CURRICULUM VITAE

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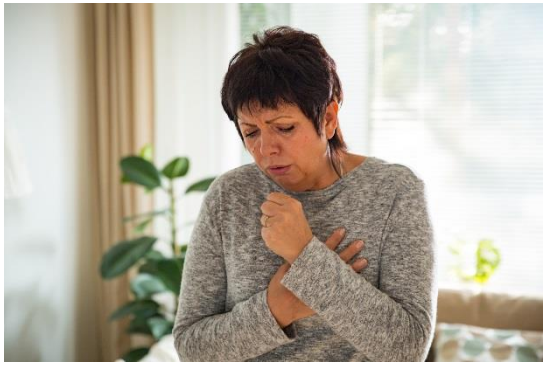
Case Study : Patient with Uncontrolled Asthma due to Incorrect Device Choice

Irawaty Djaharuddin

Departemen Pulmonologi & Kedokteran Respirasi FK UNHAS

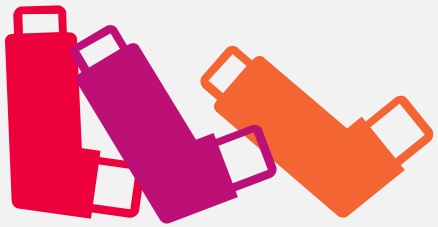
Case: Incorrect device choice

- Patient, female 43 years old and has had asthma for 4 years (hospitalised 9 months ago with an exacerbation)
- Dispensing history shows that she only obtains her asthma medication sporadically
- When asked, patient reveals that she doesn’t get much benefit out of her inhaler and that has trouble remembering individual steps in using her inhaler
- Doctor decided to check her inhalation technique to investigate whether she is using her existing device correctly
- Patient was getting a few key steps wrong so her doctor organised inhaler technique re-training with a monthly follow up appointment
- The importance of taking her medication correctly and continuously in order to achieve good asthma control was also emphasised



The choice and correct use of inhaler device is vital for good asthma control

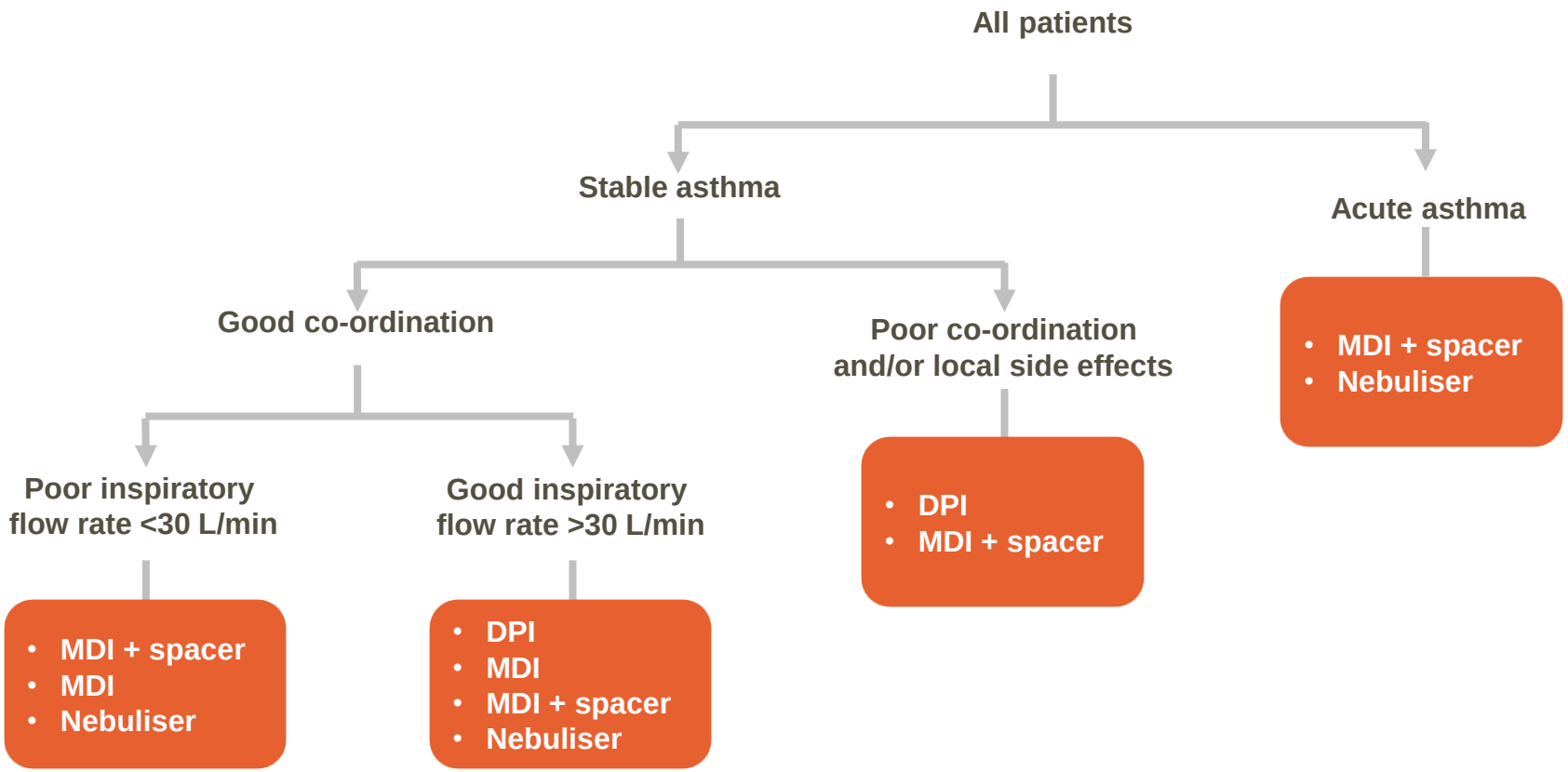
- Optimal asthma control depends on the drug and device selected, and on educating patients in the importance of adherence and inhaler technique[1]
- Incorrect inhaler use is extremely common[2-4]
- The main challenges in asthma drug delivery are non-adherence and improper device use[5]
- Improper device use can cause local side effects as well as insufficient drug delivery[6]



- Select a drug that is effective
- and well tolerated[3]
- Ensure that healthcare professionals are trained in asthma care and inhaler device use[7]
- Choose an inhaler that:[8]
  - is easy to use
  - requires minimal coordination
  - has minimal maintenance requirements
  - patients can use correctly
  - patients prefer
- Constantly train and monitor patient inhaler technique[8]

1. Scichilone N. Adv Ther. 2015;32:285–92; 2. Sanchis J et al. Chest. 2016;150:394–406; 3. Roche N et al. EMJ Respir 2013;1:64-71; 4. Sulaiman I et al. J Allergy Clin Immunol Pract. 2016;4:900–909.e2; 5. Newman S. Ther Deliv 2017;8:647-61; 6. Nelson HS. Ann Allergy Asthma Immunol 2016;117:606-12; 7. Boise E, Rotella M. Int Forum Allergy Rhinol 2015; 5:71-5; 8. Lavorini F. Breathe 2008;5:121-31.

Choosing an appropriate inhaler: a suggested approach



DPI, dry powder inhaler; MDI, metered dose inhaler

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Capstick T & Clifton I. Expert Rev Respir Med 2012;6:91–103; Dekhuijzen P et al. Respiratory Medicine 2013;107:1817e1821; Haughney J et al. Respir Med 2010;104:1237-45; Nelson H. Ann Allergy Asthma Immunol 2016; 606-12.

Many factors can influence patient satisfaction with treatment choice

When choosing a device, patient preference should be taken into account. Patients generally will only use an inhaler that they like and feel comfortable with

Therapy factors[1]	Device factors[2,3]	Other related factors[1]
Treatment (including medication)	Ability to use device	Physician communication
Symptoms, side effects	Level of actuation/inhalation coordination required	Disease history
HRQL and functionality	Ability to generate sufficient inspiratory flow	Treatment history
Expectations of therapy	Convenience	
Satisfaction with medication	Availability and cost	

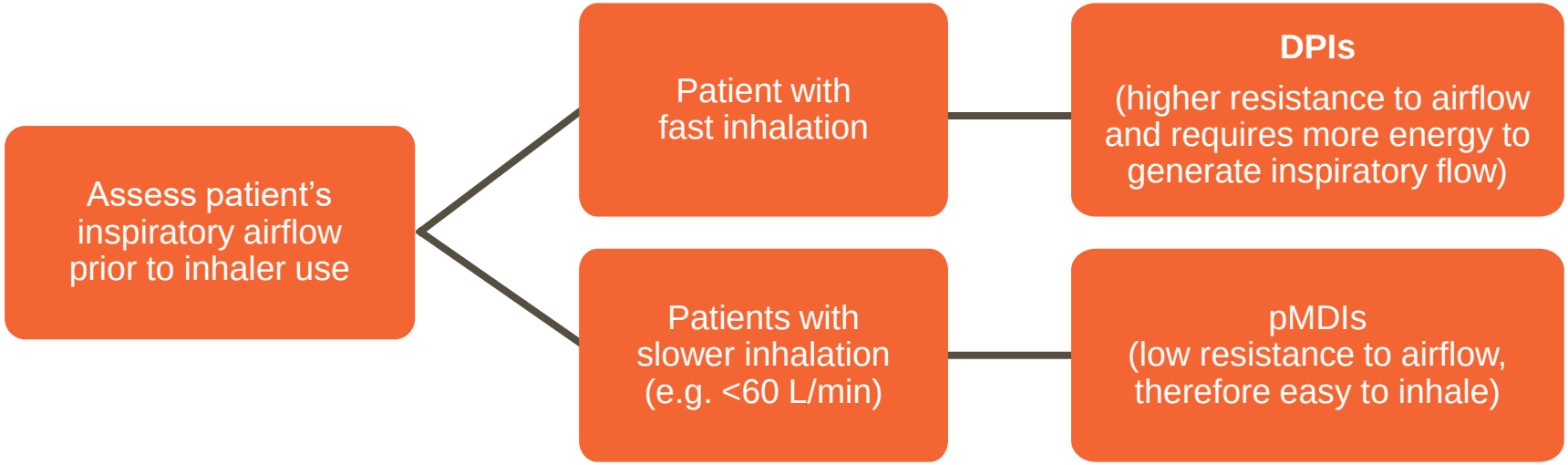
Table illustrating factors that can influence the patient's satisfaction with their medication (inhaler device or other treatment). Major factors are those that reflect clinical improvements attributed to the treatment, and how these match patient expectations. Patient preference may directly influence both expectations (by providing confidence in the treatment) and satisfaction, through a sense of ownership in the device selection decision.

HRQL, health-related quality of life

1. Anderson P. Eur Respir Rev 2005;14(96);109–116; 2. Vincken W et al. Prim Care Respir J. 2010;19:10−20; 3. Capstick GD & Clifton I. Expert Rev Resp Med. 2012;6(1):91−103.

Achieving optimal technique is dependent on the patient's ability as well as device type

– Achieving optimal inspiratory flow with DPIs and coordinating actuation and inhalation with pMDIs are crucial in determining whether a patient has an appropriate inhaler technique

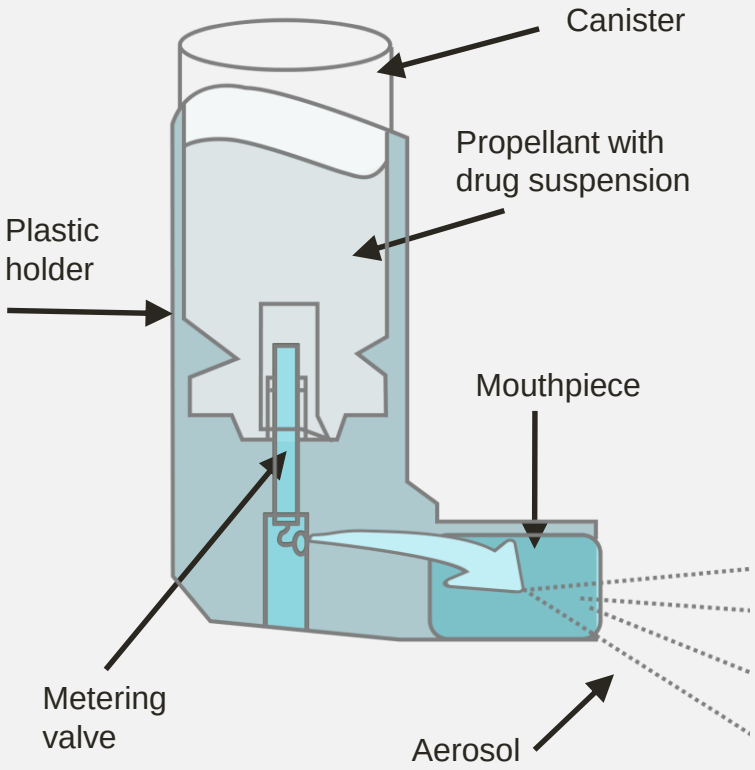


DPI: dry powder inhaler; pMDI: pressurised metered dose inhaler.

The MDI device

Metered Dose Inhaler (MDI)

- Delivers a specific amount (metered dose) of aerosolized medication with each actuation
- Key components include:
  - **Metal canister** containing the drug formulation
  - **Drug formulation** made up of the drug, a liquefied gas propellant ± excipients
  - **Metering valve** allows a metered quantity to be dispensed with each actuation
  - Actuator (or mouthpiece) which allows the patient to operate the device and directs the aerosol into the patient's lungs
  - **Dust cap** for mouthpiece



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Metered Dose Inhaler (MDI)

Advantages

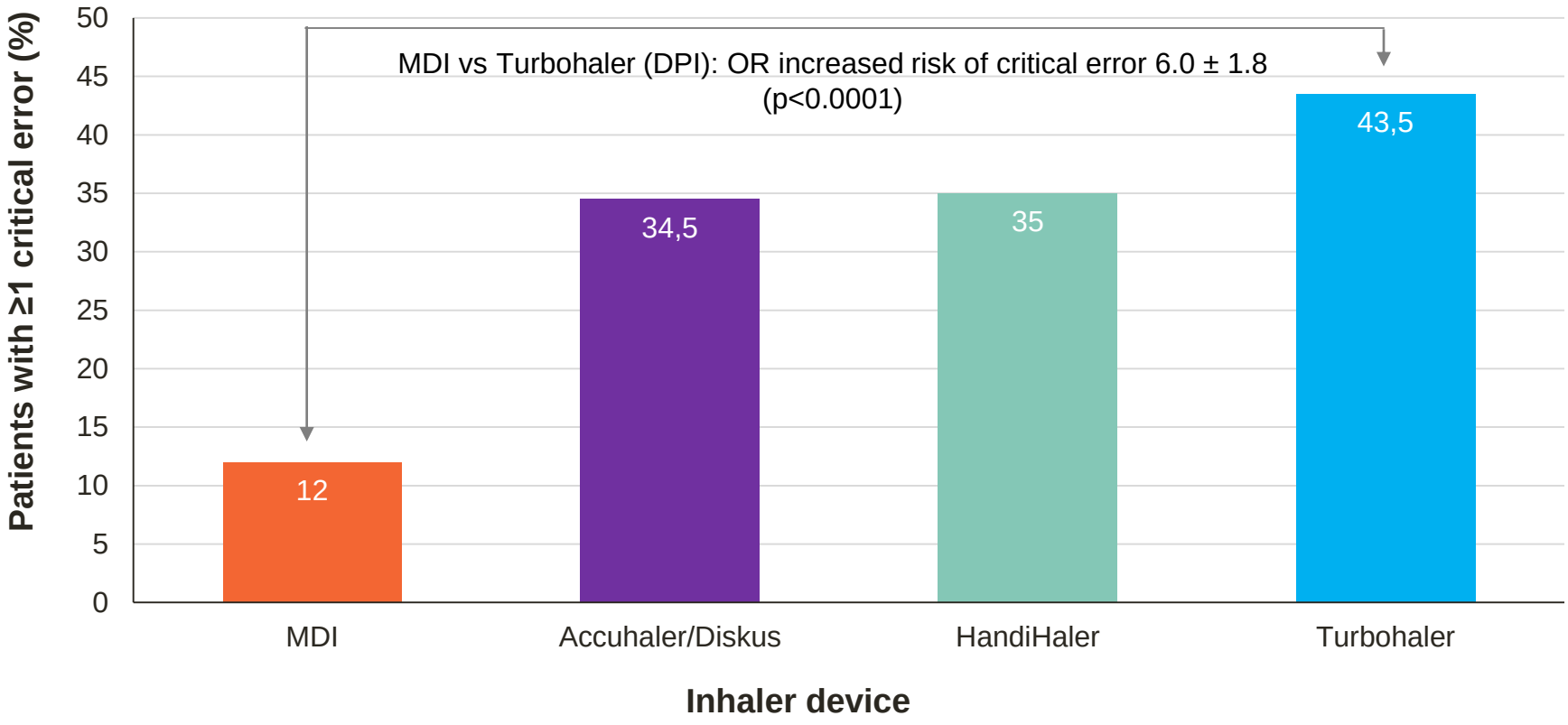
- Small in size, unobtrusive, convenient to carry
- Easy and quick to operate
- Dose counter to measure how many doses remain
- Multi-dose capability
  - allows for quick drug delivery
  - protects the drug from contamination during usage

Disadvantages

- Drug delivery is highly dependent on patient technique
- Inability to coordinate inhaler actuation with inspiration can result in suboptimal lung deposition
- Patients may have difficulty using MDIs, especially the elderly, very young, and patients with arthritis
- High aerosol velocity leads to deposition of ~80% of actuated dose in oropharynx

1. Hess DR. Respir Care. 2008;53:699–725; 2. Rees J. BMJ. 2005;331:504-506.

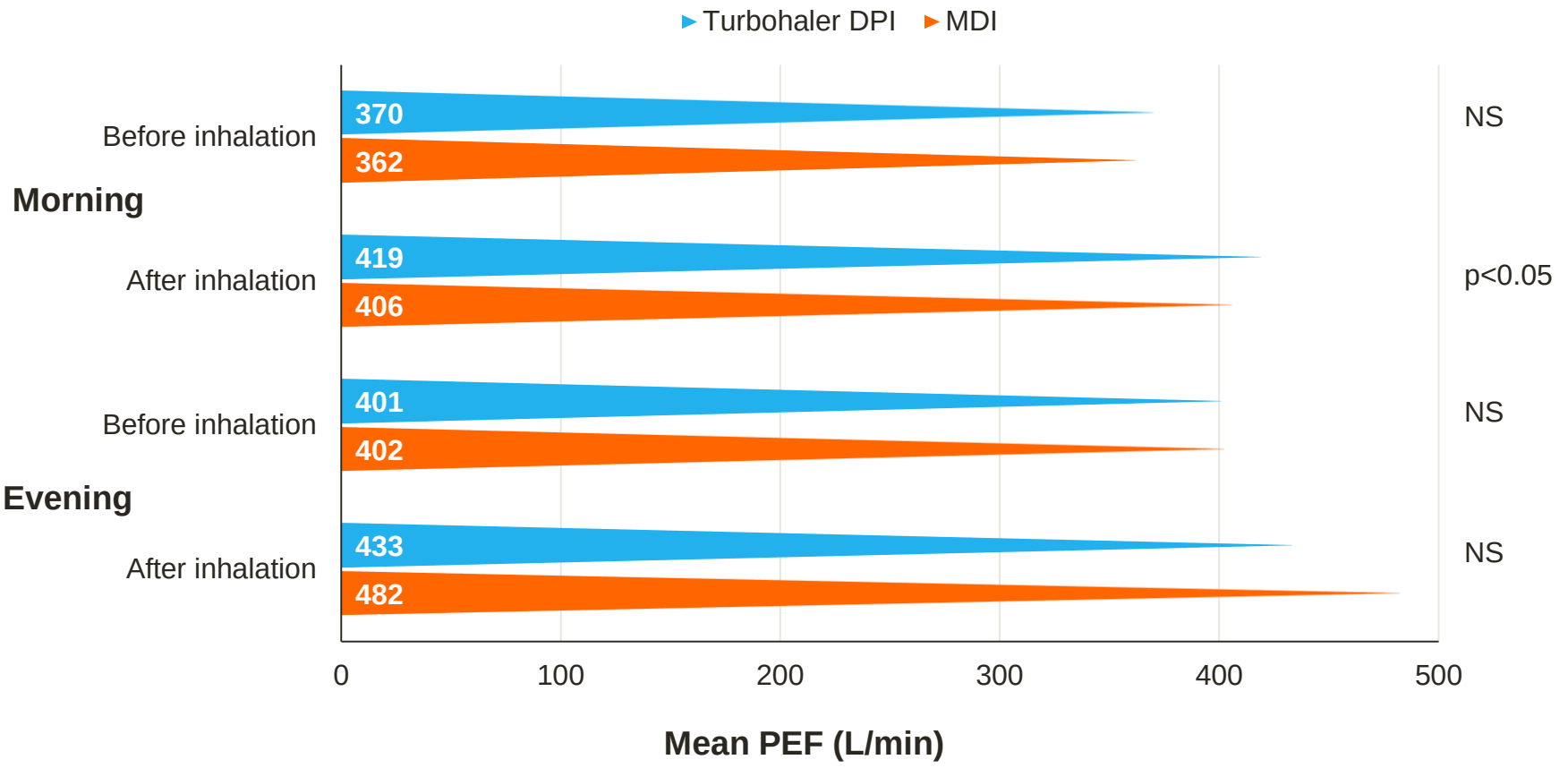
Inhaler mishandling is more common with Turbohaler (DPI) than MDIs



MDI, metered dose inhaler; OR, odds ratio.
Observational study of the prevalence of inhaler mishandling; n=1664 patients with asthma (42%) or COPD (52%) experienced using inhalation devices. Mean (SD) age 62 (16) years.

The same results were first presented in Melani AS et al. Respir Med. 2011;105(6):930–938. This graph has been independently created by GSK from the original data.

Clinical efficacy of MDI and the Turbohaler (DPI) is comparable



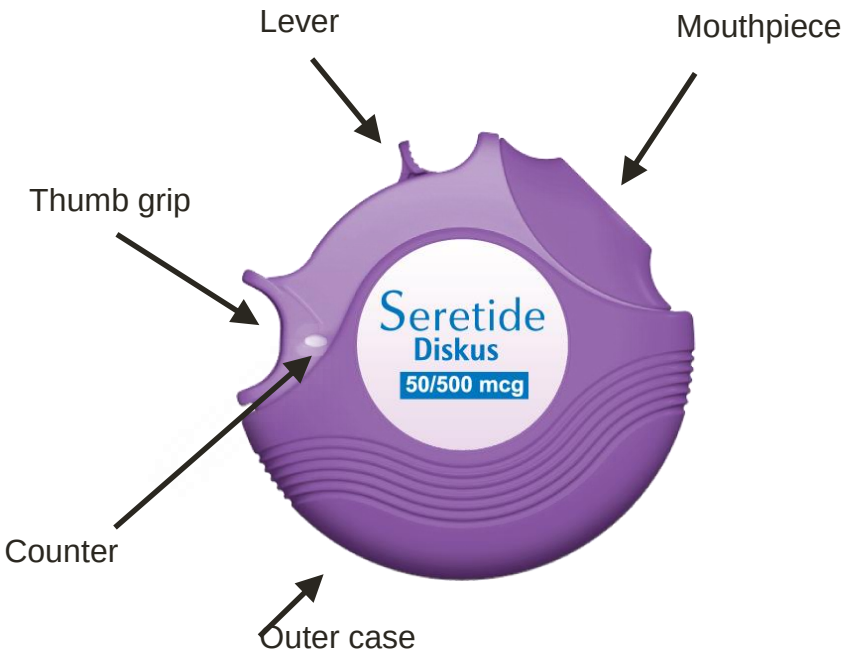
DPI, dry-powder inhaler; MDI, metered-dose inhaler; NS, not significant; PEF, peak expiratory flow.
Administration of 0.5 mg terbutaline sulphate via Turbohaler DPI and MDI for 2 weeks to asthma patients, mean (range) age 46 (20–66) years, n=19.

The same results were first presented in Osterman K et al. Allergy. 1989;44(4):294–297. This figure has been independently created by GSK from the original data.

The Diskus device

Dry Powder Inhalers (DPIs)

- Deliver medication to the lungs in the form of a dry powder.
- Medication is commonly held either in a capsule for manual loading or in a proprietary form from inside the inhaler.
- Most DPIs rely on the force of patient inhalation to entrain powder from the device and subsequently break-up the powder into particles that are small enough to reach the lungs.



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Rees J. BMJ 2005; 331: 504-506. Hess D. Respiratory Care 2008; 53: 699-725.

Dry Powder Inhalers (DPIs)

Advantages

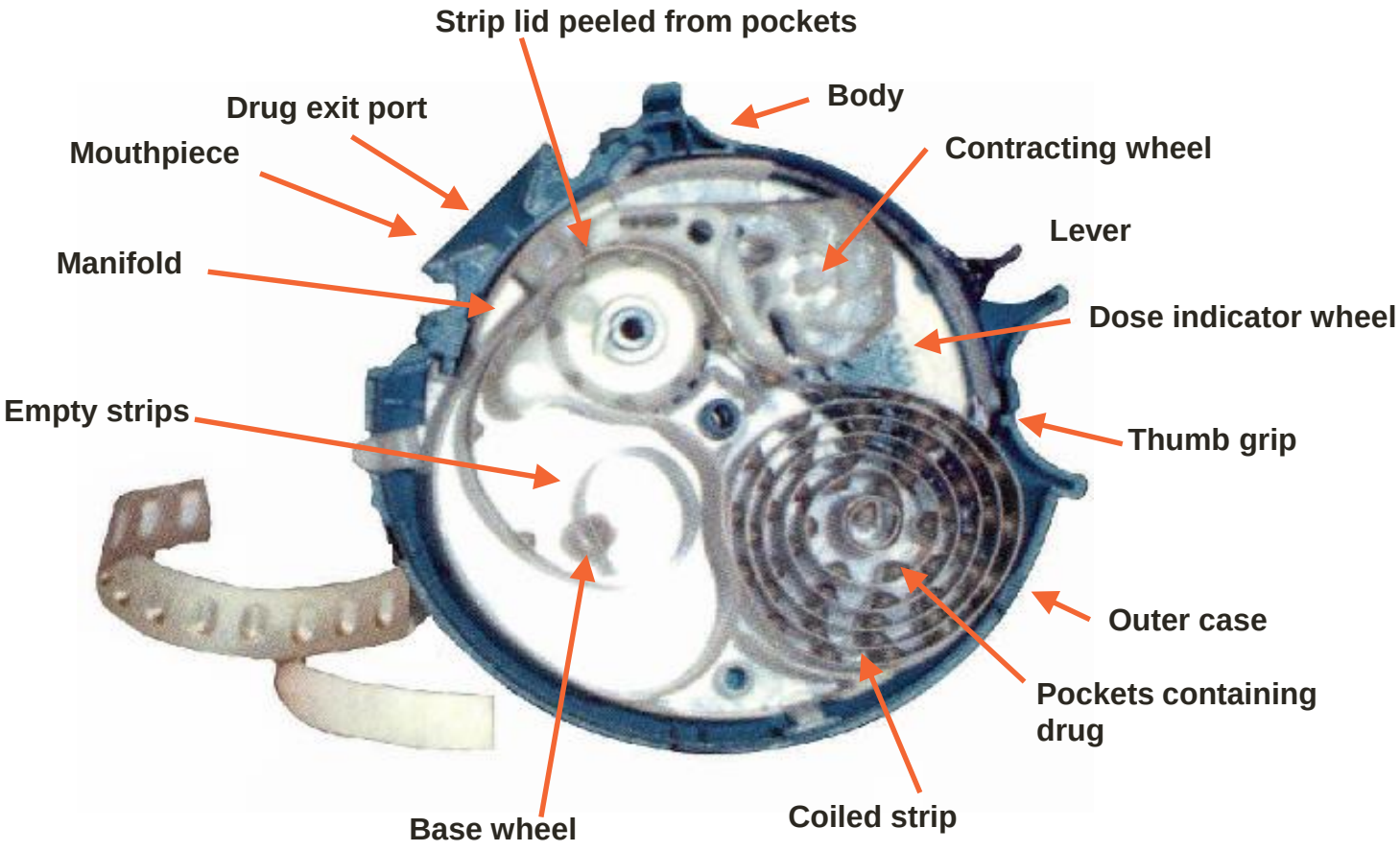
- DPIs do not require coordination between actuation and inhalation
- Multiple dose DPIs have up to 200 doses, so unlike unit-dose DPIs, there is no need for reloading for each dose
- Environment-friendly as they do not use propellant

Disadvantages

- May induce provocative cough
- Time needed to load the medication capsule for unit-dose DPIs
- Most DPIs need a minimum inspiratory flow rate to deliver the appropriate dose
- Insufficient inspiratory flow rates may lead to reduced dose delivery and incomplete deaggregation of powder
  - hence such DPIs can normally be used only in older children and adults
- If a patient exhales directly toward the device, the powder can be blown out

Hess D. Respir Care 2008; 53 (6): 699-725. Rees J. Br Med J 2005; 331: 504-506.

Cross-section through the Accuhaler/Diskus



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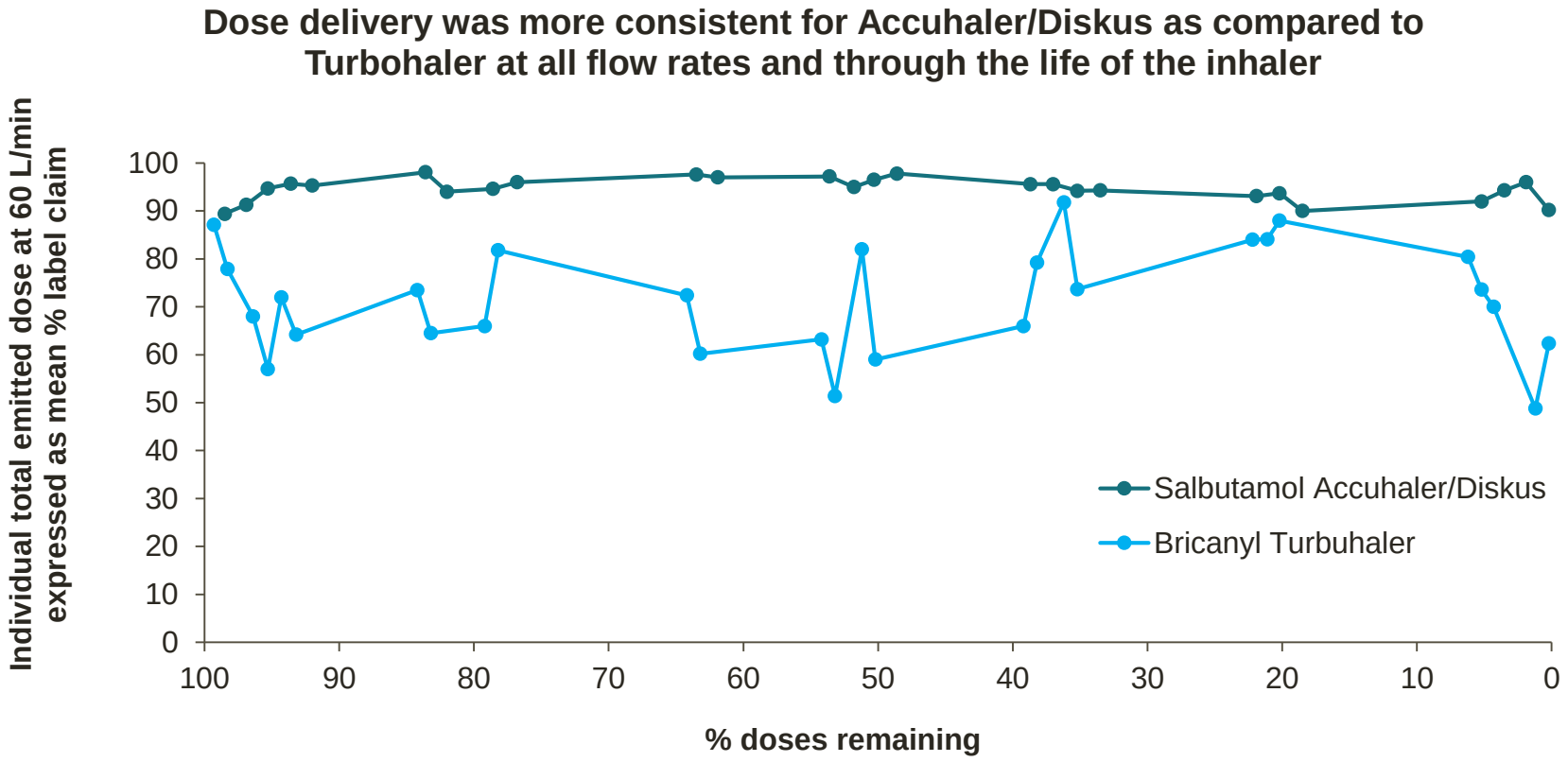
Accuhaler/Diskus exhibits a more consistent dose and fine particle generation vs. Turbohaler

This study uses in vitro test methods to compare the capability of four alternative Devices to deliver an accurate and precise dose of salbutamol

These results were first presented in Prime D et al. J Aerosol Med. 1999;12(2):75–84. This figure has been independently created from the original by GSK.

Compared with the Turbohaler, the Accuhaler/Diskus showed a high level of dose consistency



In vitro comparison of drug delivery characteristics of salbutamol Accuhaler/Diskus and terbutaline Turbohaler

Malton A et al. J Pharm Med 1996;6:35-48. PLEASE NOTE COPYRIGHT PERMISSON WILL BE REQUIRED TO USE THIS SLIDE

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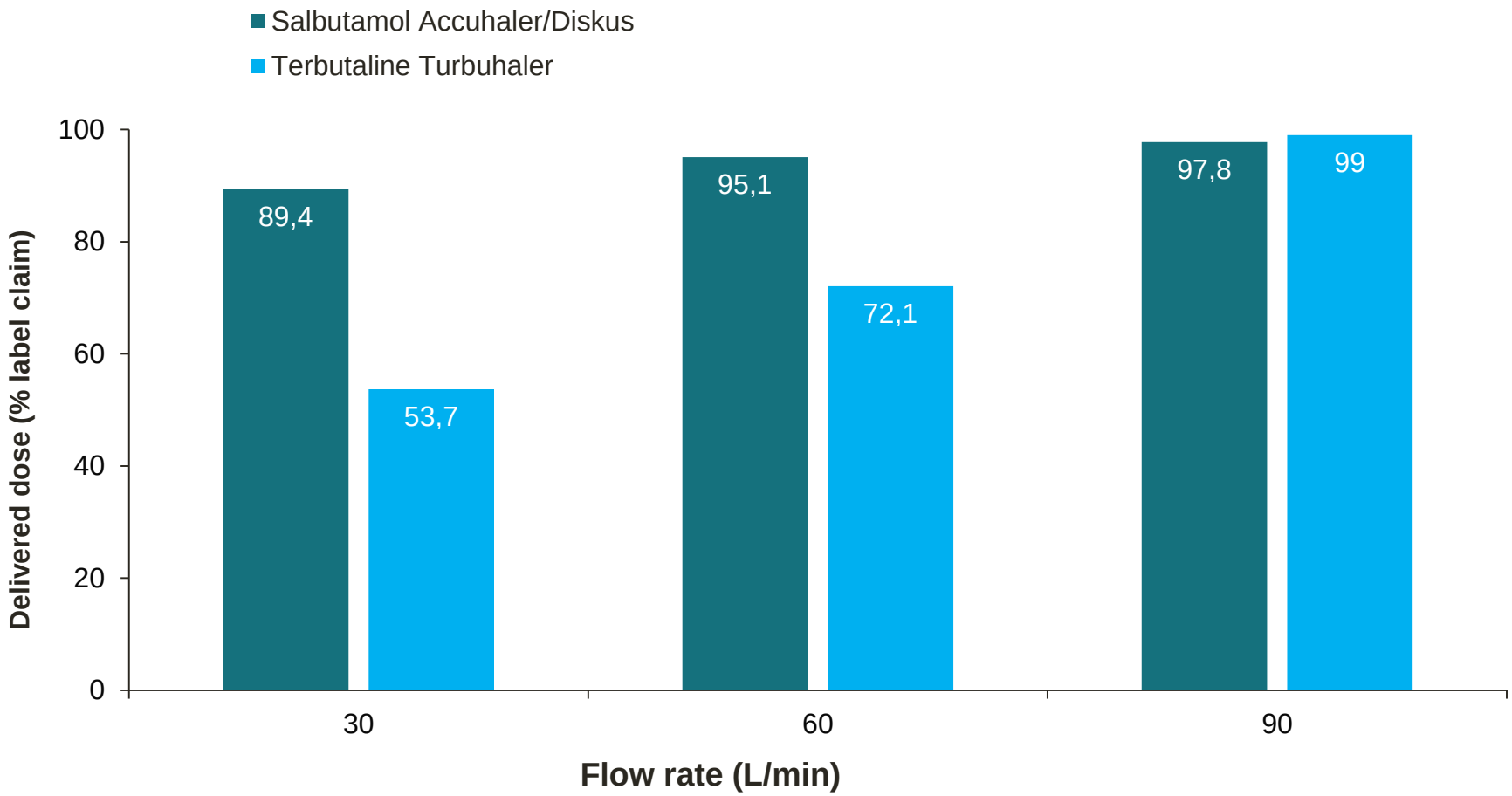
Accuhaler/Diskus emitted dose* is greater than Turbohaler at lower inspiratory flow rates



Delivered dose data (% label claim) measured *in vitro* for two inhalers at various flow rates; median for 10 determinations from six devices
**In vitro* study; does not necessarily correlate with clinical effectiveness.

The same results were first published in Malton A et al. J Pharm Med. 1996;6:35–48. This figure has been independently created by GSK from the original data.

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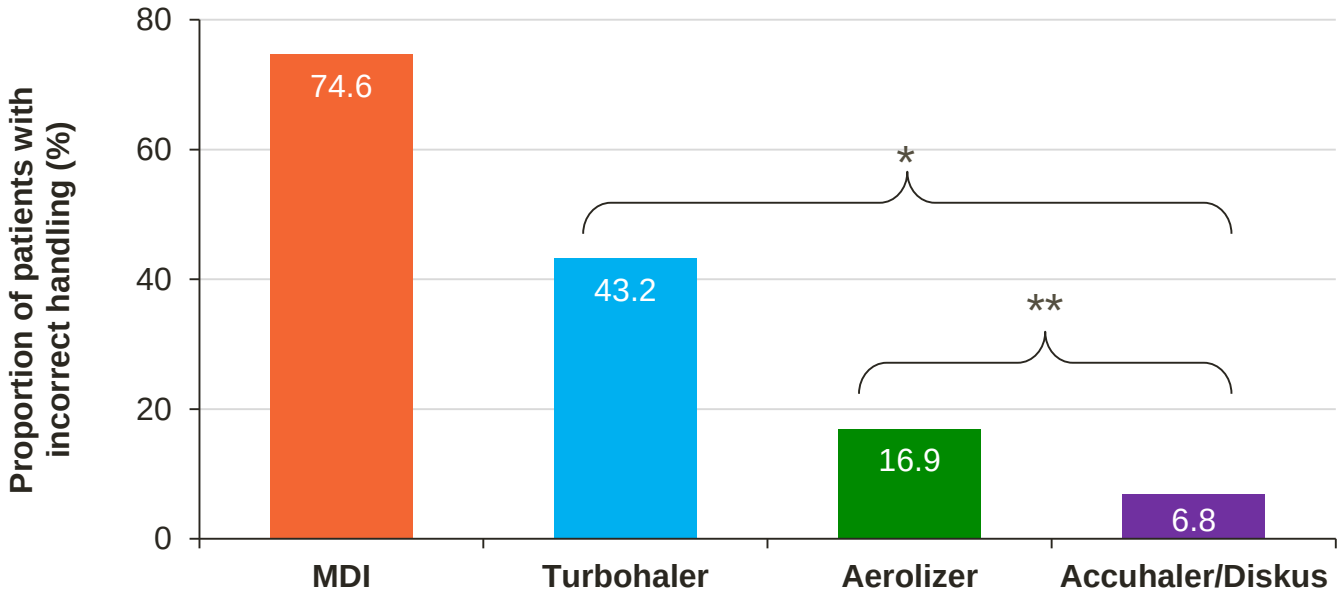
Handling errors were lower in patients using Accuhaler/Diskus vs Turbohaler

- Handling errors were significantly lower in patients using:
  - DPIs as compared to those using MDI
  - Accuhaler/Diskus as compared to those using Turbohaler



* p < 0.001 vs Accuhaler/Diskus

** p < 0.031 vs Accuhaler/Diskus

Prospective, cross-sectional, observational study to assess handling errors in 300 patients using MDI or different DPIs

DPI, dry-powder inhaler; MDI, metered-dose inhaler

Khassawneh BY et al. Respir Care. 2008;53(3):324–328.

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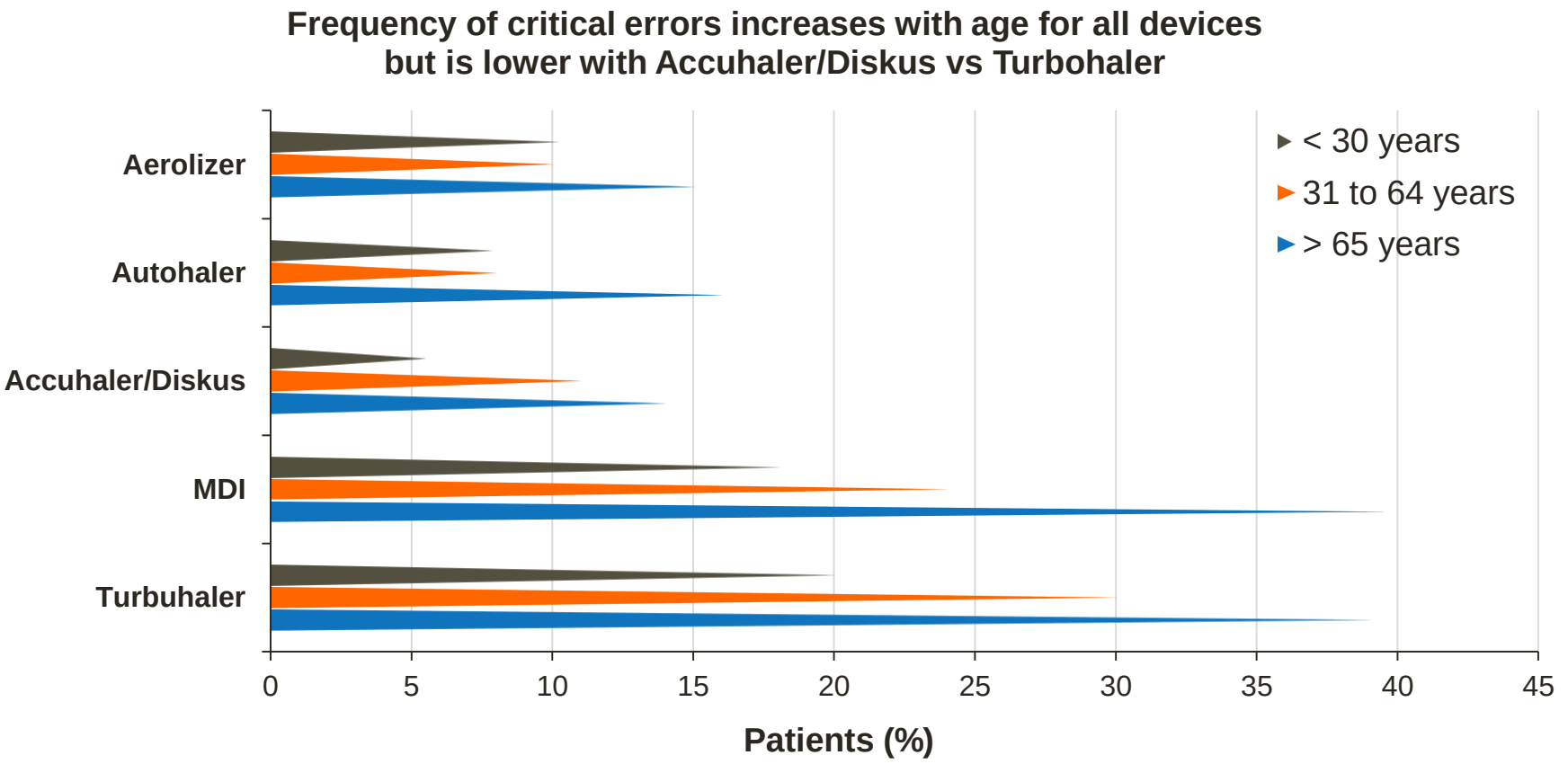
Critical errors increase with age for all devices but are lower with Accuhaler/Diskus vs Turbohaler



Observational study to evaluate the handling of inhalers by patients in real-world, primary care setting

MDI, metered-dose inhaler.

The same results were first presented in Molimard M et al. J Aerosol Med. 2003; 16:249-54. This figure has been independently created by GSK from the original data.

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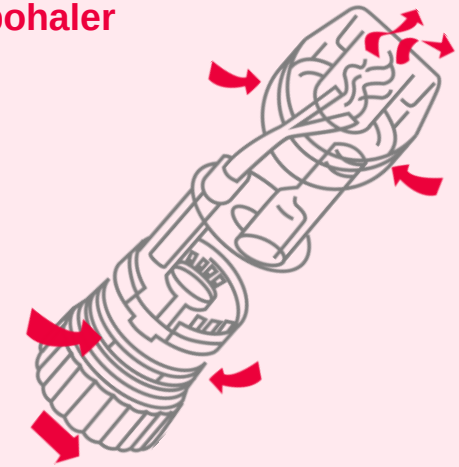
Why is the Accuhaler/Diskus successful?

Characteristics	Diskus	Turbohaler
		
Inspiratory Flow Rate (IFR)	Can be operated by patients with low IFR (minimum 30 L/min)[1]	May be more variable to IFR (minimum 60 L/min), especially during an asthma attack, in children & the elderly[1]
Protection from humidity	Drug is protected and can be used in humid environments[2]	Vulnerable to humidity and moisture[3]
Dose consistency	Pre-measured blister ensuring consistency dose to dose	Dose is measured by actuating device
Dose counter	Enables patient to know the number of doses remaining	Warning when 20 doses are remaining

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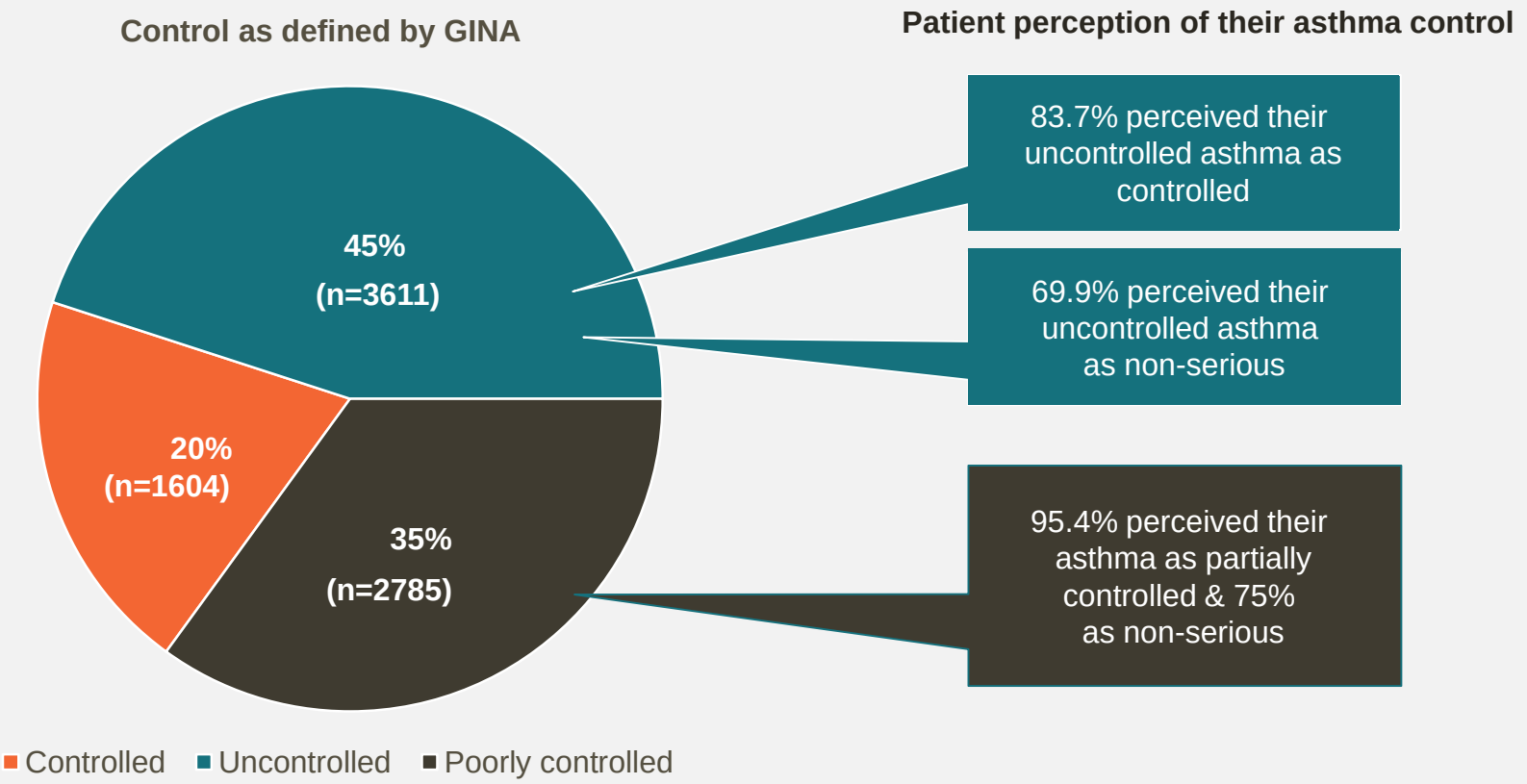
1. Hill LS, Slater AL. Resp Med 1998;92:105-110; 2. Fluticasone propionate (inhaled formulations) Global Datasheet, Version 33; 18 April 2018; 3.Symbicort Turbohaler PIL September 2017. Available at: https://www.medicines.org.uk/emc/files/pil.1326.pdf. Accessed September 2018.

Regular maintenance dosing v. single maintenance and reliever therapy

Real-world data: Many patients have poor perception of their asthma control



- Survey of 8,000 patients with asthma from 11 Eurpoean countries
- Over 80% of the patients with acute exacerbations (oral steroid use, ED visits or hospitalisations in the previous year) regarded their asthma as controlled
- 934 patients required hospitalisation but 57.9% of them still considered their asthma to be non-serious

GINA: Global Initiative for Asthma

The same results were first published in Price D, *et al. NPJ Prim Care Respir Med* 2014;24:14009. This graph has been independently created by GSK from the original.

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Regular maintenance dosing vs. single maintenance and reliever therapy: Effects on exacerbations (4 studies)

Data from double-blind randomized clinical trials

Outcome	Maintenance and reliever therapy n/N	Regular maintenance dosing (at a higher ICS dose)	Odds Ratio (95% CI)	P-value for overall effect	Heterogeneity
Patients with exacerbations requiring oral steroids	342/4202 8.1%	516/4894 10.5%	0.75 [0.65, 0.87]	Z=3.85; p=0.00012	I^2=0%
Patients with severe exacerbations (hospitalisation or ER visit)	118/3321 3.6%	225/4447 5.1%	0.72 [0.57, 0.90]	Z=2.83; p=0.0047	I^2=0%
Patients with serious adverse events	176/4215 4.2%	213/4915 4.3%	0.92 [0.74, 1.13]	Z=0.82; p=0.41	I^2=0%

Favours maintenance and reliever therapy Favours regular maintenance dosing

ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; SABA: short-acting β_2-agonist; ER: emergency room

The same results were first published in Kew K *et al. Cochrane Database Syst Rev* 2013;Issue 12:CD009019.
This graph has been independently created by GSK from the original.

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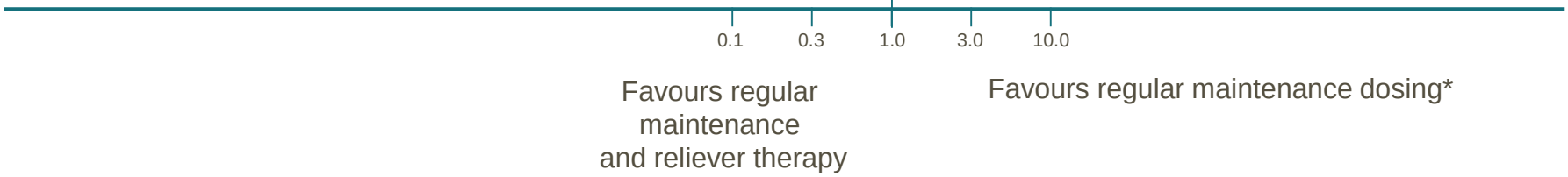
Regular dosing versus single maintenance and reliever therapy vs. current best practice

Data from open-label randomised controlled trials (13 trials)

Outcome	Maintenance and reliever therapy (n/N)	Regular maintenance dosing (n/N)	Odds Ratio (95% CI)	P-value for overall effect	Heterogeneity
Patients with exacerbations requiring oral steroids	257/4433 5.8%	304/4408 6.9%	0.83 [0.70, 0.98]	Z=2.18; p=0.03	I^2=0%
Patients with exacerbations requiring hospitalisation	21/4433 0.5%	26/4408 0.6%	0.81 [0.45, 1.44]	Z=0.72; p=0.47	I^2=0%
Discontinuation due to adverse events (AEs)	88/4224 4.2%	31/4187 4.3%	2.85 [1.89, 4.30]	Z=4.98; p=0.00001	I^2=0%



* Current best practice

AE: adverse events; ICS: inhaled corticosteroid; OCS: oral corticosteroids; LABA: long-acting β_2-agonist; SABA: short-acting β_2-agonist

The same results were first published in Cates C *et al. Cochrane Database Syst Rev* 2013;Issue 4:CD007313.
This graph has been independently created by GSK from the original.

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Continued impact on asthma symptoms following single maintenance and reliever therapy: 7 clinical studies

Weighted averages for asthma control endpoints at baseline and during maintenance and reliever therapy

Total number of patients receiving Budesonide/formoterol maintenance and reliever therapy	**6,603**	
Study durations	6-12 months	
Asthma control endpoints	**Baseline**	**Treatment**
Symptom-free days (%)	13.2%	46.0%
As-needed reliever use (inhalations/day)	2.18	0.92
Reliever-free days (%)	14.7%	56.1%
Nights with awakenings due to asthma (%)	27.7%	11.5%
Severe exacerbations* (events/patient/year)	0.22	

- On average, patients on maintenance and reliever therapy:
  - needed reliever at least once per day,
  - experienced nocturnal symptoms every 7–10 nights,
  - were asymptomatic <50% of the study time, and
  - rate of severe asthma exacerbation was ~one in five patients per year

* Severe exacerbation in this study was extended beyond the usual clinical definition to include not only a hospital or emergency department stay, but also a short course of prednisone or a decrease in morning PEF≥ 30% from baseline on 2 or more consecutive days

Chapman KR *et al. Thorax* 2010;65:747-752.

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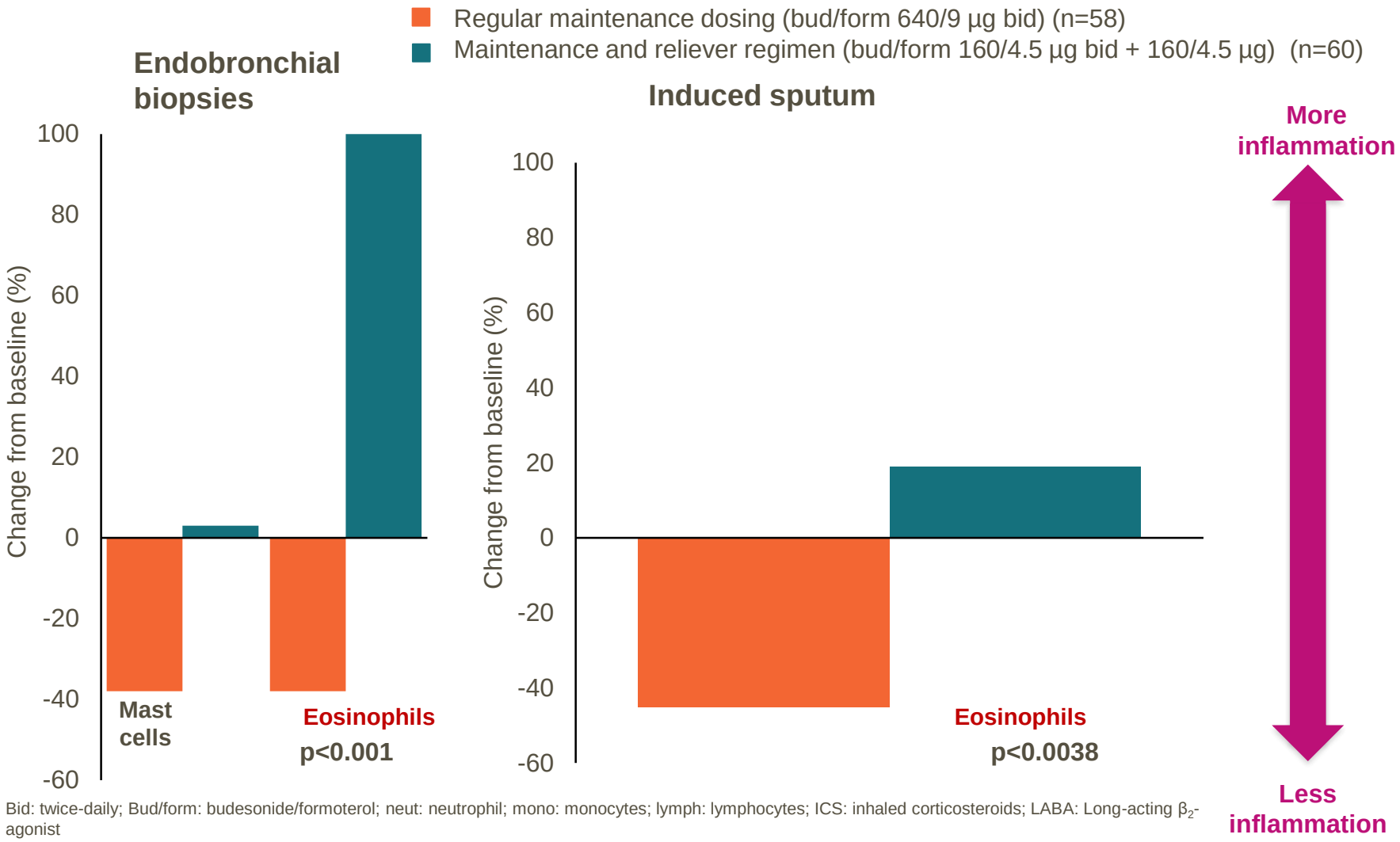
One year of single maintenance and reliever therapy increased bronchial inflammation vs. regular maintenance ICS/LABA dosing



Bid: twice-daily; Bud/form: budesonide/formoterol; neut: neutrophil; mono: monocytes; lymph: lymphocytes; ICS: inhaled corticosteroids; LABA: Long-acting β_2-agonist

The same results were first published in Pavord I *et al. J Allergy Clin Immunol* 2009;123(5):1083–1089.
These graphs has been independently created by GSK from the original.

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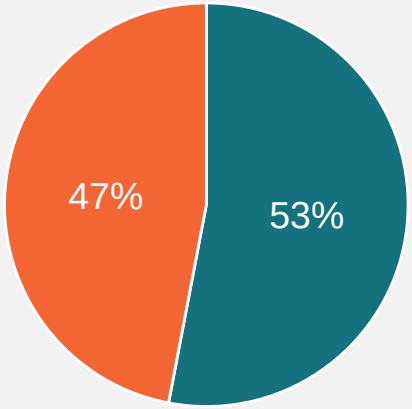
Prescription data confirm inappropriate SABA co-prescribing with single maintenance and reliever prescriptions in the UK



A single maintenance and reliever therapy prescription is often accompanied with a SABA prescription

53% of the patients prescribed a single maintenance and reliever therapy were also co-prescribed rescue SABA

– 15.6% of first prescriptions for single maintenance and reliever therapy included a SABA co-prescription

Possible reasons for inappropriate SABA prescriptions:

– Prescriber confusion

– Patient using the maintenance and reliever therapy and SABA as rescue

– Patient confusion (requesting routine SABA refill)

Potential patient impact of inappropriate SABA prescriptions:

– Overuse of β_2-agonist, with risk of adverse events

– Insufficient ICS dosing and poor asthma control

SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid

The same results were first published in DiSantostefano R *et al. J Prim Care Respir Med*. 2016;26:16038.
This figure has been independently created by GSK from the original.

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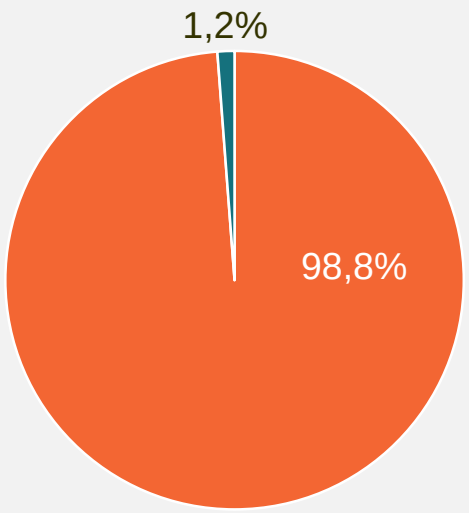
Single maintenance and reliever therapy prescribing demonstrates confusion in clinical setting: UK



Of 14,072 first prescriptions for budesonide/formoterol (2013):

- only 1.2% of patients were prescribed Symbicort maintenance and reliever therapy
- mean of 4.7 budesonide/formoterol inhalers were dispensed over the following year, suggesting poor adherence with Symbicort maintenance and reliever therapy

Dispensing of >12 inhalers/year would be expected for maintenance and reliever therapy. Possible issues:

- Poor overall adherence/inadequate patient education
- Use of separate SABA for reliever therapy
- Use of maintenance and reliever therapy as a reliever only, with risk of earlier treatment failure

SABA: short-acting β_2-agonist

DiSantostefano R *et al. J Prim Care Respir Med*. 2016;26:16038.

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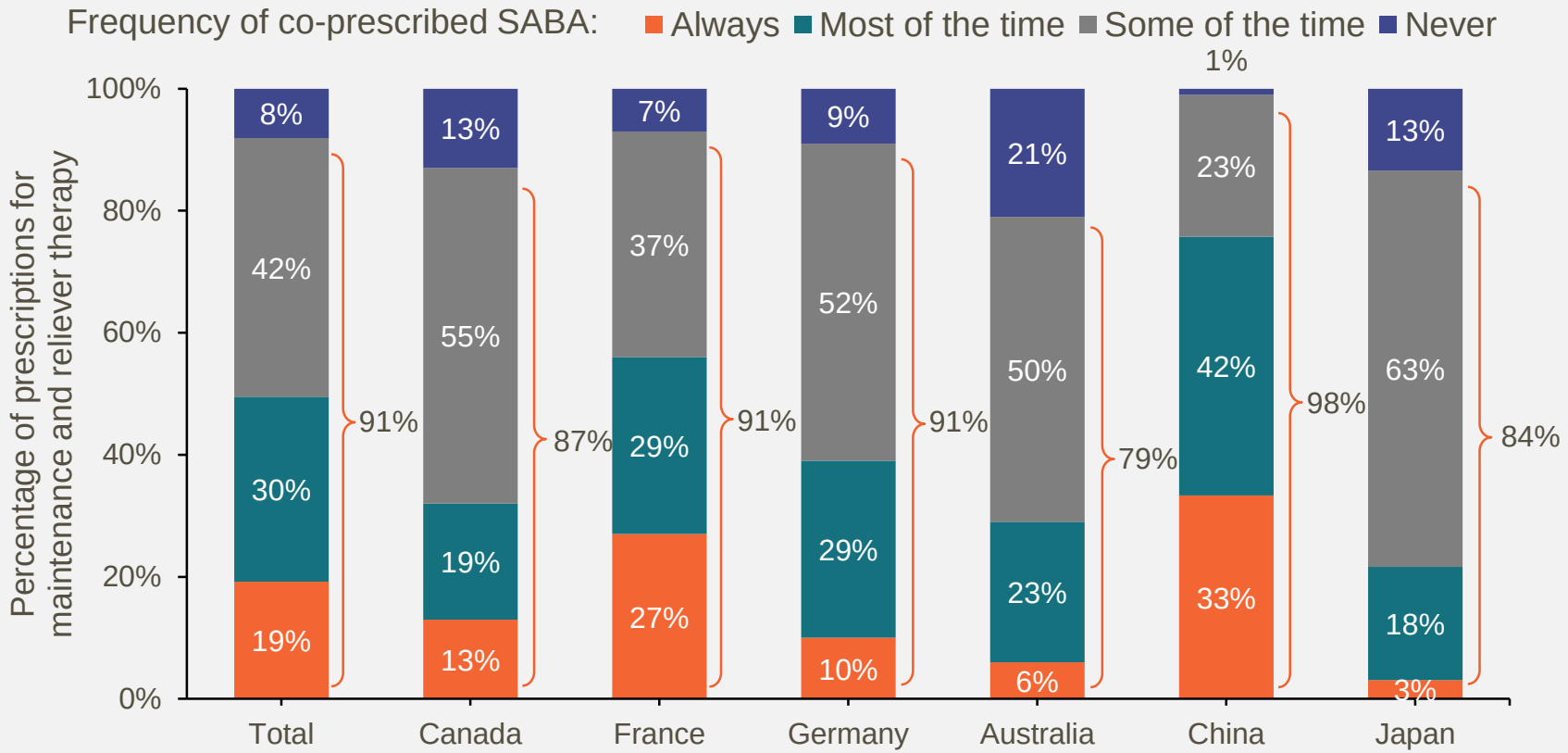
Real-world confusion with single maintenance and reliever therapy

SABA co-prescribed at least some of the time in over 90% of prescriptions



Respondents: physicians who have prescribed maintenance and reliever therapy
Base: Total (n=1,286), Canada (n=248), France (n=112), Germany (n=180), Australia (n=269), China (n=281), Japan (n=196);
SABA: short-acting β_2-agonist

The same results were first published in Hinds D *et al. Am J Respir Crit Care Med* 2016;193:A1708.
This graph has been independently created by GSK from the original.

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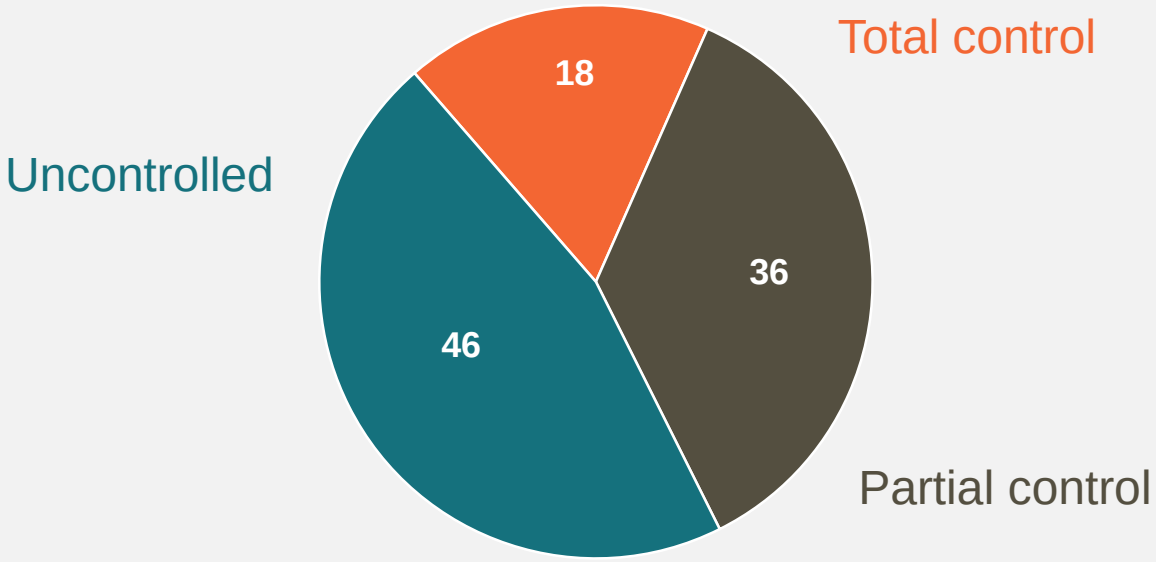
After 1 year of single maintenance and reliever therapy[1,2]

A retrospective analysis of data from 5 studies: 5246 patients on maintenance and reliever therapy assessed according to GINA-derived[3] asthma control



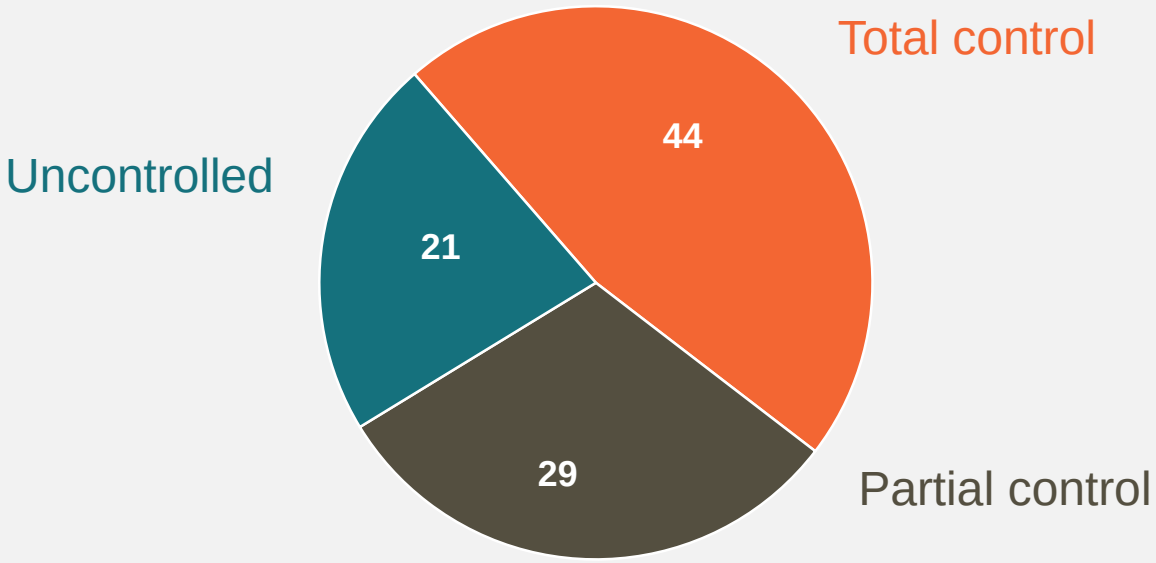
This is a weekly control measure. GINA: Global Initiative for Asthma; Patients all had ≥ 1 exacerbation in previous year.

1. The same results were first published in Bateman E *et al. J Allergy Clin Immunol*. 2010;125:600–608. This graph has been independently created by GSK from the original. 2. GSK DoF RF/SFC/0030/17. 3. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2018, available from www.ginasthma.org.

ID/AST/0016/18 AD: 05/10/2018 ED: 05/10/2020

Patients with GINA-defined asthma control maintain it after 1 year of regular maintenance therapy

The Gaining Optimal Asthma control (GOAL) study[1-3]: 585 patients with moderate asthma taking fluticasone/salmeterol assessed according to GINA-defined[4] asthma control



This is a weekly control measure.

At baseline, all patients had uncontrolled asthma (GINA-defined); mean exacerbation rate 0.6 events in previous year
Exacerbations: Asthma requiring hospitalization and/or course of oral steroids or antibiotics

1. The same results were first published in Bateman E *et al. Eur Respir* J 2007;29(1):56–63 and 2. *Bateman E, et al. Am J Respir Crit* Care Med 2004;170: 836-44. This graph has been independently created by GSK from the original. 3. GSK DoF RF/SFC/0031/17. 4. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2018, available from www.ginasthma.org.

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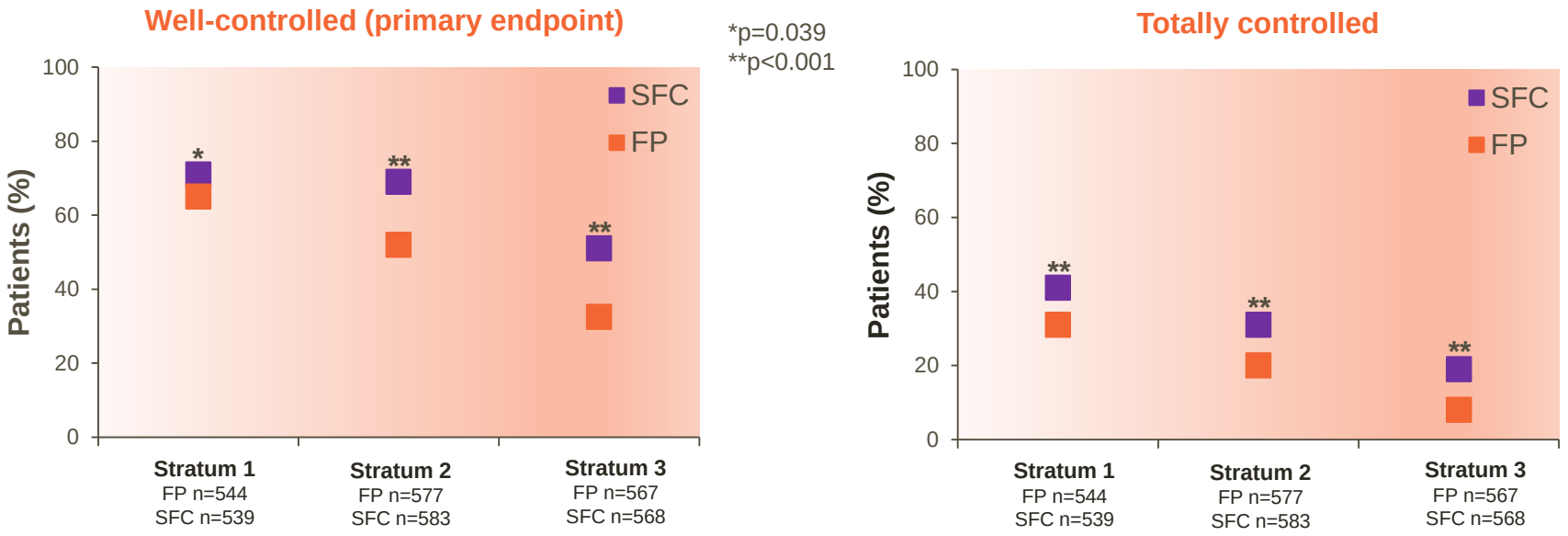
More patients achieved guideline defined asthma control was significantly greater with SFC versus FP

Percentage of patients with well-controlled (primary endpoint) or totally controlled asthma



The odds of achieving well-controlled/totally controlled asthma at the same or lower dose of ICS for SFC vs. FP in Stratum 1 increased by at least 40% (well-controlled: p=0.003; totally controlled: p<0.001) and was more than double in both Stratum 2 (well-controlled and totally controlled: p<0.001) and Stratum 3 (well-controlled and totally controlled: p<0.001).

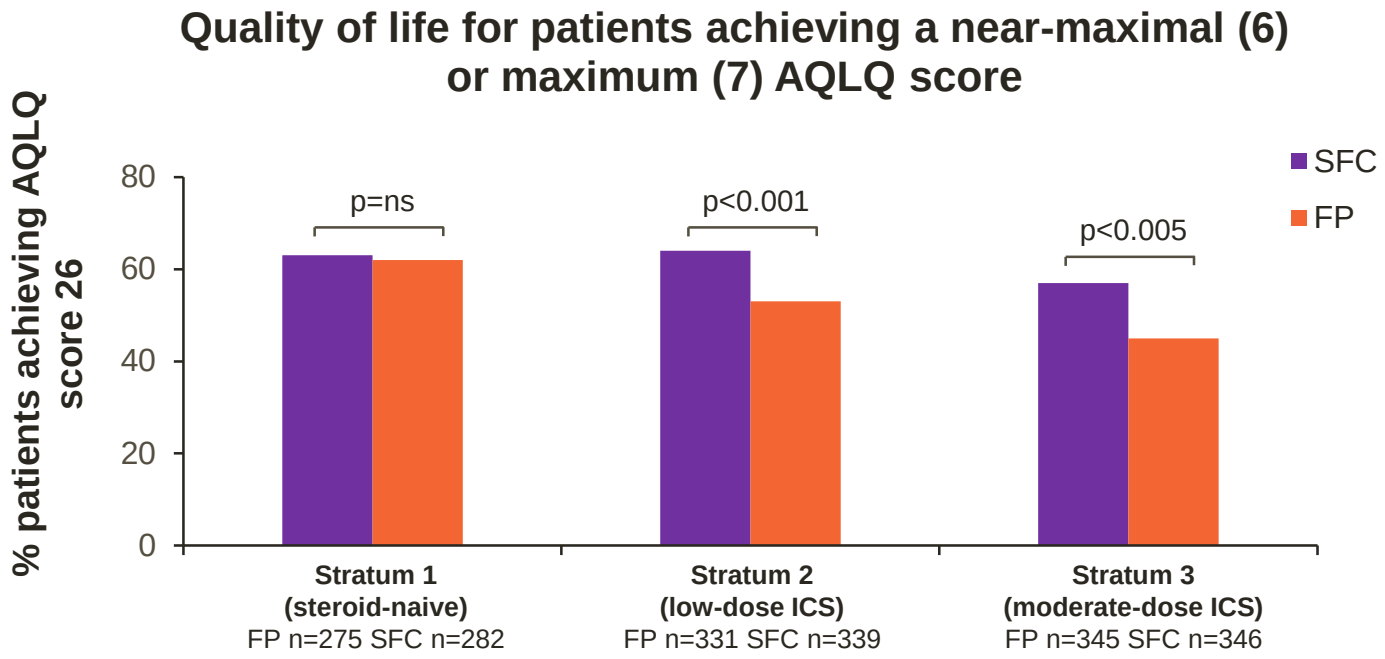
This was a 1-year, stratified, randomised, double-blind, parallel-group study (n=3421 randomised) in patients (≥12 to <80 years) with persistent asthma who received either SFC (50/100 µg bid) and SFC (50/250 µg bid) up to a maximum of SFC (50/500 µg bid) or FP (100 µg bid) and FP (250 µg bid) up to a maximum of FP (500 µg bid).

FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate combination.

The same results were first published in Bateman et al. *Am J Respir Crit Care Med.* 2004;170:836-844. These graphs have been independently created by GSK from the original.

ID/AST/0017/18 AD: 08/10/2018 ED: 08/10/2020

Patients achieve near normal QoL with SFC vs. FP



A significantly higher percentage of patients achieving AQLQ score ≥6 for SFC versus FP in Stratums 2 and 3

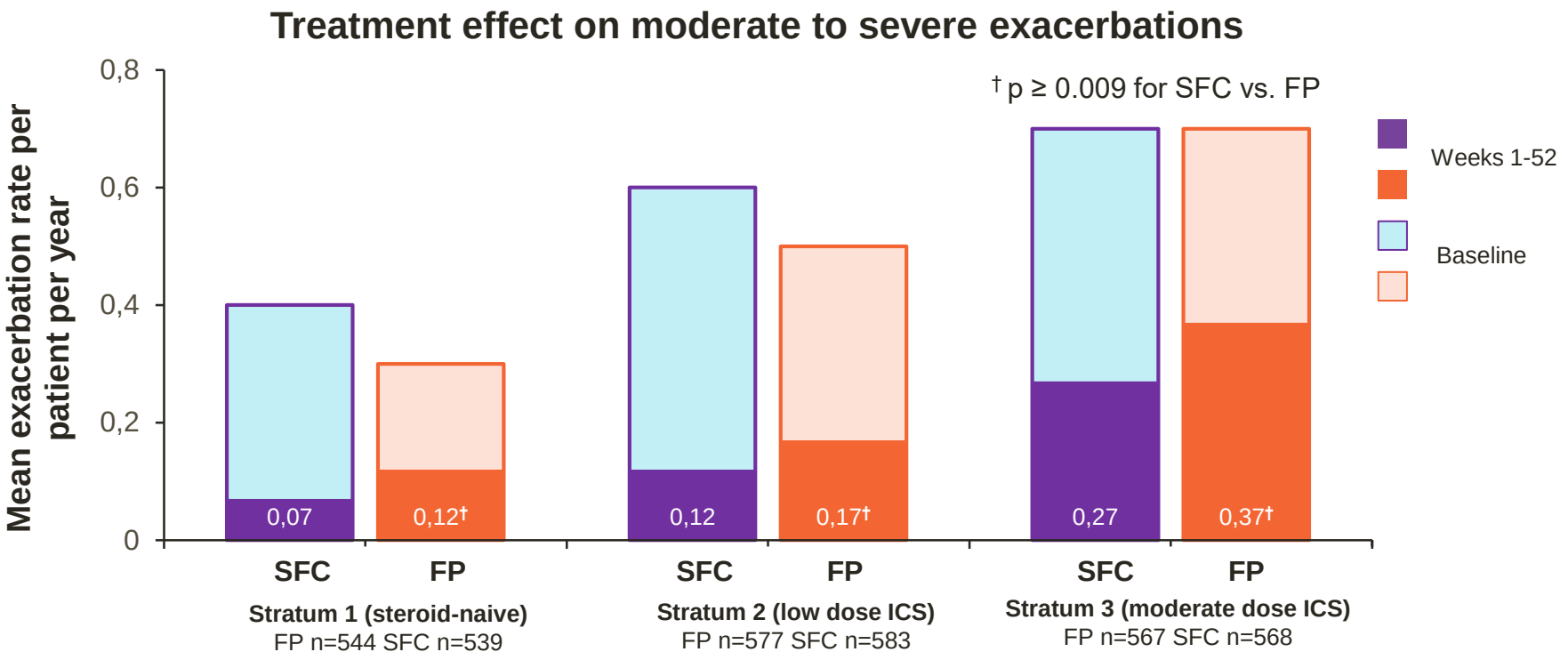
This was a 1-year, stratified, randomised, double-blind, parallel-group study (n=3421 randomised) in patients (≥12 to <80 years) with persistent asthma who received either SFC (50/100 µg bid) and SFC (50/250 µg bid) up to a maximum of SFC (50/500 µg bid) or FP (100 µg bid) and FP (250 µg bid) up to a maximum of FP (500 µg bid).

AQLQ, Asthma Quality of Life Questionnaire; FP, fluticasone propionate; ICS, inhaled corticosteroid; SFC, salmeterol/fluticasone propionate combination; QoL Quality of life

The same results were first published in Bateman et al. *Am J Respir Crit Care Med.* 2004;170:836-844. This graph has been independently created by GSK from the original.

ID/AST/0017/18 AD: 08/10/2018 ED: 08/10/2020

Patients had significantly lower exacerbation rate with SFC vs. FP



There were significantly fewer exacerbations* in the SFC group compared with the FP group (†p ≥ 0.009)

* Requiring either oral steroids or hospitalisation / emergency visit.

This was a 1-year, stratified, randomised, double-blind, parallel-group study (n=3421 randomised) in patients (≥12 to <80 years) with persistent asthma who received either SFC (50/100 µg bid) and SFC (50/250 µg bid) up to a maximum of SFC (50/500 µg bid) or FP (100 µg bid) and FP (250 µg bid) up to a maximum of FP (500 µg bid).

FP, fluticasone propionate; ICS, inhaled corticosteroid; SFC, salmeterol/fluticasone propionate combination.

The same results were first published in Bateman et al. *Am J Respir Crit Care Med.* 2004;170:836-844. This graph has been independently created by GSK from the original.

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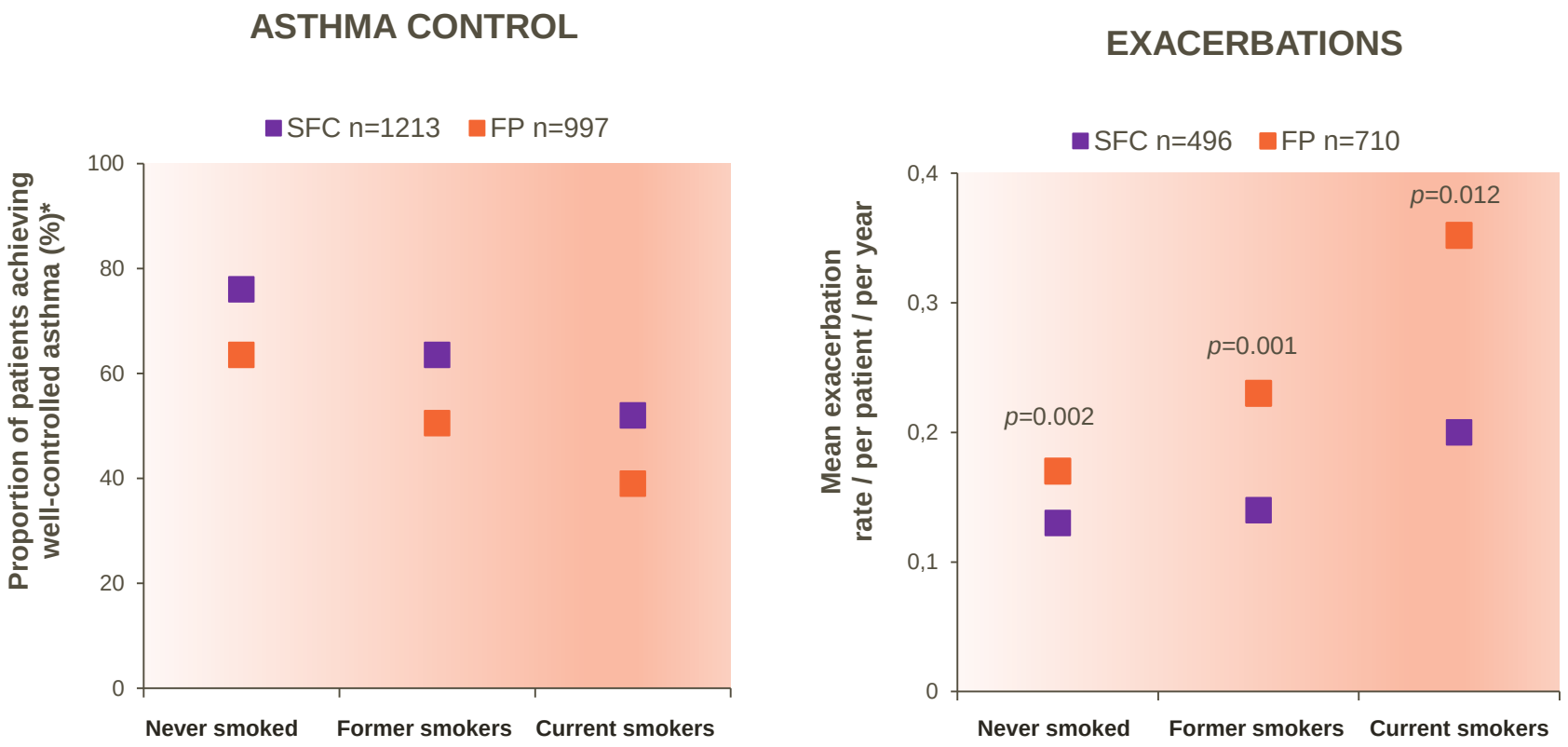
SFC was clinically superior to FP in asthma patients irrespective of smoking status



These are post-hoc results from a 1-year, stratified, randomised, double-blind, parallel-group study (n=3421 randomised) in patients (≥12 to <80 years) with persistent asthma who received either SFC (50/100 µg bid) and SFC (50/250 µg bid) up to a maximum of SFC (50/500 µg bid) or FP (100 µg bid) and FP (250 µg bid) up to a maximum of FP (500 µg bid).
* Statistical significance was not given in the paper. Strata are combined/pooled for this analysis.

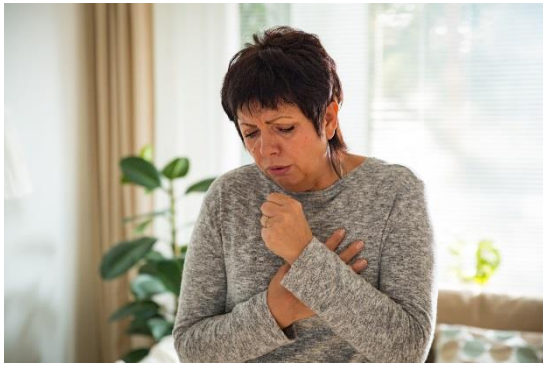
FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate combination.

These figures were first published in Pedersen et al. *J Allergy Clin Immunol.* 2007;120:1036-1042. These graphs have been independently created by GSK from the original.

ID/AST/0017/18 AD: 08/10/2018 ED: 08/10/2020

Case: monthly review

- With the correct support from her healthcare provider, patient now feels confident in using her device
- Regular follow-ups reinforce this confidence and also allows patient's healthcare provider to assess whether she is still achieving good symptom control
- As patient appears happy with her treatment, she has been taking her medication correctly and continuously
- As treatment effectiveness and adherence are good, patient will stay on her current device for the foreseeable future



Thank you