

Public health considerations of benefit and risk with LABAs

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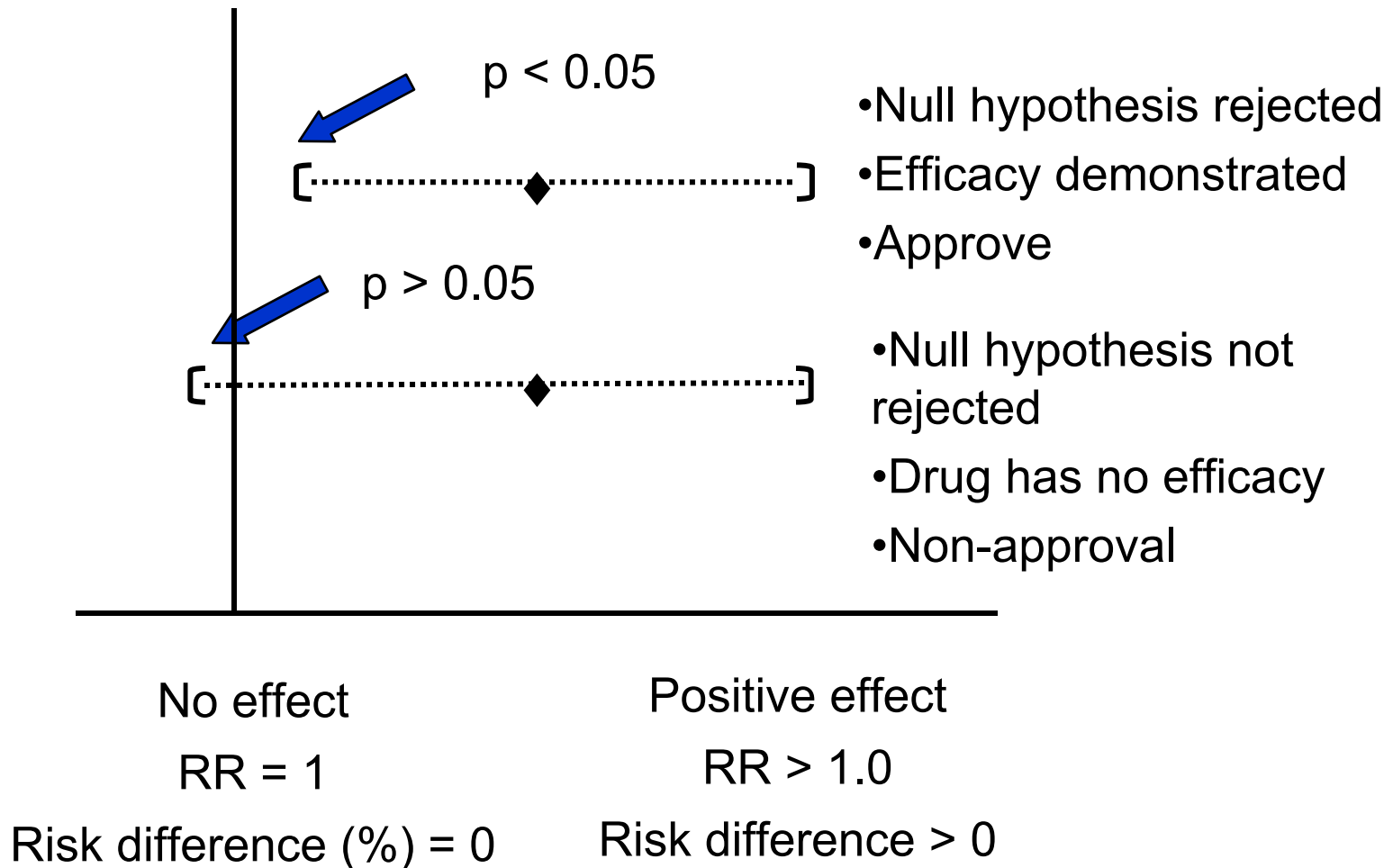
Outline

- Describe the asymmetric handling of benefit and risk in drug development and approval process
- Demonstrate uncertainty created by low power to exclude asthma mortality risk with non-Serevent LABAs
 - Foradil pivotal trials
- Summarize of evidence addressing presence or absence of important clinical benefits with LABAs
- Contrast the decision-making paradigms in controlled trials and in public (population) health
- Focus on Advair health benefits and mortality risk
 - Why? Largest population exposure; more data to work with
 - Asymmetric power
 - Absence of proof \neq proof of absence
- Conclusions and recommendations

The current drug approval paradigm:
Asymmetric handling of efficacy and safety
(surrogates for benefit and risk) (1)

- **Pivotal trials are powered to show efficacy**
 - Pre-specified value for efficacy “success”
 - Null hypothesis: drug does not work
 - Pre-specified type I (α) error
 - Probability of finding a difference, given there is none
 - Minimize false positives
 - “Regulator’s risk” set at $\alpha \leq 0.05$
 - Pre-specified type II (β) error
 - Probability of failing to find a difference, given there is one
 - Minimizes false negatives
 - “Company’s risk” set at $\beta=0.1-0.2$ (Power=80%-90%)
 - Statistical tests to reject null hypothesis (no efficacy)
 - $p < 0.05$
 - lower bound of 95% CI excludes null

Current drug approval paradigm: Statistics and decision-making for efficacy

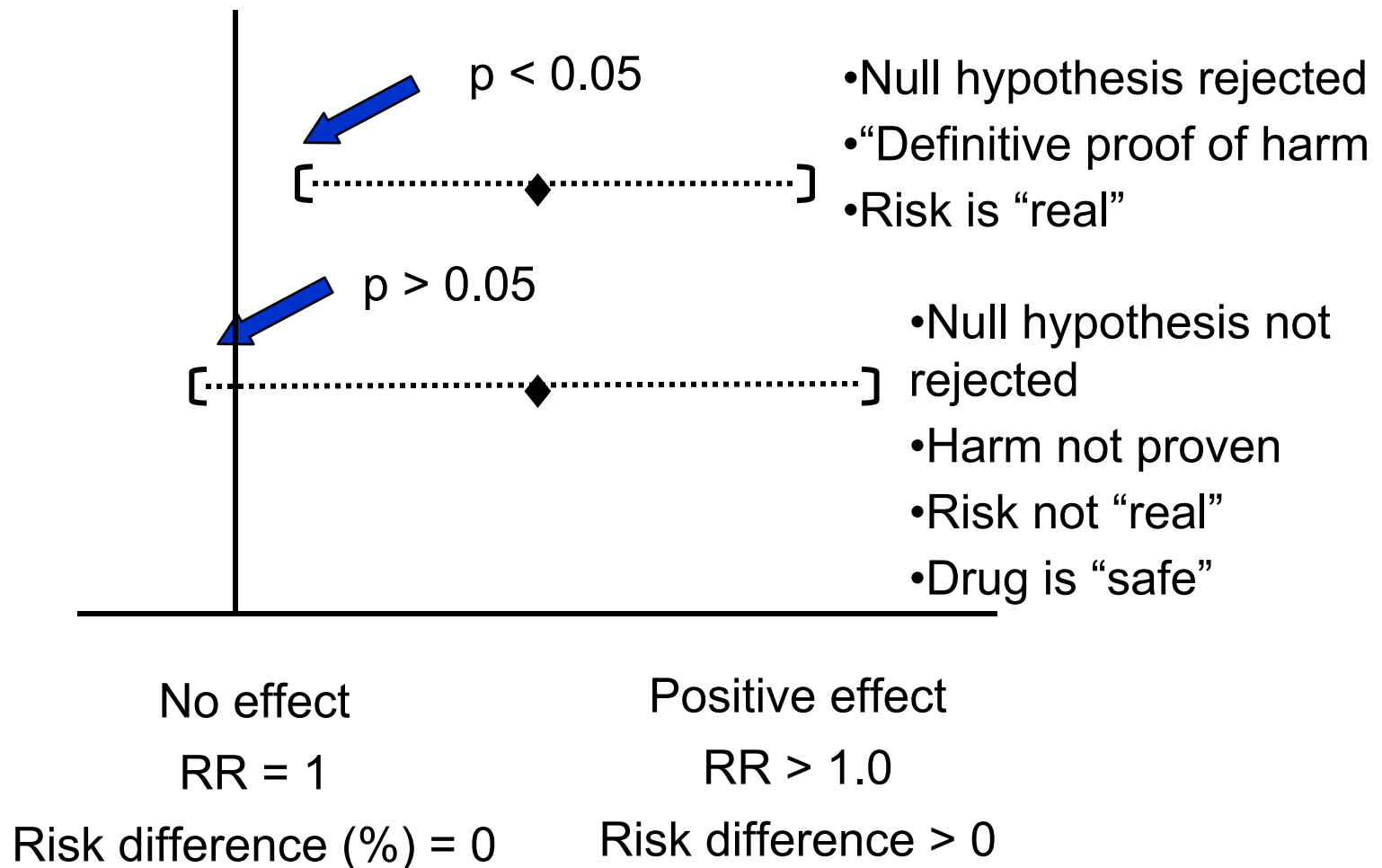


The current drug approval paradigm:
Asymmetric handling of efficacy and safety
(surrogates for benefit and risk)

- **Pivotal trials not powered to demonstrate safety or exclude harm**

- No pre-specified value for safety “success”
 - What level of serious harm is acceptable in exchange for the pre-specified efficacy?
 - Do the pivotal trials exclude this pre-specified value of acceptable harm?
- Null hypothesis: drug is safe (rather than harmful)
 - Why is there an *a priori* presumption of safety? Inherent bias endangers public
 - Why aren't drugs presumed *a priori* to carry a pre-specified level of unacceptable risk that must be excluded to “prove” safety? Would provide rational basis for B-R
- FDA insistence on “definitive” proof to reject its presumption of safety
 - Trials not powered to meet this level of certainty (why would any company try)
 - Amounts to “free-ride” for drug; high risk for the public
- No attention to type II (β) error to minimize false negative conclusions of safety
 - Typical β (to show harm) $\gg \gg 0.5$ (Power $\ll \ll 50\%$)
 - FDA concludes: Absence of proof of harm = proof of absence of harm but this is clearly a false construct
- Focus on p-values and confidence intervals
 - Insistence on “definitive” proof of harm
 - “Loaded dice;” the House (the drug) more likely to win; the Public loses

Current drug approval paradigm: Statistics and decision-making for safety (must “prove” harm, not “prove” safety)



Efficacy

- *A priori* presumption
 - Drug does not work
 - Can be tested
- Regulatory practice
 - Trials show that drug does work
- Randomized controlled trials
 - High probability of finding efficacy
 - Low probability of failing to find efficacy
 - Low probability of erroneously concluding efficacy



Evidence-based?



Stacked deck?

Safety

- *A priori* presumption
 - Drug is safe
 - Can not be tested
 - (Not: drug is harmful)
 - Can be tested
- Regulatory practice
 - Trials fail to definitively prove harm, rather than “prove” safety
- Randomized controlled trials
 - Low probability of finding harm
 - High probability of failing to find harm
 - High probability of erroneously concluding safety

Serevent Nationwide Surveillance

BMJ 1993; 306:1034-37

Outcome	Salmeterol (n=16 787)	Salbutamol (n=8393)	Relative risk	Significance
Deaths:				
Respiratory and related to asthma	12 (0.07)	2 (0.02)	3.00	* p=0.105
Other obstructive airways disease	4 (0.02)	1 (0.01)	2.00	* p=0.506
Other respiratory causes	2 (0.01)	1 (0.01)	1.00	* p=1.000

Relative risk	Significance
3.00	* p=0.105

(95% CI 0.7-27.6)

FDA focus

Potential mortality risk
(equivalent to 1.7 per 100 per year)

Asthma mortality in SNS and SMART

	SNS	SMART	Combined
Incidence ($\times 10^{-4}$ pyrs)			
Standard therapy		5.5	
Salbutamol	7.7		6.0
Salmeterol	23.2	20.7	22.9
Attributable risk	15.5	17.4	16.9 (7-27)
Relative risk	3.0	4.3	3.8 (1.4-12.7)

Estimated asthma mortality attributable to salmeterol and all LABAs since approval

Excess asthma mortality and hospitalizations can be estimated from attributable risk and measures of salmeterol use

		<u>Excess asthma deaths (95% CI)</u>	
1994-2004	Serevent	5460	(1180-9820)
	All LABAs	9330	(2790-15960)
<hr/>			
2005-2007	Serevent	280	(120-450)
	All LABAs	5150	(2120-8180)

Foradil NDA, 12 µg bid:

All pivotal studies (adult and children) combined

Serious asthma exacerbations

	Formoterol	Albuterol	Placebo
Adult studies (040, 041)	N=275	N=272	
Child study (049)	N=171		N=176
Combined	N=446	N=272	N=176
Cases	9	2	0
Pyrs	235	63	176
Incidence (per 10 ⁴)	383	317	0
Attributable risk	vs. A: 66 (-441-572)		
NNH	vs. A: ≥ 17		

What is the mortality risk with Foradil based on the NDA package approved by FDA?

- Pivotal studies small, low power
 - 0 cases observed in 235 pyrs
- Inability to exclude extremely high mortality risks
 - 95% CI for asthma mortality: 0-1.6 per 100 pyrs
- For asthma mortality with Foradil, cannot exclude:

Upper bound of 95% CI

- | | |
|--|-----------------------------|
| • Incidence ($\times 10^{-4}$ pyrs) | 157 (c/w 34 for salmeterol) |
| • Attrib risk ($\times 10^{-4}$ pyrs) | 151 (c/w 27 for salmeterol) |
| • NNH | 66 (c/w 366 for salmeterol) |
- Conclusion:
 - We have no idea, but false assurance
 - Could be extremely high (probably is)

Summary measures of clinical health benefits with single-entity LABAs compared to albuterol in pivotal trials in adults

	Serevent				Foradil			
	SLG-311	SLG-312	SLD-311	SLD-312	2302	2303 ¹	040	041
Δ AQOL	---	---	---	---	-0.01	-0.25	---	---
Δ Asthma score	-0.2	---	-0.1	---	-0.06	“not stat sig”	-0.3	-0.1
Δ Rescue use (puffs/d)	-0.5	-1.7	0	-0.6	-0.26		“not different”	“not different”

¹ One patient in Foradil group was hospitalized and intubated with life-threatening exacerbation (note: one out of 80)

Summary measures of clinical health benefits with combination LABA-ICS products compared to ICS in pivotal trials in adults

	Advair		Symbicort	
	3002	3003	716	717
Δ AQOL ¹	0.43	0.45	0.16	0.29
Δ Asthma score ²	18% \uparrow in sx-free days	16% \uparrow in sx-free days	-0.03	-0.15
Δ Rescue use (puffs/d)	21% \uparrow in rescue-free days	22% \uparrow in rescue-free days	-0.35	-0.46

¹ Δ AQOL < 0.5 not clinically important

² Δ asthma score < 0.4 is “small at best”

Comparison and interpretation of clinical “benefit” measures in adults

	Symbicort 716	Symbicort 717	Advair 3002	Advair 3003	Clinical interpretation ¹
Δ AQOL	0.16	0.29	0.43	0.45	“not meaningful”
Δ Asthma score	-0.03	-0.15	---	---	“not meaningful”
Δ Rescue use	-0.35	-0.46	---	---	“not important”
Δ Symptom- free days	1% ↑	11% ↑	18% ↑	16% ↑	?
Δ Rescue free days	11% ↑	19% ↑	21% ↑	22% ↑	?

¹ Paraphrased quotations from FDA medical officer reviews of LABA NDAs

Comparison and interpretation of clinical “benefit” measures in children

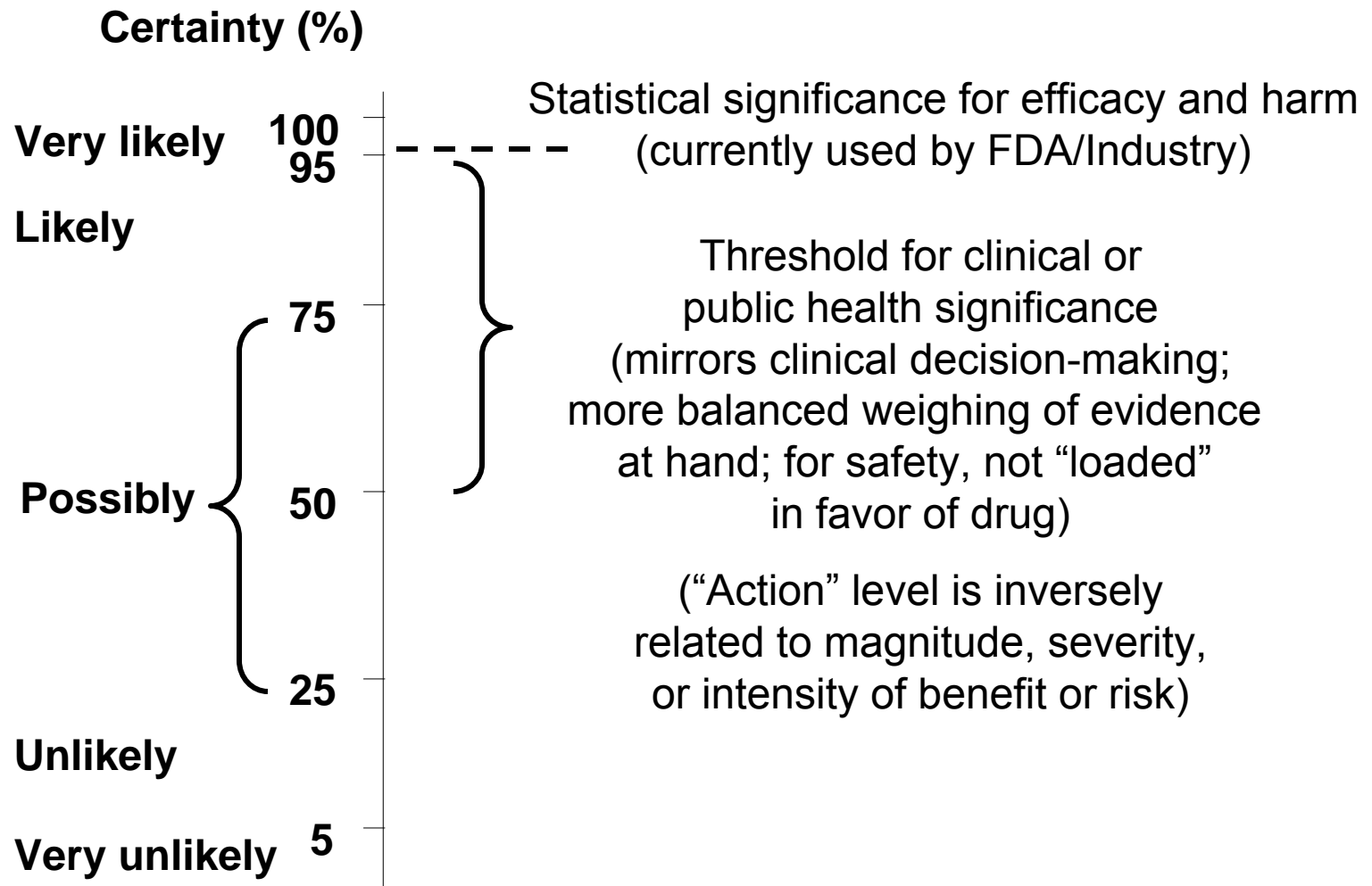
	Serevent	Foradil		Advair
	390	049	DP/PD2	30031
Daytime asthma score	-0.3	-0.07	-0.12	-0.1
Nighttime asthma score		-0.09	-0.07	
Daytime rescue use	-0.3	-0.08	-0.14	-0.1
Nighttime rescue use		-0.09	-0.08	

Level of certainty regarding asthma mortality risk with combination LABA-ICS products in children and adolescents

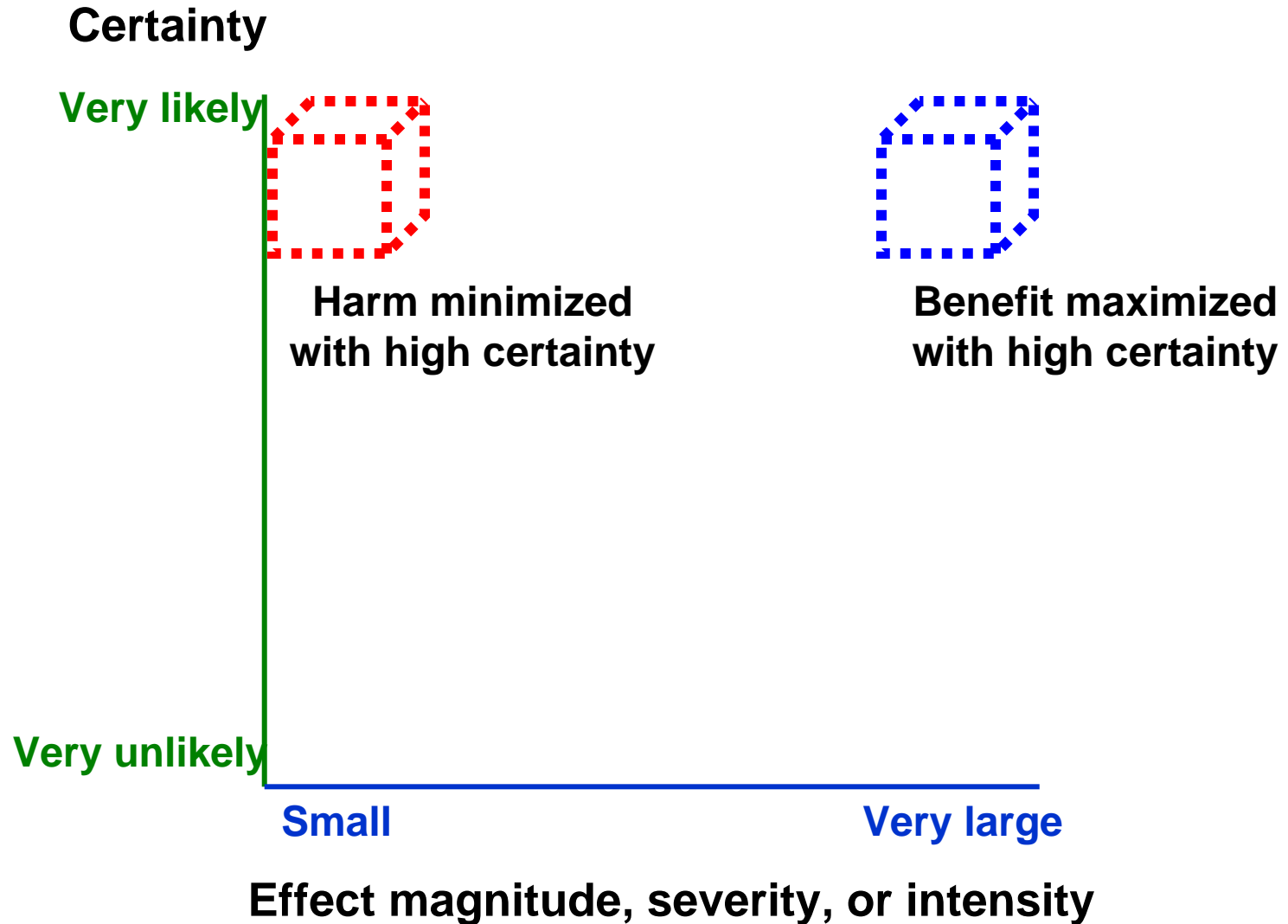
Total LABA-ICS database in children and adolescents ¹ N=2,394 Pyrs=1,085			
Hazard ratio	Power to detect hazard ratio ($\alpha=0.05$)	Person-years needed to exclude hazard ratio ($\alpha=0.05$)	
		90% power	95% power
10	34%	4,900	5,884
15	52%	2,946	3,537
25	77%	1,629	1,956
43	95%	900	1,081
50	97%	770	920

¹ Database from Dr. Levenson's review

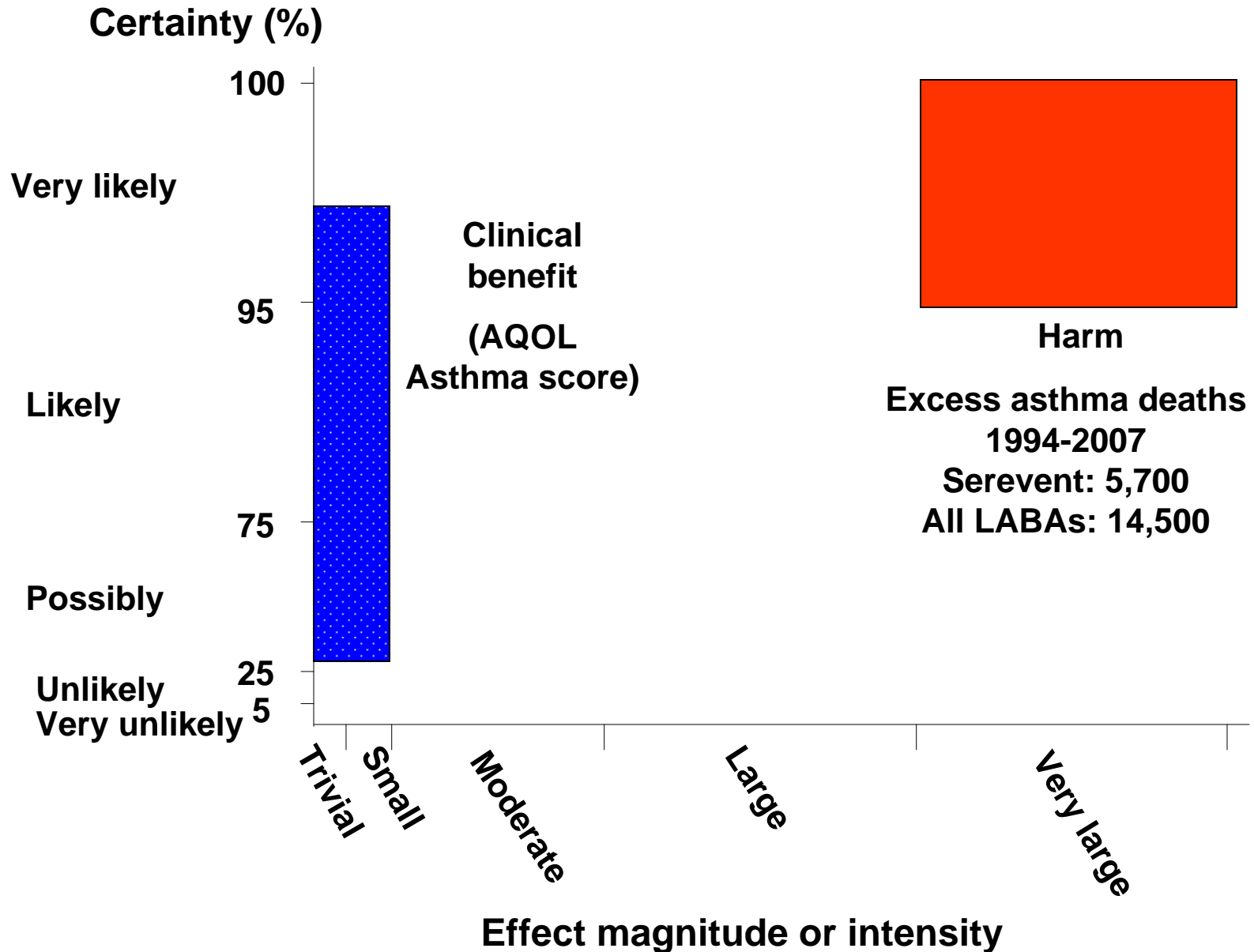
Decision-making paradigms in drug approval and public health



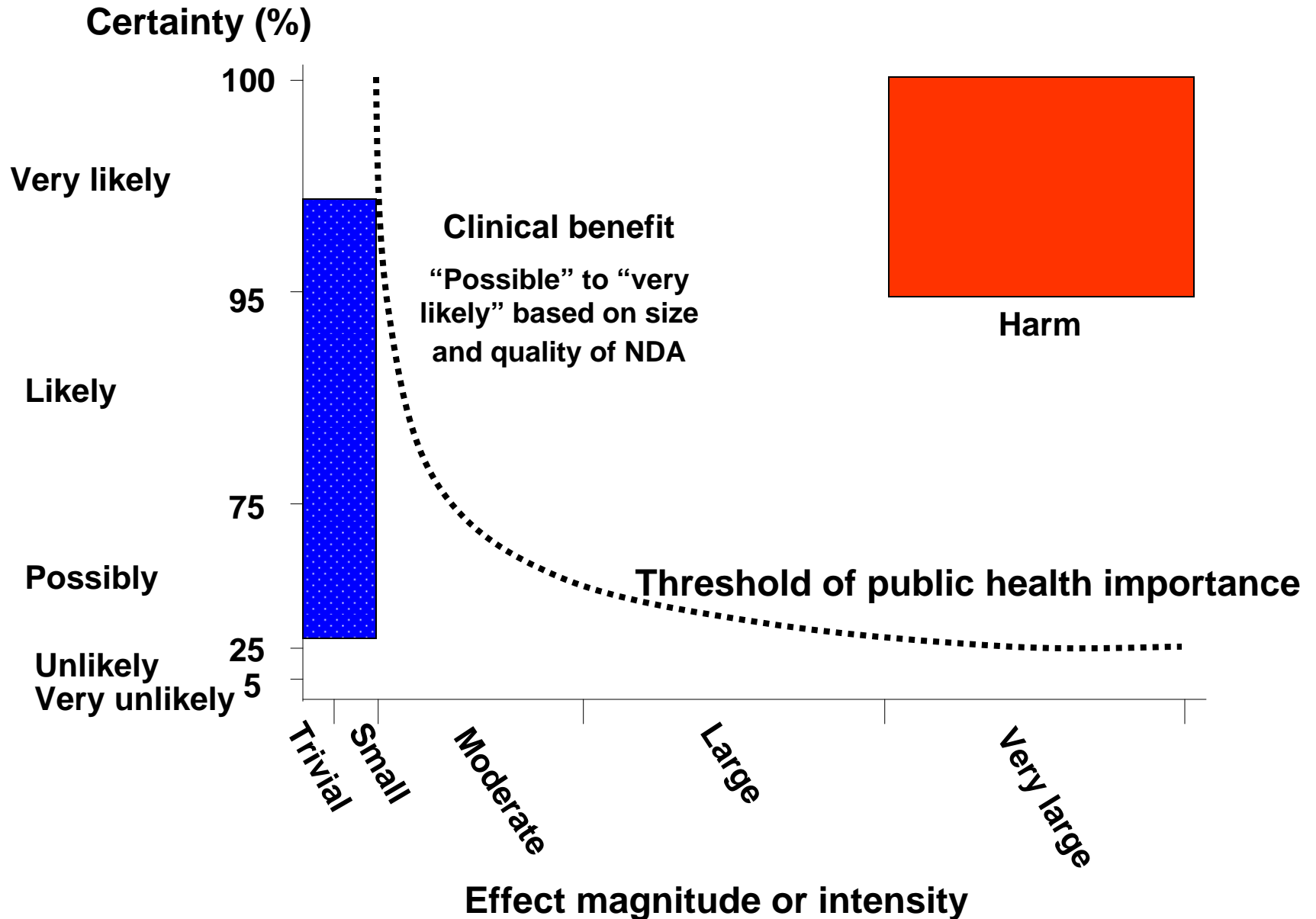
Characteristics of an ideal drug



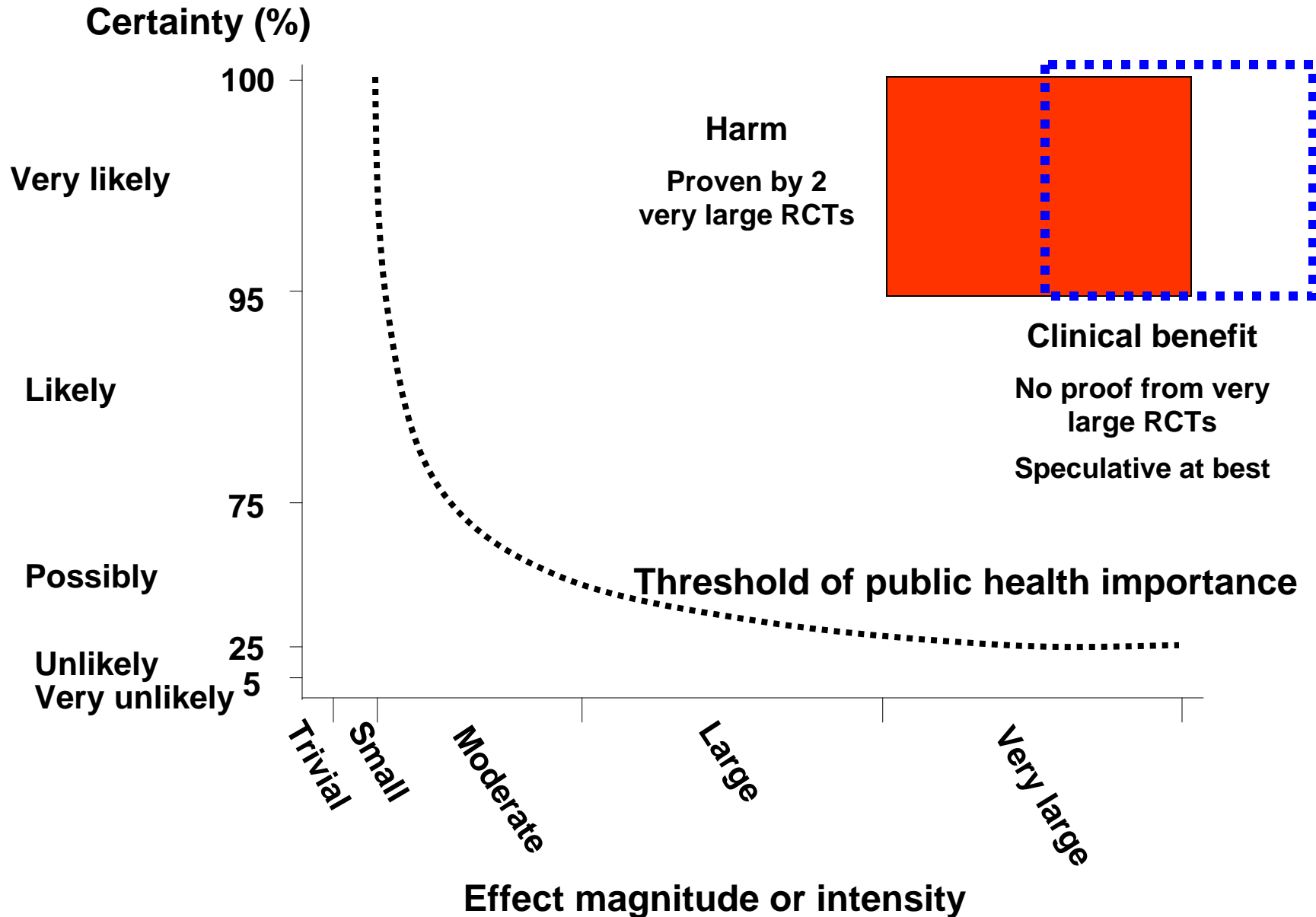
Clinical benefits and asthma mortality risk with LABAs, compared to existing alternative therapies (1)



Clinical benefits and asthma mortality risk with LABAs, compared to existing alternative therapies (2)



Clinical benefits and asthma mortality risk with LABAs, per FDA's Office of New Drugs



Attributable risk of the composite outcome in LABA-treated patients, and the baseline risk of the composite outcome in the control groups from the LABA clinical trials

	Attributable risk per 10 ⁴ pyrs (composite outcome) ¹		Incidence rate per 10 ⁴ pyrs (composite outcome)
Serevent	86	Serevent control	289 ¹
Foradil	147	Foradil control	228 ¹
Advair	3	Advair control	63¹
Symbicort	273	Symbicort control	94 ¹
		SNS control	395
		SMART control	275

¹ Derived from Dr. Levenson's review

Asymmetry in handling of benefits and risks in pivotal trials for approval of Advair and Symbicort

	Benefits			Asthma mortality		
	Outcome measure	Power		Power 10-fold ↑	Power 50-fold ↑	Power 100-fold ↑
Advair (3002)	FEV ₁ (Δ 0.25L)	80%	Advair (3002, 3003)	8%	31%	56%
	AQOL (Δ 0.5)	88%				
Symbicort (716)	FEV ₁ (Δ 0.25L)	95%	Symbicort (716, 717)	10%	40%	68%

- Power: without a telescope, the moon has no craters
 - Does that mean the moon really has no craters?
- Given such low power, how could anyone objectively conclude that Advair or Symbicort is safe?
 - Or that their clinical health benefits exceed their risks, considering risk has not been adequately or accurately measured?

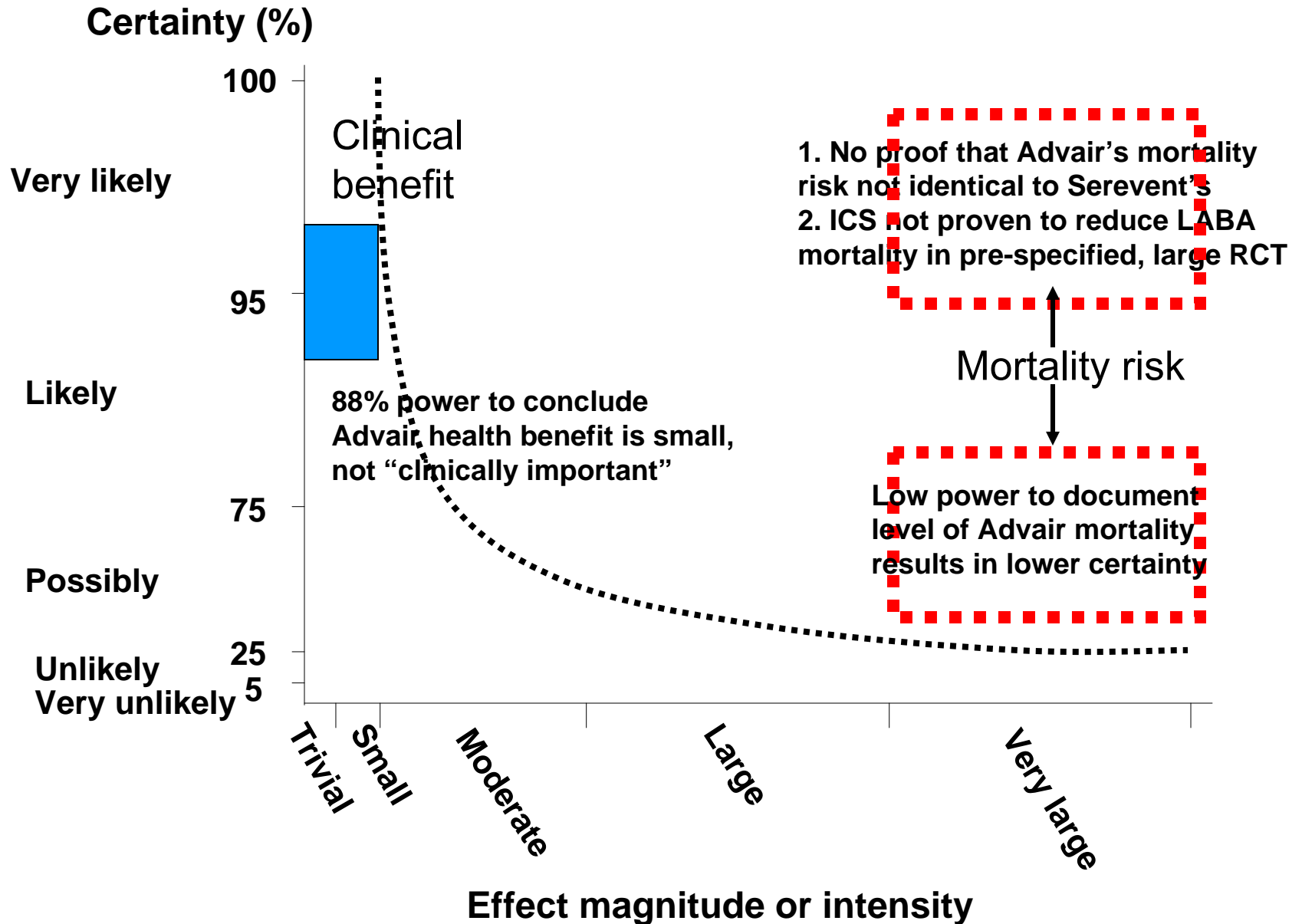
Level of certainty regarding asthma mortality risk with Advair from total controlled database

	Total Advair database ¹ N=13,212 Pyr=6,402	
Hazard ratio ²	Power to detect hazard ratio ($\alpha=0.05$)	Person-years needed to exclude hazard ratio ($\alpha=0.05$; power=90%)
1.5	6%	360,800
3	28%	36,080
5	62%	13,530
10	96%	4,900

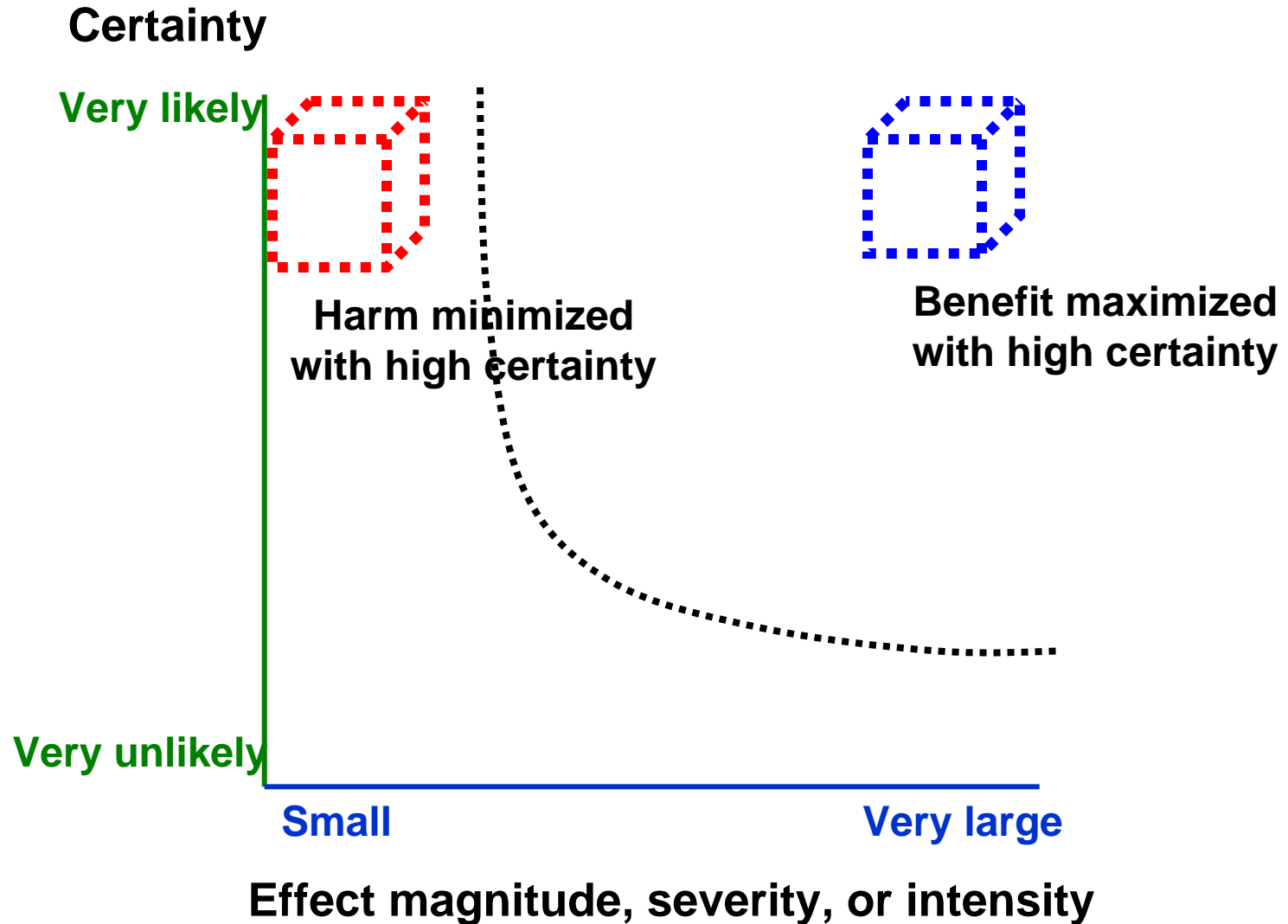
¹ Based on Dr. Levenson's review

² Background rate from SNS and SMART (6 per 10⁴ per year)

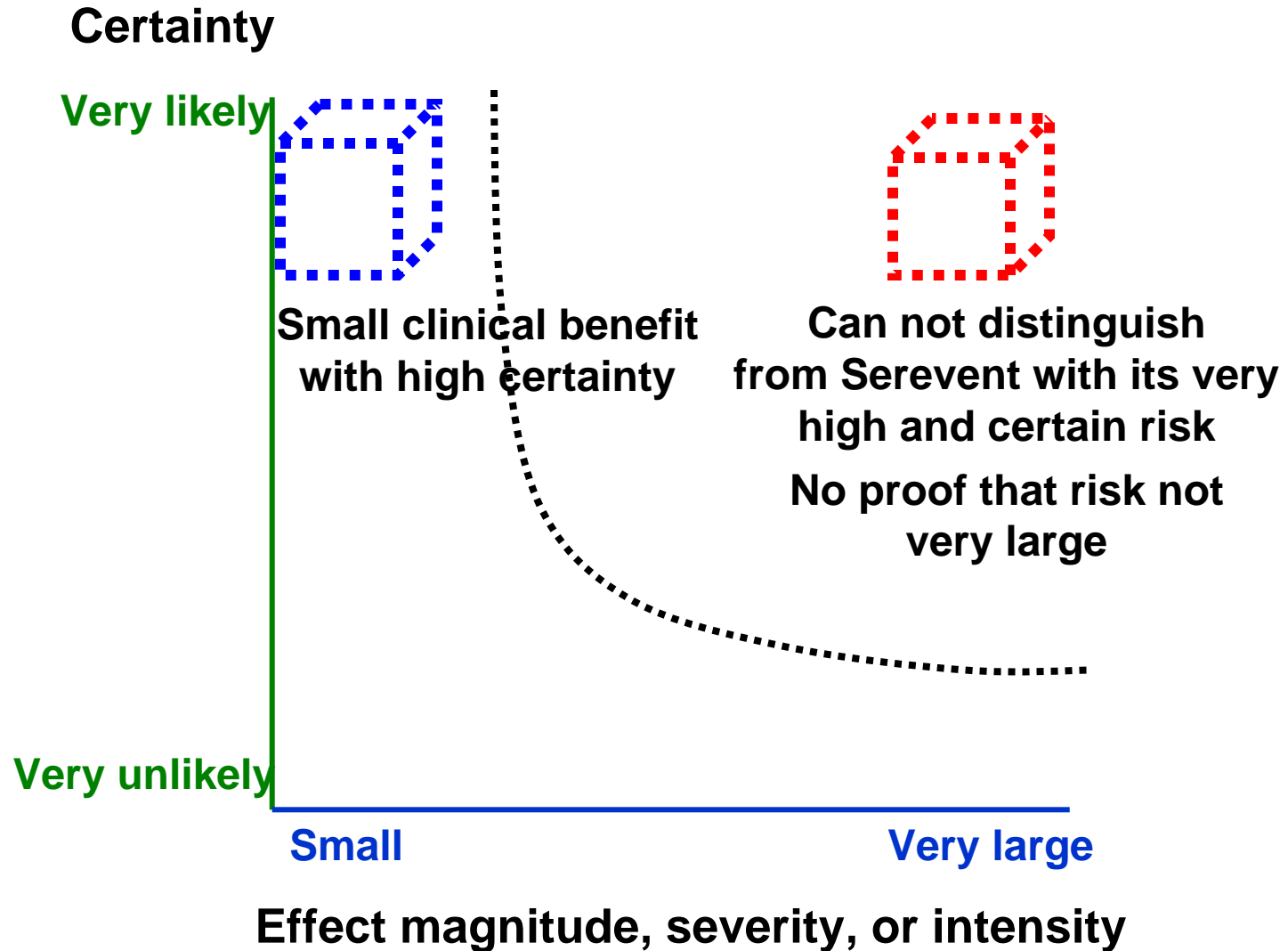
Clinical benefits and asthma mortality risk with Advair, compared to existing alternative therapies (ICS)



Characteristics of an ideal drug



Characteristics of Advair: Antithesis of an “ideal drug”



Conclusions (1)

- **Single-entity LABA products should be withdrawn from the market**
 - Generally trivial to small clinical benefit compared to albuterol
 - In children (vs. placebo), clinical benefit is even less
 - Nearly 50% of use without any ICS
 - Serevent is known with high certainty to confer high mortality risk
 - Combination (LABA-ICS) products ensure ICS use and compliance with labeling
 - But here's the contradiction: ICS not shown to reduce LABA asthma mortality risk
 - What's the rationale for concluding that ICS should be used with LABAs?

Conclusions (2)

- **Asthma indication for use of all combination LABA-ICS products in children and adolescents should be withdrawn**
 - Inadequately studied; “safety” unproven and no evidence to prove that benefit exceeds risk
 - Trivial clinical benefit, if any, compared to placebo
 - High potential for substantially increased asthma mortality risk
 - Absence of proof of mortality risk \neq proof of absence of such risk
 - We have sufficient evidence to exclude a 43-fold or greater increase in asthma mortality risk, but not lower risk than this
 - No health benefit commensurate with this level of risk has been demonstrated or proven
 - There is no basis to conclude that LABA-ICS are “safe and effective” or that “benefits exceed risks” in these age-groups
 - Strong suggestion of inverse age-related mortality risk

Conclusions (3)

- **Asthma indication for use of all combination LABA-ICS products in adults should be withdrawn**
 - While it is clear that LABA-ICS is superior to ICS alone with respect to measures of bronchodilation, this does not translate into “clinically meaningful” health benefits
 - Even for Advair, where most favorable data is available, no evidence that asthma hospitalizations are prevented
 - The LABA component of these products are known to confer a substantial increase in asthma mortality
 - No evidence from randomized trials that the ICS component reduces or reverses mortality risk of LABA
 - Even for Advair, no proof that mortality risk not same as Serevent (28% chance of detecting a true HR=3)
 - FDA maintains, as a matter of stated policy, that ICS component does not alter LABA mortality risk (check the label)

Advair label, 2008

WARNING: RISK OF ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, **may** increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients on placebo). (5.1)

Why “may” and not “does”?

enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 1 and Figure 1). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%, relative risk 4.37 [95% CI: 1.25, 15.34]).

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR DISKUS, or other asthma-controller therapy modifies the risk of asthma-related death.

Conclusions (4)

- **Asthma indication for use of all combination LABA-ICS products in adults should be withdrawn**
 - LABA-ICS products are statistically indistinguishable from single entity LABAs (Dr. Levenson's presentation)
 - Cannot exclude nearly 10-fold increase in asthma mortality
 - “Approved indication” is equivalent to an FDA endorsement or recommendation that a product be used for a specified disorder
 - Given the above, with such small proven clinical benefit, how can we justify exposing millions of patients to what we must conclude is an extremely high risk of death?
 - On what basis can we conclude that LABA-ICS products are “safe and effective” if efficacy measures of bronchodilation do not predict or translate to “clinically meaningful” health benefits, and asthma mortality risk is proven to be high?
 - At best, LABA-ICS products have been inadequately and insufficiently studied to justify marketing
 - This has arisen because of FDA's asymmetric and biased handling of efficacy and safety

Final thoughts (1)

- Asthma is a serious disorder affecting millions
- Current therapies inadequate to manage symptoms or improve functioning in a substantial subgroup of patients
 - No “silver bullets” or “wonder drugs”
 - Need and desire (patients, practitioners) for more effective and safer therapies
 - But we must be guided by evidence, not desire or unproven speculation, especially if high mortality risks are likely
- As with any drug used to treat a disease affecting large numbers, some patients will show remarkable response
 - With LABA-ICS products, such response is unproven, and must be rare, if randomized controlled trials are to be believed.
 - If LABA-ICS are life-saving for some patients, we don't know how to identify them and we have no evidence-based reason to speculate such properties
 - Likewise we are unable to identify patients most likely to experience mortality or life-threatening events due to LABA-ICS. However, strong evidence exists that mortality risk is real
 - “Russian roulette” at a cost of perhaps over 14,000 lives and rising, for no proven substantial health benefit
- Diamonds (color, clarity, cut, carat), zircons, and glass
 - LABA-ICS are closer to glass than diamonds (clinical benefits) but they command diamond prices (mortality risk)

Final thoughts (2)

- Committee is faced with many intertwined issues
- In a new era of “Safety First,” proclaimed earlier this year by FDA:
 - Is FDA’s asymmetric assessment of efficacy and safety in the best interests of the public? Is it fair, objective, balanced?
 - Is the current paradigm that presumes safety and requires “definitive proof” of harm, acceptable as a matter of public health policy?
 - If it is acceptable, why not extend the same presumption to efficacy and do away with the requirement for evidence?
- Regarding LABAs
 - Better therapeutic options for asthma are sorely needed, but such options must be supported by evidentiary proof
 - FDA is authorized to approve drugs that are “safe and effective”
 - Patients’ willingness to accept mortality risk is not a basis for approval or continued marketing and is not rational public policy (paying diamond prices for a zircon or piece of glass is not rational)
 - If safety hasn’t been adequately or accurately assessed and if it has been treated differently from efficacy, how can FDA conclude that a drug is “safe” or that benefit exceeds risk?
 - It’s time for honest, objective, and evidence-based decision-making
 - The best available evidence strongly suggests that all LABA products confer substantially increased asthma mortality risks, while conferring small if any, meaningful health benefits. Bronchodilation is a very imperfect surrogate for health benefit
 - With a high degree of certainty, many thousands have died because of the LABAs they used. What proven, not speculative, health benefit justifies these deaths? No RCT has shown that LABAs rescue anyone from the grave