Täiskasvanute astma käsitlus esmatasandil
Tõendusmaterjali kokkuvõte

Kliiniline küsimus nr 12

Kliinilise küsimuse tekst: Kas astma diagnoosiga patsientidele, kellel on kaasuv krooniline kardiovaskulaarhaigus, tohib kasutada β-blokaatoreid vs mittekasutamisega

Kokkuvõte, sh kriitiliste tulemusnäitajate kaupa:

Mitteselektiivsed β-blokaatorid võivad esile kutsuda bronhospasmi, seda nii suu kaudu kui ka lokaalselt silmatilkadena manustades (ülevaateartikkel Covar 2005, ka Kaiserman 2009). Võrreldes KOK-haigetega taluvad astmahaiged mitteselektiivseid β-blokaatoreid halvemini (Kotlyar 2002). Seetõttu nende ravimite kasutamine on seotud olulise riskiga.

Kardioselektiivsete ehk β1-blokaatorite kasutamisest astmahaigetel on tõendusmaterjal nende kasutamise pigem poolt kerge ja mõõduka raskusega astma korral kindlate kardiovaskulaarhaiguste raviks: ägeda koronaarhaiguse ajal, müokardi infarkti järgselt sekundaarseks preventsiooniks.

Cochrane andmebaasi süstemaatilises ülevaates (Salpeter 2002, täiendatud 2011) järeldati, et kerge või mõõduka raskusega astma või COPD korral **kardioselektiivsed beeta-blokaatorid lühiajalisel kasutamisel hingamisfunktsiooni ei häireid esile ei kutsu**: FEV1 nende kasutamise järgselt oluliselt ei muutunud, sümptomite tekkeriskis olulist erinevust ei olnud (riskierinevus e *risk difference* 0.01 [-0.02, 0.04]), hooravi vajadus oluliselt ei muutunud (inhalatsioone patsiendinädala kohta -0.11 [-6.75, 6.54]). Teisi tulemusnäitajaid ei käsitletud.

Teises süstemaatilises ülevaates (Self 2013) järeldati, et kardioselektiivsete beeta-blokaatorite kasutamise kohta vaid **hüpertensiooni** raviks (ilma kaasuva südamepuudulikkuse või koronaahaiguseta) on andmeid väga vähe.

Küll aga on suurtest vaatlusuuringutest saadud tõendeid, et kardioselektiivsed beeta-blokaatorid astma ja KOK-haigetel
-**vähendavad müokardi-infarkti aegset suremust**: ravi beeta-blokaatoritega 24 tunni jooksul hospitaliseerimisest vähendas oluliselt suremust: OR 0.52, 95% CI 0.45-0.60 (Olenchock 2009)- -- **vähendavad müokardi-infarkti järgset suremust:** 1-aasta suremus RR 0.85 (95% CI 0.73-1.00), raske astma korral olulist erinevust ei ilmnenud (Chen 2001)

Ei leidnud ühtegi RCT ega suurt vaatlusuuringut, mis käsitleks kardioselektiivsete beeta-blokaatorite kaustamist astmahaigetel **südamepuudulikkuse** raviks. Publitseeritud on ekspertide arvamusi (1, 2 3), et oht kardioselektiivsete β-blokaatorite kasutamisel astmahaigetele on väike ning samas on beeta-blokaatoritest suur kasu südamepuudulikkuse ravis, mistõttu nendest hoidumine astma JA südamepuudulikkusega patsientidel ei ole õigustatud.

Siiski võib kardioselektiivsete beeta-blokaatorite kasutamine astmahaigete poolt suurendada EMOsse pöördumisi: RR 1.40 (95% CI 1.20-1.62), kuigi üldhospitaliseerimise riski osas olulist erinevust ei ilmnenud: RR 0.89 (95% CI 0.53-1.50)(Brooks 2007)

Ravijuhendid

Kokkuvõte ravijuhendites leiduvatest soovitustest:

Seda küsimust ei käsitle üldse järgmised ravijuhendid: Canada 2010-2012, ISCI-2012, VaDoD-2011. GEMA-2009 juhendis loetletakse astmat ägestavate tegurite hulgas ka β-blokaatorid, eraldi nende kasutamist ei käsitleta.

Napisõnaliselt käsitleb seda küsimust SIGN-2011: β-blokaatorid, k.a. silmatilgad on astma korral vastunäidustatud (viiteid ja tõendusmaterjali tugevuse astet toodud ei ole).

EPR – 2007: soovitab mitte kasutada mitteselektiivseid beeta-blokaatoreid, k.a. silmatilku (tõendusmaterjali tase kord B, kord C). Kardioselektiivsete beeta-blokaatorite kohta soovitust ei ole sõnastatud.

Selgitav tekst järgmine: Mitteselektivsed beeta-blokaatorid võiva esile kutsuda astmahoo (Odeh et al. 1991; Schoene et al. 1984 = juhukirjeldused, kui timololsilmatilgad põhjustasid astmahoo), kuigi kardioselektiivsed beeta-blokaatorid nagu betaksolool võivad olla paremini tlutavadtolerated (Dunn et al. 1986 = betaksolool silmatilkadena on paremini talutav kui timolool). Kergevõivad taluda kardioselektiivseid beeta-blokaatorieid , seetõttu võib neid peale hoolikat kaalumist südame-veresoonkonna haiguste ravis kasutada (*therefore, if needed for managing cardiovascular disorders, these agents may be administered after careful evaluation*) (Salpeter 2002) ja mõõduka obstruktsiooniga patsiendid A recent systematic review, primarily of single dose or short-term

GINA-2012 – Suu kaudu või silmatilkadena manustatavad beeta-blokaatorid võivad esile kutsuda bronhospasmi (tõendusmaterjali tase A), vajalik tihe jälgimine, kui neid preparaate astmapatsientidel kasutada (viide ülevaateartiklile Covar 2005). Beeta-blokaatoritest on tõendatult kasu ägeda koronaarsündroomi ravis ja südame isheemiatõve teiseses ennetuses (Olenchock 2009).

2012 ESC südamepuudulikkuse juhend: tekstis lause, et astma korral (aga mitte KOK korral) on β-blokaatorid vastunäidustatud. Viiteid ja tõendusmaterjali tugevust toodud ei ole.

Süstemaatilised ülevaated[1]

Kokkuvõte	**Viide kirjandusallikale**
BACKGROUND: Beta-blocker therapy has mortality benefit in patients with hypertension, heart failure and coronary artery disease, as well as during the perioperative period. These drugs have traditionally been considered contraindicated in patients with reversible airway disease. **OBJECTIVES:** To assess the effect of cardioselective beta-blockers in patients with asthma or COPD. **SEARCH STRATEGY:** up to May 2002 (Update – juuni 2011) **SELECTION CRITERIA:** Randomized, blinded, placebo-controlled trials of single dose or continued treatment of the effects of cardioselective beta-blockers in patients with reversible airway disease. **DATA COLLECTION AND ANALYSIS:** Two independent reviewers extracted data from the selected articles, reconciling differences by consensus. Beta1-blockers were divided into those with or without intrinsic sympathomimetic activity (ISA). Interventions were: administration of single or continued beta1-blocker, and response to beta2-agonist given after the study drug. **MAIN RESULTS:** Nineteen studies on single-dose treatment and 10 studies on continued treatment met the inclusion criteria. Single dose cardioselective beta-blocker produced a 7.46% (95% CI 5.59, 9.32) reduction in FEV1, but with a 4.63% (95% CI 2.47, 6.78) increase in FEV1 with beta2-agonist, compared to placebo. Treatment lasting 3 - 28 days produced no change in FEV1 (-0.42%; 95% CI -3.74, 2.91), symptoms or inhaler use, whilst maintaining a 8.74% (95% CI 1.96, 15.52) response to beta2-agonist. There was no significant change in FEV1 treatment effect for those patients with COPD: single doses -5.28% (95% CI -10.03, -0.54%), continued treatment 1.07% (CI -3.3, 5.44. With continued treatment there was no significant difference in	Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for reversible airway disease. Cochrane Database Syst Rev. 2002; (4):CD002992. (new search for studies and content updated in 2011, conclusions did not change, published in issue 11, 2011.) http://www.ncbi.nlm.nih.gov/pubmed/12519582 Põhimõtteliselt sama: Ann Intern Med. 2002 Nov 5;137(9):715-25. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. Salpeter SR, Ormiston TM, Salpeter EE. Ja Heart Fail Monit. 2003;4(2):45-54.

[1] Otsing Pubmedis 07.08.2013 "Asthma"[Mesh] AND "Adrenergic beta-Antagonists"[Mesh] AND (Meta-Analysis[ptyp] OR systematic[sb]) 17 vastet, asjakohased toodud tabelis

FEV1 response for beta1-blockers without ISA compared to those with IS: -3.22% (96%CI -7.79, 1.36) compared to 2.72% (95% CI -2.12, 7.59). Those without ISA produced a 12.0% increase in FEV1 after beta2-agonist administration compared to placebo (95%CI 4.12,19.87) while beta1-blockers with ISA produced no change compared to placebo (-0.60% [95%CI -13.93, 12.73). These results were obtained in a small number od studies of few patients. The difference was not significant. **REVIEWER'S CONCLUSIONS:** Cardioselective beta-blockers given in mild - moderate reversible airway disease or COPD, do not produce adverse respiratory effects in the short term. Given their demonstrated benefit in conditions such as heart failure, cardiac arrhythmias and hypertension, these agents should not be withheld from such patients, but long term safety (especially their impact during an acute exacerbation) still needs to be established.	Beta-blocker use in patients with congestive heart failure and concomitant obstructive airway disease: moving from myth to evidence-based practice. Ormiston TM, Salpeter SR.
Benefits outweigh risks of cardioselective beta-blocker therapy in patients with nonsevere asthma and a history of heart failure or myocardial infarction (MI). This review summarizes the risks versus benefits of using cardioselective beta-blockers in the treatment of hypertension in patients with asthma. METHODS: We searched the English literature from 1976 to 2011 via PubMed, EMBASE, and SCOPUS using the following search terms: "beta-blocker treatment of hypertension" AND "asthma"; "cardioselective beta-blockers" AND "asthma." When pertinent articles were found, we assessed relevant articles cited in those papers. All studies related to cardioselective beta-blocker use in patients with asthma and hypertension were included. RESULTS: Seven studies with patient populations ranging from 10 to 17 patients evaluated cardioselective beta-blockers in patients with asthma and hypertension. Atenolol and/or immediate-release metoprolol were evaluated in these studies. The duration of beta-blocker therapy in four studies was 1-8 weeks; two studies were single dose and one investigation lasted 8 months. Metoprolol and atenolol were generally well tolerated except at higher doses such as metoprolol >100 mg daily. CONCLUSION: In the absence of concomitant cardiovascular disease, routine use of beta-blockers for the treatment of hypertension in patients with asthma should be avoided.	Self TH, Wallace JL, Soberman JE. Cardioselective beta-blocker treatment of hypertension in patients with asthma: when do benefits outweigh risks? J Asthma. 2012 Nov;49(9):947-51 http://www.ncbi.nlm.nih.gov/pubmed/22974249

Viited

Kokkuvõte (abstrakt või kokkuvõtlikum info)	**Viide kirjandusallikale**
OBJECTIVES: We evaluated the use and effectiveness of beta-blocker therapy after acute myocardial infarction (AMI) for elderly patients with chronic obstructive pulmonary disease (COPD) or asthma. BACKGROUND: Because patients with COPD and asthma have largely been excluded from clinical trials of beta-blocker therapy for AMI, the extent to which these patients would benefit from beta-blocker therapy after AMI is not well defined. METHODS: Using data from the Cooperative Cardiovascular Project,	Chen J, Radford MJ, Wang Y, Marciniak TA, Krumholz HM. J Am Coll Cardiol. 2001 Jun 1;37(7):1950-6. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly

we examined the relationship between discharge use of beta-blockers and one-year mortality in patients with COPD or asthma who were not using beta-agonists, patients with COPD or asthma who were concurrently using beta-agonists and patients with evidence of severe disease (use of prednisone or previous hospitalization for COPD or asthma) compared with patients without COPD or asthma. RESULTS: Of 54,962 patients without contraindications to beta-blockers, patients with COPD or asthma (20%) were significantly less likely to be prescribed beta-blockers at discharge after AMI. After adjusting for demographic and clinical factors, we found that beta-blockers were associated with lower one-year mortality in patients with COPD or asthma who were not on beta-agonist therapy (relative risk [RR] = 0.85, 95% confidence interval [CI] 0.73 to 1.00), similar to patients without COPD or asthma (RR = 0.86, 95% CI 0.81 to 0.92). A survival benefit for beta-blockers was not found among patients concurrently using beta-agonists or with severe COPD or asthma. CONCLUSIONS: Beta-blocker therapy after AMI may be beneficial for COPD or asthma patients with mild disease. A survival benefit was not found for elderly AMI patients with more severe pulmonary disease.	patients with chronic obstructive pulmonary disease or asthma. http://www.ncbi.nlm.nih.gov/pubmed/11401137?dopt=Abstract
PURPOSE: To investigate the use of topical ocular anti-glaucoma medications by glaucomatous patients with obstructive pulmonary disease and their effect on related hospitalizations and emergency room visits. **PARTICIPANTS:** We followed the electronic medical records of all the members in a district of the largest health maintenance organization in Israel (the "central district" of Clalit Health Services) older than 20 years (317,469 members); 6597 of them were on chronic topical anti-glaucoma treatment of which 693 (10.5%) suffered from obstructive pulmonary disease (OPD). **METHODS:** In a historical cohort study, we documented all anti-glaucoma prescriptions filled in the district between January 1, 2001, and December 31, 2003, and all emergency room (ER) visits and hospitalizations in internal medicine, geriatric, or pulmonology departments. **MAIN OUTCOME MEASURES:** The rate of hospitalization and emergency room visits during treatment with each anti-glaucoma medication. **RESULTS:** Five hundred forty-four glaucomatous OPD patients (78.5%) were treated with topical beta-blockers, but only 169 (31.1%) of them received a cardio-selective beta-blocker (betaxolol). Patients treated with betaxolol each received more prescriptions per year than patients treated with timolol ($p < 0.0001$). Patients on topical betaxolol or timolol had 23.1 and 20.7 hospitalization days as well as 7.3 and 6.1 emergency room visits per 100 treatments per year, respectively, compared to a mean of 10 hospitalization days ($p < 0.0001$) and 5.0 ER visits for patients on non-beta-blocker anti-glaucoma medications. **CONCLUSIONS:** A majority of glaucomatous patients with obstructive pulmonary disease were treated with topical beta-blockers, mostly non-cardioselective (timolol). Those patients were more prone to be hospitalized or visit the emergency room while on	Kaiserman I, Fendyur A, Vinker S. Topical beta blockers in asthmatic patients-is it safe? Curr Eye Res. 2009 Jul;34(7):517-22 http://www.ncbi.nlm.nih.gov/pubmed/19899964

the medication.	
Beta blockers have a proven benefit in the management of patients with acute coronary syndromes (ACS) and for secondary prevention of coronary events. Current guidelines list such reactive airway diseases (RADs) such as asthma and chronic obstructive pulmonary disease as relative contraindications to beta-blocker use. However, the co-morbid burden of RAD and coronary heart disease is substantial, and data suggest that the treatment benefit of beta blockers is shared by patients with RAD. The Get with the Guidelines (GWTG) database was used to evaluate use of beta blockers within 24 hours of admission and at discharge in patients with ACS with (n = 12,967) and without (n = 81,140) a history of RAD. Data were collected in 435 hospitals between January 2000 and September 2006. A multivariable logistic regression model was used to determine predictors of beta-blocker treatment. In patients with no RAD history, beta-blocker prescription rates were 78.3% at admission and 88.7% at discharge; in patients with a RAD history, rates were 65.6% at admission and 77.2% at discharge. Compared with patients with no history of RAD, patients with a history of RAD were 42% less likely (odds ratio 0.58, confidence interval 0.54 to 0.62, p <0.0001) to receive a beta blocker upon admission and 55% less likely (odds ratio 0.45, confidence interval 0.41 to 0.48, p <0.0001) to receive a beta blocker at discharge in multivariable analysis. Among all other clinical factors, RAD history was the most significant predictor of likelihood of not receiving a beta blocker at admission or discharge. Receipt of beta blockers within 24 hours after admission was associated with a lower in-hospital mortality rate for patients with RAD (odds ratio = 0.52, p <0.001) and for patients without RAD (odds ratio = 0.38, p <0.001). Careful assessment of beta-blocker safety and RAD severity by physicians is needed to improve beta-blocker prescription rates in this large group of patients with ACS.	Olenchock BA, Fonarow GG, Pan W, Hernandez A, Cannon CP; Get With The Guidelines Steering Committee. Current use of beta blockers in patients with reactive airway disease who are hospitalized with acute coronary syndromes. Am J Cardiol. 2009 Feb 1;103(3):295-300. http://www.ncbi.nlm.nih.gov/pubmed/19166678
Beta-blockers are currently contraindicated in asthma because their acute administration may be associated with worsening bronchospasm. However, their effects and safety with their chronic administration are not well evaluated. The rationale for this pilot study was based on the paradigm shift that was observed with the use of beta-blockers in congestive heart failure, which once contraindicated because of their acute detrimental effects, have now been shown to reduce mortality with their chronic use. We hypothesized that certain beta-blockers may also be safe and useful in chronic asthma therapy. In this prospective, open-label, pilot study, we evaluated the safety and effects of escalating doses of the beta-blocker, nadolol, administered over 9 weeks to 10 subjects with mild asthma. Dose escalation was performed on a weekly basis based on pre-determined safety, lung function, asthma control and hemodynamic parameters. The primary objective was to evaluate safety and secondary objectives were to evaluate effects on airway hyperresponsiveness, and indices of respiratory function. The escalating administration of nadolol was well tolerated. In 8 out of the 10 subjects, 9 weeks of nadolol treatment produced a significant, dose-dependent increase in PC20 that reached 2.1 doubling doses at 40 mg (P<0.0042). However, there was also a dose-independent 5% reduction in mean FEV1 over the study period (P<0.01). We conclude that in most patients with mild asthma, the dose-escalating administration of the beta-blocker, nadolol, is well tolerated and may have beneficial effects on airway hyperresponsiveness. Our findings warrant further testing in future larger trials.	Hanania NA, Singh S, El-Wali R, Flashner M, Franklin AE, Garner WJ, Dickey BF, Parra S, Ruoss S, Shardonofsky F, O'Connor BJ, Page C, Bond RA. The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. Pulm Pharmacol Ther. 2008;21(1):134-41. http://www.ncbi.nlm.nih.gov/pubmed/17703976 vt ka 55
STUDY OBJECTIVE: To determine the rates of hospitalizations and emergency department (ED) visits during cardioselective and nonselective beta-blocker therapy in patients with asthma and/or chronic obstructive pulmonary	Brooks TW, Creekmore FM, Young DC, Asche CV, Oberg B, Samuelson WM. Pharmacotherapy. 2007

disease (COPD). DESIGN: Retrospective, observational cohort study. DATA SOURCE: Electronic medical records database. PATIENTS: A total of 11,592 adult patients with asthma and/or COPD, identified from August 1, 1997-December 31, 2005, who were taking beta-blockers for at least 30 days or had never received a beta-blocker (controls). MEASUREMENTS AND MAIN RESULTS: Of these patients, 3062 were taking cardioselective and 690 nonselective beta-blockers; 7840 were controls. The primary end point for the beta-blocker groups was the rate of hospitalizations and ED visits/patient-year of beta-blocker therapy relative to the control group. In patients with asthma with or without concomitant COPD, cardioselective beta-blockers were associated with a relative risk of 0.89 (95% confidence interval [CI] 0.53-1.50) for hospitalizations and 1.40 (95% CI 1.20-1.62) for ED visits compared with controls. Nonselective beta-blockers were associated with a relative risk of 2.47 (95% CI 1.37-4.48) for hospitalizations and 1.21 (95% CI 0.91-1.62) for ED visits. In patients with COPD only, cardioselective beta-blockers were associated with a relative risk of 0.64 (95% CI 0.43-0.96) for hospitalizations and 1.19 (95% CI 1.02-1.39) for ED visits. Nonselective beta-blockers were associated with a relative risk of 1.02 (95% CI 0.52-2.02) for hospitalizations and 0.51 (95% CI 0.33-0.80) for ED visits. CONCLUSION: In patients with asthma with or without COPD, both cardioselective and nonselective beta-blocker use increased hospitalizations and ED visits compared with controls. Thus, these patients should receive beta-blocker therapy only if their cardiac risk exceeds their pulmonary risk and if they have concomitant cardiac disease for which beta-blockers decrease mortality, such as previous acute myocardial infarction or chronic heart failure. In patients with COPD only, cardioselective beta-blockers slightly increased the risk of ED visits but reduced the risk of hospitalizations. Nonselective beta-blocker therapy in these patients reduced the rate of ED visits and total visits. These findings suggest a larger safety margin with beta-blocker therapy in patients with COPD only than in those with asthma with or without COPD.	May;27(5):684-90. Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking beta-blockers. http://www.ncbi.nlm.nih.gov/pubmed/17461703
BACKGROUND: A substantial proportion of the population with congestive heart failure (CHF) has concomitant airway disease. Little information exists on the tolerability of carvedilol in patients with chronic obstructive pulmonary disease (COPD). In this study, we assessed the tolerability and efficacy of carvedilol in patients with CHF and concomitant COPD or asthma. METHODS: Between 1996 and 2000, a total of 487 patients began receiving open-label carvedilol. Forty-three (9%) had COPD (n = 31) or asthma (n = 12). Spirometry supported clinical diagnosis in all, and full pulmonary function testing supported diagnosis in 71%. Sixty percent began carvedilol therapy in the hospital and underwent measurement of peak expiratory flow rates (PEFR) before and after dosing. RESULTS: In patients with COPD, mean forced expiratory volume in one second (FEV(1)) was 62% +/- 13% predicted, reversibility was 4% +/- 4% with bronchodilators, and FEV(1)/FVC was 62% +/- 8%. Mean PEFR was 325 +/- 115 liter/min before the dose and increased by 17% 2 hours after the carvedilol dose (p = 0.04). In patients with asthma, mean FEV(1) was 80% +/- 17% predicted, reversibility was 13% +/- 7%, and FEV(1)/FVC was 74% +/- 11%. Mean PEFR was	J Heart Lung Transplant. 2002 Dec;21(12):1290-5. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. http://www.ncbi.nlm.nih.gov/pubmed/12490274

407 +/- 161 liter/min before the dose with no significant change 2 hours after the dose. Carvedilol was introduced safely in 84% of patients with COPD, with only 1 patient withdrawn from therapy for wheezing. In contrast, only 50% of patients with asthma tolerated carvedilol. Survival at 2.5 years was 72%. In survivors, left ventricular end-diastolic diameter decreased from 76 +/- 11 mm to 72 +/- 14 mm (p = 0.01), left ventricular end-systolic diameter decreased from 65 +/- 13 mm to 60 +/- 15 mm (p = 0.01), and fractional shortening increased from 14% +/- 7% to 17% +/- 7% (p = 0.05) at 12 months. CONCLUSIONS: Patients with CHF and COPD tolerated carvedilol well with no significant reversible airflow limitation, but patients with CHF and asthma tolerated carvedilol poorly. The effect of carvedilol on left ventricular dimensions and function in patients with concomitant airway diseases was similar to that seen in our general group of patients. Asthma remains a contraindication to beta-blockade.	
Ülevaateartikkel	Immunol Allergy Clin North Am. 2005 Feb;25(1):169-90. Medications as asthma triggers. Covar RA, Macomber BA, Szefler SJ. http://www.ncbi.nlm.nih.gov/pubmed/15579370

Otsistrateegiad:

Otsing 07.08.2013 "Asthma"[Mesh] AND "Adrenergic beta-Antagonists"[Mesh] AND (Randomized Controlled Trial[ptyp] AND "2003/08/11"[PDat] : "2013/08/07"[PDat]), 11 vastet, ükski neist pole küsimusele vastav RCT

Seejärel otsing astma ja beeta-blokaatorite MeSH terminitega ja piiranguks <10 aastat pubitseerimisest "Asthma"[Mesh] AND "Adrenergic beta-Antagonists"[Mesh] AND ("2003/08/11"[PDat] : "2013/08/07"[PDat]), 120 vastet **(Vt allpool)**

"Asthma"[Mesh] AND "Adrenergic beta-Antagonists"[Mesh] AND ("2002/04/01"[PDAT] : "3000/12/31"[PDAT]), s.t. alates Salpeter 2002-2003 meta-analüüsidesse haaratud ajaperioodi lõpust: 138 vastet, neist 1 asjakohane.

Spetsiaalselt südamepuudulikkuseleele suunatud otsing 15.08.2013 ("Asthma"[Mesh] AND "Heart Failure"[Mesh]) AND "Adrenergic beta-Antagonists"[Mesh], 22 vastet

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