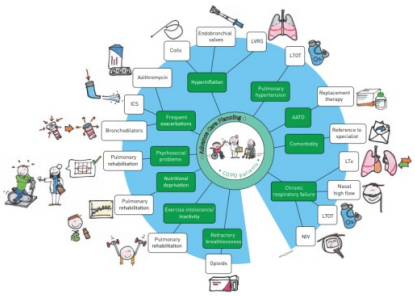
Innovatie bij COPD

En hoe integreer je dat met ACP?



Eline v.d. Ploeg, longarts i.o. (e.a.b.van.der.ploeg@umcg.nl)
Marlies van Dijk, longarts (m.van.dijk05@umcg.nl)
26-05-2023

1

Inhoud

- Korte inleiding
- Keuzemenu van behandelbare kenmerken
- Discussie: ACP en innovatie

2

2

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Disclosure belangen sprekers	
Geen potentiële belangenverstrengeling	Eline
Speakers fee ‘ERS in oranje’ (AstraZeneca; Boehringer Ingelheim; Chiesi, GSK; Sanofi)	Marlies

3

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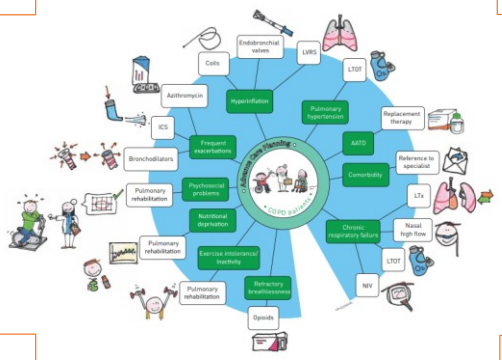
Het keuzemenu

Hyperinflatie

Bronchitis

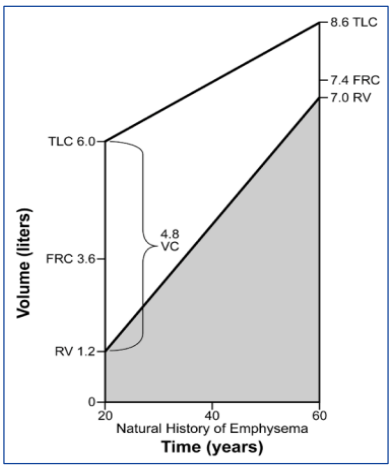


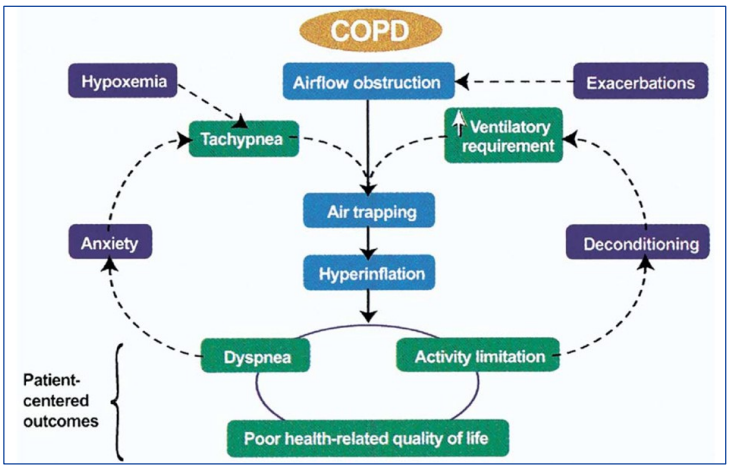
Exacerbaties

Refractaire dyspnoe

4

Hyperinflatie - inleiding

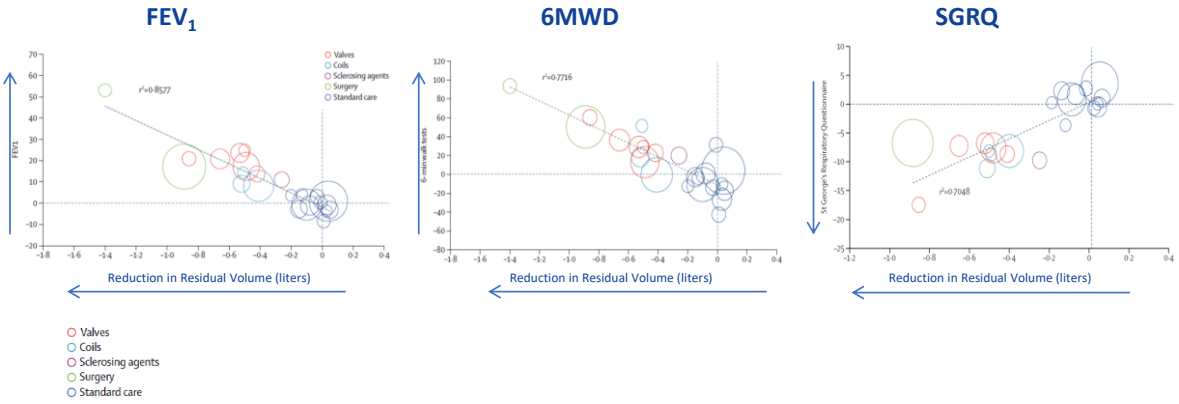




Cooper et al, *AJM*, 2006

5

Hyperinflatie als behandelbaar kenmerk



vGeffen et al, *Lancet Resp Med*, 2019

6

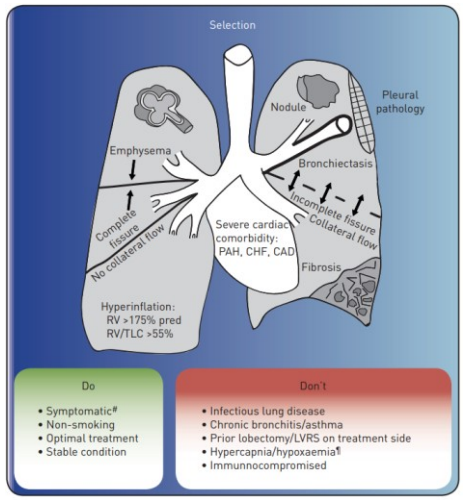
Patiëntenselectie - Indicaties

- Hoge ziektelast en een behandelwens
- Optimale behandeling COPD
- Uitgesproken hyperinflatie:
  - Post-bronchodilator in de Bodybox
  - RV>175% (of >200% bij homogeen verdeeld emfyseem)
- Emfyseem en een 'behandeltarget'

7

Patiëntenselectie - Contraindicaties

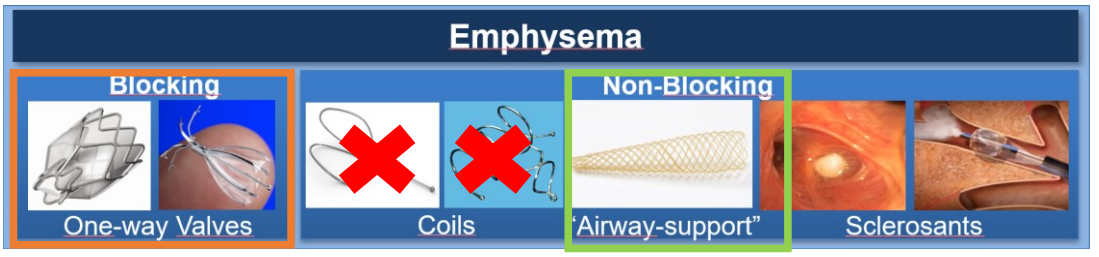
- PaO_2 <6.0 kPa, $PaCO_2$ >8.0 kPa
- Ernstige PHT (RVSP >55 mmHg)
- Hartfalen (LVEF < 40%)
- Belangrijke afwijkingen op de CT



Hartman et al, *Eur Resp Rev*, 2019

8

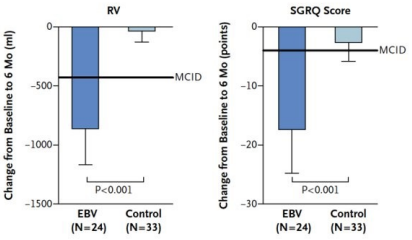
Welke bronchoscopische opties zijn er?

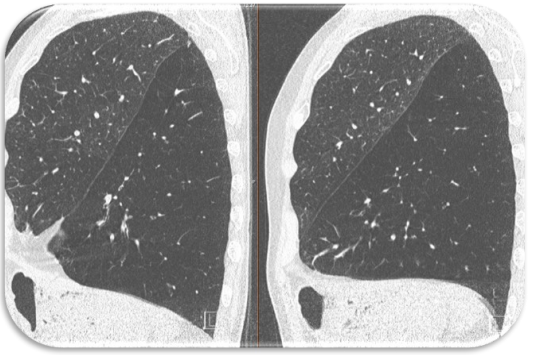


9

Ventielbehandeling

- Meest emfysemateuze longkwab
- Afsluiten met éénrichtingsventielen
  - Inductie volumeverlies



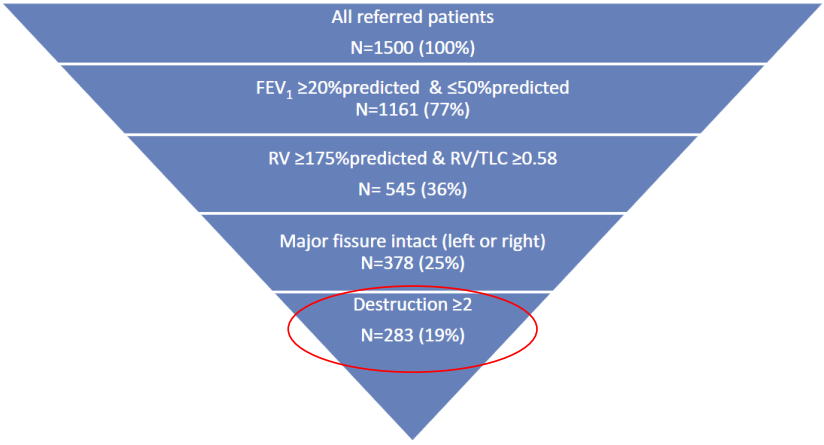


Klooster et al, *NEJM*, 2015

10

Patiëntenselectie - ventielbehandeling

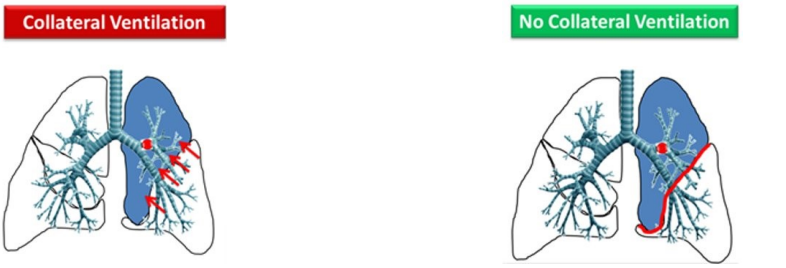
Endobronchial Valves

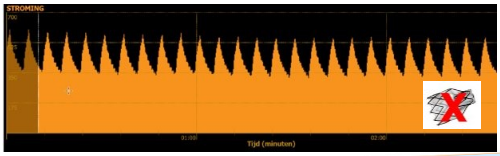


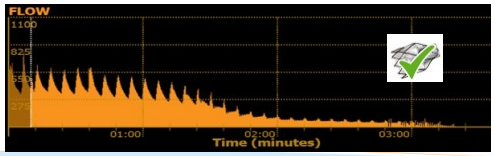
Welling et al, *Int J Chron Obstruct Pulmon Dis*, 2020

11

Vaker behandelen met ventielen ?







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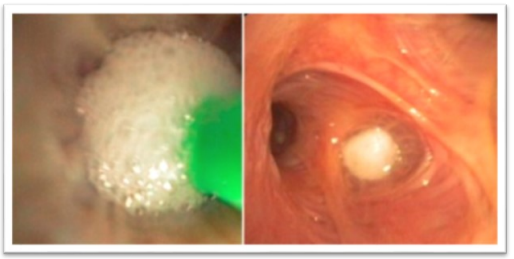
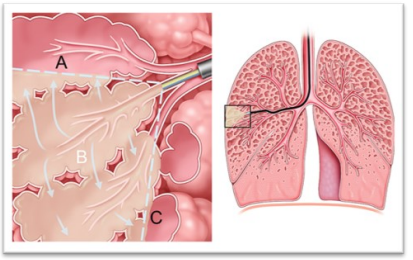
CONVERT Trial

- ‘Lijmen’ van de fissuur bij collaterale ventilatie

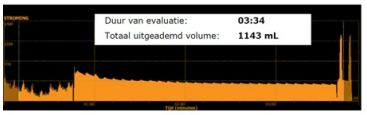




13

Voorbeeld

Chartis measurement → CV+



CONVERT-TRIAL

- Prospective, open-label, multi-center studie
  - N=140
- Patienten met een geschikte longkwab, maar collaterale ventilatie

Doel

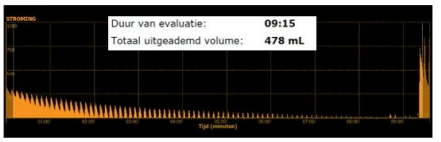
- Collaterale ventilatie opheffen
- Nadien ventielplaatsing

Vertrouwelijk

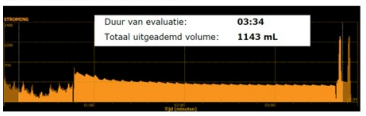
14

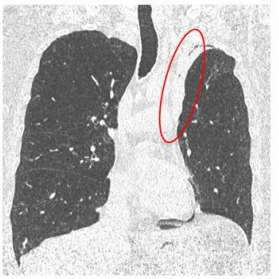
Voorbeeld

Chartis measurement → CV-



Chartis measurement → CV+



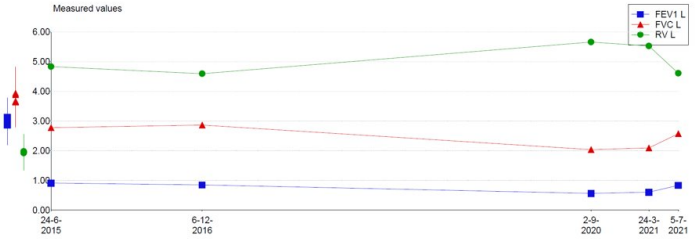


Vertrouwelijk

15

Voorbeeld

	baseline	6 week FU	
FEV_1	0,61 L (21%)	0,83 L (31%)	**+27%**
RV	5,53 L (282%)	4,61 L (163%)	**-920 ml**
RV/TLC	72%	64%	



Vertrouwelijk

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Interim analyse CONVERT

- N= 40
- Fissuur compleetheid: 89.5 % (79.5-97.7 %)
- Uitkomst
  - Opheffen collaterale ventilatie: 79% (31/40)
  - Reductie volume longkwab (6 wk): 1.1 ± 0.6 L.

ERS 2020

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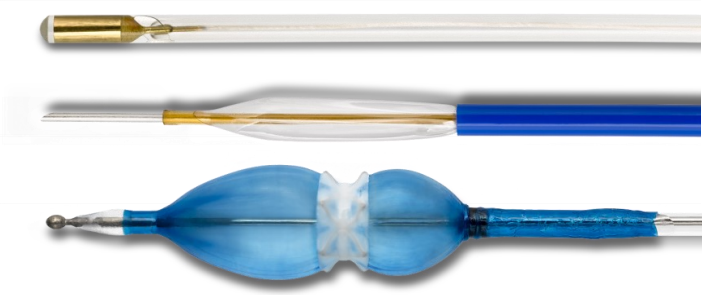
Airway bypass



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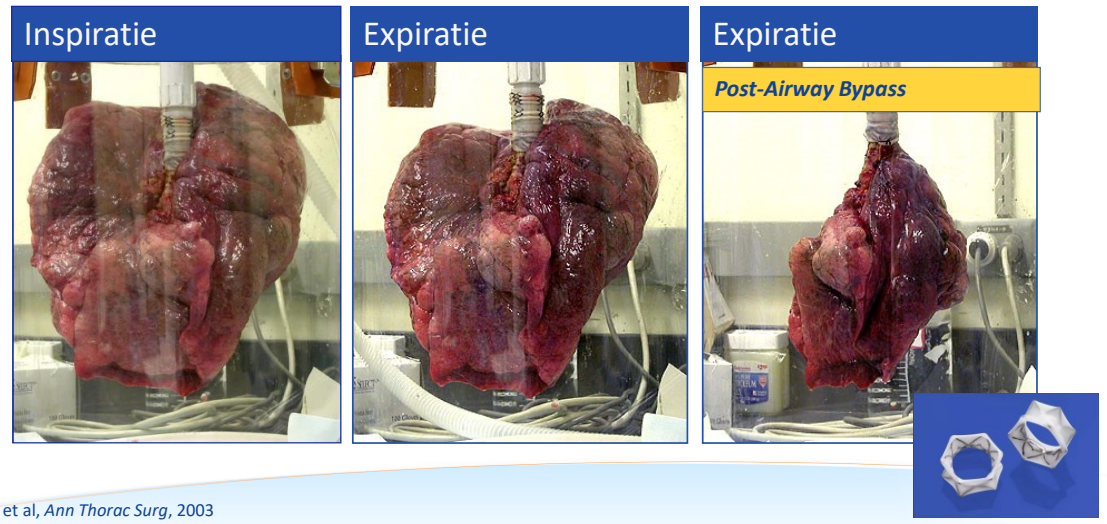
Airway bypass



Lausberg et al, *Ann Thorac Surg*, 2003

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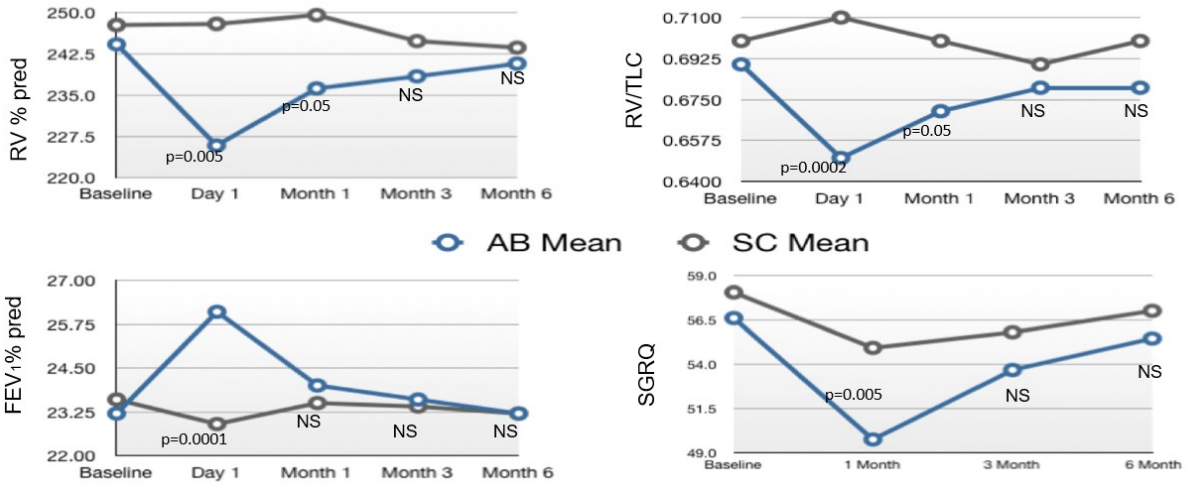
Airway bypass – EASE trial (n=315)



Shah et al, *Lancet*, 2011

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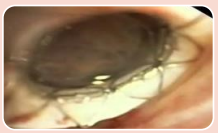
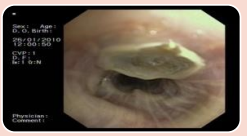
Airway bypass

Patent
- Open
- No tissue at distal end



Lung parenchyma

Mucous & Secretions



Stent 'Fibrosis'

Shah et al, *Lancet*, 2011

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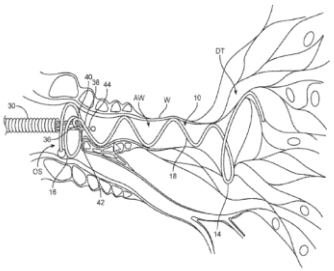
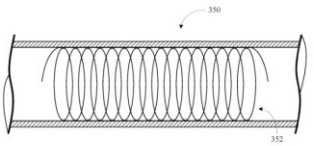
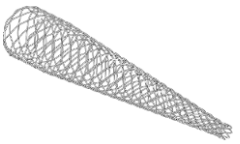
Alternatief - Airway support



US20210186512A1
(FreeFlowMedical)



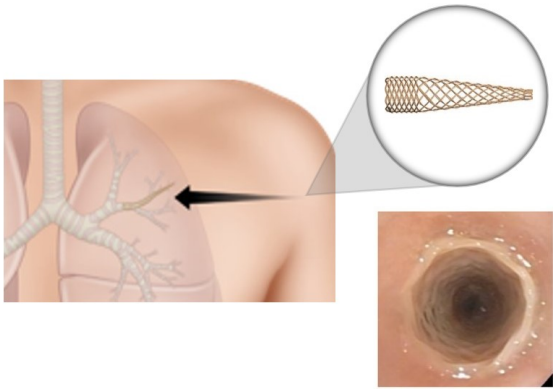
US20220280279A1
(Apreo)

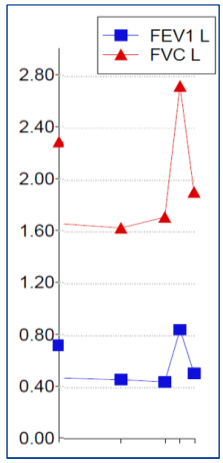


US20220354631A1
(Pulmair)

22

Implantable artificial bronchus





Vertrouwelijk

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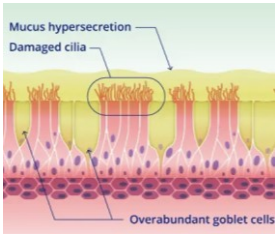
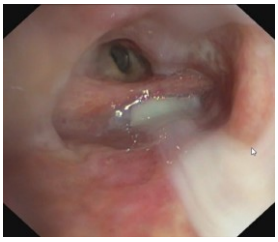
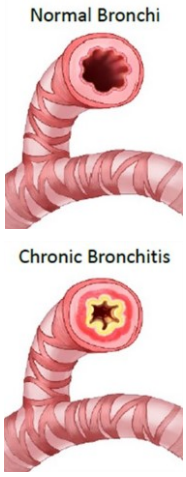
Chronische bronchitis - inleiding







Definitie: De aanwezigheid van een productieve hoest gedurende ≥3 maanden in 2 opeenvolgende jaren

Kenmerken: Luchtweginflammatie, hypersecretie van mucus en ineffectieve klaring door dysfunctie trilhaarepitheel

Prevalentie: 14-74% van patiënten met COPD

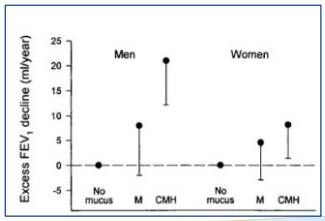
Kim et al, *Curr Op Pulm Med*, 2015

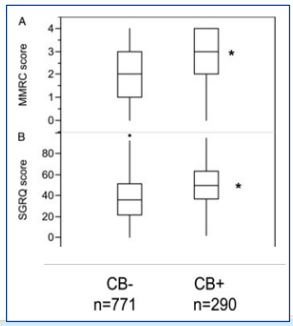
24

Chronische bronchitis - inleiding

Geassocieerd met:

- Ernstiger luchtwegobstructie
- Meer klachten
- Beperktere inspanningstolerantie
- Slechtere kwaliteit van leven
- Meer en ernstiger exacerbaties





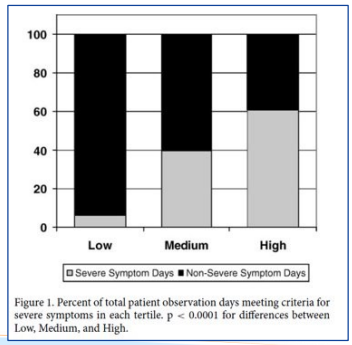


Figure 1. Percent of total patient observation days meeting criteria for severe symptoms in each tertile. p < 0.0001 for differences between Low, Medium, and High.

Vestbo et al, *AJRCCM*,1996; Kim et al, *Chest*, 2011

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Chronische bronchitis – huidige behandeling

Target mechanism	Smoking cessation	Physical measures	Expectorants	SABAs	LABAs	LAMA	Glucocorticoids (ICS)	PDE-4	Antioxidants
Reduce overproduction of mucus	X					X*	X		X
Control inflammation							X	X	
Increase ciliary transport and reduce mucus tenacity	X	X*	X*	X*	X				X
Modify cough	X								

*Evidence is not conclusive or lacking for Chronic Bronchitis patients

Kim et al, *AJRCCM*, 2013

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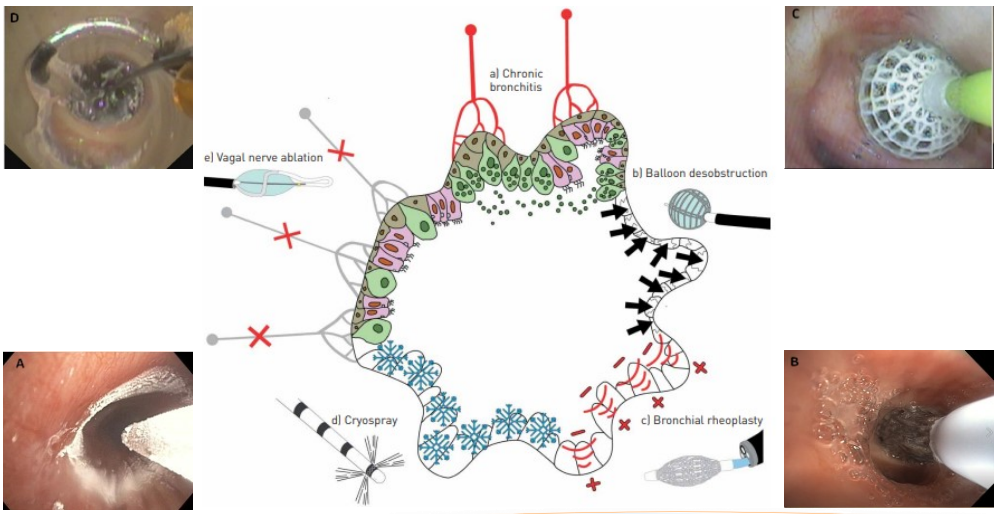
Bronchoscopische technieken

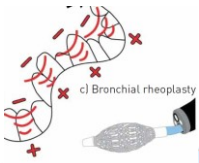


Hartman et al, *ERR*, 2021

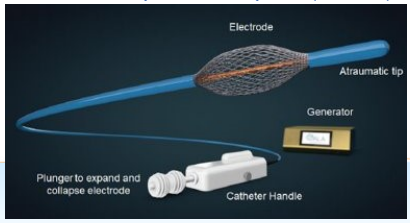
27

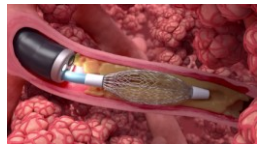
Rheoplastiek

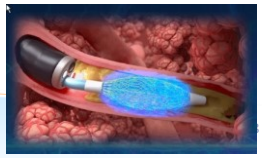
- Toediening van hoog frequente energiepulsen aan het luchtwegepitheel en de submucosa:
  - Behandeling van de 2e tot 7e luchtweggeneratie
  - 2 behandelingen van 30-60 minuten (1 maand interval)
  - Dagbehandeling
- Doel: Regeneratie van het epitheel met minder slijmbekercellen d.m.v. apoptose



The Gala Airway Treatment System (RheOx™)







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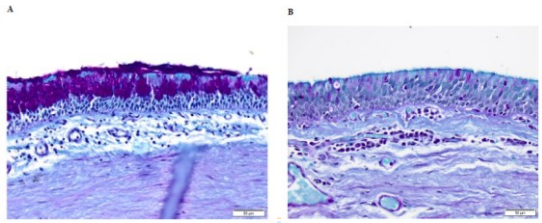
Rheoplastiek – Resultaat tot nu toe

- 1 publicatie: 30 patiënten, open-label
- In luchtwegbiopten (n=54) 39% reductie slijmbekercellen
- 4 SAE's gerelateerd aan de behandeling, zonder blijvende schade

TABLE 3 Results of multicentre RheOx bronchial rheoplasty study [30]

	RCT	Subjects	Time point	Result
Quality of life				
SGRQ total score change	No	30	3 months	−16.9±20.0
	No	29	12 months	−15.2±20.4
CAT total score change	No	30	3 months	−8.8±7.6
	No	29	12 months	−7.0±8.9
Chronic bronchitis symptoms#				
CAT change in question on phlegm	No	30	3 months	−1.8±1.1
	No	29	12 months	−1.7±1.5
CAT change in question on cough	No	30	3 months	−1.4±1.3
	No	29	12 months	−1.1±1.6
Lung function	No	29/30	3 and 12 months	No sign changes
Exercise capacity	Not reported			



Vooraf 120 dagen na

Vallipour et al, *AJRCCM*, 2020

29

Rheoplastiek – Huidig onderzoek

- In 2021
- Start RCT in de US en Europa: *Rhesolve studie*
  - Sham gecontroleerd, dubbelblind
  - N=270
  - 2 jaar Follow up
  - Primair eindpunt: Verandering in kwaliteit van leven

Past Present Future

ClinicalTrials.gov Identifier: NCT04677465

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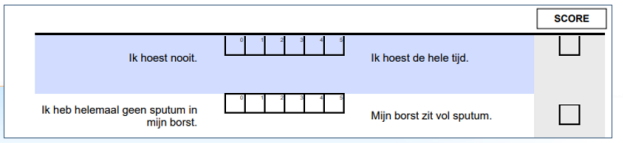
Rheoplastiek – Patientselectie

- COPD, FEV_1 >30%
- Aanwezigheid van chronische bronchitis (CAT vraag 1+2: ≥ 6 punten)
- Roken > 6 mnd gestaakt
- Symptomatisch (CAT > 10; SGRQ >25 punten)

- Geen astma, bronchiectasieën of ernstig emfyseem
- Geen electronische devices (Pacemaker, ICD)
- Geen hartritmestoornis in de afgelopen 2 jaren



ClinicalTrials.gov Identifier: NCT04677465

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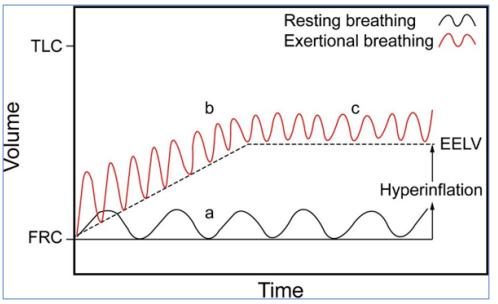
Refractaire dyspnoe - inleiding

- Dyspnoe meest voorkomende symptoom bij COPD
- Disbalans tussen:
  - Vraag naar adem en kunnen voldoen aan deze vraag
- Dynamische hyperinflatie veelvoorkomend



O'Donnell et al; *ERR*; 2006

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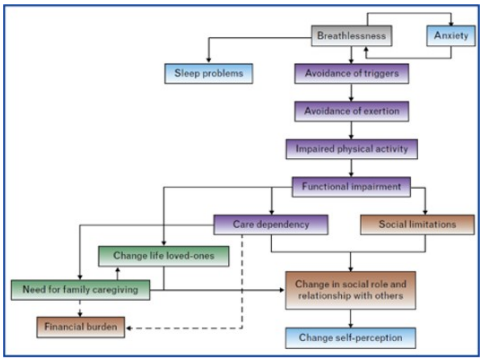
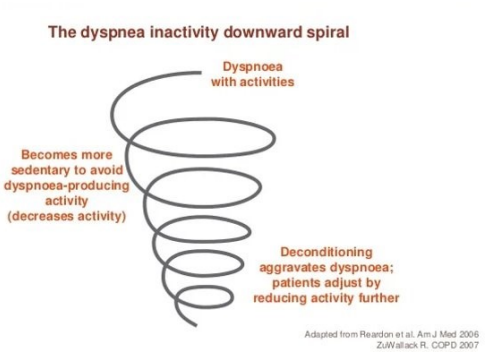
Vicieuze cirkel





Hoe deze cirkel te doorbreken?

Handheld NIV of PEP-buddy™?

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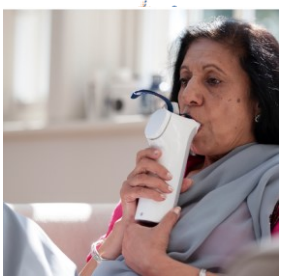
Handheld NIV



- Vitabreath - Philips
- Draagbaar, maar (nog) zware batterij
- Geeft 18 cm$H_2$0 inspiratoire druk en 8 cm $H_2$0 PEEP
- Doel om dyspnoe te verminderen na dagelijkse activiteiten
  - Actiever, meer participatie, meer conditie

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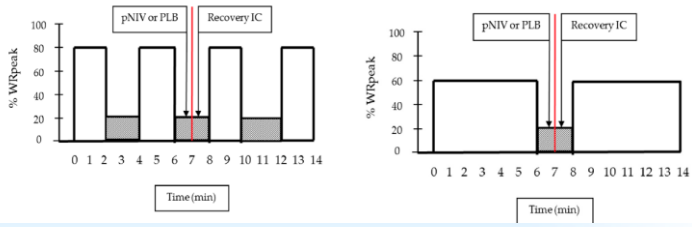
Article

Intermittent Use of Portable NIV Increases Exercise Tolerance in COPD: A Randomised, Cross-Over Trial

Ioannis Vogiatzis [1,2,*,†], Nikolaos Chynkiamis [1,†], Matthew Armstrong [1], Nicholas D. Lane [2,3], Tom Hartley [2,3], William K. Gray [2] and Stephen C. Bourke [2,3]

- Gerandomiseerde, open label cross over studie
- 24 patiënten met COPD GII-IV met dynamische hyperinflatie

- Inspanning op matige of hoge intensiteit
  - Handheld NIV (pNIV) of pursed lip breathing (PLB)
  - Uithoudingsvermogen getest op 2 en 12 weken
  - 24 weken follow up



Vogiatzis et al, *J Clin Med*, 2019

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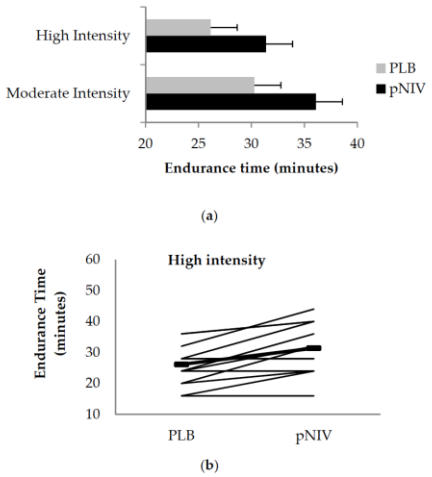
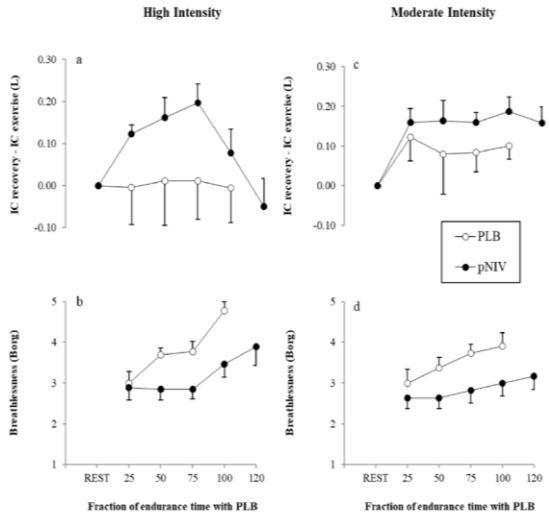
Uitkomsten inspanning





Vogiatzis et al, *J Clin Med*, 2019

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Uitkomsten angst

Table 4. Effects of the use of VitaBreath device on anxiety, symptom burden and ability to perform tasks.

Question	Pre-VitaBreath	Post-VitaBreath	*p*-Value
How anxious are you about becoming short of breath (SOB)? 1 = Not at all anxious 10 = Very anxious	7.50 (5.25–8.75)	4.00 (2–5.75)	0.001 * 20 improvements 2 worse 2 ties
How long did it take you to recover from SOB?			0.002 * 17 improvements 3 worse 4 ties
<1 min	0 (0%)	6 (25%)	
2–3 min	7 (29.2%)	9 (37.5%)	
4–5 min	3 (12.5%)	4 (16.7%)	
5–7 min	5 (20.8%)	1 (4.2%)	
7–10 min	5 (20.8%)	2 (8.3%)	
More than 10 min	4 (16.7%)	2 (8.3%)	

- 23/24 patiënten gebruikten het apparaat dagelijks na 16 weken

Vogiatzis et al, *J Clin Med*, 2019

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Effect of portable noninvasive ventilation on thoracoabdominal volumes in recovery from intermittent exercise in patients with COPD

N. Chynkiamis,[1] N. D. Lane,[2,4] D. Megaritis,[1] J. Manifield,[1] I. Loizou,[1] C. Alexiou,[1] S. Riazati,[1] A. LoMauro,[3] S. C. Bourke,[2,4*] and I. Vogiatzis[1,2*]

[1]*Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle Upon-Tyne, United Kingdom;* [2]*Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, Newcastle Upon-Tyne, United Kingdom;* [3]*Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milano, Italy; and* [4]*Translational and Clinical Research Institute, Newcastle University, Newcastle Upon-Tyne, United Kingdom*

- 14 patiënten met COPD (FEV1 55% ± 22%)
- Twee fietstesten 5x 2 minuten met pNIV tijdens herstel
- Meten van dynamische hyperinflatie en thoracoabdominale volumes

Chynkiamis et al, *J of Appl Phys*, 2021

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Resultaten

Table 2. *Breathing pattern and symptoms during acute application of pNIV and PLB*

	Responders			Nonresponders		
	pNIV	PLB	*P*	pNIV	PLB	*P*
V_T, L	1.9 ± 0.7	1.4 ± 0.5	0.002	1.1 ± 0.3*	1.2 ± 0.4	0.369
bf, breaths/min	21 ± 3	22 ± 5	0.478	27 ± 5*	20 ± 4	0.002
V_E, L/min	39.0 ± 16.6	32.5 ± 12.4	0.009	29.1 ± 7.6	23.4 ± 9.2	0.018

- Responders gebruikten abdominale spieren om DH tegen te gaan
- Hogere BMI geassocieerd met betere respons
  - Minder hyperinflatie in rust

Chynkiamis et al, *J of Appl Phys*, 2021

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PEP-buddy

- Dynamische hyperinflatie draagt bij aan dyspnoe bij COPD patienten
- Met name dyspnoe bij inspanning (80%)
- Pursed lip breathing
  - Wisselend behaalde drukken door patiënten, niet altijd consequent

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PEP-buddy

- Manometry optimized positive expiratory pressure (PEP) breathing
- Draagbaar om de hals
- Creëert ongeveer 4-10 cm H20 aan druk bij expiratie
- Hypothese:
  - Afname V/Q mismatch
  - Afname dynamische hyperinflatie door afname ademfrequentie
  - Preventie van luchtwegcollaps

Zafar, *Chest*, 2021
Zafar, *Resp Care*, 2023

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A Hands-free, Oral, Positive Expiratory Pressure Device for Exertional Dyspnea and Desaturation in COPD

- Pilot studie
- 32 patiënten met COPD (FEV_1 45±14%) met dyspnoe d'effort tijdens 6MWD
- Exclusie: patiënten met recente opname, LTOT
- Gebruiken van PEP buddy tijdens inspanning, rust

Zafar, *Resp Care*, 2023

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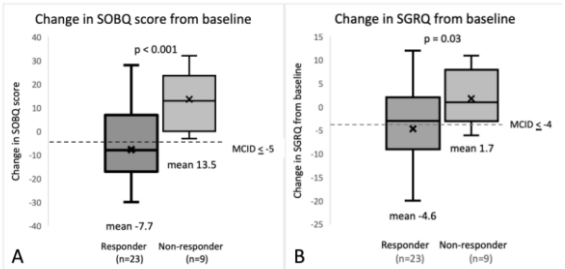
Uitkomsten

- Overall
  - BORG 3.8 vs 3.6 (PEP)
  - SOBQ 52.8 vs 51.1(PEP)
  - SGRQ 50.1 vs 47.2 (PEP)
- 23/32 responders
  - Lagere FEV_1 (40% vs 57%, p<0.01)
  - Lagere FVC (69% vs 82%, p=0.03)



Zafar, *Resp Care*, 2023

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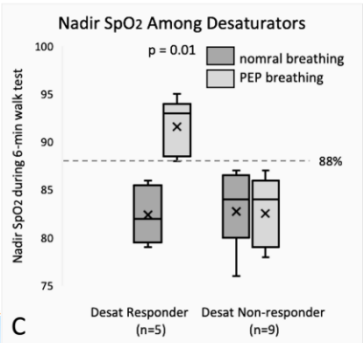
Desaturatie

- 14/32 deelnemers desatureerden (<88%) vooraf bij inspanning
  - 5 deelnemers geen desaturatie met PEP Buddy
  - 9 deelnemers desatureerden nog steeds (6 wel een dyspnoe respons)



Zafar, *Resp Care*, 2023

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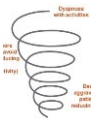
Refractaire dyspnoe - Conclusie

- Beiden gemakkelijke add-on innovatie voor COPD patiënten
- Met name bij dynamische hyperinflatie, desaturatie
- Nog meer onderzoek nodig voor goede patiëntenselectie, werkingsmechanisme en kwaliteit van leven
- Wat vinden jullie hiervan? Zouden jullie deze opties bespreken?



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Exacerbaties - inleiding

- Voorkomen van exacerbaties belangrijk:
  - Afname levensverwachting, kwaliteit van leven
- Hoge kosten en druk op de zorg
  - COPD zorguitgaven 753 miljoen/jaar
  - 2019 34, 960 opnames met 243,505 opname dagen!
  - ~50% kosten van zorguitgaven op basis van ziekenhuisopnames bij exacerbaties
- 20% van de patienten wordt binnen twee jaar 3x of vaker opgenomen
- Inmiddels roflimulast, macroliden; wie schrijft dit voor? Is er meer?

RIVM, VZinfo, opendata CBS

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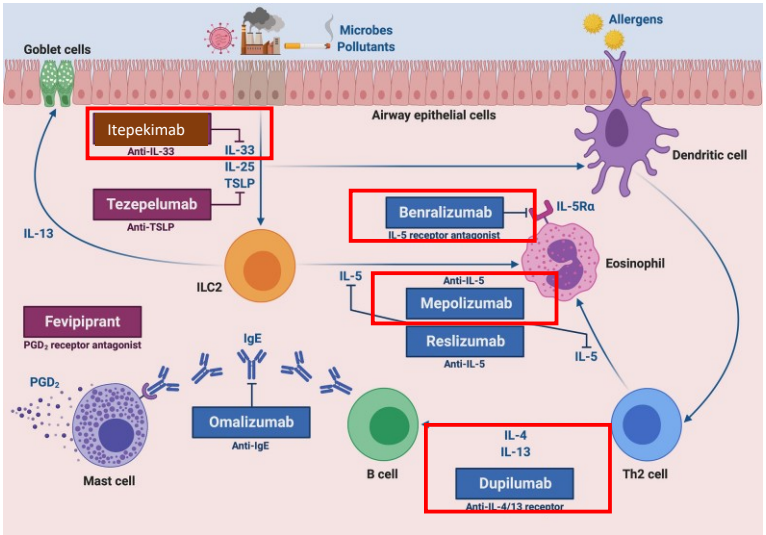
Biologicals bij exacerbaties



Pelaia, *Front Immunol*, 2020

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Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial

Klaus F Rabe, Bartolome R Celli, Michael E Wechsler, Raolat M Abdulai, Xiaodong Luo, Maarten M Boomsma, Heribert Staudinger, Julie E Horowitz, Aris Baras, Manuel A Ferreira, Marcella K Ruddy, Michael C Nivens, Nikhil Amin, David M Weinreich, George D Yancopoulos, Helene Goulaouic

- Gerandomiseerde, dubbel blinde, fase 2a studie in 10 landen
- COPD, 40-75jr, >10 PY, huidige of gestopte rokers, standaardtherapie toegestaan, min 2 matige of 1 ernstige exacerbatie
- Exclusie: gebruik van macroliden, roflimulast of montelukast
- 24-52 weken, om de 2 weken injectie

Rabe, *Lancet resp med*, 2021

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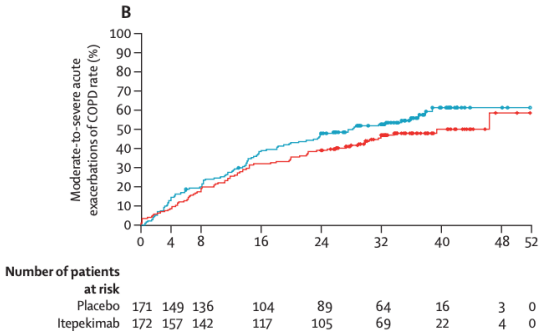
Resultaten



- 19% reductie in exacerbatie frequentie, niet significant
- Maar..

Rabe, *Lancet resp med*, 2021

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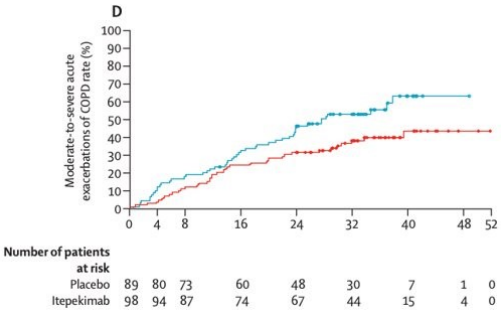
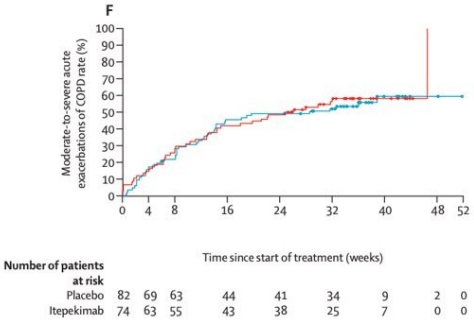
Resultaten

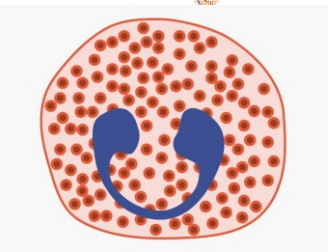




- Bij gestopte rokers: 42% risicoreductie én 0.9L FEV1 verbetering!
- Goed getolereerd, weinig bijwerkingen

Rabe, *Lancet resp med*, 2021

Maar ook anti IL-5!



- Eosinofilie >2% verhoogd risico op exacerbaties in COPD

4 grote RCT's:

- Mepolizumab: >150 eosinofielen bij screening of >300 in afgelopen jaar, 1500 deelnemers, triple therapie
- Benralizumab: >220 eosinofielen bij screening, 2436 deelnemers, duale of triple therapie

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Mepolizumab

- METREX
  - 1.7 exac/ jaar in placebo vs 1.4 in mepolizumab (p=0.04)
- METREO
  - Geen significant verschil tussen exacerbaties per jaar
- In beide studies geen verbetering SGRQ of CAT
- Geen verbetering van longfunctie

Pavord, *NEJM*, 2021

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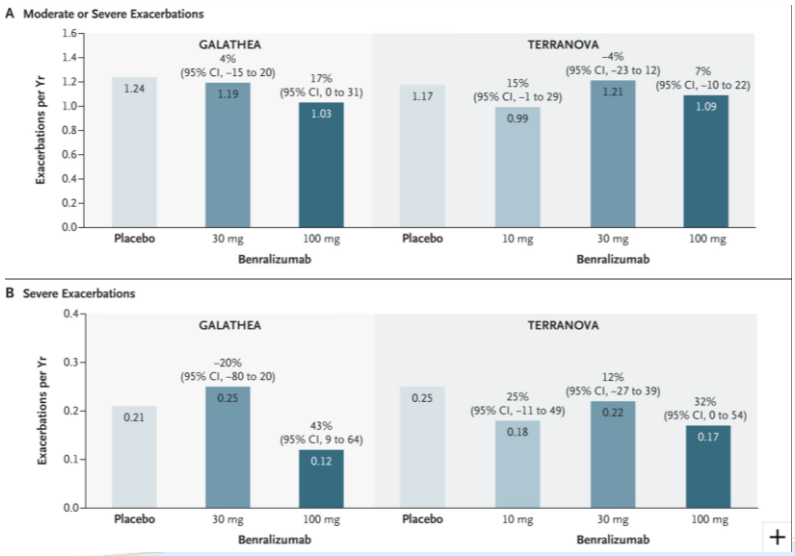
Benralizumab



Criner, *NEJM*, 2021

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Vers van de pers!

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

Surya P. Bhatt, M.D., M.S.P.H., Klaus F. Rabe, M.D., Ph.D., Nicola A. Hanania, M.D., Claus F. Vogelmeier, M.D., Jeremy Cole, M.D., Mona Bafadhel, M.D., Ph.D., Stephanie A. Christenson, M.D., Alberto Papi, M.D., Dave Singh, M.D., Elizabeth Laws, Ph.D., Leda P. Mannent, M.D., Naimish Patel, M.D., et al., for the BOREAS Investigators*

Article Figures/Media Metrics May 21, 2023
DOI: 10.1056/NEJMoa2303951

- Fase 3, dubbel blind, gerandomiseerde studie
- COPD FEV1 30-70%, ≥ 300 eosinofielen bij screening met ≥ 3 maanden klachten van bronchitis
- Triple therapie
- Onduidelijk of roflumilast en azitromycine exclusiecriteria waren

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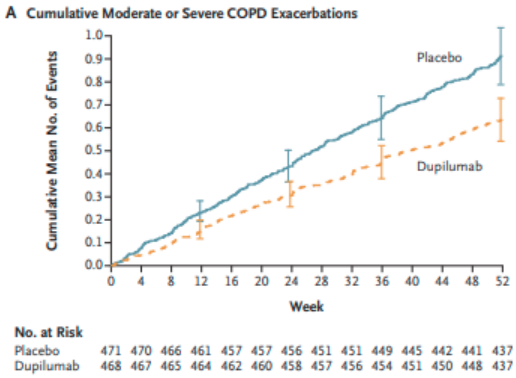
Resultaten

- Rate ratio exacerbaties dupilimab vs. placebo groep 0.70 (0.58 to 0.86) <0.001

End Point	Placebo (N=471)	Dupilumab (N=468)	P Value
Change in SGRQ total score from baseline to wk 52			
Least-squares mean change (95% CI)	−6.4 (−8.0 to −4.8)	−9.7 (−11.3 to −8.1	
Least-squares mean difference vs. placebo (95% CI)	—	−3.4 (−5.5 to −1.3)	0.002
SGRQ total score improvement ≥4 points at wk 52			
Percentage of patients (95% CI)	43.1 (38.6 to 47.7)	51.5 (46.9 to 56.1)	
Odds ratio vs. placebo (95% CI)	—	1.4 (1.1 to 1.9)	0.009



Bhatt, *NEJM*, 2023

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Kosten biologicals vs opname?

Disclaimer: Geen exacte wetenschap!

- Dupilumab: Circa 16,380 euro per jaar
- Circa 35.000 opnames per jaar, waarvan 50% >1 keer
  - 20% van patienten met COPD met rec. exacerbaties heeft eosinofilie
  - 10% in aanmerking voor Dupilumab?

- 3500 patienten Dupilumab/jaar: 57 miljoen euro
- Reductie van 30% ziekenhuisopnames: 13 miljoen euro

- Proportioneel?

RIVM, VZinfo, opendata CBS

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Biologicals voor exacerbaties - conclusie

- Anti-IL33
  - Bij niet-rokers effect op exacerbaties
- Anti-IL5
  - Wisselende uitkomsten
  - Patientenselectie belangrijk: afkappunt eosinofielen?
- Anti-IL4
  - Exacerbatie frequentie significant gereduceerd met 30%
  - Effect van roken?
- Gevolgen voor patiënt? Kosten?
- Patiëntselectie is key!

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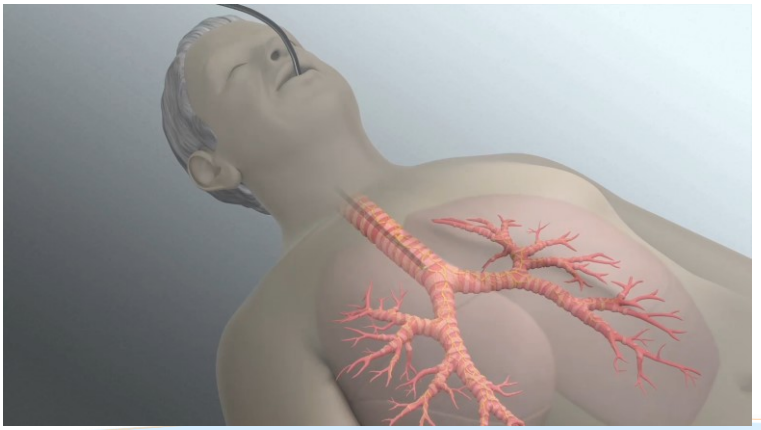
Exacerbaties – bronchoscopische optie

- Targeted long deneratie (TLD)



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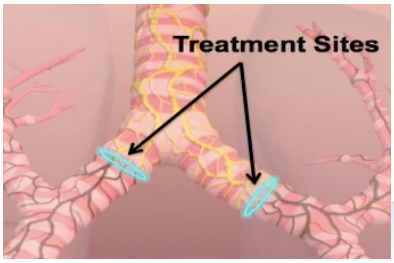
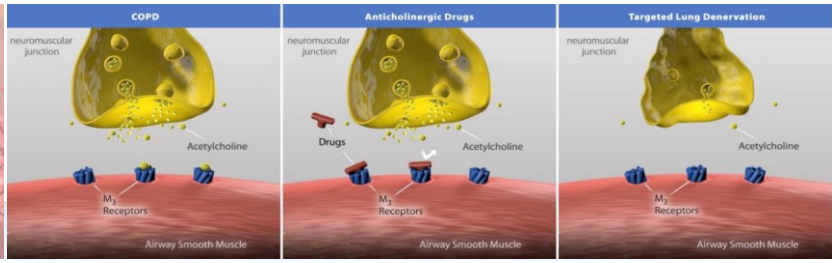
Targeted long denervatie

- Toediening van radiofrequente energie in de LHB en RHB
- Doel: Parasympatische zenuwgeleiding onderbreken
- Bronchoscopie onder anesthesie in dagbehandeling
- Onder doorlichting met plaatsing oesofagusballon





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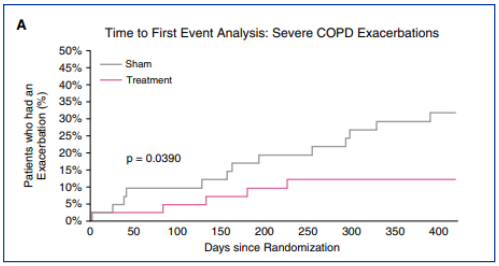
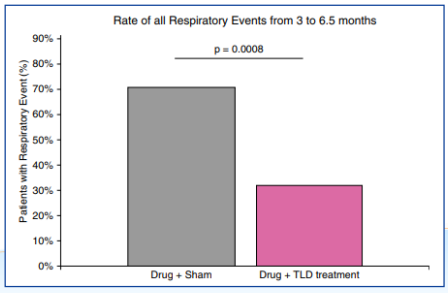
Targeted lung denervation – AIRFLOW-2

- Gerandomiseerde, sham-gecontroleerde dubbelblinde RCT (n=82)
- Geen significant verschil in FEV_1, kwaliteit van leven, inspanningsvermogen
- Wel minder 'respiratoire events'





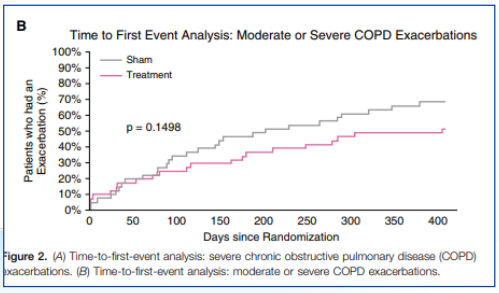


Figure 2. (A) Time-to-first-event analysis: severe chronic obstructive pulmonary disease (COPD) exacerbations. (B) Time-to-first-event analysis: moderate or severe COPD exacerbations.

Slebos et al, *AJRCCM*, 2019

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Targeted lung denervation – AIRFLOW-3

- Gerandomiseerde, sham-gecontroleerde dubbelblinde RCT (n=480)
- Gestart in 2019, naar verwachting dit jaar laatste inclusie
- Inclusie: Patiënten met Gold E, FEV_1 >25% en LAMA gebruik
- Primair eindpunt: COPD-exacerbaties

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Advance care planning en innovaties

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Advance care planning en innovaties

- Wat denken jullie van de besproken innovaties? Ga je ze (in de toekomst) bespreken met de patiënt?
- Innovaties in studieverband?
- Hoe zou je innovaties bespreken met een patiënt in combinatie met ACP? Wie heeft de regie?

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