosteroids: a quasi-cohort study

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Limitation

1. Selection bias: LAMA user?
2. Adjust: age, gender, comorbidity
3. ICS user: 60 days prior pneumonia
4. Not observed dose response



	No. with pneumonia	No. quasi-cohort (person-days)	Quasi-rates per 1000 person-years	Rate ratio	
				Crude	Adjusted ^a (95% CI)
Total number	1928	19 275	2.63		
Non-users^b	1515	17 442	2.29	1.00	Ref
Current users	413	1833	5.93	2.59	1.83 (1.57, 2.14)
Secondary analysis – dose^c					
Low dose	31	180	4.54	1.98	1.60 (1.06, 2.45)
Moderate dose	72	342	5.54	2.42	1.53 (1.12, 2.08)
High dose	310	1311	6.23	2.72	1.96 (1.64, 2.34)
Secondary analysis – type					
Budesonide	96	362	6.98	3.05	2.67 (2.05, 3.49)
Fluticasone	240	970	6.52	2.85	1.93 (1.58, 2.36)
Other ICSs	77	501	4.05	1.77	1.23 (0.92, 1.63)

Retrospective, health care data (Korea)

Table 1. Clinical characteristics according to inhaled corticosteroid use

Characteristics	ICS (-)		ICS (+)		P value
	No.	%	No.	%	
Total	447,855	100.0	281,488	100.0	
Age (yr)	56.7 ± 18.34		57.9 ± 17.66		< 0.001
Male (%)	172,121	38.4	121,641	43.2	< 0.001
Insurance type					< 0.001
Medical insurance	418,306	93.4	257,173	91.4	
Medical aid	29,549	6.6	24,315	8.6	
Hospital type					
Primary	404,262	90.3	195,198	69.3	< 0.001
Secondary	24,902	5.6	31,582	11.2	< 0.001
Tertiary	37,647	8.4	120,396	42.8	< 0.001
Comorbidity					
Ischemic heart disease	9,515	2.1	11,676	4.1	< 0.001
Osteoporosis	7,733	1.7	8,405	3.0	< 0.001
Depressive disorder	3,617	0.8	4,086	1.5	< 0.001
Arthritis	15,238	3.4	9,154	3.3	< 0.001
Diabetes mellitus	28,774	6.4	27,581	9.8	< 0.001
Congestive heart failure	4,879	1.1	6,035	2.1	< 0.001
Hypertension	56,962	12.7	54,287	19.3	< 0.001
Anemia	3,792	0.8	3,620	1.3	< 0.001
Metabolic syndrome	21,577	4.8	26,028	9.2	< 0.001
Allergic rhinitis	285,877	63.8	196,663	69.9	< 0.001
Malignancy	2,585	0.6	5,521	2.0	< 0.001
Charlson comorbidity index	1.3 ± 0.65		1.4 ± 18.28		< 0.001

ICS, inhaled corticosteroids

Claims for asthma, July 2013 and June 2014, HIRA
P: >15 years old with at least 2 outpatient visit,
Inpatient care with systemic steroid/asthma

Limitation

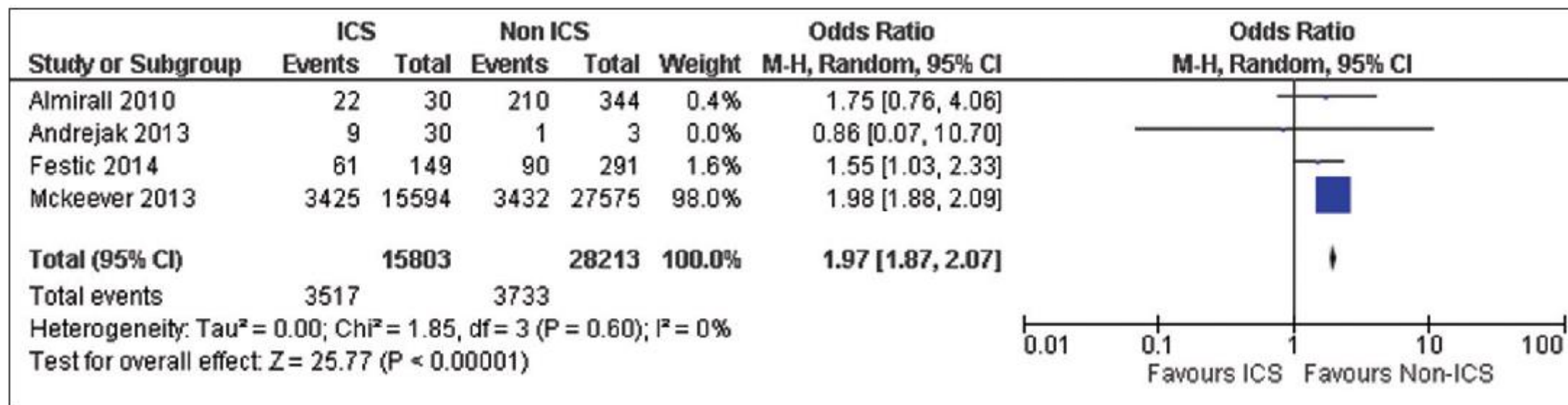
1. Primary clinics (87.8%)
2. Adjust: age, gender, comorbidity
3. Confounding factor: age, comorbidity, hospitalization, ER visit
4. Exclusion of COPD?

Complications

Pneumonia	43,978	9.8	50,237	17.8	< 0.001
Empyema	92	0.02	284	0.10	< 0.001
ARDS, acute respiratory failure	72	0.02	131	0.05	< 0.001
Pneumothorax	175	0.04	541	0.19	< 0.001
Pneumomediastinum	24	0.01	48	0.02	< 0.001

ICS, inhaled corticosteroids; ER, emergency room; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

Meta-analysis of observational study



Risk of bias

Table 5 Risk of bias assessment of observational studies

Study	Outcome	Preintervention		At intervention	Postintervention			
		Confounding	Participant selection	Intervention classification	Deviation from intended intervention	Missing data	Measurement of outcomes	Reporting results
Sasagawa <i>et al</i> ²²	Bone density	Critical	Serious	Serious	Low	No information	No information	Low
Sosa <i>et al</i> ²⁰	Bone density	Serious	Serious	Low	Low	No information	Moderate	Low
Langhammer <i>et al</i> ²¹	Bone density	Low	Moderate	Low	Low	No information	No information	Low
Israel <i>et al</i> ¹⁸	Bone density	Low	Moderate	Moderate	Low	Low	Low	Low
McKeever <i>et al</i> ²³	Pneumonia	Low	Moderate	Moderate	Low	Serious	Moderate	Low
Qian <i>et al</i> ²⁴	Pneumonia	Moderate	Serious	Moderate	Low	Low	Low	Low
Ekbom <i>et al</i> ²⁵	Pneumonia	Moderate	Moderate	Low	Low	No information	Low	Low
Kim <i>et al</i> ²⁶	Pneumonia	Moderate	Low	Serious	Low	No information	Serious	Low
Lee <i>et al</i> ²⁷	TB	Low	Low	Serious	Low	No information	Low	Low
Brode <i>et al</i> ²⁸	NTM	Low	Low	Low	Low	No information	No information	Low
Smeeth <i>et al</i> ²⁹	Cataracts	Moderate	Low	Moderate	Low	Low	Low	Low

NTM, non-tuberculous mycobacterial; TB, tuberculosis.

Aged ≥ 16 years hospitalized with CAP, Barcelona, 2003-2005 (N=663)

Confounding factor of ICS User



Inhaled corticosteroids and systemic inflammatory response in community-acquired pneumonia: A prospective clinical study

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- ICS user**
- older
 - Higher hx of pneumonia, CAP severity
 - Lower TNF-alpha
 - Lower mortality rate (30,60days)

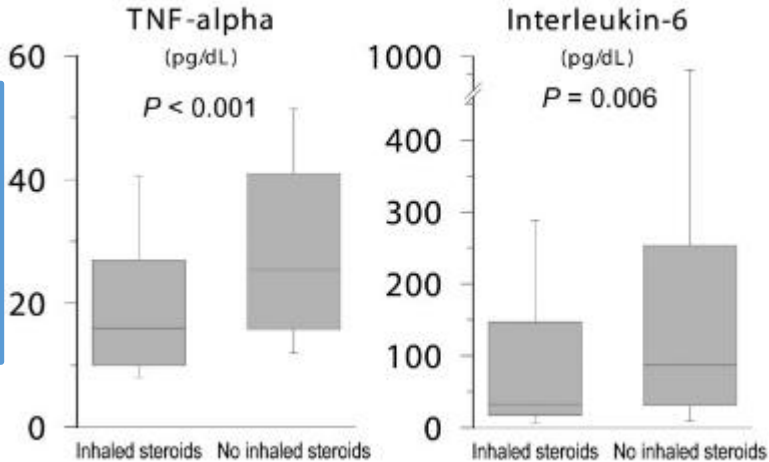


Table 1 Patients' characteristics on admission

	No ICS (n = 535)	ICS (n = 128)	P
Gender (male/female)	336/199	91/37	0.098
Age, years	65 ± 18	72 ± 11	<0.001
Smoking (current or former)	303 (57%)	92 (74%)	0.002
Alcohol abuse (current or former)	67 (13%)	17 (14%)	0.89
Chronic respiratory disease			
COPD	130 (24%)	80 (63%)	<0.001
Asthma	12 (2%)	28 (22%)	<0.001
Bronchiectasis	7 (1%)	4 (3%)	0.29
Pulmonary sequelae of tuberculosis	10 (2%)	6 (5%)	0.13
Other	9 (2%)	2 (2%)	NA
Other comorbidities			
Chronic heart disease	90 (17%)	29 (23%)	0.17
Chronic renal failure	29 (5%)	7 (6%)	>0.99
Chronic liver disease	21 (4%)	2 (2%)	0.30
Cancer	20 (4%)	5 (4%)	>0.99
Diabetes mellitus	95 (18%)	31 (24%)	0.13
Neurological disease	119 (22%)	16 (13%)	0.020
Previous antibiotics	178 (33%)	42 (33%)	0.99
Macrolides	36 (7%)	6 (5%)	0.52
Fluoroquinolones	27 (5%)	10 (8%)	0.31
Cephalosporins	26 (5%)	12 (9%)	0.082
Penicillins	65 (12%)	9 (7%)	0.14
Other	27 (5%)	5 (4%)	NA
Pneumonia in the previous year	117 (22%)	60 (47%)	<0.001
Previous influenza vaccination	215 (40%)	71 (56%)	0.002
Previous pneumococcal vaccination	72 (14%)	33 (26%)	0.001

Confounding factor-exclusion of COPD

Source	Age group	No. of patients	COPD excluded	Study type	Result	95% CI
Kim et al. [12]	>15 years	831,613	No; LAMA users included	Asthma ICS/asthma non-ICS	OR: 1.38	1.36-1.41
Ekbom et al. [13]	20-44 years	7,284	No; asthma self-reported diagnosis	Hospitalization/no-hospitalization	HR: 3.35	1.97-5.02
McKeever et al. [14]	18-80 years	43,169	Yes	Pneumonia/no pneumonia	OR: 1.24	1.5-1.79
Festic et al. [15]	43-70 years	1,234	Yes; asthma and COPD reported separately	Asthma ICS/asthma non-ICS	OR: 1.07 for asthma	0.61-1.87
					OR: 1.4 for COPD	0.95-2.09
To et al. [16]	16-83 years	62	Yes	Asthma ICS/asthma non-ICS	No difference	
Almirall et al. [17]	>14 years	2,662	Yes; asthma and COPD reported separately	Pneumonia/pneumonia (case-control)	OR: 1.1 for asthma	0.4-3.00
					OR: 3.26 for COPD	1.07-9.98

Discussion and conclusion

- Many RCT showed that there is no association with ICS use and pneumonia in asthma patients
- Several observational retrospective study had many limitations especially study design (retrospective), selection bias, and confounding factor and these study can't show causality
- ICS is not associated with risk of pneumonia in asthma