급성 허혈성 뇌졸중의 항혈전치료

김 준 태
전남의대 신경과

Antithrombotic Therapy in Acute Ischemic Stroke

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CONTENTS

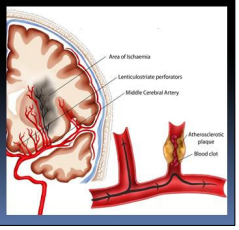
- Antiplatelets
  - Guidelines
  - Unsettled issues
  - Other agents
- Anticoagulations
  - Guidelines

Anti-thrombotics in AIS

1) Halting the progression of an intra-arterial thrombus
2) Forestalling early recurrent embolization
3) Maintaining collateral flow to the area of ischemia
4) Preventing rethrombosis or reocclusion after recanalization

Clinical...
- Neurological deterioration
- Recurrence (new stroke)

Radiological...
- Infarct growth
- New ischemic lesions



Non-cardioembolic Stroke or TIA

- Antiplatelets
  - Aspirin
  - Combination aspirin+ER-DP
  - Clopidogrel

RR of stroke, MI, or death about 22%

  - Combination aspirin+clopidogrel

Within 24 hours of a minor ischemic stroke or TIA for 90 days

LOE B. Based on the CHANCE trial

when continued for 2-3 years, increases the risk of hemorrhage

LOE A. Based on the CHARISMA, MATCH trial

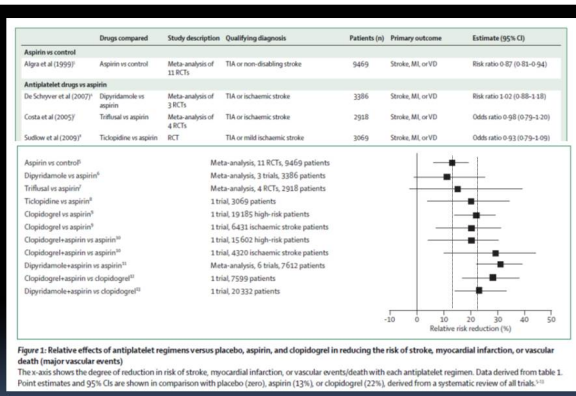


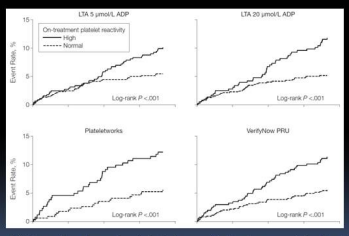
Figure 1: **Relative effects of antiplatelet regimens versus placebo, aspirin, and clopidogrel in reducing the risk of stroke, myocardial infarction, or vascular death (major vascular events)**
The x-axis shows the degree of reduction in risk of stroke, myocardial infarction, or vascular events/death with each antiplatelet regimen. Data derived from table 1. Point estimates and 95% CIs are shown in comparison with placebo (zero), aspirin (13%), or clopidogrel (22%), derived from a systematic review of all trials.[5,12]

Hankey GJ, Lancet Neurol 2010

2014 AHA/ASA guidelines

- Resistance or nonresponsiveness of antiplatelet agents
- Patients who have a stroke while undergoing therapy
- Combination of OAC and antiplatelets

- non-responders to aspirin and clopidogrel



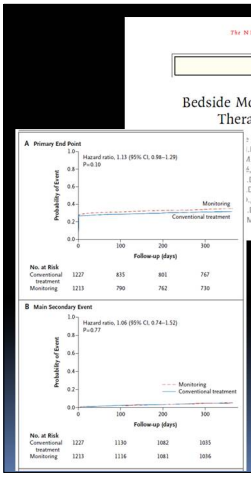
High on-treatment platelet reactivity is associated with atherothrombotic events after PCI

Breet NJ et al. JAMA 2010

- non-responders to aspirin and clopidogrel

✓ Intuitive to switch to an alternative therapy or add a second drug ???

The cause of the differential patient response to platelet function test : multifactorial, related to comorbid conditions such as DM, genetic factor, and concomitant drug use…



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting

Platelet-function monitoring with adjustment of antiplatelet therapy as needed before and after stent implantation did not reduce the rate of cardiovascular events, as compared with a conventional treatment strategy without measurement of the effect of antiplatelet drugs.

… do not support the routine use of platelet-function testing in patients undergoing coronary stenting.

Clinical Outcomes Using a Platelet Function-Guided Approach for Secondary Prevention in Patients With Ischemic Stroke or Transient Ischemic Attack

Jeremiah P. Depta, MD; Jeffrey Fowler, DO; Eric Novak, MS; Irene Katzan, MD, MS; Suzanne Bakdash, MD, MPH; Kandice Kottke-Marchant, MD, PhD; Deepak L. Bhatt, MD, MPH

✓ Modifying antiplatelet therapy after platelet function testing may be associated with increased death, bleeding, or ischemic events compared with patients without any antiplatelet therapy modification.
✓ Increasing antiplatelet therapy in patients with aspirin and/or clopidogrel nonresponse was not associated with better, or even similar, clinical outcomes as in those without modification of their antiplatelet regimen but rather was associated with higher event rates.
✓ The results do not provide support for testing, as the strategy of antiplatelet therapy modification was not associated with any evidence of better outcomes.

	Acute ARU (aspirin 300mg)		
	ARU <550 IU	ARU ≥550 IU	
ARU on day 5			
ARU <550 IU	263 (90.4%)	39 (67.2%)	302(86.5%)
ARU ≥550 IU	28 (9.6%)	19 (32.8%)	47 (13.5%)
	291 (83.4%)	58 (16.6%)	349

75-mg Clopidogrel

Nonresponder Definition ≥ 230 PRU		Period 1 Responder	Period 1 Nonresponder	Total
Period 2	Responder	147 (70.0)	17 (8.1)	164 (78.1)
	Nonresponder	16 (7.6)	30 (14.3)	46 (21.9)
	Total	163 (77.6)	47 (22.4)	210 (100)
Kappa = 0.544				

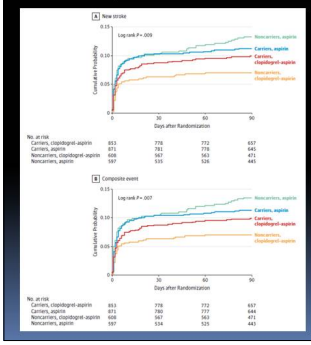
Nonresponder Definition ≥ 208 PRU		Period 1 Responder	Period 1 Nonresponder	Total
Period 2	Responder	122 (58.1)	25 (11.9)	147 (70.0)
	Nonresponder	21 (10.0)	42 (20.0)	63 (30.0)
	Total	143 (68.1)	67 (31.9)	210 (100)
Kappa = 0.488				

Kim JT, Stroke 2015
Hochholer W, JACC 2014

Original Investigation

Association Between *CYP2C19* Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack

Yilong Wang, MD, PhD; Xingquan Zhao, MD, PhD; Jinxi Lin, MD, PhD; Hao Li, PhD; S. Claiborne Johnston, MD, PhD; Yi Lin, MD, PhD; Yuesong Pan, MD; Liping Liu, MD, PhD; David Wang, DO, FAHA, FAAN; Chunxue Wang, MD, PhD; Xia Meng, MD, PhD; Jianfeng Xu, MD, PhD; Yongjun Wang, MD; for the CHANCE Investigators



- ✓ The use of A+C compared with A alone reduced the risk of a new stroke only in the subgroup of patients who were not carriers of the *CYP2C19* loss of-function alleles.
- ✓ These findings support a role of *CYP2C19* genotype in the efficacy of this treatment.

Wang Y, JAMA 2016 e-pub

- Biological antiplatelet resistance; increased rates of vascular events _ from observational study
- Platelet function guided modification; no evidence _ from RCT, observational study

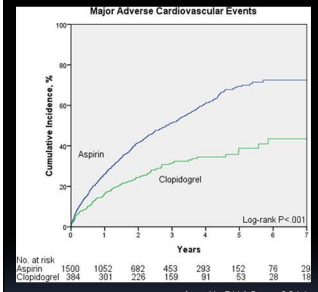
? Lack of evidence; design, small size
? Different strategies; addition, change, timing…

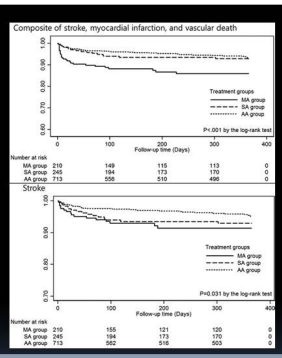
- Prior aspirin (antiplatelet) users
  - Less severe stroke in LAA
  - Better functional outcome
  - More bleeding after IV tPA

Park JM, Ann Neurol 2016
Xian Y, JAMA Neurol 2016

- ✓ There is no evidence that increasing the dose of aspirin provides additional benefit.
- ✓ Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin (Class IIb; LOE C)

2014 AHA/ASA guidelines





Lee M, BMJ Open 2014

… clopidogrel initiation was associated with fewer recurrent vascular events than aspirin reinitiation.

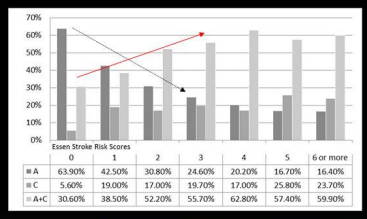
… compared with maintaining aspirin, switching to or adding alternative antiplatelet agents may be better in preventing subsequent vascular events in patients who experienced a new ischemic stroke while taking aspirin.

Detailed antiplatelet regimes after ischemic stroke

Tx	N (%)	Regimens	N (%)
MA group	212 (18.1%)	Aspirin mono	212
SA group	246 (21.0%)	Clopidogrel mono	198 (80.5%)
		Cilostazol mono	24 (9.8%)
		Other monot	11 (4.5%)
		Non-aspirin combi	13 (5.2%)
AA group	714 (60.9%)	Asp+Clop combi	622 (87.1%)
		Asp+Cilo combi	75 (10.5%)
		Asp+other combi	17 (2.4%)

Kim JT, Stroke 2016 (Supplement)

Essen Stroke Risk scores and antiplatelet strategies



	0	1	2	3	4	5	6 or more
A	63.90%	42.50%	30.80%	24.60%	20.20%	16.70%	16.40%
C	5.60%	19.00%	17.00%	19.70%	17.00%	25.80%	23.70%
A+C	30.60%	38.50%	52.20%	55.70%	62.80%	57.40%	59.90%

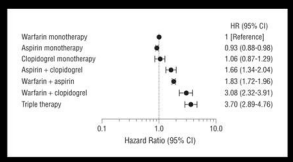
	Clopidogrel vs ASP				Asp+clop vs ASP			
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
ESRS, binary:								
1 or more (vs 0)	9.16 (2.15 39.05)	0.003	7.27 (1.68 31.44)	0.008	4.72 (2.29 9.75)	<.0001	3.67 (1.75 7.69)	0.0006
2 or more (vs 0-1)	2.33 (1.57 3.54)	<.0001	2.26 (1.48 3.45)	0.0002	3.06 (2.23 4.20)	<.0001	2.82 (2.04 3.91)	<.0001
3 or more (vs 0-2)	2.04 (1.56 2.66)	<.0001	2.05 (1.54 2.68)	<.0001	2.08 (1.69 2.55)	<.0001	2.04 (1.64 2.52)	<.0001
ESRS, ordinal 1 point increase	1.57 (1.25 1.50)	<.0001	1.39 (1.26 1.53)	<.0001	1.34 (1.25 1.45)	<.0001	1.34 (1.24 1.45)	<.0001

CRCS-5, unpublished data

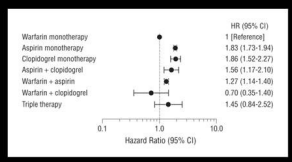
- Combination of OAC + antiplatelet in AF patients
  - CAD + AF in AIS
  - ICAS + AF in AIS
  - CAS/PCI + AF in AIS

Study	Mono (N)	Combi (N)	Annual bleeding risk	P
Shireman et al.	8131	1963	1.3% vs 1.9%	0.052
Flaker et al.	3172	481	2.3% vs 3.9%	0.01
Hart et al.	1780	1756	0.05% vs 1.2%	0.009

Risk of major bleeding
; substantially increased with combination therapy



Hazard ratios (HRs) for the risk of nonfatal (n = 12,191) and fatal (n=1381) bleeding associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs.



Hazard ratios (HRs) for the risk of nonfatal (n = 9785) and fatal (n=3537) Ischemic stroke associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs.

Risk of major bleeding
; substantially increased with combination therapy

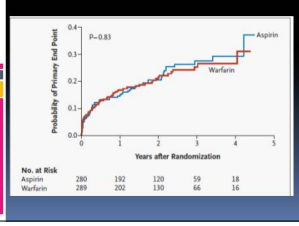
No additional effects for prevention
in combination therapy

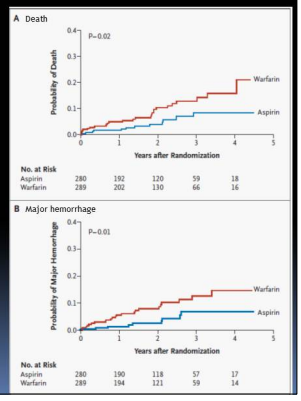
Hansen ML, Arch Intern Med 2010

- MI/ICAS+AF
  - Asp vs warfarin in MI
  - Asp vs warfarin in ICAS

No obvious rationale for adding aspirin to warfarin in CAD patients with AF, unless they have a coronary stent

- MI/ICAS+AF
  - Asp vs warfarin in MI
  - Asp vs warfarin in ICAS





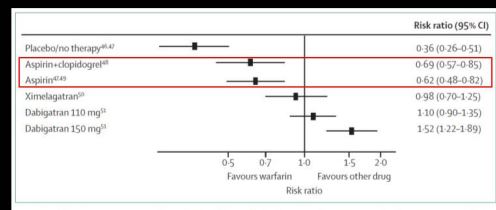


Figure 3: Indirect comparisons of the relative effects of placebo or no therapy, antiplatelet regimens (aspirin and clopidogrel, and aspirin alone), and anticoagulant regimens (ximelagatran and dabigatran), when compared with warfarin, in reducing the risk of stroke and systemic embolism among patients with atrial fibrillation in clinical trials

Hankey GJ, Lancet Neurol 2010

Symptomatic ICAS + AF in AIS

1) Asp + warfarin
2) Asp + Clop
3) Asp + Clop + warfarin
4) Warfarin

Warfarin + Aspirin (+ Clopidogrel) — Only in acute stage ?

Risk of major bleeding
; substantially increased with combination therapy

No additional effects for prevention
in combination therapy

- END
  - Aspirin vs aspirin + clopidogrel (or cilostazol)
  - Progressive/new/edema ...

Anecdotal
Pilot
Small sample

... Inconclusive

Cilostazol combined with aspirin prevents early neurological deterioration in patients with acute ischemic stroke: A pilot study

Clopidogrel Plus Aspirin Prevents Early Neurologic Deterioration and Improves 6-Month Outcome in Patients With Acute Large Artery Atherosclerosis Stroke

Clopidogrel plus aspirin *versus* aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke

- CHANCE trial
  - Early recurrent stroke
  - Early deterioration (new + progression?)
- POINT trial
  - Early deterioration (new + progression)

- Radiological outcomes
  - New ischemic lesions
  - Infarct growth

STROKE

Dual Antiplatelet Therapy With Clopidogrel and Aspirin in Symptomatic Carotid Stenosis Evaluated Using Doppler Embolic Signal Detection
The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial

Articles

Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial

- Radiological outcomes
  - New ischemic lesions

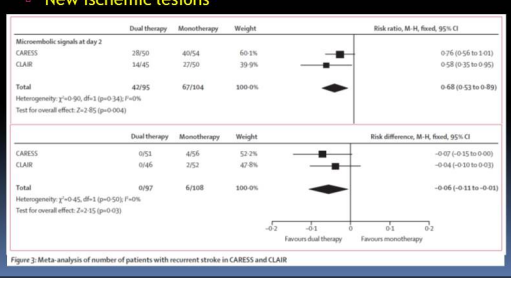


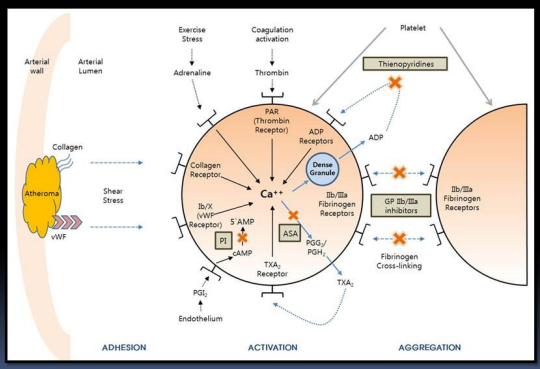
Figure 3: Meta-analysis of number of patients with recurrent stroke in CARESS and CLAIR

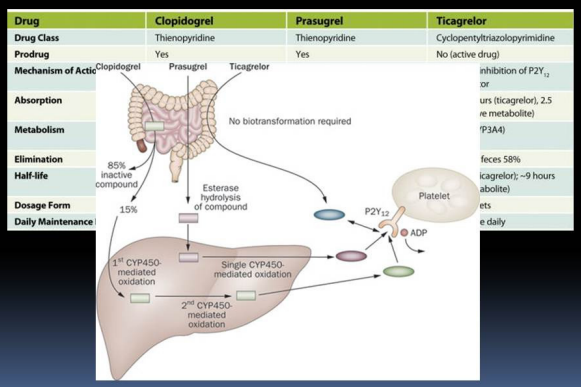
- Radiological outcomes
  - New ischemic lesions
  - Infarct growth

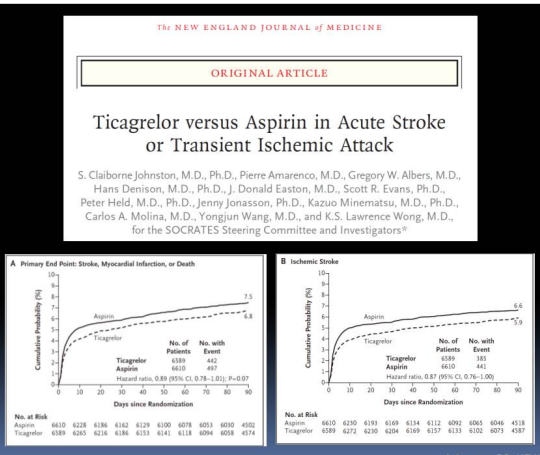
Recurrent Ischemic Lesions After Acute Atherothrombotic Stroke
Clopidogrel Plus Aspirin Versus Aspirin Alone

	Clopidogrel Plus Aspirin	Aspirin	RR or OR (95% CI)	*P* Value
Primary outcome, n/total n (%)				
Newly developed ischemic lesion	61/167(36.5)	60/167(35.9)	1.02 (0.77–1.35)	0.91*

- Other or New antiplatelets
  - Cilostazol
  - Triflusal
  - Ticagrelor







Johnston SC, NEJM 2016

- Guideline

Cardioembolic Stroke

- Non-valvular AF
  - Dabigatran
  - Apixaban
  - Ribaroxaban
  - Edoxaban
  - Warfarin

Cardioembolic Stroke

- Non-valvular AF
  - Dabigatran
  - Apixaban
  - Ribaroxaban
  - Edoxaban
  - ~~Warfarin~~

Leading opinion

The king is dead (warfarin): direct thrombin and factor Xa inhibitors: the next Diadochian War?

Hans-Christoph Diener[1]*, John Eikelboom[2], Christopher B. Granger[3], and Werner Hacke[1]

Int J Stroke. 2012

$CHADS_2$		$CHADS_2$		CHA_2DS_2-VASc	
Congestive heart failure			Prevalence (%)	Stroke rate at 1 year, % (95% CI)	Prevalence (%)	Stroke rate at 1 year, % (95% CI)
Hypertension	0	22%	1·7% (1·5-1·9)	8%	0·8% (0·6-1·0)
Age ≥75 years	1	31%	4·7% (4·4-5·1)	12%	2·0% (1·7-2·4)
Diabetes mellitus	2	23%	7·3% (6·9-7·8)	18%	3·7% (3·3-4·1)
Stroke, transient ischaemic attack, or thromboembolism	3	15%	15·5% (14·6-16·3)	23%	5·9% (5·5-6·3)
Maximum score	4	7%	21·5% (20·0-23·2)	19%	9·3% (8·7-9·9)
CHA_2DS_2VASc	5	2%	19·7% (16·9-22·9)	12%	15·3% (14·3-16·2)
Congestive heart failure/LV dysfunction	6	0·2%	22·4% (14·6-34·3)	6%	19·7% (18·2-21·4)
Hypertension	7	..	..	2%	21·5% (18·7-24·6)
Age ≥75 years	8	..	..	0·4%	22·4% (16·3-30·8)
Diabetes mellitus	9	..	..	0·1%	23·6% (10·6-52·6)
Stroke, transient ischaemic attack, or thromboembolism					
Vascular disease (previous MI, PAD, or aortic plaque)					
Age 65-74 years					
Sex category (female sex)					
Maximum score					

All patients in this study were discharged from a hospital in Denmark between 1997 and 2006 with non-valvular atrial fibrillation, were not anticoagulated, and were followed up for 1 year. CHA_2DS_2-VASc scores: 0=no antithrombotic therapy recommended. 1=antithrombotic therapy with oral anticoagulation or antiplatelet therapy recommended (preferably oral anticoagulation). ≥2=oral anticoagulation recommended.

LV=left ventricular. MI=myocardial infarction. PAD=peripheral artery

Olesen JB, BMJ 2011
Hankey GJ, Lancet Neurol 2014

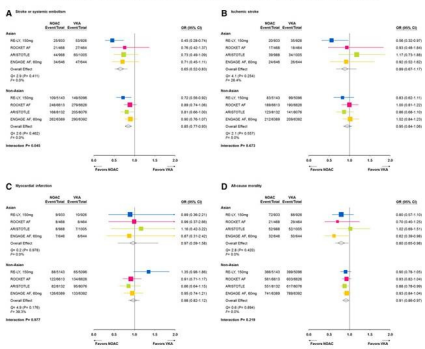
	Dabigatran etexilate	Apixaban	Rivaroxaban
Coagulation target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Bioavailability	6%	60%	66%
Plasma protein binding	35%	87%	95%
Dosing in atrial fibrillation	110 mg twice a day or 150 mg twice a day	5 mg twice a day	20 mg once a day
Onset of action	0·5-2 h	3-4 h	3-4 h
Duration of peak plasma concentration	0·5-2 h	3-4 h	2·5-4 h
Half-life*	12-14 h	12 h	7-11 h
Renal clearance	80%	25%	66% (half unchanged, half inactive metabolites)
Routine monitoring	No	No	No
Drug interactions	P-glycoprotein inhibitors†	P-glycoprotein inhibitors†; CYP3A4‡	P-glycoprotein inhibitors†; CYP3A4‡

*In patients with normal renal function. †P-glycoprotein inhibitors include azole antifungals (eg, ketoconazole, itraconazole, voriconazole, posaconazole) and protease inhibitors (eg, ritonavir). ‡Cytochrome p450 isoenzyme inhibitors include azole antifungals, protease inhibitors (eg, atazanavir), and macrolide antibiotics (eg, clarithromycin).

Table 3: Pharmacological properties of new oral anticoagulants

Alberts MJ, Lancet Neurol 2014

Efficacy outcomes of stroke or systemic embolism (A), ischemic stroke (B), myocardial infarction (C), and all-cause mortality (D) for the standard-dose non–vitamin K antagonist (VKA) oral anticoagulants (NOACs) vs VKAs. CI indicates confidence interval; and OR, odds ratio.



Kang-Ling Wang et al. Stroke. 2015;46:2555-2561

American Heart Association.

JAMA Internal Medicine | Original Investigation

Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Ya-Hui Hsueh, PhD; Rima Izem, PhD; Mary Ross Southworth, PharmD; Yuqin Wei, MS; Jiemin Liao, MA; Margie R. Goulding, PhD; Katrina Mott, MHS; Yoganand Chillarige, MPA; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc Published online October 3, 2016.