Kroonilise sageduskontrolli ravim

Kliiniline küsimus

Kas kroonilise sageduskontrolli strateegia puhul tuleks kodade virvendusarütmia patsientidel esmavalikuna eelistada BBL vs KKB vs muid ravimeid?

Olulised tulemusnäitajad

väga olulised: surm, elukvaliteet, südame löögisageduse eesmärkväärtuse (nt ≤100 x/min) saavutamine, tõsine kõrvaltoime;

mõõdukalt olulised: hospitaliseerimine, ravi katkestama sundiv kõrvaltoime, südamepuudulikkus.

Kliinilise tõenduse kokkuvõte

Kroonilise sageduskontrolli saavutamiseks on kasutusel beeta-adrenoblokaatorid (BBL), kaltsiumikanalite mittedihüdropüridiinsed blokaatorid (KKB), digoksiin ja, harvem, amiodaroon.

AFFIRM uuringus (Olshansky 2004) näisid BBL kõige efektiivsemad ja olid enim kasutatud ravimiklass sageduskontrolli saavutamiseks, ent selle uuringu eesmärgiks ei olnud sageduskontrolli ravimite omavaheline võrdlus. On tohutu hulk ajaloolisi uuringuid, mis võrdlevad väikestel patsiendirühmadel üksikute ravimite lühiajalist mõju südame löögisagedusele võrreldes platseeboga. Valdavalt on need ebaadekvaatse metoodikaga ning ei kajasta tulemusnäitajaid, mida töörühm oluliseks pidas.

Värske tõenduse ülevaade on esitatud NICE 2014 juhendis. Kui ristuva uuringikavaga uuringud kõrvale jäeti, leiti 3 asjakohast kliinilist uuringut

Study	Intervention/comparison	Population	Outcomes	Comments
Khand 2003[232]	Digoxin versus beta-blocker	Persistent AF and heart failure	Rate control Left ventricular ejection function (LVEF%)	All patients received open label digoxin in phase 1
Mulder 2012[317]	Beta-blocker versus placebo	AF and heart failure	All-cause mortality Rehospitalisation with heart failure	All patients were >70 years old
Tse 2001B[435]	Digoxin versus amiodarone	Chronic AF	Rate control	Small study numbers

BBL vs platseebo KVA ja südamepuudulikkusega patsientidel:

- väga madala kvaliteediga andmed ühest uuringust (N=738) näitavad, et 21 kuu pikkuse kasutamise järel ei erinenud suremus BBL ja platseebo rühmades (sama kinnitas hilisem meta-analüüs, Kotecha 2014)
- väga madala kvaliteediga andmed ühest uuringust (N=100) näitasid, et 21 ravikuul rehospitaliseeriti südamepuudulikkuse tõttu rohkem beeta-blokaatorit kasutanud patsiente võrrelduna platseeboga.
- Väga madala kvaliteediga andmed ühest uuringust (N=46) näitasid, et 6ndal ravikuul on digoksiin efektiivsem kui beetablokaator 24 tunni keskmise südamelöögisageduse langetamisel KVA ja südamepuudulikkusega patsientidel,
- madala kvaliteediga andmed ühest uuringust (N=100) näitasid, et pärast 6 kuulist kasutamist puudub kliiniline erinevus dikoksiini ja beetablokaatori vahel LVEFi muutuse osas.
- väga madala kvaliteediga andmed ühest uuringust (N=15) näitasid, et puudus kliiniline erinevus digoksiini ja amiodaroonil toimel vatsakeste sagedusele füüsilisel koormusel.

Teiste ravijuhendite soovitused samal teemal

AHA 2014 juhend

I klassi soovitused

- paroksüsmaalse, persisteeriva ja permanentse KVA korral kasutage vatsakeste sageduse ohjamiseks beetablokaatorit või mittedihüdropüridiinset kaltsiumikanali blokaatorit (tõenduse tase B)

IIb klassi soovitused

- suukaudset amiodarooni võib vatsakeste sageduse ohjamiseks kasutada, kui teised ravimid ei anna piisavat efekti või on vastunäidustatud (tõenduse tase C)

III klassi soovitused

- ärge kasutage mittedihüdropüridiinset kaltsiumikanali blokaatorit südemapuudulikkuse dekompensatsiooniga patsiendil, see võib hemodünaamikahäiret süvendada (tõenduse tase C)
- KVA ja pre-eksitatsiooniga patsientidel ärge kasutage digoksiini, mittedihüdropüridiinset kaltsiumikanali lokaatorit ega i/v amiodarooni, kuna need võivad suurendada vatsakeste löögisagedust ja põhjustada vatsakeste fibrillatsiooni (tõenduse tase B).
- ärge kasutage dronedarooni vatsakeste sageduse ohjamiseks permanentse kodade virvenduse puhul, kuna see suurendab insuldi, müokardiinfarkti, süsteemse emboolia või südamesurma liit-tõenäosust (tõenduse tase B).

Kanada ravijuhend

- soovitame vatsakeste sageduse ohjamiseks (KVA ja KLA puhul) esmaselt kasutada BBL või KKB, kui patsiendil ei ole anamneesis MI või vasaku vatsakese düsfunktsiooni (tugev soovitus, mõõduka kvaliteediga tõendus) 2010
- soovitame pigem mitte kasutada digoksiini esmase ravimina vatsakeste sageduse ohjamiseks füüsiliselt aktiivsetel patsientidel ning jätta see kasutamiseks inaktiivsetel ja vasaku vatsakese düsfunktsiooniga patsientidel (nõrk soovitus, mõõduka kvaliteediga tõendus) 2010
- kui BBL või KKB ei taga vatsakeste löögisageduse eesmärgi saavutamist, võib lisada digoksiini (nõrk soovitus, mõõduka kvaliteediga tõendus) 2010
- digoksiini võib kaaluda patsientidel, kellel on tahhükardiast tingitud sümptomid ning kellel ravivastus BBl ja/või KKB-le on ebapiisav või kellel need on vastunäidustatud või kes neid ei talu (nõrk soovitus, keskmise kvaliteediga tõendus) 2016
- soovitame mitte kasutada dronedarooni permanentse KVA-ga patsientidel ega ainult sageduskontrolli eesmärgil (tugev soovitus, kõrge kvaliteediga tõendus) 2012
- soovitame mitte kasutada dronedarooni patsientidel, kel on anamneesis südamepuudulikkus või kelle VV väljutusfraktsioon on 40% või madalam (tugev soovitus, mõõduka kvaliteediga tõendus) 2012
- amiodarooni kasutamine vatsakeste sageduse ohjamiseks peaks olema erandlik, juhtudel, kui teised raviviisid ei sobi või ei ole efektiivsed (nõrk soovitus, madala kvaliteediga tõendus) 2010
- soovitame BBL vatsakeste sageduse ohjamiseks patsientidel, kellel on anamneesis MI või VV düsfunktsioon (tugev soovitus, kõrge kvaliteediga tõendus) 2010

ESC 2016 ravijuhend

- KVA patsientidel, kelle LVEF on 40% või kõrgem, on soovitav südame löögisageduse ohjamiseks kasutada BBL, digoksiini, diltiaseemi või verapamiili (IB)
- KVA patsientidel, kelle LVEF on alla 40%, on soovitav südame löögisageduse ohjamiseks kasutada BBL ja/või digoksiini (IB)
- Kombinatsioonravi tuleks kaaluda, kui monoteraapia ei taga eesmärksageduse saavutamist (IIA C)
- Permanentse KVA patsientidel, kellel kardioversiooni plaanis pole, ei tohi südame löögisageduse ohjamiseks üldjuhul kasutada antiarütmikume (III A)

NICE ravijuhend

- kasutage patsientidel, kes vajavad vatsakeste löögisageduse aeglustamist, esmaselt monoteraapiat tavalise BBL või löögisagedust aeglustava toimega KKB-ga.
- valige ravim vastavalt patsiendi sümptomitele, südame löögisagedusele, kaasuvatele haigustele ja patsiendi eelistusele.
- kaaluge digoksiini monoteraapia kasutamist üksnes füüsiliselt väheaktiivsetel patsientidel
- kui monoteraapia ei leevenda sümptomeid ja sümptomid on arvatavalt tingitud vatsakeste kõrgest löögisagedusest, kaaluge kahe ravimi kombineerimist (BBL, KKB, digoksiin).
- ärge kasutage amiodarooni pikaajaliselt vatsakeste löögisageduse aeglustamiseks.

Ref-s, evidence tables

Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JGF. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? Journal of the American College of Cardiology. 2003; 42(11):1944-1951

Study	Khand 2003{KHAND2003}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in United Kingdom; Setting: NR
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People with heart failure and AF
Subgroup analysis within study	Not applicable
Inclusion criteria	NR
Exclusion criteria	HR at rest <60 beats/min; systolic BP <90mmHg,; sick sinus syndrome or complete heart block; current treatment with a beta-blocker or HR lowering calcium channel antagonist or >200mg amiodarone; recent major cardiovascular event or procedure; asthma or reversible obstructive airways disease; serum creatinine >250micromol/l or significant hepatic disease, ; uncorrected significant valvular heart disease or any life-threatening non-cardiac disease.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): cardedilol 68.6 (9.4); placebo 68.4 (9.8). Gender (M:F): 29M/ 16F. Ethnicity:
Further population details	1. Age:
Extra comments	Persistent AF (>1 month) and heart failure who were receiving digoxin and diuretics.
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Rate control drugs - Digoxin. Phase 1: open label digoxin (as previously prescribed); double-blind carvedilol placebo. Phase 2: double-blind digoxin; double-blind carvedilol placebo. Duration 6 months. Concurrent medication/care: NR (n=20) Intervention 2: Rate control drugs - Beta blockers. Phase 1 (4 months): open label digoxin (as previously prescribed); double-blind carvedilol (starting dose 3.125mg bid, increased at 2 week intervals to the target dose of 25mg bid (up titration period of 2 months) or, for patients weighing >85kg, 50mg bid. Phase 2(6 months): double blind digoxin placebo; double-blind carvedilol (continued from phase 1). Duration 6 months. Concurrent medication/care:
	NR
Funding	Study funded by industry (Roche Pharmaceuticals)

RESULTS (NUMBERS ANALYSED): DIGOXIN versus BETA BLOCKERS

Protocol outcome 1: Rate control - heart rate (time or amount of people) at latest follow-up
- Actual outcome for People with heart failure and AF: HR at 6 months at 6 months; Group 1: mean 75.5 (SD 10.6); n=20, Group 2: mean 88.8 (SD 18.7); n=16

Protocol outcome 2: Left ventricular function - number of people/ejection fraction as % at latest follow-up
- Actual outcome for People with heart failure and AF: LVEF (%) at 6 months; Group 1: mean 27.2 % (SD 11.7); n=21, Group 2: mean 21.6 % (SD 11); n=20

Protocol outcomes not reported by the study	Mortality (long-term) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Quality of life at latest follow-up

Table 49: Clinical evidence profile: Beta-blocker versus digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta blocker	digoxin	Relative (95% CI)	Absolute		
Mortality												
0	-	-	-	-	-	-	-	-	-	-	–	CRITICAL
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	–	CRITICAL
24-h mean HR at 6 months (Better indicated by lower values) [232]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	16	20	-	MD 13.1 higher (2.83 to 23.37 higher)	VERY LOW	CRITICAL
LVEF (%) (Better indicated by lower values) [232]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	16	20	-	MD 5.6 lower (13.04 lower to 1.84 higher)	LOW	IMPORTANT

a. Unclear blinding and allocation concealment
b. Confidence interval crossed 2 MIDs
c. Confidence interval crossed one MID

Mulder BA, van Veldhuisen DJ, Crijns HJGM, Bohm M, Cohen-Solal A, Babalis D et al. Effect of nebivolol on outcome in elderly patients with heart failure and atrial fibrillation: insights from SENIORS. European Journal of Heart Failure. 2012; 14(10):1171-1178

Study	Mulder 2012{MULDER2012}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=738)
Countries and setting	Conducted in Multiple countries; Setting: unclear
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People with heart failure and AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): nebivolol group: 77 (5); placebo: 77 (5). Gender (M:F): Define. Ethnicity:
Further population details	1. Age:
Extra comments	all patients were >70 years and had heart failure
Indirectness of population	No indirectness
Interventions	(n=361) Intervention 1: Rate control drugs - Beta blockers. Medication was titrated over a 16 week period from a starting dose of 1.25mg daily to a target of 10mg daily. During the first 4 months of follow-up patients were closely monitored as medication was carefully titrated. Target dose of nebivolol was 10mg or the maximum tolerated dose for the individual patient. For the duration of the maintenance phase it was advised to maintain the same individual dose of the study drug until the end of the follow-up period. During the titration phase, patients were required to attend study visits at 1-2 week intervals. In this phase they were seen at least 5 times. The maximum period of drug titration was 16 weeks and the minimum 4 weeks.. Duration 21 months. Concurrent medication/care: unclear (n=377) Intervention 2: Placebo. Identical placebo tablets. Duration 21 months. Concurrent medication/care: unclear
Funding	Study funded by industry (Menarini Richerche SpA, Italy. Funding for additional statistical analyses to the Clinical trials and Evaluation Unit in London.)
RESULTS (NUMBERS ANALYSED): BETA BLOCKERS versus PLACEBO Protocol outcome 1: Mortality (long-term) at latest follow-up - Actual outcome for People with heart failure and AF: All-cause mortality at 21 months; Group 1: 67/361, Group 2: 72/377 Protocol outcome 2: Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up - Actual outcome for People with heart failure and AF: Heart failure hospitalisation at 21 months; Group 1: 72/361, Group 2: 58/377	
Protocol outcomes not reported by the study	Rate control - heart rate (time or amount of people) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Left ventricular function - number of people/ejection fraction as % at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Quality of life at latest follow-up

Table 48: Clinical evidence profile: B-blocker versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blocker	Control	Relative (95% CI)	Absolute		
Mortality[317]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	67/361 (18.6%)	72/377 (19.1%)	RR 0.97 (0.72 to 1.31)	6 fewer per 1000 (from 53 fewer to 59 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Rate control												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Rehospitalisation with heart failure[317]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	72/361 (19.9%)	58/377 (15.4%)	RR 1.3 (0.95 to 1.78)	46 more per 1000 (from 8 fewer to 120 more)	LOW	IMPORTANT

a. Randomisation and allocation concealment unclear
b. Confidence interval crossed 2 MIDs
c. Confidence interval crossed 1 MID

Tse HF, Lam YM, Lau CP, Cheung BM, Kumana CR. Comparison of digoxin versus low-dose amiodarone for ventricular rate control in patients with chronic atrial fibrillation. Clinical and Experimental Pharmacology and Physiology. 2001; 28(5-6):446-450

Study	Tse 2001{TSE2001B}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in Hong Kong (China)
Line of therapy	2nd line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: chronic AF
Stratum	Persistent/permanent AF
Subgroup analysis within study	Not applicable
Inclusion criteria	not stated
Exclusion criteria	intolerance of amiodarone or digoxin or contraindication to their therapy; amiodarone therapy in the past 6 months; class III or IV heart failure; clinically significant valvular heart disease; unstable angina or recent MI in the past 6 months; implanted pacemaker
Age, gender and ethnicity	Age - Mean (SD): 63 (9). Gender (M:F): 13 M/ 3F. Ethnicity: Chinese
Further population details	1. Age:
Extra comments	all patients had previously failed an attempt to restore and maintain sinus rhythm
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Rate control drugs - Amiodarone. dose/quantity, brand name, extra details. Duration 24 weeks. Concurrent medication/care: warfarin (n=7) Intervention 2: Rate control drugs - Digoxin. 0.25mg daily or -.125mg daily if bodyweight <50kg or serum creatinine >200mmol/l. Duration 24 weeks. Concurrent medication/care: warfarin
Funding	Academic or government funding (Committee on Research Conference Grant)

RESULTS (NUMBERS ANALYSED): DIGOXIN versus AMIODARONE

Protocol outcome 1: Quality of life at latest follow-up
- Actual outcome for Persistent/permanent AF: SF-36 Role: physical at 24 weeks
- Actual outcome for Persistent/permanent AF: SF-36 Bodily pain at 24 weeks
- Actual outcome for Persistent/permanent AF: SF-36 Physical functioning at 24 weeks
- Actual outcome for Persistent/permanent AF: SF-36 General health at 24 weeks
- Actual outcome for Persistent/permanent AF: SF-36 Social functioning at 24 weeks
- Actual outcome for Persistent/permanent AF: SF-36 Vitality at 24 weeks
- Actual outcome for Persistent/permanent AF: SF-36 Mental health at 24 weeks
- Actual outcome for Persistent/permanent AF: SF-36 Role: emotional at 24 weeks;
- Actual outcome for Persistent/permanent AF: % reduction in VR during ambulatory exercise at 24 weeks; Group 1: mean 27 (SD 13); n=7, Group 2: mean 25 (SD 12); n=9
- Actual outcome for Persistent/permanent AF: % reduction in VR during peak exercise at 24 weeks; Group 1: mean 13 (SD 12); n=7, Group 2: mean 12 (SD 10); n=8

Protocol outcomes not reported by the study	Rate control - heart rate (time or amount of people) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up; Left ventricular function - number of people/ejection fraction as % at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Mortality (long-term) at latest follow-up

Table 47: Clinical evidence profile: digoxin versus amiodarone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digoxin	Amiodarone	Relative (95% CI)	Absolute		
% reduction in VR during ambulatory exercise[435]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7	8	-	MD 2 higher (10.72 lower to 14.72 higher)	VERY LOW	CRITICAL
% reduction in ventricular rate (VR) from baseline during peak exercise[435]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7	8	-	MD 1 higher (10.27 lower to 12.27 higher)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a Randomisation method unclear, blinding unclear; differences in SF-36 scores between groups at baseline
b CI crosses both MIDs

BACKGROUND: Atrial fibrillation and heart failure often coexist, causing substantial cardiovascular morbidity and mortality. β blockers are indicated in	Kotecha D et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation:an individual-patient data meta-analysis. Lancet 2014;384:2235–2243.

patients with symptomatic heart failure with reduced ejection fraction; however, the efficacy of these drugs in patients with concomitant atrial fibrillation is uncertain. We therefore meta-analysed individual-patient data to assess the efficacy of β blockers in patients with heart failure and sinus rhythm compared with atrial fibrillation.

METHODS:

We extracted individual-patient data from ten randomised controlled trials of the comparison of β blockers versus placebo in heart failure. The presence of sinus rhythm or atrial fibrillation was ascertained from the baseline electrocardiograph. The primary outcome was all-cause mortality. Analysis was by intention to treat. Outcome data were meta-analysed with an adjusted Cox proportional hazards regression. The study is registered with Clinicaltrials.gov, number NCT0083244, and PROSPERO, number CRD42014010012.

FINDINGS:

18,254 patients were assessed, and of these 13,946 (76%) had sinus rhythm and 3066 (17%) had atrial fibrillation at baseline. Crude death rates over a mean follow-up of 1·5 years (SD 1·1) were 16% (2237 of 13,945) in patients with sinus rhythm and 21% (633 of 3064) in patients with atrial fibrillation. β-blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm (hazard ratio 0·73, 0·67-0·80; p<0·001), but not in patients with atrial fibrillation (0·97, 0·83-1·14; p=0·73), with a significant p value for interaction of baseline rhythm (p=0·002). The lack of efficacy for the primary outcome was noted in all subgroups of atrial fibrillation, including age, sex, left ventricular ejection fraction, New York Heart Association class, heart rate, and baseline medical therapy.

INTERPRETATION:

Based on our findings, β blockers should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant heart failure and atrial fibrillation.