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Original Research

β-Blockers and Asthma: Surprising findings from the FAERS database

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ABSTRACT

Introduction: β-Blockers are essential for cardiovascular disease management but can induce respiratory issues, particularly with non-selective β-blockers. Their safety in asthmatic patients is debated.
Objective: This study investigates the link between different classes of β-blockers and the risk of asthma and asthma-like adverse events (AEs) using data from the Food and Drug Administration's Adverse Event Reporting System (FAERS).
Methods: β-Blockers were first reviewed according to European Society of Cardiology classification and then using the Vashistha and Kumar classification. The risk associated with different β-blocker classes was evaluated through disproportionality analysis using the reporting odds ratio (ROR).
Results: Among 251,145 AEs reported for β-blockers, 4104 were asthma-related. Selective β_1-blockers had a higher asthma risk signal (ROR: 1.15) compared to non-selective β-blockers (ROR: 0.90). α- and β-Blockers showed the lowest risk (ROR: 0.51). The Vashistha and Kumar classification detailed risk profiles for various β-blockers, highlighting differences even within the same class. Dual α- and β-blockers, hydrophilic, and lipophilic β-blockers posed lower asthma risks, while selective β_1-blockers had higher risks regardless of intrinsic sympathomimetic activity.
Conclusion: Although the signals detected by disproportionality analysis are only candidate risks, the risk stratification resulting from our analysis highlights the need for cautious β-blocker selection in asthmatic patients or those predisposed to asthma. Furthermore, despite the limitations associated with the FAERS data, the study reveals significant variability in risk among different β-blocker classes, crucial for clinical decisions and patient management. Drugs like esmolol, metoprolol, nebivolol, and nadolol may be safer for asthmatic patients, whereas betaxolol, bisoprolol, timolol, and propranolol should be avoided.

1. Introduction

β-Blockers are a class of medications widely used to treat cardiovascular diseases (CVDs) such as hypertension, angina, and heart failure [1]. They work by blocking the β-adrenoceptors (β-ARs), which play a key role in the regulation of cardiovascular function by the sympathetic nervous system [2]. The expert consensus document published by the European Society of Cardiology (ESC) in 2004 classified β-blockers into three classes: non-selective ($\beta_1 + \beta_2$)-blockers, selective β_1-blockers, and α_1-and β-blockers [3] (Table 1). In contrast, Vashistha and Kumar's classification is much more detailed, with β-blockers divided into seven classes according to their pharmacokinetics, pharmacodynamics and mechanism of action: selective β_1-blockers without intrinsic sympathomimetic activity (ISA), selective β_1-blockers with ISA, non-selective β-blockers without ISA, non-selective β- blockers with ISA, dual α- and β-blockers, lipophilic β-blockers, and hydrophilic β-blockers [4] (Table 1).

Despite their efficacy in managing CVDs, β-blockers have been associated with respiratory adverse events (AEs), including bronchospasm and exacerbation of respiratory symptoms. They also neutralize the effectiveness of β_2-agonists [1,2]. These medications can trigger both moderate and severe asthma exacerbations, as well as elevate mortality rates among patients with severe chronic obstructive pulmonary disease (COPD) [1,5].

Although β-blockers can worsen pulmonary function in individual patients, they are not contraindicated in either COPD or asthma. The

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ESC guidelines recommend that the use of cardioselective β_1-blockers should be encouraged, starting with low doses combined with close monitoring for signs of airway obstruction (wheezing and shortness of breath with prolonged expiration) [6]. Indeed, the use of β-blockers (including both β_1-selective and nonselective agents) in patients with COPD and CVD is not only safe but also reduces their all cause and in-hospital mortality [7]. However, patients with classical pulmonary asthma may have their condition worsened by the use of nonselective β-blockers or agents with low β_1-selectivity [7]. Nevertheless, the latest ESC guidelines for the management of elevated blood pressure and hypertension have reiterated the concept that cardioselective β_1-blockers may be used in low dose in chronic asthma [8].

It is noteworthy that while both cardioselective and non-cardioselective β-blockers are correlated with diminished FEV_1 and FVC values, only the non-cardioselective β-blockers, which impact the functionality of both β_1-and β_2-ARs, show a significant reduction in the FEV_1/FVC ratio, a measure to assess airflow obstruction [9]. Furthermore, in patients with reactive airway disorder, single doses of both cardioselective β_1-blockers and non-selective β-blockers may result in a slight reduction in lung function during the initial phase of treatment [10]. However, this decline is only temporary.

To shed more light on the possible respiratory risk associated with the use of cardioselective β_1-blockers, the World Health Organization's (WHO) global database of individual case safety reports (VigiBase) was searched in February 2020 for reports of fatal asthma or bronchospasm involving the use of cardioselective β_1-blockers up to December 2019 [11]. VigiBase contains reports of more than 40 million suspected adverse drug reactions submitted by member countries of the WHO International Drug Monitoring Programme since 1968 [12]. It is hosted by the Uppsala Monitoring Center. Any health care provider or patient can submit a report.

Analysis of the data revealed 6 deaths out of 583 cases of asthma and 12 out of 1015 cases of bronchospasm. The use of inhalers was reported in 5 cases, indicating pre-existing lung disease. All cases were considered as possible asthma due to insufficient differentiation from COPD. In 4 cases, the use of a cardioselective β_1-blocker was unlikely to be the cause of the event, as bronchospasm was not the main cause of death. The AEs were not considered to be attributable to the β-blocker itself, but rather to the concomitant drugs used to treat comorbidities, including sepsis, pneumonia, heart disease and kidney cancer. Another report provided minimal information beyond a list of drugs administered (salbutamol, beclomethasone, metoprolol and anesthetics) and the only recorded clinical reaction, asthma. While the anesthetics may have been the primary cause of the reaction, the possibility of β-blocker involvement cannot be excluded. The VigiBase data also showed that 13 deaths occurred in the absence of a pre-existing asthma and were associated with adverse drug reactions coded as asthma (n = 2) or bronchospasm (n = 11). All this reinforces the idea that although asthma is not an absolute contraindication to the use of cardioselective β_1-blockers [7,8], these drugs should be prescribed with caution [13].

The choice of appropriate drugs to treat CVD is often an absolute necessity [1,14]. However, when a cardioselective β_1-blocker is prescribed, the risk of bronchoconstriction, although minimal, is still present in patients with concomitant asthma [15]. Therefore, the objective should be to choose a cardioselective β_1-blocker that offers maximum safety, although this is complicated by the conflicting and often anecdotal data in the literature.

The aim of this study was to ascertain whether there is a β-blocker that is less harmful to an asthmatic patient. To do this, the association between different classes of β-blockers and the risk of asthma and asthma-like AEs was assessed using data from the Food and Drug Administration's Adverse Event Reporting System (FAERS).

2. Methods

2.1. The FAERS database

The FAERS database is a publicly available repository of AE reports submitted to the FDA, directly by healthcare providers and consumers, or indirectly through manufacturers, from the United States and other countries using MedWATCH program submission forms [16]. It contains information on drug and biologic products, including the type of AE, patient demographics, and other relevant clinical data. This database represents a valuable resource for the post-marketing surveillance of drug safety. It provides useful insight into the AE profile of medications due to the widespread exposure of a particular drug in the real-world population and the large sample size, which includes a wide variety of AE reports [17].

2.2. Data extraction and categorization

FAERS categorises AEs using the preferred term (PT) level of standardised terminology found in the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. In this study, AEs coded under PTs designated as "respiratory, thoracic and mediastinal disorders" were examined as outcomes of interest. A more focused approach included standardised MedDRA queries. Specifically, "allergic bronchitis", "allergic cough", "allergic respiratory symptoms", "asthma", "asthmatic

Table 1
–Classes of β-blockers divided according to the expert consensus document published by the European Society of Cardiology in 2004 [3] or the classification proposed by Vashistha and Kumar [4].

European Society of Cardiology			Vashistha and Kumar	
Selectivity	Adrenoreceptor	Examples	Class	Examples
Selective β_1-blockers	β_1-AR > β_2-AR	Metoprolol (also inverse agonist), Bisoprolol (also inverse agonist), Atenolol, Esmolol, Betaxolol (also Ca^{2+} entry blocker), Acebutolol (also with ISA), Nebivolol (also activates endothelial nitric oxide synthase), Celiprolol (also α_2-AR blocker with ISA)	Selective β_1-blockers without ISA	Atenolol, Betaxolol, Bisoprolol, Esmolol, Metoprolol, Nebivolol
Non-selective	β_2-AR < β_1-AR	Propranolol (also inverse agonist), Alprenolol (also inverse agonist), Nadolol (also inverse agonist), Sotalol, Pindolol (also inverse agonist), Bopindolol (also inverse agonist), Timolol (also inverse agonist)	Selective β_1-blockers with ISA	Acebutolol, Celiprolol
α_1- and β-blockers	β_2-AR < β_1-AR	Bucindolol (also inverse agonist), Carvedilol, Labetalol (also inverse agonist)	Non-selective β-blockers without ISA	Nadolol, Propranolol, Timolol
			Non-selective β-blockers with ISA	Bopindolol, Pindolol
			Dual α- and β-blockers	Carvedilol, Labetalol
			Lipophilic β-blockers	Propranolol, Labetalol
			Hydrophilic β-blockers	Sotalol, Nadolol, Atenolol

ISA, intrinsic sympathomimetic activity.

crisis", "asthma exercise induced", "bronchial hyperreactivity", "bronchial irritation", "bronchial obstruction" "bronchospasm", "bronchospasm paradoxical", "bronchostenosis", "reversible airway obstruction", and "wheezing" were examined. It was recognised that each report could include one or more respiratory AEs, as emphasised by FAERS.

β-Blockers were first divided into classes according to the ESC classification [3] and then according to the Vashistha and Kumar classification [4]. It was important to use both classifications because, although the broader categories of the ESC classification are easier for lay people to understand, they do not provide specific risk profiles for individual drugs. This could lead to making generalisations that are less accurate and therefore less useful for clinical decision making.

2.3. Signal detection

Disproportionality analysis is an important tool in pharmacovigilance research because it helps to identify possible signals of drug-related AEs [18,19]. In this approach, the incidence of AEs associated with a particular drug is compared with the incidence of AEs associated with all other drugs. The principle is that a signal is generated during data extraction when the incidence rate of a particular AE for a particular drug dramatically exceeds the background incidence rate recorded in the database. This deviation from the norm must meet a predefined threshold or set of criteria to be considered statistically significant.

The European Medicines Agency uses two key measures for this analysis: the reporting odds ratio (ROR) and the proportional reporting ratio (PRR) [20]. The ROR is the ratio of the probability of reported cases with a given drug to the probability of reported cases without that drug [21]. If there are at least three cases, a lower bound of the 95 % confidence interval (CI) greater than 1 is considered statistically significant [22]. The PRR is calculated as the ratio of the proportion of reported cases of a particular AE in people exposed to a specific drug to the proportion of the same event in people exposed to all or several other drugs [23]. However, according to Rothman et al. [24], ROR may theoretically be a less biased technique than PRR. Furthermore, Chen et al. found that ROR outperformed other methods in terms of signal precocity [25]. Another advantage of ROR is that it allows for multivariate logistic regression, which considers confounding and interaction effects [21].

As only odds ratios can be obtained for studies in which it is typically not possible to estimate the population at risk [26], as in the case of our investigation, we performed a disproportionality analysis to assess the potential association between β-blockers and the risk of asthma and asthma-like AEs and calculated the ROR.

2.4. Ethical statement

Data in the FAERS database are anonymized. Therefore, ethics committee approval was not required for this analysis.

3. Results

A total of 251,145 AEs associated with the use of β-blockers had been reported to FAERS by March 31, 2024. Of these AEs, 4104 were classified as asthma-related events (Table 2).

Table 2
– Number of reported cases of all adverse events (Total) and asthma-related events (Asthma) by classification, β-blocker class and individual β-blocker.

European Society of Cardiology				Vashistha and Kumar			
Total 204,051 Asthma 4104							
Class	***β-blocker***	***Total***	***Asthma***	***Class***	***β-blocker***	***Total***	***Asthma***
Selective β_1- blockers	Acebutolol	130,404	2954	Selective β_1-blockers without ISA	Atenolol	127,689	2885
	Atenolol	2261	67		Betaxolol	2,6470	423
	Celiprolol	26,470	423		Bisoprolol	2244	124
	Betaxolol	454	2		Esmolol	31,597	1006
	Bisoprolol	2244	124		Metoprolol	816	11
	Esmolol	31,597	1006		Nebivolol	58,386	1186
	Metoprolol	816	11			8176	135
	Nebivolol	58,386	1186				
		8176	135				
Non-selective	Alprenolol	45,907	840	Selective β_1-blockers with ISA	Acebutolol	2715	69
	Bopindolol	2	0		Celiprolol	2261	67
	Nadolol	3	0			454	2
	Pindolol	3401	39				
	Propranolol	1205	18				
	Sotalol	24,976	445				
	Timolol	3076	38				
		13,244	300				
α_1- and β- blockers	Bucindolol	27,740	310	Non-selective β- blockers without ISA	Nadolol	41,621	784
	Carvedilol	12	0		Propranolol	3401	39
	Labetalol	22,056	265		Timolol	24,976	445
		5672	45			13,244	300
				Non-selective β- blockers with ISA	Alprenolol	1210	18
					Bopindolol	2	0
					Pindolol	3	0
						1205	18
				Dual α_1- and β-AR blockers	Bucindolol	27,740	310
					Carvedilol	12	0
					Labetalol	22,056	265
						5672	45
				Lipophilic β-blockers	Labetalol	30648	490
					Propranolol	5672	45
						24,976	445
				Hydrophilic β-blockers	Atenolol	32,947	500
					Nadolol	26,470	423
					Sotalol	3401	39
						3076	38

3.1. β-blockers categorized according to the ESC classification

When the risk of asthma was assessed by categorizing the β-blockers according to the ESC classification [3] (Table 2, Fig. 1 A), one of the most surprising findings was that selective β_1-blockers demonstrated a higher signal for a risk of inducing asthma and asthma-like AEs in comparison to non-selective β-blockers. The findings suggested that individuals who use selective β_1-blockers are 15 % more likely to report asthma-related events compared to those who do not use these drugs (ROR: 1.15, 95 % CI: 1.08 to 1.23). Conversely, the ROR for non-selective β-blockers (ROR: 0.90, 95 % CI: 0.83 to 0.97) suggested a slightly decreased risk of asthma-related events, with a 10 % lower likelihood of reporting such events compared to those who were not using these medications. The 95 % CI below 1 confirms statistical significance, unexpectedly suggesting these drugs may be safer for asthmatic patients compared to selective β_1-blockers.

Notably, the ROR for α_1-and β-blockers (0.51, 95 % CI: 0.46 to 0.58) indicated a significantly reduced risk of asthma-related events. The probability of patients using these drugs reporting asthma or asthma-like AEs was 49 % lower than that of patients not using these drugs. The lower limit of 95 % CI was found to be well below 1, thereby confirming the robustness of this finding.

3.2. β-blockers categorized according to the Vashistha and Kumar classification

A clearer understanding of the specific safety profile of each drug in asthma was obtained by analyzing individual β-blockers according to the Vashistha and Kumar classification [4]. By examining each class separately, the analysis provided a detailed understanding of the risk profile of each class and even individual drugs within these classes (Table 2, Fig. 1B and 2).

The lowest signal for a risk of asthma and asthma-like AEs was observed in patients treated with dual α- and β-blockers (ROR 0.51, 95 % CI 0.46 to 0.58), hydrophilic β-blockers (ROR 0.71, 95 % CI 0.65 to 0.79), and lipophilic β-blockers (ROR 0.76, 95 % CI 0.69 to 0.84). This

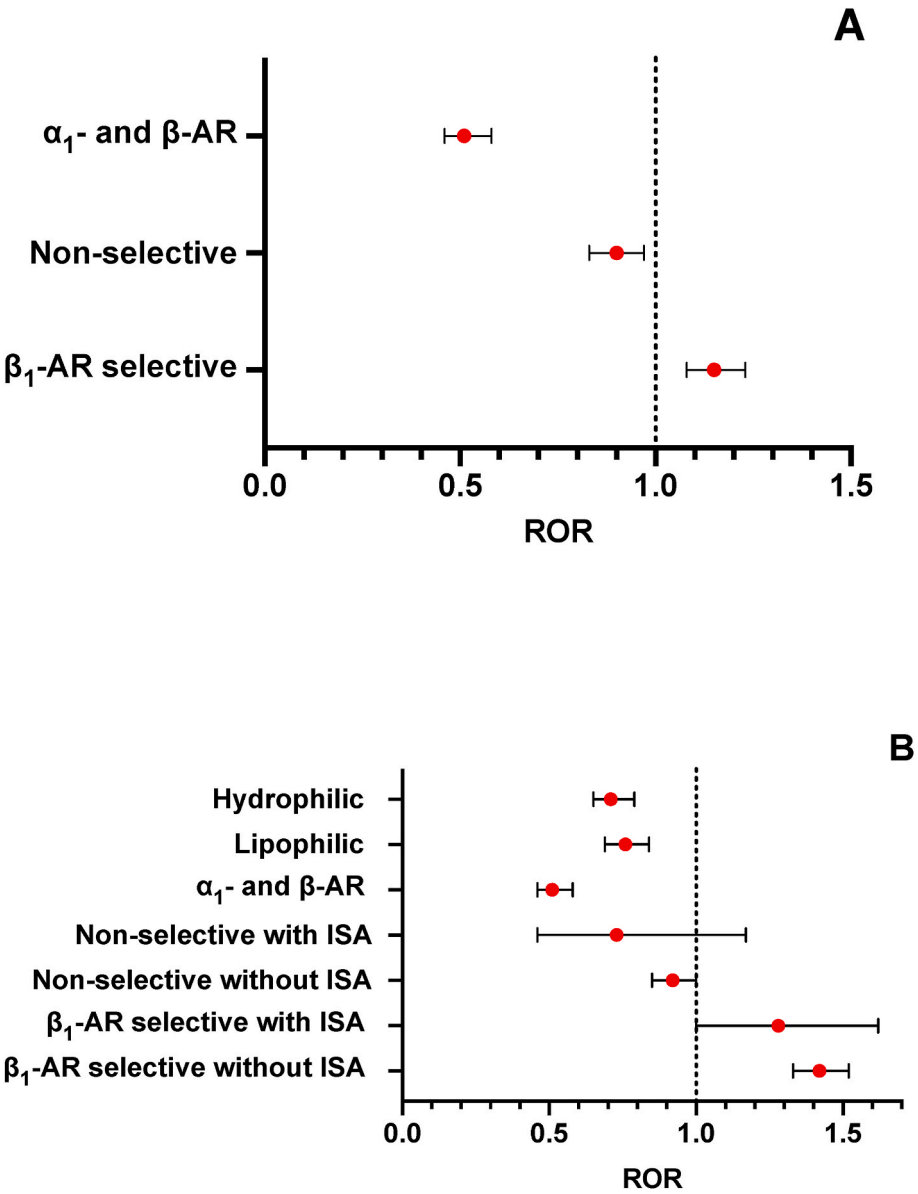

Fig. 1. – Disproportionality rate (ROR with 95 % CI) of asthma and asthma-like AEs registered in the FAERS database up to March 31, 2024 by β-blocker class according to the classification of the European Society of Cardiology (A) and that proposed by Vashistha and Kumar (B) compared with all other reports of AEs associated with β-blocker use.

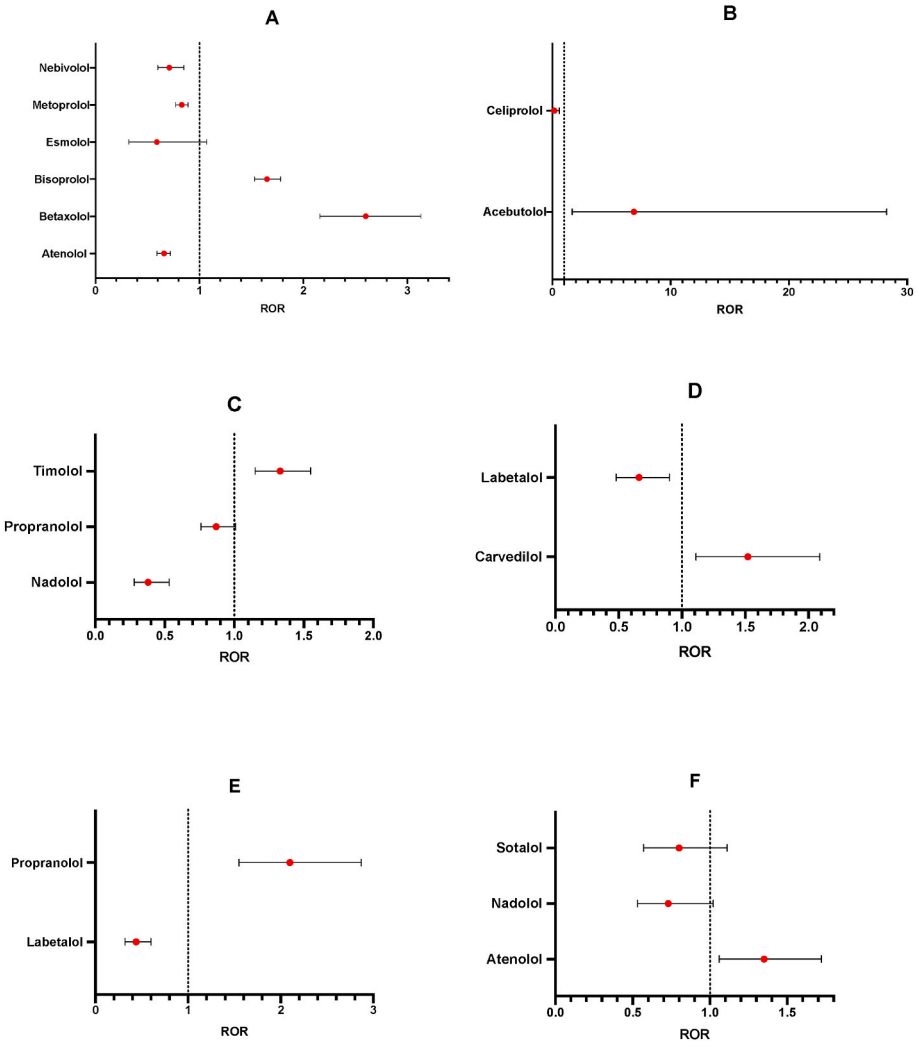

Fig. 2. – Disproportionality rate (ROR with 95 % CIs) of reports of asthma and asthma-like AEs recorded in the FAERS database up to March 31, 2024 for each β-blocker in the context of its class according to the Vashistha and Kumar classification, compared with all other reports of AEs associated with β-blocker use. A, Selective β_1-blockers without ISA; B, Selective β_1-blockers with ISA; C, Non-selective β-blockers without ISA; D, dual α_1-and β-blockers; E, lipophilic β-blockers; F, hydrophilic β-blockers.

reduction was highly statistically significant for the first two classes and moderate but statistically significant for lipophilic β-blockers.

Conversely, non-selective β-blockers without ISA showed a neutral to slightly protective effect (ROR 0.92, 95 % CI 0.85 to 1.00), but there was considerable variability in the signal for a risk of asthma-related events between the individual β-blockers, with timolol being able to increase this signal (ROR 1.33, 95 % CI 1.15 to 1.55), propranolol showing a neutral to slightly increased risk of asthma (ROR 0.87, 95 % CI 0.76 to 1.01), and nadolol having a low signal for a risk of asthma-related events (ROR 0.38, 95 % CI 0.28 to 0.53).

Non-selective β-blockers with ISA showed a trend towards a reduced risk (ROR 0.73, 95 % CI 0.46 to 1.17), although the lack of statistical significance due to the wide confidence interval suggests that their use should be approached with caution until more definitive data are available. It should be noted that only pindolol has had reports of asthma and asthma-like AEs.

The ROR of selective β_1-blockers with ISA was 1.42 (95 % CI 1.33 to 1.52), indicating a 42 % increased risk of asthma and asthma-like AEs. This is a statistically significant finding, suggesting a higher risk with these drugs. Selective β_1-blockers without ISA also showed an increased risk of asthma-related events (ROR 1.28, 95 % CI 1.00 to 1.62], with the upper limit of the 95 % CI indicating marginal statistical significance). In any case, there were some differences between the individual agents in both classes. In the selective β_1-blocker class without ISA, atenolol, esmolol, metoprolol and nebivolol showed a low risk of asthma-related events. Their RORs were 0.66, 95 % CI 0.59 to 0.72; 0.59, 95 % CI 0.32 to 1.07; 0.83, 95 % CI 0.77 to 0.89; and 0.71, 95 % CI 0.60 to 0.85, respectively. However, betaxolol (ROR 2.60, 95 % CI 2.16 to 3.13) and bisoprolol (ROR 1.65, 95 % CI 1.53 to 1.78) showed higher risks. Selective β_1-blockers with ISA also exhibited a mixed profile. Acebutolol showed a significantly higher risk of asthma-related events (ROR 6.90, 95 % CI 1.68 to 28.27), whereas celiprolol was associated with a very low ROR (0.15, 95 % CI 0.04 to 0.59).

It is important to note that a significant distinction emerged between labetalol (ROR 0.66, 95 % CI 0.48 to 0.90) and carvedilol (ROR 1.52, 95 % CI 1.11 to 2.09) with regard to their classification as dual α- and β-AR blockers. Furthermore, atenolol showed a signal for an increased risk of asthma (ROR 1.35 95 % CI 1.06 to 1.72) in comparison to sotalol (ROR 0.80, 95 % CI 0.57 to 1.11) and nadolol (ROR 0.73 95 % CI 0.53 to 1.02) within the context of hydrophilic β-blockers. However, it exhibited a notable reduction in asthma risk when considered with other selective β_1-blockers without ISA. In the context of lipophilic β-blockers, propranolol demonstrated a notable increase in the risk of asthma, as evidenced by the ROR (2.10, 95 % CI: 1.55–2.87). In contrast, as previously stated, when considered in the context of non-selective β-blockers without ISA, it exhibited a neutral to slightly increased signal for a risk of

asthma (ROR 0.87 95 % CI 0.76 to 1.01).

4. Discussion

The use of β-blockers, a cornerstone in the management of several CVDs including hypertension, angina, heart failure and arrhythmias, requires careful consideration in patients with asthma or other reactive airway diseases due to the potential risk of bronchoconstriction and exacerbation of respiratory symptoms. As the safety margin of these drugs is narrower than in COPD, the latest European Society of Hypertension guidelines recommend against using β-blockers to treat hypertension in patients with asthma [27].

Our analysis suggests that selective β_1-blockers without ISA should be avoided in asthma patients due to an appreciably elevated risk, whereas selective β_1-blockers with ISA should be used with caution due to a moderately elevated risk. However, this finding contrasts with the evidence from a meta-analysis of patients treated with long-term cardioselective β_1-blockers, which indicated no increased risk of exacerbation, death or asthma [28]. Analysis of pharmacovigilance databases was also very reassuring regarding the tolerability of selective β_1-blockers in asthmatics [28].

Nevertheless, one of the more intriguing aspects of our analysis was the emergence of a number of differences between the individual drugs in the two classes. To explain these differences, it could be argued that the pharmacology of cardioselective β_1-blockers suggests that none of the currently available β-blockers exhibit absolute selectivity for β_1-ARs [2]. While cardioselective β_1-blockers tend to demonstrate less pronounced β_2-AR antagonism compared to non-selective β-blockers, several of them show minimal preference for β_1-ARs over β_2-ARs [29].

The aforementioned hypothesis does not, however, account for the AEs observed with bisoprolol and acebutolol, which have been demonstrated to possess high affinity for β_1-ARs [2]. It is possible that additional pharmacological properties are involved [30]. Nebivolol is a highly selective β_1-AR blocker that also activates endothelial nitric oxide synthase. The potential role of nitric oxide in airway control is well established [31]. Celiprolol is a β_1-AR blocker with partial β_2-agonist activity, weak blockade of postjunctional α_1-ARs and prejunctional α_2-AR effects.

Non-selective β-AR blockers without ISA also demonstrated considerable variability. They are typically avoided in asthma patients due to the inherent risk of β_2-AR blockade in the airways, which may result in bronchoconstriction [2]. However, while timolol exhibited a markedly elevated risk of asthma-related events, nadolol showed a significantly reduced risk. Timolol is the most prescribed non-selective β-AR blocker eye drop [32]. It has greater selectivity for the β_2-AR than other commonly used non-selective β-AR blockers [32]. Nadolol is also an inverse agonist [33]. This implies that when it binds to β-ARs, it not only blocks the effects of adrenaline and noradrenaline, but also induces a reduction in basal receptor activity below the level observed in the absence of any ligand (agonist or antagonist), thereby shifting the balance of spontaneously active receptors towards the inactive state [34]. By attenuating basal receptor activity, inverse agonists may potentially elicit bronchodilation in the absence of external agonists [35]. There is evidence that nadolol has beneficial effects on airway hyperresponsiveness [36].

Although there is evidence that the infusion of propranolol is associated with a significantly higher risk of developing an asthma attack, predominantly in patients with a pre-existing history of asthma [37], our data indicate that this β-blocker, when considered within the broader category of non-selective β-AR blockers without ISA, exhibits a neutral to slightly increased risk of asthma-related events. It is noteworthy that the administration of propranolol in patients with hypertension and anxiety was associated with increased β_2-AR bronchodilating function, which is contrary to the anticipated outcome [38]. It can be reasonably deduced that propranolol may not fully block the activity of β_2-ARs, as it has the potential to induce inverse agonism [2]. In a rat model of passive cigarette smoking, Guo and colleagues observed that one-month course of propranolol treatment enhanced β_2-AR-mediated relaxation [39]. Concurrently, it attenuated the contractile response to acetylcholine by reducing noradrenaline. In contrast, metoprolol, which is a selective β_1-AR blocker with ISA, reduced blood catecholamine levels but did not increase airway smooth muscle responsiveness to β_2-AR agonists. A single-center, randomized, double-blind, placebo-controlled trial conducted in the United Kingdom revealed that patients with chronic asthma who received 80 mg/d of propranolol did not experience any AE [40,41]. However, propranolol is associated with a higher risk of asthma-related problems if it is classified as a lipophilic β-blocker. Being lipophilic, propranolol is capable of crossing cell membranes and affecting lung tissue, which may result in a worsening of asthma symptoms. Conversely, β-blockers with a hydrophilic profile, such as sotalol and nadolol, demonstrated a lower risk, potentially due to their limited penetration into lung tissue, which in turn leads to a diminished likelihood of bronchoconstriction.

There was little data on non-selective β-AR blockers with ISA in the FAERS database, but these drugs should generally be avoided in asthma patients as they can worsen respiratory symptoms.

The dual α- and β-AR blockers demonstrated a significantly lower risk of AEs, which may be attributed to their ability to cause vasodilation and reduce airway resistance. However, carvedilol exhibited a higher risk, whereas labetalol demonstrated a comparatively lower risk. The differential risk profiles of carvedilol and labetalol for asthma-related AEs can be ascribed to their distinct pharmacological properties. The higher risk of carvedilol can be attributed to its significant β_2-AR antagonism [25], which can lead to bronchoconstriction. Conversely, the lower risk of labetalol is may be due to its balanced adrenergic blockade. It exhibits a higher affinity for α_1-ARs compared to β_1-or β_2-ARs and a lower affinity for β_2-ARs than carvedilol [29,42]. This difference should be carefully considered when selecting a dual α- and β-AR blocker for patients with asthma or those at risk of respiratory complications.

In any case, when interpreting the results of our analysis, it is important to recognize the limitations associated with the FAERS data. Thus, although the results of this study are compelling, they do not provide conclusive evidence that β-blockers lead to asthma-related AEs.

The FDA itself has highlighted that relying on FAERS data alone is an inadequate approach for determining the safety profile of a drug [16,43]. Indeed, there is currently no definitive evidence linking the reported event, whether an AE or a medication error, to the drug in question. This is because the FDA does not require definitive evidence establishing a causal link between a product and an event. AE reports are voluntarily submitted by healthcare providers, consumers and manufacturers, which may result in false, exaggerated, inaccurate, incomplete or delayed information. The information provided in these reports is limited to the observations and perspectives of the reporters. Although it is recommended that both consumers and healthcare professionals report any AEs, it is essential to recognize that such reactions may be linked to the underlying disease being addressed, may result from other medications taken simultaneously, or may occur due to various other reasons. In any case, reports are often not sufficiently detailed for accurate evaluation, nor are they subject to medical review, which increases the risk of misclassification.

Furthermore, it is not possible to establish a definitive causal relationship between a drug and an AE based on FAERS data, as the database lacks the comprehensive patient population data necessary for such an analysis. Additionally, not all AEs or medication errors associated with a given product are reported to the FDA and, conversely, duplicate reporting occurs when both consumers and sponsors submit the same report.

These limitations preclude the precise calculation of the incidence of AEs and only approximate estimates based on signal strength (ROR value) can be derived.

We must also highlight that the analysis is subject to inherent bias

due to the spontaneous reporting mechanism of FAERS. The likelihood of reporting can be influenced by various factors, such as the time a product has been on the market and the level of media coverage an event receives [44]. First, the number of reports tends to increase in the first two years after a drug is launched and then decreases [45], a phenomenon known as the Weber effect, although this pattern is not always consistent [46]. Table 3 shows the year of the first inclusion of AE reports in the FAERS database for each of the β-blockers analyzed, divided into classes according to the Vashistha and Kumar classification. Signal numbers and scores can also fluctuate in the years following a drug's launch, with the number of signals supported depending on the period after launch [47]. The reporting of AEs tends to accelerate when an AE associated with a drug is the subject of media attention. This phenomenon, known as the notoriety effect [48], can result in the reporting of similar cases involving other drugs in the same class, a process known as the ripple effect [48]. Conversely, signal values can be suppressed when many reports link the same AE to several drugs, known as the masking or cloaking effect [49]. It is important to give these dynamics careful consideration, particularly in the context of newly launched drugs, and to analyze the temporal context in pharmacovigilance studies [50].

Nevertheless, apart from these important considerations, our analysis of the FAERS database indicates that the risk of asthma-related AEs associated with different classes of β-blockers is subject to variation. This variability underscores the importance of selecting an appropriate β-blocker based on the individual patient profile, particularly in those with underlying respiratory disease.

5. Conclusion

The Global Initiative for Asthma report mentions the use of β-blockers in patients with asthma, highlighting that these agents, even those used for ophthalmic purposes, can cause bronchospasm and may even be implicated in some asthma deaths, but also that they are useful in the treatment of CVD, for example by reducing mortality in asthmatics hospitalized for an acute coronary event [51]. It therefore recommends that the use of β-blockers in asthma patients should be on a case-by-case basis and always under the supervision of a specialist. Other clinical guidelines for the treatment of asthma around the world also provide recommendations. The Japanese guidelines for adult asthma suggest that avoidance is the rule, but the risk/benefit of β_1-selective blockers should be carefully evaluated in patients with comorbid CVD [52]. Conversely the British Thoracic Society's guideline recommends that all β-blockers, including eye drops, be contraindicated [53] and the guideline of the National Heart, Lung, and Blood Institute in the USA advises avoiding nonselective β-blocker use in patients with asthma [54].

Table 3
– The year of the first inclusion of AE reports in the FAERS database for each of the β-blockers analyzed, divided into classes according to the Vashistha and Kumar classification [4].

Class	*β-blocker*	Year of the first inclusion of AE reports in the FAERS database
Selective β_1-AR blockers without ISA	Atenolol	1981
	Betaxolol	1985
	Bisoprolol	1992
	Esmolol	1987
	Metoprolol	1978
	Nebivolol	1998
Selective β_1-AR blockers with ISA	Acebutolol	1985
	Celiprolol	1997
Non-selective β-AR blockers without ISA	Nadolol	1980
	Propranolol	1969
	Timolol	1996
Non-selective β-AR blockers with ISA	Alprenolol	2011
	Bopindolol	2000
	Pindolol	1982
Dual α_1- and β-AR blockers	Bucindolol	2005
	Carvedilol	1995
	Labetalol	1984
Lipophilic β-blockers	Labetalol	1984
	Propranolol	1969
Hydrophilic β-blockers	Atenolol	1981
	Nadolol	1980
	Sotalol	1989

ISA, intrinsic sympathomimetic activity.

These recommendations are conflicting. This can lead to confusion among prescribing physicians and inappropriate denial of treatment to patients with CVD and concomitant asthma or COPD. For example, a substantial proportion of patients with heart failure with reduced ejection fraction (at least one-quarter to one-third) also present with respiratory conditions such as asthma or COPD [55]. Despite the evident clinical indications and the proven benefits of β-blockers in these patients, some individuals with asthma are being denied this treatment due to the recommendations set forth in guidelines. However, the presence of asthma or COPD should not preclude the use of β-blockers.

The decision to prescribe β-blockers to asthmatic patients must be based on a thorough assessment of their clinical characteristics and the severity of their asthma. This evaluation should include spirometry with bronchodilator reversibility testing and an evaluation of the degree of airway hyperresponsiveness. Furthermore, the potential advantages of β-blockers in the context of CVD warrant consideration. In any case, it is essential to weigh the potential benefits of β-blockers for CVD against the potential risk of worsening respiratory symptoms, particularly in those with known airway disorders in order to determine whether the benefits outweigh the risks. Obviously, the choice of the β-blocker should be linked to the best safety profile [56].

Given the lack of specific guidelines on the use of β-blockers in patients with asthma and CVD, the results of our study, which complement and extend those from the VigiBase analysis [11], may be useful in this regard.

Although we acknowledge the important limitations of our study and that the signals detected by disproportionality analysis are, in any case, only candidate risks, we reiterate, as others have done [11], that there is significant variability in the risk of asthma-related asthma between the different classes of β-blockers and, within each class, with the individual β-blocker.

Our data derived from the use of β-blockers in real life suggest that in patients with asthma or at risk of asthma, esmolol, metoprolol, nebivolol and nadolol should be preferred because of their lower risk profile, whereas betaxolol, bisoprolol, acebutolol, propranolol and timolol should be avoided because of their higher risk of inducing asthma-related events. In patients without a known airway disorder, the individual risk profiles should be considered to avoid potential exacerbation of latent or undiagnosed asthma (Table 4). Drugs such as atenolol and bisoprolol should be used with caution, particularly in patients with a history or symptoms suggestive of reactive airway disorder. However, it should be noted that a recent network meta-analysis of randomized controlled trials found that oral timolol and intravenous propranolol increased asthma attacks, regardless of asthma history, whereas celiprolol, bisoprolol, practolol and sotalol decreased, them [37].

Also the discrepancy between our analysis and what is reported in the literature on bisoprolol should be noted. Bisoprolol does not appear to be associated with a significantly increased risk of asthma exacerbations in patients with mild or moderate asthma [57]. However, it has also been shown that bisoprolol 10 mg for 6 weeks significantly reduced FEV_1 in patients with stable angina and moderate persistent bronchial asthma [58]. Furthermore, the VigiBase analysis revealed that bisoprolol was the third most prevalent cardioselective β_1-blocker, following metoprolol and atenolol, in relation to the occurrence of asthma episodes and bronchospasm [11].

CRediT authorship contribution statement

Mario Cazzola: Writing – original draft, Visualization,

Table 4
– β-blockers that may be considered safer for asthmatic patients and those that should be avoided, divided into classes according to the Vashistha and Kumar classification [4].

Class	ROR of the class	β-Blockers (Indicated/ Lower Risk)	β-Blockers (Contraindicated/ Higher Risk)
Selective β1-AR blockers without ISA	1.28	Atenolol (ROR 0.66), Esmolol (ROR 0.59), Metoprolol (ROR 0.83), Nebivolol (ROR 0.71)	Betaxolol (ROR 2.60), Bisoprolol (ROR 1.65)
Selective β1-AR blockers with ISA	1.42	Celiprolol (ROR 0.15)	Acebutolol (ROR 6.90),
Non-selective β-blockers without ISA	0.92	Nadolol (ROR 0.38), Propranolol (ROR 0.87)	Timolol (ROR 1.33)
Non-selective β-blockers with ISA	0.73		Pindolol
Dual α_1- and β-AR blockers	0.51	Labetatol (ROR 0.66)	Carvedilol (ROR 1.52)
Lipophilic β-blockers	0.76	Labetatol (ROR 0.44)	Propranolol (ROR 2.10)
Hydrophilic β-blockers	0.71	Nadolol (ROR 0.73), Sotalol (ROR 0.80)	Atenolol (ROR 1.35)

ISA, intrinsic sympathomimetic activity; ROR, reporting odds ratio.

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