Short Acting Beta Agonist Use Associated with Increased Mortality and Morbidity in Asthma Patients: A Systematic Review and Meta-Analysis

Yiyun Hu[1], Janice Y. Kung[2], Dimitri Galatis[3], Hoan Linh Banh[4]

[1]Department of Pharmacy, The Second Xiangya Hospital, Central South University, Changsha, Hunan; [2]University of Alberta, John W. Scott Health Sciences Library; [3]University of Alberta, Faculty of Pharmacy and Pharmaceutical Sciences; [4]University of Alberta, Faculty of Medicine and Dentistry, Department of Family Medicine

Corresponding authors: Yiyun Hu, Department of Pharmacy, the Second Xiangya Hospital of Central South University, 139 Renmin Middle Rd. Changsha, Hunan, China, 410008; email: huyiyun89@126.com; Hoan Linh Banh, Faculty of Medicine and Dentistry/Department of Family Medicine, University of Alberta; 6-10 University Terrace, Edmonton, AB, T6G 2C6, Canada; email: hoan@ualberta.ca

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ABSTRACT -- Purpose: Short acting β2 agonists are recommended to be used ≤ 2 canisters per year. It is suggested that overuse of β2 agonists will lead to increased morbidity and mortality. This study aimed to determine if overuse of β2 agonists result in increased morbidity and mortality. **Methods:** We performed a systematic review and meta-analysis of the literature to determine if overuse of β2 agonists cause increase mortality, ICU admissions, hospitalization, and exacerbation. **Results:** A total of 11,888 publications were identified and 4260 duplications were removed, resulting in 7268 abstracts that were screened and 7254 irrelevant studies that were excluded. Ultimately, 14 studies were included. The overall pooled estimated odds ratio (OR) for mortality was 0.83 (95% CI: 0.66, 1.05), 0.99 for ICU admission (95% CI: 0.80, 1.21), 1.22 for hospitalization (95% CI: 0.96, 1.31), and 0.99 for exacerbation (95% CI: 0.85, 1.15). **Conclusion:** There is no statistical difference in mortality, ICU admission rate, hospitalization, or exacerbation with using β2 agonists.

INTRODUCTION

Asthma is a chronic airway inflammatory disease which presents with symptoms of wheezing, shortness of breath, chest tightness and cough (1). Currently, the Global Initiative for Asthma (GINA) recommends the use of low dose inhaled corticosteroid (ICS) and formoterol (a rapid onset long acting β2 agonist) combination for symptom relief and if that is not possible, then the use of ICS on schedule and short acting β2 agonist (SABA) as needed for relief (1). It is not recommended to treat asthma with SABA as monotherapy (1). β2 agonists are a potent bronchodilator and play an important role in symptom relief. Although it is recommended that all patients with asthma should have a SABA inhaler, regular use of SABA causes hyperresponsiveness (2). Studies showed that overuse of SABA occurs in patients with worsening asthma control who seek them for relief due to ICS underuse (3). SABA overuse, although prevalent, has been associated with worsening of asthma control and increased risk of death (4-7). Results from the studies are conflicting and have created controversy in the recommendations for asthma treatment. We performed a systematic review and meta-analysis of the literature to determine effects of SABA overuse in asthma patients. The primary outcome is mortality. The secondary outcomes are: 1) intensive care unit (ICU) admission; 2) hospitalization; and 3) exacerbation. The systematic review and meta-analysis are registered on PROSPERO (CRD42021279882).

METHODS

The reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement (8). The

medical librarian (JYK) developed and executed comprehensive searches in Ovid MEDLINE, Ovid Embase, CINAHL, and Cochrane Library (via Wiley) on October 28, 2021. To capture all relevant literature concerning the use of short acting beta agonists in asthma patients, relevant keywords and controlled vocabulary were carefully selected. Searches were limited to English language. Refer to Appendix I for full-text search strategies. A total of 11,888 results were retrieved and, after removing duplicates, 7,628 unique results remained for the initial title and abstract screening in a web-based tool called Covidence (www.covidence.org). In addition to subscription databases, the research team reviewed the first 200 Google Scholar results for inclusion. Bibliographies from included studies were also reviewed (Appendix I).

Data extraction and quality assessment

The references were independently reviewed by two authors (YYH, HLB). Disagreements were resolved by a third author (DG). The data was independently extracted by two authors (YYH, HLB). This included: subject demographic characteristics, first author, year of publication, design of the study, population, intervention, comparator, sample size, and all outcome measures. The meta-analysis consisted of observational studies with the following inclusion criteria: 1) asthma patients, 2) SABA use, 3) mortality, 4) intensive care unit (ICU) admission, 5) hospitalization, 6) exacerbation. Exclusion criteria were: 1) non asthma patients, and 2) no SABA use.

STATISTICAL ANALYSIS

The pooled estimates of odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to compare the OR of clinical outcomes between the SABA group and no SABA group based on the events of reported mortality, ICU admission, hospitalization, and exacerbation. The inverse variance method was used for outcomes represented by OR with a 95% CI. I^2 statistic was applied to inspect heterogeneity. For $I^2 < 50\%$ and p value > 0.1, heterogeneity was acceptable. For $I^2 > 50\%$ and p value < 0.1, the random effect or a meta-regression method to find sources for the obvious heterogeneity was performed. Because the meta-analysis had less than 10 studies, the funnel plot and Egger test were not used to assess the presence of small study effects. Because the included studies are observational studies, the quality of the studies were not assessed as they all have a high risk of bias. All the statistical analyses were performed in Review Manager (RevMan. version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2021).

RESULTS

A total of 11,888 publications were identified and 4260 duplications were removed, resulting in 7268 abstracts that were screened and 7254 irrelevant studies that were excluded. Ultimately, 13 observational studies and one RCT (Dennis) were included (Figure 1). The three SABAs included in the studies were salbutamol, albuterol, and fenoterol in either metered dose inhaler or nebulizer. Most of the comparators used in the studies were inhaled corticosteroids, oral steroids, or salmeterol. The characteristics of the studies are summarized in Table 1. One study (Strunk) focused on the pediatric population. One study by Pearce (16) only examined patients with asthma between the ages of 4 and 45. One study by Crane (12) reported two separate ORs for metered dose inhaler and nebulizer. Splitzer et al. (19) reported the odds ratio for each SABA use.

Effect of SABA use on mortality

A total of 28,179 patients were included in the analysis. The overall pooled estimated odds ratio (OR) for all studies was 0.83 (95% CI: 0.66, 1.05) using a random effect model with low observed heterogeneity ($I^2 = 0\%$, $p = 0.64$) (Figure 2). After removing two studies from the analysis due to small sample sizes (Pearce 2009 and Splitzer) (Figure 2A), the OR was 0.83 (95% CI: 0.65, 1.04). Thus, did not affect the results.

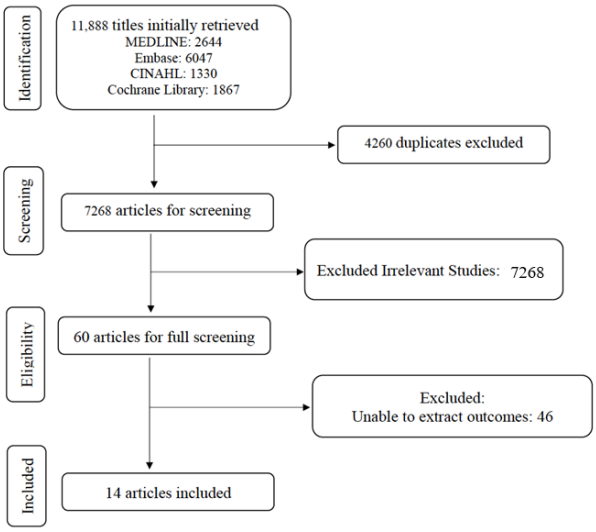


Figure 1. PRISMA.

Effect of SABA use and ICU admission

Even though only four studies reported OR for ICU admission, a total of 371,374 patients were included. The pooled estimated OR was 0.99 (95% CI: 0.80, 1.21) using a random effect model with low observed heterogeneity ($I^2 = 0\%$, $p = 0.90$) (Figure 3).

Effect of SABA use and hospitalization

Only 2 studies were included in the analysis for hospitalization with 368,700 patients. The pooled estimated OR was 1.22 (95% CI: 0.96, 1.31) using a random effect model with low observed heterogeneity ($I^2 = 0\%$, $p = 0.43$) (Figure 4).

Effect of SABA use and exacerbation

The exacerbation analysis included five studies with 35,752 patients. The pooled estimated OR was 0.99 (95% CI: 0.85, 1.15) using a random effect model with low observed heterogeneity ($I^2 = 0\%$, $p = 0.65$) (Figure 5).

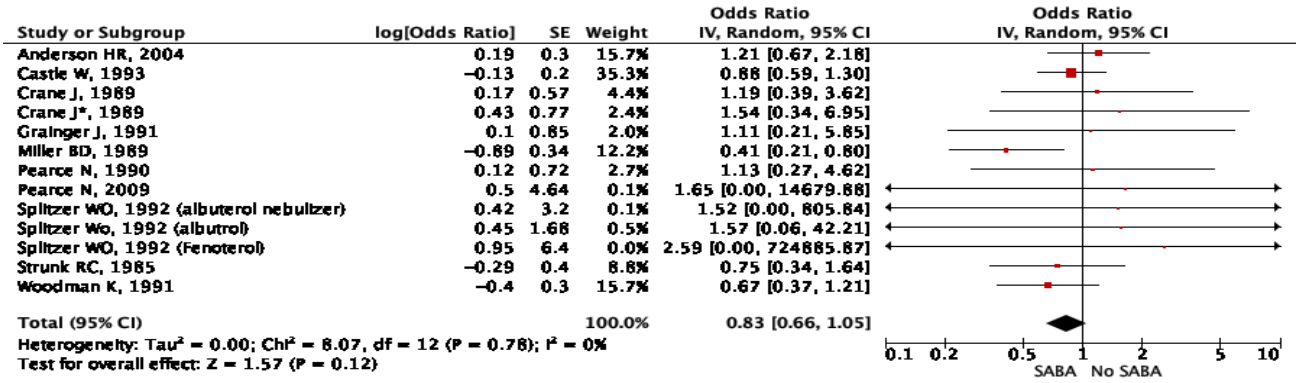
DISCUSSION

This meta-analysis showed that SABA use or overuse did not affect mortality, ICU admission, hospitalization, or exacerbation. Most studies defined overuse as using more than 1 canister of 200 doses per month as per GINA recommendation (1). The studies in the analysis included all three SABAs (salbutamol, albuterol, and fenoterol). SABAs are selective β2 agonists which have a rapid onset and are short acting agents. β2 receptors are a combination of G proteins, and adenylyl cyclase (23). Activation of the β2 receptors result in the smooth muscle of the lung, dilation, and opens the airway (24). SABAs are effective in acute asthma symptom control. Crane et al. in 1989, (12) published a case-control study suggesting that overuse of fenoterol increased the risk of death in patients with asthma in New Zealand. The theory was that fenoterol is less beta-selective than salbutamol. The exact mechanism for the increased death is still unclear. Long-term use of SABA, however, could be associated with tachyphylaxis and hyperresponsiveness (25). In this meta-analysis, Splitzer et al. examined the risk of death with each SABA use. Although the results are statistically significant, the sample size is very small as the confidence intervals are extremely wide. Removal of these two studies did not alter the results. Three studies (Castle, Eisner, and Fitzgerald) had significantly larger sample sizes and the ORs are not statistically significant.

Studies also showed that persistent use of SABA did not prompt the health care professionals to make changes to the asthma management (26-27). Currently, GINA recommends that patients who are well controlled should have no need for SABA more than two inhalations a week which equates to two canisters a year (1). It is important for all primary care providers to monitor the use SABA on a regular basis to avoid overuse.

LIMITATIONS

The meta-analysis consists of 14 observational studies, and they all have high risk of publication bias. In addition, the data in the studies were collected from the 1990's except for two studies (Bateman and Van Ganse). Most of these studies did not disclose concurrent treatments such theophylline or systemic corticosteroids which may lead to increase mortality and morbidity. Lastly, potential confounders such as



*nebulizer

Figure 2. Forest plot for SABA use and mortality.

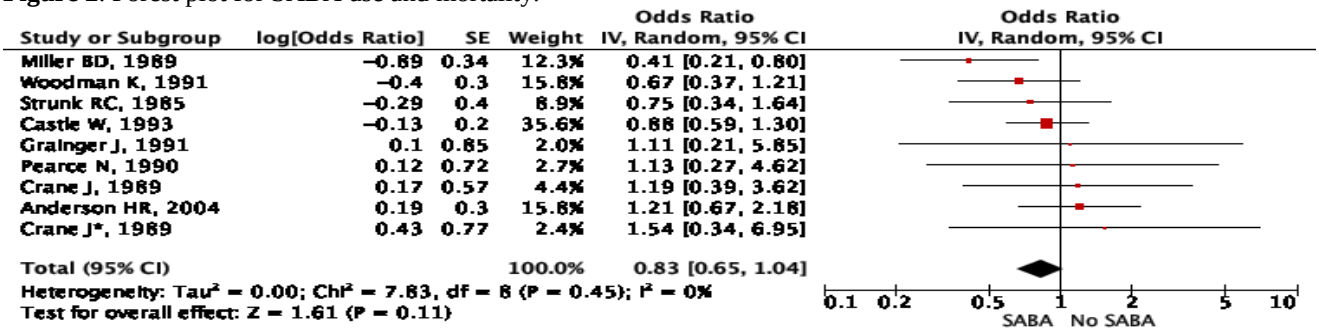


Figure 2A. Forest plot for SABA use and mortality after two studies (Pearce and Splitzer) with small sample sizes were removed.

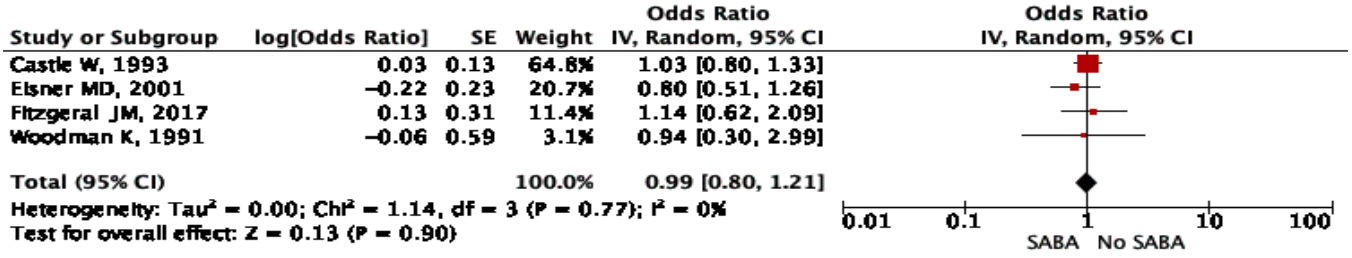


Figure 3. Forest plot for SABA use and ICU admission.

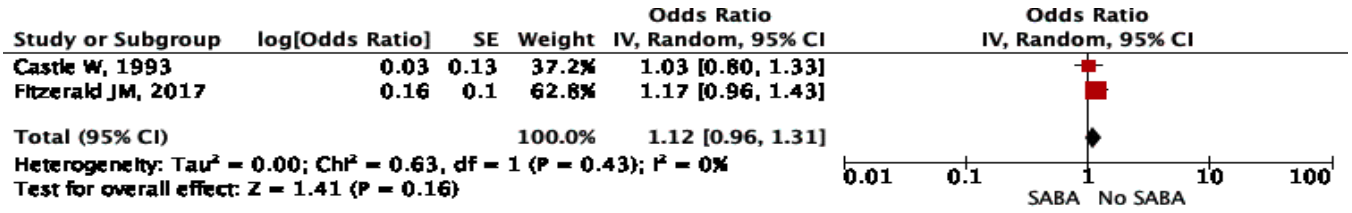


Figure 4. Forest plot for SABA use and hospitalization

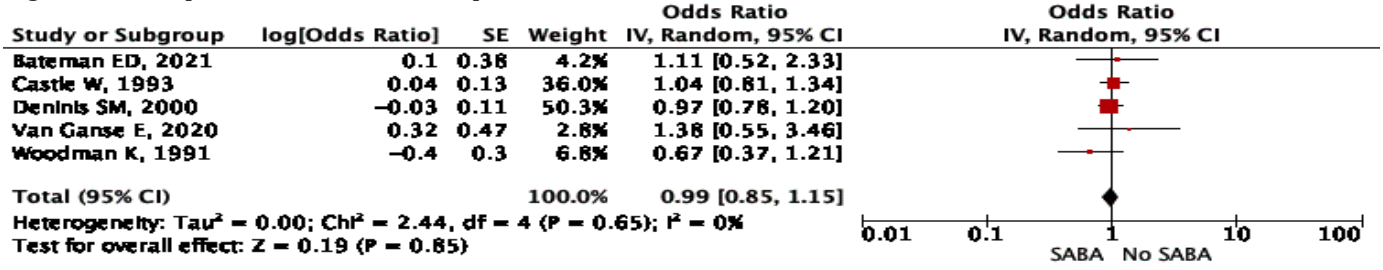


Figure 5. Forest plot for SABA use and exacerbation.

Table 1. Characteristics of the studies (10-23)

Author, year	Journal	Patient characteristics, sample size	Outcomes	SABA	Comparator
Anderson HR, 2004	BMJ	n = 1064, (G1 = 532, G2 = 532)	Mortality	Fenoterol	Salmeterol
Bateman ED, 2021	Eur Respir J	n = 8351	Exacerbation	β2 agonist	No β2 agonist
Castle W, 1993	BMJ	n = 25180 (G1 = 7082 G2 = 14113)	Mortality Hospital admission Exacerbation	Salbutamol	Salmeterol
Crane J, 1989	Lancet	n = 585 (G1 = 117, G2 = 468)	Mortality Hospital admission	Fenoterol Salbutamol	No β2 agonist
Dennis SM, 2000	Lancet	n = 983 (G1 = 486, G2 = 487)	Exacerbation	Salbutamol	Placebo
Eisner MD, 2001	Eur Respir J	n = 2344, (G1 = 1550, G2 = 794)	ICU admission	β2 agonist	ICS
Fitzerald JM, 2017	Resp Med	343,520	ICU admission Hospitalization	β2 agonist	No β2 agonist
Grainer J, 1991	Thorax	n = 539 (G1 = 121, G2 = 427)	Mortality	β2 agonist	No β2 agonist
Miller BD, 1989	Am J Dis Child	n = 24 (G1 = 12, G2 = 12)	Mortality	β2 agonist	No β2 agonist
Pearce N, 1990	Thorax	n = 138, (G1 = 69, G2 = 69)	Mortality	Salbutamol, fonoterol	No β2 agonist
Splitzer WO, 1992	NEJM	n = 277 (G1 = 44, G2 = 233)	Mortality	β2 agonist	No β2 agonist
Strunk RC, 1985	JAMA	n = 42 (G1 = 22, G2 = 21)	Mortality	β2 agonist	No β2 agonist
Van Ganse E, 2020	Ann Allergy Asthma Immunol	n = 908	Exacerbation	β2 agonist	No β2 agonist
Woodman K, 1991	Clin Pharmcacol Ther	n = 330 (G1 = 58, G2 - 227)	Mortality Exacerbation	β2 agonist	No β2 agonist

administration of inhaled corticosteroids, which could affect clinical outcomes, were given to patients in many of the studies and may cause bias.

CONCLUSION

There is no statistical difference in mortality {0.83 (95% CI: 0.66, 1.05)}, ICU admission rate {1.22 (95% CI: 0.96, 1.31)}, hospitalization {1.22 (95% CI: 0.96, 1.31)}, and exacerbation {0.99 (95% CI: 0.85, 1.15)} in asthma patients with SABA use.

CONFLICT OF INTEREST. All authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTION. HLB conceived and conceptualized the research idea. JK conducted comprehensive searches. YH and HLB reviewed the search, performed the screening and full text assessment. DG resolved any conflicts. YH. and HLB completed the quality assessment and data extraction. HLB performed the data analyses, HLB. And YH interpreted the results. YH. and HLB contributed to the draft manuscript. All authors contributed to the revisions and final proof reading.

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Appendix I. Search Strategies

Database	Search Strategy
MEDLINE **Ovid MEDLINE(R) ALL** 1946 to October 04, 2021	1. (short acting adj2 (beta agonist* or bronchodilator*)).mp. 2. (short acting adj2 (beta 2-agonist* or beta2 agonist*)).mp. 3. exp Adrenergic beta-2 Receptor Agonists/ 4. (albuterol or fenoterol or isoetharine or levalbuterol or metaproterenol or orciprenaline or pirbuterol or salbutamol or terbutaline).mp. 5. SABA*.ti,ab,kf. 6. or/1-5 7. asthma*.mp. or exp Asthma/ 8. exp Mortality/ 9. (mortalit* or death* or dying or fatalit*).ti,ab,kf. 10. morbidit*.mp. 11. (exacerbat* or worse*).mp. 12. exp Critical Care/ 13. (intensive care or critical care or ICU).ti,ab,kf. 14. exp Hospitalization/ or (hospitali?ation* or hospitali?ed).mp. 15. (admission* or admitt* or readmission* or re-admission*).ti,kf. or (admission* or admitt* or readmission* or re-admission*).ab. /freq=2 16. or/8-15 17. 6 and 7 and 16 18. limit 17 to english language
Embase **Ovid Embase** 1974 to 2021 October 04	1. (short acting adj2 (beta agonist* or bronchodilator*)).mp. 2. (short acting adj2 (beta 2-agonist* or beta2 agonist*)).mp. 3. exp beta 2 adrenergic receptor stimulating agent/ 4. (albuterol or fenoterol or isoetharine or levalbuterol or metaproterenol or orciprenaline or pirbuterol or salbutamol or terbutaline).mp. 5. or/1-4 6. asthma*.ti,ab,kw. or exp *asthma/ 7. exp *mortality/ 8. (mortalit* or death* or dying or fatalit*).ti,ab,kw. 9. morbidit*.mp. 10. (exacerbat* or worse*).ti. or (exacerbat* or worse*).ab. /freq=2 11. exp *intensive care/

12. (intensive care or critical care or ICU).ti,ab,kw.
13. (hospitali?ation* or hospitali?ed).ti,kw. or (hospitali?ation* or hospitali?ed).ab. /freq=2
14. (admission* or admitt* or readmission* or re-admission*).ti,kw. or (admission* or admitt* or readmission* or re-admission*).ab. /freq=2
15. or/7-14
16. 5 and 6 and 15
17. limit 16 to english language

CINAHL	S1	(short acting N2 (beta agonist* or bronchodilator*))
	S2	(short acting N2 (beta 2-agonist* or beta2 agonist*))
	S3	(MH "Adrenergic Beta-Agonists+")
	S4	albuterol or fenoterol or isoetharine or levalbuterol or metaproterenol or orciprenaline or pirbuterol or salbutamol or terbutaline
	S5	SABA*
	S6	S1 OR S2 OR S3 OR S4 OR S5
	S7	(MH "Asthma+") OR "asthma*"
	S8	(MH "Mortality+")
	S9	mortalit* or death* or dying or fatalit*
	S10	morbidit*
	S11	exacerbat* or worse*
	S12	(MH "Critical Care+")
	S13	"intensive care" or "critical care" or ICU
	S14	(MH "Hospitalization+")
	S15	hospitali?ation* or hospitali?ed
	S16	TI ((admission* or admitt* or readmission* or re-admission*) OR AB ((admission* or admitt* or readmission* or re-admission*)
	S17	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
	S18	S6 AND S7 AND S17 [Limit to English language]
Cochrane Library	#1	(short acting NEAR/2 (beta agonist* or bronchodilator*))
	#2	(short acting NEAR/2 (beta 2 agonist* or beta2 agonist*))
	#3	[mh "Adrenergic beta-2 Receptor Agonists"]
via Wiley	#4	albuterol or fenoterol or isoetharine or levalbuterol or metaproterenol or orciprenaline or pirbuterol or salbutamol or terbutaline
(Cochrane	#5	SABA*:ti,ab,kw
Reviews, Trials)	#6	{OR #1-#5}
	#7	[mh Asthma] or asthma*
	#8	[mh Mortality]
	#9	(mortalit* or death* or dying or fatalit*):ti,ab,kw
	#10	morbidit*
	#11	exacerbat* or worse*
	#12	[mh "Critical Care"]
	#13	("intensive care" or "critical care" or ICU):ti,ab,kw
	#14	[mh Hospitalization]
	#15	hospitali?ation* or hospitali?ed
	#16	(admission* or admitt* or readmission* or re-admission*):ti,ab,kw
	#17	{OR #8-#16}
	#18	#6 AND #7 AND #17
Google Scholar	(short acting beta agonists OR SABA) AND asthma AND (mortality OR death OR morbidity OR "critical care" OR "intensive care")	