

Dr. Sunny Kaul

Consultant in Respiratory & Intensive Care
Medicine

Royal Brompton & Harefield NHS Foundation
Trust

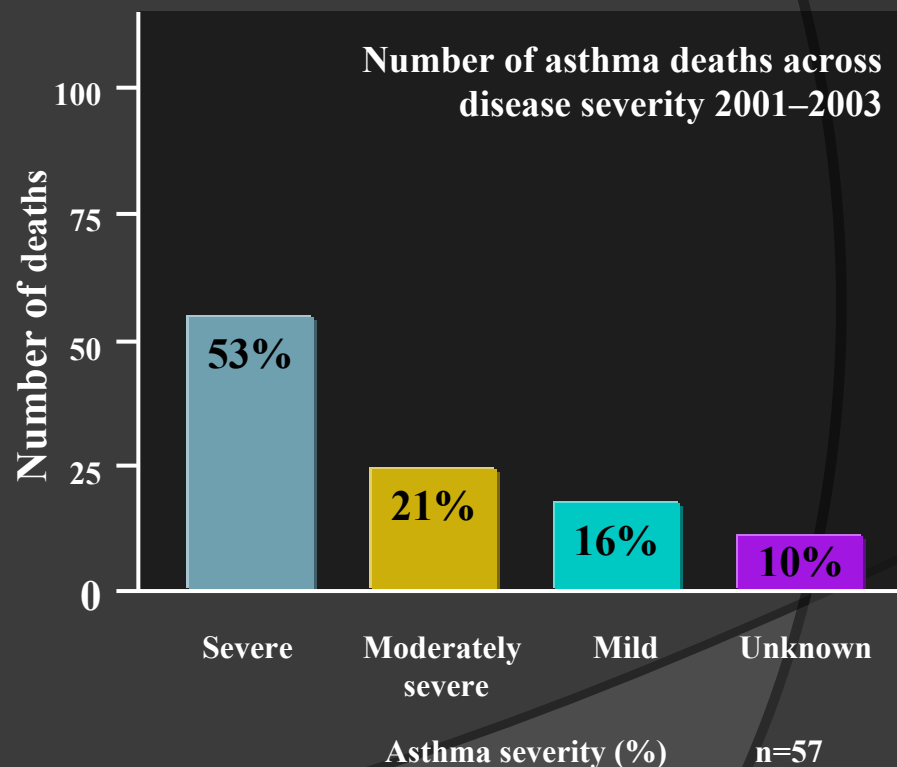
Roadmap

- Few Facts n Figures – Asthma
- Diagnosis – BTS Guidelines
- Treatment – BTS Guidelines

● Facts n Figures

Asthma deaths occur across disease severity^{1,2}

- It is a myth that only severe asthma can prove fatal
- Asthma deaths occur across disease severity with deaths occurring in those patients whose asthma is considered mild-to-moderate



EPIDEMIOLOGY

- 10-15% population
- Asthma care likely to cost average PCT £4.5million per year
- Average PCT (330,000 pts) will have
 - – 45,000 with diagnosed asthma
 - – >400 emergency admissions/yr
- **1 in 4 have severe asthma that is under treated**

Asthma and the NHS – the financial burden

Treating a patient with uncontrolled asthma costs **3 times more** than treating a patient whose asthma is controlled

S

HS



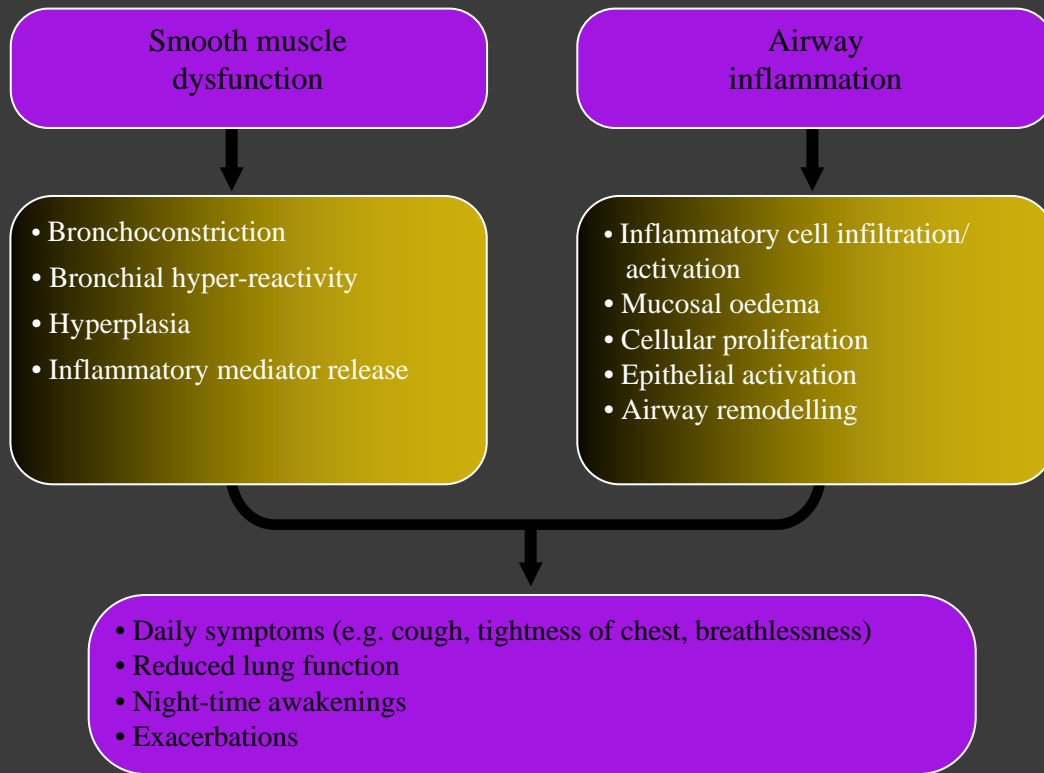
Patient burden

- Over 50% accept lifestyle limitations due to their asthma
- Over one third experience daily symptoms
- Over 70% experience night-time awakening



What is asthma?

- Asthma is a two-part problem comprising:
 - Airway inflammation and smooth muscle dysfunction





Asthma pathology¹

- Inflammation of the lungs
- Smooth muscle hyperplasia
- Basement membrane thickening
- Mucous gland hyperplasia
- Mucosal epithelial sloughing
- Tissue oedema



Airway remodelling¹

- ⦿ Changes occurring as a consequence of inflammation in the airways have been termed remodelling
- ⦿ The epithelium, basement membrane and smooth muscle are all affected
- ⦿ These changes contribute to a loss of lung function
- ⦿ If inflammation is untreated, this can lead to airway remodelling

⦿ Diagnosis – BTS Guidelines



Diagnosis

- The diagnosis of asthma is a clinical one
- There is no standardised definition, therefore, it is not possible to make clear evidence based recommendations on how to make a diagnosis
- Central to all definitions is the presence of symptoms and of variable airflow obstruction

Features that increase the probability of asthma in adults

- >1 of the following: wheeze, breathlessness, chest tightness, cough, particularly if:
 - worse at night and early morning
 - in response to exercise, allergen exposure and cold air
 - after taking aspirin or beta blockers
 - Personal/family history of asthma/atopy
- Widespread wheeze heard on auscultation of the chest
- Unexplained low FEV₁ or PEF
- Unexplained peripheral blood eosinophilia

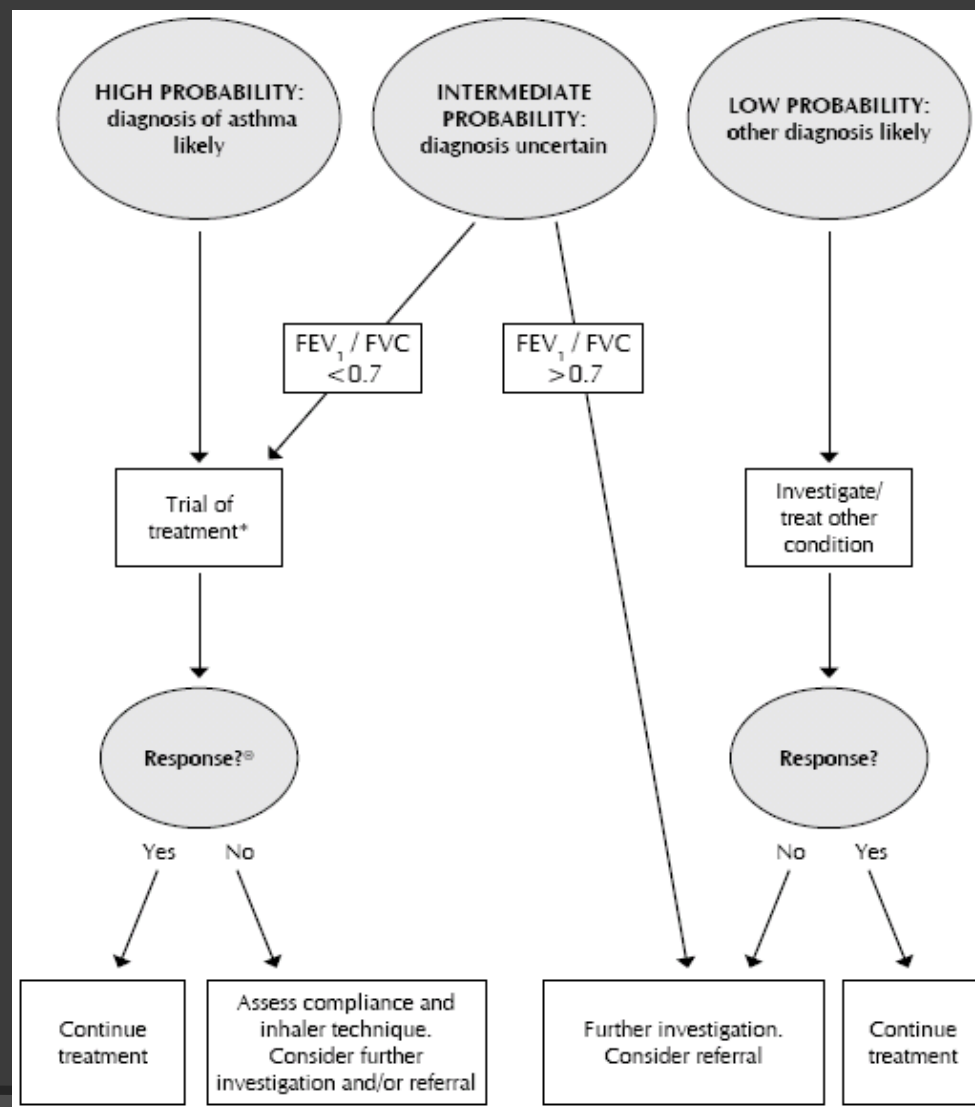


Features that lower the probability of asthma

- Prominent dizziness, light-headedness, peripheral tingling
- Chronic productive cough in the absence of wheeze or breathlessness
- Repeatedly normal physical examination of chest when symptomatic
- Voice disturbance
- Symptoms with colds only
- Significant smoking history (>20 pack-years)
- Cardiac disease
- Normal PEF or spirometry when symptomatic

- ⦿ Reconsider the diagnosis of asthma in those who do not respond
- ⦿ Preferred approach in patients with an **intermediate probability** of having asthma is to carry out further investigations, including an explicit trial of treatments for a specified period, before confirming a diagnosis and establishing maintenance treatment

Following clinical assessment in adults



CRITERIA FOR SPECIALIST REFERRAL

- ⦿ Diagnosis unclear
- ⦿ Unexpected clinical findings (clubbing, crackles etc)
- ⦿ Unexplained restrictive spirometry
- ⦿ Suspected occupational asthma
- ⦿ Persistent non-variable breathlessness
- ⦿ Monophonic wheeze or stridor
- ⦿ Prominent systemic features (myalgia, weight loss, fever)
- ⦿ Chronic sputum production
- ⦿ CXR shadowing
- ⦿ Marked blood eosinophilia
- ⦿ Poor response to asthma treatment
- ⦿ Severe asthma exacerbation

Monitoring asthma in primary care

- Symptomatic asthma control using RCP '3 questions',
- Asthma Control Questionnaire or Asthma Control Test (ACT™)
- Lung function (spirometry/PEF)
- Exacerbations
- Inhaler technique
- Compliance (prescription refill frequency)
- Bronchodilator reliance (prescription refill frequency)
- Possession of and use of self management plan/personal action plans

RCP 3 QUESTIONS

3 questions to be asked at every consultation:

In the last week/month:

1. Have you had any difficulty sleeping because of your asthma symptoms (including cough)?
2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?
3. Has your asthma interfered with your usual activities (e.g. housework, work/school, etc)?

Asthma Control Test™ (ACT)

Score

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time

1

Most of the time

2

Some of the time

3

A little of the time

4

None of the time

5

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day

1

Once a day

2

3 to 6 times a week

3

Once or twice a week

4

Not at all

5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?

4 or more nights a week

1

2 or 3 nights a week

2

Once a week

3

Once or twice

4

Not at all

5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day

1

1 or 2 times per day

2

2 or 3 times per week

3

Once a week or less

4

Not at all

5

5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all

1

Poorly controlled

2

Somewhat controlled

3

Well controlled

4

Completely controlled

5

Copyright 2002, QualityMetric Incorporated.
Asthma Control Test Is a Trademark of QualityMetric Incorporated.

Patient Total Score



Step 1: Mild intermittent asthma

- ⦿ Prescribe inhaled short acting β_2 agonist (SABA) as short term reliever therapy for all patients with symptomatic asthma
- ⦿ Good asthma control is associated with little or no need for short-acting β_2 agonist
- ⦿ Using two or more canisters of β_2 agonists per month or > 10-12 puffs per day is a marker of poorly controlled asthma that puts individuals at risk of fatal or near-fatal asthma
- ⦿ Patients with high usage of inhaled short-acting β_2 agonists should have their asthma management reviewed



Step 2: Regular preventer therapy

- ⦿ Inhaled steroids are the recommended preventer drugs for adults in order to achieve overall treatment goals
- ⦿ Consider inhaled steroids if any of the following:
 - Using inhaled β_2 agonist three times a week or more
 - Symptomatic three times a week or more
 - Waking one night a week



Step 2: Regular preventer therapy

- Adults:
 - 200-800mcg/day BDP*(reasonable starting dose 400mcg per day for many adults)

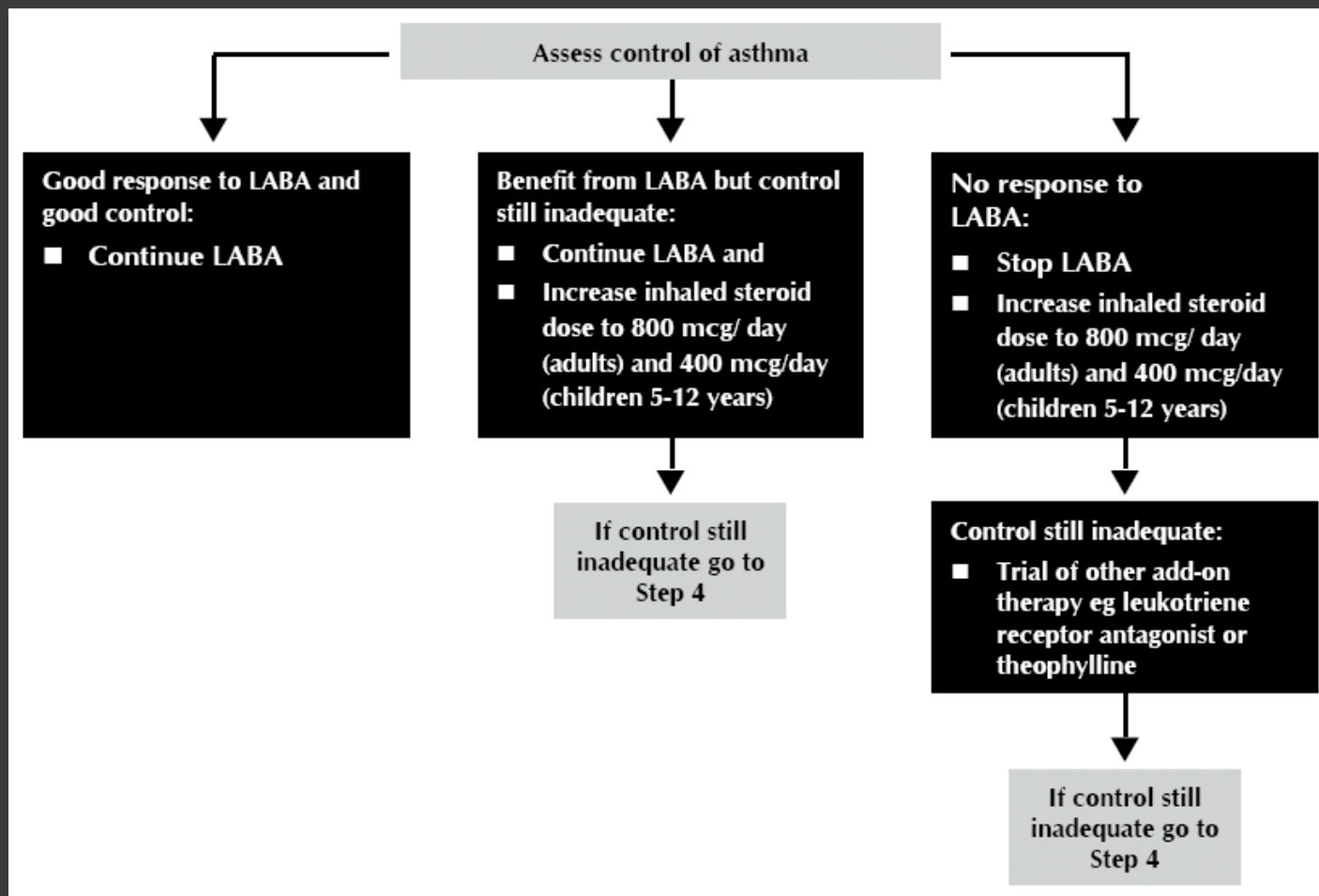
*All doses in the guideline refer to beclometasone given via CFC-MDI (metered dose inhaler).
Beclometasone 400mcg = budesonide 400mcg = fluticasone propionate 200mcg

Step 3: Initial add-on therapy

- A proportion of patients may not be adequately controlled at step 2
- Adults and Children 5-12:
 - First choice as add-on therapy is an inhaled long-acting β_2 agonist (LABA), which should be considered before going above a dose of 400mcg BDP* and certainly before going above 800mcg

*All doses in the guideline refer to beclometasone given via CFC-MDI (metered dose inhaler). Beclometasone 400mcg = budesonide 400mcg = fluticasone propionate 200mcg

Step 3: Initial add-on therapy





LABA safety

- Within the guideline it is mentioned that the UK Regulatory agency and guideline development group reviewed the balance of risks and benefits LABAs in the management of asthma and concluded that LABAs can continue to be used in conjunction with inhaled steroids

Combination inhalers

- There is no difference in efficacy in giving inhaled steroid and LABA in combination or in separate inhalers
- Combination inhalers have the advantage of guaranteeing that LABAs are not taken without inhaled steroid
- In adult patients at step 3 who are poorly controlled:
 - the use of budesonide/formoterol in a single inhaler as rescue medication instead of a SABA, in addition to its regular use as a controller treatment, has been shown to be an effective
 - This management technique has not been investigated with other inhalers
 - Before instituting this management careful patient education is required

Step 4: Persistent poor control

- Essentially unchanged
- Green = Adults

Consider trials of:

- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

STEP 4

Persistent poor control



Step 5: Continuous or frequent use of oral steroids

- Essentially unchanged
- Green = Adults

Use daily steroid tablet
in lowest dose providing
adequate control

Maintain high dose inhaled
steroid at 2000 mcg/day*

Consider other treatments to
minimise the use of steroid
tablets

Refer patient for specialist care

STEP 5

**Continuous or frequent
use of oral steroids**



Stepping down

- Stepping down therapy once asthma is controlled is recommended
- Regular review of patients as treatment is stepped down is important
- Patients should be maintained at the lowest possible dose of inhaled steroid
- Reductions should be slow, decreasing dose by ~25-30% every three months

Adolescents

- ⦿ Asthma is common and underdiagnosed
- ⦿ See them on their own for part of consultation
- ⦿ Complementary and alternative medicine widespread and marker for non-adherence

Summary

- Asthma still a very important disease
- BTS guidelines - updates
- Questions?



LOOKING AT THE EVIDENCE BASE IN MORE DEPTH - STUDY SELECTION CRITERIA

Selected double-blind, randomised controlled trials

At least 6 months treatment duration

Published in peer-reviewed medical journal

ICS or ICS/LABA as regular controller treatment or
Bud/form as maintenance and rescue treatment

Exacerbation data as per ERS/ATS taskforce
guidance

Patients were “uncontrolled” prior to randomisation

STUDIES

	GOAL <i>Bateman ED et al</i>	CONCEPT <i>Fitzgerald JM et al</i>	EXCEL <i>Dahl R et al</i>	Jarjour NN et al 2006	Busse WW et al 2003	
Design	- R,DB,PG - 12 months - n = 3421	- R,DB,DD, PG - 12 months - n = 688	- R,DB,DD,PG - 6 months - n = 1391	- R,DB,PG (3-part run-in) - 6 months - n = 288	- R,DB,PG (3-part run-in) - 6 months - n = 308	
1°	Well-controlled asthma	Symptom-free days	All Exacerbations	Proportion of pts who remained in study	Proportion of pts who remained in study	
	STAY <i>O'Byrne PM et al</i>	STEP <i>Scicchitano R et al</i>	SMILE <i>Rabe KF et al</i>	STEAM <i>Rabe KF et al</i>	COMPASS <i>Bateman ED et al</i>	AHEAD <i>Bousquet J et al</i>
Design	- R,DB,PG - 12 months - n = 2760	- R,DB,DD,PG - 12 months - n=1890	- R,DB,PG - 12 months - n = 3394	- R,DB,PG - 6 months - n= 697	- R,DB,DD,PG - 6 months - n = 3335	- R,DB,DD,PG - 6 months - n = 2309
1°	Severe Exacerbations	Severe Exacerbations	Severe Exacerbations	Lung Function	Severe Exacerbations	Severe Exacerbations

BASELINE CHARACTERISTICS

Study	Mean FEV ₁ % pred	% Symptom-free days	Rescue use (inh/day)	% Rescue- free days	% Nights with awakenings and/or symptoms	Exacerbation History* (% pts with ≥1 in past year)
GOAL Bateman ED	76%	15	1.9	26	35	31%
CONCEPT Fitzgerald JM	82%	5	1.3	32	27	14-17%
EXCEL Dahl R	78-79%	7-8	2.3	25-26	69*	41-42%
Jarjour NN	81%	42	0.9	59	N/A	N/A
Busse WW	81%	44	0.8	65	N/A	N/A
STAY O'Byrne PM	73%	23-24	2.4-2.5	8	20-22	100%
STEP Scicchitano R	70%	10	1.9	29	23	100%
SMILE Rabe KF	72%	12	1.8-1.9	14-15	30-31	100%
STEAM Rabe KF	75%	30	1.6	24	13	N/A
COMPASS Bateman ED	72-73%	9	2.3	9	32-34	100%
AHEAD Bousquet J	70-71%	11	2.2-2.3	9-10	32	100%

Age= 35-46 years; ACQ=1.8-2.1 * Nights with symptoms

- Consider regular, dosing studies as a group and SMART studies a separate group
- Both groups fairly comparable in terms of frequency of daily asthma symptoms, rescue use & age of patients
- Also, for studies which measured ACQ, the baseline scores were also comparable and ranged from 1.8 to 2.1
- Now consider two other baseline characteristics available to us, in general, the patients in the regular, stable dosing studies had a somewhat higher FEV1 % predicted than the Symbicort SMART studies
- Based on studies that looked at exacerbation history, regular stable dosing studies had a lower percent of patients with at least one exacerbation requiring systemic steroid treatment, ER treatment and/or hospitalization

BASELINE CHARACTERISTICS

Study	Mean FEV ₁ % pred	% Symptom-free days	Rescue use (inh/day)	% Rescue- free days	% Nights with awakenings and/or symptoms	Exacerbation History* (% pts with ≥1 in past year)
GOAL Bateman ED	76%	15	1.9	26	35	31%
CONCEPT Fitzgerald JM	82%	5	1.3	32	27	14-17%
EXCEL Dahl R	78-79%	7-8	2.3	25-26	69*	41-42%
Jarjour NN	81%	42	0.9	59	N/A	N/A
Busse WW	81%	44	0.8	65	N/A	N/A
STAY O'Byrne PM	73%	23-24	2.4-2.5	8	20-22	100%
STEP Scicchitano R	70%	10	1.9	29	23	100%
SMILE Rabe KF	72%	12	1.8-1.9	14-15	30-31	100%
STEAM Rabe KF	75%	30	1.6	24	13	N/A
COMPASS Bateman ED	72-73%	9	2.3	9	32-34	100%
AHEAD Bousquet J	70-71%	11	2.2-2.3	9-10	32	100%

Age= 35-46 years; ACQ=1.8-2.1 * Nights with symptoms

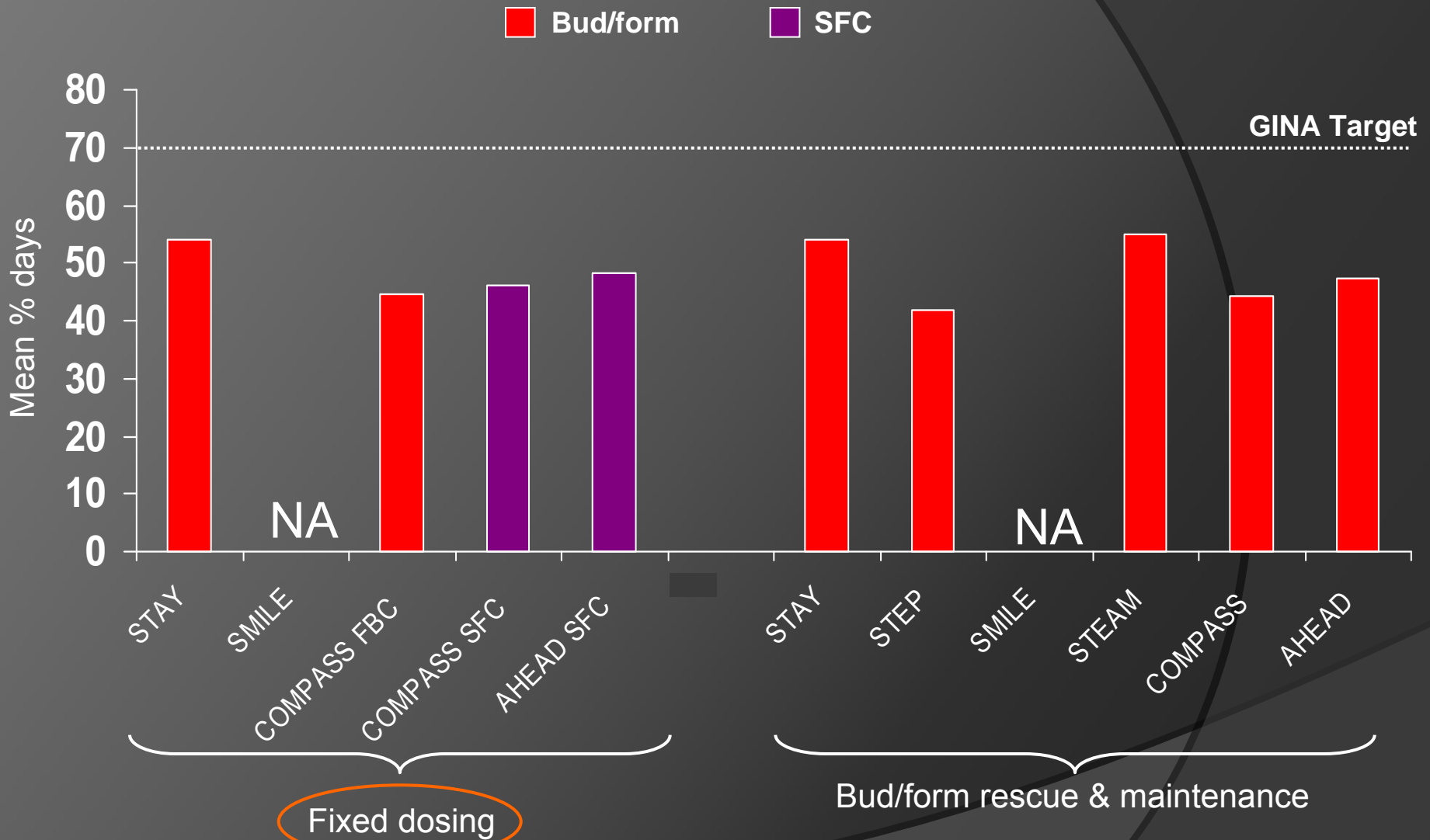
- ⦿ However, there are two important points to consider in regard to baseline characteristics
- ⦿ First, guidelines state that the targets for asthma control are achievable for all patient populations regardless of their asthma severity
- ⦿ Second, for this exercise, we were comparing outcomes to guideline targets and not comparing outcomes between studies

BASELINE CHARACTERISTICS

Study	Mean FEV ₁ % pred	% Symptom-free days	Rescue use (inh/day)	% Rescue- free days	% Nights with awakenings and/or symptoms	Exacerbation History* (% pts with ≥1 in past year)
GOAL Bateman ED	76%	15	1.9	26	35	31%
CONCEPT Fitzgerald JM	82%	5	1.3	32	27	14-17%
EXCEL Dahl R	78-79%	7-8	2.3	25-26	69*	41-42%
Jarjour NN	81%	42	0.9	59	N/A	N/A
Busse WW	81%	44	0.8	65	N/A	N/A
STAY O'Byrne PM	73%	23-24	2.4-2.5	8	20-22	100%
STEP Scicchitano R	70%	10	1.9	29	23	100%
SMILE Rabe KF	72%	12	1.8-1.9	14-15	30-31	100%
STEAM Rabe KF	75%	30	1.6	24	13	N/A
COMPASS Bateman ED	72-73%	9	2.3	9	32-34	100%
AHEAD Bousquet J	70-71%	11	2.2-2.3	9-10	32	100%

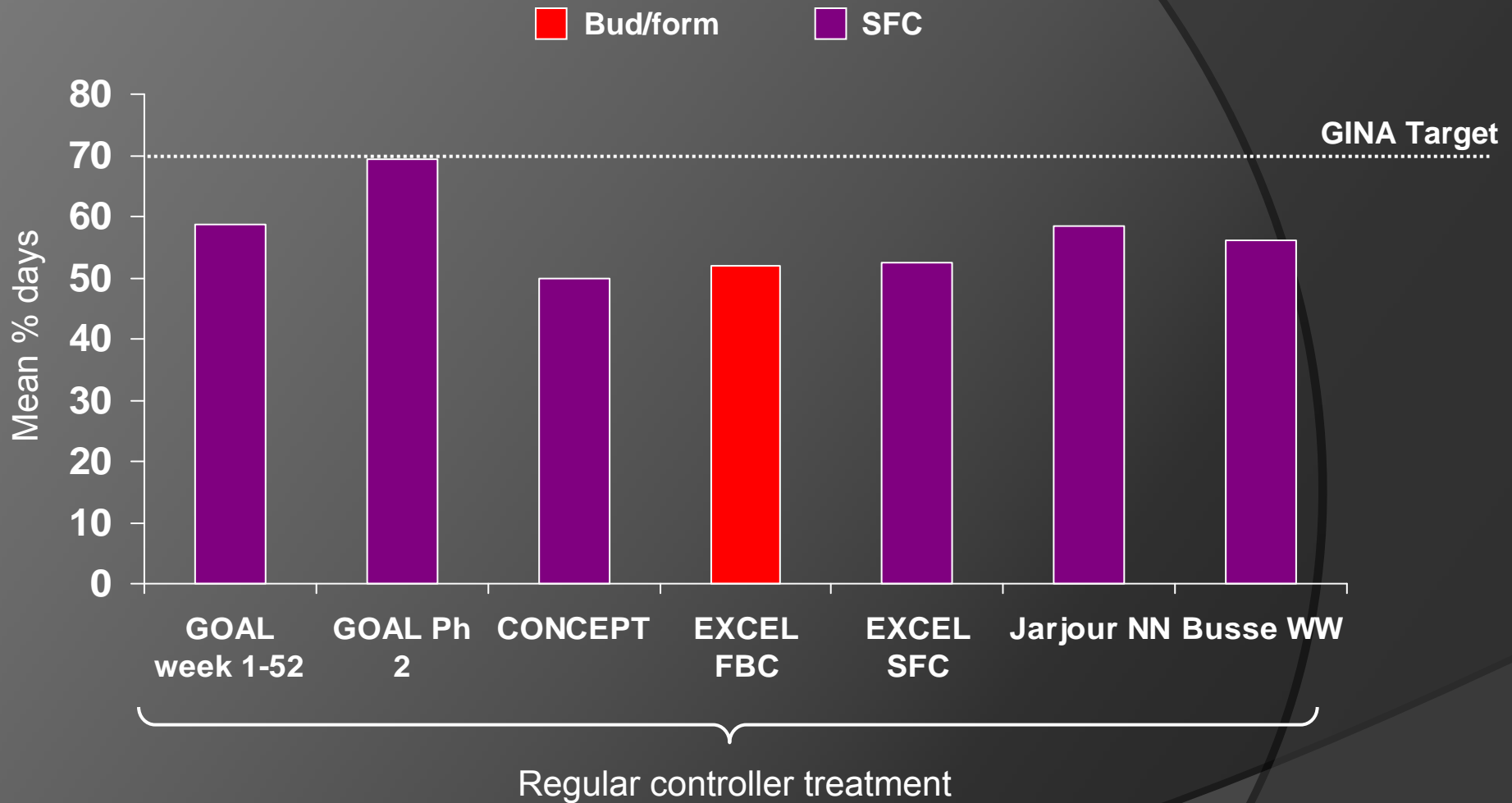
Age= 35-46 years; ACQ=1.8-2.1 * Nights with symptoms

SYMPTOM-FREE DAYS ON TREATMENT



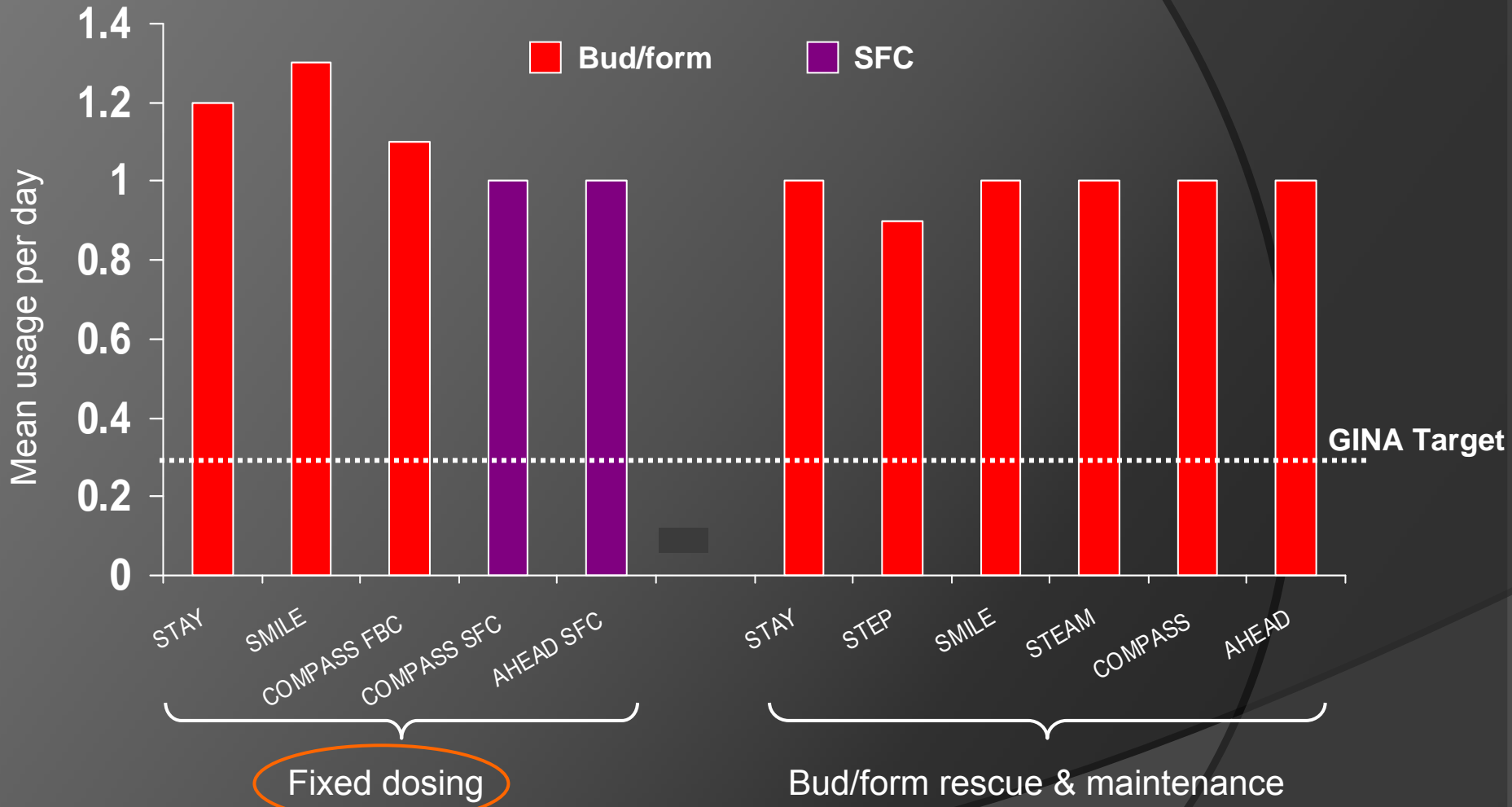
GINA objective: daily symptoms < twice a week

SYMPTOM-FREE DAYS ON TREATMENT



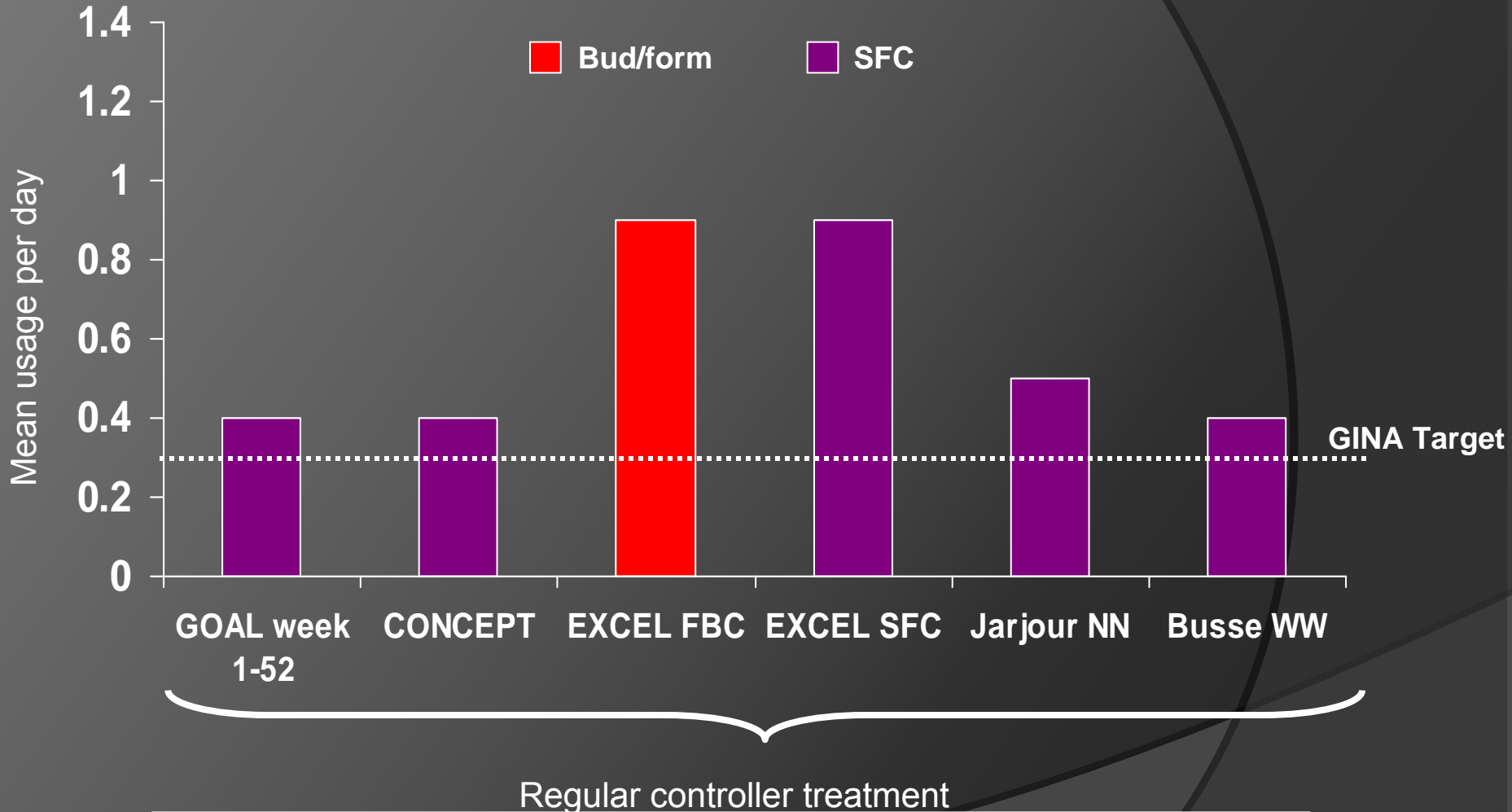
GINA objective: daily symptoms < twice a week

DAILY RESCUE USE ON TREATMENT



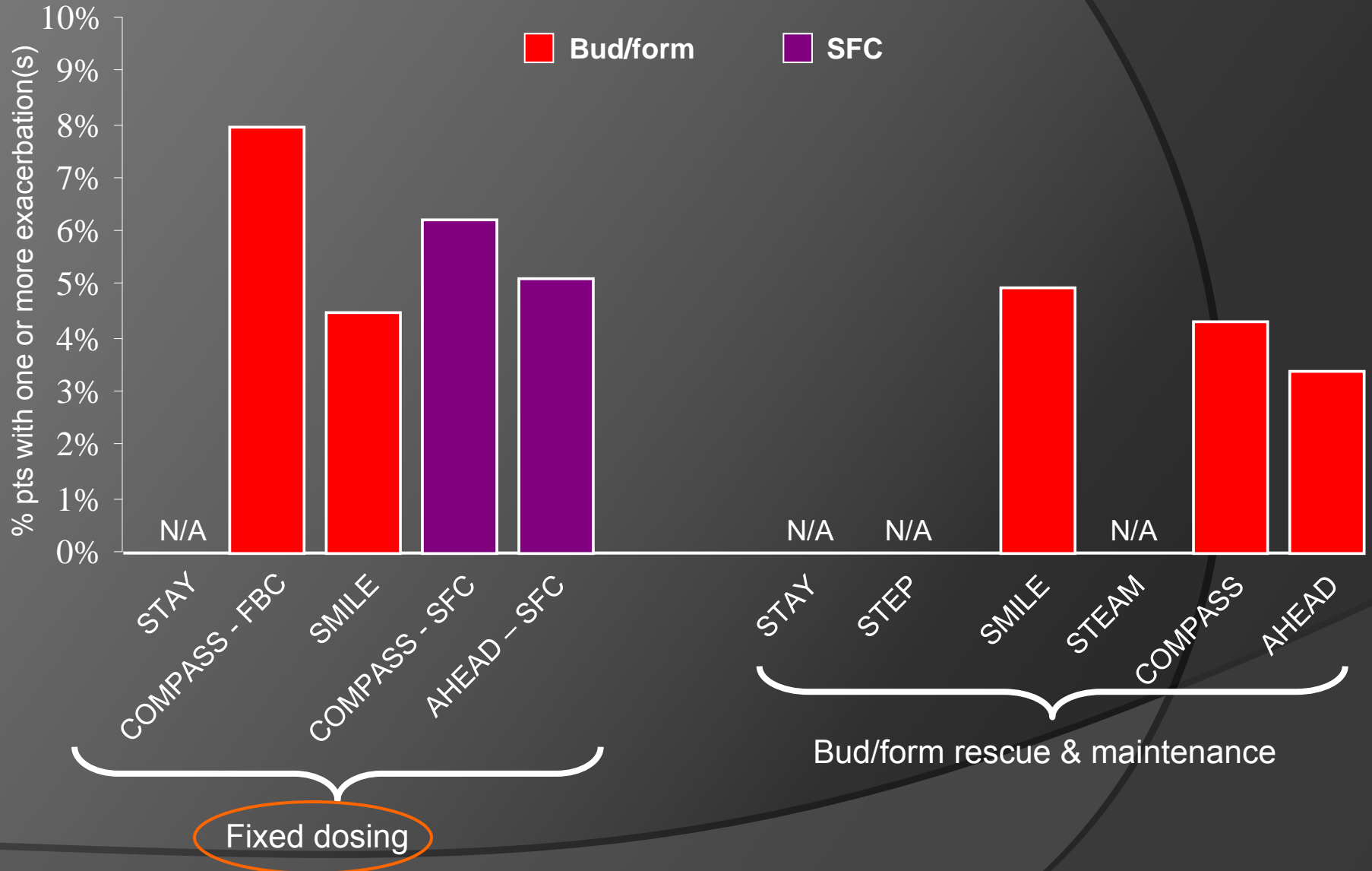
GINA objective: rescue < twice a week

DAILY RESCUE USE ON TREATMENT

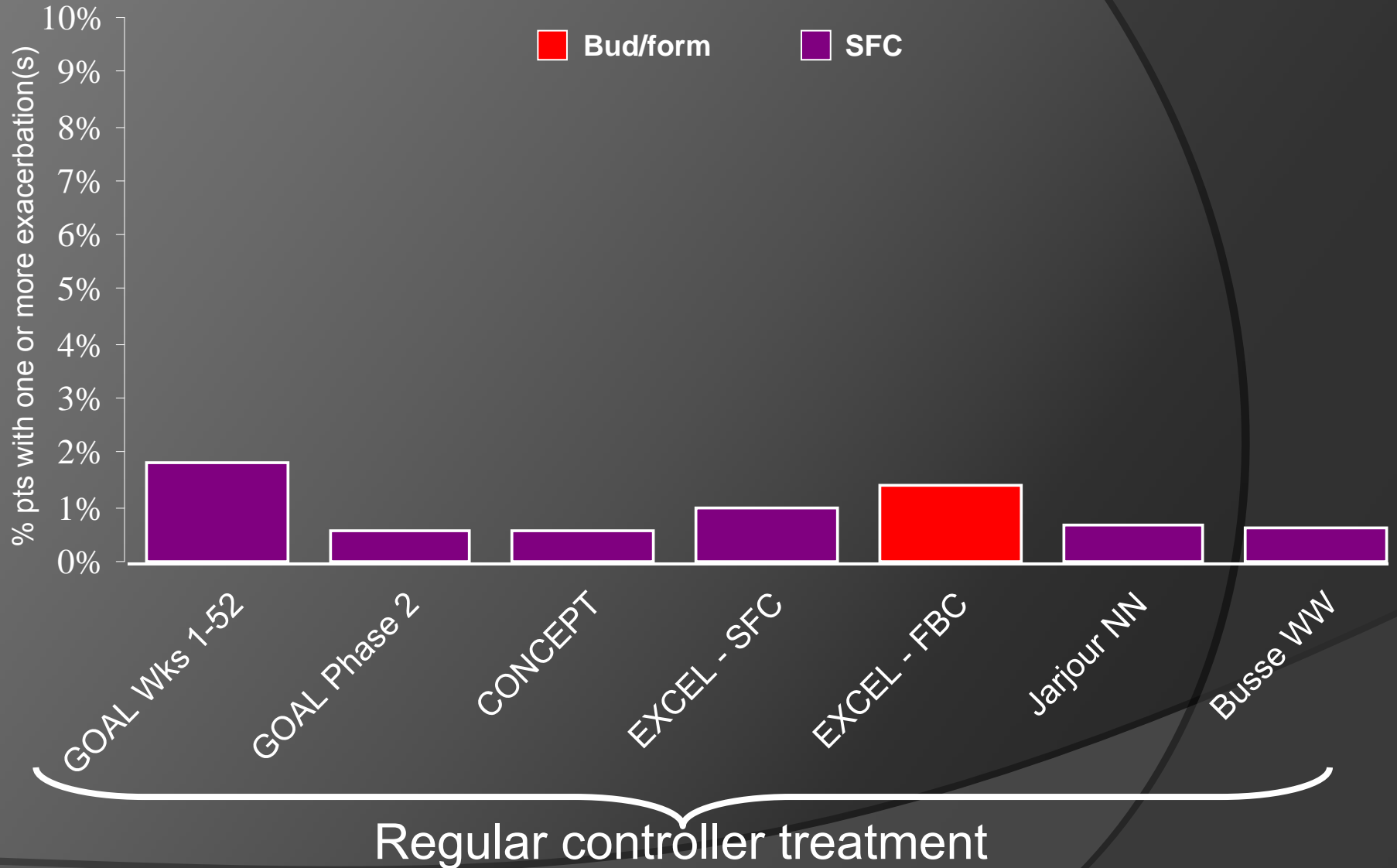


GINA objective: rescue < twice a week

EXACERBATIONS REQUIRING ER TREATMENT OR HOSPITALISATION



EXACERBATIONS REQUIRING ER TREATMENT OR HOSPITALISATION



One could suppose...

Under-treatment of underlying inflammation means that when an exacerbation occurs it is more likely to be severe and require hospitalisation

Primary end point : Time to first severe exacerbation

TREATMENT STRATEGIES FOR ASTHMA: CONCLUSION

Bud/form as rescue and maintenance treatment is a possible option but there is a lack of data that it meets the GINA criteria of asthma control

Regular controller treatment can achieve and maintain GINA guideline-defined control including prevention of exacerbations

- Chapman KR, Barnes NC, Greening AP, et al. Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal. *Thorax* 2010;65:747e52

- The use of a combination inhaler containing budesonide and formoterol as both maintenance and quick relief therapy (SMART) has been recommended as an improved method of using inhaled corticosteroid/long-acting β agonist (ICS/LABA) therapy
- Published double-blind trials show that budesonide/formoterol therapy delivered in SMART fashion achieves better asthma outcomes than budesonide monotherapy or lower doses of budesonide/formoterol therapy delivered in constant dosage

- ⦿ Attempts to compare budesonide/formoterol SMART therapy with regular combination ICS/LABA dosing using other compounds have been confounded by a lack of blinding and unspecified dose adjustment strategies
- ⦿ The asthma control outcomes in SMART-treated patients are poor;
- ⦿ it has been reported that only 17.1% of SMART-treated patients are controlled.

- In seven trials of 6–12 months duration, patients using SMART have
- 1. Used quick reliever daily (weighted average 0.92 inhalations/day)
- 2. Awakened with asthma symptoms once every 7–10 days (weighted average 11.5% of nights),
- 3. Suffered asthma symptoms more than half of days (weighted average 54.0% of days)
- 4. Had a severe exacerbation rate of one in five patients per year (weighted average 0.22 severe exacerbations/patient/year)

These poor outcomes may reflect the recruitment of a skewed patient population

- Although improvement from baseline has been attributed to these patients receiving additional ICS therapy at pivotal times, electronic monitoring has not been used to test this hypothesis nor the equally plausible hypothesis that patients who are non-compliant with maintenance medication have used budesonide/formoterol as needed for self-treatment of exacerbations
- Although the long-term consequences of SMART therapy have not been studied, its use over 1 year has been associated with significant increases in sputum and biopsy eosinophilia

- ① At present, there is no evidence that better asthma treatment outcomes can be obtained by moment-to-moment symptom-driven use of ICS/LABA therapy than conventional physician-monitored and adjusted ICS/LABA therapy

Summary

- Asthma still very important disease
- BTS guidelines Work in real life (GOAL Study)!
- Step 3: a few observations
- High quality care is cost-effective care
- 21 Century - guidelines/meritocracy we should about achieving the gold standard :
- Clinical & Cost Effectiveness
- Questions?