Boezemfibrilleren

Medicamenteuze behandeling

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Definitie

- Ongeorganiseerde asynchrone, gefractioneerde atriale electrische activiteit, herkenbaar door afwezigheid van P-toppen en de aanwezigheid van kleine irregulaire oscillaties.
- Meestal irregulaire pols

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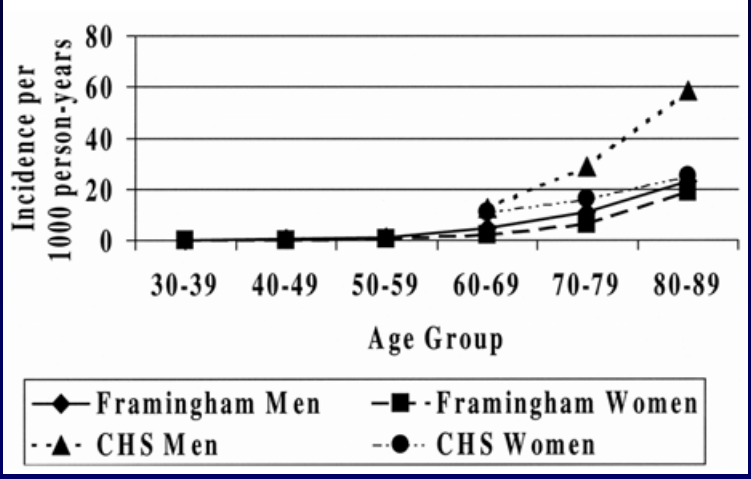
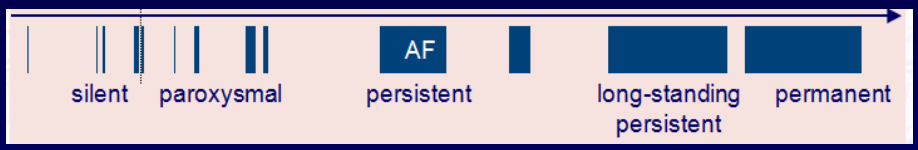
Classificatie

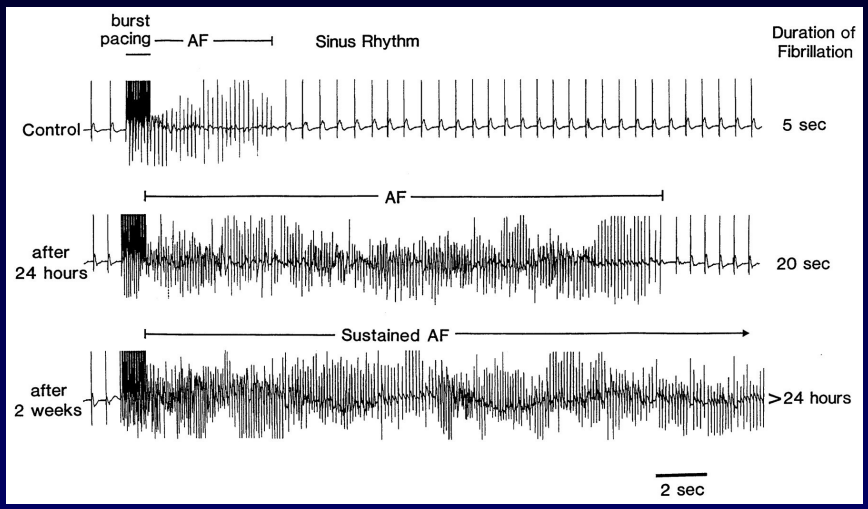
- Paroxysmaal: spontaan terminerend binnen zeven dagen (>50 % termineert <24 uur.
- Persisterend: langer dan zeven dagen en niet geaccepteerd.
- Permanent: geaccepteerd.

Incidentie



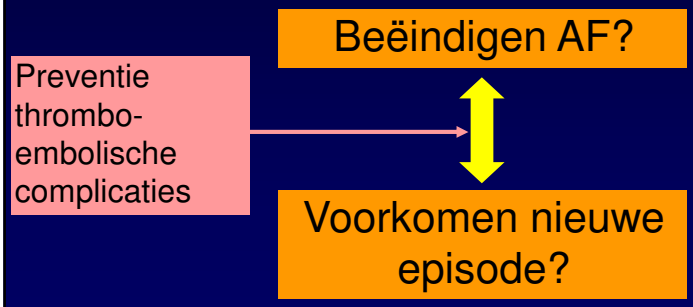
Natuurlijk beloop





Wijffels et al. *Circulation 1995*

Atrium Fibrilleren
Behandeling



Casus 1

- Man 19 jaar, “avondje zuipen met de mannen”, onwelwording.
- LO: dronken, snelle irregulaire inaequale pols, verder gb.
- ECG: boezemfibrilleren; 185/min.
- Dag later: nuchter, boezemfibrilleren; 170/min.

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Casus 2

- Vrouw 63 jaar, palpitaties ‘s nachts, niet heel heftig, maar wel eerste keer.
- LO: snelle irregulaire inaequale pols, verder gb.
- ECG: boezemfibrilleren; 135/min.

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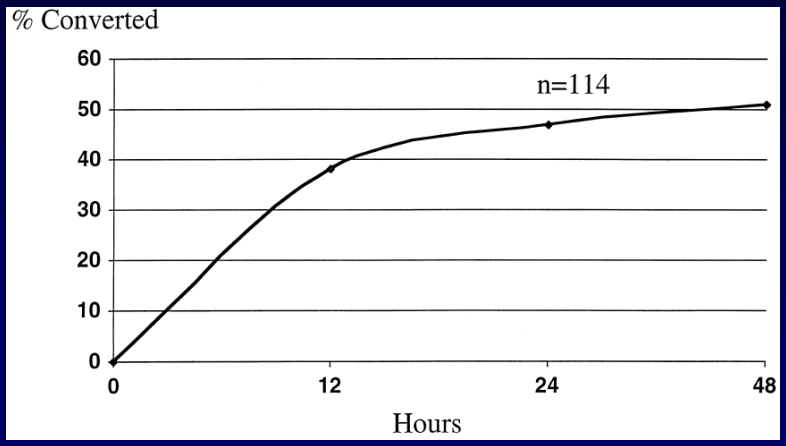
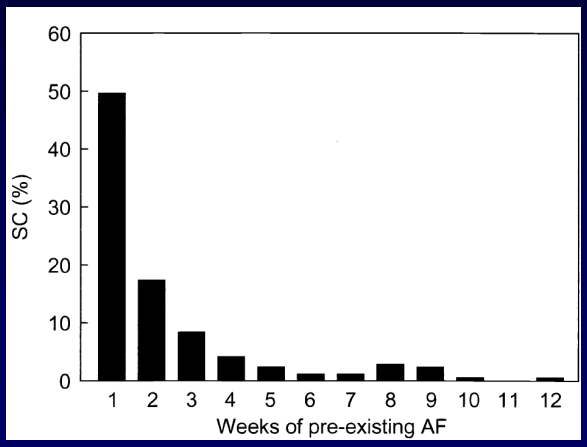
Spontane conversie

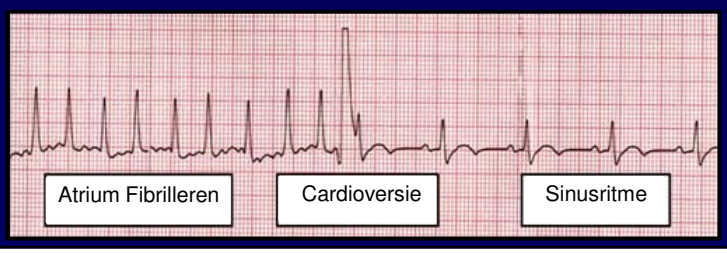


Spontane conversie



Atrium Fibrilleren
Beëindigen

1. Spontaan
   - meestal < 1 dag
2. Medicamenteus
   - Infuus
   - 'Pill in the Pocket'
3. Electrische cardioversie



Casus 1

- Man 19 jaar, avondje zuipen met de mannen, onwelwording.
- LO: dronken, snelle irregulaire inaequale pols, verder gb.
- ECG: boezemfibrilleren; 185/min.
- Dag later: nuchter, boezemfibrilleren; 170/min.
- Klaarmaken voor cardioversie: spontane conversie naar sinusritme

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Casus 2

- Vrouw 63 jaar, palpitaties ‘s nachts, niet heel heftig, maar wel eerste keer.
- LO: snelle irregulaire inaequale pols, verder gb.
- ECG: boezemfibrilleren; 135/min.
- ‘s Ochtends onveranderd. Wat te doen?

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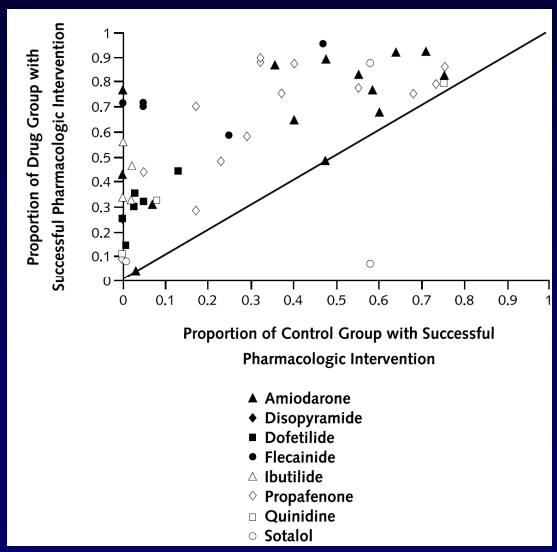
Medicamenteuze conversie



Ann Intern Med. 2003;139:1018-1033

Medicamenteuze conversie

Level of Evidence	Drug	Trials with Control Group				Range of Sustained Ventricular Arrhythmia in All Trials that Reported Side Effects
		Trials	Patients in Drug Group	Odds Ratio of Conversion Compared with Control (95% CI)*	*P* Value	
		n				%
Strong	Ibutilide	4	552	30.7 (10.9–86)	<0.01	0–9
	Flecainide	5	128	13.2 (6.4–27.4)	<0.01	0–2
	Dofetilide	6	716	6.7 (4.5–10)	<0.01	1–12
	Propafenone	14	680	3.9 (2.3–6.8)	<0.01	0–2
	Amiodarone	15	484	3.2 (2.5–5.1)	<0.01	0
Moderate	Quinidine	3	99	2.9 (1.2–6.9)	0.02	0–12
Inconclusive	Disopyramide	1	13	7.0 (0.3–153)	0.10	Not reported
	Sotalol	3	115	1.1 (0.1–6.9)	>0.2	0–2

* Control indicates placebo, calcium-channel blockers, β-blockers, or digoxin.

Ann Intern Med. 2003;139:1018-1033

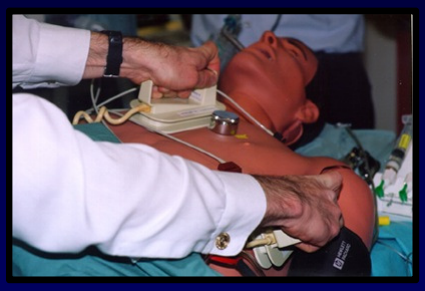
Medicamenteuze conversie (effectiviteit)

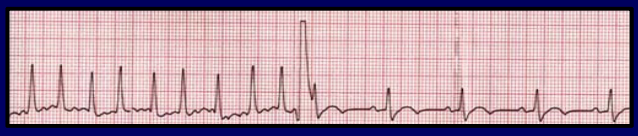
- Zeker niet beter dan placebo:
  - Digoxine, betablokkers, calciumantagonisten
- Waarschijnlijk niet beter dan placebo:
  - Sotalol, dysopyramide
- Waarschijnlijk beter dan placebo:
  - Quinidine
- Zeker beter dan placebo:
  - Amiodaron, flecaïnide, ibutilide, vernakalant, dofetilide, propafenon en 36 andere

Electrische conversie

- >90% succesvol
- Diepe sedatie nodig
- Complicaties:
  - Embolie
  - Spierpijn, brandwonden

Atrium Fibrilleren
Cardioversie





Behandeling lange termijn

- Frequentie-controle = ‘Rate control’
- Ritme-controle = ‘Rhythm control’

Casus 3

- Man 72 jaar komt op poli, sinds drie weken last van wat onrustig gevoel in de borst.
- VG: hypertensie
- ACE-remmer, thiazidediureticum
- ECG: Boezemfibrilleren 110/min, verder gb.

Casus 4

- Vrouw, 70 jaar, sinds drie maanden paar keer per dag in rust minuten durend palpitaties.
- VG: PCI RCA bij eenvatslijden drie jaar eerder.
- ASA, statine.
- Holter: PAF 140/min, SR 60-80/min.
- Echo: geringe AoI, verder gb.

Atrium Fibrilleren
Ritme-therapie

1. Rhythm control ⟷ Rate control

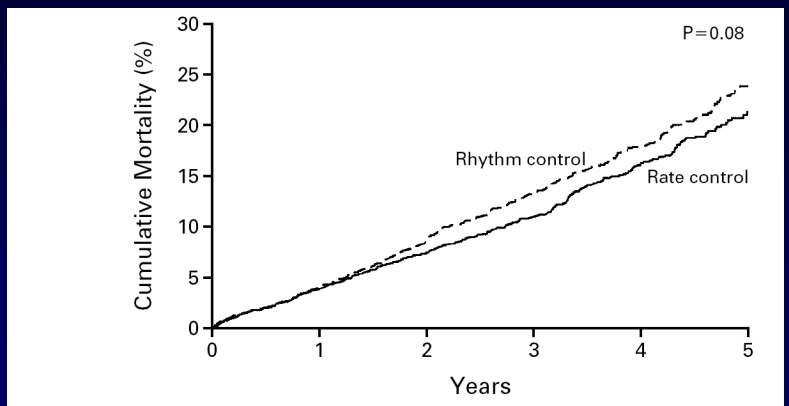
SR nastreven
- Medicamenteus
- Cardioversie
- Catheterablatie
- Chirurgie

AF accepteren
- Medicamenteus
- Pacemaker en Ablatie Hisbundel

AFFIRM-studie

- 4060 patiënten
- Ouder dan 65 jaar of andere risico's op CVA/overlijden
- Recidiverend persisterend
- Primaire eindpunt: mortaliteit
- Follow-up 5 jaar

AFFIRM-studie

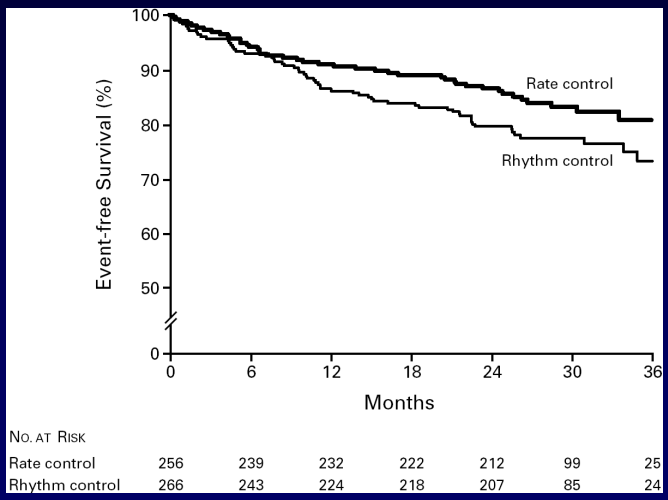


No. of Deaths	number (percent)					
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

RACE-studie

- 522 patiënten
- Recidiverend persisterend na cardioversie
- Primaire eindpunt: cardiovasculaire mortaliteit + hartfalen + CVA + pacemaker + bijwerkingen medicatie + bloeding
- Follow-up 36 maanden

RACE-studie



PIAF-studie

- Diltiazem versus amiodaron
- 252 patiënten
- Boezemfibrilleren 7-360 dagen bestaand
- Primaire eindpunt: boezemfibrilleren-gerelateerde symptomen
- Follow-up 12 maanden

PIAF-studie

	Mean baseline and mean change from baseline at month 12 (SD)		
	Group A: diltiazem	Group B: amiodarone	US norm*
Physical functioning			
Baseline	60 (25)	63 (28)	84
Month 12	+7 (26)†	+8 (26)†	
Physical role function			
Baseline	32 (38)	41 (41)	81
Month 12	+20 (57)‡	+17 (51)†	
Bodily pain			
Baseline	67 (30)	69 (31)	75
Month 12	+10 (31)‡	+8 (36)	
General health			
Baseline	47 (17)	52 (19)	72
Month 12	+3 (17)	+3 (20)	
Vitality			
Baseline	45 (20)	50 (22)	61
Month 12	+10 (19)‡	+7 (21)‡	
Social functioning			
Baseline	72 (25)	74 (25)	83
Month 12	+8 (28)†	+10 (29)‡	
Emotional role function			
Baseline	62 (45)	62 (45)	81
Month 12	+3 (51)	0 (45)	
Mental health			
Baseline	63 (20)	67 (19)	74
Month 12	+5 (20)†	+4 (17)	

*Data from reference 11. †p<0·05 for within-group difference from baseline. ‡p<0·01 for within-group difference from baseline. +Indicates changes.

Gunstige effect van sinusritme wordt tenietgedaan door de benodigde antiarrhythmica

Covariates Significantly Associated With Survival

Covariate	*P*	HR	HR: 99% Confidence Limits Lower	Upper
Age at enrollment*	<0.0001	1.06	1.05	1.08
Coronary artery disease	<0.0001	1.56	1.20	2.04
Congestive heart failure	<0.0001	1.57	1.18	2.09
Diabetes	<0.0001	1.56	1.17	2.07
Stroke or transient ischemic attack	<0.0001	1.70	1.24	2.33
Smoking	<0.0001	1.78	1.25	2.53
Left ventricular dysfunction	0.0065	1.36	1.02	1.81
Mitral regurgitation	0.0043	1.36	1.03	1.80
Sinus rhythm	<0.0001	0.53	0.39	0.72
Warfarin use	<0.0001	0.50	0.37	0.69
Digoxin use	0.0007	1.42	1.09	1.86
Rhythm-control drug use	0.0005	1.49	1.11	2.01

*Per year of age.

Corley, Circulation, 2004

Rate and rhythm control of AF

Recommendations	Class[a]	Level[b]
Rate control should be the initial approach in elderly patients with AF and minor symptoms (EHRA score 1).	I	A
Rhythm control is recommended in patients with symptomatic (EHRA score ≥ 2) AF despite adequate rate control.	I	B
Rate control should be continued throught a rhythm control approach to ensure adequate control of the ventricular rate during recurrences of AF.	I	A
Rhythm control as an initial approach should be considered in young symptomatic patients in whom catheter ablation treatment has not been ruled out.	IIa	C
Rhythm control should be considered in patients with AF secondary to a trigger or substrate that has been corrected (e.g. ischaemia, hyper-thyroidism).	IIa	C
Rhythm control in patients with AF and AF-related heart failure should be considered for improvement of symptoms.	IIa	B

[a]Class of recommendation. [b]Level of evidence.
AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

Casus 3

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- VG: hypertensie
- ACE-remmer, thiazidediureticum
- ECG: Boezemfibrilleren 110/min, verder gb.
- Rate control

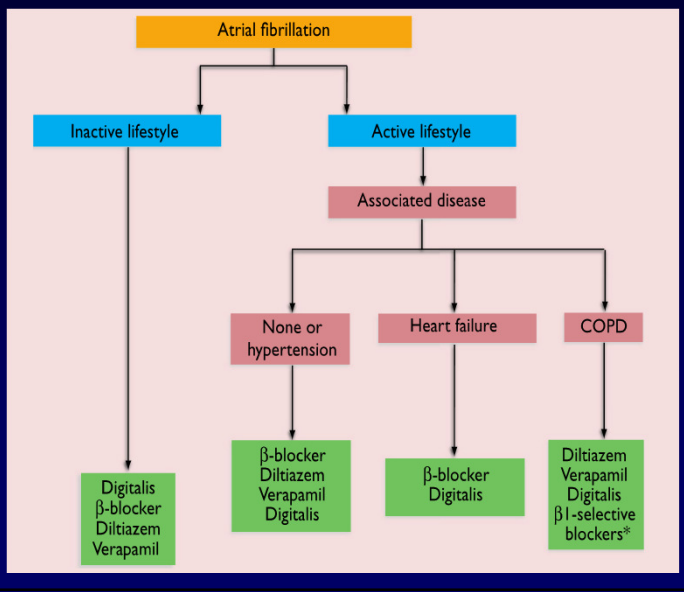
Casus 4

- Vrouw, 70 jaar, sinds drie maanden paar keer per dag in rust minuten durend palpitaties.
- VG: PCI RCA bij eenvatslijden drie jaar eerder.
- ASA, statine.
- Holter: PAF 140/min, SR 60-80/min.
- Echo: geringe AoI, verder gb.
- Rhythm control

‘Rate control’

- Digoxine
  - In rust effectief, bij inspanning niet.
- Calciumantagonisten
  - Diltiazem en verapamil effectief in rust en bij inspanning.
- Beta-blokkers
  - Atenolol, metoprolol, timolol, pindolol, en nadolol zijn effectief
  - Xamoterol, celiprolol en labetolol zijn niet effectief

Welk middel?



'Rate control': ablatie bundel van His

- Zeer effectief
- Geen 'rate control' medicatie meer nodig
- Pacemaker

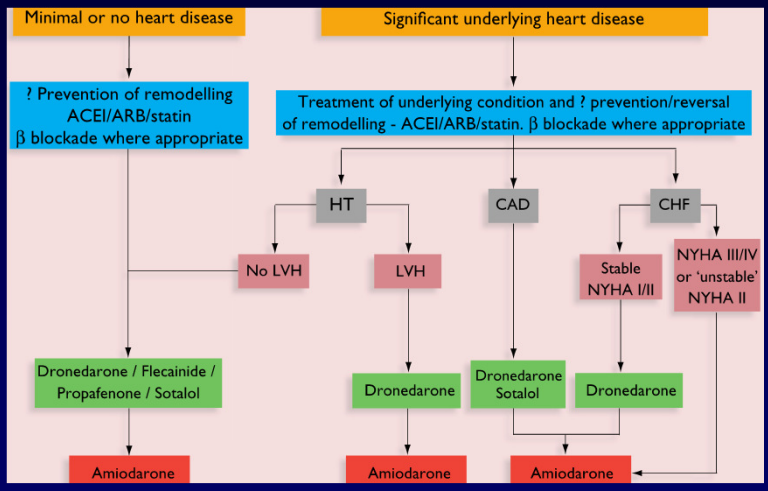
´Rhythm control´

1. Behandelen oorzaak (zelden)
2. Medicamenteus
3. Catheter-ablatie
4. Chirurgisch

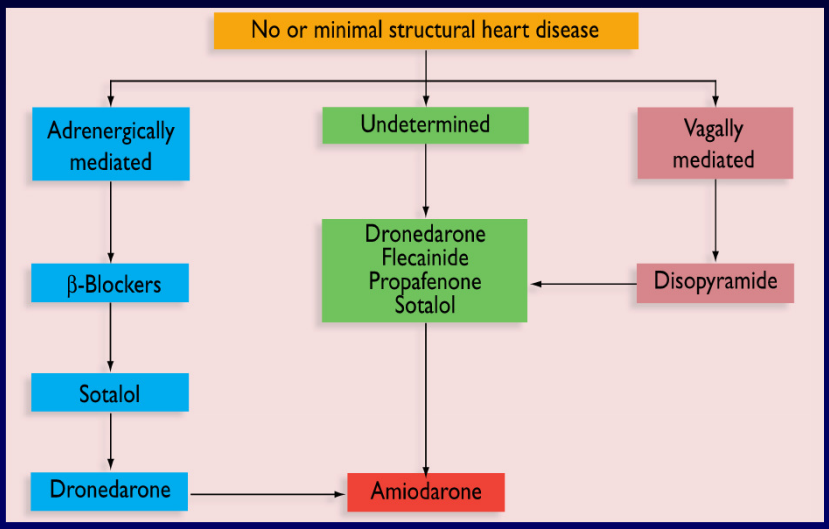
´Rhythm control´, medicamenteus

- Gewone Beta-blokkers *(m.n. metoprolol, atenolol)*
  - Redelijk effectief
  - Ook goede ´rate control´
- Bijzondere betablokker *(sotalol)*
  - Effectiever dan gewone betablokker
  - Matige ´rate control´
  - Pro-arrhythmogeen
- Klasse I middelen *(m.n. flecainide en propafenon)*
  - Effectief
  - Combinatie met betablokker of calciumantagonist
  - Pro-arrhythmogeen
- Amiodaron
  - Meest effectief
  - Veel en deels onomkeerbare bijwerkingen

Rhythm control medicatie



Rhythm control medicatie



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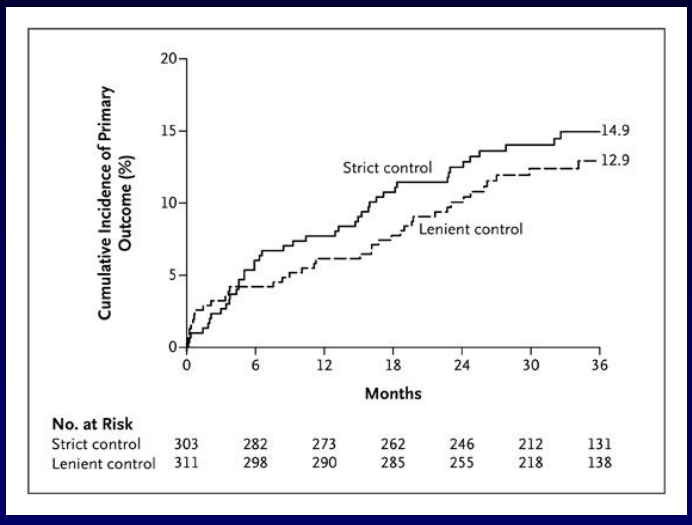
- ECG: Boezemfibrilleren 110/min, verder gb.
- Rate control: betablokker

Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.



Van Gelder IC et al. N Engl J Med 2010;362:1363-1373.

The NEW ENGLAND JOURNAL of MEDICINE

Casus 4

- Vrouw, 70 jaar, sinds drie maanden paar keer per dag in rust minuten durend palpitaties.
- VG: PCI RCA bij eenvatslijden drie jaar eerder.
- ASA, statine.
- Holter: PAF 140/min, SR 60-80/min.
- Echo: geringe AoI, verder gb.
- Rhythm control: flecainide + betablokker/calciumantagonist

Sotalol: contra-indicaties

- Nierinsufficiëntie
- QT-tijdverlengende medicatie
- Algemene contra-indicaties van niet-selectieve betablokkers
- Gevorderd structureel hartlijden.

Sotalol: bij start

- ECG
- Lab (creat, kalium en bij diarree of diuretica Magnesium)

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Sotalol: Follow-up

- Na twee dagen ECG
- Twee keer per jaar ECG, lab (creat, kalium en bij diarree of diuretica Magnesium) en check interacties.

Sotalol: Klinisch instellen

- ICD-dragerschap
- Significant coronarialijden
- Bradycardie
- Hoog-normale QTc.

Amiodaron: contra-indicaties

- QT-tijd verlengende medicatie

Amiodaron: bij start

- Lab (Transaminasen en TSH/FT4)
- Thoraxfoto
- Voorlichting zonbescherming
  - Armen bedekken
  - Hoed
  - Minimaal SPF 30

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Amiodaron: Follow-up

- ECG na ongeveer een maand.
- Elke zes maanden lab (transaminasen, TSH/FT4 en bij digoxine gebruik digoxinespiegel) en check interacties
- Jaarlijks thoraxfoto
- Als visusklachten: oogarts.
- Dosis zo laag mogelijk.

Amiodaron: Klinisch instellen

- In principe niet nodig

Flecainide: contra-indicaties

- Structurele hartziekten
- Tweede- en derdegraads AV-blok
- Trifasciculair- en bifasciculair blok
- Aspecifiek verlengd QRS (>120ms)
- Ventriculaire tachycardieën
- Shock
- Coronarialijden
- Significante nier- of leverinsufficiëntie
- QT-tijd verlengende medicatie
- Boezemflutter (relatief)

Flecainide: bij start

- Twee maal daags kortwerkend preparaat starten (in principe 2dd100mg)
- ECG
- Betablokker erbij (of evt calciumantagonist)
- Interacties checken.

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Flecainide: Follow-up

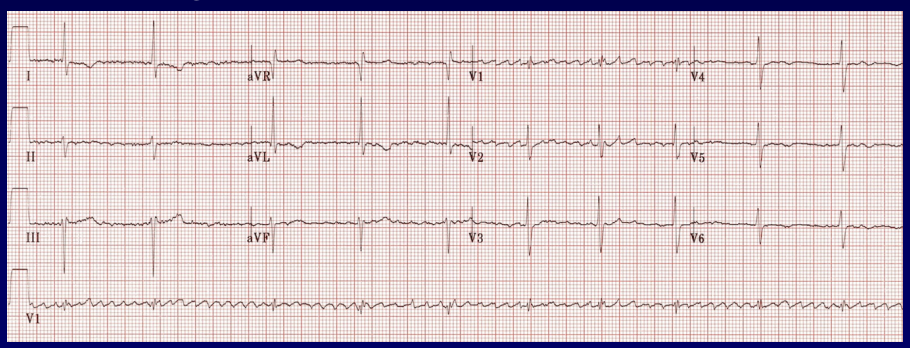
- Na vijf giften (dus op derde dag) ECG en inspanningstest ter beoordeling van QRS-breedte.
- Nadien voorkeur voor een maal daags CR-preparaat of anders twee maal daags retard-preparaat.
- Jaarlijks ECG, inspanningstest en checken interacties.

Flecainide: Klinisch instellen

- ICD-drager
- Bradycardie
- Geringe structurele hartziekte

Casus 5

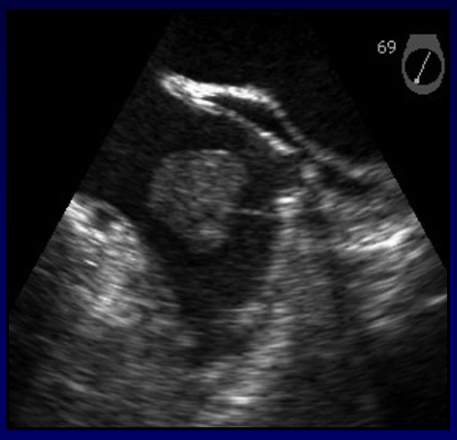
- Man 75 jaar, sinds drie maanden progressief kortademig bij inspanning.
- VG: permanent AF
- Med: Acenocoumarol, metoprolol ret 50mg 1dd1

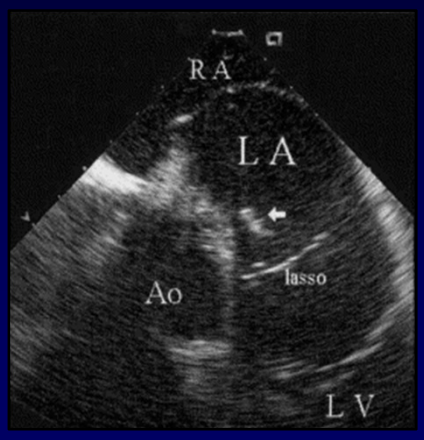


Casus 6

- Vrouw, 57 jaar, palpitaties in aanvallen sinds drie weken.
- VG: PAF, waartegen betablokker
- Holter: symptomatische nsVT's

LA Stolsel





Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors
Previous stroke
TIA or systemic embolism
Age ≥ 75 years

Clinically relevant non-major risk factors
CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%]
Hypertension
Diabetes mellitus
Age 65-74 years
Female sex
Vascular disease

AF= atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radionuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.

Risk factor-based point-based scoring system - CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 ans	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65-74	1
Sex category [i.e. femal sex]	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/y)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Original Article

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators

N Engl J Med
Volume 361(12):1139-1151
September 17, 2009

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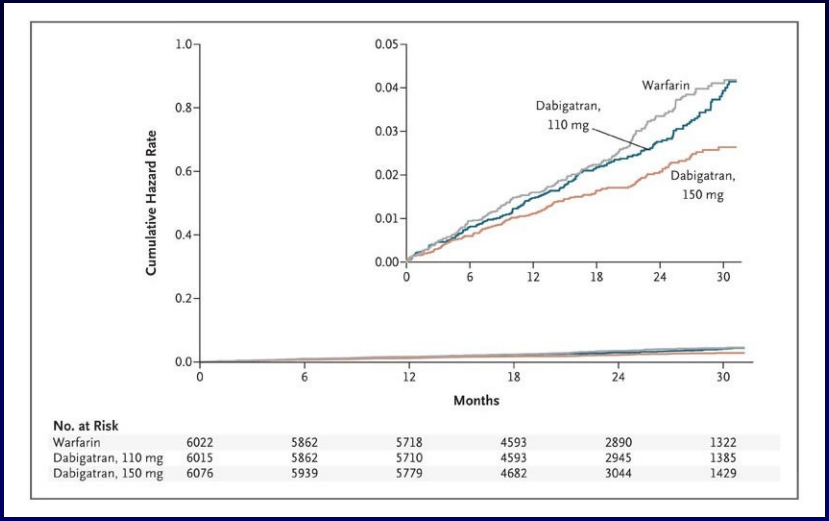
Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group



Connolly SJ et al. N Engl J Med 2009;361:1139-1151

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Safety Outcomes, According to Treatment Group

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
† Gastrointestinal bleeding could be life threatening or non–life threatening.
‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Connolly SJ et al. N Engl J Med 2009;361:1139-1151

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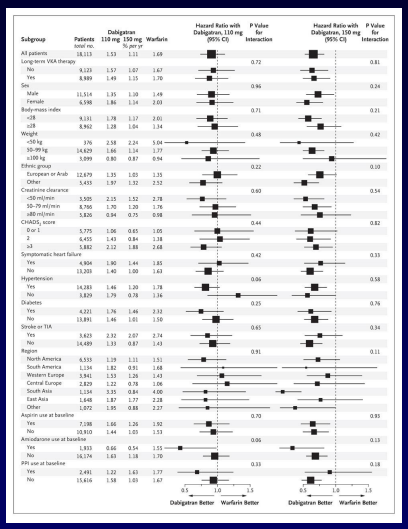
Relative Risk of the Primary Outcome of Stroke or Systemic Embolism with Dabigatran versus Warfarin, According to Subgroup



Connolly SJ et al. N Engl J Med 2009;361:1139-1151

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators

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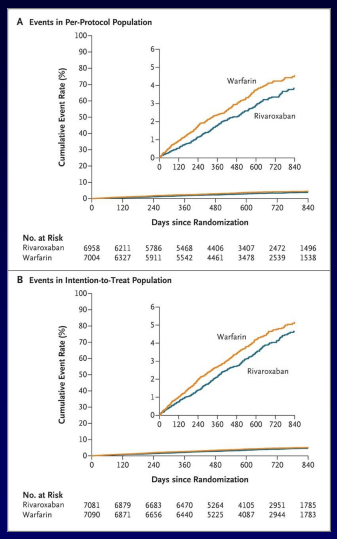
The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.



Patel MR et al. N Engl J Med 2011;365:883-891

Rates of Bleeding Events.

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

Patel MR et al. N Engl J Med 2011;365:883-891

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators

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September 15, 2011

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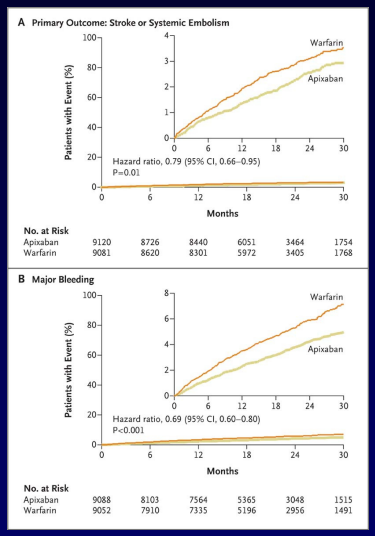
Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes.



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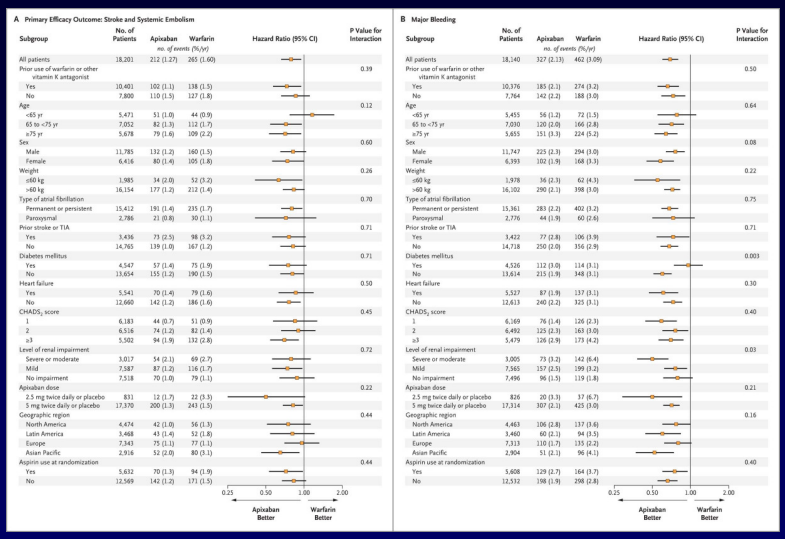
Relative Risks of the Primary Efficacy and Safety Outcomes, According to Major Prespecified Subgroups.



A Primary Efficacy Outcome: Stroke and Systemic Embolism

Subgroup	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	Hazard Ratio (95% CI)	P Value for Interaction
All patients	18,201	212 (1.27)	265 (1.60)		
Prior use of warfarin or other vitamin K antagonist					0.39
Yes	10,401	102 (1.1)	138 (1.5)		
No	7,800	110 (1.5)	127 (1.8)		
Age					0.12
<65 yr	5,471	51 (1.0)	44 (0.9)		
65 to <75 yr	7,052	82 (1.3)	112 (1.7)		
≥75 yr	5,678	79 (1.6)	109 (2.2)		
Sex					0.60
Male	11,785	132 (1.2)	160 (1.5)		
Female	6,416	80 (1.4)	105 (1.8)		
Weight					0.26
≤60 kg	1,985	34 (2.0)	52 (3.2)		
>60 kg	16,154	177 (1.2)	212 (1.4)		
Type of atrial fibrillation					0.70
Permanent or persistent	15,412	191 (1.4)	235 (1.7)		
Paroxysmal	2,786	21 (0.8)	30 (1.1)		
Prior stroke or TIA					0.71
Yes	3,436	73 (2.5)	98 (3.2)		
No	14,765	139 (1.0)	167 (1.2)		
Diabetes mellitus					0.71
Yes	4,547	57 (1.4)	75 (1.9)		
No	13,654	155 (1.2)	190 (1.5)		
Heart failure					0.50
Yes	5,541	70 (1.4)	79 (1.6)		
No	12,660	142 (1.2)	186 (1.6)		
$CHADS_2$ score					0.45
1	6,183	44 (0.7)	51 (0.9)		
2	6,516	74 (1.2)	82 (1.4)		
≥3	5,502	94 (1.9)	132 (2.8)		
Level of renal impairment					0.72
Severe or moderate	3,017	54 (2.1)	69 (2.7)		
Mild	7,587	87 (1.2)	116 (1.7)		
No impairment	7,518	70 (1.0)	79 (1.1)		
Apixaban dose					0.22
2.5 mg twice daily or placebo	831	12 (1.7)	22 (3.3)		
5 mg twice daily or placebo	17,370	200 (1.3)	243 (1.5)		
Geographic region					0.44
North America	4,474	42 (1.0)	56 (1.3)		
Latin America	3,468	43 (1.4)	52 (1.8)		
Europe	7,343	75 (1.1)	77 (1.1)		
Asian Pacific	2,916	52 (2.0)	80 (3.1)		
Aspirin use at randomization					0.44
Yes	5,632	70 (1.3)	94 (1.9)		
No	12,569	142 (1.2)	171 (1.5)		

0.25 0.50 1.00 2.00
Apixaban Better | Warfarin Better

B Major Bleeding

Subgroup	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	Hazard Ratio (95% CI)	P Value for Interaction
All patients	18,140	327 (2.13)	462 (3.09)		
Prior use of warfarin or other vitamin K antagonist					0.50
Yes	10,376	183 (2.1)	274 (3.2)		
No	7,764	142 (2.2)	188 (3.0)		
Age					0.64
<65 yr	5,455	56 (1.2)	72 (1.5)		
65 to <75 yr	7,030	120 (2.0)	166 (2.8)		
≥75 yr	5,655	151 (3.3)	224 (5.2)		
Sex					0.08
Male	11,747	225 (2.3)	294 (3.0)		
Female	6,393	102 (1.9)	168 (3.3)		
Weight					0.22
≤60 kg	1,978	36 (2.3)	62 (4.3)		
>60 kg	16,102	290 (2.1)	398 (3.0)		
Type of atrial fibrillation					0.75
Permanent or persistent	15,361	283 (2.2)	402 (3.2)		
Paroxysmal	2,776	44 (1.9)	60 (2.6)		
Prior stroke or TIA					0.71
Yes	3,422	77 (2.8)	106 (3.9)		
No	14,718	250 (2.0)	356 (2.9)		
Diabetes mellitus					0.003
Yes	4,526	112 (3.0)	114 (3.1)		
No	13,614	215 (1.9)	348 (3.1)		
Heart failure					0.30
Yes	5,527	87 (1.9)	137 (3.1)		
No	12,613	240 (2.2)	325 (3.1)		
$CHADS_2$ score					0.40
1	6,169	76 (1.4)	126 (2.3)		
2	6,492	125 (2.3)	163 (3.0)		
≥3	5,479	126 (2.9)	173 (4.2)		
Level of renal impairment					0.03
Severe or moderate	3,005	73 (3.2)	142 (6.4)		
Mild	7,565	157 (2.5)	199 (3.2)		
No impairment	7,496	96 (1.5)	119 (1.8)		
Apixaban dose					0.21
2.5 mg twice daily or placebo	826	20 (3.3)	37 (6.7)		
5 mg twice daily or placebo	17,314	307 (2.1)	425 (3.0)		
Geographic region					0.16
North America	4,463	106 (2.8)	137 (3.6)		
Latin America	3,460	60 (2.1)	94 (3.5)		
Europe	7,313	110 (1.7)	135 (2.2)		
Asian Pacific	2,904	51 (2.1)	96 (4.1)		
Aspirin use at randomization					0.40
Yes	5,608	129 (2.7)	164 (3.7)		
No	12,532	198 (1.9)	298 (2.8)		

0.25 0.50 1.00 2.00
Apixaban Better | Warfarin Better

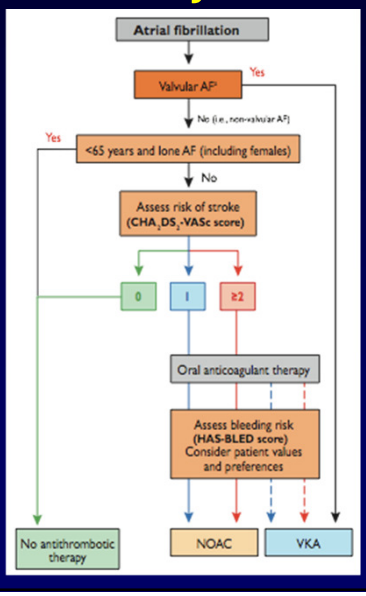
Granger CB et al. N Engl J Med 2011;365:981-992

The NEW ENGLAND JOURNAL of MEDICINE

ESC-guidelines 2012

The NOACs so far tested in clinical trials have all shown non-inferiority compared with VKAs, with better safety, consistently limiting the number of ICH. On this basis, this guideline now recommends them as broadly preferable to VKA in the vast majority of patients with non-valvular AF, when used as studied in the clinical trials performed so far. Since there is still limited experience with these agents, strict adherence to approved indications and careful post-marketing surveillance are strongly recommended.

Richtlijn ESC



Voordelen NOACs	Nadelen NOACs
•Geen lab-controle •Iets minder kans op complicaties	•Geen antidotum (nog) •Kans op therapie-ontrouw, met mgl direct ernstige gevolgen •Geen lab-test voor meten effectiviteit •Duur (inclusief antidota)

Contra-indicaties NOACs

- Bloedingscomplicatie onder VKA
- Te verwachten lage therapietrouw
- Ernstige nierinsufficientie
- Jonger dan 18 jaar
- Zwanger/borstvoeding
- Stabiele INR onder VKA
- etc

NOACs: kiezen

	Dabigatran (RE-LY)[70,71]	Rivaroxaban (ROCKET-AF)[3]	Apixaban (ARISTOTLE)[4]
Drug characteristics			
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	60–80	50
Time to peak levels, h	3	3	3
Half-life, h	12–17	5–13	9–14
Excretion	80% renal	2/3 liver, 1/3 renal	25% renal, 75% faecal
Dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.
Dose in renal impairment	110 mg b.i.d.	15 mg o.d. (if CrCl 30-49 mL/min)	2.5 mg b.i.d.
Special considerations	Intestinal absorption is pH-dependent and is reduced in patients taking proton pump inhibitors	Higher levels expected in patients with renal or hepatic failure	
	Increased risk of bleeding in patients taking verapamil/amiodarone/quinidine/ketoconazole	Activity lower in fasted patients so should be taken after food	

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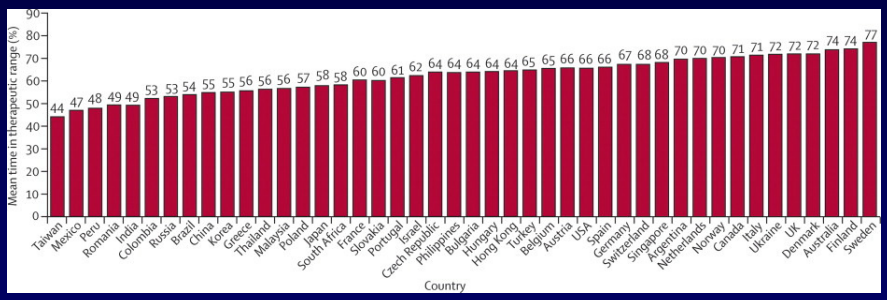
12.000 euro per QALY, maar ook in Nederland?



Leidraad begeleide introductie NOACs (11/2012)

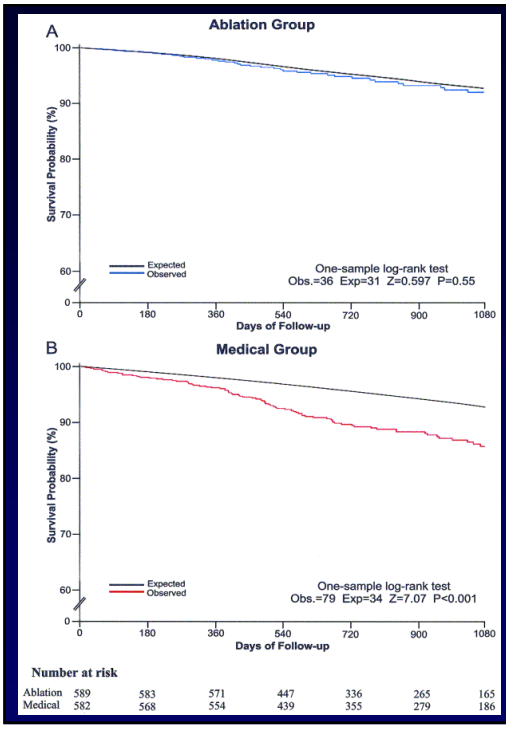
- Invoeren na regionale afspraken over:
  - Spoedeisende situaties
  - Indicaties
  - Beleid rond electieve ingrepen
  - Wanneer en welke lab-testen
- Vervolgen veiligheid na introductie

www.begeleidezelfzorg.nl

- Doseerarts krijgt inzage in actuele medicatie van de apotheek, inclusief alerts.
- Eenvoudig intercollegiaal consult met internist-vasculair geneeskundige.
- Via uw eigen toegangssite kunt u inzage krijgen in actuele dossier.
- Patiënt kan 7 dagen per week meten en advies opvragen.
- Doorgedoseerd door internisten.
- Geen wachtlijst zelfmeetcursus.
- Registratie alle mogelijke complicaties.
- Eventueel hulp via wijkverpleging van Buurtzorg.
- Er komt therapietrouwprogramma voor patienten op NOACs.

Casus 7

- Vrouw, 55 jaar, nieuwe palpitaties
- VG: boezemflutter (2x in 2 jaar)
- Med: Acenocoumarol
- Holter: PAF; 120-130/min in rust.
- Wat te doen?



Overleving na pulmonaalvene-isolatie gelijk aan gepaarde algemene levensverwachting

(niet gerandomiseerd, groepen vergelijkbaar behoudens aantal geprobeerde anti-arrhythmica)

Pappone, JACC, 2003