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合併使用 budesonide 及 formoterol 與單獨使用 budesonide 產生嚴重氣喘症狀之評估[1]

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壹、 背景

依照氣喘治療指引 GINA 2016[2]，氣喘長期目標是要控制氣喘的病情，盡可能減少氣喘惡化及副作用的產生。階梯式的療法可以針對輕、中、及重度的氣喘病患使用不同強度的藥物以達到長期目標的療效。其中，在中重度的患者需要吸入型的類固醇加上長效性的支氣管擴張劑 LABA(long acting beta2 agonist)來作控制，但因曾經有大型研究指出使用 salmeterol 這個 LABA 藥物會較使用 SABA 類藥物或安慰劑有較高的氣喘相關性死亡與其他與嚴重性氣喘相關的症狀[3,4]，此篇研究即是探討合併使用類固醇與長效性支氣管擴張劑 formoterol 的安全性。

貳、 研究方法

此篇 26 週的雙盲研究來自於多個醫療中心，收納病人為 12 歲以上有持續性氣喘至少 1 年、每日接受氣喘藥物治療、及

在過去一年曾經有 1 至 4 次氣喘惡化，使用 budesonide 併 formoterol 或 budesonide 單用的病人;曾有過危及生命的氣喘、4 次以上獨立的氣喘惡化、2 次以上因氣喘住院、在隨機分配的 7 天內產生不穩定氣喘、及抽菸超過 10 年的病人則排除在外。起始收納人數為 12,460 人，其中 767 人因故被排除，故納入實驗的人數為 11,693 人；將納入實驗人數以 1:1 隨機分配的方式分為兩組，分別為 budesonide-formoterol 組 5,846 人和 budesonide 組 5,847 人，其中再分高劑量與低劑量組，分別為低劑量的 budesonide 80μg-formoterol 4.5μg 組 1,645 人和 budesonide 80μg 組 1,646 人，以及高劑量的 budesonide 160μg-formoterol 4.5μg 組 4,201 人和 budesonide 160μg 組 4,201 人，使用方法為每日兩次。主要終點(end point)主要評估嚴重氣喘的事件發生情況(包含氣喘相關死亡、插管、以及住院)，安全評估包含嚴重的不良反應發生情況、因不良反應而停止用藥、以及因氣喘惡化而停止用藥。此實驗也評估藥物之療效，其主要終點就是氣喘惡化。

參、 研究結果

此實驗自 2011 年至 2015 年，收納共 11,693 位病人，經過實驗過程後，共有 11,551 人完成實驗。

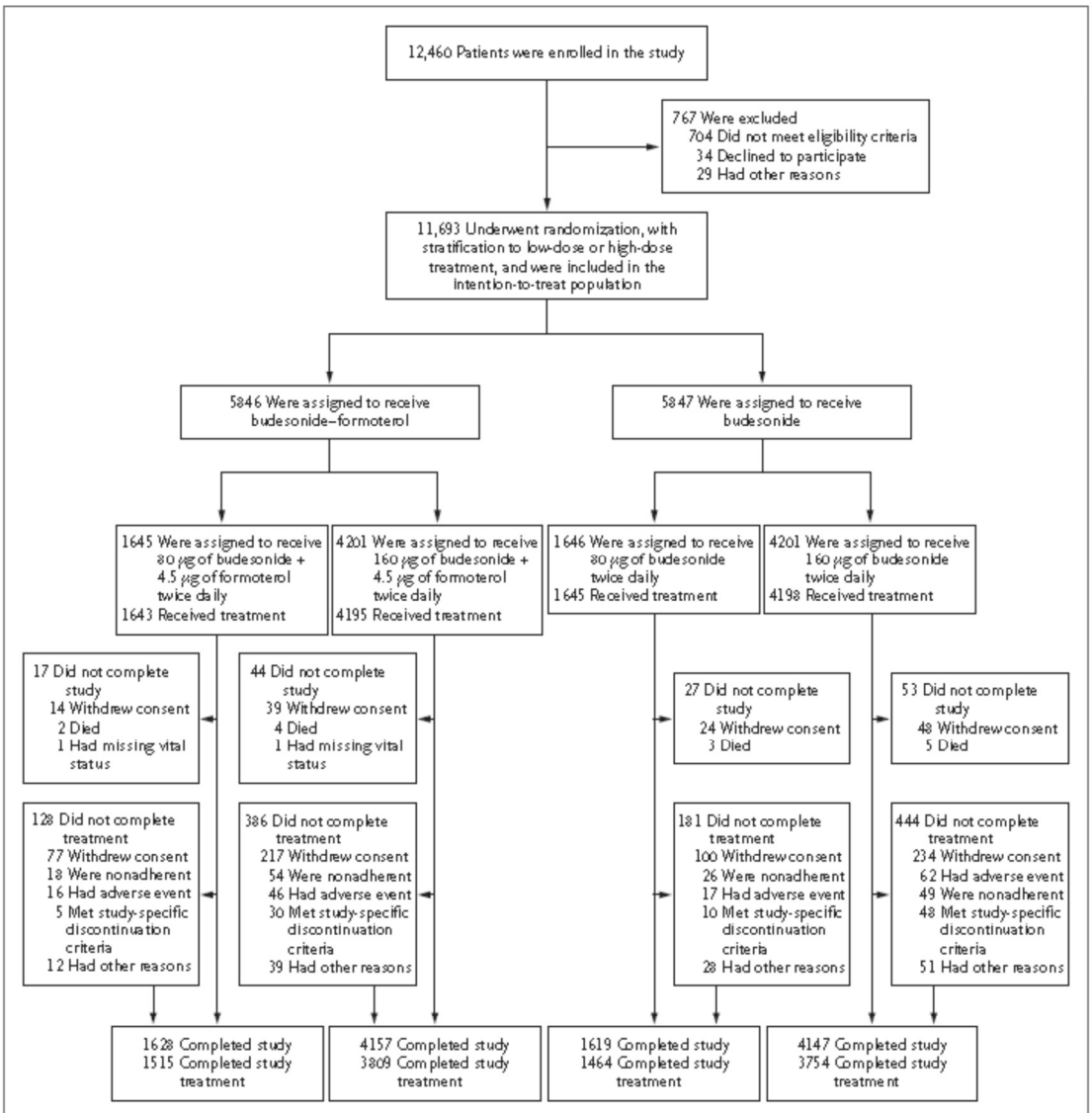


Figure 1. Screening, Randomization, and Follow-up.

All patients who underwent randomization to treatment were included in the intention-to-treat population, regardless of whether they received treatment. Each dose of medication was provided through two actuations of a pressurized metered-dose inhaler. Owing to missing information in the electronic case-report form, one patient in the group receiving 160 μg of budesonide was not included in the number of patients who completed the study, but the patient underwent follow-up for the complete duration of the study. The study-specific discontinuation criteria are related to asthma exacerbation.

此實驗分為兩組，分別為 budesonide-formoterol 組及 budesonide 組，經分析後表示此兩組人在基本資料上無顯著不同。

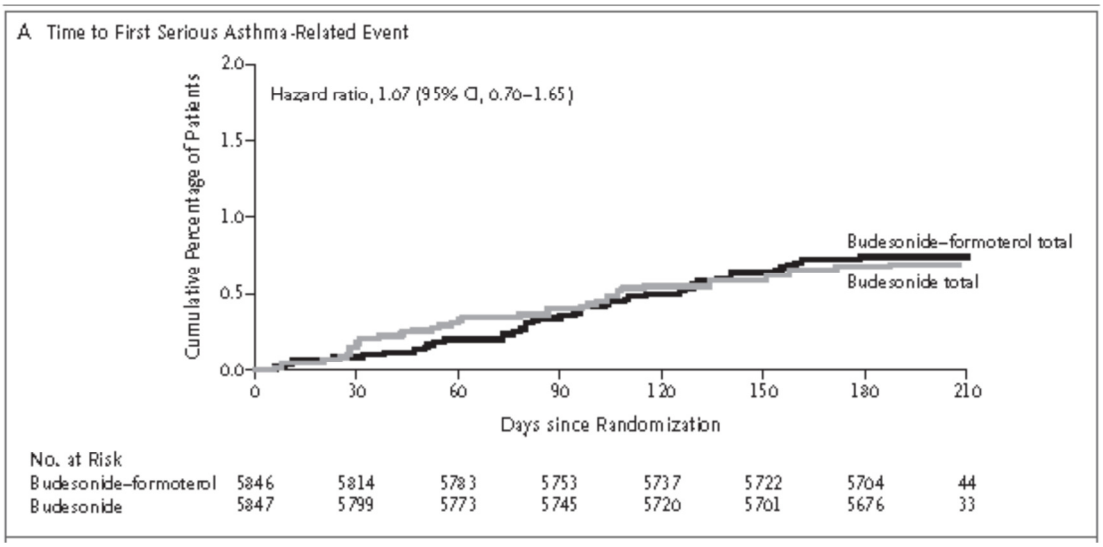
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Low Dose		High Dose		Total	
	Budesonide–Formoterol 80 μg + 4.5 μg (N=1645)	Budesonide 80 μg (N=1646)	Budesonide–Formoterol 160 μg + 4.5 μg (N=4201)	Budesonide 160 μg (N=4201)	Budesonide–Formoterol (N=5846)	Budesonide (N=5847)
Age — yr	39.3±18.4	40.4±18.2	45.1±16.7	44.7±16.8	43.4±17.4	43.5±17.3
Age group — no. (%)						
12–17 yr	304 (18.5)	277 (16.8)	328 (7.8)	359 (8.5)	632 (10.8)	636 (10.9)
18–64 yr	1188 (72.2)	1208 (73.4)	3384 (80.6)	3360 (80.0)	4572 (78.2)	4568 (78.1)
≥65 yr	153 (9.3)	161 (9.8)	489 (11.6)	482 (11.5)	642 (11.0)	643 (11.0)
Female sex — no. (%)	1043 (63.4)	1032 (62.7)	2806 (66.8)	2788 (66.4)	3849 (65.8)	3820 (65.3)
Race — no. (%)†						
White	1150 (69.9)	1137 (69.1)	2900 (69.0)	2866 (68.2)	4050 (69.3)	4003 (68.5)
Black	111 (6.7)	103 (6.3)	285 (6.8)	298 (7.1)	396 (6.8)	401 (6.9)
Asian	267 (16.2)	291 (17.7)	581 (13.8)	616 (14.7)	848 (14.5)	907 (15.5)
Other	117 (7.1)	115 (7.0)	435 (10.4)	421 (10.0)	552 (9.4)	536 (9.2)
Smoking status — no. (%)						
Never	1439 (87.5)	1383 (84.0)	3502 (83.4)	3538 (84.2)	4941 (84.5)	4921 (84.2)
Current	47 (2.9)	53 (3.2)	139 (3.3)	127 (3.0)	186 (3.2)	180 (3.1)
Former	159 (9.7)	210 (12.8)	560 (13.3)	536 (12.8)	719 (12.3)	746 (12.8)
Mean time since asthma diagnosis — yr	14.7	15.3	15.5	15.5	15.3	15.4
Mean ACQ-6 score at randomization‡	1.2±0.9	1.2±0.9	1.4±0.9	1.4±0.9	1.4±0.9	1.4±0.9
Asthma-control status at randomization — no. (%)						
Controlled: ACQ-6 <1.5	1154 (70.2)	1186 (72.1)	2321 (55.2)	2342 (55.7)	3475 (59.4)	3528 (60.3)
Uncontrolled: ACQ-6≥1.5	491 (29.8)	460 (27.9)	1880 (44.8)	1859 (44.3)	2371 (40.6)	2319 (39.7)
Exacerbations in past 12 mo — no. (%)						
0	1 (0.1)	2 (0.1)	6 (0.1)	6 (0.1)	7 (0.1)	8 (0.1)
1	1444 (87.8)	1403 (85.2)	3433 (81.7)	3421 (81.4)	4877 (83.4)	4824 (82.5)
2	161 (9.8)	197 (12.0)	611 (14.5)	599 (14.3)	772 (13.2)	796 (13.6)
3	35 (2.1)	39 (2.4)	120 (2.9)	141 (3.4)	155 (2.7)	180 (3.1)
≥4	4 (0.2)	4 (0.2)	31 (0.7)	32 (0.8)	35 (0.6)	36 (0.6)
Daily dose of inhaled glucocorticoid — no. (%)§						
None	474 (28.8)	464 (28.2)	103 (2.5)	120 (2.9)	577 (9.9)	584 (10.0)
Low	1068 (64.9)	1062 (64.5)	707 (16.8)	689 (16.4)	1775 (30.4)	1751 (29.9)
Medium	76 (4.6)	84 (5.1)	2823 (67.2)	2815 (67.0)	2899 (49.6)	2899 (49.6)
High	27 (1.6)	36 (2.2)	568 (13.5)	577 (13.7)	595 (10.2)	613 (10.5)

* Plus–minus values are means ±SD. At the time of randomization, patients were stratified to a low dose or a high dose of inhaled glucocorticoids on the basis of asthma control and prior asthma therapy. According to a post hoc analysis, there were no significant between-group differences in baseline characteristics.
† Race was self-reported.
‡ The six-item Asthma Control Questionnaire (ACQ-6) assesses asthma symptoms on a scale of 0 to 6, with higher values indicating worse symptoms.
§ On the basis of the latest dose taken within 4 weeks before randomization, a low dose was defined as 250 μg or less of beclomethasone dipropionate with a hydrofluoroalkane propellant (BDP-HFA) or fluticasone propionate or 400 μg or less of budesonide, a medium dose as 251 to 500 μg of BDP-HFA or fluticasone propionate or 401 to 800 μg of budesonide, and a high dose as more than 500 μg of BDP-HFA or fluticasone propionate or more than 800 μg of budesonide.[14]

在主要終點的評估中，budesonide-formoterol 組有 43 人產生嚴重氣喘問題，總共 49 個問題產生，而 budesonide 組有 40 人產生嚴重氣喘問題，總共 45 個問題產生；有兩個氣喘相關死亡案例，皆為 budesonide-formoterol 組。統計學上顯示無論在高劑量或者在低

劑量的情況下，budesonide-formoterol 組及 budesonide 組沒有顯著的風險差異(hazard ratio, 1.07; 95% confidence interval [CI], 0.70 to 1.65)。



在任何情況的死亡方面，budesonide-formoterol 組有 6 人，budesonide 組有 8 人；在兩組皆有 2.1%人產生嚴重不良反應，budesonide-formoterol 組有 1.6%因不良反應而停藥，budesonide 組則有 2.3%。

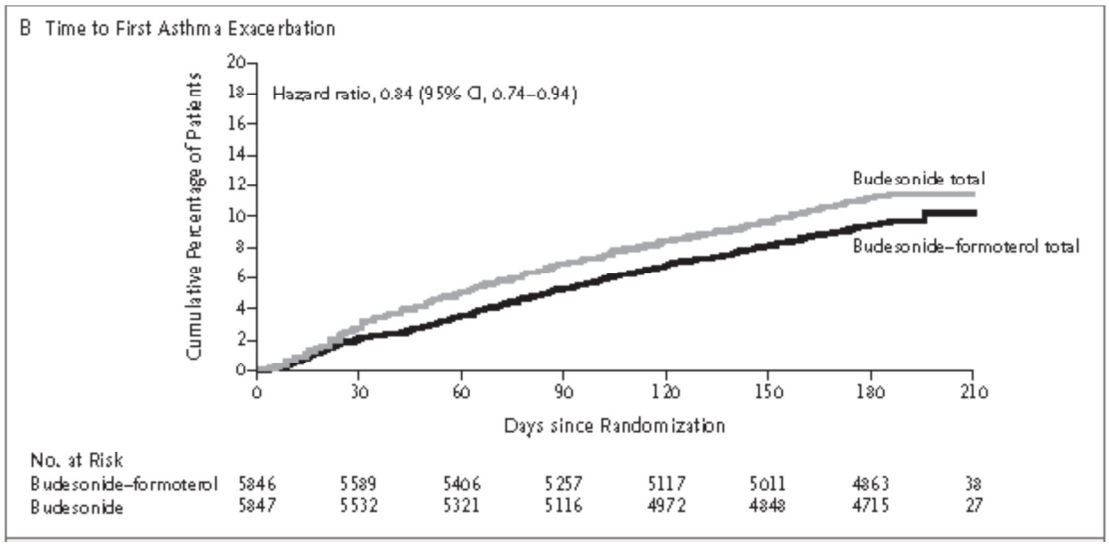
Table 3. Rates of Adverse Events.*

Event	Low Dose		High Dose		Total	
	Budesonide–Formoterol 80 μg + 4.5 μg (N=1645)	Budesonide 80 μg (N=1646)	Budesonide–Formoterol 160 μg + 4.5 μg (N=4201)	Budesonide 160 μg (N=4201)	Budesonide–Formoterol (N=5846)	Budesonide (N=5847)
	number (percent)					
Any serious adverse event	21 (1.3)	31 (1.9)	104 (2.5)	92 (2.2)	125 (2.1)	123 (2.1)
Any adverse event leading to study discontinuation	20 (1.2)	27 (1.6)	73 (1.7)	105 (2.5)	93 (1.6)	132 (2.3)
Any adverse event with outcome of death	2 (0.1)	3 (0.2)	4 (0.1)	5 (0.1)	6 (0.1)	8 (0.1)

* All data in this table were derived from the intention-to-treat population, which comprised all patients who were randomly assigned to treatment.

在主要療效終點方面，budesonide-formoterol 組有 539 人回報了 637 件氣喘惡化情況，budesonide 組則有 633 人回報了 762 件氣喘

惡化情況，在氣喘惡化的風險來說，budesonide-formoterol 組比 budesonide 組低 16.5%(hazard ratio, 0.84; 95% CI, 0.74 to 0.94; P=0.002)。



肆、 參考資料

1. Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, Fjallbrant H, Jorup C, Martin UJ. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. N Engl J Med. 2016 Sep 1;375(9):850-60.
2. Global Initiative for Asthma (GINA). 2016 GINA report: global strategy for asthma management and prevention. 2016 (http://ginasthma.org/2016-gina-report -global-strategy-for-asthma-management -and-prevention/).
3. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993;306:1034-7.
4. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.