Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-325 Mepolizumab

Stand: März 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Mepolizumab zur Behandlung der COPD **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Änderung der Arzneimittel-Richtlinie, Anlage XII: Beschlüsse über die Nutzenbewertung von neuen Arzneimitteln nach § 35a SGB V - Fluticasonfuroat/Vilanterol (Beschluss vom 20.03.2014) - Indacaterol/Glycopyrronium (Beschluss vom 08.05.2014) - Olodaterol (Beschluss vom 17.07.2014) - Tiotropium/ Olodaterol (Beschluss vom 04.02.2016) - Umeclidinium/Vilanterol (Beschluss vom 08.01.2015) - Aclidiniumbromid/Formoterol (Beschluss vom 16.07.2015) - Aclidiniumbromid (erneute Nutzenbewertung, Beschluss vom 07.04.2016) - Umeclidinium (Beschluss vom 21.07.2016) - Fluticasonfuroat/Umeclidinium/Vilanterol (Beschluss vom 16.08.2018; neues Anwendungsgebiet Beschluss 02.05.2019) - Dupilumab (Beschluss vom 6.02.2025) IQWiG Abschlussbericht - Tiotropiumbromid (IQWiG Bericht A05-18 vom 26.06.2012)
Die Vergleichstherapie soll nach dem allgemein anerkannten	

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Mepolizumab zur Behandlung der COPD Kriterien gemäß 5. Kapitel § 6 VerfO	
Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Mepolizumab	Geplantes Anwendungsgebiet laut Beratungsanforderung: Nucala ist angezeigt bei Erwachsenen als zusätzliche Erhaltungstherapie für unkontrollierte chronisch obstruktive Lungenerkrankung (COPD) mit einem inhalativen Kortikosteroid (ICS), einem langwirksamen Beta2-Agonisten (LABA) und einem langwirksamen Muskarinantagonisten (LAMA), die durch erhöhte Blut-Eosinophile gekennzeichnet ist
SAMA: Anticholinergika, kurzwirksam	
Ipratropiumbromid R03BB01 generisch	Ipratropiumbromid wird zur Therapie von reversiblen Bronchospasmen in Zusammenhang mit chronisch obstruktiver Lungenerkrankung (COPD) eingesetzt. (FI Ipratropium Teva)
LAMA: Anticholinergika, langwirksame	
Tiotropiumbromid R03BB04 Spiriva Respimat	Spiriva Respimat ist indiziert als dauerhaft einzusetzender Bronchodilatator zur Befreiung von Symptomen bei chronischer obstruktiver Lungenerkrankung (COPD)). (FI Spiriva Respimat)
Aclidiniumbromid R03BB05 Bretaris/Eklira Genuair	Bretaris Genuair bzw. Eklira Genuair werden als bronchodilatatorische Dauertherapie zur Befreiung von Symptomen bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD) angewendet. (FI Bretaris/Eklira Genuair)
Umeclidiniumbromid R03BB07 Incruse Ellipta	Incruse Ellipta ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) angezeigt. (FI Incruse Ellipta)
Glycopyrroniumbromid R03BB06 Seebri Breezhaler	Seebri Breezhaler ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt. (FI Seebri Breezhaler)
SABA: Selektive Beta2-Adrenozeptor-Agonisten, kurzwirksame	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Beispielhaft Salbutamol R03AC02 generisch	Symptomatische Behandlung von Erkrankungen mit reversibler Atemwegsobstruktion, wie z. B. Asthma bronchiale oder chronisch obstruktive bronchiale Erkrankung (COPD) mit reversibler Komponente. (FI Sultanol Inhalationslösung)
LABA: Selektive Beta2-Adrenozeptor Agonisten, langwirksame	
Salmeterol R03AC12 generisch	Zur Langzeitbehandlung von Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z. B. Asthma bronchiale (anfallsweise auftretende Atemnot durch Atemwegsverkrampfung, insbesondere nächtliches Asthma), chronische Bronchitis und Blählunge (Lungenemphysem). (FI Serevent)
Formoterol R03AC13 generisch	Forair ist ebenfalls angezeigt zur Erleichterung der bronchialobstruktiven Symptome bei Patienten mit chronisch-obstruktiver Atemwegserkrankung (COPD) (FI Forair)
Indacaterol R03AC18 Onbrez Breezhaler	Onbrez Breezhaler wird angewendet zur bronchialerweiternden Erhaltungstherapie der Atemwegsobstruktion bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD). (FI Onbrez Breezhaler)
Olodaterol R03AC19 Striverdi Respimat	Striverdi Respimat ist indiziert als Bronchodilatator zur Dauerbehandlung bei chronischer obstruktiver Lungenerkrankung (COPD). (FI Striverdi Respimat)
Xanthine	
Beispielhaft Theophyllin R03DA04 generisch	Bronchospasmolytikum/Antiasthmatikum. Behandlung und Verhütung von Atemnotzuständen aufgrund von Verengung der Atemwege (Bronchokonstriktion) bei Patienten mit persistierendem Asthma bronchiale oder mittel- bis schwergradiger obstruktiver Atemwegserkrankung (z. B. chronische Bronchitis und Lungenemphysem). (FI Theophyllin retard-ratiopharm)
Phosphodiesterase-4-Inhibitoren	
Roflumilast, oral R03DX07 Daxas	Daxas ist indiziert zur Dauertherapie bei erwachsenen Patienten mit schwerer COPD (chronisch-obstruktive pulmonale Erkrankung, FEV 1 nach Anwendung eines Bronchodilatators weniger als 50 % vom Soll) und chronischer Bronchitis sowie häufigen Exazerbationen in der Vergangenheit, begleitend zu einer bronchodilatatorischen Therapie. (FI Daxas)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Glucokortikosteroide	
Glucokortikosteroide, inhalativ	
Beispielhaft Beclometason R03BA01 generisch	Zur Behandlung von Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z. B. bei - Asthma bronchiale - chronisch obstruktiver Bronchitis (FI (Beclometason-ratiopharm)
Glucokortikosteroide, oral	
Beispielhalft Prednisolon H02AB06 generisch	Pneumonologie […] - akute Exazerbation einer COPD (DS: b), empfohlene Therapiedauer bis zu 10 Tage (FI Prednisolon acis)
Kombinationen: Selektiver Beta2-Adrenozeptor-Agonist + Anticholinergikum	
Salbutamol + Ipratropiumbromid R03AK04 generisch	Zur Behandlung von Bronchospasmen bei Patienten, die an chronisch obstruktiver Lungenkrankheit (COPD) leiden und eine regelmäßige Behandlung mit Ipratropiumbromid und Salbutamol benötigen. (FI Ipramol Teva Steri-Neb)
Fenoterol + Ipratropiumbromid R03AK03 generisch	Berodual Respimat ist indiziert zur Vorbeugung und Behandlung von Bronchospasmen bei Asthma und chronischer obstruktiver Atemwegserkrankung (COPD). Eine begleitende entzündungshemmende Behandlung sollte stets in Betracht gezogen werden. (FI Berodual Respimat)
Indacaterol + Glycopyrroniumbromid R03AL04 Ultibro Breezhaler	Ultibro Breezhaler ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt. (FI: Ultibro Breezhaler)
Vilanterol + Umeclidiniumbromid R03AL03	ANORO ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) angezeigt. (FI ANORO)

II. Zugelassene Arzneimittel im Anwendungsgebiet

ANORO	
Formoterol + Aclidiniumbromid R03AL05 Brimica Genuar	Brimica Genuar ist indiziert als bronchodilatatorische Erhaltungstherapie zur Linderung von Symptomen bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD). (FI Brimica Genuar)
Tiotropium/ Olodaterol R03AL06 Spiolto Respimat	Spiolto Respimat ist indiziert als Bronchodilatator zur Dauerbehandlung, um bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) die Symptome zu lindern. (FI Spiolto Respimat)
Kombinationen: Selektiver Beta2-Adrenozeptor-Agonist + Glucokortikosteroid	
Salmeterol + Fluticason R03AK06 generisch	ATMADISC ist angezeigt für die symptomatische Behandlung von Patienten mit COPD mit einem FEV 1 < 60 % des Normwertes (vor Anwendung eines Bronchodilatators) und wiederholt aufgetretenen Exazerbationen, die trotz regelmäßiger bronchienerweiternder Therapie signifikante Symptome aufweisen. (FI atmadisc Diskus)
Formoterol + Budesonid R03AK07 Symbicort	Symbicort Turbohaler 160/4,5 Mikrogramm/Dosis Pulver zur Inhalation ist angezeigt zur symptomatischen Behandlung von Erwachsenen im Alter von 18 Jahren und älter mit COPD, die ein forciertes exspiratorisches Einsekundenvolumen (FEV 1) < 70 % des Normwertes (nach Bronchodilatation) und Exazerbationen in der Vorgeschichte aufweisen, trotz einer regelmäßigen Behandlung mit Bronchodilatatoren (siehe auch Abschnitt 4.4). (FI Symbicort Turbohaler)
Vilanterol + Fluticasonfuroat R03AK10 Relvar Ellipta	Relvar Ellipta ist angezeigt für die symptomatische Behandlung von Erwachsenen mit COPD mit einem FEV_1<70% des Normwerts (nach Anwendung eines Bronchodilatators), die trotz regelmäßiger bronchodilatatorischer Therapie Exazerbationen in der Vorgeschichte aufweisen. (FI Relvar Ellipta)
Kombinationen: Selektiver Beta2-Adrenozeptor-Agonist + Glucokortikosteroid + Anticholinergikum	
Beclometason / Formoterol / Glycopyrronium R03AL09 Trimbow	Zur Erhaltungstherapie bei erwachsenen Patienten mit moderater bis schwerer chronisch obstruktiver Lungenerkrankung (COPD), die mit einer Kombination aus einem inhalativen Kortikosteroid und einem langwirksamen Beta-2-Agonisten oder einer Kombination aus einem langwirksamen Beta-2-Agonisten und einem langwirksamen Muskarin-Antagonisten nicht ausreichend eingestellt sind (zu den Wirkungen hinsichtlich Symptomkontrolle und Prävention von Exazerbationen siehe Abschnitt 5.1). (FI Trimbow)
Umeclidinium/ Vilanterol/ Fluticason	Trelegy Ellipta ist angezeigt für die Erhaltungstherapie bei erwachsenen Patienten mit moderater bis schwerer chronisch obstruktiver Lungenerkrankung (COPD), die mit einer Kombination aus einem inhalativen Kortikosteroid und einem langwirksamen Beta 2 -Agonisten oder mit einer Kombination aus

II. Zugelassene Arzneimittel im Anwendungsgebiet	
R03AL08 Trelegy Ellipta	einem langwirksamen Beta 2 -Agonisten und einem langwirksamen Muscarinrezeptor-Antagonisten nicht ausreichend eingestellt sind (zu den Wirkungen hinsichtlich Symptomkontrolle und Vermeidung von Exazerbationen siehe Abschnitt 5.1). (FI Trelegy Ellipta)
Antikörper	
Dupilumab D11AH05 Dupixent	Dupixent ist angezeigt als Add-on-Erhaltungstherapie bei erwachsenen Patienten mit durch eine erhöhte Anzahl an Eosinophilen im Blut gekennzeichneter chronisch obstruktiver Lungenerkrankung (COPD), die trotz einer Kombinationstherapie aus einem inhalativen Corticosteroid (ICS), einem langwirksamen Beta-2-Agonisten (LABA) und einem langwirksamen Muskarinantagonisten (LAMA) oder, falls ICS nicht angebracht ist, einer Kombinationstherapie aus LABA und LAMA unzureichend kontrolliert ist (siehe Abschnitt 5.1). (FI Dupixent)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-325 (Mepolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. Februar 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AECOPD	Acute exacerbation of COPD
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BDP	Bedometasone dipropionate
BUD	Budesonid
CAT	COPD Assessment Test
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
CNS	Zentrales Nervensystem
COPD	Chronic obstructive pulmonary disease
ECRI	ECRI Guidelines Trust
FDC	Fixed dose combination
FEV1/FEVD	Forced expiratory volume in one second
FF	Fluticasone furoate
FOR	Formoterol
FP	Fluticasone propionate
FVC	Forced Vital Capacity
G-BA	Gemeinsamer Bundesausschuss
GDG	Guideline development group
GIN	Guidelines International Network
GLY/GB	Glycopyrronium
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
ICS	Inhaled Corticosteroide
IND	Indacaterol
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonists
LoE	Level of Evidence
LTOT	Long term oxygen therapy
MACE	Major adverse cardiovascular events

MCID	Minimal clinically important difference
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-analysis
NNT	Number needed to treat
OLO	Olodaterol
OR	Odds Ratio
PDE4	Phosphodiesterase-4 (inhibitor)
PEF	Peak expiratory flow
QoL	Quality of Life
RCT	Randomised controlled trial
RR	Relatives Risiko
SABA	Short-acting beta 2 agonist
SAE	Serious adverse events
SAL	Salmeterol
SAMA	Short-acting muscarinic antagonists
SGRQ	St George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
SUCRA	Surface under the cumulative ranking curve
TDI	Transitional Dyspnoea Index
TIO	Tiotropium
TRIP	Turn Research into Practice Database
UMEC	Umeclidinium
VA/DoD	Veterans Affairs/Department of Defense
VI	Vilanterol
VIL	Vilanterol trifenatate
WHO	World Health Organization

1 Indikation

Unkontrollierte chronisch obstruktive Lungenerkrankung

Hinweis zur Synopse: Vorliegend wird auch Evidenz zu Patientinnen und Patienten mit kontrollierter COPD dargestellt.

Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation chronisch obstruktive Lungenerkrankung (COPD) durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 08.01.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 2276 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 12 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Janjua S et al., 2020 [6].

Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease (Review)

Fragestellung

To evaluate the efficacy and safety of oral PDE_4 inhibitors for management of stable COPD.

Methodik

Population:

- Adults (over 18 years of age) with COPD

Intervention /Komparator:

- orally administered PDE_4 inhibitor (roflumilast, cilomilast, tetomilast) vs placebo.
- concomitant therapy: inhaled or oral corticosteroids, inhaled long-acting betaT-agonists, or anticholinergics, or both

Endpunkte:

- Primary outcomes
  - Changes in lung function from baseline including forced expiratory volume in one second (FEVD), forced vital capacity (FVC), or peak expiratory flow (PEF)
  - Quality of life (e.g. total score on St George's Respiratory Questionnaire (SGRQ))
- Secondary outcomes
  - Incidence of COPD exacerbations
  - Symptoms (breathlessness on Borg and other scales and Shortness of Breath Questionnaire; composite measures (summary symptom score))
  - Exercise tolerance (six-minute walk test)
  - Adverse events (number of participants experiencing one or more adverse event, e.g. gastrointestinal, central nervous system (CNS), and cardiovascular adverse events; change in weight; withdrawal rates)
  - Serious adverse events
  - Mortality

Recherche/Suchzeitraum:

The previously published version included searches up to October 2016. We updated the search for this version from 2016 to 9 March 2020.

Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, through the Cochrane Register of Studies Online, PsycINFO Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO, Allied and Complementary Medicine Database (AMED) EBSCO

Weekly searches of MEDLINE Ovid, Embase Ovid

Qualitätsbewertung der Studien:

Two review authors (SJ, RF) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anmerkung FBMed: Die Extraktion der Ergebnisse beschränkt sich auf Roflumilast.

Anzahl eingeschlossener Studien:

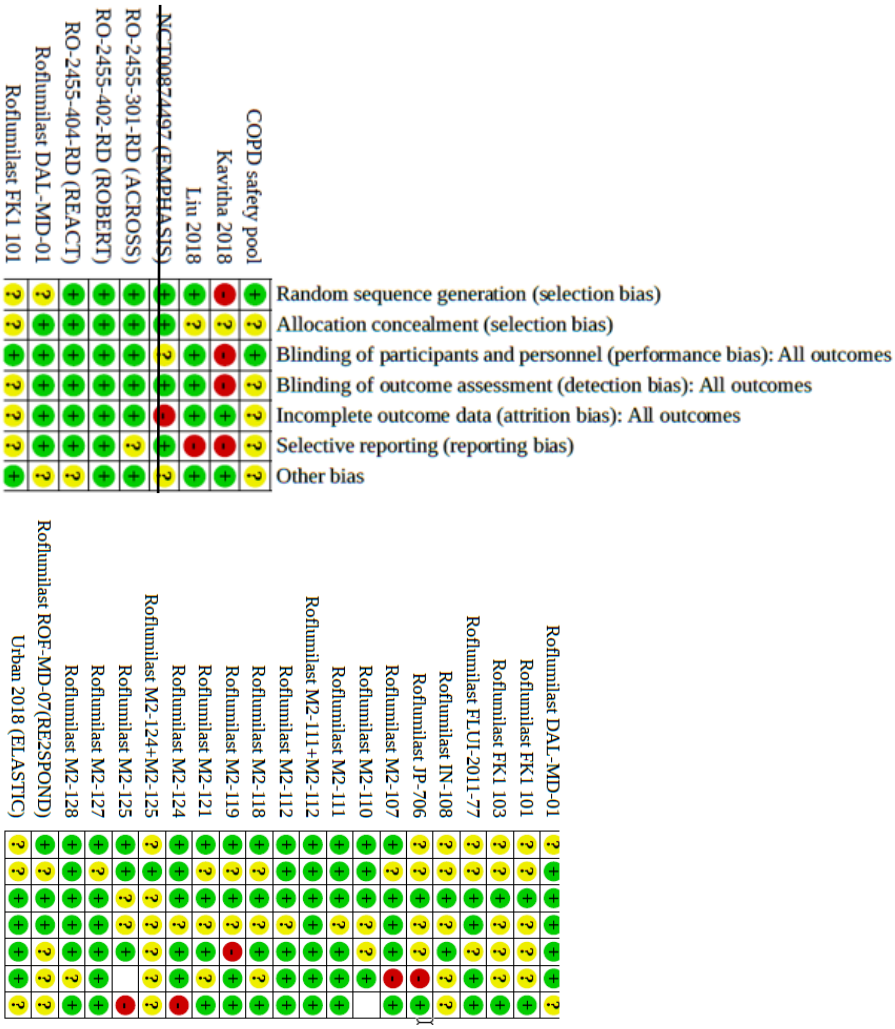
Of the 42 studies [included in this review], **27 studies examined roflumilast**, 14 trials studied cilomilast and one trial explored the use of tetomilast.

Charakteristika der Population:

The mean age of participants in these trials ranged from 60 to 70 years, with the proportion of male participants between 49% and 96%. Mean FEVD (% predicted) in trials that reported it ranged from 33% to 51%. Most trials included participants at all stages of COPD; however limitation to those with severe and very severe COPD occurred in RO-2455-301-RD (ACROSS), RO-2455-404-RD (REACT), Roflumilast DAL-MD-01, Roflumilast M2-111, Roflumilast M2-112, Roflumilast M2-124, Roflumilast M2-125, and Roflumilast ROFMD-07(RE2SPOND).

The duration of roflumilast treatment in studies ranged from 12 to 52 weeks.

Qualität der Studien:



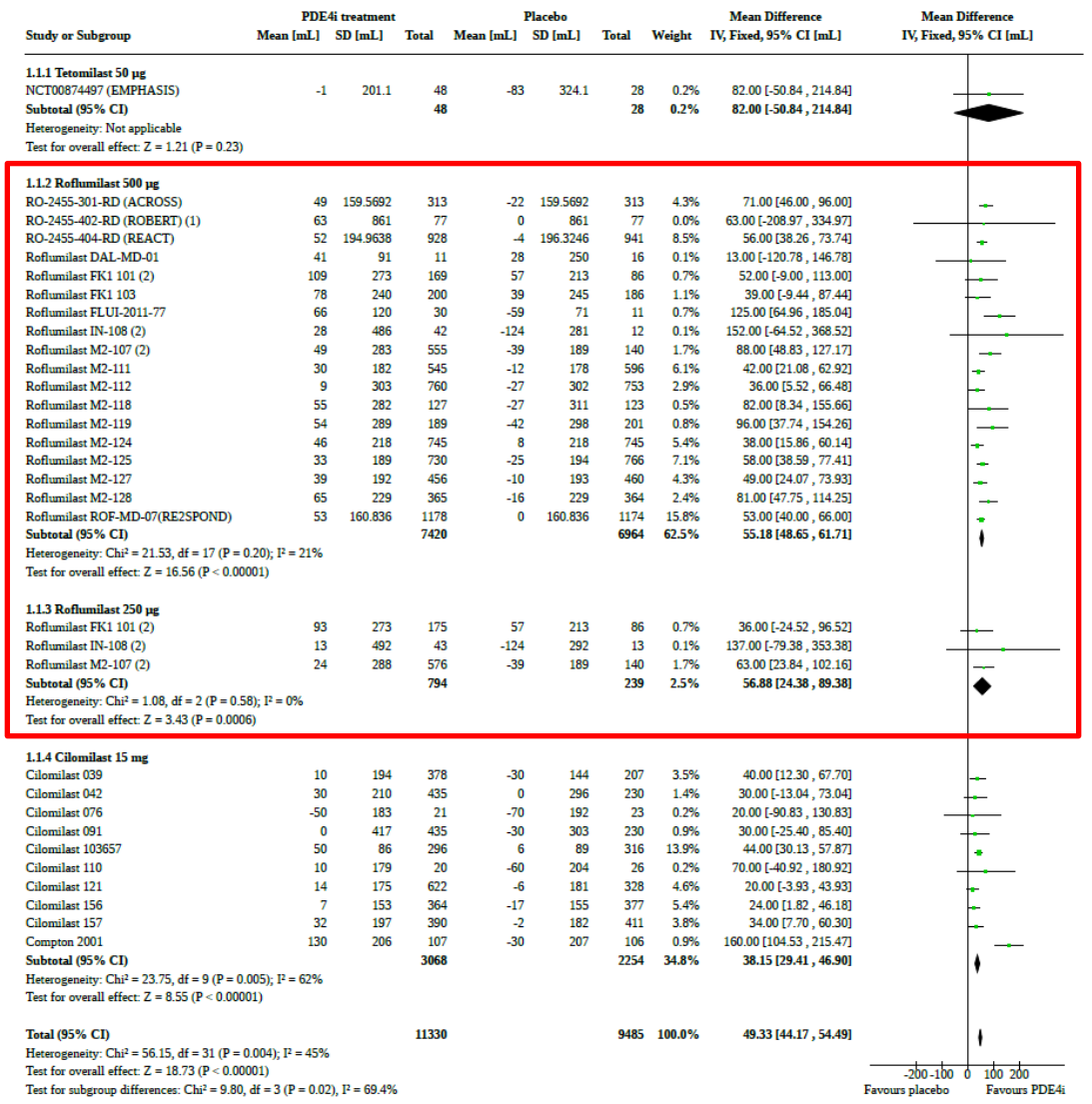
Studienergebnisse:

Anmerkung FBMed: Bei der Ergebnisextraktion wurde sich auf die primären Endpunkte fokussiert.

Change in FEV_1

We included 32 studies in the main analysis (participants = 20,815). Eighteen studies compared roflumilast 500 Gg with placebo, three studies compared roflumilast 250 Gg with placebo […].

Figure 3. Forest plot of comparison: 1 PDE_4 inhibitor versus placebo (2020 update), outcome: 1.1 FEV_1 (by drug) [mL].



Study or Subgroup	PDE4i treatment Mean [mL]	SD [mL]	Total	Placebo Mean [mL]	SD [mL]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mL]
1.1.1 Tetomilast 50 µg								
NCT00874497 (EMPHASIS)	-1	201.1	48	-83	324.1	28	0.2%	82.00 [-50.84 , 214.84]
Subtotal (95% CI)			**48**			**28**	**0.2%**	**82.00 [-50.84 , 214.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.21 (P = 0.23)								
1.1.2 Roflumilast 500 µg								
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	4.3%	71.00 [46.00 , 96.00]
RO-2455-402-RD (ROBERT) (1)	63	861	77	0	861	77	0.0%	63.00 [-208.97 , 334.97]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	8.5%	56.00 [38.26 , 73.74]
Roflumilast DAL-MD-01	41	91	11	28	250	16	0.1%	13.00 [-120.78 , 146.78]
Roflumilast FK1 101 (2)	109	273	169	57	213	86	0.7%	52.00 [-9.00 , 113.00]
Roflumilast FK1 103	78	240	200	39	245	186	1.1%	39.00 [-9.44 , 87.44]
Roflumilast FLUI-2011-77	66	120	30	-59	71	11	0.7%	125.00 [64.96 , 185.04]
Roflumilast IN-108 (2)	28	486	42	-124	281	12	0.1%	152.00 [-64.52 , 368.52]
Roflumilast M2-107 (2)	49	283	555	-39	189	140	1.7%	88.00 [48.83 , 127.17]
Roflumilast M2-111	30	182	545	-12	178	596	6.1%	42.00 [21.08 , 62.92]
Roflumilast M2-112	9	303	760	-27	302	753	2.9%	36.00 [5.52 , 66.48]
Roflumilast M2-118	55	282	127	-27	311	123	0.5%	82.00 [8.34 , 155.66]
Roflumilast M2-119	54	289	189	-42	298	201	0.8%	96.00 [37.74 , 154.26]
Roflumilast M2-124	46	218	745	8	218	745	5.4%	38.00 [15.86 , 60.14]
Roflumilast M2-125	33	189	730	-25	194	766	7.1%	58.00 [38.59 , 77.41]
Roflumilast M2-127	39	192	456	-10	193	460	4.3%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	2.4%	81.00 [47.75 , 114.25]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	15.8%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**7420**			**6964**	**62.5%**	**55.18 [48.65 , 61.71]**
Heterogeneity: Chi² = 21.53, df = 17 (P = 0.20); I² = 21%								
Test for overall effect: Z = 16.56 (P < 0.00001)								
1.1.3 Roflumilast 250 µg								
Roflumilast FK1 101 (2)	93	273	175	57	213	86	0.7%	36.00 [-24.52 , 96.52]
Roflumilast IN-108 (2)	13	492	43	-124	292	13	0.1%	137.00 [-79.38 , 353.38]
Roflumilast M2-107 (2)	24	288	576	-39	189	140	1.7%	63.00 [23.84 , 102.16]
Subtotal (95% CI)			**794**			**239**	**2.5%**	**56.88 [24.38 , 89.38]**
Heterogeneity: Chi² = 1.08, df = 2 (P = 0.58); I² = 0%								
Test for overall effect: Z = 3.43 (P = 0.0006)								
1.1.4 Cilomilast 15 mg								
Cilomilast 039	10	194	378	-30	144	207	3.5%	40.00 [12.30 , 67.70]
Cilomilast 042	30	210	435	0	296	230	1.4%	30.00 [-13.04 , 73.04]
Cilomilast 076	-50	183	21	-70	192	23	0.2%	20.00 [-90.83 , 130.83]
Cilomilast 091	0	417	435	-30	303	230	0.9%	30.00 [-25.40 , 85.40]
Cilomilast 103657	50	86	296	6	89	316	13.9%	44.00 [30.13 , 57.87]
Cilomilast 110	10	179	20	-60	204	26	0.2%	70.00 [-40.92 , 180.92]
Cilomilast 121	14	175	622	-6	181	328	4.6%	20.00 [-3.93 , 43.93]
Cilomilast 156	7	153	364	-17	155	377	5.4%	24.00 [1.82 , 46.18]
Cilomilast 157	32	197	390	-2	182	411	3.8%	34.00 [7.70 , 60.30]
Compton 2001	130	206	107	-30	207	106	0.9%	160.00 [104.53 , 215.47]
Subtotal (95% CI)			**3068**			**2254**	**34.8%**	**38.15 [29.41 , 46.90]**
Heterogeneity: Chi² = 23.75, df = 9 (P = 0.005); I² = 62%								
Test for overall effect: Z = 8.55 (P < 0.00001)								
Total (95% CI)			**11330**			**9485**	**100.0%**	**49.33 [44.17 , 54.49]**
Heterogeneity: Chi² = 56.15, df = 31 (P = 0.004); I² = 45%								
Test for overall effect: Z = 18.73 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.80, df = 3 (P = 0.02), I² = 69.4%								

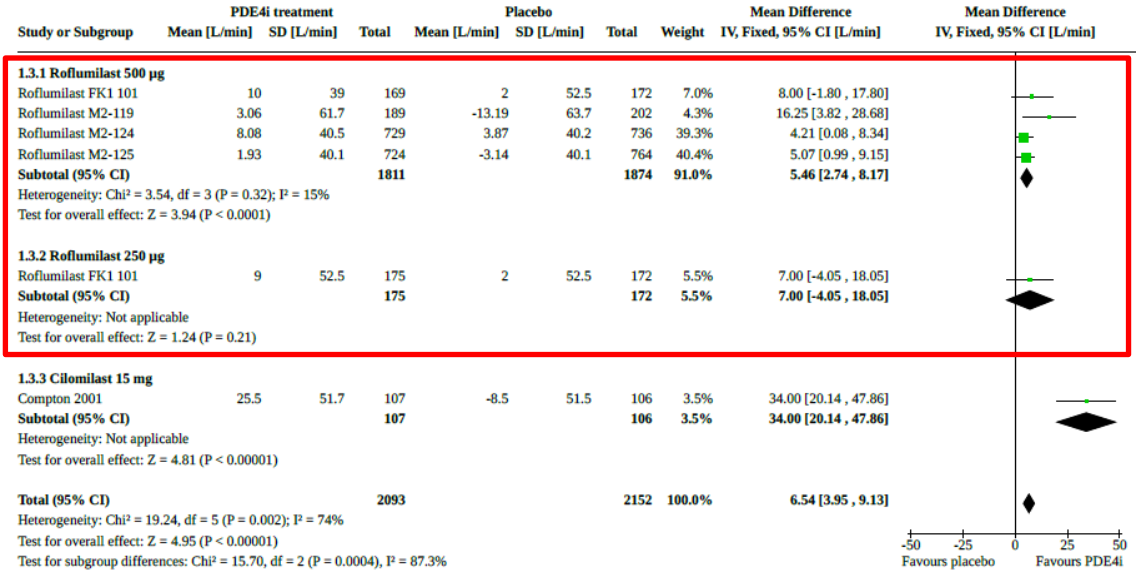
Footnotes

(1) Units converted from L to mL, standard deviations obtained by imputing participant number in each group in the calculator from GIV analysis. Mean differences for each treatment group were not availal

(2) The participant number in the placebo group was halved to avoid double counting

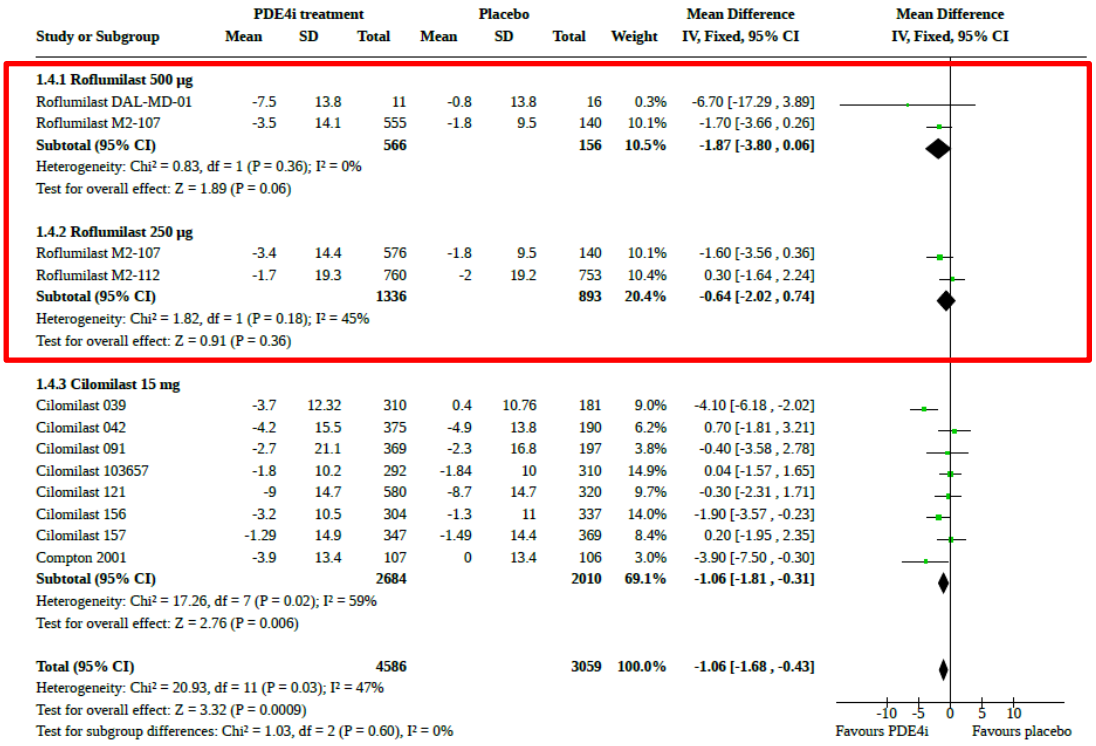
Change in PEF from baseline

Analysis 1.3. Comparison 1: PDE$_4$ inhibitor versus placebo (2020 update), Outcome 3: PEF



Change in quality of life (SGRQ)

Figure 5. Forest plot of comparison: 1 PDE$_4$ inhibitor versus placebo (2020 update), outcome: 1.4 SGRQ total score.

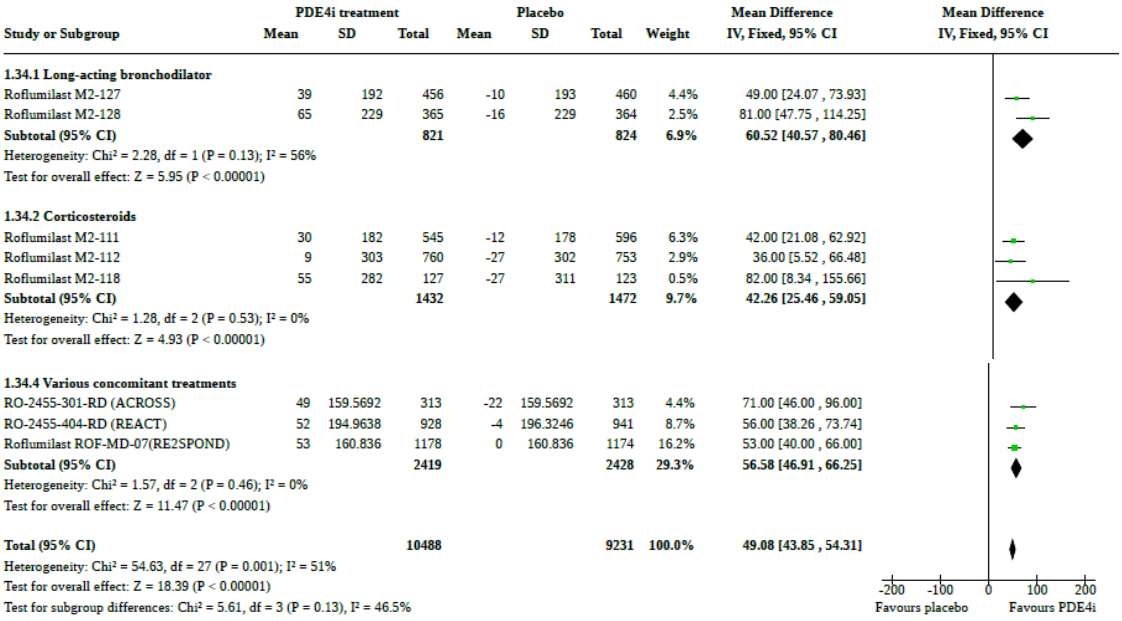


Subgroup analysis: concomitant therapies – FEV$_1$

With respect to PDE$_4$ inhibitor use with concomitant therapies (Analysis 1.34), the largest increases in FEV$_1$ were seen in two trials where participants were taking regular, long-acting bronchodilators: in one trial, salmeterol (Roflumilast M2-127), and in the other, tiotropium (Roflumilast M2-128) (MD 60.52 mL, 95% CI 40.57 to 80.46). The next largest improvements were seen in trials for which all concomitant medications (including long-acting bronchodilators if previously received) were continued (RO-2455-301-RD (ACROSS); RO-2455-404-RD (REACT); Roflumilast ROF-MD-07(RE2SPOND) (MD 56.58 mL, 95% CI 46.91 to 66.25) (Analysis 1.34). A similar improvement in FEV$_1$ was seen when participants were

taking corticosteroids (MD 42.26 mL, 95% CI 25.46 to 59.05) (Analysis 1.34). Improvements in FEV_1 were also noted in trials where only a PDE_4 inhibitor was taken (apart from shortacting $beta_2$ agonists) (MD 44.80 mL, 95% CI 37.69 to 51.91) (test for subgroup differences: Chi = 5.61, df = 3 (P = 0.13)

Analysis 1.34. Comparison 1: PDE_4 inhibitor versus placebo (2020 update), Outcome 34: FEV_1 (additional medication)



Anmerkung/Fazit der Autoren

Lung function: Based on data from 32 trials (low-certainty evidence), we found that both roflumilast and cilomilast led to greater improvements in lung function from baseline, as measured by forced expiratory volume in one second (FEV1), forced vital capacity (FVC), or peak expiratory flow rate (PEF), compared with placebo. Furthermore, improvement in lung function was seen regardless of the severity of the disease. This improvement in FEV1 lung function occurred whether or not PDE4 inhibitor treatment was given in addition to other COPD treatments, such as long-acting beta2- agonists (LABAs) or anticholinergics or inhaled corticosteroids (ICSs).

Quality of life: Data show only a small improvement in quality of life as assessed by St George's Respiratory Questionnaire (SGRQ) total score. Quality of life had been chosen as a primary outcome because of concerns as to whether or not the adverse effects of PDE4 inhibitors might outweigh any beneficial COPD-related events. The average change in SGRQ total score was 1.06 units (over a duration between 6 and 12 months).

Implications for practice: Phosphodiesterase-4 (PDE4) inhibitors are oral medicines that may be taken in combination with other standard chronic obstructive pulmonary disease (COPD) treatments. Most evidence has been gathered for roflumilast at a dose of 500 Ig daily and cilomilast at 15 mg twice daily. PDE4 inhibitors join an increasing list of treatments for COPD that improve short-term lung function and reduce exacerbations, but they have not been shown to increase life expectancy. Most trials to date have been one year in duration (with the exception of one study of nearly two years' duration). In contrast to longacting bronchodilators, PDE4 inhibitors have minimal benefit for symptoms on a day-to-day basis, or for quality of life, and are often associated with adverse effects, especially gastrointestinal effects and headaches. Roflumilast is associated with greater weight loss and increased psychiatric symptoms compared with placebo. Findings of this review provide cautious support for the use of PDE4 inhibitors in COPD. In accordance with GOLD

2020 guidelines, PDE4 inhibitors may have a place as add-on therapy for a subgroup of people with persistent symptoms or exacerbations despite optimal COPD management (e.g. people who are not controlled on fixeddose long-acting beta2-agonist (LABA) and inhaled corticosteroid (ICS) combinations).

Kommentare zum Review

- Da zur Zeit der Erstellung der Evidenzsynopse lediglich Roflumilast zugelassen ist, beschränkt sich die Extraktion der Ergebnisse auf diesem Wirkstoff.
- Most of the roflumilast trials were funded by pharmaceutical companies including AstraZeneca and GlaxoSmithKline.

3.2 Systematische Reviews

Lai CC et al., 2022 [8]

The impact of 52-week single inhaler device triple therapy versus dual therapy on the mortality of COPD patients: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

The present study conducted a systematic review and meta-analysis of the previous literature to determine the effect of 52 weeks single inhaler device triple therapy compared with dual therapy (LABA/LAMA or ICS/LABA) on all-cause mortality in patients with COPD.

Methodik

Population:

- patients with COPD

Intervention:

- single inhaler device triple therapy comprised of ICS, LABA, and LAMA

Komparator:

- dual therapies comprised of either LABA/LAMA or ICS/LABA

Endpunkte:

- Primary outcome: all-cause mortality.
- Secondary outcomes: the annual rate of moderate/severe COPD exacerbations, changes in the trough FEV1 in lung function from baseline, the change in the St. George's Respiratory Questionnaire (SGRQ) from baseline, the risk of pneumonia, respiratory tract infection, adverse events, and cardiovascular events

Recherche/Suchzeitraum:

- We searched for articles in the PubMed, Cochrane library, Web of Science, and Embase databases from their inception to 6 July 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs included 10,274 patients who received triple therapy and 12,395 patients who received LABA/LAMA or ICS/LABA dual therapy

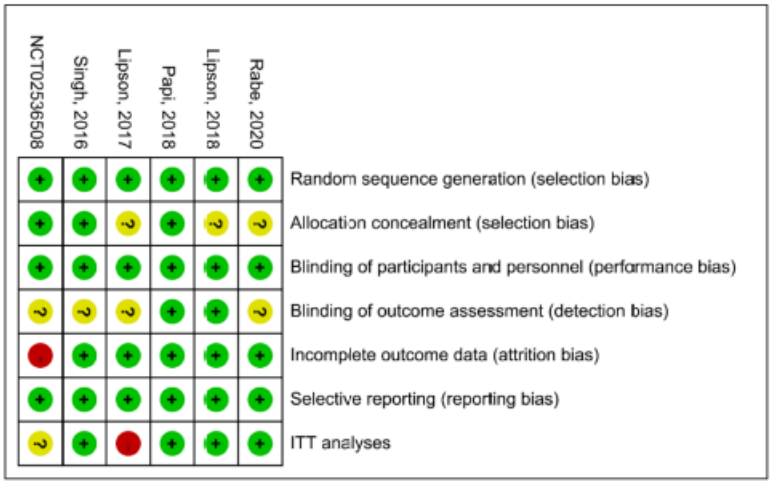
Charakteristika der Population:

Table 1. Characteristics of enrolled studies.

Study	Study Site	No of Participants	Study Period	Inclusion Criteria					Inhalation Therapy		Primary Outcome
				FEV1	Exacerbation history in previous year	Symptom scores	Excluded asthma	Others	Fixed triple	Comparator	
Lipson et al., 2018 (IMPACT) [20]	37 countries	10,355	2014–2017	FEV_1 of 50-80%	≥1 moderate/severe exacerbation if FEV_1 < 50% or ≥2 moderate exacerbations or one severe exacerbation if FEV1 of 50-80%	CAT score ≥ 10	No	≥40 years; MCID: 2 point; use LAMA, a LABA, or an ICS alone or in combination	FF/UME/VIL	FF/VIL or UME/VIL	Annual rate of moderate or severe COPD exacerbations
Papi et al., 2018 (TRIBUTE) [21]	187 sites in 17 countries	1532	2015–2017	FEV1 < 50%	≥1 moderate or severe exacerbation	CAT score ≥ 10	Yes	≥40 years; current or ex-smoker; used ICS/LABA, ICS/LAMA or LABA/LAMA for ≥2 months	BDP/FOR/GB	IND/GB	Moderate to severe COPD exacerbation rate for 52 weeks
Singh et al., 2016 (TRIOLOGY) [22]	159 sites in 14 countries	1368	2014–2016	FEV_1 < 50%	≥1 moderate/severe exacerbation	CAT score ≥ 10	Yes	≥40 years; current or ex-smoker; used ICS/LABA, ICS/LAMA or LABA/LAMA for ≥2 months	BDP/FOR/GB	BDP/FOR	Moderate to severe COPD exacerbation rate for 52 weeks
Rabe et al., 2020 (ETHOS) [24]	740 sites in 26 countries	8509	2015–2019	FEV1 of 25-65%;	≥1 moderate/severe exacerbation if FEV1 < 50% or ≥2 moderate exacerbations or one severe exacerbation if FEV1 ≥ 50%	CAT score ≥ 10	Yes	40 to 80 years; MICD: 2 point; receiving at least two inhaled maintenance therapies at the time of screening; a smoking history of at least 10 pack-years	BUD/FOR/GB	GB/FOR or BUD/FOR	Annual rate of moderate or severe COPD exacerbations
Lipson et al., 2017 (FULFIL)—extension population [33]	160 sites in 15 countries	430	2015–2016	FEV_1 < 50% or 50%-80%	≥2 moderate exacerbations or ≥1 severe exacerbation if FEV1 ≥ 50%	CAT score ≥ 10	Yes	≥40 years; receiving daily maintenance therapy for COPD for at least 3 months	FF/UME/VIL	BUD/FOR	Lung functionand health-related quality of life
NCT02536508 [34]	64 cites in US	627	2015–2017	NA	NA	NA	No	40 to 80 years, moderate to very severe COPD	BUD/FOR/GB	GB/FOR or BUD/FOR	Percent change from baseline in BMD of the lumbar spine

BDP, beclometasone dipropionate; BMD, bone mineral density; FOR, formoterol fumarate, GB, glycopyrronium; IND, indacaterol; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol; BUD, budesonide; FF, fluticasone furoate; MCID, minimum clinically important difference; COPD Assessment Test, CAT; inhaled corticosteroid, ICS; long-acting b2-agonist, LABA; long-acting muscarinic antagonist, LAMA.

Qualität der Studien:



Studienergebnisse:

Primary outcome: Mortality

- Risk of death was significantly lower in the ICS/LABA/LAMA FDC group compared to the LABA/LAMA group (RR = 0.69, 95% CI = 0.53–0.90, p = 0.007). By contrast, no significant difference in mortality was found between the ICS/LABA/LAMA FDC group and the ICS/LABA group (RR = 0.94, 95% CI = 0.72–1.24, p = 0.66)

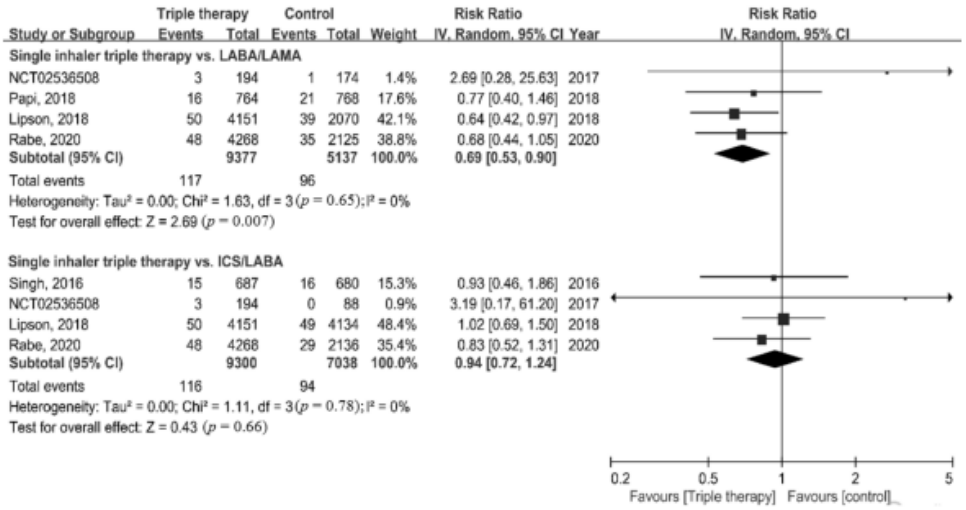


Figure 2. Forest plots for association of triple therapy with all-cause mortality.

Secondary Outcomes:

- For secondary outcomes, patients receiving ICS/LABA/LAMA FDC therapy had a significantly lower rate of moderate or severe exacerbations compared with LABA/LAMA or ICS/LABA dual therapy (RR = 0.76, 95% CI = 0.73–0.80, p < 0.001 for LABA/LAMA; RR = 0.84, 95% CI = 0.78–0.90, p < 0.001 for ICS/LABA) (Figure 3A). A significant improvement in SGRQ was observed in the single inhaler device triple therapy group compared with the dual therapy group (MD = -1.70, 95% CI = -1.72–-1.68, p < 0.001 for LABA/LAMA; MD = -1.37, 95% CI = -1.59–-1.14, p < 0.001 for ICS/LABA) (Figure 3B). ICS/LABA/LAMA FDC was associated with a significantly improved FEV1 compared with the two dual therapy groups (MD = 0.04, 95% CI = 0.01–0.07, p = 0.006 for LABA/LAMA; MD = 0.11, 95% CI = 0.06-0.15, p < 0.001 for ICS/LABA) (Figure 3C). However, high significant heterogeneity was observed in assessment of annual rate of moderate or severe exacerbations (p = 0.03, I2 = 78.6%), the change in the SGRQ score (p = 0.004, I2 = 88.2%), and the change in FEV1 (p = 0.02, I2 = 80.9%). Regarding the risk of adverse events, the risk of pneumonia in the ICS/LABA/LAMA FDC group was higher than in the LABA/LAMA group (RR = 1.43, 95% CI = 1.21–1.68, p < 0.001). There was no difference in the risk of adverse events, serious adverse events, cardiovascular events, and respiratory tract infections between the ICS/LABA/LAMA FDC group and the dual therapy groups

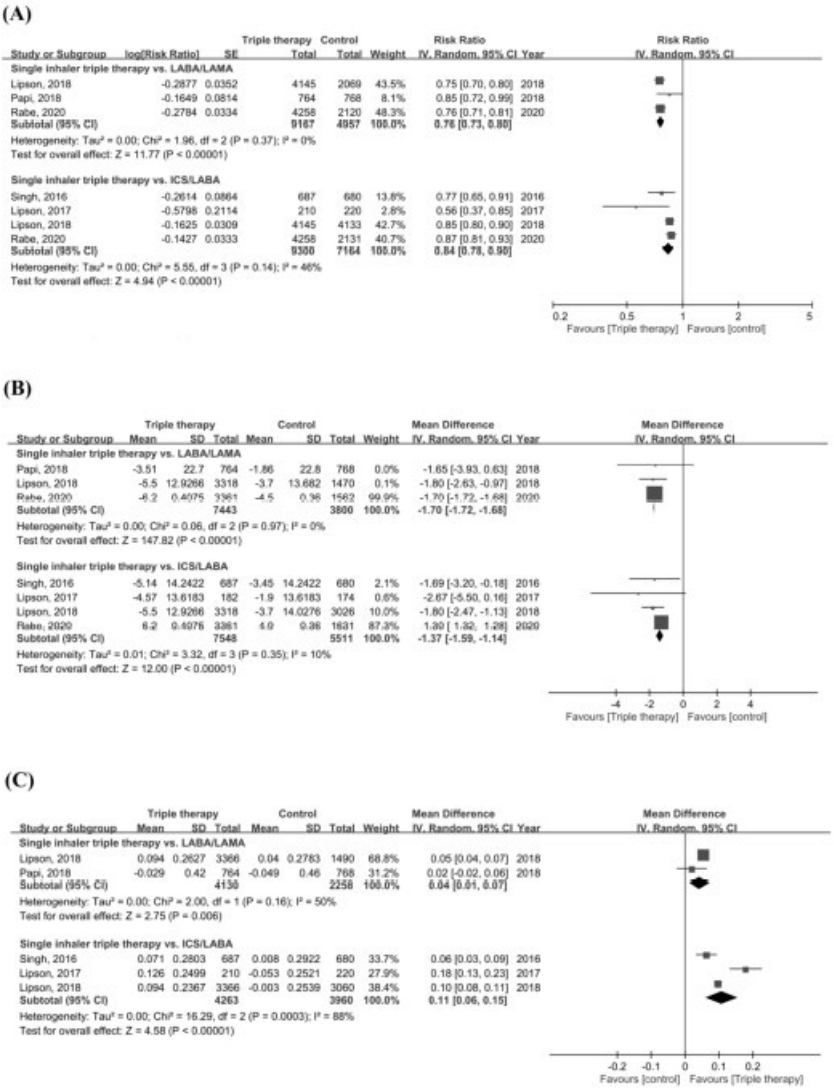


Figure 3. Forest plots for secondary outcomes. **(A)** Annual rate of moderate or severe COPD exacerbation, **(B)** change of SGRQ, and **(C)** change of FEV1.

-

Anmerkung/Fazit der Autoren

This meta-analysis indicated that COPD patients with ICS/LABA/LAMA FDC single inhaler device triple therapy could reduce 31% mortality rate compared to those with LABA/LAMA dual therapy. In addition, ICS/LABA/LAMA FDC therapy can also result in 24% and 16% lower rate of moderate or severe COPD exacerbations than LABA/LAMA and ICS/LABA, respectively. Moreover, ICS/LABA/LAMA FDC therapy is also associated with better lung function and quality of life compared with LABA/LAMA or ICS/LABA dual therapy. However, more pneumonia was found in triple therapy as compared with LABA/LAMA dual therapy. Therefore, more attention should be paid to the risk pneumonia while using ICS/LABA/LAMA FDC therapy in order to obtain a better outcome in COPD moderate or severe exacerbations and mortality.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor

- Koarai A et al., 2021 [7]

In the patients with symptomatic moderate and severe COPD and a history of exacerbations, triple therapy causes a higher incidence of pneumonia than LAMA/ LABA, but is still a more preferable treatment due to the lower incidence of exacerbations, higher trough FEV1 and better QOL score. In these patients, triple therapy was also superior to LAMA/LABA due to the lower mortality and better dyspnea score.

- Long H et al., 2021 [10]

  Our meta-analysis suggests a beneficial effect of single inhaler triple therapy in terms of mortality, frequency of moderate or severe COPD exacerbation episodes, and lung function in symptomatic COPD patients. However, ICS/LAMA/LABA FDC is associated with an increased risk of pneumonia compared to LABA/LAMA FDC.

Chen H et al., 2021 [4]

Dual bronchodilator versus inhaled corticosteroid/long-acting β(2)-agonist in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials

Fragestellung

Therefore, we undertook this meta-analysis to systematically evaluate the efficacy and safety of dual bronchodilator and ICS/LABA in patients with COPD

Methodik

Population:

- patients aged ≥ 40 years with stable, moderate to very severe COPD according to GOLD 2019

Intervention:

- dual bronchodilator (LAMA/LABA) maintenance therapy […]. All kinds of dual bronchodilator at their approved doses were included.

Komparator:

- any ICS/ LABA combination

Endpunkte:

- The efficacy and safety endpoints included the improvement of lung function, COPD exacerbations, symptoms, and quality of life (St. George's Respiratory Questionnaire [SGRQ] score). And the safety endpoints included the risk of pneumonia, adverse cardiovascular events, serious adverse events (SAEs), all-cause mortality, and withdrawals due to adverse events

Recherche/Suchzeitraum:

- searched Cochrane Library, PubMed, Embase, and Clinical Trials.gov (from inception until September 2020) for published randomized controlled trials (RCTs)

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 eligible RCTs enrolled a total of 21,496 participants, of whom 9,871 received dual bronchodilator as intervention treatment and 11,625 received ICS/LABA as a control treatment

Charakteristika der Population:

Characteristics of the included RCTs.

Authors	Age (years)		No. of patients		Interventions		Duration (months)	Endpoints[1]
	DB	ICS/LABA	DB	ICS/LABA	DB (ug)	ICS/LABA (ug)		
Rabe et al. 2008 [25]	62 ± 9	62 ± 9	304	301	Tio 18 qd, F 12 bid	SFC 50/500 bid	1.5	②③⑤⑪
Vogelmeier et al. 2013 [8]	63.2 ± 8.2	63.4 ± 7.7	467	466	Inda/Glyco 110/50 qd	SFC 50/500 bid	6	②③⑦⑧⑨⑩⑪
Hoshino et al. 2015 [26]	72 ± 7	69 ± 6	22	21	Tio/Inda 18/150 qd	SFC 50/250 bid	4	②
Zhong et al. 2015 [27]	64.8 ± 7.8	65.3 ± 7.9	372	369	Inda/Glyco 110/50 qd	SFC 50/500 bid	6	②③④⑤⑥⑦⑧⑨⑪
Donohue et al. 2015 [9]	62.5 ± 9.1	63 ± 8.9	353	353	UMEC/VI 62.5/25 qd	SFC 50/250 bid	3	③④⑤⑥⑦⑧⑨⑪
Donohue et al. 2015 [9]	63.2 ± 8.6	64 ± 8.5	349	348	UMEC/VI 62.5/25 qd	SFC 50/250 bid	3	③④⑤⑥⑦⑧⑨⑪
Singh et al. 2015 [13]	61.8 ± 8	61.4 ± 8.1	358	358	UMEC/VI 62.5/25 qd	SFC 50/500 bid	3	③④⑤⑥⑦⑧⑨⑩⑪
Beeh et al. 2016 [14]	63.6 ± 7.6	63.6 ± 7.6	433	429	Tio/Olo 5/5 or 2.5/5 qd	SFC 50/500 or 50/250 bid	1.5	②③⑦⑧⑨⑪
Vogelmeier al. 2016 [28]	63.5 ± 8.1	63.3 ± 7.5	467	466	Acl/Form 400/12 bid	SFC 50/500 bid	6	③⑤⑦⑧⑨⑩⑪
Wedzicha et al. 2016 [10]	64.6 ± 7.9	64.5 ± 7.7	1678	1680	Inda/Glyco 110/50 qd	SFC 50/500 bid	12	①⑦⑧⑨⑩⑪
Frith et al. 2018 [11]	65 ± 9.1	65.1 ± 8.4	248	250	Inda/Glyco 110/50 qd	SFC 50/500 bid	3	②⑦⑧⑨⑩⑪
Ferguson et al. 2018 [15]	65.1 ± 7.7	65.2 ± 7.2	625	314	GFF 18/9.6 bid	BFF 320/9.6 bid	6	②④⑤⑦⑧⑨⑩⑪
Lipson et al. 2018 [12]	65.2 ± 8.3	65.3 ± 8.3	2070	4134	UMEC/VI 62.5/25 qd	FF/VI 100/25 qd	12	③⑤⑦⑧⑨⑩⑪
Rabe et al. 2020 [16]	64.8 ± 7.6	64.6 ± 7.6	2125	2136	GFF 18/9.6 bid	BFF 320/9.6 bid	12	①⑦⑧⑨⑩⑪

RCT, randomized controlled trial; DB, dual bronchodilator; ICS/LABA, inhaled corticosteroid/long-acting beta2-agonist; Tio, tiotropium; F, formoterol; SFC, salmeterol/ fluticasone propionate; Inda/Glyco, indacaterol/glycopyrronium; Tio/Inda, tiotropium/indacaterol; UMEC/VI, umeclidinium/vilanterol; Tio/Olo, tiotropium/olodaterol; Acl/Form, Aclidinium/Formoterol; GFF, glycopyrrolate/formoterol; BFF, budesonide/formoterol fumarate; FF/VI, fluticasone furoate/vilanterol.

[1] Endpoints trough forced expiratory volume in the first second (trough FEV_1); ② forced vital capacity (FVC); ③ COPD exacerbation; ④ Transitional Dyspnea Index (TDI) score; ⑤ COPD assessment test (CAT) score; ⑥ St. George's Respiratory Questionnaire (SGRQ) score; ⑦ risk of pneumonia; ⑧ adverse cardiovascular events; ⑨ serious adverse events (SAE); ⑩ all-cause mortality; ⑪ withdrawals due to adverse events.

Qualität der Studien:

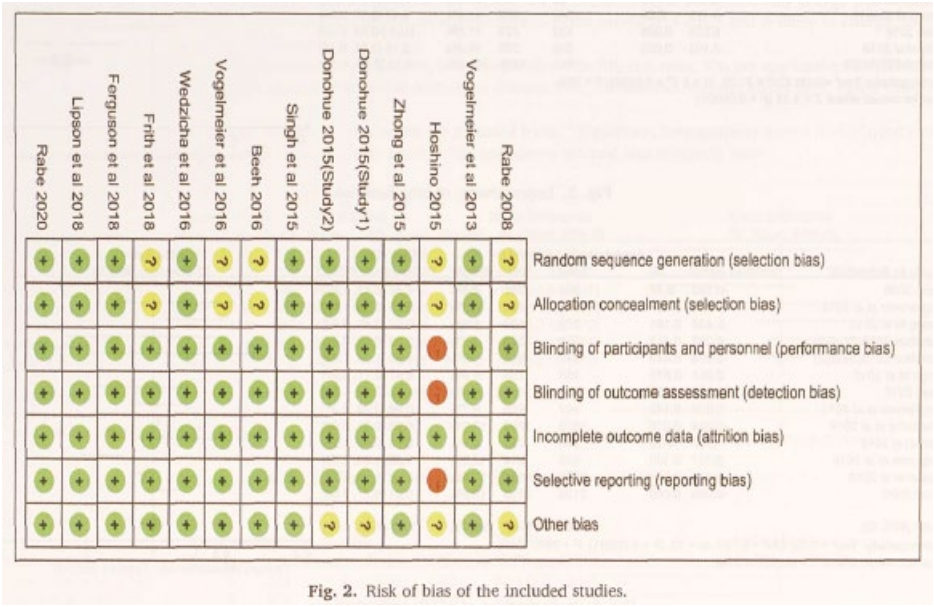


Fig. 2. Risk of bias of the included studies.

Studienergebnisse:

Improvement of lung function

- Thirteen trials reported trough FEV1 of patients after treatment, and 6 trials reported FVC. Subgroup analyses were conducted based on different parameters of lung function. **Dual bronchodilator showed a greater improvement** in both trough FEV1 (MD = 0.06 L, 95% CI International Immunopharmacology 93 (2021) 107447 30.04–0.07, P < 0.001) and FVC (FVC: MD = 0.12 L, 95% CI: 0.07–0.16, P < 0.001) in patients with COPD. Due to the substantial heterogeneity (I2 ≥ 50%) among the included trials, a random-effect model was used to analyze the pooled results. The evidence provided by the above results were graded as high quality.

Improvement of COPD exacerbations

- COPD exacerbations were included in 13 trials. There was **no significant difference** in the incidence of exacerbations between dual bronchodilator and ICS/LABA. Because of the obvious heterogeneity across the included trials (I2 =79%), a random effect model was selected to analyze data. The evidence provided by the pooled result was graded as low quality

Improvement of symptoms

- Symptoms were evaluated by the TDI score in 5 trials and by CAT score in 4 trials respectively. Subgroup analyses were conducted according to different COPD assessment questionnaires. There were **no significant differences** in the symptoms improvement between these two treatments, whether according to TDI score or CAT score. The evidence provided by the above results were graded as moderate quality and low quality.

Improvement of quality of life

- Quality of life was evaluated by the SGRQ score in 7 trials. **No significant difference** was found for the improvement of quality of life when comparing these two treatments. The evidence provided by the pooled result was graded as high quality.

Risk of pneumonia

- Twelve trials provided data on pneumonia. **Dual bronchodilator significantly reduced** the risk of pneumonia versus ICS/LABA (RR = 0.62, 95% CI: 0.53–0.72, P < 0.001), and the pooled result was graded as high-quality evidence.

Adverse cardiovascular events

- Ten trials provided data on adverse cardiovascular events. There was **no significant difference** in the incidence of adverse cardiovascular events between these two treatments. The evidence provided by the pooled result was graded as high quality.

Serious adverse events

- Twelve trials provided data on serious adverse events. There was **no significant difference** in the incidence of various serious adverse events when comparing these two treatments. The evidence provided by the pooled result was graded as high quality.

All-cause mortality

- Eleven trials provided data on all-cause mortality. **No significant difference** was found for all-cause mortality between these two treatments. The evidence provided by the pooled result was graded as moderate quality.

Withdrawals due to adverse events

- Information on withdrawals due to various adverse events was provided in 13 trials. **No significant difference** was found for withdrawals due to adverse events between these two treatments. The evidence provided by the pooled result was graded as high quality.

Anmerkung/Fazit der Autoren

Dual bronchodilator is superior to ICS/LABA in improving lung function and is associated with a lower risk of pneumonia in patients with COPD. There are no significant differences in other essential efficacy and safety profiles between these two maintenance treatments. Dual bronchodilator may be more beneficial for COPD patients than ICS/LABA.

Shuai T et al., 2021 [12]

Low-dose theophylline in addition to ICS therapy in COPD patients: a systematic review and meta-analysis

Fragestellung

we conducted this meta-analysis to explore the efficacy and safety of adding theophylline to ICS therapy in COPD to provide reliable evidence for clinicians.

Methodik

Population:

- COPD patients

Intervention/ Komparator:

- compared the efficacy between ICS plus theophylline therapy and without theophylline therapy

Endpunkte:

- hazard ratio (HR) for exacerbation frequency, HR for hospitalization rate, HR for mortality, improvement of FEV1, and changes in inflammatory or anti-inflammatory biomarkers

Recherche/Suchzeitraum:

- We conducted searches in electronic database such as PubMed, Web Of Science, Cochrane Library, and Embase from inception to October 31th, 2020

Qualitätsbewertung der Studien:

- We assessed the methodology quality of randomized controlled trials based on Cochrane Handbook for Systematic Reviews of Interventions
- We used the Newcastle–Ottawa Scale (NOS) to assess the quality of the cohort studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 studies included; 4/7 RCT, 3/7 Cohort
- A total of 47,556 participants were included from 7 studies and the sample size for a single study ranged between 24 and 10,816.

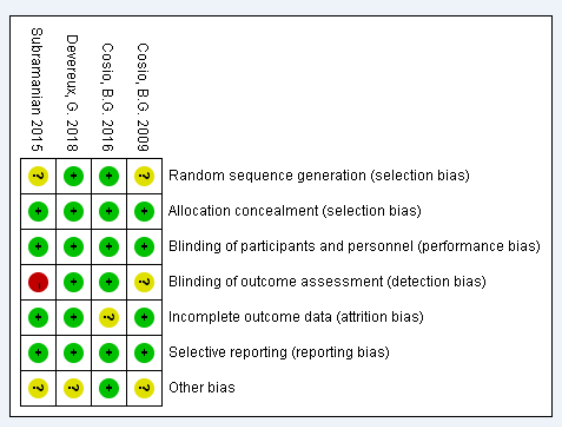
Charakteristika der Population:

Table 1. Characteristic of included studies (n = 7).

Study	Year	Design	N	Age	Male%	Smoker %	Duration	Intervention	Dosage(T)	NOS	outcome
Cyr, M.C.	2007	Cohort	21760/ 10697	72.5±7.9/71.2 ±7.9	66.7/ 65.1	NA	172±269/ 185±237 days	T+ICS/LABA+ICS	346±204 mg	7	①②
Cosio, B.G.	2009	RCT	16/19	67.6±1.3/66.7 ±1.7	100/0	NA	3 months	T/ST	100mg bid	NA	④
Lee, T.A.	2009	Cohort	1850/ 10816	71.4/69.0	94.0/ 91.5	NA	2002.10–2003.3	a.T+ICS/ICS; b.T+ICS+LABA/ ICS+LABA; c.T+ICS+SABA/ICS +LABA; d.T+ICS+LABA+SABA/ ICS+LABA+SABA	10–20 μg/ml	5	①②③④
Subramanian	2015	RCT	24/26	57.96 ± 7.47/ 54.46 ± 10.49	87.5/ 96.2	50/57.7	60 days	T+ICS+LABA/ICS+LABA	> 50 kg: 400 mg; 40–50 kg: 300 mg; < 40 kg: 200 mg qd	NA	⑤
Cosio, B.G.	2016	RCT	34/36	68.09 ± 8.37/ 67.82 ± 9.34	83.3/ 79.4	32.4/ 36.1	52 weeks	T+ICS+LABA/ICS+LABA	100mg bid	NA	①④
Devereux, G.	2018	RCT	788/779	68.3 ±8.2/68.5 ±8.6	53.9/ 53.7	31.4/ 32.0	52 weeks	T+ICS/ICS	200mg qd or bid	NA	①②③
Wilairat, P.	2019	Cohort	474/237	70.02 ±10.68/ 70.29±11.41	73.84/ 75.53	2.95/ 6.33	2011.1–2015.12	T+ICS+LABA/ICS+LABA	≤200mg qd or >200mg qd	6	①②

Outcome: ①exacerbation rate; ②hospitalization rate; ③mortality; ④FEV1; ⑤HDAC or inflammatory biomarkers. Abbreviations: T: theophylline; ICS: Inhaled corticosteroids; LABA: long-acting beta-2 agonists; ST: standard therapy; IPR: ipratropium; PBO: placebo; NA: not applicable; NOS: Newcastle-Ottawa Scale.

Qualität der Studien:



Studienergebnisse:

Exacerbation rate of COPD

- we conducted a subgroup analysis based on study design. RCTs and cohort studies both indicated that adding theophylline to ICS did not reduce COPD exacerbation (fig 3)

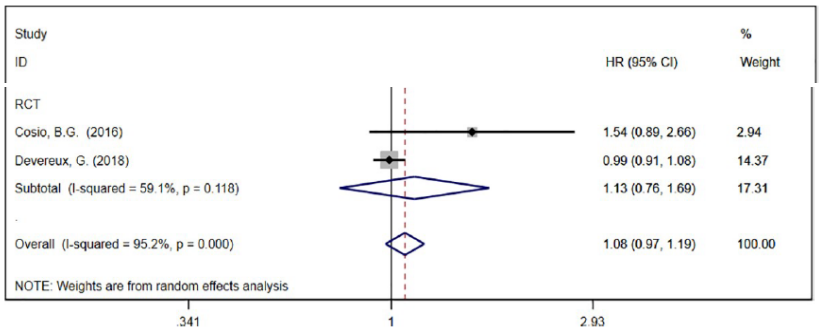


Fig 3. Forest plot of acute exacerbation rate (Subgroup analysis based on study design).

Anmerkung/Fazit der Autoren

In this systematic review and meta-analysis, low-dose theophylline as an add-on therapy to ICS did not reduce the exacerbation rate of COPD. Instead, the hospitalization rate and mortality increased. There was a controversy concerning the anti-inflammatory effect of low-dose theophylline. Furthermore, theophylline as an add-on therapy to ICS improved lung function compared with non-theophylline group. Thus, we do not recommend adding low-dose theophylline to ICS therapy in COPD patients based on current evidence.

Lipari M et al., 2020 [9]

Dual- versus mono-bronchodilator therapy in moderate to severe COPD: a meta-analysis

Fragestellung

the primary objective of this meta-analysis is to evaluate the efficacy of dual therapy with LABA + LAMA compared with monotherapy with LAMA for moderate to severe COPD

Methodik

Population:

- adult patients with moderate to severe COPD

Intervention/ Komparator:

- LABA + LAMA with long-acting bronchodilator monotherapy (LAMA) in adult patients with moderate to severe COPD

Endpunkte:

- FEV1 and SGRQ scores at baseline and 12 weeks
- incidence of adverse events, serious adverse events, and cardiovascular events at 12 weeks

Recherche/Suchzeitraum:

- PubMed, CINAHL, and Web of Science databases
- from inception through March 2020

Qualitätsbewertung der Studien:

- Jadad scoring system

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 full-text RCTs
- 6086 patients

Charakteristika der Population:

Table 1. Included Studies.

Study	Inclusion criteria	Duration	Study outcomes: Primary outcome	Study outcomes: Secondary outcome	Jadad score
Mahler et al (a)[23]	≥40 Years with moderate to severe COPD, with a smoking history ≥10 pack-years and PB FEV_1 ≤65% and ≥30% of predicted normal and PB FEV_1/FVC <70% at screening	12 Weeks	n = 1134 AUC FEV_1 Change from Baseline • Moderate COPD (n = 259): I +T vs T LSM 120 mL, 95% CI = 90-160 mL; $P \leq 0.001$ • Severe or very severe COPD (n = 302): I +T vs T LSM 130 mL, 95% CI = 100-160 mL $P \leq 0.001$	Difference in trough FEV_1 change from baseline • Moderate COPD (n = 259): LSM 90 mL; 95% CI = 50-130 mL; $P \leq 0.001$ • Severe or very severe COPD (n = 302): LSM 70 mL; 95% CI = 30-110 mL; $P \leq 0.001$ Any adverse effect • I + T (n = 570): 45.4% • T (n = 561): 41.2%	5
Mahler et al (b)[23]			n = 1142 AUC FEV_1 change from baseline • Moderate COPD (n = 259): I +T vs T LSM 130 mL; 95% CI = 90-160 mL; $P \leq 0.001$ • Severe or very severe COPD (n = 302): I +T vs T LSM 110 mL; 95% CI = 80-140 mL; $P \leq 0.001$	Difference in trough FEV_1 change from baseline • Moderate COPD (n = 261): LSM 90 mL; 95% CI = 60-120 mL; $P \leq 0.001$ • Severe or very severe COPD (n = 304): LSM 60 mL; 95% CI = 30-90 mL $P \leq 0.001$ Any adverse effect • I + T (n = 572): 43.0% • T (n = 570): 40.2%	5
Bateman et al[15]	≥40 Years, with moderate-to-severe stable COPD and a smoking history of ≥10 years	26 Weeks	n = 2144 Treatment difference, trough FEV_1 change from baseline • I + G vs I: LSM 0.07 L; $P < 0.001$ • I + G vs G LSM 0.09 L; $P < 0.001$	Treatment difference, trough FEV_1 • I + G vs T: LSM 0.08 L; $P < 0.001$ Any adverse event • I + G (n = 474) = 55.1% • G (n = 476) = 61.3% • T (n = 480) = 57.3% Serious adverse events • I + G (n = 474) = 4.6% • G (n = 476) = 6.1% • T (n = 480) = 4.0% MACE • I + G (n = 474) = 0% • G (n = 476) = 1.5% • T (n = 480) = 0.8%	5
Donohue et al[9]	≥40 Years with a clinically established history of COPD and smoking history of ≥10 pack-years, had a PB FEV_1/FVC <0.70 and a PB FEV_1 of <70% of predicted normal values and a score of ≥2 on the modified Medical Research Council (mMRC) Dyspnea Scale	24 Weeks	n = 1532 Trough FEV_1 change from baseline[a] • V + U (n = 413): LSM 0.171 L, SE ±0.0126 • U (n = 418): LSM 0.119 L, SE ±0.0126 • V (n = 421): LSM 0.076 L, SE ±0.0127	SGRQ score change from baseline • V + U (n = 413): −8.07, SE ±0.749 • U (n = 418): −7.25, SE ±0.753 • V (n = 421): −7.75, SE ±0.760 Any adverse effect • V + U (n = 413): 51% • U (n = 418): 52% • V (n = 421): 48% Serious adverse events • V + U (n = 413): 5% • U (n = 418): 6% • V (n = 421): 6%	3
Celli et al[10]	≥40 Years with a clinically established history of COPD and smoking history of ≥10 pack-years, had a PB FEV_1/FVC <0.70 and a PB FEV_1 of <70% of predicted normal values and a score of ≥2 on the mMRC Dyspnea Scale	24 Weeks	n = 1489 Trough FEV_1 change from baseline[a] • V + U (n = 403): LSM 0.207 L, ±SE 0.0119 • U (n = 404): LSM 0.129 L, ±SE 0.0119 • V (n = 404): LSM 0.093 L, ±SE 0.0121	Any adverse event • V + U (n = 403): 52% • U (n = 404): 53% • V (n = 404) = 53% Serious adverse event • V + U (n = 403): 6% • U (n = 404): 5% • V (n = 404) = 5%	5

Table 1. (continued).

Study	Inclusion criteria	Duration	Study outcomes: Primary outcome	Study outcomes: Secondary outcome	Jadad score
Donohue et al[11]	≥40 Years of age, with a smoking history of ≥10 pack-years and an established clinical history of COPD, patients had a post-salbutamol FEV_1/FVC ratio <0.70 and a post-salbutamol FEV_1 ≥35% and ≤80% of predicted values	52 Weeks	n = 563 Any adverse effect • U + V (n = 226): 53.1% • U (n = 227): 58.1% • P (n = 109): 52.3% Serious adverse events • U + V (n = 226): 6.2% • U (n = 227): 7.5% • P (n = 109): 6.4% Cardiac adverse events • U + V (n = 226): 15% • U (n = 227): 22% • P (n = 109): 23%	Trough FEV_1 change from baseline • U + VI (n = 226): 0.231 L (95% CI = 0.153-0.310) • U (n = 227): 0.178 L (95% CI = 0.098-0.258)	
Decramer et al (a)[12]	≥40 Years with moderate to very severe COPD	24 Weeks	n = 1141 Trough FEV_1 change from baseline[a] • V + U (n = 207): LSM 0.211, ±SE 0.018 • T (n = 203): LSM 0.121, ±SE 0.019 • V (n = 205): LSM 0.121, ±SE 0.019	SGRQ change from baseline • V + U (n = 207): LSM −6.87, ±SE 1.02 • T (n = 203): LSM −7.62, ±SE 1.05 • V (n = 205): LSM −8.29, ±SE 1.06	5
Decramer et al (b)[12]			n = 1191 Trough FEV_1 change from baseline[a] • V + U (n = 217): LSM 0.208, ±SE 0.018 • T (n = 215): LSM 0.149, ±SE 0.018 • U (n = 222): LSM 0.186 ±SE 0.018	SGRQ change from baseline • V + U (n = 217): LSM −9.95, ±SE 0.98 • T (n = 215): LSM −9.78, ±SE 0.95 • U (n = 222): LSM −8.40, ±SE 0.97 Any adverse events • V + U (n = 212) = 51% • T (n = 208) = 39% • V (n = 209) = 47% Serious adverse events • V + U (n = 212) = 3% • T (n = 208) = 6% • V (n = 209) = 7%	5
Singh et al[18]	≥40 Years of age with moderate to severe COPD with a smoking history ≥10 pack-years	24 Weeks	n = 1729 1-Hour postdose FEV_1 change from baseline • F + A (n = 385): LSM 0.299 L • A (n = 385): LSM 0.174 L • F (n = 384): LSM 0.160 L	SGRQ change from baseline • F + A (n = 385): −7.2 • A (n = 385): −5.8 • F (n = 384): −5.6 Any adverse events • F + A (n = 385): 50.4% • A (n = 385): 49.4% • F (n = 384): 56.5% Serious adverse events • F + A (n = 385): 6% • A (n = 385): 4.2% • F (n = 384): 3.6%	5
ZuWallack et al (a)[21]	≥40 Years of age with moderate to severe COPD, PB FEV_1 ≥30% and <80% of predicted normal, and PB FEV_1/FVC <70% with a smoking history ≥10 pack-years	12 Weeks	n = 1132 AUC 0-3 hours FEV_1 • O + T (n = 527): mean 0.313, ±SE 0.010 • T (n = 525): mean 0.196, ±SE 0.010 Trough FEV_1 change from baseline[a] • O + T (n = 527): mean 0.297, ±SE 0.009 • T (n = 525): mean 0.191, ±SE 0.009	SGRQ mean score at 12 weeks • O + T (n = 1039): 41.2, ±SE 0.33 • T (n = 1055): 43.1, ±SE 0.33 Any adverse event • O + T (n = 567): 45.3% • T (n = 565): 42.8% Serious adverse events • O + T (n = 567): 7.1% • T (n = 565): 4.6%	3

Table 1. (continued).

Study	Inclusion criteria	Duration	Study outcomes: Primary outcome	Study outcomes: Secondary outcome	Jadad score
ZuWallack et al (b)[21]		12 Weeks	n = 1135 AUC 0-3 hours FEV_1 • O + T (n = 523): mean 0.297, ±SE 0.010 • T (n = 538): mean 0.191 ±SE 0.010 Trough FEV_1 change from baseline[a] • O + T (n = 523): mean 0.175, ±SE 0.009 • T (n = 538): mean 0.135, ±SE 0.009	SGRQ mean score at 12 weeks • O + T (n = 1039): 41.2, ±SE 0.33 • T (n = 1055): 43.1, ±SE 0.33 Any adverse event • O + T (n = 566): 40.1% • T (n = 569): 43.2% Serious adverse events • O + T (n = 566): 4.2% • T (n = 569): 4.7%	3
Maleki-Yazdi et al[13]	>40 Years with moderate to very severe COPD and an established clinical history of COPD	24 Weeks	n = 905 Trough FEV_1 change from baseline[a] • V + U (n = 454): LSM 0.208, ±SE 0.0114 • T (451): 0.093, ±SE 0.0115	SGRQ change from baseline • V + U (n = 454): −7.21, ±SE 0.538 • T (451): −5.17, ±SE 0.548 Any adverse event • V + U (n = 454): 44% • T (451): 42% Any serious adverse event • V + U (n = 454): 4% • T (451): 4% Any cardiovascular event • V + U (n = 454): 2% • T (451): 2%	5
Asai et al[16]	≥40 Years with moderate to severe COPD, a smoking history of ≥10 pack-years, a PB FEV_1 ≥30% and <80% of the predicted normal, and a PB FEV_1/FVC <0.70 at screening	• SHINE: 26 weeks • ARISE: 52 weeks	n = 340 Trough FEV_1 change from baseline • I + G (n = 161): LSM 1.50 L • T (n = 79): LSM 1.42 L	SGRQ total score • I + G (n = 161): 28.84 • T (n = 79): 32.42 Any adverse event • I + G (n = 161): 65.2% • T (n = 79): 65.8%	1
Hashimoto et al[17]	≥40 Years with moderate to severe COPD, a smoking history of ≥10 pack-years, a PB FEV_1 ≥30% and <80% of the predicted normal, and a PB FEV_1/FVC <0.70 at screening	26 Weeks	n = 182 Trough FEV_1 change from baseline • I + G (n = 42) vs I (n = 41): 90 mL; $P = 0.015$ • I+G (n = 42) vs G (n = 40): 100 mL; $P = 0.004$ • I +G (n = 42) vs T (n = 40): 90 mL; $P = 0.017$ • I +G (n = 42) vs P (n = 19): 280 mL; $P < 0.001$	Any adverse event • I + G (n = 42): 50% • T (n = 40): 77.5% • I (n = 41): 65.9% • G (n = 40): 60.0% • P (n = 19): 62.2%	5
Buhl et al[22]	≥40 Years with moderate-to-severe COPD, a smoking history of ≥10 pack-years, a PB FEV_1 <80% of the predicted normal, and a PB FEV_1/FVC <0.70 at screening	24 Weeks	n = 5163 Prespecified analysis • Any adverse event ○ T + O (n = 1029): 74% ○ T (n = 1033): 73.3% ○ O (n = 1038): 76.6% • Serious adverse events ○ T + O (n = 1029): 16.4% ○ T (n = 1033): 16.7% ○ O (n = 1038): 17.4% • MACE ○ T + O (n = 1029): 2.3% ○ T (n = 1033): 1.8% ○ O (n = 1038): 2.4%		2

Table 1. (continued)

Study	Inclusion criteria	Duration	Study outcomes: Primary outcome	Study outcomes: Secondary outcome	Jadad score
D'Urzo et al[19]	≥40 Years of age with moderate to severe COPD, PB FEV_1 ≥30% and <80% of predicted normal, and PB FEV_1/FVC <70% with a smoking history ≥10 pack-years	28 Weeks	n = 921 Any adverse event • F + A (n = 182): 65.9% • A (n = 194): 67.5% • F (n = 192): 64.6% Serious adverse event • F + A (n = 182): 7.7% • A (n = 194): 67.5% • F (n = 192): 64.6%		5
Kerwin et al[14]	≥40 Years of age with a diagnosis of COPD PB FEV_1 of ≤70% and ≥50% of normal predicted values, mMRC Dyspnea Scale score of ≥1	12 Weeks	n = 494 Trough FEV_1 change from baseline[a] • V + U (n = 224): LSM 74 mL ±SE 15.5 • T (n = 225): LSM −14 mL ±SE 15.5	SGRQ change total score • V + U (n = 225): LSM −3.23 ±SE 0.59 • T (n = 232): LSM −2.67 ±SE 0.59 Any adverse event • V + U (n = 247): 30% • T (n = 247): 31% Cardiac adverse events • V + U (n = 247): 1.6% • T (n = 247): 1.2%	5
Sethi et al[20]	≥40 Years with stable, moderate to very severe symptomatic COPD (PB FEV_1/FVC <70% and PB FEV_1 <80% of predicted at screening, and a COPD Assessment Test score ≥10 at screening and randomization)	24 Weeks	n = 1583 Trough FEV_1 change from baseline • F + A (n = 314) vs T (n = 475): 19 mL; *P*, ns • F + A (n = 314) vs A (n = 475): 14 mL; *P*, ns • F + A (n = 314) vs F (n = 319): 55 mL; *P* < 0.001	SGRQ total score change from baseline • A + F (n = 314): 4.68 • T (n = 475): 5.58 • A (n = 475): 4.95 • F (n = 319): 3.96 Any adverse event • A + F (n = 314): 58.3% • T (n = 475): 60.0% • A (n = 475): 60.8% • F (n = 319): 65.8% Serious adverse event • A + F (n = 314): 7.3% • T (n = 475): 7.8% • A (n = 475): 8.6% • F (n = 319): 6.9% MACE • A + F (n = 314): 0.6% • T (n = 475): 0.6% • A (n = 475): 0.4% • F (n = 319): 1.3%	5

Abbreviations: A, aclidinium; AUC, standardized area under the curve; COPD, chronic obstructive pulmonary disease; F, formoterol; FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity; G, glycopyrronium; I, indacaterol; LSM, least-squares mean; MACE, major adverse cardiac event; O, olodaterol; P, placebo; PB, postbronchodilator; SGRQ, St George Respiratory Questionnaire; T, tiotropium; U, umeclidinium; V, vilanterol.
[a]Primary outcome used in our analysis.

Qualität der Studien:

Siehe Table 1

Studienergebnisse:

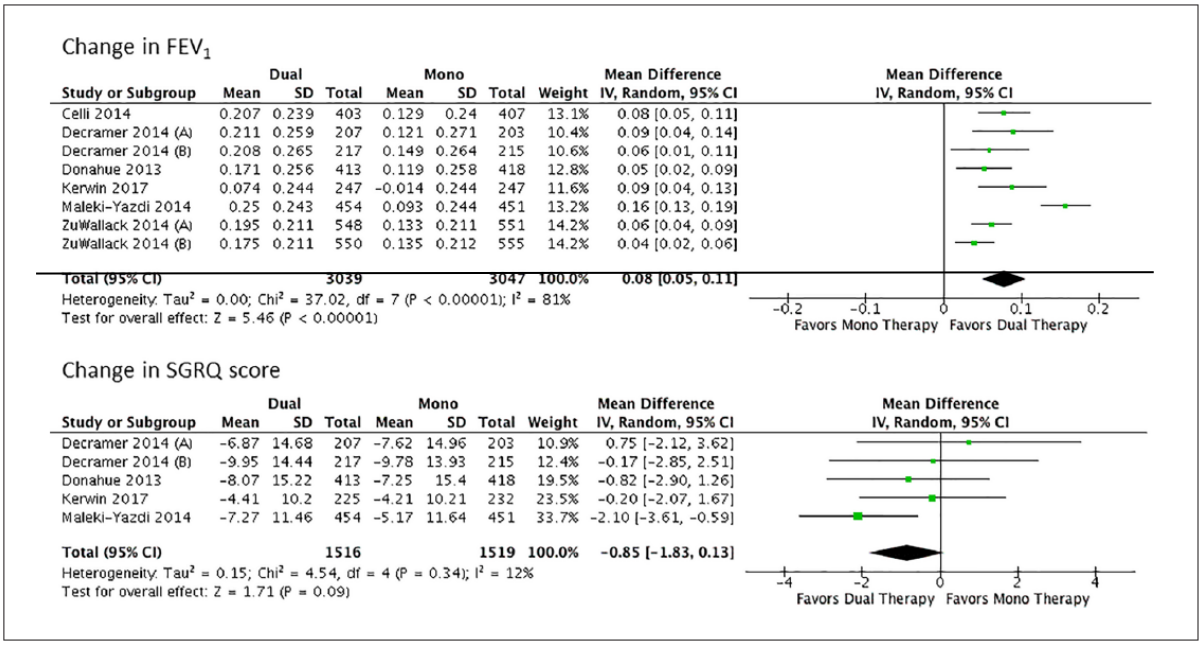


Figure 2. Efficacy as measured by FEV_1 and SGRQ score.
Abbreviations: FEV_1, forced expiratory volume at 1 s; SGRQ, St George Respiratory Questionnaire.

The 18 studies included in this meta-analysis had a total of 6086 patients. FEV1 change from baseline to 12 weeks was reported in 8 of the 18 studies and increased an average of 80 mL more with dual therapy versus monotherapy (mean difference [MD] = 0.08 L; 95% CI = 0.05-0.11 L; I2 = 81%; P < 0.00001).

Changes in SGRQ scores from baseline to 12 weeks were reported in 5 of 18 studies and did not differ between the dual therapy and monotherapy groups (MD = −0.85; 95% CI = −0.83-0.13; I2 = 12%; P = 0.34). Of the 8 studies reporting FEV1 outcomes, 5 reported SGRQ outcomes.

All 18 studies reported on any adverse events. Overall adverse events did not differ between the groups (odds ratio [OR] = 1.00; 95% CI = 0.92-1.09; I2 = 27%; P = 0.14). There was no difference in serious adverse events, which were reported in 11 studies (OR = 1.01; 95% CI = 0.86-1.18; I2 = 20%; P = 0.75). In addition, there was no difference in cardiac adverse event rates reported in 6 studies (OR = 0.88; 95% CI = 0.58-1.34; I2 = 20%; P = 0.29). Figures 2 and 3 display the forest plots for these analyses. Post hoc subgroup analysis of 3 trials that compared dual therapy (umeclidinium/vilanterol) with LABA monotherapy (vilanterol) in 2053 patients showed that dual therapy resulted in a mean improvement in FEV1 at 12 weeks of 100 mL compared with LABA monotherapy (MD = 0.10 L; 95% CI = 0.08, 0.12; I2 = 0%; P < 0.00001).

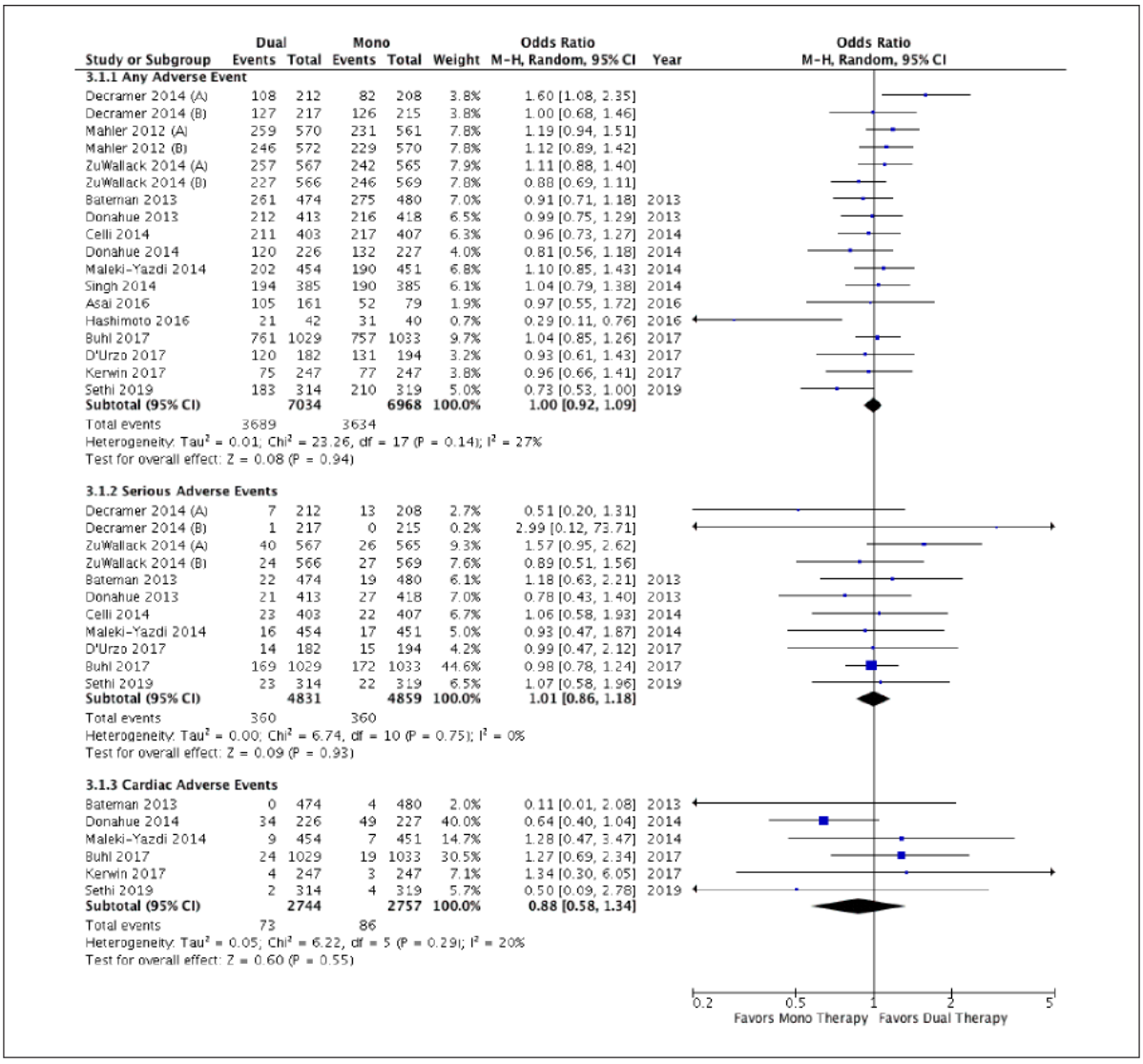


Figure 3. Adverse events.

Anmerkung/Fazit der Autoren

Patients receiving dual bronchodilator therapy showed a greater improvement in lung function without increasing adverse events. Although combination therapy did not significantly improve symptom scores compared with monotherapy, any further improvement in FEV1 resulting from combined LABA + LAMA may benefit patients with COPD in the long-term.

Kommentare zum Review

Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

3.3 Leitlinien

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024[5].

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

Zielsetzung/Fragestellung

goal was to produce recommendations for management of COPD based on the best scientific information available.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- This 2025 GOLD Report is the second update of the 2023-revised report
- Following systematic literature searches and double-blind review by the GOLD Science Committee, the GOLD report has been updated to include key peer-reviewed research publications from January 2023 to July 2024. In total, 164 new references have been added to the GOLD 2025 report.

LoE

Description of Levels of Evidence — Table A

Evidence Category	Sources of Evidence	Definition
A	Randomized controlled trials (RCTs)	Evidence is from endpoints of well-designed RCTs that provide consistent findings in the population for which the recommendation is made without any important limitations.
	Rich body of high quality evidence without any significant limitation or bias	Requires high quality evidence from ≥ 2 clinical trials involving a substantial number of subjects, or a single high quality RCT involving substantial numbers of patient without any bias.
B	Randomized controlled trials (RCTs) with important limitations	Evidence is from RCTs that include only a limited number of patients, post hoc or subgroup analyses of RCTs or meta-analyses of RCTs.
	Limited body of evidence	Also pertains when few RCTs exist, or important limitations are evident (methodologic flaws, small numbers, short duration, undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent).
C	Non-randomized trials Observational studies	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	Panel consensus judgment	Provision of guidance is deemed valuable but clinical literature addressing the subject is insufficient. Panel consensus is based on clinical experience or knowledge that does not meet the above stated criteria.

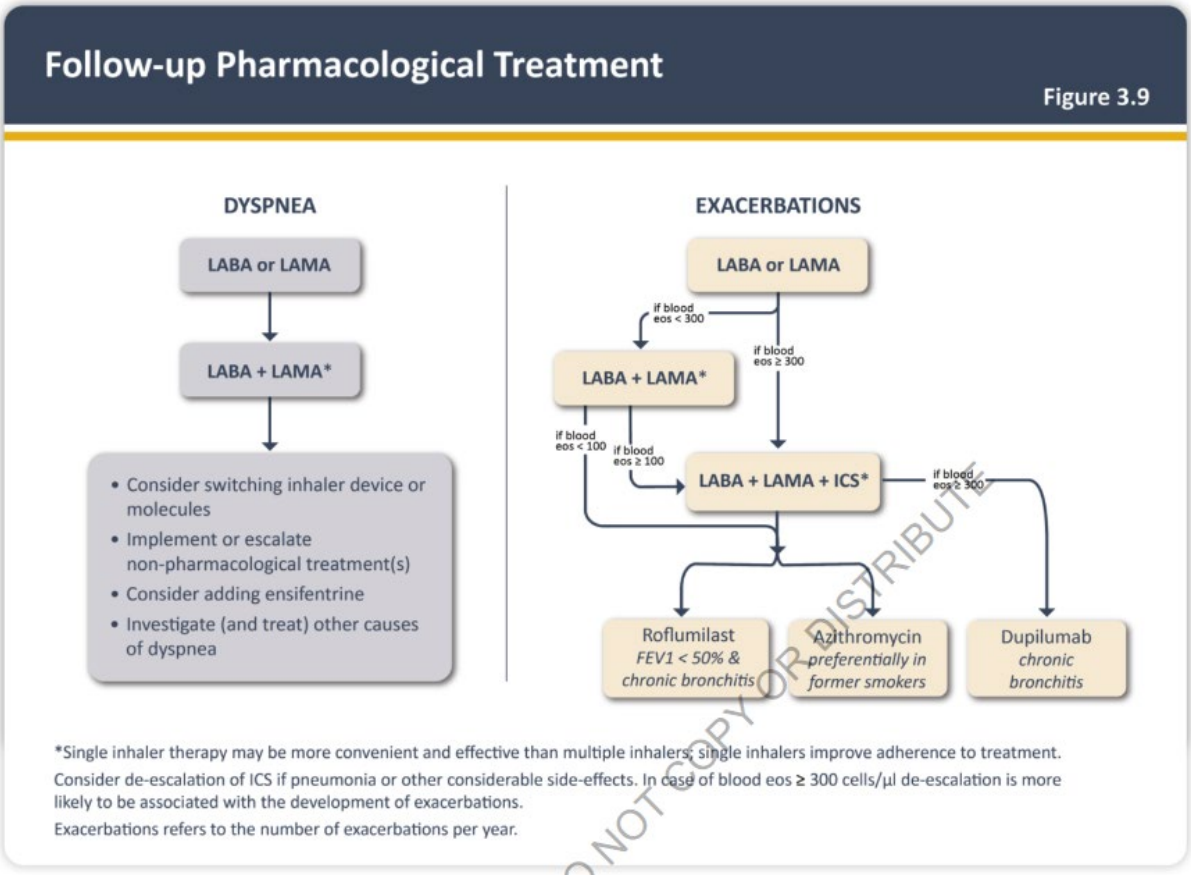
GoR

- Grade of Recommendation nicht klar differenziert vom Level of Evidence

Sonstige methodische Hinweise

Levels of evidence have been assigned to evidence-based recommendations where appropriate. Evidence levels are indicated in boldface type enclosed in parentheses after the relevant statement e.g., (Evidence A). The methodological issues concerning the use of evidence from meta-analyses were carefully considered when i) treatment effect (or effect size) was consistent from one study to the next, and we needed to identify the common effect; ii) the effect varied from one study to the next, and there was a need to identify the reason for the variation.

Empfehlungen



The follow-up pharmacological treatment algorithm (Figure 3.9) can be applied to any patient who is already taking maintenance treatment(s) irrespective of the GOLD group allocated at treatment initiation. If response to initial treatment is appropriate, maintain it. If not:

- Check adherence, inhaler technique and possible interfering comorbidities.
- The need to target primarily dyspnea/activity limitation or to prevent further exacerbations should be evaluated in each patient. Consider the predominant treatable trait to target (dyspnea or exacerbations).
  - Use the exacerbation pathway if both exacerbations and dyspnea need to be targeted.
- If a change in treatment is considered necessary, then select the corresponding algorithm for dyspnea (Figure 3.9 left column) or exacerbations (Figure 3.9 right column)
- Identify which box corresponds to the patient's current treatment and follow the suggested algorithm.

Dyspnea

- For patients with persistent breathlessness or exercise limitation on bronchodilator monotherapy, (703) the use of two long-acting bronchodilators is recommended.
- If the addition of a second long-acting bronchodilator does not improve symptoms, we suggest:
  - Considering switching inhaler device or molecules.
  - Implementing or escalating non-pharmacological treatment(s) e.g., pulmonary rehabilitation.
  - Considering adding ensifentrine if available.

- At all stages, dyspnea due to other causes (not COPD) should be investigated and treated appropriately. Inhaler technique and adherence should be considered as causes of inadequate treatment response. Rehabilitation should also be considered.

Exacerbations

- For patients with persistent exacerbations on bronchodilator monotherapy, escalation to LABA+LAMA isrecommended.
- In patients who develop further exacerbations on LABA+LAMA therapy we suggest escalation to LABA+LAMA+ICS.
- A beneficial response after the addition of ICS may be observed at blood eosinophil counts ≥ 100 cells/µL, with a greater magnitude of response more likely with higher eosinophil counts. (496)
- If patients treated with LABA+LAMA and eosinophil counts < 100 cells/µL still have exacerbations the following options may be considered:
  - Among those who are not currently smoking, consider adding azithromycin. (704,705) Consideration to the development of resistant organisms should be factored into decision-making.
  - Among those with FEV1 < 50%, symptoms of chronic bronchitis and history of prior severe exacerbation, consider adding roflumilast. (706-708)
- If patients treated with LABA+LAMA+ICS (or those with eosinophil counts < 100 cells/µL) still have exacerbations the following options may be considered:
  - Among those with eosinophils ≥ 300 cells/µl and symptoms of chronic bronchitis, consider adding dupilumab. (700,701)
  - Among those who are not currently smoking, consider adding azithromycin. (704,705) Consideration to the development of resistant organisms should be factored into decision-making.
  - Among those with FEV1 < 50%, symptoms of chronic bronchitis and history of prior severe exacerbation, consider adding roflumilast. (706-708)
- Patients treated with LABA+LAMA+ICS should not have the ICS component withdrawn unless the inhaled corticosteroids were started inappropriately, there has been no response to ICS, they experience significant side-effects, or severe or recurrent pneumonia. The risks and benefits of discontinuing ICS should be considered. If blood eosinophils are ≥ 300 cells/µL de-escalation is more likely to be associated with the development of exacerbations. (709,710)

Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Figure 3.17

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Single inhaler triple therapy compared to dual LABD therapy relative risk reduction: IMPACT: HR 0.72 (95% CI: 0.53, 0.99)[1a] ETHOS: HR 0.51 (95% CI: 0.33, 0.80)[1b]	Symptomatic people with a history of frequent and/or severe exacerbations
Non-pharmacological Therapy			
Smoking cessation[2]	Yes	HR for usual care group compared to intervention group (smoking cessation) HR 1.18 (95% CI: 1.02, 1.37)[2]	Asymptomatic or mildly symptomatic
Pulmonary rehabilitation[3#]	Yes	Old trials: RR 0.28 (95% CI 0.10, 0.84)[3a] New trials: RR 0.68 (95% CI 0.28, 1.67)[3b]	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks after discharge)
Long-term oxygen therapy[4]	Yes	NOTT: ≥ 19 hours of continuous oxygen vs ≤ 13 hours: 50% reduction[4a] MRC: ≥ 15 hours vs no oxygen: 50% reduction[4b]	PaO_2 ≤ 55 mmHg or < 60 mmHg with *cor pulmonale* or secondary polycythemia
Noninvasive positive pressure ventilation[5]	Yes	12% in NPPV (high IPAP level) and 33% in control HR 0.24 (95% CI 0.11, 0.49)[5]	Stable COPD with marked hypercapnia
Lung volume reduction surgery[6]	Yes	0.07 deaths/person-year (LVRS) vs 0.15 deaths/person-year (UC) RR for death 0.47 (p = 0.005)[6]	Upper lobe emphysema and low exercise capacity

*RCT with pre-specified analysis of the mortality outcome (primary or secondary outcome); #Inconclusive results likely due to differences in pulmonary rehabilitation across a wide range of participants and settings.

1. a) IMPACT trial (Lipson et al. 2020) and b) ETHOS trials (Martinez et al. 2021); 2.Lung Health Study (Anthonisen et al. 2005); 3. a) Puhan et al. (2011) and b) Puhan et al. 2016; 4. a) NOTT (NOTT, 1980) and b) MRC (MRC, 1981); 5. Kohlein trial (Kohlein et al. 2014); 6. NETT trial (Fishman et al. 2003)

ICS: inhaled corticosteroid; IPAP: inspiratory positive airway pressure; LABA: long-acting beta$_2$-agonist; LABD: long-acting bronchodilator; LAMA: long-acting anti-muscarinic; LTOT: long-term oxygen therapy; NPPV: noninvasive positive pressure ventilation; LVRS: lung volume reduction surgery; UC: usual treatment control group.

Maintenance Medications in COPD*

Figure 3.18

Generic Drug Name	Inhaler Type	Nebulizer	Oral/Injectable Delivery	Duration of Action
BETA$_2$-Agonists				
Short-acting (SABA)				
Fenoterol	MDI	✓	tablet, solution	variable
Levalbuterol	MDI	✓		variable
Salbutamol (albuterol)	MDI & DPI	✓	syrup, tablet	variable
Terbutaline	DPI		tablet	variable
Long-acting (LABA)				
Arformoterol		✓		12 hours
Formoterol	DPI	✓		12 hours
Indacaterol	DPI			24 hours
Olodaterol	SMI			24 hours
Salmeterol	MDI & DPI			12 hours
Anticholinergics				
Short-acting (SAMA)				
Ipratropium bromide	MDI	✓		6-8 hours
Oxitropium bromide	MDI	✓		7-9 hours
Long-acting (LAMA)				
Aclidinium bromide	DPI			12 hours
Glycopyrronium bromide	DPI		solution	variable
Tiotropium	DPI, SMI, MDI			24 hours
Umeclidinium	DPI			24 hours
Glycopyrronium		✓		12 hours
Revefenacin		✓		24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)				
Fenoterol/ipratropium	SMI	✓		6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓		variable
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)				
Formoterol/aclidinium	DPI			12 hours
Formoterol/glycopyrronium	MDI			12 hours
Indacaterol/glycopyrronium	DPI			12-24 hours
Vilanterol/umeclidinium	DPI			24 hours
Olodaterol/tiotropium	SMI			24 hours
Methylxanthines				
Aminophylline			solution, injectable	variable
Theophylline (SR)			tablet, capsule, elixir, solution, injectable	variable
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)				
Formoterol/beclometasone	MDI, DPI			12 hours
Formoterol/budesonide	MDI, DPI			12 hours
Formoterol/mometasone	MDI			12 hours
Salmeterol/fluticasone propionate	MDI, DPI			12 hours
Vilanterol/fluticasone furoate	DPI			24 hours
Triple Combination in One Device (LABA+LAMA+ICS)				
Fluticasone/umeclidinium/vilanterol	DPI			24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI			12 hours
Budesonide/formoterol/glycopyrrolate	MDI			12 hours
Phosphodiesterase-3 and/or -4 Inhibitors				
Roflumilast			tablet	24 hours
Ensifentrine		✓		12 hours
Mucolytic Agents				
Erdosteine			capsule, suspension	12 hours
Carbocysteine†			capsule, packet, solution,syrup	6-8 hours
N-acetylcysteine†		✓	solution, tablet	2-6 hours
Biologics				
Dupilumab			injectable	2 weeks

*This list is not exhaustive. Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

Bronchodilators

Bronchodilators are medications that increase FEV1 and/or change other spirometric variables (Figure 3.19). They act by altering airway smooth muscle tone and the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Bronchodilators tend to reduce dynamic hyperinflation at rest and during exercise,(306,892) and improve exercise performance. The extent of

these changes, especially in patients with severe and very severe COPD, is not easy to predict from the improvement in FEV1 measured at rest.(893,894)

Bronchodilator dose-response (FEV1 change) curves are relatively flat with all classes of bronchodilators.(895-901) Increasing the dose of either a beta2-agonist or an anticholinergic by an order of magnitude, especially when given by a nebulizer, appears to provide subjective benefit in acute episodes(902) but is not necessarily helpful in stable disease.(903) Bronchodilator medications in COPD are most often given on a regular basis to prevent or reduce symptoms. Toxicity is also dose-related (Figure 3.18). Use of short acting bronchodilators on a regular basis is not generally recommended.

Beta2-agonists

The principal action of beta2-agonists is to relax airway smooth muscle by stimulating beta2-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. There are short-acting (SABA) and long-acting (LABA) beta2-agonists. The effect of SABAs usually wears off within 4 to 6 hours.(897,898) Regular and as- needed use of SABAs improve FEV1 and symptoms.(904) LABAs show duration of action of 12 or more hours and do not preclude additional benefit from as-needed SABA therapy.(905)

Formoterol and salmeterol are twice-daily LABAs that significantly improve FEV1 and lung volumes, dyspnea, health status, exacerbation rate and number of hospitalizations,(906) but have no effect on mortality or rate of decline of lung function. Indacaterol is a once daily LABA that improves breathlessness,(907,908) health status(908) and exacerbation rate.(908) Some patients experience cough following the inhalation of indacaterol. Oladaterol and vilanterol are additional once daily LABAs that improve lung function and symptoms.(909,910)

Adverse effects

Stimulation of beta2-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in susceptible patients. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta2-agonists, regardless of route of administration. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics,(911) and oxygen consumption can be increased under resting conditions in patients with chronic heart failure,(912) these metabolic effects decrease over time (i.e., show tachyphylaxis). Mild falls in partial pressure of oxygen (PaO2) can occur after administration of both SABAs and LABAs(913) but the clinical significance of these changes is uncertain. Despite prior concerns related to the use of beta2- agonists in the management of asthma, no association between beta2-agonist use and loss of lung function or increased mortality has been reported in COPD.(906,914,915)

Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.(916) Short-acting antimuscarinics (SAMAs), namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction.(917) Long-acting muscarinic antagonists (LAMAs), such as tiotropium, aclidinium, glycopyrronium bromide (also known as glycopyrrolate), umeclidinium and revefenacin have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect.(916)

A systematic review of RCTs concluded that ipratropium, a short acting muscarinic antagonist, alone provided small benefits over short-acting beta2-agonist in terms of lung function, health status and requirement for oral steroids.(918) Among LAMAs, some are administered once a day (tiotropium, umeclidinium, revefenacin), others twice a day (aclidinium), and some are approved for once daily dosing in some countries and twice daily dosing in others (glycopyrrolate).(916,919) LAMA treatments improve symptoms, including cough and sputum and health status.(916,920,921) They also improve the effectiveness of pulmonary rehabilitation(922,923) and reduce exacerbations and related hospitalizations.(920) Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment.(924,925)

Adverse effects

Inhaled anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects observed with atropine.(916,926) Extensive use of this class of agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of mouth.(917,927) Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship.(928) Some patients using ipratropium report a bitter, metallic taste. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported.(929,930) In a large, long-term clinical trial in COPD patients, tiotropium added to other standard therapies had no effect on cardiovascular risk.(889) Although there were some initial concerns regarding the safety of tiotropium delivery via the Respimat®(931) inhaler, the findings of a large trial observed no difference in mortality or exacerbation rates when comparing tiotropium in a dry-powder inhaler and the Respimat® inhaler.(932) There are less safety data available for the other LAMAs, but the rate of anti-cholinergic side effects for

drugs in this class appears to be low and generally similar. Use of solutions with a facemask can precipitate acute glaucoma, probably as a direct result of the contact between the solution and the eye.(933-935)

Methylxanthines

Controversy remains about the exact effects of xanthine derivatives. They may act as non-selective phosphodiesterase inhibitors, but have also been reported to have a range of non-bronchodilator actions, the significance of which is disputed.(936-938) Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD.

Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome P450 mixed function oxidases. Clearance of the drug declines with age. Many other physiological variables and drugs modify theophylline metabolism. Enhanced inspiratory muscle function has been reported in patients treated with methylxanthines,(936) but whether this reflects a reduction in gas trapping or a primary effect on the respiratory skeletal muscles is not clear. All studies that have shown efficacy of theophylline in COPD were performed with sustained-release preparations.

There is evidence for a modest bronchodilator effect compared with placebo in stable COPD.(939) Addition of theophylline to salmeterol produces a greater improvement in FEV1 and breathlessness than salmeterol alone.(940,941) Earlier studies reported contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates.(942,943) A study that investigated the effectiveness of adding low-dose theophylline to ICS in COPD patients at increased risk of exacerbation showed no difference compared with placebo in the number of COPD exacerbations over a one-year period.(944) A large placebo-controlled trial showed no effect of oral theophylline alone or in combination with prednisolone 5 mg daily on exacerbations of severe COPD.(945)

Adverse effects

Toxicity is dose-related, which is a particular problem with xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given.(937,939) Methylxanthines are non-specific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). Other side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum levels of theophylline. These medications have significant interactions with commonly used medications such as erythromycin (but not azithromycin), certain quinolone antibiotics (ciprofloxacin, but not ofloxacin), allopurinol, cimetidine (but not ranitidine), serotonin uptake inhibitors (fluvoxamine) and the 5- lipoxygenase inhibitor zileuton.

Combination bronchodilator therapy

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with a lower risk of side-effects compared to increasing the dose of a single bronchodilator.(946,947) Combinations of SABAs and SAMAs are superior compared to either medication alone in improving FEV1 and symptoms.(948) Treatment with formoterol and tiotropium in separate inhalers has a bigger impact on FEV1 than either component alone.(949) There are numerous combinations of a LABA and LAMA in a single inhaler available (Figure 3.18). These combinations improve lung function compared to placebo;(946) this improvement is consistently greater than long-acting bronchodilator monotherapy effects although the magnitude of improvement is less than the fully additive effect predicted by the individual component responses.(950) Single inhalers improve adherence to treatment.(951) In studies where patient reported outcomes (PROs) are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on PROs compared to monotherapies.(952-955) In one clinical trial, combination LABA+LAMA treatment had the greatest improvement in quality of life compared to placebo or its individual bronchodilator components in patients with a greater baseline symptom burden.(956) A clinical trial showed that LABA+LAMA improved lung function and symptoms versus long-acting bronchodilator monotherapy in symptomatic patients with low exacerbation risk and not receiving inhaled corticosteroids.(695) The LABA+LAMA combination demonstrated favorable improvements compared with the monotherapies for the majority of outcomes irrespective of baseline HRQoL.(957) These clinical trials deal with group mean data, but symptom responses to LABA+LAMA combinations are best evaluated on an individual patient basis. A lower dose, twice daily regimen for a LABA+LAMA has also been shown to improve symptoms and health status in COPD patients(958) (Figure 3.19). These findings have been shown in people across different ethnic groups (Asian as well as European).(959)

Most studies with LABA+LAMA combinations have been performed in patients with a low rate of exacerbations. One study in patients with a history of exacerbations indicated that a combination of long-acting bronchodilators is more Be sure to read and understand the paragraph entitled Important Purpose & Liability Disclaimer 85 effective than long-acting bronchodilator monotherapy for preventing exacerbations.(960) Another large study found that combining a LABA with a LAMA did not reduce exacerbation rate as much as expected compared with a LAMA alone.(961) Another study in patients with a history of exacerbations showed that a combination LABA+LAMA decreased exacerbations to a greater

extent than an LABA+ICS combination.(962) However, another study in a population with high exacerbation risk (≥ 2 exacerbations and/or 1 hospitalization in the previous year) reported that LABA+ICS decreased exacerbations to a greater extent than a LABA+LAMA combination at higher blood eosinophil concentrations.(496) A large observational pharmaco-epidemiological study found similar effectiveness of LABA+LAMA and LABA+ICS but a significantly higher risk of pneumonia in those treated with LABA+ICS.(963)

Inhaled corticosteroids (ICS)

General considerations

In vitro evidence suggests that COPD-associated inflammation has limited responsiveness to corticosteroids. Moreover, some drugs including beta2-agonists, theophylline or macrolides may partially facilitate corticosteroid sensitivity in COPD.(964,965) The clinical relevance of this effect has not yet been fully established. In vivo data suggest that the dose-response relationships and long-term (> 3 years) safety of ICS in people with COPD are unclear and require further investigation.(962) Because the effects of ICS in COPD can be modulated by the concomitant use of long-acting bronchodilators, these two therapeutic options are discussed separately. Both current and ex-smokers with COPD benefit from ICS use in terms of lung function and exacerbation rates, although the magnitude of the effect is lower in heavy or current smokers compared to light or ex-smokers.(496,966)

Efficacy of ICS (alone)

Most studies have found that regular treatment with ICS alone does not modify the long-term decline of FEV1 nor mortality in people with COPD.(967) Studies and meta-analyses assessing the effect of regular treatment with ICS alone on mortality in people with COPD have not provided conclusive evidence of benefit.(967) In the TORCH trial, a trend toward higher mortality was observed for patients treated with fluticasone propionate alone compared to those receiving placebo or salmeterol plus fluticasone propionate combination.(844) However, an increase in mortality was not observed in COPD patients treated with fluticasone furoate in the Survival in Chronic Obstructive Pulmonary Disease with Heightened Cardiovascular Risk (SUMMIT) trial.(968) In moderate COPD, fluticasone furoate alone or in combination with vilanterol was associated with slower decline in FEV1 compared with placebo or vilanterol alone by on average 9 mL/year.(969) A number of studies have investigated whether there is a relationship between ICS treatment and risk of lung cancer with conflicting results.(970)

ICS in combination with long-acting beta agonist (LABA+ICS)

In patients with moderate to very severe COPD and exacerbations, an ICS combined with a LABA is more effective than either component alone in improving lung function, health status and reducing exacerbations.(971,972) Clinical trials powered on all-cause mortality as the primary outcome failed to demonstrate a statistically significant effect of LABA+ICS combination therapy on survival.(844,968)

Adverse effects

There is high quality evidence from RCTs that ICS use modifies the airway microbiome(977) and is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.(967) This excess risk has been confirmed in ICS studies using fluticasone furoate, even at low doses.(978) Patients at higher risk of pneumonia include those who currently smoke, are aged ≥ 55 years, have a history of prior exacerbations or pneumonia, a body mass index (BMI) < 25 kg/m2, a poor MRC dyspnea grade and/or severe airflow obstruction.(979,980) Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of developing pneumonia.(981) In studies of patients with moderate COPD, ICS by itself or in combination with a LABA did not increase the risk of pneumonia.(968,980)

Results from RCTs have yielded varied results regarding the risk of decreased bone density and fractures with ICS treatment, which may be due to differences in study designs and/or differences between ICS compounds.(887,978,982-984) Results of observational studies suggest that ICS treatment could also be associated with increased risk of diabetes/poor control of diabetes,(985) cataracts,(986) and mycobacterial infection.(987) An increased risk of tuberculosis has been found in both observational studies and a meta-analysis of RCTs.(988-990) In the absence of RCT data on these issues, it is not possible to draw firm conclusions.(991) ICS and lung cancer incidence is discussed in Chapter 5.

Management of patients currently on LABA+ICS

In general, if there is an indication for ICS use then LABA+LAMA+ICS has been shown to be superior to LABA+ICS (Figure 3.22). For patients currently on LABA+ICS, it is important to review whether there was a relevant prior exacerbation history and whether there was a previous positive response to ICS treatment. Using this information, the following should be considered:

- If there was no relevant exacerbation history, then consider changing to LABA+LAMA (Figure 3.22).
- If there was a previous exacerbation history but currently there are no exacerbations this suggests a positive response to treatment.(992-997) If dyspnea persists despite treatment with LABA+ICS, escalation to LABA+LAMA+ICS should be considered.(998-1001)
- If the patient is currently suffering with exacerbations, then blood eosinophil counts can be used to guide treatment; if < 100 cells/µl then consider changing to LABA+LAMA, while ≥ 100 cells/µl suggests that LABA+LAMA+ICS should be used (Figure 3.22).

- The benefits and risks of ICS withdrawal should be carefully considered, with a blood eosinophil count > 300 cells/µl being an indicator of increased risk of exacerbations with ICS withdrawal.

Triple therapy (LABA+LAMA+ICS)

The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches(1002) and has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA+LAMA and LABA+ICS.(493,495,496,1003-1010) A post-hoc analysis of one of the RCTs that evaluated the effects of LABA+LAMA+ICS showed that triple therapy improved clinical outcomes versus dual therapy regardless of smoking status.(1011)

A post-hoc pooled analysis of three triple therapy clinical trials in COPD patients with severe airflow obstruction and a history of exacerbations showed a non-significant trend for lower mortality (assessed as a safety outcome) with triple inhaled therapy compared to non-ICS based treatments.(1012) Two large one-year randomized controlled trials (named IMPACT and ETHOS) were reviewed earlier in Chapter 3 (see 'Therapeutic interventions that reduce COPD mortality') and provide new evidence on mortality reduction with fixed-dose inhaled triple combinations compared to dual bronchodilation.(699,1013)

Oral glucocorticoids

Oral glucocorticoids have numerous side effects, including steroid myopathy(1014) which can contribute to muscle weakness, decreased functionality, and respiratory failure in people with very severe COPD. Systemic glucocorticoids for treating acute exacerbations in hospitalized patients, or during emergency department visits, have been shown to reduce the rate of treatment failure, the rate of relapse and to improve lung function and breathlessness.(1015) Conversely, prospective studies on the long-term effects of oral glucocorticoids in stable COPD are limited.(1016,1017) Therefore, while oral glucocorticoids play a role in the acute management of exacerbations, they have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.

Phosphodiesterase-4 (PDE4) inhibitor

The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.(1018) Roflumilast is a once daily oral medication with no direct bronchodilator activity. Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations.(1019) The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators,(1020) and in patients who are not controlled on fixed-dose LABA+ICS combinations.(706) The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.(705,708) There has been no study directly comparing roflumilast with an inhaled corticosteroid.

Adverse effects

Roflumilast has more adverse effects than inhaled medications for COPD.(1021) The most frequent are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Adverse effects have led to increased withdrawal rates from clinical trials. Adverse effects seem to occur early during treatment, are reversible, and diminish over time with continued treatment. In controlled studies an average unexplained weight loss of 2 kg has been seen and weight monitoring during treatment is advised, in addition to avoiding roflumilast treatment in underweight patients. Roflumilast should also be used with caution in patients with depression.

Antibiotics

In older studies prophylactic, continuous use of antibiotics had no effect on the frequency of exacerbations in COPD(1022,1023) and a study that examined the efficacy of chemoprophylaxis undertaken in winter months over a period of 5 years concluded that there was no benefit.(1024) Later studies have shown that regular use of some antibiotics may reduce exacerbation rate.(1025,1026)

Azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (250 mg two times per day) for one year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care.(704,1027,1028) Azithromycin use was associated with an increased incidence of bacterial resistance, prolongation of QTc interval, and impaired hearing tests.(704) A post-hoc analysis suggests lesser benefit in active smokers.(705) There are no data showing the efficacy or safety of chronic azithromycin treatment to prevent COPD exacerbations beyond one-year of treatment.

Pulse therapy with moxifloxacin (400 mg/day for 5 days every 8 weeks) in patients with chronic bronchitis and frequent exacerbations had no beneficial effect on the exacerbation rate overall.(1029) Long-term doxycycline did not reduce exacerbations, although there may be responder subgroups.(1030)

Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine, erdosteine)

In COPD patients not receiving ICS, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC) may reduce exacerbations and modestly improve health status.(1031-1034) In contrast, it has been shown that erdosteine may have a significant effect on (mild) exacerbations irrespective of concurrent treatment with ICS. Due to the heterogeneity of studied populations, treatment

dosing and concomitant treatments, currently available data do not allow precise identification of the potential target population for antioxidant agents in COPD.(1035)

Phosphodiesterase 3 and 4 (PDE 3 & PDE4) inhibitors

Ensifentrine is a novel, first-in-class, inhaled dual inhibitor of PDE3 and PDE4 with both anti-inflammatory activity and bronchodilator effects. PDE3 inhibition, through modulation of cyclic GMP levels, causes smooth muscle relaxation.(1036) In parallel phase III studies, ensifentrine, delivered via standard jet nebulizer, significantly improved lung function(1036) and dyspnea but had inconsistent effects on quality of life. A reduction in exacerbation rate was suggested but the patient populations were not enriched for exacerbation risk. In addition, the studies were not designed to assess the impact of ensifentrine on top of LABA+LAMA or LABA+LAMA+ICS making it difficult to fully position this agent in our treatment algorithm (Figure 3.9).(501,700-702) Studies did not find safety or tolerability issues.(1037) Ensifentrine is currently only available in the United States.

Other drugs with potential to reduce exacerbations

Four large phase 3 studies have investigated the efficacy of the anti-IL-5 monoclonal antibody mepolizumab(1038) and the anti-IL-5 receptor-□ antibody benralizumab(1039) in patients with COPD, who had a history of two or more exacerbations in the last year and increased blood eosinophil count. The studies showed inconsistent effects on exacerbation reduction, and none have received regulatory approval for treatment of COPD. Currently, large randomized trials are been conducted to investigate whether these and other biologic treatments are effective in a population who have more compelling evidence of eosinophilic or type II airway inflammation.(701)

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13. In two large, phase 3, double-blind, randomized trials, patients with COPD, chronic bronchitis, a history of two or more moderate exacerbations or one or more severe exacerbation(s) in the last year despite treatment with LABA+LAMA+ICS, and blood eosinophil count of ≥ 300 cells/µL who received dupilumab had fewer exacerbations, better lung function and improved health status over 52 weeks.(700,701)

Nedocromil and leukotriene modifiers have not been tested adequately in COPD patients and the available evidence does not support their use. (1040,1041)

There was no evidence of benefit, and some evidence of harm, including malignancy and pneumonia, following treatment with an anti-TNF-alpha antibody (infliximab) in moderate to severe COPD.(1042)

A recent Cochrane meta-analysis did not show sufficient evidence to support the use of immunostimulants.(1043)

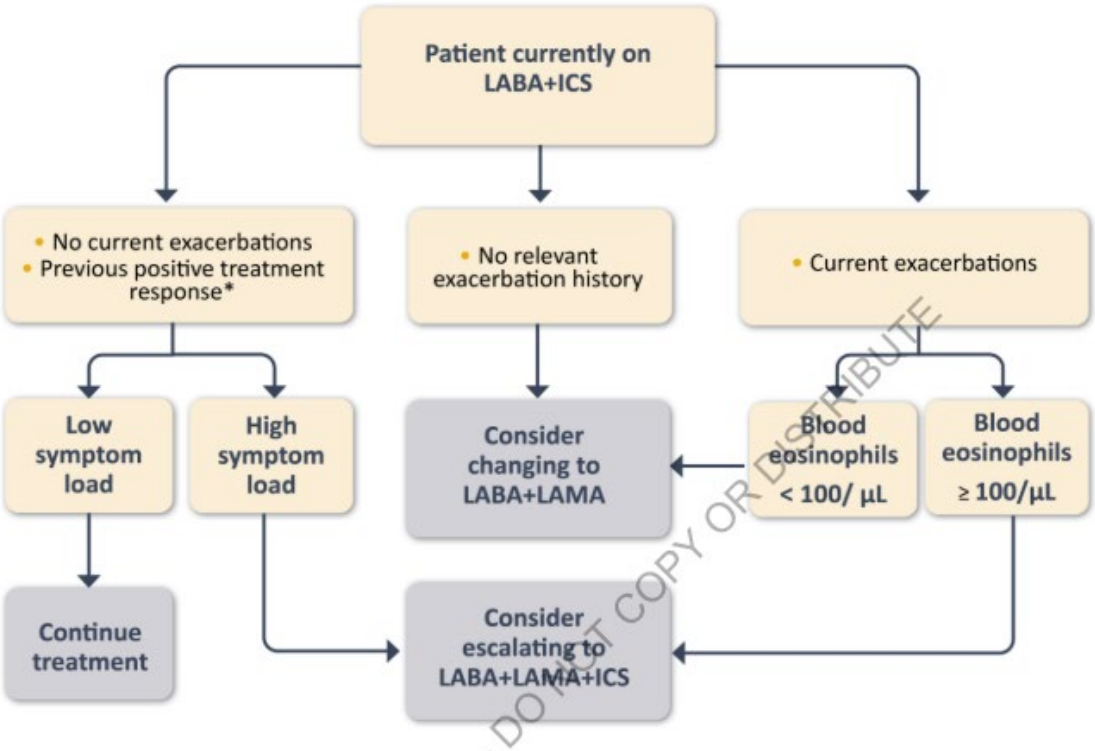
An RCT of the selective β1 receptor blocker metoprolol in patients with moderate or severe COPD, who did not have an established indication for beta-blocker use, showed it did not delay the time until the first COPD exacerbation compared to the placebo group and hospitalization for exacerbation was more common among the patients treated with metoprolol.(1044,1045) There is no evidence that beta-blockers should be used in people with COPD who do not have a cardiovascular indication for their use.

Simvastatin did not prevent exacerbations in people with COPD who had no metabolic or cardiovascular indication for statin treatment.(1046) An association between statin use and improved outcomes (including decreased exacerbations and mortality) has been reported in observational studies of people with COPD who received them for cardiovascular and metabolic indications.(1047)

There is no evidence that supplementation with vitamin D has a positive impact on exacerbations in unselected patients.(1048) In a meta-analysis vitamin D supplementation reduced exacerbation rates in patients with low baseline vitamin D levels,(1049) but a more recent study has shown no effect.(1050)

Management of Patients Currently on LABA+ICS

Figure 3.22



*Patient previously had exacerbations and responded to LABA+ICS treatment

Other Pharmacological Treatments

Figure 3.23

Alpha-1 Antitrypsin Augmentation Therapy	• Intravenous augmentation therapy may slow down the progression of emphysema **(Evidence B)**
Antitussives	• There is no conclusive evidence of a beneficial role of antitussives in people with COPD **(Evidence C)**
Vasodilators	• Vasodilators do not improve outcomes and may worsen oxygenation **(Evidence B)**
Opioids	• Low-dose long acting oral and parenteral opioids may be considered for treating dyspnea in COPD patients with severe disease **(Evidence B)**
Pulmonary Hypertension Therapy	• Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD **(Evidence B)**

Pulmonary Rehabilitation, Self-Management and Integrative Care in COPD

Figure 3.24

Pulmonary Rehabilitation	• Rehabilitation is indicated in all patients with relevant symptoms and/or a high risk for exacerbation **(Evidence A)** • Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients **(Evidence A)** • Pulmonary rehabilitation reduces hospitalization among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) **(Evidence B)** • Pulmonary rehabilitation leads to a reduction in symptoms of anxiety and depression **(Evidence A)**
Education and Self-Management	• Education is needed to change patient's knowledge but there is no evidence that used alone it will change patient behavior **(Evidence C)** • Self-management intervention with communication with a health care professional improves health status and decreases hospitalizations and emergency department visits **(Evidence B)**
Integrated Care Programs	• Integrative care and telehealth have no demonstrated benefit at this time **(Evidence B)**
Physical Activity	• Physical activity is a strong predictor of mortality **(Evidence A)**. People with COPD should be encouraged to increase their level of physical activity although we still do not know how to best ensure the likelihood of success

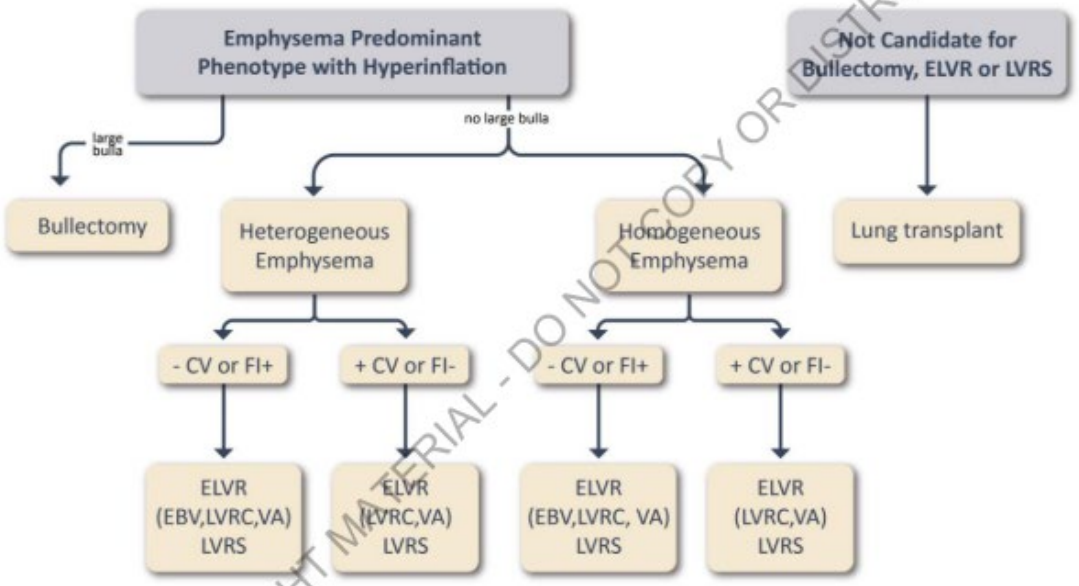
Overview of Current and Proposed Surgical and Bronchoscopic Interventions for People with COPD

Figure 3.25

Symptoms	Chronic Mucus Production	Exacerbations	Dyspnea
Disorders	• Chronic bronchitis	• Acute and chronic bronchitis • Bulla • Emphysema • Tracheobronchomalcia	• Bulla • Emphysema • Tracheobronchomalcia
Surgical and Bronchoscopic Interventions	• Nitrogen cryospray • Rheoplasty	• Targeted lung denervation	• Giant bullectomy • Large airway stenting • EBV • Coil • Thermal vapor ablation • Lung sealants • LVRS • Lung transplantation

Surgical and Interventional Therapies in Advanced Emphysema

Figure 3.26



Note: not all therapies are clinically available in all countries. Long term ELVR outcomes or direct comparisons to LVRS are unknown.

Definition of abbreviations: CV, collateral ventilation measure by Chartis; FI + fissure integrity > 90% by HRCT; FI-, fissure integrity < 90% by HRCT; ELVR, Endoscopic Lung Volume Reduction, EBV, Endobronchial Valve; VA, Vapor Ablation; LVRC, Lung Volume Reduction Coil; LVRS, Lung Volume Reduction Surgery. Modified from Vogelmeier, AJRCCM, 2017.

Management of Severe but not Life-threatening Exacerbations*

Figure 4.5

Assess severity of symptoms, blood gases, chest radiograph

Administer supplemental oxygen therapy, obtain serial arterial blood gas, venous blood gas and pulse oximetry measurements

Bronchodilators:

- Increase doses and/or frequency of short-acting bronchodilators
- Combine short-acting beta 2-agonists and anticholinergics
- Consider use of long-acting bronchodilators when patient becomes stable
- Use spacers or air-driven nebulizers when appropriate

Consider oral corticosteroids

Consider antibiotics (oral) when signs of bacterial infection are present

Consider noninvasive mechanical ventilation (NIV)

At all times:

- Monitor fluid balance
- Consider subcutaneous heparin or low molecular weight heparin for thromboembolism prophylaxis
- Identify and treat associated conditions (e.g., heart failure, arrhythmias, pulmonary embolism etc.)

Key Points for the Management of Exacerbations

Figure 4.6

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**
- Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not normally be more than 5 days **(Evidence A)**
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should normally be 5 days **(Evidence B)**
- Methylxanthines are not recommended due to increased side effect profiles **(Evidence B)**
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival **(Evidence A)**

Interventions that Reduce the Frequency of COPD Exacerbations

Figure 4.11

Intervention Class	Intervention
Bronchodilators	LABAs LAMAs LABA + LAMA
Corticosteroid-containing regimens	LABA + ICS LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast Dupilumab
Anti-infectives	Vaccines Long Term Macrolides
Mucoregulators	N-acetylcysteine Carbocysteine Erdosteine
Various others	Smoking Cessation Rehabilitation Lung Volume Reduction Vitamin D Shielding measures (e.g., mask wearing, minimizing social contact, frequent hand washing)

Bundesärztekammer (BÄK) et al., 2021 [2,3]

Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

Nationale VersorgungsLeitlinie COPD; Langfassung, 2. Auflage, Version 1

Zielsetzung/Fragestellung

Nationale VersorgungsLeitlinien sollen die Versorgung von Patient*innen in Deutschland verbessern durch aktuelle wissenschaftlich begründete Empfehlungen zu Diagnostik, Behandlung und Rehabilitation sowie zu einem strukturierten und optimierten Management der Erkrankung. Dazu gehört insbesondere auch eine verbesserte Kommunikation zwischen den Behandelnden über alle Sektoren- und Fächergrenzen hinaus sowie der Einbezug der Patient*innen in alle Behandlungsentscheidungen.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft teilweise zu (Evidenz über Hintergrundtext identifizierbar);
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu (am 25. Juni 2021 verabschiedet, 5-jährige Überarbeitung angestrebt).

Recherche/Suchzeitraum:

- Die strukturierte Leitlinienrecherche wurde vom 22.02.2017 bis 22.03.2017 durchgeführt.
- Systematische Recherchen wurden in Medline via Pubmed und der Cochrane-Datenbank durchgeführt. Recherche bis 01/2019.

LoE

- Evidenzbewertung mit dem AMSTAR-Tool, AMSTAR-2-Tool, in Anlehnung an das Cochrane Risk of Bias Tool, entsprechend den Empfehlungen zur „Bewertung des Biasrisikos (Risiko systematischer Fehler) in klinischen Studien: ein Manual für die Leitlinienerstellung“ und mit dem QUADAS-2-Tool.
- Evidenzqualität: Für den Fall, dass eine Bewertung nach GRADE bereits durch die Autor*innen der systematischen Übersichtsarbeit erfolgt war, wurde diese übernommen. Wenn eine Bewertung nach GRADE nicht zur Verfügung stand, oder Primärstudien aus systematisch durchgeführten Recherchen für die Formulierung von Empfehlungen herangezogen wurden, wurde die Präzision, Direktheit und Konsistenz der Evidenz, sowie endpunktbezogene Studienqualität betrachtet und narrativ beschrieben. Daraus ergab sich eine Bewertung der Evidenzqualität in Anlehnung an GRADE von hoch bis sehr gering. Eigene GRADE-Bewertungen wurden nicht vorgenommen, da auch keine eigenen Metaanalysen durchgeführt wurden.

GoR

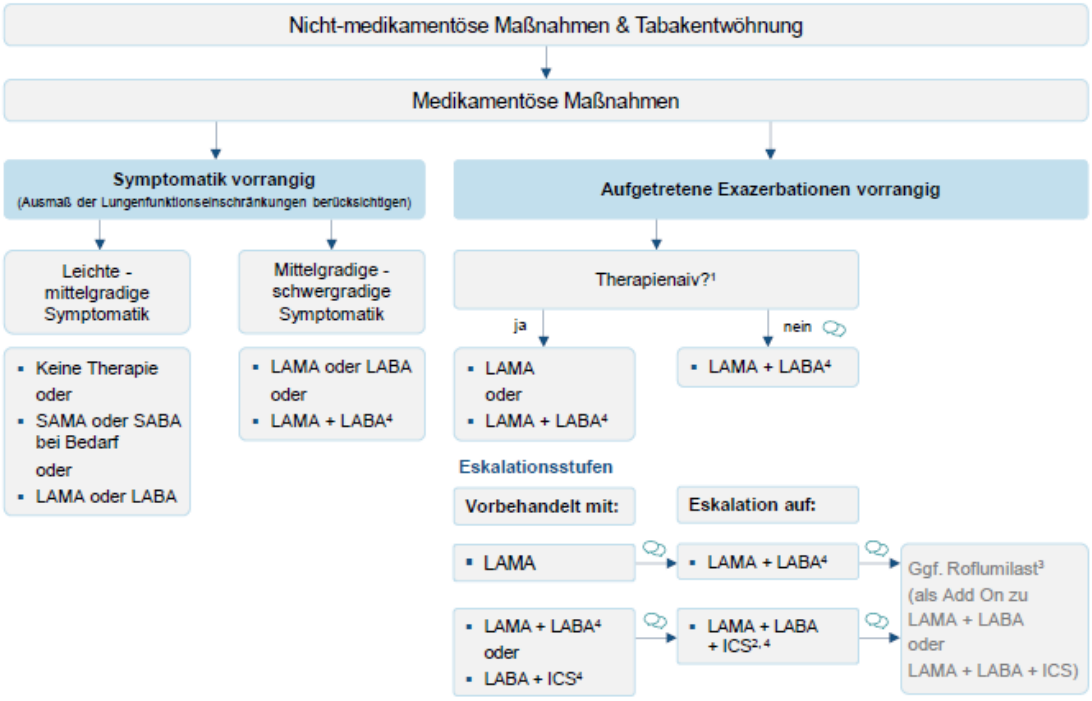
Tabelle 3: Schema zur Graduierung von NVL-Empfehlungen, modifiziert nach [7,9]

Empfehlungsgrad	Beschreibung	Formulierung	Symbol
A	Starke Positiv-Empfehlung	Soll	⇑⇑
B	Abgeschwächte Positiv-Empfehlung	Sollte	⇑
0	Offene Empfehlung	Kann	⇔
B	Abgeschwächte Negativ-Empfehlung	Sollte nicht	⇓
A	Starke Negativ-Empfehlung	Soll nicht	⇓⇓

Medikamentöse Therapie

Empfehlungen/Statements	Empfehlungs-grad
5-1 Patient*innen mit COPD sollen gemäß dem Algorithmus Medikamentöse Langzeit-behandlung (Abbildung 4) behandelt werden.	⇑⇑

Abbildung 4: Medikamentöse Langzeitbehandlung



[1] Bei bereits mit der Kombination LABA/ICS vorbehandelten Patient*innen ist die Überprüfung der Indikation für eine ICS-Gabe zu prüfen.
[2] Die Kombination LAMA/LABA/ICS kann bei höheren Eosinophilenwerten zum Einsatz kommen. Vor Eskalation ist generell die Indikation für ein ICS zu prüfen.
[3] Die Gabe von Roflumilast ist bei Patient*innen mit COPD möglich, die trotz Therapie wiederholt exazerbieren, dem „chronische Bronchitis"-Phänotyp zuzuordnen sind und eine FEV1 < 50% haben. Roflumilast kann hierbei als Add On sowohl zusätzlich zu der Kombination LABA/LAMA als auch zu LAMA/LABA/ICS gegeben werden.
[4] Wenn Patient*innen mit COPD über einen längeren Zeitraum beschwerdearm oder beschwerdefrei sind; sie von einer Eskalation nicht profitieren oder unerwünschte Nebenwirkungen auftreten, ist die Möglichkeit der Deeskalation medikamentöser Therapiemaßnahmen unter engmaschiger Kontrolle zu prüfen.

LAMA: Langwirkende Anticholinergika (long-acting muscarinic antagonist), LABA: Langwirkende Beta-2-Sympathomimetika (long-acting beta2-agonist), ICS: Inhalatives Corticosteroid, SABA: kurzwirkende Beta-2-Sympathomimetika, SAMA: kurzwirkende Anticholinergika

- Evidenzbasis: Der Algorithmus zur medikamentösen Langzeitbehandlung beruht auf einer strukturierten Recherche nach aggregierter Evidenz. Für die Interpretation der

einzelnen Evidenzen geht die Leitliniengruppe von Gruppeneffekten aus. Zur Frage des Stellenwertes der Triple-Therapie sowie Roflumilast wurden zusätzlich systematische Recherchen nach RCTs durchgeführt; ebenso zu möglichen kardialen Nebenwirkungen unter LAMA oder LABA-Therapie. Die Evidenz für die einzelnen Therapiestufen wird jeweils im zugehörigen Abschnitt beschrieben

- Erläuterung zur Darstellung des Algorithmus: Der Algorithmus wird in 2 Behandlungspfade unterteilt. Der linke Pfad empfiehlt mögliche medikamentöse Therapieoptionen für Patient*innen, bei denen die Schwere der Hauptsymptome im Vordergrund steht (siehe Kapitel 2.7 Strukturierte Symptomerfassung). Die rechte Seite stellt mögliche Therapien bei Patient*innen da, welche vermehrt Exazerbationen in der Anamnese oder im Krankheitsverlauf erlebt haben (siehe Kapitel 2.7.1 Erfassung von Exazerbationen). In den unterschiedlichen Therapiestufen sind teils mehrere Alternativen pro Kasten (z. B. Mono- oder Kombitherapie) aufgeführt. Welche davon im individuellen Fall in Frage kommen, müssen Ärzt*innen und Patient*innen vor dem Hintergrund der persönlichen Umstände sowie der zu erwartenden Wirkungen und Nebenwirkungen entscheiden. Mit der Reihenfolge in den Kästen ist explizit keine Gewichtung verbunden.

Inhalative Therapie

*Initiale Behandlung therapienaiver Patient*innen*

Keine medikamentöse Therapie

- Zum Stellenwert des Verzichts auf medikamentöse Maßnahmen bei gering symptomatischen Patient*innen ohne Exazerbationen konnte keine Evidenz identifiziert werden. Basierend auf der klinischen Erfahrung der Leitlinien-gruppe sieht der Algorithmus bei einer vorrangig leichten bis mittelschweren Symptomatik (siehe Kapitel 2.7 Struk-turierte Symptomerfassung) nach individueller Einschätzung des Gesundheitszustandes der Patient*innen auch den Verzicht auf medikamentöse Therapie und die Ausschöpfung nicht-medikamentöser Therapiemaßnahmen als Option vor (siehe Kapitel 4 Nicht-medikamentöse Therapie). Ziel ist, die COPD-Symptomatik mit dem geringstmög-lichen Risiko an unerwünschten Wirkungen zu verbessern. Bei Patient*innen, die wenig unter ihrer Symptomatik leiden, ist es daher nach Einschätzung der Leitliniengruppe möglich zu prüfen, in wie weit nicht-medikamentöse Maßnahmen die Beschwerden wirksam lindern können. Dies wird durch andere Leitlinien ebenfalls gestützt [9]. Da eine schwere Exazerbation eine gefährliche Notfallsituation darstellt und die medikamentöse Behandlung das Auf-treten von Exazerbationen reduzieren kann, wird der Verzicht auf eine medikamentöse Behandlung nicht empfohlen, wenn in der Vorgeschichte bereits schwere Exazerbationen aufgetreten sind.

Bedarfsmedikation

- Evidenzbasis: In der strukturierten Recherche konnte 1 Cochrane-Review [154] identifiziert werden.
- Rationale: Nach den Daten aus einer strukturierten Recherche und basierend auf der klinischen Erfahrung sowie anderen Leitlinien sieht die Leitliniengruppe eine ausschließlich bedarfsorientierte Therapie mit einem SAMA oder SABA als Behandlungsoption bei mild bis mittelgradiger COPD-Symptomatik. Sie zeichnen sich aus durch einen schnellen Wirkungsbeginn und eine Wirkdauer von 4-6 Stunden und sind daher in der Bedarfs- und Notfallanwendung einsetzbar. Da keine Überlegenheit einer Wirkstoffgruppe gezeigt werden konnte, ist es gerechtfertigt, die Bedarfsmedikation entsprechend des individuell besseren Ansprechens der Patient*innen auf die jeweilige Medikation zu wählen. Bei der ausschließlich bedarfsorientierten Therapie besteht erfahrungsgemäß die Gefahr der Verschleierung

einer Progression durch zu häufigen Gebrauch. Das kann dazu führen, dass nicht rechtzeitig eine Langzeittherapie initiiert wird. Die Leitliniengruppe weist darauf hin, dass eine Langzeittherapie mit kurzwirksamen Bronchodilatatoren aufgrund des Nebenwirkungsprofils nicht indiziert ist. Steht die Vermeidung von weiteren Exazerbationen im Fokus der Therapie, sieht die Leitliniengruppe keine Indikation für bedarfsweisen Einsatz von SABA oder SAMA.

Langwirksame Bronchodilatatoren

- Evidenzbasis: In der strukturierten Recherche konnten zwei Cochrane-Reviews [155,156] identifiziert werden, welche die Wirkun-gen von langwirksamen Muskarinantagonisten und langwirksamen Beta-2-Agonisten untersuchten.
- Rationale: Die Evidenzqualität wird als moderat eingeschätzt. LAMA sind im Vergleich zu Placebo prinzipiell wirksam, zudem sind LAMA und LABA hinsichtlich Mortalität und Verbesserung der Symptomatik vergleichbar. Hinsichtlich der Ver-meidung von Exazerbationen scheinen LAMA überlegen. Daraus leitet die Leitliniengruppe die Indikation für ein LAMA oder ein LABA bei therapienaiven Patient*innen mit COPD ohne stattgehabte Exazerbationen ab. Ebenso begründen die Daten die Indikation eines LAMA bei Patient*innen mit höherer Exazerbationsfrequenz.
- Sicherheit: Zur Klärung, welche langwirksame Bronchodilatatorgruppe (LAMA oder LABA) als inhalative Dauertherapie weni-ger kardiale Nebenwirkungen verursacht, wurde eine zusätzliche systematische Recherche durchgeführt. Es wur-den hauptsächlich Registerstudien identifiziert [157–162], jedoch keine prospektiven Studien mit adjustizierten End-punkten. Auf Basis dieser Ergebnisse – zusammen mit der Schwierigkeit, Kausalzusammenhänge aus Registern abzuleiten – kann nach Einschätzung der Leitliniengruppe keine Überlegenheit von einem LABA oder einem LAMA als initiale Dauertherapie hinsichtlich möglicher kardialer Nebenwirkungen abgeleitet werden. Die Vermutung, dass insbesondere Tiotropium eine sichere Dauertherapie diesbezüglich ist, konnte durch die Recherche nicht bestätigt werden.

*Therapieeskalation bei vorbehandelten Patient*innen*

LAMA/LABA

- Evidenzbasis: Zum Stellenwert der Kombinationstherapie aus LAMA und LABA konnten in der strukturierten Recherche zwei Cochrane-Reviews [163,164] identifiziert werden.
- Rationale: Die Evidenzqualität wird als überwiegend moderat bis hoch eingeschätzt. Die vorliegende Evidenz stützt die Kom-bination von LAMA und LABA als nächste Eskalationsstufe. Erhielten Patient*innen initial bereits ein LAMA, können schwere Exazerbationen durch die zusätzliche Gabe eines LABA wahrscheinlich nicht verhindert werden, jedoch könnten diese nach Einschätzung der Leitliniengruppe zu einer zusätzlichen Symptomverbesserung führen.
- Mit ICS vorbehandelte Patient*innen: Die Leitliniengruppe weist auf Basis ihrer klinischen Erfahrung – und gestützt durch die Daten der DACCORD-Studien [33] – darauf hin, dass ein großer Anteil der Patient*innen mit COPD im vertragsärztlichen Bereich bereits mit der Kombination ICS/LABA vorbehandelt ist und empfiehlt (siehe Abbildung 4 und Empfehlung 5-2) die Indikation für eine ICS-Gabe regelmäßig zu überprüfen und dies abzusetzen, wenn die Indikation nicht (mehr) besteht

LAMA/LABA/ICS (Triple-Therapie)

- Evidenzbasis: In der strukturierten Recherche wurde ein Cochrane-Review identifiziert, der den Stellenwert einer Triple-Therapie aus LAMA, LABA und ICS untersuchte [165]. Dieser konnte jedoch innerhalb des Suchzeitraumes (09/2016) keine RCTs einschließen. Eine zusätzlich durchgeführte systematische Recherche zum Thema ergab acht neuere

RCTs [166–173]. Von diesen thematisierten 5 RCTs [166–169,172] die Eskalation von einer LABA/ICS- oder LAMA/LABA-Kombination auf die Triple-Therapie.

- Rationale: Die Evidenzqualität wird für Patient*innen mit stattgehabten Exazerbationen als moderat eingeschätzt; bei Patient*innen ohne stattgehabte Exazerbationen als sehr gering. Auf Basis der identifizierten Evidenz und klinischer Überlegungen sieht die Leitliniengruppe in der Triple-Therapie eine Möglichkeit der Therapieeskalation für Patient*innen mit COPD, bei welchen – trotz Therapie mit einer LAMA/LABA- Kombination – weiterhin Exazerbationen vorrangig sind. Die Daten der hier eingeschlossenen 5 RCTs zeigen unter Einsatz der Triple-Therapie eine Ver-besserung des Endpunktes Exazerbationen; die Konfidenzintervalle sind zumeist eng, was für eine ausreichende Präzision dieses Endpunktes spricht (Ausnahme Ferguson [167]: Vergleich Triple-Therapie vs. LABA/ICS). Die Übertragbarkeit dieses Effektes (Direktheit) ist zumeist begrenzt auf Patient*innen mit COPD und stattgehabten Exazerbationen im letzten Jahr – 4/5 der identifizierten RCTs hatten dies als Einschlusskriterium definiert. Bei Patient*innen ohne Exazerbationen hat die Triple-Therapie dagegen keinen großen Stellenwert, da der Effekt auf die Symptomatik kaum untersucht wurde und nicht plausibel erscheint. In 3/5 der identifizierten Studien ergaben sich zudem Hinweise darauf, dass bei einer höheren Eosinophilenzahl im Differentialblutbild die Triple-Therapie eine stärkere Reduktion künftiger Exazerbationen erzielen kann. Hier sieht die Leitliniengruppe eine mögliche Indikation für die zusätzliche Gabe eines ICS (siehe den folgenden Abschnitt). Anhaltspunkte für ein eventuell erhöhtes An-sprechen auf die inhalative Steroidgabe können – neben der erhöhten Eosinophilenzahl – ein diagnostisch gesi-chertes Asthma oder eine Atopie, erhebliche Variationen der FEV1 über einen längeren Zeitraum (mindestens 400 ml), oder eine über den Tag erhebliche Variation des maximal expiratorischen Flusses (mindestens 20%) sein [9].

Roflumilast

- Evidenzbasis: In der strukturierten Recherche konnte ein Cochrane-Review [182] zum Thema identifiziert werden.
- Rationale: Die Evidenzqualität wird als gering eingeschätzt. Auch wurden in die identifizierte systematische Übersichtsarbeit keine Studien eingeschlossen, die die Wirksamkeit von Roflumilast als Add-on speziell zu einer Triple-Therapie untersuchen. Dennoch einigt sich die Gruppe auf Basis der vorhandenen Evidenz darauf, Roflumilast als letzte Eskalationsstufe zu einer Triple-Therapie (LAMA/LABA/ICS) zu empfehlen, wenn wegen erhöhter Exazerbations-gefahr weiterhin Handlungsbedarf besteht. In einigen Fällen ist Roflumilast auch statt ICS eine Option als Add-on zu einer LAMA/LABA-Kombination, nämlich, wenn ICS-Kontraindikationen bestehen, da von einem ähnlichen, ent-zündungsmildernden Wirkungsansatz ausgegangen werden kann. Die Gabe von Roflumilast ist demnach bei Patient*innen mit COPD möglich, die trotz Therapie wiederholt exazerbieren, dem „chronische Bronchitis“-Phänotyp zuzuordnen sind (siehe Kapitel 1.2 Epidemiologie) und eine FEV1 < 50% haben. Dies entspricht den Formulierungen der EMA-Dokumente [183]. Um das Risiko gastrointesti-naler Nebenwirkungen zu reduzieren, ist ein stufenweises Aufdosieren der Medikation möglich.

<u>Orale Steroidtherapie</u>

Die Leitlinie adressiert an dieser Stelle diejenigen Patient*innen, welche ohne eine dauerhafte orale Steroidtherapie als Therapieoption nicht zurechtkommen. Nach der klinischen Erfahrung der Leitliniengruppe gibt es eine geringe Anzahl von Patient*innen, die zeitweise nicht ohne diese Option zu führen sind.

- Evidenzbasis: Ein in der strukturierten Recherche identifizierter Cochrane-Review [188] untersuchte die Effekte oral applizierter Steroide gegenüber einer Placebo-Gabe bei Patient*innen mit COPD.
- Rationale: Auf Basis ihrer klinischen Erfahrungen sieht die Leitliniengruppe keine belastbare Evidenz für die dauerhafte Gabe von OCS (Orale Corticosteroide), insbesondere aufgrund der potenziellen Schäden. In den seltenen Fällen, in denen sich eine orale Steroidgabe vorübergehend dennoch nicht vermeiden lässt, ist es wichtig, diese dann mit einer möglichst niedrigen wirksamen Dosierung durchzuführen. Grundsätzlich sind die kontinuierliche Überprüfung der Indikation und entsprechende Absatzversuche geboten.

Prophylaktische Therapie mit Antibiotika

- Evidenzbasis: In der strukturierten Recherche wurde ein Cochrane-Review zum Stellenwert der prophylaktischen Therapie mit Antibiotika identifiziert [189].
- Rationale: Die Leitliniengruppe schließt aus den Daten der strukturierten Recherche mit moderater Evidenzqualität, dass die prophylaktische Gabe von Antibiotika im Einzelfall zwar eine mögliche Option für die Reduktion von Exazerbationen zu sein scheint. Diese kommt jedoch nicht als Standardbehandlung in Betracht, vor allem vor dem Hintergrund der steigenden Anzahl von Antibiotikaresistenzen sowie spezifischer Nebenwirkungen einzelner Substanzen. Im Sinn des „Antibiotic Stewardship“ muss der dauerhafte Einsatz von Antibiotika zur Prophylaxe sehr kritisch geprüft und gegen die gesamtgesellschaftlichen Schäden abgewogen werden.

Mukolytika

Empfehlungen/Statements	Empfehlungs-grad
5-8 Bei symptomatischen Patient*innen mit überwiegend bronchitischen Beschwerden können ausgewählte Mukolytika (z. B. N-Acetylcystein) als Dauertherapie und in angemessener Dosierung zur Vermeidung von Exazerbationen eingesetzt werden.	⇔

- Evidenzbasis: Die Empfehlung 5-8 basiert auf einer systematischen Recherche nach aggregierter Evidenz sowie der klinischen Erfahrung der Leitliniengruppe. Es werden vier Meta-analysen herangezogen: [190-193]
- Rationale: Die Evidenzqualität wird als überwiegend moderat eingeschätzt. Mukolytika nehmen nach Einschätzung der Leitli-niengruppe einen hohen Stellenwert in der Selbstmedikation bei Patient*innen mit COPD ein. Der Vorteil einer oralen Einnahme kann möglicherweise eine wichtige Therapieoption insbesondere für ältere Menschen darstellen. Auf Basis der vorhandenen Evidenz wurde aufgrund der überwiegend moderaten Evidenzqualität bei gleichzeitigen generell erhöhten Risiken für Adhärenzbeeinträchtigung und Wechselwirkungen durch Polypharmazie für Mukoly-tika eine offene Empfehlung formuliert, wenn die Vermeidung von Exazerbationen im Vordergrund steht. Besonders hinzuweisen ist darauf, dass Wirksamkeit für Mukolytika nur in entsprechend hoher Dosierung und als Dauertherapie gezeigt wurde.

Antitussiva

- Die S2k-Leitlinie zur Diagnostik und Therapie von erwachsenen Patienten mit Husten [126] sieht die Indikation für eine antitussive Therapie insbesondere bei unproduktivem Reizhusten bzw. bei Husten mit geringen Sekretmengen (bei akuten Atemwegsinfektionen). Falls es keine (Erkältungsinfekt, akute virale Bronchitis) oder keine schnell und effektiv wirkende kausale Therapie gibt, ist die vorübergehende Verordnung von Hustenstillern eine Option.

- Wenn jedoch eine Sekretretention zu Husten führt, ist die Förderung der Expektoration das zentrale Prinzip in der physikalischen und medikamentösen Therapie. Antitussiva sind hierbei nur in Ausnahmefällen indiziert, zum Bei-spiel nachts für Hustendämpfung in Kombination mit Expektorantien tagsüber. [126]

Betablocker

- Evidenzbasis: Zum Umgang mit Betablockern bei Patient*innen mit COPD konnte in der strukturierten Recherche ein Cochrane-Review identifiziert werden [195].
- Stellenwert: Die identifizierten Daten lassen wenige Rückschlüsse auf Patient*innen mit COPD und kardiovaskulären Indikationen für eine Beta-Blocker-Therapie zu. Es ergeben sich jedoch Hinweise, dass die Indikation für Patient*innen mit schwergradiger COPD und einem hohen Risiko für schwere Exazerbationen strenger gestellt werden muss.

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Bourbeau J et al., 2023 [1]

Canadian Thoracic Society Clinical

Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence

Zielsetzung/Fragestellung

The overall objective of this CTS guideline is to help clinicians match pharmacological treatment to the clinical status of individuals with stable COPD. This is an important step toward personalizing therapy based on individual characterization. The specific objective is to provide clinical guidance with evidence-based recommendations from a systematic review with a meta-analysis and expertinformed clinical remarks to optimize maintenance pharmacological therapy aimed at alleviating dyspnea and improving health status, preventing exacerbations and reducing mortality for individuals with stable COPD.

Methodik

- Repräsentatives Gremium – trifft teilweise zu (Patient*innenbeteiligung unklar);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;

- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu (The guideline will be formally reviewed every three years or sooner to determine the need for and nature of any updates).

Recherche/Suchzeitraum

- In addition to the studies included in our previous guidelines, a comprehensive search of literature was performed from MEDLINE,EMBASE, and COCHRANE libraries from the end date of the 2019 guideline search (October 18, 2018, to June 9, 2022) for PICO 1 and 2, and from 1974 to June 9, 2022, for PICO 3.

LoE

- GRADE

GoR

- Following open and extensive discussions, the entire panel proposed wording and/or updates to prior recommendations, and where applicable, any required change to the strength of the recommendation. They based the strength of each recommendation on the GRADE quality of evidence[20] and synthesis of clinical judgment.
- Recommendations were then voted upon using a six-point voting scale, whereby it was defined a priori that a recommendation would only be accepted if each panel member voted for option 1, 2, or 3 (“wholeheartedly agree,” “agree,” or “can support”). For a recommendation to be accepted, it had to be voted on by 75% of the eligible panel members and achieve ratings 1, 2, or 3 by 80% of the voting panelists. In the event of a failure to reach 80% of votes with ratings 1, 2, or 3, another period of discussionensued, whereby dissenting opinions were heard and considered.
- The recommendation was revised as necessary and followed by a second round of voting using a three-point scale, for which acceptance of a recommendation required a majority (80%) of panelists to choose option 1 or 2. Throughout this process all recommendations achieved acceptance. We also included practical clinical advice within “Clinical Remarks” attached to recommendations. This advice represents the consensus opinion of panel members based on their expertise.

Empfehlungen

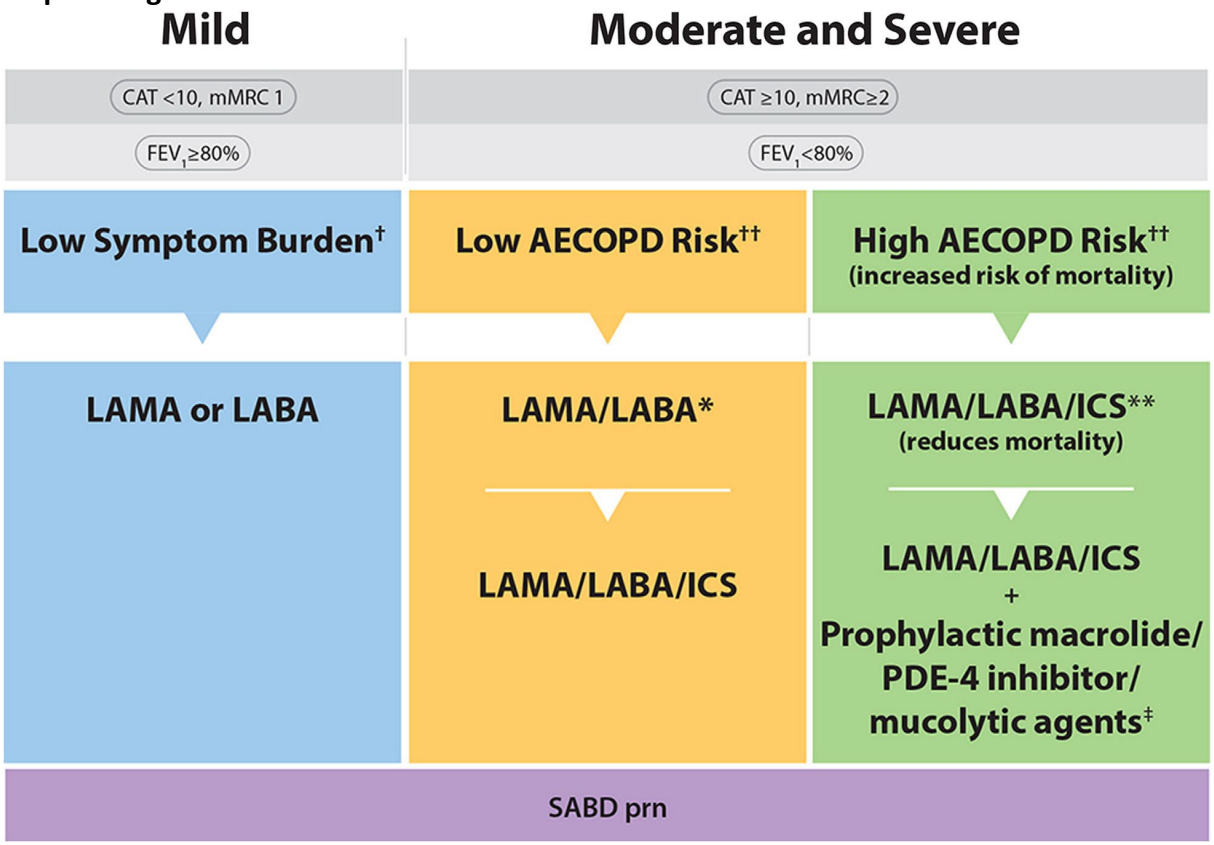


Figure 3 – COPD pharmacotherapy. This figure promotes an evidence-informed approach that aligns proven effective treatments with spirometry, symptom burden, risk of future exacerbations, and mortality risk. Because of the clinical heterogeneity in COPD, spirometry should not be used in isolation to assess disease severity and this is why it is also important to perform a thorough clinical evaluation of the patient, including symptom burden and risk of exacerbations that permits the implementation of treatments that are specific for subpopulations. SABD prn (as needed) should accompany all recommended therapies across the spectrum of COPD.†Symptom burden encompasses shortness of breath, activity limitation, and impaired health status.††Individuals are considered at "Low Risk of AECOPD" if # 1 moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids) and did not require hospital admission/ED visit. Individuals are considered at "High Risk of AECOPD" if $ 2 moderate AECOPD or $ 1 severe exacerbation in the last year (severe AECOPD is an event requiring hospitalization or ED visit).* LAMA/LABA single inhaled dual therapy is preferred over ICS/LABA inhaled combination therapy considering the additional improvements in lung function and the lower rates of adverse events such as pneumonia. ICS/LABA combination therapy should be used in individuals with concomitant asthma. There is no universally accepted definition of concomitant asthma. The 2017 CTS Position Statement on COPD Pharmacotherapy provides guidance on the assessment of patients who may have concomitant asthma.**Triple inhaled ICS/LAMA/LABA combination therapy should preferably be administered in a single inhaler triple therapy (SITT), and not in multiple inhalers (see text), although we acknowledge that some patients continue to prefer separate inhalers. þOral pharmacotherapies in this group include prophylactic macrolide, and PDE-4 inhibitor and mucolytic agents for patients with chronic bronchitis. AECOPD, acute exacerbation of COPD; CAT, COPD assessment test; ICS, inhaled corticosteroid; LABA, longacting ß2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council; SABD prn, short-acting bronchodilator as needed.

PICO 1

TABLE 1] 2023 Recommendations for PICO 1. How Does a Clinician Choose Appropriate Maintenance Pharmacotherapies in Individuals With Stable COPD to Reduce Symptom Burden, for Example, Dyspnea and Exercise Intolerance, and Improve Health Status?

2023 Recommendations to Reduce Symptom Burden and Improve Health Status	Strength of Recommendation	Certainty of Evidence	Evidence From Meta-Analysis: Online Supplement Table 1	Evidence From Meta-Analysis: Online Supplement 2
P.1.A. In individuals with stable COPD, at low risk of exacerbations§, with low symptom burden and health status impairment (CAT < 10, mMRC 1), and only mildly impaired lung function (FEV_1 ≥ 80% predicted), we recommend starting initial monotherapy with either LAMA or LABA.	**Strong**	***Moderate to high certainty*** of greater improvements in dyspnea, exercise tolerance, and health status with LAMA or LABA compared to placebo.	1.1 a, b	Tables 16, 17; Pages 127, 128.
Clinical remark: All studies have characterized individuals with spirometry-based COPD although not all have classified disease severity by FEV_1, mMRC, and/or CAT exactly as we have in order to compare either LAMA or LABA monotherapy to placebo; however, the panel valued the importance of providing a precise consensus working definition of COPD with mild symptom burden for recommending regular long-acting bronchodilator therapy.		***Low certainty*** of greater improvements in dyspnea, exercise tolerance, and health status with LAMA monotherapy compared to LABA monotherapy.	1.1 c	Table 1; Figures: 1-13; Pages 5-23.
		Low certainty of greater improvement in physical activity with LAMA or LABA compared to placebo.	1.1 d	n/a
P.1.B. In individuals with stable COPD, at low risk of exacerbations§, with a moderate to high symptom burden/health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted), we recommend starting LAMA/LABA dual therapy as initial maintenance therapy.	**Strong**	***Moderate to high certainty*** of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to LAMA monotherapy.	1.2 a	Table 2; Figures: 14-23; Pages 24-40.
Clinical remarks: This recommendation reflects the strength and quality of evidence and high importance to patients and clinicians of alleviating dyspnea and improving health status as key treatment goals of COPD, particularly in individuals with moderate to high symptom burden/health status impairment.		***Moderate certainty*** of greater improvements in dyspnea, exercise intolerance, and health status with LAMA/LABA compared to LABA monotherapy.	1.2 b	Table 3; Figures: 24-34; Pages 41-50.
Note that improvement in exercise capacity may not lead to improvement in physical activity without adding a behavioral intervention.		***Low certainty*** of greater improvement in physical activity with LAMA/LABA compared to placebo.	1.3	Table 18; Page 129.
LAMA/LABA dual therapy is preferred to ICS/LABA combination therapy due to significant improvement in lung function and lower rates of pneumonia. However,		***Low certainty*** of greater improvements in dyspnea, exercise intolerance, and health status	1.5	Table 4; Figures: 35-46; Pages 51-62.

2023 Recommendations to Reduce Symptom Burden and Improve Health Status	Strength of Recommendation	Certainty of Evidence	Evidence From Meta-Analysis: Online Supplement Table 1	Evidence From Meta-Analysis: Online Supplement 2
ICS/LABA combination therapy is preferred to LAMA/LABA dual therapy in individuals who have COPD with concomitant asthma.		with LAMA/LABA compared to ICS/LABA combination therapy.		
P.1.C. In individuals with stable COPD, at low risk of exacerbations§, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted) despite LAMA/LABA dual therapy or ICS/LABA combination therapy, we recommend step-up to a LAMA/LABA/ICS triple combination therapy.	**Strong**	***Moderate certainty*** of greater improvements in dyspnea and health status with LAMA/LABA/ICS compared to LAMA/LABA dual therapy or ICS/LABA combination therapy.	1.6 a, b	Tables 7, 8; Figures: 71-92; Pages 90-107.
Clinical remark: The best option to alleviate dyspnea and other symptoms as well as to improve health status is to combine optimal pharmacotherapy with pulmonary rehabilitation.				
P.1.D. In individuals with stable COPD, at low risk of exacerbations§, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted) despite LAMA/LABA/ICS triple combination therapy, we suggest not stepping down to LAMA/LABA dual therapy.	**Weak**	***Low to moderate certainty*** of lack of harm from step down from LAMA/LABA/ICS to LAMA/LABA dual therapy.	1.7	Table 10; Figures: 101-103; Pages 115-117.
For patients taking LAMA/LABA dual therapy, we suggest not stepping down to LAMA or LABA monotherapy.	**Weak**	***Insufficient evidence.***		
Clinical Remark: This recommendation reflects the high importance that both patients and clinicians ascribe to alleviating dyspnea and improving health status, particularly in individuals with moderate to high symptom burden/health status impairment. Withdrawing ICS may result in worsening of health status and lung function in some patients. Therefore, we prioritized these outcomes over the risk of adverse events including pneumonia with use of LAMA/LABA/ICS triple combination therapy. However, stepping down may be considered in patients in whom the step				

2023 Recommendations to Reduce Symptom Burden and Improve Health Status	Strength of Recommendation	Certainty of Evidence	Evidence From Meta-Analysis: Online Supplement Table 1	Evidence From Meta-Analysis: Online Supplement 2
up did not result in improved symptoms or health status or because of adverse effects that are of significant importance. No studies of step-down have assessed the impact on dyspnea.				
P.1.E. In individuals with stable COPD, at low risk of exacerbations§, currently on LAMA monotherapy, LABA monotherapy, or LAMA/LABA dual therapy, we do not suggest adding any of the following oral medications: **- Phosphodiesterase-4-inhibitors** **- Mucolytics** **- Statins** **- Anabolic steroids** **- Oral Chinese herbal medicines** **- Theophylline**	**Weak**	***Low certainty*** of no improvements in dyspnea, exercise tolerance, physical activity levels, and/or health status with oral therapies compared to placebo.	1.8	Tables 12-20; Pages 118-131.
Clinical remark: There are limited studies assessing theophylline, which showed equivocal changes in health status. Although there is evidence of a modest improvement in FEV_1 with theophylline, the panel placed greater weight on the risk of adverse events and drug interactions.				
P.1.F. In all individuals with stable COPD and at a low risk of exacerbations§, we recommend against treatment with ICS monotherapy.	**Strong**	***Low certainty*** of no improvements in dyspnea, exercise tolerance, physical activity levels, and/or health status with ICS monotherapy compared to placebo.		Table 19; Page 130.
Clinical Remark: When indicated in patients with COPD, ICS should only be administered as part of combination therapy (see above). The panel placed greater weight on the increased risk of adverse events (eg, pneumonia).				

AECOPD, acute exacerbation of COPD; CAT, COPD assessment test; ICS, inhaled corticosteroid; LABA, long-acting ß2-agonist;; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council; P.1., Patients/population (P); Intervention(s) (I), Comparison/comparator (C); and Outcome (O), (PICO)1.
§Patients are considered at "Low Risk of AECOPD" if ≤1 moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids) and did not require hospital admission/ED visit.

PICO 2

TABLE 2] 2023 Recommendations for PICO 2. How Does a Clinician Choose Appropriate Maintenance Pharmacotherapies in Individuals With Stable COPD to Reduce the Risk of AECOPD?

2023 Recommendations to Reduce the Risk of Acute Exacerbations	Strength of Recommendation	Certainty of Evidence	Evidence From Meta-Analysis: Supplement Table 1	Evidence From Meta-Analysis: Supplement 2
P.2.A. In individuals with stable COPD, at low risk of exacerbations§, a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted), we recommend starting LAMA/LABA dual therapy as initial maintenance therapy.	**Strong**	***Moderate certainty*** of greater reduction in rate of exacerbation with LAMA/LABA dual therapy compared to LAMA monotherapy.	2.4 a	Table 22; Figures: 118-122; Pages 137-14.
Clinical Remark: LAMA/LABA dual therapy is preferred to ICS/LABA combination therapy due to significant improvement in lung function and lower rates of pneumonia. However, ICS/ LABA combination therapy is preferred to LAMA/LABA dual therapy in individuals who have COPD with concomitant asthma.		***Low to moderate certainty*** of greater reduction in rate of exacerbation with LAMA/LABA dual therapy compared to LABA monotherapy.	2.4 b	Table 23; Figures: 123-126; Pages 142-144.
		Low to moderate certainty of greater reduction in rate of exacerbation with LAMA/LABA dual therapy compared to ICS/LABA combination therapy.	2.6	Table 24; Figures: 127-129; Pages 145-148.
P.2.B. In individuals with stable COPD, at high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted), we recommend the use of LAMA/LABA/ICS triple combination therapy.	**Strong**	***Low to moderate certainty*** of greater reduction in rate of exacerbation with LAMA/LABA/ICS triple combination therapy compared to LAMA monotherapy.	2.7 a	Table 29; Figures: 147-151; Pages 164-167.
Clinical Remark: The panel placed high value on the reduction of exacerbations and mortality as demonstrated in several studies when LAMA/LABA/ICS triple combination therapy was used in this high-risk population compared to LAMA/LABA dual therapy or ICS/LABA combination therapy.		***Moderate certainty*** of greater reduction in rate of exacerbation with LAMA/LABA/ICS triple combination therapy compared to ICS/LABA combination therapy.	2.7 b	Table 28; Figures: 142-146; Pages 160-163.
		Moderate certainty of greater reduction in rate of exacerbation with LAMA/LABA/ICS triple combination therapy compared to LAMA/LABA dual therapy.	2.7 C	Table 27; Figures: 137-141; Pages 157-159.

2023 Recommendations to Reduce the Risk of Acute Exacerbations	Strength of Recommendation	Certainty of Evidence	Evidence From Meta-Analysis: Supplement Table 1	Evidence From Meta-Analysis: Supplement 2
P.2.C. In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted), we do not suggest step down from LAMA/LABA/ICS triple combination therapy to LAMA/LABA dual therapy.	**Weak**	***Low certainty** of benefit of stepdown from LAMA/LABA/ICS to LAMA/LABA*	2.8	Table 30; Figure: 152-154; Pages 168-170.
Clinical Remark: Withdrawing ICS may lower health status and lung function. Withdrawing ICS may also be associated with an increased risk of moderate-severe AECOPD, especially in patients with blood eosinophils counts ≥ 300 cells/μL.				
P.2.D. In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted) who continue to exacerbate (either moderate or severe) despite being on LAMA/LABA/ICS triple combination therapy, we recommend the addition of macrolide maintenance therapy.	**Strong**	***Moderate certainty** of greater reduction in rate of exacerbation with addition of oral macrolide to LAMA/LABA/ICS*	2.11	Table 35; Page 179.
Clinical Remark: the benefits of macrolide maintenance therapy studied over 1 year should be weighed against the risks of microbial resistance, hearing impairment and cardiac arrhythmia related to QT prolongation/drug interactions.				
P.2.E. In individuals with stable COPD, with a Chronic Bronchitic Phenotype at a high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted) who continue to exacerbate despite being on LAMA/LABA/ICS triple combination therapy, we suggest the addition of either Roflumilast or N-acetylcysteine.	**Weak**	***Low certainty** of greater reduction in rate of exacerbation with the addition of roflumilast compared to placebo?*	2.9	Table 40; Page 184.
		***Moderate certainty** of the addition of N-acetylcysteine.*	2.10	Table 32; Figures: 157; Page 173.

AECOPD, acute exacerbation of COPD; CAT, COPD assessment test; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council; P.2., Patients/population (P); Intervention(s) (I); Comparison/comparator (C); and Outcome (O), (PICO) 2.
§Patients are considered at "Low Risk of AECOPD" if ≤ 1 moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids) *and* did not require hospital admission/ Emergency Department visit.
*Patients are considered at "High Risk of AECOPD" if ≥ 2 moderate AECOPD or ≥1 severe AECOPD in the last year (severe AECOPD is an event requiring hospitalization or ED visit).

PICO 3

TABLE 3] 2023 Recommendations for PICO 3. How Does a Clinician Choose Appropriate Maintenance Pharmacotherapies in Individuals With Stable COPD to Reduce Mortality?

2023 Recommendations to Reduce Mortality	Strength of Recommendation	Certainty of Evidence	Evidence From Meta-Analysis: Supplement Table 1	Evidence From Meta-Analysis: Supplement 2
P.3.A. In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted), we recommend the use of LAMA/LABA/ICS triple combination therapy over LABA/LAMA dual therapy.	**Strong**	*Moderate certainty* for greater reduction in mortality with LAMA/LABA/ICS triple combination compared to LABA/LAMA dual therapy.	3.2	Table 41; Figures 162-164; Pages 186-188.
Clinical remark: Triple combination therapy is preferred to LABA/LAMA dual therapy because of the greater benefit in reducing mortality (secondary or other outcome) and also the additional benefits of preventing moderate-severe AECOPD (primary outcomes in these RCTs) and improving dyspnea, health status, lung function (secondary outcomes), in this well-defined population of patients.				
P.3.B. In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden/health status impairment (CAT ≥ 10, mMRC ≥ 2) and impaired lung function (FEV_1 < 80% predicted) we recommend the use of LAMA/LABA/ICS triple combination therapy over ICS/LABA combination therapy.	**Weak**	*Moderate certainty* for greater reduction in mortality with LAMA/LABA/ICS triple combination therapy compared to ICS/LABA combination therapy.	3.3	Table 42; Figures: 165-167; Pages 189-192.
Clinical remark: Although triple therapy has not shown superiority in reducing mortality (secondary or other outcome) compared to ICS/LABA, it has shown greater benefit on other important outcomes such as preventing moderate-severe AECOPD (primary outcomes in these RCTs) and improving dyspnea, health status, lung function (secondary outcomes), in this well-defined population of patients.				

AECOPD, acute exacerbation of COPD; CAT, COPD assessment test; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, Modified Medical Research Council; P.3., Patients/population (P); Intervention(s) (I); Comparison/comparator (C); and Outcome (O), (PICO) 3; RCTs, randomized controlled trials.
*Patients are considered at "High Risk of AECOPD" if ≥ 2 moderate AECOPD *or* ≥ 1 severe exacerbation in the last year (severe AECOPD is an event requiring hospitalization or ED visit).

Department of Veterans Affairs & Department of Defense, 2021 [11]

VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease; Version 3.0

Zielsetzung/Fragestellung

This CPG provides an evidence-based framework for evaluating and managing care for patients with COPD toward improving clinical outcomes. Successful implementation of this CPG will:

- Assess the patient's condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care
- Emphasize the use of patient-centered care using individual risk factors and event history
- Minimize preventable complications and morbidity
- Optimize individual health outcomes and quality of life (QoL)

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Embase	01/01/2014 – 02/21/2020	Embase.com
Medline	01/01/2014 – 02/21/2020	Embase.com
PubMed In Process & Non-Indexed Citations	01/01/2014 – 02/21/2020	pubmed.ncbi.nlm.nih.gov

LoE

- GRADE

GoR

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend …
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against …
Weak against	We suggest against …
Strong against	We recommend against …

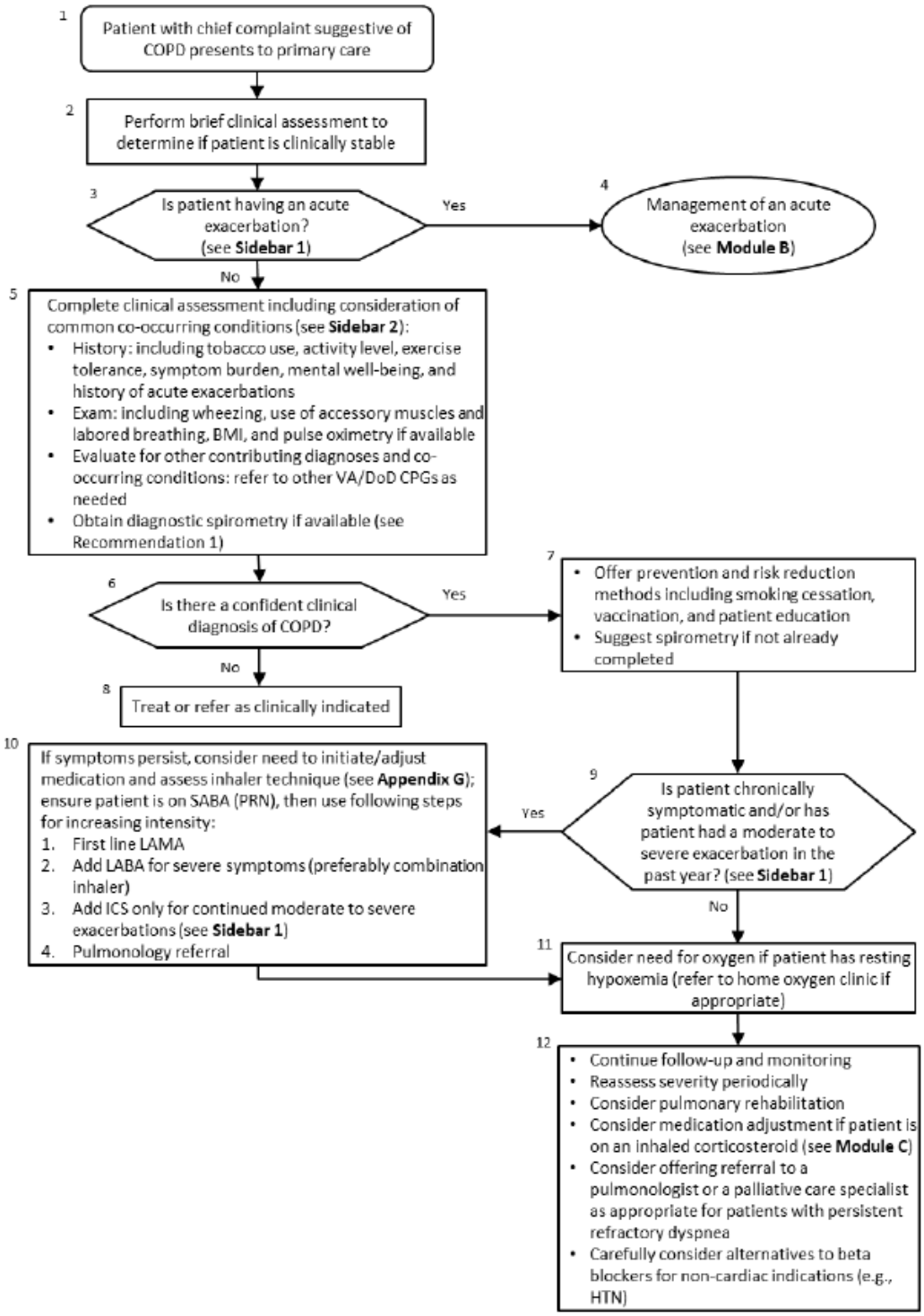
It is important to note that a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care).

Sonstige methodische Hinweise

- The 2021 VA/DoD COPD CPG is the third update to this CPG.

Algorithm

A. Module A: Management of COPD in Primary Care



Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CPG: clinical practice guideline; HTN: hypertension; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting antimuscarinic agent; PRN: pro re nata (as needed); SABA: short-acting beta 2-agonist; VA/DoD: Department of Veterans Affairs/Department of Defense

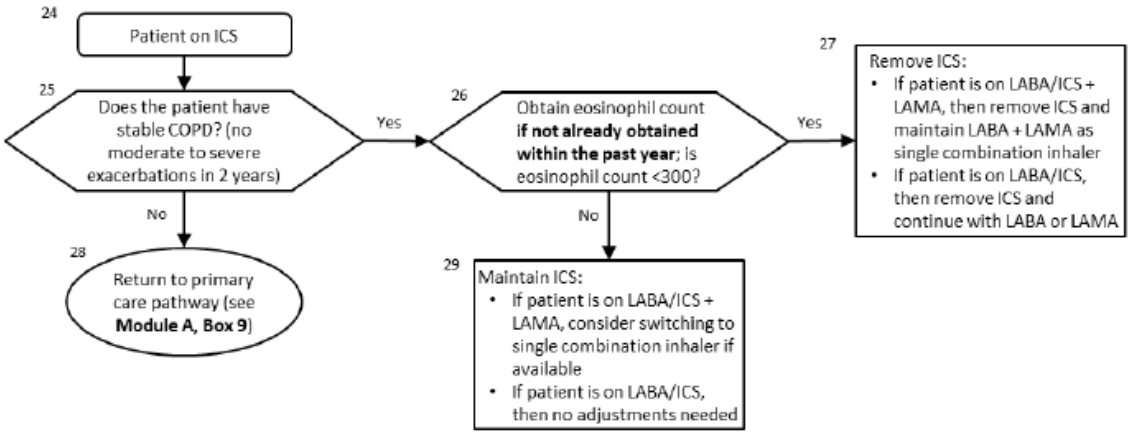
Sidebar 1: Definition of Exacerbations
Increased dyspnea above day-to-day variability with or without change in sputum amount or color. Moderate to severe exacerbations are those that require antibiotics and/or systemic corticosteroids. Patients with exacerbation within the past six months would be considered to have "severe COPD."

Abbreviations: COPD: chronic obstructive pulmonary disease

Sidebar 2: Common Co-occurring Conditions
• CVD • CHF • Pulmonary embolism • Sleep disorders • Poor nutritional status (both under and over nutrition) • Gastroesophageal reflux • Depression • Anxiety

Abbreviations: CHF: congestive heart failure; CVD: cardiovascular disease

C. Module C: Inhaled Corticosteroids Usage



Abbreviations: COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting antimuscarinic agent

Recommendations

Topic	#	Recommendation	Strength[a]	Category[b]
Diagnosis & Classification	1.	We suggest post-bronchodilator spirometry to confirm clinical diagnosis of COPD.	Weak for	Reviewed, New-replaced
	2.	There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD.	Neither for nor against	Reviewed, New-added
Risk Reduction	3.	We recommend smoking cessation for prevention and risk reduction of COPD.	Strong for	Reviewed, New-replaced
	4.	We suggest routine vaccination for influenza and pneumococcal pneumonia for prevention and risk reduction of COPD exacerbations.	Weak for	Reviewed, New-replaced
	5.	We recommend offering inhaled long-acting muscarinic antagonists as first-line therapy in patients with symptomatic COPD.	Strong for	Reviewed, New-replaced
	6.	We recommend against offering an inhaled long-acting beta agonist as first-line therapy in patients with symptomatic COPD, unless a long-acting muscarinic antagonist is not tolerated or is contraindicated.	Strong against	Reviewed, New-added
	7.	We recommend against offering an inhaled corticosteroid in patients with symptomatic COPD as a first-line therapy.	Strong against	Not reviewed, Amended
	8.	For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a long-acting muscarinic antagonist, we suggest adding a long-acting beta agonist to long-acting antimuscarinic agent therapy.	Weak for	Reviewed, New-replaced
	9.	If choosing dual therapy, we recommend against offering long-acting beta agonists with inhaled corticosteroids for patients with COPD.	Strong against	Reviewed, New-added
	10.	In patients with COPD who are on combination therapy with a long-acting antimuscarinic agent/long-acting beta agonist and continue to have COPD exacerbations, we suggest adding an inhaled corticosteroid as a third medication.	Weak for	Reviewed, New-replaced
	11.	There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy.	Neither for nor against	Reviewed, New-added
	12.	We suggest considering withdrawal of inhaled corticosteroids in patients with COPD without moderate to severe exacerbations in the last two years.	Weak for	Reviewed, New-added

Topic	#	Recommendation	Strength[a]	Category[b]
First-line Therapy	13.	There is insufficient evidence to recommend for or against the use of N-acetylcysteine preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	Neither for nor against	Reviewed, Amended
	14.	There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not).	Neither for nor against	Reviewed, New-replaced
	15.	We recommend providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia (PaO_2 <55 mm Hg and/or SaO_2 ≤88%) or chronic stable resting moderate hypoxemia (PaO_2 56 – 59 mm Hg or SaO_2 >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale).	Strong for	Not reviewed, Not changed
	16.	We suggest against routinely offering ambulatory long-term supplemental oxygen for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.	Weak against	Reviewed, Not changed
	17.	In patients with COPD, we suggest starting or continuing cardio-selective beta-blockers only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).	Weak for	Reviewed, Amended
	18.	We suggest offering a supported self-management program that includes a written action plan with exacerbation management, smoking cessation, and exercise.	Weak for	Reviewed, New-replaced
	19.	We suggest offering telehealth support that includes telemonitoring and/or mobile applications.	Weak for	Reviewed, New-replaced

[a] For additional information, see Grading Recommendations.

[b] For additional information, see Recommendation Categorization and Appendix D.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2025) am 03.01.2025

#	Suchschritt
1	[mh "Pulmonary Disease, Chronic Obstructive"]
2	(chronic NEXT obstructive NEXT (airway* OR lung OR pulmonary) NEXT disease*):ti,ab,kw
3	(COPD OR COAD):ti,ab,kw
4	(chronic NEXT bronchitis):ti,ab,kw
5	("chronic airflow obstruction"):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from Jan 2020 to present, in Cochrane Reviews

Leitlinien und systematische Reviews in PubMed am 03.01.2025

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchschritt	Treffer
	Leitlinien	
1	"Pulmonary Disease, Chronic Obstructive"[mh]	71185
2	"chronic obstructive pulmonary disease*"[tiab] OR "chronic obstructive airways disease*"[tiab] OR "chronic obstructive airway disease*" OR "chronic obstructive lung disease*"[tiab] OR "chronic bronchitis"[tiab] OR "chronic airflow obstruction"[tiab] OR COPD[tiab] OR COAD[tiab]	101738
3	#1 OR #2	121876
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])	1248
5	(#4) AND ("2020/01/01"[PDAT] : "3000"[PDAT])	281
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])	281
	systematische Reviews	
7	Pulmonary Disease, Chronic Obstructive/therapy[majr]	21534

#	Suchschritt	Treffer
8	(#2) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR 64harmacothe*[tiab] OR 64harmacothe*[tiab] OR 64harmacotherapy*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])	60554
9	#7 OR #8	67663
10	(#9) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])	4793
11	(#10) AND ("2020/01/01"[PDAT] : "3000"[PDAT])	2032
12	(#11) NOT "The Cochrane database of systematic reviews"[Journal]	2003
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])	1989
	systematische Reviews ohne Leitlinien	
14	(#13) NOT (#6)	1942

Iterative Handsuche nach grauer Literatur, abgeschlossen am 08.01.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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2. **Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).** Nationale VersorgungsLeitlinie COPD; Langfassung, 2. Auflage, Version 1 [online]. AWMF-Registernummer nvl-003. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2021. [Zugriff: 06.01.2025]. URL: https://register.awmf.org/assets/guidelines/nvl-003l_S3_COPD_2024-12.pdf.
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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

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Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Datum der Erstellung	30. Januar 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Erwachsene mit unkontrollierter chronisch obstruktiver Lungenerkrankung (COPD) mit einem inhalativen Kortikosteroid (ICS), einem langwirksamen Beta2-Agonisten (LABA) und einem langwirksamen Muskarinantagonisten (LAMA), die durch erhöhte Blut-Eosinophile gekennzeichnet ist.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Bei den hier in Augenschein zu nehmenden Patientinnen und Patienten ist offenbar bereits eine inhalative Triple-Therapie (ICS/LABA/LAMA) etabliert. Diese Kombination kommt für Patientinnen und Patienten infrage, bei denen im Differenzialblutbild höhere Eosinophilenwerte gemessen wurden oder aber eine Historie gehäufter Exazerbationen im Vorfeld der Hinzunahme eines inhalativen Kortikosteroids (ICS) dokumentiert ist. (1) Zuallererst sind wichtige nichtmedikamentöse Begleitmaßnahmen bei allen COPD-Patientinnen und -Patienten vorzunehmen und zu etablieren: Dies beinhaltet grundsätzlich das individualisierte Finden eines geeigneten Inhalationsdevices, die Schulung der richtigen Inhalationstechnik, physiotherapeutische und rehabilitative Maßnahmen (Lungensport o. Ä.), Rauchentwöhnung sowie eine Infektprophylaxe im Sinne von Wahrnehmung der entsprechenden Indikationsimpfungen (Influenza, COVID, RSV, Pneumokokken). Für den Fall, dass unter der Triple-Therapie keine stabile Phase erreicht werden kann und sich Symptome verschlechtern oder es häufiger zu Exazerbationen kommt, ist die Überprüfung bzw. das Absetzen von ICS empfohlen. Und zwar für folgende Konstellationen (1): • Eosinophile < 100 Zellen/µl im Differenzialblutbild und • keine klinischen asthmatischen Komponenten vorhanden oder • in der Vergangenheit unter ICS eine Pneumonie aufgetreten.

Als weitere medikamentöse Therapieoption bei Patientinnen und Patienten mit COPD, die unter optimierter Therapie häufiger exazerbieren und dem bronchitischen Phänotyp zuzuordnen sind sowie eine FEV-1 von < 50 % haben, kann der Phosphodiesterase-4(PDE4)-Inhibitor Roflumilast zusätzlich zu der Triple-Kombination in Tablettenform verabreicht werden (1).

Seit 2024 ist darüber hinaus als Add-On-Erhaltungstherapie Dupilumab für Patientinnen und Patienten mit COPD, die eine erhöhte Bluteosinophilie aufweisen, zugelassen. Aus den Studien BOREAS und NOTUS sind Anhaltspunkte für einen (geringen) Zusatznutzen für die entsprechenden Patientinnen und Patienten ableitbar (2-4).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Die Behandlungsentscheidung wird in der Regel individuell und idealerweise leitliniengerecht vorgenommen. Die Therapie beinhaltet die oben genannten nichtmedikamentösen und medikamentösen Maßnahmen. Die Schulung der Inhalationstechnik und das Finden des individuell geeigneten Devices, mit dem COPD-Patientinnen und Patienten optimal zurechtkommen, ist eine wesentliche Aufgabe der behandelnden Ärztinnen und Ärzte. Eine Dosissteigerung oder eine „Stufentherapie“ wie zum Beispiel beim Asthma bronchiale ist bei der Behandlung der COPD per se nicht vorgesehen. Vielmehr fließen die Symptomatik, Exazerbationshäufigkeit, Lungenfunktion, Bildgebung, Blutgasanalysen und die individuelle, patientenseitige Fähigkeit ein Inhalationssystem optimal bedienen zu können, in die Therapieentscheidung mit ein.

Die kritische Überprüfung des sinnvollen Einsatzes inhalativer Kortikosteroide (ICS), wie oben aufgeführt, ist ebenfalls regelmäßige fachärztliche Aufgabe.

Roflumilast ist eine mögliche Add-on-Option, jedoch lediglich bei einer FEV-1 < 50 % und häufigen Exazerbationen in näherer Vergangenheit (1). Die Empfehlung hierzu ist schwach und unerwünschte Arzneimittelwirkungen häufig, sie limitieren daher den Einsatz. Um diese Indikation als Option zu eruieren, sind Lungenfunktionsuntersuchungen unabdingbar.

Regelmäßige Messungen der Eosinophilenzahlen aus dem Differenzialblutbild sind empfehlenswert, um die neue Therapieoption Dupilumab bei entsprechend erhöhten Eosinophilen-Werten evaluieren zu können. (2)

Zur Vervollständigung möglicher Therapieoptionen sollten darüber hinaus folgende, bislang nicht erwähnte, nichtmedikamentöse Therapiemaßnahmen bedacht werden:

- Bei Vorliegen einer respiratorischen hyperkapnischen Insuffizienz sollte eine nichtinvasive Beatmung (NIV) evaluiert werden.
- Bei Patientinnen und Patienten mit Lungenemphysem, die symptomatisch sind und bei denen alle konservativen Maßnahmen (einschließlich Rehabilitation) ausgeschöpft wurden, können darüber hinaus Lungenvolumenreduktionsverfahren (operativ vs. endoskopisch) erwogen werden (5).

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