Atriyal Fibrilasyonda Akılcı İlaç Tedavisi

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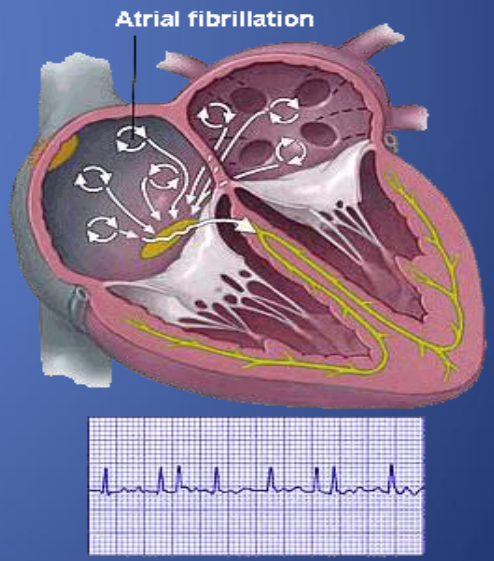
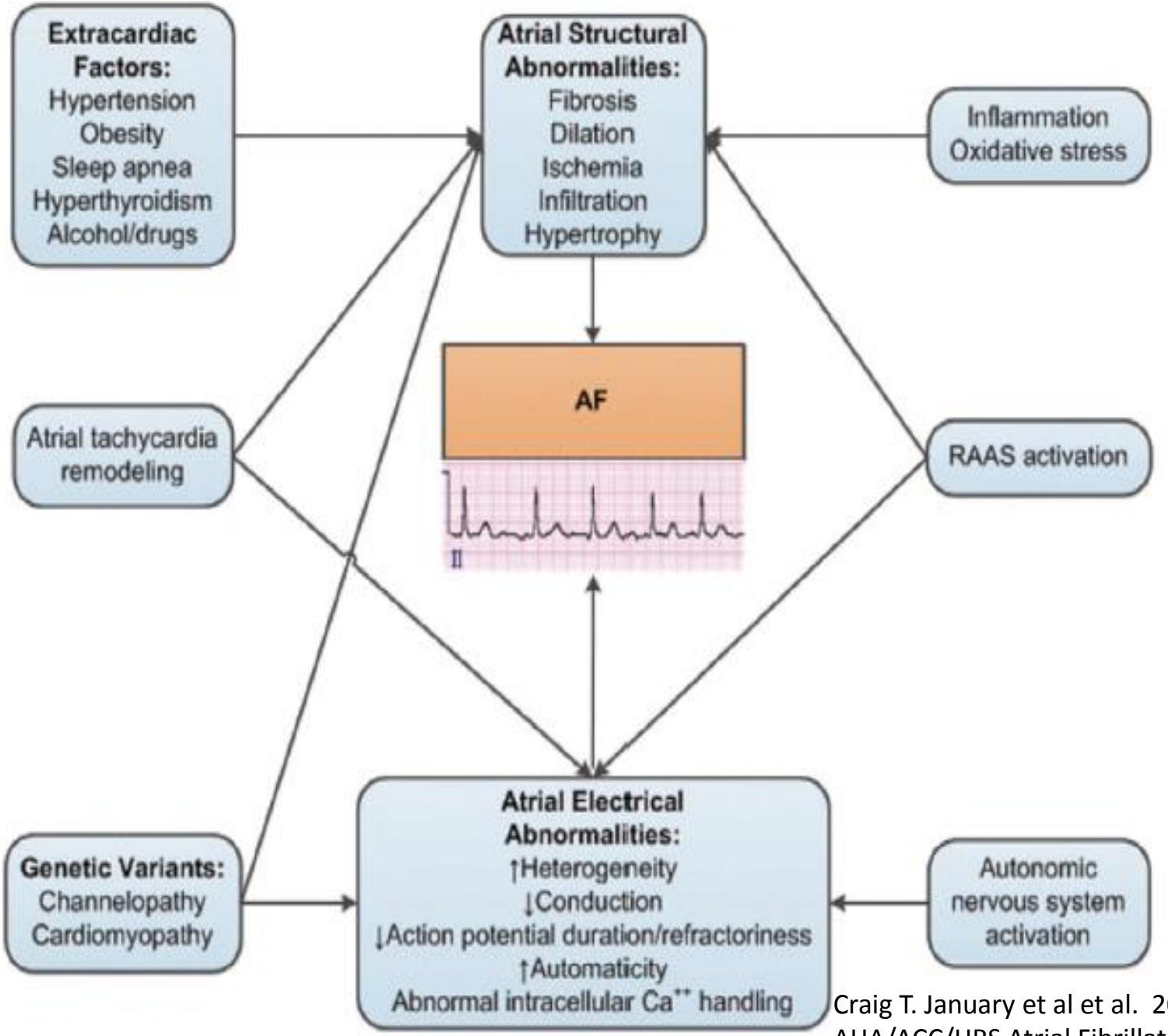
Kardiyoloji Anabilim Dalı

Epidemiyoloji

- Atriyal fibrilasyon en sık gözlenen kronik ritim bozukluğudur.
- Genel toplumda sıklığı % 1-2
  - 40 yaş altında < % 0.5
  - 80 yaş üstü > % 5-15
- İnme riskininde 5 kat artış
- Ölüm riskinde 2 kat artış



Camm et al. European Heart Journal (2010) 31, 2369–2429



Craig T. January et al et al. 2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Akılcı İlaç Kullanımı

- Kişilerin klinik bulgularına ve bireysel özelliklerine göre; uygun ilacı, uygun süre ve dozda, en uygun maliyetle ve kolayca sağlayabilmeleri olarak tanımlanmaktadır.

Akılcı ilaç kullanımı, ucuz veya indirimli ilaç kullanımı anlamına gelmez

Akılcı İlaç Kullanımı

- Hastalığın patofizyolojisi ve ilaçların etki mekanizmaları
- İlaçların yan etki profili ve ilaç etkileşimleri
- Risk-yarar oranı
- Maliyet-etkinlik

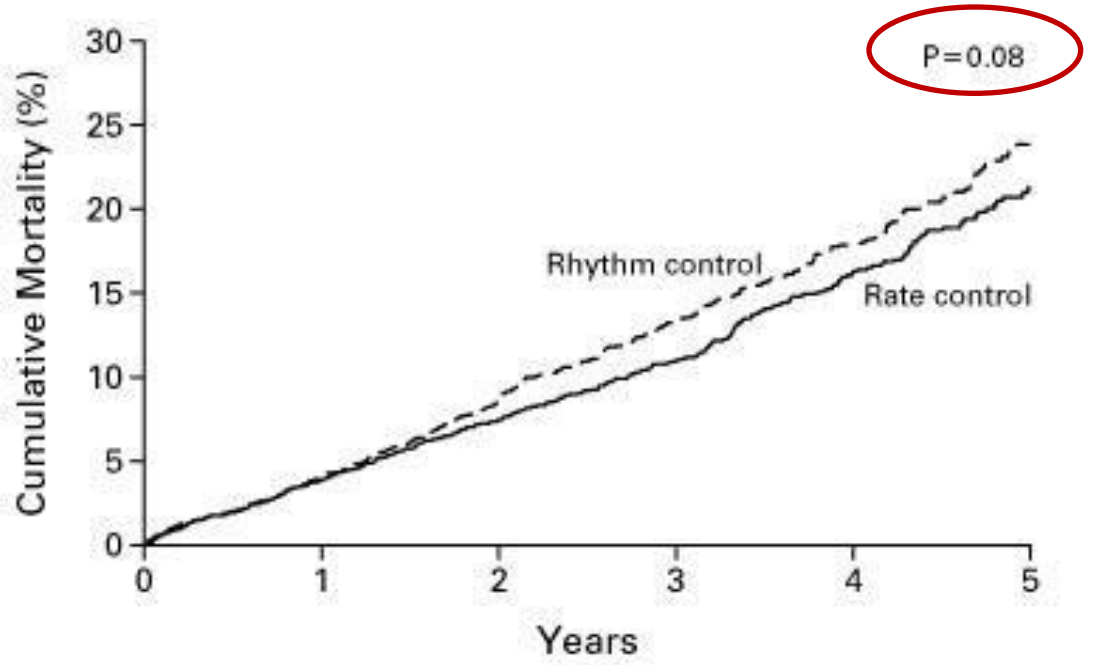
Tedavi yaklaşımı

- AF tipinin belirlenmesi
- Altta yatan nedenlerin araştırılması
- Hız kontrolü
- Ritim kontrolü
- Tromboembolinin önlenmesi

Tedavi yaklaşımı

- **Ritim kontrolü**
  - ✓ Kardiyoversiyon
  - ✓ **Antiaritmik ilaçlar**
  - ✓ Ablasyon
- **Embolik olayların engellenmesi**
- **Hız kontrolü**
  - ✓ Kalp hızının kontrol altına alınması
  - ▪ **İlaçlar**
  - ▪ AV nod ablasyonu + kalıcı kalp pili

AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) Çalışması



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)

N Engl J Med 2002; 347:1825-1833

Hız-Ritim kontrolü?

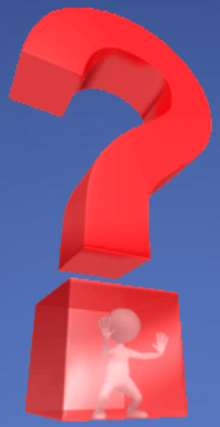
Atriyal Fibrilasyonda Hız ve Ritim Kontrolü Çalışmaları					
ÇALIŞMA	**YIL**	**HASTA SAYISI**	**PRİMER SONLANIM NOKTASI**	**HAZARD RATİO**	**P DEĞERİ**
PIAF	2000	252	Semptomatik iyileşme	1,1	0,31
AFFIRM	2002	4060	Tüm Nedenlere Bağlı Mortalite	0,87	0,08
RACE	2002	522	Birleşik sonlanım noktası	0,73	0,99
STAF	2003	200	Birleşik sonlanım noktası	1,09	0,99
HOT CAFE	2004	205	Birleşik sonlanım noktası	1,98	>0,71
AF-CHF	2008	1376	Kardiyovasküle r Mortalite	0,94	0,59
PABA-CHF	2008	81	Birleşik sonlanım noktası	MULTIPLE	<0,001

Birleşik sonlanım noktası→kardiyovasküler kaynaklı ölüm, kalp yetersizliği, tromboembolik komplikasyon,kanama, pil imp.,ilaç yan etkisi

E. Kevin Heist et al.*Circulation. 2011;124:2746-2755*

Hız Kontrolü

- Persistan AF
- Asemptomatik hasta
- ≥ 65 yaş
- Kardiyoversiyona uygun olmayan hasta (AF > 1 yıl, dilate LA > 5,5 cm, multiplkardiyoversiyona rağmen AF)
- Komorbid durumların varlığı
- Antiaritmik tedavi başarısızlığı veya yan etkisi
- Hasta tercihi



Ritim Kontrolü

- Paroksismal AF veya yeni tanı AF
- Semptomatik hasta
- < 65 yaş
- Lone AF ve tetikleyici faktörlere bağlı AF (hipertiroidi, alkol, kafein, cerrahi sonrası)
- AF'ye bağlı taşikardiyomiyopati
- Hız kontrolüne rağmen semptomatik olan hasta
- Hasta tercihi

Bajpai A et al. British Medical Bulletin 2008;88:75-94.

Hız Kontrolü

- Basit
- Ucuz
- Daha az toksik
- Daha az invaziv işlem

Hız Kontrolü Hedefleri-RACE II Çalışması

STRICT RATE CONTROL:<80 bpm
LENİENT RATE CONTROL:<110 bpm

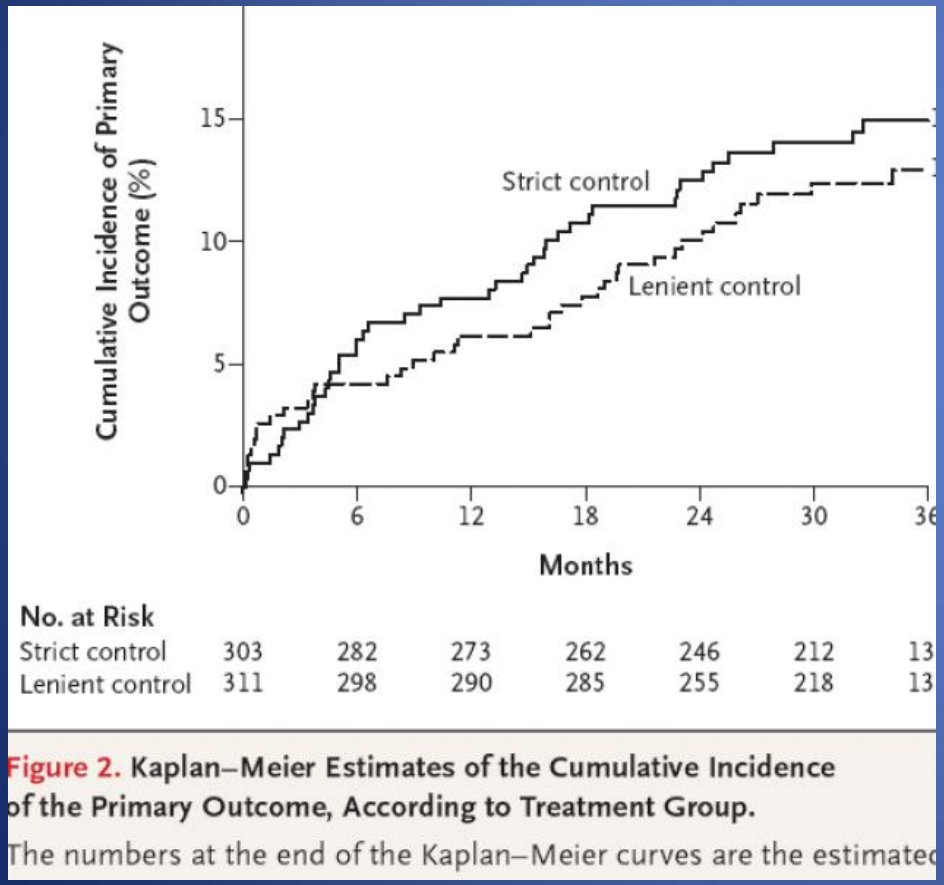


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.

The numbers at the end of the Kaplan–Meier curves are the estimated

- Ilımlı hız kontrolü (istirahat kalp hızı < 110/dk)
  - –Persistan
  - –Asemptomatik
  - –EF > % 40
- Semptomatik hasta istirahat
  - – kalp hızı 80-100/dk

Van Gelder et al. NEJM 2010;362:1363-73

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2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

A heart rate control (resting heart rate <80 bpm) strategy is reasonable for symptomatic management of AF	IIa	B
Lenient rate control strategy (resting heart rate <110 bpm) may be reasonable with asymptomatic patients and LV systolic function is preserved	IIb	B

European Heart Journal (2010) 31, 2369–2429
doi:10.1093/eurheartj/ehq278

ESC GUIDELINES

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

It is reasonable to adopt a stricter rate control strategy when symptoms persist or tachycardiomyopathy occurs, despite lenient rate control: resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm. After achieving the strict heart rate target, a 24 h Holter monitor is recommended to assess safety.	IIa	B

Hız kontrolü-Farmakolojik tedavi

- Beta blokerler
- Non dihidropiridin grubu kalsiyum kanal blokerleri
- Digoksin
- Amiadoran/dronedarone
- Sotalol

Beta Blokerler

- AFFIRM çalışması sonuçlarında beta blokerler en etkili hız kırıcı ajanlar olarak bulunmuştur. (beta bloker 70% kalsiyum kanal blokerleri 54% başarılı)*.

- Esmolol, propranolol, metoprolol ıv verilen beta blokerler.

- Karvedilolün digoksin ile kombinasyonu sol ventrikül fonksiyonlarını iyileştirir**.

*.N Engl J Med 2002; 347:1825-1833

**. Khand AU et al.J Am Coll Cardiol. 2003;42:1944-51.

Non Dihidropiridin Kalsiyum Kanal Blokerleri

- Diltiazem ve verapamil L tipi kalsiyum kanalları üzerinden direk AV noda etkilidir. Intravenöz ve oral kullanımları mevcuttur.

- Egzersiz ve istirahat kalp hızını azaltır ve egzersiz toleransını artırırlar.

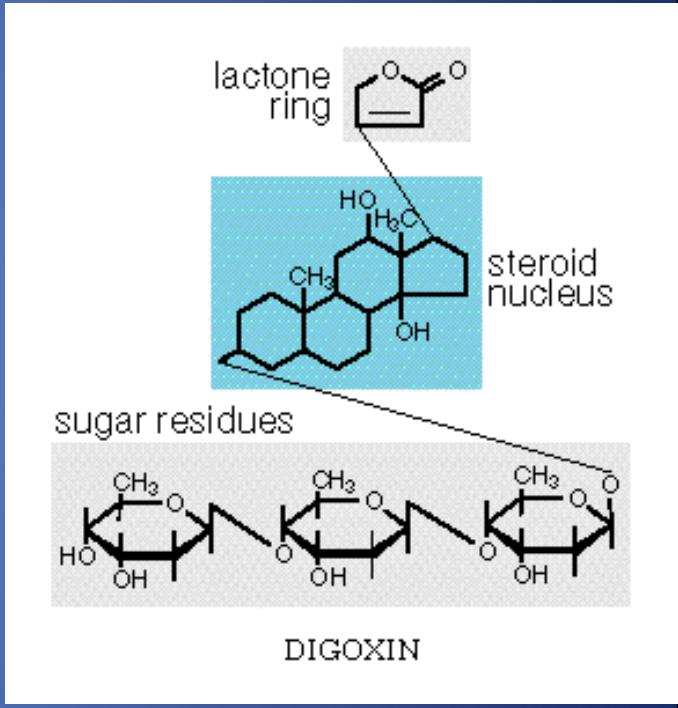
- Negatif inotrop etkilerinden dolayı sistolik fonksiyonları baskılanmış ve akut kalp yetersizliğinde olan hastalarda kullanılmamalıdır.

- Korunmuş ejeksiyon fraksiyonlu kalp yetersizliği hastalarında tercih edilecek tedavi yaklaşımıdır.

Lundstrom T et al. J Am Coll Cardiol. 1990;16:86-90.
Phillips BG et al. Pharmacotherapy. 1997;17:1238-45

Digoksin

- Hücre zarı Na/K ATPase kanalını bloker eder ve hücre içi Na ve Ca miktarı artar.
- Vagomimetik etkisi ile AV ve SA nodda indirek baskılanmaya yol açar
- İstirahat kalp hızına etkilidir egzersiz kalp hızına etkisi yoktur*.
- Intravenöz kullanımında etki başlangıcı 1 saat geçer.
- Bir Beta bloker veya kalsiyum kanal blokeri ile kombine edilmelidir.



Goodman & Gilman's Pharmacology Chapter 33. Pharmacotherapy of Congestive Heart Failure

*Farshi C et al. J Am Coll Cardiol. 1999;33:304-10

Digoksin

Yan Etkiler

- Görsel halusilasyonlar
- Bulantı kusma iştahsızlık
- Ekstrasistoller
- Av blok, sinusal arrest
- Böbrek fonksiyon bozukluğu olanlarda doz ayarlanmalı

İlaç Etkileşimleri

- Amiodaron→Digoksin %70
- Verapamil→Digoksin %50-75
- Propafenon→Digoksin 30%
- Kinidin →Digoksin50-75%
- Dronedaron→Digoksin %150

Goodman & Gilman's Pharmacology Chapter 33. Pharmacotherapy of Congestive Heart Failure
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Digoksin

- AFFIRM çalışması post hoc analizinde cinsiyet ve kalp yetersizliği olmasından bağımsız olarak mortaliteyi artırdığı gösterilmiştir. Bir başka subgrup analizinde bu bulgu desteklenmemiştir.*-***.

- DIG (Digitalis Investigation Group) çalışmasında 0.9 ng/mL üzerinde serum değerleri artmış mortalite ile ilişkili**.

- Digoksin bu sonuçlardan sonra ikinci seçenek ajan olarak ve özellikle kalp yetersizliği olan hastalarda önerilmektedir.

*Whitbeck M.G. Et al. European heart journal. 2012
**N Engl J Med. 1997;336:525-33.
*** Gheorghiade M et al.Eur Heart J. 2013;34:1489-97.

Amiodaron

- Sempotolitik ve AV nodu baskılayıcı
- Pre-eksitasyonu olmayan kritik hastalarda
- Kronik kullanımı ile ilgili veri sınırlı
- Uzun dönem kullanımını sınırlayacak yan etkiler

Dronedaron

- İyodinden fakir, daha az toksik.
- İstirahat kalp hızını ortalama 12 atım/dk ve egzersiz kalp hızını azalttığı gösterildi*.
- Permanent AF lerde KY, inme, ölüm ve hospitalizasyon ihtiyacını arıtırıyor**.
- Kalp yetersizliği ve sol ventrikül sistolik fonksiyon bozukluğu olanlarda MI inme ve mortaliteyi artırıyor***.

*Davy JM et al. (ERATO) study. Am Heart J. 2008;156:527-9.
**Connolly SJ et al N Engl J Med.2011;365:2268-76.
***Kober L et al . N Engl J Med. 2008;358:2678-87.

Table 10. AF Rate Control Common Medication Dosage

	Intravenous Administration	Usual Oral Maintenance Dose
Beta blockers		
Metoprolol tartrate	2.5–5.0 mg IV bolus over 2 min; up to 3 doses	25–100 mg BID
Metoprolol XL (succinate)	N/A	50–400 mg QD ESC→ 200MG ÜST DOZ
Atenolol	N/A	25–100 mg QD
Esmolol	500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV	N/A
Propranolol	1 mg IV over 1 min, up to 3 doses at 2 min intervals	10–40 mg TID or QID
Nadolol	N/A	10–240 mg QD
Carvedilol	N/A	3.125–25 mg BID
Bisoprolol	N/A	2.5–10 mg QD
Nondihydropyridine calcium channel antagonists		
Verapamil	(0.075-0.15 mg/kg) IV bolus over 2 min, may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion	180–480 mg QD (ER) ESC→360 MG ÜST DOZ
Diltiazem	0.25 mg/kg IV bolus over 2 min, then 5-15 mg/h	120–360 mg QD (ER)
Digitalis glycosides		
Digoxin	0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h	0.125–0.25 mg QD
Others		
Amiodarone	300 mg IV over 1 h, then 10–50 mg/h over 24 h	100–200 mg QD

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IV beta blockers or nondihydropyridine calcium channel blocker recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated	I	B
IV amiodarone can be useful for rate control in critically ill patients without pre-excitation	IIa	B
With pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or amiodarone, should not be administered	III: Harm	B

AKUT HIZ KONTROLÜ-ESC

European Heart Journal (2010) 31, 2369–2429
doi:10.1093/eurheartj/ehq278

ESC GUIDELINES

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Amiodaronun preeksitasyon sendromunda kullanımı AHA/ACC/HRS 2014 kılavuzunda önerilmiyor.

Nebojsa M et al. J Cardiovasc Electrophysiol. 2011;22:1077-8

Recommendations for acute rate control

Recommendations	Class[a]	Level[b]
In the acute setting in the absence of pre-excitation, i.v. administration of β-blockers or non-dihydropyridine calcium channel antagonists is recommended to slow the ventricular response to AF, exercising caution in patients with hypotension or heart failure.	I	A
In the acute setting, i.v. administration of digitalis or amiodarone is recommended to control the heart rate in patients with AF and concomitant heart failure, or in the setting of hypotension.	I	B
In pre-excitation, preferred drugs are class I antiarrhythmic drugs or amiodarone.	I	C
When pre-excited AF is present, β-blockers, non-dihydropyridine calcium channel antagonists, digoxin, and adenosine are contraindicated.	III	C

Uzun Dönem Hız Kontrolü-ACC/AHA/HRS

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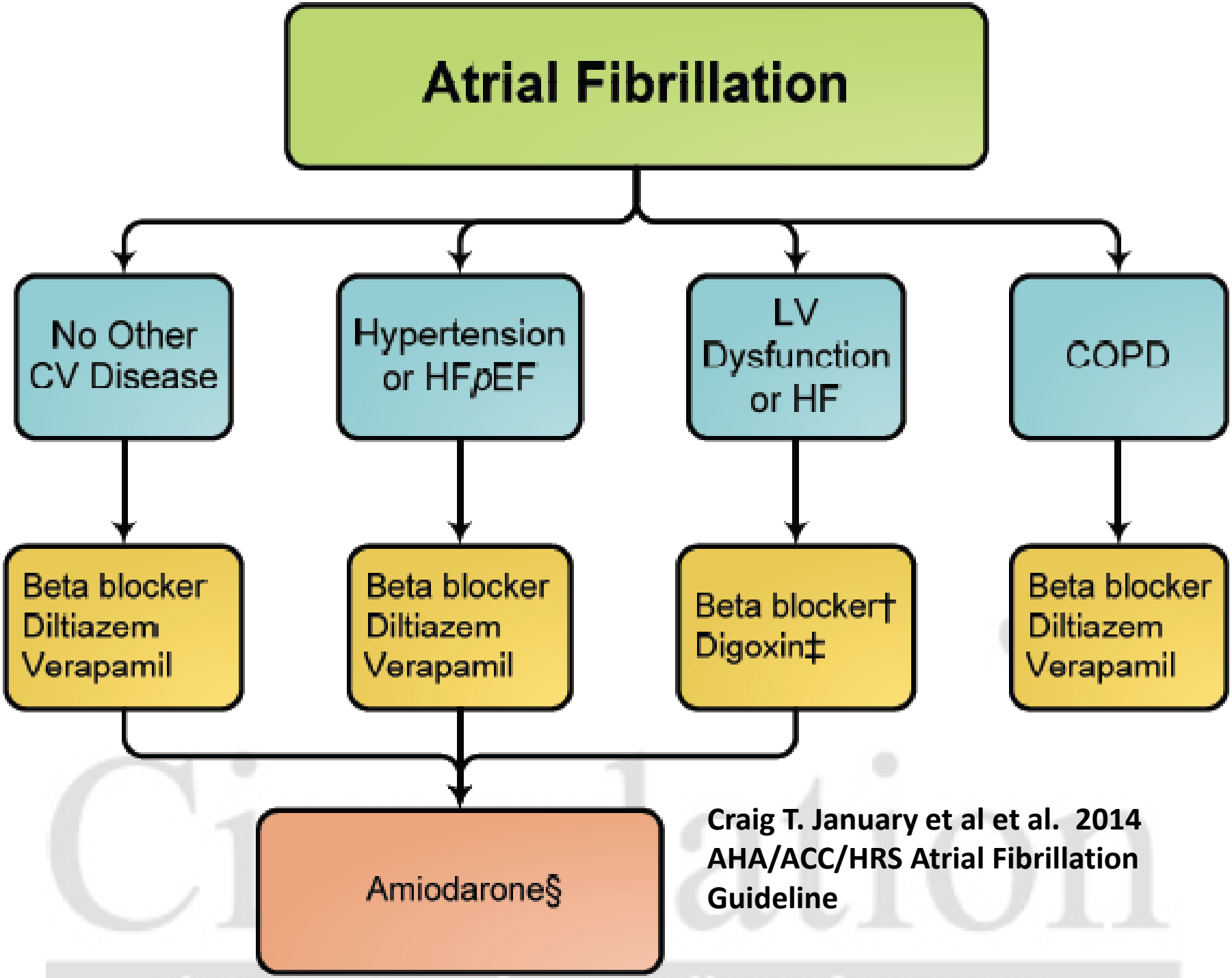
Control ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF	I	B
For AF, assess heart rate control during exertion, adjusting pharmacological treatment as necessary	I	C
Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated	IIb	C
Nondihydropyridine calcium channel antagonists should not be used in decompensated HF	III: Harm	C
With pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or amiodarone, should not be administered	III: Harm	B
Dronedarone should not be used to control ventricular rate with permanent AF	III: Harm	B

Uzun Dönem Hız Kontrolü-ESC

Rate control using pharmacological agents (β-blockers, non-dihydropyridine calcium channel antagonists, digitalis, or a combination thereof) is recommended in patients with paroxysmal, persistent, or permanent AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia.	I	B
In patients who experience symptoms related to AF during activity, the adequacy of rate control should be assessed during exercise, and therapy should be adjusted to achieve a physiological chronotropic response and to avoid bradycardia.	I	C
In pre-excitation AF, or in patients with a history of AF, preferred drugs for rate control are propafenone or amiodarone.	I	C

It is reasonable to achieve rate control by administration of dronedarone in non-permanent AF except for patients with NYHA class III–IV or unstable heart failure.	IIa	B
Digoxin is indicated in patients with heart failure and LV dysfunction, and in sedentary (inactive) patients.	IIa	C
Rate control may be achieved by administration of oral amiodarone when other measures are unsuccessful or contraindicated.	IIb	C
Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF.	III	B



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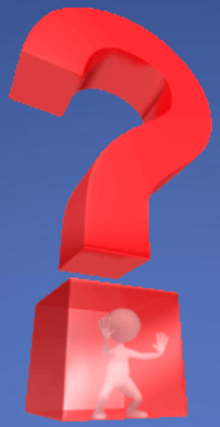
Ritim Kontrolü

- Daha fazla hastaneye yatış
- Daha pahalı
- Daha fazla yan etki
- Daha fazla invaziv işlem

Hız Kontrolü

- Persistan AF
- Asemptomatik hasta
- ≥ 65 yaş
- Kardiyoversiyona uygun olmayan hasta (AF > 1 yıl, dilate LA > 5,5 cm, multiplkardiyoversiyona rağmen AF)
- Komorbid durumların varlığı
- Antiaritmik tedavi başarısızlığı veya yan etkisi
- Hasta tercihi



Ritim Kontrolü

- Paroksismal AF veya yeni tanı AF
- Semptomatik hasta
- < 65 yaş
- Lone AF ve tetikleyici faktörlere bağlı AF (hipertiroidi, alkol, kafein, cerrahi sonrası)
- AF'ye bağlı taşikardiyomiyopati
- Hız kontrolüne rağmen semptomatik olan hasta
- Hasta tercihi

Bajpai A et al. British Medical Bulletin 2008;88:75-94.

Ritim Kontrolü

- Ritim kontrolü benimsendiğinde AF rekürensini engellemek içi antiaritmik tedavi planlanmalı
- İlaç seçimini etkinlikten çok güvenlik profili belirlemeli
- Potansiyel proaritmi riski değerlendirilmeli

Kinidin

- Sınıf 1a antiaritmik
- AF ve ventriküler taşikardi tedavisinde
- Vagolitik, α bloker, Na ve yüksek dozda K kanal blokajı
- Yan etki→diare, çinkonizm ve trombositopeni, QT uzaması, torsades de pointes(verapamil azaltır)
- P-glikoprotin inhibisyonu sonucu serum digoksin düzeyini yükseltir.

Disopiramid

- Sınıf 1a antiaritmik
- Na kanal blokajı, antikolinerjik ve negatif inotropik
- Vagatoni ile indüklenen AF tedavisinde etkili
- HKMP ye AF eşlik ettiğinde etkili
- Dar açılı glokom, prostat hipertrofisi ve myasteni gravisde kullanılmamalı

Flekainid-Propafenon


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outpatient Treatment of Recent-Onset Atrial Fibrillation with the "Pill-in-the-Pocket" Approach

- Sınıf 1c antiaritmik
- Yapısal kalp hastalığı olmayan hasta
- MI ve sol ventrikül disfonksiyonu olan hastalarda kontraendike→ ventriküler proaritmi
- Pill in the pocket*
  - Etkili ve güvenli
- Flekainidin ve propafenonun AF'yi hızlı ventrikül yanıtlı atriyal fluttera dönüştürme potansiyeli nedeniyle eşzamanlı atriyoventriküler düğüm blokajı önerilmektedir**.
- Flekainin özellikle 24 saatten kısa süre önce başlayan AF lerde etkili(%67-92 başarı 6 saat)
- Propafenon başarı oranı %41-91 arasında değişmekte.
- Yan etki→baş dönmesi, görme bozukluğu, metalik tat

*Alboni P. Et al N Engl J Med 2004;351:2384-91.

**ESC 2010 GuidelinesEuropean Heart Journal (2010) 31, 2369–2429

Sotalol

- Sınıf 3 antiaritmik, potasyum kanal (I_{KR}) ve Beta bloker, günde çift doz(2x80→2x240)
- Renal klerens (GFR:30-60→günde tek doz)
- QT uzaması→mortalite artış nedeni
- Sinus ritmine döndürmede başarısız ancak sinus ritminin idamesinde diğer antiaritmikler kadar etkili

Lafuente LC. Et al Cochrane Database Syst Rev. 2007;CD005049.

Dofetilide

- Sınıf 3 antiaritmik
- Selektif potasyum kanal bloker (I_{KR})
- Renal klerens→doz ayarlaması
- Sinus ritminin devamının sağlanmasında , sinus ritmine çevirmeden daha etkili(SAFIRE-D çalışması*).
- 24 saat içinde %70 36 saat içinde %91 kardiyoversiyon başarısı gösterildi (SAFİRE-D).
- Post-MI ve kalp yetersizliğinde güvenli (DIAMOND çalışması**)
- QT uzaması→Torsade de Pointes

Efficacy and Safety of Oral Dofetilide in Converting to and Maintaining Sinus Rhythm in Patients With Chronic Atrial Fibrillation or Atrial Flutter

The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study

***Circulation*. 2000;102:2385-2390.**

**Pedersen OD et al Circulation. 2001;104:292-6.

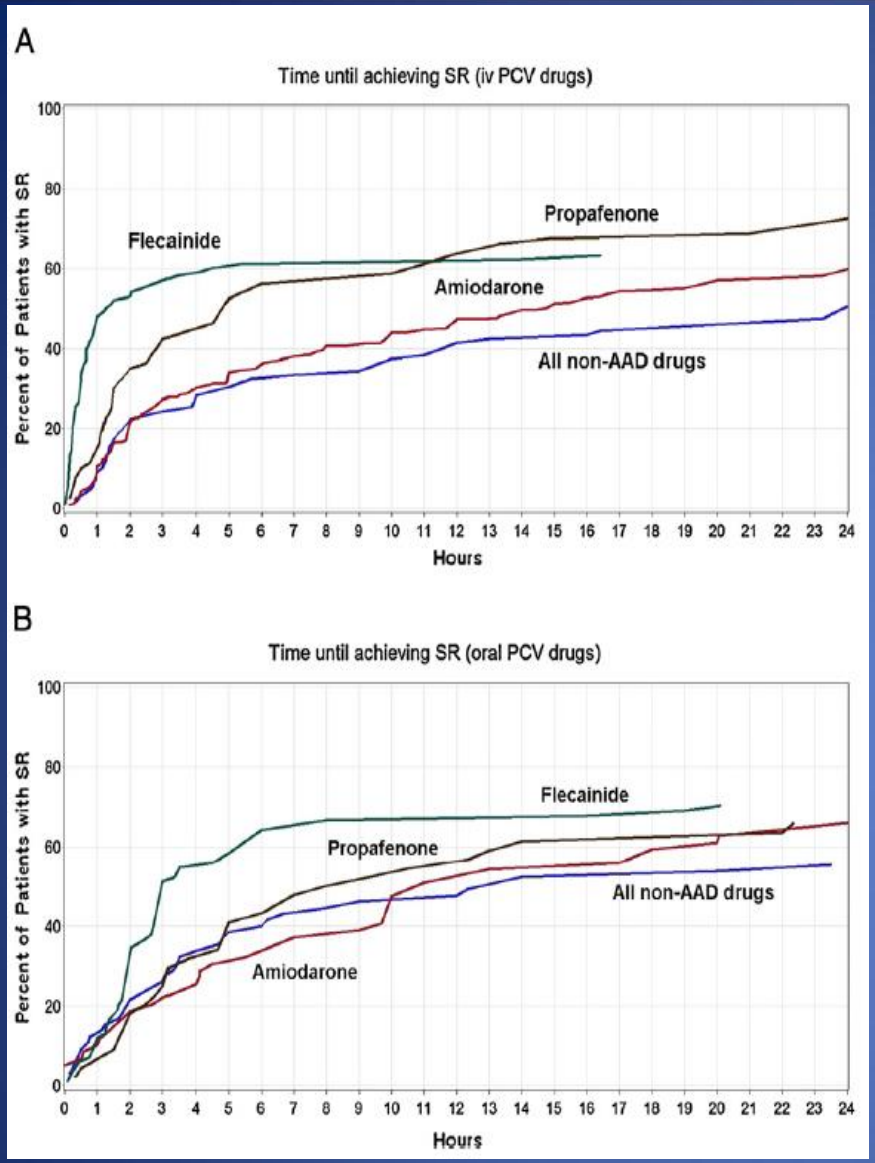
İbutilide

- Sadece ıv formu olan sınıf 3 antiaritmik.
- 30 dk dan kısa sürede %50 hastada sinus ritmini sağlamakta
- Atriyal flutterda daha başarılı.
- Elektriksel kardiyoversiyon başarısını artırır.
- QT aralığını uzatır, EF<%30 ve hipokalemi durumunda kullanılmamalı.

Abi-Mansour P et al. Am Heart J. 1998;136(4 Pt 1):632
Oral H et al. N Engl J Med. 1999;340:1849-54.

Amiodaron

- Sınıf 3 antiaritmik, iyodinize
- Multıkanal bloker(K, Na, Ca), α ve β bloker
- Yarılanma ömrü haftalar sürüyor ve yağ dokuda depolanıyor.
- En etkili antiaritmik(Sotalol, propofenon, dranedaron ile karşılaştırmalı çalışmaları.)
- CYP3A4 ve CYP2C9 inhibisyonu→varfarin etkisi artar
- P-glikoprotein inh→digoksin klerensi azalır



- Altı haftalık oral amidaron yüklemesi ile kardiyoversiyon oranı %25
- Amidaron ıv yükleme tedavisini plasebo ile karşılaştıran çalışmada konversiyon oranları %80-%40
- Elektriksel kardiyoversiyon başarısını artırır.

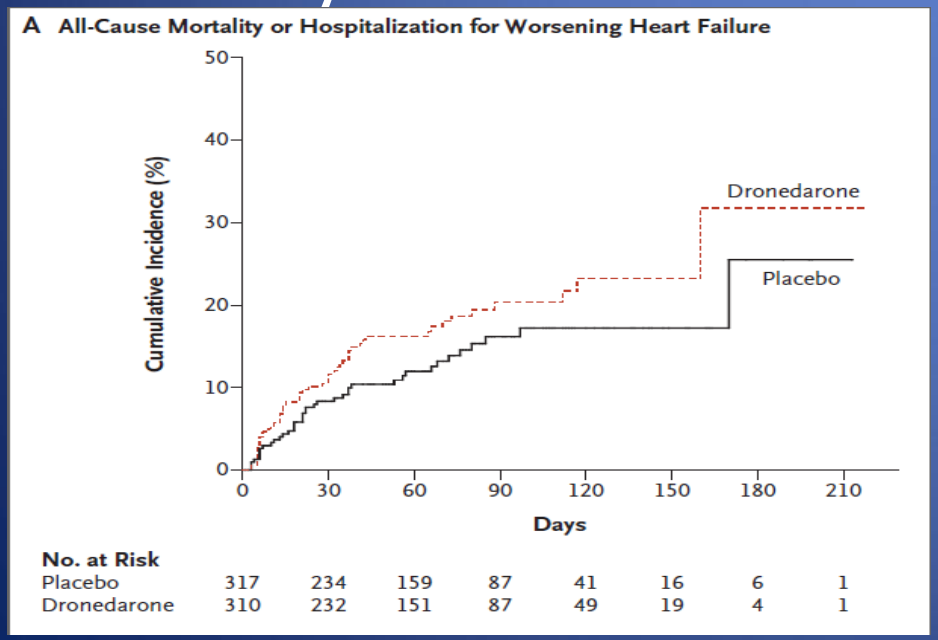
CrijnsHJ et al. RHYTHM-AFstudy. Int JCardiol. 2014; 172:588–594.
Singh BN et al N Engl J Med. 2005;352(18):1861.
Vardas PE et alChest. 2000;117(6):1538

Amiodaron-Yan Etkisi

- Pulmoner hipersensitivite ve kronik intertisyel fibrosiz
- Hepatit
- Tiroidit (hipo-hipertroidizm)
- Fotosensitivite
- Ciltte mavi-gri renk değişimi
- Ataxi, tremor, alopesi
- Sinus bradikardisi, QT uzaması

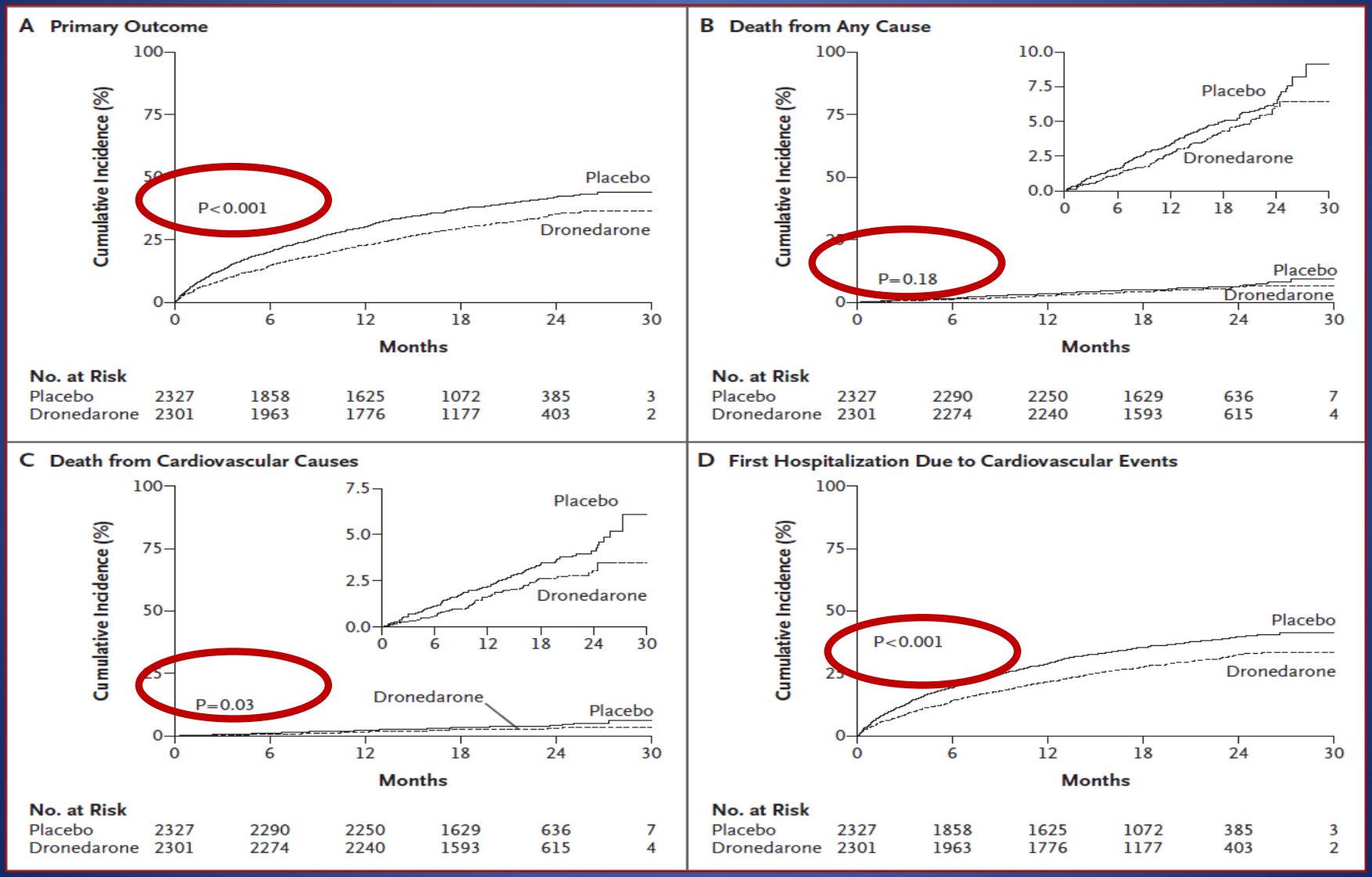
Dronedaron

- Sınıf 3 antiaritmik, multikanal bloker
- Yapı amiodarone benzer ancak daha az toksik
- Kalp yetersizliği hastalarında mortaliteyi artırıyor→kontraendike*(ANDROMEDA)



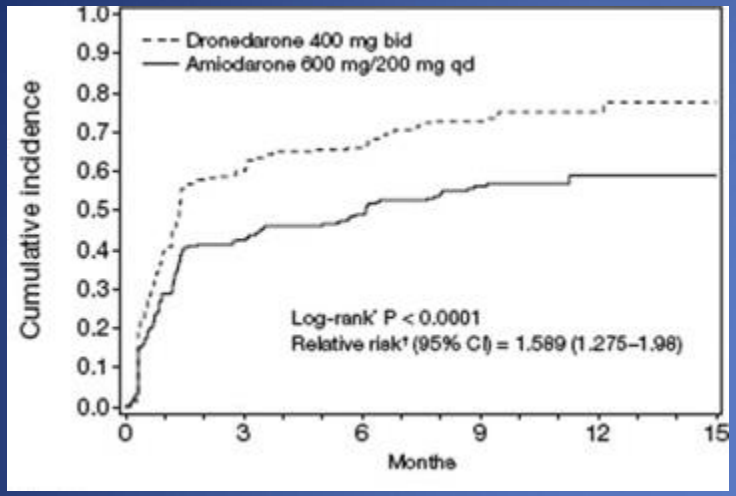
*ANDROMEDA investigators N Engl J Med 2008;358:2678-87

Kalp yetersizliği olmayan AF hastalarında extrakardiyak yan etki oluşturmadan hospitalizasyon ve mortaliteyi azalttığı gösterildi.(**ATHENA- PLASEBO KONTROLLÜ)**



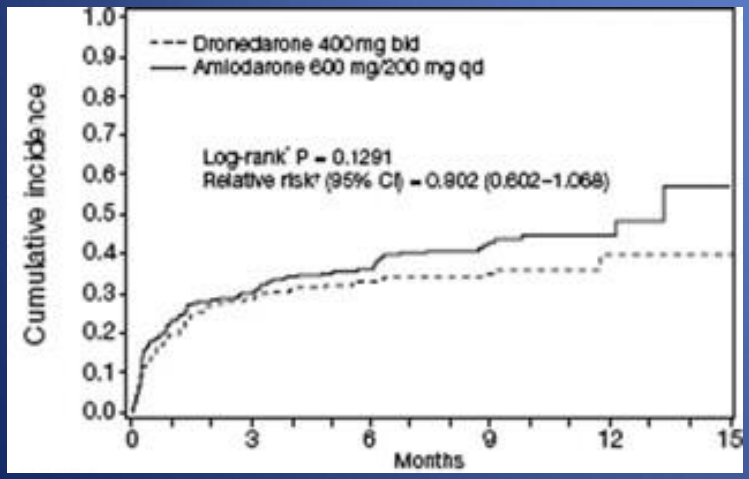
ATHENA Investigators. N Engl J Med. 2009;360:668–678.

The DIONYSOS Amiodaron&Dronedaron



AF REKÜRENSİ

risk oranı (RO) 1.59; %95 GA 1.28–1.98; *P* <0.0001



GÜVENLİK SONLANIM NOKTASI

RO 0.80; %95 GA 0.60–1.07; *P* = 0.129

PALLAS→Kardiyovasküler olaylar için yüksek riskli permanent AF hastaları Dronedaron&Plasebo

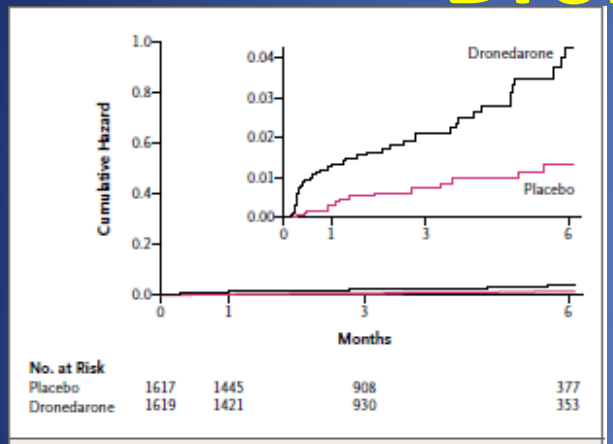


Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

Primer sonlanım noktaları →inme, MI, sistemik embolizm, kardiyovasküler nedenli ölüm dronedaron grubunda fazla **P=0,002**

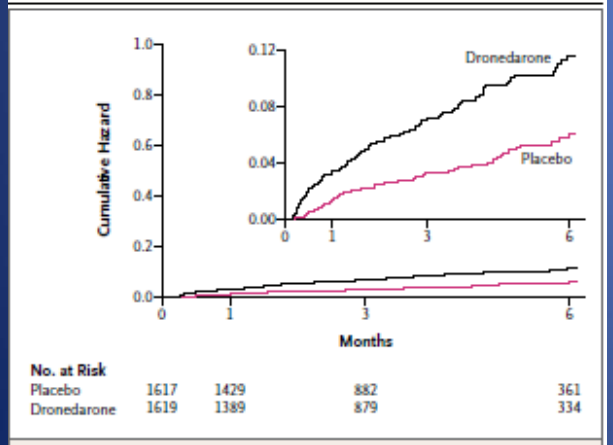


Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

Kardiyovasküler nedenli planlanmayan hospitalizasyon dronedaron gurubunda fazla **P=0,02**

Pallas trial. N Engl J Med 2011;365:2268-76.

Dronedaron

- Bradikardi, QT uzaması
- CYP 3A4 ile metobolize olur.
- CYP 2D6 ve P-glikoprotein inh.→dıgoksin ve dabigatran serum seviyesini artırır
- Verapamil ve diltizem (CYP3A4 inh) ile kullanılabilir ancak doz ayarlanmalıdır.
- Hepatotoksik

Vernakalant

- Multipl iyon kanalı blokeri.
- Atriyal selektif
- Atriyal refrakterliği uzatıp, hıza bağımlı atriyal iletiyi yavaşlatır, fakat ventriküler repolarizasyondan sorumlu akımlar üzerinde çok az etkisi vardır.

Vernakalant Hydrochloride for Rapid Conversion of Atrial Fibrillation

A Phase 3, Randomized, Placebo-Controlled Trial

ACT trial

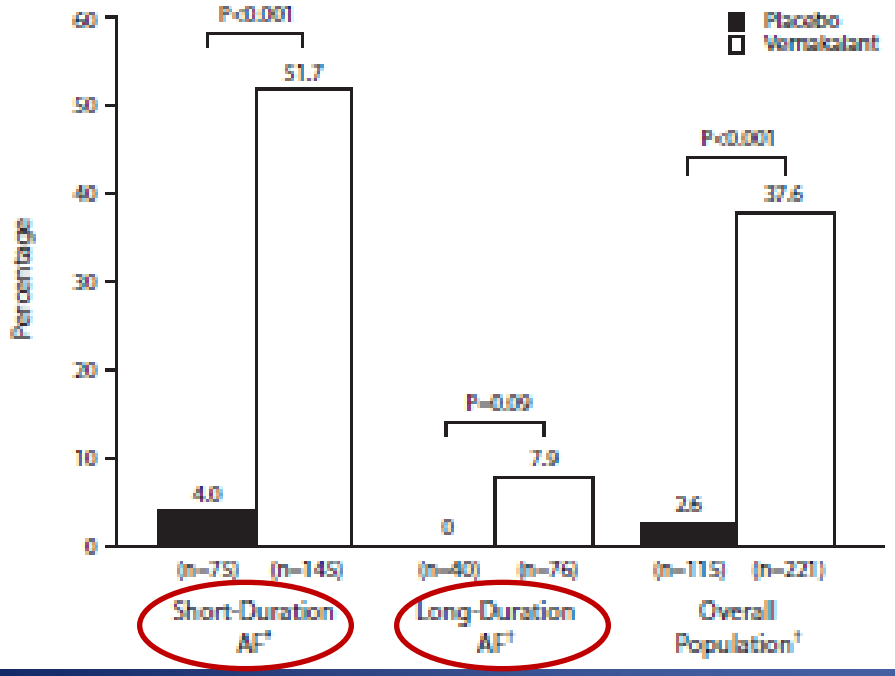


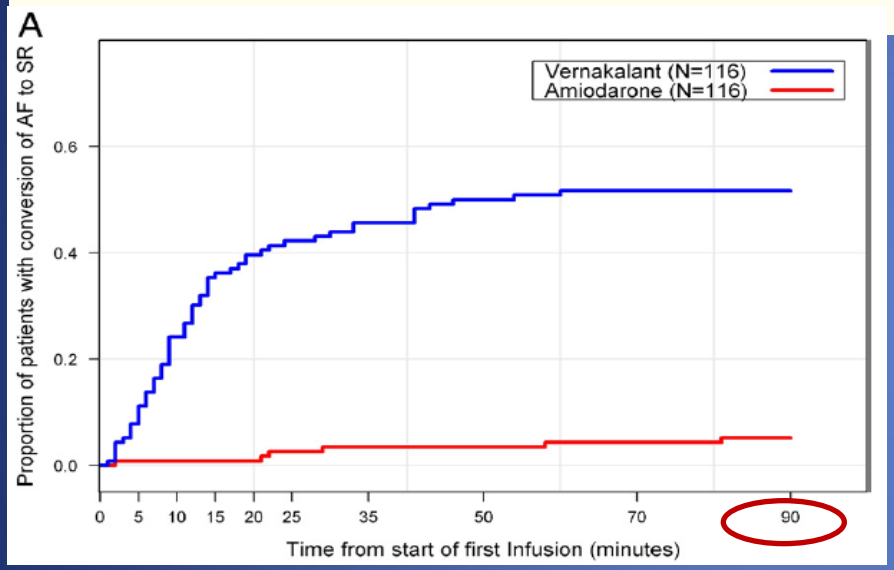
Table 2. Success Rates in Patients With AF Lasting 3 to 48 Hours and 3 to 7 Days

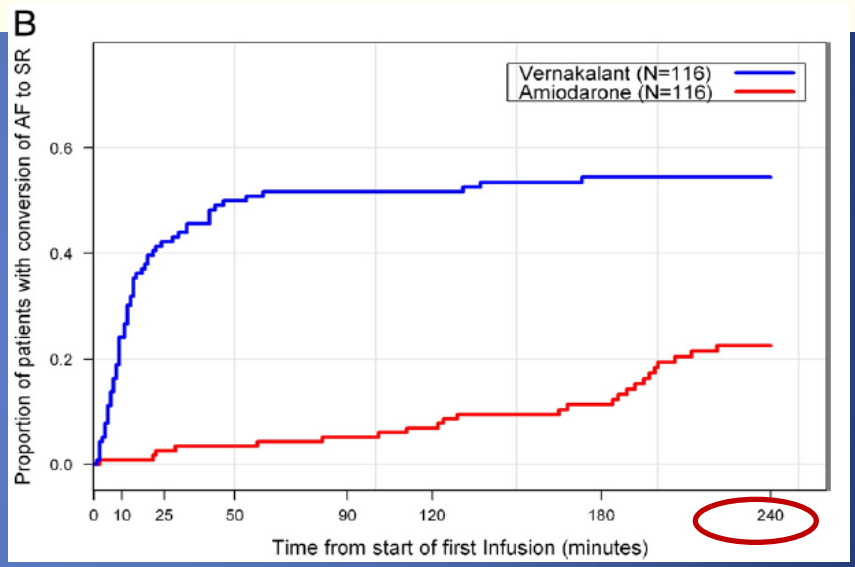
	Conversion to Sinus Rhythm, n (%)	Difference of Success (95% CI), %	*P*
AF lasting 3 to 48 h			
Vernakalant (n=103)	64 (62.1)	57.2 (46.4–68.0)	<0.001
Placebo (n=61)*	3 (4.9)		
AF lasting 3 to 7 d			
Vernakalant (n=42)	10 (23.8)	23.8 (10.9–36.7)	0.048
Placebo (n=16)*	0		

*Two patients given placebo in the long-duration AF group were reassigned after randomization for this nonprespecified analysis based on actual AF duration.

Roy D et al. Circulation 2008;117:1518–1525

A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation





infüzyon sonrası ilk 90 dk (%51,7'ye karşı %5,2; P<0,0001) ve 4 saat içinde (%54,4'e karşı %22,6; P<0,0001) sinüs ritminin sağlanmasında vernakalant intravenöz amiodarondan anlamlı derecede üstün.

AVRO çalışması

Camm AJ et al. J Am Coll Cardiol 2011;57:313–321

Vernakalant

- Vernakalant, AF süresi ≤7 gün veya kalp cerrahisi sonrası ≤3 gün olan hastaların kardiyoversiyonunda etkilidir .90 dk içerisinde, hastaların yaklaşık %50'sinde ve ortalama 8-14 dakikada kardiyoversiyon sağlar.

- Vernakalant infüzyonu 10 dakikada 3 mg/kg dozunda uygulanır ve eğer 15 dakika sonrasında AF sebat ederse ikinci bir infüzyon 2 mg/ kg dozunda verilebilir.

- IDKMP dahil kompanse hastalarda güvenli ancak VT ve hipotansiyon riskini artırabilir.

- Vernakalant, <100 mmHg hipotansiyon, yakın zamanda (<30 gün) akut koroner sendrom, NYHA sınıf III ve IV kalp yetersizliği, ciddi aort darlığı ve QT intervalinde uzama (düzeltilmemiş QT >440 ms) olan hastalarda kontrendikedir.

Beta Bloker

- Sinus ritminin idamesinde başarılı değiller.
- Post operatif dönem, tirotoksikoz gibi adrenerjik indüced AF gelişimini azaltabilir.

Antiaritmik İlaç Etkinliği

	Drug	OR of recurrence (95%CI)
Most effective	Amiodarone	0.19 (0.14–0.27)
	Dofetilide	0.28 (0.20–0.38)
	Flecainide	0.31 (0.16–0.60)
Some efficacy	Propafenone	0.37 (0.28–0.48)
	Quinidine	0.51 (0.40–0.65)
	Sotalol	0.53 (0.44–0.65)
	Dronedarone	0.60 (0.47–0.76)
No demonstrable benefit	Betablocker	0.74 (0.49–1.13)
	Verapamil	Unable to estimate
	Digoxin	Unable to estimate

Table 12. Recommended Drug Doses for Pharmacological Cardioversion of AF

Drug	Route of Administration	Dosage		Potential Adverse Effects
Amiodarone	Oral	600–800 mg daily in divided doses to a total load of up to 10 g, then 200 mg QD as maintenance		Phlebitis (IV), hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, increased INR
	IV	150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to oral dosing		
Dofetilide	Oral	CrCl (mL/min)	Dose (mcg BID)	QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age
		>60 40–60 20–40 <20	500 250 125 Not recommended	
Flecainide	Oral	200–300 mg x 1*		Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease
Ibutilide	IV	1 mg over 10 min; may repeat 1 mg once if necessary (weight <60 kg use 0.01 mg/kg)		QT prolongation, torsades de pointes, hypotension
Propafenone	Oral	450–600 mg x 1*		Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease

*Recommended given in conjunction with a beta blocker or nondihydropyridine calcium channel antagonist adı

ESC Flekainid 10 dakika boyunca 2 mg/kg i.v.

ESC propafenon 10 dakika boyunca 2 mg/kg i.v.

Craig T. January et al et al. 2014 AHA/ACC/HRS Atrial Fibrillation Guideline

AHA/ACC önerileri

Pharmacological cardioversion		
Flecainide, dofetilide, propafenone, and IV ibutilide are useful for cardioversion of AF or atrial flutter provided contraindications to the selected drug are absent	I	A
Amiodarone is reasonable for pharmacological cardioversion of AF	IIa	A
Propafenone or flecainide ("pill-in-the-pocket") to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting	IIa	B
Dofetilide should not be initiated out of hospital	III: Harm	B

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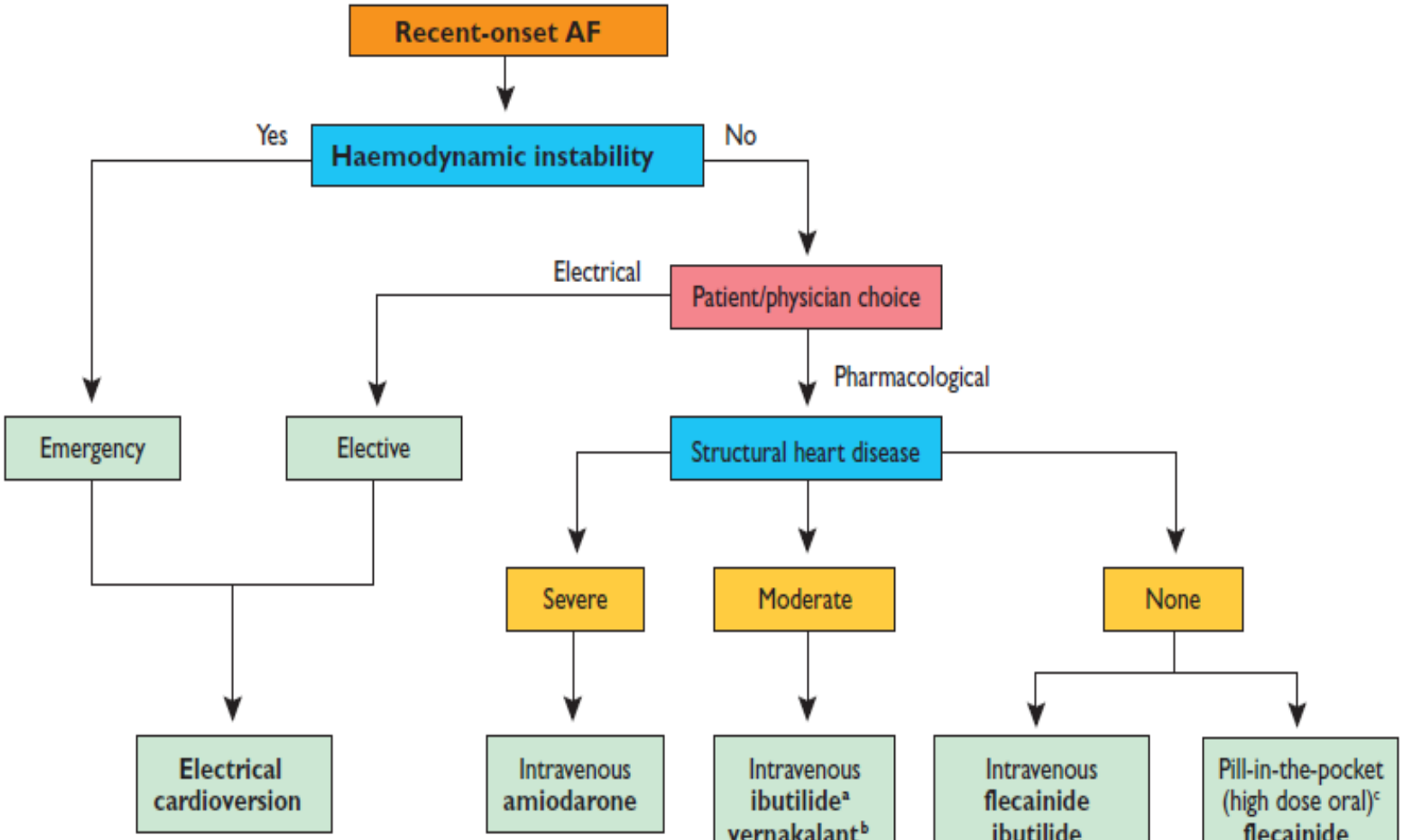
ESC Önerileri

Recommendations	Class[a]	Level[b]
When pharmacological cardioversion is preferred and there is no structural heart disease, i.v. flecainide or propafenone is recommended for cardioversion of recent-onset AF.	I	A
In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended.	I	A
In selected patients with recent-onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) should be considered, provided this treatment has proven safe during previous testing in a medically secure environment.	IIa	B
In patients with recent-onset AF, structural heart disease, but without hypotension or manifest congestive heart failure, ibutilide may be considered. Serum electrolytes and the QTc interval must be within the normal range, and the patients must be closely monitored during and for 4 h after the infusion because of risk of proarrhythmia.	IIb	A
Digoxin (LoE A), verapamil, sotalol, metoprolol (LoE B), other β-blocking agents and ajmaline (LoE C) are ineffective in converting recent-onset AF to sinus rhythm and are not recommended.	III	A B C

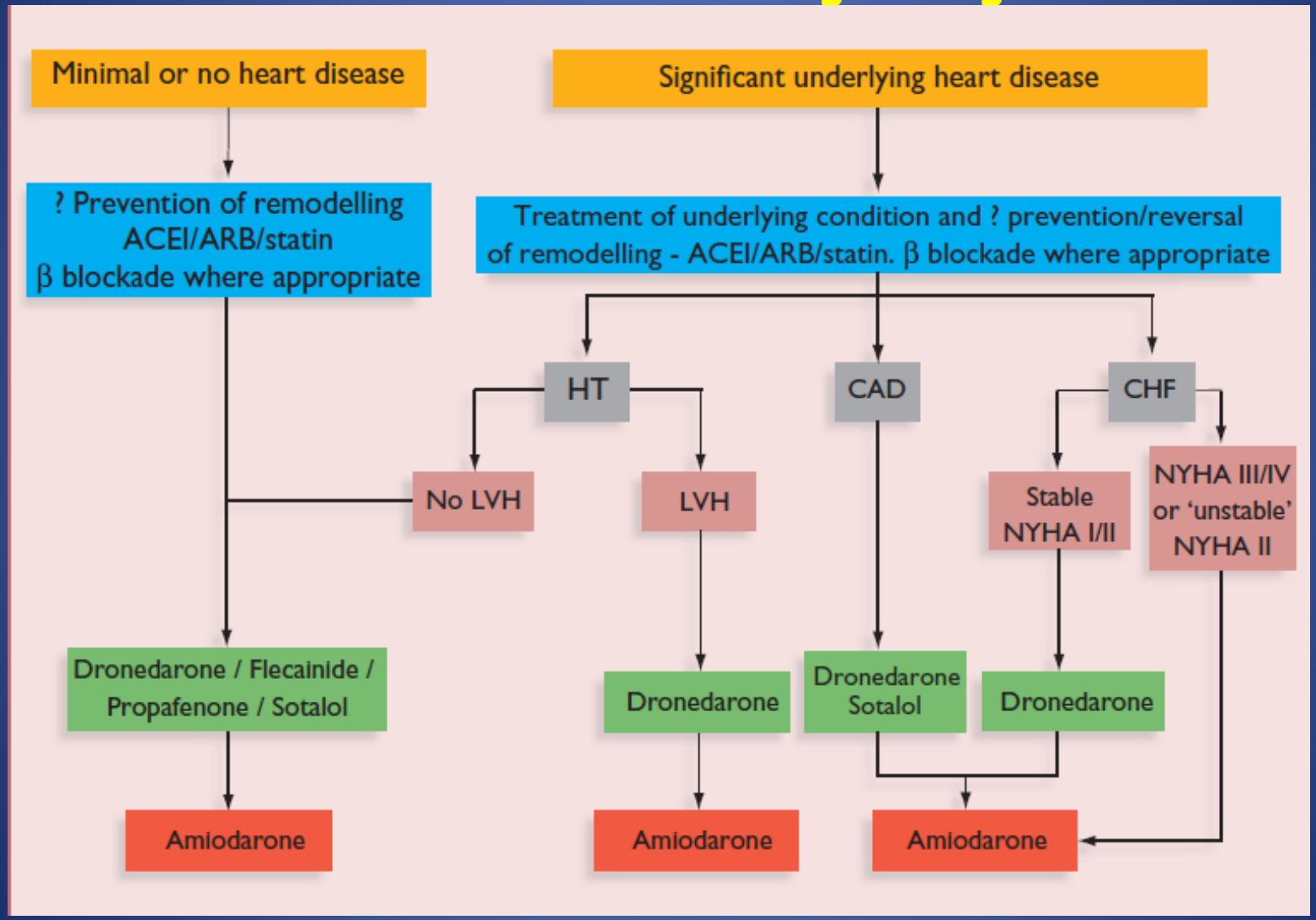
Recommendations	Class[a]	Level[b]	Ref[c]
When pharmacological cardioversion is preferred and there is no or minimal structural heart disease, intravenous flecainide, propafenone, ibutilide, or vernakalant are recommended.	I	A	120, 121, 123, 124, 126, 127, 131–134
In patients with AF ≤7 days and moderate structural heart disease [but without hypotension <100 mm Hg, NYHA class III or IV heart failure, recent (<30 days) ACS, or severe aortic stenosis], intravenous vernakalant may be considered. Vernakalant should be used with caution in patients with NYHA class I–II heart failure.	IIb	B	120, 121, 124, 128
Intravenous vernakalant may be considered for cardioversion of postoperative AF ≤3 days in patients after cardiac surgery.	IIb	B	122

ESC 2010 GuidelinesEuropean Heart Journal (2010) 31, 2369–2429
ESC 2012 Uptodated European Heart Journal (2012) 33, 2719–2747



[a]Ibutilide should not be given when significant left ventricular hypertrophy (≥1.4 cm) is present.
[b]Vernakalant should not be given in moderate or severe heart failure, aortic stenosis, acute coronary syndrome or hypotension. Caution in mild heart failure.
[c]'Pill-in-the-pocket' technique – preliminary assessment in a medically safe environment and then used by the patient in the ambulatory setting.

Antiaritmik İlaç Seçimi



ESC 2010 Guidelines European Heart Journal (2010) 31, 2369–2429

Öneriler→ACC/AHA/HRS

6.2.1. Antiarrhythmic Drugs to Maintain Sinus Rhythm: Recommendations

Class I

1. **Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended.** ***(Level of Evidence: C)***
2. **The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities** ***(Level of Evidence: A)*****:**
   a. **Amiodarone (314, 347-349)**
   b. **Dofetilide (332, 336)**
   c. **Dronedarone (350-352)**
   d. **Flecainide (347, 353)**
   e. **Propafenone (347, 354-357)**
   f. **Sotalol (347, 355, 358)**
3. **The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug.** ***(Level of Evidence: C)***
4. **Owing to its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated. (314, 354, 359-362).** ***(Level of Evidence: C)***

Class IIa

1. **A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy.** ***(Level of Evidence: C)***

Class IIb

1. **It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF, when the drug has reduced the frequency or symptoms of AF.** ***(Level of Evidence: C)***

Class III: Harm

1. **Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent** ***(Level of Evidence: C)*** **including dronedarone (282).** ***(Level of Evidence: B)***
2. **Dronedarone should not be used for treatment of AF in patients with New York Heart Association (NYHA) class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks (283).** ***(Level of Evidence: B)***

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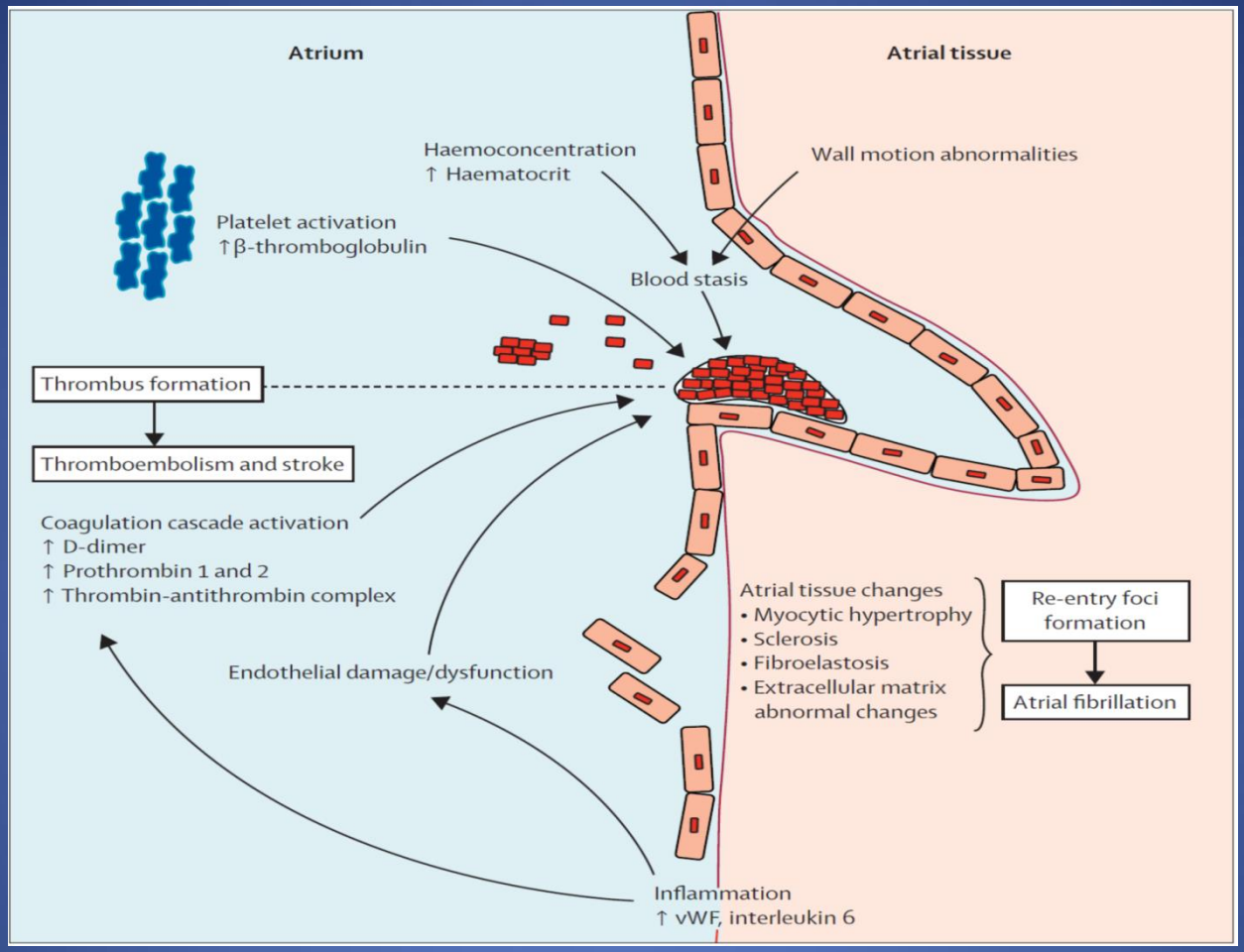
Öneriler→ESC

Recommendations	Class[a]	Level[b]
The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease:		
• amiodarone	I	A
• dronedarone	I	A
• flecainide	I	A
• propafenone	I	A
• d,l-sotalol	I	A
Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy), or dronedarone (LoE A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (LoE C).	I	A / C
In patients with severe heart failure, NYHA class III and IV or recently unstable (decompensation within the prior month) NYHA class II, amiodarone should be the drug of choice.	I	B
In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.	I	A

β-Blockers are recommended for prevention of adrenergic AF.	I	C
If one antiarrhythmic drug fails to reduce the recurrence of AF to a clinically acceptable level, the use of another antiarrhythmic drug should be considered.	IIa	C
Dronedarone should be considered in order to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.	IIa	B
β-blockers should be considered for rhythm (plus rate) control in patients with a first episode of AF.	IIa	C
Disopyramide may be considered in patients with vagally mediated AF.	IIb	B
Dronedarone is not recommended for treatment of AF in patients with NYHA class III and IV, or with recently unstable (decompensation within the prior month) NYHA class II heart failure.	III	B
Antiarrhythmic drug therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning permanent pacemaker.	III	C

ESC 2010 Guidelines European Heart Journal (2010) 31, 2369–2429

Atriyal Fibrilasyon – Sol Atriyal Appendiks – Trombüs Oluşumu



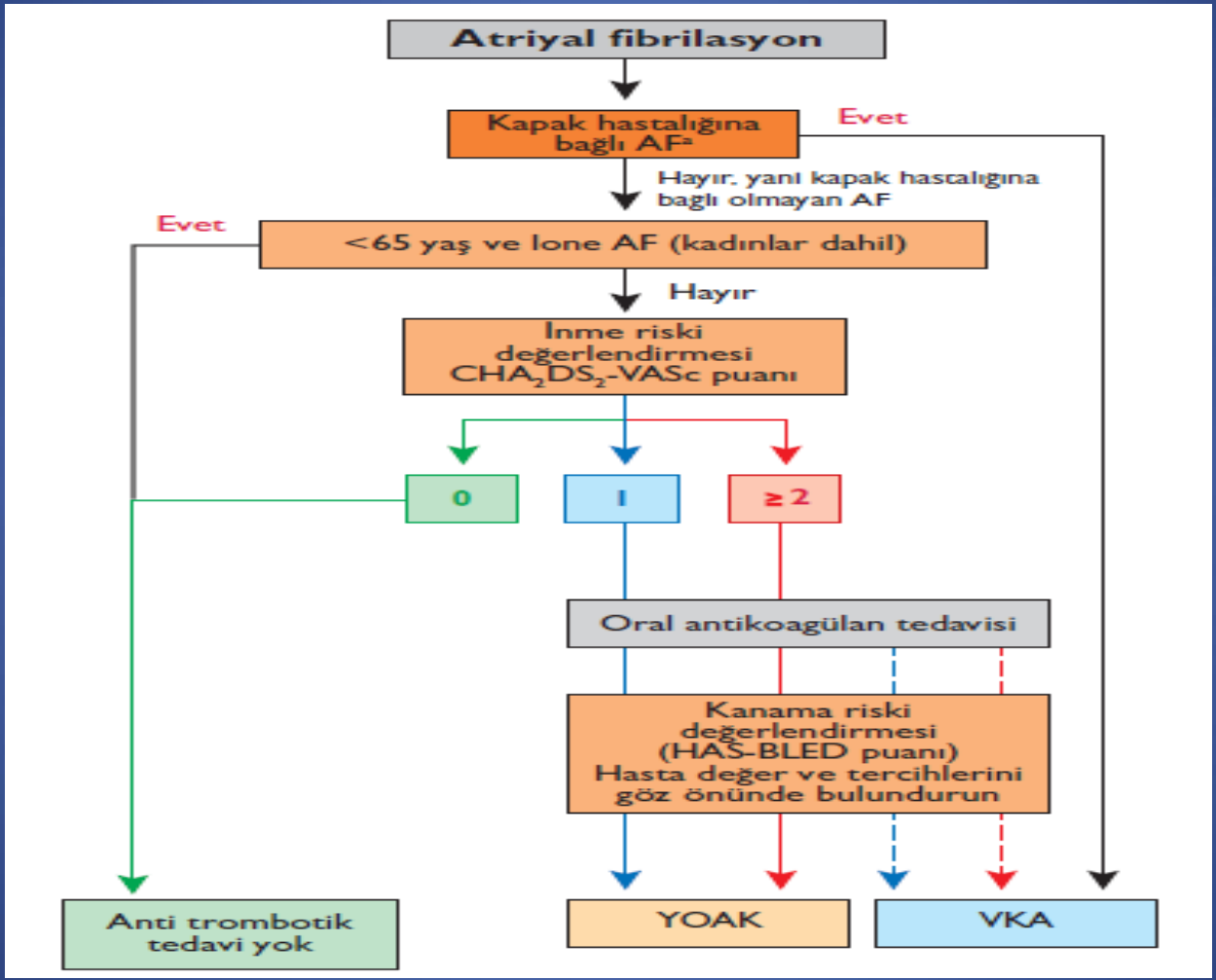
AF ye bağlı inme 50-59 yaş arasında %1,5 iken 80 yaş üstü bu oran %20 yi geçmektedir

AF ile ilişkili inmelerin morbidite ve mortalitesi daha yüksektir.

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

Heart disease and stroke statisticsCirculation 2011;123:e18–e209.

Antikoagülasyon



Camm AJ. 2012 focused update. European Heart Journal (2012) 33, 2719–2747

Antikoagülasyon-CHADS-VASc SKORU

0 düşük risk
1 orta risk
≥ yüksek risk

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc		Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores	
	Score		Adjusted Stroke Rate (% per y)
$CHADS_2$		$CHADS_2$*	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 y	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc		CHA_2DS_2-VASc†	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 y	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65–74 y	1	6	9.8
Sex category (i.e., female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

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Antikoagülasyon-HASBLED skoru

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

≥ 3 yüksek risk

AHA/ACC 2014

Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences	I
Antithrombotic therapy selection based on risk of thromboembolism	I
CHA_2DS_2-VASc score recommended to assess stroke risk	I
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis	I
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥ 2, oral anticoagulants recommended. Options include:	
• Warfarin	I
• Dabigatran, rivaroxaban, or apixaban	I
With warfarin, determine INR at least weekly during initiation and monthly when stable	I
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR	I
Re-evaluate the need for anticoagulation at periodic intervals	I

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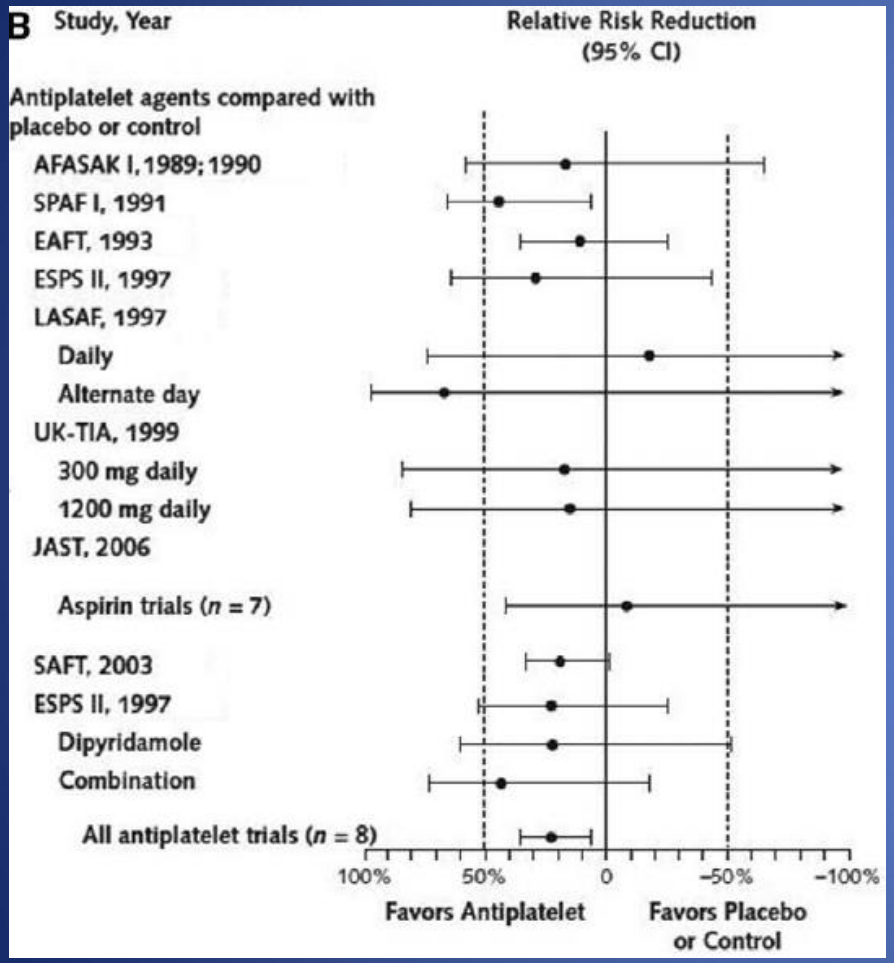
Aspirin



- SPAF çalışması inmeden korumada plasebodan üstün olduğunu gösterdi
- Primer profilkaside %19 relatif risk azalması sağladı
- BAFTA çalışmasında 75 yaş üstü hastalarda warfarin aspirine önemli kanama riskini artırmadan üstün bulundu

Aguilar M. Cochrane Database Syst Rev. 2005;(4):CD001925.
Mant J , (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007;370:493–503.

Klopidogrel+ASA

- ACTİVE-W çalışması warfarinin %40 relatif risk azalması sağladığını gösterdi.
- ACTİVE-A çalışması kombinasyonun tek başına ASA tedavisine göre %28 relatif risk azalması sağladığı ancak major kanama riskini %57 artırdığını gösterdi.
- ASA&Klopidogrel karşılaştıran çalışma yok
- AVERROES çalışması ASA ve Apixabanı karşılaştırdı ve apixaban üstünlüğü nedeniyle erken sonlandırıldı

Connolly SJ, Lancet. 2006;367:1903–12. 199.
Connolly SJ. N Engl J Med. 2009;360:2066–78
Connolly SJ, N Engl J Med. 2011;364:806–17.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

With nonvalvular AF and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy	IIa
With nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered	IIb

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2012) **33**, 2719–2747
doi:10.1093/eurheartj/ehs253

ESC GUIDE

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation

Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa

Öneriler

ESC

When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended.	I
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III

AHA

With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:	
Warfarin	I
Dabigatran, rivaroxaban, or apixaban	I
With moderate-to-severe CKD and CHA_2DS_2-VASc scores ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered	IIb
Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits	III: No Benefit