Effects of short- and long-acting beta-agonists on asthma exacerbations: a prospective cohort

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All authors critically reviewed the manuscript and have given their final approval of the version to be published.

EVG and MdB provided supervision, conceived and designed the study, interpreted the data, and drafted the manuscript. NT contributed to data acquisition. AD, MB, LL, SH, SS, GH, OG and MF contributed to study design and interpretation of data. EVG is the guarantor of the study.

All authors agree to be accountable for all aspects of the work related to its accuracy or integrity.

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Registration

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Keywords: prospective cohort, asthma, short-acting beta-agonists, long-acting beta-agonists, exacerbations

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Dr. Van Ganse reports the receipt of personal fees from PELyon for work outside the scope of the submitted manuscript.

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Abbreviations

AEx	asthma exacerbation
CATI	computer-assisted telephone interview
CI	confidence interval
EHR	Electronic Health Record
FDA	Food and Drug Administration
FDC	fixed-dose combination
GLLM	generalized linear mixed model
GP	General Practitioner
ICS	inhaled corticosteroids
LABA	long-acting β-agonist
LTRA	leukotriene receptor antagonist
NS	non-significant
OCS	oral corticosteroids
OR	odds ratio
RCT	randomized controlled trial
SABA	short-acting β-agonist

ABSTRACT (255 words)

Background. In asthma, short- and long-acting β-agonists (SABAs and LABAs) should be used together with inhaled corticosteroids (ICS), and regular use is inappropriate.

Objective. To assess the relationship between patterns of use of therapy and asthma exacerbations (AEx).

Methods. Asthmatic patients (6-40 years) were enrolled in France and the United Kingdom. Prescribing data, Computer-Assisted Telephone Interviews (CATIs), and text messages assessed medication use and AEx over a maximum period of 24 months. Generalized linear mixed models provided AEx risks associated with therapy.

Results. Among the 908 patients (median age: 20.0 years, 46.6% women, 24.5% children) answering a total of 4,248 CATIs over 486 (±235) days, regular (i.e. daily) use was more frequent for single LABAs and Fixed Dose Combinations (FDCs) than for single ICS (75.6%, 70.1%, and 65.4% of investigated periods of use, respectively). Regular (i.e. daily or almost daily) SABA use was observed for 21.1% of periods of use. Altogether, 265 patients (29.2%) experienced ≥1 AEx. ORs for AEx risk related to regular vs. no use of FDCs, single ICS, and single LABAs were 0.98 (95% CI=[0.73-1.33]), 0.90 (95% CI=[0.61-1.33]), and 1.29 (95% CI=[0.76-2.17]), respectively, after adjustment for cotherapy, socio-demographic, and disease characteristics. The OR was 2.09 (95% CI=[1.36-3.21]) in regular SABA users.

Conclusion. ICS and FDCs were often used intermittently whereas SABAs and LABAs could be used regularly, and exacerbations were frequent. Compared to non-users, the risk of exacerbation increased moderately under regular use of single LABAs, while it doubled, significantly, in regular SABA users, likely in relationship with poor overall asthma control.

INTRODUCTION

The safety of long-acting β-agonists (LABAs) remains controversial in patients with asthma, prompting regulators to contraindicate LABAs for use as single agents to treat asthma [1]. GINA guidelines also emphasize the need to avoid a regular use of short-acting β-agonists (SABAs) without concurrent ICS use, a situation frequently observed in routine care, where overreliance on SABAs and poor adherence to ICS are common [2, 3]. Recent clinical trials have compared LABAs in fixed dose combinations (FDCs) with ICS, obtaining reassuring findings regarding the occurrence of nonlethal exacerbations [4-8]. Evidence is nonetheless limited in the context of routine clinical care, where inappropriate use of therapy may impact safety and effectiveness [9]. A systematic review assessing the risks associated with LABAs in combination with ICS compared to ICS alone could not reach robust conclusions [10].

To investigate the effect of LABAs on asthma outcomes under real-life conditions, the European Medicines Agency requested an observational study collecting prospective information on actual medication use and ensuing outcomes. Therefore, a study employing a longitudinal design with repeated assessments of asthma therapy use and exacerbations over time was considered appropriate to examine LABA safety in real life, based on the assumption that potential risks of would vary between periods of regular use and periods without use, and according to co-therapy with ICS. In a context of increased awareness regarding inappropriate use of SABAs in routine care and the potential impact on outcomes, the study simultaneously collected data on the use of SABAs, allowing assessments of both short- and long-acting bronchodilators [9].

METHODS

Study design and study population

The methods of the study have been described [11]. Briefly, this was a prospective, field study of a cohort of patients with persistent asthma recruited and followed from 2013 to 2015. The study population included patients with asthma aged 6-40 years who were recruited in primary care in France and the United-Kingdom (UK). In the UK, the study identified patients from THIN, a network of Electronic Health Records (EHRs), whereas in France patients were directly identified by General Practitioners in their practices.

Data collection

Trained interviewers administered computer-assisted telephone interviews (CATIs) to patients aged 12-40 years and to parents/caregivers of patients aged 6-11 years immediately after inclusion, and then every four months during a maximum follow-up period of 24 months. CATIs assessed the type of asthma medications prescribed at the time of interviews, and patient-reported use and occurrence and type of asthma exacerbations (AEx) during the last 4 months [12]. Patients also received monthly text messages inquiring whether they had experienced a new AEx since the last study contact. A positive answer triggered an additional CATI with questions on medication use prior to AEx to ensure that data were collected as close to the AEx as possible. Socio-demographic data (gender, age, and country of residence) were obtained from medical records.

Measures

Outcome

Asthma exacerbation (AEx) was defined as a new OCS course for asthma (≥3 days), an unscheduled medical contact for asthma, a hospital contact (emergency room visit and/or overnight hospitalization) and/or death due to asthma. AEx events were reported by patients themselves or their caregivers at each

CATI, including the type of event. The date of AEx was recorded, and multiple AEx events within 15 days were considered a single event.

Reported medication use

Medication use was assessed at each CATI, separately for each inhaler reported used in the period assessed. The questions had been validated before starting patients' inclusions: they assessed distinct patterns of use for specific time periods[12]. LABA use was assessed separately for single LABA inhalers, regardless of whether they were administered monotherapy or with ICS, and for FDC inhalers. The assessment was based on a question inquiring about the number of days of LABA or ICS use during the 7 days preceding CATIs, and when an AEx was reported, the 7 days before the occurrence of the AEx; answers were grouped in 3 categories (none: 0 days of use; irregular use: 1-6 days of use; and regular use: 7 days of use). The use of short-acting β-agonists (SABAs) in the last four weeks was measured based on CATI questions inquiring about the frequency of SABA use; responses were grouped into 'irregular use' (once or twice weekly or less than once a week) and 'regular use' (daily or almost every day). No prescribed SABAs was considered as 'no use'.

Severity markers

For all patients, the 12 months before inclusion -the "pre-study period"- was used to verify inclusion criteria –e.g., repeated prescribing of controller therapy- and to assess the severity of asthma [11]. The number of OCS courses prescribed during this pre-study period was obtained from medical records.

The daily doses of ICS reported at the first CATI were computed from patient-reported information on the type of ICS prescribed and daily dosage, and were reported as the beclomethasone equivalent dose according to GINA equivalence computations [13]; values were grouped into 3 categories according to µg of the beclomethasone equivalent doses in teenagers and adults (12+) and children (6-11): high (> 1,000 µg and >400 µg, respectively), medium (500-1,000 µg and 200-400 µg, respectively), and low: (≤500 µg and ≤200 µg, respectively).

The use of leukotriene receptor antagonists (LTRAs) at inclusion was assessed from prescribing data at the first CATI, coded as a binary variable (yes/no).

Data analyses

Descriptive analyses

Analyses were based on all available CATI reports; reports contained complete data due to mandatory completion rules in the CATI online forms. First, patients' baseline characteristics were summarized as counts and percentages. Next, patient-reported medication uses were described: the purpose was to identify inappropriate use, ie "**irregular"** use among FDC and ICS users, and "**regular"** use among users of LABA in single inhalers, and SABA users. Finally, the frequency of asthma exacerbations (AEx) during follow-up was presented, including the type of AEx.

Risk of asthma exacerbation (AEx) during medication use

For each medication, we investigated whether the reported use was associated with an AEx occurrence. A multilevel logistic regression approach was used (Generalized Linear Mixed Models with CATI reports nested within patients, and a variance component structure to account for correlations among time points), in which a patient's use was allowed to change over time. Treatment variables (FDCs, ICS, single LABAs, SABAs) were entered in the model to detect a potential impact on AEx; '0 days' of use or absent prescription was considered the reference group. For all medications, a "regular use" was assumed to maximize the probability of observing a potential impact -positive or negative- on exacerbations. The model was adjusted for age, gender, country, and markers of severity (dose of ICS prescribed at inclusion, annual number of episodes of use of OCS before inclusion, prescribed LTRA at inclusion).

RESULTS

Baseline sample characteristics

The analyses included data from 908 patients who completed at least one CATI (Figure 1). The median age of the participants was 20.0 years; 46.6% were female, and 55.8%, 19.7% and 24.5% were adults, teenagers and children, respectively. At inclusion, 28.9% of patients were prescribed ICS without LABAs, 59.0% were prescribed LABA/ICS FDCs, 9.1% were prescribed LABAs and ICS in distinct inhalers, and 3.0% (n=27) were prescribed LABAs without ICS. In parallel, 84.7% of patients were using SABAs at inclusion. At the initial CATI, LTRAs were used by 198 (21.8%) patients, and 710 patients (78.2%) were prescribed low or medium doses of ICS. The average number of OCS courses during the 12 months before inclusion was 0.45 (±0.90) (Table 1). Missing data only concerned markers of baseline severity (OCS, and ICS daily doses: 3.2% and 2.6% missing values, respectively), which were replaced with the most frequent values.

FIGURE 1

TABLE 1

Medication use during follow-up

Participants were followed for 486 (±235) days. Four thousand two hundred fourty-eight CATIs were conducted (4,120 regular CATIs and 128 CATIs performed after AEx detection). The global answer rate to text messages was 66.5%, and 55.2% of the patients answered greater than 80% of the text messages.

Figure 2 illustrates the use of medications before the CATIs. Of the 2,246 CATIs reporting the use of FDCs by 564 patients, 29.9% reported an irregular use of FDCs (1 to 6 days). ICS use was reported by 288 patients in 941 CATIs: use was irregular in 34.6% of the CATIs.

Single LABA use with or without concomitant ICS use was declared by 84 patients in 308 CATIs, and regular use (7-day use) was reported in 75.6% of their CATIs. SABA use was reported by 827 patients in 3696 CATIs: use was regular in 21.1% of the CATIs.

FIGURE 2

Occurrence of asthma exacerbation (AEx)

During follow-up, 29.2% of patients experienced ≥1 AEx, with an average of 2.0 (±1.8) AEx events per patient. AEx events mostly consisted of new OCS courses (80% of AEx), often with unscheduled medical visits (72% of AEx). Few (3.3%) asthma-related hospital contacts were reported, and no asthma-related death occurred (Table 2).

TABLE 2

Risk of AEx during medication use

No significantly increased risks of AEx were associated with patient-reported medication use over time when comparing periods of regular use with periods of nonuse of FDCs (0.98, 95% CI: 0.73-1.33) and single ICS (0.90, 95% CI: 0.61-1.33). By contrast, the risk of AEx non-significantly increased with regular use of single LABAs (1.29, 95% CI: 0.76-2.17), while increase was larger and significant with regular use of SABAs (2.09, 95% CI: 1.36-3.21).

A greater number of AEx events occurred in French than in British patients (1.72, 95% CI: 1.06-2.81). Women had a significantly increased risk of AEx compared to men (1.39, 95% CI: 1.08-1.78), and children displayed a significantly increased risk compared to adults (1.40, 95% CI: 1.05-1.87). All three markers of severity were significantly associated with an increased risk of AEx: (1.29, 95% CI: 1.16-

248 1.43) for pre-study OCS courses; (1.42, 95% CI: 1.07-1.88) for medium versus low initial dose and
249 (1.52, 95% CI: 1.11-2.08) for high versus low ICS initial dose, and (1.49, 95% CI: 1.15-1.94) for use of
250 LTARs at inclusion. (Table 3; Figure 3).

251

252 TABLE 3

253 FIGURE 3

DISCUSSION

Our prospective cohort followed 908 patients with persistent asthma in France and in the UK, including 222 children, with 4,248 assessments of the actual use of therapy and occurrence of exacerbations. High proportions of patients did not make appropriate use of controller therapy, with 29.9% and 34.6% of CATIs revealing an irregular use of FDCs and ICS, respectively. By contrast, when patients used LABAs in single inhalers, they mostly used it regularly (75.6% of CATIs), and many patients declared a regular use of SABAs (21.1% of CATIs). Altogether, 29% of the patients experienced an exacerbation: when compared to periods of non-use, the risk decreased slightly, but not significantly so, under regular FDC and ICS use while it increased moderately -albeit not significantly- during regular use of single LABAs inhalers, and even more under regular use of SABAs, with a significant doubling of the risk. A significantly higher risk was observed in France than in the UK, in female patients, in children aged 6-12 years compared to adults, and in patients with more severe asthma.

For FDCs, our 'real world' results complement the findings of recent RCTs comparing the occurrence of serious adverse outcomes in patients treated with FDCs compared with ICS monotherapy, where FDCs and ICS were associated with similar rates of these outcomes [7, 8]. Our data are consistent with a recent observational study conducted with claims data that reported a 20% decreased risk of asthma-related hospitalization in patients treated with FDCs compared to LABAs and ICS in distinct inhalers [14], highlighting the absence of risk when patients used LABAs concomitantly with ICS and not as a monotherapy, as advised by guidelines [15, 16]. Interestingly, in our study, FDCs and ICS were declared to be used irregularly in 30% and 35% of episodes of use, supporting observations of common inappropriate use of asthma controller therapy, and so contributing to the increased risk of exacerbations recorded in patients using short- or long-acting bronchodilators in single inhalers.[9] SABA or LABA and ICS use in distinct inhalers may indeed become an at-risk treatment use when patients preferentially use their bronchodilator at the expense of ICS therapy [17]. Although this pattern of use was not directly observed in our study, differential use between LABA and ICS has been documented by a study showing that 17.7% of patients receiving LABAs and ICS in distinct inhalers had episodes of treatment with LABA monotherapy[18]. Consistent results were retrieved from a US study examining Medicaid enrollees

[19]. Notably, in our study, patients reported irregular (1-6 days) use of ICS in 35% of declared episodes of use, supporting the assumption that LABAs -and SABAs- are occasionally used without simultaneous ICS therapy [9].

For bronchodilators in single inhalers use, the data reveal that the majority of LABAs uses tended to be regular (>75%), and regular use increased the odds of exacerbations with 29% compared to periods of non-use, in agreement with available evidence [20]. However, the number of patients using single LABA inhalers decreases fastly, as shown by recent studies [21], precluding more robust findings from this study population. Nonetheless, the use of LABAs in monotherapy is contra-indicated in asthma, and the identification of patients still relying on this therapy suggests that additional efforts are needed to raise prescribers' awareness of the risks related to this use. Less expected was the regular use of SABAs declared in 21% of the CATIs, while more than 80% of the patients used SABAs. This implies that many SABA users had periods of regular use, despite recommendations [13]. This observation is likely related to the overall low level of control observed in the study population, with patients reporting a poor control of asthma in more than 50% of the interviews [22]. Combined with the known irregularity of use of inhaled corticosteroids [23], this finding contributes to the increased risk of exacerbation in regular SABA users, a situation much more common than regular LABA use, as illustrated by our analysis of adherence data [22]. This underlines the need of further emphasizing the appropriate use of SABAs [2, 3].

The findings on the effects of socio-demographic characteristics and asthma severity on the risk of exacerbations are consistent with published evidence. First, women had an increased risk of exacerbations compared to men, as previously reported in relation to poorer asthma control and exacerbation occurrence [24]. Second, more frequent exacerbations were observed in France than in the UK. This difference might in part be attributed to differences in health care systems and the management of asthma in the two countries. Also, exacerbations occurred more often in children than in adults, consistent with previous reports [25]. Potential explanations include a higher prevalence of viral infections or better reporting of asthma outcomes by caregivers in this study. [26]. Last, higher risks of exacerbation were observed to correlate with pre-study severity markers -prior use of OCS, higher doses of ICS, and

cotherapy with LTRAs-, which represents a validation of their use to control confounding effects due to asthma severity.

Part of the results should be interpreted with some caution given the small sample of patients using LABAs in single inhalers, in contrast to the high prevalence of SABA use. Significant changes in LABA use in favor of FDCs at the expense of single LABA and ICS inhalers have indeed been observed recently. In France, a 2.4-fold decrease in the number of users of LABA monotherapies was identified between 2006 and 2016: from 4.1% to 1.7%[21]. In the UK, the prevalence of single LABA use also decreased sharply from 11.3% to 5.4% between 2007 and 2011 [9]. Moreover, frequent changes in asthma medication prescription and use were identified during the follow-up period in our study population. Therefore, to optimize data analysis, a GLM model was used, taking into account distinct periods of therapy in individual patients, to compare the occurrence of exacerbations between periods "at risk" - periods where patients used medications with potential impact on exacerbations- and periods with no such use. Our findings that sorted exacerbations according to prior patterns of use of medications (none, irregular, regular) appropriately reflected routine care, and identified the real-world uses of therapy that put the patients at maximal risk of adverse outcome. The study thus provides information that complements studies focused on fatal and near-fatal outcomes, or on head-to-head comparisons between treatment strategies.

Only 8.4% of the patients contacted in the UK agreed to participate. The enrollment process was however complex, as potential subjects had to be identified by the practice, before receiving information and providing specific agreements by mail. The selection bias did not affect the findings, as the study investigated the relationship between different patterns of use of therapy, and exacerbations. Furthermore, a parallel study conducted on another population of British patients showed similar data, with common overuse of SABAs and relative underuse of ICS 9, supporting the validity of our findings. The response rates to texting or the failure to accurately recall details may also have contributed to some irregularities in data acquisition, but this limitation affected all treatment groups in a similar way, and it was unlikely to impact the findings, as significant efforts were made to contact all patients regularly by CATIs and text messages, independently of their treatment and of the study hypotheses. In parallel,

studies that rely on telephone interviews without actually reviewing medical records or ordering specific tests always have some inherent weaknesses.

Other potential limitations were the moderate severity of asthma in the study, as a result of the enrolment from primary care practices, and the age range (6-40) imposed by the need to prevent inclusion of COPD, as asthma may be difficult to distinguish from COPD in primary care. These limitations possibly hampered the generalizability of our findings, but recent data confirm that asthmatic patients managed in primary care may experience major outcomes, supporting the clinical relevance of our findings [3].

In conclusion, the study provides valid insights into the relationship between the use of short- and long-acting bronchodilators and the occurrence of adverse outcomes in a real-world population of patients with asthma in two different countries. It is one of the few studies providing detailed and prospective patient-reported data on medication use and effects through close patient follow-up, allowing valid investigations of medication use and effects.

The study also represented an opportunity to investigate asthma management in primary care settings in more depth in France and the UK from patient and health care professional perspectives [27, 28]. The study supports the reassuring results obtained for LABA/ICS FDCs in recent randomized trials [7, 8]. It also highlighted the low number of patients who are currently receiving single LABAs, notably in monotherapy, suggesting that recommendations have in part been implemented [1]. However, the observed overuse of SABAs (more than 20% of SABA uses) is a major concern, which is also the case -despite limited and decreasing use-, for the extended use of LABAs in single inhalers, and both situations warrant educational efforts towards health care professionals and patients (self-management training). Others risk factors for exacerbations were identified such as severity, female gender, age, and country [28].

In summary, the results corroborate findings from clinical trials on FDC safety, and support the validity of the recent GINA recommendations, advising against regular bronchodilator use, certainly in the absence of concomitant ICS therapy [13].

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TABLES

Table 1: Patients' characteristics at inclusion (N=908)

Characteristics	N (%)
Gender	
Male	485 (53.4%)
Female	423 (46.6%)
Age at inclusion	
18-40 years	507 (55.8%)
12-17 years	179 (19.7%)
6-11 years	222 (24.5%)
Country	
United Kingdom	161 (17.7%)
France	747 (82.3%)
Medications at inclusion	
ICS without LABAs	262 (28.9%)
LABAs/ICS FDCs	536 (59.0%)
LABAs + ICS (distinct inhalers)	83 (9.1%)
LABAs in monotherapy (without ICS)	27 (3.0%)
Prescribed daily dose of ICS at the initial CATI in µg (1) (2)	
Low	411 (45.3%)
Medium	299 (32.9%)
High	198 (21.8%)
Prescribed leukotriene receptor antagonists at the initial CATI (1)	
No	710 (78.2%)
Yes	198 (21.8%)
SABA use at the initial CATI	
Daily or almost ('regular')	205 (22.6%)
Less frequent use ('irregular')	564 (62.1%)

Nonuse	139 (15.3%)
	Mean (SD)
# of OCS courses during the pre-study period (1)(3)	0.45 (0.90)

437 [(1)] Markers of asthma severity. [(2)] High: > 1,000 µg of the beclomethasone equivalent dose (>400 µg in children); medium:
438 500 to 1,000 µg of the beclomethasone equivalent dose (200 to 400 µg in children); low: ≤500 µg of the beclomethasone
439 equivalent dose (≤200 µg in children). [(3)] The pre-study period corresponds to the one-year selection period before inclusion.
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441

442 **Table 2: Characteristics of asthma exacerbations (AEx) during follow-up**

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	N patients	% of patients affected during follow-up [(1)] (n=908)	% of patients affected per year (among all CATIs performed)[(1)] (n=461)
Any OCS course	212	23.3%	24.9%
Any unscheduled medical visit for asthma	190	20.9%	20.4%
Any hospital contact (Emergency Room visit or hospital admission due to asthma)	30	3.3%	2.6%
Death due to asthma	0	0	0
Any outcome (overall)	265	29.2%	30.6%

444 [(1)] Percentages were not mutually exclusive, as patients could be prescribed an OCS course during a medical contact.

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446 **Table 3: Risk of asthma exacerbations during follow-up in groups stratified according to medication use and patient**
447 **characteristics (4,248 CATIs in 908 patients)**
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Variable		Odds ratio	95% CIs		p-value
			Lower	Upper	
Single LABA use [(1) (2)]	0 day	.	.	.	.
	1 to 6 days	0.45	0.11	1.93	0.29
	7 days	1.29	0.76	2.17	0.34
LABA/ICS FDC use [(2)]	0 day	.	.	.	.
	1 to 6 days	0.93	0.64	1.35	0.70
	7 days	0.98	0.73	1.33	0.91
Single ICS use [(2)]	0 day	-			
	1 to 6 days	0.64	0.36	1.14	0.13
	7 days	0.90	0.61	1.33	0.59
SABA use (past 4 weeks) [(2)]	No use	-			
	Irregular use	1.26	0.86	1.85	0.24
	Regular use	2.09	1.36	3.21	0.01
Country	United Kingdom	.	.	.	.
	France	1.72	1.06	2.81	0.03
Gender	Male	.	.	.	.
	Female	1.39	1.08	1.78	0.01
Age group	18-40 years	.	.	.	.
	12-17 years	0.87	0.60	1.25	0.44
	6-11 years	1.40	1.05	1.87	0.02
# of OCS courses during the pre-study period		1.29	1.16	1.43	<0.01
Prescribed daily ICS dose (µg of the beclomethasone equivalent dose) at initial CATI [(3)]	Low	.	.	.	.
	Medium	1.42	1.07	1.88	0.02
	High	1.52	1.1	2.08	0.01

Prescribed leukotriene receptor antagonists (LTRAs) at initial CATI	No	.	.	.	.
	Yes	1.49	1.15	1.94	0.01

(1) LABAs were used with ICs in distinct inhalers or in monotherapy.

(2) Time-varying measurements obtained at each CATI.

(3) High: > 1,000 µg of the beclomethasone equivalent dose (>400 µg in children); medium: 500 to 1,000 µg of the beclomethasone equivalent dose (200 to 400 µg in children); low: ≤500 µg of the beclomethasone equivalent dose (≤200 µg in children).

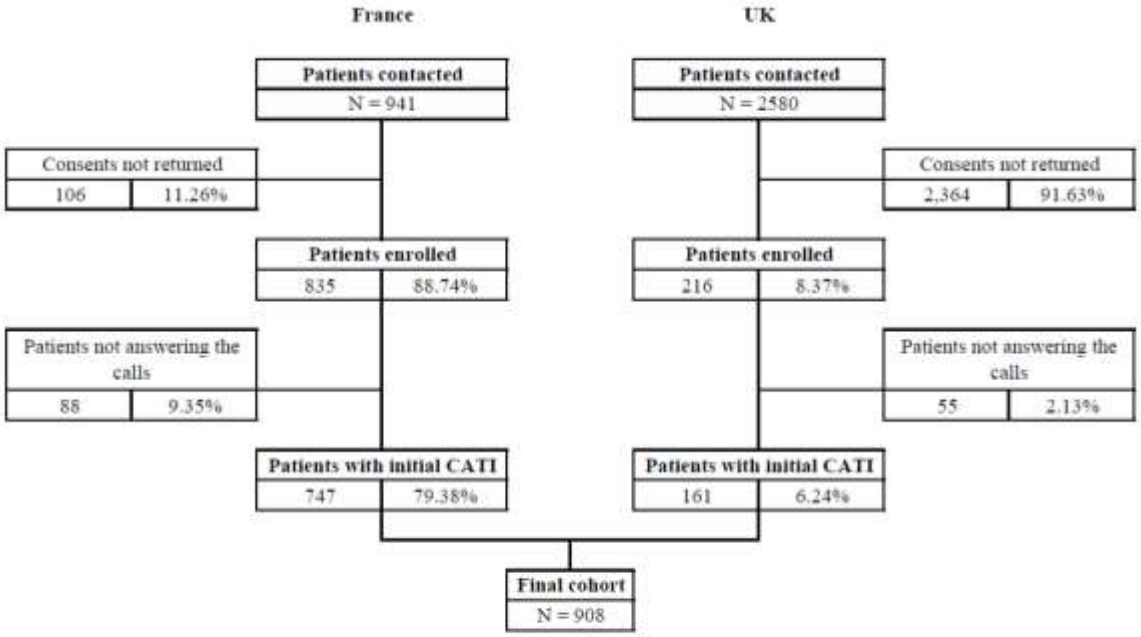

Figure 1 : Patient flowchart in France and the United Kingdom

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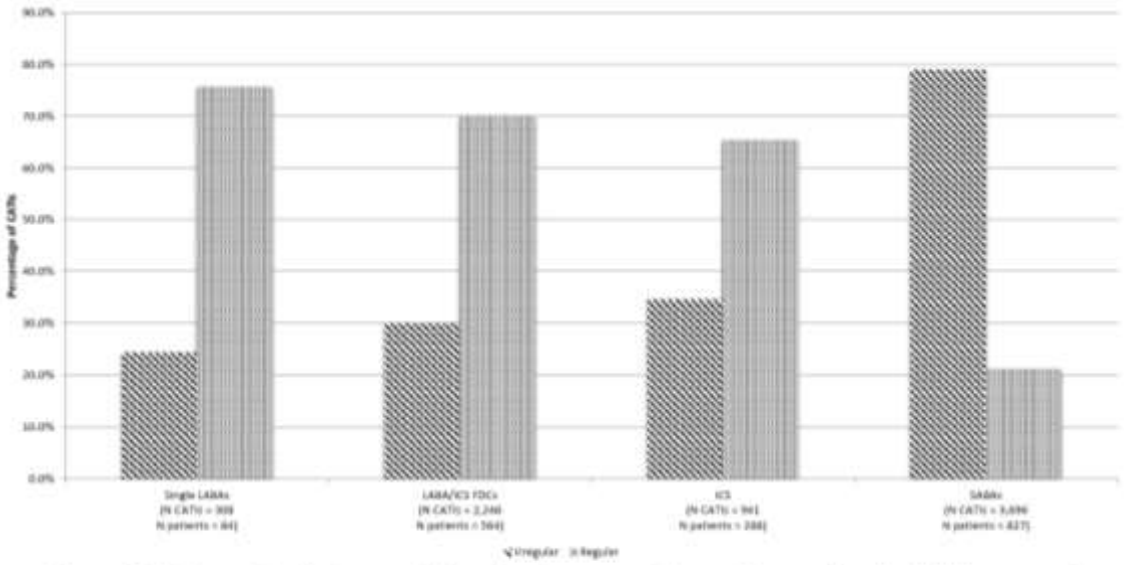

Figure 2: Patterns of patient-reported treatment use over the week preceding the CATI or preceding the reported date of occurrence of an Aex
(7 days for single LABAs, FDCs et ICS ; 4 weeks for SABAs)

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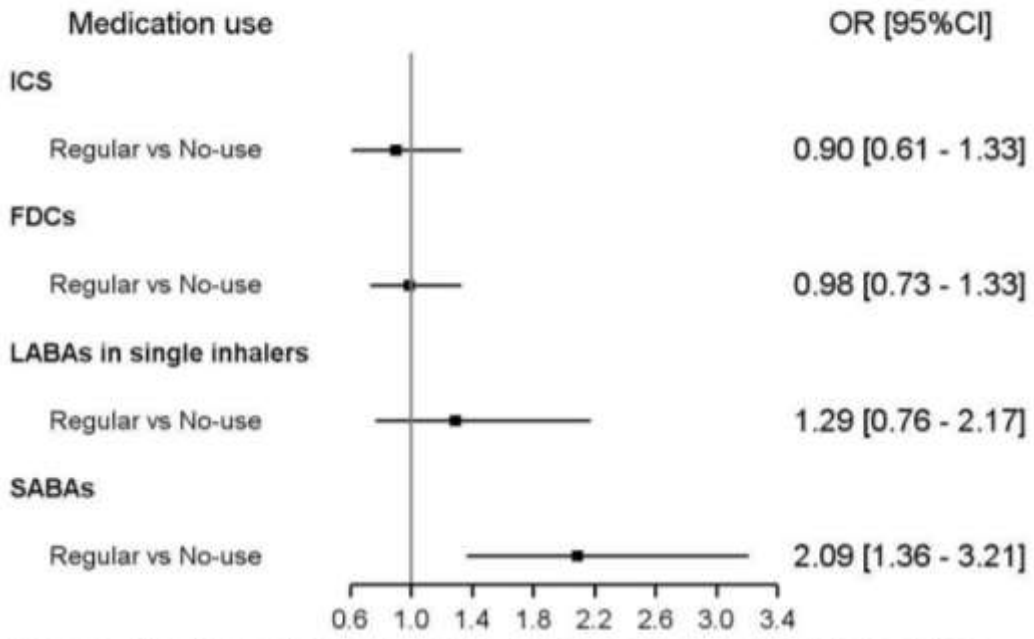

Figure 3: ORs of exacerbations in regular users vs. non users of distinct asthma medication

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