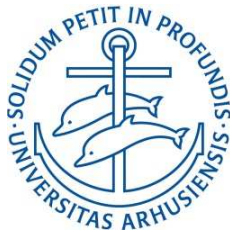


Prognostic Benefits of AF Ablation Stroke, AF Burden and OAC

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Dept. of Cardiology, Aarhus University Hospital
Denmark*



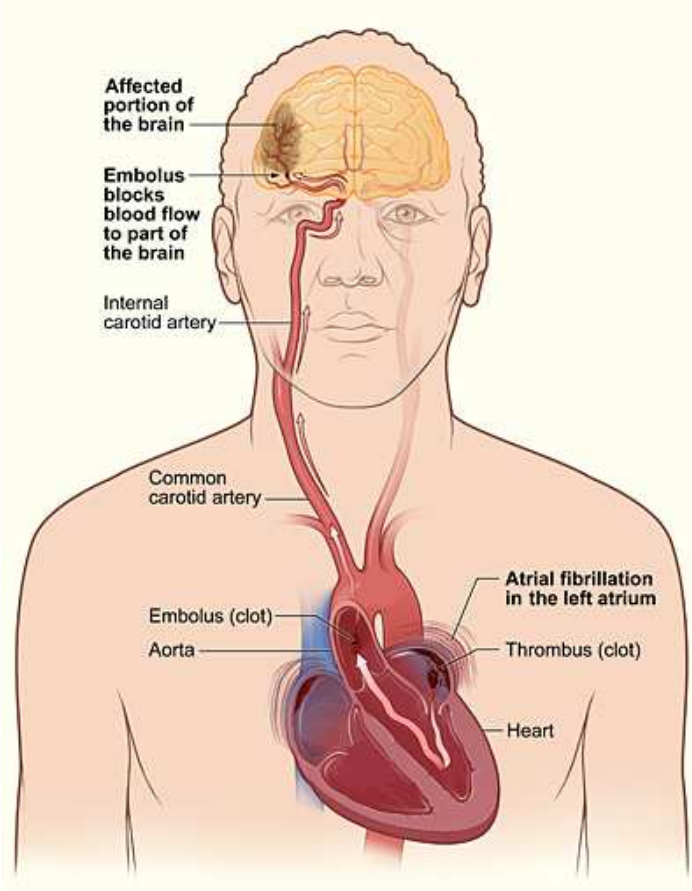
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Patient CASE

- 63 y - male with parox. AF, hypertension and DM
- EHRA class II, AF often during/after exercise
- No effect of flecainide/beta blockers referred PVI
- *“I am afraid of the stroke risk my GP talked about, can I still get that after this operation?”*
- *“Can I stop medical treatment after the operation?”*



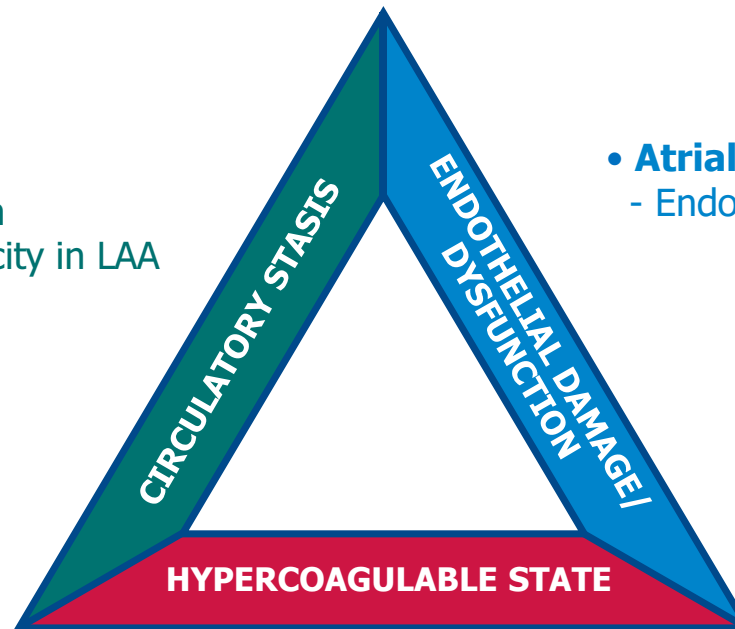
Ischemic Stroke in AF



AF and Thrombus Formation

Virchow's triad

- **Atrial fibrillation**
 - Stasis in left atrium
 - Reduced flow velocity in LAA



- **Atrial fibrillation**
 - Endocardial damage and dysfunction

- **Atrial fibrillation**
 - Increased thrombogenesis
 - Inflammation
 - Coagulation cascade activation

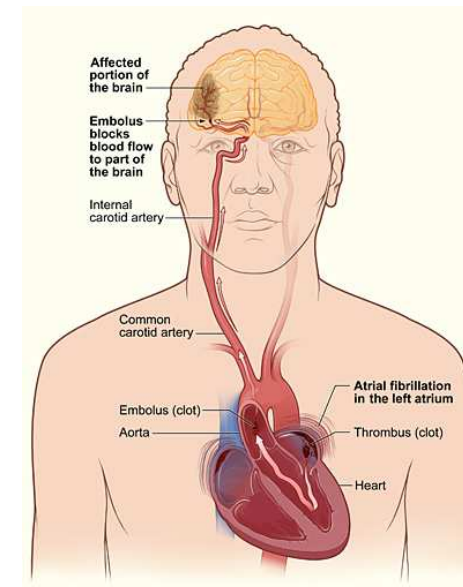
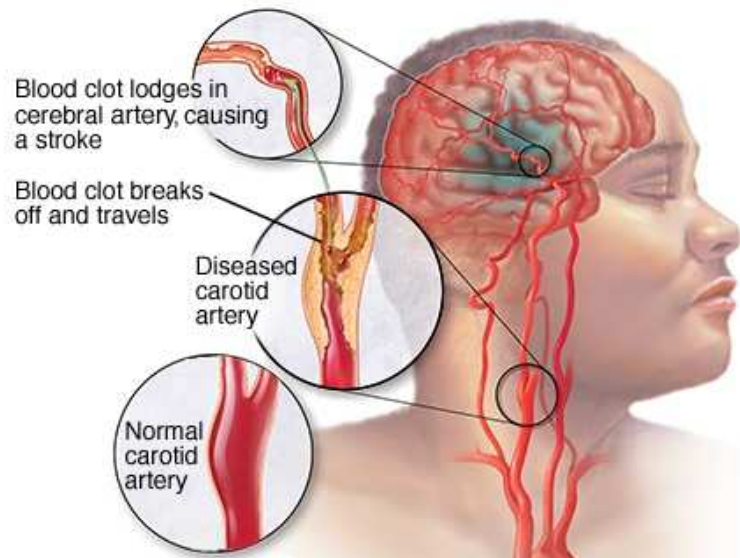
Adapted from Watson T et al. Lancet 2009;373:155–66



Other causes of Ischemic stroke in AF

- Up to 25% of ischemic strokes in AF is not LA thromboembolism:^{1,2}
 - Embolus from LV, through PFO/ASD or valve.
 - Atherosclerotic plaques.
 - Cerebrovascular disease.

1. AHA/ACC/ESC Guidelines. *Circulation* 2006;114:e257–354;
2. Bogousslavsky J et al. *Neurology* 1990;40:1046–50



Risk Factors of Stroke and AF

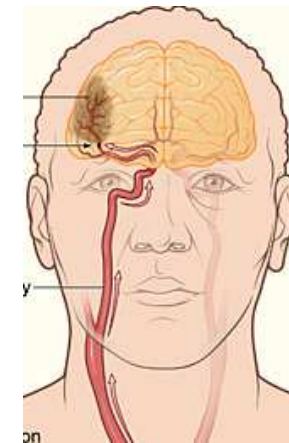
Heart failure

Vascular disease

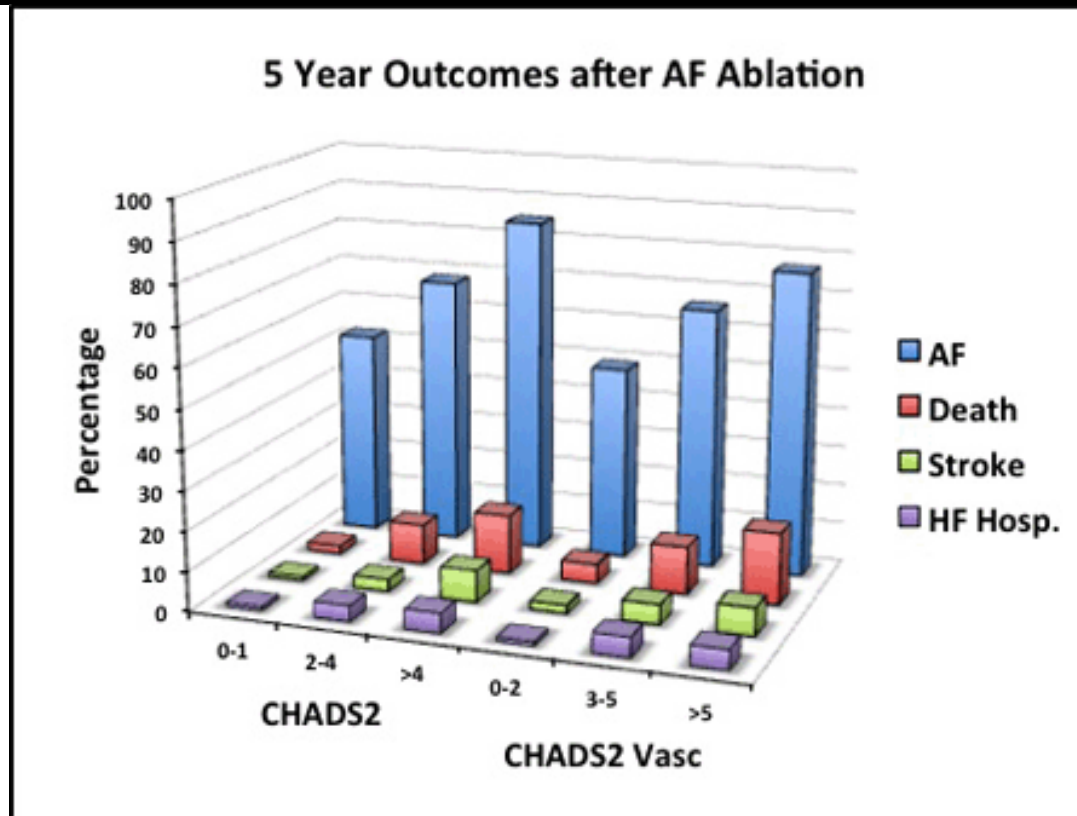
Hypertension

Diabetes

Obesity



Risk Factors of Stroke and AF



- Single center cohort
- 1st AF ablation
- 2179 patients

Jacobs V et al Heart Rhythm 2014



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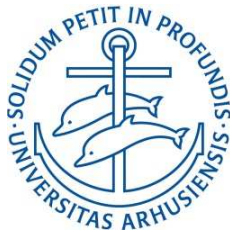
Modifying Stroke Risk Factors

- Congestive heart failure (maybe - antihypertensive drugs)
- Hypertension (antihypertensive drugs)
- Diabetes (metformin?, Semaglutide)
- Vascular disease (Antiplatelet and lipid reduction)
- Age ? Can you lower your risk score?
- Atrial fibrillation
 - RFA critical colleagues: “Just Botox?”

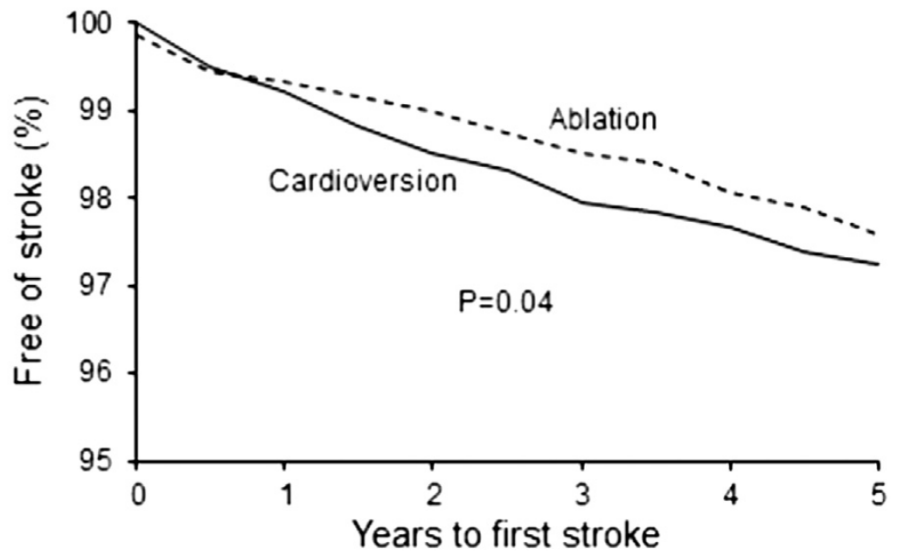


What can we expect?

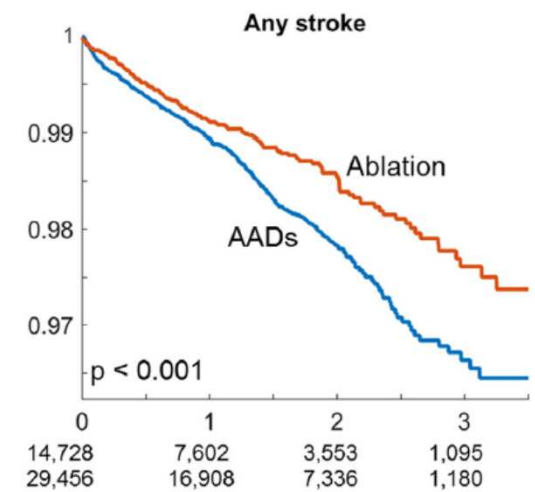
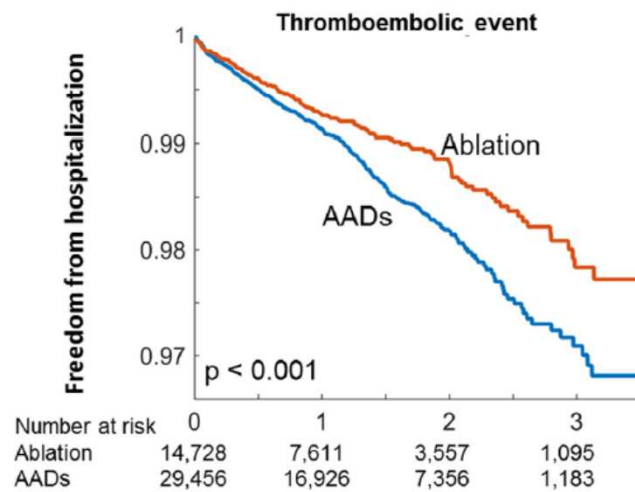
- If we eliminate AF we only reduce stroke rate by maximum 75%.
Incidence of 2%/y, RFA eliminate AF in 50 %,decrease incidence to 1,25%/y
- Same patients that have high recurrence and high stroke risk
 - Effective ablation – difficult in these patients
 - Complication – higher in these patients
- In some patients AF is the main cause of stroke and in others a “symptom” of other underlying causes.



Observational Data – Propensity Matched



No. at risk	0	1	2	3	4	5
Ablation	12,122	9,373	5,759	3,508	2,122	1,277
Cardioversion	12,122	9,095	5,432	3,231	1,985	1,163



CHA₂DS₂-VASc ≥ 2

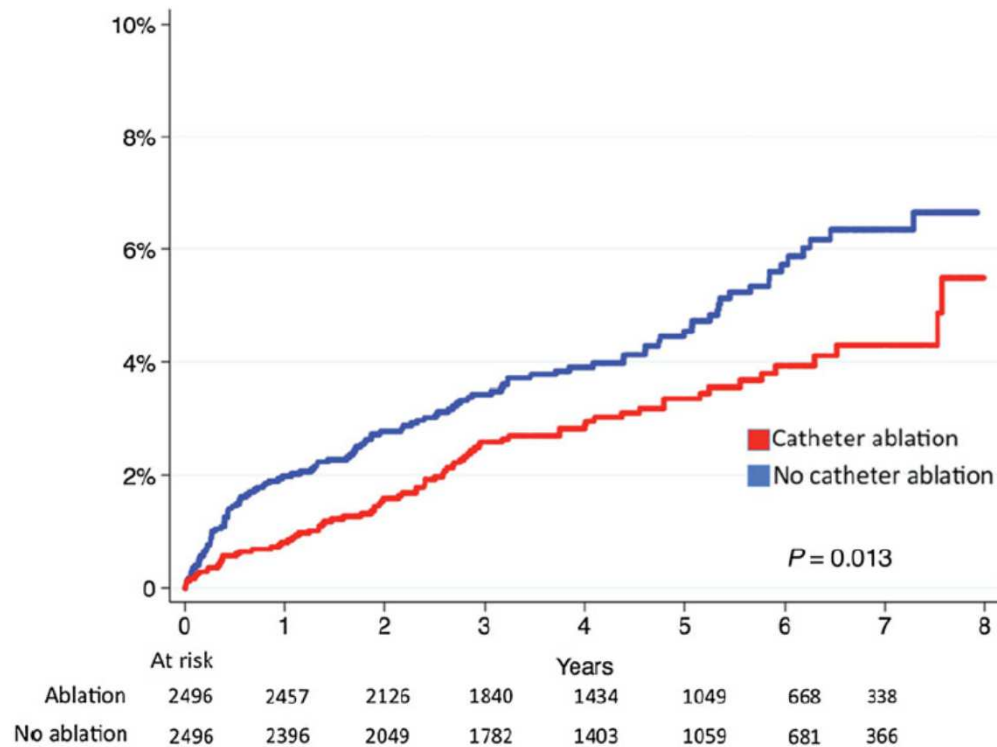
Noseworthy PA Heart Rhythm 2015

Mansour M et al Am j Cardiol 2018

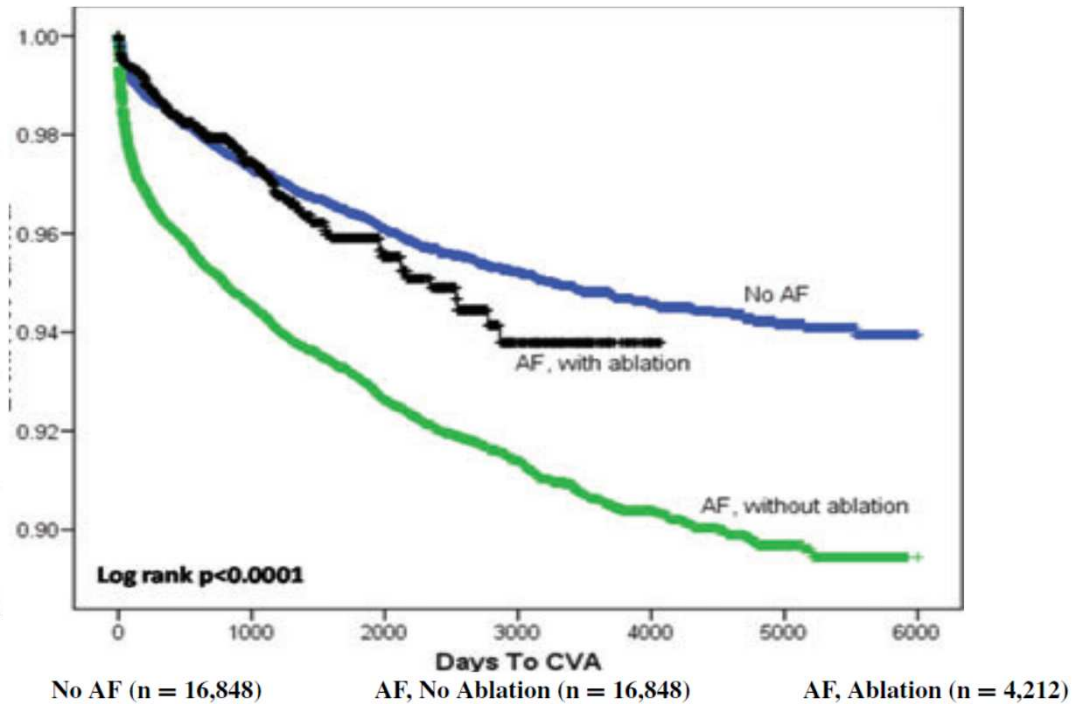


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Observational Data – Propensity Matched



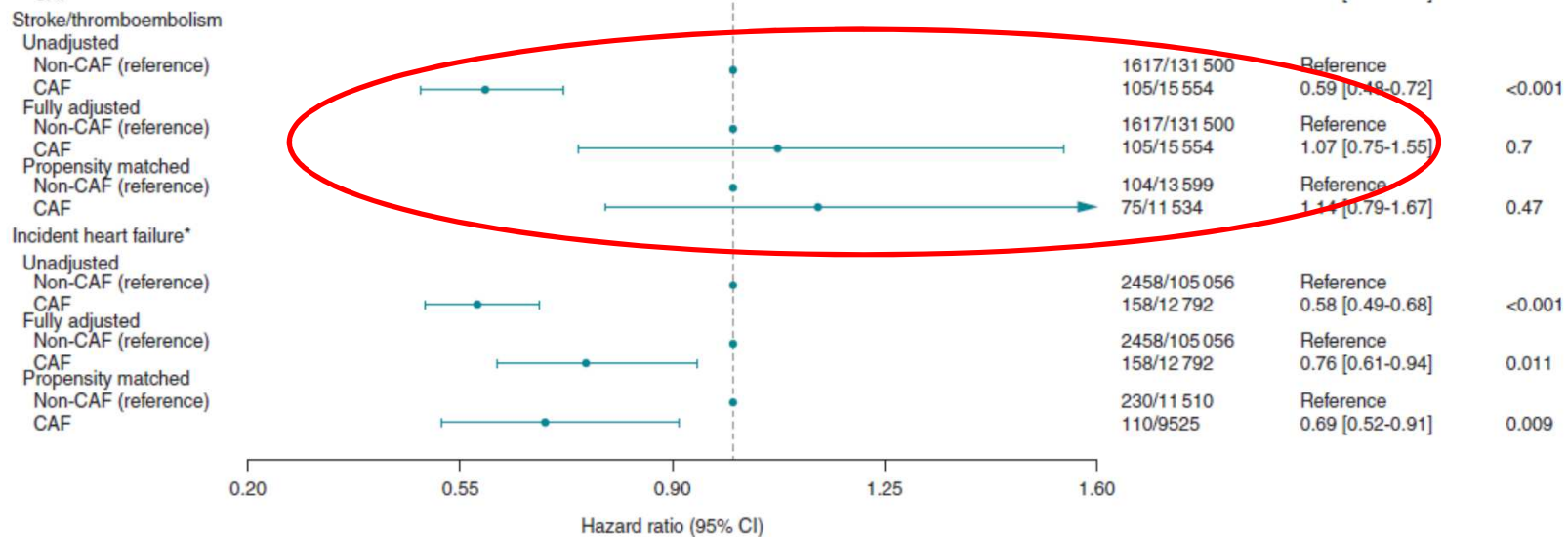
Frieberg L et al *European Heart Journal* 2016



Bunch TJ et al *J Cardiovasc. Electrophysiology* 2011

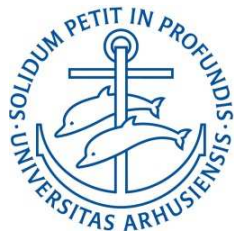


Observational Data – Propensity Matched



Modin D et al. *Europace* 2019

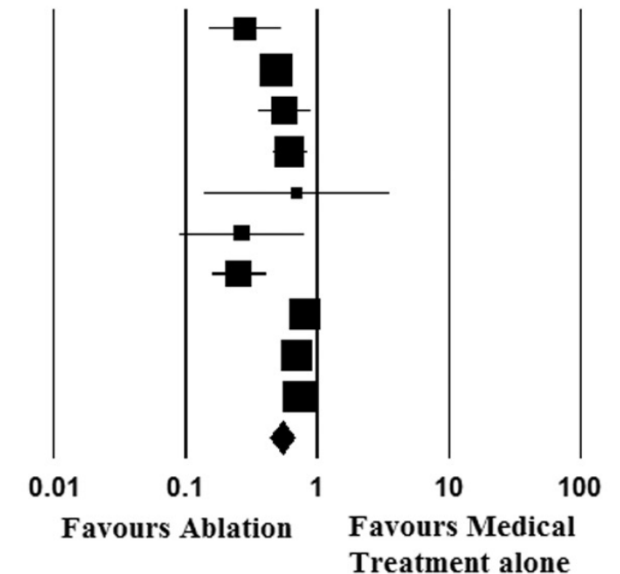
- Including patients undergoing 1st DC to balance type of AF
- Matched RFA vs No-RFA
- 2262:2261 patients



Earlier RCT and observational studies Ablation vs. ADD and Stroke Risk

OBSERVATIONAL STUDIES

		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Pappone et al 2003	Stroke or TIA	0.282	0.150	0.531	-3.927	0.000
Bunch et al 2011	Stroke or TIA	0.487	0.404	0.588	-7.495	0.000
Hunter et al 2011	Stroke or TIA	0.563	0.352	0.901	-2.396	0.017
Reynolds et al 2012	Stroke or TIA	0.616	0.455	0.835	-3.126	0.002
Blandino et al 2013	Stroke or TIA	0.703	0.138	3.581	-0.424	0.672
Lin et al 2013	Stroke or TIA	0.267	0.090	0.787	-2.393	0.017
Chang et al 2014	Stroke or TIA	0.254	0.158	0.408	-5.658	0.000
Noseworthy et al 2015	Stroke or TIA	0.807	0.646	1.008	-1.886	0.059
Friberg et al 2016	Stroke or TIA	0.696	0.524	0.925	-2.500	0.012
Saliba et al 2017	Stroke or TIA	0.725	0.585	0.899	-2.935	0.003
		0.540	0.431	0.676	-5.372	0.000



Meta analysis Barra S et al. Int J Cardiol 2018



CABANA and Stroke

	Events, No. (%)		Kaplan-Meier 4-Year Event Rate, %				
	Catheter Ablation Group (n = 1108)	Drug Therapy Group (n = 1096)	Catheter Ablation Group (n = 1108)	Drug Therapy Group (n = 1096)	Absolute Reduction	Hazard Ratio (95% CI) ^a	P Value
Disabling stroke	3 (0.3)	7 (0.6)	0.1	0.7	0.6	0.42 (0.11-1.62)	.19

	Disabling Stroke*	Any Stroke
Ablation Group (n=1108)		
≤30 days after ablation	0	4
>30 days after ablation	3	22
Never ablated (n=102)	0	1
Total	3	27
Drug Therapy Group (n=1096)		
≤30 days after initiating drug	1	3
>30 days after initiating drug	6	35
Never started drug therapy (n=4)	0	1
Total	7	39

Expected 4 y risk - 2,7% vs. 4,2 % - power of 90% N≈ **6500** pt.

NNT – 67 pt. reduce 1 stroke over 4 y.

Actual sample size and effects - **Power ≈ 50%**

“No difference in stroke rate RFA vs AAD”



Packer DL et al. JAMA 2019

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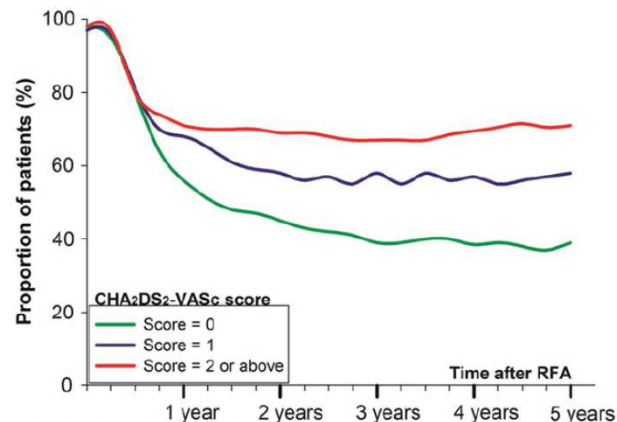
AF Ablation and Stroke Risk

- RCTs have not demonstrated risk reduction
 - Low power
 - Low risk population
- Most large observational studies indicates a risk reduction.
 - Propensity matched
 - Who get RFA?





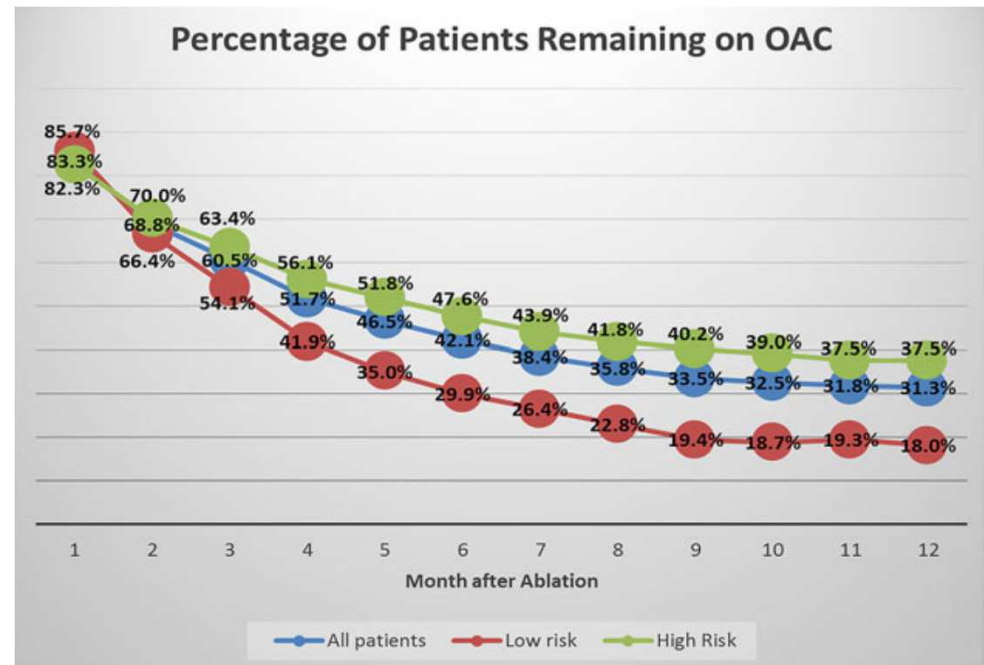
What do we do with OAC?



Number of patients under observation						
CHA ₂ DS ₂ -VASc score	1 year	2 years	3 years	4 years	5 years	
Score = 0	1275	644	484	386	335	281
Score = 1	1268	785	618	564	475	392
Score = 2 or above	1507	1047	944	846	744	655

Figure 1 Persistence in use of oral anticoagulation therapy after first-time radiofrequency ablation according to the CHA₂DS₂-VASc score: the proportion of patients receiving oral anticoagulation therapy by years.

Karasoy D et al. EHJ 2015



Noseworthy PA et al. JAHA 2015

20-40 % continues OAC without indication and 20-60 % stop OAC despite an indication



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Stroke Risk after PVI ±OAC

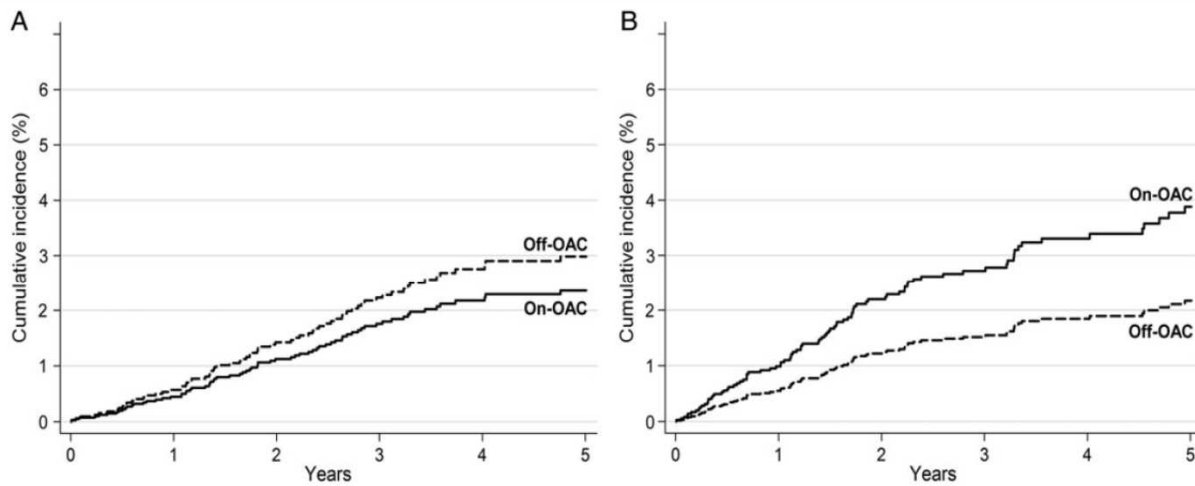


Figure 3 The cumulative incidences of thromboembolism and serious bleeding according to oral anticoagulation therapy. (A) Thromboembolism, adjusted for the components of CHA₂DS₂-VASc score and (B) serious bleeding, adjusted for the components of HAS-BLED score.

	On-OAC		Off-OAC	
	N	IR (95% CI)	N	IR (95% CI)
Thromboembolism	36	0.56 (0.40–0.78)	35	0.64 (0.46–0.89)
CHA ₂ DS ₂ -VASc = 0	8	0.50 (0.25–1.00)	13	0.51 (0.30–0.88)
CHA ₂ DS ₂ -VASc = 1	3	0.14 (0.05–0.44)	10	0.59 (0.32–1.10)
CHA ₂ DS ₂ -VASc ≥ 2	25	0.93 (0.63–1.38)	12	0.97 (0.55–1.71)
Serious bleeding	63	0.99 (0.77–1.27)	24	0.44 (0.29–0.65)
HAS-BLED ≤ 1	28	0.73 (0.51–1.07)	18	0.43 (0.27–0.69)
HAS-BLED = 2	23	1.31 (0.87–1.98)	4	0.40 (0.15–1.06)
HAS-BLED ≥ 3	12	1.45 (0.82–2.56)	2	0.60 (0.15–2.42)

N, number of events; IR, incid-years; HR, hazard ratio.

Nation wide danish register - 4050 patients from 3 mo. after 1st PVI

Karasoy D et al. EHJ 2015



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Stroke Risk after PVI ±OAC

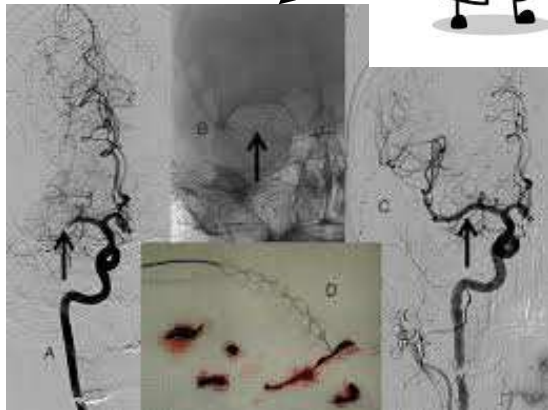
Table 2. Cardiovascular Events per Year of Follow-up After PVI

CHA ₂ DS ₂ -VASC Score	Events While Taking Warfarin Sodium, No. (% per Year)			Events While Not Taking Warfarin Sodium, No. (% per Year)		
	Ischemic Stroke	Intracranial hemorrhage	Death	Ischemic Stroke	Intracranial hemorrhage	Death
<2	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.1)
≥2	4 (0.3)	2 (0.2)	6 (0.5)	5 (1.6) ^a	0	3 (0.9)

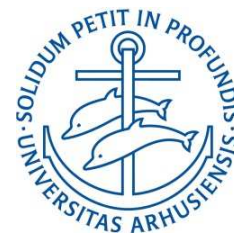
CHA2DS2-VASc score	Adjusted stroke rate %/ year
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Sjalander S et al. JAMA Cardiology 2017

6551 AF ablation - 4361 1st PVI - 1551 registered OAC (Wafarine)



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Stroke Risk after PVI ±OAC

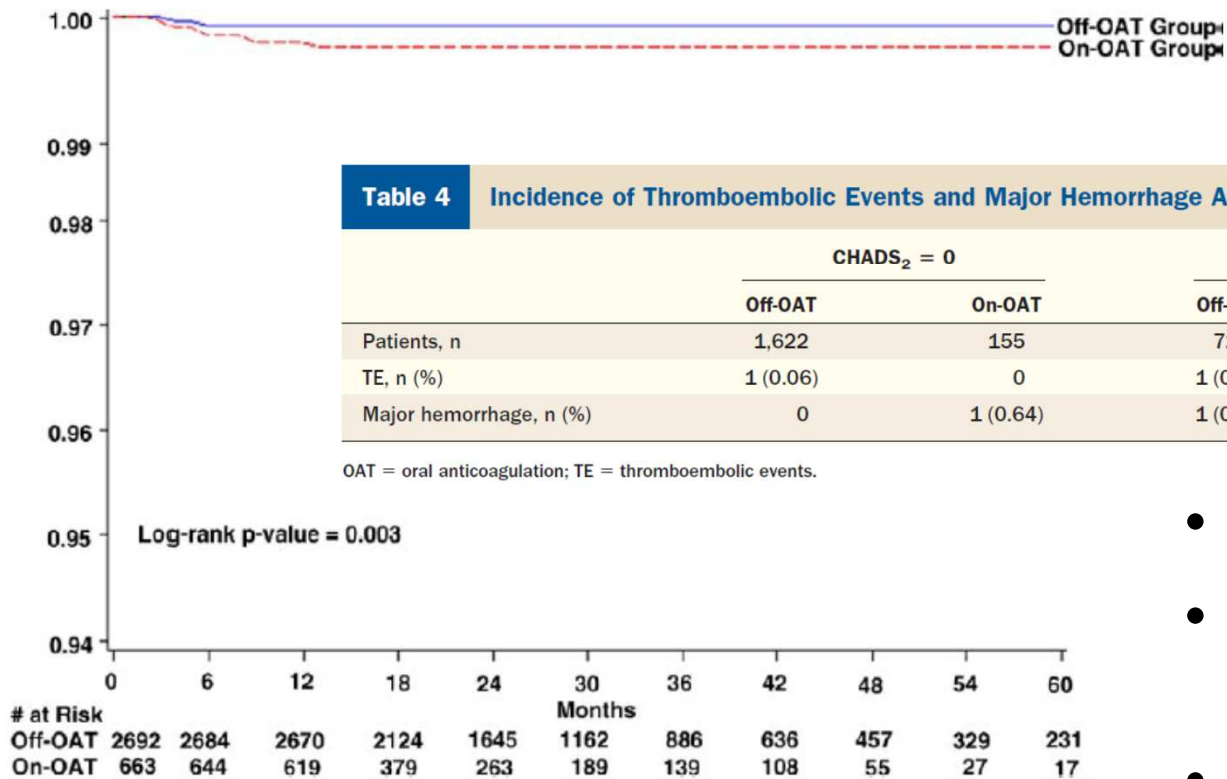


Table 4 Incidence of Thromboembolic Events and Major Hemorrhage According to CHADS₂ Score in Off- and On-OAT Groups

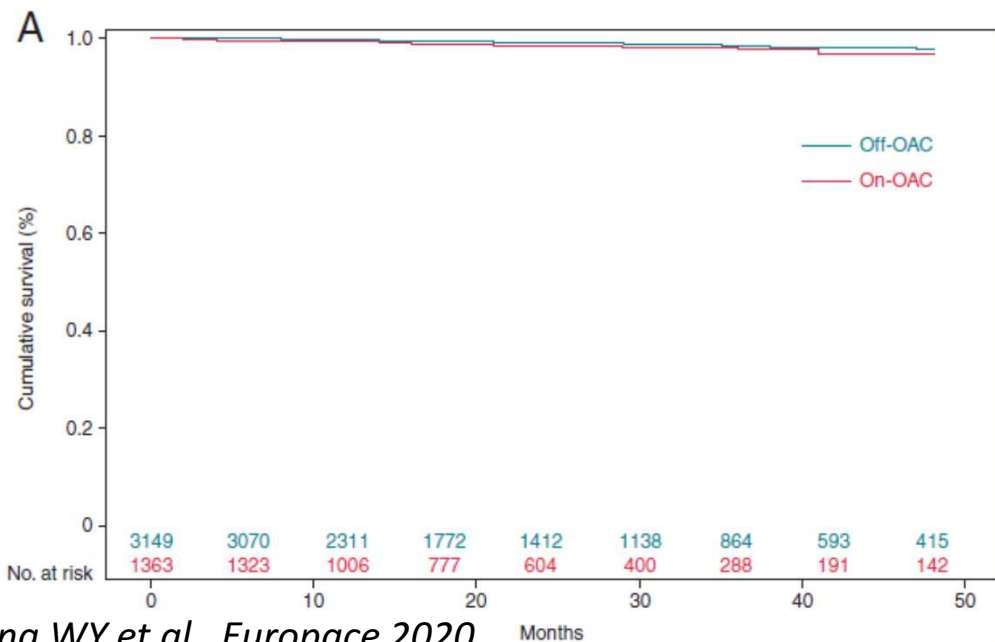
	CHADS ₂ = 0		CHADS ₂ = 1		CHADS ₂ ≥ 2	
	Off-OAT	On-OAT	Off-OAT	On-OAT	Off-OAT	On-OAT
Patients, n	1,622	155	723	261	347	247
TE, n (%)	1 (0.06)	0	1 (0.14)	1 (0.38)	0	2 (0.81)
Major hemorrhage, n (%)	0	1 (0.64)	1 (0.14)	2 (0.8)	0	10 (4)

- No AF recurrence
- Different FU strategy recurrence and endpoints
- OAC-off got antiplatelet

Themistoclakis et al. JACC 2010



Stroke Risk after PVI ±OAC



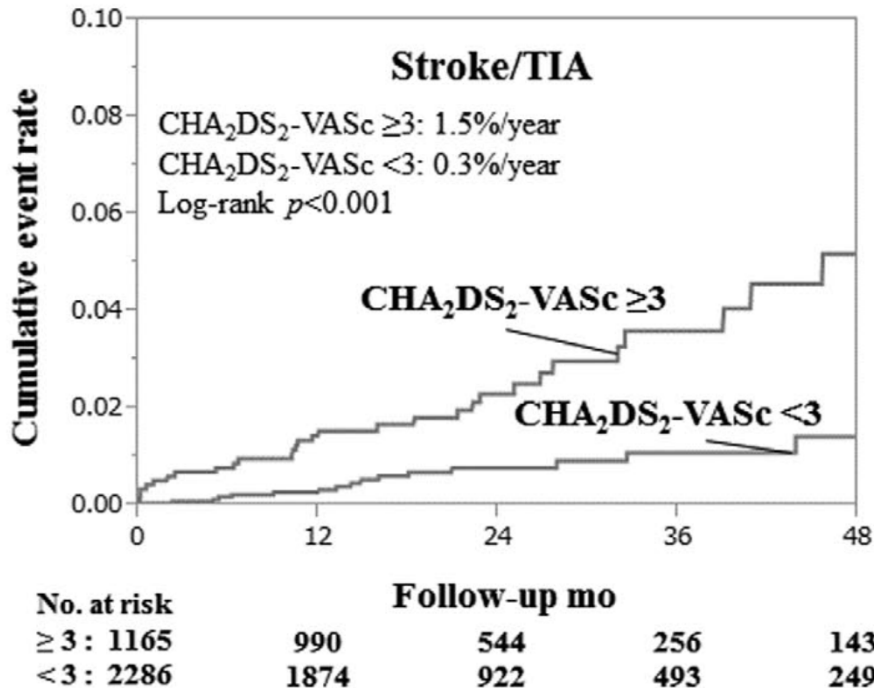
Yang WY et al. *Europace* 2020

- 3 mo. blanking 6 mo. free AF
- Censored at recurrence
- Repetitive 24 Holter
- ≈60% → antiplatelet
- Self-reported outcome
- Previous stroke and DM predictors

	Off-OAC	On-OAC
	Overall	Overall
	n IR (95% CI)	n IR (95% CI)
Thromboembolism ^a		
Intermediate-risk	10 0.36 (0.19–0.67)	3 0.35 (0.11–1.08)
High-risk	24 0.69 (0.46–1.03)	19 1.11 (0.71–1.74)
Major bleeding ^b		
Low-risk	4 0.13 (0.05–0.36)	3 0.29 (0.09–0.91)
Intermediate-risk	4 0.17 (0.06–0.44)	5 0.46 (0.19–1.11)
High-risk	4 0.44 (0.17–1.18)	1 0.21 (0.03–1.48)



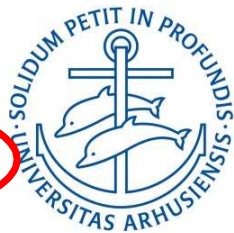
Stroke Risk after PVI OAC vs. CHA₂DS₂-VASc



- Multicenter AF Register
- 3541 pt.
- 53 % stopped OAC

	Stroke/TIA			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (+1 year)	1.06 (1.03–1.10)	0.003	1.03 (0.99–1.07)	0.16
Female	0.94 (0.48–1.72)	0.85		
BMI (+1 kg/m ²)	1.00 (0.92–1.00)	0.92		
AF type				
Paroxysmal	Ref.		Ref.	
Persistent	1.07 (0.54–2.00)	0.64	0.91 (0.45–1.73)	0.76
Long-standing persistent	3.38 (1.55–6.76)	0.003	3.07 (1.31–6.63)	0.012
Ablation sessions ≥2	1.54 (0.63–3.24)	0.32		
Comorbidities				
Hypertension	2.01 (1.11–3.85)	0.020		
Diabetes	1.73 (0.89–3.16)	0.11		
Heart failure	2.17 (1.15–3.90)	0.019		
Stroke/TIA	2.09 (0.91–4.22)	0.08		
Vascular disease	2.46 (1.20–4.64)	0.015		
CHA ₂ DS ₂ -VASc	1.44 (1.24–1.68)	<0.001	1.31 (1.06–1.60)	0.015
Echocardiography variables				
LVEF (+1%)	0.99 (0.96–1.02)	0.40		
LAd (+1 mm)	1.06 (1.02–1.10)	0.006	1.04 (0.99–1.08)	0.12
Post-ablation therapy				
Warfarin (vs. DOAC)	1.40 (0.76–2.51)	0.28		
Antiplatelet therapy	1.15 (0.40–2.63)	0.78		
AAD use	1.25 (0.69–2.19)	0.45		
Hb (mg/dL)	0.85 (0.71–1.01)	0.07		
CrCl (mL/min)	0.99 (0.98–1.00)	0.11		
AF recurrence	1.34 (0.76–2.34)	0.31		
OAC discontinuation	0.44 (0.24–0.78)	0.004	0.74 (0.39–1.35)	0.32

Okumure Y et al. Circulation J 2019



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Stroke Risk after PVI ±OAC

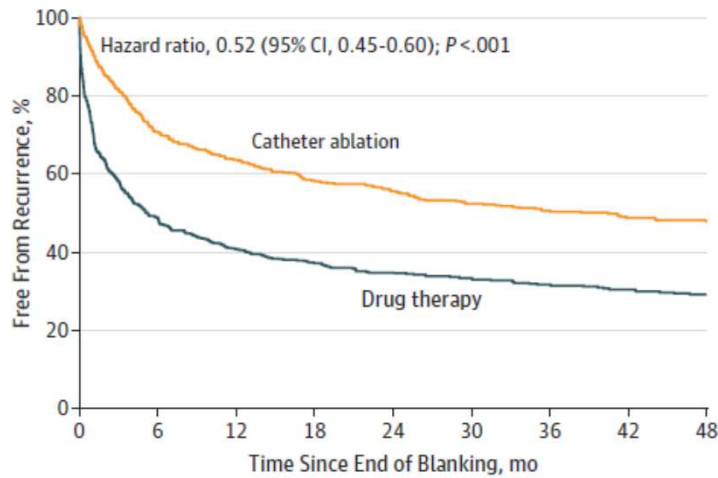
- Ranging from
 - Low risk off-OAC 0.1 – 0.5 %/Y
 - High risk off-OAC 0.0 – 1.6 %/Y

CHADS2 score	Adjusted stroke rate % / year	CHA2DS2-VASc score	Adjusted stroke rate % / year
0	1.9	0	0
1	2.8	1	1.3
2	4.0	2	2.2
3	5.9	3	3.2
4	8.5	4	4.0
5	12.5	5	6.7
6	18.2	6	9.8
		7	9.6
		8	6.7
		9	15.2

- Observational multicenter studies or registers
- AF recurrence? Different monitoring strategies.
- Most on 1st time PVI
- Some are taking clopidogrel/aspirin anyway - *why not continue with NOAC?*



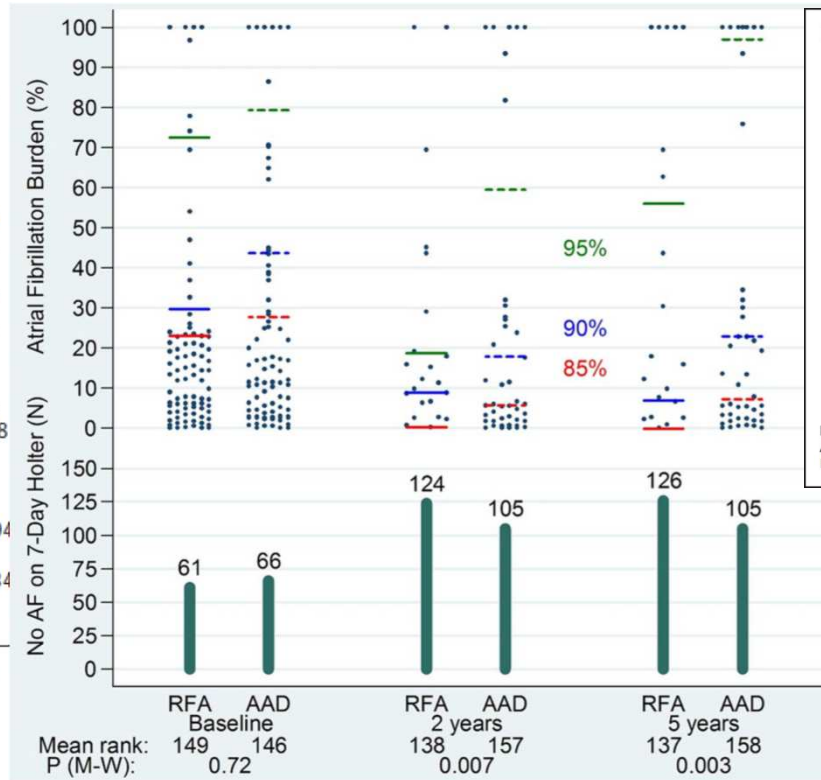
Effect of Ablation on AF Burden



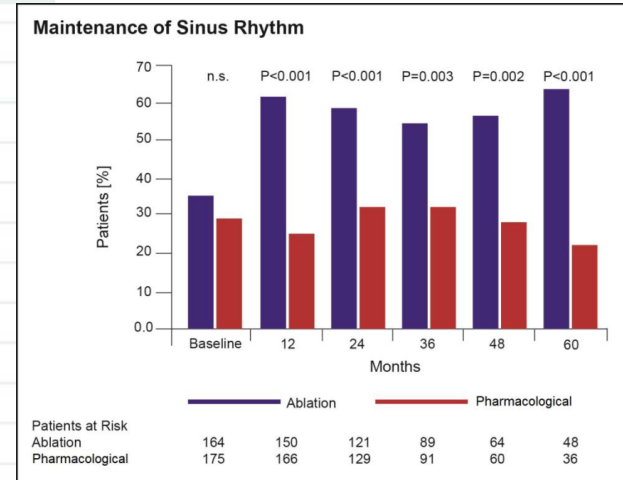
No. at risk	0	6	12	18	24	30	36	42	48
Drug therapy	629	304	252	212	181	157	131	115	94
Catheter ablation	611	432	381	328	291	241	201	163	134

Freedom from recurrence of atrial fibrillation following the blanking period in 1240 patients who used the study electrocardiogram event recorders

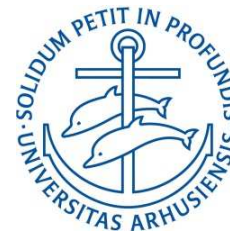
CABANA Packer DL et al. JAMA 2019



MANTRA-PAF 5y FU Nielsen JC et al. JAMA 2017



Marrouche N et al. NEJM 2018



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Continuous monitoring

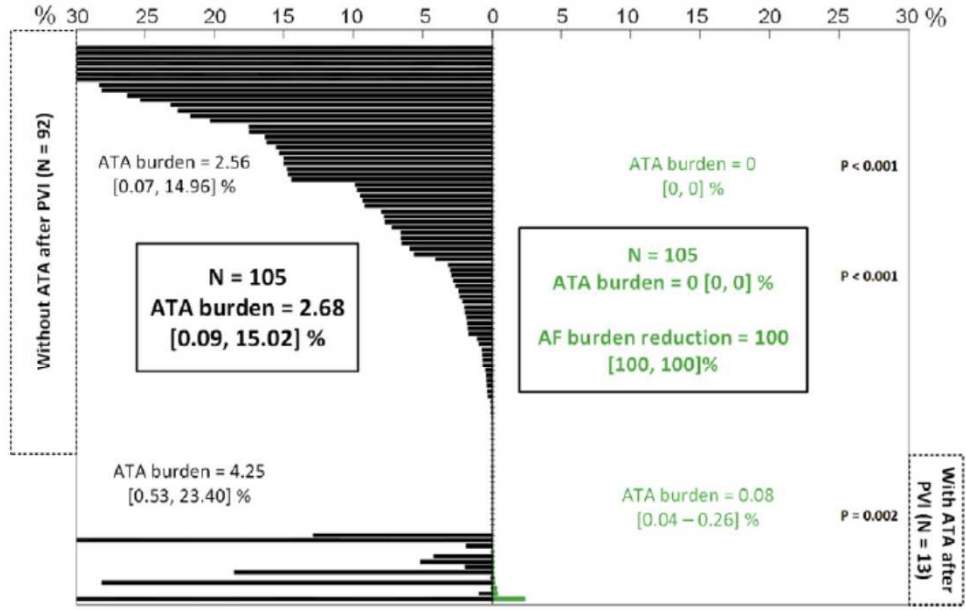
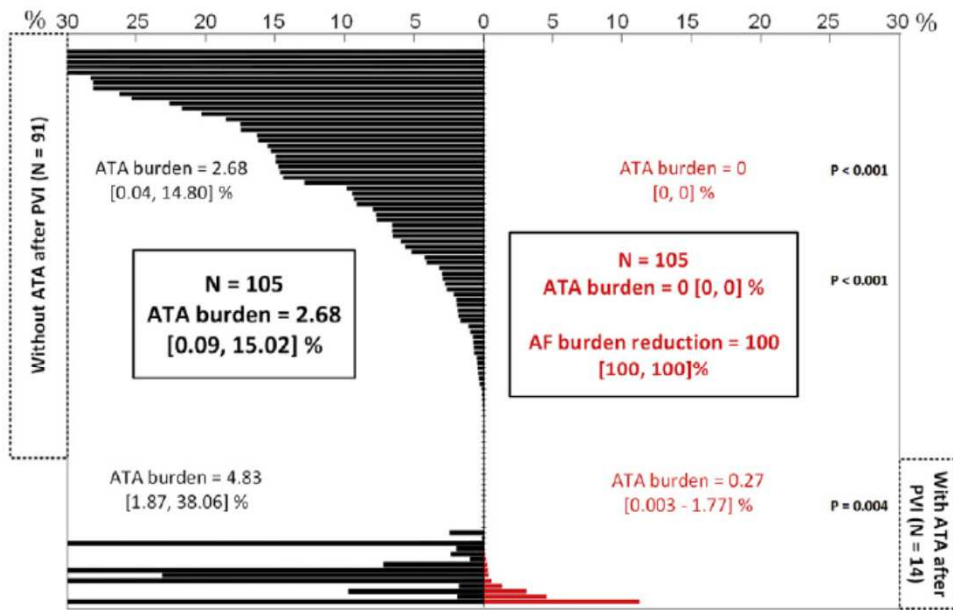
ATA burden before and after PVI in all patients (n=105)

% of time spent in ATA before PVI (65 [61, 78] monitoring days)

% of time spent in ATA during 3-12 months after PVI (270 [270, 270] monitoring days)

% of time spent in ATA before PVI (65 [61, 78] monitoring days)

% of time spent in ATA during 12-24 months after PVI (360 [360, 360] monitoring days)

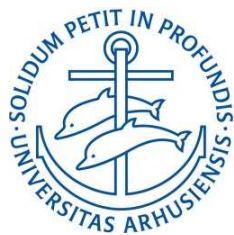
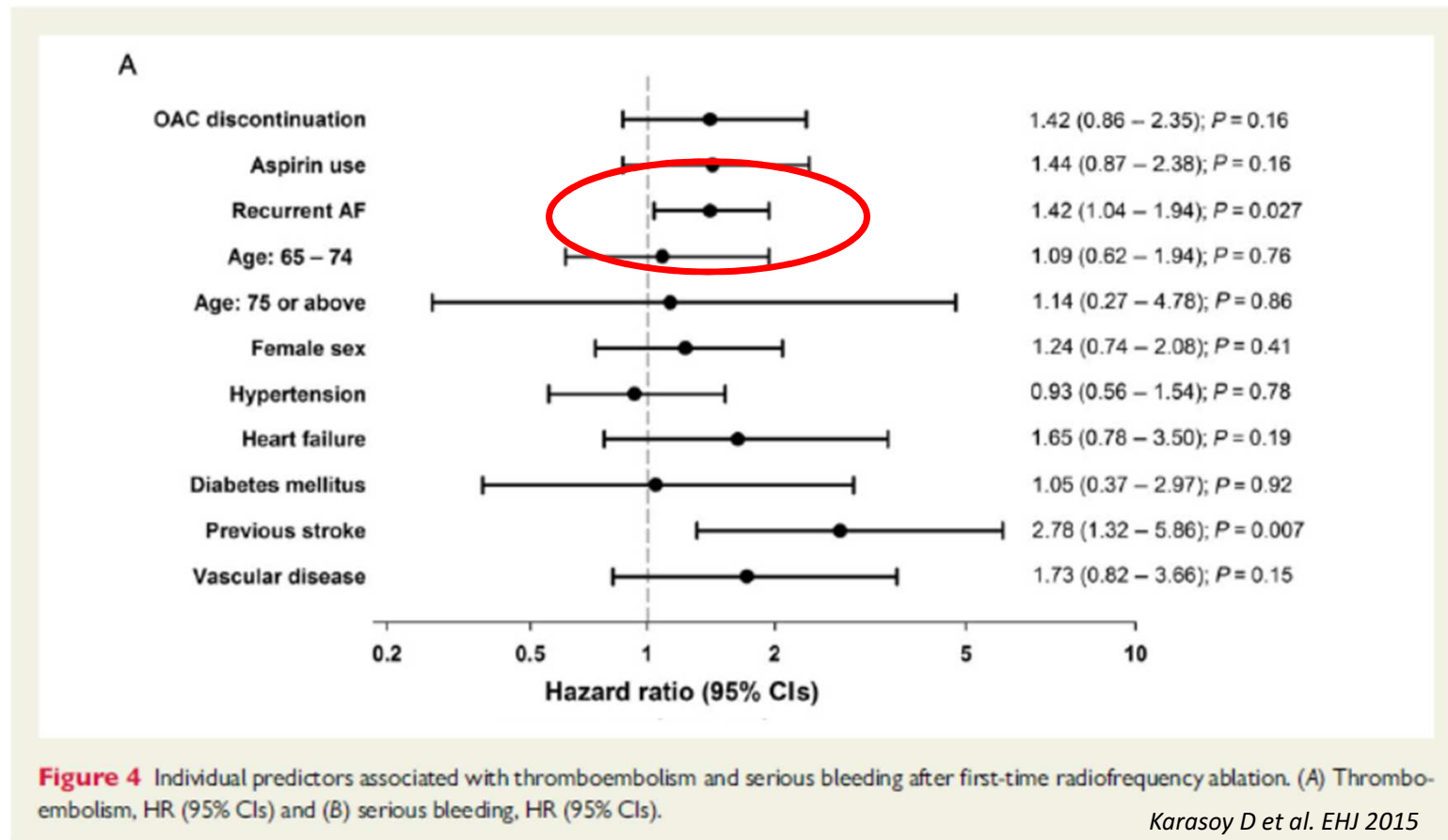


Close to Cure Duytschaever M et al. Heart Rhythm 2019



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Stroke Risk - AF Recurrence



Stroke Risk - AF Recurrence

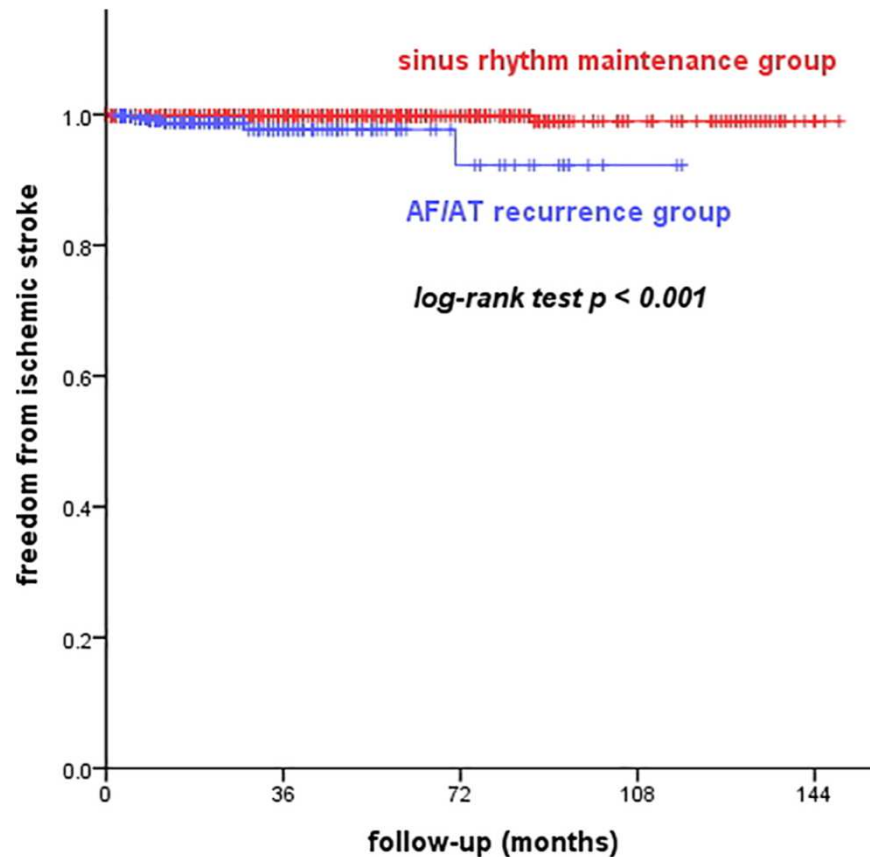


Table 3. Distribution of ischerece and SR maintenance groups.

CHA ₂ DS ₂ -VASc	AF recurrence (n = 619)		SR maintenance (n = 929)	
	Patients	Events	Patients	Events
0	228	2 (0.9)	439	1 (0.2)
1	205	4 (1.9)	287	0
2	113	0	115	0
3	45	0	65	0
4	18	0	18	1 (5.5)
5	9	1 (11.1)	4	1 (25.0)
6	1	0	1	0
≥7	0	0	0	0
Total	619	7 (1.1)	929	3 (0.3)

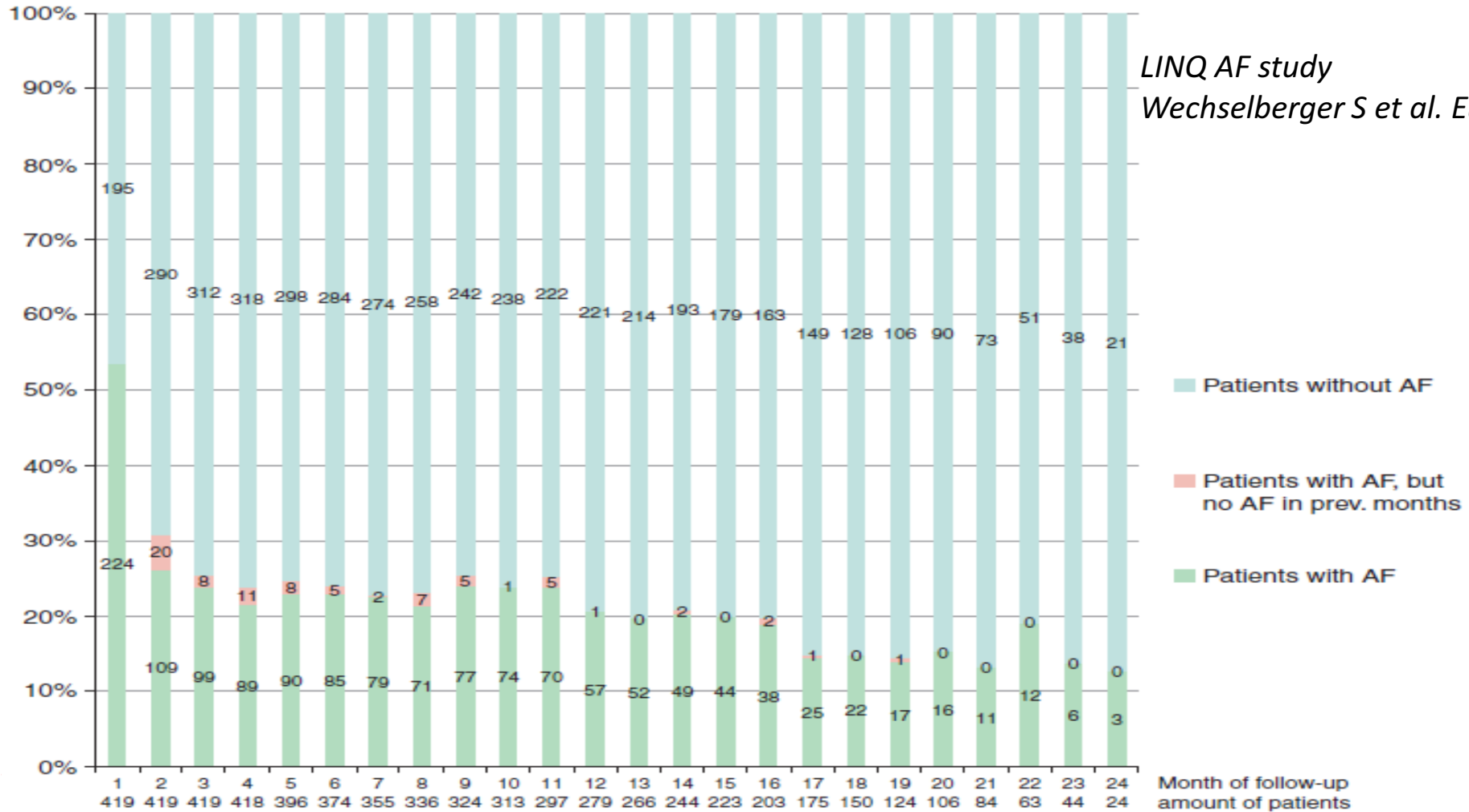
Kim DH et AL PLOsone 2018



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Continuous monitoring

LINQ AF study
Wechselberger S et al. Europace 2018



Month of follow-up
amount of patients



EMB

Continuous monitoring to guide OAC

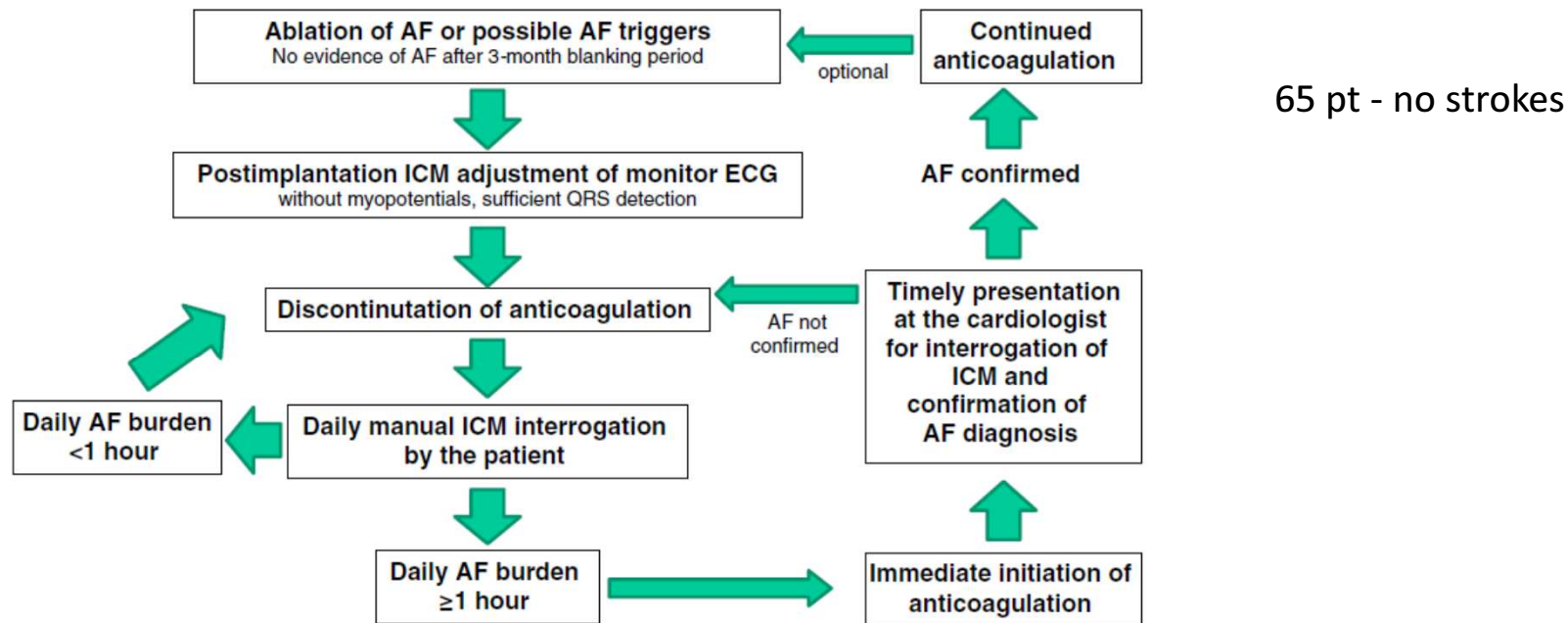
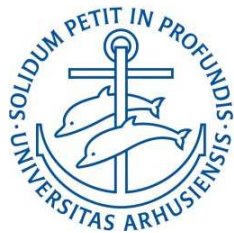


Figure 1. Flow-chart of patient selection and follow-up. AF = atrial fibrillation; ECG = electrocardiogram; ICM = implantable cardiac monitor.

Zuern C et al. PACE 2015



EMB 2020

Risk of TE with Device detected AF

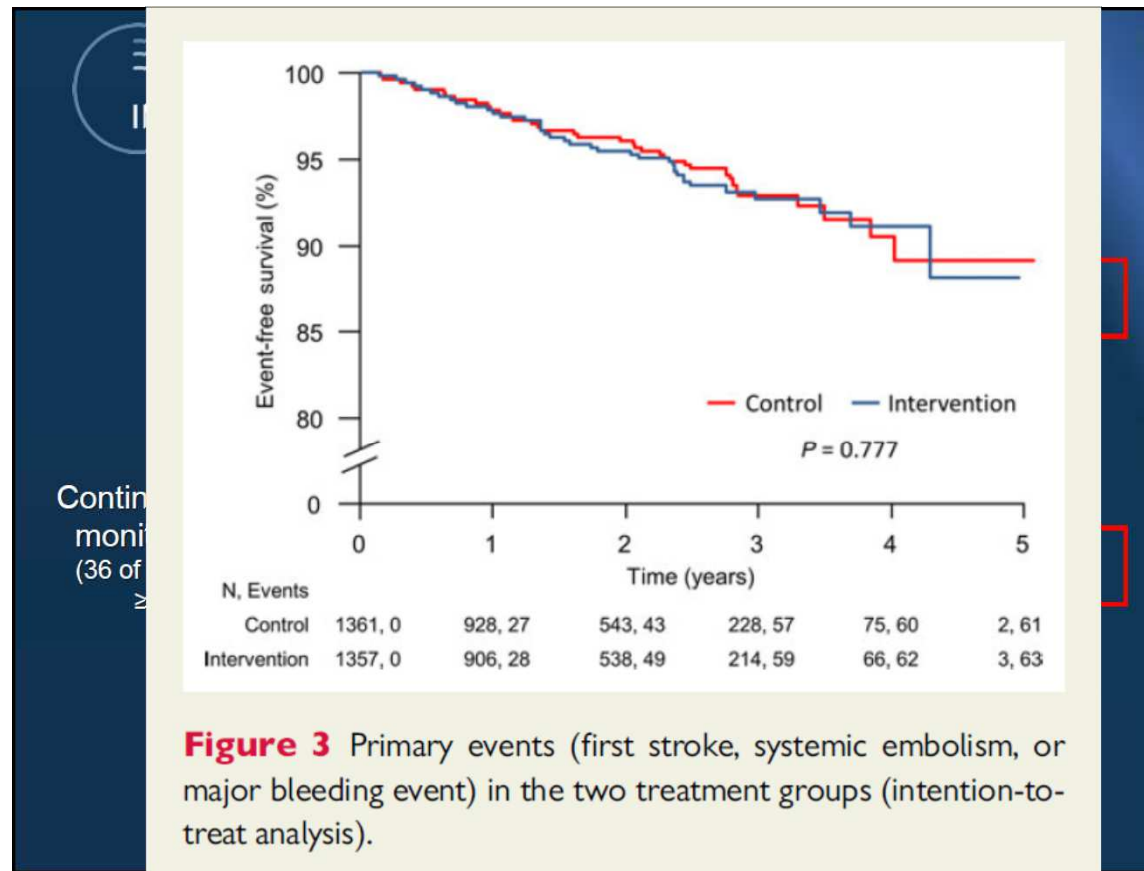
- From RE-LY, ARISTOTLE, ENGAGE AF TIMI48
- Ischemic stroke 0.9-1,2 %/yr (5% placebo)
- Intracranial bleeding 0.3-0.8 %/yr

Duration	TE %/yr (95% CI)	TE %/yr
0	0.69	0.69
≤0.86 h	1.23 (0.15 to 4.46)	
0.87 to 3.63 h	0 (0 to 2.08)	0.62
3.64 to 17.72	1.18 (0.14 to 4.28)	0.80
>17.72 h	4.89 (1.96 to 10.07)	

CHA ₂ DS ₂ -VASc score	Patients (n= 7329)	Adjusted stroke rate (%/year) ^b
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%



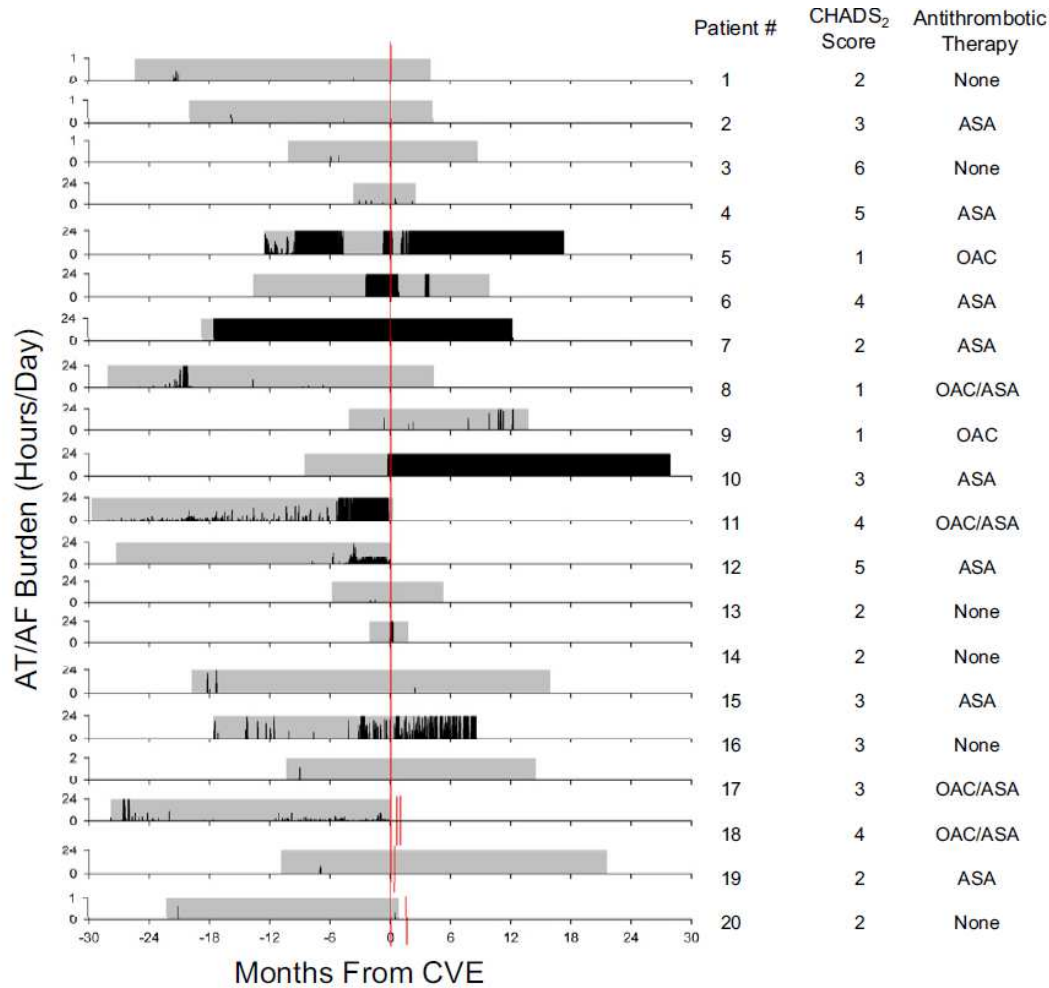
Start Stop Strategy



Martin D et al. European Heart Journal 2015



Timing of Stroke and AF

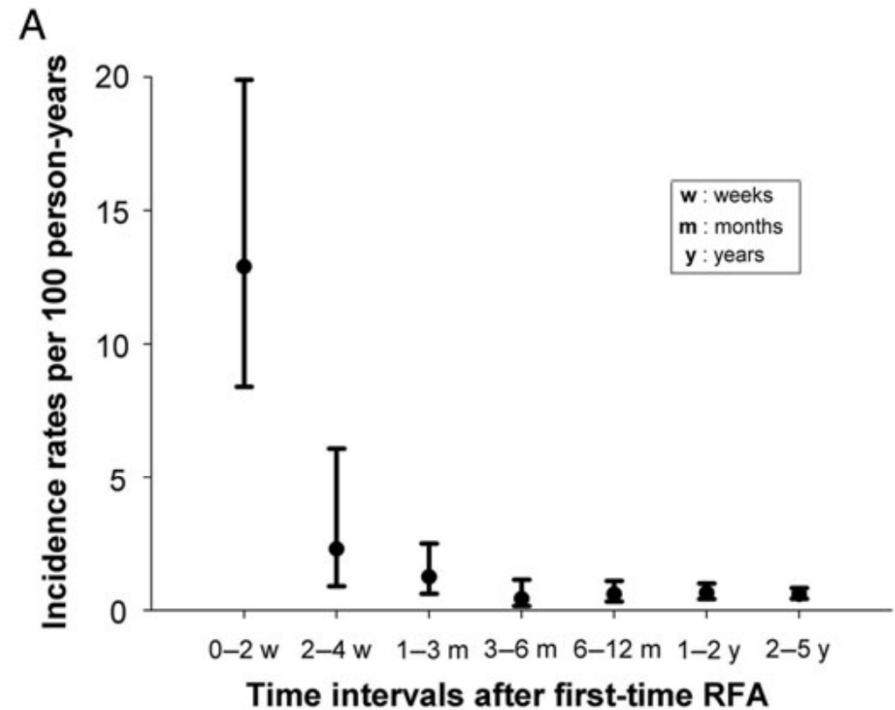


Daoud et al. HR 2011



Future studies OCEAN

- 1572 pt.
- 1 y after AF ablation
- No AF on 2-3 24h-Holter
- Rivaroxaban vs Aspirin
- CHA₂DS₂-VASc ≥ 1
- Stroke, embolism, or MR lesion >15 mm



Incidence rates	12.9	2.30	1.25	0.43	0.60	0.65	0.60
95% lower CI	8.35	0.86	0.63	0.16	0.34	0.42	0.43
95% upper CI	20.0	6.11	2.50	1.15	1.10	1.00	0.83
Number of events	20	4	8	4	11	20	36
Person-years	154	174	639	926	1809	3092	5995

Take Home Messages

- No well powered RCT have tested if AF ablation reduces the risk of stroke!
We can not conclude that it does or doesn't
- After RFA - **lower** stroke risk with **similar risk scores** ± OAC!
- Association between recurrence and risk of stroke
 - Device detected AF - lower risk of stroke with similar risk scores.
- Re-evaluate OAC ≥3-12 months after AF ablation
 - CHA₂DS₂-VASc <2 stop OAC
 - CHA₂DS₂-VASc ≥2 discuss risk with patient - CHA₂DS₂-VASc 2-3 and SR stop OAC
 - Periodic and continuous AF monitoring adds information – *know your population!*

Detailed Registers on Follow-up AND well powered RCT!!!!!!

