REVIEW
ASTHMA

The safety of cardioselective β_1-blockers in asthma: literature review and search of global pharmacovigilance safety reports

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ABSTRACT

Introduction: Beta-blockers are key in the management of cardiovascular diseases but blocking airway β_2-receptors can cause severe and sometimes fatal bronchoconstriction in people with asthma. Although cardioselective β_1-blockers may be safer than non-selective β-blockers, they remain relatively contraindicated and under-prescribed. We review the evidence of the risk associated with cardioselective β_1-blocker use in asthma.

Methods: We searched "asthma" AND "beta-blocker" in PubMed and EmbaseOvid from start to May 2020. The World Health Organization (WHO) global database of individual case safety reports (VigiBase) was searched for reports of fatal asthma or bronchospasm and listed cardioselective β_1-blocker use (accessed February 2020). Reports were examined for evidence of pre-existing asthma.

Results: PubMed and EmbaseOvid searches identified 304 and 327 publications, respectively. No published reports of severe or fatal asthma associated with cardioselective β_1-blockers were found. Three large observational studies reported no increase in asthma exacerbations with cardioselective β_1-blocker treatment. The VigiBase search identified five reports of fatalities in patients with pre-existing asthma and reporting asthma or bronchospasm during cardioselective β_1-blocker use. Four of these deaths were unrelated to cardioselective β_1-blocker use. The circumstances of the fifth death were unclear.

Conclusions: There were no published reports of cardioselective β_1-blockers causing asthma death. Observational data suggest that cardioselective β_1-blocker use is not associated with increased asthma exacerbations. We found only one report of an asthma death potentially caused by cardioselective β_1-blockers in a patient with asthma in a search of VigiBase. The reluctance to use cardioselective β_1-blockers in people with asthma is not supported by this evidence.

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There are no published reports of asthma deaths associated with cardioselective β1-blocker use and only one possible death in WHO VigiBase reports. Despite widespread concerns, asthma deaths associated with cardioselective β1-blockers are very rare. https://bit.ly/3if6TuY

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Introduction

Cardiovascular diseases are common among people with asthma with some adjusted models showing approximately double the risk of coronary heart disease and stroke [1–3]. In one prospective cohort study people with asthma had a 60% higher risk of cardiovascular events in a 10-year follow-up [4]. β_2-agonist medications are fundamental in the current management of both asthma and other obstructive lung diseases such as COPD [5, 6]. On the other hand, β-antagonists, more commonly known as β-blockers, are a cornerstone of management of cardiovascular disease such as heart failure and after myocardial infarction [7]. Although these treatments primarily target different receptor subtypes (β_1 *versus* β_2), concern about the specificity of the available drugs for these receptor subtypes has led to uncertainty about the management of patients with both obstructive airways and cardiovascular diseases.

First-generation non-selective β-blockers caused alarm with reports of severe bronchospasm and fatalities, in some instances after only ocular administration [8, 9]. This led to β-blockers being absolutely contraindicated in asthma. "Cardioselective" β_1-blockers were developed to preferentially block cardiac β_1-adrenoceptors with less activity at airway β_2-receptors. However, this selectivity is not complete, and concerns about the safety of cardioselective β_1-blockers in patients with airways disease persist. Observational studies suggest that using cardioselective β_1-blockers to treat cardiovascular disease is not associated with increased exacerbations in COPD [10, 11]. Guidelines support the use of cardioselective β_1-blockers in COPD where there is a clear indication for their use [12, 13]. However, a recent randomised placebo-controlled trial of the cardioselective β_1-blocker metoprolol in patients with COPD was stopped early due to concerns about a greater number of severe exacerbations in the metoprolol group [14]. The safety of cardioselective β_1-blockers to treat cardiovascular disease in asthma remains unclear.

Many clinicians remain reluctant to use cardioselective β_1-blockers in people with asthma [15, 16]. As a result, large numbers of people with asthma may be denied the cardiovascular benefits of β-blocker medications. It is also recognised that it can be difficult to distinguish between asthma and COPD and other comorbid disease in elderly people further adding to the challenges of appropriate medication prescribing [17, 18].

This narrative literature review first considers the pharmacology of cardioselective β_1-blockers with respect to their use in asthma. We then review the published evidence of cardioselective β_1-blocker use in asthma and also look at the WHO global database of individual case safety reports (VigiBase) for any details of reported asthma-related fatalities with cardioselective β_1-blocker use [19].

Understanding the pharmacology

β-adrenoceptors

There are three known subtypes of β-adrenoceptor: β_1-, β_2- and β_3-adrenoceptors. $Beta_1$-adrenoceptors are found predominantly in the heart where the β_1:β_2 adrenoceptor ratio is around 7:3 and catecholamine stimulation leads to positive ionotropic and chronotropic effects [20]. $Beta_2$-adrenoceptors are found predominantly in bronchial smooth muscle but also in heart, skeletal muscle and peripheral blood vessels [21]. $Beta_3$-adrenoceptors are found primarily in adipose tissue and the bladder but are also found in the cardiac atria and peripheral vasculature where they are involved in mediation of metabolic effects [22]. The relevance of β_3-blockade to cardiovascular and respiratory health is not clear but as β_3-receptors do not seem be involved in airway smooth muscle function they will not be considered further in this review [22].

Relative β_1-selectivity

Early "non-selective" β-blockers (such as propranolol, sotalol and timolol) bind and inhibit both β_1- and β_2-adrenoceptors. Cardioselective β_1-blockers (such as metoprolol, bisoprolol and atenolol) have a greater inhibition of β_1-adenoceptors than β_2-adrenoceptors. Some cardioselective β_1-blockers have less β_2-blocking effect than others [23–25]. This has been quantified *in vitro* with the relative affinity for β_1-adrenoceptors:β_2-adrenoceptors ranging from 13.5 (bisoprolol) to 2.3 (metoprolol) (table 1) [26]. The selectivity of cardioselective β_1-blockers is also dose dependent: with increasing doses of any cardioselective β_1-blocker the selectivity becomes less marked [26, 27].

Intrinsic sympathomimetic activity and inverse agonism

Unoccupied β-adrenoceptors have a baseline level of activity. Most β-blockers not only prevent the binding of catecholamines, but also influence the baseline level of activity of the adrenoceptor [28]. β-blockers that cause an increase in baseline receptor activity on binding are described as having intrinsic sympathomimetic activity (ISA), also sometimes called weak partial agonist activity (figure 1) [29]. Examples of β-blockers with ISA include labetalol and acebutolol (table 1). A meta-analysis of β-blocker treatment after myocardial infarction found that β-blockers with ISA were associated with a higher

TABLE 1 Commonly used β-blockers and their relative β-adrenoceptor selectivity and partial agonist and inverse agonist properties

	Cardioselective β_1-blockers (relative selectivity of β_1 *versus* β_2)	Nonselective β-blockers (relative selectivity of β_1 *versus* β_2)
Partial agonist/ISA	Acebutolol (2.4[#])	Labetalol (2.5[#])
	Practolol (>14.1[#])	Alprenolol (16.2[#])
Inverse agonist	Metoprolol (2.3[#], 6.0[¶])	Carvedilol (4.5[#])
	Atenolol (4.7[#], 5.7[¶])	Propranolol (8.3[#])
	Bisoprolol (13.5[#], 19.6[¶])	Sotalol (12.0[#])
	Nebivolol (40.6[¶])	Nadolol (23.4[#])
		Timolol (25.7[#])

A relative selectivity ratio of 1 demonstrated equal activity at both β_1- and β_2-adrenoceptors. ISA: intrinsic sympathomimetic activity. [#]: according to Baker [26] using cell lines expressing human adrenoceptors; [¶]: according to Ladage *et al.* [49] in their review figure.

all-cause mortality compared to β-blockers without ISA [30]. Current guidelines suggest avoiding β-blockers with ISA for treating cardiovascular disease [31].

β-blockers that cause a decrease in baseline receptor activity are described as inverse agonists, also sometimes called negative intrinsic activity [28, 32, 33]. Examples of inverse agonists include metoprolol, bisoprolol, atenolol, nebivolol, carvedilol, nadolol, propranolol and timolol.

Temporal effect

A pharmacokinetic temporal phenomenon of β-blockers is well established in heart failure with initial negative inotropic effects causing lethargy and low blood pressure usually improving within a week of treatment. To avoid these unwanted symptoms, clinicians are advised to start with a low dose and slowly up-titrate β-blocker therapy ("start low, go slow" approach) [12]. In reactive airways disease, single doses of both cardioselective and non-selective β-blockers have been consistently found to decrease the forced expiratory volume in 1 s (FEV_1) compared to placebo [34]. Pooled results in a meta-analysis by Salpeter *et al.* [34] suggest that this initial drop in FEV_1 resolves over a few days or weeks.

Interactions with β-agonist therapy

In a meta-analysis of people with asthma, the response to β-agonist therapy, as measured by FEV_1 increase from baseline, showed a mean 16% increase after a single dose of a cardioselective β_1-blocker compared to a 23% increase after placebo and a 1% decline after a non-selective β-blocker [24]. However, the

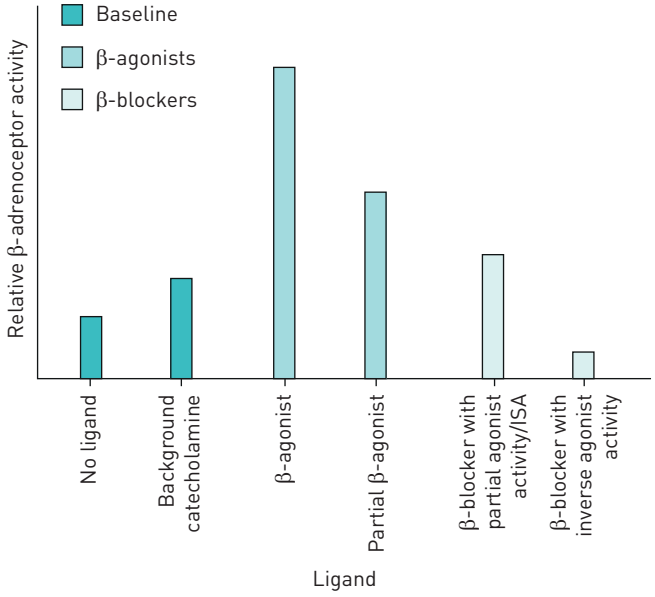

FIGURE 1 Pictorial representation of β-adrenoceptor activity in the presence of background catecholamines, β-agonists and β-blockers. ISA: intrinsic sympathomimetic activity.

bronchodilator response to β-agonist therapy is maintained during continuous treatment with cardioselective β_1-blockers [35–37].

Methods

Review of cardioselective β_1-blockers in asthma

We reviewed evidence of whether use of cardioselective β_1-blockers altered safety outcomes among people with asthma, as defined by decrease in FEV_1, asthma exacerbations, hospital admissions and fatalities. A search of the terms "asthma" AND "beta-blockers" was undertaken in the databases of biomedical published literature: PubMed and EmbaseOvid. In EmbaseOvid we used "asthma" with a focus AND "beta adrenergic receptor blocking agent" with a focus and "beta-blocker" as a keyword. In PubMed "asthma" AND "beta adrenergic blocking agent" were both recognised terms for medical subject headings, MeSH. Both searches were limited to results with abstracts and English language. PubMed and EmbaseOvid were searched on 24 May 2020, and 304 and 237 publications were identified, respectively. MB selected studies that were relevant for asthma and cardioselective β_1-blocker use. The inclusion criteria included studies of clinical impact of an oral, intravenous or topical cardioselective β_1-blocker on people with a clinical diagnosis of asthma. Exclusion criteria included cell-based studies, inhaled β-blocker use only and studies of non-selective β-blockers only. These studies were analysed along with further searching of the reference lists of these papers. The results are summarised in table 2 with individual studies detailed in the supplementary material. PRISMA is an evidenced-based minimum set of items for reporting in systematic reviews and meta-analyses; the PRISMA flow diagram is shown in figure 2. Data were collected on the type of study, the number of participants, the specific β_1-blocker used, impact on FEV_1, exacerbations and number of fatalities.

Search of World Health Organization global database for individual case safety reports

We also undertook a search of global pharmacovigilance safety reports. VigiBase holds reports of over 20 million suspected adverse drug reactions submitted from national pharmacovigilance centres since 1968 with currently 140 countries contributing [19]. VigiBase is held by the Uppsala Monitoring Centre. Any healthcare provider or patient can submit a report.

VigiBase (accessed February 2020) was interrogated for reports of asthma-related fatalities occurring in patients taking cardioselective β_1-blockers up to December 2019. The anatomical, therapeutic, chemical classification was used to identify reports with cardioselective β_1-blockers as suspect medicines. The Medical Dictionary for Drug Regulatory Authorities was used to identify reports that included as suspected adverse reactions categorised as asthma, bronchospasm and asthma crisis (table 3). From these reports, those with a fatal outcome were included for assessment. MB and RS independently reviewed the details of all 18 fatal cases. Reports with a documented history of asthma or COPD or concomitant medicines that suggested pre-existing asthma or COPD were identified (table 4).

Results

Published reports

The 127 publications that were identified in this review are summarised in table 2 and detailed in the supplementary material. Key reports are discussed below.

A meta-analysis by Salpeter *et al.* [34] (updated in 2011) included 19 single-dose and 10 continued-dose placebo-controlled randomised trials in reactive airways disease. They found no difference in FEV_1, respiratory symptoms or incidence of inhaler use with continued cardioselective β_1-blocker exposure [34].

TABLE 2 Summary studies included in review

Type of study	Publications found in the search and considered in the review
Meta-analysis or systematic review	4 (3 meta-analyses, 1 systematic review)
Randomised controlled trial	53 (765 participants in total of which 682 people with asthma and 83 with reversible airways disease)
Non-randomised trial	31 (106 915 participants in total of which 63 763 were asthma alone, 43 152 were asthma or COPD)
Literature review	12 (9 asthma, 1 obstructive lung disease, 1 reversible airways disease and 1 on adverse reactions to β-blockers)
Other	27 (8 case reports, 7 murine models, 7 guinea pig models, 4 opinion articles, 1 questionnaire)

Studies that could be allocated to two categories are included in the highest tier (for example, meta-analysis above non-randomised trial).

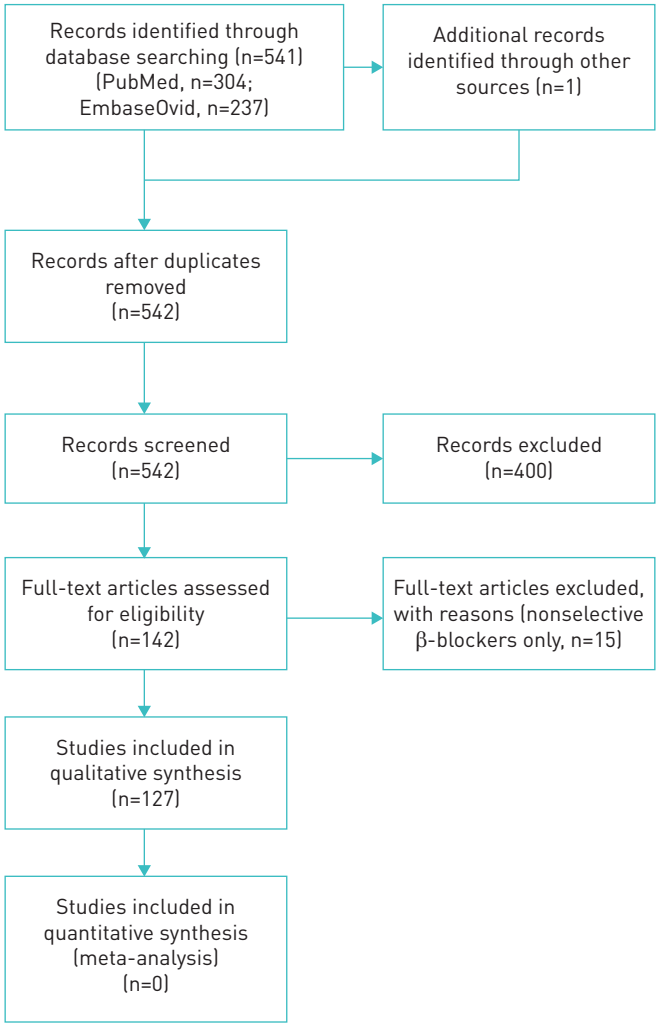

FIGURE 2 PRISMA flow diagram of articles considered in the literature review.

Morales *et al.* [38] undertook a meta-analysis and population-based study of topical β-blockers (delivered as eye drops) in people with asthma. The meta-analysis showed that eye drops have similar effects to systemic administration of β-blockers, with a drop in FEV_1 from baseline for non-selective β-blockers (11% lower) and cardioselective β_1-blockers (6% lower). The population-based nested case–control study, which included 4865 people with asthma and ocular hypertension, found a 4.8-fold increase in moderate

TABLE 3 Summary of VigiBase total and fatal reports for cardioselective β_1-blockers with asthma or bronchospasm as reported suspected adverse reactions from start to December 2019

Cardioselective β_1-blockers	Reactions coded as asthma		Reactions coded as bronchospasm	
	Total	Of which were fatal	Total	Of which were fatal
Metoprolol	286	4	322	6
Atenolol	141	1	385	3
Bisoprolol	95	0	108	1
Nebivolol	29	0	32	0
Betaxolol	18	0	86	0
Acebutolol	5	1	30	0
Celiprolol	6	0	41	1
Landiolol	1	0	0	0
Esmolol	1	0	11	1
Esatenolol	1	0	0	0

TABLE 4 VigiBase data: clinical details of all five reported fatalities with cardioselective β1-blocker use in patients with an adverse drug reaction of asthma or bronchospasm who had evidence of pre-existing asthma

Report	Year	Cardioselective β_1-blockers				Reported adverse drug reactions
		Name	Dose	Duration	Indication	
1	1985	Metoprolol	Not stated	1.1 years	Not stated	Asthma (general anaesthetic medications listed)
2	2017	Metoprolol	100 mg by mouth once daily	Not stated	Hypertension	Asthma, sepsis, pneumonia, emphysema, decreased immune response, renal cancer
3	2018	Acebutolol	600 mg by mouth once daily	Not stated	Not stated	Asthma, acute MI, cardiogenic shock, metastatic renal cancer
4	2009	Atenolol	50 mg once daily	Not stated	Not stated	Bronchospasm, acute MI, cardiac failure, aspiration, sudden cardiac death
5	2019	Atenolol	Not stated	11 years	Hypertension	Asthma, viral pneumonia (immunosuppressant medicines listed)

MI: myocardial infarction.

asthma exacerbations after ocular single-dose non-selective β-blocker use. There was no significant increase in risk after continuous non-selective β-blocker administration or single or continuous cardioselective β_1-blocker use.

Another systematic review by the same group included 32 studies of people with asthma given single doses of cardioselective β_1-blockers (330 patient exposures) and also non-selective β-blockers (301 patient exposures) [24]. They found that FEV_1 was decreased after a single dose of both cardioselective β_1-blockers (7% lower than baseline) and non-selective β-blockers (10% lower than baseline). As mentioned above, the response to β-agonist after cardioselective β_1-blockers (FEV_1 16% increase from baseline) was better than the response after non-selective β-blockers (1% decrease) but lower than the response to β-agonist after placebo (23% increase).

A randomised placebo-controlled crossover trial of 19 adults with mild or moderate asthma given bisoprolol daily for a minimum of 2 weeks found no difference in exacerbations between the groups [37]. Rescue β-agonist therapy after a controlled bronchoconstriction was also non-inferior with bisoprolol treatment.

Non-randomised studies also did not find an association between cardioselective β_1-blocker use and asthma exacerbations. A nested case–control study in a general practice database cohort of 35 502 patients with both asthma and cardiovascular disease found no evidence of a higher risk of moderate or severe asthma exacerbations among 5017 patients who had been prescribed cardioselective β_1-blockers compared to controls matched for age, sex and duration of follow-up [39]. However, this study found a higher risk of exacerbations with the prescription of non-selective β-blockers [39]. Similar findings were made in another nested case–control study of 10 934 people admitted with a first asthma exacerbation requiring corticosteroids compared to 74 415 controls [40]. A 1-year cohort study of 8390 US army veterans who had asthma or COPD and concurrent heart disease found that there was no difference in hospital admissions related to asthma or COPD among the 2810 who had been treated with cardioselective β_1-blockers compared to 5293 receiving only non-β-blocker heart medications [41]. Another observational study in the USA investigated 1062 Medicare beneficiaries aged over 65 with cardiovascular disease and COPD/asthma and found that half were on β-blockers but that their use did not appear to influence the occurrence of cardiac events, pulmonary events or death [42].

Nebivolol is a highly cardioselective β_1-blocker with inverse agonist properties. A non-randomised study of patients with chronic heart failure with concomitant obstructive airways disease treated with nebivolol, up-titrated over 24 weeks, included 13 asthmatics who showed no significant decrease in FEV_1 at the final 24-week visit [43].

In a slightly different clinical context, Sultana *et al.* [44] suggested that the use of β-blockers was a risk factor for exacerbation related to thunderstorm asthma but grouped non-selective and cardioselective β_1-blockers together. Among users of cardioselective β_1-blockers there was no statistically significant increase in risk.

We found no published reports of fatalities or severe bronchospasm associated with use of cardioselective β_1-blockers in asthma. By contrast we found six separate case reports of severe or fatal bronchospasm following non-selective β-blocker use in asthmatics.

The National Review of Asthma Deaths investigating the cause of 195 asthma deaths in the UK between 2012 and 2013 reported four deaths due to "Drugs (nonsteroidal anti-inflammatory drugs, aspirin or beta-blockers)" [45]. Unfortunately, this provided no details on whether any of these deaths were associated with cardioselective β_1-blockers, and we have been unable to obtain this information from the authors of the report.

VigiBase reports

Table 3 shows the number of reports that included asthma or bronchospasm as an adverse reaction and a cardioselective β_1-blocker as a suspect medicine. Of the 583 reports of asthma and 1015 reports of bronchospasm a total of six and 12 fatalities were identified. Five reports noted use of inhalers suggesting pre-existing obstructive lung disease (we could not adequately differentiate between asthma or COPD, but all have been included as potentially having asthma), four reported asthma as an adverse reaction and one referenced bronchospasm (table 4). Four of these cases listed other medicines that were suspected to have caused or contributed to the adverse reactions as well as the β-blocker. A range of concomitant conditions was reported including: sepsis, viral pneumonia, cardiac disorders and renal cancer. Bronchospasm did not appear to be the primary cause of death, and therefore these four deaths were deemed unlikely to be caused by cardioselective β_1-blocker use. One report (Report 1 in table 4) included little information other than naming medications (salbutamol, beclomethasone, metoprolol and also general anaesthetic agents started on the same day), and the only clinical reaction reported was asthma. While the reaction could have been caused by the anaesthetic drugs, it is possible that this death may have been related to β-blocker use. Hence, we identified this as the single potential asthma fatality in VigiBase related to the use of a cardioselective β_1-blocker in a patient with asthma.

There were also 13 fatalities without evidence of pre-existing asthma in the reports but with an adverse drug reaction coded as asthma (n=2) or bronchospasm (n=11) (table 3). It is possible that these people had undiagnosed asthma and only developed symptoms when they took β-blockers or simply that known pre-existing asthma was not recorded in the reports. Of these 13 fatalities four of these patients had respiratory-related deaths and all four were associated with metoprolol. Four of the 13 were considered non-respiratory. There was insufficient information in the reports for the remaining five patients to determine the likely cause of death.

Discussion

We found no evidence that treatment with cardioselective β_1-blockers, given systemically or topically as eye drops, causes an increase in moderate or severe asthma exacerbations, and we found no reports of fatalities in people with asthma using cardioselective β_1-blockers in the published literature. We found only one potential asthma death caused by cardioselective β_1-blockers in the international pharmacovigilance database (VigiBase), and interpretation of the cause of death in this case was limited by insufficient information. These findings suggest that asthma-related deaths caused by cardioselective β_1-blockers are likely to be very rare.

A major limitation of this review is publication and reporting bias. It is also possible that these adverse effects are so rare because clinicians have avoided cardioselective β-blockers in patients with asthma, in particular in those with severe or problematic asthma. We do not know how many asthmatics are prescribed cardioselective β_1-blockers worldwide, but Morales *et al.* [39] found that 14% of a UK population with diagnosed asthma and cardiovascular disease in a general practice database were prescribed cardioselective β_1-blockers. Among a general practice data set of 1071 people with asthma and cardiovascular disease from the USA, 9% of those aged between 60 and 69 years had been prescribed β-blockers in the previous year [46]. In light of this, it seems that to have only one fatality that can potentially be linked to use of cardioselective β_1-blockers in asthma in the VigiBase database is reassuringly low.

A strength of this review is the use of VigiBase data in addition to the published literature. Given that β-blockers have been available for many years, it is reasonable to expect that any major concerns would turn up on such a reporting system. However, as the VigiBase information comes from a variety of sources, the probability that a suspected adverse effect is drug-related is not the same in all cases. Reports can be submitted by any person – not necessarily a clinician – and most reports of fatal asthma or bronchospasm submitted to VigiBase had minimal clinical information making the correct assignment of the likely association between cardioselective β_1-blocker use and asthma fatalities difficult. This variation in clinical information also limited the VigiBase analysis, as we were unable to explore other outcomes such as hospitalisation. Another limitation of the VigiBase data is that of under-reporting, which as a result of fear of litigation, lack of awareness of the reporting system or even the assumption that bronchospasm following β-blocker administration was expected, may prevent some cases from being reported.

Implications for clinical practice

Guidelines have shifted from previously stating that all β-blockers are contraindicated in asthma to recommending that prescription of cardioselective β_1-blockers should be done under specialist supervision on a "case-by-case basis" [5]. Nevertheless, concerns over the safety of cardioselective β_1-blockers in asthma persist, and this remains a difficult area for prescribers, resulting in underutilisation of β-blockers in people with asthma [47]. Clinically there must be a balance of risk and benefit behind each decision to treat a person with asthma with a β-blocker as outlined in the recent report from the Global Initiative for Asthma (GINA) [48]. If there is a clinical indication and perceived clinical benefit from a β-blocker for a person with asthma, this review suggests that using highly selective β_1-blockers, such as bisoprolol, at the lowest effective dose, is likely to minimise the risk of problematic β_2-blocking bronchospasm.

Future research

Major studies of the cardiovascular benefits of β-blockers have excluded patients with asthma – the cardiac benefits for these patients can only be extrapolated from studies from which they have been excluded. This should be addressed with future studies including these participants.

To support the safe and appropriate prescribing of cardioselective β_1-blockers to a growing cohort of people with asthma and cardiovascular disease, research clarifying to what extent rescue β_2-agonist therapy is affected by use of regular cardioselective β_1-blocker therapy and understanding of the dose at which each drug becomes insufficiently selective is needed.

Conclusions

The pharmacology of cardioselective β_1-blockers indicates that cardioselectivity is not complete. Small reductions in lung function have been observed after single doses in people with asthma, but this adverse effect appears to resolve with continued treatment. Observational studies have found no increase in moderate or severe asthma exacerbations in people with asthma taking regular cardioselective β_1-blockers. We found no reports of asthma deaths caused by cardioselective β_1-blockers in the published literature and only one possible death that was clearly in an asthmatic patient in the VigiBase data, for which there was insufficient detail to establish clear causality. Absence of evidence of fatal asthma is not necessarily evidence that it does not occur. However, these findings suggest that, despite widespread concerns, fatalities or serious asthma exacerbations due to cardioselective β_1-blocker use are likely to be extremely rare. The reluctance to use cardioselective β_1-blockers in people with asthma is not supported by this evidence.

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Data availability: Data available from the corresponding author upon reasonable request.

Author contributions: M. Bennett, C. Chang and R. Hancox were involved in the design and review process. M. Tatley and R. Savage were involved in review and data collection from VigiBase.

Conflict of interest: M. Bennett reports grants from Waikato Medical Research Foundation during the conduct of the study. C.L. Chang has nothing to disclose. M. Tatley has nothing to disclose. R. Savage has nothing to disclose. R.J. Hancox reports a proposed research grant on a related topic and travel to meetings supported by GSK, and travel to meetings supported by Boehringer Ingelheim and AstraZeneca, outside the submitted work.

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