Cardiovascular disease in asthma patients: From mechanisms to therapeutic implications

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ABSTRACT

Cardiovascular disease (CVD) is often associated with asthma, and asthma patients have an increased risk of CVD mortality. Our understanding of the bidirectional risk of CVD and asthma has been based on several observational studies. However, specific pathogenetic mechanisms underlying the development of cardiovascular comorbidities in patients with asthma have not yet been fully determined. Such cardiovascular complications in patients with asthma have been attributed to airway and systemic inflammation present in both asthma and CVD. Indeed, there is evidence that mast cells, eosinophils, inflammatory cytokines, and immunoglobulin E increase in both lungs of patients with asthma and in injured heart and vessels of CVD patients. These findings suggest that allergic asthma and CVD may share pathogenic pathways. Understanding these pathways is critical to the choice of pharmacological interventions. Currently, the most appropriate therapeutic approach lies in using the best available evidence to optimize the management of both asthma and CVD. Therapy should be optimized to take advantage of the favorable benefits that each medication may have on both organs while minimizing the likelihood of adverse effects on the lungs and heart. It is noteworthy that inhaled β_2-agonists provide benefits in patients with acute decompensated heart failure. Furthermore, inhaled corticosteroids may reduce the risk of atherosclerosis. On the other hand, asthma is not an absolute contraindication to using cardio-selective β_1-blockers, but these medications should be prescribed with caution, especially if they are necessary to prevent acute cardiovascular events, and alternative treatment options are unavailable. In addition, when aspirin intake causes the onset of hypersensitivity, $P2Y_{12}$ inhibitors (e.g., clopidogrel, prasugrel, and ticagrelor) are effective and safe treatment alternatives.

Key words: asthma, cardiovascular disease, comorbidity, mechanisms, therapeutic approaches

ASTHMA HETEROGENEITY

Asthma is a heterogeneous condition characterized by airway hyperresponsiveness, variable airflow obstruction that can become permanent over time and chronic inflammation [1, 2]. However, not all of these characteristics are usually present, and one or two may prevail when large cohorts of asthma patients are analyzed [3]. Furthermore, asthma must be divided into at least two main endotypes according to their type 2 (T2) inflammation. It is defined as $T2_{high}$ characterized by upregulation of T2 immune pathways (ie, interleukin [IL]-4 and IL-13 gene sets) and eosinophilic airway inflammation or $T2_{low}$ (usually characterized by neutrophilic or paucigranulocytic airway inflammation) [4]. Patients with $T2_{high}$ asthma are more allergic and have more eosinophils and airway hyperresponsiveness than patients with low expression [5]. $T2_{low}$ asthma remains poorly understood. It encompasses extremely late-onset asthma, obesity-related asthma, smoking-related asthma, neutrophilic asthma, and asthma with mild inflammation [6].

Age at the onset of asthma has emerged as a crucial determinant in differentiating between endotypes [7]. Patients with early-onset (or childhood-onset) asthma are often atopic, with T2-predominant inflammation and a favorable prognosis. On the other hand, patients with adult-onset or late-onset asthma are

frequently nonatopic, have a poor prognosis, and are more likely to have permanent airway obstruction. The absence of clinical allergy in late-onset asthma indicates that the T2 pathway is distinct from, and likely more complex than, the one associated with the early-onset allergic phenotype [8]. A T2 inflammatory process in the lung is achievable in the absence of mucosal-specific immunoglobulin (Ig)E and clinical allergic responses [8]. Some people have sputum neutrophilia mixed in with their eosinophilic process. This mixed inflammatory process suggests that other immune pathways interact with T2 immunity, including activation of IL-33 and IL-17 pathways [8].

Chest tightness, wheezing, and coughing can limit everyday activities, impair function, and disturb sleep [1, 2]. Asthma management aims not only to establish adequate control of symptoms and relieve them when they occur but also to reduce the risk of asthma-related exacerbations and mortality, prolonged airflow limitation, and treatment-related adverse effects.

The basis of asthma management includes inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABAs) [1, 2]. However, long-acting muscarinic receptor antagonists (LAMAs), CysLT receptor antagonists (CysLTRAs), oral corticosteroid (OCS), and biological therapies such as omalizumab that target IgE (preventing it from binding to receptors on basophils and mast cells), mepolizumab and reslizumab (monoclonal antibodies [mAbs] that target interleukin-5 [IL-5]), benralizumab (an IL-5 receptor α [IL-5 R]-directed cytolytic mAb), or dupilumab (an anti-IL-4 receptor α mAb that blocks both IL-4 and IL-13 signaling) are accessible as alternatives. In addition, growing evidence demonstrates the benefits of treating asthma with the triple regimen of ICS, LABA, and LAMA [9, 10].

Asthma guidelines and therapeutic strategies still provide treatment recommendations disregarding the complexity of asthma and advocate a progressive approach, increasing or de-escalating therapy by shifting to a higher or lower step, depending on the frequency and severity of the patient's symptoms [11].

However, it is critical to identify the particular component of asthma that drives symptoms in each patient before therapy selection [12]. Eosinophilic airway inflammation usually responds to standard treatment with corticosteroids and biologics although biological therapies are suggested only in patients with severe asthma [1, 2]. $T2_{low}$ asthma is not responsive to treatment with ICSs, but instead, it is a predictor of response to antibiotics [6, 12]. Macrolides, including clarithromycin and azithromycin, have demonstrated their effectiveness [12]. No interventions have been evaluated for this specific inflammatory endotype although preliminary evidence suggests therapies targeting the IL-6 pathway may be beneficial. Asthmatics with paucigranulocytic airway inflammation may not warrant anti-inflammatory treatment as symptoms in these patients may be driven solely by smooth muscle dysfunction (airway hyperresponsiveness) [6, 12]. Therefore, these patients may benefit from smooth muscle-directed therapies such as additional bronchodilators and LAMAs, mast-cell directed therapies, or in the most severe cases, bronchial thermoplasty [6, 12].

COMORBIDITIES AND ASTHMA

Adult-onset asthma may share metabolic and inflammatory components with other diseases such as obesity, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease (CVD), and psychiatric disorders [7]. Asthma, mainly in individuals with neutrophilic airway inflammation, causes systemic inflammation, with an increase in circulating proinflammatory cytokines such as IL -6 and tumor necrosis factor-α (TNF-α), as well as high-sensitive C-reactive protein (CRP) [13]. Systemic inflammation, a phenomenon common for many nonrespiratory disorders and asthma, constitutes a possible link between these disorders and at least certain endotypes of asthma [14].

Numerous comorbid diseases, including gastroesophageal reflux, allergic rhinitis, obesity, depression, diabetes mellitus, and CVD, have been associated with asthma [15].

These comorbidities can affect the course of asthma and its severity as well as its treatment modality. Therefore, the identification of such comorbidities, a thorough evaluation of their effects, and appropriate treatment that may reduce their impact must become a fundamental part of the approach to a patient with asthma [15].

Since asthma and CVD constitute major public health problems, there is genuine interest in determining the extent of any association between them and in understanding how one disease affects the other. Regrettably, epidemiological research on this relationship has produced contradictory evidence.

ARE ASTHMA AND CVD ASSOCIATED?

Some epidemiological studies found a strong link between asthma and CVD, particularly coronary artery disease (CAD), acute myocardial infarction (AMI), and arterial hypertension [16, 17]. Arterial hypertension shows the strongest association with asthma [18]. In a recent systematic review and meta-analysis that analyzed data from 5 493 776 subjects, the strength of association with asthma was weak for CAD, moderate for heart failure (HF), hypertension, cardiovascular comorbidities, and pulmonary hypertension, and strong for hypertensive cardiomyopathy [19]. In severe asthma, cardiovascular comorbidities, CAD, and HF were moderately associated while hypertension was strongly associated. Furthermore, arterial hypertension has been associated with established measures of adult asthma severity, as evidenced by the use of more than 6 canisters of short-acting β-agonists (SABAs), history of emergency department visits or hospitalization, and corticosteroid administration in an US case-control study [20].

The CVD risk has been reported to be from 32% [21] to 42% [22], and it is higher in asthmatics than in people without asthma. Analysis of 30 cohort studies comprising

4 157 823 participants showed that asthma and CVD had stronger links in women than in men (39% vs. 19%) and that patients with late-onset were at higher risk than patients with early-onset asthma (39% vs. 26%) [19]. Women have an increase in the prevalence rate of asthma, which is temporally correlated with variations in estrogen levels [23]. However, overweight women (body mass index, 25-30) with adult-onset asthma had a stronger association with CVD than those with adult-onset asthma who were not overweight [24]. Furthermore, asthma is associated with increased risk of CVD among smokers [25] and among adults whose asthma is work-related [26].

However, several other investigations found only modest or no connections between asthma and CVD. According to the Atherosclerosis Risk in Communities (ARIC) study conducted in the United States, those who had ever had asthma had an adjusted relative risk of coronary heart disease of 0.87 (95% CI, 0.66–1.14), while those who currently had asthma had an adjusted relative risk of 0.69 (95% CI, 0.46–1.05) [27]. Although CVD and hypertension were more common in individuals with asthma than in the general population, an Italian population-based retrospective cross-sectional analysis revealed that there was only a weak correlation between asthma and these conditions [18]. A Polish epidemiological study revealed no increased prevalence of comorbidity between cardiovascular diseases and asthma, with only ischemic heart disease (IHD) showing an odds ratio (OR) >1 [28]. Furthermore, asthma significantly reduced the risk of atherosclerosis (OR, 0.33) in patients with asthma compared to controls.

Asthma, particularly the uncontrolled eosinophilic phenotype, is a risk factor for CVD, not only in the classic form with coronary artery occlusion but also in vasospastic episodes without occlusion [29].

Several population-based cohort studies have concluded that asthma is associated with increased risk of CAD of up to about 30% [16, 30]. However, it has been reported that only those with asthma and an allergy have an elevated risk of CAD [31]. In any case, women with adult-onset asthma appear to have a higher risk of CAD [32].

In subjects with active asthma, defined as current users of asthma medications, the risk of acute myocardial infarction (AMI) is estimated to be 29% higher than in subjects without asthma, regardless of high-sensitivity (hs) CRP levels, smoking history, physical activity levels, or sex [33]. Inactive asthma, defined as the lack of asthma-related events within one year before AMI, does not increase the risk of AMI. On the other hand, current asthma, characterized by the occurrence of any asthma-related episodes, including asthma symptoms (cough with wheezing, shortness of breath, and tightness in the chest), the use of asthma medications, unexpected surgery visits for asthma, emergency room visits for asthma, or hospitalization for asthma within a year before the index date of AMI, increases the risk of AMI [34]. Asthma exacerbations have been found to correlate with significantly higher risk of AMI, particularly in the initial 1-week interval after acute exacerbation [35]. Data from the Korean Genome and Epidemiology Study prospective cohort from 2004 to 2016 showed that asthma was mainly associated with IHD in the older age (≥53 years) group and the untreated asthma group [36].

Patients with asthma are at increased risk of all-cause and CVD mortality [23]. Chinese research using data from the National Health and Nutrition Examination Survey from 2001/2002 to 2013/2014 showed that people with current childhood-onset asthma had a slightly higher CVD death rate than those with current adulthood-onset asthma [37]. However, according to an Australian study, asthma in children did not affect CVD mortality and CAD, HF, or major CVD events in adults [38]. Adult asthma is greatly influenced by factors intrinsic to the body, such as hormones and chest wall stiffness [30]. These inherent variables may increase the risk of CAD, but cigarette smoking also has an impact on adult asthma and is a risk factor for CAD [30]. In a sample of more than 400 000 Taiwanese adults, patients with active, but not with inactive, asthma were more likely to die from CVD [39]. The risk of death from CAD was increased similarly. However, in a sensitivity analysis that excluded people with previous heart disease, only the relationship with CVD mortality persisted. Men had a higher correlation with active asthma than women regarding CVD mortality. Patients with asthma who had moderate to severe acute exacerbation during the previous year had higher mortality following CVD events [40].

PATHOGENETIC MECHANISMS LINKING ASTHMA TO CVD

Cardiovascular complications in patients with asthma can be attributed to the inflammation present in asthma and CVD. However, the specific pathogenetic mechanisms that can facilitate the development of cardiovascular comorbidities have not yet been fully determined.

Despite the limitations of translating animal responses into humans, it should be noted that experimentally, acute and chronic allergic lung inflammation evoked in mice by sensitization and challenge with ovalbumin facilitated atheroma formation, regardless of whether lung inflammation occurred before, after, or concurrently with atherogenesis [41]. Pathological changes in the arteries have also been demonstrated in asthmatic patients [42]. Asthma is associated with pre-atherosclerotic vascular changes, such as increased arterial stiffness, and especially with a higher prevalence of overt atherosclerosis than in subjects without asthma. The severity of asthma is related to more pronounced pathological vascular alterations [42]. Furthermore, subjects with persistent asthma exhibited not only a more significant carotid plaque burden but also higher levels of serum inflammatory biomarkers (IL-6 and hs-CRP) than those without asthma [43].

Chronic airway inflammation in asthma could contribute to systemic inflammation [44], suggesting that the vasculature is systemically exposed to inflammation

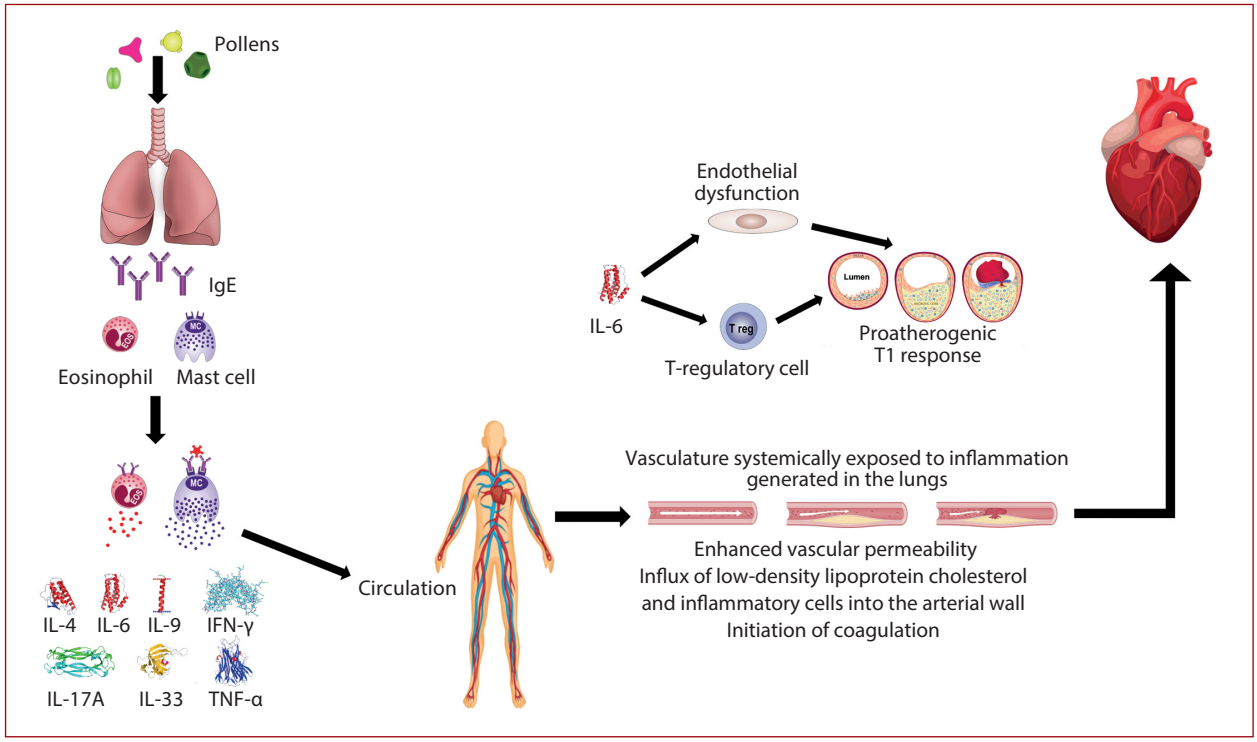

Figure 1. Some pathogenetic mechanisms linking asthma to cardiovascular disease
Abbreviations: IL, interleukin; IFN-, interferon γ, IgE, immunoglobulin E

generated in the lungs [45] (Figure 1). Female sex hormones have been shown to increase allergic lung inflammation in animal models [46]. This may suggest that systemic inflammatory responses are triggered more strongly in women with asthma than in men, leading to a pro-inflammatory state that puts women with asthma at increased risk of developing CVD [46].

Atherosclerosis has long been recognized as a chronic inflammatory disease characterized by inflammation and immunological dysfunction [47]. Several inflammatory cells, including macrophages, monocytes, lymphocytes, neutrophils, and mast cells, which are present in the walls of asthmatic bronchoalveolar and atherosclerotic vessels, play an important role in the pathogenesis of both diseases and perform comparable functions [48]. T1 cells appear to be the key driver for atherosclerotic CVD [49]. Nevertheless, IgE concentrations are higher in coronary events [49]. However, it is unclear whether this is due to their involvement in the genesis of the coronary event or to the inflammatory response caused by the tissue damage that occurred during the event [50].

In any case, IgE-triggered mast cells and eosinophil leucocytes have been proposed as potential essential players [51]. Both types of cells, by producing chemokines and cytokines, particularly IL-4, IL-6, IL-9, IL-17A, and IL-33, but also interferon-γ and TNF-α [45], enhance vascular permeability and admission of low-density lipoprotein cholesterol and inflammatory cells into the arterial wall. Furthermore, evidence shows that mast cells accumulate excessively in injured endothelium, which on one hand stimulates the formation of foam cells and atherosclerotic plaques, and on the other hand, is an important factor in plaque degradation and initiation of coagulation due to cytokines released from granules and proteolytic enzymes [52].

IL-6 is a crucial effector cytokine in the atherosclerotic T1 process, as it directly inhibits T-regulatory cells, allowing the proatherogenic T1 response to occur [53]. IL-6 also causes endothelial dysfunction, the first step in arterial damage and the production of atherosclerotic plaques, spreads inflammation and predicts future atherosclerotic CVD events [54, 55].

The shared inflammatory mechanisms of asthma and CVD from the 5-lipoxygenase enzymatic pathway may contribute to long-term concomitant airway and atherosclerosis [56]. Cysteinyl-leukotrienes (CysLTs) operate as powerful smooth muscle constrictors in the airways, causing tissue edema and signaling eosinophil recruitment. Furthermore, they profoundly influence left ventricular function, heart rate, and coronary artery tone, causing myocardial depression when secreted by immunologically activated human cardiac mast cells. There is also evidence that CysLTs can increase the probability of thrombosis by activating platelets and clotting factors with subsequent coronary thrombosis [57].

Human heart mast cells generate chymase and renin, which locally activate the angiotensin system and cause arteriolar vasoconstriction [58]. Furthermore, when immunologically activated, they also secrete histamine and platelet-activating factor, with their well-known harmful effects on asthma and CVD [58].

Smooth muscle remodeling is another process that can be induced by inflammatory mediators. Hyperplasia and aberrant smooth muscle cell contraction leading to airway constriction in asthma are also recognized as characteristics of vascular remodeling and endothelial abnormalities seen in CVD [59].

Uncontrolled asthma, particularly in patients with a T2 inflammatory profile or significant eosinophilic activation, can promote a procoagulant state [16]. However, most patients with asthma do not experience thromboembolic events [16] although increasing evidence suggests that asthma is associated with greater risks of pulmonary embolism [60].

ASTHMA, CVD, AND MUTUAL PHARMACOLOGICAL INTERFERENCES

There is a possibility that therapeutic approaches used to treat asthma can cause or worsen CVD [61, 62], but drugs used to treat CVD can also adversely affect asthma [62]. On the other hand, there is growing evidence that some asthma medications can improve CVD and that different CVD treatments can reduce the severity of asthma [62].

Inhaled β_2-agonist treatment can increase the incidence of acute AMI, atrial fibrillation (AF), congestive HF, cardiac arrest, and sudden cardiac mortality in asthmatic patients [61]. This risk is higher in people with long QT syndrome [59]. The increased risk of AMI, which is not limited to β_2-agonists but also involves ICSs, generally occurs primarily in the first 3 months of therapy and then decreases [63]. Furthermore, long-term intensive use (more than 13 prescriptions in a year) of an ICS and a SABA has also been associated with increased risk of AMI [62]. Some patients with asthma may have stronger sympathetic responses to β_2-agonists contributing to their increased cardiovascular risk [64]. However, this possibility is negated by retrospectively collected data from the Taiwan National Health Insurance database [65]. The results showed that new bronchodilator users, but not previous users, had a reduced risk of coronary vasospastic angina possibly because new users would be less susceptible to increased sympathetic activity and thus vasospasm. The ability of inhaled β_2-agonists to induce benefits in patients with acute decompensated HF is important. In fact, they improve cardiovascular hemodynamics, increase cardiac output, reduce peripheral vascular resistance, and reduce pressure in the pulmonary circulation [61]. Furthermore, bronchoconstriction in patients with HF is frequently reversible with inhaled β_2-agonists, and the resulting decrease in the work of breathing might potentially further reduce cardiac workload [61]. In any case, a recent nested case-control analysis conducted using the UK Clinical Practice Research Datalink of patients with asthma suggested that the use of SABA or ICS/LABA combination therapy was not associated with increased risk of major adverse cardiovascular events (CVE) defined as the first occurrence of stroke, HF, AMI, arrhythmia, or cardiovascular death compared with ICS [66].

Similarly, other drugs used to treat asthma can adversely affect the heart. For example, ipratropium bromide, a short-acting muscarinic antagonist (SAMA), was associated with a 69% increase in the risk of arrhythmias in 12–24-year old patients with asthma who used this SAMA at high-dose (more than 114 mcg) [67]. However, the risk was not statistically significant in low-dose SAMA users (114 mcg or less). Furthermore, it should be noted that LAMAs, such as tiotropium, glycopyrronium, and umeclidinium, demonstrated safety and tolerability comparable to placebo when added to ICS therapy in different treatment stages in adults with symptomatic asthma [68].

Even at therapeutic blood concentrations, theophylline can cause tachycardia and serious arrhythmias, of which multifocal atrial tachycardia may herald sudden cardiac death [69].

Although not explicitly studied in patients with asthma, those receiving high-dose corticosteroid treatment (7.5 mg equivalent of prednisone per day) have an increased risk of developing CAD or HF [70]. Furthermore, the risk of AF occurrence with 7.5 mg equivalent of prednisone per day is six-fold higher than in patients who did not receive the drug [71]. Apparently, the risk of CVE when using oral doses of prednisolone >10 mg per day is higher during the first 30 days than during the longer period [72].

Interestingly, given higher levels of IgE in patients with CVD and their association with IHD [50], omalizumab has been reported to increase the risk of CVE, as well as arterial and venous thromboembolic events, in individuals with moderate to severe asthma [73]. However, the study that described these findings included individuals with a much higher CAD burden who received omalizumab. In fact, a subsequent pooled analysis of 25 omalizumab-related randomized controlled trials and 2 extension studies did not find evidence of any elevated cardiovascular risk [74]. Nonetheless, there are sporadic case reports in which omalizumab has been associated with arterial and venous thromboembolic events [75]. Furthermore, French pharmacovigilance research demonstrated that omalizumab was associated with hypertension, ventricular arrhythmia, and venous thromboembolism to a significantly greater extent than mepolizumab, reslizumab, and benralizumab [76].

Since inhaled bronchodilators must always be administered in combination with ICS in patients with asthma, ICS treatment was compared to ICS-LABA treatment using real-world data; no significant differences were found between the two groups [77]. However, in women with asthma, the use of ICS is associated with significantly lower cardiovascular and all-cause mortality [78]. On the other hand, patients who had received much lower mean daily doses of ICS in the previous two years were reported to have greater atherosclerotic alterations [74]. ICSs may reduce the risk of atherosclerosis in two ways: directly through absorption across the lungs and exerting a direct impact on the artery wall, or indirectly by lowering the airway inflammatory response [79].

The documentation that CysLTs cause inflammatory changes and induction of immunothrombosis and, consequently, have also been implicated in CVD is the reason why the use of a CysLTRA has been suggested to cause a reduction in AMI and the risk of atherosclerosis [57, 80]. Results of a recent observational retrospective 3-year study of 800 adult asthmatic patients suggest that montelukast, a potent and selective $CysLT_1RA$, may play a role in the prevention of incidental myocardial ischemia events in the elderly asthmatic population [81]. However, although ICS plus CysLTRA treatment in older adults is associated with lower risk of CVEs than ICS plus LABA treatment, its risk of exacerbating asthma is higher [82].

β-Blockers are frequently used in the treatment of CVD, but they can deleteriously impact asthma patients. Over time, evidence has accumulated on their ability to cause bronchoconstriction, neutralize the effectiveness of β_2-agonists, and induce moderate and severe asthma exacerbations [83, 84]. However, this unfavorable impact on the heart is mainly observed with non-selective β-blockers while cardio-selective β-blockers, which are 13 to 19 times more potent in blocking β_1-adrenoceptors (ARs) than β_2--ARs [85], are better tolerated than non-selective β-blockers. Still they are not completely risk-free, mainly in patients with unstable asthma or those with severe airway obstruction [86]. Therefore, asthma is not an absolute contraindication, but these medications should still be prescribed with caution especially if cardio-selective β_1-blockers are necessary in acute CVEs and alternative treatment options are unavailable [86]. The choice could possibly fall on drugs more suitable for concomitant CVD and asthma, such as nebivolol, a selective for β_1-AR with nitric oxide-mediated vasodilatory effects and is metabolically neutral, or celiprolol, a β-blocker possessing strong β_1-AR antagonist and mild β_2-AR agonist properties. But even in this case the risk of bronchoconstriction, even if small, cannot be ruled out [87]. Chronic use of nonselective β-blockers with β_2-AR inverse agonist characteristics, such as nadolol, which exert their beneficial effects on airway epithelial cells and immune cells by inhibiting constitutive pro-inflammatory signaling through non-canonical β-arrestin-2-mediated signaling may be another choice [88]. In fact, it is well tolerated, may have favorable effects on airway hyperresponsiveness, and does not neutralize the effectiveness of salbutamol according to two small clinical studies that were not supported by larger research [89, 90].

Statin use is the cornerstone of CVD prevention [91]. Furthermore, even in smokers with asthma, statins improve the anti-inflammatory effects of ICSs [92]. However, a 2020 Cochrane review concluded that statin therapy was unsuccessful for asthma [93]. Nevertheless, a recent meta-analysis of 8 observational studies and 11 randomized controlled tirals (RCTs) on asthma demonstrated that statins can reduce exacerbations and improve asthma management [94]. Furthermore, statins have been shown to improve asthma symptoms and lower levels of hs-CRP, sputum eosinophil ratio, and IL-6 without affecting lung function in people with asthma [95].

Due to its role in the development of pro-inflammatory mediators in the lungs, the renin-angiotensin system may have a role in the pathophysiology of asthma. There is substantial meta-analytical evidence linking high circulating ACE concentrations with the onset of asthma [96]. The high levels of angiotensin II and renin found in patients with severe asthma during exacerbations compared to those without exacerbations cause bronchoconstriction, smooth muscle cell hyperplasia, and lung inflammation [97]. As a result, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 (AT1) receptor blockers may be beneficial for people with asthma. However, contrary to expectations, ACE inhibitors were linked to higher asthma morbidity in patients with hypertension and asthma, including increased use of SABAs, systemic corticosteroids, and emergency department visits or hospitalization [20]. These events are quite rare, although potentially serious, and generally occur in the first few weeks of treatment [98]. On the contrary, a small reduction in airway hyperresponsiveness was observed with AT1 receptor blockers [99].

There is no evidence that calcium channel blockers worsen asthma when administered orally [62]. On the contrary, they may be useful for improving lung function, particularly in exercise-induced asthma [100]. Additionally, calcium channel blockers reduce the annual decline in lung function in asthmatic patients. This effect is thought to be caused by their inhibitory action on inflammation and airway remodeling [101].

Aspirin is the cornerstone for treating ischemic heart disease and secondary prevention of ischemic and valvular heart disease. Aspirin intake can cause the onset of hypersensitivity, known as aspirin-exacerbated respiratory disease (AERD), characterized by symptoms such as rhinorrhea, sneezing, nasal congestion, ocular tearing, bronchospasm, skin flushing, hives, and hypotension [102]. After aspirin administration, changes in arachidonic acid metabolism may cause an imbalance between pro-inflammatory and anti-inflammatory substances, resulting in an overproduction of CysLTs, IL-33/thymic stromal lymphopoietin, and prostaglandin $(PG)D_2$ and diminished production (or increased catabolism) of PGE_2 in the respiratory tract [103]. AERD affects a considerable number of patients with asthma, with a prevalence of about 7% [104] and becomes higher in those who also have nasal polyposis, with estimates ranging from 30 to 40% [105].

Antithrombotic agents that do not include aspirin, such as $P2Y_{12}$ inhibitors (e.g., clopidogrel, prasugrel, and ticagrelor) are treatment alternatives for people who are allergic to aspirin [106]. Clopidogrel was recommended in 2014 by the American College of Cardiology Foundation/American Heart Association guidelines for the management of patients with non-ST-segment elevation acute coronary syndromes in those with aspirin hypersensitivity, with a loading dosage followed by daily maintenance [107].

Compared to aspirin alone, $P2Y_{12}$ inhibitor monotherapy for secondary prevention is linked with a considerable reduction in atherothrombotic events without increased risk of serious bleeding [108]. However, dual antiplatelet therapy is suggested during acute coronary syndromes, particularly after percutaneous coronary intervention [109]. Aspirin desensitization is possible for these individuals; however, many "standard" desensitization methods take several days, rendering them problematic in emergency situations [110].

Nevertheless, patients with AERD who are on a stable asthma regimen and have a predicted baseline forced expiratory volume in 1 second (FEV_1) of at least 70% can be safely desensitized to aspirin using a 90-minute dose escalation protocol, beginning at 40.5 mg, and identifying desensitization as tolerance of the repeated provocation dose and at least one subsequent aspirin dose, bringing total cumulative daily dose to ≥325 mg [111]. This procedure is often performed in a single day. Furthermore, there is some evidence that treatment with omalizumab can help reduce respiratory symptoms during aspirin desensitization and potentially restore aspirin tolerance without the need for aspirin desensitization [112].

CONCLUSION

In conclusion, accumulating evidence has emerged to suggest associations between asthma and CVD. As a result, our understanding of the bidirectional risk of CVD and asthma has increased although knowledge about this association and its mechanisms remain incomplete. Indeed, the clinical evidence supporting the hypothesis that asthma confers an elevated CVD risk in patients is not univocal, and the specific biological mechanisms that may facilitate the development of cardiovascular comorbidities are unclear because they often overlap and sometimes conflict with each other. Understanding these biological mechanisms is critical for choosing pharmacological interventions. Currently, the most appropriate therapeutic approach lies in using the best available evidence to optimize the management of both asthma and CVD. In any case, it will be necessary to conduct specific clinical trials studying the effect on clinical outcomes of drugs known to be helpful for both CVD and asthma.

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