Let’s Dilate! Novel bronchodilators for asthma management?

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Learning Objectives

- **Review the current guidelines focusing on ICS/β agonist use as rescue.**
- **Identify and address how new studies support combined therapy in rescue management**
- **Define the potential molecular mechanisms by which ICS/β agonist interactions enhance therapeutic efficacy.**

Outline

- **Revised guidelines**
- **Review evidence supporting new guideline-driven approaches to rescue therapy in asthma**
- **Examine the molecular mechanisms of steroid-β agonist interactions**
- **Summary**

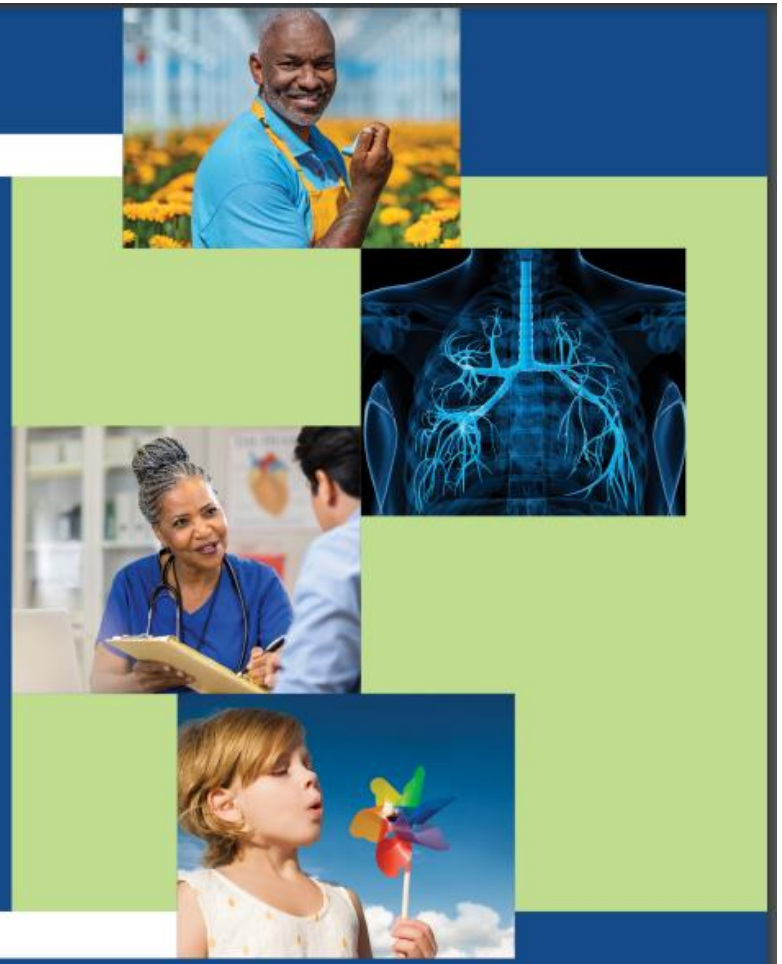
- **Jill is a 51-year-old**, nonsmoking woman who presents to your office for a second opinion due to her **25-year history of asthma** and “sinus problems.” She has been to the ED once in the past year for an asthma exacerbation but has never been hospitalized.
- Although, at times, she may not need her albuterol rescue inhaler for up to a month, she sometimes needs it daily and experiences nocturnal awakening, needing albuterol up to 2 to 3 times per month.

What reliever can we offer Jill?

2020 FOCUSED UPDATES TO THE

Asthma Management Guidelines

December 3, 2020



National Heart, Lung, and Blood Institute

2020 Focused Updates to the Asthma Management Guidelines

A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group

nhlbi.nih.gov/AsthmaGuidelines

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Are we SMART?

2020 Focused Updates to the Asthma Management Guidelines: Clinician's Guide

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2020 FOCUSED UPDATES TO THE Asthma Management Guidelines

CLINICIAN'S GUIDE

SINGLE MAINTENANCE AND RELIEVER THERAPY (SMART) IMPLEMENTATION GUIDANCE AND CONSIDERATIONS FOR SHARED DECISION MAKING

- **Target population:** Individuals 4 years and older with a severe exacerbation in the prior year are particularly good candidates for SMART to reduce exacerbations.
- **Who should not receive this treatment:** Do not use ICS-formoterol as reliever therapy in individuals taking ICS-salmeterol as maintenance therapy.
- **Treatment:** Inhaled ICS-formoterol in a single inhaler. This form of therapy has only been studied with formoterol as the long-acting beta$_2$-agonist (LABA).
  - ✓ SMART is appropriate for Step 3 (low-dose ICS) and Step 4 (medium-dose ICS) treatment.
  - ✓ Individuals whose asthma is uncontrolled on maintenance ICS-LABA with SABA as quick-relief therapy should receive the preferred SMART if possible before moving to a higher step of therapy.
  - ✓ ICS-formoterol should be administered as maintenance therapy with 1–2 puffs once or twice daily (depending on age, asthma severity, and ICS dose in the ICS-formoterol preparation) and 1–2 puffs as needed for asthma symptoms.
  - ✓ Maximum number of puffs per day is 8 (36 mcg formoterol) for children ages 4–11 years and 12 (54 mcg formoterol) for individuals ages 12 years and older.
  - ✓ Advise individuals to contact their physician if they need to exceed maximum number of puffs.
  - ✓ Dose of formoterol was based on 4.5 mcg/inhalation, the most common preparation used in the studies reviewed.
- **Potential benefits:** In studies this treatment consistently reduced asthma exacerbations requiring unscheduled medical visits or systemic corticosteroids and in some studies improved asthma control and quality of life. Reduced exposure to oral corticosteroids and to ICS treatment suggest that the intervention might reduce future corticosteroid-associated harms.
- **Potential risks:** Studies found no difference in documented harms between this type of therapy and daily ICS, or ICS-LABA, with SABA as quick relief therapy.

ORIGINAL ARTICLE

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

Papi A et al. N Engl J Med 2022;386:2071-2083

RESEARCH SUMMARY

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Papi A et al. DOI: 10.1056/NEJMoa2203163

CLINICAL PROBLEM

Patients typically treat acute asthma symptoms with short-acting β_2-agonist (SABA) rescue therapy. However, SABAs do not treat inflammation, leaving patients at risk for severe exacerbations. Whether rescue therapy with a fixed-dose combination of a SABA (albuterol) plus a glucocorticoid (budesonide) can improve outcomes is unknown.

CLINICAL TRIAL

Design: A multinational, phase 3, double-blind, randomized trial evaluated the safety and efficacy of as-needed use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, in patients with uncontrolled moderate-to-severe asthma receiving inhaled glucocorticoid-containing maintenance therapy.

Intervention: Adults and adolescents were randomly assigned to receive, on an as-needed basis, 180 μg of albuterol plus 160 μg of budesonide, 180 μg of albuterol plus 80 μg of budesonide, or 180 μg of albuterol; the treatments were delivered through a single metered-dose inhaler. Children 4 through 11 years of age were assigned only to the lower-dose combination group or the albuterol-alone group. Participants continued their baseline glucocorticoid-containing maintenance therapies. The primary efficacy end point was the first severe asthma exacerbation in a time-to-event analysis.

RESULTS

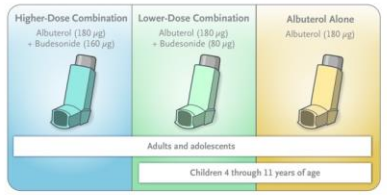
Efficacy: 3123 patients were assessed with respect to the efficacy end points. During a minimum follow-up of 24 weeks, the higher-dose combination of albuterol–budesonide significantly reduced the risk of severe asthma exacerbations, as compared with albuterol alone. The difference between the lower-dose combination and albuterol alone was not significant.

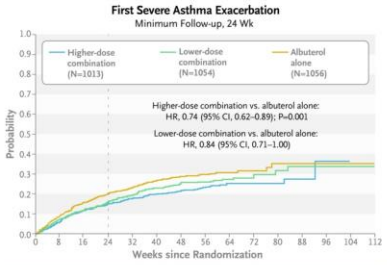
Safety: The incidence of adverse events was similar across the three trial groups.

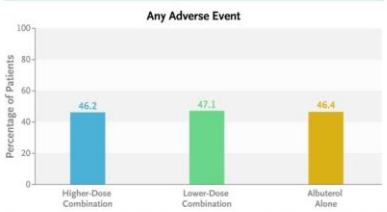
LIMITATIONS AND REMAINING QUESTIONS

- The fraction of exhaled nitric oxide level was not measured, a limitation that precludes direct assessment of antiinflammatory effects.
- A small number of children 4 to 11 years of age were included; thus, no conclusions in this age group could be drawn.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

Among patients with uncontrolled moderate-to-severe asthma receiving inhaled glucocorticoid-containing maintenance therapy, as-needed use of 180 μg of albuterol plus 160 μg of budesonide reduced the risk of severe asthma exacerbations, as compared with albuterol alone, without increasing the incidence of adverse events.

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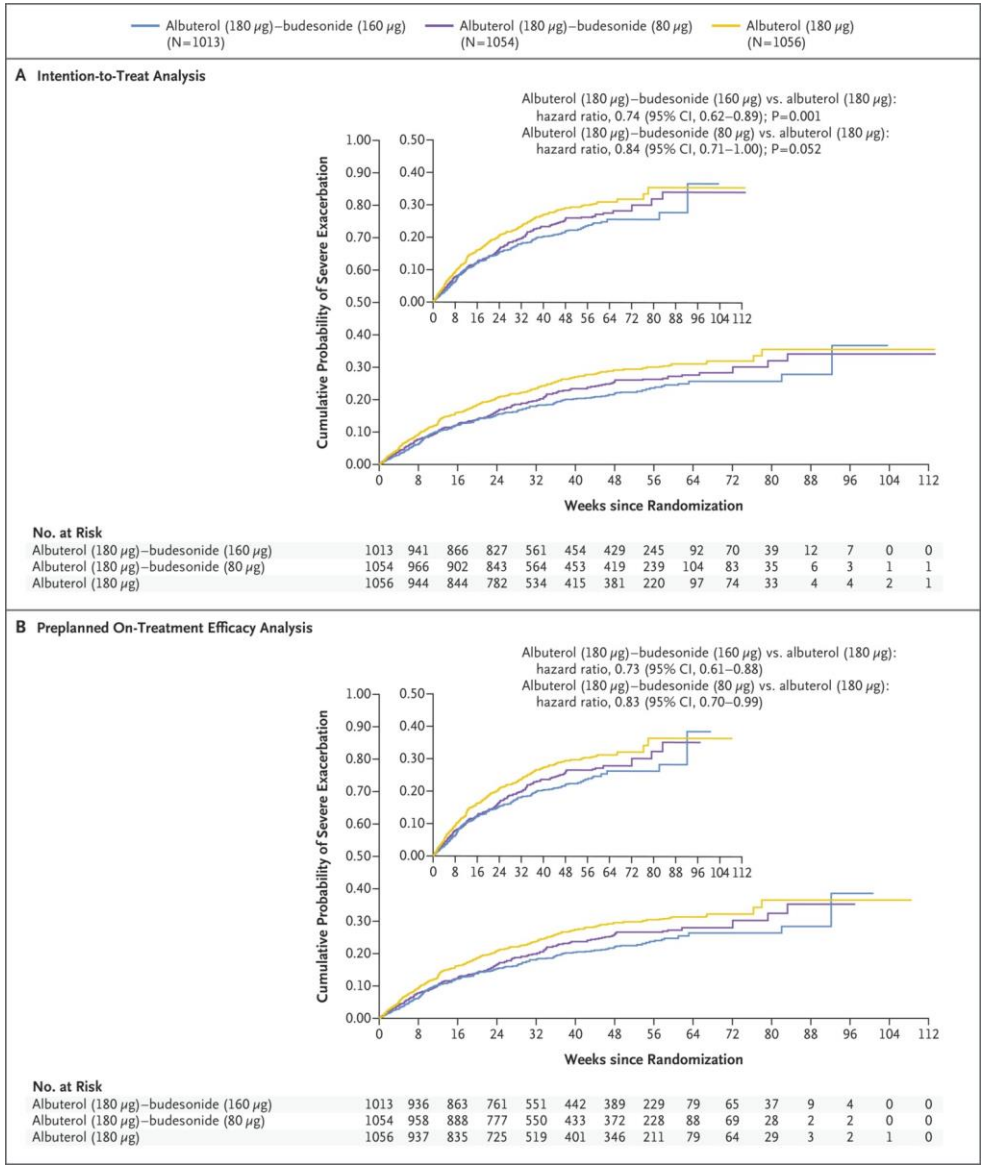
Time-to-Event Analysis of the First Event of Severe Asthma Exacerbation (Primary End Point).



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Papi A et al. N Engl J Med 2022;386:2071-2083

Intention-to-Treat and Preplanned On-Treatment Efficacy Analyses of the Secondary End Points.

Table 2. Intention-to-Treat and Preplanned On-Treatment Efficacy Analyses of the Secondary End Points.*

Analysis	Intention-to-Treat Analysis				Preplanned On-Treatment Efficacy Analysis			
	Adults and Adolescents†		Adults, Adolescents, and Children‡		Adults and Adolescents†		Adults, Adolescents, and Children‡	
	Albuterol (180 μg)–Budesonide (160 μg)	Albuterol (180 μg)	Albuterol (180 μg)–Budesonide (80 μg)	Albuterol (180 μg) Alone	Albuterol (180 μg)–Budesonide (160 μg)	Albuterol (180 μg)	Albuterol (180 μg)–Budesonide (80 μg)	Albuterol (180 μg)
Annualized rate of severe asthma exacerbation								
Patients — no.	1013	1014	1054	1056	1013	1014	1054	1056
Severe exacerbations — no.	345	427	372	441	334	413	354	426
Annualized rate (95% CI)	0.43 (0.33–0.58)	0.58 (0.44–0.77)	0.48 (0.37–0.63)	0.60 (0.46–0.79)	0.45 (0.34–0.60)	0.59 (0.44–0.78)	0.49 (0.37–0.64)	0.61 (0.46–0.80)
Rate ratio (95% CI)	0.75 (0.61–0.91)	Reference	0.81 (0.66–0.98)	Reference	0.76 (0.62–0.93)	Reference	0.80 (0.66–0.98)	Reference
Annualized total dose of systemic glucocorticoid§								
Patients — no.	1012	1011	1052	1052	1012	1011	1052	1052
Median value (5th–95th percentile) — mg/yr	0.0 (0.0–459.2)	0.0 (0.0–484.3)	0.0 (0.0–494.4)	0.0 (0.0–600.8)	0.0 (0.0–496.1)	0.0 (0.0–622.1)	0.0 (0.0–487.0)	0.0 (0.0–615.9)
Mean value — mg/yr	83.6±247.7	130.0±630.3	94.7±318.2	127.6±619.8	86.2±262.9	129.3±657.2	95.5±335.4	127.1±646.2
Response analysis at wk 24¶								
ACQ-5								
Patients — no.	1013	1014	1052	1055	1013	1014	1052	1055
Patients with response — no. (%)	682 (67.3)	636 (62.7)	690 (65.6)	656 (62.2)	677 (66.8)	630 (62.1)	681 (64.7)	650 (61.6)
Odds ratio (95% CI)	1.22 (1.01–1.46)	Reference	1.15 (0.96–1.37)	Reference	1.22 (1.02–1.47)	Reference	1.13 (0.95–1.35)	Reference
AQLQ+12								
Patients — no.	994	993	987	NA	994	993	987	NA
Patients with response — no. (%)	515 (51.8)	464 (46.7)	496 (50.3)	NA	508 (51.1)	461 (46.4)	489 (49.5)	NA
Odds ratio (95% CI)	1.25 (1.04–1.50)	Reference	1.13 (0.94–1.36)	NA	1.23 (1.02–1.48)	Reference	1.11 (0.93–1.34)	NA

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Adverse Events Occurring in at Least 2% of Patients in Any Trial Group

Table 3. Adverse Events Occurring in at Least 2% of Patients in Any Trial Group.*

Event	Albuterol (180 μg)–Budesonide (160 μg) (N=1015)	Albuterol (180 μg)–Budesonide (80 μg) (N=1055)	Albuterol (180 μg) (N=1057)
	number of patients (percent)		
Any adverse event	469 (46.2)	497 (47.1)	490 (46.4)
Nasopharyngitis	76 (7.5)	61 (5.8)	54 (5.1)
Headache	44 (4.3)	50 (4.7)	50 (4.7)
Covid-19	43 (4.2)	52 (4.9)	46 (4.4)
Upper respiratory tract infection	26 (2.6)	31 (2.9)	26 (2.5)
Bronchitis	25 (2.5)	27 (2.6)	28 (2.6)
Hypertension	22 (2.2)	27 (2.6)	26 (2.5)
Asthma	18 (1.8)	20 (1.9)	35 (3.3)
Back pain	27 (2.7)	23 (2.2)	20 (1.9)
Influenza	21 (2.1)	23 (2.2)	14 (1.3)
Sinusitis	15 (1.5)	17 (1.6)	24 (2.3)

* Adverse events are sorted in decreasing total frequency of preferred term in the *Medical Dictionary for Regulatory Activities*, version 24.0. Patients with multiple events in the same category are counted only once in that category.

Conclusions

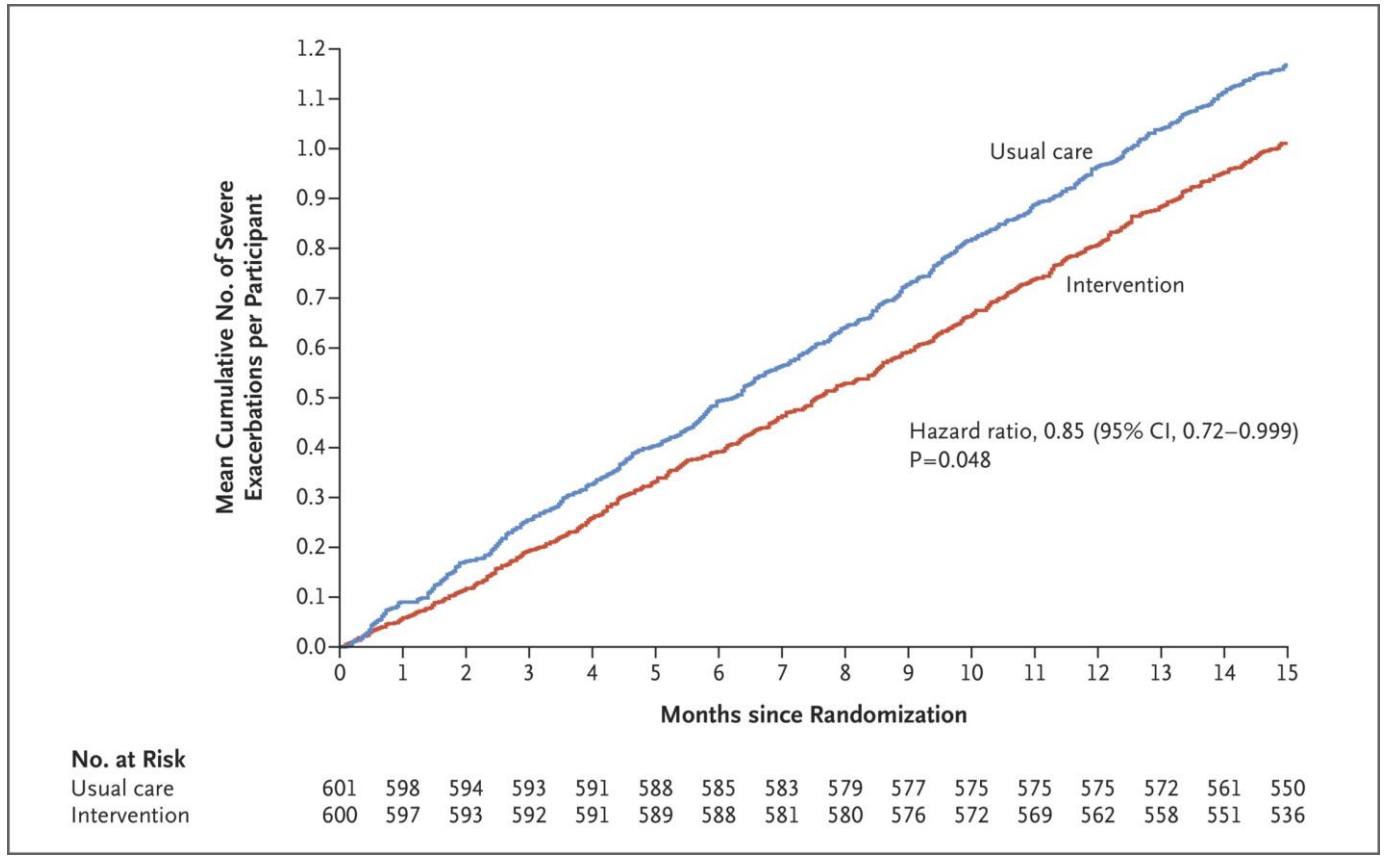
The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies.

Papi A et al. N Engl J Med 2022;386:2071-2083

ORIGINAL ARTICLE

Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma

Elliot Israel, M.D., Juan-Carlos Cardet, M.D., M.P.H., Jennifer K. Carroll, M.D., M.P.H., Anne L. Fuhlbrigge, M.D., Lilin She, Ph.D., Frank W. Rockhold, Ph.D., Nancy E. Maher, M.P.H., Maureen Fagan, D.N.P., F.N.P.-B.C., Victoria E. Forth, M.M.S., P.A.-C., Barbara P. Yawn, M.D., Paulina Arias Hernandez, M.S.W., Jean M. Kruse, B.A., et al.



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Israel E et al. N Engl J Med2022;386:1505-1518

Conclusions

Among Black and Latinx adults with moderate-to-severe asthma, provision of an inhaled glucocorticoid and one-time instruction on its use, added to usual care, led to a lower rate of severe asthma exacerbations.

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Israel E et al. N Engl J Med 2022;386:1505-1518

Why does combined ICS and β agonists as rescue work better than either alone?

Provides enhanced anti-inflammatory action when asthma becomes uncontrolled with an impending exacerbation.

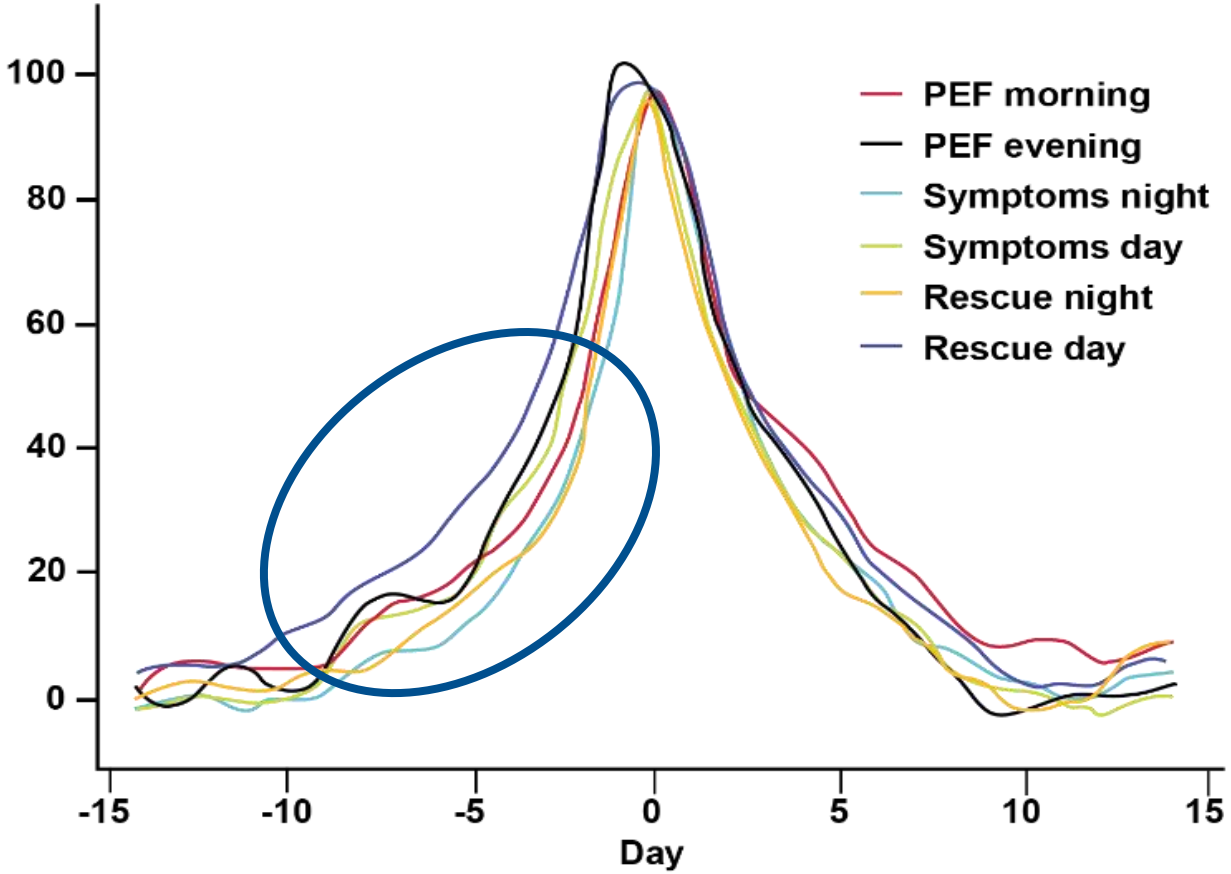
Provides improved bronchodilation unrelated to effects on inflammation.

Both processes are operative.

Again, let's Consider Jill:

Although, at times, she may not need her albuterol rescue inhaler for up to a month, she sometimes needs it daily and experiences nocturnal awakening, needing albuterol up to 2 to 3 times per month.

Predicting an Exacerbation



Tattersfield AE, et al. *Am J Respir Crit Care Med*. 1999;160(2)594-599.

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Genomic and non-Genomic Effects of GC

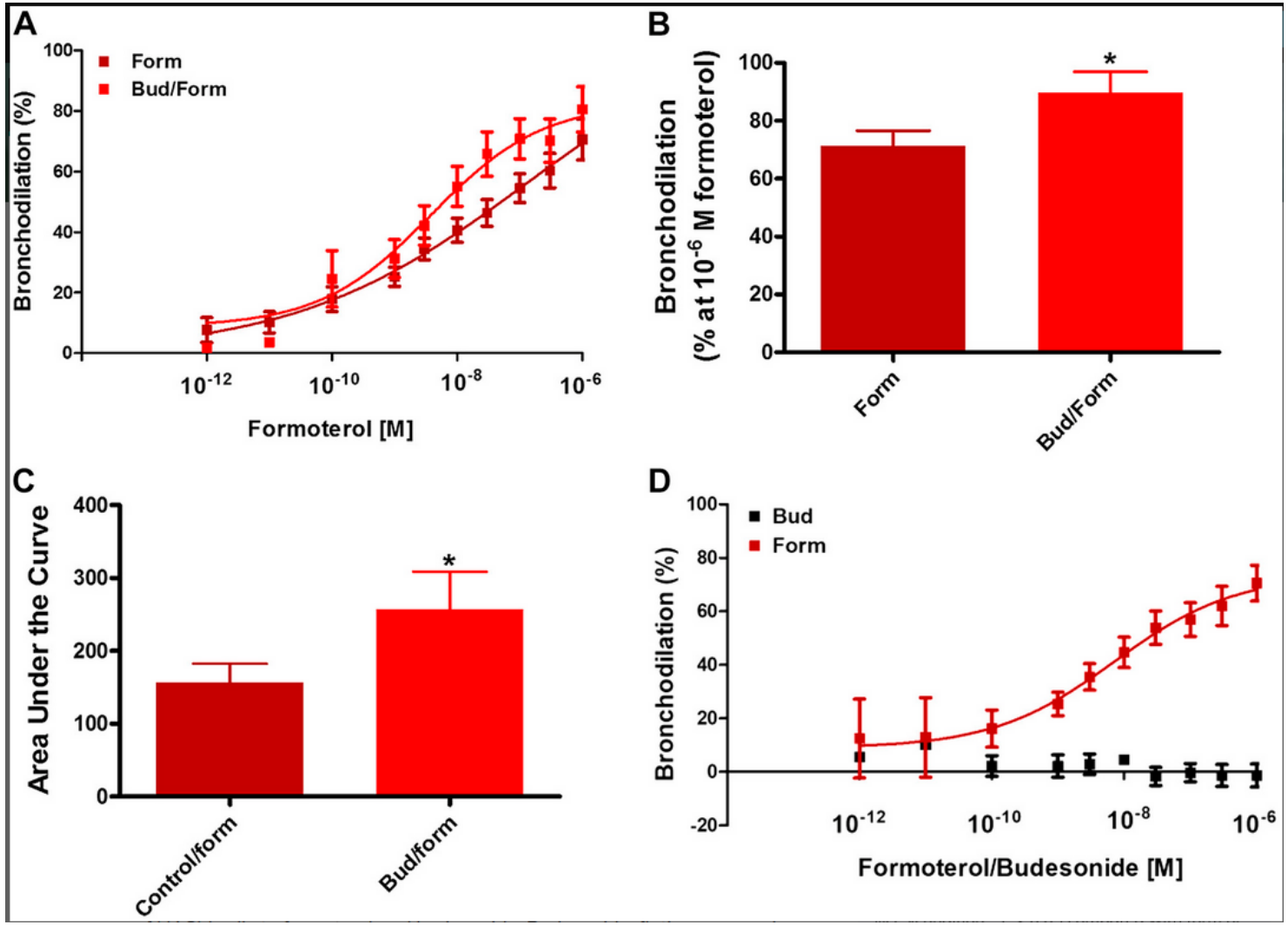
Table 1. Various Criteria (Either Alone or in Combination) Used to Distinguish Genomic Effects from Non-genomic Effects of GCs

GC effect	Acute (simultaneous or within 30 min)	Chronic (delayed)
Genomic effects	–	+
Inhibitory effects of cycloheximide or actinomycin D	–	+
GR involvement	– or +	+
Inhibitory effects of RU486	– or +	+
Type of GR involved	None, membrane GR or cytosolic GR	Cytosolic GR
GR-independent mechanisms	GC interaction with membrane	None

What is known about non-genomic effects of GC's?

- Genomic and non-genomic effects involve distinct mechanisms of action but play complementary roles in mediating the anti-inflammatory effects of GCs.
- GCs are mostly used in asthma as a 'controller' therapy because of their delayed effects, but since GCs recently have been shown to 'rapidly' enhance the effects of bronchodilators, they could be used also as a 'rescue' therapy, especially in combination with β_2 agonists.
- Compelling evidence proposed the emerging role of (airway) structural cells as a major target for GC non-genomic effects that act through poorly understood, cell-specific mechanisms.
- Both inflammatory pathways and non-inflammatory pathways such as calcium mobilization, muscle tone, and reactive oxygen species are targets for the GC non-genomic effects.

GC rapidly enhance cAMP levels and Bronchodilation



Am J Physiol Lung Cell Mol Physiol 318: L345–L355, 2020.

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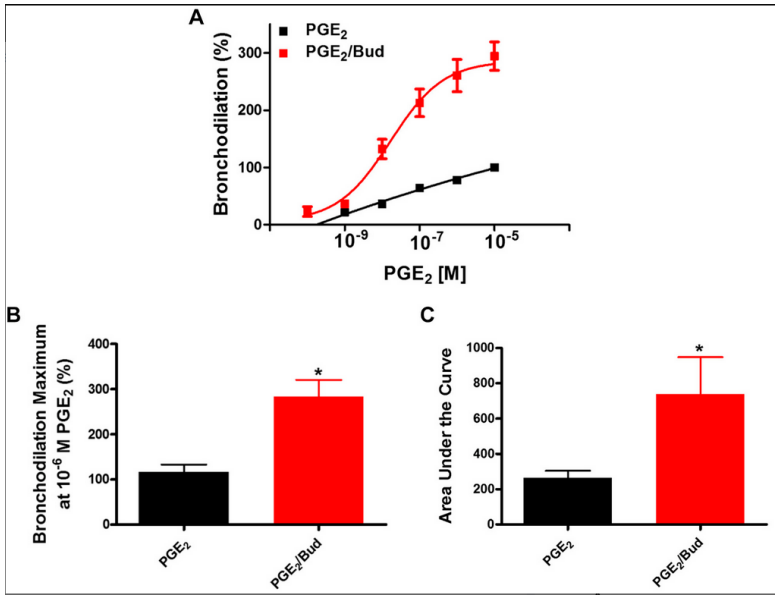

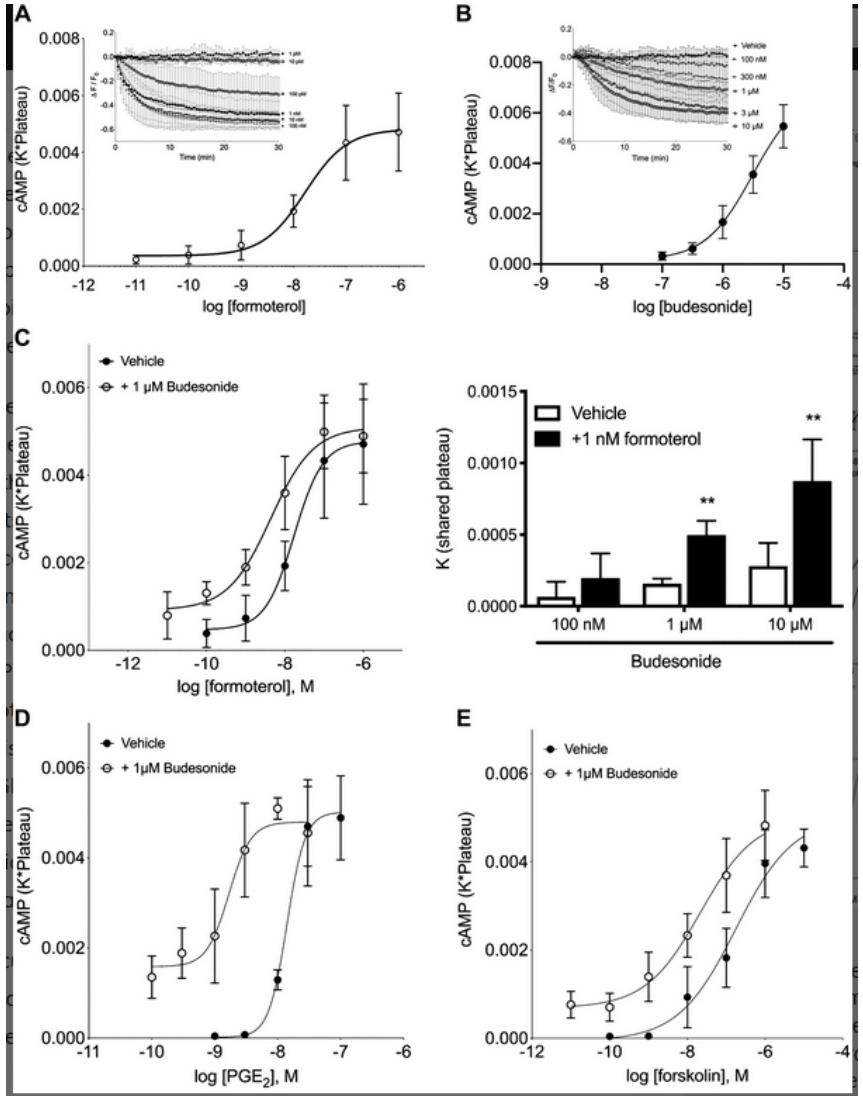

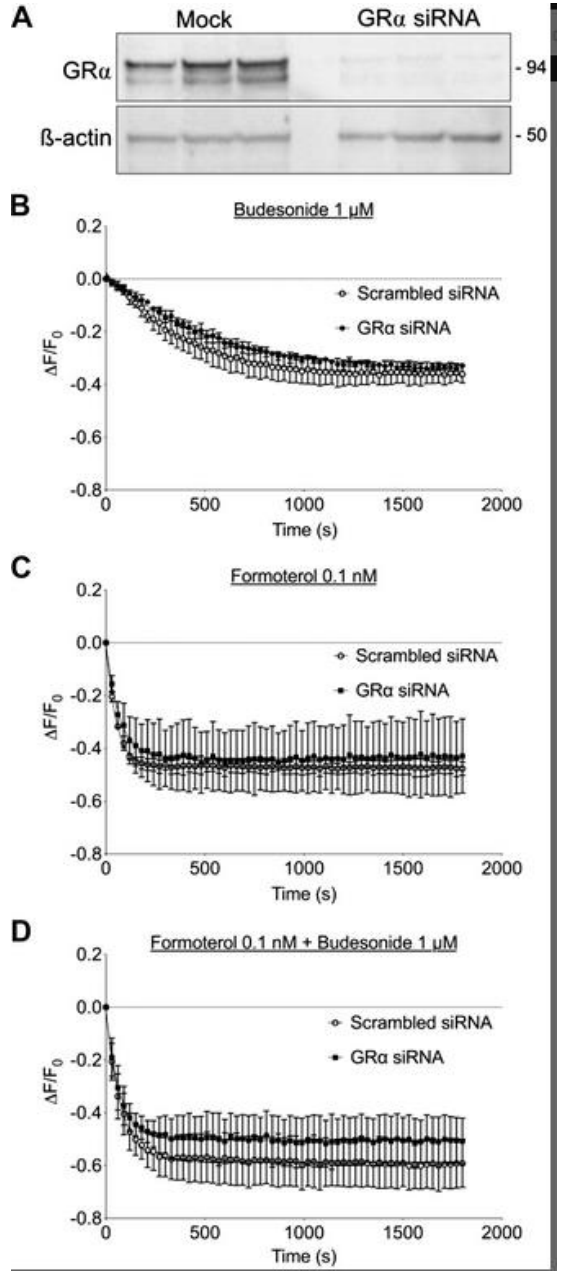

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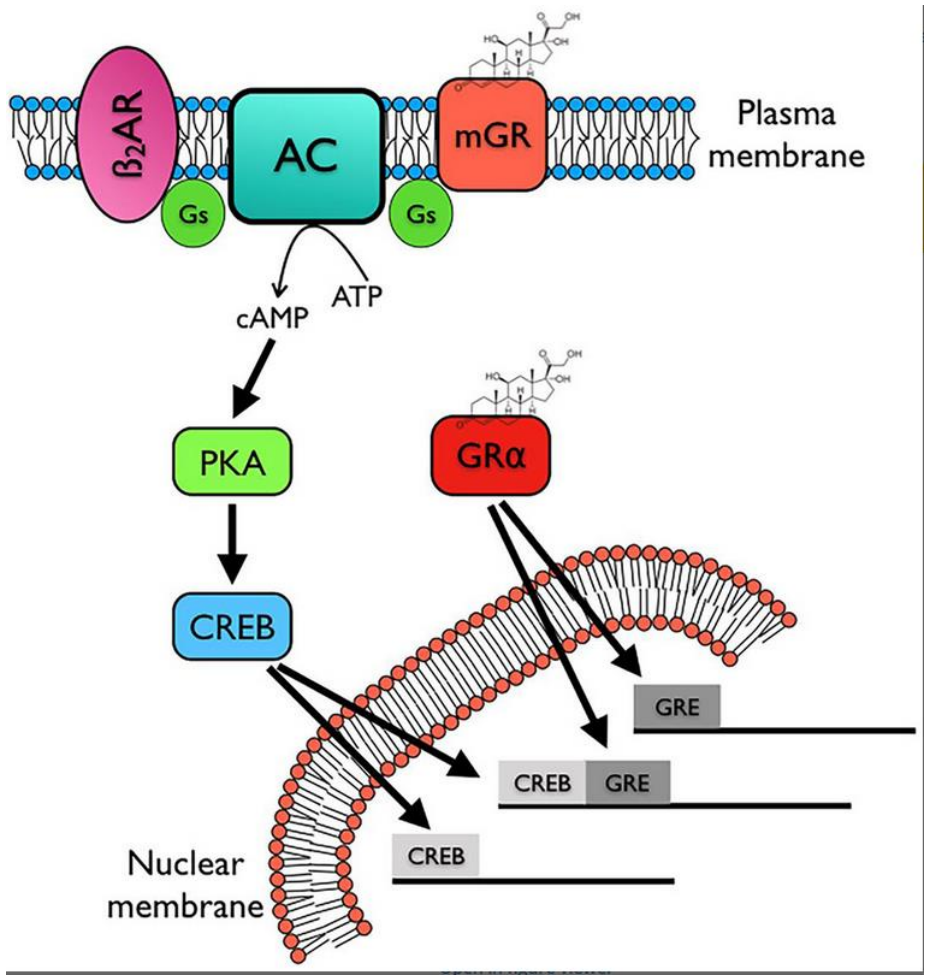
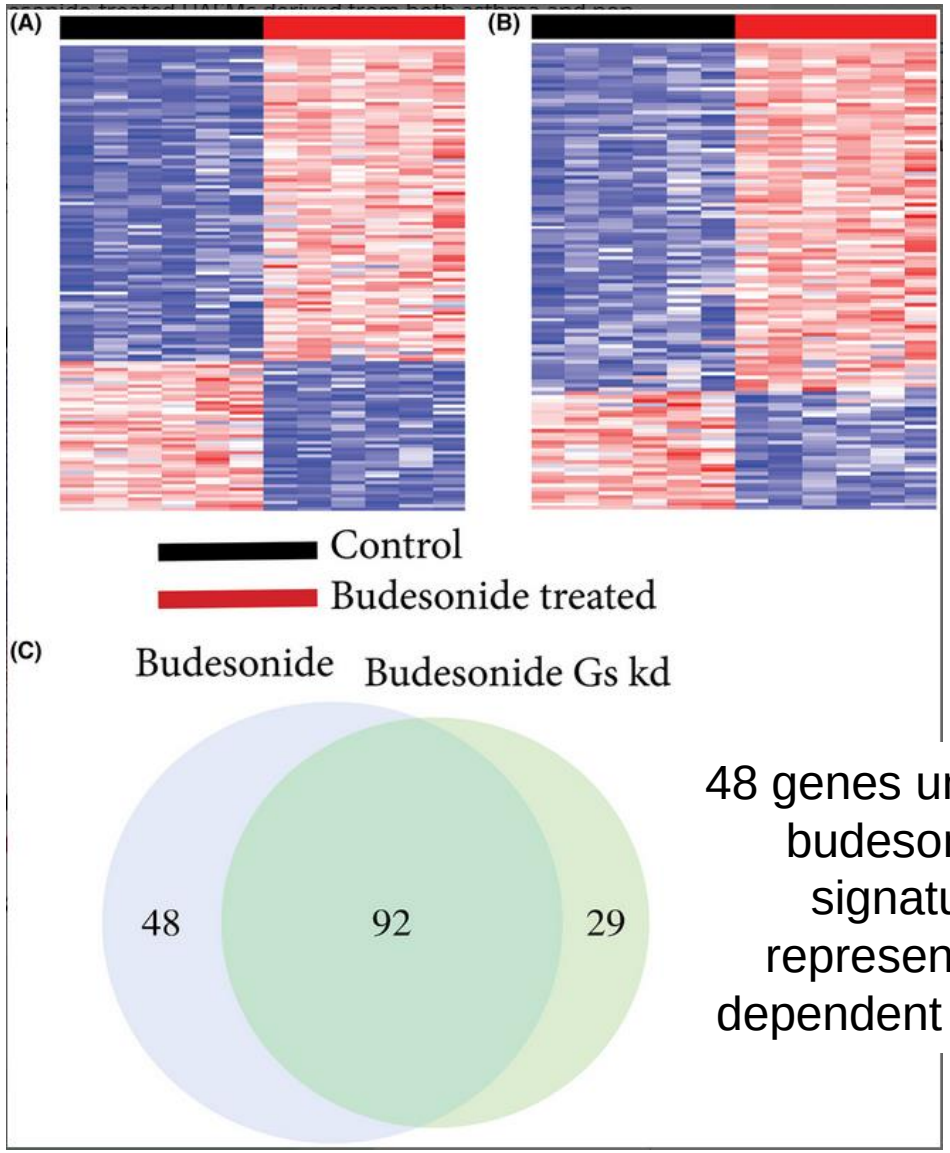
Am J Physiol Lung Cell Mol Physiol 318: L345–L355, 2020.

Some GC genomic effects require activation of $G\alpha_s$.





48 genes unique to budesonide signature represent $G_{\alpha s}$ dependent activity

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THE FASEB JOURNAL

The FASEB Journal. 2020;34:2882–2895.

Summary

- Recent guidelines embrace the use of as needed ICS/β agonist therapy in asthma.
- Trials now show that ICS/short-acting β agonist combinations can decrease exacerbation rates compared with either drug alone.
- A pragmatic trial of ICS and SABA in combination also shows a decrease in exacerbation rates compared with either drug alone.
- Compelling evidence suggests that GC's and β agonists together enhance bronchodilation that is independent of GR expression and occurs immediately.
- Studies also suggest that about 30% of GC effects are dependent on the expression and activation of $G\alpha_s$.
- Designing a GC solely to act through non-genomic pathways may prevent some of the GC side effects often engendered by GC genomic effects

Why does combined ICS and β agonists as rescue work better than either alone?

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Thank You

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