Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-B-187 Fluticasonfuroat/ Umeclidiniumbromid/Vilanteroltrifenatat

Stand: Februar 2017

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *chronisch-obstruktiver Lungenerkrankung (COPD)* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1400 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 38 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

- bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD)

Berücksichtigte Wirkstoffe/Therapien:

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen:

AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft
AE	adverse effect/event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
COPD	chronic obstructive pulmonary disease
DAHTA	Deutsche Agentur für Health Technology Assessment
FEV1	Forced expiratory volume in the first second
FSC	fluticasone propionate/salmeterol
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
ICS	inhaled corticosteroids
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
MCID	minimal clinically important difference
MD	Mean difference
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NNTB	number needed to treat for benefit
RCT	randomized controlled trial
RD	Risk difference
RR	risk ratio
SAE	severe adverse effect/event
SGRQ	St. George’s Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
TDI	Transition Dyspnea Index
TD-LABA	bid long-acting b 2 -agonist
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WMD	weighted mean difference
bid	Twice daily
ATS	American Thoracic Society
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	health-related quality of life
SABA	short-acting beta2-agonists
TIO	tiotropium
VAS	visual analogue scale
AE	adverse event
FPS	fluticasone/salmeterol
FP	fluticasone propionate

BDF	budesonide/formoterol
MF/F	mometasone furoate and formoterol
MF	mometasone furoate
BID	twice daily
MDI	metered-dose inhaler

Umeclidinium-Vilanterol-Fluticason zur Behandlung der COPD

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

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 Abschnitt II. Zugelassene Arzneimittel im Anwendungsgebiet COPD*
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 - Umeclidinium (Beschluss vom 21.07.2016) - Aclidiniumbromid (erneute Nutzenbewertung, Beschluss vom 07.04.2016) - Aclidiniumbromid/Formoterol (Beschluss vom 16.07.2015) - 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) IQWiG Abschlussbericht - Tiotropiumbromid (IQWiG Bericht A05-18 vom 26.06.2012)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche (COPD)*

II. Zugelassene Arzneimittel im Anwendungsgebiet COPD

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fach-/Gebrauchsinformation)
Zu bewertendes Arzneimittel:	
Umeclidinium-Vilanterol-Fluticason	Trelegy Ellipta ist angezeigt für die Erhaltungstherapie bei erwachsenen Patienten mit moderater bis schwerer chronisch obstruktiver Lungenerkrankung (COPD), die mit einer Kombination aus einem inhalativen Kortikosteroid und einem langwirksamen Beta-2-Agonisten nicht ausreichend eingestellt sind (zu den Wirkungen hinsichtlich Symptomkontrolle siehe Abschnitt 5.1).
SABA: Selektive Beta2-Adrenozeptor-Agonisten, kurzwirksame	
Beispielhaft Salbutamol R03AC02 generisch	Zur Verhütung und Behandlung von Atemwegserkrankungen mit reversibler Obstruktion, wie z. B. Asthma bronchiale oder chronische Bronchitis. Hinweis: Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindung mit einer entzündungshemmenden Dauertherapie erfolgen.
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).
Formoterol R03AC13 generisch	Prophylaxe und Behandlung der Bronchokonstriktion bei Patienten mit reversibler oder irreversibler COPD einschließlich chronischer Bronchitis und Emphysem.
Indacaterol R03AC18 Onbrez®	Onbrez® Breezhaler® ist für die bronchialerweiternde Erhaltungstherapie der Atemwegsobstruktion bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt. (Onbrez® Breezhaler®, Oktober 2014)
Olodaterol R03AC19	Striverdi Respimat ist indiziert als Bronchodilatator zur Dauerbehandlung bei chronischer obstruktiver Lungenerkrankung (COPD). (Striverdi® Respimat®, November 2013)

II. Zugelassene Arzneimittel im Anwendungsgebiet COPD	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fach-/Gebrauchsinformation)
Striverdi® Respimat®	
SAMA: Anticholinergika, kurzwirksame	
Ipratropiumbromid R03BB01 generisch	Ipratropiumbromid wird zur Therapie von reversiblen Bronchospasmen in Zusammenhang mit chronisch obstruktiver Lungenerkrankung (COPD) eingesetzt.
LAMA: Anticholinergika, langwirksame	
Tiotropiumbromid R03BB04 Spiriva® Respimat®	Tiotropium ist indiziert als dauerhaft einzusetzender Bronchodilatator zur Befreiung von Symptomen bei chronischer obstruktiver Lungenerkrankung (COPD).
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.
Umeclidiniumbromid R03BB07 Incruse®	Incruse® ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) angezeigt.
Glycopyrroniumbromid R03BB06 Seebri® Breezhaler®	Seebri® Breezhaler® ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt.
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). Hinweis: Es wird empfohlen die Dauertherapie dieser Erkrankungen mit Theophyllin in Kombination mit anderen, die Bronchien

II. Zugelassene Arzneimittel im Anwendungsgebiet COPD	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fach-/Gebrauchsinformation)
	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.
Phosphodiesterase-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.
Glucokortikosteroide	
Glucokortikosteroide, inhalativ	
Beispielhaft Beclometason R03BA01 generisch	Zur Behandlung von Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z. B. bei – Asthma bronchiale – chronisch obstruktive Bronchitis Hinweis: nicht zur Behandlung von plötzlich auftretenden Atemnotanfällen (akuter Asthmaanfall oder Status asthmaticus) geeignet.
Glucokortikosteroide, oral	
Beispielhalft Prednisolon H02AB06 generisch	- akute Exazerbation einer COPD (DS: b), empfohlene Therapiedauer bis zu 10 Tagen.
Kombinationen: Selektiver Beta2-Adrenozeptor-Agonist + Anticholinergikum	
Salbutamol + Ipratropiumbromid	Zur Behandlung von Bronchospasmen bei Patienten, die an chronisch obstruktiver Lungenkrankheit (COPD) leiden und eine regelmäßige Behandlung mit Ipratropiumbromid und Salbutamol benötigen.

II. Zugelassene Arzneimittel im Anwendungsgebiet COPD	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fach-/Gebrauchsinformation)
R03AK04 generisch	
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.
Indacaterol + Glycopyrroniumbromid R03AL04 Ultibro® Breezhaler®	Ultibro Breezhaler ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt.
Vilanterol + Umeclidiniumbromid R03AL03 ANORO®	ANORO® ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) angezeigt.
Formoterol + Aclidiniumbromid R03AL05 Brimica® Genuar®	Brimica® Genuar® ist indiziert als bronchodilatatorische Erhaltungstherapie zur Linderung von Symptomen bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD).
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.
Kombinationen: Selektiver Beta2-Adrenozeptor-Agonist + Glucokortikosteroid	
Salmeterol + Fluticason R03AK06	wird bei der symptomatischen Behandlung von Patienten mit COPD angewendet, die eine $FEV<_1$ 60% des vorhergesagten Normwerts (vor Anwendung eines Bronchodilatators) und wiederholt Exazerbationen aufweisen und trotz kontinuierlicher Therapie mit Bronchodilatatoren an signifikanten Symptomen leiden.

II. Zugelassene Arzneimittel im Anwendungsgebiet COPD	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fach-/Gebrauchsinformation)
generisch	
Formoterol + Budesonid R03AK07 Symbicort®	Symptomatische Behandlung von Patienten mit schwerer COPD (FEV_1 <50% des Normwertes) und wiederholten Exazerbationen in der Vorgeschichte, die trotz einer regelmäßigen Behandlung mit lang wirksamen Bronchodilatatoren erhebliche Symptome aufweisen.
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.

Quellen: Fachinformationen, Lauer-Taxe

IQWiG Berichte/G-BA Beschlüsse

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), 2013 [20]. Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für das DMP chronisch obstruktive Lungenerkrankung; Abschlussbericht; Auftrag V12-01	**5.4.5.7 Versorgungsaspekt „Medikamentöse Maßnahmen“ (1.5.7 der DMP-Richtlinie)** *DMP-Richtlinie* Zur medikamentösen Therapie sind mit der Patientin oder dem Patienten ein individueller Therapieplan zu erstellen und Maßnahmen zum Selbstmanagement zu erarbeiten (siehe auch strukturierte Schulungsprogramme [Ziffer III 4]). Vorrangig sollen unter Berücksichtigung der Kontraindikationen und der Präferenzen der Patientinnen und Patienten Medikamente verwendet werden, deren positiver Effekt und Sicherheit im Hinblick auf die unter Ziffer III 1.3 genannten Therapieziele in prospektiven, randomisierten, kontrollierten Studien nachgewiesen wurde. Dabei sollen vorrangig diejenigen Wirkstoffe / Wirkstoffgruppen oder Kombinationen bevorzugt werden, die diesbezüglich den größten Nutzen erbringen. Da das Ansprechen auf Medikamente individuell und im Zeitverlauf unterschiedlich sein kann, ist ggf. ein Auslassversuch unter Kontrolle der Symptomatik und der Lungenfunktion zu erwägen. Sofern im Rahmen der individuellen Therapieplanung andere Wirkstoffgruppen oder Wirkstoffe als die in dieser Anlage genannten verordnet werden sollen, ist die Patientin oder der Patient darüber zu informieren, ob für diese Wirkstoffgruppen oder Wirkstoffe Wirksamkeitsbelege bzgl. der unter Ziffer III 1.3 genannten Therapieziele vorliegen. Ziel der medikamentösen Therapie ist es insbesondere, die Symptomatik (vor allem Husten, Schleimretention und Luftnot) zu verbessern und Exazerbationen zeitnah zu behandeln sowie deren Rate zu reduzieren. In der medikamentösen Behandlung der COPD werden Bedarfstherapeutika (Medikamente, die z. B. bei Atemnot eingenommen werden) und Dauertherapeutika (Medikamente, die als Basistherapie regelmäßig eingenommen werden) unterschieden. Vorrangig sollten folgende Wirkstoffgruppen verwendet werden: 2) Dauertherapie: • lang wirksames Anticholinergikum, • lang wirksames Beta-2-Sympathomimetikum. • In begründeten Einzelfällen: • Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung), • inhalative Glukokortikosteroide (bei schwerer und sehr schwerer COPD, insbesondere dann, wenn häufige Exazerbationen auftreten oder Zeichen eines Asthma bronchiale bestehen). Bei gehäuft auftretenden Exazerbationen können mukoaktive Substanzen (Acetylcystein, Ambroxol, Carbocistein) erwogen werden. In der Inhalationstherapie ist nur die im Bronchialsystem deponierte

	Medikamentenmenge wirksam. Diese hängt stark ab von der individuellen Anatomie der Atemwege, dem Atemmuster, der Partikelgröße und dem Inhalationssystem. Es sollten daher das Inhalations-system und die Schulung individuell an die Bedürfnisse und Fähigkeiten (insbesondere Alter und Koordination) angepasst werden. Darüber hinaus ist es sinnvoll, in der Dauertherapie bei Verwendung mehrerer inhalativer Medikamente für alle Präparate den gleichen Typ von Inhalationssystem einzusetzen. Nach einer initialen Einweisung in die Inhalationstechnik sollte diese in jedem Dokumentationszeitraum mindestens einmal überprüft werden. *Aussagen der eingeschlossenen Leitlinien* 6 der eingeschlossenen Leitlinien (BTS 2007, NICE 2010, ACP 2011, CTS 2011, GOLD 2013 und RNAO 2010) enthalten Empfehlungen zur medikamentösen Therapie der COPD. Der Versorgungsaspekt „Medikamentöse Maßnahmen“ (1.5.7 der DMP-Richtlinie) wurde der Übersichtlichkeit halber in Unterpunkte untergliedert. Im Folgenden werden zunächst allgemeine Empfehlungen zur medikamentösen Therapie beschrieben. Anschließend werden Bronchodilatatoren und Kortikosteroide einzeln, gefolgt von weiteren medikamentösen Maßnahmen, dargestellt. Alle Angaben zur medikamentösen Behandlung von Exazerbationen werden gesondert im Versorgungsaspekt „Exazerbationen / Atemwegsinfekte“ (1.5.7.2 der DMP-Richtlinie) behandelt. *Abgleich mit den Anforderungen der DMP-Richtlinie zu „Allgemeine Aussagen der eingeschlossenen Leitlinien“* Mehrere Leitlinien geben mit überwiegend mittlerer / niedriger GoR- / LoE-Kategorie Empfehlungen zu allgemeinen Aspekten der medikamentösen Therapie. Die Empfehlungen stimmen im Wesentlichen mit der DMP-Richtlinie überein. Es ergibt sich kein Aktualisierungs- bzw. Ergänzungsbedarf. *Abgleich mit den Anforderungen der DMP-Richtlinie zu „Aussagen der eingeschlossenen Leitlinien zu Bronchodilatatoren“* Eine Leitlinie gibt mit hoher LoE-Kategorie die Empfehlung, dass bevorzugt inhalative Zubereitungen in der medikamentösen Therapie eingesetzt werden sollen. Die Leitlinie beinhaltet im Vergleich zur DMP-Richtlinie eine zusätzliche Empfehlung. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden. Eine Leitlinie gibt mit hoher LoE-Kategorie die Empfehlung, dass lang wirksame Anticholinergika und Beta-2-Sympathomimetika kurz wirksamen vorgezogen werden sollen. Die Leitlinie beinhaltet im Vergleich zur DMP-Richtlinie eine zusätzliche Empfehlung. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden. 2 Leitlinien geben mit uneinheitlicher GoR- / LoE-Kategorie und eine Leitlinie ohne Angaben zu GoR und nicht zuordenbarem LoE Empfehlungen zur Kombinationstherapie von lang wirksamen Beta-2-Sympathomimetika mit lang wirksamen Anticholinergika. Die Leitlinien beinhalten im Vergleich zur DMP-Richtlinie zusätzliche Empfehlungen. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden.

	Eine Leitlinie gibt mit hoher GoR-Kategorie Empfehlungen zum Einsatz von Theophyllin in Kombination mit Beta-2-Sympathomimetika oder Anticholinergika, wenn die Monotherapie mit Bronchodilatatoren nicht zur Verbesserung der Symptomatik führt. Die Leitlinie beinhaltet im Vergleich zur DMP-Richtlinie zusätzliche Empfehlungen. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden. *Abgleich mit den Anforderungen der DMP-Richtlinie zu „Aussagen der eingeschlossenen Leitlinien zu Kortikosteroiden"* Eine Leitlinie gibt mit hoher LoE-Kategorie eine negative Empfehlung für die alleinige Monotherapie mit inhalativen Kortikosteroiden. Die Leitlinie enthält im Vergleich zur DMP-Richtlinie eine zusätzliche Empfehlung. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden. Eine Leitlinie gibt mit hoher LoE-Kategorie eine negative Empfehlung zum Einsatz von oralen Kortikosteroiden zur Langzeittherapie. Die Leitlinie beinhaltet im Vergleich zur DMP-Richtlinie eine zusätzliche Empfehlung. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden. Eine Leitlinie gibt mit hoher GoR-Kategorie eine negative Empfehlung zum Einsatz von Kortikosteroiden im Reversibilitätstest zur Voraussage des wahrscheinlichen Therapie-ansprechens. Es handelt sich hierbei um eine im Vergleich zur DMP-Richtlinie zusätzliche Empfehlung. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden.
Gemeinsamer Bundesausschuss (G-BA) [11]. Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Umeclidinium vom 21. Juli 2016	**I. Die Anlage XII wird in alphabetischer Reihenfolge um den Wirkstoff Umeclidinium wie folgt ergänzt:** Zugelassenes Anwendungsgebiet (laut Zulassung vom 28. April 2014): „Incruse® ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt." **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) Erwachsene Patienten mit COPD ab einem mittleren Schweregrad (50 % ≤ FEV1[1] < 80 % Soll)[2]: **Zweckmäßige Vergleichstherapie:** Langwirksame Beta-2-Sympathomimetika oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Tiotropium:** Ein Zusatznutzen ist nicht belegt. b) Bei darüberhinausgehenden Schweregraden (30 % ≤ FEV1 < 50 % Soll bzw. FEV1 < 30 % Soll oder respiratorische Insuffizienz) mit ≥ 2 Exazerbationen pro Jahr: **Zweckmäßige Vergleichstherapie:**

	Langwirksame Beta-2-Sympathomimetika oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen und zusätzlich inhalative Corticosteroide (ICS). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. 1 FEV1: exspiratorische Einsekundenkapazität. 2 Diese Population enthält Patienten mit COPD-Schweregrad II (keine Einschränkung hinsichtlich der Anzahl an Exazerbationen) und Patienten mit COPD-Schweregraden ≥ III mit < 2 Exazerbationen pro Jahr.
Gemeinsamer Bundesausschuss (G-BA), 2016 [9]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Aclidiniumbromid vom 7. April 2016	**I. Die Anlage XII wird wie folgt geändert:** 1. Die Angaben zu Aclidiniumbromid in der Fassung der Beschlüsse vom 21. März 2013 und 20. Juni 2013 (BAnz AT 02.05.2013 B1 bzw. BAnz AT 18.07.2013 B1) werden aufgehoben. 2. Anlage XII wird in alphabetischer Reihenfolge um den Wirkstoff Aclidiniumbromid wie folgt ergänzt: **Zugelassenes Anwendungsgebiet (laut Zulassung vom 20. Juli 2012):** „Eklira® Genuair® / Bretaris® Genuair® wird als bronchodilatatorische Dauertherapie bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD) angewendet, um deren Symptome zu lindern." **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** 1. Erwachsene Patienten mit COPD ab einem mittleren Schweregrad (50 % ≤ FEV11 < 80 % Soll)2: 1 FEV1: exspiratorische Einsekundenkapazität. 2 Diese Population enthält Patienten mit COPD-Schweregrad II (keine Einschränkung hinsichtlich der Anzahl an Exazerbationen) und Patienten mit COPD-Schweregraden ≥ III mit < 2 Exazerbationen pro Jahr. **Zweckmäßige Vergleichstherapie:** Langwirksame Beta-2-Sympathomimetika oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Formoterol:** a. Patienten mit Schweregrad II (50 % ≤ FEV1 < 80 % Soll): **Ein Zusatznutzen ist nicht belegt.** b. Patienten mit Schweregrad III (30 % ≤ FEV1 < 50 % Soll) und < 2 Exazerbationen pro Jahr: **Hinweis auf einen beträchtlichen Zusatznutzen.**

	c. Patienten mit Schweregrad IV (FEV1 < 30 % Soll oder respiratorische Insuffizienz) und < 2 Exazerbationen pro Jahr: **Ein Zusatznutzen gilt als nicht belegt.** 2. Bei darüberhinausgehenden Schweregraden (30 % ≤ FEV1 < 50 % Soll bzw. FEV1 < 30 % Soll oder respiratorische Insuffizienz) mit ≥ 2 Exazerbationen pro Jahr: **Zweckmäßige Vergleichstherapie:** Langwirksame Beta-2-Sympathomimetika oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen und zusätzlich inhalative Corticosteroide (ICS). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen gilt als nicht belegt.
Gemeinsamer Bundesausschuss (G-BA) 2016 [10]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Tiotropium/Olodaterol vom 04. Februar 2016	**Zugelassenes Anwendungsgebiet1** Spiolto® Respimat® ist indiziert als Bronchodilatator zur Dauerbehandlung, um bei erwachsenen Patienten mit chronisch obstruktiver Lungenerkrankung (COPD) die Symptome zu lindern. **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) Erwachsene Patienten mit COPD ab einem mittleren Schweregrad (50 % ≤ FEV12 < 80 % Soll)[3]: **Zweckmäßige Vergleichstherapie:** langwirksame Beta-2-Sympathomimetika oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Tiotropium:** Hinweis für einen geringen Zusatznutzen. b) bei darüberhinausgehenden Schweregraden (30 % ≤ FEV1 < 50 % Soll bzw. FEV1 < 30 % oder respiratorische Insuffizienz) mit ≥ 2 Exazerbationen pro Jahr: **Zweckmäßige Vergleichstherapie:** langwirksame Beta-2-Sympathomimetika oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen und zusätzlich inhalative Corticosteroide (ICS) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Tiotropium und zusätzlich ICS:** Anhaltspunkt für einen geringeren Nutzen. 1 laut Zulassung vom 01. Juli 2015 2 FEV1: exspiratorische Einsekundenkapazität 3 Diese Population enthält Patienten mit COPD-Schweregrad II (keine Einschränkung über die Anzahl der Exazerbationen) und Patienten mit COPD-Schweregraden ≥ III mit < 2 Exazerbationen pro Jahr.

Gemeinsamer Bundesausschuss (G-BA), 2015 [16]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Aclidiniumbromid/Formoterol vom 16. Juli 2015	**Zugelassenes Anwendungsgebiet:** Aclidiniumbromid/Formoterol (Duaklir® Genuair® / Brimica® Genuair®) ist angezeigt zur bronchodilatatorischen Erhaltungstherapie zur Linderung von Symptomen bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD). Teilpopulation a) Patienten mit COPD mit einem mittleren Schweregrad 50 % ≤ FEV1 < 80 % Soll (entspricht Stufe II) **Zweckmäßige Vergleichstherapie:** – langwirksame Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit dem langwirksamen Beta-2-Sympathomimetika Formoterol:** Hinweis für einen geringen Zusatznutzen Teilpopulation b) Patienten mit COPD mit < 2 Exazerbationen pro Jahr, 30 % ≤ FEV1 < 50 % Soll (entspricht Stufe III) **Zweckmäßige Vergleichstherapie:** – langwirksame Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit dem langwirksamen Beta-2-Sympathomimetika Formoterol:** Hinweis für einen beträchtlichen Zusatznutzen Teilpopulation c) Patienten mit COPD mit < 2 Exazerbationen pro Jahr, ≤ FEV1 < 30 % Soll oder respiratorische Insuffizienz (entspricht Stufe IV) **Zweckmäßige Vergleichstherapie:** – langwirksame Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit dem langwirksamen Beta-2-Sympathomimetika Formoterol:** Ein Zusatznutzen ist nicht belegt Teilpopulation d) Patienten mit einer über einen mittleren Schweregrad hinausgehenden COPD 30 % ≤ FEV1 < 50 % Soll bzw. FEV1 < 30 % oder respiratorische Insuffizienz (entspricht Stufe III und IV) mit ≥ 2

	Exazerbationen pro Jahr **Zweckmäßige Vergleichstherapie:** – langwirksame Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksame Anticholinergika (Tiotropium) oder die Kombination beider Wirkstoffklassen, zusätzlich inhalative Corticosteroide (ICS) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit dem langwirksamen Beta-2-Sympathomimetika Formoterol und zusätzlich ICS:** Ein Zusatznutzen ist nicht belegt
Gemeinsamer Bundesausschuss (G-BA), 2015 [17]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Umeclidinium/Vilanterol vom 8. Januar 2015	**Zugelassenes Anwendungsgebiet:** ANORO® ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt. a) Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) ab einem mittleren Schweregrad (50 % ≤ FEV1 < 80 % Soll) Die zweckmäßige Vergleichstherapie für die Wirkstoffkombination Umeclidinium/Vilanterol als bronchodilatatorische Dauertherapie bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD) ab einem mittleren Schweregrad (50 % ≤ FEV1 < 80 % Soll), ist: - langwirksame Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder - langwirksame Anticholinergika (Tiotropium) oder - die Kombination beider Wirkstoffklassen **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Umeclidinium/Vilanterol gegenüber Tiotropium:** Ein Zusatznutzen ist nicht belegt. b) Patienten mit COPD mit darüberhinausgehenden (siehe a)) Schweregraden (30 % ≤ FEV1 < 50 % Soll bzw. FEV1 < 30 % oder respiratorische Insuffizienz) mit ≥ 2 Exazerbationen pro Jahr Die zweckmäßige Vergleichstherapie für die Wirkstoffkombination Umeclidinium/Vilanterol als bronchodilatatorische Dauertherapie bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD) mit darüberhinausgehenden (Siehe a)) Schweregraden (30 % ≤ FEV1 < 50 % Soll bzw. FEV1 < 30 % oder respiratorische Insuffizienz) mit ≥ 2 Exazerbationen pro Jahr, ist: - zusätzlich inhalative Corticosteroide (zu langwirksamen Beta-2-Sympathomimetika [Formoterol oder Salmeterol] oder langwirksamen Anticholinergika [Tiotropium] oder der Kombination beider Wirkstoffklassen) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens von**

	Umeclidinium/Vilanterol gegenüber der zweckmäßigen Vergleichstherapie: Der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie gilt als nicht belegt.
G-BA, 2017 [18]. Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Abs. 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) … in Kraft getreten am 1. Januar 2017	**Anlage 11 Anforderungen an das strukturierte Behandlungsprogramm für Patientinnen und Patienten mit chronisch obstruktiver Lungenerkrankung (COPD)** *1.5 Therapeutische Maßnahmen* 1.5.8 Medikamentöse Maßnahmen Zur medikamentösen Therapie sind mit der Patientin oder dem Patienten ein individueller Therapieplan zu erstellen und Maßnahmen zum Selbstmanagement zu erarbeiten (siehe auch strukturierte Schulungsprogramme [Nummer 4]). Vorrangig sollen unter Berücksichtigung der Kontraindikationen und der Präferenzen der Patientinnen und Patienten Medikamente verwendet werden, deren positiver Effekt und Sicherheit im Hinblick auf die in Nummer 1.3 genannten Therapieziele in prospektiven, randomisierten, kontrollierten Studien nachgewiesen wurde. Dabei sollen vorrangig diejenigen Wirkstoffe/Wirkstoffgruppen oder Kombinationen bevorzugt werden, die diesbezüglich den größten Nutzen erbringen. Da das Ansprechen auf Medikamente individuell und im Zeitverlauf unterschiedlich sein kann, ist gegebenenfalls ein Auslassversuch unter Kontrolle der Symptomatik und der Lungenfunktion zu erwägen. Sofern im Rahmen der individuellen Therapieplanung andere Wirkstoffgruppen oder Wirkstoffe als die in dieser Anlage genannten verordnet werden sollen, ist die Patientin oder der Patient darüber zu informieren, ob für diese Wirkstoffgruppen oder Wirkstoffe Wirksamkeitsbelege bezüglich der in Nummer 1.3 genannten Therapieziele vorliegen. Ziel der medikamentösen Therapie ist es insbesondere, die Symptomatik (vor allem Husten, Schleimretention und Luftnot) zu verbessern und Exazerbationen zeitnah zu behandeln sowie deren Rate zu reduzieren. In der medikamentösen Behandlung der COPD werden Bedarfstherapeutika (Medikamente, die z. B. bei Atemnot eingenommen werden) und Dauertherapeutika (Medikamente, die als Basistherapie regelmäßig eingenommen werden) unterschieden. Vorrangig sollten folgende Wirkstoffgruppen verwendet werden: 2. Dauertherapie: 2.1. lang wirksames Anticholinergikum, 2.2. lang wirksames Beta-2-Sympathomimetikum, 2.3. Kombination von lang wirksamem Anticholinergikum und lang wirksamem Beta-2-Sympathomimetikum. 2.4. In begründeten Einzelfällen: 2.4.1 inhalative Glukokortikosteroide (bei schwerer und sehr schwerer

	COPD und zwar nur, wenn mindestens 2 Exazerbationen innerhalb von 12 Monaten auftreten oder Zeichen eines Asthma bronchiale bestehen), 2.4.2 Roflumilast für Patienten mit schwerer und sehr schwerer COPD mit Symptomen wie Auswurf und Husten, 2.4.3 Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung) nur, wenn die Wirkung von lang wirksamen Bronchodilatatoren und inhalativen Glukokortikosteroiden unzureichend ist. Bei gehäuft auftretenden Exazerbationen können mukoaktive Substanzen erwogen werden. Ein routinemäßiger Einsatz kann nicht empfohlen werden. In der Inhalationstherapie ist insbesondere die im Bronchialsystem deponierte Medikamentenmenge wirksam. Diese hängt stark ab von der individuellen Anatomie der Atemwege, dem Atemmuster, der Partikelgröße und dem Applikationssystem. Es sollte daher das Applikationssystem und die Schulung individuell an die Bedürfnisse und Fähigkeiten (insbesondere Alter und Koordination) angepasst werden. Darüber hinaus ist es sinnvoll, in der Dauertherapie bei Verwendung mehrerer inhalativer Medikamente für alle Präparate den gleichen Typ von Applikationssystem einzusetzen. Bei Patientinnen und Patienten, bei denen ein Wechsel des Applikationssystems absehbar Probleme bereiten wird, kann bei der Verordnung die Substitution durch Setzen des Aut-idem-Kreuzes ausgeschlossen werden. Nach einer initialen Einweisung in die Applikationstechnik soll diese in jedem Dokumentationszeitraum mindestens einmal überprüft werden.
Gemeinsamer Bundesausschuss (G-BA), 2014 [14]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V und Anlage IX – Festbetragsgruppenbildung Beta2-Sympathomimetika, inhalativ oral, Gruppe 1, in Stufe 2 nach § 35a Absatz 3 in Verbindung mit Absatz 4 Satz 1 SGB V Vom 17. Juli 2014	**I. Die Anlage XII wird in alphabetischer Reihenfolge um den Wirkstoff „Olodaterol“ wie folgt ergänzt:** „Olodaterol Ein medizinischer Zusatznutzen als therapeutische Verbesserung entsprechend § 35 Absatz 1b Satz 1 bis 5 SGB V von Olodaterol gegenüber den anderen Wirkstoffen der Festbetragsgruppe „Beta2-Sympathomimetika, inhalativ oral, Gruppe 1“ in Stufe 2 gilt gemäß § 35a Absatz 1 Satz 4 und 5 SGB V als nicht belegt.“ **II. In Anlage IX der Arzneimittel-Richtlinie wird die Festbetragsgruppe „Beta2-Sympathomimetika, inhalativ oral, Gruppe 1“ in Stufe 2 wie folgt gefasst:** „Stufe: 2 Wirkstoffgruppe: Beta2-Sympathomimetika, inhalativ oral Festbetragsgruppe Nr.: 1 Status: verschreibungspflichtig Wirkstoffe und Vergleichsgrößen: Formoterol (Formoterol hemifumarat-(x)-Wasser): 19 Indacaterol (Indacaterol maleat): 197,5

<table>
<tr><td></td><td>Olodaterol (Olodaterol hydrochlorid): 2,5

Salmeterol (Salmeterol xinofoat): 75,8

Gruppenbeschreibung: inhalative Darreichungsformen

Darreichungsformen: Druckgasinhalation Lösung/Suspension, einzeldosiertes Pulver zur Inhalation, Hartkapseln mit Pulver zur Inhalation, Lösung zur Inhalation, Pulver zur Inhalation“</td></tr>
<tr><td>Gemeinsamer Bundesausschuss (G-BA), 2014 [15].
Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V und Anlage IX – Festbetragsgruppenbildung Kombinationen von Glucocorticoiden mit langwirksamen Beta2-Sympathomimetika, Gruppe 1, in Stufe 3 nach § 35a Absatz 3 in Verbindung mit Absatz 4 Satz 1 SGB V vom 20. März 2014</td><td>I. Die Anlage XII wird in alphabetischer Reihenfolge um die Wirkstoffkombination „Fluticason furoat / Vilanterol“ wie folgt ergänzt:

„Fluticason furoat / Vilanterol

Ein medizinischer Zusatznutzen als therapeutische Verbesserung entsprechend § 35 Absatz 1b Satz 1 bis 5 SGB V der Kombination von Fluticason furoat und Vilanterol gegenüber den anderen Wirkstoffkombinationen der Festbetragsgruppe „Kombinationen von Glucocorticoiden mit langwirksamen Beta2-Sympathomimetika, Gruppe 1“ in Stufe 3 gilt gemäß § 35a Absatz 1 Satz 4 und 5 SGB V als nicht belegt.“

II. In Anlage IX der Arzneimittel-Richtlinie wird die Festbetragsgruppe „Kombinationen von Glucocorticoiden mit langwirksamen Beta2-Sympathomimetika, Gruppe 1“ in Stufe 3 wie folgt gefasst:
<table>
<tr><td colspan="2">„Stufe:</td><td>3</td></tr>
<tr><td colspan="2">Wirkstoffgruppe:</td><td>Kombinationen von Glucocorticoiden mit langwirksamen Beta2-Sympathomimetika</td></tr>
<tr><td colspan="2">Festbetragsgruppe Nr.:</td><td>1</td></tr>
<tr><td colspan="2">Status:</td><td>verschreibungspflichtig</td></tr>
<tr><td>Wirkstoffe und Vergleichsgrößen:</td><td>Wirkstoffe</td><td>Vergleichsgrößen</td></tr>
<tr><td>Beclometasondipropionat + Formoterol

Beclometasondipropionat, wasserfreies Formoterol hemifumarat-(x)-Wasser</td><td>200</td><td>9,82</td></tr>
<tr><td>Budesonid + Formoterol

Formoterol hemifumarat-(x)-Wasser</td><td>501</td><td>12,64</td></tr>
<tr><td>Fluticason furoat + Vilanterol

Vilanterol trifenatat</td><td>150</td><td>25</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Fluticason propionat + Formoterol
Fluticason 17-propionat Formoterol hemifumarat-(x)-Wasser</td><td>283,34</td><td>10,92</td></tr>
<tr><td>Fluticason propionat + Salmeterol
Fluticason 17-propionat Salmeterol xinafoat</td><td>523,78</td><td>92,24</td></tr>
<tr><td colspan="2">Gruppenbeschreibung:</td><td>inhalative Darreichungsformen</td></tr>
<tr><td colspan="2">Darreichungsformen:</td><td>Druckgasinhalation Lösung / Suspension, einzeldosiertes Pulver zur Inhalation, Pulver zur Inhalation“</td></tr>
</table>
</td></tr>
<tr><td>Gemeinsamer Bundesausschuss (G-BA), 2014 [13]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB Indacaterol/ Glycopyrronium vom 8. Mai 2014</td><td>
Zugelassenes Anwendungsgebiet:

Ultibro® Breezhaler®/Xoterna® Breezhaler® ist für die bronchialerweiternde Erhaltungstherapie zur Symptomlinderung bei erwachsenen Patienten mit chronisch-obstruktiver Lungenerkrankung (COPD) angezeigt.

Patienten mit COPD Stufe II

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit langwirksamen Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksamen Anticholinergika (Tiotropium) oder der Kombination beider Wirkstoffklassen:

<u>Anhaltspunkt für einen geringen Zusatznutzen</u>

Patienten mit COPD Stufe III mit höchstens einer Exazerbation pro Jahr

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit langwirksamen Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksamen Anticholinergika (Tiotropium) oder der Kombination beider Wirkstoffklassen:

<u>Hinweis für einen geringen Zusatznutzen</u>

Patienten mit COPD Stufe IV mit höchstens einer Exazerbation pro Jahr

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit langwirksamen Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksamen Anticholinergika (Tiotropium) oder der Kombination beider Wirkstoffklassen:

<u>Ein Zusatznutzen ist nicht belegt.</u>

Patienten mit COPD Stufe III und Stufe IV mit ≥ 2 Exazerbationen pro Jahr
</td></tr>
</table>

	Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie mit langwirksamen Beta-2-Sympathomimetika (Formoterol oder Salmeterol) oder langwirksamen Anticholinergika (Tiotropium) oder der Kombination beider Wirkstoffklassen zusätzlich inhalative Corticosteroide: Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2013 [12]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Aclidiniumbromid vom 21. März 2013	**Zugelassenenes Anwendungsgebiet (Stand: 20.Juli 2012)** Bretaris Genuair / Eklira Genuair wird als bronchodilatatorische Dauertherapie bei Erwachsenen mit chronisch-obstruktiver Lungenerkrankung (COPD) angewendet, um deren Symptome zu lindern.“ **a) Patienten ab Therapiestufe II** zVT: langwirksame Beta-2-Sympathomimetika (Formoterol, Salmeterol) und/oder langwirksame Anticholinergika (Tiotropiumbromid) Das Stufenschema der Nationalen Versorgungsleitlinie (NVL) COPD, Version 1.9, Januar 2012 ist zu berücksichtigen. Ausmaß und Wahrscheinlichkeit des Zusatznutzens: Ein Zusatznutzen ist nicht belegt. **b) Patienten ab Therapiestufe III/IV mit mehr als zwei Exazerbationen** zVT: langwirksame Beta-2-Sympathomimetika (Formoterol, Salmeterol) und/oder langwirksame Anticholinergika (Tiotropiumbromid) und zusätzlich inhalative Corticosteroide Das Stufenschema der Nationalen Versorgungsleitlinie (NVL) COPD, Version 1.9, Januar 2012 ist zu berücksichtigen. Ausmaß und Wahrscheinlichkeit des Zusatznutzens: Ein Zusatznutzen ist nicht belegt.

Rojas-Reyes MX et al. 2016 [33]. Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease	1. Fragestellung To assess relative effects of the following treatments on markers of exacerbations, symptoms, quality of life and lung function in patients with COPD. • Tiotropium plus LABA/ICS versus tiotropium. • Tiotropium plus LABA/ICS versus LABA/ICS.
	2. Methodik Population: with a diagnosis of COPD Intervention/Komparator: Inhaled combination corticosteroid and long-acting beta2-agonist (such as fluticasone/salmeterol, budesonide/formoterol, beclomethasone/formoterol) and tiotropium bromide versus: • inhaled tiotropium bromide alone; or • inhaled corticosteroid and long-acting beta2-agonist combination. Endpunkte: Primary outcomes: Mortality (all-cause), Exercise tolerance, Hospital admissions: all-cause and due to exacerbations, Exacerbations: all-cause, requiring short burst oral corticosteroids or antibiotics as defined by agreed criteria, Health-related quality of life (measured with a validated scale for COPD, e.g. St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRQ)), Serious adverse events non-fatal, Pneumonia. Secondary outcomes: Symptoms, Forced expiratory volume in one second (FEV1), Adverse events, Side effects, Cost-effectiveness of interventions Suchzeitraum (for this update): July 2010 to April 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 6/1 902 Qualitätsbewertung: Cochrane Risk of Bias Tool, GRADE
	3. Ergebnisdarstellung **Tiotropium plus LABA/ICS versus tiotropium** • all studies with low risk of bias • no statistically significant differences in mortality (two studies; 961 participants) • reduction in all-cause hospitalisations with the use of combined therapy (tiotropium + LABA/ICS): OR 0.61, 95% CI 0.40 to 0.92; two studies; 961 participants; number needed to treat for an additional beneficial outcome (NNTB) 19.7, 95% CI 10.75 to

	123.41; moderate quality of evidence (downgraded because of study limitations: incomplete outcome assessment in 1 study) • effect on exacerbations heterogeneous among trials, not meta-analysed • Health-related quality of life measured by St. George's Respiratory Questionnaire (SGRQ): statistically significant improvement in total scores with use of tiotropium + LABA/ICS compared with tiotropium alone (mean difference (MD) -3.46, 95% CI -5.05 to -1.87; four studies; 1446 participants); low quality of evidence (downgraded because of study limitations: unclear risk of selection bias and detection bias and incomplete outcome assessment in 1 study; unclear risk of detection bias in 1 study; incomplete outcome assessment in 1 study) • exercise tolerance not as an outcome assessed • pooled estimates did not show statistically significant differences in adverse events, serious adverse events, pneumonia **Tiotropium plus LABA/ICS versus LABA/ICS** • 1 of six studies (60 participants) also compared combined therapy (tiotropium + LABA/ICS) versus LABA/ICS therapy alone • study was affected by lack of power; therefore results did not allow to draw conclusions for this comparison
	4. Fazit der Autoren In this update we found new moderate-quality evidence that combined tiotropium + LABA/ICS therapy compared with tiotropium plus placebo decreases hospital admission. Low-quality evidence suggests an improvement in disease-specific quality of life with combined therapy. However, evidence is insufficient to support the benefit of tiotropium + LABA/ICS for mortality and exacerbations (moderate and low-quality evidence, respectively). Of note, not all participants enrolled in the included studies would be candidates for triple therapy according to current international guidance. Compared with the use of tiotropium plus placebo, tiotropium + LABA/ICS-based therapy does not increase undesirable effects such as adverse events or serious non-fatal adverse events. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Farne HA, Cates CJ, 2015 [6]. Long-acting beta2-agonist in addition to	1. Fragestellung To compare the relative effects on markers of quality of life, exacerbations, symptoms, lung function and serious adverse events in people with COPD randomised to LABA plus tiotropium versus tiotropium alone; or LABA plus tiotropium versus LABA alone.
	2. Methodik

tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease.	Population: with diagnosis of COPD Intervention/Komparator: inhaled LABA in addition to tiotropium bromide compared to inhaled tiotropium bromide alone or inhaled LABA alone; any formulation of LABA and tiotropium bromide allowed, ICS and other comedications allowed (not part of the randomised treatment) Endpunkte: • Primary outcomes: Quality of life (measured with a validated scale for COPD, e.g. St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRQ)), hospital admissions (all cause and due to exacerbations), mortality (all-cause), disease-specific mortality (if independently adjudicated) • Secondary outcomes: exacerbations (requiring short burst oral corticosteroids or antibiotics, or both), FEV1, symptoms, all-cause non-fatal serious adverse events, disease-specific serious adverse events (if independently adjudicated) Suchzeitraum: search period for this update is January 2012 to July 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 10/10 894 Qualitätsbewertung der Studien: gemäß Cochrane, GRADE
	3. Ergebnisdarstellung • all trials compared tiotropium in addition to LABA to tiotropium alone • four trials additionally compared LAMA plus LABA with LABA alone • four studies used LABA olodaterol, three used indacaterol, two used formoterol, one used salmeterol **Health-related quality of life (St George's Respiratory Questionnaire (SGRQ)** • tiotropium alone vs. tiotropium plus LABA (6 709 participants; 5 studies): o slightly larger improvement: mean difference (MD) -1.34, 95% confidence interval (CI) -1.87 to -0.80 o MD smaller than the four units that is considered clinically important o responder analysis indicated that 7% more participants receiving tiotropium plus LABA had a noticeable benefit (greater than four units) from treatment in comparison to tiotropium alone o In the control arm in one study, which was tiotropium alone, the SGRQ improved by falling 4.5 units from

	baseline and with tiotropium plus LABA the improvement was a fall of a further 1.3 units (on average). • LABA plus tiotropium vs. LABA alone (3 378 participants; 4 studies): o small but significant improvement in SGRQ (MD -1.25, 95% CI -2.14 to -0.37 o although difference smaller than four units, still an increase of 10 people with a clinically important improvement for 100 treated represented **hospital admission or mortality** • no significant differences **exacerbations, symptom scores, serious adverse events, and withdrawals** • tiotropium alone vs. tiotropium plus LABA: no significant differences with moderate heterogeneity for both exacerbations and withdrawals • LABA plus tiotropium vs. LABA alone (3 514 participants; 3 studies): improvement in exacerbation rates: odds ratio (OR) 0.80, 95% CI 0.69 to 0.93.
	4. Fazit der Autoren: The results from this review indicated a small mean improvement in health-related quality of life and FEV1 for participants on a combination of tiotropium and LABA compared to either agent alone, and this translated into a small increase in the number of responders on combination treatment. In addition, adding tiotropium to LABA reduced exacerbations, although adding LABA to tiotropium did not. Hospital admission and mortality were not altered by adding LABA to tiotropium, although there may not be enough data. While it is possible that this is affected by higher attrition in the tiotropium group, one would expect that participants withdrawn from the study would have had less favourable outcomes; this means that the expected direction of attrition bias would be to reduce the estimated benefit of the combination treatment. The results were largely from studies of olodaterol and there was insufficient information to assess whether the other LABAs were equivalent to olodaterol or each other. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)* • *vier verschiedene LABAs angewendet (salmeterol, formoterol, indacaterol, olodaterol)* • *Olodaterol am häufigsten in den Studien eingesetzt* • *there was insufficient information to assess whether the other*

	LABAs were equivalent to olodaterol or each other • *hohe Fallzahlverluste schränken Vertrauen in die Effektschätzer zu health-related quality of life, hospital admission, mortality ein (moderate quality of evidence - GRADE)*
Geake JB et al. 2015 [8]. Indacaterol, a once-daily beta2-agonist, versus twice-daily beta2-agonists or placebo for chronic obstructive pulmonary disease.	1. Fragestellung To compare the efficacy and safety of indacaterol versus placebo and alternative twice-daily long-acting beta2-agonists for the treatment of patients with stable COPD.
	2. Methodik Population: Adults older than 18 years with a confirmed spirometric diagnosis of COPD. Intervention: once-daily indacaterol at any dose Komparator: Placebo or twice-daily long-acting beta2-agonists Endpunkte: • Primary endpoints: FEV1, QoL, number of participants with a clinically significant improvement in quality of life • Secondary endpoints: 1. Peak FEV1, mean difference in dyspnea, number of participants experiencing a clinically significant improvement in dyspnea, serious adverse events, mortality, number of participants experiencing at least one protocol defined exacerbation. Suchzeitraum: We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), handsearched respiratory journals and meeting abstracts and searched the Novartis trials registry and ClinicalTrials.gov. The date of the most recent search was 8 November 2014. Anzahl eingeschlossene Studien/Patienten (Gesamt): 13/9 961 participants Qualitätsbewertung der Studien: gemäß Cochrane Hetrogenität: ….
	3. Ergebnisdarstellung *(<u>Hinweis</u>: fokussierte Darstellung auf direkte Vergleiche!)* • 10 (8 562 participants) on indacaterol vs. placebo comparison • 5 trials (4 133 participants) on indacaterol vs. twice-daily beta2-agonist comparison (salmeterol, formoterol and eformoterol) • 1 trial (90 participants) provided no data to be used in this review • 2 trials included both indacaterol versus placebo and indacaterol versus twice-daily beta2-agonist comparisons • trials between 12 weeks and 52 weeks in duration • quality of the evidence was strong, and risk of significant bias was

	minimal in most of the included studies **QoL** • Differences between indacaterol and twice-daily beta2-agonists in mean SGRQ scores (MD -0.81, 95% CI -2.28 to 0.66) and in the proportions of participants achieving clinically relevant improvements in SGRQ scores (OR 1.07, 95% CI 0.87 to 1.32) were not statistically significant, but the confidence intervals are too wide to permit the conclusion that the treatments were equivalent. **exacerbations** • Data were insufficient for analysis of differences in exacerbation rates for both placebo and twice-daily beta2-agonist comparisons.
	4. Fazit der Autoren: For patients with stable COPD, use of indacaterol versus placebo results in statistically significant and clinically meaningful improvements in lung function and quality of life. The clinical benefit for lung function is at least as good as that seen with twice-daily long-acting beta2-agonists. The comparative effect on quality of life remains uncertain, as important differences cannot be excluded. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Cheyne L et al. 2015 [2]. **"Review content assessed as up-to-date"** **Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease**	1. Fragestellung To compare the relative effects of tiotropium to ipratropium bromide on markers of quality of life, exacerbations, symptoms, lung function and serious adverse events in patients with COPD using available randomised controlled trial data.
	2. Methodik Population: We included adult patients with a diagnosis of COPD Intervention: tiotropium Komparator: ipratropium bromide; Participants were allowed inhaled steroids and other co-medications provided they were not part of the randomized treatment. Endpunkte: Lungenfuktion (FEV1), All-cause non-fatal serious adverse events (SAEs) , Hospital admissions (all-cause and due to exacerbations), Mortality (all-cause) Lebensqualität (SGRQ oder CRQ) Suchzeitraum: bis August 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 (n=1 073)
	3. Ergebnisdarstellung **all-cause non-fatal serious adverse events** (2 trials, n=1073)

	There were fewer people experiencing one or more non-fatal serious adverse events on tiotropium compared to ipratropium (odds ratio (OR) 0.50; 95% CI 0.34 to 0.73) **mortality, all-cause** (2 trials, n=1073) There was no statistically significant difference in the number of deaths between tiotropium and ipratropium (OR 1.39; 95% CI 0.44 to 4.39, moderate quality evidence) **Hospital admissions** • both studies reported fewer hospital admissions in the tiotropium group (OR 0.34; 95% CI 0.15 to 0.70, moderate quality evidence) • both studies reported fewer patients experiencing one or more exacerbations leading to hospitalisation in the people on tiotropium in both studies (OR 0.56; 95% CI 0.31 to 0.99, moderate quality evidence) **Lebensqualität** • 1 study measured quality of life using the St George's Respiratory Questionnaire (SGRQ) • mean SGRQ score at 52 weeks was lower in the tiotropium group than the ipratropium group (lower on the scale is favourable) (MD -3.30; 95% CI -5.63 to -0.97, moderate quality evidence) **exacerbations** • fewer participants suffering one of more exacerbations in the tiotropium arm (OR 0.71; 95% CI 0.52 to 0.95, high quality evidence) • reported difference in mean number of exacerbations per person per year which reached statistical significance (MD -0.23; 95% CI -0.39 to -0.07, P = 0.006, moderate quality evidence) **withdrawals** (2 trials, n=1073) • significantly fewer withdrawals from the tiotropium group (OR 0.58; 95% CI 0.41 to 0.83, high quality evidence)
	4. Fazit der Autoren This review shows that tiotropium treatment, when compared with ipratropium bromide, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of COPD), fewer exacerbations of COPD and improved quality of life. There were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable COPD, as proposed in guidelines. A recent large double-blind trial of the two delivery devices found no substantial difference in mortality

	using 2.5 µg or 5 µg of tiotropium via Respimat in comparison to 18 µg via Handihaler. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Ni H et al. 2014 [29]. **Aclidinium bromide for stable chronic obstructive pulmonary disease**	1. Fragestellung To assess the efficacy and safety of aclidinium bromide in stable COPD.
	2. Methodik Population: We included studies involving adults (over 18 years of age) diagnosed with moderate to severe COPD, Participants had evidence of airway obstruction, with clinical presentation of dyspnoea, chronic cough or sputum production Intervention/Komparator: 1. Aclidinium bromide versus placebo 2. Aclidinium bromide versus long-acting beta2-agonist (LABA) 3. Aclidinium bromide versus long-acting muscarinic antagonist (LAMA) Endpunkte: • <u>Primary outcomes:</u> Mortality (all-cause and respiratory); exacerbations requiring a short course of an oral steroid or antibiotic, or both; QoL (St George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Disease Questionnaire (CRQ)) • <u>Secondary outcomes:</u> Change in lung function (FEV1, FEV1/FVC); functional capacity by six-minute walking distance; hospital admissions due to exacerbations or from all causes; improvement in symptoms measured by the Transitional Dyspnoea Index (TDI); adverse events; non-fatal serious adverse events; withdrawals due to lack of efficacy or adverse events Suchzeitraum: Systematic search to 7 April 2014. Anzahl eingeschlossene Studien/Patienten (Gesamt): 12/9 547 Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool
	3. Ergebnisdarstellung **Quality of the evidence** • comparison of aclidinium inhalers and dummy inhalers: confidence that there are benefits in terms of the number of hospitalisations and patients' quality of life • less certain: numbers of flare-ups needing additional drugs and serious side effects • not have enough information to assess any effect on the number of deaths • not have enough information to reliably compare aclidinium with

	tiotropium or formoterol **Mortality/exacerbations** • no difference between aclidinium and placebo in o all-cause mortality (low quality) o number of patients with exacerbations requiring a short course of oral steroids or antibiotics, or both (moderate quality) **Quality of life** • Aclidinium lowered SGRQ total score with a mean difference of -2.34 (95% CI -3.18 to -1.51; I2 = 48%, 7 trials, 4442 participants) compared to placebo • More patients on aclidinium achieved a clinically meaningful improvement of at least four units decrease in SGRQ total score (OR 1.49; 95% CI 1.31 to 1.70; I2 = 34%; number needed to treat (NNT) = 10, 95% CI 8 to 15, high quality evidence) over 12 to 52 weeks than on placebo **Hospitalisations** • Aclidinium reduced number of exacerbations requiring hospitalisation by 4 to 20 fewer per 1000 over 4 to 52 weeks (OR 0.64; 95% CI 0.46 to 0.88; I2 = 0%, 10 trials, 5624 people; NNT = 77, 95% CI 51 to 233, high quality evidence) compared to placebo • no difference in non-fatal serious adverse events (moderate quality evidence) Compared to tiotropium, aclidinium did not demonstrate significant differences for exacerbations requiring oral steroids or antibiotics, or both, exacerbation-related hospitalisations and non-fatal serious adverse events (very low quality evidence). Inadequate data prevented the comparison of aclidinium to formoterol or other LABAs.
	4. Fazit der Autoren: Aclidinium is associated with improved quality of life and reduced hospitalisations due to severe exacerbations in patients with moderate to severe stable COPD compared to placebo. Overall, aclidinium did not significantly reduce mortality, serious adverse events or exacerbations requiring oral steroids or antibiotics, or both. Currently, the available data are insufficient and of very low quality in comparisons of the efficacy of aclidinium versus tiotropium. The efficacy of aclidinium versus LABAs cannot be assessed due to inaccurate data. Thus additional trials are recommended to assess the efficacy and safety of aclidinium compared to other LAMAs or LABAs. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Welsh EJ, Cates CJ, Poole P, 2013 [36].	1. Fragestellung To compare the relative effects of inhaled combination therapy and tiotropium on markers of exacerbations, symptoms, quality of life, lung function, pneumonia and serious adverse events in patients with chronic

Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease	obstructive pulmonary disease.
	2. Methodik Population: with a diagnosis of chronic obstructive pulmonary disease Intervention/Komparator: Inhaled combination corticosteroid and long-acting beta2-agonist (such as fluticasone/salmeterol, budesonide/formoterol, beclomethasone/formoterol) versus inhaled tiotropium bromide. Endpunkte: Primary outcomes: Mortality (all-cause), Hospital admission, Exacerbations; all-cause, requiring short courses of oral corticosteroids or antibiotics as defined by agreed criteria, Pneumonia Secondary outcomes: Quality of life (measured with a validated scale for COPD, e.g. St George's Respiratory Questionnaire, Chronic Respiratory Disease Questionnaire), Symptoms, Forced expiratory volume in one second (FEV1), Non-fatal serious adverse events, Adverse events, Withdrawals Suchzeitraum: latest search in November 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 3/1 528 Qualitätsbewertung: Cochrane Risk of Bias Tool, GRADE
	3. Ergebnisdarstellung • 1 large, two-year trial (INSPIRE) and 2 smaller, shorter trials found • results not pooled: number of withdrawals from each arm of the INSPIRE trial was large and imbalanced, outcome data not collected for patients who withdrew, raising concerns about the reliability of data from this study • INSPIRE: more deaths on tiotropium than on fluticasone/salmeterol (Peto odds ratio (OR) 0.55; 95%confidence interval (CI) 0.33 to 0.93) • number of withdrawals from each of the arms was 11 times larger than the observed number of deaths for participants on fluticasone/salmeterol and seven times larger for participants on tiotropium • INSPIRE: more all-cause hospital admissions in patients on fluticasone/salmeterol than those on tiotropium (Peto OR 1.32; 95% CI 1.04 to 1.67). • INSPIRE: no statistically significant difference in hospital admissions due to exacerbations (primary outcome) • no significant difference in exacerbations in patients on

	fluticasone/salmeterol compared to tiotropium • exacerbations requiring treatment with oral corticosteroids: less frequent in patients on fluticasone/salmeterol (rate ratio 0.81; 95% CI 0.67 to 0.99) • exacerbations requiring treatment with antibiotics: more frequent in patients treated with fluticasone/salmeterol (rate ratio 1.19; 95% CI 1.02 to 1.38) • more cases of pneumonia in patients on fluticasone/salmeterol than in those on tiotropium (Peto OR 2.13; 95% CI 1.33 to 3.40) • Confidence intervals for these outcomes do not reflect the additional uncertainty arising from unknown outcome data for patients who withdrew.
	4. Fazit der Autoren Since the proportion of missing outcome data compared to the observed outcome data is enough to induce a clinically relevant bias in the intervention effect, the relative efficacy and safety of combined inhalers and tiotropium remains uncertain. Further large, long term randomised controlled trials comparing combination therapy to tiotropium are required, including adequate follow-up of all participants randomised (similar to the procedures undertaken in TORCH and UPLIFT). Additional studies comparing alternative inhaled long-acting beta2-agonist/steroid combination therapies with tiotropium are also required.
Nannini LJ et al. 2013 [28]. **Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease**	1. Fragestellung To assess the efficacy and safety of combined long-acting beta2-agonist and inhaled corticosteroid (LABA/ICS) preparations, as measured by clinical endpoints and pulmonary function testing, compared with inhaled corticosteroids (ICS) alone, in the treatment of adults with chronic obstructive pulmonary disease (COPD).
	2. Methodik Population: Adult patients (age >40 years) with known, stable COPD Intervention/Komparator: • Fluticasone propionate/salmeterol (FPS) versus fluticasone propionate (FP) • Budesonide/formoterol (BDF) versus budesonide (BD) • Mometasone furoate/formoterol (MF/F) versus mometasone furoate (MF) Endpunkte: Exazerbationen, Krankenhauseinweisungen, Mortalität, Pneumonierate Lungenfunktion (FEV1), Suchzeitraum bis Juni 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 15 (n=7 814)

	Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool
	3. Ergebnisse **Exacerbation rates** (6 studies: n = 5601) - Pooled results for FPS, BDF and MF/F versus ICS alone A significant reduction was noted in the rate of exacerbations requiring oral corticosteroids with combination therapy when compared with ICS (rate ratio (RR) 0.87; 95% CI 0.80 to 0.94) **Hospitalisations due to COPD exacerbations** (10 studies:n= 7060) - Pooled results for FPS, BDF and MF/F versus ICS alone No significant difference was described between combined LABA/ICS and ICS-alone treatments in hospitalisations due to COPD exacerbations; OR 0.93 (95% CI 0.80 to 1.07) **Mortality**(12 studies; n = 7518) - Pooled results for FPS, BDF and MF/F versus ICS alone When data were combined for both treatments and their respective comparators, the odds of death were significantly lower after combination treatment than after mono-component steroid OR 0.78, (95% CI 0.64 to 0.94) **Pneumonia (**12 studies; n= 7315) - Pooled results for FPS, BDF and MF/F versus ICS alone When data were combined for both treatments and their respective comparators, the odds of pneumonia were not significantly different after combination treatment than after mono-component steroid OR (1.08, 95% CI 0.91 to 1.28)
	4. Anmerkungen der Autoren: Combination ICS and LABA offer some clinical benefits in COPD compared with ICS alone, especially for reduction in exacerbations. This review does not support the use of ICS alone when LABAs are available. Adverse events were not significantly different between treatments. Further long-term assessments using practical outcomes of current and new 24-hour LABAs will help determine their efficacy and safety. For robust comparisons as to their relative effects, long-term head-to-head comparisons are needed. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Nannini LJ et al. 2012 [27].	1. Fragestellung To assess the efficacy of combined inhaled corticosteroids (ICS) and long-acting beta2-agonist (LABA) preparations with LABAs alone in

Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease	adults with COPD.
	2. Methodik Population: erwachsene Patienten (>40 Jahre) mit stabiler COPD (keine Exazerbationen bis vor einem Monat vor Studienbeginn); Geplante Subgruppenanalysen , jedoch nicht durchgeführt. Es wurden allgemein Patienten mit stufenübergreifenden COPD Schweregraden eingeschlossen Intervention/Komparator: 1. Fluticasone and salmeterol (FPS) versus salmeterol 2. Budesonide and formoterol (BDF) versus formoterol Endpunkte: Exazerbationen, Krankenhauseinweisungen, Mortalität, Pneumonierate, Lungenfunktion (FEV1), 6-Minuten Gehstrecke, Lebensqualität, Symptomatik, Notfallmedikation, Nebenwirkungen Suchzeitraum bis November 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 14/11 794
	3. Ergebnisdarstellung Hinweis: 10 Studien zu Fluticason/Salmeterol und 4 Studien zu Budesonid/Formoterol • Signifikante Reduktion hinsichtlich Exazerbationen unter der Kombinationstherapie, wenn verglichen wird gegen LABA alleine (9 Studien, n= 9921; RR: 0,76; 95%KI: 0,68-0,84). • Es wurden keine signifikanten Unterschiede zwischen den Studien zu Fluticason/Salmeterol und Budenosid/Formoterol gefunden. • Es wurde kein Unterschied hinsichtlich der Mortalität und Krankenhauseinweisungen gezeigt. • Pneumonien traten signifikant häufiger unter der Kombinationstherapie auf (12 Studien, N=11.076 Pat; OR: 1.55; 95%KI: 1.20-2.01). Unter der Kombinationstherapie wurde eine signifikante Verbesserung der Lebensqualität (keine gepoolten Ergebnisse) sowie der Lungenfunktion (FEV1) gezeigt (keine gepoolten Ergebnisse).
	4. Anmerkungen/Fazit der Autoren Concerns over the analysis and availability of data from the studies bring into question the superiority of ICS/LABA over LABA alone in preventing exacerbations. The effects on hospitalisations were inconsistent and require further exploration. There was moderate quality evidence of an increased risk of pneumonia with ICS/LABA. There was moderate quality evidence that treatments had similar effects on mortality. Quality of life, symptoms score, rescue medication use and FEV1 improved more on ICS/LABA than on LABA, but the average differences were probably not clinically significant for these outcomes. To an individual patient the

	increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations. More information would be useful on the relative benefits and adverse event rates with combination inhalers using different doses of inhaled corticosteroids. Evidence from head-to-head comparisons is needed to assess the comparative risks and benefits of the different combination inhalers. *5. Hinweise durch FB Med* • *Effekt auf Krankenhauseinweisungen war inkonsistent.* • *Unterschiedliche Dosierungen.* • *Unterschiedlichen Kombinationen.* • *Wenig Studien zu Budesonid/Formoterol.* • *Verschiedene primäre Endpunkte.* • *Unterschiedliche Schweregrade der COPD, nicht stratifiziert.* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Chong J et al. 2012 [3]. **Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease**	1. Fragestellung To compare the relative clinical effects of tiotropium bromide alone versus LABA alone, upon measures of quality of life, exacerbations, lung function and serious adverse events, in people with stable COPD.
	2. Methodik Population Patienten mit COPD Intervention (inhalatives) Tiotropium vs. Komparator: LABAs (Begleitherapie war erlaubt.) Endpunkte: Lebensqualität (gemessen mit validierten Messinstrumenten z.B. SGRQ), Exacerbations, Mortality (all-cause) Hospital admissions; all-cause and due to exacerbations, Disease-specific mortality, if independently adjudicated, FEV1, All-cause, non-fatal serious adverse events Withdrawals, Cost and cost-effectiveness Suchzeitraum bis Feb. 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7(n=12.223)
	3. Ergebnisdarstellung • In the analysis of the primary outcomes in this review, a high level of heterogeneity amongst studies meant that we did not pool data for St George's Respiratory Questionnaire quality of life score. Subgroup analyses based on the type of LABA found statistically significant differences among effects on quality of life depending on whether tiotropium was compared with salmeterol, formoterol or indacaterol. • Tiotropium reduced the number of participants experiencing one or more exacerbations compared with LABA (odds ratio (OR) 0.86; 95% confidence interval (CI) 0.79 to 0.93). For this outcome, there was no difference seen among the different types of LABA. • There was no statistical difference in mortality observed between the treatment groups.

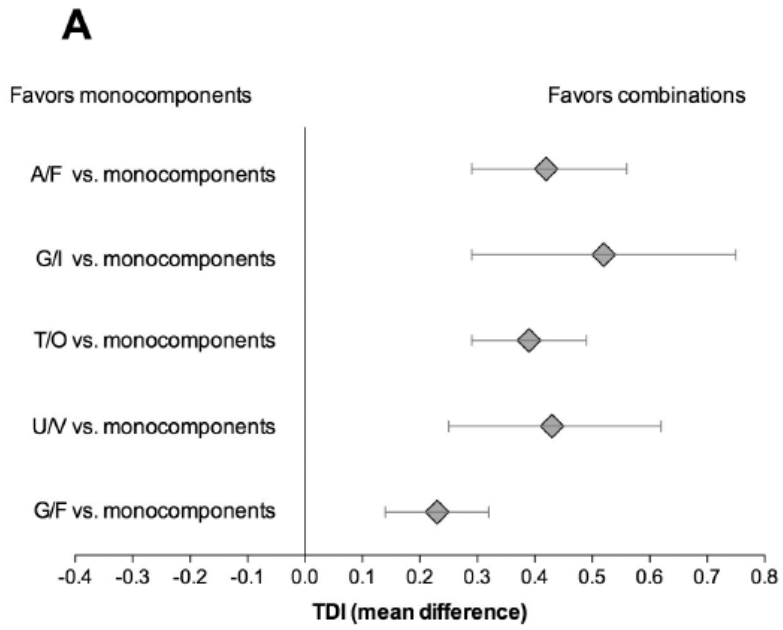
	• For secondary outcomes, tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalization compared with LABA treatment (OR 0.87; 95% 0.77 to 0.99), but not in the overall rate of all-cause hospitalisations. There was no statistically significant difference in forced expiratory volume in one second (FEV1) or symptom score between tiotropium and LABA treated participants. There was a lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABA (OR 0.88; 95% CI 0.78 to 0.99). The tiotropium group was also associated with a lower rate of study withdrawals (OR 0.89; 95% CI 0.81 to 0.99).
	4. Anmerkungen/Fazit der Autoren In people with COPD, the evidence is equivocal as to whether or not tiotropium offers greater benefit than LABAs in improving quality of life; however, this is complicated by differences in effect among the LABA types.Tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalisations, although there were no statistical differences between groups in overall hospitalisation rates or mortality during the study periods. There were fewer serious adverse events and study withdrawals recorded with tiotropium compared with LABAs. Symptom improvement and changes in lung function were similar between the treatment groups. Given the small number of studies to date, with high levels of heterogeneity among them, one approach may be to give a COPD patient a substantial trial of tiotropium, followed by a LABA (or vice versa), then to continue prescribing the long-acting bronchodilator that the patient prefers. Further studies are needed to compare tiotropium with different LABAs, which are currently ongoing. The available economic evidence indicates that tiotropium may be cost-effective compared with salmeterol in several specific settings, but there is considerable uncertainty around this finding. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Spencer S et al. 2011 [34]. **Inhaled corticosteroids versus long-acting beta2-agonists for chronic obstructive**	1. Fragestellung To determine the relative effects of inhaled corticosteroids and long-acting beta2-agonists on clinical endpoints in patients with stable COPD.
	2. Methodik Population Erwachsene COPD Patienten (Schweregrad: stufenübergreifend) Intervention/Komparator: ICS vs inhalative LABA (Formoterol vs. Beclomethason; Formoterol vs. Budesonid; Formoterol vs. Ciclesonid;

pulmonary disease	Formoterol vs. Fluticason; Formoterol vs. Mometason; Formoterol vs. Triamcinolon; Salmeterol vs. Beclomethason; Salmeterol vs. Budesonid; Salmeterol vs.Ciclesonid; Salmeterol vs.Fluticason; Salmeterol vs. Mometason; Salmeterol vs. Triamcinolon) Hinweis: langwirksame Anticholinerika wie Tiotropium, waren als Begleitmedikation erlaubt. Endpunkte: Exazerbationen, Hospitalisierungen aufgrund von Exazerbationen, Pneumonien, Gesamtmortalität, Lungenfunktion (FEV1), Lebensqualitätsparameter, Symptomatik, Notwendigkeit einer Notfallmedikation, Nebenwirkungen, Hospitalisierungen (jede Ursache), Studienabbrüche Suchzeitraum bis Aug. 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7/5 997
	3. Ergebnisdarstellung • Pneumonien: Stat. signifikant mehr Pneumonien als Nebenwirkung (OR: 1.38; 95% KI: 1.10-1.73) und als schwere Nebenwirkungen (OR: 1.48; 95%KI: 1.13 - 1.93) unter der ICS, wenn verglichen wird mit LABA. • Lebensqualität: Stat. signifikant größere Verbesserung unter einer Kortikosteroidtherapie (MD -0.74; 95% CI -1.42 to -0.06). • Andere Endpunkte: Keine stat. signifikanten Unterschiede zwischen den Interventionen, hinsichtlich der anderen Endpunkte.
	4. Fazit der Autoren: This review supports current guidelines advocating long-acting beta-agonists as frontline therapy for COPD, with regular inhaled corticosteroid therapy as an adjunct in patients experiencing frequent exacerbations. *5. Hinweise durch FB Med:* *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Karner C, Cates CJ, 2011 [23].	1. Fragestellung To assess the relative effects of adding inhaled corticosteroids to tiotropium and long-acting beta2-agonists treatment in patients with chronic obstructive pulmonary disease.

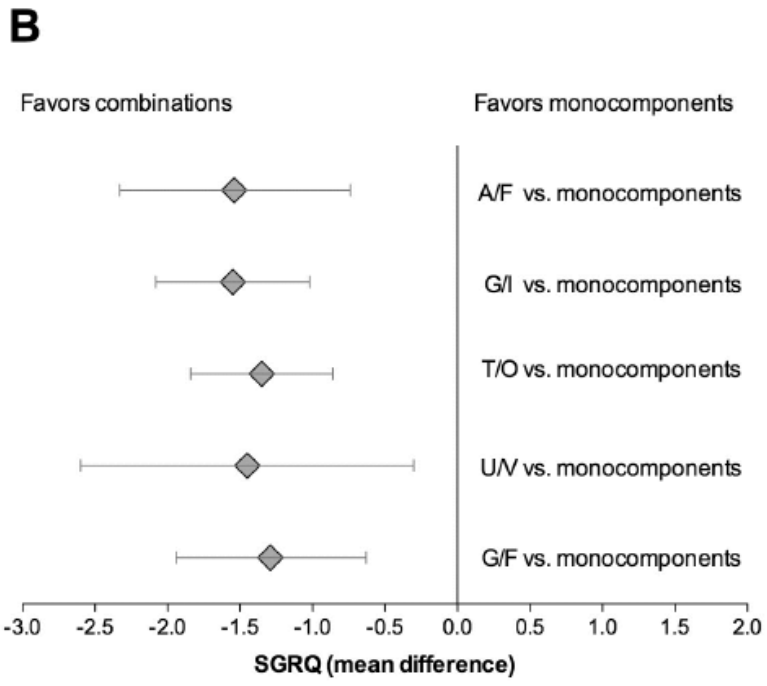
The effect of adding inhaled corticosteroids to tiotropium and long-acting beta2-agonists for chronic obstructive pulmonary disease	2. Methodik Population: patients with chronic obstructive pulmonary disease (COPD) Intervention/Komparator: inhaled corticosteroid (ICS) and long-acting beta2-agonist (LABA) combination therapy in addition to inhaled tiotropium against tiotropium and long-acting beta2-agonist (LABA) treatment Endpunkte: Primary outcomes: Quality of life (measured with a validated scale for COPD, e.g. St George's Respiratory Questionnaire, Chronic Respiratory Disease Questionnaire), Exacerbations, requiring short burst oral corticosteroids or antibiotic, or both; Pneumonia; Mortality, all-cause Secondary outcomes: Hospital admissions, all causes and due to exacerbations; Disease specific mortality, if independently adjudicated; Forced expiratory volume in one second (FEV1); Serious adverse events, all-cause, non-fatal; Withdrawals Suchzeitraum: in February 2011 Eingeschlossene Studien/Patienten (gesamt): 1/293 Qualitätsbewertung: Cochrane Risk of Bias Tool, GRADE
	3. Ergebnisdarstellung • study was of good methodological quality • but high and uneven withdrawal rates between the treatment arms • substantial uncertainty regarding the difference in effect of tiotropium + LABA and ICS and the tiotropium + LABA treatments on quality of life (MD -1.02; 95% CI -5.10 to 3.06) • considerable uncertainty and no statistically significant difference in the number of patients who had one or more exacerbations, pneumonia, mortality between the tiotropium + LABA and ICS (87/145) and the tiotropium + LABA (96/148) groups • no statistically significant difference in the number of patients admitted to hospital due to exacerbation or any cause, exacerbations, non-fatal serious adverse events, adverse events
	4. Fazit der Autoren The relative efficacy and safety of adding inhaled corticosteroid to tiotropium and a long-acting beta2-agonist for chronic obstructive pulmonary disease patients remains uncertain and additional trials are required to answer this question. *5. Hinweise durch FB Med:* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*

Systematische Reviews

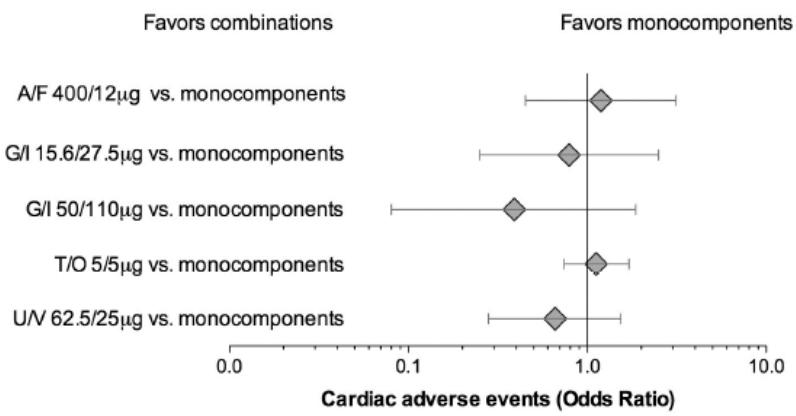
Calzetta L et al. 2016 [1]. **A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable chronic obstructive pulmonary disease**	1. Fragestellung Therefore, we carried out a systematic review with meta-analysis that incorporated the data from trials lasting at least 3 months to evaluate the effectiveness of LAMA/LABA FDCs for COPD treatment.
	2. Methodik Population: patients with COPD diagnosed by pulmonary function testing (PFT) Intervention: inhalant administration of LAMA/LABA combinations Komparator: at least one mono component Endpunkt: trough FEV1, transition dyspnea index (TDI), St. George's Respiratory Questionnaire (SGRQ), cardiac adverse events Study type: RCT Suchzeitraum: up to October 1 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 22/23 168 COPD patients (combinations, n = 10 328; 160 mono components, n = 12 840) Qualitätsbewertung der Studien: Jadad score (scale of 1 to 5, score of 5 being the highest), RCTs with Jadad score ≥3 included in meta-analysis Homogenität: moderate to high levels of heterogeneity considered for I2>50% publication bias: assessed by funnel plot and Egger’s test
	3. Ergebnisdarstellung • 14 published papers and 1 abstract presented at ERS Congress (Amsterdam, 2015) • 2 studies used aclidinium and formoterol • 3 studies used tiotropium and olodaterol • 4 studies used glycopyrronium and indacaterol • 5 studies used umeclidinium and vilanterol • 1 study used glycopyrronium and formoterol **Influence of LAMA/LABA combinations on TDI and SGRQ score vs. mono components**



- significant funnel plot asymmetry detected for the impact of aclidinium/formoterol and tiotropium/olodaterol combinations on TDI
- smaller studies showed less beneficial effect for aclidinium/formoterol combination (Egger's test P<0.1)
- smaller studies reported larger protective effect for tiotropium/olodaterol combination (Egger's test P<0.05)



Influence of LAMA/LABA combinations on cardiac adverse events vs. mono components

	B 
	4. Anmerkungen/Fazit der Autoren The gradient of effectiveness emerging from this meta-analysis is merely a weak indicator of possible differences between the various LAMA/LABA FDCs. Only direct comparisons will document if a specific LAMA/LABA FDC is better than the other. In the meanwhile, we think it is only proper consider the dual bronchodilation better than a LAMA or a LABA alone, regardless of drugs used. *5. Hinweise durch FB Med* • *No sponsor had a role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.* • *Interessenkonflikterklärungen liegen vor* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)* • *Jadad-Score weniger geeignet zur Bewertung des Verzerrungsrisikos*
Tricco AC et al. 2015 [35]. **Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis**	1. Fragestellung Our research question was 'What is the comparative safety and effectiveness of long-acting inhaled agents (ICS, LABA, LAMA), alone or in any combination, for patients with COPD?'
	2. Methodik Population: adults with COPD Intervention/ Komparator: long-acting inhaled agent in any combination compared with each other or placebo; concomitant COPD medications included if both groups received the same interventions (eg, rescue medication with a short acting β-agonist) Endpunkte: o primary outcome: proportion of patients with moderate-to-severe exacerbations (ie, worsening of COPD symptoms that may require hospitalisation, emergency department visits, treatment with oral steroids and/or antibiotics, use of rescue medication, or unscheduled visits to a walk-in clinic or to a healthcare provider)

	o secondary outcomes: number of patients experiencing mortality, pneumonia, serious arrhythmia, cardiovascular-related mortality (CVM) Suchzeitraum: until December 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 208 RCTs/134 692 Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool Zentrale Annahmen: untersucht und adäquat berücksichtigt Publication bias: inspection of funnel plots
	3. Ergebnisdarstellung (siehe auch Abbildungen im Anhang) • many trials were at a high risk of bias for many of the criteria o unclear random sequence generation: 63% o unclear allocation concealment: 84% o unclear selective outcome reporting: 55% o high (52%) or unclear (39%) risk of bias due to the 'other bias' item: mainly funding bias (many studies funded by a pharmaceutical company and included study authors who were employed by the drug manufacturer) • NMA for moderate-to-severe exacerbations: 20 RCTs, 26 141 patients with an exacerbation in the past year • 32 treatments effective versus placebo: o tiotropium, o budesonide/formoterol, o salmeterol, indacaterol, o fluticasone/salmeterol, o indacaterol/glycopyrronium, o tiotropium/fluticasone/salmeterol, o tiotropium/budesonide/formoterol • tiotropium/budesonide/formoterol most effective: 99,2% probability of being the most effective according to the Surface Under the Cumulative RAnking (SUCRA) curve • NMA on mortality: 88 RCTs, 97 526 patients o fluticasone/salmeterol more effective than placebo, formoterol and fluticasone alone • fluticasone/salmeterol most effective: SUCRA=71% • NMA on cardiovascular-related mortality (CVM): 37 RCTs, 55 156 patients o safest: salmeterol versus each OF placebo, tiotropium and tiotropium (Soft Mist Inhaler (SMR)); fluticasone versus tiotropium (SMR); and salmeterol/fluticasone versus tiotropium

	and tiotropium (SMR) • Triamcinolone acetonide most harmful: SUCRA=81% • NMA on pneumonia occurrence: 54 RCTs, 61 551 patients o 24 treatments more harmful, including 2 that increased risk of pneumonia versus placebo; fluticasone and fluticasone/salmeterol • most harmful: fluticasone/salmeterol with SUCRA=89% • NMA for arrhythmia: no statistically significant differences between agents identified • We were unable to explore other important effect modifiers, such as duration of treatment administration, as this was inconsistently reported across the included randomised trials. • no evidence for small-study effects and publication bias across all analyses
	4. Fazit der Autoren Many inhaled agents are available for COPD, some are safer and more effective than others. Our results can be used by patients and physicians to tailor administration of these agents. *5. Hinweise durch FB Med* • *Einzelergebnisse aller Studien (Effektschätzer und Konfidenzintervalle) nicht berichtet* • *unklar, ob die angewendeten statistischen Verfahren adäquat waren*
Kim JS et al. 2015 [24]. **Comparison of clinical efficacy and safety between indacaterol and tiotropium in COPD: meta-analysis of randomized controlled trials**	1. Fragestellung This study was performed to compare the clinical efficacy and safety between indacaterol and tiotropium in patients with moderate-to-severe COPD.
	2. Methodik Population: patients with stable moderate to severe COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria Intervention: inhaled indacaterol Komparator: inhaled tiotropium Endpunkt: • primary outcome: comparison of trough (24-h postdose) FEV1 • secondary outcomes: comparison of trough FEV1, St. George`s Respiratory Questionnaire (SGRQ) total score and minimal clinically important difference (MCID) of SGRQ total score at week 26, adverse events (including incidence of any adverse events, nasopharyngitis, cough, COPD worsening, serious adverse events, and serious cardiovascular events - cardiac failure and

	myocardial ischemic disease) Study type: RCTs, at least 12 weeks of follow-up Suchzeitraum: to July 1, 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4/ 6 819 subjects enrolled with 3 407 in the indacaterol 150 µg group and 3 412 subjects inthe tiotropium 18 µg group Qualitätsbewertung der Studien: Cochrane Handbook of Systematic Reviews 5.1. Heterogenität: measured by Higgins and Green I2 test, I2 ranges between 0% (no heterogeneity) and 100% (maximal heterogeneity), heterogeneity considered to be substantial at P < 0.10 and I2 > 50%, heterogeneity explored with sensitivity analysis potential publication bias: Egger's regression test, funnel-plot based Trim and Fill method, P values < 0.05 (two-tailed test) considered significant
	3. Ergebnisdarstellung A high risk of bias for blinding of participants was reported in two studies due to open labeled study (18, 20) 18. Donohue JF, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010; 182: 155–162. 19. Buhl R, et al. Blinded 12-week comparison of oncedaily indacaterol and tiotropium in COPD. Eur Respir J. 2011; 38: 797–803. 20. Bateman ED, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J. 2013; 42: 1484–1494. 21. Decramer ML, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med. 2013; 1: 524–533. **SGRQ** • similar St. George`s Respiratory Questionnaire (SGRQ) total scores and percentages of patients with SGRQ improvement (≥ 4 units) at week 26 • heterogeneity among three studies substantial (Q = 11.13 for 2 df, I2 = 82.0%, P = 0.004), without INVIGORATE study (only severe COPD patients), heterogeneity became 0% and the percentage of patients with MCID in the SGRQ at week 26 was significantly higher in those using indacaterol than in those receiving tiotropium (pooled OR = 1.40, 95% CI, 1.15 to 1.71, P = 0.001) **AEs** • incidences of nasopharyngitis, serious cardiovascular events, and serious adverse events were not different • those of cough (OR = 1.68, P < 0.001, and RR = 1.63) and COPD worsening (OR = 1.18, P = 0.003, and RR = 1.12) were higher for indacaterol than tiotropium • when one study with only severe COPD patients was removed from the meta-analysis, the difference in the incidence of COPD

	worsening between indacaterol and tiotropium became non-significant (OR = 1.13, P = 0.204, and RR = 1.09) • Ergebnisse zur Untersuchung des “publication bias“ nicht berichtet • Heterogenitätsanalysen beschrieben
	4. Anmerkungen/Fazit der Autoren The clinical efficacy and serious adverse events between indacaterol and tiotropium were equivocal in patients with moderate-to-severe COPD. Cough is a common complaint associated with indacaterol, and COPD worsening needs to be carefully monitored in severe COPD patients when treated with indacaterol. *5. Hinweise durch FB Med* • *The authors have no support or funding to report.* • *Competing Interests: Min-Ji Kim is employed by 'Samsung Biomedical Research Institute' and Jung Soo Kim, K. C. Carriere, and Hye Yun Park are employed by 'Samsung Medical Center'. This do not alter the authors' adherence to PLOS ONE policies on sharing data and materials.* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Yan JH et al. 2014 [37]. **Efficacy and safety of roflumilast in patients with stable chronic obstructive pulmonary disease: A meta-analysis.**	1. Fragestellung To assess the efficacy and safety of roflumilast in COPD patients
	2. Methodik Population: patients with diagnosed COPD according to the GOLD guidelines Intervention: Roflumilast 500 mg with or without other pharmacological treatments Komparator: Placebo with or without other pharmacological treatments Endpunkte: • Primary endpoints: forced expiratory volume in 1 s (FEV1) and the mean exacerbation rate (mild, moderate or severe) • Secondary endpoints: postbronchodilator spirometric parameters including FEV1, forced vital capacity (FVC), forced expiratory volume in 6s (FEV6), forced expiratory flow between 25% and 75% of the vital capacity (FEF25%-75%), HRQoL (St George’s Respiratory Questionnaire (SGRQ) total score), the overall mortality rate and adverse events (AEs) Suchzeitraum: from 1980 through November 20th, 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 studies with 9 675 patients (roflumilast vs. placebo: 4955 vs. 4720) including 11 RCTs were selected for this meta-analysis. Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung

	All studies had clearly defined eligibility criteria, therapies, and reasons for patient exclusion except two unpublished RCTs. Allocation sequence generation and concealment were adequately described in 7 studies. Primäre Endpunkte: • roflumilast significantly reduces mean exacerbation rate (WMD =-0.23; 95% CI = -0.33 to -0.13; p < 0.00001; I^2= 18%) • changes of mean exacerbation rate (23%) greater than the MCID of exacerbation rate (≥22%) Sekundäre Endpunkte: • roflumilast failed to improve SGRQ total score • changes of SGRQ total score lower than the MCID (≥4 units) Sicherheit: • overall mortality rate did not differ between roflumilast and placebo • roflumilast associated with increases in o withdrawals due to AEs (RR: 1.62; 95% CI : 1.44 to 1.82; p < 0.00001) o number of patients experiencing any AEs (RR = 1.08; 95% CI = 1.02 to 1.14; p < 0.007) o diarrhoea (RR = 3.75; 95% CI = 2.70 to 5.21; p < 0.00001) o headache (RR= 2.32; 95% CI = 1.79 to 3.02; p < 0.00001) o nausea (RR = 3.16; 95% CI = 2.01 to 4.96; p < 0.00001) o insomnia (RR = 2.41; 95% CI = 1.24 to 4.66; p < 0.009) o weight loss (RR = 4.37; 95% CI = 2.88 to 6.61; p < 0.00001) • roflumilast not associated with changes in nasopharyngitis, upper respiratory tract infection, influenza, and vomiting
	4. Fazit der Autoren Roflumilast significantly reduces the mean exacerbation rate in COPD patients. Although there are insufficient clinical evidence on other clinical endpoints and high risk of some adverse events, roflumilast therapy may benefit COPD patients. Further studies are needed to pay more attention to the long-term efficacy and safety of roflumilast. *5. Hinweise durch FB Med* • *None of the authors have any conflicts of interest to declare.* • *No current external funding sources for this study.* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Rodrigo GJ et al., 2014 [31]. **Efficacy and Safety of a Fixed-Dose Combination of**	1. Fragestellung This systematic review assessed the efficacy and safety of the fixed-dose combination of the long-acting b 2 -agonist indacaterol and long-acting muscarinic antagonist glycopyrronium (QVA149) compared with its monocomponents (glycopyrronium and indacaterol) and tiotropium for the treatment of moderate to severe COPD.

Indacaterol and Glycopyrronium for the Treatment of COPD A Systematic Review	2. Methodik Population: adult patients aged ≥ 40 years with stable moderate to severe COPD according GOLD Intervention: Inhaled QVA149 Komparator: Tiotropium or glycopyrronium or indacaterol Endpunkte: • Primäre Endpunkte: FEV 1 ,serious AEs (SAEs), serious cardiovascular events (SCVEs) as primary outcomes • Sekundäre Endpunkte: Dyspnea (Transition Dyspnea Index [TDI] total score), health status (St. George's Respiratory Questionnaire [SGRQ] total score), rescue medication use, COPD exacerbations, and withdrawals (total and due to AEs) Suchzeitraum: Systematic literature search 2014. Anzahl eingeschlossene Studien/Patienten (Gesamt): 5/4 842 Qualitätsbewertung der Studien: Cochrane instrument
	3. Ergebnisdarstellung All studies showed a low risk of bias. <u>QVA149 vs Tiotropium:</u> • no significant differences in SAEs (13.1% vs 12.3%) and SCVEs (1.7% vs 2.3%), without significant heterogeneity among studies • QVA149 significantly reduced o dyspnea as a mean change from baseline (- 0.63 points of TDI; P<0002) and o the use of rescue medication (- 0.63 puff s/d; P<0001), compared with tiotropium • QVA149 showed a 19% greater likelihood of experiencing a minimal clinical important difference (MCID) in TDI (≥ 1 point), with NNTB =11. • mean change from baseline SGRQ total score significantly higher with QVA149 than tiotropium (-2.64 units; P<.04) • percentage of patients receiving QVA149 with an MCID in the SGRQ (≥4 units of total score) significantly higher, compared with those receiving tiotropium (63.2% vs 54.2%; P<0001; NNTB = 11). • QVA149 reduced number of exacerbations significantly compared with tiotropium, with NNTB = 19 (estimate based on data from two long-term studies) • nonsignificant differences in the rate of o any AE (70.7% vs 69.9%) o total withdrawals (15.7% vs 16.2%) o withdrawals due to AEs (5.7% vs 4.5%) <u>QVA149 vs Glycopyrronium</u> • no significant differences in SAEs (15.7% vs 17.1%) and SCVEs (1.9% vs 2.5%) • QVA149 significantly improved health status more than

	glycopyrronium • significant reductions in the use of rescue medication (-0.59; P<0001), and the SGRQ total score (-2.18 units; P<04) in patients receiving QVA149 • QVA149 significantly increased the rate of patients achieving an MCID in the SGRQ total score (63.2% of patients receiving QVA149 vs 55.0% of those receiving glycopyrronium; P<.04; NNTB= 12) • QVA149 significantly reduced exacerbations compared with glycopyrronium (NNT= 25) • nonsignificant differences in the rate of any AE (78.0% vs 81.1%), total withdrawals (17.3% vs 21.2%), and withdrawals due to AEs (5.4% vs 6.6%). <u>QVA149 vs Indacaterol</u> • 1 trial presented this comparison: no pooled analysis of data • overall incidence of AEs similar across both treatment groups • most frequently reported AE: exacerbation (28.9% and 32.1% in the QVA149 and indacaterol groups, respectively)
	4. Fazit der Autoren: Once-daily, inhaled QVA149 showed superior efficacy compared with glycopyrronium and the current standard of care, tiotropium, in patients with moderate to severe COPD. *5. Hinweise durch FB Med* • *The authors have reported to CHEST the following confl icts of interest: Dr Rodrigo has participated as a lecturer, speaker, and advisor in scientifi c meetings and courses under the sponsorship of Air Products and Chemicals Inc , Almirall SA, AstraZeneca plc, Boehringer Ingelheim GmbH, Esteve SA, GlaxoSmithKline plc, Merck & Co Inc, and Novartis AG. Dr Plaza has participated as a lecturer and speaker in scientifi c meetings and courses under the sponsorship of AstraZeneca plc, GlaxoSmithKline plc, Esteve SA, and Merck & Co Inc.* • *The authors have reported to CHEST that no funding was received for this study.* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)*
Karabis A et al., 2013 [22]. **Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance**	1. Fragestellung The efficacy of aclidinium was compared with tiotropium and glycopyrronium, using a network meta-analysis (NMA) of randomized controlled trials (RCTs) in moderate-to-severe COPD patients.
	2. Methodik Population: Adults with COPD, as defined by GOLD guidelines. Studies with high proportions (30%) of mild and/or very severe patients were excluded. Intervention: aclidinium 400 µg BID, glycopyrronium 50 µg OD, tiotropium 18 µg OD, or tiotropium 5 µg OD, administered using any inhalation

treatment of moderate to severe COPD patients: a systematic review and network meta-analysis	device Komparator: Studies that compare any of the interventions against each other or placebo Endpunkte: FEV1 at 12 weeks and 24 weeks; St George's Respiratory Questionnaire (SGRQ) total score at 12 weeks and 24 weeks; the proportion of patients within each group achieving a clinically meaningful change (at least four units) in SGRQ total score at 12 weeks and 24 weeks; Transition Dyspnea Index (TDI) total score at 12 weeks and 24 weeks; the proportion of patients within each group achieving a clinically meaningful change (at least one unit) in TDI focal score at 12 weeks and 24 weeks Suchzeitraum: from July 1989 to October 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 21/22 542 Qualitätsbewertung der Studien: Jadad Score
	3. Ergebnisdarstellung All studies scored at least 3 out of 5, indicating good-quality RCTs. • aclidinium 400 µg BID (3 studies) • tiotropium 5 µg OD (3 studies) • tiotropium 18 µg OD (13 studies) • glycopyrronium 50 µg OD (2 studies). **Quality of Life** Aclidinium resulted in higher improvement in SGRQ score at 24 weeks, compared to tiotropium 5 µg (difference in CFB, −2.44 [95% CrI −4.82, −0.05]); and comparable results to tiotropium 18 µg (−1.80 [95% CrI −4.52, 0.14]) and glycopyrronium (−1.52 [95% CrI −4.08, 1.03]). **Dyspnea** • Improvements in TDI score were comparable for all treatments.
	4. Fazit der Autoren: Maintenance treatment with aclidinium 400 µg BID is expected to produce similar improvements in lung function, health-related quality of life, and dyspnea compared to tiotropium 5 µg OD; tiotropium 18 µg OD; and glycopyrronium 50 µg OD. *5. Hinweise durch FB Med* • *This study was conducted by MAPI Consultancy on behalf of Almirall SA (Barcelona, Spain) and Forest Research Institute (FRI; Jersey City, NJ, USA), who funded the study and the writing of this manuscript. All authors participated in the design and conduct of the study, as well as drafting and revising the manuscript. Leandro Lindner is an employee of Almirall SA. Michelle Mocarski is an*

	employee of FRI. Andreas Karabis and Eline Huisman are employees of MAPI Consultancy and served as paid consultants to Almirall and FRI during the conduct of this study and the preparation of this manuscript. Andrew Greening has no conflict of interest to declare in this work. • *Almirall pU von Aclidiniumbromid* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)* • *Jadad-Score weniger geeignet zur Bewertung des Verzerrungsrisikos* • *Bayesische Netzwerk-Meta-Analyse mit Markov-Ketten-Monte-Carlo (MCMC)-Simulationen, aber ohne Ergebnisse aus paarweise vergleichenden Meta-Analysen* • *Berichtsqualität ermöglicht keine (abschließende) Bewertung, der Untersuchung der zentralen Annahmen (Ähnlichkeit, Homogenität, Konsistenz) und des adäquaten Umgangs mit den Ergebnissen*
Chung VC et al., 2013 [4]. **Indacaterol for chronic obstructive pulmonary disease: systematic review and meta-analysis**	1. Fragestellung Beyond dosage, answers to three additional questions are needed for clarifying the role of indacaterol in treating stable COPD: What is the comparative effectiveness of indacaterol versus (i) existing b2 agonists of formoterol and salmeterol?; (ii) the anticholinergic tiotropium? (iii) Does the addition of indacaterol to tiotropium offer additional benefits to patients? We attempted to answer these questions by conducting a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy and safety of indacaterol.
	2. Methodik Population: adults with stable COPD Intervention: indacaterol Komparator: control therapies (placebo or other drugs) Endpunkt: change in FEV1 value (with a minimum duration of 12 weeks), exacerbation at or beyond 1 year, changes in Transition Dyspnoea Index (TDI), St George's Respiratory Questionnaire (SGRQ) scoring, and BODE index (with a minimal duration of 6 months) Study type: RCTs Suchzeitraum: till 30 Jan 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12/10 977 Qualitätsbewertung der Studien: Cochrane risk of bias tool

	Heterogenität: chi-squared testes, at a significance level of p= 0.1. I2 statistic was calculated to estimate total variation across studies, I2 ,25% indicator of low heterogeneity level, 25–50% moderate level, higher than 50% high level, heterogeneity explored with sensitivity analysis, random effects meta-analysis separately for each outcome publication bias (for primary outcome of FEV1): Egger's test conducted
	3. Ergebnisdarstellung Risk of bias amongst included studies was mediocre overall (Table 2), with poor reporting on methodological details. **Indacaterol versus Placebo** <u>Changes in SGRQ, TDI, BODE Index, exacerbation rate and worsening of symptoms.</u> • improving of SGRQ scoring above the MID value at 26th week reported by one trial using 150 ug • another trial testing 150 ug and 300 ug did not find clinically relevant improvements at the same time point • indacaterol (150 and 300 ug) improved TDI at 26th and 52nd weeks at its MID value of 1 unit • 6 RCTs reported worsening of COPD symptoms (dyspnea, cough, sputum purulence/volume, or wheeze) at the end of the study • Pooled results (subgroup limited to six trials (n= 2,787) using <150 ug), the RR was 0.84 (95%CI: 0.70 to 1.00, I2 = 0%) **Indacaterol versus other long acting b2 agonist bronchodilators** <u>Changes in SGRQ, TDI and exacerbations.</u> • no clinically relevant difference between salmeterol and indacaterol observed in SGRQ and TDI • differences between formoterol and indacaterol on SGRQ and TDI below MID threshold • No trial under this comparison reported exacerbation rate at one year. **Indacaterol versus Tiotropium** Both estimates were below MID threshold, and similar efficacies between the two drugs were also observed in the outcomes of SGRQ and TDI. **Indacaterol plus Tiotropium versus Tiotropium plus Placebo** None of the pre-specified secondary outcomes were reported in the trials. **Safety** • Indacaterol users significantly more likely to experience nasopharyngitis, compared to placebo (RR = 1.22, 95%CI: 1.01 to 1.47, I2 = 15%) • subgroup analysis: result statistically significant only at dosage >150 ug (RR >150 ug =1.27, 95%CI: 1.04 to 1.54, I2 = 0%; RR

	≤150 ug = 1.24, 95%CI: 0.80 to 1.91) • difference between the two effect sizes was statistically insignificant (p value of In RR = 0.92)
	4. Anmerkungen/Fazit der Autoren Indacaterol is safe and beneficial for patients with COPD at dosage ≤150ug. It may serve as a good alternative to existing bronchodilators, or as an add-on to tiotropium for unresponsive patients. Use of higher dosage requires further justification. *5. Hinweise durch FB Med* • *The authors have no support or funding to report.* • *The authors have declared that no competing interests exist.* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)* • *Ergebnisse bestätigt im CR Geake JB, 2015 (siehe oben)*
Rodrigo GJ et al,. 2012 [32]. **Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: A systematic review**	1. Fragestellung … when symptoms are not adequately controlled with monotherapy, guidelines recommended the addition of a LABA to a LAMA ("dual" long-acting bronchodilator therapy), the addition of an ICS to a LABA ("combined" therapy), or even a LABA plus an ICS to a LAMA ("triple" therapy), although data supporting these different therapeutic approaches are limited to date. The objective of this systematic review is to assess the efficacy of these therapeutic combinations compared with tiotropium monotherapy in COPD patients.
	2. Methodik Population: adult patients aged greater than 40 years with stable COPD satisfying American Thoracic Society/European Respiratory Society, or Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria Intervention: tiotropium plus LABA ("dual" long-acting bronchodilator therapy), LABA plus ICS ("combined" therapy) and tiotropium plus LABA plus ICS ("triple" therapy) Komparator: tiotropium monotherapy Endpunkte: • Primary outcomes: forced volume in the first second (FEV1) (pre and post bronchodilator test), use of rescue medications, health-related quality of life (HRQoL) (St. George Respiratory Questionnaire [SGRQ]), dyspnea, and COPD exacerbations • Secondary outcomes measures: all-cause mortality, withdrawals during treatment period, and severe adverse effects (SAE). A serious adverse event was defined as any untoward medical occurrence that results in sometimes death, is life-threatening, requires inpatient hospitalization, or results in persistent or

	significant disability/incapacity. Studienauswahl: more than 2 weeks of duration, randomized (parallel group or cross sectional) controlled trials without language restriction Suchzeitraum: bis 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 20/6 803 Qualitätsbewertung der Studien: according to recommendations outlined in Cochrane Handbook Heterogeneity: measured by I2 test (<40% might be unimportant, 40%-60% might be moderate, and 60%-100% may be substantial), outcomes with statistically significant differences but with moderate to substantial heterogeneity, 95% predictive intervals were calculated to address the distribution of true effects sizes Publication bias of primary outcomes was evaluated by visual inspection of funnel plots
	3. Ergebnisdarstellung • only four long-term trials (≥24 weeks) • allocation concealment adequate in 8 studies • data were not collected for patients who withdraw in 12 studies • 10 trials were sponsored by the pharmaceutical industry • due to small number of studies, publication bias cannot be excluded Because selected studies differed in the mixes of participants and interventions, a random-effects meta-analysis was performed to address this variation across studies in all outcomes. **Tiotropium plus LABA ("dual" long-acting bronchodilator therapy) compared with tiotropium monotherapy** • 10 trials 14. Aaron SD, et al. Tiotropium in combination with placebo, salmeterol, or fluticasoneesalmeterol for treatment of chronic obstructive pulmonary disease. A randomized trial. Ann Intern Med 2007;146:545e55. 17. Hanania NA, et al. Efficacy and safety of nebulized formoterol as add-on therapy in COPD patients receiving maintenance tiotropium bromide. Results from a 6-week, randomized, placebo-controlled, clinical trial. Drugs 2009;69:1205e16. 23. Novartis. CQAB149B2341 trial. Available from: http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/displayFile.do?trialResult¼3901. [accessed 14.02.11]. 24. Novartis. CQAB149B2351 trial. Available at: http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/displayFile.do?trialResult¼3903. [accessed 14.02.11]. 26. Tashkin DP, et al. Concomitant treatment with nebulized formoterol and tiotropium in subjects with COPD: a placebo-controlled trial. Respir Med 2008;102:479e87. 27. Tashkin DP, et al. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. COPD 2009;6:17e25. 28. Terzano C, et al. Rational timing of combination therapy with tiotropium and formoterol in moderate and severe COPD. Respir Med 2008;102:1701e7. 29. van Noord JA, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J 2005;26: 214e22.

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outcome	references	n	Mean duration, weeks (range)	Measure 95 % CI	p	I2 %	95 % prediction interval
Mean rescue medication (puffs/day)	[17,25 - 30]	1357	10 (4 - 24)	WMD = - 0.75 (- 1.17, - 0.32)	0.0006	90	- 2.04, 0.55
Final change in SGRQ	[14,15,25,26,30]	1205	20 (6 - 54)	WMD = - 1.81 (- 3.11, _- 0.51)	0.006	9	-
TDI	[14,25 - 27,29]	981	24 (12 - 54)	WMD 0 - 1.15 (- 1.81, - 0.48)	0.0007	66	- 2.55, 0.26
Patients with COPD exacerbations	[14,17,25,26,28 - 30]	1501	30 (4 - 54)	OR = 0.94 (0.57, 1.57)	0.82	68	-
Serious adverse effects	[14,17,22,23,25,26,30]	2273	17 (6 - 54)	OR = 1.02 (0.71, 1.48)	0.90	0	-
Pneumonia	[14,25]	433	33 (13 - 54)	OR = 1.00 (0.10, 9.73)	0.99	0	-
Prematurely discontinued patients	[14,17,22,23,25,26, 28 - 30]	3774	17 (4 - 54)	OR = 0.96 (0.77, 1.20)	0.73	0	-
Withdrawals due to adverse events	[14,17,22,23,25,26]	3490	17 (6 - 54)	OR = 0.99 (0.62, 1.59)	0.96	31	-
Withdrawals due to treatment failure	[14,22,23,26,30]	3206	22 (6 - 54)	OR = 1.04 (0.54, 2.03)	0,6	0	-

COPD = Chronic obstructive pulmonary disease; n = number of subjects; LABA; OR = Odds ratio; SGRQ = Saint George Respiratory Questionnaire; TDI = Transitional dyspnea index; WMD = weighted mean difference.

LABA plus ICS (“combined” therapy) compared with tiotropium monotherapy

- 7 trials

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32. Wedzicha JA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19e26.

outcome	references	n	Mean duration,	Measure 95 % CI	p	I2 %

			weeks (range)			
Mean rescue medication (puffs/day)	[15,16,19,20,25]	404	9 (4 – 13)	WMD = - 0,4 (- 0,76; - 0,03)	0,03	0
Final change in SGRQ	[22,23]	1479	60 (16 – 104)	WMD = - 2,07 (- 2,49; - 1,64)	0,0001	0
TDI	[19,20,25]	237	10 (4 – 13)	WMD = - 0,42 (- 0,96; 0,03)	0,13	71
Patients with COPD exacerbations	[19,25,32]	802	43 (12 – 104)	OR = 1,12 (0,9; 1,4)	0,31	0
Serious adverse effects	[15,19,20,32]	1610	31 (4 – 104)	OR = 1,33 (1,04; 1,69)	0,02	0
Pneumonia	[20,32]	1378	54 (4 – 104)	OR = 2,22 (1,35; 3,63)	0,002	0
Prematurely discontinued patients	[16,19,20,25,32]	1620	29 (4 – 104)	OR = 0,9 (0,45; 1,8)	0,77	34
Withdrawals due to adverse events	[15,19,20,25,32]	1667	28 (4 – 104)	OR = 1,02 (0,73; 1,44)	0,9	0
Withdrawals due to treatment failure	[19,32]	1448	58 (12 – 104)	OR = 0,8 (0,5; 1,29)	0,36	0

COPD = Chronic obstructive pulmonary disease; n = number of subjects; LABA; OR = Odds ratio; SGRQ = Saint George Respiratory Questionnaire; TDI = Transitional dyspnea index; WMD = weighted mean difference.

LABA/ICS plus tiotropium (“triple” therapy) compared with tiotropium monotherapy

- 6 trials

14. Aaron SD, et al. 2007

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outcome	references	n	Mean duration, weeks (range)	Measure 95 % CI	p	I2 %	95 % prediction interval
Final change in SGRQ	[14,18,33]	991	26 (12 – 54)	WMD = 3,95 (6,18; - 1,73)	0,0005	81	- 5,41; - 2,49
TDI	[14,26]	353	30 (6 – 54)	WMD = 0,99 (2,99; 1,0)	0,33	81	-
Patients with COPD exacerbations	[14,21,33]	1303	27 (12 – 54)	OR = 0,65 (0,36; 1,19)	0,17	75	-
Serious adverse effects	[14,21,33]	1303	27 (12 – 54)	OR = 0,68 (0,4; 1,14)	0,14	0	-
Pneumonia	[14,33]	961	33 (12 – 54)	OR = 1,27 (0,3; 5,36)	0,74	0	-
Prematurely discontinued patients	[14,21,33]	1033	26 (12 – 54)	OR = 0,65 (0,37; 1,12)	0,12	71	-
Withdrawals due to adverse events	[14,21,33]	1033	26 (12 – 54)	OR = 1,01 (0,59; 1,74)	0,96	0	-
All-cause mortality	[14,33]	961	33 (12 – 54)	OR = 1,79 (0,54; 5,89)	0,34	0	-

	COPD = Chronic obstructive pulmonary disease; n = number of subjects; LABA; OR = Odds ratio; SGRQ = Saint George Respiratory Questionnaire; TDI = Transitional dyspnea index; WMD = weighted mean difference.
	4. Anmerkungen/Fazit der Autoren "Dual" and "triple" therapy seem like the most promising for patients with moderate to very severe COPD. However, data are still scarce and studies too short to generate a strong recommendation. Future studies should examine long-term efficacy and safety. *5. Hinweise durch FB Med* • *Unterschiede zwischen den Studien in: Studiendauer, Stichprobenumfang, Endpunkte (primär/sekundär)* • *The funding for this study came from salary support for Drs. Rodrigo, Castro-Rodriguez and Plaza. No sponsorship from institutions or pharmaceutical industry was provided to conduct this study.* • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)* • *viele patientenrelevante Endpunkte mit heterogenen Ergebnissen* • *Forest Plots nicht dargestellt, Ergebnisse der Einzelstudien unbekannt* • *zusammenfassend solide Ergebnisse: Lebensqualitätsvorteil der „dualen", „combined" und „triple" Therapie im Vergleich zur Monotherapie (klinische Relevanz unklar), Vorteil bei „rescue medication" der „combined" Therapie im Vergleich zur Monotherapie, Schadenspotential der „kombinierten" Therapie im Vergleich zur Monotherapie* • *Ergebnisse zum Vergleich „Tiotropium plus LABA ("dual" long-acting bronchodilator therapy) compared with tiotropium monotherapy" bestätigt im CR Farne HA, 2015 (siehe oben)* • *Ergebnisse zum Vergleich „LABA plus ICS ("combined" therapy) compared with tiotropium monotherapy" unterscheiden sich von CR Welsh EJ, 2013 (siehe oben),* • *Ergebnisse zum Vergleich "LABA/ICS plus tiotropium ("triple" therapy) compared with tiotropium monotherapy" bestätigt im CR Rojas-Reyes MX, 2016 (siehe oben)*
Rodrigo GJ et al., 2012 [30]. **Comparison of Indacaterol with Tiotropium or twice-daily long-acting beta-agonists**	1. Fragestellung The objective of this systematic review was to explore the efficacy and safety of inhaled indacaterol in comparison with tiotropium or TD-LABA in moderate-severe COPD.
	2. Methodik Population: adult patients aged >40 years with stable moderate to severe COPD satisfying American Thoracic Society/European Respiratory Society or GOLD (Global Initiative for Chronic Obstructive Lung Disease) diagnostic criteria Intervention: inhaled Indacaterol

for stable COPD: A systemtic review	Komparator: tiotropium, salmeterol, formoterol monotherapy (2x täglich) Endpunkte: FEV1, Notwendikeit einer Notfallmedikation, Dyspnoe (TDI Index), Gesundheitszustand (SGRQ), Exazerbationen, Nebenwirkungen (schwere), Studienabbrüche, Mortalität (jede Ursache), andere Vitalaparameter Suchzeitraum: bis Dez. 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5/5 920 Qualitätsbewertung der Studien: according to recommendations outlined in Cochrane Handbook Heterogeneity: measured by I2 test (<40% might be unimportant, 40%-60% might be moderate, and 60%-100% may be substantial) Publication bias of primary outcomes was evaluated by visual inspection of funnel plots
	3. Ergebnisdarstellung • all studies judged to have a low risk of bias Because selected studies differed in the mixes of participants and interventions, a random-effects meta-analysis was performed to address this variation across studies in all outcomes. **Indacaterol vs. Tiotropium:** • Stat. signifikante und klinisch signifikante Reduktionen hinsichtlich der Notwendigkeit an Notfallmedikation (-0.57 puffs/days, p<0.0001) und Dyspnoe (43% höhere Wahrscheinlich den minimal klinisch relevanten Unterschied zu erreichen) unter Indacaterol, verglichen gegen Tiotropium. • Zusätzlich zeigte sich, dass der MCID hinsichtlich des Gesundheitszustandes eher unter einer Indacaterolgabe erreicht wurde, als mit Tiotropium (OR= 1.43; 95% KI:1.22, 1.68; p= 0.00001). **Indacaterol vs. LABA:** • Die Lungenfunktion (FEV1), war am Ende der Behandlung stat. signifikant besser in der Indacaterolgruppe, wenn verglichen wird mit einer LABA Therapie (80 ml, p=0.00001). • Stat. signifikante Vorteile unter Indacaterol gegenüber LABAs hinsichtlich der Dyspnoe (61% höhere Wahrscheinlich den minimal klinisch relevanten Unterschied zu erreichen; p = 0.008), und dem Gesundheitszustand (21% höhere Wahrscheinlich den minimal klinisch relevanten Unterschied zu erreichen; p=0.04). Allgemein: Vergleichbares Sicherheitsprofil und Verträglichkeit zwischen den Interventionen.
	4. Anmerkungen/Fazit der Autoren Available evidence suggests that indacaterol may prove useful as an alternative to tiotropium or TD-LABA due to its effects on health status,

	dyspnea, and pulmonary function. *5. Hinweise durch FB Med* • *kleine Anzahl an Studien* • *study funded by salary support from Hospital Central de las Fuerzas Armadas for Dr Rodrigo .*
Yohannes AM et al., 2011 [38]. **Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes**	1. Fragestellung To systematically review recent evidence on the effectiveness of tiotropium versus placebo, ipratropium, and long-acting-β2-agonists on outcomes relevant to patients with stable COPD, including health-related quality of life, dyspnea, exacerbations and hospitalizations.
	2. Methodik Population: adult patients ≥40 y old with stable COPD consistent with American Thoracic Society/European Respiratory Society or GOLD diagnostic criteria, who had not had an exacerbation in the 4 weeks before the study Intervention: Tiotropium Komparator: with placebo, ipratropium bromide, or long-acting beta agonists (LABA, salmeterol, or formoterol) Endpunkte: Gesundheitsbezogene Lebensqualität, Dyspnoe, Exazerbationen und Krankenhauseinweisungen Suchzeitraum bis Januar 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 16/16 301 Qualitätsbewertung der Studien: Jadad score, score of < 3 regarded as methodologically poor quality Heterogeneity: I2 test used with values of 25%, 50%, and 75%, representative of low, moderate, and high heterogeneity, respectively; if > 25% a random-effect model used
	3. Ergebnisdarstellung • Tiotropium zeigte eine stat. signifikante Verbesserung der gesundheitsbezogenen Lebensqualität, wenn verglichen wird mit Plazebo (OR:1.61, 95% KI 1.38–1.88, P < .001) und Ipratropium (OR: 2.03, 95% KI: 1.34–3.07, p= 0.001). • Tiotropium verbesserte stat. signifikant die Inzidenz von Dyspnoe wenn verglichen wird mit Plazebo (OR 1.96, 95% KI 1.58–2.44, p < 0.001) und Ipratropium (OR: 2.10, 95% KI 1.28–3.44, p=0 .003). • Tiotropium reduzierte stat. signifikant das Risiko auf eine Exazerbation (OR: 0.83, 95% KI 0.72–0.94, p=0 .004) und damit assoziierten Krankenhauseinweisungen (OR 0.89; 95% KI 0.80–0.98, p=0 .02), jedoch nicht schwere unerwünschte Ereignisse (p=0 .19) wenn

	verglichen wird gegen Plazebo. • Vermehrtes Auftreten der Nebenwirkung ,,trockener Mund'' unter Tiotropium (7.4%) verglichen mit Ipratropium (3.9%), Salmeterol (1.6%) und und Plazebo (2.0%).
	4. Anmerkungen/Fazit der Autoren In stable COPD, tiotropium showed superior efficacy in improving quality of life and dyspnea, compared to placebo and ipratropium. However, tiotropium's differences with salmeterol were less clear. *5. Hinweise durch FB Med* • *Für den Vergleich von Tiotropium und Ipratropium oder LABA, waren oft nur ein oder zwei Studien vorhanden.* • *Problem der doppelten Berücksichtigung von Patienten von sich überschneidenden Publikationen.* • *Möglicherkeit des Publikations-Bias.* • *Jadad-Score weniger geeignet zur Bewertung des Verzerrungsrisikos* • *Dr Vestbo has disclosed relationships with GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, Pfizer, and Nycomed. Dr Yohannes and Mr Willgoss have disclosed no conflicts of interest.*
McIvor RA et al., 2011 [26]. **BMJ Clinical Evidence: COPD**	1. Fragestellung What are the effects of maintenance drug treatment in stable COPD?
	2. Methodik Population: Patients with stable COPD Intervention: inhaled anticholinergics, inhaled anticholinergics plus beta2 agonists, inhaled beta2 agonists, inhaled corticosteroids, inhaled combinations Komparator: any of the interventions above, Placebo Endpunkt: Study type: systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up, no minimum length of follow-up required, except for long-acting anticholinergics (6-month follow-up required), all studies described as "open", "open label", or not blinded unless blinding was impossible excluded We aimed for a minimum follow-up of 1 year for maintenance treatment, but, where we did not identify studies with this length of follow-up, reported on studies of shorter duration. Suchzeitraum: bis April 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): k.A. Qualitätsbewertung der Studien: GRADE

3. Ergebnisdarstellung

ANTICHOLINERGICS (INHALED)

• Inhaled anticholinergics improve lung function and symptoms and reduce exacerbations in stable COPD compared with placebo.

• It is unclear whether inhaled anticholinergics or inhaled beta2 agonists are the more consistently effective drug class in the treatment of COPD.

• Anticholinergics are associated with an increased rate of dry mouth.

<u>Anticholinergics (short-term treatment) versus placebo:</u>

- Ipratropium in the short term seems no more effective at improving symptoms or the need for rescue bronchodilators (moderate-quality evidence).
- Short-term treatment with ipratropium is no more effective at improving quality of life (moderate-quality evidence).

18. Dahl R, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:778–784.

<u>Anticholinergics (long-term treatment) versus placebo:</u>

- Tiotropium seems no more effective at reducing allcause mortality at 2 to 48 months (moderate-quality evidence).

21. Rodrigo GJ, et al. Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. Respir Med 2009;103:1421–1429.

24. Tonnel AB, et al. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. Int J Chron Obstruct Pulmon Dis 2008;3:301–310.

- Tiotropium used long term is more effective at 12 to 52 weeks at reducing COPD exacerbations (high-quality evidence).
- Long-term treatment with tiotropium seems more effective at 6 to 12 months at improving quality of life (moderate-quality evidence).

22. Rodrigo GJ, Nannini LJ.Tiotropium for the treatment of stable chronic obstructive pulmonary disease: a systematic review with meta-analysis. Pulm Pharmacol Ther 2007;20:495–502.

24. Tonnel AB, et al. 2008

BETA2 AGONISTS (INHALED)

• Inhaled beta2 agonists improve lung function and symptoms and reduce exacerbations in stable COPD compared with placebo.

• It is unclear whether inhaled anticholinergics or inhaled beta2 agonists are the more consistently effective drug class in the treatment of COPD.

<u>Short-acting beta2 agonists (short-term treatment) versus placebo:</u>

- Short-acting beta2 agonists (short-term treatment) may be more effective at improving daily breathlessness scores in people with stable COPD (very low-quality evidence).

26. Sestini P, et al. Short-acting beta2 agonists for stable chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.

28. Donohue JF, et al. Evaluation of the efficacy and safety of levalbuterol in subjects with COPD. COPD 2006;3:125–132.

<u>Short-acting beta2 agonists (long-term treatment) versus placebo:</u>

- no systematic review of only long-term treatment with short-acting beta2 agonists versus placebo

<u>Long-acting beta2 agonists (short-term or long-term treatment) versus placebo:</u>

- Long-acting beta2 agonists (short-term or long-term treatment) seem no more effective at reducing mortality (moderate-quality evidence).

32. Rodrigo GJ, et al.Safety of long-acting betaagonists in stable COPD: a systematic review. Chest 2008;133:1079–1087.

- Long-acting beta2 agonists (short-term or long-term treatment) seem more effective at reducing the rate of COPD exacerbations and at improving symptoms (assessed by the Chronic Disease Respiratory Questionnaire and Transitional Dyspnoea Index) (moderate-quality evidence).

30. Shukla VK, et al. Long-acting beta2 agonists for the maintenance treatment of chronic obstructive pulmonary disease in patients with reversible and non-reversible airflow obstruction: a systematic review of clinical effectiveness. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 2006. Available at: http://www.cadth.ca/media/pdf/219_LABA_tr_e_no-appendices.pdf (last accessed 28 April 2011).

32. Rodrigo GJ, et al.Safety of long-acting betaagonists in stable COPD: a systematic review. Chest 2008;133:1079–1087.

37. Baumgartner RA, et al. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, doubledummy, placebo- and active-controlled trial. Clin Ther 2007;29:261–278.

38. Beier J, et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily beta(2)-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. Pulm Pharmacol Ther 2007;20:740–749.

- Long-acting beta2 agonists (short-term or long-term treatment) may be no more effective at improving quality of life (moderate-quality evidence).

32. Rodrigo GJ, et al. 2008.

ANTICHOLINERGICS PLUS BETA2 AGONISTS (INHALED).

• Combined treatment with inhaled anticholinergics and beta2 agonists may improve symptoms and lung function and reduce exacerbations compared with either treatment alone, although long-term effects are unknown.

• We found no clinically important information from RCTs comparing long-term treatment with a combination of anticholinergics and beta2 agonists versus no active treatment.

<u>Short-acting anticholinergic plus short-acting inhaled beta2 agonist (short-term treatment) versus shortacting beta2 agonist alone:</u>

- Combining a short-acting anticholinergic drug (ipratropium) with a short-acting beta2 agonist for 12 weeks is more effective at improving exacerbations, but ipratropium plus a short-acting beta2 agonist seems no more effective at 85 days at improving the dyspnoea component of the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

29. Sin DD, et al. Contemporary management of chronic obstructive pulmonary disease: scientific

review. JAMA 2003;290:2301–2312.

44. Appleton S, et al. Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.

- Ipratropium plus a short-acting beta2 agonist seems no more effective than short-acting beta2 agonist alone at 85 days at improving fatigue, emotion, and mastery components of the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

44. Appleton S, et al. 2010.

<u>Short-acting anticholinergic plus short-acting inhaled beta2 agonist (short-term treatment) versus shortacting</u>

<u>anticholinergic alone:</u>

- Combining a short-acting anticholinergic drug (ipratropium) with a short-acting beta2 agonist for 12 weeks seems as effective a short-acting anticholinergic alone at improving exacerbations (moderatequality evidence).

29. Sin DD, et al. 2003.

ANTICHOLINERGICS VERSUS BETA2 AGONISTS (INHALED)

• It is unclear whether inhaled anticholinergics or inhaled beta2 agonists are the more consistently effective drug class in the treatment of COPD.

• Short-acting anticholinergics seem to be associated with a small improvement in quality of life compared with beta2 agonists.

• Long-acting inhaled anticholinergic drugs may improve lung function compared with long-acting beta2 agonists.

• We found no clinically important results from RCTs comparing long-acting anticholinergics versus short-acting beta2 agonists in the treatment of people with COPD.

<u>Short-acting anticholinergic versus short-acting beta2 agonist:</u>

- Ipratropium seems modestly more effective than a short-acting beta2 agonist at improving the dyspnoea component of the Chronic Respiratory Disease Questionnaire (moderate-quality evidence).

44. Appleton S, et al. 2010

- Ipratropium seems modestly more effective
- than a short-acting beta2 agonist at improving fatigue, emotion, and mastery components of the Chronic Respiratory
- Disease Questionnaire (moderate-quality evidence).

44. Appleton S, et al. 2010

<u>Short-acting anticholinergic versus long-acting beta2 agonist:</u>

- Ipratropium and the long-acting beta2 agonists
- salmeterol and formoterol seem equally effective at improving COPD exacerbations (moderate-quality evidence).

30. Shukla VK, et al. 2006.

- Ipratropium and the long-acting beta2 agonists
- salmeterol and formoterol seem equally effective at 12 weeks at improving total score on the Chronic Respiratory
- Disease Questionnaire (moderate-quality evidence).

45. Appleton S, et al. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.

<u>Long-acting anticholinergic versus long-acting beta2 agonist:</u>

- Tiotropium and salmeterol are equally effective
- at reducing all-cause mortality (high-quality evidence).
- Tiotropium and salmeterol are equally effective
- at improving COPD exacerbations (high-quality evidence).

48. Barr RG, et al.Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. Thorax 2006;61:854–862.

- Tiotropium and salmeterol seem equally effective
- at improving St George's Respiratory Questionnaire scores (moderate-quality evidence).

30. Shukla VK, et al. 2006.

THEOPHYLLINE

• Theophylline may improve lung function compared with placebo, but adverse effects limit its usefulness in stable COPD.

• Theophylline has a narrow therapeutic range and is associated with adverse effects such as diarrhoea, headache, irritability, seizures, and cardiac arrhythmias. The usefulness of theophyllines is limited by adverse effects and the need for frequent monitoring of blood concentrations.

<u>Theophylline (long-term treatment) versus placebo:</u>

- Theophylline (long-term treatment) seems more effective at 12 months at reducing the frequency
- and duration of acute COPD exacerbations (moderate-quality evidence).

53. Zhou Y, et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. Respirology 2006;11:603–610

CORTICOSTEROIDS (INHALED)

• Inhaled corticosteroids reduce exacerbations in COPD and reduce decline in FEV1, but the beneficial effects are small.

• Combined inhaled corticosteroids plus long-acting beta2 agonists improve lung function and symptoms and reduce exacerbations compared with placebo, and may be more effective than either treatment alone.

• Long-term treatment with inhaled corticosteroids may predispose to adverse effects such as skin bruising, oral candidiasis, and pneumonia.

<u>Inhaled corticosteroids (long-term treatment) versus placebo:</u>

- Inhaled corticosteroids (long-term treatment) seem no more

effective at reducing mortality at 3 years in people with moderate to severe COPD (moderate-quality evidence).

35. Calverley PM, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775–789.

62. Drummond MB, et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and metaanalysis. JAMA 2008;300:2407–2416.

- Inhaled corticosteroids (long-term treatment) seem more effective at improving dyspnea and at reducing COPD exacerbations in people with moderate to severe COPD (moderate-quality evidence).

61. Agarwal R, et al. Inhaled corticosteroids vs placebo for preventing COPD exacerbations: a systematic review and metaregression of randomized controlled trials. Chest 2010;137:318–325.

63. Mahler DA, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:1084–1091.

64. Hanania NA, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 2003;124:834–843.

- Inhaled corticosteroids (long-term treatment) seem more effective at improving health-related quality of life in people with COPD (moderate-quality evidence).

58. Yang IA, et al. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.

64. Hanania NA, et al. 2003

Comment: Many of the RCTs of inhaled corticosteroids have been done in people with moderate to severe COPD (FEV1 <50% predicted) and hence apply only to that population. The lifetime risk of fractures in people who take corticosteroids for longer than 3 to 4 years is unknown. The Global Initiative on Obstructive Pulmonary Disease has therefore advocated the use of inhaled corticosteroids only in people with an FEV1 <50% predicted, and frequent exacerbations (at least 3 exacerbations in the past 3 years).

CORTICOSTEROIDS PLUS LONG-ACTING BETA2 AGONISTS (INHALED)

• Combined inhaled corticosteroids plus long-acting beta2 agonists improve lung function, symptoms, and healthrelated quality of life and reduce exacerbations compared with placebo, and may be more effective than either treatment alone.

<u>Corticosteroid plus long-acting beta2 agonist versus placebo:</u>

- Combined inhaled corticosteroids plus long-acting beta2 agonists are more effective at reducing all-cause mortality in people with moderate to severe disease (high-quality evidence).

65. Nannini L, et al. Combined corticosteroid and longacting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.

66. Tashkin DP, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. Drugs 2008;68:1975–2000.

67. Zheng JP, et al. The efficacy and safety of combination salmeterol (50 microg)/fluticasone propionate (500 microg) inhalation twice daily via accuhaler in Chinese patients with COPD. Chest 2007;132:1756–1763.

- An inhaled corticosteroid plus a long-acting beta2 agonist is more effective at reducing COPD exacerbation rates in people with moderate to severe disease (moderate-quality evidence).

65. Nannini L, et al. 2010.

67. Zheng JP, et al. 2007

68. Sin DD, et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:1207–1214.

- Corticosteroids plus long-acting beta2 agonists seem more effective at improving health-related quality of life in people with moderate to severe disease (moderate-quality evidence).

65. Nannini L, et al. 2010.

68. Sin DD, et al. 2008

<u>Corticosteroid plus long-acting beta2 agonist versus corticosteroid alone:</u>

- Fluticasone plus salmeterol is more effective at 3 years than fluticasone alone at reducing all-cause mortality in people with moderate to severe disease.
- However, we don't know how budesonide plus formeterol compares with budesonide alone (high-quality evidence).

66. Tashkin DP, et al. 2008

69. Nannini LJ, et al. Combined corticosteroid and longacting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.

- An inhaled corticosteroid plus a long-acting beta2 agonist seems more effective at reducing COPD exacerbations in people with moderate to severe disease (moderate-quality of evidence).

68. Sin DD, et al. 2008

69. Nannini LJ, et al. 2010

- A corticosteroid plus a long-acting beta2 agonist seems more effective at improving health-related quality of life in people with moderate to severe disease (moderate-quality evidence).

69. Nannini LJ, et al. 2010

<u>Corticosteroid plus long-acting beta2 agonist versus beta2 agonist alone:</u>

- Fluticasone plus salmeterol seems no more effective at 3 years than salmeterol alone at reducing all-cause mortality in people with moderate to severe disease (moderate-quality evidence).
- An inhaled corticosteroid plus a long-acting beta2 agonist may be more effective at reducing COPD exacerbations in people with moderate to severe disease (low-quality evidence).

70. Rodrigo GJ, et al.Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. Chest 2009;136:1029–1038.

- A corticosteroid plus a long-acting beta2 agonist may be more effective at improving health-related quality of life in people with moderate to severe disease (low-quality evidence).

70. Rodrigo GJ, et al. 2009

71. Nannini LJ, et al. Combined corticosteroid and longacting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 2,

	2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.
	4. Anmerkungen/Fazit der Autoren In this systematic review, we present information relating to the effectiveness and safety of the following interventions: alpha1 antitrypsin, antibiotics (prophylactic), anticholinergics (inhaled), beta2 agonists (inhaled), corticosteroids (oral and inhaled), general physical activity enhancement, inspiratory muscle training, nutritional supplementation, mucolytics, oxygen treatment (long-term domiciliary treatment), peripheral muscle strength training, psychosocial and pharmacological interventions for smoking cessation, pulmonary rehabilitation, and theophylline. 5. Hinweise durch FB Med • *Spirometrieergebnisse nicht patientenrelevant (hier nicht berichtet)* • *Interventionen nur berichtet wenn relevante Evidenz identifiziert wurde*

Leitlinien

Criner GJ et al., 2015 [5]. **American College of Chest Physicians (CHEST) and Canadian Th oracic Society (CTS) joint evidence-based guideline (AECOPD Guideline)** Prevention of acute exacerbations of COPD	Fragestellung Key question 2: In patients aged > 40 y who are previous or current smokers with COPD, does maintenance inhaled therapy prevent acute exacerbations?
	Methodik Grundlage der Leitlinie: Kreis aus „experts in pulmonology and respiratory therapy“ und Methodiker*innen, Interessenkonflikte dargelegt und bewertet (Teilnahme an Formulierung und Abstimmung zu Empfehlungen untersagt), Formulierung von klinischen Fragestellungen und PICO-Schemen, systematische Suche, Auswahl und Bewertung (AGREE, DART - Documentation and Appraisal Review Tool, Cochrane Risk of Bias tool) der Literatur zur Frage, ggf. Metaanlysen berechnet, GRADE-Profile erstellt, Konsensusprozess über Webinars und online-Surveys, abschließende Expertenkonsulation Suchzeitraum: Leitlinienrecherche am 30.01.2013, Cochrane-Recherche am 25.04.2013 (limited to systematic reviews published between 2007 and 2013), PubMed-Recherche am 29.04.2013 (limited to reviews published between 2008 and 2013) **LoE**

TABLE 3] Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

GoR: siehe Anhang

Sonstige methodische Hinweise

The PICO 2 inhaled therapies group reviewed 49 systematic reviews and determined that 30 were relevant. Of the 30 systematic reviews, 11 were used to directly inform the evidence base.

Two panelists in the PICO 2 inhaled therapies group were permitted to write recommendations, and they worked with the other panelists in the group to draft supporting text.

Recommendations were not made in instances where the panelists believed the data insufficient or inconclusive to warrant a recommendation. In instances where there was insufficient evidence but a recommendation was still warranted, a weak suggestion was developed, and consensus based (CB) replaced the grade.

- *Quellenangaben im Hintergrundtext zur Empfehlung*
- *keine Hinweise auf formale Konsensusverfahren*
- *jährliche Aktualisierung geplant*

Freitext/Empfehlungen/Hinweise

PICO 2: Does Maintenance Inhaled Therapy Prevent/Decrease Acute Exacerbations of COPD?

11. In patients with moderate to severe COPD, we recommend the use of long-acting b 2 -agonist compared with placebo to prevent moderate

to severe acute exacerbations of COPD (Grade 1B).

144. Singh S, et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials . BMJ . 2011 ; 342 : d3215 .

145. Wise RA, et al ; TIOSPIR Investigators . Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med . 2013 ; 369 (16): 1491 - 1501 .

146. Karner C, et al. Tiotropium versus placebo for chronic obstructive pulmonary disease . Cochrane Database Syst Rev . 2012 ;(7): CD009285 .

13. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1A).

142. Vestbo J, et al . Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary . Am J Respir Crit Care Med . 2013 ; 187 (4): 347 - 365 .

147. O'Donnell DE, et al . Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care . Can Respir J . 2008; 15(suppl A): 1A - 8A.

148. O'Donnell DE, et al . Eff ects of tiotropium on lung hyperinfl ation, dyspnoea and exercise tolerance in COPD . Eur Respir J . 2004 ; 23 (6): 832 - 840 .

149. Celli B , et al . Improvement in resting inspiratory capacity and hyperinfl ation with tiotropium in COPD patients with increased static lung volumes . Chest . 2003 ; 124 (5): 1743 - 1748 .

150. O'Donnell DE, et al. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease . Eur Respir J . 2004 ; 24 (1): 86 - 94 .

23. Tashkin DP, et al ; UPLIFT Study Investigators . A 4-year trial of tiotropium in chronic obstructive pulmonary disease . N Engl J Med . 2008 ; 359 (15): 1543 - 1554 .

151. Calverley PM, et al ; TORCH Investigators . Salmeterol and fl uticasone propionate and survival in chronic obstructive pulmonary disease . N Engl J Med . 2007; 356(8): 775- 789.

152. Chong J, et al. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease . Cochrane Database Syst Rev . 2012 ;(9): CD009157 .

153. Vogelmeier C, et al ; POET-COPD Investigators . Tiotropium versus salmeterol for the prevention of exacerbations of COPD . N Engl J Med . 2011 ; 364 (12): 1093 - 1103 .

140. Wootton R . Twenty years of telemedicine in chronic disease management—an evidence synthesis . J Telemed Telecare . 2012 ; 18 (4): 211 - 220 .

14. In patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared with long-acting b 2 - agonist to prevent moderate to severe acute exacerbations of COPD (Grade 1C).

154. Appleton S, et al . Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease . Cochrane Database Syst Rev . 2006;(3): CD006101.

155. Brown D ea. A randomized, double blind, parallel, multi-centre comparison of inhalation solution with albuterol inhalation solution following single-dose and chronic administration (85 days) in patients with chronic obstructive pulmonary disease. Boehringer Ingelheim unpublished report USA U91-0865, 1991 .

156. Brown D ea. A randomized, double blind, parallel, multicenter comparison of Atrovent (ipratropium bromide) inhalation solution with metaproterenol inhalation solution following single-dose and chronic administration (85 days) in patient with chronic obstructive pulmonary disease. Boehringer Ingelheim unpublished report USA U91-0866, 1991 .

157. Friedman M . A multicenter study of nebulized bronchodilator solutions in chronic obstructive pulmonary disease . Am J Med . 1996; 100(suppl 1): S30- S39.

158. Rennard SI, et al. Extended therapy with ipratropium is associated with improved lung function in patients with COPD. A retrospective analysis of data from seven clinical trials . Chest . 1996 ; 110 (1): 62 - 70 .

159. Tashkin DP, et al . Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease. A 90-day multi-center study . Am J Med . 1986; 81 (5A): 81 - 90 .

160. Tashkin DP, et al . Results of a multicenter study of nebulized inhalant bronchodilator

	solutions . Am J Med . 1996; 100(suppl 1): S62- S69.154- 160 161. COMBIVENT Inhalation Aerosol Study Group . In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more eff ective than either agent alone. An 85-day multicenter trial . Chest . 1994 ; 105 (5): 1411 - 1419 . 162. COMBIVENT Inhalation Solution Study Group . Routine nebulized ipratropium and albuterol together are better than either alone in COPD . Chest . 1997 ; 112 (6): 1514 - 1521 . 163. Colice GL . Nebulized bronchodilators for outpatient management of stable chronic obstructive pulmonary disease . Am J Med . 1996; 100(suppl 1): S11- S18.161 - 163 15. In patients with moderate to severe COPD, we suggest the use of a short-acting muscarinic antagonist compared with short-acting b 2 - agonist monotherapy to prevent acute mild-moderate exacerbations of COPD (Grade 2C). 154. Appleton S, et al . Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease . Cochrane Database Syst Rev . 2006;(3): CD006101. 164. Campbell S. For COPD a combination of ipratropium bromide and albuterol sulfate is more eff ective than albuterol base . Arch Intern Med . 1999 ; 159 (2): 156 - 160 . 157. Friedman M. 1996 160. Tashkin DP, et al . 1996 161. COMBIVENT 1994 162. COMBIVENT 1997 163. Colice GL . 1996 165. Alexander KM ea. A randomized, double blind, parallel, multicenter comparison of Combivent (ipratropium bromide and albuterol sulfate) inhalation solution with its components following single-dose and chronic administration (85 days) in patients with chronic pulmonary disease. Boehringer Ingelheim unpublished report: USA U92-0801, 1992 . 166. Gross N, et al . Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease . Respiration . 1998 ; 65 (5): 354 - 362 . 167. Levin DC, et al . Addition of anticholinergic solution prolongs bronchodilator eff ect of beta 2 agonists in patients with chronic obstructive pulmonary disease . Am J Med . 1996; 100(suppl 1): S40- S48. 16. In patients with moderate to severe COPD, we suggest the use of short-acting muscarinic antagonist plus short-acting b 2 - agonist compared with shortacting b 2 - agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B). 142. Vestbo J, et al. GOLD 2013 147. O'Donnell DE, et al. 2008 168. van Noord JA, et al. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease . Th orax . 2000; 55(4): 289- 294. 169. Mahler DA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD . Chest . 1999 ; 115 (4): 957 - 965 . 170. Cramer JA, et al. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease . Can Respir J . 2007 ; 14 (1): 25 - 29 . 154. Appleton S, et al. 2006 141. Kew KM, et al. Long-acting beta2-agonists for chronic obstructive pulmonary disease . Cochrane Database Syst Rev . 2013 ;(10): CD010177 . 17. In patients with moderate to severe COPD, we suggest the use of long-acting b 2 -agonist monotherapy compared with short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD (Grade 2C). 148. O'Donnell DE, et al. 2004

	150. O'Donnell DE, et al. 2004 171. O'Donnell DE, et al. Dynamic hyperinfl ation and exercise intolerance in chronic obstructive pulmonary disease . Am J Respir Crit Care Med . 2001 ; 164 (5): 770 - 777 . 146. Karner C, et al. 2012 172. Anthonisen NR, et al. Eff ects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. Th e Lung Health Study . JAMA . 1994 ; 272 (19): 1497 - 1505 . 142. Vestbo J, et al. GOLD 2013 147. O'Donnell DE, et al. 2008 173. Cheyne L, et al. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease . Cochrane Database Syst Rev . 2013 ;(9): CD009552 . 144. Singh S, et al. 2011 145. Wise RA, et al. 2013 174. Loke YK, et al. Tiotropium and the risk of death in COPD . N Engl J Med . 2014 ; 370 (5): 480 - 481 175. Verhamme KM, et al. Tiotropium and the risk of death in COPD . N Engl J Med . 2014 ; 370 (5): 481 - 482 . 176. Jenkins CR. Tiotropium and the risk of death in COPD . N Engl J Med . 2014 ; 370 (5): 482 - 483 . 18. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with a short-acting muscarinic antagonist to prevent acute moderate to severe exacerbations of COPD (Grade 1A). 154. Appleton S, et al. 2006 19. In patients with moderate to severe COPD, we suggest the combination use of a short-acting muscarinic antagonist plus long-acting b 2 -agonist compared with long-acting b 2 -agonist monotherapy to prevent acute mild to moderate exacerbations of COPD (Grade 2C). 177. Sethi S, et al. Infl ammation in COPD: implications for management . Am J Med . 2012 ; 125 (12): 1162 - 1170 . 178. Izquierdo Alonso JL, et al. Th e excessive use of inhaled corticosteroids in chronic obstructive pulmonary disease . Arch Bronconeumol . 2012 ; 48 (6): 207 - 212 . 179. de Miguel-Díez J, et al. Inappropriate overuse of inhaled corticosteroids for COPD patients: impact on health costs and health status . Lung . 2011; 189(3): 199- 206. 180. Barnes PJ. Inhaled corticosteroids in COPD: a controversy . Respiration . 2010 ; 80 (2): 89 - 95 . 181. Price D, et al. Risk-to-benefi t ratio of inhaled corticosteroids in patients with COPD . Prim Care Respir J . 2013 ; 22 (1): 92 - 100 . 182. Zervas E, et al. Inhaled corticosteroids in COPD: pros and cons . Curr Drug Targets . 2013 ; 14 (2): 192 - 224 . 183. Barnes PJ. Role of HDAC2 in the pathophysiology of COPD . Annu Rev Physiol . 2009 ; 71 : 451 - 464 . 184. Barnes PJ. Glucocorticosteroids: current and future directions . Br J Pharmacol . 2011 ; 163 (1): 29 - 43 . 185. Mercado N, et al . Decreased histone deacetylase 2 impairs Nrf2 activation by oxidative stress . Biochem Biophys Res Commun . 2011 ; 406 (2): 292 - 298 . 186. Jen R, et al. Eff ects of inhaled corticosteroids on airway infl ammation in chronic obstructive pulmonary disease: a systematic review and meta-analysis . Int J Chron Obstruct Pulmon Dis . 2012 ; 7 : 587 - 595 . 22. Calverley P, et al ; TRial of Inhaled Steroids ANd long-acting beta2 agonists study group . Combined salmeterol and fl uticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial . Lancet . 2003 ; 361 (9356): 449 - 456 .

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	anticholinergic/long-acting b 2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C). 24. For patients with stable COPD, we recommend maintenance combination of inhaled corticosteroid/long-acting b 2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C). 25. For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting b 2–agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).
Management of Chronic Obstructive Pulmonary Disease Working Group, 2014 [25]. **Department of Veterans Affairs (VA)/Department of Defense (DoD)** Clinical practice guideline for the management of chronic obstructive pulmonary disease	Fragestellung KQ5: In patients with COPD, what is the evidence that stepped therapy with the following drug classes, or combinations, improves outcomes? a. long-acting beta agonists (LABA) b. short-acting beta agonists (SABA) prn (as needed) c. SABA regularly administered d. short-acting anticholinergics e. long-acting anticholinergics f. inhaled corticosteroids g. phosphodiesterase 4 inhibitors h. chronic macrolides (e.g., azithromycin; chronic usage is defined as longer than 3 weeks) i. theophylline j. N-acetylcysteine What is the evidence that certain subpopulations (e.g. COPD patients over 65 years) have increased benefits or risks from stepped therapy?
	Methodik Grundlage der Leitlinie: The guideline development process for the 2014 CPG consisted of the following steps: 1. Formulating evidence questions (KQs); 2. Conducting the systematic review; 3. Convening a three and one-half day face-to-face meeting with the CPG Champions and Work Group members; and 4. Drafting and submitting a final CPG on the management of COPD to

	the VA/DoD EBPWG – Update der Version von 2007 – Suchzeitraum: January 1, 2005 to February 2014 *Weitere Kriterien für die Qualität einer LL:* • *transparente Ergebnisdarstellung* • *Empfehlungen mit Literaturstellen verknüpft* LoE/GoR: The GRADE of a recommendation is based on the following elements: • Four decision domains used to determine the strength and direction (described above); • Relative strength (Strong or Weak); • Direction (For or Against). Using these elements, the grade of each recommendation is presented as part of a continuum: • Strong For (or "We recommend offering this option …"); • Weak For (or "We suggest offering this option …"); • Weak Against (or "We suggest not offering this option …"); • Strong Against (or "We recommend against offering this option …"). Sonstige methodische Hinweise *This CPG is designed to assist primary care providers in treating and managing patients with COPD. It addresses the following elements.*
	Freitext/Empfehlungen/Hinweise <u>Recommendation 12.</u> We suggest offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). <u>Discussion</u> Both LABAs and LAMAs, such as tiotropium, are important in the management of patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). We recommend tiotropium (a LAMA) as first-line maintenance therapy (in addition to SABA for rescue therapy) because this medication is more effective than LABAs as a group in preventing COPD exacerbations and COPD-related hospitalizations with fewer serious adverse events. LAMAs (specifically tiotropium) have been shown to improve FEV1 and QoL and to prevent moderate to severe exacerbations in patients with confirmed, stable COPD who continue to have respiratory symptoms, despite the use of as-needed short-acting bronchodilators. [82] Compared to LABAs as a group, tiotropium reduces the frequency of

	COPD exacerbations. However, this is a weak recommendation because there is no difference in all-cause hospitalization rates, mortality, symptom improvement, and FEV1 between tiotropium and LABAs. [85] The confidence in the available evidence is moderate, and the benefits-harm balance may slightly favor tiotropium over LABAs as first-line therapy. Further harm-benefit or cost-benefit analysis research is needed to compare these two medication classes. Evidence[6]: 82.Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonarydisease. *Cochrane Database Syst Rev.* 2012;7:Cd009285. 85.Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronicobstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012;9:Cd009157. **GRADE Strength of Recommendation: weak for** 6 For new recommendations, developed by the 2014 guideline Work Group, the literature cited corresponds directly to the 2014 evidence review. This can include articles that were captured as part of an included study (e.g., an RCT that was included in a systematic review). For new recommendations which did not cite evidence identified through the systematic evidence review, "additional evidence" is listed. These are studies that support the recommendation, but which were not systematically identified through a literature review. For recommendations that have been carried over from the 2007 VA/DoD COPD CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to relevant studies that support the recommendation, but which were not systematically identified through a literature review.
Institute for Clinical Systems Improvement (ICSI), 2016 [21]. **Diagnosis and Management of Chronic Obstructive Pulmonary Disease (COPD)**	Fragestellung Siehe "Management of Chronic Obstructive Pulmonary Disease Working Group. 2014 [25]"
	Methodik ICSI has endorsed with qualifications the Veteran's Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease. Using the ICSI endorsement process, this document has been reviewed by the ICSI COPD work group. **Literature Search** The VA/DoD literature search covered the time period from January 1, 2005 to February 2014. ICSI replicated this search to include January 2014 – February 2015. Additional articles were provided by work group members and discussed by the work group prior to inclusion. **GRADE Methodology** Following a review of several evidence rating and recommendation writing systems, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation

	(GRADE) system.
	Freitext/Empfehlungen/Hinweise **Recommendation** #12 – We suggest offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea or cough). **Strength of Recommendation** Weak for **Agree without Qualification** Yes **Qualification Statement** Agree **Literature (New) Search Support** Oba Y, Lone NA. Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: a network meta-analysis and meta-regression. Ther Adv Respir Dis 2015;9:3-15. Mathioudakis AG, et al. Comparative mortality risk of tiotropium administered via handihaler or respimat in COPD patients: are they equivalent? Pulm Pharmacol Ther 2014a;28:91-97. Mathioudakis AG, et al. Tiotropium HandiHaler improves the survival of patients with COPD: a systematic review and meta-analysis. J Aerosol Med Pulm Drug Deliv 2014b;27:43-50.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

GOLD, 2017 [19]. **Global Initiative for Chronic Obstructive Lung Disease** Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Update 2016)	Das Vertrauen in die Empfehlungen dieser Leitlinie ist eingeschränkt. Im Methodenteil der Leitlinie wird nur unzureichend transparent gemacht, dass die Schritte der evidenzbasierten Aufbereitung der Inhalte stattgefunden haben. *„Process: To produce a GOLD report, a PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda MD, USA) search was completed using search search fields established by the Committee: 1) COPD, All fields: Adult: 19+ years, only items with abstracts, Clinical Trial, Meta-analysis; Human.* *The literature included in the review for this 2017 update was published from 2015 to 2016. Publications in peer reviewed journals not captured by PubMed may be submit-ted to the Chair, GOLD Science Committee, providing the full paper, including ab-stract, is submitted in (or translated into) English."* Empfehlungen sind zudem nicht als solche hervorgehoben, sondern befinden sich im Fließtext. Da die GOLD auch in den Studien zitiert wird, wurden die relevanten Inhalte der GOLD 2017 hier dennoch extrahiert. **Table A. Description of levels of evidence** **Evidence category** / **Sources of evidence** / **Definition** **A** — Randomized controlled trials (RCTs). Rich body of high quality evidence without any significant limitation or bias — 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. Requires high quality evidence from ≥ 2 clinical trials involving a substantial number of subjects, or a single high quality RCT involving substantial numbers of patients without any bias. **B** — Randomized controlled trials (RCTs) with important limitations. Limited Body of Evidence — Evidence is from RCTs that include only a limited number of patients, post hoc or subgroup analyses of RCTs or meta analyses of RCTs. 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. PHARMACOLOGIC THERAPY FOR STABLE COPD

Table 3.4. 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)**.
• Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms **(Evidence A)**.
• Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms **(Evidence A)**.
• 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)**.
• Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy **(Evidence A)**.
• Combination treatment with a LABA and LAMA reduces exacerbations compared to monotherapy **(Evidence B)** or ICS/LABA **(Evidence B)**.
• Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**.
• Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**.

Table 3.5. Anti-inflammatory therapy in stable COPD
Inhaled corticosteroids
• 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)**.
• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.
• Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms and health status **(Evidence A)** and reduces exacerbations **(Evidence B)** compared to ICS/LABA or LAMA monotherapy.
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:
» A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)**.
» A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations **(Evidence B)**.
Antibiotics
• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)**.
• Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**.
Mucolytics/antioxidants
• Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations **(Evidence B)**.
Other anti-inflammatory agents
• 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.

Table 3.7. Other pharmacological treatments
Alpha-1 antitrypsin augmentation therapy
• Intravenous augmentation therapy may slow down the progression of emphysema **(Evidence B)**.
Antitussives
• There is no conclusive evidence of a beneficial role of antitussives in patients with COPD **(Evidence C)**.
Vasodilators
• Vasodilators do not improve outcomes and may worsen oxygenation **(Evidence B)**.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 11.10.2016

#	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,ab,kw
3	#1 or #2
4	(chronic NEXT bronchitis):ti,ab,kw or (emphysema):ti,ab,kw or (Chronic NEXT obstructive NEXT airways NEXT disease):ti,ab,kw or (Chronic NEXT obstructive NEXT lung NEXT disease):ti,ab,kw or (COAD OR COLD):ti,ab,kw
5	#3 or #4
	#5 from 2011 to 2016

SR, HTAs in Medline (PubMed) am 09.01.2017

#	Suchfrage
1	("pulmonary disease, chronic obstructive/drug therapy"[Majr]) OR "pulmonary disease, chronic obstructive/therapy"[Majr]
2	("chronic obstructive pulmonary disease"[Title/Abstract]) OR copd[Title/Abstract] OR (chronic[Title/Abstract] AND obstructive[Title/Abstract] AND (pulmonary[Title/Abstract] OR lung[Title/Abstract]) AND disease[Title/Abstract])
	chronic[Title/Abstract] OR COAD[Title/Abstract]
3	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
4	(#2) AND #3
5	(#1) OR #4
6	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
7	((#6) AND ("2012/01/01"[PDAT] : "2017/01/09"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 09.01.2017

#	Suchfrage
1	"Pulmonary Disease, Chronic Obstructive"[Majr]
2	("chronic obstructive pulmonary disease"[Title/Abstract]) OR copd[Title/Abstract] OR (chronic[Title/Abstract] AND obstructive[Title/Abstract] AND (pulmonary[Title/Abstract] OR lung[Title/Abstract] AND disease[Title/Abstract])
3	(#1) OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
5	(#4) AND ("2012/01/01"[PDAT] : "2017/01/09"[PDAT])
6	(#5) NOT ((comment[Publication Type]) OR letter[Publication Type])
7	(#6) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

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Anhang:

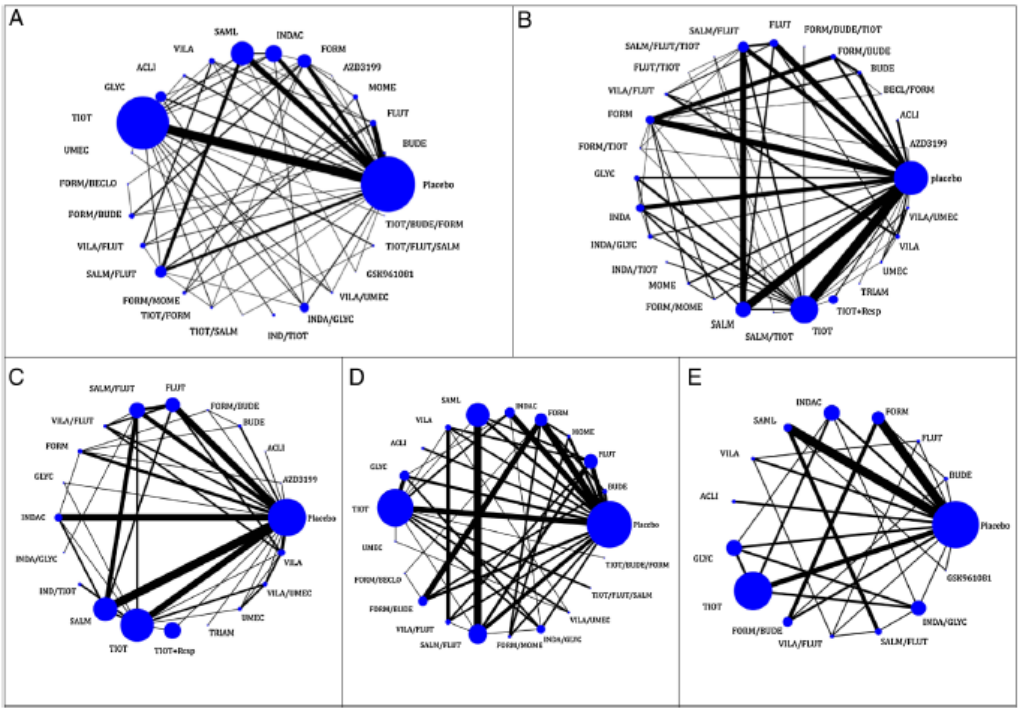

Figure 3 Network meta-analysis plots. (A) Exacerbation, (B) mortality, (C) cardiovascular-related mortality, (D) pneumonia and (E) serious arrhythmia. Nodes are proportional to the number of patients included in the corresponding treatments, and edges are weighted according to the number of studies included in the respective comparisons. BECL, beclomethasone; BUDE, budesonide; FLUT, fluticasone; MOME, mometasone; TRIAM, triamcinolone acetonide; AZD3199, AZD3199 (ultra LABA); FORM, formoterol; INDAC, indacaterol ; SALM, SAML, salmeterol; VILA, vilanterol; ACLI, aclidinium bromide; GLYC, glycopyrronium bromide; DAROT, darotropium bromide; TIOT, tiotropium; UMEC, umeclidinium; FORM/BECLO, BECL/FORM, formoterol/beclomethasone; FORM/BUDE, formoterol/budesonide; VILA/FLUT, vilanterol/fluticasone; SALM/FLUT, salmeterol/ fluticasone/; FORM/MOME, formoterol/mometasone; TIOT/BUDE, tiotropium/budesonide; TIOT/FLUT, FLUT/TIOT, tiotropium/ fluticasone; TIOT/FORM, FORM/TIOT, tiotropium/formoterol; TIOT/SALM, tiotropium/salmeterol; IND/TIOT, indacaterol/tiotropium; INDA/GLYC, indacaterol/glycopyrronium; VILA/UMEC, vilanterol/umeclidinium; GSK961081, GSK961081; FORM/IPRATR, formoterol+ipratropium bromide; TIOT/FLUT/SALM, tiotropium/fluticasone/salmeterol; TIOT/BUDE/FORM, FORM/BUDE/TIOT, tiotropium/budesonide/formoterol; BUDE/FORM/IPRATR, budesonide/formoterol/ipratropium bromide; TIOT+Resp, Tiotropium Respimat (Soft Mist Inhaler).

Abbildung 1: Grafik der Netzwerke aus Tricco AC, et al. 2015 [35].

Table 3 Statistically significant network meta-analysis results

Treatment comparison	NMA estimate OR (95% CI)	CI	MA estimate OR (95% CI)	CI	Number of studies (Number of patients)	MA Heterogeneity variance
Exacerbation past year—20 studies, 17 treatments, 26 141 patients						
FLUT/SALM vs SALM	0.85	0.75–0.97	0.82	0.70–0.95	4 (2784)	0.00
TIOT vs INDAC	0.83	0.72 to 0.96	0.83	0.72 to 0.96	1 (3439)	–
TIOT vs SALM	0.82	0.73 to 0.93	0.84	0.76 to 0.92	1 (7376)	–
SALM vs placebo	0.79	0.64 to 0.97	0.80	0.58 to 1.09	1 (634)	–
INDAC vs placebo	0.78	0.61 to 1.00				
BUDE/FORM vs FORM	0.76	0.64 to 0.91	0.76	0.62 to 0.93	4 (3080)	0.01
FLUT/F vs VILA	0.75	0.62 to 0.92	0.75	0.61 to 0.94	2 (1624)	0.00
INDAC/GLYC vs TIOT	0.74	0.60 to 0.91	0.74	0.60 to 0.91	1 (1466)	–
INDAC/GLYC vs FLUT/SALM	0.71	0.55 to 0.92				
FLUT/SALM vs Placebo	0.67	0.53 to 0.85				
TIOT vs Placebo	0.65	0.53 to 0.79	0.64	0.50 to 0.83	1 (1003)	–
BUDE/FORM vs placebo	0.64	0.45 to 0.91	0.55	0.36 to 0.83	1 (519)	–
INDAC/GLYC vs GLYC	0.63	0.51 to 0.78	0.63	0.51 to 0.77	1 (1469)	–
INDAC/GLYC vs INDAC	0.62	0.48 to 0.79				
INDAC/GLYC vs SALM	0.61	0.48 to 0.78				
TIOT/FLUT/SALM vs placebo	0.58	0.35 to 0.96				
INDAC/GLYC vs FORM	0.57	0.36 to 0.90				
TIOT/BUDE/FORM vs INDAC/GLYC	0.48	0.28 to 0.83				
INDAC/GLYC vs placebo	0.48	0.36 to 0.64				
TIOT/BUDE/FORM vs TIOT/FLUT/SALM	0.40	0.21 to 0.80				
TIOT/BUDE/FORM vs BUDE/FORM	0.36	0.19 to 0.69				
TIOT/BUDE/FORM vs TIOT	0.36	0.22 to 0.59	0.36	0.22 to 0.59	1 (660)	–
TIOT/BUDE/FORM vs FLUT/SALM	0.35	0.21 to 0.58				
TIOT/BUDE/FORM vs TIOT/SALM	0.33	0.17 to 0.65				
TIOT/BUDE/FORM vs BECL/FORM	0.32	0.15 to 0.65				
TIOT/BUDE/FORM vs BUDE	0.31	0.16 to 0.60				
TIOT/BUDE/FORM vs GLYC	0.30	0.18 to 0.52				
TIOT/BUDE/FORM vs INDAC	0.30	0.18 to 0.50				
TIOT/BUDE/FORM vs SALM	0.30	0.18 to 0.49				
TIOT/BUDE/FORM vs FLUT	0.29	0.14 to 0.60				
TIOT/BUDE/FORM vs FORM	0.28	0.15 to 0.52				
TIOT/BUDE/FORM vs placebo	0.23	0.14 to 0.40				
Between-study heterogeneity variance for NMA			0.00			
Design-by-treatment interaction model for inconsistency χ^2 (df, p value, heterogeneity)			3.37 (4, 0.498, 0.00)			
Mortality overall—88 studies, 28 treatments, 97 526 patients						
FORM vs FLUT/SALM	1.64	1.01 to 2.67				0.00
FLUT/SALM vs Placebo	0.78	0.63 to 0.96	0.81	0.66 to 1.00	6 (4852)	0.00
FLUT/SALM vs FLUT	0.75	0.60 to 0.94	0.76	0.62 to 0.93	3 (3752)	0.00
Between-study heterogeneity variance for NMA			0.00			
Design-by-treatment interaction model for inconsistency χ^2 (df, p value, heterogeneity)			31.44 (50, 0.982, 0.00)			
Cardiovascular-related mortality—37 studies, 20 treatments, 55 156 patients						
TIOT+Resp vs SALM	2.32	1.38 to 3.88				
TIOT vs SALM	2.00	1.23 to 3.26	1.32	0.46 to 3.81	1 (7798)	–
TIOT+Resp vs FLUT/SALM	1.87	1.14 to 3.06				
TIOT+Resp vs FLUT	1.75	1.04 to 2.94				
TIOT vs FLUT/SALM	1.61	1.02 to 2.56	2.12	0.95 to 4.72	1 (1448)	–
SALM vs placebo	0.63	0.45 to 0.88	0.60	0.42 to 0.87	4 (5171)	0.00
Between-study heterogeneity variance for NMA			0.00			
Design-by-treatment interaction model for inconsistency χ^2 (df, p value, heterogeneity)			11.79 (27, 0.995, 0.00)			

Abbildung 2: statistisch signifikante Ergebnisse aus Tricco AC, et al. 2015 [35].

Table 3 Continued

Treatment comparison	NMA estimate OR (95% CI)	CI	MA estimate OR (95% CI)	CI	Number of studies (Number of patients)	MA Heterogeneity variance
Pneumonia—54 studies, 21 treatments, 61 551 patients						
FLUT/VILA vs ACLI	3.15	1.07 to 9.24				
FLUT/VILA vs BUDE	2.83	1.10 to 7.25				
FLUT/SALM vs ACLI	2.81	1.30 to 6.07				
FLUT/VILA vs GLYC	2.59	1.09 to 6.18				
FLUT/SALM vs BUDE	2.52	1.44 to 4.43				
FLUT/SALM vs GLYC	2.31	1.47 to 3.64				
FLUT/VILA vs TIOT	2.25	1.02 to 4.96				
FLUT vs BUDE	2.21	1.25 to 3.92				
FLUT/SALM vs FORM	2.09	1.29 to 3.37				
FLUT/SALM vs TIOT	2.00	1.52 to 2.64	2.20	1.33 to 3.62	1 (1323)	–
FLUT/SALM vs INDAC	1.95	1.20 to 3.17				
FLUT/SALM vs placebo	1.90	1.53 to 2.34	1.75	1.44 to 2.13	4 (3872)	<0.0001
FLUT/VILA vs VILA	1.87	1.18 to 2.96	1.90	1.20 to 3.01	4 (2442)	0.00
FLUT/SALM vs SALM	1.70	1.38 to 2.09	1.69	1.40 to 2.04	8 (7613)	0.00
FLUT vs placebo	1.66	1.32 to 2.08	1.60	1.32 to 1.95	5 (4258)	0.00
SALM vs FLUT	0.67	0.54 to 0.84	0.68	0.56 to 0.83	2 (3174)	0.00
INDAC vs FLUT	0.58	0.36 to 0.95				
TIOT vs FLUT	0.57	0.43 to 0.75				
FORM vs FLUT	0.55	0.33 to 0.90				
INDAC/GLYC vs FLUT	0.51	0.31 to 0.85				
GLYC vs FLUT	0.49	0.31 to 0.78				
INDAC/GLYC vs FLUT/SALM	0.45	0.27 to 0.75	0.11	0.01 to 2.09	1 (522)	–
ACLI vs FLUT	0.41	0.19 to 0.88				
INDAC/GLYC vs FLUT/VILA	0.40	0.16 to 0.98				
Between-study heterogeneity variance for NMA			0.01			
Design-by-treatment interaction model for inconsistency χ^2 (d.f., p value, heterogeneity)			34.33 (31, 0.311, 0.00)			

ACLI, aclidinium bromide; BECL, beclomethasone; BUDE, budesonide; d.f., degrees of freedom; FLUT, fluticasone; FORM, formoterol; GLYC, glycopyrronium bromide; INDAC, indacaterol; MA, meta-analysis; NMA, network meta-analysis; SALM, salmeterol; TIOT, tiotropium; TIOT +Resp, Tiotropium Respimat (Soft Mist Inhaler); VILA, vilanterol.

Abbildung 3: Fortsetzung statistisch signifikanter Ergebnisse aus Tricco AC, et al. 2015 [35].

Table 1. Study characteristics

Author, year, (study duration)	Inclusion criteria				Interventions and Sample Size (n)				Primary Outcome	Concomitant drugs allowed
	Age	FEV_1	Smoke Hx	Exacerbation	Triple therapy	Dual or combination therapy	Monotherapy	No inhaled therapy		
Aaron, 2007 [28] 12 months	≥35 years	<65% predicted	≥10 pack-years	At least 1 in previous 12 months requiring antibiotics or steroids	18 μg tio OD plus FPS 500/50 μg /puff 1P BID (n = 145)	18 μg tio OD plus S 25 μg/puff 2P BID (n = 148)	18 μg tio OD plus placebo 2 P BID (n = 156)	NA	Proportion of patients experiencing at least 1 exacerbation	Albuterol, oxygen, antileukotrienes, methylxanthines
Welte, 2009 [27] 3 months	≥40 years	≤50% predicted	≥ 10 pack- years	History requiring antibiotics or steroids	18 μg tio OD plus BDF 320/9 μg /puff 1P BID(n = 329)	NA	18 μg tio OD plus placebo1P BID(n = 331)	NA	FEV_1	Terbutlaine
Cazzola, 2007 [26] 3 months	≥50 years	<70% predicted	≥20 pack- years/ current smoker	Not a criterion	18 μg tio OD plus FPS 250/25 μg /puff 2P BID (n = 29)	FPS 500/50 μg/puff 1P BID plus placebo 1P OD (n = 26)	18 μg tio OD plus placebo 1 P BID (n = 26)	NA	FEV_1	Salbutamol, theophylline
Fang, 2008 [25] 12 months	NR	25%–70% predicted	Not a criterion	At least 1 in previous 36 months requiring antibiotics or steroids	18 μg tio OD plus FPS 250/50 μg /puff BID (n = 33)	FPS 250/50 μg/puff BID (n = 32)	18 μg tio OD (n = 32)	(n = 29)	FEV_1	Albuterol

FEV_1 = forced expiratory volume in the first second of expiration; Hx = history; NA = not applicable; NR = not reported; μg = micrograms; tio = tiotropium; OD = once daily; P = puff; BID = twice daily; FPS = fluticasone/salmeterol; BDF = budesonide/formoterol; S = salmeterol.

Abbildung 4: Eigenschaften der eingeschlossenen Studien aus Gaebel K, et al. 2011 [7]

TABLE 4] American College of Chest Physicians Grading System

Grade of Recommendation	Balance of Benefit vs Risk and Burdens (Strength of the Recommendation: Level 1 or 2)	Methodological Strength of Supporting Evidence (Quality of Body of Evidence: A, B, C, or CB)	Implications
Graded evidence-based guideline recommendations			
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balance with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ, depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balance with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies	Best action may differ, depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Nongraded consensus-based suggestions			
Consensus based	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on confidence in the estimate of effect and may change the estimate.

Abbildung 5: aus Criner GJ et al., 2015 [5]