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Literature Review

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The role of beta-agonist therapy for chronic obstructive airway disease in patients with coexistent atrial fibrillation

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Abstract

Background: *New advances have been made in medicine, but the incidence and prevalence of chronic obstructive pulmonary disease (COPD) are evident, and it is established as the fourth cause of death in the United States representing a high cost for the healthcare system. This condition has been related to atrial fibrillation due to the changes in the lungs and vasculature. Based on this history, we seek to evaluate the outcome of AF in the patients with COPD and its relationship with medical therapy utilized to treat this pulmonary condition with the objective of establishing the relationship between the use of beta-agonist therapy for obstructive airway disease in patients with AF.*

Discussion: *Cell receptors participate in multiple reactions and the sympathetic response is received via the alpha- and beta-receptors are related to the hemodynamic of the vasculature of the lungs and cardiovascular system. The beta-blockade agents are one of the most common medication classes used for rate control in cardiac arrhythmias, but the side effect could be COPD exacerbation; on the other hand, beta-adrenergic or beta-agonist as a therapy for this pulmonary condition could increase the heart rate leading to AF decompensation. There is a clear dilemma in our patients who have airway disease and AF since the treatment for one might worsen the other. The clear benefit in morbidity and mortality of beta-blocker therapy, especially beta1-selective, outweighs the potential for any pulmonary side-effects related to ex-acerbation of COPD or airway disease.*

Conclusion: *There is clear data showing the evidence of the potential paradoxical side-effect between COPD and AF therapies, given the exacerbation of one due to treatment of the other, benefits versus risks should be discussed and the medical decision should be made based on them. The deteriorated cardiac condition can rapidly predispose to critical complications leading to death, which is why the use of beta-blockade agents will be chosen over possible complications with pulmonary disease. In other words, the benefit should outweigh the risk based on the best outcome for the patient.*

Keywords: Atrial Fibrillation, Pulmonary Disease, Obstructive Pulmonary Disease, Chronic Obstructive Pulmonary Disease (COPD), B-Agonist, Atrial Fibrillation, B-Block (Selective, Non-Selective), Digitalis, Other Antiarrhythmic.

Introduction

The new era in cardiovascular diseases has come with great advances in the diagnosis and management of arrhythmias. It is well known that electrophysiology procedures such as ablation and mapping now have different newer approaches.

During the recent decades the world has faced the epidemiological change from acute and infectious disease as first cause of death to the chronic diseases, given the new treatment and advances in medicine, these conditions have not only occupied the first positions as cause of death worldwide, they are also leading the list of most common condition for disability causing a disproportional cost in the health system and creating a critical crises in our community due to the conflict between the severity, medications and copayments.

Due to the increasing incidence and prevalence of chronic obstructive pulmonary disease (COPD), the Center for Disease Control (CDC) has established it has the fourth cause of death in the United States and one of the conditions of highest cost. The cost is directly proportional to the severity of the disease, especially in those patients who are on multiple inhalation

therapy, nebulization, oral agents, oxygen supplementation, and also rehabilitation requirements as we could see this disease could tremendously affect the quality of life of our patients. This condition is a chronic, progressive inflammatory process affecting the lungs and consequently causes changes in the dynamics of the pulmonary blood vessels.

As established by the "International Journal of COPD," the chronic obstructive pulmonary disease is associated with arrhythmias, more specifically Atrial Fibrillation (AF), an arrhythmia that in more than 90% of the cases originates in the pulmonary veins [1]. Taiwan was one of the first countries relating AF and COPD, finding that patients with COPD had more hospital readmissions and more prevalence of cardiovascular disease including diabetes mellitus, dyslipidemia, hypertension as well as cerebrovascular accidents and congestive heart failure [2].

AF could be described as an age-related arrhythmia that would be associated with several co-morbidities and its mortality can be up to 5% per year despite treatment including addressing the anticoagulation therapy for potential complications like the increased risk of stroke; cardiac events, sudden death, heart failure, and myocardial infarction are frequently seen in patient with this arrhythmias, but one-third of deaths are due to non-vascular causes like cancer, respiratory diseases, and infections, then the remaining AF patients die from stroke or hemorrhage (Approximately 6% each), or other causes [3]. The ENGAGE AF-TIMI 48 trial has found that sudden cardiac death was the single most common cause of death and responsible for approximately a third of all deaths and probably half of all cardiovascular deaths in atrial fibrillation patients; the most common factors related to sudden cardiac death in these patients were: male, left ventricular hypertrophy in the electrocardiogram, ejection fraction <50%, New York Heart Association functional class III–IV and prior myocardial infarction, non-use of beta blockade agents, use of digitalis and tachycardia [4]. According with WebMD patients with AF could reach over 750,000 admission per year, consuming $8,705 extra yearly and the national total amount could reach 26 billion and 75% of this is related to admissions, the social security office reports AF as a cause of disability due to persistent symptoms [5].

In the other hand, the Center for Disease Control and Prevention have reported that chronic lower respiratory disease, mainly chronic obstructive pulmonary disease, is the fourth leading cause of death in the US, its prevalence is directly related with tobacco smoke as the primary cause, but also the exposure to secondhand smoke, fumes, and genetics are also importantly related [6].

Based on the historic correlation between AF and its origin in the pulmonary blood vessels, its relation with the homodynamic, the importance of the rate or rhythm control, and the relation between COPD, its treatment and the changes produced in the lungs and pulmonary vasculature, we seek to evaluate the outcome of AF in the patients with COPD and its relation with medical therapy utilized to treat this pulmonary condition.

Objective

Our objective is to establish the relationship between the use of beta-agonist therapy for obstructive airway disease in patients with atrial fibrillation, then correlate their role in the exacerbation of this arrhythmia and its outcome.

Method

This is a descriptive retrospective review of thirty-five studies to determine the outcome of patients with AF who use beta-agonist therapy for COPD. The studies reviewed were obtained from The Center for Disease Control and Prevention, New England Journal of Medicine, The Lancet Journal, International Journal Chronic Obstructive Pulmonary Disease, StatPearls Internet Publishing, Respiratory Medicine, Journal of the American College of Cardiology, American Journal Respiratory Critical Care Medicine, Proceedings of the National Academy of Sciences of the United States of America, Journal of Cardiothoracic Surgery, Journal of the American Medical Association Internal Medicine, CHEST Journal, Annals of Thoracic Surgery, European Journal of Cardiothoracic Surgery, Dovepress Open Access, Cochrane Database of Systematic Reviews, cvpharmacology.com, and The First Aid For The USMLE Step 1 2019 by McGraw-Hill Education.

Discussion

The pulmonary dynamics are based in bronchoconstriction and bronchodilation, managed by the signaling received in via cell receptors. Multiple factors could affect the course of COPD, promoting exacerbation and potential complications; these could be infections, environmental contaminant, medications side effects, or non-compliance with medications. Besides the multiple reasons for complication, most of them have a common denominator, which is the cell receptors interaction as the cause.

These cell receptors participate in multiple reactions in different organ systems and the sympathetic response is received via the alpha- and beta-receptors. The mechanism of beta-receptors is related to ATP-cAMP conversion via adenylyl cyclase for protein kinase A. This results in calcium influx into myocardial cells and inhibition of myosin light chain kinase in smooth muscle cells. These receptors are responsible for increasing contractility, heart rate, lipolysis and renin release via beta1-receptors; bronchodilatation, ciliary relaxation, decrease uterine tone, increase of aqueous humor, insulin release, lipolysis and vasodilatation via beta2-receptors; and increase in thermogenesis of skeletal muscle, lipolysis and urinary bladder relaxation via beta3-receptors (Table 1) [7]. Since both heart rate and rhythm control are equally effective in AF therapy, most of the time our goal is to control heart rate [7-9]. The reason beta-blockade agents have an important role in the treatment of these arrhythmias is due to its blockade effects of both beta1 and beta2 receptors, resulting in heart rate reduction. On the other hand, airway diseases such as COPD, require beta-adrenergic therapy to stimulate the beta2-receptors preventing further bronchospasm and producing bronchodilatation [10,11].

Table 1: Function sympathetic receptors.

Receptor	Symbol	Function
Alpha-1	α- 1	Increase intestinal muscle contraction, increase bladder muscle contraction, increase vascular smooth muscle contraction, promotes mydriasis via pupillary dilator muscle contraction.
Alpha-2	α- 2	Decrease adrenergic or sympathetic signaling, decrease aqueous humor, decrease insulin release and lipolysis. Increase platelet aggregation.
Beta-1	β- 1	Increase heart muscle contractility and heart rate, increase lipolysis and the renin release.
Beta-2	β- 2	Promotes vasodilation (More effect in lungs), increase the insulin release, lipolysis, and aqueous humor production. Tocolysis (Decrease of uterine tone) and relaxation of the ciliary muscle.
Beta-3	β- 3	Increase the thermogenesis in skeletal muscle, bladder relaxation, and lipolysis

Beta-blockade agents are one of the most common medication classes used for rate control in cardiac arrhythmias, but their effects are not limited to the cardiovascular system [12]. They are further classified as selective referring to the beta1-receptor and non-selective which means both beta1 and beta2-receptors; the latter might cause bronchoconstriction due to blockade of the beta2 moiety [13]. Given the variety of beta-blockers available, however, we have the possibility to choose a beta1-selective blocker, and in theory it should not have any significant effect on the lungs (Table 2.1 and 2.2) [14].

Table 2.1: Beta blockade agents.

Receptor	Action	Drugs
Selective	β-1>β-2	Metoprolol, bisoprolol, atenolol, esmolol, betaxolol, acebutol (Partial), nebivolol
Non-Selective	β-1=β-2	Carvedilol (Also α blockade), labetalol (Also α blockade), propranolol, nadolol, timolol, pindolol (Partial)
Others	β-2	Olodaterol, vilanterol
We could summarize the mechanism and use of this agent as: Decrease of SA and AV nodal activity due to the decrease in CAMP and calcium current. Used for supra ventricular tachycardia, ventricular rate control for atrial fibrillation and atrial flutter. Decrease oxygen consumption due to the decrease in heart rate and contractility Related to decrease in mortality in myocardial infarction. Proven to reduce the mortality in heart failure (Metoprolol, bisoprolol, carvedilol) Most common side effects: COPD Exacerbation, impotence, bradycardia, atrioventricular blockade, masking of the symptoms of hypoglycemia, dyslipidemia (Specially Metoprolol), sedation and sleep alterations. Exacerbation of Prinzmetal angina (Propanolol).		

Table 2.2: Beta blockade agents.

Drug	Descriptions
Acebutolol	Cardioselective beta-adrenergic blocking agent. selectivity for the beta-1-receptor is lost at high doses
Atenolol	Competitive, beta-1-selective adrenergic antagonist, similar to metoprolol. Atenolol has a longer plasma half-life than does metoprolol, which allows for once-daily dosing. renally eliminated, minimally metabolized,
Betaxolol	Competitive, beta-1-selective adrenergic antagonist. Betaxolol is one of the most potent and selective of the beta-blockers available. Its selectivity for the beta-1-receptor makes it a preferred agent in patients with bronchospastic pulmonary disease
Bisoprolol	Oral beta-adrenergic antagonist. Bisoprolol is cardioselective (beta-1-receptor-specific)
Carvedilol	Combined alpha- and nonselective beta-blocker. Although it has some pharmacologic similarities to labetalol, the ratio of beta to alpha-1 effects is much greater for carvedilol than for labetalol. The ratio of beta to alpha-1 effects is much greater for carvedilol than for labetalol. The ratio of beta-blockade to alpha1-blockade for carvedilol is in the order of 10 to 100:1.

Labetalol	Combined selective, competitive alpha1-blocker and nonselective, competitive beta-blocker. Labetalol blocks beta1-receptors in the heart, beta2-receptors in bronchial and vascular smooth muscle, and alpha1-receptors in vascular smooth muscle. Its pharmacodynamic action is primarily mediated by beta-blockade, with an alpha- to beta-receptor activity ratio of 1:3 when given orally and 1:7 when given intravenously
Metoprolol	Competitive, beta-1 selective (cardioselective) adrenergic antagonist, selectivity for the beta1-receptor is lost at higher doses. At doses>400 mg/day, metoprolol also can competitively block beta2-adrenergic receptors in the bronchial and vascular smooth muscles, potentially causing bronchospasm.
Nadolol	Oral, nonselective, beta-adrenergic receptor antagonist
Nebivolol	Beta-1 selective (cardioselective) adrenergic antagonist.
Penbutolol	Oral nonselective beta-blocker
Pindolol	Oral, nonselective, beta-receptor antagonist with intrinsic sympathomimetic activity. Pindolol is the beta-blocker with the highest degree of ISA and nonselective antagonist qualities. The effect of ISA, as with beta-blockade in general, can be selective or nonselective in nature.
Propranolol	Prototype of the beta-adrenergic receptor antagonists. It is a competitive, nonselective beta-blocker without intrinsic sympathomimetic activity
Timolol	Nonselective, beta-adrenergic receptor antagonist. Timolol does not demonstrate appreciable intrinsic sympathomimetic or membrane-stabilizing activities.

Similarly, the effect of beta-adrenergic or beta-agonist use is not limited to the lungs [15]. Its effect reflects the increase in heart rate, myocyte contractility and release of renin given the rebound effect in higher blood pressure, increase in heart rate and cardiac demand, thereby providing an ideal environment for AF decompensation from a cardiovascular perspective and due to the polypharmacy and high incidence of atrial fibrillation in the elderly population, it is important to recognize drugs or other agents as a potential cause and it would contribute to a diagnosis and management of drug-induced AF more efficiently [16]. The treatment with bronchodilator and the frequency of them would depend in the persistency or severity of the obstructive pulmonary disease as well as the cause of the exacerbation of the symptoms (Algorithm 2). The local pulmonary treatment is addressed with the bronchodilators, which could be short acting or long acting (Table 3 and 4).

Table 3: Beta adrenergic agents.

Action	Drugs	Function
Short Acting	Albuterol	Relaxes smooth muscle. Use for acute exacerbation.
Long Acting	Salmeterol, formeterol	Longer acting. Used for prophylaxis.
We could summarize the mechanism and use of this agent as: Promotes bronchial smooth muscle relaxation. Short acting is used to treat acute exacerbation versus the long acting that is use for control or prophylaxis. Most common side effects: Anxiety, Tachycardia, and arrhythmia exacerbation.		

Table 4: Beta adrenergic agents.

Albuterol	Moderately selective oral and Inhaled short-acting beta-2-receptor agonist (SABA)
Epinephrine	Nonselective adrenergic agonist with a high affinity for beta1-, beta2-, and alpha1-receptors. It exhibits dose-dependent effects; beta-adrenergic effects (e.g., inotropy, vasodilation) are more pronounced at low doses and alpha-adrenergic effects (e.g., vasoconstriction) at high doses
Formeterol	Long-acting beta-2 receptor agonist (LABA) given twice daily via nebulizer. Formoterol has more than a 200-fold greater agonist activity at beta-2 receptors (primarily in the lung) than at beta-1 receptors
Indacaterol	Long-acting beta-2 agonist (LABA) given once-daily.
Levalbuterol	Moderately selective short-acting beta-2-receptor agonist (SABA). It is a moderately selective beta2-adrenergic agonist that stimulates receptors of the smooth muscle
Metaproterenol	Oral and inhaled synthetic beta-2 and beta-1 agonist that is structurally and pharmacologically similar to isoproterenol. It is more selective for beta-2 receptors than isoproterenol.
Olodaterol	Inhaled long-acting beta-2 adrenergic agonist (LABA) that is given once daily.

Pirbuterol	Inhaled sympathomimetic bronchodilator agent similar in structure to albuterol. It was a relatively selective beta-2 receptor agonist. Discontinued in the united states.
Salmeterol	Long-acting inhaled beta-2 agonist (LABA) that is given twice daily.
Terbutaline	Oral and parenteral bronchodilator and is a systemic short-acting beta-2 adrenergic agonist (SABA). Terbutaline is an oral and parenteral bronchodilator and is a systemic short-acting beta-2 adrenergic agonist (SABA).

There is a clear dilemma in our patients who have airway disease and AF since the treatment for one might worsen the other. On one side we have the need to break the bronchoconstriction with a bronchodilatory agent which stimulates the beta receptors causing as consequence a potential increase of heart rate, but on the other side, we have the atrial fibrillation requiring beta-blockade agent to control the rate, but these agents will potentially promote a bronchoconstriction blocking the beta adrenergic signaling. These discrepancies in the effects of pharmacotherapy between both conditions explain the high tolerance for beta-blockers in COPD patients who are actively utilizing aerosolized beta2-agonists [17]. Multiple theories and hypotheses have been exposed while some authors have related the long acting beta adrenergic or the chronic use of beta agonist to less adverse events related with cardiac arrhythmias, Bond et al demonstrated that acute therapy with beta-blockade increased bronchoreactivity, while chronic therapy did not; they described acute therapy as 28 days or less [18].

The side-effects could vary between cases, due to baseline arrhythmia control and how critical or severe the COPD exacerbation might be. The literature has shown different results in specific cases or types of patients, such as those surgical and/or critically ill where both therapies (beta-blockers and beta-agonists) have been highly needed and used. Yamanashi et al showed the potential benefit of beta-agonists post-operatively in patients undergoing thoracic surgery due to malignancy in COPD patients. In their study, the administration of beta-agonist therapy did not show any increase in the incidence of AF chronic obstructive pulmonary disease patients underwent lobectomy or segmentectomy due to non-small-cell lung cancer [19]. Other investigators reported that older individuals with COPD who were new users of long-acting β-agonists and anticholinergics were associated with increased risks of cardiovascular events, reason why they conclude that close monitoring of COPD patients requiring long-acting bronchodilators is needed regardless of drug class; in other words there is an increased risk of cardiovascular events in the presence of beta-agonist treatment [20]. In a cohort of 5226 Holter Monitor COPD patients, 40% had atrial tachycardia. Hanrahan et al. showed that patients with COPD have an increased incidence of atrial tachycardia in the presence of long-acting beta-agonists, in this large cohort atrial tachycardia increased by 2%-5% with LABA treatment but more serious arrhythmias were infrequent and did not increase with inhaled LABA therapy, the administration of this medication did not increase mean heart rate [21].

Pauwel et al. concluded that the use of formoterol with 100 µg bid or a four times higher dose (400 µg bid) of the ICS budesonide showed a significant decrease in severe exacerbation of asthma [22], while O'Byrnes et al described the improvement of the patient with mild persistent asthma after formoterol was added to budesonide [23].

Following patients with pulmonary malignancy or thoracic surgery, AF has been noted. The reason why both can be considered as risk factors for the development of post-operative atrial arrhythmias [24] might be elucidated by an increase in vagal tone, cardiac inflammatory process, pulmonary dynamics, right heart anomalies and hypoxia [25,26].

In our hospital facility, a retrospective review of 46 of patients with established atrial fibrillation (AF) and airways disease on Beta Agonist therapy was conducted and presented in HFSA 2020, were elderly (28 pts were 65 or above), minority (38pts were Black/African American and Hispanic) patients were predominant. 52% of patients had pulmonary hypertension, and 27 pts had Heart Failure (HF). A total of 16pts had COPD, of which 11 were on Beta-Blockers (BB). Overall, BB was used in 60.86% pts (24 Selective vs. 4 Non-Selective). A total of 11 pts had recurrent hospitalization (RH); HF exacerbation was the most common cause with 36% (4pts), followed by AF-RVR 27.27% (3pts). The 63.63% (7pts) were on Beta Blocker; 45.45% (5pts) had PHTN; 27.27% (3pts) had COPD on Beta-Blockers. Regarding the patients with COPD on BB shown to tend recurrent hospitalization (RH), there were not patients with COPD who were not on BB with RH. In our data, there was a clear relationship between atrial fibrillation with coexistence heart failure on beta-blocker therapy and re-hospitalization. Beside the chronic obstructive pulmonary disease has been related to structural and hemodynamic cardiac affections, in our review, it did not show a major impact regarding re-hospitalization.

The clear benefit in morbidity and mortality of beta-blocker therapy directed to multiple comorbidities like cardiac arrhythmias and heart failure (Table 5 and 6) [27-30]; especially beta1-selective, outweighs the potential for any pulmonary side-effects related to exacerbation of COPD or airway disease [31].

Upon literature review, we found significant data focusing on the beta-blockade aspect of the pharmacotherapy for atrial fibrillation (Table 5). Affirm trial published in 2002 was one of the first randomized, multi-center trials where 4060 patients were enrolled and they concluded that there was no survival benefit with the rhythm, control strategy, Rate control was preferable over rhythm control due to lower risk of adverse effects. RACE II trial another multi-center randomized control trial which enrolled 614 patients. Results showed that lenient rate control (<110 BPM) was non-inferior to strict rate control (<80 bpm), and it was much easier to achieve. The benefits of Beta blockade were applied to patients with heart failure in the CIBIS-II trial published in 1999. This trial was stopped early as interim analysis showed significant mortality benefit in heart failure with reduced ejection fraction with NYHA class III and Class IV symptoms. In 2003, Results of the COMET trial were published which showed significant superiority interns of survival benefit for Carvedilol (Combined

alpha-1 and nonselective beta-blocker) over metoprolol (Competitive, beta-1 selective/cardioselective adrenergic antagonist) when used in the treatment of chronic heart failure with reduced LV ejection fraction.

Table 5: Evidence based, beta blockade.

Literature	Brief explanation of the findings
A comparison of rate control and rhythm control in patients with atrial fibrillation (AFFIRM Trial)	Rate control was non-inferior to rhythm control. Rate control possibly superior in elderly and patients with co-morbid.
Lenient versus strict rate control in patients with atrial fibrillation (RACE Trial)	Strict rate control (<80 bpm) was not better than lenient (<110 bpm) control
The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II Trial)	Bisoprolol improved mortality in NYHA 3-4
Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET Trial)	Carvedilol superior to metoprolol reducing mortality in NYHA II+ & EF<35%

There was very limited research on the role of beta-agonist therapy in COPD/Atrial fibrillation. Shah V et al. in 2016 suggested correcting the underlying respiratory decompensation while treating patients with Atrial fibrillation as they render the treatment of AF ineffective and that presence of AF is a predictor for increased mortality for COPD-related hospitalizations. Chen CY et al. enrolled 882 patients with both COPD and AF along with 2646 patients with COPD without AF and analyzed hospitalization outcomes and concluded that the length of hospital stays and the in-hospital mortality rate were significantly higher in AF patients with COPD than in those without COPD. There were no specific outcomes related to the use of beta-agonist therapy in either group.

Van Gestel YR et al evaluated the use of beta blocker therapy in 3371 consecutive patients in a single institution who underwent major vascular surgery and results showed that in carefully selected patients with COPD, the use of cardioselective beta-blockers appears to be safe and associated with reduced mortality. The most closely related analysis was by Yamanashi, K et al. in 2017 where they retrospectively analyze 174 COPD patients who were administered Beta-2 agonist therapy perioperatively while undergoing lobectomy or segmentectomy. Increased incidence of postoperative atrial arrhythmias including Atrial fibrillation was not observed (Table 6).

Table 6: Evidence based, beta adrenergic.

Literature	Brief summary
Shah V, Desai T, Agrawal A (2016) The Association between Chronic Obstructive Pulmonary Disease (COPD) and Atrial Fibrillation: A Review.	Correct the underlying respiratory decompensation while treating patients with AF as they render the treatment of AF ineffective
Chen CY, Liao KM (2018) The impact of atrial fibrillation in patients with COPD during hospitalization. Int J Chron Obstruct Pulmon Dis 13:2105-2112.	the length of hospital stays, and the in-hospital mortality rate were significantly higher in AF patients with COPD than in those without COPD.
Ling Y, Saleem W, Shee CD (2008) Concomitant use of β-blockers and β2-agonists. European Respiratory 31:905-906.	Co-prescription of β-blockers and β2-agonists may often be inadvertent and that in some patients with airways disease, β-blockers could be stopped or a cardioselective β1-antagonist substituted.
van Gestel YR, Hoeks SE, Sin DD, Welten GM, Schouten O, et al. (2008) Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis Am J Respir Crit Care Med 178(7):695-700.	Cardioselective beta-blockers were associated with reduced mortality in patients with COPD undergoing vascular surgery. In carefully selected patients with COPD, the use of cardioselective beta-blockers appears to be safe and associated with reduced mortality.
Yamanashi K, Marumo S, Sumitomo R, et al. (2017) Long acting β2-adrenocepter agonists are not associated with atrial arrhythmias after pulmonary resection. J Cardiothorac Surg 19;12(1):35.	Perioperative administration of long-acting β2-adrenoceptor agonists might not increase the incidence of postoperative atrial arrhythmias in chronic obstructive pulmonary disease patients.
Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, et al.(2013) Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med 173(13):1175-1185.	Among older individuals with COPD, new use of long-acting β-agonists and anticholinergics is associated with similar increased risks of cardiovascular events. Close monitoring of COPD patients requiring long-acting bronchodilators is needed

As outlined in table 4, several landmark clinical trials have proven the mortality benefit of Beta-blockers in heart failure patients especially reduced ejection fraction, reason why it is established as a first-line therapy and must be prescribed as a part of pharmacological therapy in the absence of contraindications.
The cardiac remodeling observed in heart failure occurs due to the structural and functional changes as a cause of molecular and cellular changes involving cardiac myocytes. One of the reasons for these changes is the chronic stimulation of Beta 1- adrenergic receptors, the same stimulus that is inhibited by beta blockers [32-35].

Beta blockade therapy works improving the outcome of patients with cardiomyopathy via multiple modalities including decreasing the deleterious effects of catecholamine stimulation on the myocytes, also increases the responsiveness of the myocardium to inotropic and chronotropic function and thus improves contractility by upregulating beta-1 receptor density in the myocardium [36,37]. Although both COPD and atrial fibrillation have existed for a long time and there is substantial research in both, there is not enough evidence in the concurrent management of the complex co-presentation. The most significant being the lack of Randomized clinical trials. We recommend there is a role for future studies focusing on populations with co-existing COPD and atrial fibrillation like the one conducted by Chen CY et al. with further emphasis and subgroups based on the level of each disease namely advanced COPD requiring home oxygen therapy. Atrial fibrillation can be sub-grouped based on comorbidities like heart failure, history of stroke, etc, and outcomes based on beta-agonist therapy.

Conclusion

There is no doubt about the relation between atrial fibrillation and cardiac events in the presence of comorbid (Age, sex, heart failure, persistent arrhythmia, etc) and medication side effects; clear data have shown the evidence of the potential paradoxical side-effect between COPD and AF therapies, given the exacerbation of one due to treatment of the other, reason why benefits versus risks should be discussed and the medical decision has to be taken based on them. Elderly population has a higher risk for side effects, the main reason for this is the higher incidence of arrhythmias especially atrial fibrillation and potential side effect from the polypharmacy in this population, reason why the fast recognition of the potential side effects and exacerbation of the any arrhythmia in a timely matter is highly important, as well as the consideration for alternatives therapies like digoxin [38], calcium channel blockers [39,40] , or amiodarone [41]. Deteriorated cardiac condition can rapidly predispose to critical complications leading to death, which is why the use of beta-blockade agents will be chosen over possible complications with pulmonary disease based on the morbidity and mortality benefit. The clinician must establish the risk based on the on the possible complications like risk of stroke (Current ECG, CHADS2-VASc and NIHSS scores could be used), respiratory failure (CAT Score could be used), or exacerbation of their baseline conditions. In other words, and besides further data would be needed in this population of patients, the benefit should outweigh the risk based on the best outcome for the patient.

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