Kliiniline küsimus nr 7

Kliinilise küsimuse tekst: Kas astma diagnoosiga püsiravi vajavatele patsientidele tuleks ravi tiitrimisel (step-up) suurendada IKS annust (monoteraapia) vs IKS (algannusele) LABA lisamine (kombineeritud ravi)?

Lühendid: IKS=inhaleeritav glükokortikosteroid; LABA= pikatoimeline β2-agonist

Kokkuvõte, sh kriitiliste tulemusnäitajate kaupa:

Ravi ülestiitrimisel saavutatakse mõõdukalt/mõnevõrra paremad ravitulemused *(modest improvement)*, kui madalas annuses inhaleeritavale kortikosteroidile lisatakse pikatoimeline β2-agonist (kombineeritud ravi) võrreldes sellega, kui suurendatakse inhaleeritava kortikosteroidi annust (monoteraapia).
Andmed põhinevad Cochrane'i andmebaasi 2010. a avaldatud süstemaatilisel ülevaatel ja 48 kliinilise katse meta-analüüsil, mis hõlmab kuni 2008.a. maini läbi viidud uuringuid. Lisaks peale seda publitseeritud kahe kliinilist katse tulemused on samasuunalised. Meta-analüüsi hõlmatud uuringutes oli kombineeritud ravi rühmas beklometasooni või selle ekvivalentannuse (BDP-eq) mediaan 400 µg/ööpäevas ning monoteraapia rühmas BDP-eq mediaan 1000 µg/ööpäevas, lisandunud kliinilistes katsetes oli kombineeritud ravi rühmas budesoniidi annus 200-400 µg/ööpäevas ning monoteraapia rühmas budesoniidi annus 800 µg/ööpäevas. LABA annused olid: salmeterool 50mcgx2 või formoterool 12mcgx2 (v.a. kokku 3 uuringut, kus olid kas 2x suuremad või väiksemad LABA annused)

Meta-analüüsi alusel oli osa tulemusnäitajatest paremad kombineeritud ravi saanute hulgas ning mitte ühelgi juhul ei olnud tulemusnäitajad paremad monoteraapiat saanute hulgas. Tulemusnäitajad olid täpsemalt järgmised:

- elukvaliteedi muutus AQLQ skoori alusel 0.10 [-0.06, 0.26] (statistiliselt mitteoluline)
- astma ägenemiste esinemine, mis vajavad suukaudset kortikosteroidravi RR 0.88 [0.78, 0.98] (statistiliselt oluline erinevus), **NNT 73** (uuringute mediaankestus 12 nädalat)
- päevaste sümptomite esinemine: päevaste sümptomite skoori muutus -0.26 [-0.35, -0.17], sümtomiteta päevade arvu suurenemine 9.18 päeva [6.02, 12.33 päeva] võrra (mõlemal puhul statistiliselt oluline erinevus)
- öösümptomid/unehäired: sümptomiteta ööde arvu muutus -2.10 [-7.98, 3.79] (statistiliselt mitteoluline), öiste ärkamiste arvu muutus-0.03 [-0.10, 0.04] (statistiliselt mitteoluline)
- hooravi vajaduse vähenemine (kordi ööpäevas) -0.20 [-0.29, -0.11](statistiliselt oluline erinevus)
- ravi kõrvaltoimete esinemine: tõsised kõrvaltoimed RR 0.82 [0.50, 1.34], kõik kõrvaltoimed RR 0.99 [0.95, 1.03] (statistiliselt mitteolulised erinevused).

Meta-analüüsis mittekajastunud (hiljem publitseeritud) kliiniliste katsete tulemused on meta-analüüsi tulemustega samasuunalised.

Samadele järeldustele jõuab ka:

Jonas DE, Wines RCM, DelMonte M et al. In: Drug Class Review: Controller Medications for Asthma: Final Update 1 Report. OR, USA (2011).
http://www.ncbi.nlm.nih.gov/pubmed/22132427
(tõendusmaterjali kvaliteet: tugev)

Kombineeritud ravi kõrvaltoimete kohta publitseeriti 2013 .a märtsis Cochrane'i andmebaasi süstemaatiline ülevaade, mis hõlmas 35 täiskasvanutel ja noorukitel läbi viidud uuringut (kokku 13 447 uuritavat). Salmoterool-ICS ravi saanute hulgas leidis aset 7/6986 surmajuhtu ning samas annuses ICS ravi saanute hulgas 7/ 6461 surmajuhtu (Peto šansisuhe (OR) 0.90; 95% CI 0.31-2.60, tõendusmaterjali kvaliteet mõõdukas). Statistiliselt olulist erinevust ei olnud ka mittefataalsete tõsiste kõrvaltoimete osas (Peto OR 1.15; 95% CI 0.91 to 1.44, tõendusmaterjali kvaliteet mõõdukas).

Formoterooli ja salmoterooli kõrvaltoimete võrdluse osas publitseeriti 2012. a märtsis Cochrane'i andmebaasi süstemaatiline ülevaade, mis hõlmas 4 uuringut. Uuritavate hulgas astmaga seotud surmajuhtumeid ei olnud. Mittefataalsete ravi tõsiste kõrvaltoimete osas formoterooli ja salmeterooli vahel statistiliselt olulisi erinevusi ei ilmnenud (Peto šansisuhe (OR) 0.77; 95% CI 0.46-1.28).

Ei leidnud siiski ühtegi RCT küsimuse kohta, et kui algannuses IKS ja LABA ei ole andnud soovitud efekti, kas siis suurendada IKS annust või lisada kolmas toimeaine (otsistrateegia 28.11.2013: ("Asthma"[Mesh] AND "Glucocorticoids"[Mesh]) AND "Adrenergic beta-Agonists"[Mesh] AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields]) AND Randomized Controlled Trial[ptyp] n=72, ükski pole asjakohane ("Asthma/drug therapy"[Mesh] AND "Drug Therapy, Combination"[Mesh]) AND "Glucocorticoids"[Mesh] AND (Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) 06.02.2014 –n=138, mitte ühtegi asjakohast

Ravijuhendid

Kokkuvõte ravijuhendites leiduvatest soovitustest:

Enamiku ravijuhendite soovitustes eelistatakse kombinatsioonravi ICS annuse suurendamisele:

- Kõige uuem seda küsimust põhjaliku süstemaatilise ülevaate alusel käsitlenud ravijuhend (Canada 2012) annab tugeva soovituse: kui madalas annuses ICS monoteraapiaga ei saavutata astma kontrolli, soovitatakse esimese eelistusena lisada madalas annuses ICS-le LABA, mitte suurendada ICS annust.
- Kindel soovitus kombinatsioonravi eelistamise kohta ravi ülestiitrimisel on ka GINA-2012 juhendis, SIGN-2012 juhendis, GEMA-2010 juhendis ja NICE-TA138 analüüsis.
    - SIGN juhendis soovitatakse kaaluda enne ICS annuse suurendamist üle 400

µg BDP-eq LABA lisamist raviskeemi; lisada LABA kindlasti enne, kui suurendada ICS annust >800 µg BDP-eq.

- GINA 2012 juhendi taskuversioonis soovitatakse LABA lisamist madalas annuses ICS ravile, põhitekstis soovitatakse aga LABA lisamist mõõdukas annuses ICS ravile.
- GEMA-2010 juhendis on eelistatud valikuks madalas annuses ICS-le LABA lisamine. Alternatiivina soovitatakse ka ICS annuse suurendamist mõõduka annuseni või ICS-LTRA kombinatsiooni, kui individuaalne riskianalüüs viitab LABA kasutamise riskidele.
- Va/Dod 2009 juhendis soovitatakse madalas annuses ICS ravi korral kaaluda nii ICS annuse suurendamist kui ka LABA lisamist, kusjuures ICS annuse suurendamine on ohutum, aga LABA lisamine tõhusam. Juba mõõdukas/kõrges annuses ICS ravile soovitatakse kindlasti lisada LABA.

Mõlemaid siinkohal kaalutavaid alternatiive soovitavad võrdväärsete valikutena EPR-3 2007 ja ISCI-2012 (viidates EPR-3 2007), samuti NVL-2011, kus aga pigem soovitatakse alguses suurendada ICS annuseid ja seejärel lisada LABA, otsustamisel tuleb arvestada patsiendi seisundiga.

ICS madal annus:

- budesoniid ööpäevases annuses 200-400 µg ehk ≤400 µg (Canada 2010/2012, SIGN, GINA)
- budenosiid ööpäevases annuses ≤600 µg (EPR-3 2007, ISCI ja VaDoD)

ISC mõõdukas annus:

- budesoniid ööpäevases annuses 401-800 µg (Canada 2010/2012, SIGN, GINA)
- budenosiid ööpäevases annuses 601-1200 µg (EPR-3 2007, ISCI ja VaDoD).

Kõigis seda küsimust käsitlevates ravijuhistes soovitatakse enne medikamentoosse ravi muutmist hinnata astma diganoosi korrektsust, ravimi inhaleerimistehnikat, ravisoostumust, jätkuvat ekspositsiooni riskiteguritele, kaasuvaid haigusi.

Kokkuvõtted süstemaatilistest ülevaadetest:
("Asthma"[Mesh] AND "Glucocorticoids"[Mesh]) AND "Adrenergic beta-Agonists"[Mesh] AND (systematic[sb] OR Meta-Analysis[ptyp]) n=32

Süstemaatiline ülevaade ja meta-analüüs hõlmas kokku 48 kliinilist katset 15 155 uuritavaga, nendest 14 000 täiskasvanud. Uuritavatel oli enne uuringu algust senise ICS raviga ebapiisavalt kontrollitud astma. Katsetes võrreldi 1) kombinatsioonravi inhaleeritava kortikosteroidraviga (ICS) mediaanannuses 400 µg BDP-eq (beklometasoon või selle ekvivalentannus) koos salmeterooli või formoterooliga ning 2) monoteraapia ICS-ga mediaanannuses 1000 µg BDP-eq. Katsete kestus enamasti 24 nädalat või vähem. Kombinatsioonravi saanute hulgas oli süsteemset kortikosteroidravi vajavate astma ägenemiste risk oluliselt väiksem (RR 0.88, 95% CI 0.78 - 0.98, 27 uuringut, N = 10,578), absoluutne riski vähenemine 11.45% → 10%, NNT 73 (kliiniliste katsete kestuse mediaan 12 nädalat). Haiglaravi vajaduse osas ja tõsiste kõrvaltoimete osas olulisi erinevusi ei olnud (vastavalt RR 1.02, 95% CI 0.67 -	Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma.

1.56 ja RR 1.12, 95% CI 0.91-1.37). The combination of LABA and ICS resulted in significantly greater but modest improvement from baseline in lung function, symptoms and rescue medication use than with higher ICS dose. Despite no significant group difference in the risk of overall adverse events (RR 0.99, 95% CI 0.95 to 1.03), there was an increase in the risk of tremor (RR 1.84, 95% CI 1.20 to 2.82) and a lower risk of oral thrush (RR 0.58, 95% CI 0.40 to 0.86)) in the LABA and ICS compared to the higher ICS group. There was no significant difference in hoarseness or headache between the treatment groups. The rate of withdrawals due to poor asthma control favoured the combination of LABA and ICS (RR 0.65, 95% CI 0.51 to 0.83).	Cochrane Database Syst Rev. 2010 Apr 14;(4):CD005533. http://www.ncbi.nlm.nih.gov/pubmed/20393943
Süstemaatilise ülevaate eesmärk oli võrrelda astma ägenemiste korral 1)patsiendi enda poolt ambulatoorses ravis algatatud ICS annuse suurendamist ja 2) jätkamist endise ICS annusega. Tulemused: Five RCTs (four parallel-group and one cross-over) involving a total of 1250 patients (28 children and 1222 adults) with mild to moderate asthma were included. The mean daily baseline ICS dose was 555 mcg (range 200 mcg to 795 mcg) and the mean daily ICS dose achieved following increase was 1520 mcg (range 1000 mcg to 2075 mcg), in CFC beclomethasone dipropionate equivalents. Three parallel-group studies in adults (two doubling and one quadrupling; mean achieved daily dose of 1695 mcg with a range of 1420 to 2075 mcg), involving 1080 patients contributed data to the primary outcome. There was no significant reduction in the need for rescue oral corticosteroids when patients were randomised to the increased ICS compared to stable maintenance dose groups (OR 0.85, 95% CI 0.58 to 1.26). There was no significant difference in the overall risk of non-serious adverse events associated with the increased ICS dose strategy, but the wide confidence interval prevents a firm conclusion. No serious adverse events were reported. AUTHORS' CONCLUSIONS: In adults with asthma on daily maintenance ICS, a self-initiated ICS increase to 1000 to 2000 mcg/day at the onset of an exacerbation is not associated with a statistically significant reduction in the risk of exacerbations requiring rescue oral corticosteroids. More research is needed to assess the effectiveness of increased ICS doses at the onset of asthma exacerbations (particularly in children).	http://www.ncbi.nlm.nih.gov/pubmed/21154378 Cochrane Database Syst Rev. 2010 Dec 8;(12):CD007524. doi: 10.1002/14651858.CD007524.pub3. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Quon BS, Fitzgerald JM, Lemière C, Shahidi N, Ducharme FM.
Objectives: To assess the risk of mortality and non-fatal serious adverse events in trials which randomised patients with chronic asthma to regular salmeterol and inhaled corticosteroids in comparison to the same dose of inhaled corticosteroids. *Results.* We have included 35 studies (13,447 participants) in adults and adolescents. We judged that the overall risk of bias was low, and we obtained data on serious adverse events from all studies. All except 542 adults (and none of the children) who were randomised to salmeterol were given fluticasone in the same (combination) inhaler.Seven deaths occurred in 6986 adults on regular salmeterol with inhaled corticosteroids (ICS), and seven deaths in 6461 adults on regular inhaled corticosteroids at the same dose. The difference was not statistically significant (Peto odds ratio (OR) 0.90; 95% confidence interval (CI) 0.31 to 2.60, moderate quality evidence). The risk of dying from any cause in adults on ICS was 10 per 10,000, and on salmeterol and ICS we would expect between 3 and 26 deaths per 10,000. Non-fatal	Cates CJ, Jaeschke R, Schmidt S, Ferrer M. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2013 Mar 28;3:CD006922. http://www.ncbi.nlm.nih.gov/pubmed/23744625

serious adverse events of any cause were reported in 167 adults on regular salmeterol with ICS, compared to 135 adults on regular ICS; again this was not a statistically significant increase (Peto OR 1.15; 95% CI 0.91 to 1.44, moderate quality evidence). The frequency of serious adverse events was 21 per 1000 in the adults treated with ICS and 24 per 1000 in those treated with salmeterol and ICS. The absolute difference in the risk of non-fatal serious adverse events was an increase of 3 per 1000, that was not statistically significant (risk difference (RD) 0.003; 95% CI -0.002 to 0.008). Asthma-related serious adverse events were reported in 29 and 23 adults in each group respectively, a non-significant difference (Peto OR 1.12; 95% CI 0.65 to 1.94, moderate quality evidence). *Conclusions* We found no statistically significant differences in fatal or non-fatal serious adverse events in trials in which regular salmeterol was randomly allocated with ICS, in comparison to ICS alone at the same dose. Although 13,447 adults and 1862 children have now been included in trials, the frequency of adverse events is too low and the results are too imprecise to confidently rule out a relative increase in all cause mortality or non-fatal adverse events with salmeterol used in conjunction with ICS. However, the absolute difference between groups in the risk of serious adverse events was very small. We could not determine whether the increase in all cause non-fatal serious adverse events reported in the previous meta-analysis on regular salmeterol alone is abolished by the additional use of regular ICS. We await the results of large ongoing surveillance studies mandated by the FDA to provide more information. There were no asthma-related deaths and few asthma-related serious adverse events. Clinical decisions and information for patients regarding regular use of salmeterol have to take into account the balance between known symptomatic benefits of salmeterol and the degree of uncertainty and concern associated with its potential harmful effects.	Vt ka samalaadne ülevaade sarnaste tulemustega formoterooli kohta: http://www.ncbi.nlm.nih.gov/pubmed/23744625
Aim: To evaluate the clinical efficacy, safety, and cost effectiveness of long-acting beta2-agonist and inhaled corticosteroid (LABA-ICS) combination therapy for adults (12 years of age or older) diagnosed with persistent asthma. *Results:* The studies that were identified during the economic review had weaknesses in analysis, funding, and use of comparators. This supported the need for a full economic analysis from the Canadian context. In comparing all four strategies, the incremental QALYs gained from introducing a LABA earlier are small at 12 weeks and one year. The total costs are higher the earlier a LABA is introduced. For treatment-naive patients, the incremental cost per QALY gained from treatment with LABA plus ICS instead of ICS monotherapy is $3.3 million. For asthma that is uncontrolled on low-dose ICS, the incremental cost per QALY gained from treatment with LABA plus lowdose ICS instead of medium-dose ICS monotherapy is $1.6 million. For asthma that is uncontrolled on medium-dose ICS, the incremental cost per QALY gained from treatment with LABA plus medium-dose ICS instead of high-dose ICS monotherapy is $190,000. The results were insensitive to changes in relevant parameters. *Conclusions:* For most patients with persistent asthma, the initial and only therapy needed is inhaled corticosteroid (ICS). The clinical review found statistically important, but not clinically meaningful, benefits from switching to combination therapy in managing most asthma not controlled by ICS. A primary economic analysis from a Canadian perspective found that the later a long-acting beta2-agonist (LABA) is introduced into therapy, the more cost	Bond K, Coyle D, O'Gorman K, Coyle K, Spooner C, Lemičre C, Vandermeer B, Tjosvold L, Rowe BH. Long-Acting Beta2-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation. [CADTH Technology report number 122, November 2009]. http://www.cadth.ca/index.php/en/publication/941

effective the treatment strategy becomes. The analysis suggests that introducing LABA before patients have tried high-dose ICS therapy is not justified.	
Aim: compare the risks of mortality and non-fatal serious adverse events in trials which have randomised patients with chronic asthma to regular formoterol versus regular salmeterol.The date of the most recent search was January 2012. **Results:** The review included four studies (involving 1116 adults and 156 children). All studies were open label and recruited patients who were already taking inhaled corticosteroids for their asthma, and all studies contributed data on serious adverse events. All studies compared formoterol 12 µg versus salmeterol 50 µg twice daily. The adult studies were all comparing Foradil Aerolizer with Serevent Diskus, and the children's study compared Oxis Turbohaler to Serevent Accuhaler. There was only one death in an adult (which was unrelated to asthma) and none in children, and there were no significant differences in non-fatal serious adverse events comparing formoterol to salmeterol in adults (Peto odds ratio (OR) 0.77; 95% confidence interval (CI) 0.46 to 1.28), or children (Peto OR 0.95; 95% CI 0.06 to 15.33). Over a six-month period, in studies involving adults that contributed to this analysis, the percentages with serious adverse events were 5.1% for formoterol and 6.4% for salmeterol; and over a three-month period the percentages of children with serious adverse events were 1.3% for formoterol and 1.3% for salmeterol. **AUTHORS' CONCLUSIONS:** We identified four studies comparing regular formoterol to regular salmeterol (without randomised inhaled corticosteroids, but all participants were on regular background inhaled corticosteroids). The events were infrequent and consequently too few patients have been studied to allow any firm conclusions to be drawn about the relative safety of formoterol and salmeterol. Asthma-related serious adverse events were rare and there were no reported asthma-related deaths.	Cates CJ, Lasserson TJ. Regular treatment with formoterol versus regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2012 Mar 14;3:CD007695. http://www.ncbi.nlm.nih.gov/pubmed/22419326
http://www.ncbi.nlm.nih.gov/pubmed/22926172 - uuritavaks lapsed, järeldus samasuunaline Pediatrics. 2012 Sep;130(3):e650-7. doi: 10.1542/peds.2012-0162. Epub 2012 Aug 27. **A systematic review of long-acting β2-agonists versus higher doses of inhaled corticosteroids in asthma.** Castro-Rodriguez JA, Rodrigo GJ. **Source** Department of Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile. jacastro17@hotmail.com **Abstract** **OBJECTIVE:** To compare the efficacy of inhaled corticosteroids (ICS) plus long-acting β2 agonist (LABA) versus higher doses of ICS in children/adolescents with uncontrolled persistent asthma. **METHODS:** Randomized, prospective, controlled trials published January 1996 to	

January 2012 with a minimum of 4 weeks of LABA+ICS versus higher doses of ICS were retrieved through Medline, Embase, Central, and manufacturer's databases. The primary outcome was asthma exacerbations requiring systemic corticosteroids; secondary outcomes were the pulmonary function test (PEF), withdrawals during the treatment period, days without symptoms, use of rescue medication, and adverse events. **RESULTS:** Nine studies (n = 1641 patients) met criteria for inclusion (7 compared LABA+ICS versus double ICS doses and 2 LABA+ICS versus higher than double ICS doses). There was no statistically significant difference in the number of patients with asthma exacerbations requiring systemic corticosteroids between children receiving LABA+ICS and those receiving higher doses of ICS (odds ratio = 0.76; 95% confidence interval: 0.48-1.22, P = .25, I(2) = 16%). In the subgroup analysis, patients receiving LABA+ICS showed a decreased risk of asthma exacerbations compared with higher than twice ICS doses (odds ratio = 0.48; 95% confidence interval: 0.28-0.82, P = .007, I(2)= 0). Children treated with LABA+ICS had significantly higher PEF, less use of rescue medication, and higher short-term growth than those on higher ICS doses. There were no other significant differences in adverse events. **CONCLUSIONS:** There were no statistically significant group differences between ICS+LABA and double doses of ICS in reducing the incidence of asthma exacerbations but it did decrease the risk comparing to higher than double doses of ICS.	
Results from large trials support greater efficacy with the addition of a LABA to an ICS than with a higher dose ICS (high SOE for ≥ 12, low <12) and greater efficacy with the addition of a LABA to an ICS over continuing the current dose of ICS alone for poorly controlled persistent asthma (high SOE). SOE=strenght of evidence **ICS+LABA compared with higher dose ICS** **(addition of LABA to ICS compared with increasing the dose of ICS)** We found 4 systematic reviews with meta-analysisand 33 RCTs (37 publications),that included head-to-head comparisons between an ICS+LABA with a higher dose ICS meeting our inclusion/exclusion criteria. Seven trials included children, and 2 enrolled an exclusively pediatric population under 12 years of age. Overall, results from a good quality systematic review with meta-analysis and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with an increased dose of ICSs. Those treated with ICSs plus LABAs had an increased rate of tremor (N = 10, RR 2.96, 95% CI: 1.60, 5.45). Indirect evidence from meta-analysis of placebo-controlled trials suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline. Just one of the RCTs enrolled an exclusively pediatric population < 12 years of age (four included some subjects < 12) and results are not necessarily applicable to pediatric populations. **Detailed Assessment** **Direct Evidence** We found 4 systematic reviews with meta-analysis and 33 RCTs that included head-to-head comparisons between an ICS+LABA with a higher dose ICS meeting our inclusion/exclusion criteria. These trials compared the	Drug Class Review: Controller Medications for Asthma: Final Update 1 Report [Internet]. Portland (OR): Oregon Health & Science University; 2011 Apr. Editors Jonas DE, Wines RCM, DelMonte M, Amick HR, Wilkins TM, Einerson BD, Schuler CL, Wynia BA, Shilliday BB. http://www.ncbi.nlm.nih.gov/pubmed/22132427

addition of a LABA to an ICS with increasing the dose of the ICS. Twenty-one of the 33 (64%) administered the ICS and LABA in a single inhaler and twelve (36%) administered the ICS and LABA in separate inhalers. Although 6 trials included children, just one enrolled an exclusively pediatric population under 12 years of age.103 The trials are described in the Key Question 1 section of the report. The largest systematic review reported no difference in overall withdrawals (all reasons) (N = 39, RR 0.92, 95% CI: 0.84 to 1.00), overall side events (N = 30, RR 0..99, 95% CI: 0.95 to 1.03), or specific side effects, with the exception of an increase rate of tremor in the LABA group (N = 11, RR 1.84, 95% CI: 1.20 to 2.82), however this result became insignificant when a single study using a higher dose of LABA was removed from the analysis. The rate of withdrawals due to poor asthma control favored the combination of LABA and ICS (N = 29, RR 0.71, 95% CI: 0.56 to 0.91). The overall adverse events, withdrawals due to adverse events, and specific adverse events for the included RCTs appear consistent with these findings (Evidence Tables A and B).	Page 101, Table 19

Viited täiendavatele kliinilistele katsetele

Otsistrateegia: ("Asthma"[Mesh] AND "Glucocorticoids"[Mesh]) AND "Adrenergic beta-Agonists"[Mesh] AND (Randomized Controlled Trial[ptyp] AND ("2008/03/01"[PDAT] : "3000/12/31"[PDAT]))

Kokkuvõte (abstrakt või kokkuvõtlikum info)	Viide kirjandusallikale
In this double-blind, randomized, parallel group study, asthmatics with moderate to severe disease used budesonide (400 mcg/day) for 5 weeks (run-in period); then they were randomized to use budesonide (800 mcg/day--BUD group) or budesonide plus formoterol (400 mcg and 24 mcg/day, respectively--FORMO group) for 9 weeks (treatment period). Home PEF measurements, symptom daily reporting, spirometry, sputum induction (for differential cell counts and sputum cell cultures), and hypertonic saline bronchial challenge test were performed before and after treatments. TNF-alpha, IL-4 and eotaxin-2 levels in the sputum and cell culture supernatants were determined. Morning and night PEF values increased in the FORMO group during the treatment period (p<0.01), from 435+/-162 to 489+/-169 and 428+/-160 to 496+/-173 L/min, respectively. The rate of exacerbations in the FORMO group was lower than in the BUD group (p<0.05). Neutrophil counts in sputum increased in both groups (p<0.05) and leukocyte viability after 48 h-culture increased in the FORMO group (p<0.05). No other parameter changed significantly in either group. This study showed that adding formoterol to budesonide improved home PEF and provided protection from exacerbations, although increase of leukocyte viability in cell culture may be a matter of concern and needs further investigation.	Menezes MB, Teixeira AL, Terra Filho J, Vianna EO. Inflammatory and functional effects of increasing asthma treatment with formoterol or double dose budesonide. Respir Med. 2008 Oct;102(10):1385-91. http://www.ncbi.nlm.nih.gov/pubmed/18632258
OBJECTIVES: To evaluate the effect of increasing the ICS dosage vs adding LABAs on the time spent with well-controlled asthma or poorly controlled asthma.METHODS: Post hoc analysis of the Formoterol and Corticosteroid Establishing Therapy study, which compared a fourfold increase in the budesonide dose with and without formoterol. RESULTS: Time with well-controlled asthma was improved by 19% (95% confidence interval [CI], 3 to 35%; p = 0.017) by adding formoterol, 24	O'Byrne PM, Naya IP, Kallen A, Postma DS, Barnes PJ. Increasing doses of inhaled corticosteroids compared to adding

microg/d, to therapy with budesonide, 200 microg/d, compared to 2% (95% CI, -9 to 12%; p = 0.76) with therapy with budesonide, 800 microg/d, alone. Time with well-controlled asthma was further improved by 29% (95% CI, 13 to 47%; p < 0.001) by adding formoterol to therapy with budesonide, 800 microg/d. Time with poorly controlled asthma was significantly reduced using the same interventions by 43% (95% CI, 25 to 57%), 22% (95% CI, 7 to 44%), and 50% (95% CI, 30 to 64%), respectively. Adding formoterol to budesonide was significantly more effective in increasing time with well-controlled asthma when compared to increasing the budesonide dose fourfold (increase, 16%; 95% CI, 1 to 33%; p = 0.035), with a trend for a greater reduction in time with poor control (decrease, 21%; 95% CI, -5 to 42%).	long-acting inhaled beta2-agonists in achieving asthma control. Chest. 2008 Dec;134(6):1192-9. http://www.ncbi.nlm.nih.gov/pubmed/18689590