Siinusrütmi säilitava ravimi valik

Kliiniline küsimus

Kas siinusrütmi säilitavaks raviks tuleks eelistada mõnd konkreetset ravimirühma/ravimit: BBL vs Ic vs III?

Olulised tulemusnäitajad

Surm, ajuinfarkt, trombemboolia, elukvaliteet, tõsine kõrvaltoime.

Mõõdukalt olulised: hospitaliseerimine, KVA taasteke (sek preventsioonil), ravi katkestama sundiv kõrvaltoime, südamepuudulikkus, aeg KVA esimese taastekkeni, siinusrütmi püsimine 12 kuud.

Kliinilise tõenduse kokkuvõte

Enamike uuringute kliinilise tõenduse kvaliteet on väga madal kuni keskmine.

Suremus: Ravim vs platseebo.

Madala kvaliteediga tõendus, et propafenoon võib olla kliiniliselt efektiivsem surmade vähendamises võrreldes platseeboga, kuid on ka potentsiaalne risk, et propafenoon võib suremust tõsta (5 uuringut, N=1098)

Madala kvaliteediga tõendus, et sotalool on vähem efektiivne kui platseebo suremuse vähendamises (12 uuringud, N=3002)

Madal-väga madal tõendus, et disopüramiid, beeta-blokaatorid ja amiodaroon võivad olla vähem efektiivsed surmade vähendamises võrreldes platseeboga, kuid on ka võimalus, et eelmainitud ravimid vähendavad suremust (8 uuringut, N=1381)

Suremus: Aniarütmikum vs antiarütmikum.

Väga madala kvaliteediga tõendus:

Disopüramiid võib olla efektiivsem võrreldes teiste 1C ravimitega, kuid on potentsiaal, et teised 1C klassi antiarütmikumid võivad vähendada suremust (1 uuring, N=66)

Flekainiid võib olla efektiivsem võrreldes propafenooniga, kuid on potentsiaal, et ka propafenoon võib suremust vähendada (1 uuring, N=297)

Amiodaroon võib olla efektiivsem I klassi antiarütmikumidest, on potensiaal, et amiodaroon võib vähendada suremust (1 uuring, N=643)

Amiodaroon võib olla efektiivsem sotaloolist, kuid on potentsiaal, et sotalool võib vähendada suremust (1 uuring, N=1113)

III klassi antiarütmikumid võivad olla efektiivsemad kui I klassi antiarütmikumid, kuid on potentsiaal, et I klassi antiarütmikumid vähendavad suremust (1 uuring, N=2875)

Väga madala kvaliteediga tõendusmaterjal viitas, et amiodaroon võib olla kliiniliselt vähem efektiivne dronedaroonist, kuid on potentsiaal, et amiodaroon võib vähendada suremust (1 uuring, N=504)

Väga madala kvaliteediga tõendusmaterjal viitas, et sotalooli ja I klassi antiarütmikumide vahel ei ole kliinilist erinevust, välja arvatud kinidiini puhul (4 uuringut, N=594).

AF kodumine: Ravim vs platseebo

Nõrga kuni keskmise tugevusega tõendus näitab, et flekaniid, propafenoon, amiodaroon ja sotalool on kliiniliselt efektiivsed võrreldes platseeboga (24 uuringut, N=4249)

Madala kvaliteediga tõendus näitab, et disopüramiid ja beeta-blokaatorid võivad olla kliiniliselt efektiivsed võrreldes platseeboga (4 uuringud, N=708)

AF kordumine: Antiarütmikum vs antiarütmikum.

Tõendus näitab, et amiodaroon on kliiniliselt efektiivsem võrreldes:

- I klassi antiarütmikumidega (keskmise kvaliteediga tõendus, 4 uuringut, N=643)
- Sotalool (keskmise kvaliteediga tõendus, 5 uuringut, N=1113)
- Dronedaroon (Kõrge kvaliteediga tõendus, 1 uuring, N=504)

Väga madala kvaliteediga tõendus näitab, et järgnevate ravimite vahel ei pruugi olla olulisi erinevusi:

- Flekainiid ja propafenoon (2 uuringut, N=297)
- Sotalool ja I klassi antiartümikumid väljaarvatud qvinidiin (4 uuringut, N=594)
- Sotalool ja Beeta-blokaatorid (2 uuringut, N=263)

Madala kvaliteediga tõendus viitas, et III klassi antiarütmikumide ja I klassi antiartümikumide vahel ei pruugi olla erinevust, kuid trend viitas suuremale III klassi antiarütmikumide efektiivsusele (7 uuringut, N=1603)

Ravimite ära jätmine kõrvaltoimete tõttu: ravimid vs platseebo

Madala kuni keskmise kvaliteediga tõendus, et disopüramiidi, flekainiidi, propafenooni, beeta-blokaatori, amiodarooni ja sotalooli tarvitamise korral esines rohkem ravimite ära jätmist kõrvaltoimete tõttu võrreldes platseeboga (26 uuringut, N=4838)

Ravimite ärajätmine kõrvaltoimete tõttu: antiartümikum vs antiarütmikum

Esines rohkem ravimite katkestamist kõrvaltoimete tõttu võrreldes võrdlusega järgnevatel juhtudel:

- I klassi ravimid võrreldes disopüramiidiga (madal tõenduse kvaliteet, 1 uuring, N=113)
- I klassi ravimid võrreldes amiodarooniga (Väga madal tõenduse kvaliteet, 4 uuringut, N=652)
- Amiodaroon võrreldes dronedarooniga (keskmise kvaliteediga tõendus, 1 uuring, N=504)
- I klassi ravimid välja arvatud kinidiin võrreldes sotalooliga (madala kvaliteediga tõendus, 4 uuringut, N=567)
- Sotalool võrreldes teiste beeta-blokaatoritega (madala kvaliteediga tõendus, 2 uuringut, N=263).

Väga madala kvaliteediga tõendus näitas, et järgnevatel juhtudel esines rohkem ravimi ära jätmist kõrvaltoimete tõttu:

- Propafenoon võrreldes flekainiidiga, kuid efektiivsuse suund eelistas propafenooni (2 uuringut, N=297)
- Amiodaroon võrreldes sotalooliga, kuid efektiivsuse suund eelistas amiodarooni (4 uuringut, N=618)
- I klassi ravimid võrreldes III klassi ravimitega, kuid efektiivsuses oli eelis III klassi ravimeil (7 uuringut, N=>100)

Teiste ravijuhendite soovitused samal teemal

Enamik ravijuhendeid soovitab kaaluda antiarütmikumi vajadust siinusrütmi säilitamisel ja hinnata antiarütmikumi potentsiaalseid kõrvaltoimeid ja proarütmilisi toimeid enne ravi alustamist. Soovitatakse ka tuvastada ja kõrvaltada kõik teised muudetavad rütmihäiret soodustavad faktorid enne antiartümilise ravi alustamist.

AHA 2014 juhendi kohaselt tuleb lähtuda antiarütmikumi valikul esmaselt ohutusest. AHA ravijuhend toob ära tabelina erinevate antiarütmikumide annused ja vältimiskriteeriumid.

Kanada ravijuhend (2010) rõhutab suremuse erinevuse puudumist rütmikontrolli ja frekventsikontrolli strateegia vahel ja hoiatab antiartümikumide kõrvaltoimete eest.

Siinusrütmi säilitamist antiartümikumidega soovitatakse hinnata individuaalselt koostöös patsiendiga.

Siiski soovitatakse suukaudset antiarütmikumi patsientidel, kellel on korduv AF paroksüsm ja kellel on soovitud rakendada rütmikontrollivat ravi (tugev soovitus, keskmise kvaliteediga tõenduspõhisus).

Normaalse väljutusfraktisooniga ja ilmas südame isheemiatõveta patsientidel soovitatakse kasutada IC antiarütmikumie koos beeta-blokaatoriga (tugev soovitus, madala kvaliteediga tõenduspõhisus).

Langenud väljutusfraktsiooniga patsientidel (EF alla 35%) on ainukeseks antiarütmikumi valikuks amiodaroon.

ESC 2016 ravijuhend soovitab antiarütmikumi valikut kaaluda vastavalt patsiendi kaasuvatele haigustele, võimalikule proarütmiale, kõrvaltoimetele ja patsiendi valikule.

- Dronedaroon, flekainiid, propafenoon või sotalool on soovitatud korduva KVA ennetamiseks normaalse südamefunktsiooniga ja ilma vasaku vatsakese hüpertroofiata patsientidel (IA).
- Dronedaroon on soovitaud KVA ennetamiseks stabiilse koronaarhaigusega patsientidel ilma südamepuudulikkuseta (IA).
- Amiodaroon on soovitatud KVA ennetamiseks südamepuudulikkusega patsientidel (IB).

- Kuigi amiodaroon on efektiivsem kui teised antiarütmikumid, siis kõrvaltoimete tõttu soovitatakse seda kasutada II valiku preparaadina (IIa,C).
- AKEI, ARB ja BBL soovitatakse kaaluda südamepuudulikkuse ja langenud väljutusfraktsiooniga patsientidel, et ennetada KVA uue episoodi teket (IIa, A).

NICE ravijuhend soovitab pikaaegse rütmikontrolli rakendamisel arvestada patsiendi soovidega, kaasnevate haigustega ja korduva KVA tekkeriski tõenäosusega.

Kui pikaaegset rütmikontrolli vajatakse, siis on soovitatutud esmavaliku preparaadina kasutada standardset beeta-blokaatorit (mitte sotalool), kui ei ole vastunäidustusi.

Kui beeta-blokaator on vastunäidustatud või ebaefektiivne, siis soovitatakse hinnata sobivust teiste antiartümikumide jaoks, arvestades konkreetsete ravimite kõrvaltoimeid ja proarütmilist efekti.

Dronedaroon on soovitatud siinusrütmi hoidmiseks pärast kardioversiooni patisentidel, kelle:

- KVA ei ole kontrollitud esmavaliku preparaadiga (beeta-blokaator)
- Patsientidel, kellel on vähemalt 1 järgnevast:
    - Hüpertenisoon, mis vajab vähemalt 2 erinevat ravimigruppi
    - Diabeet
    - Eelnev TIA, ajuinsult või süsteemne embol
    - Vasaku koja diameeter 50 mm või suurem
    - Vanus 70 aasta või vanem
- Kellel ei ole vasaku vatsakese süstoolset düsfunktsiooni
- Kellel ei ole anamneesis või praegust südamepuudulikkust

Kaaluda amiodarooni tarvitamist vasaku vatsakese düsfunktsiooni või südamepuudulikkuse korral.

Ei soovitata tarvitada 1C klassi antiarütmikume nagu flekainiid ja propafenoon teadaoleva südame isheemiatõvega või strukturaalse südamehaigusega patsientidel.

Soome ravijuhend soovitab kasutada esmavaliku preparaadina BBL.

Kui on vaja täiendav antiarütmikum lisada, siis soovitatakse lähtuda eelkõige ohutusest ja kaasuvatest haigustest ning südamehaiguste profiilist.

Amiodaroon on soovitatud patsientidele, kellel muud ravimid on olnud ebaefektiivsed või kellel kaasnevate haiguste tõttu ei ole võimalik teisi antiarütmikume kasutada (südamepuudulikkus, südame isheemiatõbi).

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Vt NICE 2014

Table 73: Clinical evidence profile: mortality- antiarrhythmic versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Individual antiarrhythmic - Class 1a: Disopyramide [226,289]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/75 (2.7%)	0/71 (0%)	OR 7.56 (0.47 to 122.66)	-	VERY LOW	CRITICAL
Individual antiarrhythmic - Class 1c: Flecainide [80,420,439]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/71 (0%)	0/78 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Individual antiarrhythmic - Class 1c: Propafenone [40,130,250,366,424]												
5	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	0/720 (0%)	2/378 (0.5%)	OR 0.05 (0 to 1.02)	5 fewer per 1000 (from 5 fewer to 0 more)	LOW	CRITICAL
Individual antiarrhythmic - Class II: Beta-blockers [256,329]												
2	randomised trials	no serious risk of bias	serious[f]	no serious indirectness	very serious[b]	none	3/280 (1.1%)	1/282 (0.4%)	OR 2.75 (0.39 to 19.56)	6 more per 1000 (from 2 fewer to 62 more)	VERY LOW	CRITICAL
Individual antiarrhythmic - Class III: Amiodarone [83,167,246,408]												
4	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	very serious[b]	none	13/428 (3%)	3/245 (1.2%)	OR 1.96 (0.68 to 5.67)	11 more per 1000 (from 4 fewer to 53 more)	VERY LOW	CRITICAL
								0%		-		
Individual antiarrhythmic - Class III: Sotalol [40,42,69,76,80,145,249,291,351,361,408,410]												
12	randomised trials	serious[h]	no serious inconsistency	no serious indirectness	serious[e]	none	34/1791 (1.9%)	5/1211 (0.4%)	OR 2.47 (1.21 to 5.05)	6 more per 1000 (from 1 more to 16 more)	LOW	CRITICAL

a. Allocation concealment was unclear in both studies
b. Confidence interval crossed both MIDs
c. Allocation concealment was unclear in 2/3 studies
d. Allocation concealment was unclear in 4/5 studies
e. Confidence interval crossed 1 MID
f. I2= 66%, p= 0.31
g. Allocation concealment was unclear in 3/4 studies
h. Allocation concealment was unclear in 8/12 studies

Table 74: Clinical evidence profile: mortality - antiarrhythmic versus antiarrhythmic

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
Comparing antiarrhythmic drugs - Disopyramide versus other Class I drugs [110]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/60 (1.7%)	0/25 (0%)	OR 6.09 (0.12 to 313.90)	149 more per 1000 (from 32 fewer to 885 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Flecainide versus Propafenone [16,90]												
2	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/145 (0%)	1/152 (0.7%)	OR 0.14 (0 to 6.96)	6 fewer per 1000 (from 7 fewer to 37 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Class I drugs [7,178,249,449]												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
4	randomised trials	serious[d]	very serious[e]	no serious indirectness	serious[f]	none	16/311 (5.1%)	28/332 (8.4%)	OR 0.59 (0.31 to 1.11)	33 fewer per 1000 (from 57 fewer to 8 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Dronedarone [266]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	5/255 (2%)	2/249 (0.8%)	OR 2.32 (0.52 to 10.32)	10 more per 1000 (from 4 fewer to 69 more)	LOW	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Sotalol [7,178,246,332,408]												
5	randomised trials	serious[g]	serious[h]	no serious indirectness	serious[f]	none	34/584 (5.8%)	39/529 (7.4%)	OR 0.77 (0.47 to 1.25)	16 fewer per 1000 (from 38 fewer to 17 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Sotalol versus Class I drugs other than quinidine [7,80,250,376]												
4	randomised trials	serious[i]	serious[j]	no serious indirectness	very serious[b]	none	15/243 (6.2%)	17/251 (6.8%)	OR 0.94 (0.44 to 1.99)	4 fewer per 1000 (from 37 fewer to 59 more)	VERY LOW	CRITICAL
								0%		-		
Comparing antiarrhythmic drugs - Sotalol versus Other Beta-blockers [77,361]												
2	randomised trials	serious[k]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/133 (0%)	0/130 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Comparing antiarrhythmic drugs - Class III versus Class I drugs [7,80,146,249,250,376,449]												
7	randomised trials	serious[l]	serious[m]	no serious indirectness	very serious[b]	none	42/1353 (3.1%)	39/1522 (2.6%)	OR 0.79 (0.49 to 1.26)	5 fewer per 1000 (from 13 fewer to 6 more)	VERY LOW	CRITICAL

a. Allocation concealment was unclear
b. Confidence interval crossed both MIDs
c. Allocation concealment was unclear in 1/2 studies
d. Allocation concealment was unclear in 3/4 studies
e. I2=85%, p=0.01
f. Confidence interval crossed 1 MID
g. Allocation concealment was unclear in 4/5 studies
h. I2=59%, p=0.09
i. Allocation concealment was unclear in 2/4/ studies
j. I2=57%, p=0.13
k. Allocation concealment was unclear in both studies
m. Allocation concealment was unclear in 4/8 studies
13 I2=42%, p=0.11

Table 75: Clinical evidence profile: withdrawal due to adverse events – antiarrhythmic versus control

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiarrhythmic	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Individual antiarrhythmic - Class 1a: Disopyramide [226,289]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	9/75 (12%)	2/71 (2.8%)	OR 3.85 (1.13 to 13.18)	72 more per 1000 (from 4 more to 248 more)	LOW	IMPORTANT
Individual antiarrhythmic - Class 1c: Flecainide [80,420,439]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/71 (9.9%)	0/78 (0%)	OR 9.14 (1.94 to 42.94)	-	MODERATE	IMPORTANT
Individual antiarrhythmic - Class 1c: Propafenone [40,130,250,366,424]												
5	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[b]	none	94/720 (13.1%)	23/378 (6.1%)	OR 1.69 (1.09 to 2.62)	38 more per 1000 (from 5 more to 84 more)	LOW	IMPORTANT
Individual antiarrhythmic - Class II: Beta-blockers [256,329]												
2	randomis	serio	no serious	no serious	no serious	none	22/280 (7.9%)	6/282	OR 3.38	47 more per	MODER	IMPORT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiarrhythmic	Placebo	Relative (95% CI)	Absolute	Quality	Importance
	ed trials	us[a]	inconsistency	indirectness	imprecision			(2.1%)	(1.57 to 7.25)	1000 (from 12 more to 115 more)	ATE	ANT
Individual antiarrhythmic - Class III: Amiodarone [83,179,246]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/161 (12.4%)	1/113 (0.9%)	OR 5.55 (2.24 to 13.72)	38 more per 1000 (from 11 more to 100 more)	MODERATE	IMPORTANT
Individual antiarrhythmic - Class III: Sotalol [40,42,70,77,80,146,248,291,352,361,410]												
11	randomised trials	serious[e]	serious[f]	no serious indirectness	no serious imprecision	none	251/1530 (16.4%)	102/1079 (9.5%)	OR 1.61 (1.25 to 2.06)	49 more per 1000 (from 21 more to 82 more)	LOW	IMPORTANT

a. Allocation concealment was unclear in both studies
b. Confidence interval crossed 1 MID
c. Allocation concealment was unclear in 2/3 studies
d. Allocation concealment was unclear in 4/5 studies
e. Allocation concealment was unclear in 7/11 studies
f. I2=52%, p=0.001

Table 76: Clinical evidence profile: withdrawals due to adverse events- antiarrhythmic versus antiarrhythmic drugs

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
Comparing antiarrhythmic drugs - Disopyramide versus other Class I drugs [110]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	6/60 (10%)	12/53 (22.6%)	OR 0.37 (0.14 to 1.03)	129 fewer per 1000 (from 187 fewer to 5 more)	LOW	IMPORTANT
Comparing antiarrhythmic drugs - Flecainide versus Propafenone [16,90]												
2	randomised trials	serious[c]	very serious[d]	no serious indirectness	very serious[e]	none	12/145 (8.3%)	18/152 (11.8%)	OR 0.68 (0.32 to 1.43)	35 fewer per 1000 (from 77 fewer to 43 more)	VERY LOW	IMPORTANT
Comparing antiarrhythmic drugs - Amiodarone versus Class I drugs [7,178,249,449]												
4	randomised trials	serious[f]	very serious[7]	no serious indirectness	serious[b]	none	46/359 (12.8%)	62/293 (21.2%)	OR 0.55 (0.36 to 0.84)	83 fewer per 1000 (from 28 fewer to 123 fewer)	VERY LOW	IMPORTANT
Comparing antiarrhythmic drugs - Amiodarone versus Dronedarone [266]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	45/255 (17.6%)	32/249 (12.9%)	OR 1.45 (0.89 to 2.35)	48 more per 1000 (from 12 fewer to 129 more)	MODERATE	IMPORTANT
Comparing antiarrhythmic drugs - Amiodarone versus Sotalol [7,178,246,332]												
4	randomised trials	serious[f]	serious[h]	no serious indirectness	very serious[e]	none	42/340 (12.4%)	31/278 (11.2%)	OR 1.19 (0.73 to 1.95)	18 more per 1000 (from 28 fewer to 85 more)	VERY LOW	IMPORTANT
Comparing antiarrhythmic drugs - Sotalol versus Class I drugs other than quinidine [7,250,376]												
4	randomi	serious[i]	serious[j]	no serious	no serious	none	32/290 (11%)	56/277	OR 0.45	100 fewer per	LOW	IMPORT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
	sed trials			indirectness	imprecision			(20.2%)	(0.28 to 0.72)	1000 (from 48 fewer to 136 fewer)		ANT
Comparing antiarrhythmic drugs - Sotalol versus Other Beta-blockers [77,361]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	15/133 (11.3%)	5/130 (3.8%)	OR 2.86 (1.15 to 7.11)	64 more per 1000 (from 6 more to 183 more)	LOW	IMPORTANT
Comparing antiarrhythmic drugs - Class III versus Class I drugs [7,80,146,249,250,376,449]												
7	randomised trials	serious[l]	very serious[m]	no serious indirectness	serious[b]	none	244/1448 (16.9%)	299/1527 (19.6%)	OR 0.79 (0.65 to 0.96)	34 fewer per 1000 (from 6 fewer to 59 fewer)	VERY LOW	IMPORTANT

a. Allocation concealment was unclear
b. Confidence interval crossed 1 MID
c. Allocation concealment was unclear in 1/2 studies
d. I2=72%; p=0.05
e. Confidence interval crossed both MIDs
f. Allocation concealment was unclear in 3/4 studies
g. I2=91%, p=<0.0001
h. I2=61%, p=0.05
i. Allocation concealment was unclear in 2/4 studies
j. I2=71%, p=0.05
k. Allocation concealment was unclear in both studies
l. Allocation concealment was unclear in 4/7 studies
m. I2=82%, p=<0.00001

Table 77: Clinical evidence profile: AF recurrence- antiarrhythmic versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiarrhythmic	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Individual antiarrhythmic - Class 1a: Disopyramide [226,289]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	40/75 (53.3%)	49/71 (69%)	OR 0.52 (0.27 to 1.01)	153 fewer per 1000 (from 315 fewer to 2 more)	LOW	CRITICAL
Individual antiarrhythmic - Class 1c: Flecainide [80,420,439]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/71 (43.7%)	56/78 (71.8%)	OR 0.31 (0.16 to 0.6)	277 fewer per 1000 (from 114 fewer to 429 fewer)	MODERATE	CRITICAL
Individual antiarrhythmic - Class 1c: Propafenone [40,130,250,366,424]												
5	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	376/720 (52.2%)	276/378 (73%)	OR 0.37 (0.28 to 0.48)	230 fewer per 1000 (from 165 fewer to 299 fewer)	MODERATE	CRITICAL
Individual antiarrhythmic - Class II: Beta-blockers [256,329]												
2	randomised trials	no serious risk of bias	serious[e]	no serious indirectness	serious[b]	none	172/280 (61.4%)	203/282 (72%)	OR 0.62 (0.44 to 0.88)	105 fewer per 1000 (from 26 fewer to 189 fewer)	LOW	CRITICAL
Individual antiarrhythmic - Class III: Amiodarone [83,167,246,408]												
4	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	200/428 (46.7%)	209/245 (85.3%)	OR 0.19 (0.14 to 0.27)	329 fewer per 1000 (from 243 fewer to 405 fewer)	MODERATE	CRITICAL
Individual antiarrhythmic - Class III: Sotalol [40,42,70,77,80,146,250,291,352,361,409,411]												
12	randomis	serious[g]	serious[h]	no serious	no serious	none	1197/1791	955/12	OR 0.51	133 fewer per	LOW	CRITICA

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiarrhythmic	Placebo	Relative (95% CI)	Absolute	Quality	Importance
	ed trials			indirectness	imprecision		(66.8%)	11 (78.9%)	(0.43 to 0.6)	1000 (from 97 fewer to 173 fewer)		L

a. Allocation concealment was unclear in both studies
b. Confidence interval crossed 1 MID
c. Allocation concealment was unclear in 2/3 studies
d. Allocation concealment was unclear in 4/5 studies
e. I2=52%, p=0.15
f. Allocation concealment was unclear in 3/4 studies
g. Allocation concealment was unclear in 8/12 studies
h. I2=57%, p=<0.0001

Table 78: Clinical evidence profile: AF recurrence - antiarrhythmic versus antiarrhythmic

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
Comparing antiarrhythmic drugs - Disopyramide versus other Class I drugs [110]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	26/60 (43.3%)	27/53 (50.9%)	OR 0.76 (0.36 to 1.6)	68 fewer per 1000 (from 237 fewer to 115 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Flecainide versus Propafenone [16,91]												
2	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[b]	none	49/145 (33.8%)	56/152 (36.8%)	OR 0.87 (0.54 to	32 fewer per 1000 (from 129	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
									1.4)	fewer to 81 more)		
Comparing antiarrhythmic drugs - Amiodarone versus Class I drugs [7,179,249,449]												
4	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/311 (45.7%)	229/332 (69%)	OR 0.36 (0.26 to 0.5)	245 fewer per 1000 (from 163 fewer to 323 fewer)	MODERATE	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Dronedarone [266]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	116/255 (45.5%)	163/249 (65.5%)	OR 0.45 (0.31 to 0.63)	194 fewer per 1000 (from 110 fewer to 285 fewer)	HIGH	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Sotalol [7,179,246,332,409]												
5	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	284/584 (48.6%)	363/529 (68.6%)	OR 0.43 (0.34 to 0.54)	202 fewer per 1000 (from 145 fewer to 260 fewer)	MODERATE	CRITICAL
Comparing antiarrhythmic drugs - Sotalol versus Class I drugs other than quinidine [7,80,250,376]												
4	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[b]	none	150/243 (61.7%)	157/251 (62.5%)	OR 0.98 (0.67 to 1.45)	5 fewer per 1000 (from 97 fewer to 82 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Sotalol versus Other Beta-blockers [77,361]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute		
2	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	very serious[b]	none	88/133 (66.2%)	83/130 (63.8%)	OR 1.1 (0.64 to 1.9)	22 more per 1000 (from 108 fewer to 132 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Class III versus Class I drugs [7,80,146,249,250,376,449]												
7	randomised trials	serious[g]	serious[h]	no serious indirectness	no serious imprecision	none	806/1353 (59.6%)	966/1522 (63.5%)	OR 0.89 (0.76 to 1.04)	27 fewer per 1000 (from 66 fewer to 9 more)	LOW	CRITICAL

a unclear allocation concealment
b CI crosses both MIDs
c unclear allocation concealment in 1/2 studies
d unclear allocation concealment in 3/4 studies
e unclear allocation concealment in 4/5 studies
f unclear allocation concealment in both studies
g unclear allocation concealment in 4/7 studies
h I2=69%; p=0.001

Table 72: Summary of studies included in the review

Study	Population	Intervention/comparison	Outcomes
A-COMET II[291]	Symptomatic AF; persistent for >48 hours, <6 months duration N=658	Sotalol/ placebo/ (azimilide- not included in this review)	Mortality Recurrence rate Drug withdrawal due to side effects
AFFIRM 2003[7]	AF	Amiodarone/ sotalol	Mortality Recurrence rate
Aliot 1996[16]	Paroxysmal AF documented any time before (70% in last year) N=97	Flecainide/ Propafenone	Mortality Stroke Recurrence rate Drug withdrawal due to side effects
Bellandi 2001[40]	Recurrent AF	Sotalol/ Propafenone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Benditt 1999[42]	AF or atrial flutter documented in the last 3 months. Type: paroxysmal or recent-onset 77%, persistent 23%. N=253	Sotalol/ placebo	Mortality Stroke Recurrence rate Drug withdrawal due to side effects
Carunchio 1995[80]	Recurrent AF with >3 episodes in previous year N=66	Flecainide/ sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects

Channer 2004[83]	Persistent AF (mean duration: 6 months) N=99	Amiodarone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
DAPHNE 2008[76]	Bradycardia-tachycardia sinus node disease with history of several episodes of AF/atrial flutter and needing a pacemaker	Sotalol/ beta-blockers (atenolol or metoprolol)	Recurrence rate Drug withdrawal due to side effects
Dogan 2004[130]	Recent onset and persistent AF	Propafenone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
DYONISOS 2010[265]	Documented AF for >72 hours	Amiodarone/ dronedarone	Mortality Recurrence rate Drug withdrawal due to side effects Patients developing heart failure

Study	Population	Intervention/comparison	Outcomes
EMERALD 2000[69]	Persistent AF (1 week to 1 year, mean duration <6 months) N=535	Dofetilide/ Sotalol/ Placebo	Mortality Recurrence rate Drug withdrawal due to side effects
FAPIS 1996[90]	Paroxysmal recurrent AF with>2 episodes in the last 4 months	Flecainide/ Propafenone	Mortality Recurrence rate Drug withdrawal due to side effects
GEFACA 2001[167]	Persistent AF lasting>2 months	Amiodarone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Karlson 1998[225]	Persistent AF	Disopyramide/ placebo	Mortality Stroke Adverse events AF recurrence
Kochiadakis 2000[246]	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 64%, persistent 34% (mean duration: 10 months). N=186	Amiodarone/ Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects

Kochiadakis 2004A[249]	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 63%, persistent 37% (mean duration: 8 months). N=146	Amiodarone/ propafenone	Mortality Recurrence rate Drug withdrawal due to side effects
Kochiadakis 2004B[247]	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 59%, persistent 41% (mean duration: 8 months). N=254	Propafenone/ Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects

Study	Population	Intervention/comparison	Outcomes
Kuhlkamp 2000[256]	Persistent AF lasting 2 days to 1 year (mean duration: 3 months) N=394	B-blocker/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Lloyd 1984[289]	Persistent AF lasting 1 month to 3 years (mean duration: NS). N=82	Disopyramide/ placebo	Mortality Stroke Recurrence rate Drug withdrawal due to side effects
Nergardh 2007[329]	Persistent AF of less than 1 year (mean duration: 5 months). N=168	B-blocker/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Niu 2006[332]	Any type of AF: 41% paroxysmal, 59% persistent (mean duration: NS). N=102	Amiodarone/ Sotalol	Mortality Recurrence rate Drug withdrawal due to side effects
PAFAC 2004[145]	Persistent AF lasting >7 days (mean duration: 15 months). N=848	Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects

PITAGORIA 2008[178]	Recurrent symptomatic AF in patients with sinus node disease and an indication for pace-maker. Type of AF: 53% paroxysmal, 46% persistent (mean duration NS). N=176	Amiodarone/ Class 1C (flecainide or Propafenone)/ Sotalol	Mortality Stroke Drug withdrawal due to side effects
Plewan 2001[361]	Persistent AF (mean duration: 9 months). N=128	Sotalol/ B-blocker	Mortality Recurrence rate Drug withdrawal due to side effects
PRODIS 1996[109]	Persistent AF (mean duration: 5 months). N=56	Disopyramide/ Propafenone	Mortality Recurrence rate Drug withdrawal due to side effects
RAFT 2003[366]	Previous symptomatic AF documented in the last year. Type: NS. N=523	Propafenone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects

Study	Population	Intervention/comparison	Outcomes
Reimold 1993[376]	Any symptomatic AF or atrial flutter. Type: paroxysmal 46%, persistent 53% (mean duration: 36 months). N=100	Propafenone/ Sotalol	Mortality Recurrence rate Drug withdrawal due to side effects
SAFE-T 2005[408]	Persistent AF lasting 3 days to 1 year (mean duration NS. N=655	Amiodarone/ Sotalol/ placebo	Mortality Recurrence rate
Singh 1991[410]	Persistent AF or atrial flutter lasting 2 weeks to 1 year (mean duration: 3 months). N=34	Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
SOPAT 2004[351]	Paroxysmal AF documented in the last 1 month (mean duration: NS). N=1033	Sotalol/ placebo	Mortality Stroke Recurrence rate Drug withdrawal due to side effects