Näidisvorm G
Tõendusmaterjali kokkuvõte

Kliiniline küsimus nr **4**

Kliinilise küsimuse tekst: **Kas astma diagnoosiga patsientidele tuleb määrata hooravile lisaks püsiravi (hooravi või hooravi+püsiravi või hooravi asemel püsiravi).**

Kokkuvõte, sh kriitiliste tulemusnäitajate kaupa:

Regulaarne pikaajaline farmakoloogiline ravi aitab ennetada astma ägenemisi.
Monoteraapiatest on astma ägenemiste ennetamiseks kõige tõhusam pikaajaline kortikoidsteoidravi.(Sin 2004)
11 randomiseeritud platseebovõrdlusega kliinilise uuringu meta-analüüsis selgus, et pikaajaline ravi inhaleeritavate kortikosteroididega (IKS) vähendas astma ägenemisi 55% võrra võrreldes platseebo või lühitoimeliste β2-agonistidega (RR 0.46; 95%CI, 0.34-0.62). Randomiseeritud kliinilise uuringu tõsise astma ägenemisega patsientide alarühma tulemusnäitajaid analüüsides järeldati, et pikaajaline ravi inhaleeritavate kortikosteroidide madalate annustega aeglustab kopsufunktsiooni langust (O'Byrne 2009)
Baasravi analüüsivas süstemaatilises ülevaates leiti mõõduka tugevusega tõendusmaterjali, et erinevad inhaleeritavate kortikosteroidide toimeained on sarnase tõhususega erinevate tulemusnäitajate osas (astma sümptomite kontroll, ägenemiste ennetamine, hooravi vajaduse vähendamine). (Jonas 2011[0]),

Milline IKS algannus? Cochrane'i andmebaasi süstemaatilises ülevaates (Powell 2004) järeldati, et madal või mõõdukas algannus on sama tõhus kui kõrge algannus.

Alaküsimused:
Kas astma baasravi alustada juba kerge või alles keskmise raskusega püsiva astma korral?

Ühes 7241 patsienti hõlmanud ja 3 aastat kestnud topeltpimedas randomiseeritud kliinilises uuringus (Pauwels, 2003, nn START-uuring[7]) on näidatud, et kerge püsiva astma korral on ICS püsiravi (400 µg budesoniidi päevas) saanute hulgas oluliselt vähem tõsiseid astma ägenemisi kui platseeborühmas, vastavalt 33 juhtu ja 55 juhtu 1000 patsiendi kohta; HR (*hazard ratio*) 0,56 [0,41-0,71].

Kas kerge püsiva astmaga patsientidele määrata pidev e igapäevane (*daily*) või vahelduv e pausidega (*intermittent*) baasravi?

Cochrane andmebaasi 2013. a süstemaatilises ülevaates (Chauhan 2013)[6] hinnati nii laste kui ka täiskasvanute vastavaid uuringuid, tõendusmaterjali hinnati pigem madalaks, ei ole uuringuid, mis oleksid kestnud kauem kui 1 aasta. Vt ka NEJM publitseeritud RCT (Boushey 2005)
Vastav Cochrane ülevaate GRADE tabel koos **absoluutsete efektidega** on toodud allpool

Commented [MO1]: Tehnilistel põhjustel on 2. ja 3. veeru pealkirjad nihkes, viga parandatud lisatud selgitavate kastikeste abil.

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Summary of findings for the main comparison. Intermittent 'as needed' ICS versus daily ICS for persistent asthma in children and adults

Intermittent 'as needed' ICS versus daily ICS for persistent asthma in children and adults
Patient or population: Children and adults with persistent asthma.
Settings: Outpatients
Intervention: Intermittent 'as needed' ICS versus daily ICS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Daily ICS	Intermittent ICS				
Patients with 1 or more exacerbations requiring oral corticosteroids (duration 12 to 52 weeks)	**19 per 100**	**20 (17 to 25) per 100**	**RR 1.07** (0.87 to 1.32)	**1204** (7 studies)	⊕⊕⊖⊖ **low** [1,2]	
Patients with serious adverse health events (duration 12 to 52 weeks)	**2 per 100**	**2 (1 to 4) per 100**	**RR 0.82** (0.33 to 2.03)	**1055** (6 studies)	⊕⊕⊖⊖ **low** [1,2]	
Patients with at least 1 exacerbation requiring emergency department/ acute care visit (duration 12 to 52 weeks)	**15 per 100**	**18 (14 to 20) per 100**	**RR 1.08** (0.9 to 1.3)	**1055** (6 studies)	⊕⊕⊖⊖ **low** [1,2]	
Change from baseline AM PEFR (%) (duration 44 to 52 weeks)		The mean change from baseline am PEFR (%) in the intermittent groups was **2.56% lower** than daily ICS group (4.49 to 0.63 lower)	**MD -2.56** (-4.49 to -0.63)	**350** (3 studies)	⊕⊕⊕⊖ **moderate** [2]	
Proportion of asthma control days over the period (duration 44 to 52 weeks)		The mean proportion of asthma control days over the period in the intermittent groups was 9% **lower** than daily ICS group (4% to 14%)	**MD -0.09** (-0.14 to -0.04)	**330** (3 studies)	⊕⊕⊕⊖ **moderate** [2]	
Change from baseline mean daily use of β_2-agonists (puffs/ day) (duration 24 to 44 weeks)		The mean change from baseline mean daily use of β_2-agonists (puffs/ day) in the intermittent groups was **0.12 puffs/ day higher** than daily ICS group (0 to 0.23 higher)	**MD 0.12** (0.00 to 0.23)	**442** (3 studies)	⊕⊕⊕⊖ **moderate** [2]	

1 Confidence intervals were too wide to exclude important differences between treatments for this outcome.
2. Diversity of ways in which intermittent ICS regimens were implemented and the variety of participants in the trials limits the confidence in our estimate of the treatment effects

pidev püsiravi vahelduv püsiravi

Märkus: sellest tabelist puuduvad tehnilistel põhjustel pdf-variandis olevad järgmised 2 rida:
- laste pikkuse muutus: vahelduva ravi rühmas pikkus 0,14 cm pikem (0,13-0.69 cm), n=523, uuringute kvaliteet mõõdukas
-uuringu katkestamine 14/100 uuritava kohta mõlemas rühmas, rühmade vahel statistilisi erinevusi ei ole: OR 1.05(0,75-1,46)

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Tulemusnäitajad:
Elukvaliteet: Std MD -0.16 [-0.36, 0.04](statistiliselt mitteoluline)
Astma ägenemine –ei ole erinevust ühegi näitaja osas
Suremus (astmast tingitud või olenemata põhjusest e *all-cause mortality*) - NA
Päevaste sümptomite esinemine – vahelduval ravil vähem sümptomivabu päevi: Std MD -0.15 (95% CI -0.28 to -0.03) ja -9% (95% CI -14% to -4%),
Öösümptomid/unehäired: MD -0.03 [-0.08, 0.02](statistiliselt mitteoluline)
Hooravi vajadus: suurenes vahelduva ravi rühmas 0.12 SABA annust/päevas (95% CI 0 to 0.23)
Hospitaliseerimine (olenemata põhjusest) - NA
Ravi katkestamine kõrvaltoime tõttu: OR 1.05 (0,75-1,46) statistiliselt olulist erinevust ei ole
Füüsilise aktiivsuse piiratus - NA

Selle kohta, kas kerge astma korral vahelduv püsiravi/baasravi võiks pikema aja jooksul põhjustada kopsude funktsiooninäitajate halvenemist võrreldes pideva püsiravi/baasravi kasutamisega, andmeid veel ei ole.
START-uuringu lõppedes jälgiti osa patsientidest veel kuni 10 a jooksul (Busse 2008, Haahtela 2009)[7a, 8a]: kokku 13 aastat kestnud uuringuperioodi lõpus olid nii koheselt püsiravi saanud patsientide kui ka 2 aasta võrra edasilükatud püsiraviga patsientide kopsude funktsiooninäitajad normi piires.

Kas astma hooraviks või püsiraviks sobib LABA monoteraapia (ilma IKS)?
LABA monoteraapia võib põhjustada tõsiseid mittesoovitavaid toimeid.
Ühes meta-analüüsis (Salpeter 2006)[1], mis hõlmas 19 uuringut 33 826 osavõtjaga selgus, et LABA kasutamine suurendab astma ägenemistest põhjustatud hospitaliseerimisi (OR, 2.6 [95% CI, 1.6 - 4.3]) ja eluohtlike tüsistuste tekkimist (OR, 1.8 [CI, 1.1 - 2.9]) võrreldes platseebo kasutamisega. Haiglaravi vajasid rohkem nii salmeteroolravi (OR, 1.7 [CI, 1.1 - 2.7]) kui ka formoterooliravi saanud patsiendid (OR, 3.2 [CI, 1.7 - 6.0]). LABA monoteraapiat saanute hulgas oli 6 kuu jooksul hospitaliseerimist vajavate patsientide osakaal suurem 0,7 protsendipunkti võrra (CI, 0.1% - 1.3%), samuti oli suurem astmaga seotud surmajuhtude risk OR 3.5 [CI, 1.3 - 9.3]).
Astmast tingitud surmajuhtude tõusu täheldati LABA monoteraapiat saanute hulgas ka Cochrane'i andmebaasi 2009. a süstemaatilise ülevaate andmetel (Walters 2007)[2]: lisandus 1 surmajuhtum iga 1250 [CI 700 – 10 000] patsiendi kohta, kes oli saanud LABA-monoteraapiat 6 kuud.
Ka kolmas süstemaatiline ülevaade on kooskõlas eelpooltoodud tulemustega (Rodrigo 2009)[2a]: Kolmandas süstemaatilises ülevaates (Rodrigo 2009) võeti kokku β_2-agonistidega monoteraapia kohta võrdluses platseeboga ning võrdlsKokku analüüsiti 92 kliinilist katset 74 092 osavõtjaga. Kooskõlas teiste ülevaadetega näidati ka selles astmast tingitud surmajuhtude suurenemist β_2-agonistidega monoteraapiat saanute hulgas võrreldes platseeborühmaga (RR 3.83; 95%CI, 1.21-12.14). IKS ja β_2-agonistidega kombineeritud ravi saanute hulgas aga esines oluliselt vähem astma ägenemisi (RR=0.73; 95% CI, 0.67-0.79) ning hospitaliseerimisi (RR=0.58, 95%CI, 0.45-0.74),

Ei leidnud aga ühtegi RCT, mis otseselt võrdleks SABA ja LABA monoteraapiat.

LABA kombineerituna ICS on ohutuselt sarnane ISC monoteraapiale (Jaeschke 2008, Ducharme 2010, ka Cates 2013 – vt EvSu7)

Kas SABA püsiravina või vastavalt vajadusele hooravina?
Cochrane'i andmebaasi 2003.a. valminud ja 2009. a. üle vaadatud süstemaatilise ülevaate (Walters 2003)[3] andmetel ei ole lühitoimeliste β2-agonistide (SABA) regulaarsel kasutamisel selgeid kliinilisi eeliseid SABA vajadusel kasutamise ees, kuid pideva SABA kasutamise ravikulu on suurem. Samas ei ole leitud olulist erinevust nende ravitaktikate ohutuses.

Tulemusnäitajad:
Elukvaliteet: skoori keskmine erinevus (MD) 0.01 [-0.24, 0.26] (ei ole statistiliselt oluline)
Astma ägenemine OR 0.86 [0.71, 1.04] (ei ole statistiliselt oluline)
Suremus (astmast tingitud või olenemata põhjusest e *all-cause mortality) – ei olnud surmajuhtusid*
Päevaste sümptomite esinemine – ilma päevaste sümptomiteta päevade osakaal (%) MD 6.70% [2.68, 10.72%] – erinevus pideva SABA kasuks; teiste indikaatorite osas statistiliselt olulisi erinevusi ei olnud
Öösümptomid/unehäired – statistiliselt olulisi erinevusi ei olnud
Sümptomskoor (kogu ööpäev) MD 0.26 [0.00, 0.52] – erinevus vajadusel SABA kasuks
Hooravi vajadus - NA
Hospitaliseerimine (olenemata põhjusest) – ei olnud analüüsitud
Ravi kõrvaltoimed: 1.03 [0.72, 1.49] (ei ole statistiliselt oluline)
Füüsilise aktiivsuse piiratus – ei olnud analüüsitud
Ravikulu – suurem pideva SABA ravi korral

Kas astma hooraviks määrata SABA või formoterool/ICS?
Cochrane'i andmebaasi 2013. a süstemaatilises ülevaates (Cates 2013)[4] hinnati formoterool4,5µg/budenosiidi 160µg (FOR/BUD) kasutamist nii püsiraviks kui ka hooraviks võrreldes senise parima praktikaga, milleks oli ICS püsiraviks/SABA hooraviks.
FOR/BUD ravi saanutel esines vähem suukaudset kortikosteroidravi vajavaid ägenemisi (OR 0.83; 95% CI 0.70 to 0.98), samas aga rohkem ravi katkestamisi kõrvaltoimete tõttu OR 2,85 [1,89-4,3). Vastav GRADE tabel koos **absoluutsete efektidega** on toodud allpool. Elukvaliteedi osas olid tulemused väga heterogeensed ja neid meta-analüüsis ei kombineeritud (I^2=68%).

Commented [MO2]: Tehnilistel põhjustel on 2. ja 3. veeru pealkirjad vehtuses. 2. veerg: kontrollrühm (ICS+ SABA vajadusel) , 3. veerg FOR/BUD nii säilitusraviks kui ka hooraviks)

[Type text]

Summary of findings for the main comparison. 160/4.5 mcg BDF single inhaler therapy compared to current best practice for adult asthma that is not controlled on ICS

160/4.5 µg BDF single inhaler therapy compared to current best practice for adults with asthma that is not controlled on ICS
Patient or population: adults with asthma that is not controlled on ICS
Settings: community
Intervention: 160/4.5 µg BDF single inhaler therapy
Comparison: current best practice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Assumed risk Current best practice	kontroll	FOR/BUD				
Patients with exacerbations causing hospitalisation Follow-up: mean 6 months	**6 per 1000**	**5 per 1000** (3 to 8)	**OR 0.81** (0.45 to 1.44)	8841 (8 studies)	⊕⊕⊖⊖ **low** [1,2]	
Patients with exacerbations treated with oral steroids Follow-up: mean 6 months	**70 per 1000**	**59 per 1000** (50 to 69)	**OR 0.83** (0.70 to 0.98)	8841 (8 studies)	⊕⊕⊕⊖ **moderate** [1]	
Fatal serious adverse events Follow-up: mean 6 months	**1 per 1000**	**1 per 1000** (0 to 5)	**OR 1.95** (0.53 to 7.21)	8841 (8 studies)	⊕⊕⊖⊖ **low** [1,2]	
Serious adverse events (non-fatal) Follow-up: mean 6 months	**20 per 1000**	**24 per 1000** (18 to 32)	**OR 1.20** (0.90 to 1.60)	8841 (8 studies)	⊕⊕⊖⊖ **low** [1,2]	
Discontinuation due to adverse events Follow-up: mean 6 months	**7 per 1000**	**21 per 1000** (14 to 31)	**OR 2.85** (1.89 to 4.3)	8411 (7 studies)	⊕⊕⊕⊖ **moderate** [1]	

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unblinded trials
[2] Confidence interval cannot rule out important differences in either direction
BDF: budesonide plus formoterol; ICS: inhaled corticosteroids

Canadian Thoracic Society viis läbi tõendusmaterjali süstemaatilise ülevaate, mis hõlmas kuni 2011.a. septembrini läbi viidud uuringuid. Tõendusmaterjali süstemaatilise ülevaate alusel sõnastati järgmised soovitused: SABA on sobiv hooravim kõigis vanuserühmades ja raskusastmete korral ja eelistatud hooravim kerge astmaga patsientidel, nii püsiravita kui ka ICS püsiravil patseintidele. LABA monoteraapia (k.a. formeterool monoteraapia ilma ICS) hooraviks ei sobi. Mõõduka raskusega mittekontrollitud astmaga patsientidel, kel on soodumus ägenemistele (s.t. kindlal alarühmal), võib kasutada budenosiid/formoterooli hooraviks lisaks LABA/ICS säilitusravile.
Ekvipotentne 12 mcg formoterooli ja 200 mcg salbutamooli (http://thorax.bmj.com/content/47/1/30.full.pdf)

Täiendav RCT: Papi A, Corradi M, Pigeon-Francisco C, Baronia R, Siergiejko Z, Petruzzelli S, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med 2013;1:23-31
http://www.ncbi.nlm.nih.gov/pubmed/24321801

Ravijuhendid

Ravijuhendite soovitused langevad kokku järgnevas:

- Kõigil patsientidel peab olema võimalus kasutada vajadusel hooravi.
- Vahelduva astmaga patsientidel (intermittent asthma) piisab ainult hooravist (reliever therapy), (EPR-3 2007, SIGN-2012, GINA-2012, Canada 2010, GEMA-2009. VA/DoD, NVL 2011)
- Püsiva astmaga (persistent asthma) patsiendid vajavad püsiravi (controller therapy), millele vajadusel lisaks hooravi. (EPR-3 2007, SIGN-2012. GINA-2012, GEMA-2009, VA/DoD, NVL-2011)

Ehk: püsiravi vajavad kõik need patsiendid, kellel esineb vähemalt 1 mittekontrollitud astma tunnustest (*one or more indicators of poor control*) (Canada 2010).

- Canada 2012 juhend soovitab kerge püsiva astma korral pidevat (*daily*) püsiravi, mitte vahelduvat (*intermittent*) püsiravi (s.t. juhul, kui tekib astma kontrolli kaotus). Teistes juhendites seda küsimust käsitletud ei ole.

Ravijuhendite soovitustes püsiravi lisamise näidustuse kohta ja hooraviks soovitatavate ravimpreparaatide kohta on erinevusi. Hooravi soovitused on eriti põhjalikult käsitletud Canada 2012 juhendis.

Püsiravi lisamise näidustused :

- SABA > 2 korda nädalas (EPR-3 2007, SIGN-2012; GEMA-2010), >3 korda nädalas (Canada 2010)
- Sümptomid (köha, wheeze, hingeldus kestusega kuni mõned tunnid) > 2 korra nädalas (EPR-3 2007, SIGN-2012, GINA-2012, GEMA-2010)
- Öine ärkamine < 2 korda kuus (EPR 3 2007), ≥1 kord nädalas (Canada 2010, SIGN 2012),

või episoodide ajal öine ärkamine <2 korda nädalas, episoodide vahelisel perioodil ei esine öiseid ärkamisi (GINA-2012)

- Kopsufunktsioon: episoodide vahelisel perioodil normaalne (GINA-2012) või < 90% *personal best* (GEMA 2009)
- Astma tõttu puudumine töölt või koolist (GEMA-2009)
- Füüsilise aktiivsuse piiratus (GINA-2012)

- Suukaudset kortikosteroidravi nõudnud ägenemine viimase kahe aasta jooksul (s.t. selle järgne inhaleeritav ICS peaks kestma 2 aastat)(SIGN-2012)

Hooraviks soovitatavad ravimid:
- Canada 2010-2012: kiiretoimelised β2-agonistid: SABA (salbutamool, terbutaliin või fenoterool). SABA on sobiv hooravim kõigis vanuserühmades ja raskuastmete koral ja eelistatud hooravim kerge astmaga patsientidel (nii püsiravita kui ka ICS püsiravil. LABA monoteraapia (k.a. formeterool monoteraapia ilma ICS) hooraviks ei sobi. Mõõduka raskusega mittekontrollitud astmaga patsientidel, kel on soodumus ägenemistele (s.t. kindlal alarühmal), võib kasutada budenosiid/formoterooli hooraviks nii, et säilitusravi ICS jääb samaks. (*in exacerbation-prone adults with moderate asthma and poor control on a fixed dose maintenance ISC/LABA combination, we suggest the use of BUD/FOR as reliever be considered at the same maintenance ICS dose*). Ipratroopiumbromiid nendele patsientidele, kes kõrvaltoimete tõttu ei talu SABA.
- EPR-3 2007: inhaleeritav lühitoimeline β2-agonist (short-acting beta agonist e SABA) albuterool=salbutamool, levalbuterool, pirbuterool. Formoterooli ei soovita uuringuandmete vähesuse tõttu.
- SIGN-2012: inhaleeritav SABA
- GINA-2012: kiiretoimeline β2-agonist (rapid-acting β2-agonist e RABA): SABA või LABA formoterool (formoterool ainult ICS regulaarsel püsiravil patsientidele). Alternatiiviks inhaleeritavad antikoliinergilised ained, kiiretoimelised suukaudsed β2-agonistid, kiiretoimeline teofülliin.
- GEMA-2010: SABA
- VA/DoD: SABA
- NVL-2011: RABA: fenoterool, formoterool, salbutamool, terbutaliin.

Võib kasutada ka muid ravimeid: ipratroopiumbromiid, fenoterool/ipratroopiumbromiidi fikseeritud kombinatsioon (*Eestis Berodual nime all*), kiiretoimeline teofülliin, suukaudne SABA, süsteemne CS.

Süstemaatilised ülevaated

Kokkuvõte	Viide kirjandusallikale	Nr
Sh: Efficacy studies provide moderate evidence that ICSs do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits), or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons. (p 180)	Daniel E Jonas, MD, MPH, Roberta C M Wines, MPH, Marcy DelMonte, PharmD, BCPS, Halle R Amick, MSPH, Tania M Wilkins, MS, Brett D Einerson, MPH, Christine L Schuler, MD, Blake A Wynia, MPH, and Betsy Bryant Shilliday, PharmD, CDE, CPP. **Drug Class Review: Controller Medications for Asthma. Final Update 1 Report. Drug Class Reviews.** Portland (OR): Oregon Health & Science University; April **2011**. http://www.ncbi.nlm.nih.gov/books/NBK56695/	Jonas 2011
PURPOSE: To assess the risk for severe, life-threatening, or fatal asthma exacerbations associated with long-acting beta-agonists. DATA SOURCES: English- and non-English-language searches of MEDLINE, EMBASE, and Cochrane databases; the U.S. Food and Drug Administration Web site; and references of selected reviews through December 2005. STUDY SELECTION: Randomized, placebo-controlled trials that lasted at least 3 months and evaluated long-acting beta-agonist use in patients with asthma. All trials allowed the use of as-needed short-acting beta-agonists. DATA EXTRACTION: Outcomes measured were Peto odds ratio (OR) and risk difference of severe exacerbations requiring hospitalization, life-threatening exacerbations requiring intubation and ventilation, and asthma-related deaths. The OR for asthma-related deaths was obtained from the Salmeterol Multi-center Asthma Research Trial (SMART). DATA SYNTHESIS: Pooled results from 19 trials with 33 826 participants found that long-acting beta-agonists increased exacerbations requiring hospitalization (OR, 2.6 [95% CI, 1.6 to 4.3]) and life-threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]) compared with	Salpeter SR, Buckley NS, Ormiston TM,Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Annals Intern Med 2006;144(12):904-12. http://www.ncbi.nlm.nih.gov/pubmed/16754916	Salpeter 2006 1

placebo. Hospitalizations were statistically significantly increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and formoterol (OR, 3.2 [CI, 1.7 to 6.0]) and in children (OR, 3.9 [CI, 1.7 to 8.8]) and adults (OR, 2.0 [CI, 1.1 to 3.9]). The absolute increase in hospitalization was 0.7% (CI, 0.1% to 1.3%) over 6 months. The risk for asthma-related deaths was increased (OR, 3.5 [CI, 1.3 to 9.3]), with a pooled risk difference of 0.07% (CI, 0.01% to 0.1%). LIMITATIONS: The small number of deaths limited the reliability in assessing this risk, and 28 studies did not report information on the outcomes of interest. CONCLUSIONS: Long-acting beta-agonists have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma-related deaths.		
Asthma is a common respiratory disease among both adults and children and short acting inhaled beta-2 agonists are used widely for 'reliever' bronchodilator therapy. Long acting beta-2 agonists (LABA) were introduced as prospective 'symptom controllers' in addition to inhaled corticosteroid 'preventer' therapy (ICS). In this updated review we have included studies in which patients were either not on ICS as a group, or in which some patients, but not all, were on ICS to complement previous systematic reviews of studies where LABA was given in patients uniformly receiving ICS. We have focussed particularly on serious adverse events, given previous concerns about potential risks, especially of death, from regular beta-2 agonist use. OBJECTIVES: This review aimed to determine the benefit or detriment on the primary outcome of asthma control with the regular use of LABA compared with placebo, in mixed populations in which only some were taking ICS and in populations not using ICS therapy. SEARCH STRATEGY: until October 2005. SELECTION CRITERIA: All randomised studies of at least four weeks duration, comparing a LABA given twice daily with a placebo, in chronic asthma. Selection criteria to this updated review have been altered to accommodate recently published Cochrane reviews on combination and addition of LABA to ICS therapy. Studies in which all individuals were uniformly taking ICS were excluded from this review. MAIN RESULTS: Sixty-seven studies (representing 68 experimental comparisons) randomising 42,333 participants met the inclusion criteria. Salmeterol was used as long-acting agent in 50 studies and formoterol fumarate in 17. The treatment period was four to nine weeks in 29 studies, and 12 to 52 weeks in 38 studies. Twenty-four studies did not permit the use of ICS, and forty permitted either inhaled corticosteroid or cromones (in three studies this was unclear). In these studies between 22% and 92% were taking ICS,	Walters EH, Gibson PG, Lasserson TJ, Walters JA. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD001385. http://www.ncbi.nlm.nih.gov/pubmed/17253458	Walters 2007 2

with a median of 62%. There were significant advantages to LABA treatment compared to placebo for a variety of measurements of airway calibre including morning peak expiratory flow (PEF), evening PEF and FEV1. They were associated with significantly fewer symptoms, less use of rescue medication and higher quality of life scores. This was true whether patients were taking LABA in combination with ICS or not. Findings from SMART (a recently published surveillance study) indicated significant increases in asthma related deaths, respiratory related deaths and combined asthma related deaths and life threatening experiences. The absolute increase in asthma-related mortality was consistent with an increase of around one per 1250 patients treated with LABA for six months, but the confidence intervals are wide (from 700 to 10,000). Post-hoc exploratory subgroups suggested that African-Americans and those not on inhaled corticosteroids were at particular risk for the primary end-point of death or life-threatening asthma event. There was also a suggestion of an increase in exacerbation rate in children. Pharmacologically predicted side effects such as headache, throat irritation, tremor and nervousness were more frequent with LABA treatment. AUTHORS' CONCLUSIONS: LABA are effective in the control of chronic asthma in the "real-life" subject groups included. However there are potential safety issues which call into question the safety of LABA, particularly in those asthmatics who are not taking ICS, and it is not clear why African-Americans were found to have significant differences in comparison to Caucasians for combined respiratory-related death and life threatening experiences, but not for asthma-related death.		
Safety of long-acting beta agonists (LABA) has been questioned and recent evidence suggested a detrimental effect on asthma control as well as an increased risk of death. OBJECTIVE: To evaluate the safety of regular use of LABA compared with placebo or LABA added to inhaled corticosteroids (ICS) compared with ICS in persistent asthma. METHODS: Primary outcomes were asthma exacerbations (AE) requiring systemic corticosteroids or hospitalization, life-threatening exacerbations and asthma-related deaths. RESULTS: We identified 92 randomized clinical trials with 74,092 subjects. LABA (as monotherapy) reduced exacerbations requiring corticosteroids (Relative Risk [RR]=0.80; 95% CI, 0.73-0.88), without detrimental effects on hospitalizations or life-threatening episodes. Contrarily, LABA showed a significant increase in asthma-related deaths (Relative Risk=3.83; 95% CI, 1.21-12.14). Subgroup analysis suggests that children, patients receiving salmeterol, and a duration of treatment>12 weeks are associated with a higher risk of serious adverse effects; also there was a protective effect of concomitant use of ICS. On the other hand, combination of LABA/ICS reduced exacerbations	Rodrigo GJ, Moral VP, Marcos LG, Castro-Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. Pulm Pharmacol Ther. 2009 Feb;22(1):9-19. http://www.ncbi.nlm.nih.gov/pubmed/19026757	Rodrigo 2009 2a

(RR=0.73; 95% CI, 0.67-0.79), and hospitalizations (RR=0.58, 95% CI, 0.45-0.74). Combined therapy was also equivalent to ICS in terms of life-threatening episodes and asthma-related deaths. Again, children and use of salmeterol were associated with an increased risk of some severe outcomes as compared with adults and formoterol users, respectively. CONCLUSIONS: This review reinforced the international recommendations in terms of the use of LABA remains the preferred add-on therapy to ICS for patients whose disease cannot adequately controlled with ICS, and that LABA cannot be prescribed as a monotherapy. Nevertheless, in spite of the protective effect of the ICS, children and salmeterol use still show an increased risk of non-fatal serious adverse events.		
INTRODUCTION: It has been postulated that inhaled long acting beta-agonists (LABAs) when used as monotherapy in asthma may increase the incidence of asthma related deaths, intubations and hospitalizations, but concomitant use of inhaled corticosteroids (ICS) may modify this effect. OBJECTIVES: To assess the safety of formoterol in patients with asthma using ICS. PATIENTS AND METHODS: We conducted a systematic review and meta-analysis of parallel group, blinded, randomized controlled trials with at least 12 weeks of treatment examining the impact of twice a day formoterol on asthma-related and total morbidity and mortality in patients concurrently using ICS. Our main analysis considering impact of LABAs (salmeterol and formoterol) has already been published. In this report we present detailed information from studies investigating use of twice daily formoterol among patients receiving ICS. RESULTS: The search yielded 16 relevant studies included in this analysis. Among over 10,000 participants (5,996 taking formoterol with over 4,000 patient-years observation in formoterol groups) there were 2 asthma-related deaths (both in formoterol groups) and no asthma-related non-fatal intubations. The risk of asthma-related hospitalizations (odds ratio [OR] 0.59, 95% CI 0.37-0.93) and asthma-related serious adverse events (mostly hospitalizations) [OR 0.58, 95% CI 0.37-0.91] were significantly lower in patients on formoterol and ICS compared to patients on ICS alone. The OR for total mortality was	Jaeschke R, O'Byrne PM, Nair P, Mejza F, Leśniak W, Brozek J, Thabane L, Cheng J, Bała M, Schünemann HJ, Sears MR, Guyatt G. The safety of formoterol among patients with asthma using inhaled corticosteroids. Systematic review and meta-analysis. Pol Arch Med Wewn. 2008 Nov;118(11):627-35. http://www.ncbi.nlm.nih.gov/pubmed/18776152	Jaeschke 2008 2b

1.22, 95% CI 0.38-3.90, reflecting 7 deaths in formoterol groups and 3 deaths in control groups respectively. CONCLUSIONS: In patients with asthma using inhaled corticosteroids formoterol decreased the risk of asthma-related hospitalizations. There were too few asthma-related deaths and intubations to establish formoterol's relative impact on these outcomes.		
Inhaled short-acting beta-2 agonists are the major class of bronchodilators used for relief of symptoms in asthma. There has been concern that excessive uncontrolled use of beta-2 agonists might have contributed to rises in asthma mortality seen in some countries. International consensus guidelines now generally recommend using short-acting beta-2 agonists only for relief of symptoms on an as needed basis. OBJECTIVES: To assess the effects of using short-acting inhaled beta-2 agonists regularly or only on demand in asthmatic adults and children on indices of asthma control. SEARCH STRATEGY: Searches were carried out of the Cochrane Airways Group "Asthma and Wheez* RCT" register in 1997, 1999 and 2002. SELECTION CRITERIA: Randomised controlled trials in which the short-acting beta-2 agonist was given regularly in the experimental group, together with an inhaled bronchodilator for relief of symptoms ('rescue use'). The control group consisted of matching placebo inhaled regularly, with an inhaled bronchodilator for 'rescue use'. MAIN RESULTS: 800 abstracts were identified for the first version and 60 papers were requested for full assessment. In this update 15 studies were added to the 34 trials which met the entry criteria for the first version in 2000. No clinically or statistically significant differences were found in airway calibre measurements. The regular treatment groups required less rescue medication, -0.80 puffs/24 hours (95% CI -0.07 to -1.30) and -0.42 puffs/daytime (95% CI -0.12 to -0.72), and had fewer days with asthma symptoms, -6.7% (95% CI -2.7 to -10.7). There was no significant difference in the odds ratio for the occurrence of at least one major asthma exacerbation either in parallel group or cross over studies. REVIEWER'S CONCLUSIONS: In general, these results support current guidelines, although it has given reassuring evidence against concerns over regular use of inhaled short-acting beta-2 agonists. Vaadatud üle ka 2009, järelduste sisu ei muutunud: Respiratory guidelines (BTS,GINA etc) have limited short-acting beta-2 agonists to as needed use, presumably because of the safety concerns referred to above. This review would in general confirm the rationale of these guidelines, although it has put these concerns into quantitative perspective. There no clear and categorical	Walters EH, Walters J. Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Cochrane Database Syst Rev. 2003;(2):CD001285. http://www.ncbi.nlm.nih.gov/pubmed/12804401 Republished: Cochrane Database Syst Rev. Vol 4, 2009; järeldused ei muutunud	Walters 2003 3

advantage in using short-acting beta-2 agonists regularly. In addition there would be a financial penalty related to the greater use of medication on a regular bronchodilator regime. However, the lack of significant clinical detriment to using beta-2 agonists regularly means that more consideration should be given to patient preferences and circumstances, without dogmatic proscription on this matter. Management guidelines should reflect this reality.		
BACKGROUND: Inhaled corticosteroids (ICS) form the basis of maintenance therapy in asthma and their efficacy is well established. However, the optimal starting dose of ICS is not clearly established. Recent reviews demonstrate a relatively flat efficacy curve for ICS and increasing side effects with increasing ICS doses. High doses are frequently prescribed and there are now reports of significant side effects occurring with high dose ICS use. These issues demonstrate the need to establish the optimal starting dose of ICS in asthma. OBJECTIVES: To establish the optimal starting dose of ICS by evaluating the efficacy of initial high dose ICS with low dose ICS in subjects with asthma, not currently on ICS. SEARCH STRATEGY: Date of last search: January 2003 SELECTION CRITERIA: Randomised controlled trials of two different doses of the same ICS in adults and children with asthma with no concomitant ICS or OCS. DATA COLLECTION AND ANALYSIS: Trial quality was assessed and data were extracted independently by two reviewers. Study authors were contacted for confirmation. Trials were analysed according to the following ICS dose comparisons: step down vs constant dose ICS (n=7); high vs moderate (n=11); high vs low (n=9); moderate vs low (n=11); fold change in dose (all studies). MAIN RESULTS: 31 papers reporting the results of 26 trials were included in the review. For studies that compared a step down approach to a constant moderate/low ICS dose, there were no significant differences in lung function, symptoms, rescue medications or asthma control between the two treatment approaches. Significant but clinically small improvements in percent predicted FEV(1) (WMD 5.32, 95% CI 0.65 to 9.99) and non significant improvements in the change in morning PEF were found for high dose ICS compared to moderate dose ICS. There were no significant differences in efficacy between high and low dose ICS. For moderate dose ICS, compared to low dose ICS, there were significant improvements in the change in morning PEF l/min from baseline (WMD 11.14, 95% CI 1.34 to 20.93) and nocturnal symptoms (SMD -0.29, 95% CI -0.53 to -0.06). Commencing ICS at double or quadruple a base moderate or low dose had no greater effect than commencing with the base dose. Several studies reported greater	Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. Cochrane Database Syst Rev. 2004;(2):CD004109. http://www.ncbi.nlm.nih.gov/pubmed/15106238	Powell 2004

improvement in airway hyperresponsiveness for high dose ICS. REVIEWERS' CONCLUSIONS: For patients with asthma who require ICS, commencing with a moderate dose ICS is equivalent to commencing with a high dose ICS and down-titrating. The small significant benefits of commencing with a high ICS dose are not of sufficient clinical benefit to warrant its use when compared to moderate or low dose ICS. Initial moderate ICS dose appears to be more effective than initial low ICS dose. High dose ICS may be more effective than moderate or low dose ICS for airway hyperresponsiveness. There is no benefit in doubling or quadrupling ICS in subjects with stable asthma.		
Traditionally inhaled treatment for asthma has used separate preventer and reliever therapies. The combination of formoterol and budesonide in one inhaler has made possible a single inhaler for both prevention and relief of symptoms (single inhaler therapy or SiT). OBJECTIVES: To assess the efficacy and safety of budesonide and formoterol in a single inhaler for maintenance and reliever therapy in asthma compared with maintenance with inhaled corticosteroids (ICS) (alone or as part of current best practice) and any reliever therapy. SEARCH METHODS:Until February 2013. SELECTION CRITERIA: Parallel, randomised controlled trials of 12 weeks or longer in adults and children with chronic asthma. Studies had to assess the combination of formoterol and budesonide as SiT, against a control group that received inhaled steroids and a separate reliever inhaler. MAIN RESULTS: We included 13 trials involving 13,152 adults and one of the trials also involved 224 children (which have been separately reported). All studies were sponsored by the manufacturer of the SiT inhaler. We considered the nine studies assessing SiT against best practice to be at a low risk of selection bias, but a high risk of detection bias as they were unblinded.In adults whose asthma was not well-controlled on ICS, the reduction in hospital admission with SiT did not reach statistical significance (Peto odds ratio (OR) 0.81; 95% confidence interval (CI) 0.45 to 1.44, eight trials, N = 8841, low quality evidence due to risk of detection bias in open studies and imprecision). The rates of hospital admission were low; for every 1000 people treated with current best practice six would experience a hospital admission over six months compared with between three and eight treated with SiT. The odds of experiencing exacerbations needing treatment with oral steroids were lower with SiT compared with control (OR 0.83; 95% CI 0.70 to 0.98, eight trials, N = 8841, moderate quality evidence due to risk of detection bias). For every 100 adults treated with current best practice over six months, seven required a	Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013 Apr 30;4:CD007313. Märkus: ei hõlma Papi et al. 2013 RCT http://www.ncbi.nlm.nih.gov/pubmed/23633340	Cates 2013 4

course of oral steroids, whilst for SiT there would be six (95% CI 5 to 7). The small reduction in time to first severe exacerbation needing medical intervention was not statistically significant (hazard ratio (HR) 0.94; 95% CI 0.85 to 1.04, five trials, N = 7355). Most trials demonstrated a reduction in the mean total daily dose of ICS with SiT (mean reduction was based on self-reported data from patient diaries and ranged from 107 to 385 µg/day). Withdrawals due to adverse events were more common in people treated with SiT (OR 2.85; 95% CI 1.89 to 4.30, moderate quality evidence due to risk of detection bias).Three studies including 4209 adults compared SiT with higher dose budesonide maintenance and terbutaline for symptom relief. The studies were considered as low risk of bias. The run-in for these studies involved withdrawal of LABA, and patients were recruited who were symptomatic during run-in. The reduction in the odds of hospitalisation with SiT compared with higher dose ICS did not reach statistical significance (Peto OR; 0.56; 95% CI 0.28 to 1.09, moderate quality evidence due to imprecision). Fewer patients on SiT needed a course of oral corticosteroids (OR 0.54; 95% CI 0.45 to 0.64, high quality evidence). For every 100 adults treated with ICS over 11 months, 18 required a course of oral steroids, whilst for SiT there would be 11 (95% CI 9 to 12). Withdrawals due to adverse events were more common in people treated with SiT (OR 0.57; 95% CI 0.35 to 0.93, high quality evidence).One study included children (N = 224), in which SiT was compared with higher dose budesonide. There was a significant reduction in participants who needed an increase in their inhaled steroids with SiT, but there were only two hospitalisations for asthma and no separate data on courses of oral corticosteroids. Less inhaled and oral corticosteroids were used in the SiT group and the annual height gain was also 1 cm greater in the SiT group, (95% CI 0.3 cm to 1.7 cm).The results for fatal serious adverse events were too rare to rule out either treatment being harmful. There was no significant difference found in non-fatal serious adverse events for any of the comparisons. AUTHORS' CONCLUSIONS: Single inhaler therapy has now been demonstrated to reduce exacerbations requiring oral corticosteroids against current best practice strategies and against a fixed higher dose of inhaled steroids. The strength of evidence that SiT reduces hospitalisation against these same treatments is weak. There were more discontinuations due to adverse events on SiT compared to current best practice, but no significant differences in serious adverse events. Our confidence in these conclusions is limited by the open-label design of the trials, and by the unknown adherence to treatment in the current best practice arms of the trials.Single inhaler therapy can reduce the risk of asthma exacerbations needing oral corticosteroids in comparison with fixed dose maintenance ICS and separate relief medication. The reduced odds of exacerbations with SiT compared with higher dose ICS should be viewed in the context of the possible impact of LABA withdrawal during study run-in. This may have made the study populations more likely to respond to SiT.Single inhaler therapy is not currently licensed for children under 18 years of age in the United Kingdom and there is currently very little research evidence for this		

approach in children or adolescents.		
Daily inhaled corticosteroids (ICS) are the recommended mainstay of treatment in children and adults with persistent asthma. However, often, ICS are used intermittently by patients or recommended by physicians to be used only at the onset of exacerbations. **OBJECTIVES:** The aim of this review was to compare the efficacy and safety of intermittent versus daily ICS in the management of children and adults with persistent asthma and preschool-aged children suspected of persistent asthma. **SEARCH METHODS:** We searched the Cochrane Airways Group Specialised Register of trials (CAGR) and the ClinicalTrials.gov web site up to October 2012. **SELECTION CRITERIA:** We included randomised controlled trials (RCTs) that compared intermittent ICS versus daily ICS in children and adults with persistent asthma. No co-interventions were permitted other than rescue relievers and oral corticosteroids used during exacerbations. **DATA COLLECTION AND ANALYSIS:** Two review authors independently assessed trials for inclusion, methodological quality and extracted data. The primary efficacy outcome was the number of patients with one or more exacerbations requiring oral corticosteroids and the primary safety outcome was the number of patients with serious adverse health events. Secondary outcomes included exacerbations, lung function tests, asthma control, adverse effects, withdrawal rates and inflammatory markers. Equivalence was assumed if the risk ratio (RR) estimate and its 95% confidence interval (CI) were between 0.9 and 1.1. Quality of the evidence was assessed using GRADE. **MAIN RESULTS:** Six trials (including one trial testing two relevant protocols) met the inclusion criteria for a total of seven group comparisons. The four paediatric trials (two involving preschool children and two school-aged children) and two adult parallel-group trials, lasting 12 to 52 weeks, were of high methodological quality. A total of 1211 patients with confirmed, or suspected, persistent asthma contributed to the meta-analyses. There was no statistically significant group difference in the risk of patients experiencing one or more exacerbations requiring oral corticosteroids (1204 patients; RR 1.07; 95% CI 0.87 to 1.32; the large confidence interval translates into a risk of exacerbations in the intermittent ICS group varying between 17% and 25%, assuming a 19% risk with daily ICS). Age, severity of airway obstruction, step-up protocol used during exacerbations and trial duration did not significantly influence the primary efficacy outcome. No group difference was observed in the risk of patients with serious adverse health events (1055 patients; RR 0.82; 95% CI 0.33 to 2.03). Compared to the daily ICS group, the intermittent ICS group displayed a smaller improvement in change from baseline peak expiratory flow rate (PEFR) by 2.56% (95% CI -4.49% to -0.63%), fewer symptom-free days (standardised mean difference	Chauhan BF, Chartrand C, Ducharme FM. Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. Cochrane Database Syst Rev. 2013 Feb 28;2:CD009611. http://www.ncbi.nlm.nih.gov/pubmed/23450606 Vt ka GRADE tabel	Chauhan 2013 6

(SMD) -0.15 (95% CI -0.28 to -0.03), fewer asthma control days -9% (95% CI -14% to -4%), more use of rescue β2-agonists by 0.12 puffs/day (95% CI 0 to 0.23) and a greater increase from baseline in exhaled nitric oxide of 16.80 parts per billion (95% CI 11.95 to 21.64). There was no significant group difference in forced expiratory volume in one second (FEV1), quality of life, airway hyper-reactivity, adverse effects, hospitalisations, emergency department visits or withdrawals. In paediatric trials, intermittent ICS (budesonide and beclomethasone) were associated with greater growth by 0.41 cm change from baseline (532 children; 95% CI 0.13 to 0.69) compared to daily treatment. **AUTHORS' CONCLUSIONS:** In children and adults with persistent asthma and in preschool children suspected of persistent asthma, there was low quality evidence that intermittent and daily ICS strategies were similarly effective in the use of rescue oral corticosteroids and the rate of severe adverse health events. The strength of the evidence means that we cannot currently assume equivalence between the two options.. Daily ICS was superior to intermittent ICS in several indicators of lung function, airway inflammation, asthma control and reliever use. Both treatments appeared safe, but a modest growth suppression was associated with daily, compared to intermittent, inhaled budesonide and beclomethasone. Clinicians should carefully weigh the potential benefits and harm of each treatment option, taking into account the unknown long-term (> one year) impact of intermittent therapy on lung growth and lung function decline.		
CONTEXT: Over the last 2 decades, many new pharmacological agents have been introduced to reduce the growing morbidity associated with asthma, but the long-term effects of these agents on exacerbations are unclear. OBJECTIVE: To systematically review and quantitatively synthesize the long-term effects of inhaled corticosteroids, long-acting beta2 agonists, leukotriene pathway modifiers/receptor antagonists, and anti-IgE therapies on clinical outcomes and particular clinically relevant exacerbations in adult patients with chronic asthma. DATA SOURCES: MEDLINE, EMBASE, and Cochrane databases were searched to identify relevant randomized controlled trials and systematic reviews published from January 1, 1980, to April 30, 2004. We identified additional studies by searching bibliographies of retrieved articles and contacting experts in the field.	Sin DD, Man J, Sharpe H, Gan WQ, Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. JAMA. 2004 Jul 21;292(3):367-76. http://www.ncbi.nlm.nih.gov/pubmed/15265853 täistekst http://jama.jamanetwork.com/article.aspx?articleid=199101	Sin 2004 8

STUDY SELECTION AND DATA EXTRACTION: Included trials were double-blind, had follow-up periods of at least 3 months, and contained data on exacerbations and/or forced expiratory volume in 1 second. The effects of interventions were compared with placebo, short-acting beta2 agonists, or each other. DATA SYNTHESIS: Inhaled corticosteroids were most effective, reducing exacerbations by nearly 55% compared with placebo or short-acting beta2 agonists (relative risk [RR], 0.46; 95% confidence interval [CI], 0.34-0.62; P<.001 for heterogeneity). Compared with placebo, the use of long-acting beta2 agonists was associated with 25% fewer exacerbations (RR, 0.75; 95% CI, 0.64-0.88; P =.43 for heterogeneity); when added to inhaled corticosteroids, there was a 26% reduction above that achieved by steroid monotherapy (RR, 0.74; 95% CI, 0.61-0.91; P =.07 for heterogeneity). Combination therapy was associated with fewer exacerbations than was increasing the dose of inhaled corticosteroids (RR, 0.86; 95% CI, 0.76-0.96; P =.65 for heterogeneity). Compared with placebo, leukotriene modifiers/receptor antagonists reduced exacerbations by 41% (RR, 0.59; 95% CI, 0.49-0.71; P =.44 for heterogeneity) but were less effective than inhaled corticosteroids (RR, 1.72; 95% CI, 1.28-2.31; P =.91 for heterogeneity). Use of monoclonal anti-IgE antibodies with concomitant inhaled corticosteroid therapy was associated with 45% fewer exacerbations (RR, 0.55; 95% CI, 0.45-0.66; P =.15 for heterogeneity). CONCLUSIONS: Inhaled corticosteroids are the single most effective therapy for adult patients with asthma. However, for those unable or unwilling to take corticosteroids, the use of leukotriene modifiers/receptor agonists appears reasonable. Long-acting beta2 agonists may be added to corticosteroids for those who remain symptomatic despite low-dose steroid therapy. Anti-IgE therapy may be considered as adjunctive therapy for young adults with asthma who have clear evidence of allergies and elevated serum IgE levels.		
SAMA BACKGROUND: Anticholinergic agents such as ipratropium bromide are sometimes used in the treatment of chronic asthma. They effect bronchodilation and have also been used in combination with beta2-agonists in the management of chronic asthma. OBJECTIVES: To examine the effectiveness of anticholinergic agents versus placebo and in comparison with beta2-agonists or as adjunctive therapy to beta2-agonists.	Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults. Cochrane Database Syst. Rev. 3, CD003269 (2004). Update Cohrane andmebaasis 2010, muutusteta. Enam rohkem ei updeidita ka, kuna SAMAdel	Westby 2004

SEARCH STRATEGY: August 2003 (Update august 2008, muutusteta). SELECTION CRITERIA: Randomised trials or quasi-randomised trials were considered for inclusion. Studies assessing an anticholinergic agent versus placebo or in combination/comparison with beta2-agonists were included. In practice, all beta2-agonists were short acting. Short-term (less than 24 hours duration) and longer-term studies were separated; the latter are reported in this review and the former in the review, "Anticholinergic agents for chronic asthma in adults short term". MAIN RESULTS: The studies analysed were in two groups: those comparing anticholinergics with placebo and those comparing the combination of anticholinergics with short acting beta2-agonists versus short acting beta2-agonists alone. The former group had 13 studies involving 205 participants included in this review, and the latter 9 studies involving 440 patients. Generally methodological quality was poorly reported, and there were some reservations with respect to the quality of the studies. Despite the limited number of studies that could be combined, anticholinergic agents in comparison with placebo resulted in more favourable symptom scores particularly in respect of daytime dyspnoea (WMD -0.09 (95%CI -0.14, -0.04, 3 studies, 59 patients). Daily peak flow measurements also showed a statistically significant improvement for the anticholinergic (e.g. morning PEF: WMD =14.38 litres/min (95%CI 7.69, 21.08; 3 studies, 59 patients). However the clinical significance is small and in terms of peak flow measurements equates to approximately a 7% increase over placebo. The more clinically relevant comparison of a combination of anticholinergic plus short acting beta2-agonist versus short acting beta2-agonist alone gave no evidence in respect of symptom scores or peak flow rates of any significant differences between the two regimes. Again there are reservations with respect to the quality of the information from which these conclusions are drawn. REVIEWERS' CONCLUSIONS: Overall this review provides no justification for routinely introducing anticholinergics as part of add-on treatment for patients whose asthma is not well controlled on standard therapies. This does not exclude the possibility that there may be a sub-group of patients who derive some benefit and a trial of treatment in individual patients may still be justified. The role of long term anticholinergics such as tiotropium bromide has yet to be established in patients with asthma and any future trials might draw on the messages derived from this review.	astma baasravis enam rolli ei ole.	
OBJECTIVES: To assess the comparative efficacy, safety and side-effects of long-acting beta-2 agonists and theophylline in the maintenance treatment of adults and adolescents with asthma. SELECTION CRITERIA: All included studies were RCTs involving adults and children with	Tee AK, Koh MS, Gibson PG, Lasserson TJ, Wilson AJ, Irving LB. Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma.	Tee 2007

clinical evidence of asthma. These studies must have compared oral sustained release and/or dose adjusted theophylline with an inhaled long-acting beta-2 agonist. DATA COLLECTION AND ANALYSIS: Until Nov 2006 MAIN RESULTS: Thirteen studies with a total of 1344 participants met the inclusion criteria of the review. They were of varying quality. There was no significant difference between salmeterol and theophylline in FEV(1) predicted (6.5%; 95% CI -0.84 to 13.83). However, salmeterol treatment led to significantly better morning PEF (mean difference 16.71 L/min, 95% CI 8.91 to 24.51) and evening PEF (mean difference 15.58 L/min, 95% CI 8.33 to 22.83). Salmeterol also reduced the use of rescue medication. Formoterol, used in two studies was reported to be as effective as theophylline. Bitolterol, used in only one study, was reported to be less effective than theophylline. Participants taking salmeterol experienced fewer adverse events than those using theophylline (Parallel studies: Relative Risk 0.44; 95% CI 0.30 to 0.63, Risk Difference -0.11; 95% CI -0.16 to -0.07, Numbers Needed to Treat (NNT) 9; 95% CI 6 to 14). Significant reductions were reported for central nervous system adverse events (Relative Risk 0.50; 95% CI 0.29 to 0.86, Risk Difference -0.07; 95% CI -0.12 to -0.02, NNT 14; 95% CI 8 to 50) and gastrointestinal adverse events (Relative Risk 0.30; 95% CI 0.17 to 0.55, Risk Difference -0.11; 95% CI -0.16 to -0.06, NNT 9; 95% CI 6 to 16). AUTHORS' CONCLUSIONS: Long-acting beta-2 agonists, particularly salmeterol, are more effective than theophylline in improving morning and evening PEF, but are not significantly different in their effect on FEV1. There is evidence of decreased daytime and nighttime short-acting beta-2 agonist requirement with salmeterol. Fewer adverse events occurred in participants using long-acting beta-2 agonists (salmeterol and formoterol) as compared to theophylline.	Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001281. http://www.ncbi.nlm.nih.gov/pubmed/17636663	
PURPOSE: To review the literature to determine whether inhaled ipratropium bromide provides additive benefits to adults with acute asthma who are being treated with beta-agonists in an emergency department. SUBJECTS AND METHODS: English-language studies, both published (1978 to 1999) and unpublished, were retrieved using Medline, Science Citation Index, Current Contents, bibliographic reviews of primary research, review articles, consultation with experts, and the register of Medical Editors' Trial Amnesty. Only randomized, double-blind, controlled trials that enrolled patients having an exacerbation of asthma were included. The main outcome measure was pulmonary function; hospital admission rate was also evaluated. RESULTS: Ten studies including 1,483 adults with acute asthma were selected (mean age 32 +/- 13 years, 36% men). The overall effect size in SD units of pulmonary function showed a significant benefit from ipratropium (effect size 0.14, 95% confidence interval	Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med. 1999 Oct;107(4):363-70. http://www.ncbi.nlm.nih.gov/pubmed/10527039	Rodrigo 2009

[CI]: 0.04 to 0.24, P = 0.008). Study-specific effect sizes ranged from 0.03 to 0.63. This pooled effect size was equivalent to a 10% (95% CI: 2% to 18%) increase in forced expiratory volume in 1 second (FEV1) or peak expiratory flow in the ipratropium group compared with the control group. Analysis of the four studies that included patients with extreme obstruction (FEV1 or peak flow <35% of predicted at presentation) showed substantial improvement with ipratropium therapy (effect size 0.38, 95% CI: 0.09 to 0.67). In the five trials (1,186 patients) that studied the effect of ipratropium administration on hospital admissions, pooled results revealed that ipratropium reduced admission rates significantly (odds ratio 0.62, 95% CI: 0.44 to 0.88, P = 0.007). CONCLUSIONS: The addition of ipratropium to beta-agonist therapy offers a statistically significant, albeit modest, improvement in pulmonary function, as well as a reduction in the rate of hospital admissions.		

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Kokkuvõte (abstrakt või kokkuvõtlikum info)	Viide kirjandusallikale	Viide
RATIONALE: To evaluate the association between asthma exacerbations and the decline in lung function, as well as the potential effects of an inhaled corticosteroid, budesonide, on exacerbation-related decline in patients with asthma. OBJECTIVES: To determine whether severe asthma exacerbations are associated with a persistent decline in lung function. METHODS: The START (inhaled steroid treatment as regular therapy in early asthma) study was a 3-year, randomized, double-blind study of 7,165 patients (5-66 yr) with persistent asthma for less than 2 years, to determine whether early intervention with low-dose inhaled budesonide prevents severe asthma-related events (exacerbations requiring hospitalization or emergency treatment) and decline in lung function. MEASUREMENTS AND MAIN RESULTS: There were 315 patients who experienced at least one severe asthma exacerbation, of which 305 were analyzable, 190 in the placebo group and 115 in the budesonide group. In the placebo group, the change in post-bronchodilator FEV(1) % predicted from baseline to the end of the study, in patients who did or did not experience a severe exacerbation was -6.44% and -2.43%, respectively (P < 0.001). A significant difference was seen in both children and in adults, but not in adolescents. In the budesonide group, the change in the post-bronchodilator FEV(1) % predicted in patients who did or did not experience a severe exacerbation was -2.48% and -1.72%, respectively (P = 0.57). The difference in magnitude of reduction afforded by budesonide, in patients who experienced at least one severe asthma-related event compared with those who did not, was statistically significant	Am J Respir Crit Care Med. 2009 Jan 1;179(1):19-24. doi: 10.1164/rccm.200807-1126OC. Epub 2008 Oct 31. Severe exacerbations and decline in lung function in asthma. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW; START Investigators Group. http://www.ncbi.nlm.nih.gov/pubmed/18990678	O'Byrne 2009

(P = 0.042). CONCLUSIONS: Severe asthma exacerbations are associated with a more rapid decline in lung function. Treatment with low doses of inhaled corticosteroid is associated with an attenuation of the decline.		
Although inhaled glucocorticosteroids are recommended for persistent asthma, their long-term effect on recent onset, mild, persistent asthma has yet to be established. METHODS: We did a randomised, double-blind clinical trial in 7241 patients in 32 countries to assess the effects of budesonide in patients who had had mild persistent asthma for less than 2 years and who had not had previous regular treatment with glucocorticosteroids. Patients aged 5-66 years received either budesonide or placebo once daily for 3 years in addition to their usual asthma medications. The daily budesonide dose was 400 microg, or 200 microg for children younger than 11 years. The primary outcome was time to first severe asthma-related event, and analysis was by intention to treat. FINDINGS: 198 of 3568 patients on placebo and 117 of 3597 on budesonide had at least one severe asthma exacerbation; hazard ratio 0.56 (95% CI 0.45-0.71, p<0.0001). Patients on budesonide had fewer courses of systemic corticosteroids and more symptom-free days than did those on placebo. Compared with placebo, budesonide increased postbronchodilator forced expiratory volume in 1 s (FEV1) from baseline by 1.48% (p<0.0001) after 1 year and by 0.88% (p=0.0005) after 3 years (expressed as percent of the predicted value). The corresponding increase in prebronchodilator FEV1 was 2.24% after 1 year and 1.71% after 3 years (p<0.0001 at both timepoints). The effect of treatment on all outcome variables was independent of the baseline lung function (prebronchodilator or postbronchodilator) or baseline medication. In children younger than 11 years, 3-year growth was reduced in the budesonide group by 1.34 cm. The reduction was greatest in the first year of treatment (0.58 cm) than years 2 and 3 (0.43 cm and 0.33 cm, respectively). INTERPRETATION: Long-term, once-daily treatment with low-dose budesonide decreases the risk of severe exacerbations and improves asthma control in patients with mild persistent asthma of recent onset.	Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM; START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003 Mar 29;361(9363):1071-6. http://www.ncbi.nlm.nih.gov/pubmed/12672309	Pauwels 2003
The Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study enrolled 7241 patients aged 5 to 66 years with recent-onset, mild persistent asthma to assess early intervention with the inhaled corticosteroid budesonide on long-term asthma control. OBJECTIVE: The open-label phase of the START study was included to determine the effect on lung	Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, O'Byrne PM; START Investigators Group. The Inhaled Steroid Treatment As	Busse 2008 7a

function and asthma control of adding budesonide to the reference group patients who had not initially received inhaled corticosteroids. METHODS: Patients were randomized to double-blind treatment with budesonide, 200 mug (those aged < 11 years) or 400 mug once daily, or placebo plus the usual asthma therapy for 3 years, after which all patients received 2 years of open-label treatment with budesonide once daily. RESULTS: During the full 5-year study period, postbronchodilator FEV(1) percent predicted decreased, irrespective of randomized treatment during the double-blind phase, by an average of 2.22% (SE, 0.15%). However, patients with inhaled budesonide in the double-blind phase had a significantly lower risk (odds ratio, 0.61; P < .001) of a severe asthma-related event during the full 5-year study period than those in the reference group. Moreover, patients in the reference group used more additional asthma medications during both the open-label and double-blind phases. CONCLUSIONS: In mild persistent asthma early intervention with inhaled budesonide was associated with improved asthma control and less additional asthma medication use.	Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy Clin Immunol. 2008 May;121(5):1167-74. http://www.ncbi.nlm.nih.gov/pubmed/18405951	
Abstract BACKGROUND: In a 3-year study, adult patients who recently developed asthma (symptoms for less than 1 year) were treated for 2 years with the inhaled corticosteroid (ICS) budesonide (early therapy) or terbutaline. During the third year of the study, terbutaline-treated patients received budesonide (delayed therapy). Differences in lung function and bronchial responsiveness to histamine were observed between the 2 groups. OBJECTIVE: We compared the effects of early versus delayed budesonide therapy after a 10-year follow-up period (13 years after the study began) and current real-life data. METHODS: Of the original 103 patients, 90 were re-examined 13 years after study initiation. After the third year of the study, all patients had their medications, including the dose of ICS, individually adjusted. RESULTS: After the follow-up period, lung function was within the normal range for the entire group (all patients); bronchial responsiveness significantly improved compared with baseline data. No statistically significant differences in clinical or functional variables were found between patients given early or delayed budesonide therapy. However, the delayed therapy group had a higher neutrophil count and higher concentrations of eosinophilic cationic protein and myeloperoxidase in induced sputum. This group had also used more asthma medication and hospital days.	Haahtela T, Tamminen K, Kava T, Malmberg LP, Rytilä P, Nikander K, Persson T, Selroos O. Thirteen-year follow-up of early intervention with an inhaled corticosteroid in patients with asthma. J Allergy Clin Immunol. 2009 Dec;124(6):1180-5. http://www.ncbi.nlm.nih.gov/pubmed/20004779	Haahtela 2009 8a

CONCLUSIONS: Patients with relatively mild asthma who received ICS within 12 months of their first asthma symptoms or after a 2-year delay achieved equally good functional control of asthma after 10 years of individualized therapy. However, the delayed therapy group exhibited slightly less optimal disease control and more signs of airway inflammation.		
Although guidelines recommend daily therapy for patients with mild persistent asthma, prescription patterns suggest that most such patients use these so-called controller therapies intermittently. In patients with mild persistent asthma, we evaluated the efficacy of intermittent short-course corticosteroid treatment guided by a symptom-based action plan alone or in addition to daily treatment with either inhaled budesonide or oral zafirlukast over a one-year period. METHODS: In a double-blind trial, 225 adults underwent randomization. The primary outcome was morning peak expiratory flow (PEF). Other outcomes included the forced expiratory volume in one second (FEV1) before and after bronchodilator treatment, the frequency of exacerbations, the degree of asthma control, the number of symptom-free days, and the quality of life. RESULTS: The three treatments produced similar increases in morning PEF (7.1 to 8.3 percent; approximately 32 liters per minute; P=0.90) and similar rates of asthma exacerbations (P=0.24), even though the intermittent-treatment group took budesonide, on average, for only 0.5 week of the year. As compared with intermittent therapy or daily zafirlukast therapy, daily budesonide therapy produced greater improvements in pre-bronchodilator FEV1 (P=0.005), bronchial reactivity (P<0.001), the percentage of eosinophils in sputum (P=0.007), exhaled nitric oxide levels (P=0.006), scores for asthma control (P<0.001), and the number of symptom-free days (P=0.03), but not in post-bronchodilator FEV1 (P=0.29) or in the quality of life (P=0.18). Daily zafirlukast therapy did not differ significantly from intermittent treatment in any outcome measured. CONCLUSIONS: It may be possible to treat mild persistent asthma with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen. Further studies are required to determine whether this novel approach to treatment should be recommended.	Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Chinchilli VM, Craig TJ, Dimango EA, Deykin A, Fagan JK, Fish JE, Ford JG, Kraft M, Lemanske RF Jr, Leone FT, Martin RJ, Mauger EA, Pesola GR, Peters SP, Rollings NJ, Szefler SJ, Wechsler ME, Israel E; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med. 2005 Apr 14;352(15):1519-28. http://www.ncbi.nlm.nih.gov/pubmed/15829533	Boushey 2005
Short-acting β-agonist (SABA) use is well established in predicting asthma events in adults. However, this predictive ability has yet to be established in a pediatric population together with an assessment of amount of use. OBJECTIVE: To identify the number of SABA canisters that best predicts future asthma-related exacerbations and the optimal length of time for measurement of SABA use in pediatric and adult asthma patients.	*Ägenemiste ennustamine vastavalt SABA kasutusele* Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting β-agonist use and its ability to predict future asthma-related outcomes.	Stanford 2012

METHODS: Asthma patients were identified from a Medicaid and a commercially insured database (January 1, 2004, through December 31, 2005, and January 1, 2004, through June 30, 2006, respectively). Following the date of first asthma medication, an assessment period (3, 6, or 12 months) was used to measure SABA use. Asthma-related exacerbations were identified in the subsequent 12-month period. Receiver operating characteristic curve analyses and logistic regression were used to select the critical values of SABA use and optimal assessment periods and to conduct incremental analysis, respectively. RESULTS: A total of 33,793 Medicaid and 101,437 commercial patients met the study criteria. Use of 3 or more SABA canisters during 12 months was identified in both pediatric Medicaid and commercial populations to best predict an increased risk of an asthma-related exacerbation. For adults, use of 2 or more SABA canisters was found as the critical value with shorter optimal assessment periods of 3 and 6 months. Each additional SABA canister resulted in an 8% to 14% and 14% to 18% increase in risk of an asthma-related exacerbation in children and adults, respectively. CONCLUSION: The study identified critical values of SABA use that predict future asthma events. Each additional SABA canister predicted increases in exacerbation risk in children and adults.	Ann Allergy Asthma Immunol. 2012 Dec;109(6):403-7. http://www.ncbi.nlm.nih.gov/pubmed/23176877	
BACKGROUND: Divergent strategies have emerged for the management of severe asthma. One strategy utilises high and fixed doses of maintenance treatment, usually inhaled corticosteroid/long-acting β2-agonist (ICS/LABA), supplemented by a short-acting β2-agonist (SABA) as needed. Alternatively, budesonide/formoterol is used as both maintenance and reliever therapy. The latter is superior to fixed-dose treatment in reducing severe exacerbations while achieving similar or better asthma control in other regards. Exacerbations may be reduced by the use of budesonide/formoterol as reliever medication during periods of unstable asthma. We examined the risk of a severe exacerbation in the period after a single day with high reliever use. METHODS: Episodes of high reliever use were quantified and exacerbations occurring post-index day with these episodes were examined post hoc in two double-blind studies comparing the efficacy and safety of budesonide/formoterol maintenance and reliever therapy (Symbicort SMART™, Turbuhaler®) 160/4.5 μg twice daily plus as needed with similar or higher maintenance doses of ICS/LABA plus SABA or formoterol. RESULTS: Budesonide/formoterol maintenance and reliever therapy significantly reduced the risk of episodes of high reliever use (>6 inhalations/day) vs. all alternative ICS/LABA	Buhl R, Kuna P, Peters MJ, Andersson TL, Naya IP, Peterson S, Rabe KF. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. Respir Res. 2012 Jul 20;13:59. http://www.ncbi.nlm.nih.gov/pubmed/22816878	

regimens. With conventional fixed-dose treatment the need for exacerbation treatment within 21 days ranged from 6.0-10.1% of days post-index for all regimens compared with 2.5-3.4% of days with budesonide/formoterol maintenance and reliever therapy. CONCLUSIONS: Budesonide/formoterol maintenance and reliever therapy reduces the incidence of high reliever episodes and the exacerbation burden immediately following these episodes vs. alternative ICS/LABA plus SABA regimens at up to double the maintenance dose of ICS.		
BACKGROUND: Asthmatics treated with long-acting beta-agonists have a reduced bronchodilator response to moderate doses of inhaled short acting beta-agonists during acute bronchoconstriction. It is not known if the response to higher doses of nebulised beta-agonists or other bronchodilators is impaired. We assessed the effect of long-acting beta-agonist treatment on the response to 5 mg nebulised salbutamol and to ipratropium bromide. METHODS: Two double-blind, placebo-controlled, crossover studies of inhaled formoterol 12 mug twice daily in patients with asthma.High-dose salbutamol: 36 hours after the last dose of 1 week of formoterol or placebo treatment, 11 subjects inhaled methacholine to produce a 20% fall in FEV1. Salbutamol 5 mg was then administered via nebuliser and the FEV1 was monitored for 20 minutes. Ipratropium: 36 hours after the last dose of 1 week of formoterol or placebo treatment, 11 subjects inhaled 4.5% saline to produce a 20% fall in FEV1. Salbutamol 200 mug or ipratropium bromide 40 mug was then inhaled and the FEV1 was monitored for 30 minutes. Four study arms compared the response to each bronchodilator after formoterol and placebo. Analyses compared the area under the bronchodilator response curves, adjusting for changes in pre-challenge FEV1, dose of provocational agent and FEV1 fall during the challenge procedure RESULTS: The response to nebulised salbutamol was 15% lower after formoterol therapy compared to placebo (95% confidence 5 to 25%, p = 0.008). The response to ipratropium was unchanged. CONCLUSION: Long-acting beta-agonist treatment induces tolerance to the bronchodilator effect of beta-agonists, which is not overcome by higher dose nebulised salbutamol. However, the bronchodilator response to ipratropium bromide is unaffected. (väike uuring, uuritavaid 11)	Haney S, Hancox RJ. Overcoming beta-agonist tolerance: high dose salbutamol and ipratropium bromide. Two randomised controlled trials. Respir Res. 2007 Mar 6;8:19.	Haney 2007

The two drugs were compared in 44 asthmatics in a double-blind, randomized crossover, placebo-controlled study. There were four test days on which each patient received the following sequences of drugs: sal-sal-ipra, sal-sal-placebo, ipra-ipra-sal, and ipra-ipra-placebo. Baseline forced expiratory volume in 1 sec (FEV1) was similar on the four days. The change in FEV1 produced by salbutamol when given as the first bronchodilator was 0.50 +/- 0.30 L as compared to a change of 0.39 +/- 0.27 L produced by ipratropium ($p < 0.01$). Both salbutamol and ipratropium resulted in statistically similar further improvements in FEV1 when given as the second drug. There was, however, a wide patient-to-patient variability in response, with some patients showing greater improvement with salbutamol and others with ipratropium.	Chhabra SK, Pandey KK. Comparison of acute bronchodilator effects of inhaled ipratropium bromide and salbutamol in bronchial asthma. J Asthma. 2002 Aug;39(5):375-81.	Chhabra 2002
University of Groningen and the Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, and Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands. h.a.m.kerstjens@umcg.nl Abstract BACKGROUND: Some patients with asthma have frequent exacerbations and persistent airflow obstruction despite treatment with inhaled glucocorticoids and long-acting beta-agonists (LABAs). METHODS: In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5 µg) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1 second (FEV(1)) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year. RESULTS: The patients had a mean baseline FEV(1) of 62% of the predicted value; the mean age was 53 years. At 24 weeks, the mean (±SE) change in the peak FEV(1) from baseline was greater with tiotropium than with placebo in the two trials: a difference of 86±34 ml in	Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012 Sep 27;367(13):1198-2007. http://www.ncbi.nlm.nih.gov/pubmed/22938706	Kerstjens 2012

trial 1 (P=0.01) and 154±32 ml in trial 2 (P<0.001). The predose (trough) FEV(1) also improved in trials 1 and 2 with tiotropium, as compared with placebo: a difference of 88±31 ml (P=0.01) and 111±30 ml (P<0.001), respectively. The addition of tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79; P=0.03). No deaths occurred; adverse events were similar in the two groups. CONCLUSIONS: In patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov numbers, NCT00772538 and NCT00776984.).		
BACKGROUND: Long-acting beta-agonist (LABA) therapy improves symptoms in patients whose asthma is poorly controlled by an inhaled glucocorticoid alone. Alternative treatments for adults with uncontrolled asthma are needed. METHODS: In a three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma, we evaluated the addition of tiotropium bromide (a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease but not asthma) to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison). RESULTS: The use of tiotropium resulted in a superior primary outcome, as compared with a doubling of the dose of an inhaled glucocorticoid, as assessed by measuring the morning peak expiratory flow (PEF), with a mean difference of 25.8 liters per minute (P<0.001) and superiority in most secondary outcomes, including evening PEF, with a difference of 35.3 liters per minute (P<0.001); the proportion of asthma-control days, with a difference of 0.079 (P=0.01); the forced expiratory volume in 1 second (FEV1) before bronchodilation, with a difference of 0.10 liters (P=0.004); and daily symptom scores, with a difference of -0.11 points (P<0.001). The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and increased the prebronchodilator FEV1 more than did salmeterol, with a difference of 0.11 liters (P=0.003).	Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger L, Engle LL, DiMango EA, Fahy JV, Israel E, Jarjour N, Kazani SD, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Szefler SJ, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Bleecker ER; National Heart, Lung, and Blood Institute Asthma Clinical Research Network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010 Oct 28;363(18):1715-26.	Peters 2010

CONCLUSIONS: When added to an inhaled glucocorticoid, tiotropium improved symptoms and lung function in patients with inadequately controlled asthma. Its effects appeared to be equivalent to those with the addition of salmeterol. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00565266.).		
According to international treatment guidelines, inhaled rapid-acting β2 agonists should be used for the control of symptoms in patients with asthma. We compared the efficacy and safety of an extrafine combination inhaler containing a corticosteroid (beclometasone) plus a rapid-onset, long-acting β2 agonist (formoterol) with a short-acting β2 agonist (salbutamol) as reliever strategies in patients taking beclometasone—formoterol combination as maintenance treatment. Methods In a double-blind trial undertaken in 183 centres in 14 European countries over 48 weeks, patients (aged ≥18 years) with asthma that was not fully controlled, with a forced expiratory volume in 1 s (FEV1) of at least 60% predicted, had a 2-week run in. During this period, patients were treated with a combination of beclometasone 100 μg and formoterol 6 μg per one inhalation twice daily plus salbutamol 100 μg as required delivered by use of a pressurised metered-dose inhaler. They were then randomly assigned in a 1:1 ratio with a computer-generated randomisation list to receive beclometasone 100 μg plus formoterol 6 μg or salbutamol 100 μg as reliever in addition to maintenance with beclometasone 100 μg plus formoterol 6 μg twice daily. Primary outcome was the time to first severe exacerbation (admission to hospital or visit to emergency department, or use of systemic steroids for ≥3 consecutive days). Secondary outcomes were number of severe exacerbations (events per 100 patients per year), time to and number of mild exacerbations, additional exacerbation variables, lung function, symptom scores, and asthma control. Analysis was by intention to treat. The study is registered with ClinicalTrials.gov, number NCT00861926. Findings 1714 patients were randomly assigned to the as-needed beclometasone—formoterol (n=857) and as-needed salbutamol groups (n=857), and 1701 were analysed (852 and 849, respectively). 326 severe exacerbations were reported by 251 patients during the study, and 99 versus 152 patients had at least one exacerbation during the 48 weeks, respectively. Compared with beclometasone—formoterol plus salbutamol as needed,	Papi A, Corradi M, Pigeon-Francisco C, Baronia R, Siergiejko Z, Petruzzelli S, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med 2013;1:23-31	

beclometasone—formoterol for both maintenance and reliever treatment significantly increased the time to first exacerbation (209 days vs 134 days) by 75 days, with a 36% reduction in risk (hazard ratio 0·64 [95% CI 0·49 to 0·82]; p=0·0005), and the estimated probability was 12% and 18%, respectively (p=0·0003). The number of days with mild asthma exacerbations was also lower with as-needed beclometasone—formoterol than with as-needed salbutamol (56·04 days per patient per year vs 65·11 days per patient per year; 0·86 [0·76 to 0·98]; p=0·021). From the run-in period to week 48, both treatments improved symptoms (mean change −1·59 [—1·94 to −1·25] in the as-needed beclometasone—formoterol group vs −1·44 [—1·78 to −1·10] in the as-needed salbutamol group, difference −0·15 [—0·60 to 0·30]; p=0·507), percentage of asthma control days (9·5% [7·3 to 11·8] vs 10·9% [8·7 to 13·1], respectively, −1·4 [—4·3 to 1·6]; p=0·359), use of reliever (—0·29 [—0·38 to −0·20] vs −0·27 [—0·36 to −0·19], respectively, −0·02 [—0·13 to 0·10]; p=0·794), and lung function (FEV1, 0·090 [0·060 to 0·120] vs 0·090 [0·060—0·120], respectively, 0·001 [—0·040 to 0·040]; p=0·969), and were well tolerated (patients with serious adverse events, 32 [4%] and 41 [5%], respectively). Interpretation Our results lend support to the use of the combination of a single inhaled corticosteroid plus a rapid-onset, long-acting β2 agonist for maintenance and relief in patients with moderate to severe asthma and provide encouraging data for the formulation of beclometasone—formoterol for this use.		
Ainult madalat ja mõõdukat IKS algannust võrreldud pole. (Otsistrateegia 25.11.2013 "Asthma"[Mesh] AND "Glucocorticoids"[Mesh] AND "low dose"[All Fields] AND "medium dose"[All Fields] AND (systematic[sb] OR Randomized Controlled Trial[ptyp]), n=1, asjakohaseid vasteid ei ole). Madala ja mõõduka algannuse osas on võrdlust Powell 2004 süstemaatilises ülevaates.		

Täiendav küsimus: **Mida kasutada astma hooraviks, kui patsient kõrvaltoimete tõttu beeta-agonisti ei talu?**

"Asthma"[Mesh] AND reliever[All Fields] AND (systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) n=104, aga asjakohaseid ei ole
"Asthma"[Mesh] AND reliever[All Fields] AND "agonist intolerance"[All Fields] AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp])) n=0

"Theophylline"[Mesh] AND "Asthma"[Mesh] AND (systematic[sb] OR Meta-Analysis[ptyp]) n=39

1) Travers AH, Jones AP, Camargo CA Jr, Milan SJ, Rowe BH. Intravenous beta(2)-agonists versus intravenous aminophylline for acute asthma. Cochrane Database Syst Rev. 2012 Dec 12;12:CD010256. http://www.ncbi.nlm.nih.gov/pubmed/23235686
Pole asjakohane.

2) Tee AK, Koh MS, Gibson PG, Lasserson TJ, Wilson AJ, Irving LB. Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001281.
http://www.ncbi.nlm.nih.gov/pubmed/17636663
LABA salmeterool tõhusam ja paremini talutav kui teofülliin, formoterooli ja teofülliini tõhususes erinevust ei selgunud, kuid ei ole vastust küsimusele, mida kasutada siis, kui patsient ei talu SABA/LABA.

SAMA (short-acting muscarinic antagonist) hooraviks SABA **aseme**l?
SAMA=ipratroopium (Atrovent); LAMA=tiotroopium (Spiriva)
Süstemaatilised ülevaated:
"Ipratropium"[Mesh] AND "Asthma"[Mesh] AND (systematic[sb] OR Meta-Analysis[ptyp]) n=21, 2 teemakohast

Astma hooraviks SAMA+SABA vs SABA monoteraapia hinnati ühes meta-analüüsis (Rodrigo 1999). See meta-analüüs hõlmas 10 EMO osakondades läbi viidud uuringut ja 1483 patsienti. SAMA+SABA rühmas suurenes FEV1 või PEF 10% võrra ((95% CI: 2% to 18%) ning vähenes haiglaravile suunamise šanss (OR 0.62, 95% CI: 0.44 to 0.88) võrreldes platseebo+SABA.

SAMA toimet astma püsiravis on hinnatud 2004. a publitseeritud Cochrane andmebaasi süstemaatilises ülevaates (Westby 2004; töörühma poolt üle vaadatud ka 2010.a, muutusteta):
- SAMA vs platseebo: 13 uuringut kokku 205 uuritavaga. Uuringute metodoloogiline kvaliteet oli madal. SAMA kasutajatel oli võrreldes platseeborühmaga mõnevõrra vähem päevasümptomeid ning FEV1 mõnevõrra suurenes (ligikaudu 7% võrra). Üheksas uuringus (uuritavaid kokku 440).
- SABA+SAMA kombineeritud ravi vs SABA monoteraapia: 9 uuringut kokku 440 uuritavaga. Uuringute metodoloogiline kvaliteet oli madal. SABA+SAMA ei olnud ühegi uuritava tulemusnäitaja osas tõhusam kui SABA monoteraapia.

Peale 1999.a. publitseeritud uuringud: Otsing "Ipratropium"[Mesh] AND "Asthma"[Mesh] AND (Randomized Controlled Trial[ptyp] AND ("1999/01/01"[PDAT] : "3000/12/31"[PDAT])) annab 19 vastet, nende hulgas üks väike RCT ipratroopium *vs* salbutamool (Chhabra 2002, n=44): statistiliselt olulisi nende vahel erinevusi ei ilmnenud.
Ühes väikeses uuringus (Haney 2007, n=11) oli näha, et LABA (konkreetset formoterooli) foonil SABA toime väheneb (nn tolerants beeta-agonistide suhtes), kuid SAMA toime ei muutu.

Küll aga on leitud, et **ravi ülestiitrimisel** on **LAMA** lisamisest teatud juhtudel kasu (Peters 2010; Kerstjens 2012)

Inhaleeritav magneesiumsulfaat vs SABA:
There is currently no good evidence that inhaled MgSO(4) can be used as a substitute for inhaled β(2)-agonists.

Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, Rowe BH. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2012 Dec 12;12:CD003898. http://www.ncbi.nlm.nih.gov/pubmed/23235599