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: 2023-B-319 Dupilumab

Stand: Dezember 2023

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

Dupilumab 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) IQWiG Abschlussbericht - Tiotropiumbromid (IQWiG Bericht A05-18 vom 26.06.2012)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen	Siehe systematische Literaturrecherche

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Kriterien gemäß 5. Kapitel § 6 VerfO	**Dupilumab zur Behandlung der COPD**
Therapie im Anwendungsgebiet gehören.	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Dupilumab	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Dupilumab ist angezeigt als Add-on-Erhaltungstherapie bei Erwachsenen mit chronisch obstruktiver Lungenerkrankung mit Typ-2-Inflammation, die trotz Dreifach- oder Zweifach-Therapie, sofern inhalative Kortikosteroide kontraindiziert sind, nicht ausreichend kontrolliert ist.
SAMA: Anticholinergika, kurzwirksam	
Ipratropiumbromid R03BB01 generisch	Ipratropiumbromid wird zur Therapie von reversiblen Bronchospasmen in Zusammenhang mit chronisch obstruktiver Lungenerkrankung (COPD) eingesetzt. Stand FI Ipratropium Teva: 09/2014
LAMA: Anticholinergika, langwirksame	
Tiotropiumbromid R03BB04 Spiriva Respimat	Tiotropium ist indiziert als dauerhaft einzusetzender Bronchodilatator zur Befreiung von Symptomen bei chronischer obstruktiver Lungenerkrankung (COPD). *Stand FI: 10/2018*
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. *Stand FI: 02/2018*
Umeclidiniumbromid R03BB07 Incruse Ellipta	Incruse Ellipta ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) angezeigt. *Stand FI: 01/2019*
Glycopyrroniumbromid R03BB06 Seebri Breezhaler	Seebri Breezhaler ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt. *Stand FI: 07/2018*
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 chro-nisch obstruktive bronchiale Erkrankung (COPD) mit reversibler Komponente. *Hinweis: Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindung mit einer entzündungshemmenden Dauertherapie erfolgen.* *Stand FI (Sultanol Inhalationslösung): 10/2014*
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). *Stand FI (Serevent): 05/2018*
Formoterol R03AC13 generisch	Prophylaxe und Behandlung der Bronchokonstriktion bei Patienten mit reversibler oder irreversibler COPD einschließlich chronischer Bronchitis und Emphysem. *Stand FI (Foradil P): 07/2017*
Indacaterol R03AC18 Onbrez	Onbrez Breezhaler ist für die bronchialerweiternde Erhaltungstherapie der Atemwegsobstruktion bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt. *Stand FI: 08/2018*
Olodaterol R03AC19 Striverdi Respimat	Striverdi Respimat ist indiziert als Bronchodilatator zur Dauerbehandlung bei chronischer obstruktiver Lungenerkrankung (COPD). *Stand FI: 10/2018*
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). *Stand FI (Solosin): 08/2018* *Hinweis: Es wird empfohlen die Dauertherapie dieser Erkrankungen mit Theophyllin in Kombination mit anderen, die Bronchien erweiternden und entzündungshemmenden Arzneimitteln, wie z. B. lang wirksamen β-Sympathomimetika und Glukocortikoiden durchzuführen. Arzneimittel mit verzögerter Theophyllin-Freisetzung, wie Theophyllin retard ratiopharm, sind nicht zur Akutbehandlung des Status asthmaticus oder der akuten Bronchospastik bestimmt*.

II. Zugelassene Arzneimittel im Anwendungsgebiet

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. *Stand FI: 04/2018*
Glucokortikosteroide	
Glucokortikosteroide, inhalativ	
Beispielhaft Beclometason R03BA01 generisch	Zur Behandlung von Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z. B. bei Asthma bronchiale oder chronisch obstruktive Bronchitis. *Stand FI (Beclometason-ratiopharm): 03/2017* *Hinweis: nicht zur Behandlung von plötzlich auftretenden Atemnotanfällen (akuter Asthmaanfall oder Status asthmaticus) geeignet*.
Glucokortikosteroide, oral	
Beispielhalft Prednisolon H02AB06 generisch	Pneumologie: akute Exazerbation einer COPD, empfohlene Therapiedauer bis zu 10 Tagen. *Stand FI (Decortin H): 09/2017*
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. *Stand FI (Ipramol Teva Steri-Neb): 11/2017*
Fenoterol + Ipratropiumbromid R03AK03 generisch	indiziert zur Vorbeugung und Behandlung von Bronchospasmen bei Asthma und chronischer obstruktiver Atemwegserkrankung (COPD). Eine begleitende entzündungshemmende Behandlung sollte stets in Betracht gezogen werden. *Stand FI (Berodual Respimat: 06/2016*
Indacaterol + Glycopyrroniumbromid	Ultibro Breezhaler ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
R03AL04 Ultibro Breezhaler	*Stand FI: 05/2019*
Vilanterol + Umeclidiniumbromid R03AL03 ANORO	ANORO ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) angezeigt. *Stand FI: 01/2019*
Formoterol + Aclidiniumbromid R03AL05 Brimica Genuar	Brimica Genuar ist indiziert als bronchodilatatorische Erhaltungstherapie zur Linderung von Symptomen bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD). *Stand FI: 08/2019*
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. *Stand FI: 12/2018*
Kombinationen: Selektiver Beta2-Adrenozeptor-Agonist + Glucokortikosteroid	
Salmeterol + Fluticason R03AK06 generisch	ist angezeigt für die symptomatische Behandlung von Patienten mit COPD mit einem FEV1 < 60 % des Normwertes (vor Anwendung eines Bronchodilatators) und wiederholt aufgetretenen Exazerbationen in der Vorgeschichte, die trotz regelmäßiger bronchienerweiternder Therapie signifikante Symptome aufweisen. *Stand FI (Aerivio Spiromax): 05/2017*
Formoterol + Budesonid R03AK07 Symbicort	Symbicort Turbohaler ist angezeigt zur symptomatischen Behandlung von COPD, die ein forciertes exspiratorisches Einsekundenvolumen (FEV1) < 70 % des Normwertes (nach Bronchodilatation) und Exazerbationen in der Vorgeschichte aufweisen, trotz einer regelmäßigen Behandlung mit Bronchodilatatoren. *Stand FI: 09/2018*
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. *Stand FI: 12/2018*
Kombinationen: Selektiver Beta2-Adrenozeptor-Agonist + Glucokortikosteroid + Anticholinergikum	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Beclometason / Formoterol / Glycopyrronium R03AL09 Trimbow	Trimbow ist angezeigt zur Erhaltungstherapie bei erwachsenen Patienten mit moderater bis schwerer chronisch obstruktiver Lungenerkrankung (COPD), die mit einer Kombination aus einem inhalativen Kortikosteroid und einem langwirksamem Beta-2-Agonisten nicht ausreichend eingestellt sind. *Stand FI: 01/2019* *Anwendungsbeschränkungen: Das Arzneimittel ist nicht angezeigt zur Behandlung akuter Episoden von Bronchospasmen oder akuter Exazerbationen bei COPD (d. h. als Notfallmedikation).*
Umeclidinium/ Vilanterol/ Fluticason R03AL08 Trelegy Ellipta	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 nicht ausreichend eingestellt sind. *Stand FI: 10/2018*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-319 (Dupilumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	20. Dezember 2023

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 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.

Die Erstrecherche wurde am 18.05.2022 durchgeführt, die folgende am 23.11.2023. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse dargestellt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 2584 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 19 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Janjua S et al., 2020 [8].

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:

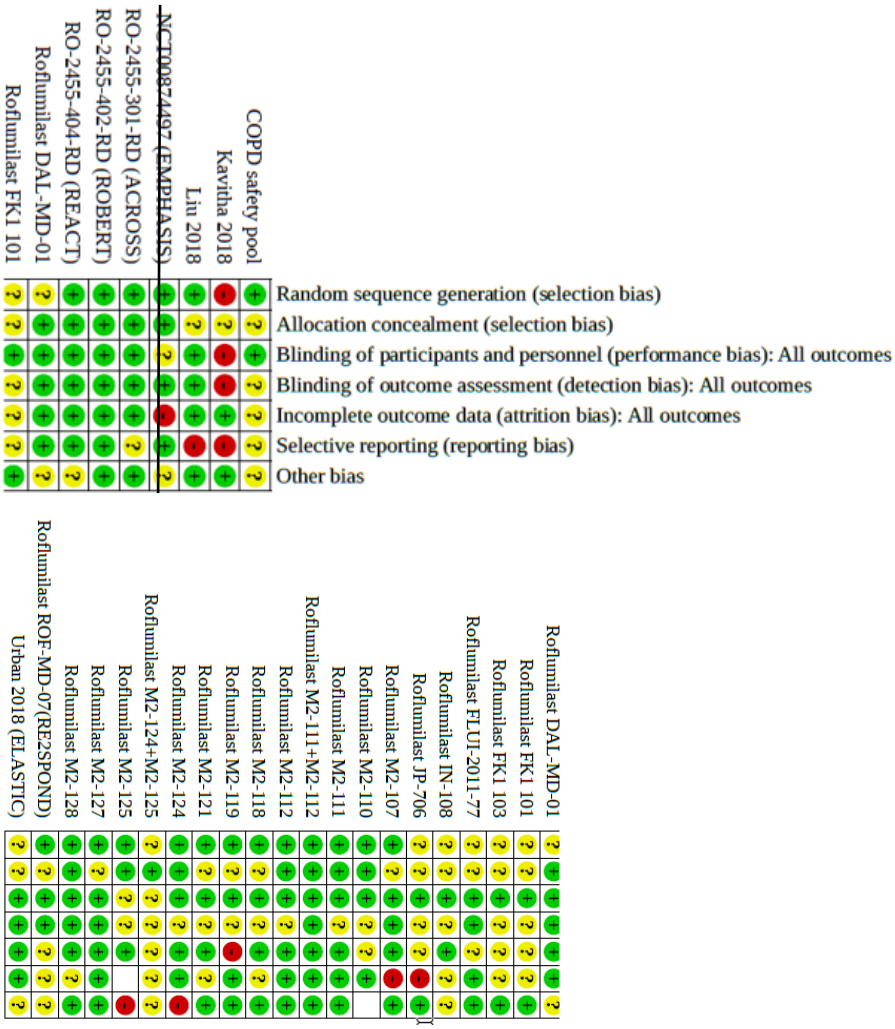
Of the 42 studies [included in this review], **27 studies examined roflumilast**, 14 trials studied cilomilast and one trial explored the use of tetomilast.

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:



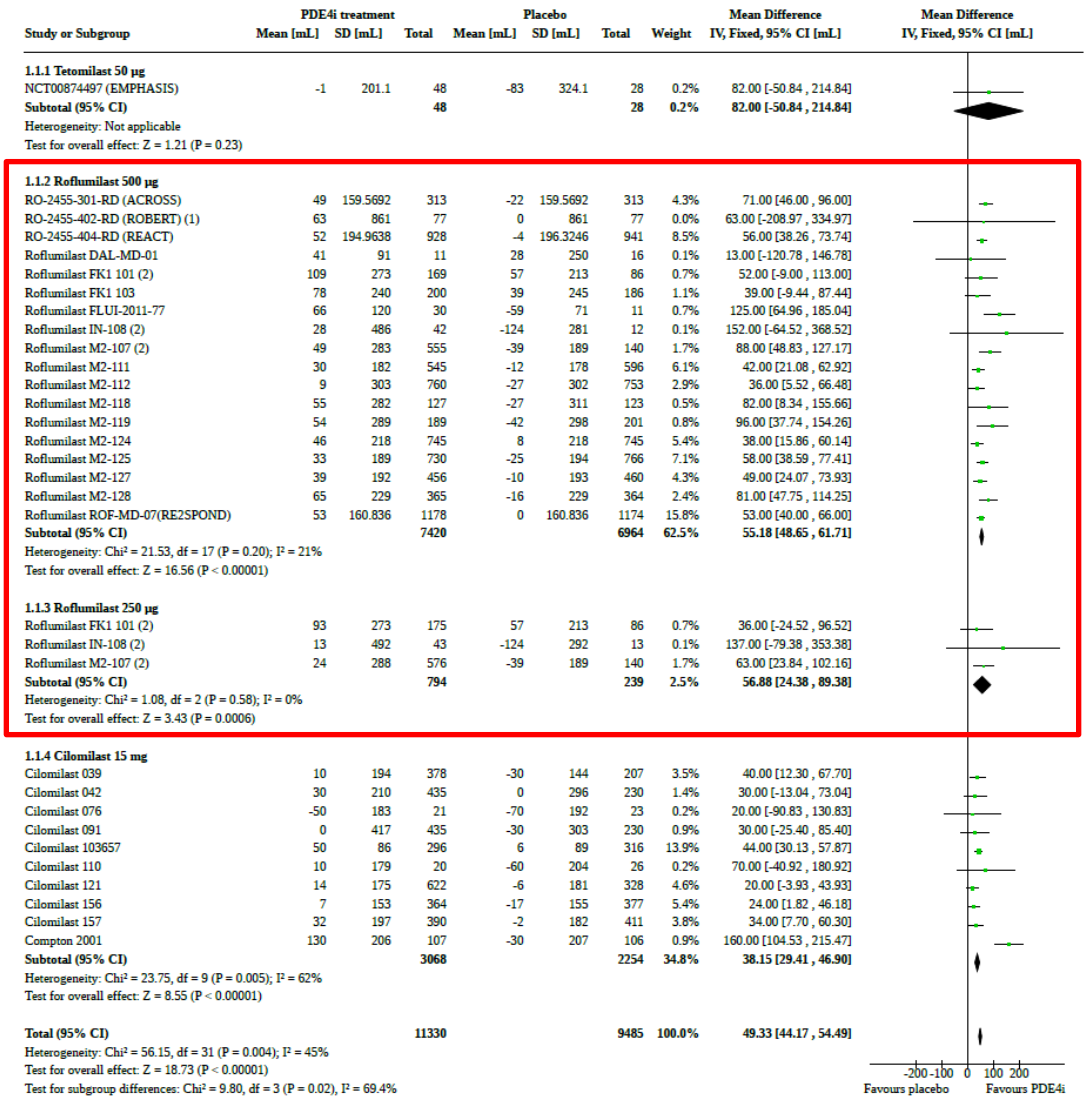
Studienergebnisse:

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%								

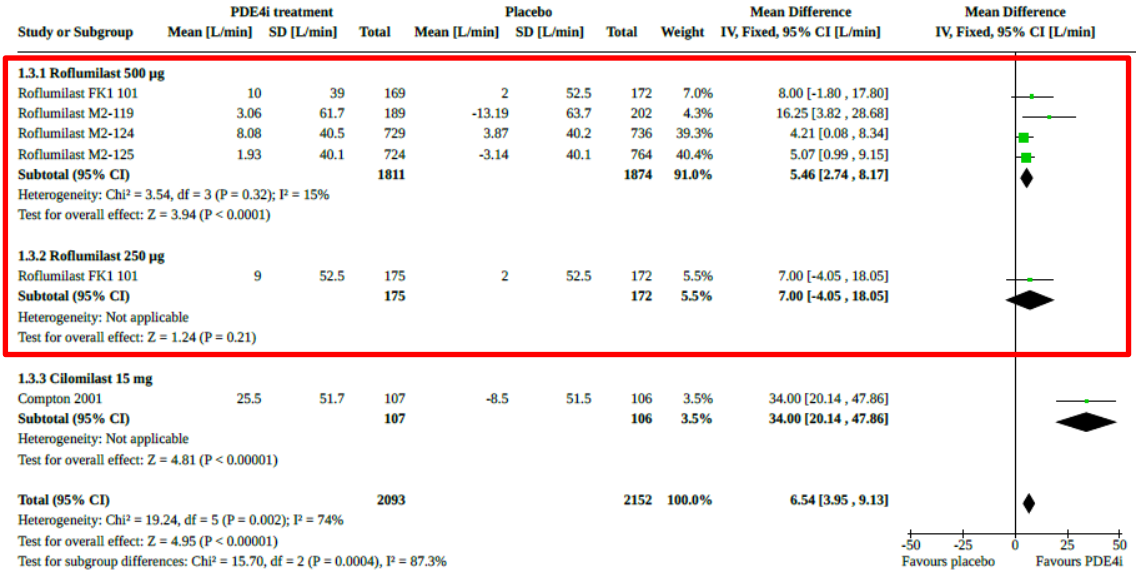
Footnotes

(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

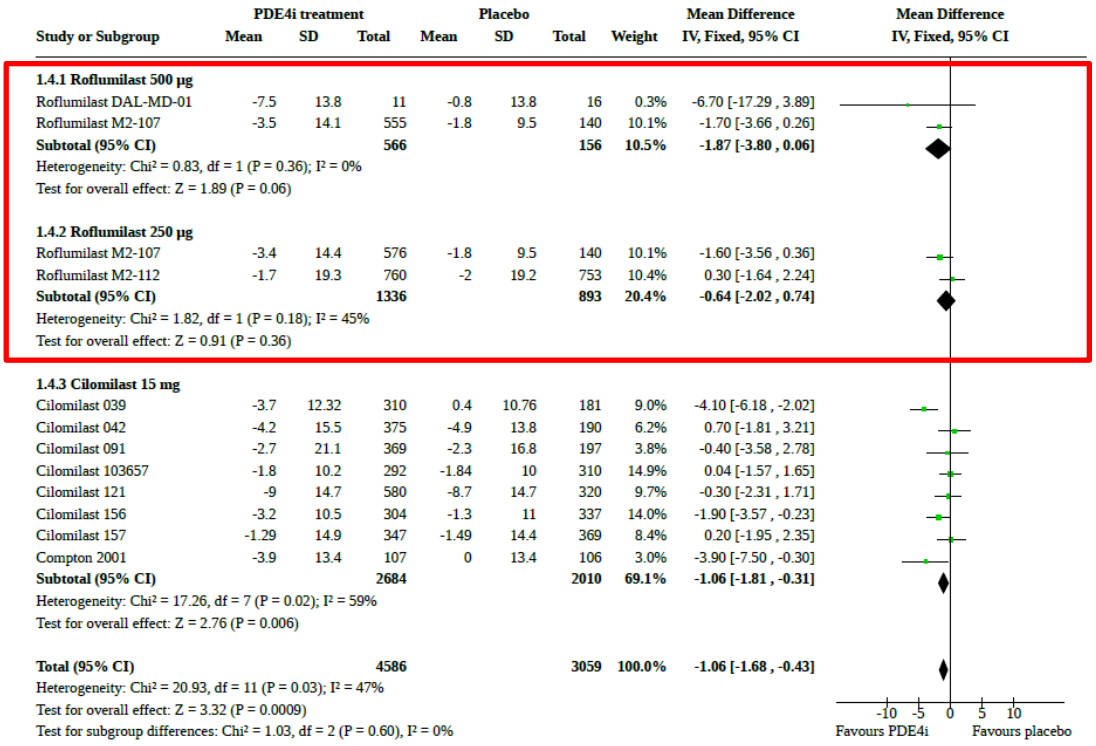
Change in PEF from baseline

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.



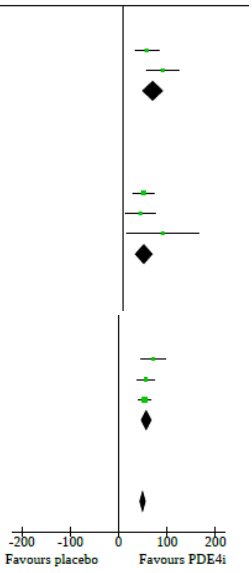
Subgroup analysis: concomitant therapies – FEV$_1$

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)

Study or Subgroup	PDE4i treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.34.1 Long-acting bronchodilator								
Roflumilast M2-127	39	192	456	-10	193	460	4.4%	49.00 [24.07 , 73.93]
Roflumilast M2-128	65	229	365	-16	229	364	2.5%	81.00 [47.75 , 114.25]
Subtotal (95% CI)			**821**			**824**	**6.9%**	**60.52 [40.57 , 80.46]**
Heterogeneity: Chi² = 2.28, df = 1 (P = 0.13); I² = 56%								
Test for overall effect: Z = 5.95 (P < 0.00001)								
1.34.2 Corticosteroids								
Roflumilast M2-111	30	182	545	-12	178	596	6.3%	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]
Subtotal (95% CI)			**1432**			**1472**	**9.7%**	**42.26 [25.46 , 59.05]**
Heterogeneity: Chi² = 1.28, df = 2 (P = 0.53); I² = 0%								
Test for overall effect: Z = 4.93 (P < 0.00001)								
1.34.4 Various concomitant treatments								
RO-2455-301-RD (ACROSS)	49	159.5692	313	-22	159.5692	313	4.4%	71.00 [46.00 , 96.00]
RO-2455-404-RD (REACT)	52	194.9638	928	-4	196.3246	941	8.7%	56.00 [38.26 , 73.74]
Roflumilast ROF-MD-07(RE2SPOND)	53	160.836	1178	0	160.836	1174	16.2%	53.00 [40.00 , 66.00]
Subtotal (95% CI)			**2419**			**2428**	**29.3%**	**56.58 [46.91 , 66.25]**
Heterogeneity: Chi² = 1.57, df = 2 (P = 0.46); I² = 0%								
Test for overall effect: Z = 11.47 (P < 0.00001)								
Total (95% CI)			**10488**			**9231**	**100.0%**	**49.08 [43.85 , 54.31]**
Heterogeneity: Chi² = 54.63, df = 27 (P = 0.001); I² = 51%								
Test for overall effect: Z = 18.39 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.61, df = 3 (P = 0.13), I² = 46.5%								



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 [10]

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

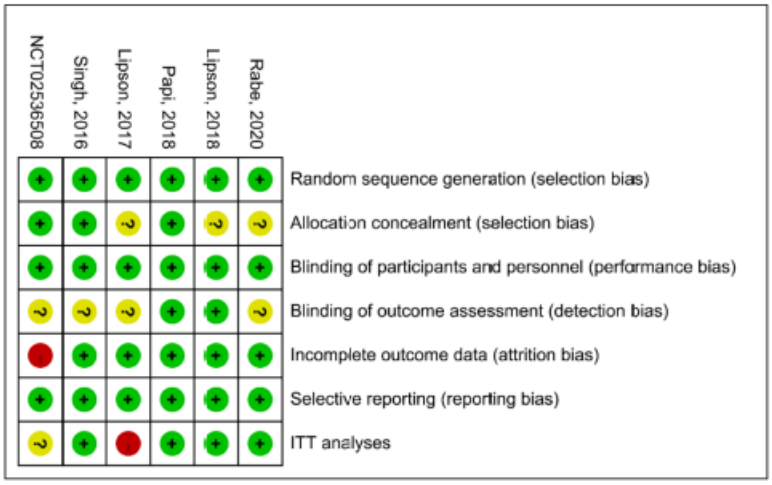
Charakteristika der Population:

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)

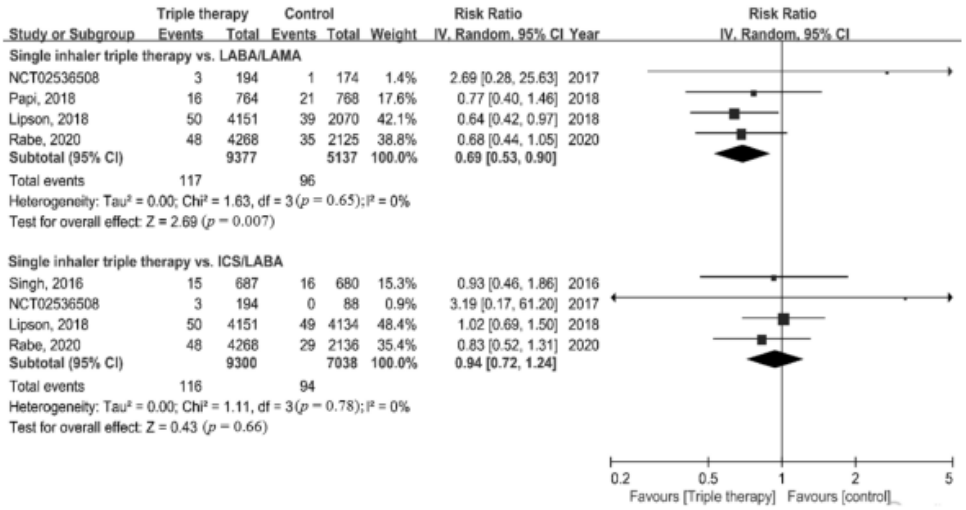


Figure 2. Forest plots for association of triple therapy with all-cause mortality.

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

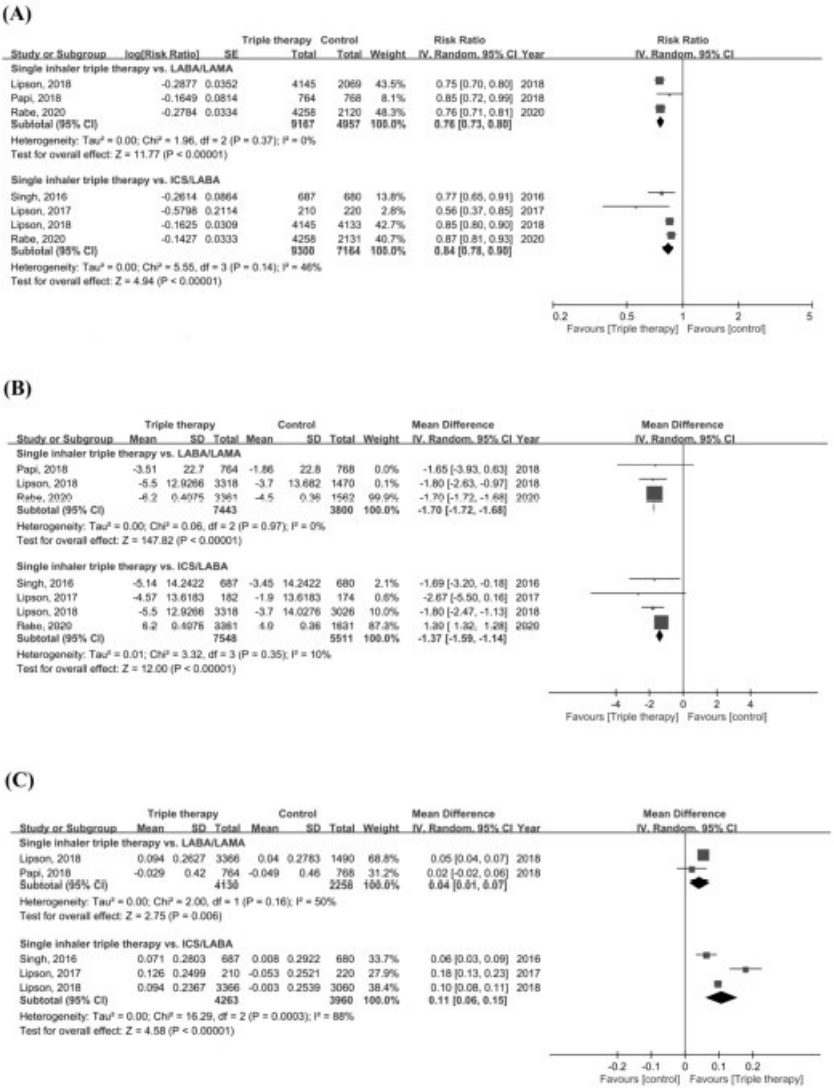


Figure 3. Forest plots for secondary outcomes. **(A)** Annual rate of moderate or severe COPD exacerbation, **(B)** change of SGRQ, and **(C)** change of FEV1.

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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 [9]

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 [12]

  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 [6]

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	③⑧⑦⑧⑨⑩⑪
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	②④⑧⑦⑧⑨⑩⑪
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	③⑧⑦⑧⑨⑩⑪
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:

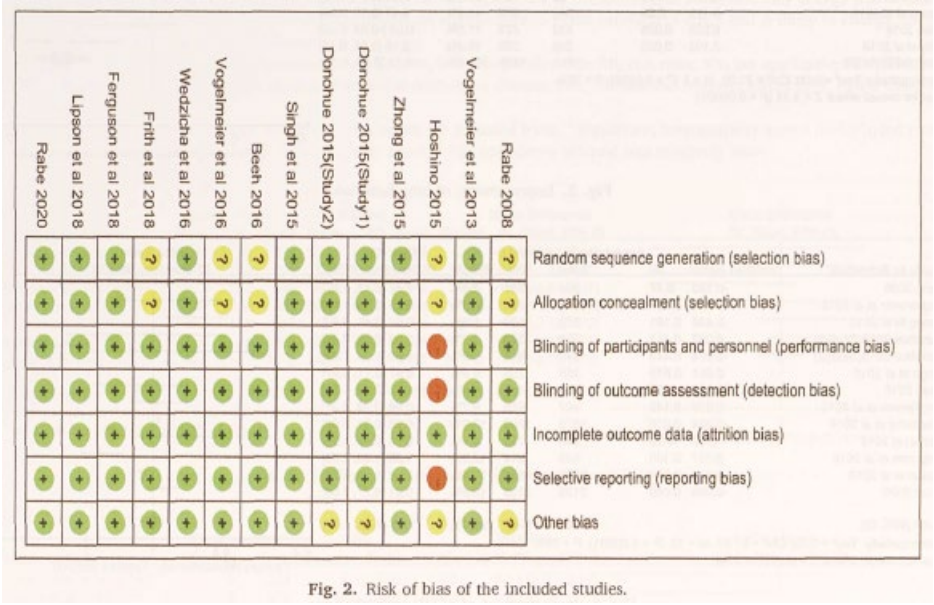


Fig. 2. Risk of bias of the included studies.

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.

Chen CY et al., 2020 [5]

LABA/LAMA fixed-dose combinations versus LAMA monotherapy in the prevention of COPD exacerbations: a systematic review and meta-analysis.

Fragestellung

The aim of this study was to systematically review the literature to investigate whether LABA/LAMA FDCs are more effective than LAMA monotherapy in preventing exacerbations.

Methodik

Population:

- patients with stable COPD

Intervention:

- LABA/LAMA

Komparator:

- LAMAs alone

Endpunkte:

- The outcomes of interest were the frequency of acute exacerbations (time to first exacerbation, rates of moderate to severe, severe and all exacerbations). Frequencies of exacerbations were also analyzed according to the treatment duration, high-risk versus low-risk populations, and tiotropium versus non-tiotropium groups.

Recherche/Suchzeitraum:

- We performed a systematic literature search to identify randomized controlled trials (RCTs) evaluating the efficacy and safety of long-acting bronchodilators for COPD using PubMed, EMBASE, Cochrane Library, and Trip databases for relevant studies published up to August 1, 2019.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- We included 10 trials in 9 articles from 2013 to 2018 with a total of 19,369 patients for analysis in this study

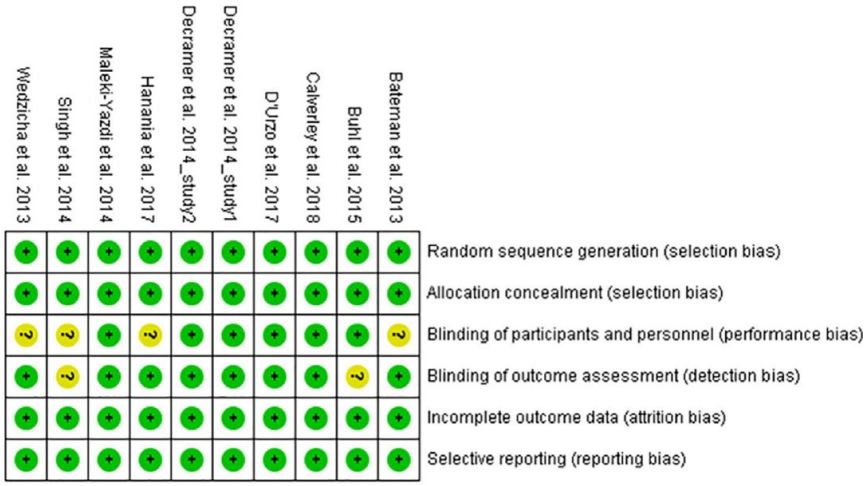
Charakteristika der Population:

Table 1. Study characteristics of the included studies.

Study	Study duration (weeks)	Number of patients	Treatment comparison/dose (µg)	Mean age (years)	Male (%)	Baseline FEV_1 % predicted	COPD severity by lung function
Bateman *et al.*[13]	26	474	Indacaterol 110/ glycopyrronium 50	64.0	76.4	55.7	Moderate (63.8%) Severe (36.1%)
		473	Glycopyrronium 50	64.3	77.2	55.1	
		480	Tiotropium 18	63.5	75.0	55.1	
Wedzicha *et al.*[14]	64	729	Indacaterol 110/ glycopyrronium 50	63.1	76.0	37.0	Severe (79.2%) Very severe (20.8%)
		740	Glycopyrronium 50	63.1	73.0	37.3	
		737	Tiotropium 18	63.6	75.0	37.4	
Decramer *et al.*[15] study 1	24	212	Umeclidinium 62.5/ vilanterol 25	63.0	70.0	48.0	Moderate (48.0%) Severe (41.2%) Very severe (10.8%)
		208	Tiotropium 18	62.6	67.0	47.8	
Decramer *et al.*[15] study 2	24	217	Umeclidinium 62.5/ vilanterol 25	65.0	65.0	47.7	Moderate (43.9%) Severe (43.2%) Very severe (12.8%)
		222	Umeclidinium 125	64.5	67.0	46.2	
		215	Tiotropium 18	65.2	71.0	47.4	
Maleki-Yazdi *et al.*[16]	24	454	Umeclidinium 62.5/ vilanterol 25	61.9	68.0	46.2	Moderate (41.4%) Severe (45.6%) Very severe (12.9%)
		451	Tiotropium 18	62.7	67.0	46.5	
Singh *et al.*[17]	24	385	Aclidinium 400/ formoterol 12	62.7	67.8	54.6	Moderate (59.2%) Severe (40.8%)
		385	Aclidinium 400	63.1	66.5	53.6	
Buhl *et al.*[12]	52	1029	Tiotropium 5/ olodaterol 5	63.8	71.2	49.3	Moderate (49.4%) Severe (38.6%) Very severe (12.0%)
		1033	Tiotropium 5	63.9	73.1	49.7	
Hanania *et al.*[18]	52	1035	Glycopyrrolate 18/ formoterol 9.6	62.7	54.3	43.4	Very severe (10.2%)
		888	Glycopyrrolate 18	62.8	55.9	42.6	
		450	Tiotropium 18	62.9	59.6	42.7	
D'Urzo *et al.*[19]	52	335	Aclidinium 400/ formoterol 12	64.2	50.1	53.2	Moderate (56.3%) Severe (43.7%)
		337	Aclidinium 400	64.4	55.8	53.0	
Calverley *et al.*[8]	52	3939	Tiotropium 5/olodaterol 5	66.5	71.0	44.6	N/A
		3941	Tiotropium 5	66.3	72.0	44.5	

AE, acute exacerbations; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second.

Qualität der Studien:



Studienergebnisse:

- Time to first exacerbation.
  - Four publications (including five RCTs, n = 5293) reported the time to first exacerbation as the endpoint (Figure 3). There was no statistical difference between the patients receiving LAMA/LABA FDCs compared with individual LAMAs (tiotropium, umeclidinium, and glycopyrronium). The HR for an exacerbation was 0.96 (95% CI 0.79–1.18; p = 0.71, I2 = 46%). Subgroup analyses according to different LAMAs (tiotropium and non-tiotropium), treatment duration (24 weeks and 52–64 weeks), and risk of exacerbations (by exacerbation history) were all not statistically significant (Supplemental Figures S1, S2, and S3).
- Moderate-to-severe exacerbations.
  - Moderate-to severe exacerbation data were available in four articles (n = 10,791). Overall, 30.0% (1620/5389) of the patients receiving LABA/LAMA FDCs experienced moderate-to-severe exacerbations, compared with 31.7% (1714/5402) of the patients receiving LAMAs alone (Figure 4). The RR was 0.96 (95% CI 0.90–1.03; p = 0.28, I2 = 16%), and no statistical difference was found. We then analyzed LABA/LAMA FDCs compared with different LAMAs (tiotropium and non-tiotropium), treatment duration (24 weeks and 52–64 weeks), and risk of exacerbations (by exacerbation history), but no statistically significant differences were found (Supplemental Figures S4, S5, and S6).
- Severe exacerbations.
  - Only two publications (n = 9349) reported severe exacerbations as one of the endpoints. There was no statistical difference between the LABA/LAMA FDCs and LAMA groups in terms of severe exacerbations [9.9% (460/4669) versus 10.8% (504/4680), respectively], with an RR of 0.92 (95% CI 0.81–1.03, p = 0.15, I2 = 0%) (Figure 5).
- All exacerbations.
  - The incidence of all exacerbations from six articles (including 9 RCTs, n = 7941) was lower in those treated with LABA/ LAMA FDCs than in those treated with LAMAs [24.0% (996/4148) versus 26.1% (991/3799), respectively], with an RR of 0.92 (95% CI 0.86– 1.00; p = 0.04, I2 = 0%) (Figure 6). Subgroup analyses showed similar efficacy in those treated with LABA/LAMA FDCs compared with those treated with different LAMAs, but slight superiority was demonstrated in those with a longer treatment duration (52–64 weeks) (RR, 0.92; 95% CI 0.85–1.00; p = 0.04) (Supplemental Figures S7 and S8). Other analyses according to the risk of exacerbations (high-risk versus low-risk, stratified by exacerbation history or lung function), demonstrated a lower rate of all exacerbations only in the high-risk population stratified by exacerbation history (RR, 0.85; 95% CI 0.74– 0.98; p = 0.03) (Supplemental Figures S9 and S10).

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis suggests that LAMA/LABA FDCs produce a small benefit in the prevention of all exacerbations compared to LAMA monotherapy, but similar efficacy in terms of time to first exacerbation, the rate of moderate-to-severe, and severe exacerbations. In addition to greater improvements in lung function, symptom scores, and health status, our findings provide evidence that LABA/LAMA FDCs are also better than LAMA monotherapy in terms of all exacerbation prevention and could be considered as the first-line treatment for COPD patients, especially in those with a history of previous exacerbations.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor

- Lipari M et al., 2020 [11]

  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.

- Mammen MJ et al., 2020 [13]

  The reduction in acute exacerbation of COPD frequency and hospital admissions as well as the observed benefits in dyspnea and quality of life favor the use of dual therapy over monotherapy for individuals with symptomatic COPD. The evidence suggests that in patients with COPD who complain of dyspnea and/or exercise intolerance, the balance of benefits of dual LABA/LAMA therapy outweighs the risks when compared with LABA or LAMA monotherapy.

Shuai T et al., 2021 [18]

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.

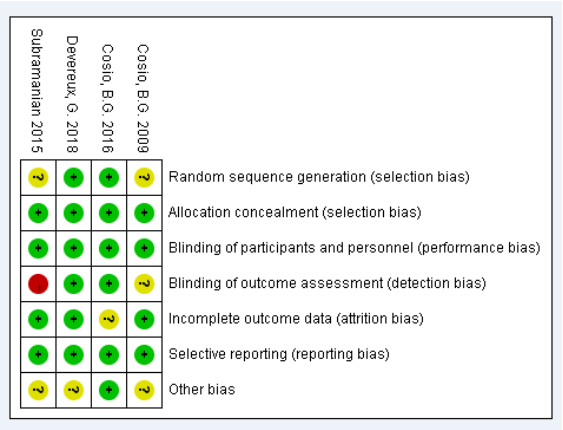
Charakteristika der Population:

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	④⑤

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)

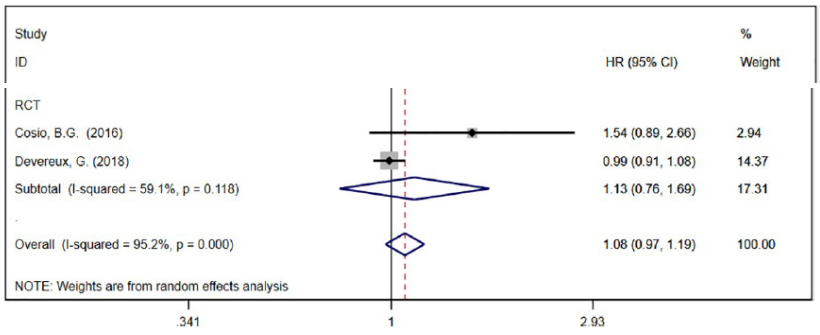


Fig 3. Forest plot of acute exacerbation rate (Subgroup analysis based on study design).

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.

Yang M et al., 2019 [19]

Inhaled corticosteroids and risk of pneumonia in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials.

Fragestellung

Inhaled corticosteroids (ICS) are generally used to treat patients with chronic obstructive pulmonary disease (COPD) who suffer from repeated exacerbations. Recently, it was reported that ICS treatment increased the risk of pneumonia in COPD patients. But it is controversial. The objective of this paper is to clarify the associations between ICS treatment and the risk of pneumonia in COPD patients

Methodik

Population:

- COPD of any severity

Intervention und Komparator:

- compared ICS with non-ICS treatment on the risk of pneumonia in COPD patients

Endpunkte:

- Pneumonia

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, Clinical Trials.gov, and Embase were searched from February 2019 to June 2019.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Twenty-five trials (N=49,982 subjects) were included

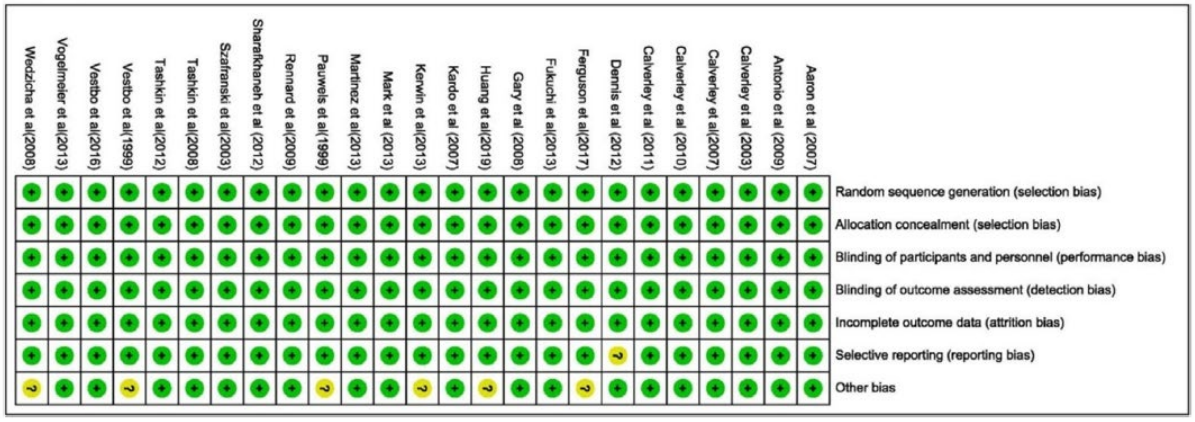
Charakteristika der Population:

Characteristics of RCTs of ICS use included in the meta-analysis.

Authors	No.of S (P/cases)		Years		Doses	Duration, months	Interventions
	ICS	controls	ICS	controls			
Gary et al. (2008)	29/394	15/388	64.9 ± 9	65.0 ± 9.1	250/50 bid	13	FSC versus S
Sharafkhaneh et al. (2012)	45/815	11/403	≥ 40	≥ 40	320/9 or 160/9 bid	12	BUD/F versus F
Aaron et al. (2007).	1/145	1/304	67.8 ± 8.9	67.9 ± 8.6	250/25 bid	13	FSC versus S
Mark et al. (2013)	177/2437	28/818	63.6 ± 9.3	63.6 ± 9.2	200or100or50/25qd	13	FF/VI versus VI
Calverley et al. (2011)	50/658	24/665	≥ 60	≥ 60	500/50 bid	24	SFC versus Tio
Antonio et al. (2009)	26/394	10/403	65.4 ± 9.1	65.3 ± 8.8	250/50 bid	13	FSC versus S
Calverley et al. (2003)	13/511	9/511	≥ 40	≥ 40	320/9;400 bid	12	BUD/F or BUD vs. F or P
Calverley et al. (2010)	5/232;7/238	1/233	63.5 ± 9.0	63.7 ± 8.8	200/24;400/24 bid	12	BDP/F vs.F; BUD/F vs. F
Dennis et al. (2012)	16/717	6/479	60.3 ± 8.7	59.2 ± 9.1	400or200/10;400 bid	13	MF/F vs. F; MF vs. P
Kardos et al. (2007)	23/507	7/487	63.8 ± 8.3	64 ± 8.2	500/50 bid	11	SFC vs S
Martinez et al. (2013)	10/816	2/408	61.7 ± 8.6	61.7 ± 8.3	200/25;100/25 qd	6	FF/VI vs. FF; FP vs.P
Rennard et al. (2009)	30/988	40/976	63.4 ± 9	62.9 ± 9.1	320/9;160/9 bid	12	BUD/FM vs. FM or P
Tashkin et al. (2012)	19/1351	9/900	60.2 ± 8.8	59.3 ± 8.8	400/10;400 bid	13	MF/F vs. F;MF vs.P
Tashkin et al. (2008)	8/1120	2/584	63.3 ± 9.0	63.4 ± 9.5	320or160/9 bid	6	BUD/F vs. FM;BUD vs.P
Vestbo et al. (1999)	16/145	24/145	59 ± 8.3	59.1 ± 9.7	400 bid	36	BUD vs.P
Pauwels et al. (1999)	33/634	16/643	52.5 ± 7.5	52.4 ± 7.7	400 bid	36	BUD vs.P
Szafranski et al. (2003)	20/406	15/406	64	64	160/9;200/4.5 bid	12	BUD/F vs.F or P
Vogelmeier et al. (2013)	4/264	0/259	63.2 ± 8.2	63.4 ± 7.7	500/50 bid	6.5	SFC vs. F
Kerwin et al. (2013)	12/618	8/412	62.6 ± 9.1	62.8 ± 9.1	100/25; 50/25 bid	6	FF/VI vs. VI or P
Ferguson et al. (2017)	3/605	6/613	63.1 ± 8.7	63.9 ± 8.7	320/9 bid	6	BUD/F vs. F
Fukuchi et al. (2013)	8/636	7/657	64.5	65.6	160/4.5 bid	3	BUD/F vs. F
Huang et al. (2019)	1/293	0/289	63.8 ± 8.8	64.4 ± 8.8	160/4.5 bid	3	BUD/F plus I + T vs. I + T
Wedzicha et al. (2008)	50/658	24/665	64	65	500/50 bid	24	SFC vs. Tio
Calverley et al. (2007)	217/3098	124/3086	65.0 ± 8.4	65.1 ± 8.2	500/50 bid	36	FP vs.P; SFC vs. F
Vestbo et al. (2016)	465/8297	377/8271	65.0 ± 8.0	65.1 ± 8.0	100/25 bid	22	FF/VI vs. VI or P

FSC, fluticasone propionate/salmeterol; ICS, inhaled corticosteroids; P, pneumonia. BUD, budesonide; F, formoterol; S, salmeterol; VI, vilanterol; FF, fluticasone furoate; Tio, tiotropium bromide; SFC, SAL plus FP combination; BDP, beclomethasone dipropionate; S, subjects; MF, mometasone furoate.

Qualität der Studien:



Studienergebnisse:

- Use of ICS and risk of pneumonia
  - Meta results revealed that high- (Peto OR, 1.98, 95% CI, 1.70–2.31; I2=0%), medium- (OR, 1.48, 95% CI, 1.02–2.16; I2=52%), and low-doses (Peto OR, 1.44, 95% CI, 1.12–1.85; I2=13%) of ICSs were all associated with an increased risk of pneumonia vs control group (Figs. 4, 5, 6). These comparisons were rated as high quality evidence by GRADE (Table 2).
- Risk of pneumonia associated with fluticasone treatment
  - Of the eligible trials, twelve assessed the use of fluticasone. The pooled results revealed that fluticasone therapy was associated with an increased risk of pneumonia vs control group (RR, 1.84, 95% CI, 1.47–2.30; I2=58%)
  - Results of the Peto approach demonstrated that high- (Peto OR, 2.01 95% CI, 1.71–2.36; I2=0%), medium- (Peto OR, 2.21 95% CI, 1.42–3.44; I2=0%), and low-doses (Peto OR, 1.73 95% CI, 1.24–2.40; I2=0%) of fluticasone treatment were all associated with an increased risk of pneumonia vs non-ICS treatment
- Risk of pneumonia associated with budesonide treatment

  - Of the eligible trials, eleven assessed the use of budesonide. Results of the Peto approach revealed that budesonide treatment was not associated with an increased risk of pneumonia vs control group (Peto OR, 1.24, 95% CI, 0.98–1.56; I2=48%)
  - Results of Mantel-Haenszel approach revealed that medium-dose budesonide treatment was also not associated with the risk of pneumonia vs control group (OR, 1.31 95% CI, 0.85–2.02; I2=56%)
- Use of ICS and risk of severe pneumonia
  - Only five studies provided information on severe pneumonia. The pooled results revealed that ICS treatment increased the risk of severe pneumonia in COPD patients (RR, 2.17, 95% CI, 1.47–3.22; I2=29%) (Fig. 14). These comparisons were rated as moderate quality evidence by GRADE

Anmerkung/Fazit der Autoren

In this meta-analysis of 25 trials (including 49,982 subjects), ICS treatment was associated with a significantly increased risk of pneumonia in patients with COPD. Similarly, ICS also increased the risk of severe pneumonia. Considering that the above pooled results might not avoid heterogeneity due to the included different types and doses of ICS, subgroup analysis was performed next. The results of subgroup analysis based on doses of ICS further verify the above views. However, subgroup analyses based on types of ICS revealed that fluticasone treatment was associated with an increased risk of pneumonia but not budesonide. In addition, it was revealed that high-, medium-, and low- doses of budesonide did not increase the risk of pneumonia.

3.3 Leitlinien

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 [7].

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:

- The GOLD 2023 Report is a major revision of the GOLD 2022 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 2021 to July 2022. In total, 387 new references have been added to the GOLD 2023 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.

Follow-up Pharmacological Treatment (Exacerbations)

Empfehlung 1

For patients with persistent exacerbations on bronchodilator monotherpay, escalation to LABA+LAMA is recommended

Empfehlung 2

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.

Empfehlung 3

If patients treated with LABA+LAMA+ICS (or those with eos < 100 cells/µL) still have exacerbations the following options may be considered: ▪

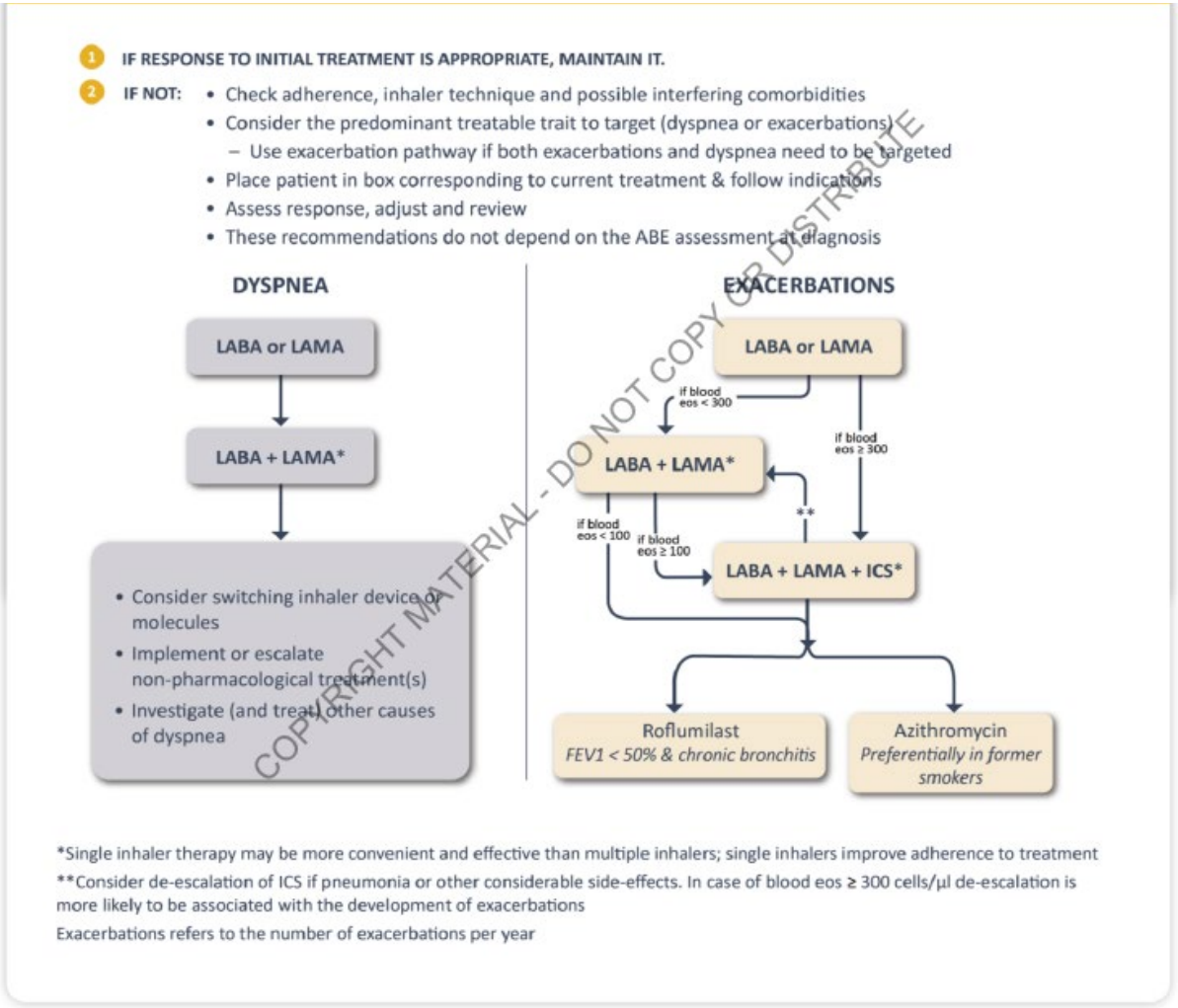
- **Add roflumilast**. This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis,(568) particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.(569,570)
- **Add a macrolide**. The best available evidence exists for the use of azithromycin, especially in those who are not current smokers.(571,572) Consideration to the development of resistant organisms should be factored into decision-making.
- **Withdrawing ICS** can be considered if pneumonia or other considerable side-effects develop. If blood eosinophils are ≥ 300 cells/µL de-escalation is more likely to be associated with the development of exacerbations.(573,574) effects that are more frequent at higher doses.

Patients under treatment with LABA + ICS

If a patient with COPD and no features of asthma has been treated – for whatever reason – with LABA+ICS and is well controlled in terms of symptoms and exacerbations, continuation with LABA+ICS is an option. However, if the patient has:

- Further exacerbations: treatment should be escalated to LABA+LAMA+ICS if the blood eosinophil count is ≥ 100 cells/µL or switched to LABA+LAMA if it is < 100 cells/µL.
- Major symptoms:

switching to LABA+LAMA should be considered.



Therapeutic interventions that reduce COPD mortality

Previous studies such as the TORCH clinical trial(697) and the SUMMIT trial(698) failed to provide evidence for the efficacy of a LABA+ICS combination compared to placebo in reducing mortality (primary outcome) in COPD patients. These trials had no requirement for a history of previous exacerbations. In the largest LAMA treatment trial UPLIFT, the intention to treat analysis, i.e., 30 days after completion of the study period, did not demonstrate a reduction in mortality (secondary outcome) compared to placebo. The majority of patients included in this study utilized an ICS. Recently, evidence has emerged from two large randomized clinical trials, IMPACT (448) and ETHOS,(566) that fixed-dose inhaled triple combinations (LABA+LAMA+ICS), reduce all-cause mortality compared to dual inhaled long-acting bronchodilation therapy. These trials were enriched for symptomatic patients (CAT ≥ 10) with a history of frequent (≥ 2 moderate exacerbations) and/or severe exacerbations (≥ 1 exacerbation requiring a hospital admission)

Bronchodilators in Stable COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Inhaled bronchodilators are recommended over oral bronchodilators (**Evidence A**)
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (**Evidence A**), and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (**Evidence A**).
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

Anti-Inflammatory Therapy in Stable COPD

Inhaled Corticosteroids	• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggesta beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • If patients with COPD have features of asthma, treatment should always contain an ICS • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Combinations can be given as single or multiple inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE4 Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: • Roflumilast improves lung function and reduces moderate and severe exacerbations **(Evidence A)**
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, azithromycin can be considered (**Evidence B**) • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators and Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)** • Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**
Other Anti-Inflammatory Agents	• Statin therapy is not recommended for prevention of exacerbations (**Evidence A**) • Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)** • Leukotriene modifiers have not been tested adequately in COPD patients

Referenzen aus Leitlinien

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.(748,749) needed use of SABAs improve FEV1 and symptoms.(755) preclude additional benefit from as-needed SABA therapy.(756) Regular and asLABAs show duration of action of 12 or more hours and

do not Formoterol and salmeterol are twice-daily LABAs that significantly improve FEV1 and lung volumes, dyspnea, health status, exacerbation rate and number of hospitalizations,(757) function. Indacaterol is a once daily LABA that improves breathlessness,(758,759) rate.(759) and exacerbation Some patients experience cough following the inhalation of indacaterol. Oladaterol and vilanterol are additional once daily LABAs that improve lung function and symptoms.(760,761) but have no effect on mortality or rate of decline of lung health status(759).

Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.(767) inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction.(768) Short-acting antimuscarinics (SAMAs), namely ipratropium and oxitropium, also block the 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.(767) 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.(769) 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).(767,770) They also improve the effectiveness of pulmonary rehabilitation(773,774) hospitalizations.(771)

versus LABA treatment.

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.(787-789).

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,(787) 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.(790) Addition of theophylline to salmeterol produces a greater improvement in FEV1 and breathlessness than salmeterol alone.(791,792) Earlier studies reported contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates.(793,794)

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.(795)

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.(796)

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.(807)

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.(803-806)

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.(562) demonstrated favorable improvements compared with the monotherapies for the majority of outcomes irrespective of baseline HRQoL.(808) The LABA+LAMA combination 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(809) been shown in people across different ethnic groups (Asian as well as European).(810) (Figure 3.19). These findings have 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 effective than long-acting bronchodilator monotherapy for preventing exacerbations.(811) 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.(812) 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.(813) 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. 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.

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.(815,816)
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.(813)
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. (448,817) 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.(818)
on mortality in people with COPD have not provided conclusive evidence of benefit.(818)
Studies and meta-analyses assessing the effect of regular treatment with ICS alone 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.(697)
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.(819)
A number of studies have investigated whether there is a relationship between ICS treatment and risk of lung cancer with conflicting results.(821)
ICS in combination with long-acting bronchodilator therapy 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.(822,823)
powered on all-cause mortality as the primary outcome failed to demonstrate a statistically significant effect of combination therapy on survival.(697,819)
Most studies that found a beneficial effect of a LABA+ICS fixed dose combination (FDC) over a LABA alone on exacerbation rate, recruited patients with a history of at least one exacerbation in the previous year.(822)
RCT conducted in a primary healthcare setting in the United Kingdom compared a LABA+ICS combination with usual care. Findings showed an 8.4% reduction in moderate-to-severe exacerbations (primary outcome) and a significant improvement in CAT™ score, with no difference in the rate of healthcare contacts or pneumonias. However, basing recommendations on these results is difficult because of the heterogeneity of treatments reported in the usual care group, the higher rate of treatment changes in the group receiving the LABA+ICS combination of interest, and the medical practice patterns unique to the UK region where the study was conducted.(824) A pragmatic 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.(820)
Triple therapy (LABA+LAMA+ICS)
The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches(851) and
has been shown to improve lung function, patient reported outcomes and reduce exacerbations when compared to LAMA alone, LABA+LAMA and LABA+ICS.(445,447,448,852-859)
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.(860)
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.(861)
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.(566,862)
Phosphodiesterase-4 (PDE4) inhibitor
The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.(867) 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: The effects on lung function are also seen

when roflumilast is added to long-acting bronchodilators, and in patients who are not controlled on fixed-dose LABA + ICS combinations. The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation. There has been no study directly comparing roflumilast with an inhaled corticosteroid.

Bundesärztekammer (BÄK) et al., 2021 [3,4]

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

<u>Grundlage der Leitlinie</u>

- 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).

<u>Recherche/Suchzeitraum:</u>

- 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.

<u>LoE</u>

- 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

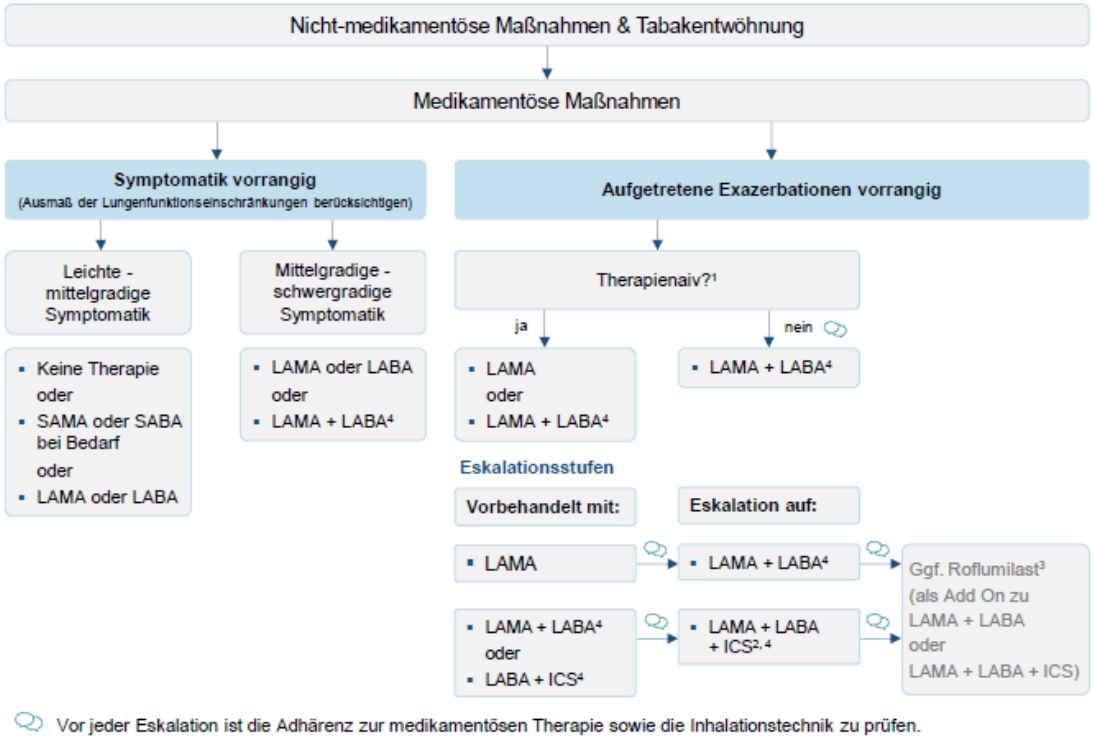
Tabelle 3: Schema zur Graduierung von NVL-Empfehlungen, modifiziert nach [7,9]

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 adjustierten 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 Pati-ent*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 [2]

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.

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- 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

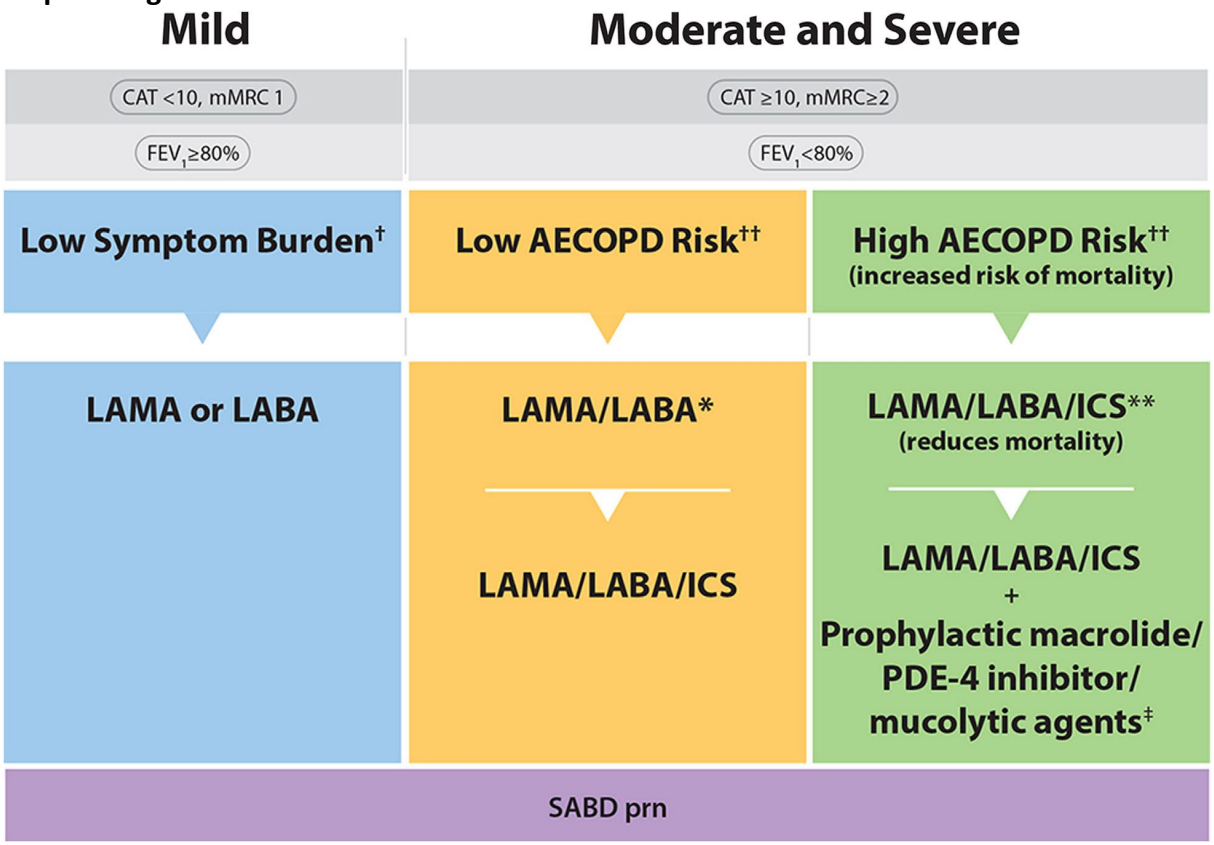

Figure 3 – COPD pharmacotherapy. This figure promotes an evidence-informed approach that aligns proven effective treatments with spirometry, symptom burden, risk of future exacerbations, and mortality risk. Because of the clinical heterogeneity in COPD, spirometry should not be used in isolation to assess 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 [14]

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

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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 …

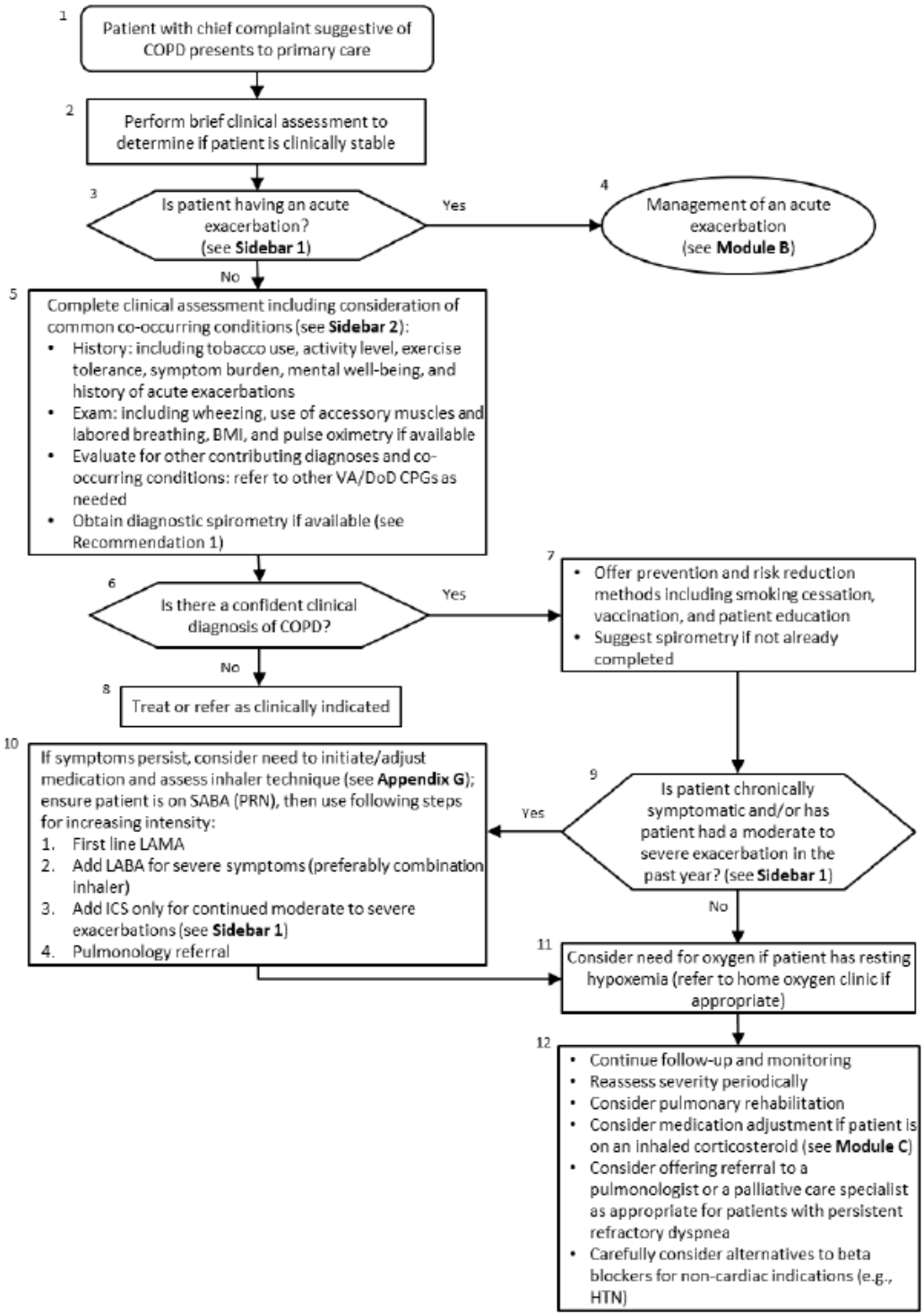
It is important to note that a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care).

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

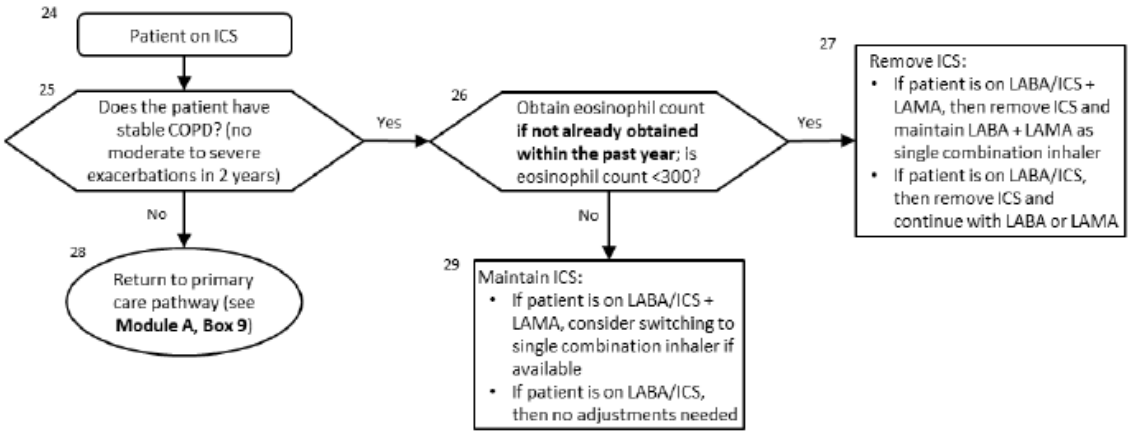
Sidebar 1: Definition of Exacerbations
Increased dyspnea above day-to-day variability with or without change in sputum amount or color. Moderate to severe exacerbations are those that require antibiotics and/or systemic corticosteroids. Patients with exacerbation within the past six months would be considered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

Nici L et al., 2020 [1,17]

American Thoracic Society

Pharmacologic management of chronic obstructive pulmonary disease.

Zielsetzung/Fragestellung

This document provides clinical recommendations for the pharmacologic treatment of chronic obstructive pulmonary disease (COPD). It represents a collaborative effort on the part of a panel of expert COPD clinicians and researchers along with a team of methodologists under the guidance of the American Thoracic Society.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium. Keine Patientenbeteiligung angegeben.
- Interessenkonflikte und finanzielle Unabhängigkeit und Umgang damit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Konsensusprozesse dargelegt. Kein externes Begutachtungsverfahren.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist im Hintergrundtext dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The literature searches queried MEDLINE, Embase, and the Cochrane Library (the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews) from 1990 to January 2019. Additional relevant publications that

were found in reference lists, were not retrieved in the original searching strategy, or were deemed eligible by the panel, and more recent studies published between January and July 4, 2019, were subsequently screened for eligibility by the methods team and included in the assessed body of evidence.

LoE und GoR

- The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)B approach to guideline development was used to rate the certainty/quality of evidence and to derive strength and direction of recommendation.

	Strong Recommendation ("We recommend . . .")	Conditional Recommendation ("We suggest . . .")
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action, and only a small minority would not. *(It is the right course of action for >95% of patients.)*	The majority of individuals in this situation would want the suggested course of action, but a sizable minority would not. *(It is the right course of action for >50% of patients.)*
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. *(It is reasonable to recommend it strongly to patients and caregivers.)*	Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision. *(Slow down, think about it, discuss it with the patient.)*
For policy makers	The recommendation can be adopted as policy in most situations, including for use as a performance indicator. *(The recommended course of action may be an appropriate performance measure.)*	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place. *(The recommended course of action is not appropriate for a performance measure.)*

Empfehlungen

PICO Question	Recommendation	Strength of Recommendation	Certainty of Evidence
1. In patients with COPD who complain of dyspnea or exercise intolerance, is LABA/LAMA combination therapy more effective than and as safe as LABA or LAMA monotherapy?	In patients with COPD who complain of dyspnea or exercise intolerance, we recommend LABA/LAMA combination therapy over LABA or LAMA monotherapy.	Strong	Moderate certainty
2. In patients with COPD who complain of dyspnea or exercise intolerance despite the use of dual therapy with LABA/LAMA, is triple therapy with ICS/LABA/LAMA more effective than and as safe as dual therapy with LABA/LAMA?	In patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy with LABA/LAMA, we suggest the use of triple therapy with ICS/LABA/LAMA over dual therapy with LABA/LAMA in those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization.	Conditional	Moderate certainty
3. In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), should the ICS be withdrawn?	In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), we suggest that the ICS can be withdrawn if the patient has had no exacerbations in the past year.	Conditional	Moderate certainty
4. In patients with COPD and blood eosinophilia, should treatment include an ICS in addition to a long-acting bronchodilator?	We do not make a recommendation for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization, for whom we suggest ICS as an additive therapy.	Conditional	Moderate certainty
5. In patients with COPD who have a history of severe and frequent exacerbations despite otherwise optimal therapy, is maintenance oral steroid therapy more effective than and as safe as no maintenance oral steroid therapy?	In patients with COPD and a history of severe and frequent exacerbations despite otherwise optimal therapy, we advise against the use of maintenance oral corticosteroid therapy.	Conditional	Low certainty
6. In patients with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, is opioid-based therapy more effective than and as safe as no additional therapy?	In individuals with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, we suggest that opioid-based therapy be considered for dyspnea management, within a personalized shared decision-making approach.	Conditional	Very low certainty

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; PICO = Population, Intervention, Comparator, and Outcomes.

Question 1:

Summary of the evidence.

The expert medical librarian initially identified 2,543 citations in MEDLINE (n = 1,086), Embase (n = 1,290), and the Cochrane Library (n = 167), with deduplication resulting in n = 1,845 warranting screening. Six additional studies were identified through other means. The majority (98.6%) were ineligible either because of a nonrigorous study methodology or lack of relevance to the PICO question, and this resulted in screeners identifying 24 studies for final review inclusion. All 24 identified studies were RCTs (5–28). The total sample size for the 24 studies was 45,441 participants; 29,589 (65.4%) of these participants were randomized to the treatment/intervention arms and 15,852 (34.6%) were in the control (comparator) arms.

Dyspnea score: assessed using the Transition Dyspnea Index or COPD Assessment Test.

Eleven studies (n = 17,650) assessed dyspnea (5, 6, 10, 15, 17, 19, 20, 22, 25–27). Because the Transition Dyspnea Index (TDI) and the COPD Assessment Test (CAT) are scored in opposite directions, changes in CAT values were multiplied by 21. The panel acknowledged that the CAT is a broader estimate of health status; however, one of its core components is dyspnea. Therefore, the panel believed that it was reasonable to use this tool as a proxy for dyspnea when other measures of dyspnea were unavailable for a particular study. The studies revealed an increased score (less breathlessness) in patients randomized to dual LABA/LAMA therapy versus monotherapy (SMD = 0.10; 95% confidence interval [CI], 0.07–0.13; P,0.001), although this did not reach the MCID threshold. There was a high certainty in the estimate of effect based on GRADE (absolute risk effect was 0.1 SDs more; 95% CI, 0.07 more to 0.13 more).

Exacerbations.

Fifteen studies (n = 22,733) assessed exacerbation risk (5, 6, 9, 10, 12–14, 17, 19–23, 26, 27). The studies revealed a reduced risk with dual LABA/LAMA therapy versus monotherapy (risk ratio [RR], 0.80; 95% CI, 0.69–0.92; P = 0.002). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 88 fewer per 1,000 patients; 95% CI, 136 fewer to 35 fewer).

Summary.

Based on the five critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be “moderate” and this certainty was assigned to the final recommendation as per GRADE guidance.

Committee discussion.

The panel noted a statistically significant decrease in exacerbations and hospital admissions among patients receiving dual therapy as opposed to monotherapy. The evidence also showed a statistically significant improvement in dyspnea and QOL with dual therapy, although these did not reach the MCID threshold. In addition, the available studies did not reveal any evidence of harm from dual therapy compared with monotherapy. Given the above evidence, we believe that patients would thus opt for dual therapy over monotherapy. The panel examined and discussed feasibility, acceptability, and health-equity issues, and concluded that dual therapy would be feasible to implement and would be acceptable to patients. The panel did note that dual long-acting bronchodilator therapy is more expensive than long-acting bronchodilator monotherapy, and that this could pose health-equity challenges to patients of limited means who might be unable to obtain the drug because of cost or lack of availability. However, a formal cost-effectiveness analysis was not performed, and the literature evidence was not fully examined in this regard. Because dual long Committee discussion. The panel noted a statistically significant decrease in

exacerbations and hospital admissions among patients receiving dual therapy as opposed to monotherapy. The evidence also showed a statistically significant improvement in dyspnea and QOL with dual therapy, although these did not reach the MCID threshold. In addition, the available studies did not reveal any evidence of harm from dual therapy compared with monotherapy. Given the above evidence, we believe that patients would thus opt for dual therapy over monotherapy. The panel examined and discussed feasibility, acceptability, and health-equity issues, and concluded that dual therapy would be feasible to implement and would be acceptable to patients. The panel did note that dual long-acting bronchodilator therapy is more expensive than long-acting bronchodilator monotherapy, and that this could pose health-equity challenges to patients of limited means who might be unable to obtain the drug because of cost or lack of availability. However, a formal cost-effectiveness analysis was not performed, and the literature evidence was not fully examined in this regard. Because dual long-acting bronchodilators are available as single inhalers, the burden of use for patients was not deemed a factor that would preclude patients from choosing dual therapy over monotherapy. However, the panel noted that if a physician chooses to prescribe two separate long-acting bronchodilator inhalers rather than a single combination dual therapy inhaler, this could increase the complexity and burden of medication use for patients. After considering these issues, and armed with moderate certainty evidence, the panel concluded that in patients with COPD who complain of dyspnea or exercise intolerance, the balance of benefits of dual LABA/LAMA therapy outweighs the risks when compared with LABA or LAMA monotherapy.

Question 2:

Summary of the evidence.

The expert medical librarian initially identified 1,482 citations in MEDLINE (n = 668), Embase (n = 768), and the Cochrane Library (n = 46), with deduplication resulting in n = 1,102 warranting screening. An additional two studies were identified through other means. The majority (99.5%) were ineligible either because of a nonrigorous study methodology or lack of relevance to the PICO question, and this resulted in screeners identifying four studies for final review inclusion. The four identified studies were multicenter RCTs (19, 29–31). The total sample size for the four RCTs was 9,313 participants; 5,700 (61.2%) of these participants were in the treatment/intervention arms and 3,613 (38.8%) were in the control (comparator) arms. Three of the four studies enrolled patients with a history of one or more exacerbations per year (19, 29, 30). In one study, patients were not required to have had an exacerbation in the past year (31).

Pneumonia.

Three studies (n = 8,964) assessed incidence of pneumonia (29–31). The studies revealed a significantly increased risk of pneumonia with triple therapy as compared with dual therapy (rate ratio, 1.39; 95% CI, 1.02–1.90; P = 0.03). There was high certainty in estimates of effect based on GRADE (absolute risk effect was 15 more pneumonias per 1,000 patients; 95% CI, 1 more to 35 more). The x2 interaction test for subgroup differences suggested similar effects in frequency of pneumonia for those with a history of one or more exacerbations in the past year and those with zero to less than one exacerbation in the past year (P = 0.74), suggesting that any differences could be explained by chance.

Hospital admissions.

One study (n = 293) evaluated the risk of all-cause hospital admissions (19). The study revealed no significant difference in risk of hospital admission with triple therapy as compared with dual therapy (rate ratio, 0.87; 95% CI, 0.62–1.24; P = 0.44). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 42 fewer per 1,000 patients; 95% CI, 123 fewer to 78 more). There were no subgroups available to analyze.

Exacerbations.

Four studies (n = 9,257) evaluated the risk of COPD exacerbations (19, 29–31). The studies revealed a significantly decreased risk of exacerbations with triple therapy as compared with dual therapy with LABA/LAMA (rate ratio, 0.71; 95% CI, 0.59–0.86; P,0.001). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 64 fewer exacerbations per 1,000 patients; 95% CI, 90 fewer to 31 fewer). The x2 interaction test for subgroup differences suggested different effects in frequency of exacerbations for those with a history of one or more exacerbations in the past year and those with zero to less than one exacerbation in the past year (P,0.001).

Committee discussion.

The panel concluded that the benefits of triple therapy with ICS/LABA/LAMA outweigh the risks as compared with treatment with LABA/LAMA dual therapy in patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy and have experienced one or more exacerbations in the past year. The panel noted that in three studies that randomized symptomatic patients with COPD who had a history of exacerbations, the benefits of triple therapy in protecting against the risk of future exacerbations outweighed the increased risk of pneumonia. In patients with COPD and a history of one or more exacerbations in the past year, the 23% rate reduction in exacerbations was believed to outweigh the 39% increased rate of pneumonia, as exacerbation events are much more common than pneumonia events in these patients. This was confirmed when the absolute risk differences were examined. Patients treated with triple therapy experienced 15 more pneumonias per 1,000 patients; however, they also experienced 230 fewer COPD exacerbations per 1,000 patients. Thus, the panel concluded that for patients with COPD and a history of exacerbations, the benefits of triple therapy outweigh the risks. However, the panel concluded that the benefits of triple therapy do not clearly outweigh the risks as compared with treatment with dual therapy in patients with COPD who have experienced zero to less than one exacerbation in the past year, because only one clinical trial that assessed this specific subgroup was available. In this study, patients with COPD and no history of exacerbations had a 17% increased relative risk of pneumonia and a 52% reduced relative risk of exacerbations. Patients treated with triple therapy experienced 15 more pneumonias per 1,000 patients, and experienced 182 fewer COPD exacerbations per 1,000 patients. Although the data from this study suggest that these patients may benefit from triple therapy, the panel believed that additional studies are needed before triple therapy can be recommended for this subgroup. The panel examined and discussed feasibility, acceptability, and health-equity issues, and concluded that the therapy options (dual therapy or triple therapy) would be feasible to implement and would be acceptable to patients. The panel did note that triple therapy is more expensive than dual long-acting bronchodilator therapy, and that this could pose health-equity challenges to patients of limited means who might be unable to obtain the drug because of cost or lack of availability. However, a formal cost-effectiveness analysis was not performed, and the literature evidence was not fully examined in this regard. Because triple therapy is available as a single inhaler, the burden of use for patients was not deemed a factor that would preclude patients from choosing triple therapy over dual therapy. However, the panel noted that if a physician chooses to prescribe two or three separate inhalers rather than a single combination triple therapy inhaler, this could increase the complexity and burden of medication use for patients. After considering these issues, the panel decided that for patients with COPD who complain of dyspnea or exercise intolerance, the balance of benefits of triple therapy with ICS/LABA/LAMA clearly outweigh the risks when compared with dual therapy with LABA/LAMA in those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization.

Question 3:

Summary of the evidence.

The expert medical librarian initially identified 1,482 citations in MEDLINE (n = 668), Embase (n = 768), and the Cochrane Library (n = 46), with deduplication resulting in n = 1,102 warranting screening. The majority (99.6%) were ineligible either because of a nonrigorous study methodology or lack of relevance to the PICO question, and this resulted in screeners identifying three studies for final review inclusion. The three identified studies were RCTs; however, one of the three studies was a subgroup analysis (32) of a larger trial (33), and thus only two studies were included for review (33, 34). The total sample size for the two studies was 3,538 participants; 1,769 (50%) of these participants were in the treatment/intervention arms and 1,769 (50%) were in the control (comparator) arms. The two studies were both multicenter trials.

Exacerbations.

Two studies (n = 3,538) evaluated the risk of COPD exacerbations (33, 34). The studies revealed no significant difference in risk of exacerbations with withdrawal of ICS and subsequent dual therapy with LABA/LAMA as compared with continued triple therapy (rate ratio, 1.07; 95% CI, 0.97–1.17; P = 0.17). There was moderate certainty in estimates of effect based on GRADE (absolute effect was 15 more exacerbation events per 1,000 patients; 95% CI, 7 fewer to 37 more). The x2 interaction test for subgroup differences suggested similar effects for the risk of COPD exacerbations for those with one or more exacerbations in the past year and those without a history of exacerbations (P = 0.88), suggesting that any differences could be explained by chance.

All-cause mortality.

Two studies (n = 3,538) evaluated all-cause mortality (33, 34). The studies revealed no significant difference in risk of death with withdrawal of ICS and subsequent dual therapy with LABA/LAMA as compared with continued triple therapy (RR, 1.09; 95% CI, 0.73–1.65; P = 0.66). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 2 more deaths per 1,000 patients; 95% CI, 7 fewer to 17 more).

Committee discussion.

According to the available evidence, withdrawal of ICS was not associated with a statistically significant difference in risk of pneumonia, all-cause mortality, or risk of COPD exacerbation. The change in QOL did not exceed the MCID threshold. Given the paucity of evidence and hence the inability to confirm the risks and benefits associated with withdrawal of ICS from triple therapy, and in light of the analysis of data from PICO question 2, which showed that triple therapy is of benefit in patients with a history of exacerbations, the panel suggests that ICS can be withdrawn and patients can be converted from triple therapy to dual therapy with LABA/LAMA if there is no history of exacerbations in the past year. The panel examined and discussed feasibility, acceptability, and health-equity issues, and concluded that withdrawal of ICS from triple therapy would be feasible to implement, would be acceptable to patients, and would pose limited (if any) health-equity challenges. A cost-effectiveness analysis was not performed, and the literature evidence was not fully examined in this regard. However, the panel believed that the costs of dual therapy versus triple therapy would not be a rate-limiting step for patients in terms of access to treatment, as dual therapy would be expected to be less expensive than triple therapy. The burden of use for patients was also not deemed to be a factor that would preclude them from choosing dual therapy over triple therapy. After considering these issues, the panel concluded that withdrawal of ICS from triple therapy can be considered for patients with COPD who do not have a history of exacerbations in the past year.

Question 4

Summary of the evidence.

The expert medical librarian initially identified 2,953 citations in MEDLINE (n = 1,734), Embase (n = 1,187), and the Cochrane Library (n = 32), with deduplication resulting in n = 1,923 warranting abstract screening. An additional seven studies were identified through other means. The majority (99.4%) were ineligible either because of a non-rigorous study methodology or lack of relevance to the PICO question, and this resulted in screeners identifying eight studies for final review inclusion. All eight identified unique studies were RCTs (29, 31, 35–40). The total sample size for the eight RCTs was 9,123 participants; 5,945 (65.2%) of these participants were in the treatment/intervention arms and 3,178 (34.8%) were in the control (comparator) arms. The chosen thresholds for the percentage of eosinophils in blood (>2% eosinophils) and the number of eosinophils per microliter of blood (>150) were based on the values presented in the studies analyzed for the review.

Pneumonia (>2% eosinophils).

Two studies (n = 4,131) assessed incidence of pneumonia in patients with >2% blood eosinophils (35, 38). The studies revealed an increased risk of pneumonia with an ICS in addition to a long-acting bronchodilator (RR, 1.99; 95% CI, 1.31–3.00; P = 0.001). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 26 more pneumonias per 1,000 patients; 95% CI, 8 more to 52 more).

Pneumonia (>150 eosinophils).

Two studies (n = 4,267) assessed incidence of pneumonia in patients with >150 blood eosinophils/ml (36, 38). The studies revealed an increased risk of pneumonia with an ICS in addition to a long-acting bronchodilator (RR, 1.55; 95% CI, 1.23–1.95; P,0.001). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 44 more pneumonias per 1,000 patients; 95% CI, 18 more to 76 more).

Exacerbations (>150 eosinophils/ml).

Six studies (n = 8,106) assessed rates of COPD exacerbations in patients with >150 blood eosinophils/ml (29, 31, 36, 38–40). The studies revealed a reduced risk of exacerbations with an ICS in addition to a long-acting bronchodilator versus a longacting bronchodilator (rate ratio, 0.70; 95% CI, 0.59–0.84; P,0.001). There was moderate certainty in estimates of effect based on GRADE. Assuming a baseline risk of COPD exacerbation in this subgroup of one exacerbation per patient per year, the absolute risk effect was 285 fewer exacerbations per 1,000 patients (95% CI, 390 fewer to 152 fewer).

Summary. Based on the five critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be “moderate” and this certainty was assigned to the final recommendation as per GRADE guidance.

Committee discussion.

According to the available evidence, the addition of ICS to a long-acting bronchodilator in patients with COPD and blood eosinophilia was associated with a significantly increased risk of pneumonia and a significantly decreased risk of exacerbations. Patients with blood eosinophilia treated with ICS plus long-acting bronchodilators experienced 26–44 more pneumonias per 1,000 patients, and 209–285 fewer COPD exacerbations per 1,000 patients. However, the panel recognized that the studies included within this PICO question analyzed the effects of ICS and long-acting bronchodilators in patients with elevated blood eosinophils as subgroup analyses. In many cases, the subgroup analyses were performed post hoc after the primary trial results had already been published. In addition, nonstandardized thresholds were used in the various studies to define “eosinophilia.” Thus, the panel believed the quality of the available studies providing the evidence was not optimal, and hence the committee was reluctant to recommend ICS for all patients with COPD and blood eosinophilia. However, given the weight of the evidence presented in PICO 2, which shows that ICS are beneficial in patients with a history of exacerbations, the panel concluded that patients with blood eosinophilia and a history of exacerbations would likewise benefit from

the addition of ICS to a long-acting bronchodilator. The panel believed that the addition of ICS to a long-acting bronchodilator in patients with blood eosinophilia and a history of exacerbations is feasible, and the burden of therapy would be acceptable to patients. A cost-effectiveness analysis was not performed because the literature was not fully examined in this regard. However, the panel did note that combination inhaled steroid/long-acting bronchodilator therapy is more expensive than long-acting bronchodilator monotherapy, and this could pose health-equity challenges to patients of limited means who might be unable to obtain the drug because of cost or lack of availability. The burden of use for patients was not deemed to be a factor that would preclude patients from choosing a long-acting bronchodilator with ICS over a long-acting bronchodilator therapy without ICS. After considering these issues, the panel did not suggest ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of one or more exacerbations in the past year.

Question 5

Summary of the evidence.

The expert medical librarian initially identified 1,500 citations in MEDLINE (n = 777), Embase (n = 664), and the Cochrane Library (n = 59), with deduplication resulting in n = 932 warranting abstract screening. The majority (98.8%) were ineligible either because of a nonrigorous study methodology or lack of relevance to the PICO question, resulting in the screeners identifying 11 studies for final review inclusion. Four of the 11 studies were RCTs (42–45). The total sample size for the four RCTs was 477 patients; 290 (60.8%) of these patients were in the treatment/intervention arms and 187 (39.2%) were in the control (comparator) arms. The four studies were a combination of single- and multicenter designs. We initially analyzed both RCT and observational (nonrandomized) evidence for this question given the available evidence, while recognizing that nonrandomized evidence can be affected by selection bias and residual confounding (e.g., confounding by indication). After the analysis, we judged the RCT evidence to be the optimal evidence on which to base this recommendation. As such, for the application of GRADE methods, we used the RCT evidence in determining the certainty of evidence, and we present the RCT evidence for the respective patientimportant outcomes.

Summary.

Based on the five critical outcomes using RCT evidence and completion of the GRADE evidence table, the overall certainty of evidence was judged to be “low” and this certainty was assigned to the final recommendation as per GRADE guidance.

Committee discussion.

The panel believed that maintenance oral steroid therapy has not been shown in clinical trials to improve clinical outcomes, and the available evidence suggests that chronic oral steroid therapy has a potential for harm. Two RCTs revealed an increased risk of adverse events with oral steroid use, suggesting excess adverse events (harms) in patients who are prescribed daily oral steroids. However, this recommendation was based on RCTs that had small sample sizes, a small number of events, short durations, and broad CIs around the point estimates. In addition, these studies occurred when there was a paucity of medications available for maintenance therapy. The quality of the underlying evidence was poor, and therefore the panel believed that a recommendation in favor of maintenance oral steroid use would be problematic given the concerns surrounding patient safety. The panel also believed that well-informed patients would place a greater value on avoiding the potential harms of adverse events and less value on the uncertain benefits of decreased dyspnea and hospital admissions. After considering these issues and the low certainty of the evidence, the panel concluded that in patients with COPD and a history of severe and frequent exacerbations, the balance of benefits of maintenance oral steroid therapy did not outweigh

the risks when compared with no steroid use. Given that the panel recommended against the intervention, issues related to feasibility, acceptability, and health equity were not discussed.

Question 6

Summary of the evidence. The expert medical librarian initially identified 576 citations in MEDLINE (n = 267), Embase (n = 193), and the Cochrane Library (n = 116), with deduplication resulting in n = 370 warranting abstract screening. The majority (96.2%) were ineligible either because of a non-rigorous study methodology or lack of relevance to the PICO question, and this resulted in screeners identifying 14 studies for final review inclusion. All of the 14 identified studies were RCTs, and 13 of these studies used a crossover design (46–59). Each RCT had a relatively small sample size and the total sample size for the 14 studies was 366 participants. There were 184 participants in the treatment/intervention arms (opioidbased treatment) across the trials (50.2%) and 182 (49.7%) in the control (comparator) arms. The majority of the 14 studies were single-center studies.

Summary.

Based on the eight critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be “very low” and this certainty was assigned to the final recommendation as per GRADE guidance.

Committee discussion.

The panel noted that in patients with advanced refractory dyspnea, there was a statistically and clinically meaningful improvement in dyspnea with opioid treatment. The panel believed that a conditional recommendation in favor of opioid use was reasonable for dyspnea management given the accumulated evidence, and that wellinformed patients might place a higher value on the improvement in dyspnea and less value on the uncertain harms of exacerbations, hospitalizations, falls, or overdoses. The panel believed that the observed benefit in dyspnea outweighed the uncertain risks. However, many of these studies were undertaken when there was a relative paucity of maintenance medications available to treat COPD, and the presumed effects of opioids might differ in today’s clinical context. Therefore, given the very low certainty of evidence, the use of opioids must be evaluated by clinicians and patients in a shared decision-making process. The panel debated the issues of feasibility, acceptability, and health equity, and felt confident that a trial of opioid therapy to determine if there was individual benefit could be implemented, would be acceptable to patients, and would pose limited (if any) health-equity challenges. A cost-effectiveness analysis was not performed, and the literature evidence was not fully examined in this regard. However, the panel also believed that opioid treatment would not be prohibitively expensive in terms of access to treatment. The burden of use for patients was also not deemed to be a factor that would preclude patients from taking opioids for advanced refractory dyspnea despite otherwise optimal COPD therapy if prescribed. After considering these issues, and armed with very low certainty evidence, the panel concluded that in individuals with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, the balance of benefits of opioid therapy may outweigh the risks when compared with no opioid use. The panel suggested that the use of opioid treatment in COPD should be carefully considered by both the clinician and the well-informed patient, underscoring the need for shared decision-making.

National Institute for Health and Care Excellence (NICE), 2018 [16]

Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care.

Leitlinienorganisation/Fragestellung

NICE's original guidance on COPD was published in 2004. It was updated in 2010, 2018 and 2019.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium einschließlich Patientenbeteiligung.
- 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.

LoE und GoR

Hierarchy of Evidence		**Grading of Recommendations**	
Ia	Evidence from systematic reviews or meta-analysis of randomised controlled trials	A	Based on hierarchy I evidence
Ib	Evidence from at least one randomised controlled trial		
IIa	Evidence from at least one controlled study without randomisation	B	Based on hierarchy II evidence or extrapolated from hierarchy I evidence
IIb	Evidence from at least one other type of quasi experimental study		
III	Evidence from non experimental descriptive studies, such as comparative studies, correlation studies and case control studies	C	Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities	D	Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II or III evidence.
DS	Evidence from diagnostic studies	DS	Evidence from diagnostic studies
NICE	Evidence from NICE guidelines or Health Technology Appraisal programme	NICE	Evidence from NICE guidelines or Health Technology Appraisal programme
HSC	Evidence from Health Service Circulars	HSC	Evidence from Health Service Circulars

Sonstige methodische Hinweise

- Surveillance report (published: 4 March 2020): „After considering all evidence and other intelligence and the impact on current recommendations, we decided that no update is necessary.” [15]

Empfehlungen

Inhaled therapy

Short-acting beta2 agonists (SABA) and short-acting muscarinic antagonists (SAMA)

- 1.2.7 Use short-acting bronchodilators, as necessary, as the initial empirical treatment to relieve breathlessness and exercise limitation. [2004]

Inhaled corticosteroids (ICS)

- 1.2.8 Do not use oral corticosteroid reversibility tests to identify which people should be prescribed inhaled corticosteroids, because they do not predict response to inhaled corticosteroid therapy. [2004]
- 1.2.9 Be aware of, and be prepared to discuss with the person, the risk of side effects (including pneumonia) in people who take inhaled corticosteroids for COPD[1]. [2010, amended 2018]

Inhaled combination therapy. Inhaled combination therapy refers to combinations of long-acting muscarinic antagonists (LAMA), long-acting beta2 agonists (LABA), and inhaled corticosteroids (ICS).

- 1.2.10 Do not assess the effectiveness of bronchodilator therapy using lung function alone. Include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. [2004]
- 1.2.11 Offer LAMA+LABA to people who:
  - have spirometrically confirmed COPD and
  - do not have asthmatic features/features suggesting steroid responsiveness and
  - remain breathless or have exacerbations despite:

having used or been offered treatment for tobacco dependence if they smoke and

optimised non-pharmacological management and relevant vaccinations and
  - using a short-acting bronchodilator. [2018]
- 1.2.12 Consider LABA+ICS for people who:
  - have spirometrically confirmed COPD and
  - have asthmatic features/features suggesting steroid responsiveness and
  - remain breathless or have exacerbations despite:

having used or been offered treatment for tobacco dependence if they smoke and

optimised non-pharmacological management and relevant vaccinations and
  - using a short-acting bronchodilator. [2018]
- 1.2.13 For people who are using long-acting bronchodilators outside of recommendations 1.2.11 and 1.2.12 and whose symptoms are under control, explain to them that they can continue with their current treatment until both they and their NHS healthcare professional agree it is appropriate to change. [2018]
- 1.2.14 Before starting LAMA+LABA+ICS, conduct a clinical review to ensure that:
  - the person's non-pharmacological COPD management is optimised and they have used or been offered treatment for tobacco dependence if they smoke
  - acute episodes of worsening symptoms are caused by COPD exacerbations and not by another physical or mental health condition
  - the person's day-to-day symptoms that are adversely impacting their quality of life are caused by COPD and not by another physical or mental health condition. [2019]
- 1.2.15 For people with COPD who are taking LABA+ICS, offer LAMA+LABA+ICS if:
  - their day-to-day symptoms continue to adversely impact their quality of life or
  - they have a severe exacerbation (requiring hospitalisation) or
  - they have 2 moderate exacerbations within a year. [2019]

- 1.2.16 For people with COPD who are taking LAMA+LABA, consider LAMA+LABA+ICS if:
  - they have a severe exacerbation (requiring hospitalisation) or
  - they have 2 moderate exacerbations within a year. [2019]
- 1.2.17 For people with COPD who are taking LAMA+LABA and whose day-to-day symptoms adversely impact their quality of life:
  - consider a trial of LAMA+LABA+ICS, lasting for 3 months only
  - after 3 months, conduct a clinical review to establish whether or not LAMA+LABA+ICS has improved their symptoms:

if symptoms have not improved, stop LAMA+LABA+ICS and switch back to LAMA+LABA

if symptoms have improved, continue with LAMA+LABA+ICS. [2019]

- 1.2.18 Document the reason for continuing ICS use in clinical records and review at least annually. [2019]
- 1.2.19 Base the choice of drugs and inhalers on:
  - how much they improve symptoms
  - the person's preferences and ability to use the inhalers
  - the drugs' potential to reduce exacerbations
  - their side effects
  - their cost.
  - Minimise the number of inhalers and the number of different types of inhaler used by each person as far as possible. [2018]
- 1.2.20 When prescribing long-acting drugs, ensure people receive inhalers they have been trained to use (for example, by specifying the brand and inhaler in prescriptions). [2018]

Oral therapy

Oral corticosteroids

- 1.2.34 Long-term use of oral corticosteroid therapy in COPD is not normally recommended. Some people with advanced COPD may need long-term oral corticosteroids when these cannot be withdrawn following an exacerbation. In these cases, the dose of oral corticosteroids should be kept as low as possible. [2004]
- 1.2.35 Monitor people who are having long-term oral corticosteroid therapy for osteoporosis, and give them appropriate prophylaxis. Start prophylaxis without monitoring for people over 65. [2004]

Oral theophylline.

In this section of the guideline, the term theophylline refers to slow-release formulations of the drug.

- 1.2.36 Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or for people who are unable to use inhaled therapy, as plasma levels and interactions need to be monitored. [2004]
- 1.2.37 Take particular caution when using theophylline in older people, because of differences in pharmacokinetics, the increased likelihood of comorbidities and the use of other medications. [2004]
- 1.2.38 Assess the effectiveness of theophylline by improvements in symptoms, activities of daily living, exercise capacity and lung function. [2004]

- 1.2.39 Reduce the dose of theophylline for people who are having an exacerbation if they are prescribed macrolide or fluoroquinolone antibiotics (or other drugs known to interact). [2004]

Oral mucolytic therapy

- 1.2.40 Consider mucolytic drug therapy for people with a chronic cough productive of sputum. [2004]
- 1.2.41 Only continue mucolytic therapy if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production). [2004]
- 1.2.42 Do not routinely use mucolytic drugs to prevent exacerbations in people with stable COPD. [2010]

Oral anti-oxidant therapy

- 1.2.43 Treatment with alpha-tocopherol and beta-carotene supplements, alone or in combination, is not recommended. [2004]

Oral anti-tussive therapy

- 1.2.44 Anti-tussive therapy should not be used in the management of stable COPD. [2004]

Oral prophylactic antibiotic therapy

- 1.2.45 Before starting prophylactic antibiotic therapy in a person with COPD, think about whether respiratory specialist input is needed. [2018]
- 1.2.46 Consider azithromycin (usually 250 mg 3 times a week) for people with COPD if they:
  - do not smoke and
  - have optimised non-pharmacological management and inhaled therapies, relevant vaccinations and (if appropriate) have been referred for pulmonary rehabilitation and
  - continue to have 1 or more of the following, particularly if they have significant daily sputum production:

frequent (typically 4 or more per year) exacerbations with sputum production

prolonged exacerbations with sputum production exacerbations resulting in hospitalisation. [2018]

- 1.2.47 Before offering prophylactic antibiotics, ensure that the person has had:
  - sputum culture and sensitivity (including tuberculosis culture), to identify other possible causes of persistent or recurrent infection that may need specific treatment (for example, antibiotic-resistant organisms, atypical mycobacteria or Pseudomonas aeruginosa)
  - training in airway clearance techniques to optimise sputum clearance (see recommendation 1.2.99)
  - a CT scan of the thorax to rule out bronchiectasis and other lung pathologies. [2018]
- 1.2.48 Before starting azithromycin, ensure the person has had:
  - an electrocardiogram (ECG) to rule out prolonged QT interval and
  - baseline liver function tests. [2018]
- 1.2.49 When prescribing azithromycin, advise people about the small risk of hearing loss and tinnitus, and tell them to contact a healthcare professional if this occurs. [2018]
- 1.2.50 Review prophylactic azithromycin after the first 3 months, and then at least every 6 months. [2018]

- 1.2.51 Only continue treatment if the continued benefits outweigh the risks. Be aware that there are no long-term studies on the use of prophylactic antibiotics in people with COPD. [2018]
- 1.2.52 For people who are taking prophylactic azithromycin and are still at risk of exacerbations, provide a non-macrolide antibiotic to keep at home as part of their exacerbation action plan (see recommendation 1.2.126). [2018]
- 1.2.53 Be aware that it is not necessary to stop prophylactic azithromycin during an acute exacerbation of COPD. [2018]

Oral phosphodiesterase-4 inhibitors

- 1.2.54 For guidance on treating severe COPD with roflumilast, see NICE's technology appraisal guidance on roflumilast for treating chronic obstructive pulmonary disease. [2018]:
  - 1.1 Roflumilast, as an add-on to bronchodilator therapy, is recommended as an option for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:
    - the disease is severe, defined as a forced expiratory volume in 1 second (FEV1) after a bronchodilator of less than 50% of predicted normal, and
    - the person has had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.
  - 1.2 Treatment with roflumilast should be started by a specialist in respiratory medicine.

Oxygen

Long-term oxygen therapy

- 1.2.55 Be aware that inappropriate oxygen therapy in people with COPD may cause respiratory depression. **[2004]**
- 1.2.56 Assess the need for oxygen therapy in people with:
  - very severe airflow obstruction (FEV1 below 30% predicted)
  - cyanosis (blue tint to skin)
  - polycythaemia
  - peripheral oedema (swelling)
  - a raised jugular venous pressure
  - oxygen saturations of 92% or less breathing air.

  Also consider assessment for people with severe airflow obstruction (FEV1 30–49% predicted). **[2004]**
- 1.2.57 Assess people for long-term oxygen therapy by measuring arterial blood gases on 2 occasions at least 3 weeks apart in people who have a confident diagnosis of COPD, who are receiving optimum medical management and whose COPD is stable. **[2004]**
- 1.2.58 Consider long-term oxygen therapy for people with COPD who do not smoke and who:
  - have a partial pressure of oxygen in arterial blood (PaO_2) below 7.3 kPa when stable **or**
  - have a PaO_2 above 7.3 and below 8 kPa when stable, if they also have 1 or more of the following:

secondary polycythaemia

peripheral oedema

pulmonary hypertension.

- 1.2.59 Conduct and document a structured risk assessment for people being assessed for long-term oxygen therapy who meet the criteria in the recommendation on considering long-term oxygen therapy. As part of the risk assessment, cover the risks for both the person with COPD and the people who live with them, including:
  - the risks of falls from tripping over the equipment
  - the risks of burns and fires, and the increased risk of these for people who live in homes where someone smokes (including e-cigarettes).

  Base the decision on whether long-term oxygen therapy is suitable on the results of the structured risk assessment. **[2018]**
- 1.2.60 For people who smoke or live with people who smoke, but who meet the other criteria for long-term oxygen therapy, ensure the person who smokes is offered smoking cessation advice and treatment, and referral to specialist stop smoking services (see the NICE guidelines on stop smoking interventions and services and medicines optimisation). **[2018]**
- 1.2.61 Do not offer long-term oxygen therapy to people who continue to smoke despite being offered smoking cessation advice and treatment, and referral to specialist stop smoking services. **[2018]**
- 1.2.62 Advise people who are having long-term oxygen therapy that they should breathe supplemental oxygen for a minimum of 15 hours per day. **[2018]**
- 1.2.63 Do not offer long-term oxygen therapy to treat isolated nocturnal hypoxaemia caused by COPD. **[2018]**
- 1.2.64 To ensure everyone eligible for long-term oxygen therapy is identified, pulse oximetry should be available in all healthcare settings. **[2004]**
- 1.2.65 Oxygen concentrators should be used to provide the fixed supply at home for long-term oxygen therapy. **[2004]**
- 1.2.66 People who are having long-term oxygen therapy should be reviewed at least once per year by healthcare professionals familiar with long-term oxygen therapy. This review should include pulse oximetry. **[2004]**

Lung surgery and lung volume reduction procedures

- 1.2.88 Offer a respiratory review to assess whether a lung volume reduction procedure is a possibility for people with COPD when they complete pulmonary rehabilitation and at other subsequent reviews, if all of the following apply:
  - they have severe COPD, with FEV1 less than 50% and breathlessness that affects their quality of life despite optimal medical treatment (see recommendations 1.2.11 to 1.2.17 in the section on inhaled combination therapy)
  - they do not smoke
  - they can complete a 6-minute walk distance of at least 140 m (if limited by breathlessness). **[2018]**
- 1.2.89 At the respiratory review, refer the person with COPD to a lung volume reduction multidisciplinary team to assess whether lung volume reduction surgery or endobronchial valves are suitable if they have:
  - hyperinflation, assessed by lung function testing with body plethysmography **and**

  - emphysema on unenhanced CT chest scan **and**
  - optimised treatment for other comorbidities. **[2018]**
- 1.2.90 Only offer endobronchial coils as part of a clinical trial and after assessment by a lung volume reduction multidisciplinary team. **[2018]**
- 1.2.91 For more guidance on lung volume reduction procedures, see the NICE interventional procedures guidance on lung volume reduction surgery, endobronchial valves and endobronchial coils. **[2018]**
- 1.2.92 Refer people with COPD for an assessment for bullectomy if they are breathless and a CT scan shows a bulla occupying at least one third of the hemithorax. **[2018]**
- 1.2.93 Consider referral to a specialist multidisciplinary team to assess for lung transplantation for people who:
  - have severe COPD, with FEV1 less than 50% and breathlessness that affects their quality of life despite optimal medical treatment (see recommendations 1.2.11 to 1.2.17 in the section on inhaled combination therapy) **and**
  - do not smoke **and**
  - have completed pulmonary rehabilitation **and**
  - do not have contraindications for transplantation (for example, comorbidities or frailty). **[2018]**
- 1.2.94 Do not use previous lung volume reduction procedures as a reason not to refer a person for assessment for lung transplantation. **[2018]**

Chronic obstructive pulmonary disease in over 16s: non-pharmacological management and use of inhaled therapies

Confirmed diagnosis of COPD

Fundamentals of COPD care:
- Offer treatment and support to **stop smoking**
- Offer **pneumococcal** and **influenza vaccinations**
- Offer **pulmonary rehabilitation** if indicated
- Co-develop a personalised **self-management plan**
- Optimise treatment for **comorbidities**

These treatments and plans should be revisited at every review

Start **inhaled therapies** only if:
- all the above interventions have been offered (if appropriate), and
- inhaled therapies are needed to relieve breathlessness and exercise limitation, and
- people have been trained to use inhalers and can demonstrate satisfactory technique

Review medication and assess inhaler technique and adherence regularly for all inhaled therapies

Offer SABA or SAMA to use as needed

If the person is limited by symptoms or has exacerbations despite treatment:

No asthmatic features or features suggesting steroid responsiveness[a]

Offer LABA + LAMA

Person has day-to-day symptoms that adversely impact quality of life

Consider 3-month trial of LABA + LAMA + ICS[b,c]

If no improvement, revert to LABA + LAMA

Person has 1 severe or 2 moderate exacerbations within a year

Consider LABA + LAMA + ICS[b,c]

Asthmatic features or features suggesting steroid responsiveness[a]

Consider LABA + ICS[b]

Person has day-to-day symptoms that adversely impact quality of life, or has 1 severe or 2 moderate exacerbations within a year

Offer LABA + LAMA + ICS[b,c]

Explore further treatment options if still limited by breathlessness or subject to frequent exacerbations (see guideline for more details)

[a] Asthmatic features/features suggesting steroid responsiveness in this context include any previous secure diagnosis of asthma or atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400 ml) or substantial diurnal variation in peak expiratory flow (at least 20%).
[b] Be aware of an increased risk of side effects (including pneumonia) in people who take ICS.
[c] Document in clinical records the reason for continuing ICS treatment.

NICE National Institute for Health and Care Excellence

This is a summary of the recommendations on non-pharmacological management of chronic obstructive pulmonary disease and use of inhaled therapies in people over 16. The guideline also covers diagnosis and other areas of management. See www.nice.org.uk/guidance/NG115

See the NICE website for information on how we use offer and consider to show strength of recommendations.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2023) am 23.11.2023

#	Suchfrage
1	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
2	(chronic NEXT obstructive NEXT pulmonary NEXT disease*):ti,ab,kw OR (COPD):ti
3	(chronic NEXT (bronchitis OR (obstructive NEXT (airways OR lung) NEXT disease*))):ti,ab,kw OR (COAD):ti
4	("chronic airflow obstruction"):ti,ab,kw
5	#1 OR #2 OR #3 OR #4
6	#5 with Cochrane Library publication date from Nov 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 23.11.2023

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

#	Suchfrage
1	Pulmonary Disease, Chronic Obstructive/therapy[majr]
2	"chronic obstructive pulmonary disease*"[tiab] OR "chronic obstructive airways disease*"[tiab] OR "chronic obstructive lung disease*"[tiab] OR "chronic bronchitis"[tiab] OR "chronic airflow obstruction"[tiab] OR COPD[ti] OR COAD[ti]
3	(#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 monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
4	(#1 OR #3) 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]

#	Suchfrage
	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])
5	(#4) AND ("2018/11/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT "The Cochrane database of systematic reviews"[Journal]
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 23.11.2023

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

#	Suchfrage
1	"Pulmonary Disease, Chronic Obstructive"[mh]
2	"chronic obstructive pulmonary disease*"[tiab] OR "chronic obstructive airways disease*"[tiab] OR "chronic obstructive lung disease*"[tiab] OR "chronic bronchitis"[tiab] OR "chronic airflow obstruction"[tiab] OR COPD[ti] OR COAD[ti]
3	(#1 OR #2) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
4	(#3) AND ("2018/11/01"[PDAT] : "3000"[PDAT])
5	(#4) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 23.11.2023

- 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

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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

Verfahrens-Nr.: 2023-B-319

Verfasser	
Name der Institution	DGf Pneumologie (DGP) Unterstützt von der DEGAM
Datum der Erstellung	2. Januar 2024

Indikation
Erwachsene mit chronisch obstruktiver Lungenerkrankung mit Typ-2-Inflammation, die trotz Dreifach- oder Zweifach-Therapie, sofern inhalative Kortikosteroide kontraindiziert sind, nicht ausreichend kontrolliert 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.)*
Behandlungsstandard in dieser Situation wäre die Gabe von Roflumilast bei Patient*innen mit COPD, 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 (Quelle NVL COPD 2. Auflage, Seite 62 medikamentöse Therapie).
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.)*
Oben aufgeführte Eskalation der Therapie mit Roflumilast berücksichtigt nicht den Status der Typ-2 Inflammation (i.e. höhere Bluteosinophilenanzahl als Indikator der Typ-2-Inflammation), sondern orientiert sich an dem klinischen Phänotyp chronische Bronchitis. Es ist jedoch die einzige empfohlen Eskalationstherapie in dieser Situation unabhängig vom Typ-2- Status. Jedoch weisen gepoolte Analysen der Roflumilast-Studien darauf hin, dass die Therapie bei höherem Typ-2-Inflammationsstatus (i.e. höhere Bluteosinophilenanzahl) wirksamer ist in der Verhinderung von Exazerbationen als bei niedrigem Typ-2-Inflammationsstatus (Martinez et al. Am J Respir Crit Care Med 2018). Diese gepoolten -Analysen haben jedoch nicht Eingang gefunden in die Therapieempfehlungen der NVL COPD.

Referenzliste:

1. NVL COPD 2.Auflage 2021
2. Martinez et al. Am J Respir Crit Care Med 2018 Nov 15;198(10):1268-1278. doi: 10.1164/rccm.201712-2493OC. Determinants of Response to Roflumilast in Severe Chronic Obstructive Pulmonary Disease. Pooled Analysis of Two Randomized Trials