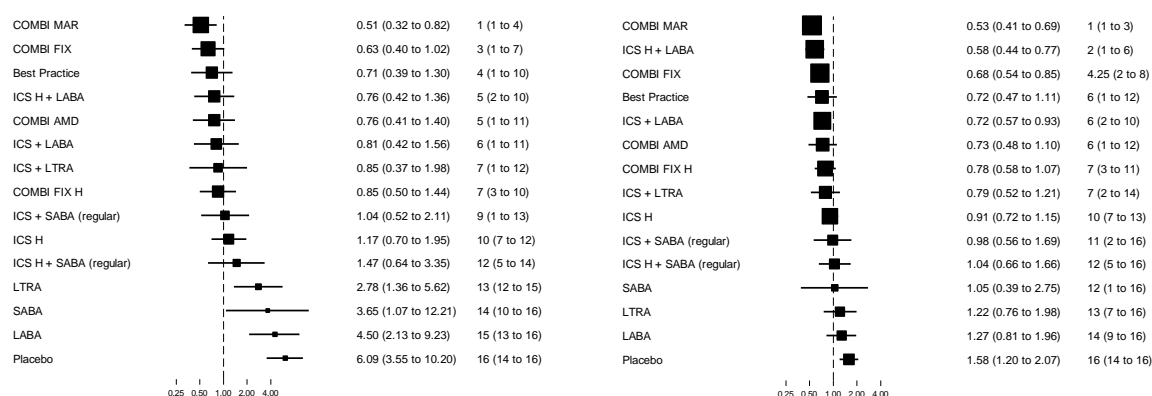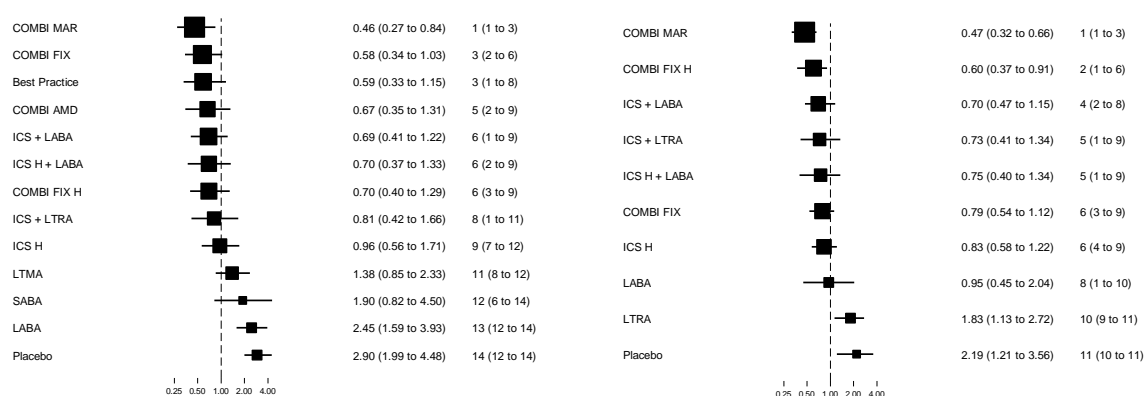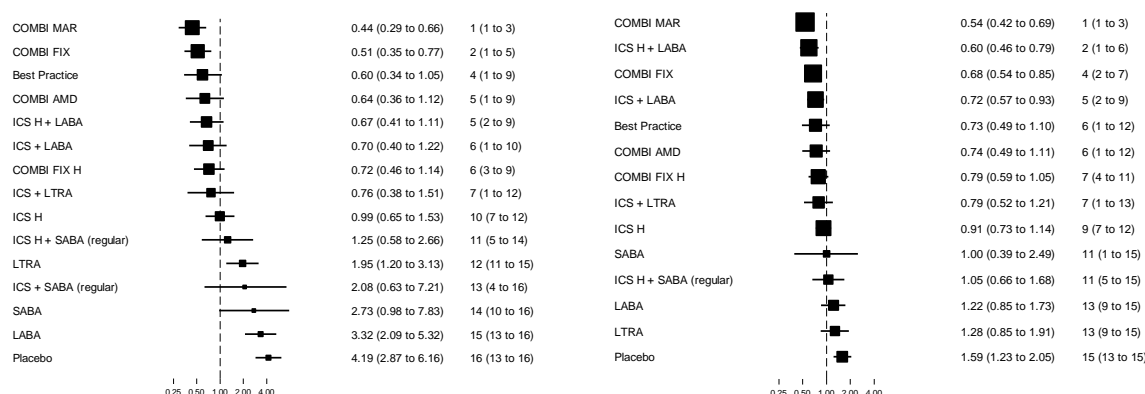**Figure S1:** Analysis of effect of strategies on exacerbations, with non-imputed data. All forest plot show rate ratios and their 95% credible intervals (95%CI), median ranks (95%CI), compared to low dose inhaled corticosteroids.

	Severe			Composite moderate or severe	
COMBI MAR	0.51 (0.32 to 0.82)	1 (1 to 4)	COMBI MAR	0.53 (0.41 to 0.69)	1 (1 to 3)
COMBI FIX	0.63 (0.40 to 1.02)	3 (1 to 7)	ICS H + LABA	0.58 (0.44 to 0.77)	2 (1 to 6)
Best Practice	0.71 (0.39 to 1.30)	4 (1 to 10)	COMBI FIX	0.68 (0.54 to 0.85)	4.25 (2 to 8)
ICS H + LABA	0.76 (0.42 to 1.36)	5 (2 to 10)	Best Practice	0.72 (0.47 to 1.11)	6 (1 to 12)
COMBI AMD	0.76 (0.41 to 1.40)	5 (1 to 11)	ICS + LABA	0.72 (0.57 to 0.93)	6 (2 to 10)
ICS + LABA	0.81 (0.42 to 1.56)	6 (1 to 11)	COMBI AMD	0.73 (0.48 to 1.10)	6 (1 to 12)
ICS + LTRA	0.85 (0.37 to 1.98)	7 (1 to 12)	COMBI FIX H	0.78 (0.58 to 1.07)	7 (3 to 11)
COMBI FIX H	0.85 (0.50 to 1.44)	7 (3 to 10)	ICS + LTRA	0.79 (0.52 to 1.21)	7 (2 to 14)
ICS + SABA (regular)	1.04 (0.52 to 2.11)	9 (1 to 13)	ICS H	0.91 (0.72 to 1.15)	10 (7 to 13)
ICS H	1.17 (0.70 to 1.95)	10 (7 to 12)	ICS + SABA (regular)	0.98 (0.56 to 1.69)	11 (2 to 16)
ICS H + SABA (regular)	1.47 (0.64 to 3.35)	12 (5 to 14)	ICS H + SABA (regular)	1.04 (0.66 to 1.66)	12 (5 to 16)
LTRA	2.78 (1.36 to 5.62)	13 (12 to 15)	SABA	1.05 (0.39 to 2.75)	12 (1 to 16)
SABA	3.65 (1.07 to 12.21)	14 (10 to 16)	LTRA	1.22 (0.76 to 1.98)	13 (7 to 16)
LABA	4.50 (2.13 to 9.23)	15 (13 to 16)	LABA	1.27 (0.81 to 1.96)	14 (9 to 16)
Placebo	6.09 (3.55 to 10.20)	16 (14 to 16)	Placebo	1.58 (1.20 to 2.07)	16 (14 to 16)

S1A Numbers of exacerbations per year, not imputed, for severe (left, 45 trials; τ^2= 0.110) and composite moderate or severe exacerbations (right, 56 trials; τ^2= 0.070).
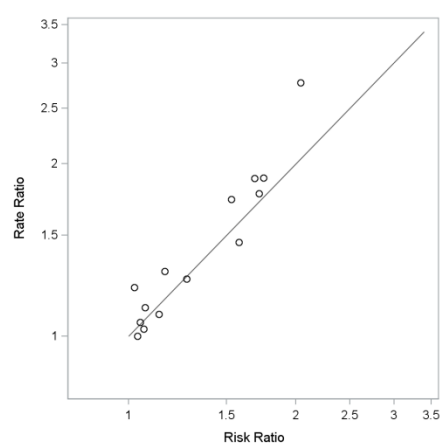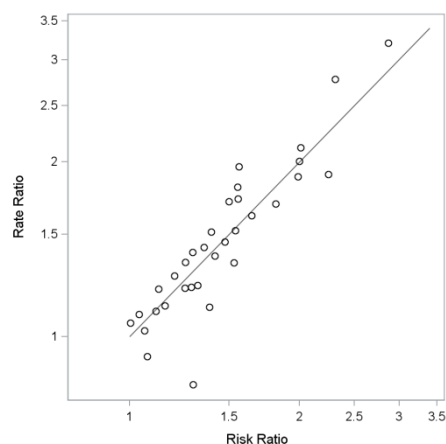

	Severe			Composite moderate or severe	
COMBI MAR	0.46 (0.27 to 0.84)	1 (1 to 3)	COMBI MAR	0.47 (0.32 to 0.66)	1 (1 to 3)
COMBI FIX	0.58 (0.34 to 1.03)	3 (2 to 6)	COMBI FIX H	0.60 (0.37 to 0.91)	2 (1 to 6)
Best Practice	0.59 (0.33 to 1.15)	3 (1 to 8)	ICS + LABA	0.70 (0.47 to 1.15)	4 (2 to 8)
COMBI AMD	0.67 (0.35 to 1.31)	5 (2 to 9)	ICS + LTRA	0.73 (0.41 to 1.34)	5 (1 to 9)
ICS + LABA	0.69 (0.41 to 1.22)	6 (1 to 9)	ICS H + LABA	0.75 (0.40 to 1.34)	5 (1 to 9)
ICS H + LABA	0.70 (0.37 to 1.33)	6 (2 to 9)	COMBI FIX	0.79 (0.54 to 1.12)	6 (3 to 9)
COMBI FIX H	0.70 (0.40 to 1.29)	6 (3 to 9)	ICS H	0.83 (0.58 to 1.22)	6 (4 to 9)
ICS + LTRA	0.81 (0.42 to 1.66)	8 (1 to 11)	LABA	0.95 (0.45 to 2.04)	8 (1 to 10)
ICS H	0.96 (0.56 to 1.71)	9 (7 to 12)	LTRA	1.83 (1.13 to 2.72)	10 (9 to 11)
LTMA	1.38 (0.85 to 2.33)	11 (8 to 12)	Placebo	2.19 (1.21 to 3.56)	11 (10 to 11)
SABA	1.90 (0.82 to 4.50)	12 (6 to 14)			
LABA	2.45 (1.59 to 3.93)	13 (12 to 14)			
Placebo	2.90 (1.99 to 4.48)	14 (12 to 14)			

S1B Patients with ≥ 1 exacerbations, not imputed, for severe (left, 43 trials; τ^2= 0.029) and composite moderate or severe exacerbations (right, 18 trials; τ^2= 0.010).

	Severe			Composite moderate or severe	
COMBI MAR	0.44 (0.29 to 0.66)	1 (1 to 3)	COMBI MAR	0.54 (0.42 to 0.69)	1 (1 to 3)
COMBI FIX	0.51 (0.35 to 0.77)	2 (1 to 5)	ICS H + LABA	0.60 (0.46 to 0.79)	2 (1 to 6)
Best Practice	0.60 (0.34 to 1.05)	4 (1 to 9)	COMBI FIX	0.68 (0.54 to 0.85)	4 (2 to 7)
COMBI AMD	0.64 (0.36 to 1.12)	5 (1 to 9)	ICS + LABA	0.72 (0.57 to 0.93)	5 (2 to 9)
ICS H + LABA	0.67 (0.41 to 1.11)	5 (2 to 9)	Best Practice	0.73 (0.49 to 1.10)	6 (1 to 12)
ICS + LABA	0.70 (0.40 to 1.22)	6 (1 to 10)	COMBI AMD	0.74 (0.49 to 1.11)	6 (1 to 12)
COMBI FIX H	0.72 (0.46 to 1.14)	6 (3 to 9)	COMBI FIX H	0.79 (0.59 to 1.05)	7 (4 to 11)
ICS + LTRA	0.76 (0.38 to 1.51)	7 (1 to 12)	ICS + LTRA	0.79 (0.52 to 1.21)	7 (1 to 13)
ICS H	0.99 (0.65 to 1.53)	10 (7 to 12)	ICS H	0.91 (0.73 to 1.14)	9 (7 to 12)
ICS H + SABA (regular)	1.25 (0.58 to 2.66)	11 (5 to 14)	SABA	1.00 (0.39 to 2.49)	11 (1 to 15)
LTRA	1.95 (1.20 to 3.13)	12 (11 to 15)	ICS H + SABA (regular)	1.05 (0.66 to 1.68)	11 (5 to 15)
ICS + SABA (regular)	2.08 (0.63 to 7.21)	13 (4 to 16)	LABA	1.22 (0.85 to 1.73)	13 (9 to 15)
SABA	2.73 (0.98 to 7.83)	14 (10 to 16)	LTRA	1.28 (0.85 to 1.91)	13 (9 to 15)
LABA	3.32 (2.09 to 5.32)	15 (13 to 16)	Placebo	1.59 (1.23 to 2.05)	15 (13 to 15)
Placebo	4.19 (2.87 to 6.16)	16 (13 to 16)			

S1C Numbers of exacerbations per year, imputed with data from patients with ≥ 1 exacerbations when numbers of exacerbations were not available, for severe (left, 57 trials; τ^2=0.102) and composite moderate or severe exacerbations (right, 61 trials; τ^2=0.070).

S1D Risk ratio (log scale) versus rate ratio (log scale) for treatment effects on exacerbations (accounting for study duration (patient years)) for severe (left) and composite moderate or severe exacerbations (right).

COMBI = combined ICS and LABA in a single inhaler; COMBI AMD = COMBI in an adjustable maintenance dose; COMBI FIX = COMBI in a fixed daily dose; COMBI MAR = COMBI as maintenance and reliever therapy; ICS (H) = inhaled corticosteroids (H=high dose ICS); LABA = long-acting beta-agonists; LTRA = leukotriene receptor antagonist; SABA = short -acting beta-agonists.

Best Practice is an open label comparator in which practitioners are free to choose therapy at their own discretion but are encouraged to treat patients according to current treatment guidelines.