Diyaliz Hastalarında Oral Antikoagülan ve Antiagregan Tedavi

Doç. Dr. Emre Tutal
Başkent Üniversitesi
Nefroloji BD

- **Antikoagülan tedavi**
  - **Warfarin**
  - **Dabigatran**
- **Antiagregan tedavi**
  - **Asetilsalisilik asit**
  - **Klopidogrel**

Diyaliz hastasında AA/AK tedavi

- **Endikasyonlar**
  - **Genel endikasyonlar**
    - **Atrial fibrilasyon**
    - **Venöz ya da arteryal trombotik hadiseler**
    - **Serebrovasküler olay**
  - **Özel endikasyonlar**
    - **AVF ya da kateter korunması**

KBY hastalarında tromboz eğilimi

- Biyokimyasal
  - Artmış prokoagülan faktörler (vWf)
  - Artmış pıhtılaşma faktör işaretçi düzeyleri (D-dimer)
  - Azalmış endojen antikoagülanlar (Antitrombin, protein c-s)
  - Azalmış fibrinolitik aktivite (plazminojen, tPA)
- Klinik
  - Artmış arterial vasküler hastalık
  - İmmobilite
  - rHuEPO kullanımı

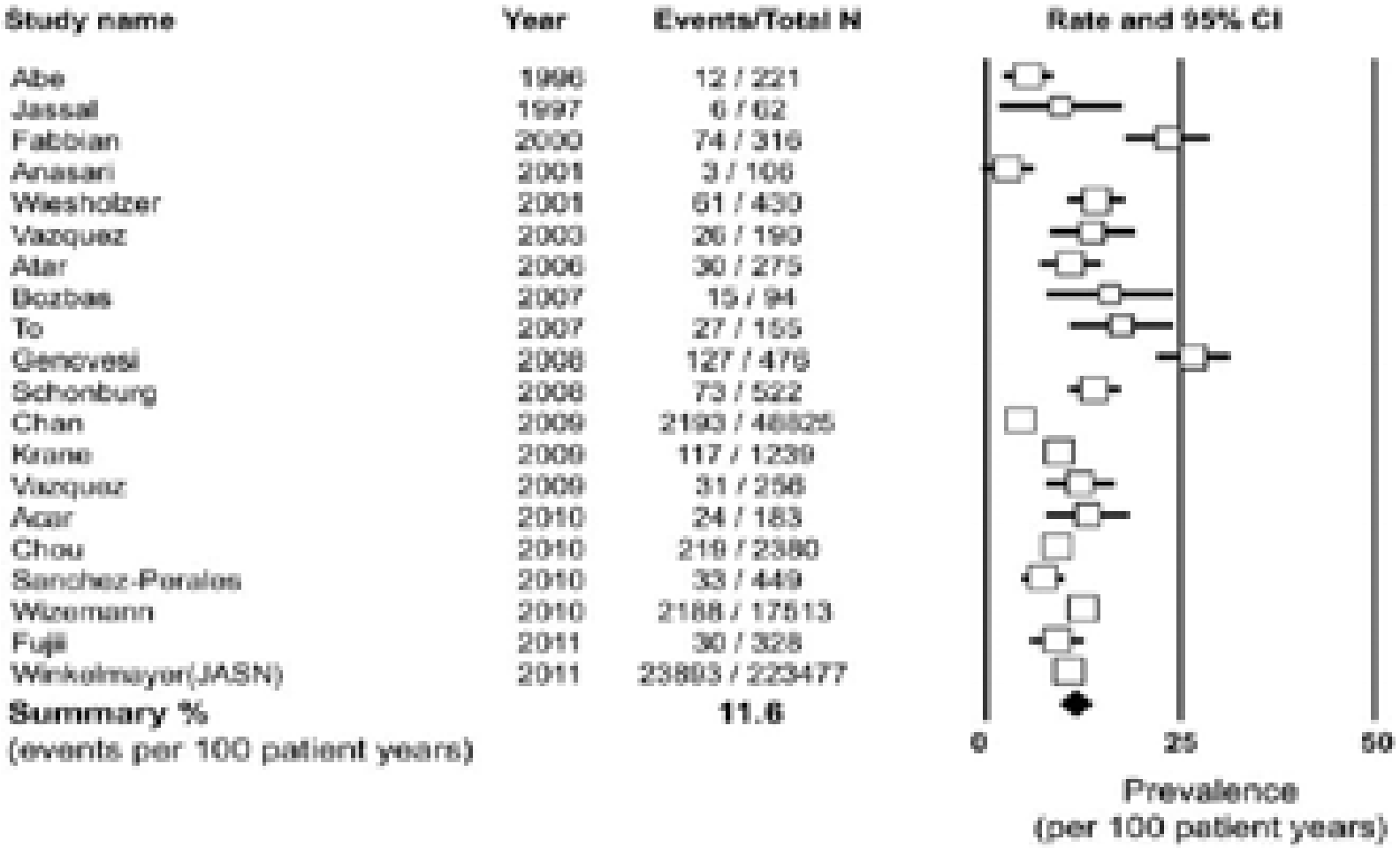
Nephrol Dial Transplant (2012) 27: 3136–3142
doi: 10.1093/ndt/gfr616

Original Articles

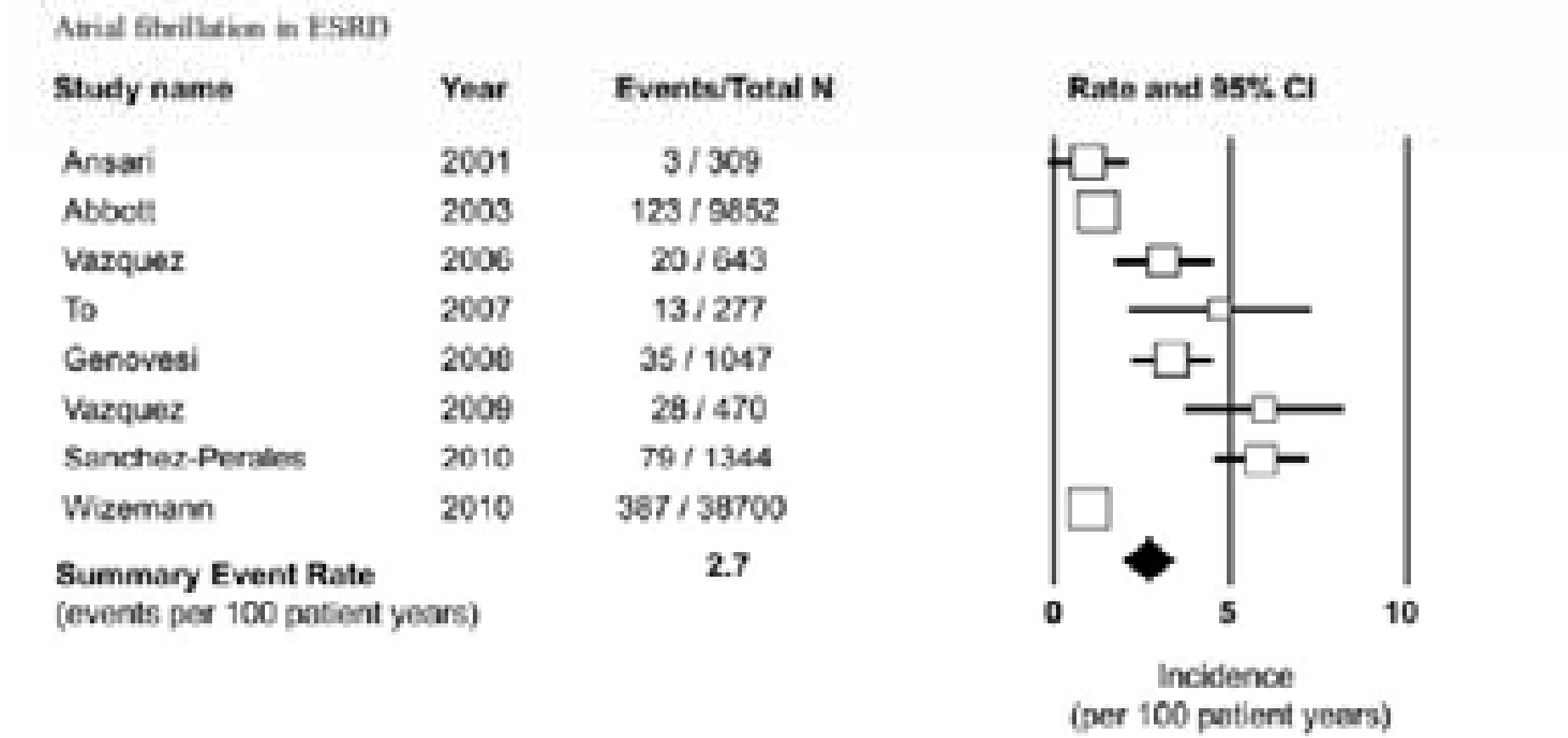
Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis

Deborah Zimmerman[1], Manish M. Sood[2], Claudio Rigatto[2], Rachel M. Holden[3], Swapnil Hiremath[1] and Catherine M. Clase[3]

1990-2011 arası 25 ana çalışmanın meta-analizi



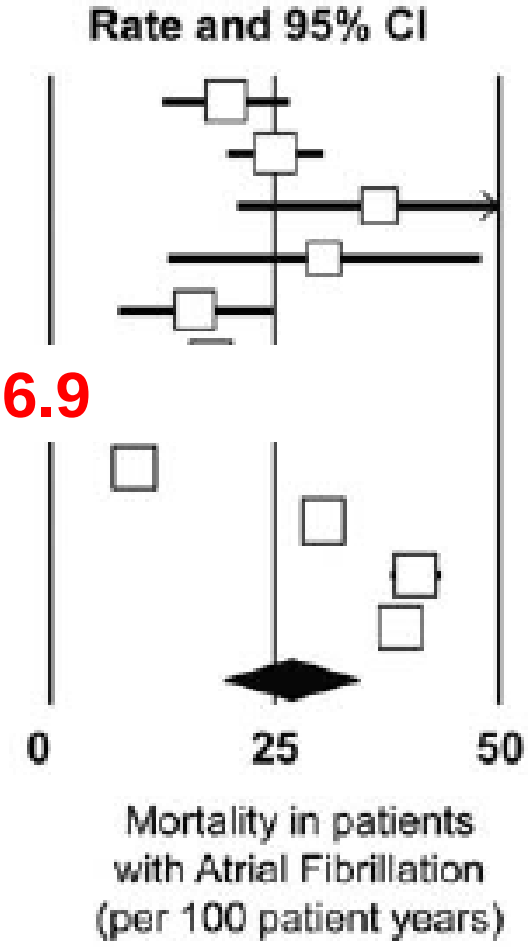
KBY popülasyonunda yıllık AF prevelansı normal popülasyona göre belirgin yüksektir (%11.6)



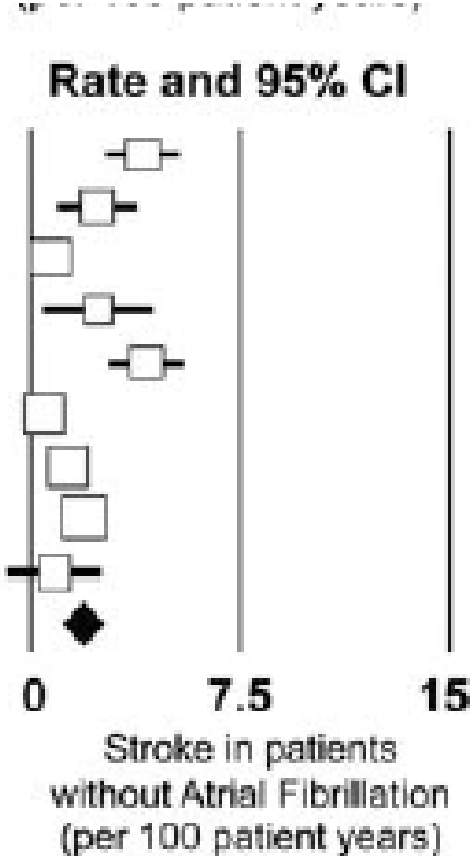
KBY popülasyonunda yıllık AF insidansı normal popülasyona göre belirgin yüksektir (%2.7)

Study name	Year	Events/Total N
Wiesholzer	2001	31 / 158
Abbott	2003	90 / 359
Vazquez	2003	21 / 57
Vazquez	2006	12 / 39
To	2007	14 / 87
G		
Va		
Chou	2010	63 / 673
Wizemann	2010	1342 / 4412
Winkelmayer(cJASN)	2011	931 / 2287
Winkelmayer(JASN)	2011	7180 / 18410
Summary Event Rate (events per 100 patient years)		26.9

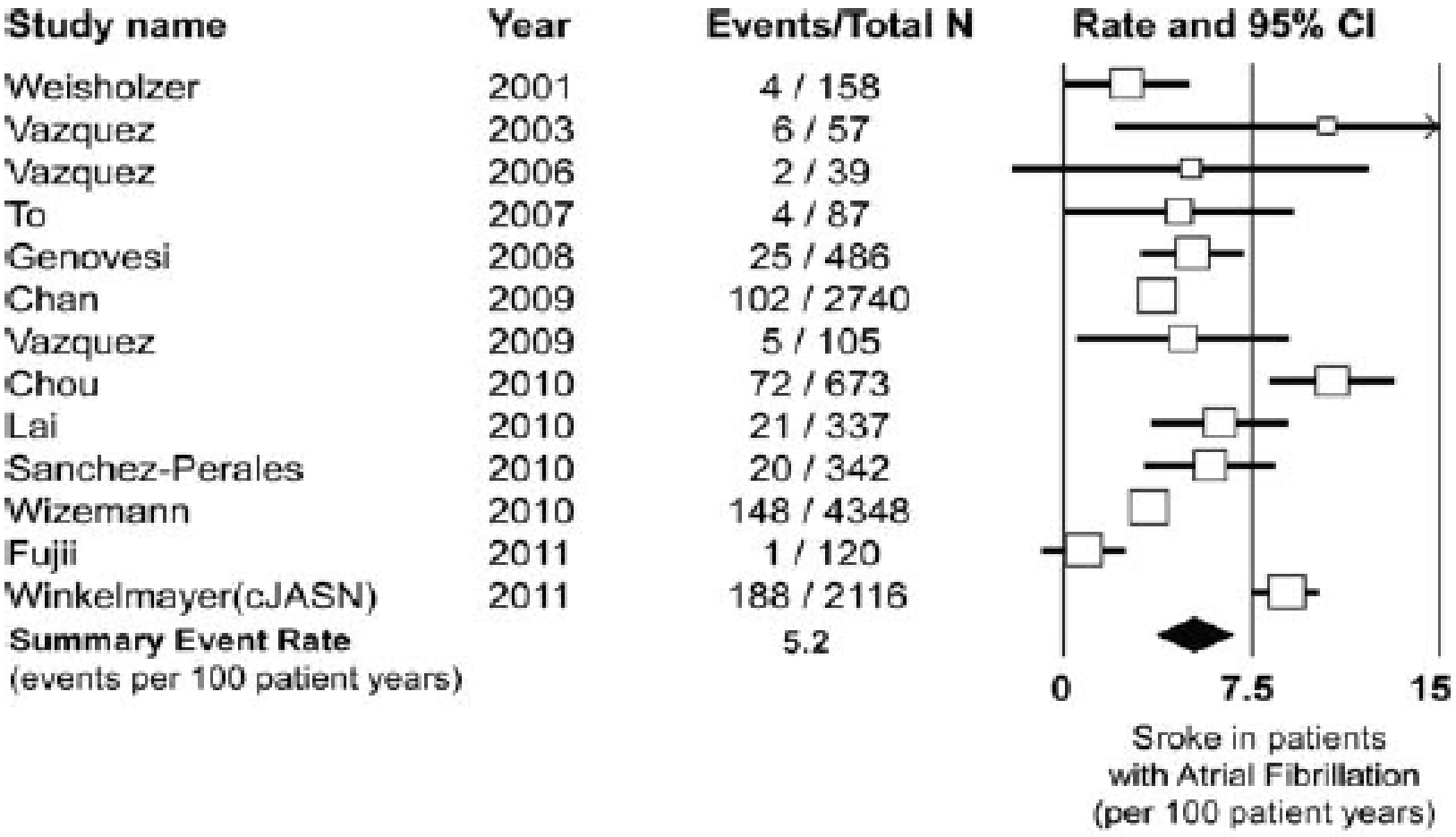
AF olan hastalarda yıllık mortalite %26.9



Study name	Year	Events/Total N
Wiesholzer	2001	38 / 954
Vazquez	2003	11 / 468
Vazquez	2006	4 / 564
To	2007	6 / 249
Genovesi	2008	39 / 942
Vazquez	2009	2 / 411
Sanchez-Perales	2010	14 / 1061
Wizemann	2010	695 / 36552
Fujii	2011	1 / 120
Summary Event Rate (events per 100 patient years)		**1.9**



AF olmayan hastalarda inme sıklığı %1.9



AF olan hastalarda inme sıklığı %5.2

Europace (2010) 12, 1666–1672
doi:10.1093/europace/euq387

REVIEW

Warfarin in haemodialysis patients with atrial fibrillation: what benefit?

Felix Yang[1]*, Denise Chou[2], Paul Schweitzer[3], and Sam Hanon[3]

[1]Division of Cardiology/Arrhythmia Offices Former 2, Department of Medicine, Montefiore Medical Center, 111 E. 210th Street, Bronx, NY 10467, USA; [2]Department of Neurology, New York Presbyterian Hospital—Cornell, New York, NY, USA; and [3]Division of Cardiology, Department of Medicine, Beth Israel Medical Center, New York, NY, USA

Received 24 July 2010; accepted after revision 19 September 2010; online publish-ahead-of-print 2 November 2010

Warfarin Farmakokinetiği

- **Dar terapötik indeks, çok sayıda ilaç ve yiyecek etkileşimi**
- **GFR < 30 mL/dk/1.73 m2 durumunda ciddi doz azaltılma gerekliliği**
- **Esas olarak karaciğer metabolizması (CYP P-450)**
- **KBY'de KC cytochrome P-450 aktivitesi %45-80 oranında azalabilir**
- **Benzer dozlarda plazma düzeyi x 1.5 artar**

- **Hemodiyaliz hastalarında kanama riski tromboz riskine göre daha fazladır? (Iseki et al. Kidney Int. 1993)**
  - **1609 diyaliz hastasının 4 yıllık takibinde**
    - **Serebral kanama riski x 10.7**
    - **Subaraknoid kanama riski x 4 kat daha fazla**
    - **Tüm vakalar beklenenden 10 ortalama 10 yıl önce gerçekleşiyor**

Stroke

American Heart Association | American Stroke Association

Decreased Glomerular Filtration Rate Is a Risk Factor for Hemorrhagic But Not for Ischemic Stroke : The Rotterdam Study

Michiel J. Bos, Peter J. Koudstaal, Albert Hofman and Monique M.B. Breteler

Stroke. 2007;38:3127-3132; originally published online October 25, 2007;
doi: 10.1161/STROKEAHA.107.489807

Table 2. Hazard Ratios for the Association Between GFR and Risk of Stroke (N=4937)

Event	GFR*	HR (95% CI) Model 1†	Model 2†	Model 3†
All stroke (n=586)	Quartile 4	1 (ref)	1 (ref)	1 (ref)
	Quartile 3	0.86 (0.65–1.14)	0.88 (0.66–1.16)	0.85 (0.64–1.13)
	Quartile 2	1.15 (0.88–1.51)	1.16 (0.89–1.52)	1.10 (0.84–1.44)
	Quartile 1	1.14 (0.84–1.54)	1.15 (0.85–1.55)	1.04 (0.77–1.41)
Ischemic stroke (n=338)	Quartile 4	1 (ref)	1 (ref)	1 (ref)
	Quartile 3	0.88 (0.63–1.22)	0.89 (0.64–1.24)	0.87 (0.62–1.20)
	Quartile 2	1.13 (0.82–1.56)	1.16 (0.84–1.60)	1.09 (0.79–1.51)
	Quartile 1	0.87 (0.59–1.29)	0.90 (0.61–1.32)	0.81 (0.54–1.20)
Hemorrhagic stroke (n=44)	Quartile 4	1 (ref)	1 (ref)	1 (ref)
	Quartile 3	1.76 (0.58–5.29)	1.79 (0.59–5.38)	1.73 (0.58–5.22)
	Quartile 2	3.06 (1.06–8.86)	3.12 (1.08–9.03)	2.92 (1.00–8.48)
	Quartile 1	4.10 (1.25–13.42)	4.14 (1.27–13.54)	3.68 (1.12–12.09)

*Thresholds for increasing quartiles were 53.9, 63.1, and 72.0 mL/min/1.73 m^2 for men and 50.4, 60.3, and 70.1 mL/min/1.73 m^2 for women.

Table 3. Hazard Ratios for the Association Between Chronic Kidney Disease and Risk of Stroke (N=4937)

Event	GFR (ml/min/1.73 m^2)	HR (95% CI) Model 1*	Model 2*	Model 3*
All stroke (n=586)	≥60 (N=2652)	1 (ref)	1 (ref)	1 (ref)
	<60 (N=2285)	1.29 (1.06–1.57)	1.28 (1.05–1.56)	1.22 (1.00–1.49)
Ischemic stroke (n=330)	≥60 (N=2652)	1 (ref)	1 (ref)	1 (ref)
	<60 (N=2285)	1.25 (0.97–1.61)	1.26 (0.98–1.63)	1.19 (0.92–1.53)
Hemorrhagic stroke (n=44)	≥60 (N=2652)	1 (ref)	1 (ref)	1 (ref)
	<60 (N=2285)	3.02 (1.45–6.27)	3.05 (1.46–6.35)	2.88 (1.38–6.01)

- **Diğer kanama komplikasyonları**
  - **GIS kanama**
    - **3-7% ölüm sebebi**
    - **İnsidans %2.5/yıl**
    - **GIS kanama öyküsü 24.7%**

- **Diyaliz hastaları genel olarak antikoagülan çalışmalarında dışarıda bırakılmıştır**
  - **the Atrial Fibrillation Follow-up Investigation of Rhythm Management study (AFFIRM)**
  - **Stroke Prevention in Atrial Fibrillation study (SPAF)**

Normal popülasyonda SVO risk skalaları

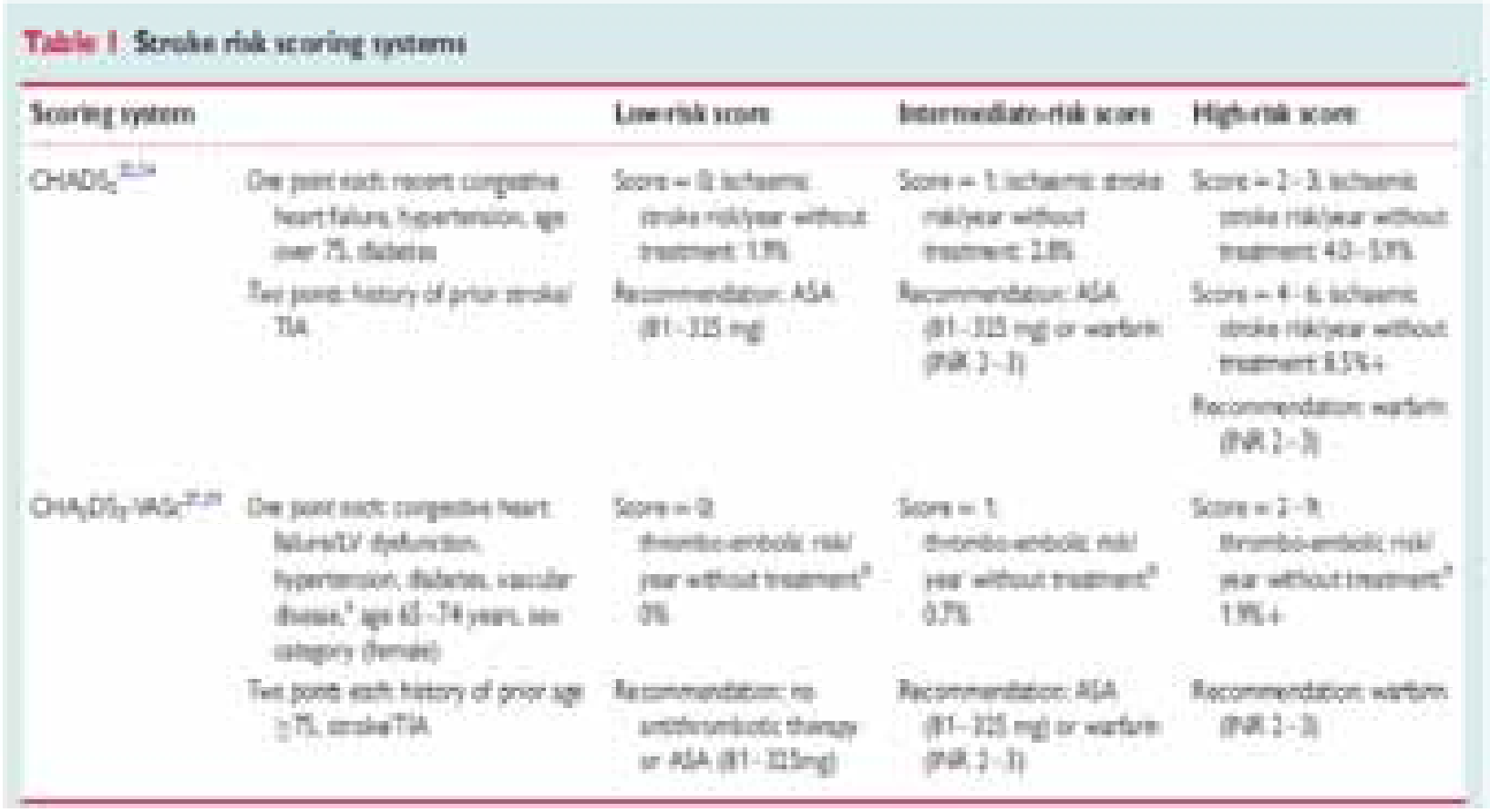


Table 1: Stroke risk scoring systems

Scoring system		Low-risk score	Intermediate-risk score	High-risk score
$CHADS_2$	One point each: recent congestive heart failure, hypertension, age over 75, diabetes Two points: history of prior stroke/TIA	Score = 0: ischaemic stroke risk/year without treatment: 1.9% Recommendation: ASA (81–325 mg)	Score = 1: ischaemic stroke risk/year without treatment: 2.8% Recommendation: ASA (81–325 mg) or warfarin (INR 2–3)	Score = 2–3: ischaemic stroke risk/year without treatment: 4.0–5.9% Score = 4–6: ischaemic stroke risk/year without treatment: 8.5%+ Recommendation: warfarin (INR 2–3)
CHA_2DS_2-VASc	One point each: congestive heart failure/LV dysfunction, hypertension, diabetes, vascular disease,[a] age 65–74 years, sex category (female) Two points each: history of prior age ≥75, stroke/TIA	Score = 0: thrombo-embolic risk/year without treatment:[b] 0% Recommendation: no antithrombotic therapy or ASA (81–325mg)	Score = 1: thrombo-embolic risk/year without treatment:[b] 0.7% Recommendation: ASA (81–325 mg) or warfarin (INR 2–3)	Score = 2–9: thrombo-embolic risk/year without treatment:[b] 1.9%+ Recommendation: warfarin (INR 2–3)

Bu popülasyonda antikoagülan tedavi %50 risk azalması sağlar

Kanama riskini öngören skalalar

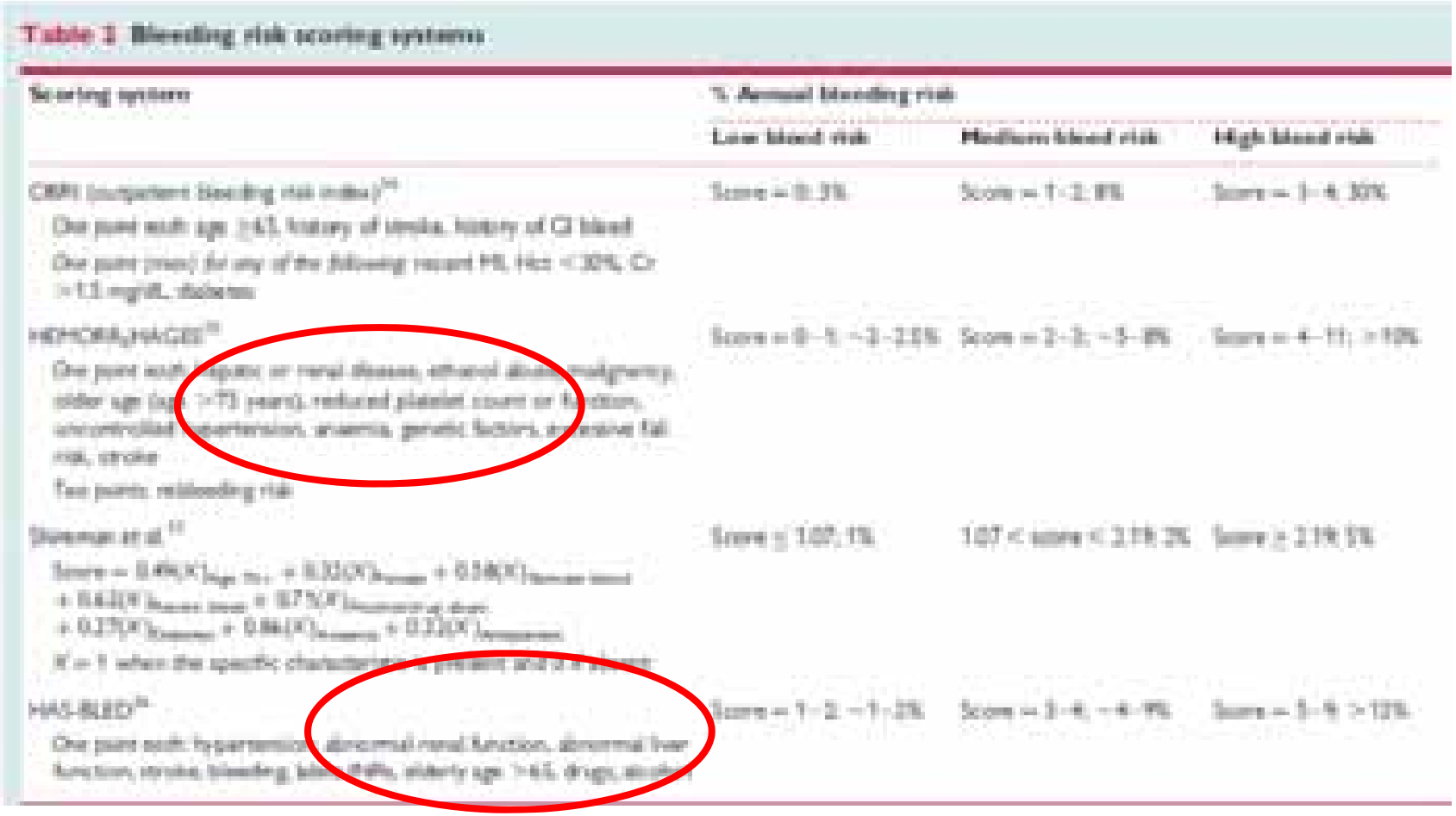


Table 1 Bleeding risk scoring systems

Scoring system	% Annual bleeding risk		
	Low bleed risk	Medium bleed risk	High bleed risk
CBRI (outpatient bleeding risk index)[20]	Score = 0: 3%	Score = 1–2: 8%	Score = 3–6: 30%
One point each: age ≥65, history of stroke, history of GI bleed			
One point (max) for any of the following: recent MI, Hct <30%, Cr >1.5 mg/dL, diabetes			
HEMORR$_2$HAGES[21]	Score = 0–1: ~1–2.5%	Score = 2–3: ~5–8%	Score = 4–11: >10%
One point each: hepatic or renal disease, ethanol abuse, malignancy, older age (>75 years), reduced platelet count or function, uncontrolled hypertension, anaemia, genetic factors, excessive fall risk, stroke			
Two points: rebleeding risk			
Sloesman et al.[11]	Score ≤ 107: 1%	107 < score < 319: 2%	Score ≥ 319: 5%
Score = $0.49(X)_{\text{age}\geq 75\text{ y}} + 0.32(X)_{\text{diabetes}} + 0.58(X)_{\text{decreased blood}}$			
$+ 0.63(X)_{\text{previous bleed}} + 0.75(X)_{\text{insufficient ad. dose}}$			
$+ 0.27(X)_{\text{malignancy}} + 0.86(X)_{\text{anaemia}} + 0.32(X)_{\text{hypertension}}$			
$X = 1$ when the specific characteristic is present and 0 if absent			
HAS-BLED[22]	Score = 1–2: ~1–2%	Score = 3–4: ~4–9%	Score = 5–9: >12%
One point each: hypertension, abnormal renal function, abnormal liver function, stroke, bleeding, labile INRs, elderly age >65, drugs, alcohol			

Use of Warfarin in People with Low Glomerular Filtration Rate or on Dialysis

Rachel M. Holden* and Catherine M. Clase†‡
*Department of Medicine, Queen's University, Kingston, Ontario, Canada, †Departments of Medicine and ‡Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

TABLE 1. Risk of stroke in National Registry of Atrial Fibrillation participants not treated with warfarin or aspirin, stratified by $CHADS_2$

$CHADS_2$ score	Predicted annualized stroke rate (95% CI)
0	1.9 (1.2–3.0)
1	2.8 (2.0–3.8)
2	4.0 (3.1–5.1)
3	5.9 (4.6–7.3)
4	8.5 (6.3–11.1)
5	12.5 (8.2–17.5)
6	18.2 (10.5–27.4)

TABLE 2. Risk of major bleeding in National Registry of Atrial Fibrillation participants prescribed warfarin, stratified by $HEMORR_2HAGES$ score

$HEMORR_2HAGES$ score	Predicted annualized major bleeding rate (95% CI)
0	1.9 (0.6–4.4)
	2.5 (1.3–4.3)
	5.3 (3.4–8.1)
	8.4 (4.9–13.6)
	10.4 (5.1–18.9)
≥5	12.3 (5.8–23.1)

Table 4—*Comparison of Major Bleeding Rates Between Patients With ESRD on OAC and the General Population*

Study	Major Hemorrhage Rate Without OAC	Major Hemorrhage Rate With OAC
ORBI low risk		3
ORBI medium risk		8
ORBI high risk		30
ESRD population		
Holden et al[23]	0.8	3.1
Elliott et al[24]	2.5–11	26–54

All data are presented as % per year.

X 5 – 10 artmış kanama riski

Warfarin-ASA kombinasyonunda kanama riski

Major Bleeding in Hemodialysis Patients

Rachel M. Holden,* Gavin J. Harman,* Miao Wang,† David Holland,* and Andrew G. Day†
*Division of Nephrology, Queen's University, and †Clinical Research Centre, Kingston General Hospital, Kingston, Ontario, Canada

Table 2. Incidence rate analysis by treatment combination*

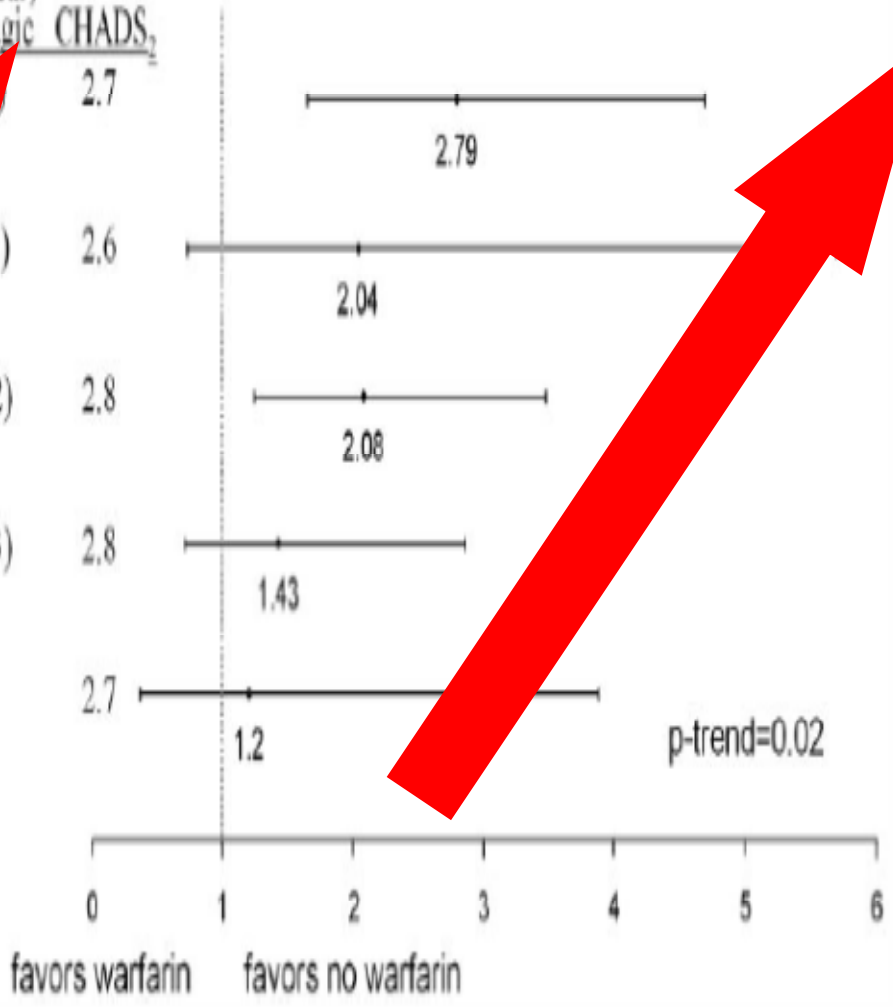
Treatment Combination	Contributed Patients*	Person-Years	Major Bleeds	IR (Exact 95% CI)	Rate Ratio (Approximate 95% CI†)	P
None	178	518.9	4	0.8% (0.2 to 2.0%)	Referent	Referent
Warfarin only	89	159.1	5	3.1% (1.0 to 7.3%)	4.1 (1.1 to 15.2)	0.07‡
Aspirin only	107	271.7	12	4.4% (2.3 to 7.7%)	5.7 (1.8 to 17.8)	0.002
Aspirin + warfarin	50	79.0	5	6.3% (2.1 to 14.8%)	8.2 (2.2 to 30.6)	0.006
Total	255	1027.9	26	2.5% (1.7 to 3.7%)		

TABLE 2. Safety of warfarin in hemodialysis patients

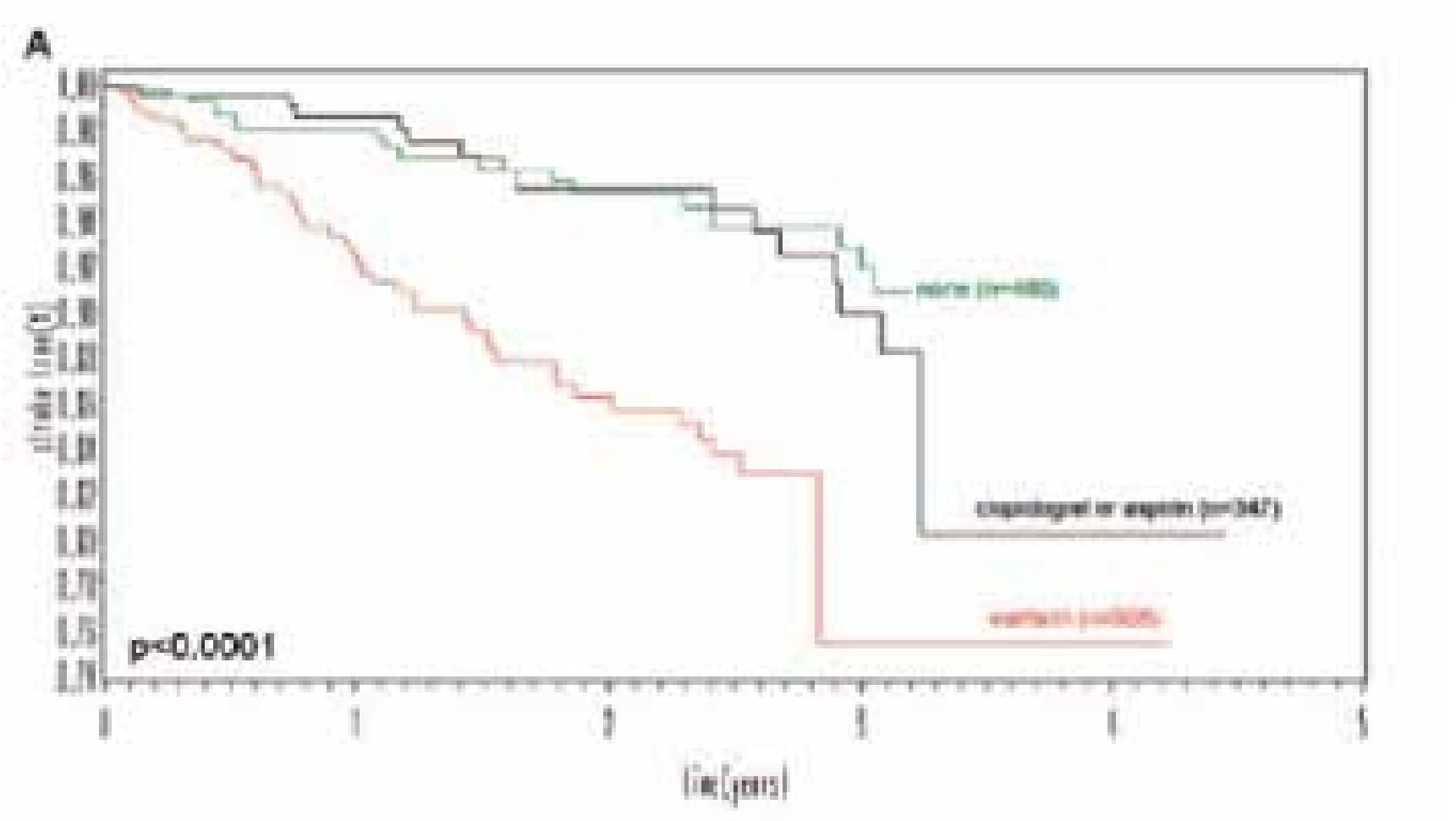
Reference	n	Target INR	Results
Mokrzycki et al. (24)	85 (41 W, 44 C)	1 mg/day (no target INR)	One patient on warfarin experienced cerebral emboli with peripheral areas of hemorrhage One patient in placebo group developed a bleeding decubitus ulcer
Zellweger et al. (26)	65 (35 W, 30 C)	INR 1.5–2.0	No major bleeds reported
Crowther et al. (29)	107 (56 W, 51 C)	INR 1.4–1.9	Six major bleeds[a] and 11 minor bleeds in warfarin group Zero major bleeds and seven minor bleeds in placebo group
Coli et al. (27)	144	INR 1.8–2.5	No reported bleeding events
Obialo et al. (25)	42 (11 W, 31 C)	INR 2.0–3.0	In the warfarin group there were two GI bleeds and one subdural hematoma with a fall versus no major bleeds in placebo group
Vazquez et al. (30)	240 (29 W, 211 C)	INR 2.0–3.0	W—26 major bleeds[b]/100 patient years C—11 major bleeds[c]/100 patient years

INR, international normalized ratio; W, warfarin group; C, control group.

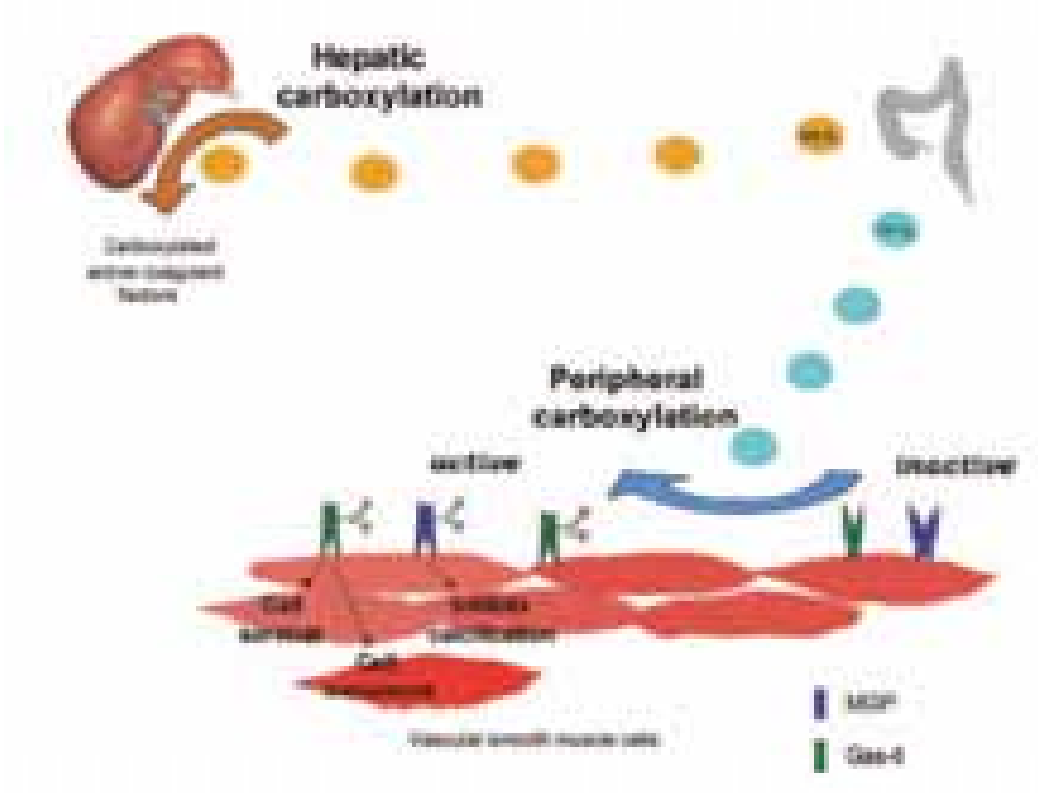
	N	strokes (strokes per pt year) ischemic	hemorrhagic	$CHADS_2$
No INR monitoring available	204	23 (0.068)	6 (0.0[illegible])	2.7
INR>3	60	3 (0.0[illegible]	[illegible]011)	2.6
INR=2-3	272	[illegible].038)	6 (0.012)	2.8
INR=1.5-1.9		9 (0.029)	4 (0.013)	2.8
INR<1.5	56	3 (0.027)	0 (-)	2.7



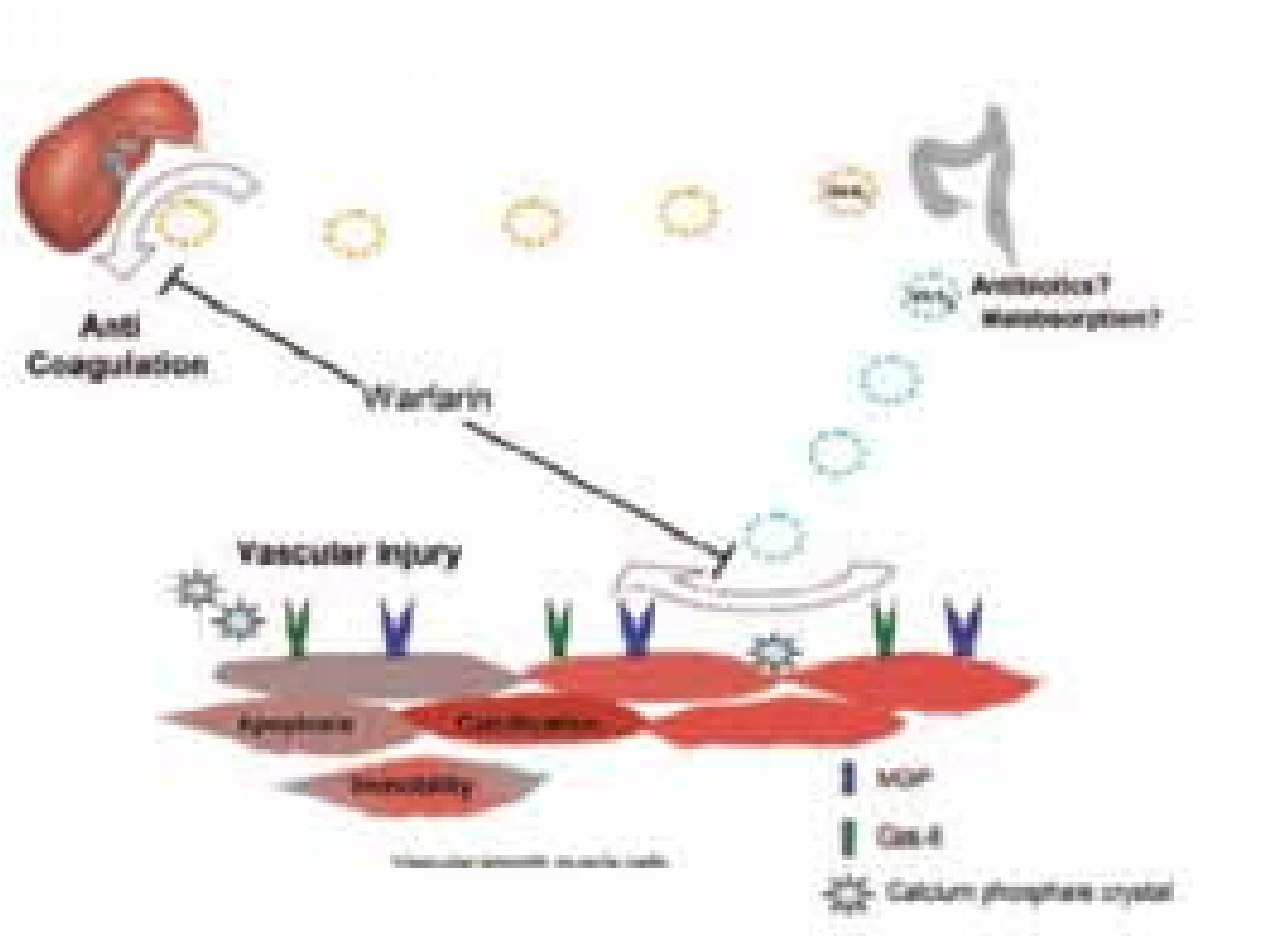
Warfarin Use Associates with Increased Risk for Stroke in Hemodialysis Patients with Atrial Fibrillation



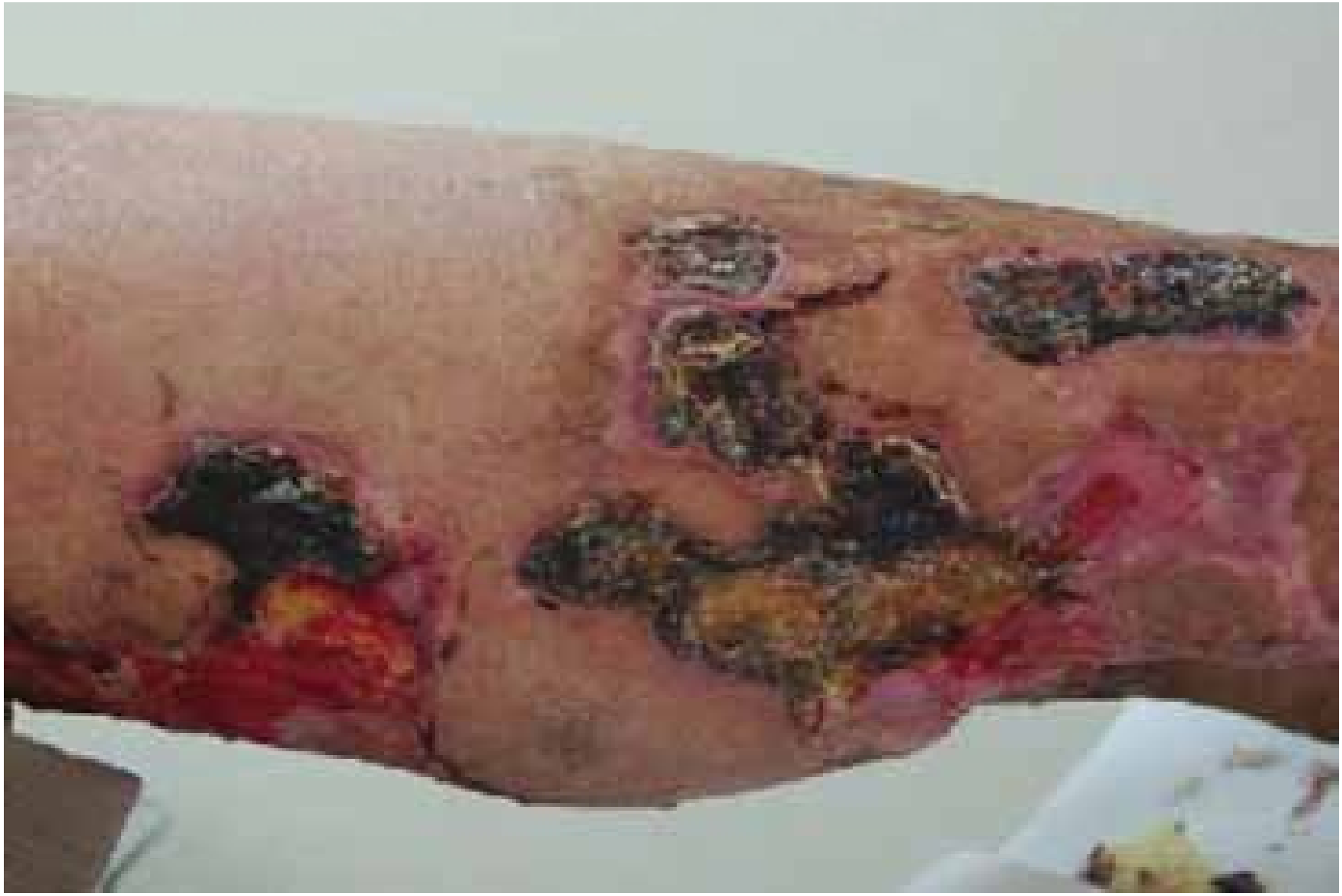
Warfarine bağlı kalsifikasyon ve kalşifilaksi



Normal koşullarda inaktif MGP ve Gas-6 proteinleri vit K bağımlı olarak karboksile edilir ve aktive hale geçerek kalsifikasyonu engeller



Antibiyotikler, diyet kısıtlamaları, malabsorbsyon ve warfarin kullanımı vitamin K sunumunu azaltarak MGP ve Gas-6 aktivasyonunu inhibe eder



KBY hastalarında OAK kullanım önerileri

- OAK lehine
  - > 75 yaş ve eşlik eden risk faktörleri (DM, HT, KKY)
  - TIA ya da inme
  - Atrial trombüs varlığı
  - Hasta tercihi
  - CHADS2 skoru > 2
  - Mitral darlık
  - Prostetik kalp kapağı
- OAK aleyhine
  - < 65 yaş ve risk faktörü yok
  - Kontrolsüz hipertansiyon
  - Antiagregan kullanımı
  - Kalşifilaksi varlığı ya da öyküsü
  - Yaygın kalsifikasyonlar
  - Malnütrisyon
  - Kanama öyküsü
  - Sık düşme öyküsü

Yeni nesil antikoagülanlar

Anticoagulant treatment: the end of the old agents?

Table 1: Comparison of pharmacokinetic and pharmacodynamic properties of three new oral anticoagulants

	Apixaban	Rivaroxaban	Dabigatran
Cmax	3–4 h	2–3 h	2 h
T ½	8–15 h	7–11 h	14–17 h
Elimination	27% renal 73% hepatic	33% renal active 33% renal inactive 33% hepatic	80% renal 20% hepatic
Dosis regimen	2×/d	1×/d	1×/d, 2×/d
Monitoring	No	No	No
Interactions	CYP3A4 P-gp	CYP3A4 P-gp	P-gp
Interferences	Yes	Yes	Yes
HIT-II	No	No	No

ORIGINAL RESEARCH ARTICLE

Influence of Renal Impairment on the Pharmacokinetics and Pharmacodynamics of Oral Dabigatran Etexilate

An Open-Label, Parallel-Group, Single-Centre Study

Joachim Stangier,[1] Karin Rathgen,[1] Hildegard Stähle,[2] and Dago Mazur[2]

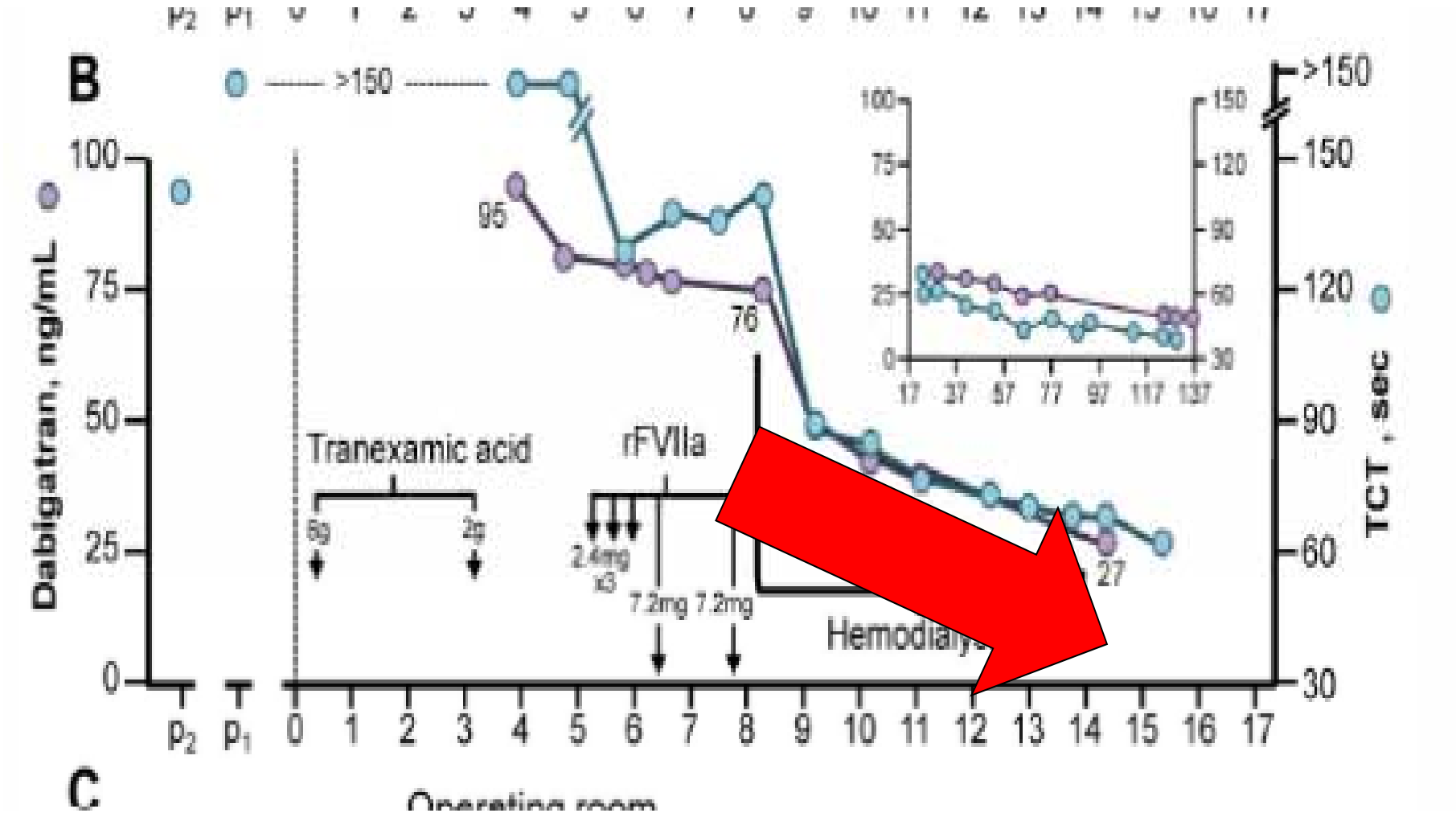
1 Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
2 PAREXEL International GmbH, Berlin, Germany

-**GFR düştükçe plazma konsantrasyonu artıyor**

-**ESRD x6**

-**ESRD'de yarı ömür 2 katına çıkıyor (14→28 sa)**

-**1 HD seansı %62-68 plazma düzeyinde azalma**


B
>150
Dabigatran, ng/mL
TCT, sec
95
76
27
Tranexamic acid
6g
2g
rFVIIa
2.4mg x3
7.2mg
7.2mg
Hemodialysis
P2
P1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
C

- **Dabigatrana bağlı kanama komplikasyonlarında kanıtlanmış tek tedavi hemodiyaliz**
- **Takipte aPTT daha uygun**

J Nephrol 2011; 24(05): 636-648
DOI: 10.5301/JN.2010.6259

Aspirin resistance in patients with chronic renal failure

Azra Meryem Tarikiulu [1], Beste Ozben [1], Mehmet Koc [2], Nurdan Papila-Topal [1], Tomris Ozben [3], Oguz Caymaz [1]

[1] Department of Cardiology, Marmara University Faculty of Medicine, Istanbul - Turkey
[2] Division of Nephrology, Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul - Turkey
[3] Department of Biochemistry, Akdeniz University Faculty of Medicine, Antalya - Turkey

	Chronic renal failure group (n=245)		Control group (n=130)	p Value*
	Hemodialysis (n=115)	Stage 3-4 CKD (n=130)		
Aspirin resistance, no. (%)	53 (46.1)	85 (34.7)	22 (16.8)	<0.001 <0.001[a,b]
Aspirin reaction unit, ARU	549 ± 60	511 ± 76	478 ± 72	<0.001 <0.001[a,b]

TABLE III
CHARACTERISTICS AND LABORATORY PARAMETERS OF ASPIRIN-RESISTANT AND ASPIRIN-SENSITIVE PATIENTS

	Aspirin-resistant patients (n=107)	Aspirin-sensitive patients (n=268)	p Value
Age (years)	63.9 ± 13.2	64.7 ± 13.6	NS
Sex (female/male)	57/50	109/159	0.027
Chronic renal failure (%)	75.4	59.7	<0.001
Hemodialysis (%)	49.5	23.1	<0.001
Blood urea nitrogen (mg/dL)	79 ± 63	50 ± 46	<0.001
Creatinine (mg/dL)	5.1 ± 4.2	3.3 ± 4.5	<0.001
C-reactive protein (mg/L)	20.1 ± 30.9	19.8 ± 40.2	NS
Hematocrit (%)	35.8 ± 6.5	38.1 ± 6.4	0.012
Platelets (10^3/mm^3)	214 ± 75	245 ± 99	0.004

Pro- and Anti-Inflammatory Cytokines in Chronic Pediatric Dialysis Patients: Effect of Aspirin

Stuart L. Goldstein,* Jocelyn C. Leung,† and Douglas M. Silverstein‡

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Clinical Journal of the American Society of Nephrology

Clin J Am Soc Nephrol 1: 974–980, 2006

Table 3. Effect of aspirin on serum cytokines in all dialysis patients[a]

Cytokine	Normal Value for Age (pg/ml)[b]	Pretreatment (pg/ml)	6 Mo of Aspirin Treatment (pg/ml)	P
Proinflammatory				
IL-1β	<10.0	20.9 ± 8.7	26.9 ± 12.3	0.7
IL-6	<0.2	10.1 ± 3.7	3.3 ± 0.3	0.1
IL-8	<5.8	69.4 ± 21.1	20.8 ± 2.3	0.04
TNF-α	<0.5	13.6 ± 2.3	4.6 ± 0.9	0.03
IL-2	<0.9	0.9 ± 0.2	0.8 ± 0.2	0.7
Anti-inflammatory				
IL-4	<1.2	1.7 ± 0.1	1.6 ± 0.2	0.8
IL-10	<1.5	6.2 ± 1.4	3.4 ± 1.2	0.07

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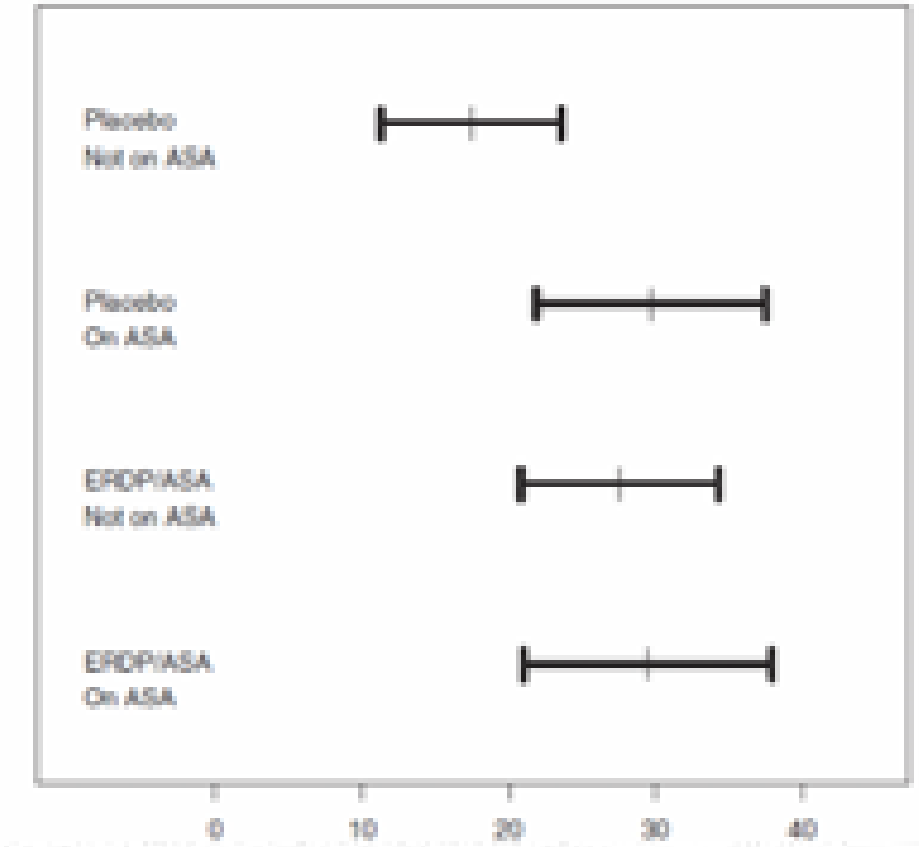
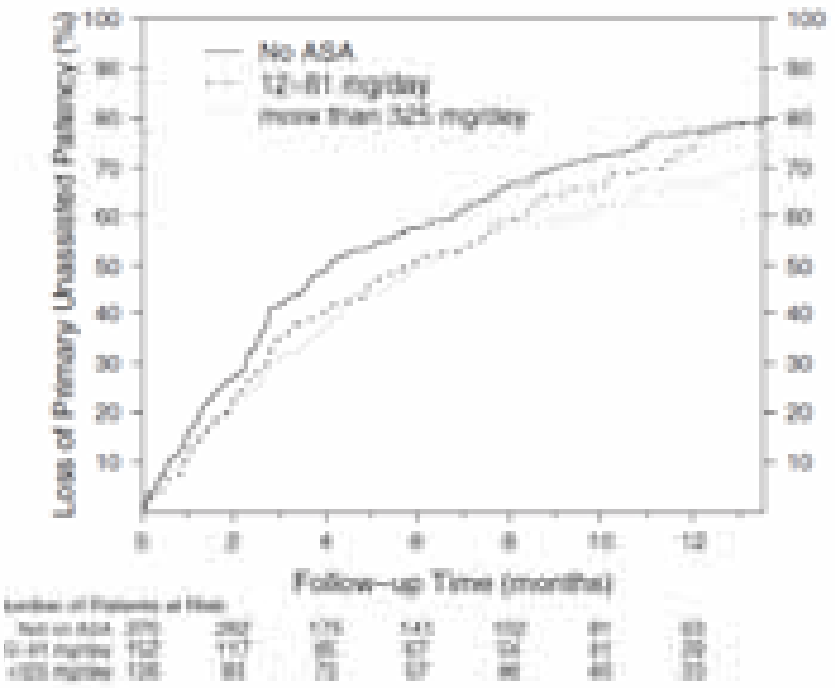
Use of Aspirin Associates with Longer Primary Patency of Hemodialysis Grafts

Bradley S. Dixon,*† Gerald J. Beck,‡ Laura M. Dember,§ Miguel A. Vazquez,‖ Arthur Greenberg,¶ James A. Delmez,** Michael Allon,†† Jonathan Himmelfarb,‡‡ Bo Hu,§ Tom Greene,§§ Milena K. Radeva,‡ Ingemar J. Davidson,‖‖ T. Alp Ikizler,¶¶ Gregory L. Braden,*** Jeffrey H. Lawson,††† James R. Cotton, Jr.,‡‡‡ John W. Kusek,§§§ and Harold I. Feldman,‖‖ for the Dialysis Access Consortium (DAC) Study Group


Placebo
Not on ASA
Placebo
On ASA
ERDP/ASA
Not on ASA
ERDP/ASA
On ASA
0
10
20
30
40
Primary Unassisted Patency (%) at 12-month follow-up


No ASA
12-81 mg/day
more than 325 mg/day
Loss of Primary Unassisted Patency (%)
Follow-up Time (months)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Dipyridamole plus Aspirin on Hemodialysis Graft Patency

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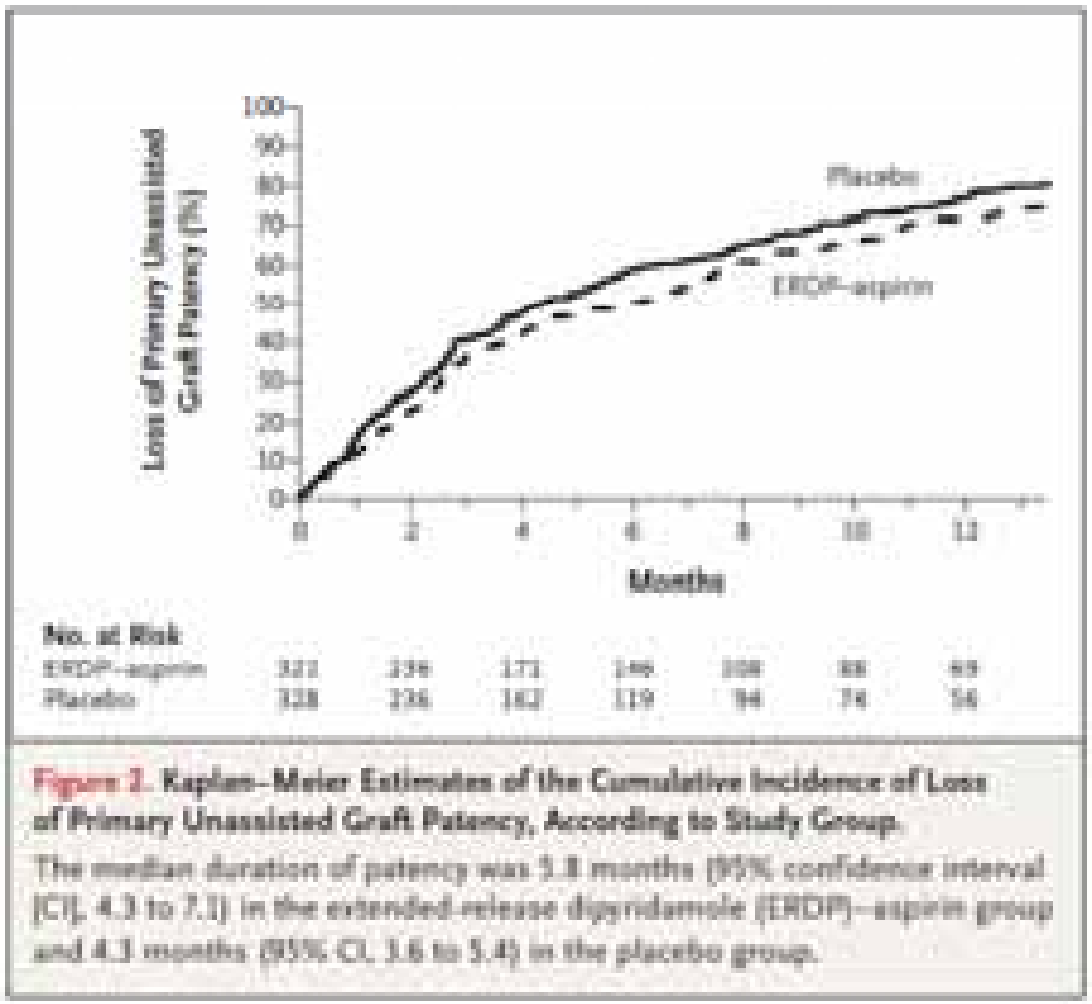

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Loss of Primary Unassisted Graft Patency, According to Study Group.

The median duration of patency was 5.8 months (95% confidence interval [CI], 4.3 to 7.1) in the extended-release dipyridamole (ERDP)–aspirin group and 4.3 months (95% CI, 3.6 to 5.4) in the placebo group.

4.5 years, with 6 additional months of follow-up. The incidence of primary unassisted patency at 1 year was 23% (95% confidence interval [CI], 18 to 28) in the placebo group and 28% (95% CI, 23 to 34) in the dipyridamole–aspirin group, an absolute difference of 5 percentage points. Treatment with dipyridamole plus aspirin significantly prolonged the duration of primary unassisted patency (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.03) and inhibited stenosis. The incidences of cumulative

Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis

A Randomized Controlled Trial

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial conducted at 9 US centers composed of academic and community nephrology practices in 2003-2007. Eight hundred seventy-seven participants with end-stage renal disease or advanced chronic kidney disease were followed up until 150 to 180 days after fistula creation or 30 days after initiation of dialysis, whichever occurred later.

Intervention Participants were randomly assigned to receive clopidogrel (300-mg loading dose followed by daily dose of 75 mg; n = 441) or placebo (n = 436) for 6 weeks starting within 1 day after fistula creation.

Table 2. Fistula Thrombosis

	No. (%) of Patients		
	Clopidogrel (n = 436)[a]	Placebo (n = 431)[a]	Relative Risk (95% Confidence Interval)[b]
Thrombosis at 6 wk (all patients)	53 (12.2)	84 (19.5)	0.63 (0.46-0.97)[c]
By location			
Forearm fistula	31 (12.9)	60 (24.7)	0.53 (0.36-0.77)
Upper arm fistula	22 (11.3)	24 (12.8)	0.89 (0.52-1.53)

[a] Six of the 441 patients randomized to clopidogrel and 5 of the 436 patients randomized to placebo were not included because patency was not evaluated.
[b] Relative risks were stratified for fistula location and center.
[c] The 95% confidence interval reported is the repeated confidence interval adjusted for interim monitoring. The repeated *P* value adjusted for interim monitoring is .016.

Table 4. Adverse Events[a]

	No. (%) of Patients		
Events	Clopidogrel (n = 441)	Placebo (n = 436)	*P* Value[b]
Any serious adverse event	67 (15.2)	81 (18.6)	.20
Bleeding	13 (2.9)	12 (2.8)	.84
Minor	0	0	> .99
Intermediate	6 (1.4)	5 (1.2)	> .99
Major	3 (0.7)	3 (0.7)	> .99
Life-threatening	4 (0.9)	4 (0.9)	> .99
Fatal	0	0	> .99
Hospitalization	64 (14.5)	77 (17.7)	.16
Ischemic heart disease	3 (0.7)	7 (1.6)	.22
Congestive heart failure	6 (1.4)	9 (2.1)	.45
Arrhythmia	1 (0.2)	7 (1.6)	.04
Hypertension	0	5 (1.1)	.03
Cerebrovascular disease	2 (0.5)	1 (0.2)	> .99
Infection	4 (0.9)	3 (0.7)	> .99
Vascular access event: study fistula	5 (1.1)	6 (1.4)	.77
Vascular access event: nonstudy access	15 (3.4)	12 (2.8)	.70
Death	4 (0.9)	4 (0.9)	> .99

J Am Soc Nephrol 14: 2313–2321, 2003

Randomized Controlled Trial of Clopidogrel plus Aspirin to Prevent Hemodialysis Access Graft Thrombosis

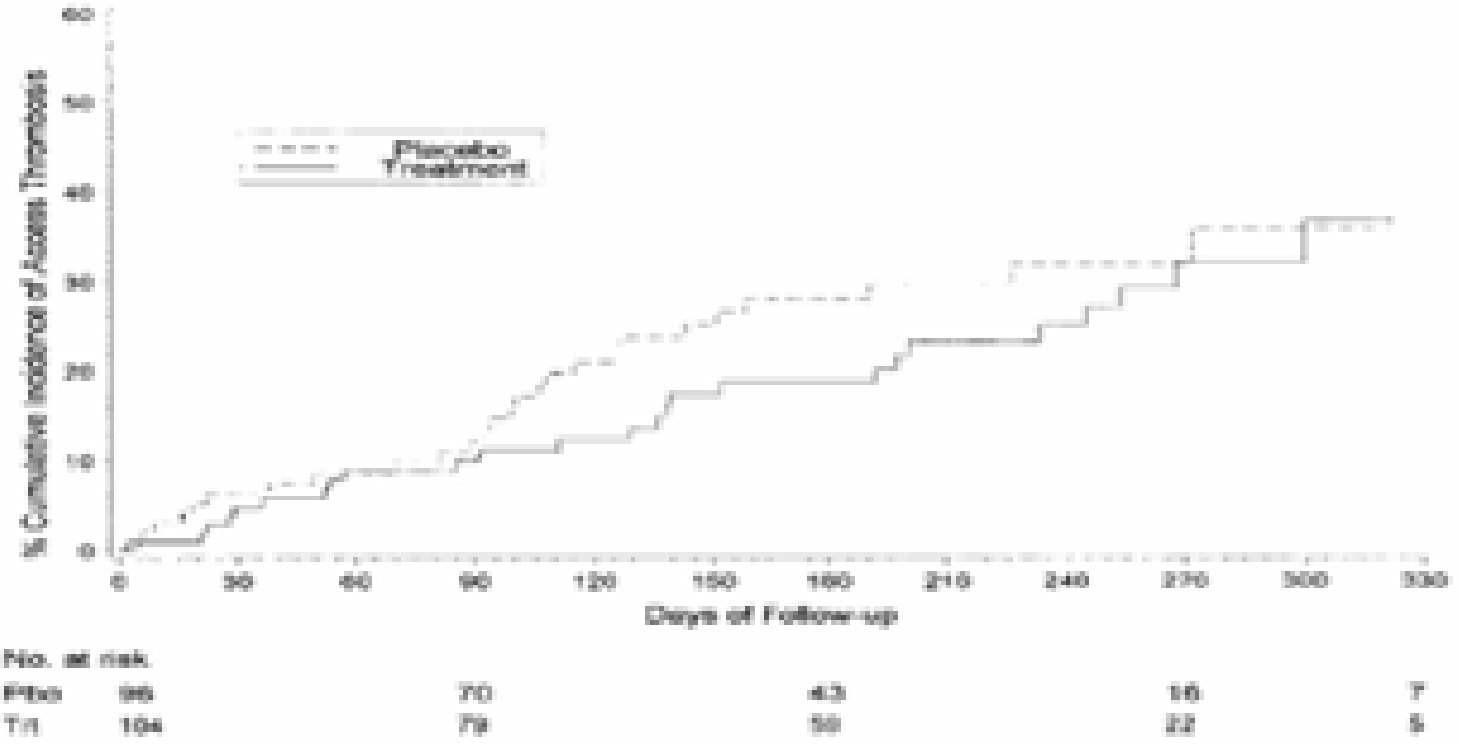

Figure 2. Cumulative incidence of first graft thromboses. The incidences were not significantly different ($P = 0.45$) for the two groups (hazard ratio, 0.81; 95% CI, 0.49 to 1.40). Plbo, placebo; Trt, treatment.

Table 2. Antiplatelet agents and access thrombosis rate in hemodialysis.

Study	Year	Trial (N)	Intervention	Duration (months)	Access thrombosis rate
Dipyridamole:					
Sreedhara[24]	1994	RCT (N = 107)	Dipyridamole 75 mg, aspirin 325 mg, both, placebo Type I: new graft Type II: recurrent thrombosis	72	Type I: 17% vs. 36% vs. 23% vs. 32% Type II: 83% vs. 58% vs. 100% vs. 80%
Dixon[25]	2009	RCT (N = 649)	Dipyridamole 200 mg + aspirin 25 mg vs. placebo	60	40% vs. 42%
Aspirin:					
Kooistra[26]	1994	RCT crossover (N = 133)	Aspirin 30 mg vs. placebo	5	16% (9.4% aspirin vs. 6.3% placebo, NS)
Clopidogrel:					
Tsamaeria[28]	2005	Prospective (N = 24)	Clopidogrel 75 mg vs. an antithrombotic therapy	Until diagnosis of thrombosis	8% vs. 92% (p = 0.001)
Dember[27]	2006	RCT (N = 677)	Clopidogrel (300 mg LD and 75 mg daily) vs. placebo	3 after AVF creation or 1 after dialysis initiation	12.2% vs. 19.3% (p = 0.018)
Kaufman[29]	2003	RCT (N = 300)	Clopidogrel 75 mg + aspirin 325 mg vs. double placebo	24	HR 0.81 (95% CI: 0.47-1.40) in favor of aspirin and clopidogrel therapy. (p = 0.45)

AVF = arteriovenous fistula; CI = confidence interval; HR = hazard ratio; LD = loading dose; MD = maintenance dose; NS = non-significant; RCT = randomized controlled trial.

Sonuç

- **KBY hastalarında kanama eğilimi tromboz eğiliminden daha ciddi bir sorundur**
- **Kardiyak ve damar yolu koruma için AP ajanlar tekli ya da kombinasyon olarak kullanılması mümkündür**
- **AK tedavide kar-zarar oranı dikkatle hesaplanmalı ve indikasyonlar normal popülasyona göre daha dar tutulmalıdır**