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STATE-OF-THE-ART PAPER

Heart Failure and Chronic Obstructive Pulmonary Disease

The Quandary of Beta-Blockers and Beta-Agonists

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The combination of heart failure and chronic obstructive pulmonary disease presents many therapeutic challenges. The cornerstones of therapy are beta-blockers and beta-agonists, respectively. Their pharmacological effects are diametrically opposed, and each is purported to adversely affect the alternative condition. The tolerability of beta-blockade in patients with mild and fixed airflow obstruction likely extends to those with more severe disease. However, the evidence is rudimentary. The long-term influence of beta-blockade on pulmonary function, symptoms, and quality of life is unclear. Low-dose initiation and gradual up-titration of cardioselective beta-blockers is currently recommended. Robust clinical trials are needed to provide the answers that may finally allay physicians' mistrust of beta-blockers in patients with chronic obstructive pulmonary disease. Beta-agonists are associated with incident heart failure in patients with pulmonary disease and with increased mortality and hospitalization in those with existing heart failure. These purported adverse effects require further investigation. In the meantime, clinicians should consider carefully the etiology of dyspnea and obtain objective evidence of airflow obstruction before prescribing beta-agonists to patients with heart failure. (J Am Coll Cardiol 2011;57:2127–38) © 2011 by the American College of Cardiology Foundation

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are global epidemics affecting in excess of 10 million patients (1,2). The cornerstones of therapy are beta-blockers and beta-agonists, respectively. The short- and long-term effects of beta-blockade are diametrically opposed: Acute negative inotropy precedes improved left ventricular systolic function. Beta-blockers confer protection from chronically elevated catecholamines and lead to up-regulation of beta-receptors. Reverse remodeling occurs. Beta-agonists exert the reverse pharmacological effects of beta-blockers. Exposure induces down-regulation and desensitization of beta-receptors (3). However, whether acute positive inotropy gives way to longer term left ventricular systolic dysfunction (LVSD) is uncertain.

Although one-third of patients with HF have concurrent COPD (4), few reports have addressed the simple therapeutic questions that interest physicians. Does "severe" or "reversible" airflow obstruction preclude $beta_1$-selective blockade? Is bronchoconstriction lessened by using a beta-blocker with $alpha_1$-antagonist activity? Do beta-blockers improve the prognosis of patients with both conditions? How safe are oral and inhaled beta-agonists in patients with HF? Here, we critically appraise the controversial issues of beta-blockers and beta-agonists in patients with HF and COPD.

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Methods

To examine beta-blockers in COPD, the CENTRAL (Cochrane Central Register of Controlled Trials) was searched for randomized, controlled, single- or double-blinded trials. Medical subject heading (MeSH) terms "respiratory tract diseases" and "adrenergic beta-antagonists" yielded 227 studies, 18 of which addressed the review objectives (5-22). Key word searches "chronic obstructive lung disease" and "beta adrenergic receptor blocking agent" or "[beta-blocker name]" identified 2 further studies (23,24). These 20 studies matched the recent Cochrane library systematic review (25). Further information was gathered searching Medline using

Abbreviations and Acronyms

CI = confidence interval
COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in 1 s
HF = heart failure
LVSD = left ventricular systolic dysfunction
MeSH = medical subject heading
OR = odds ratio

MeSH terms (restricted to humans) "lung diseases, obstructive" and "adrenergic beta-antagonists" (n = 576) (26-29).

The relationship between oral or inhaled beta-agonists and HF was examined in CENTRAL using MeSH terms "heart failure" and "adrenergic beta-agonists" (n = 187). All studies involving nebulized or inhaled beta-agonists were included (30-32). Given the unequivocal results of large randomized controlled trials investigating xamoterol (33,34), we restricted further inclusion of oral beta-agonists to larger studies lasting at least 1 month (35). Medline was searched for "heart failure" and "adrenergic beta-agonists" (n = 374) (33–38) or "albuterol" (n = 42) (30–32,39,40) or "terbutaline" (n = 25) (41) or "pirbuterol" (n = 37) (42). Substituting "cardiomyopathy, dilated" for "heart failure" located 2 additional studies (43,44). Combining the remaining beta-agonists in the MeSH hierarchy identified no new references.

Finally, Medline was searched using MeSH terms "lung diseases, obstructive" and "heart failure" (n = 969) (45,46). Bibliographies of the Cochrane review and all publications identified by the search strategies were systematically reviewed (25).

Guidelines Regarding Beta-Blocker Use in Patients With HF and COPD

The American College of Cardiology/American Heart Association guidelines for the management of HF advocate "great caution" when using beta-blockers in patients with symptomatic "reactive airways disease" (47,48). No definition of "reactive airways disease" is provided. Concerns stem from reports of acute bronchospasm in asthmatic patients given noncardioselective beta-blockers (49–51). The guidelines also state that "most patients" with COPD "remain reasonable candidates for beta-blockade." More precise advice is lacking. By contrast, the European Society of Cardiology guidelines clearly state that COPD "is not a contraindication" (1). Low-dose initiation and gradual uptitration is recommended. Furthermore, the guidance indicates, "mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation."

Properties of Beta-Blockers Approved for the Treatment of HF

Greater $beta_1$-receptor affinity provides a wider division between $beta_1$ and $beta_2$-adrenoceptor blockade, the latter mediating bronchoconstriction. Estimates of $beta_1$ affinity (so-called cardioselectivity) vary according to methodology. In vitro, $beta_1/beta_2$ selectivity ratios have been derived from receptor binding studies in a wide range of tissues using different response measures, agonists, and antagonists. $Beta_1$ selectivity is demonstrated in vivo through antagonism of biochemical and hemodynamic responses to $beta_2$ stimuli (52). Table 1 outlines the properties of beta-blockers approved for the treatment of HF (53–56). Cardioselectivity is dose-dependent. Higher plasma concentrations increase competitive antagonism of $beta_2$-adrenoceptors with only limited incremental $beta_1$-blockade (52,57,58). $Beta_2$-blockade may increase airflow obstruction in susceptible patients, possibly through unopposed parasympathetic bronchoconstriction (59,60).

Randomized Trials of Cardioselective Beta-Blockade in COPD

Only 1 small study has prospectively examined beta-blockade in patients with both HF and COPD (61). The evidence in those with COPD alone informs our daily decisions. Any review of "COPD and HF" must, therefore, objectively appraise beta-blockade in "COPD without HF." A Cochrane library meta-analysis concluded that long-term cardioselective beta-blockade is safe and well-tolerated in COPD (25,62). This meta-analysis evaluated pulmonary function in 20 randomized, controlled, crossover trials of cardioselective $beta_1$-blockers in patients with COPD (Table 2) (5–24). No study included any patients with HF.

The evidence has many limitations. Only 2 studies involved more than 20 patients (15,23), some were only single-blinded (19,20), and others lacked placebo control

Table 1 Properties of Beta-Blockers Approved for the Treatment of HF

Beta-Blocker	$Beta_1$-Selectivity (Ref. #)	Alpha-Antagonism	Intrinsic Sympathomimetic Activity	Lipid Solubility	Route of Elimination	Half-Life (h)
Carvedilol (53)	1	+	—	Moderate	Hepatic	7–10
Metoprolol tartrate (54)	40	—	—	Moderate	Hepatic	3–7
Metoprolol succinate (57)	40*	—	—	Moderate	Hepatic	20
Bisoprolol (55)	75	—	—	Low	Hepatic/Renal	10–12
Nebivolol (56)	>300	—	—	High	Hepatic	12–19

Dashes indicate that the property is not present. *The clinical cardioselectivity of metoprolol succinate controlled release/extended release is much higher than that of metoprolol tartrate because of the even beta-blockade achieved with this formulation avoiding peaks and troughs (57).
HF = heart failure.

Table 2 Randomized Controlled Trials of Cardioselective Beta-Blockers in Patients With COPD

First Author (Ref. #)	n	Duration	Severe	Reversibility	Placebo Control	Double Blind	Mean FEV_1 (l)	Mean FEV_1 (% Predicted)	Beta-Blocker	Route	Dose (mg)	Reduction FEV_1 (l)
Anderson et al. (5)	9	Single dose	—	—	Yes	Yes	—	—	Metoprolol	PO	100	—
Beil and Ulmer (22)	20	Single dose	—	—	Yes	Yes	—	—	Propranolol Atenolol Propranolol	PO	80 >100 80	—
Sorbini et al. (24)	8	Single dose	—	—	—	Yes	1.9	—	Metoprolol	PO	50, 100, 150, 200	10%
Schaanning and Vilsvik (6)	20	Single dose	—	—	Yes	Yes	1.9	—	Practolol	IV	15	6%
Perks et al. (12)	10	Single dose	—	—	Yes	Yes	1.9	—	Atenolol	PO	50, 100	—
Lammers et al. (7)	8	4 weeks	—	—	Yes	Yes	2.4	—	Oxprenolol Metoprolol Pindolol	PO	80 100 b.i.d. 10 b.i.d.	0.25 0.20
Tivenius (8)	12	2 days	—	—	Yes	Yes	1.7	50	Metoprolol	PO	50 t.i.d.	0.14
van der Woude et al. (21)	15	4 days	—	—	Yes	Yes	2.4	72	Propranolol Propranolol Metoprolol Celiprolol	PO	40 t.i.d. 80 100 200	0.41 0.33 0.25 0.09
Ranchod et al. (9)	15	3 weeks	—	—	Yes	Yes	2.3	—	Atenolol	PO	100 o.d.	0.13
Adam et al. (10)	10	Single dose	—	Yes	Yes	Yes	1.7	—	Propranolol Metoprolol Atenolol Labetalol Propranolol	PO	40 q.i.d. 100 100 200 80	0.12 0.09 0.15 0.01 0.23
von Wichert (11)	12	Single dose	—	Yes	Yes	Yes	—	—	Metoprolol	PO	100	—
Dorow et al. (13)	12	Single dose	—	Yes	Yes	Yes	1.6	—	Pindolol Bisoprolol Atenolol	PO	5 20 100	NS NS
Macquin-Mavier et al. (14)	9	Single dose	—	Yes	Yes	Yes	—	80	Bisoprolol	PO	10	—
Dorow et al. (15)	34	12 weeks	—	Yes	—	Yes	1.7	—	Acebutolol Celiprolol	PO	400 200, 400, 600	NS
McGavin and Williams (16)	9	Single dose	Yes	—	—	Yes	1.1	40	Metoprolol	PO	100	0.03
Sinclair (17)	10	Single dose	Yes	—	Yes	Yes	1.3	—	Propranolol Metoprolol Propranolol	IV	80 0.12 mg/kg 0.06 mg/kg	0.27 0.07 0.20
Wunderlich et al. (23)	35	2 days	Yes	—	Yes	Yes	1.3	—	Metoprolol	PO	100 b.i.d.	16%
Butland et al. (18)	12	4 weeks	Yes	—	Yes	Yes	—	26	Propranolol Metoprolol Atenolol	PO	80 b.i.d. 100 o.d. 100 o.d.	36% 11% 10%
Fogari et al. (19)	10	1 week	Yes	Yes	—	—	1.3	—	Atenolol Celiprolol Oxprenolol Propranolol	PO	100 200 80	NS NS 14% 16%
Fenster et al. (20)	6	1 week	Yes	Yes	Yes	—	—	45	Metoprolol	PO	50 q.i.d.	6%

b.i.d. = twice a day; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; IV = intravenously; NS = not significant; o.d. = once daily; PO = orally; q.i.d. = 4 times daily; t.i.d. = 3 times daily.

(15,16,19,24). Eleven trials involved a single treatment dose, and only 1 lasted longer than a month (15). The effect of long-term beta-blockade, therefore, is unknown. The 9 "long-term" studies (defined as more than a single treatment dose) involved 147 young, predominantly male patients with moderate airways obstruction (mean forced expiratory volume in 1 s [FEV_1]: 1.8 l). Information is particularly limited for beta-blockers conferring benefit in HF. Although many trials used metoprolol, only 2 single-dose studies used bisoprolol (13,14), and none used carvedilol or nebivolol. Most important of all, the evidence lacks the hard clinical endpoints that characterize HF trials.

Effect of Cardioselective Beta-Blockade in COPD With Reversible Airflow Obstruction

Of the 20 trials included in the Cochrane meta-analysis, 7 involved patients with reversible airflow obstruction, defined by FEV_1 improvement ≥15% following $beta_2$-agonists (10,11,13–15,19,20). Those studies show FEV_1 was unaffected by either single dose or longer duration cardioselective beta-blockade (−1.8% and −1.26%, respectively). However, the "long-term" data were derived primarily from a single randomized trial lasting just 12 weeks (15). Celiprolol, a rarely used cardioselective beta-blocker with mild $beta_2$-agonism and $alpha_2$-antagonism, caused no significant change in FEV_1 in 34 patients with moderate reversible airflow obstruction.

The longest study to date examining beta-blockade in COPD contradicts these results, but it was not included in the meta-analysis. In a randomized, double-blind, crossover trial (63), 40 patients with mild COPD and significant reversibility received bisoprolol 5 mg or atenolol 50 mg. In that study, FEV_1 declined significantly over 6 months by approximately 0.2 l in both treatment arms. Although lacking a concurrent placebo group, lung function parameters normalized during the placebo crossover period, suggesting beta-blockade directly caused bronchoconstriction.

The Cochrane meta-analysis also reported no significant inhibition of $beta_2$-agonist response by cardioselective beta-blockers. However, of the 4 small studies (10,17,19,21), only 2 included patients with significant reversibility (10,19). The minimal influence on bronchodilation is therefore unsurprising. Overall, the long-term effect of cardioselective beta-blockers in patients with COPD and significant reversibility is unknown.

Effect of Cardioselective Beta-Blockade on Severe Airflow Obstruction

The same caveats apply to the evidence for beta-blockade in patients with severe COPD. The few existing studies are small, of limited duration, predominantly used metoprolol, had no dose titration, and excluded patients with HF (Table 2). The Cochrane library separately analyzed 6 trials with mean baseline FEV_1 <1.4 l or 50% of normal predicted values (16–20,23). No significant change occurred in FEV_1 following single-dose or longer-term beta-blocker therapy (−0.71% and −3.11%, respectively) (25). However, the "long-term" results were derived from 2 studies that lasted just 1 week and recruited 16 patients (19,20). Inexplicably, the presented weighted mean difference (−3.11%) failed to incorporate 2 of the 6 referenced studies (18,23). In these, metoprolol reduced FEV_1 by 16% in 35 patients, whereas atenolol and metoprolol each significantly reduced FEV_1 by approximately 10% in 12 patients.

Effect of Cardioselective Beta-Blockade on Symptoms

Only 1 patient in each of the beta-blocker and placebo groups experienced increased respiratory symptoms in the Cochrane meta-analysis (25). The longer duration treatment ranged from just 2 days to 12 weeks. Over short periods, patients may curtail typical daily activities, thus underestimating the effect on symptoms. The perception of respiratory effort and associated distress is subjective and variable with time, reflecting a complex interaction between psychology and physiology (64). Quantification based on physical exertion also fails to reflect mental health and social functioning (65). Only 1 trial formally assessed the effect of beta-blockade on dyspnea and health-related quality of life (61). Over 4 months, bisoprolol titration in 27 patients with HF and concurrent COPD resulted in a nonsignificant improvement in dyspnea and health status assessed using generic and disease-specific questionnaires. These findings require validation in larger cohorts.

Almost all trials evaluating beta-blockade in HF excluded patients with significant pulmonary disease, documented COPD, or bronchodilator therapy (Table 3). The only trial not specifying pulmonary disease or bronchodilators within the exclusion criteria was MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) (66). Despite this, just 210 (5.3%) of the 3,991 patients enrolled had documented COPD (personal communication, J. Wikstrand, October 2009). Even in beta-blocker trials with less stringent criteria, investigators likely avoid recruiting patients with airflow obstruction. No trial publications report bronchospasm. Whether this reflects genuine tolerability, limited detection strategies, or exclusion of patients with airflow obstruction is unclear. The incidence of respiratory adverse events was similar in the metoprolol and placebo arms of MERIT-HF, including bronchospasm (respectively, 0.3% vs. 0.4%), exacerbation of COPD or bronchitis (0.4% vs. 0.4%), and pneumonia (2.0% vs. 1.9%).

Effect of Noncardioselective Beta- and Alpha-Blockade on Airflow Obstruction

Carvedilol is the only noncardioselective beta-blocker approved for treating HF. Many trials in the Cochrane meta-analysis reported adverse side effects with nonselective beta-blockers. Propranolol significantly reduced FEV_1 (8-10,16,17,19,21,23), antagonized beta-agonists

Table 3 Exclusion Criteria, Prevalence of COPD, and Respiratory Symptoms in Major Beta-Blocker Trials

Trial Acronym	Year	Exclusion Criteria	Prevalence Of COPD	Beta-Blocker	Respiratory Symptoms (Beta-Blocker vs. Placebo)
MDC	1993	Obstructive lung disease requiring $beta_2$-agonists	Not reported	Metoprolol	Not reported
CIBIS I	1994	Asthma	Not reported	Bisoprolol	Not reported
U.S. Carvedilol Trials	1996	Any condition limiting exercise or survival, such as pulmonary disease	Not reported	Carvedilol	Cough 8% vs. 10%
MOCHA	1996	Obstructive pulmonary disease requiring oral bronchodilator or steroid therapy	Not reported	Carvedilol	Respiratory disorder 5% vs. 11%
PRECISE	1996	Any condition limiting exercise or survival, such as pulmonary disease	Not reported	Carvedilol	Not reported
ANZ-Carvedilol	1997	Chronic obstructive airways disease, or current treatment with a beta-agonist	Not reported	Carvedilol	Not reported
CIBIS II	1999	Reversible obstructive lung disease	Not reported	Bisoprolol	Not reported
MERIT-HF	1999	Contraindication to beta-blockade	5.3%	Metoprolol	Not reported
RESOLVD	2000	Chronic reversible airways disease requiring therapy	Not reported	Metoprolol	Not reported
BEST	2001	Contraindication to beta-blockade, or beta-agonists	Not reported	Bucindolol	Not reported
COPERNICUS	2001	Severe primary pulmonary disease, or contraindication to beta-blocker therapy	Not reported	Carvedilol	Not reported
CAPRICORN	2001	Significant pulmonary impairment, or therapy with inhaled $beta_2$-agonists or steroids	Not reported	Carvedilol	Not reported
COMET	2003	History of asthma or chronic obstructive pulmonary disease	Not reported	Carvedilol, metoprolol	Not reported
CIBIS III	2004	Obstructive lung disease contraindicating bisoprolol treatment	Not reported	Bisoprolol	Not reported
SENIORS	2005	Regular inhaled bronchodilators, or history of bronchospasm or asthma	Not reported	Nebivolol	Not reported

ANZ-Carvedilol = Australia–New Zealand Heart Failure Research Collaborative Group Carvedilol Trial; BEST = Beta-Blocker Evaluation of Survival Trial; CAPRICORN = Carvedilol Post-Infarct Survival Controlled Evaluation; CIBIS = The Cardiac Insufficiency Bisoprolol Study; COMET = Carvedilol or Metoprolol European Trial; COPD = chronic obstructive pulmonary disease; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Study; MDC = Metoprolol in Dilated Cardiomyopathy; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MOCHA = Multicenter Oral Carvedilol Heart Failure Assessment trial; PRECISE = Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise; RESOLVD = Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot; SENIORS = Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure.

(8,10,17,19,21,23), increased dyspnea (8,9,16,17,23), and necessitated withdrawal of patients from studies (8,9,16,23). The purported mitigating effect of alpha-blockade is circumstantial at best. Two retrospective Australian analyses assessed carvedilol in patients with HF and airflow obstruction. The first (67) studied 808 consecutive patients commencing open-label treatment, excluding patients with anticipated beta-blocker intolerance. Among 89 patients with coexistent COPD or asthma, 85% tolerated carvedilol. No comments were made regarding the severity and reversibility of airflow obstruction or the reasons for intolerance. The results undoubtedly reflect selection bias rather than true tolerability. The second study (27) examined 31 patients with concomitant moderate COPD without significant reversibility (mean FEV_1: 62% predicted, reversibility: 4%). Of those patients, 84% tolerated carvedilol, with only 1 patient withdrawing due to wheezing. However, patients were predominantly young men and only 39% used inhaled bronchodilators. Applicability to real-world patients is limited.

Beta-blockers were well tolerated in 124 patients attending a community HF clinic diagnosed with moderate to severe airflow obstruction using handheld spirometry, over one-half of whom received carvedilol (26). However, many patients with established airways disease were excluded, only a minority received bronchodilators, and the FEV_1 in those prescribed carvedilol was not reported. Most recently, a randomized, open-label, triple-crossover trial examined 35 patients with coexistent COPD according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria (68). FEV_1 was significantly lower with carvedilol (1.85 l/s) than with metoprolol (1.94 l/s) and bisoprolol (2.00 l/s). To conclude, there are no robust data supporting the safety or efficacy of carvedilol, particularly in patients with moderate to severe or reversible airways disease.

Effect of Beta-Blockade on Mortality in Patients With HF and COPD

In observational studies, use of beta-blockers is consistently associated with better survival in patients with HF and concurrent COPD (46,69,70), a finding corroborated in post–myocardial infarction populations (29,71). In the Val-HeFT (Valsartan Heart Failure Trial) (46), 140 (22%) of 628 participants with physician-recorded COPD received beta-blockers. Mortality over a mean of 23 months was approximately 17%, as opposed to 31% in those with HF and COPD not prescribed beta-blockers ($p < 0.001$). The VALIANT (Valsartan in Acute Myocardial Infarction Trial) enrolled patients with myocardial infarction complicated by HF, LVSD, or both. A higher proportion of the 1,258 patients with concurrent COPD received beta-blockers (51%), with an associated lower mortality (25% vs. 35%, $p < 0.001$) (70). Finally, a retrospective Canadian study (69) examined 11,942 elderly patients hospitalized for

Table 4 Association Between Beta-Agonists and HF

First Author (Ref. #)	Population	Route	Bronchodilator	Study Design	N	Outcome	Risk Associated With Bronchodilator Use (95% CI)
Martin et al. (43)	Asthma	Oral	Bambuterol	Cohort	8,098	HF	RR: 3.41 (1.99–5.86), $p < 0.0001$
		Inhaled	Salmeterol	Cohort	15,407	HF	RR: 1.10 (0.63–1.91), $p = 0.7$
Coughlin et al. (44)	General population	Oral	Beta-agonist	Case control	387	DCM	OR: 3.4 (1.1–11.0)
		Inhaled nebulized	Beta-agonist	Case control	387	DCM	OR: 3.2 (1.4–7.1)
Sengstock et al. (38)	Cardiology clinic	Inhaled	Beta-agonist	Case control	190	DCM	OR: 1.0
Macie et al. (87)	COPD or asthma	Inhaled	Beta-agonist	Case control	59,336	HF hospitalization	OR: 1.74 (1.60–1.91)
Au et al. (37)	HF	Inhaled	Beta-agonist	Case control	1,121	HF hospitalization	OR: 1.5 (0.8–2.8), 1–2 canisters OR: 2.1 (1.0–4.3), ≥3 canisters
	General medical clinics	Inhaled	Beta-agonist	Case control	13,012	HF hospitalization	OR: 1.3 (0.9–1.8), 1–2 canisters OR: 1.1 (0.8–1.6), ≥3 canisters
Au et al. (36)	LVSD	Inhaled	Beta-agonist	Cohort	1,529	Death	RR: 0.9 (0.5–1.6), 1 canister/month RR: 1.4 (0.9–2.2), 2 canisters/month RR: 2.0 (1.3–3.2), 3 canisters/month
Singer et al. (101)	Acute HF without COPD	Inhaled	Any bronchodilator	Cohort	7,299	Death IV Vasodilator use Ventilation	OR: 1.02 (0.67–1.56) OR: 1.40 (1.18–1.67) OR: 1.69 (1.21–2.37)

CI = confidence interval; DCM = idiopathic dilated cardiomyopathy; HF = heart failure; LVSD = left ventricular systolic dysfunction; OR = odds ratio; RR = relative risk; other abbreviations as in Table 2.

HF. Mortality was lower in those with concurrent COPD who were prescribed beta-blockers, after comprehensive adjustment for age, sex, comorbidity, and propensity scores (hazard ratio: 0.78, 95% confidence interval: 0.63 to 0.95).

None of the studies assessed pulmonary function, limiting inference to patients with severe or reversible airflow obstruction. Prescribing bias is inevitable due to perceived or documented intolerance to beta-blockers. This is compounded by recruitment bias in analyses from clinical trials, whose enrolment criteria often excluded patients with significant pulmonary disease. The lower mortality of patients receiving beta-blockers may well reflect less severe lung disease.

Physiological Rationale for Adverse Beta$_2$-Agonist Effects

Reduced organ perfusion in HF results in a compensatory increase in adrenergic drive. Epinephrine and norepinephrine stimulate ventricular contraction and increase vascular resistance, maintaining cardiac output and blood pressure. Longer term, increased mechanical stress, myocardial oxygen demand, and ischemia combine with maladaptive adrenergic signaling to depress myocardial function. Beta$_1$- and beta$_2$-adrenoceptors mediate norepinephrine toxicity, fibrosis, and necrosis. Down-regulation of beta$_1$-receptors with relative preservation of the beta$_2$ subpopulation reduces the beta$_1$/beta$_2$ ratio (72). The chronotropic and inotropic responsiveness (and likewise vulnerability) of the failing myocardium to beta$_2$-agonists thereby assumes greater importance (73,74).

Beta$_2$-agonists exert numerous unfavorable cardiovascular effects: tachycardia, hypokalemia, QTC prolongation, peripheral vasodilation, disturbed autonomic modulation, and depressed heart rate variability (75–78). In susceptible patients, beta$_2$-agonists may precipitate ischemic events (79,80). Hypoxia, hypercapnia, acidosis, and excess sympathetic activity in pulmonary disease all potentially amplify these sequelae (75,81,82). When combined with the arrhythmic substrate of left ventricular dysfunction (83), the risk of life-threatening arrhythmias cannot be discounted. However, theoretical concerns may be misplaced. Although beta$_2$-agonists may exacerbate hypokalemia associated with diuretics (84), hyperkalemia induced by intensive renin angiotensin inhibition may conversely be reduced. Research is needed to define the overall influence of beta-agonists in contemporary populations.

Cautions Regarding the Adverse Associations Between Beta-Agonists and HF

Beta-agonists are associated with incident HF in patients with pulmonary disease, and with increased mortality and HF hospitalization in those with existing HF or LVSD (Table 4). These reported adverse associations merit careful scrutiny. The evidence was derived from retrospective cohort or case control analyses, all of which equated drug dispensing with drug use. Three fundamental issues under-

mined the conclusions: 1) limited multivariate adjustment; 2) confounding by collinear pulmonary disease; and 3) bias by indication. Multivariable analyses are often restricted in epidemiological studies due to residual confounding by unmeasured covariates. Cardiovascular risk factors and diseases both cluster in patients with COPD, along with underuse of beta-blockers (70,85).

Pulmonary disease may cause cardiac injury through hypoxia, arrhythmias, or even atherosclerotic mechanisms (86). The poor outcomes attributed to beta-agonists may reflect the disease for which they are prescribed. Separating the two is difficult. Dose-response relationships are limited without adjustment for severity of airflow obstruction and cumulative smoking burden (36,80). Patients using more bronchodilators may simply have more severe pulmonary disease. Both physician- and patient-mediated confounding by indication is unavoidable. Physicians may mistakenly prescribe beta-agonists or patients may increase beta-agonist use for symptoms of HF.

Beta-Agonists and Incident HF

Five reports have addressed the association between beta-agonists and incident HF in the general population or those with pulmonary disease (37,38,43,44,87). Prescription event monitoring collates physician reports of adverse events associated with newly launched drugs. Oral bambuterol, but not inhaled salmeterol, was associated with an increased incidence of HF in 8,098 patients when compared with the reference drug nedocromil (risk ratio: 3.41 [95% CI: 1.99 to 5.86], $p < 0.001$) (43). However, the bambuterol cohort received fewer prescriptions for asthma (57.3% vs. 70.2%) and more "other" indications (12.8% vs. 2.8%). Therefore, bambuterol may have unmasked previously undiagnosed HF, as suggested by the greater risk in the first month of exposure compared with months 2 to 6 (respectively, risk ratio: 4.41 [95% CI: 1.90 to 10.27] vs. 2.67 [95% CI: 1.30 to 5.47]).

Two case-control studies assessed the risk of idiopathic dilated cardiomyopathy defined by echocardiography associated with beta-agonists (38,44). Numbers of events were limited, resulting in wide confidence intervals and statistical uncertainty. Both suffered the inherent failings of case control methodology (88). In Washington, DC, oral beta-agonists were associated with a 3-fold increased risk in 387 patients compared with community-based controls selected using random digit dialing (odds ratio [OR]: 3.4, 95% CI: 1.1 to 11.0) (44). By contrast, a Detroit study (38) of 197 patients observed no significant relationship with inhaled beta-agonists, employing clinic-based controls with ischemic cardiomyopathy. Although differences between oral and inhaled administration are possible, the disparity most likely relates to choice of control groups.

Two nested case-control studies yielded equally conflicting results (37,87). The multicenter ACQUIP (Ambulatory Care Quality Improvement Project) (37) examined healthcare records from general medical clinics. Among 782 subjects hospitalized with HF, risk of admission was not related to inhaled beta-agonists after adjusting for age, cardiovascular comorbidity, beta-blocker prescription, and presence of COPD (OR: 1.3, 95% CI: 0.9 to 1.8). By contrast, the adjusted 1-year risk of HF hospitalization was increased among patients with COPD or asthma who were prescribed beta-agonists selected from the Manitoba Health database (OR: 1.74, 95% CI: 1.60 to 1.91) (87). Therefore, whether inhaled beta-agonists are implicated in the development of HF remains uncertain.

Oral Beta-Agonists in HF

Numerous small, short-term controlled studies have examined the oral beta-agonists pirbuterol, prenalterol, salbutamol, and terbutaline in patients with HF (89). The majority demonstrated acute hemodynamic improvements, including ejection fraction, cardiac index, and pulmonary capillary wedge pressure (42). Although uncommon, ventricular arrhythmias were reported (39). Only 2 studies recruited at least 20 patients and lasted longer than a month (35,42). Although symptoms and exercise tolerance improved, no beta-agonist produced a sustained improvement in systolic function. The trials lacked statistical power and were of insufficient duration to identify longer-term impairment of systolic performance.

The risk of arrhythmias is likewise uncertain. Oral sympathomimetic drugs were associated with an increased risk of arrhythmic hospitalization in a case-control study examining 298 patients previously hospitalized with HF (OR: 15.7, 95% CI: 1.1 to 228.0) (45). The confidence intervals were unfortunately wide given the low absolute number of patients receiving systemic sympathomimetics ($n = 6$). More importantly, the study failed to address the risk of sudden death outside the hospital.

Two large, randomized controlled trials investigated oral xamoterol, a partial $beta_1$-agonist. The first (33) randomized 433 patients with mild to moderate HF to receive xamoterol, digoxin, or placebo. Xamoterol improved exercise capacity, dyspnea, and fatigue. The Xamoterol in Severe Heart Failure Study aimed to extend these findings in 516 patients with New York Heart Association functional class III and IV symptoms. However, the trial was terminated prematurely due to excess mortality in the xamoterol group within 100 days of randomization (9.1% vs. 3.6%, $p = 0.02$) (34). Both sudden death and progressive pump failure contributed to the increased mortality.

Respiratory guidelines favor inhaled over oral bronchodilators due to rapid therapeutic action, greater efficacy, and fewer side effects (2). However, neither cardiologic nor pulmonary societies specifically counsel against oral agents in patients with cardiovascular disease (1,2,48,90). This lack of guidance is concerning. In the Val-HeFT, 73% of patients with HF and concurrent COPD were prescribed oral $beta_2$-agonists (46).

Nebulized Beta-Agonists in HF

Nebulized doses are typically 10× greater than standard inhalers. Two facts should be considered. Systemic adverse effects are dose-dependent (91,92), and pulmonary absorption delivers beta-agonists to the heart without first-pass metabolism. Nebulized beta-agonists may precipitate arrhythmias and myocardial ischemia (93,94). Four acute studies recruiting 44 patients in total have administered nebulized $beta_2$-agonists to patients with HF (30,32,41,95). No adverse events were reported. In 13 patients, cardiac output and ejection fraction significantly increased within 10 min of inhalation, returning to baseline after 30 min (41). The remaining 3 studies observed a reduction in airflow obstruction following nebulized salbutamol, but no consistent improvement in exercise capacity (30,32,95). Given the limited patient numbers, clinical judgment is paramount. Increasing from 2.5 to 5 mg salbutamol produces only limited incremental bronchodilation (96,97).

Inhaled Beta-Agonists in HF

Standard metered-dose beta-agonist inhalers produce only minor systemic and biochemical abnormalities (91,92,98). Whether these contribute to adverse events in patients with HF or LVSD is debatable (36,37). Among 1,529 patients with LVSD identified retrospectively through imaging records (36), all-cause mortality and HF hospitalization within 1 year were associated with beta-agonist use. The risk increased with the average number of canisters dispensed per month. The respective adjusted hazard ratios were: 0.9 and 1.3 (1 canister/month); 1.4 and 1.7 (2 canisters/month); 2.0 and 2.0 (≥3 canisters/month). However, any association is undermined by the indication for beta-agonist use: Increasing dyspnea and resulting beta-agonist prescription may simply reflect worsening HF. Without markers of HF severity, the multivariate model was unable to adjust for such confounding.

In the ACQUIP case-control study (37), beta-agonists were associated with HF hospitalization among those with existing HF (OR: 1.8, 95% CI: 1.1 to 3.0). Adjustment for age, cardiovascular comorbidity, beta-blocker prescription, presence of COPD, and a marker of disease severity (steroid use) reduced the magnitude of association (OR: 1.6, 95% CI: 1.0 to 2.7). Adding smoking status and pack-year history to the multivariate model rendered the relationship nonsignificant (OR: 1.5, 95% CI: 0.8 to 2.8). The findings reinforce concerns that the purported adverse effects of beta-agonists relate to underlying pulmonary disease and clustering of cardiovascular risk factors.

A single study has prospectively investigated inhaled beta-agonists, administering salmeterol 84 μg twice daily to 8 patients with New York Heart Association functional class II or III HF (31). Compared with placebo, salmeterol use improved FEV_1 by 6% ($p = 0.01$). Concomitant airflow obstruction limits interpretation: mild COPD was not excluded; baseline FEV_1 was reduced in all patients; and smoking history was not documented. The pharmacokinetic data proved more revealing. The steady-state trough and peak concentrations and half-life of salmeterol were at least double those reported in patients with asthma. Physicians must be wary of diminished beta-agonist hepatic metabolism in patients with HF.

Beta-Agonists in Acute HF

Inhaled beta-agonists have never been prospectively evaluated in patients with decompensated HF, although the physiological actions are appealing: enhanced cardiac output, reduced peripheral vascular resistance, and bronchodilation (99). However, numerous clinical trials have tested therapies with favorable hemodynamic activity in patients with acute HF, none of which improved mortality (1). Analogies with intravenous inotropic drugs acting through adrenergic pathways are inescapable. Acute improvement may belie myocardial injury leading to increased mortality (1,100). Evidence from 7,299 patients without COPD enrolled in the Acute Decompensated Heart Failure National Registry supports these concerns (101). Bronchodilators were administered to 14.3% of patients and associated with greater requirement for intravenous vasodilators (adjusted OR: 1.40, 95% CI: 1.18 to 1.67) and mechanical ventilation (OR: 1.69, 95% CI: 1.21 to 2.37). Hospital mortality was similar regardless of bronchodilator therapy.

Interaction Between Beta-Blockers and Beta-Agonists

The unequivocal pharmacological interaction between beta-blockers and beta-agonists is likely to influence clinical effectiveness. Nevertheless, the evidence supporting an interaction is circumstantial and derives largely from patients experiencing myocardial infarction. The effects of beta-blockers may be attenuated by beta-agonists. Less benefit was apparent in clinical trials using beta-blockers with intrinsic sympathomimetic activity after infarction (102). Beta-blocker use was also not associated with lower mortality among patients receiving concurrent beta-agonists in the Cooperative Cardiovascular Project (29). Conversely, the effects of beta-agonists, both adverse and beneficial, may be attenuated by beta-blockers. The risk of acute coronary syndromes associated with beta-agonists was lessened by concurrent beta-blockade in a case-control study using data from the Veterans Administration's ACQUIP trial (p for interaction <0.0005) (80). The aforementioned interaction between beta-blockers and beta-agonist bronchodilator response must also be considered. Whereas cardioselective beta-blockers permit bronchodilation, noncardioselective beta-blockers inhibit beta-agonist response.

Clinical Recommendations

Beta-blockers. The uncertainty arising from the paucity of evidence must be balanced against 1 certainty: Beta-blockers markedly improve symptoms and survival in patients with HF. Patients should not be denied therapy that reduces mortality by 35% (66,103,104). COPD (even moderate or severe) is not a contraindication to beta-blockers. Low-dose initiation and gradual up-titration is recommended. Cardioselectivity is paramount; metoprolol, bisoprolol, and nebivolol are candidates.

Beta-agonists. Beta-agonists are associated with increased mortality and hospitalization in patients with HF, and they fail to improve hard clinical endpoints in patients with COPD. Clinicians should only prescribe beta-agonists for clear symptom relief, after carefully considering the etiology of dyspnea and objectively documenting airflow obstruction. Oral beta-agonists should be avoided, and both the dose and frequency of nebulized therapy should be minimized. The possibility of worsening HF must always be considered when beta-agonist use increases in patients with HF and concurrent COPD.

Just as COPD and HF frequently coexist (4), so too do COPD and asthma. Even though randomized controlled trials have established the safety of long-acting beta-agonists in patients with COPD (105), concerns remain regarding safety in patients with asthma that have necessitated label changes under the Food and Drug Administration Amendments Act (106). No prospective study has addressed the safety of long-acting beta-agonists in patients with COPD and concomitant asthma. By contrast, the long-acting anticholinergic bronchodilator tiotropium has proven efficacy in both COPD and more recently asthma (107,108), with reassuring cardiovascular safety data and U.S. Food and Drug Administration approval (109,110). Moreover, another recent large randomized controlled trial has shown tiotropium to be more effective than and equally as safe as salmeterol in patients with COPD (111). Patients with HF and concomitant COPD who require regular long-acting inhaled bronchodilators, therefore, should start treatment with a long-acting antimuscarinic rather than long-acting beta-agonists.

Conclusions

The combination of HF and COPD presents complex therapeutic challenges. Many questions remain unanswered. The efficacy of beta-blockade in patients with mild and fixed airflow obstruction likely extends to those with more severe disease, though the evidence is rudimentary. The long-term influence of beta-blockade on pulmonary function, symptoms, and quality of life is unclear. Robust clinical trials are required to provide the answers that may finally allay physicians' mistrust of beta-blockers in patients with COPD. The potential adverse effects of beta-agonists likewise require further clarification. Studies should be randomized, placebo-controlled, and of sufficient magnitude to investigate clinical outcomes. The U.S. Food and Drug Administration recently convened to consider the safety of long-acting beta-agonists in asthma (106). The safety of beta-agonists in patients with HF and concurrent pulmonary disease appears equally concerning.

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