

Are Short Acting Beta Agonists Obsolete?: Con

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Conflicts of Interest

- Dr. Wenzel has received multi-site clinical trials support and accepted consulting fees from Sanofi-Genzyme, GSK AstraZeneca and Novartis

Objectives

- To provide a logical argument to continue the use of SABAs
- To provide information on the good things SABAs do
- To counter the argument that SABAs are bad

ABCs of *why* short-acting beta agonists are NOT obsolete

- Asthmatic bronchoconstriction is its *sine qua non*
- Activities beyond bronchodilation
- Adverse effects: Short on *AND* off mean less long term side effects
- Approval by FDA

Bs and Cs

- Budesonide doesn't benefit everyone
- Bronchospasm (associated with exercise)
- Beclomethasone addition can benefit
- Budget-friendly
- Combinations are very expensive
- Conclusions

Asthmatic bronchoconstriction is its *sine qua non*

- Asthma is DEFINED by beta-agonist reversible bronchoconstriction
 - 12% improvement in FEV1 with at least 200 ml improvement
- Asthma pathology is hallmarked by smooth muscle hypertrophy/hyperplasia, which *acutely* bronchodilates to short acting beta agonists

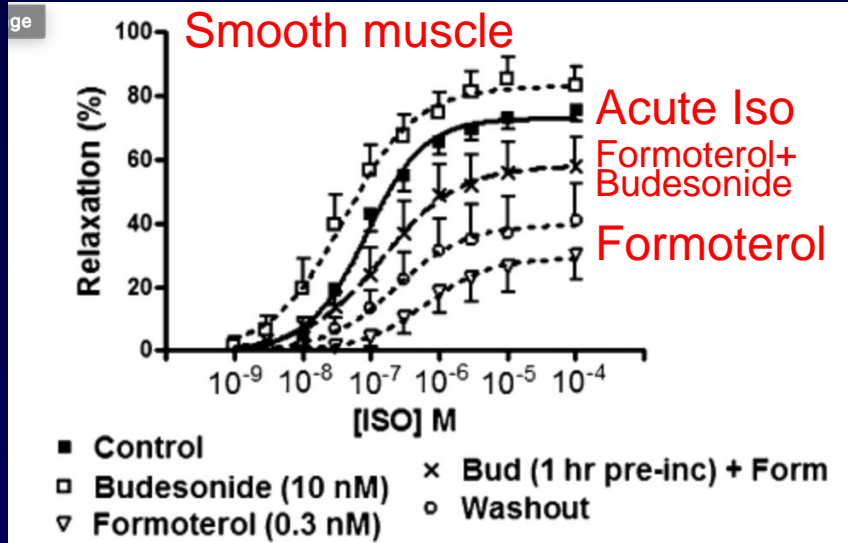
Activities beyond bronchodilation

- But there's more!
- SABAs are potent inhibitors of acute mast cell degranulation
- SABAs acutely improve ciliary beat frequency to enhance mucus clearance

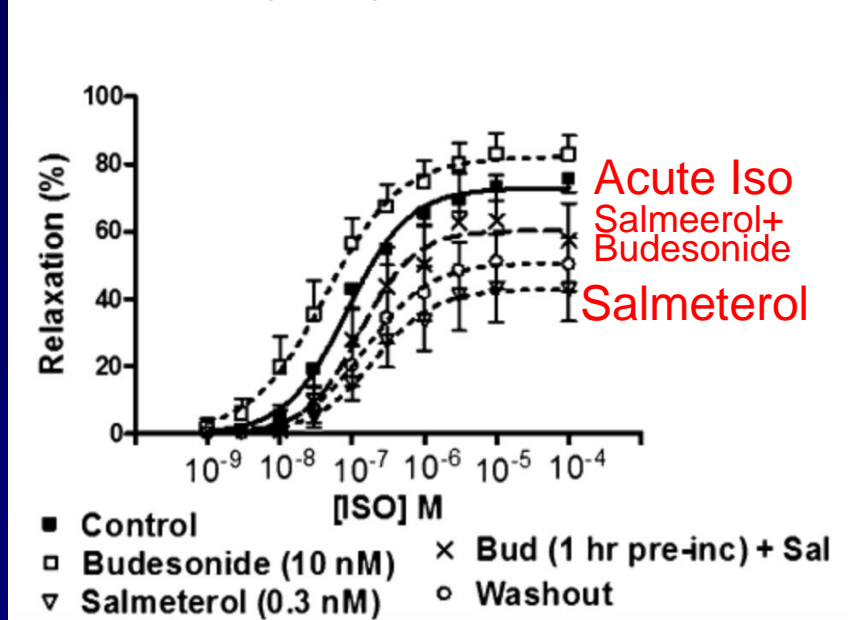
Adverse effects: Short on *AND* off mean less long term side effects

- LABAs can induce long term hypo-responsiveness/desensitization
- Regular/sustained stimulation of β 2-adrenergic receptor leads to its desensitization *in vitro* and loss of cAMP responses *in vitro* and *in vivo*

In vitro effects: depressed cAMP signaling

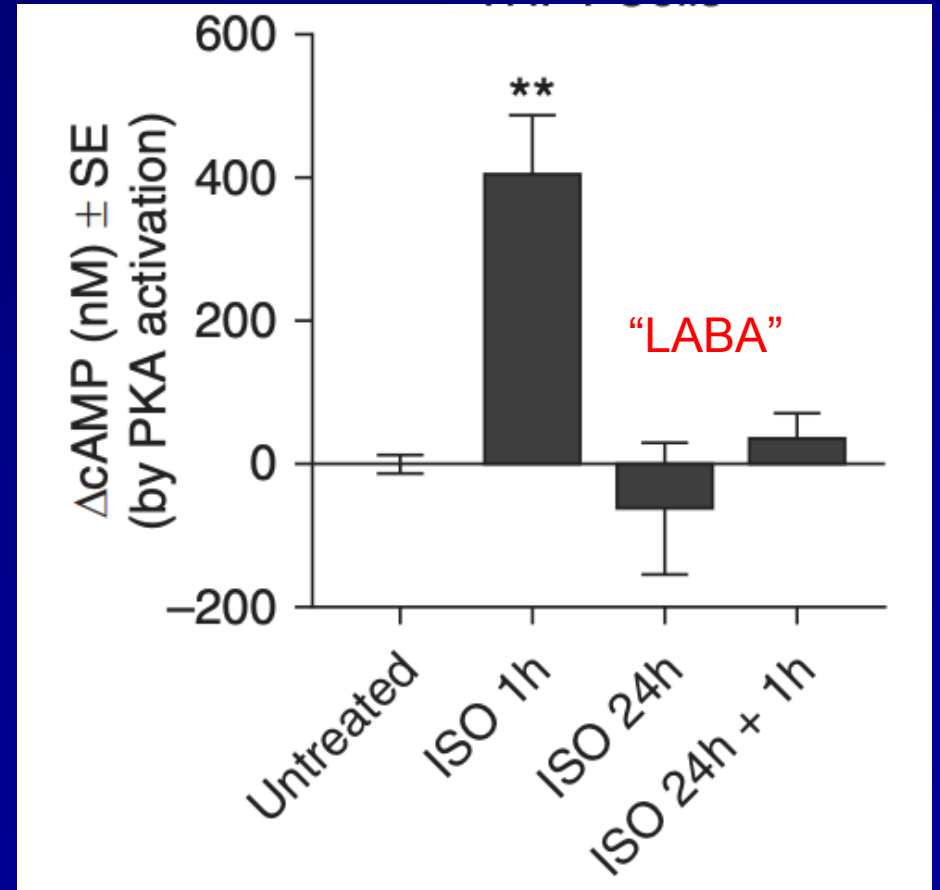


Cooper P...Panettieri R
 Br J Pharm 2011

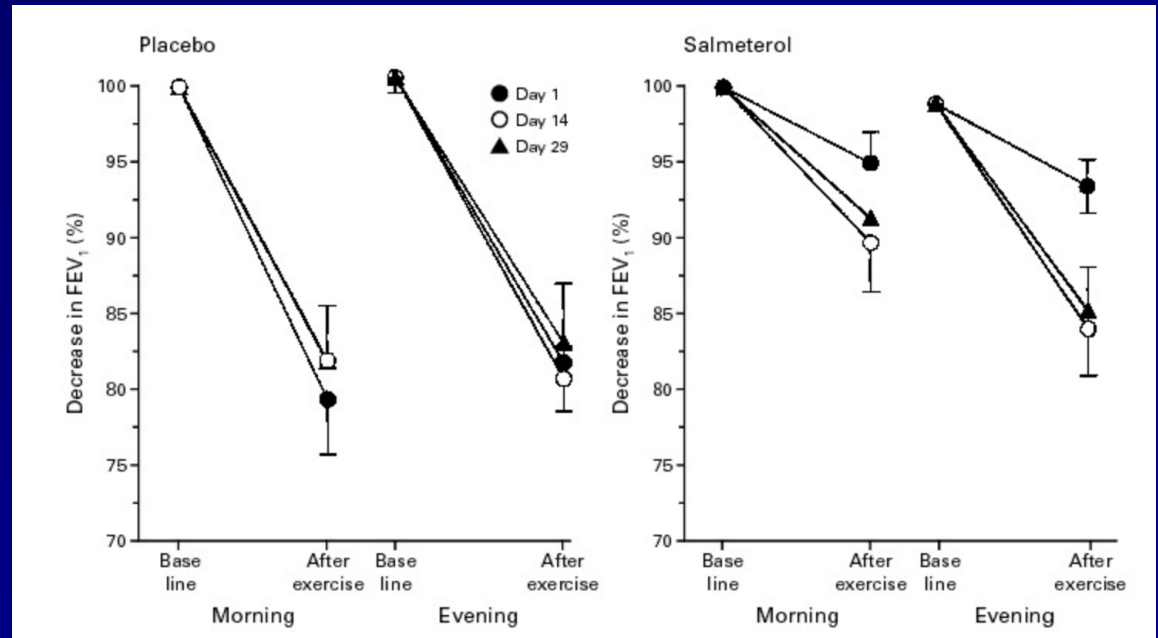
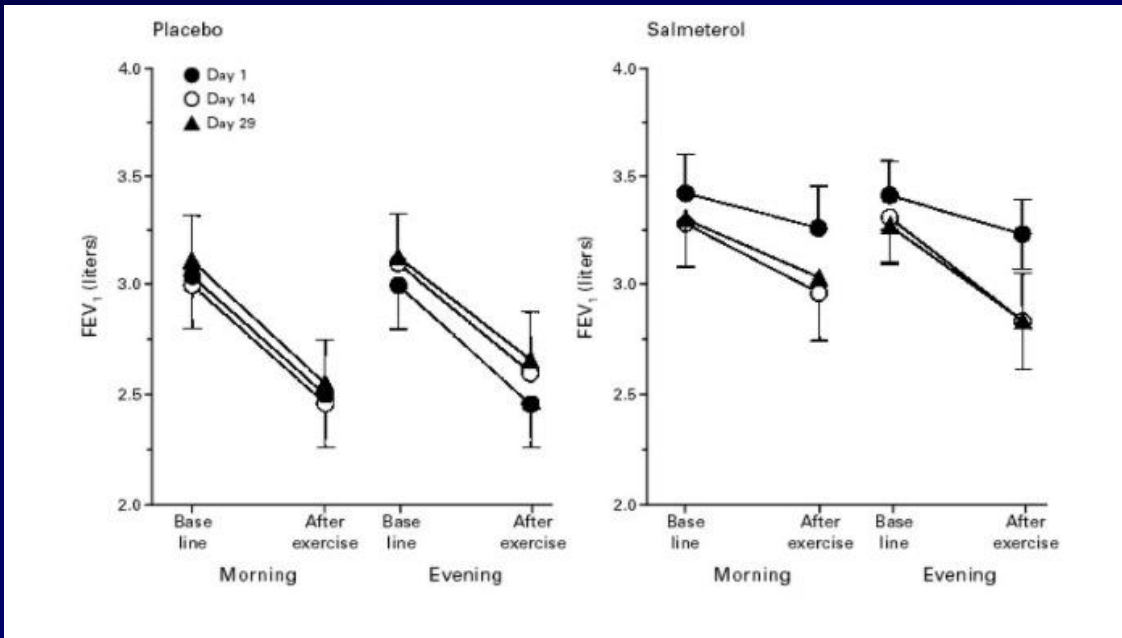


Weathington N Am J
 Resp Crit Care Med
 2019

Immune cells

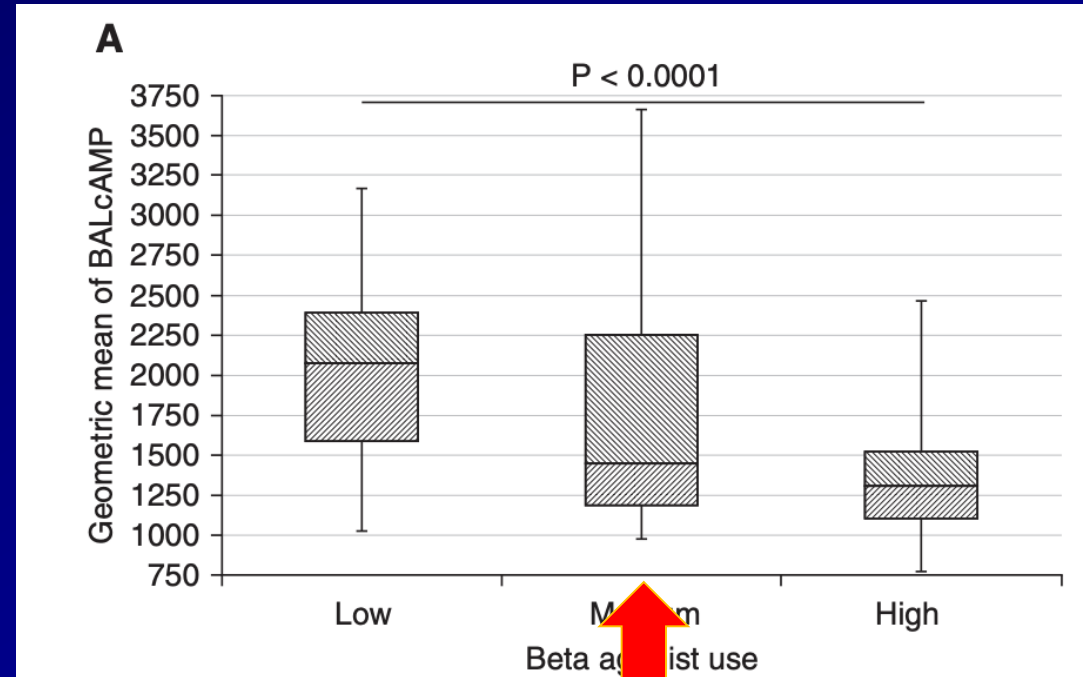
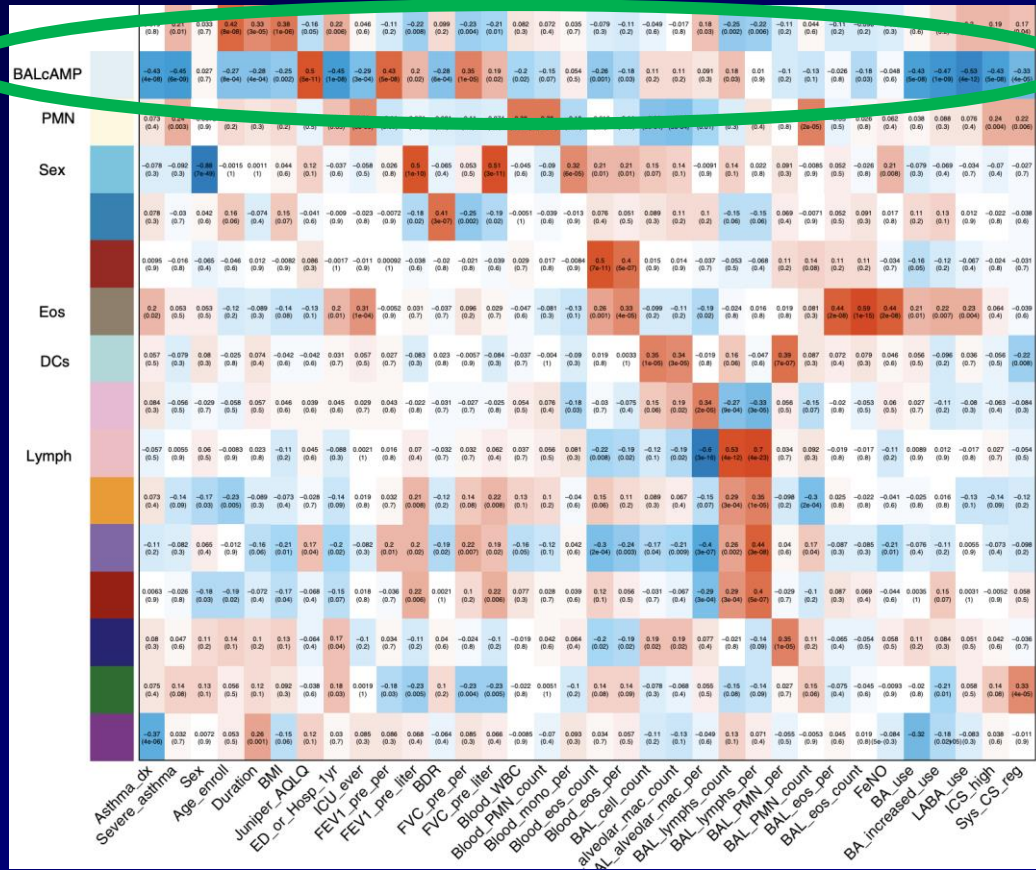


Long term use of salmeterol decreases EIB bronchoprotection



Immune effects: Depression of cAMP module corresponds to clinical severity and β -agonist use

cAMP module



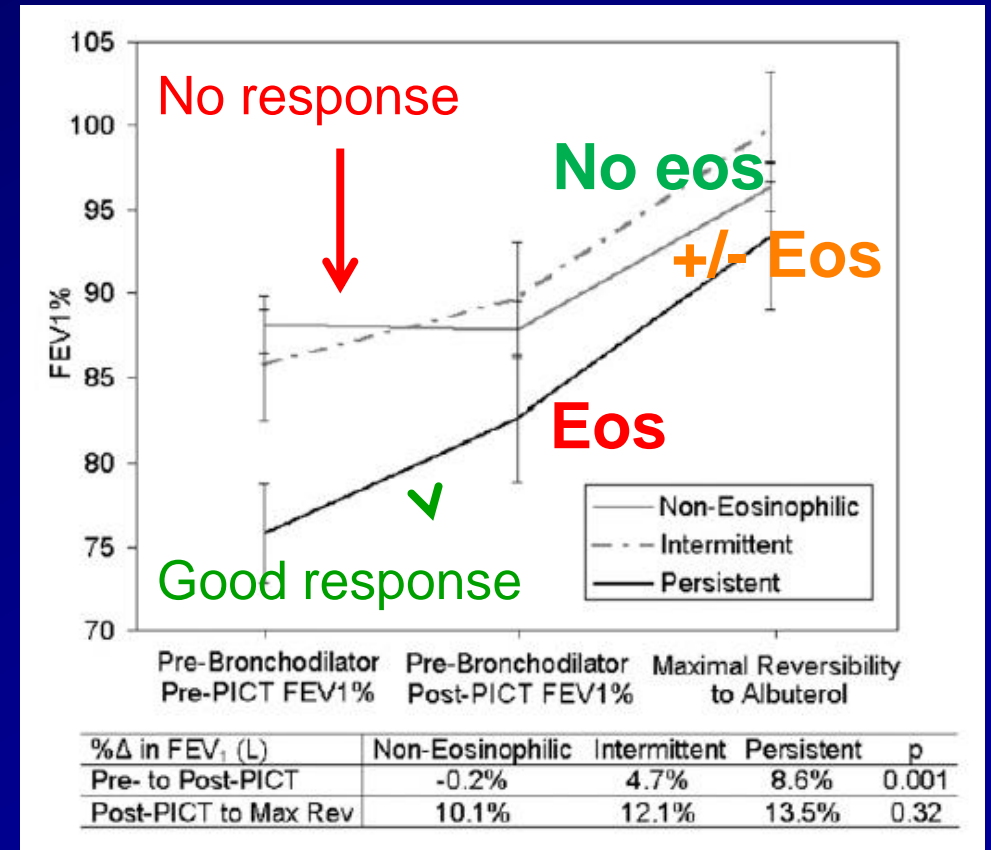
Addition of LABA-ICS

Approved by the FDA

- Albuterol approved by FDA for acute relief of bronchoconstriction
- Formoterol+Budesonide (or any other ICS) is not

Budesonide (and other ICS) don't benefit everyone

- Not all asthma responds to ICS
- All “asthma” responds to beta agonists

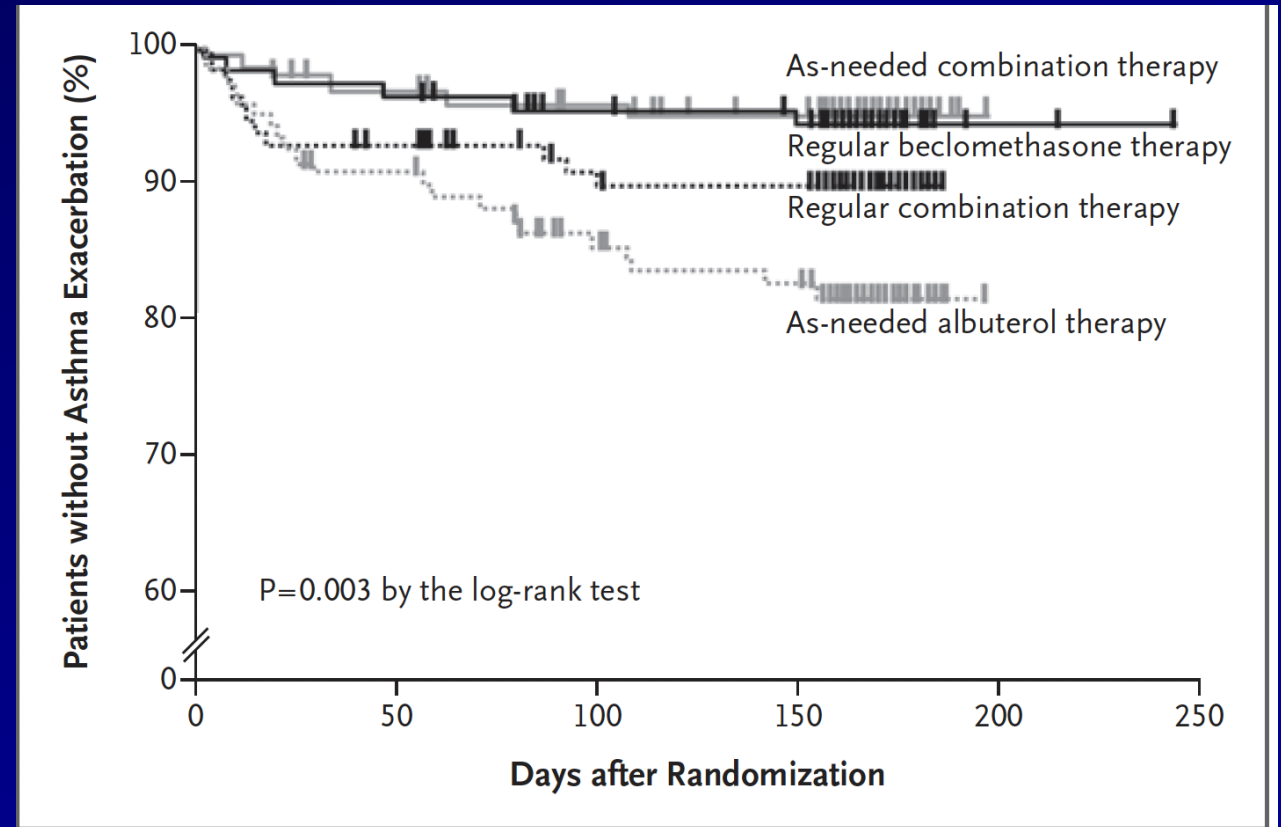


Bronchospasm (associated with exercise)

- EIB is the sole manifestation of asthma in large percent of mild asthma patients
- Up to 25% of endurance athletes report EIB as the only manifestation of asthma
- ZERO studies have compared the efficacy of SABA alone vs LABA with or without ICS for *acute* prevention of EIB

Beclomethasone addition can benefit

- Although the LABA formoterol in combination with budesonide effective as longterm as needed reliever medication SABA, in combination with ICS performs similarly
 - Even though not available as combination inhaler in US, can suggest SABA +ICS for relief *Martinez F, et al Lancet 2011*



Papa A et al N Engl J Med 2007

Budget-friendly

- Albuterol pricing has come down dramatically
- Generics now available
- Easily available for <\$20/inhaler

The screenshot displays three main options at the top: 'Free Coupons' (Prices as low as \$18.97), 'Savings Clubs' (Prices as low as \$14.69), and 'Mail Order' (No prices). Below this is a location setting prompt: 'Set your location for drug prices near you'. A promotional banner asks 'Need a prescription for albuterol?' and offers to connect with an online doctor. Below the banner is a table of pharmacy offers:

Pharmacy	Retail Price	Savings	Current Price	Action
Giant Eagle Pharmacy	\$92	Save 79%	\$18.97 with free coupon	GET FREE COUPON
Giant Pharmacy	\$80	Save 76%	\$18.97 with free coupon	GET FREE COUPON
Kroger Pharmacy	\$85	Save 77%	\$18.97 with free coupon	GET FREE COUPON
Costco	\$48	Save 60%	\$18.97 with free coupon	GET FREE COUPON

A red circle highlights the '\$18.97 with free coupon' price for all listed pharmacies.

Combinations (the right ones) are very expensive

The “right one” Symbicort

Rite Aid	\$383 retail Save 46%	\$204.48 with free coupon	GET FREE COUPON
Target (CVS)	\$281 retail Save 25%	\$209.48 with free coupon	GET FREE COUPON
CVS Pharmacy	\$281 retail Save 25%	\$209.48 with free coupon	GET FREE COUPON
Walgreens	\$282 retail Save 8%	\$258.98 with free coupon	GET FREE COUPON
Walmart	\$342 retail Save 23%	\$260.31 with free discount	GET FREE DISCOUNT
Costco	\$411 retail Save 29%	\$290.47 with free coupon	GET FREE COUPON
Giant Eagle Pharmacy	\$430 retail Save 32%	\$290.47 with free coupon	GET FREE COUPON
Giant Pharmacy	\$589 retail Save 50%	\$290.47 with free coupon	GET FREE COUPON
Weis Pharmacy	\$328 retail Save 11%	\$291.12 with free coupon	GET FREE COUPON

Dulera even more expensive

The “wrong one” (for rescue use) Air Duo

Free Coupons	Savings Clubs	Mail Order	
Prices as low as \$49.63	Prices as low as \$38.23	Prices as low as \$95	
<p>Set your location for drug prices near you</p>			
Walgreens	\$91 retail Save 45%	\$49.63 with free coupon	GET FREE COUPON
Walmart	\$86 retail Save 35%	\$55.50 with free discount	GET FREE DISCOUNT
Rite Aid	\$129 retail Save 52%	\$60.63 with free coupon	GET FREE COUPON
CVS Pharmacy	\$112 retail Save 43%	\$63.10 with free coupon	GET FREE COUPON

Generic Salmeterol-fluticasone

Conclusions

- SABAs remain a central treatment for asthma, especially in the US
- Addition of ICS for asthma Rx for EVERYONE not yet proven essential and LABA-ICS as reliever medication may be little different from SABA-ICS
- SMART therapy in US remains financially problematic and asking patients to use 2 inhalers whenever they need “relief” remains a high bar