Ne Yapalım? CHADS2VASC Skoru 5 olan ve Serebral Kanama Geçirmiş Hasta

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Ankara Yüksek İhtisas Hastanesi
Kardiyoloji Kliniği

Atriyal Fibrilasyonda Antikoagülasyon ve Serebral Kanama

- AF'da antikoagülan tedavi altındayken serebral kanama riski %0,3-3/yıl

- %45 ölüm, sadece %17 sekel olmadan iyileşiyor.

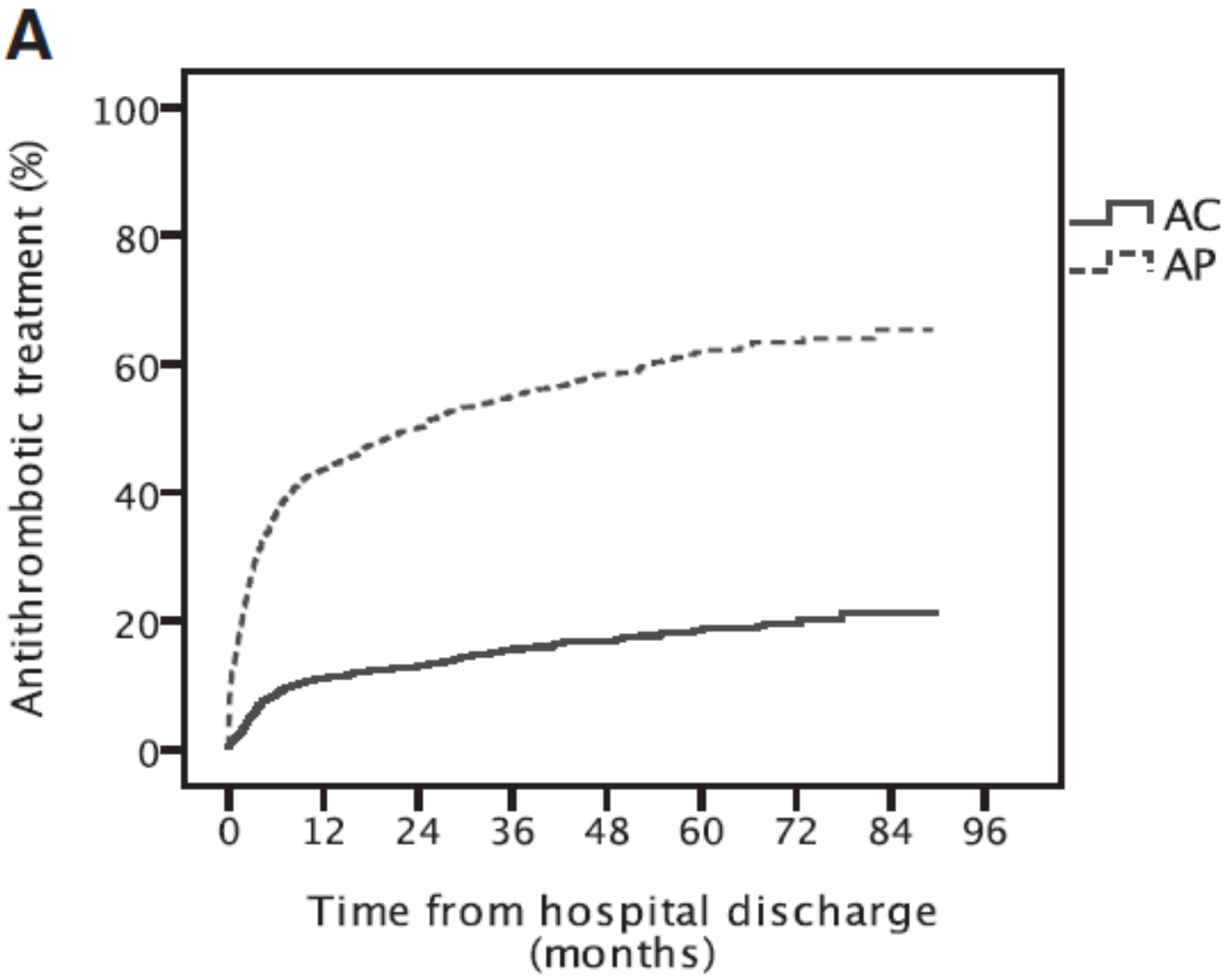
- Varfarin ilişkili kanamalarda mortalitenin >%90 nedeni serebral kanamadır. Sekellerin tümüne yakını serebral kanamaya sekonderdir.

- Kanamaların >%50'sinde INR <4

- Antikoagülan tedavinin bırakılmasının veya hiç başlanmamasının en önemli nedenlerindendir.

Antikoagülasyona Bağlı Serebral Kanamada Sorunlar

- Mortalite riski yüksek
- Hastalar yaşlı
- Hematom ekspansiyon riski yüksek ve süresi uzun
- Rekürren kanama riski yüksek (%1,7-3,7/yıl)



Stroke. 2015;46:2094-2099.

CHA_2DS_2-VASc Risk Criteria		Points	Total Score	Annual Stroke Risk (%)
C	CHF or left ventricular systolic dysfunction	1	0	0
H	Hypertension	1	1	1.3
A_2	Age ≥75 y	2	2	2.2
D	Diabetes mellitus	1	3	3.2
S_2	(Prior) Stroke or transient ischemic attack	2	4	4.0
V	Vascular disease[a]	1	5	6.7
A	Age 65-74 y	1	6	9.8
Sc	Sex category (i.e., female sex)	1	7	9.6
			8	6.7
			9	15.2

Anticoagulation therapy in atrial fibrillation after intracranial hemorrhage

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BACKGROUND The effect of oral anticoagulation therapy (OAT) in patients with atrial fibrillation (AF) with a history of intracranial hemorrhage (ICH) is poorly defined.

OBJECTIVE The purpose of this study was to evaluate the efficacy and safety of OAT in patients with AF with an ICH history.

METHODS We retrospectively compared the composite end point, including thromboembolic and major bleeding events, between patients with AF with a history of ICH who were (OAT group, n = 254) and those who were not (no-OAT group, n = 174) taking OAT.

RESULTS During a mean follow-up of 39.5 ± 31.9 months, 5.5 and 3.1 major bleeding events/100 patient-years were observed in the OAT and no-OAT groups, respectively ($P = .024$). Recurrent ICH was observed only in patient with OAT. Thromboembolic events occurred in 2.4 and 8.3 events/100 patient-years in OAT and no-OAT groups, respectively ($P < .001$). There was no significant differences in composite end points between OAT and no-OAT groups (11.5 events/100 patient-years vs 7.9 events/100 patient-years; $P = .154$). Patients with OAT who achieved a time-in-therapeutic range of ≥60% of the international normalized ratio of 2.0–3.0 demonstrated a better cumulative survival free of the composite end point ($P < .001$) than did patients without OAT. Early (<2 weeks) OAT after an index ICH did not improve composite end points because of the increased incidence of major bleeding events. However, OAT at 2 weeks after an index ICH was associated with decreased clinical events including thromboembolic events and composite end point.

CONCLUSION In patients with AF who require anticoagulation and have a history of ICH, maintaining optimal OAT with time-in-therapeutic range ≥ 60% and the initiation of OAT at least 2 weeks after an index ICH were associated with improved clinical outcomes

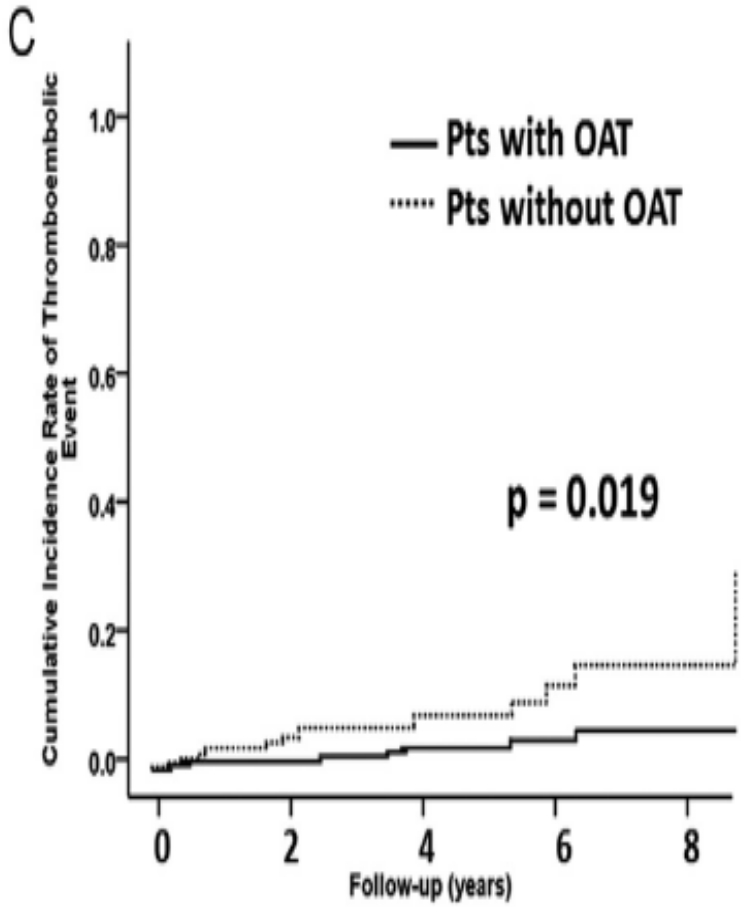
KEYWORDS Intracranial hemorrhage; Bleeding; Thromboembolic events; Anticoagulation; Atrial fibrillation

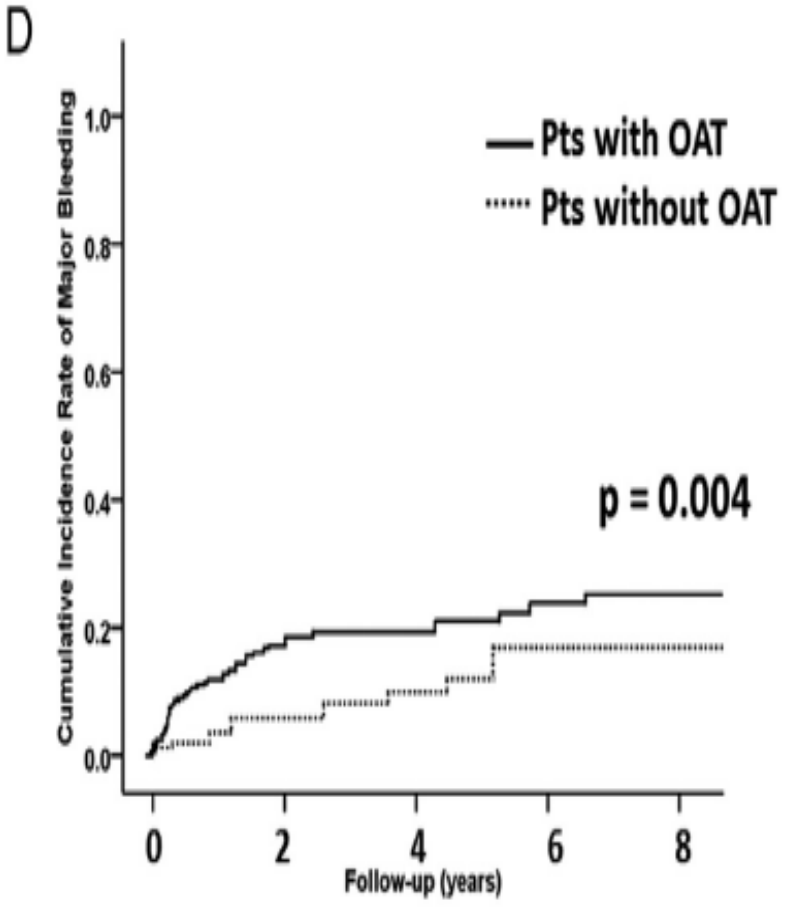
(Heart Rhythm 2016;13:1794–1802)

Table 2 Number (percentage) and incidence of clinical end points

Variable	OAT (n = 254)	No OAT (n = 174)	*P*
Composite end point	65 (25.6)	45 (25.9)	1.000
Events/100 patient-years	7.9	11.5	.154
Death	13 (5.1)	22 (12.6)	.007
Events/100 patient-years	1.4	4.8	< .001
Thromboembolic event	9 (3.6)	17 (9.8)	.012
Events/100 patient-years	2.4	8.3	< .001
Ischemic stroke	7 (2.8)	14 (8.0)	.021
Events/100 patient-years	0.8	3.3	< .001
Pulmonary thromboembolism	1 (0.4)	1 (0.6)	1.000
Events/100 patient-years	0.1	0.2	.548
Peripheral arterial embolism	1 (0.4)	1 (0.6)	1.000
Events/100 patient-years	0.1	0.2	.680
LV thrombus	0 (0)	1 (0.6)	.407
Events/100 patient-years	0	0.2	.169
Major bleeding event	46 (18.1)	13 (7.5)	.002
Events/100 patient-years	5.5	3.1	.024
Gastrointestinal tract infection	23 (9.0)	13 (7.5)	.600
Events/100 patient-years	2.6	3.1	.833
Recurrent CNS bleeding	13 (5.1)	0 (0)	.002
Events/100 patient-years	1.4	0	.006
Genitourinary tract infection	4 (1.6)	0 (0)	.150
Events/100 patient-years	0.4	0	.121
Hemoptysis	1 (0.4)	0 (0)	1.000
Events/100 patient-years	0.1	0	.560
Hematoma	1 (0.4)	0 (0)	1.000
Events/100 patient-years	0.1	0	.484
Hemoperitoneum	4 (1.6)	0 (0)	.150
Events/100 patient-years	0.4	0	.148

CNS = central nervous system; LV = left ventricle; OAT = oral anticoagulation therapy.


C
Cumulative Incidence Rate of Thromboembolic Event
1.0
0.8
0.6
0.4
0.2
0.0
Pts with OAT
Pts without OAT
p = 0.019
0
2
4
6
8
Follow-up (years)


D
Cumulative Incidence Rate of Major Bleeding
1.0
0.8
0.6
0.4
0.2
0.0
Pts with OAT
Pts without OAT
p = 0.004
0
2
4
6
8
Follow-up (years)

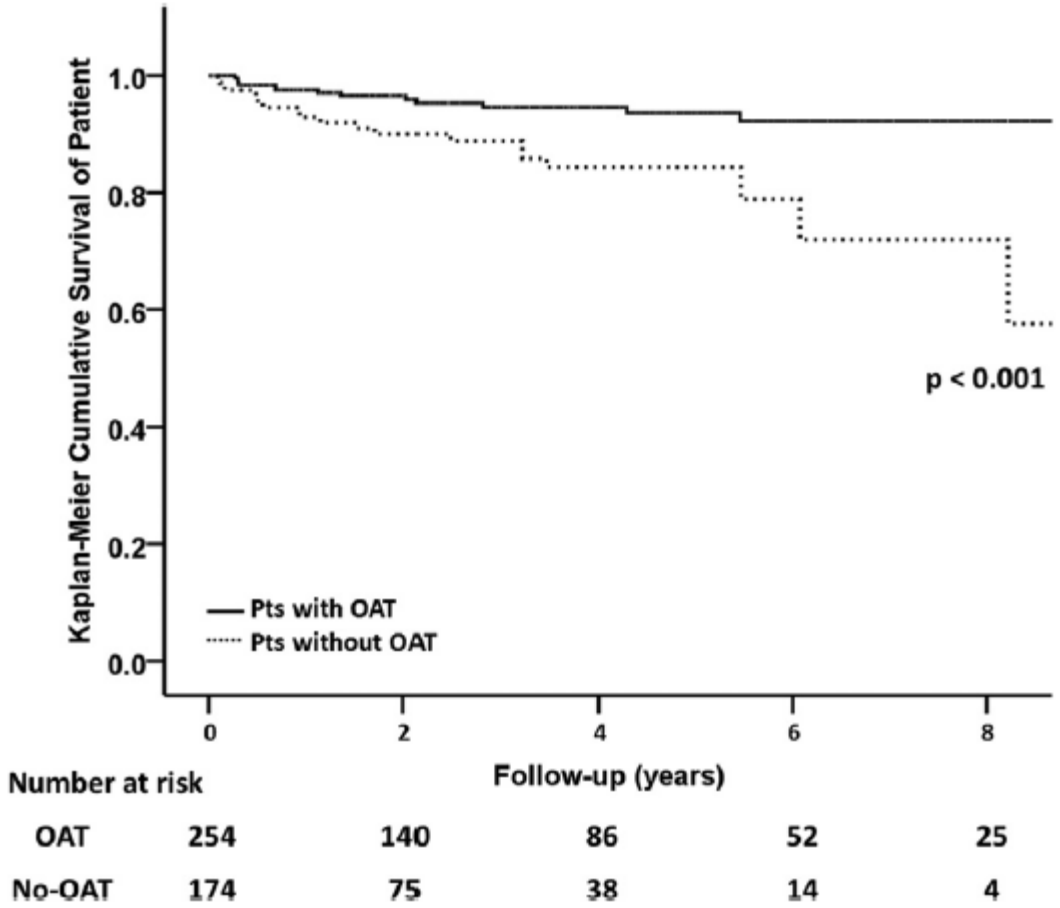


Figure 5 Kaplan-Meier cumulative survival free of all-cause mortality. Patients without OAT had a lower cumulative survival than those with OAT ($P < .001$). OAT = oral anticoagulation therapy.

Table 2. Event Rates of Various Outcomes According to Stratification on Treatment Regimen Using 1 Year of Follow-Up

Outcome	No Antithrombotic Treatment	OAC Treatment	Antiplatelet Therapy
Ischemic stroke/SE and all-cause mortality			
Events	179	43	83
Person-time (100 y)	655	316	335
Event rate (95% CI)	27.3 (23.6–31.6)	13.6 (10.1–18.3)	25.7 (20.7–31.9)
Ischemic stroke/SE			
Events	69	17	34
Person-time (100 y)	666	322	329
Event rate (95% CI)	10.4 (8.2–13.1)	5.3 (3.3–8.5)	10.3 (7.4–14.4)
All-cause mortality			
Events	130	32	69
Person-time (100 y)	682	330	353
Event rate (95% CI)	19.1 (16.0–22.6)	9.7 (6.9–13.7)	19.5 (15.4–24.7)
Recurrent ICH			
Events	57	25	18
Person-time (100 y)	662	313	339
Event rate (95% CI)	8.6 (6.6–11.2)	8.0 (5.4–11.8)	5.3 (3.3–8.4)
Major extracranial bleeding			
Events	10	5	9
Person-time (100 y)	677	329	349
Event rate (95% CI)	1.5 (0.8–2.7)	1.5 (0.6–3.7)	2.6 (1.3–5.0)

CI indicates confidence interval; ICH, intracranial hemorrhage; OAC, oral anticoagulation; and SE, systemic embolism.

Circulation. 2015;132:517-525.

Table 5

Studies on resumption anticoagulant therapy after an anticoagulant-associated ICH.

Study	Study pts N	N of pts resuming (%)	Risk of recurrent ICH at 1-year[a]	Risk of TEE at 1-year[a]	All-cause mortality at 1-year[a]
Nielsen PB et al. (2015) [104]	1752 NVAF pts	621 (35.4)	8.0% vs 8.6% HR 0.91 (95%CI 0.56-1.49)	5.3% vs 10.4% HR 0.59 (95%CI 0.33-1.03)	9.7% vs 19.1% HR 0.55 (95%CI 0.37-0.82)
Kuramatsu JB et al. (2015) [106]	566 AF pts[b]	110 (19.4)	3.9% vs 3.9%	5.5% vs 14.9%	8.2% vs 37.5%
Witt DM et al. (2015) [105]	160 pts[c]	54 (33.8)	3.7% vs 7.6% OR 0.47 (95%CI 0.10-2.30)	0% vs 1.9% stroke/CV accident	18.5% vs 31.1% OR 0.76 (95%CI 0.30–1.89)
Yung D et al. (2012) [20]	284 pts	91 (32)	< 2.5 vs 0%	Not reported	48% vs 61% OR 0.79
Poli D et al. (2014) [24]	267 pts[d]	267	2.6%	1.9% (15 events during 778 pts-years follow-up)	5.6% (44 death during 778 pts-years follow-up)

Pts indicates patients; TEE, thromboembolic events; OR, odds ratio; HR, hazard ratio; d, days; CI, confidence interval.

[a] Event rates in patients resuming vs not resuming oral anticoagulants.

[b] Data are reported only for the subgroup of AF patients.

[c] 15.4% at 1-y, if included even ICH recurrence than hematoma expansion.

[d] 19 patients (7.2%) were not taking VKAs at the index ICH.

Canadian Journal of Cardiology 28 (2012) 33–39

Clinical Research

Reinitiation of Anticoagulation After Warfarin-Associated Intracranial Hemorrhage and Mortality Risk: The Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) Study

	Warfarin restarted (n = 91)	Warfarin not restarted (n = 193)	*P* value
Death			
In-hospital	30 (33.0)	98 (50.8)	0.005
1 month	29 (31.9)	105 (54.4)	<0.001
6 months	38 (41.8)	114 (59.1)	0.006
1 year	44 (48)	118 (61)	0.04
ICH expansion or recurrrence	14 (15.4)	29 (15.0)	0.94
Death or intracranial bleeding			
1 month	32 (35.2)	106 (54.9)	0.002
1 year	46 (50.5)	118 (61.1)	0.09
Death, bleeding, or thrombotic complication at 1 year	47 (51.6)	119 (61.7)	0.11
Neurologic worsening in-hospital	39 (42.9)	101 (52.3)	0.14
Modified Rankin score < 3 at discharge	17 (18.7)	22 (11.4)	0.10
Discharge to home/retirement home	18 (19.8)	26 (13.5)	0.17

Antikoagülan tedavi başlayalım mı?

Öneri :

İnme riski >%6,5 (CHADSVASC ≥5)

Rekürren kanama riski <%1,4

İSE ANTİKOAGÜLAN BAŞLA

Table 3
Risk-benefit analysis for resuming antithrombotic therapy after intracerebral hemorrhage (ICH)

Factors Increasing Risk of Thromboembolism		Factors Increasing Risk of ICH Recurrence
Highest Risk	**Moderately High Risk**	
Mechanical valve prosthesis • Mitral position • First-generation model • With concomitant atrial fibrillation, congestive heart failure, severe mitral stenosis, or previous embolic event • Placement within previous 3 mo	Aortic mechanical valve prosthesis	Lobar ICH location
Atrial fibrillation with previous stroke	Atrial fibrillation without previous stroke but with $CHADS_2$ or CHA_2DS_2-VASc ≥1 or 2	Cerebral amyloid angiopathy
Proximal deep venous thrombosis or pulmonary embolism	Multiple previous ischemic events (cerebral, coronary, or systemic)	Age >65 y Asian ethnicity Uncontrolled hypertension Bleeding diathesis (eg, liver failure, hemophilia) Cerebral microbleeds seen on gradient-echo MRI

Neurol Clin 33 (2015) 329–345

Serebral Kanamada Rekürrens Öngördürücüleri

Yaş (>65)

Hemorajinin Lokalizasyonu (Lobar vs derin hemisferik, %15 vs %2))

Vaskülopati (amiloid vaskülopati)

Genetik risk (Apolipoprotein ϵ2 or ϵ4 genotip ve Platelet glycoprotein IIb/IIIa A1A1 genotip)

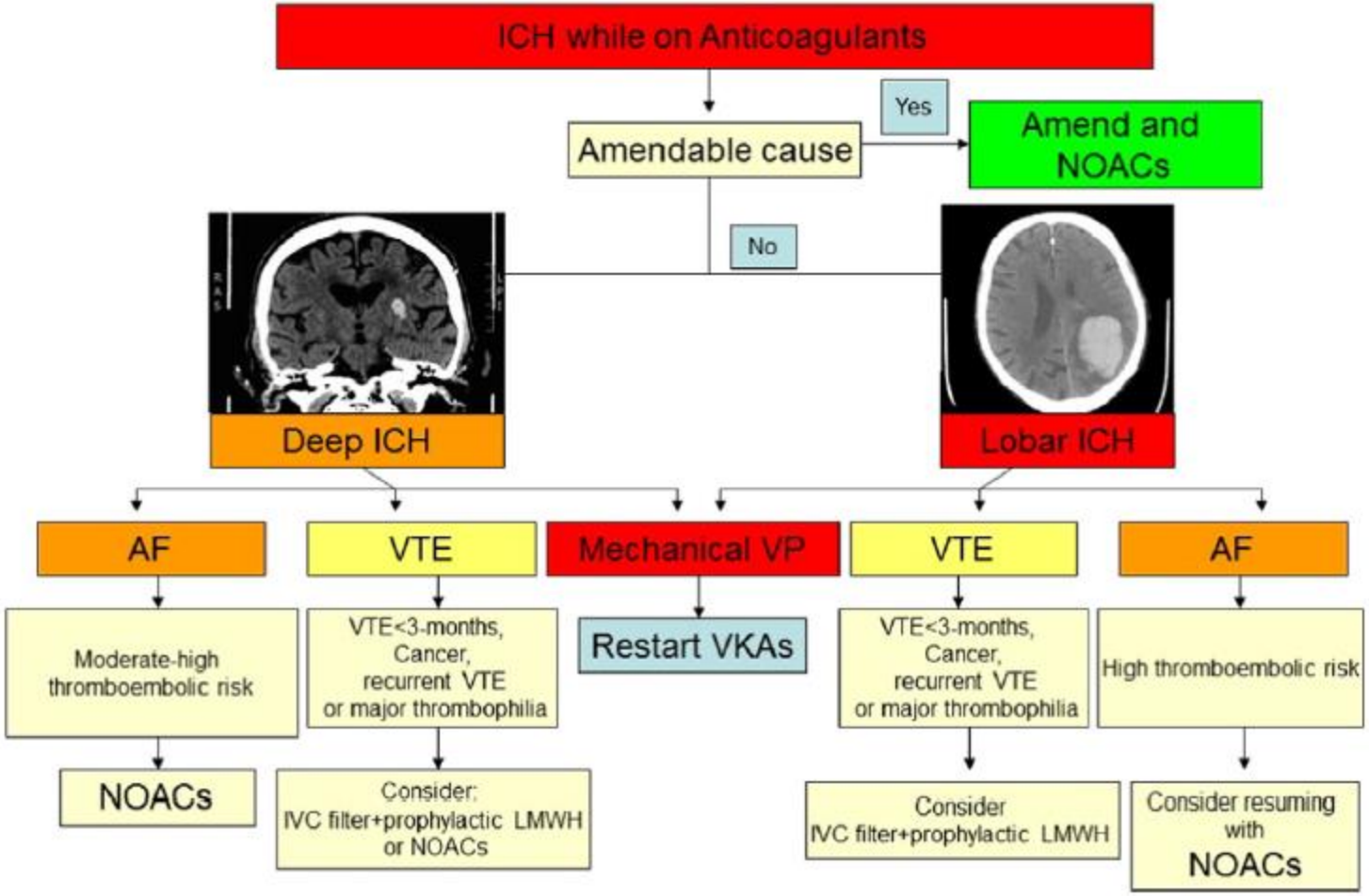
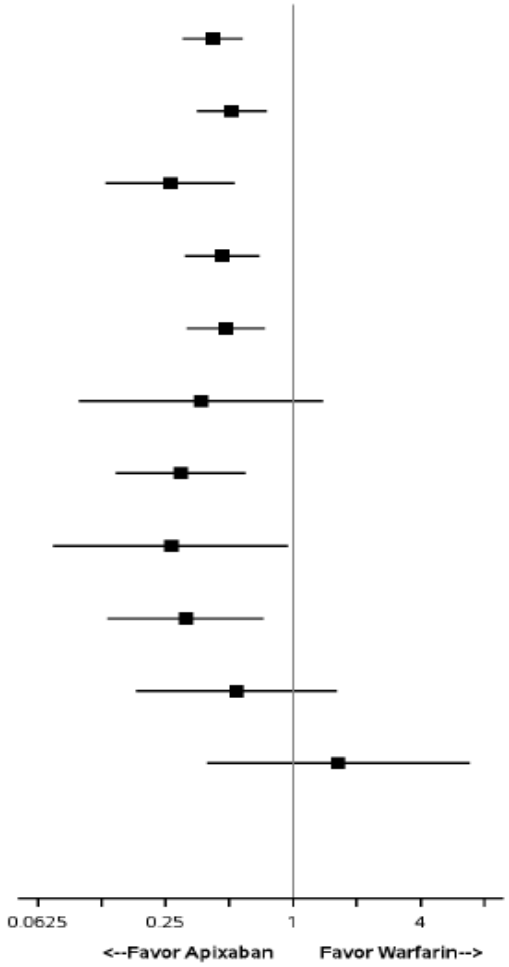


Fig. 2. Algorithm for decision making on resumption of anticoagulation after ICH.

blood®
Prepublished online March 29, 2017;
doi:10.1182/blood-2016-08-731638

Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy

	Apixaban Rate (n)	Warfarin Rate (n)	Hazard Ratio (95% CI)	p-value
All Intracranial (n = 174)	**0.33 (52)**	**0.80 (122)**	**0.417 (0.302 - 0.577)**	**<.0001**
Spontaneous (n = 119)	**0.26 (41)**	**0.51 (78)**	**0.515 (0.353 - 0.751)**	**0.0006**
Traumatic (n = 47)	**0.06 (10)**	**0.24 (37)**	**0.264 (0.131 - 0.531)**	**0.0002**
Intracerebral (n = 106)	**0.22 (34)**	**0.47 (72)**	**0.462 (0.308 - 0.695)**	**0.0002**
Spontaneous (n = 94)	**0.20 (31)**	**0.41 (63)**	**0.482 (0.314 - 0.741)**	**0.0009**
Traumatic (n = 11)	**0.02 (3)**	**0.05 (8)**	**0.367 (0.097 - 1.382)**	**0.1382**
Subdural (n = 43)	**0.06 (10)**	**0.22 (33)**	**0.296 (0.146 - 0.601)**	**0.0007**
Spontaneous (n = 14)	**0.02 (3)**	**0.07 (11)**	**0.266 (0.074 - 0.953)**	**0.0419**
Traumatic (n = 29)	**0.05 (7)**	**0.14 (22)**	**0.311 (0.133 - 0.729)**	**0.0072**
Subarachnoid (n = 14)	**0.03 (5)**	**0.06 (9)**	**0.544 (0.182 - 1.624)**	**0.2753**
Spontaneous (n = 8)	**0.03 (5)**	**0.02 (3)**	**1.637 (0.391 - 6.849)**	**0.4999**
Traumatic (n = 6)	**0.00 (0)**	**0.04 (6)**		



NOAC vs Varfarin

- Varfarin ilişkili serebral kanamada mortalite %20-55

- NOAC ilişkili serebral kanamada mortalite %20-43

van Nieuwenhuizen et al. Trials (2015) 16:393
DOI 10.1186/s13063-015-0898-4

TRIALS

STUDY PROTOCOL Open Access

Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation (APACHE-AF): study protocol for a randomised controlled trial

Koen M. van Nieuwenhuizen[1*], H. Bart van der Worp[1], Ale Algra[1,2], L. Jaap Kappelle[1], Gabriel J. E. Rinkel[1], Isabelle C. van Gelder[3], Roger E. G. Schutgens[4], and Catharina J. M. Klijn[1,5] on behalf of the APACHE-AF investigators

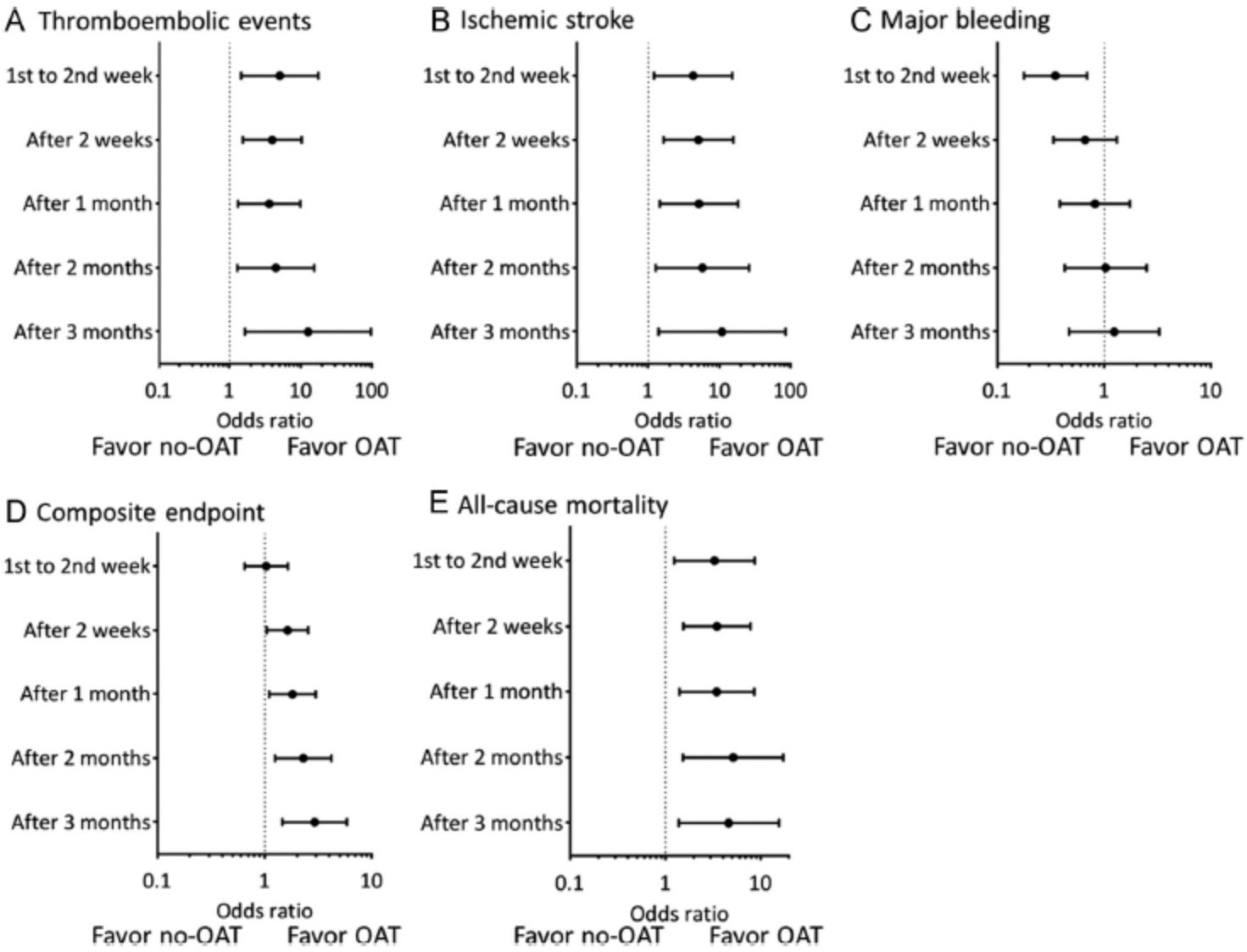
Abstract

Background: There is a marked lack of evidence on the optimal prevention of ischaemic stroke and other thromboembolic events in patients with non-valvular atrial fibrillation and a recent intracerebral haemorrhage during treatment with oral anticoagulation. These patients are currently treated with oral anticoagulants, antiplatelet drugs, or no antithrombotic treatment, depending on personal and institutional preferences.
Compared with warfarin, the direct oral anticoagulant apixaban reduces the risk of stroke or systemic embolism, intracranial haemorrhage, and case fatality in patients with atrial fibrillation. Compared with aspirin, apixaban reduces the risk of stroke or systemic embolism in patients with atrial fibrillation, and has a similar risk of intracerebral haemorrhage. Novel oral anticoagulants have not been evaluated in patients with atrial fibrillation and a recent intracerebral haemorrhage.
To inform a phase III trial, the phase II Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation (APACHE-AF) trial aims to obtain estimates of the rates of vascular death or non-fatal stroke in patients with atrial fibrillation and a recent anticoagulation-associated intracerebral haemorrhage treated with apixaban and in those in whom oral anticoagulation is avoided.

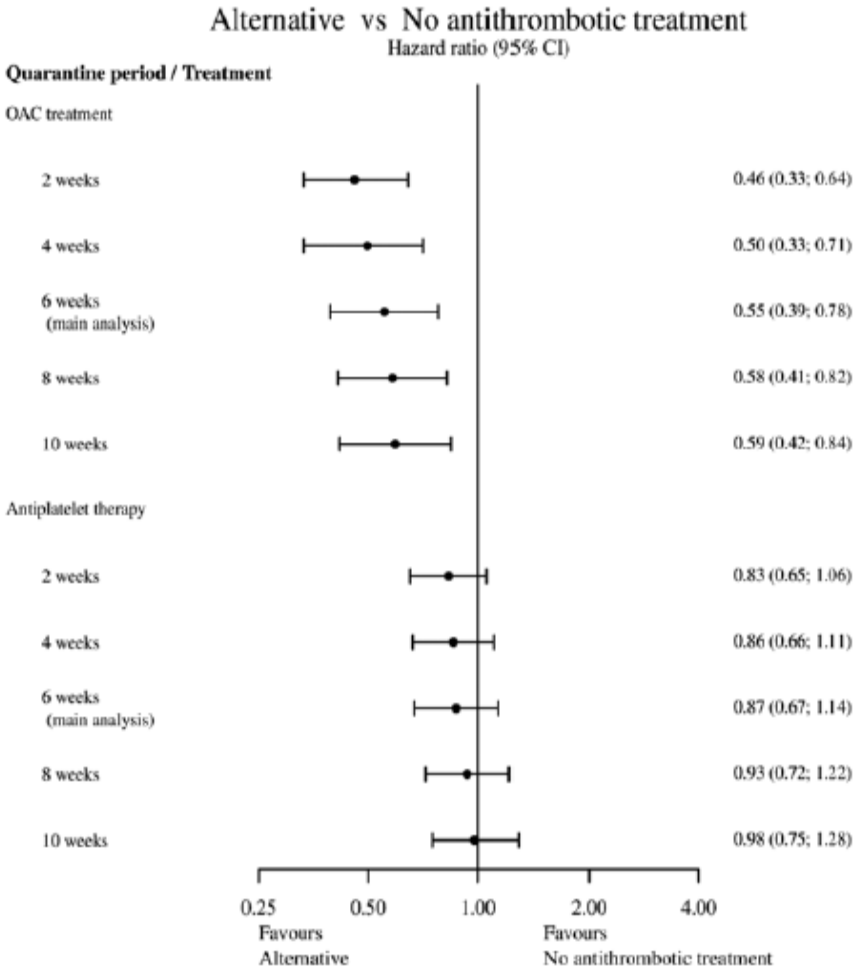
Methods/Design: APACHE-AF is a phase II, multicentre, open-label, parallel-group, randomised clinical trial with masked outcome assessment. One hundred adults with a history of atrial fibrillation and a recent intracerebral haemorrhage during treatment with anticoagulation in whom clinical equipoise exists on the optimal stroke prevention strategy will be enrolled in 14 hospitals in The Netherlands.
These patients will be randomly assigned in a 1:1 ratio to either apixaban or to avoiding oral anticoagulation. Patients in the control group may be treated with antiplatelet drugs at the discretion of the treating physician. The primary outcome is the composite of vascular death or non-fatal stroke during follow-up. We aim to include 100 patients in 2.5 years. All patients will be followed-up for the duration of the study, but at least for 1 year.
(Continued on next page)

Antikoagülasyon Ne Zaman Başlanmalı?

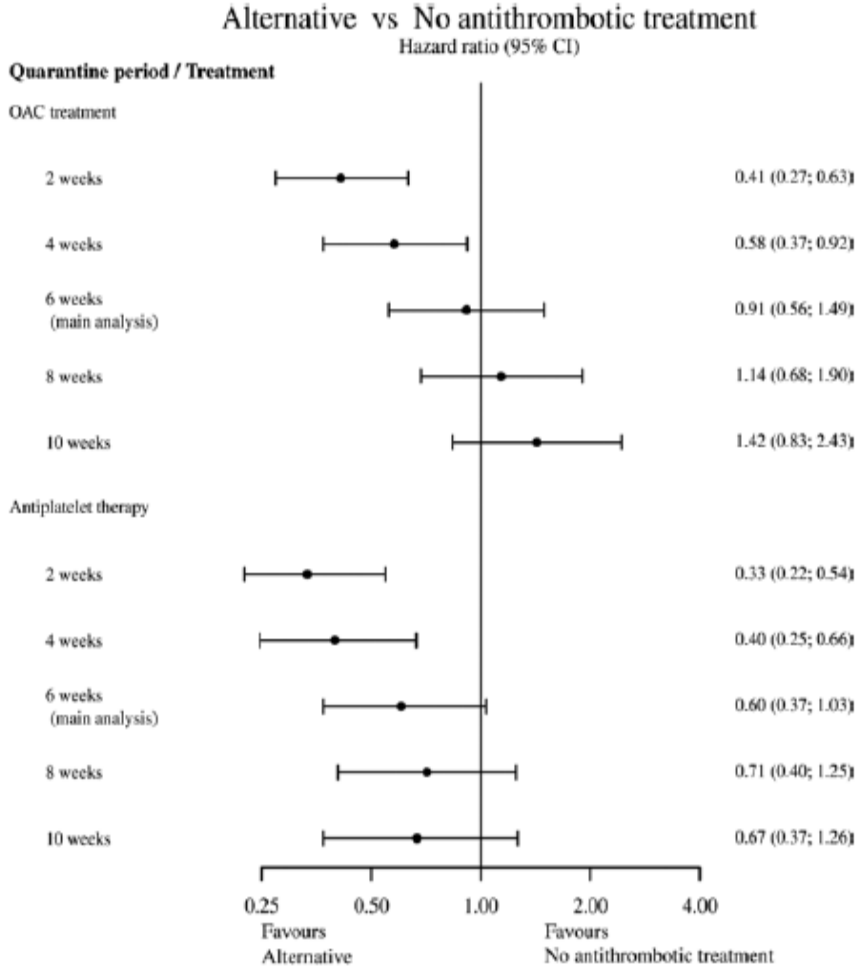
- Serebral kanama sonrası ilk hafta OAK tedavi güvenle bırakılabilir.
- 108 hastanın takibinde 8 tromboembolik olay izlenmiş (0,66 /1000 hasta yılı)
- >10 gün varfarin başlananlarda tromboembolik olay yok
- Kanama kontrol altına alınınca OAK başlanması planlanmalıdır (MR görüntüleme).



Circulation. 2015;132:517-525.



Ischemic stroke/SE and all-cause mortality



Recurrent ICH

Circulation. 2015;132:517-525.

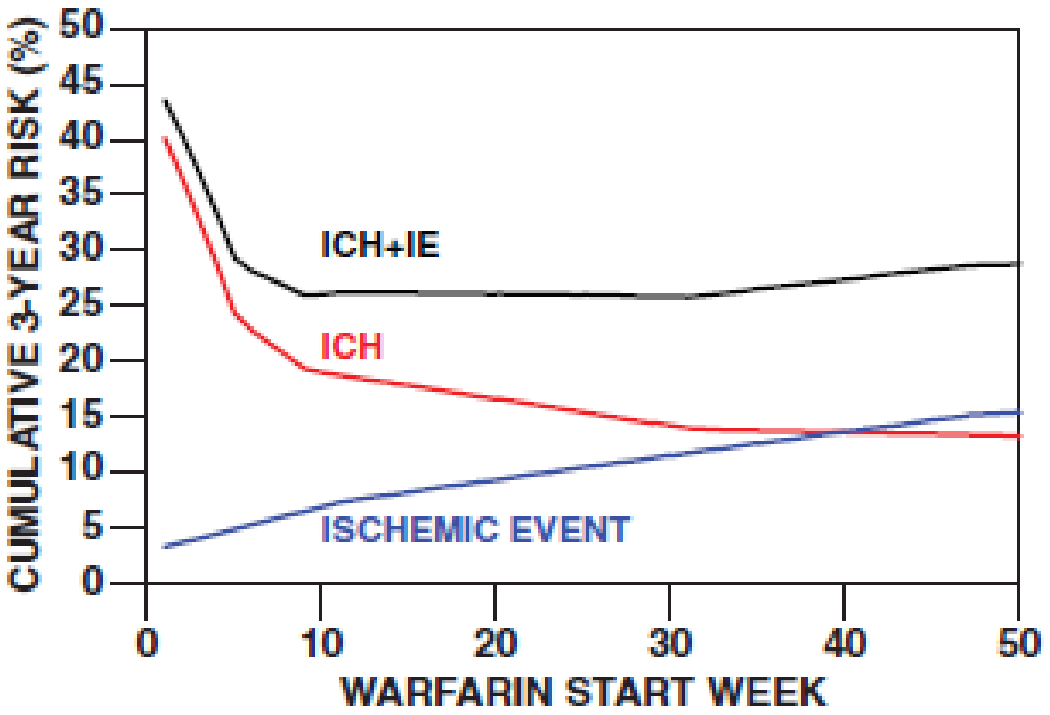


Figure 2. The "total" risk for a treatment horizon of 3 years of recurrent intracranial hemorrhage and of ischemic stroke according to the time point of resumption of anticoagulation.

Stroke. 2010;41:2860-2866.

Table 3
Restarting anticoagulation after ICH in different clinical conditions: expert interpretation of current guidelines [88–100].

Clinical condition	Ischemic stroke risk	Anticoagulant treatment after ICH?	When to restart
Atrial fibrillation	0.8 to >20% According to risk factors (Table 2)	Consider for moderate to high TE risk	> 14 days after ICH
Cardiomyopathy			
LV dysfunction without AF	1.6–4% per year	No	/
with AF	2–18% per year	As for AF patients	>14 days after ICH
LV thrombus	15% at 3 months	Always after a first ICH or ICH with amendable risk factors	As soon as possible (stable hematoma volume at CT scan) starting with sub-therapeutic doses
LA/appendage thrombi		Consider LA appendage Closure	As soon as possible if closure not indicated
Valvular disorders			
RMV	5% per year	No	
RMV with AF	> 5% per year	Always after a first ICH	>14 days after ICH
RMV and LA thrombus or previous systemic embolism	About 9%	Always after a first ICH	As soon as possible
Valve prosthesis/replacement			
Mitral/Aortic valve bioprosthesis			
-Without AF	1–2%/0.4–1.9% (17% at 3 months)	No	/
-With AF	As for AF (Table 2)	As for AF patients	>14 days after ICH
Mitral mechanical prosthesis	22% per year	Always after a first ICH	As soon as possible
Aortic mechanical prosthesis	≥ 12% per year	Always after a first ICH	As soon as possible
Double mechanical prosthesis	91%	Always after a first ICH	As soon as possible

TE = Thrombo-embolic; LV = left ventricle; RMV = rheumatic mitral valve; LA = left atrial.

Antikoagülasyona Alternatif Var mı?

Protect-AF ve PREVAIL çalışmalarının metaanalizinde LAA kapama ile hemorajik inme (%0,15'e %0,96 p=0,0004), kardiyovasküler /açıklanamayan ölüm (%1,1'e %2,3 p=0,006) ancak iskemik inme cihaz grubunda anlamlı olarak artmış (%0,2'e %1,0 p=0,05).

Sonuç

1- CHADSVASC Skoru 5 olan hastada OAK başlanmalıdır (lobar hemorajide bireysel değerlendirme sonrası)

2- Kanama kontrol altına alınınca OAK başlanabilir (>14 günden sonra)

3- NOAC tercih edilebilir

4- Kanamayı predispoze edecek etkenlerin eradikasyonu (Antiplatelet kullanımı, HT vb)