

# lääkään sydänpotilaan antitromboottinen lääkitys – onko vuotoriski liian suuri?

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Pohjolan lääkäripäivät  
22.2.2008

## Esityksen sisältö

- Korkea ikä ja hemostaasi
- lääkään potilaan vuotoriski  
antitromboottisen hoidon aikana
  - aivoverenvuoto
  - GI-vuoto
  
  - varfariini
  - ASA + muut verihiutale-estäjät

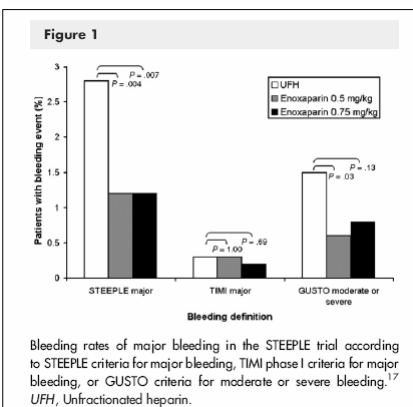
## Vuotoriskin arviointiin liittyvät ongelmat

- iäkkäät on usein poissuljettu randomisoiduista lääketutkimuksista
- merkittävän vuodon kriteerit vaihtelevat tutkimuksesta toiseen – tämä häiritsee johtopäätösten tekoa (esim. erilaisia lääkevalmisteita vertailtaessa olisi tärkeää ottaa huomioon vain oikeasti merkittävät vuodot)

### **Variation in the definitions of bleeding in clinical trials of patients with acute coronary syndromes and undergoing percutaneous coronary interventions and its impact on the apparent safety of antithrombotic drugs**

Steven R. Steinhubl, MD,<sup>a</sup> Adnan Kastrati, MD,<sup>b</sup> and Peter B. Berger, MD<sup>c</sup> Lexington, KY; Munich, Germany; and Danville, PA

**Conclusions** A task force should be initiated to formulate an internationally accepted, meaningful, and standardized approach for reporting bleeding events. A fixed definition may not work for all disease states throughout ACS and PCI. Rather, a predefined scale of bleeding can be proposed, which moves from a more liberal definition of bleeding for elective PCI to a more conservative definition in other settings such as rescue angioplasty. (Am Heart J 2007;154:3-11.)



# Hemostaasi ja ikä

Table 1  
Hemostatic changes during aging

Coagulation system proteins	
Fibrinogen	↑
Factor V	↑
Factor VII	↑
Factor VIII	↑
Factor IX	↑
Factor XIII	↑
High molecular-weight kininogen	↑
Prekallikrein levels	↑
von Willebrand factor	↑
Markers of coagulation activation <sup>a</sup>	↑
Anticoagulant proteins	
Antithrombin	Sex difference: ↑ ♀; ↓ ♂
Protein C	=; ↑
Protein S	=; ↑
Tissue factor pathway inhibitor	↑
Heparin cofactor II	↓
Fibrinolytic system proteins	
Plasmin	Sex difference: ↓ ♀; = ♂
Plasminogen activator inhibitor-1	↑
Plasmin-antiplasmin complex	↑
Thrombin-activable fibrinolysis inhibitor	↑
D-dimer	↑
Platelet function	
Bleeding time	↓
β-Thromboglobulin	↑
Platelet factor 4	↑
Aggregation to ADP and collagen	↑
Vascular endothelium	
Rigidity of vessel wall	↑
Glycosaminoglycan content of vessel wall	Alteration
Endothelial nitric oxide	↓
Endothelial nitric oxide synthase	↓
Endothelial prostacyclin	↓
Endothelial angiotensin II	↑

(↑) Increase; (=) unchanged; (↓) decrease.  
<sup>a</sup> Prothrombin fragments 1 + 2, fibrinopeptide A, activated factor VII, activation peptides of factor IX and X, thrombin-antithrombin complex.

- Yleissääntö: ikääntyminen lisää tromboosiherkkyyttä
- Ikääntymisen on kuvattu vaikuttavan
  - verisuonten seinämään
  - endoteelin ominaisuuksiin
  - verihiutaleisiin
  - hyytymistekijöihin
  - fibrinolyttiseen järjestelmään

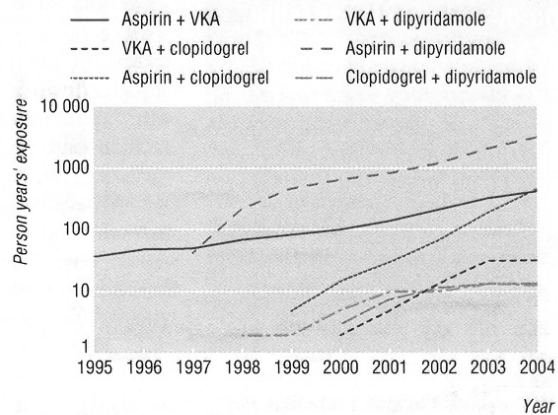
Critical Reviews in Oncology/Hematology 60 (2006) 144–151

# Sydänsairaudet ja ikä

- Ikääntyminen lisää tromboosille altistavien sydän- ja verisuonisairauksien esiintyvyyttä
  - eteisvärinä
  - sepelvaltimotauti

## Antitromboottisten lääkkeiden ja lääkeyhdistelmien käyttö lisääntyy

- esim. varfariinin käyttö lisääntyy nykyisin 10 % /v Suomessa



Use of combined antithrombotic regimens in outpatient settings. Data from Funen County, Denmark, 1995-2004. Note logarithmic y axis. VKA=vitamin K antagonist

## Antitromboottista lääkitystä käytetään edelleen liian vähän



European Heart Journal (2006) 27, 2217-2223  
doi:10.1093/eurheartj/ehi208

Clinical research  
Arrhythmia/electrophysiology

### Antithrombotic treatment is strongly underused despite reducing overall mortality among high-risk elderly patients hospitalized with atrial fibrillation

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Electrophysiology

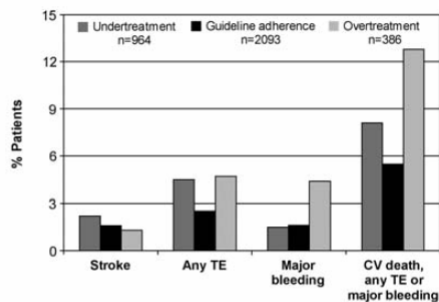
## Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation

Robby Nieuwlaat, MSc,<sup>a</sup> S. Bertil Olsson, MD,<sup>b</sup> Gregory Y.H. Lip, MD,<sup>c</sup> A. John Camm, MD,<sup>d</sup> Günter Breithardt, MD,<sup>e</sup> Alessandro Capucci, MD,<sup>f</sup> Joan G. Meeder, MD,<sup>g</sup> Martin H. Prins, MD,<sup>h</sup> Samuel Lévy, MD,<sup>i</sup> Harry J.G.M. Crijns, MD,<sup>a</sup> and on behalf of the Euro Heart Survey Investigators *Maastricht and Venlo, The Netherlands; Lund, Sweden; Birmingham and London, United Kingdom; Münster, Germany; Piacenza, Italy; and Marseille, France*

potilaiden keski-ikä 68 v

American Heart Journal  
2007;153:1006-12

Figure 2



	Absolute numbers of events			
Undertreatment	21	43	14	78
Guideline adherence	34	52	33	115
Overtreatment	5	18	17	49

Univariable absolute and proportional event rates during 1 year versus antithrombotic guideline adherence in patients at high risk for stroke. CV, Cardiovascular.

American Heart Journal  
2007;153:1006-12

## Onko ASA:sta hyötyä vanhuksille?

In an observational prospective study of 1410 patients, mean age 81 years, with prior MI and a serum LDL-C of 125 mg/dL or higher, 59% were treated with aspirin.<sup>13</sup> At 3-year follow-up, use of aspirin caused a 52% significant independent reduction in new coronary events. Use of statins caused a 54% significant independent reduction in the incidence of new coronary events.

13. Aronow WS, Ahn C. Reduction of coronary events with aspirin in older patients with prior myocardial infarction treated with and without statins. *Heart Disease*. 2002;4:159-161.

## Ikä lisää myös vuotoriskiä

- Miksi?
- Miten riskiä voi vähentää?

# AIVOVERENVUOTO

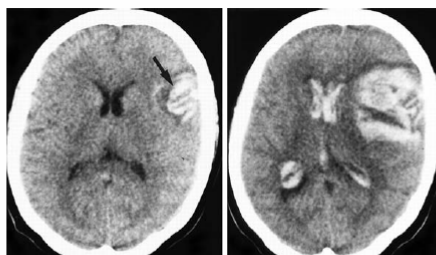


Fig. 3 Expansion of warfarin-associated intracerebral hemorrhage

J Thromb Thrombolysis (2008) 25:26–32  
DOI 10.1007/s11239-007-0101-1

## Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study



CE Lovelock, AJ Molyneux, PM Rothwell, on behalf of the Oxford Vascular Study

### Summary

Background UK stroke mortality data suggest that the incidence of haemorrhagic stroke has fallen in the past 20 years, but these data do not include deaths of individuals aged 75 years or over. Trends in the older population might differ, since cause varies with age. Our aim was to investigate changes in the population-based incidence of intracerebral haemorrhage according to age and likely aetiology.

Methods We used data from the Oxford Community Stroke Project (OCSF; 1981–86) and the Oxford Vascular Study (OXVASC; 2002–06) to investigate changes in the incidence of intracerebral haemorrhage with time, above and below age 75 years, together with associated risk factors and premorbid medications. Incidences were standardised to the 2001 census population of England and Wales.

Findings In the population aged under 75 years the incidence of intracerebral haemorrhage decreased substantially (rate ratio 0.53, 95% CI 0.29–0.95;  $p=0.03$ ), but the number of cases of intracerebral haemorrhage at all ages were similar in OXVASC and OCSF (52 vs 55 cases) as the proportion of cases occurring at 75 years and over tended to increase (2.0, 0.8–4.6;  $p=0.09$ ). The incidence of intracerebral haemorrhage associated with premorbid hypertension (blood pressure  $\geq 160/100$  mm Hg) fell overall (0.37, 0.20–0.69;  $p=0.002$ ), but the incidence of intracerebral haemorrhage associated with antithrombotic use was increased (7.4, 1.7–32;  $p=0.007$ ). Above age 75 years the proportion of cases who were non-hypertensive with lobar bleeds and presumed to have had mainly amyloid-related haemorrhages, also increased (4.0, 1.1–17;  $p=0.003$ ).

Interpretation There has been a substantial fall in hypertension-associated intracerebral haemorrhage over the past 25 years, but not in the overall number of cases of intracerebral haemorrhage in older age-groups, in part due to a rise in intracerebral haemorrhage associated with antithrombotic use. These trends, along with the expected increase in prevalence of amyloid angiopathy with the ageing population, suggest that, in contrast to projections based on mortality data below age 75 years, absolute number of cases of intracerebral haemorrhage might increase in future.

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See Reflection and Reaction

page 470

Stroke Prevention Research

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## Antitromboottisen lääkeyksen vaikutus aivoverenvuotoriskiin

TABLE 6. Estimated Absolute Rates of Primary Intracerebral Hemorrhage\*

General population, age ≈70 y	0.15%/y
<u>Aspirin</u> (any dosage)	
Atrial fibrillation or MCC	0.2%/y
Cerebrovascular disease	0.3%/y
<u>Aspirin plus clopidogrel</u>	
Atrial fibrillation	0.3%/y
Cerebrovascular disease	0.4%/y
<u>Warfarin</u> (INR 2.5)	
Atrial fibrillation	0.3–0.6%/y
Cerebrovascular disease	0.4–1.0%/y
<u>Warfarin (INR 2.5) plus aspirin</u>	
	0.5–1.0%/y

\*Absolute rates are sensitive to patient age, blood pressure, and intensity of anticoagulation. Consequently, these estimates are for general comparison only. For patients with coronary artery disease, intracerebral hemorrhage rates parallel those for atrial fibrillation if matched for age (generally younger for the former group of patients). In some studies, subdural hematomas are included with intracerebral hemorrhages as intracranial hemorrhages, resulting in ≈30% higher rates.

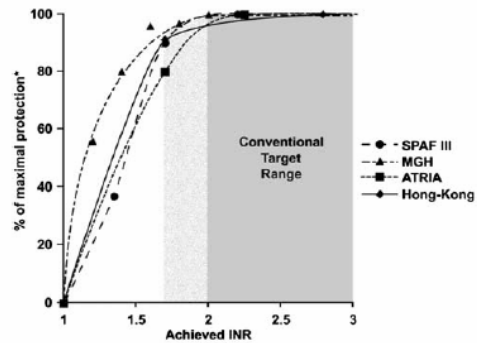
*Stroke 2005;36:1588-1593.*

## Varfariinihoito ja aivoverenvuotoriski: INR-tason merkitys

TABLE 2. Intracranial Hemorrhage vs Anticoagulation Intensity in Atrial Fibrillation Patients: 2 Recent Studies\*

Longitudinal Cohort Study		Case-Control Study†	
Absolute Rate‡		Relative Risk	
Mean Age, 71 y		Mean Age, cases=78 years, controls=75 years	
INR	Rate Per 100 Person-Years	INR	Relative Risk
<1.5	0.5	<1.5	1.4
1.5–1.9	0.3	1.5–1.9	1.2
2.0–2.5	0.3	2.0–3.0	1.0 (reference)
2.6–3.0	0.5	...	...
3.1–3.5	0.6	3.1–3.4	1.4
3.6–3.9	0.4	3.5–3.9	4.6
4.0–4.5	2.7	>4.0	8.8
>4.5	9.4	...	...

*Stroke 2005;36:1588-1593.*



\* Assumes maximal protection with INRs 2-3

Fig. 2 Relationship between achieved INRs and ischemic stroke rates in four studies: Stroke Prevention in Atrial Fibrillation (SPAF) III clinical trial [9], Massachusetts General Hospital (MGH) case-control series [11], Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) prospective cohort [12], and Hong-Kong series [10]. From Hart RG, Individualizing antithrombotic therapy to prevent stroke in patients with atrial fibrillation in Rothwell PM (ed), *Treating Individuals*, Elsevier Limited (Oxford, United Kingdom), 2007 with permission

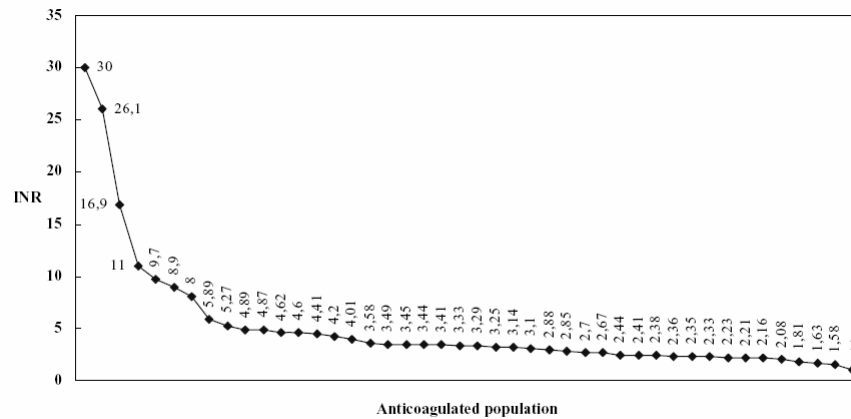
The optimal anticoagulation intensity for primary prevention of stroke (and death) in elderly atrial fibrillation patients appears to be INRs between 2.0 and 2.5 (Fig. 1)

adjustments. Available data are fewer for secondary prevention; in the two largest trials, mean achieved INRs of 2.5 and 2.9 were highly efficacious [9, 19, 20]. Current management guidelines generally advocate a target INR of 2.5 (range of 2.0–3.0) except in Japan, where lower ranges are often recommended.

J Thromb Thrombolysis (2008) 25:26–32  
DOI 10.1007/s11239-007-0101-1

Hyvä INR-kontrolli on hyvin tärkeä asia,  
mutta se ei estä kaikkia vuotoja

## Suuri osa vuodoista tulee hoitotasolla olevan INR:n aikana



2 INR in cerebral bleeding in anticoagulated population

J Thromb Thrombolysis (2006) 22:113–120

The anticoagulant levels in the bleeding cases measured according to the INR at the time of hemorrhage did not show high levels, median INR of 3.33 (range, 1.58–30), even 40% < 3 (Fig. 2). The importance of INR value may not be so determinant, and other factors, such as comorbidity, age, or time of treatment can be relevant [31–40].

The anticoagulant level in previous controls to the bleeding event was correct in 40% considering that in which the levels of appropriate anticoagulation were not surpassed in the last five controls [21, 25, 41–43].

J Thromb Thrombolysis (2006) 22:113–120

**Table 3** Predictors of CNS Bleeding during Warfarin Anticoagulation

- Advancing age ( $\geq 75$  years)
- Hypertension (especially systolic blood pressure  $\geq 160$  mmHg)
- History of cerebrovascular disease
- Intensity of anticoagulation
- Concomitant aspirin use
- “Leukoariosis” (white matter hyperdensities/hyperintensities) by CT/MRI\*
- “Microbleeds” by gradient T2 MRI\*

\* Standardized assessment/acquisition with specificity/sensitivity has not sufficiently characterized to date to permit application to care of individual patients

PROGRESS –tutkimuksessa 12 mmHg:n syst RR:n lasku vähensi aivoverenvuodon riskiä 76 % aivohalvauksen/TIA:n sairastaneilla potilailla

J Thromb Thrombolysis (2008) 25:26–32  
DOI 10.1007/s11239-007-0101-1

## Varfariinihoito ja aivoverenvuoto: riskitekijät 2

**TABLE 1. Risk Factors for Intracerebral Hemorrhage During Warfarin Anticoagulation**

Firmly established<sup>12,25–29</sup>

- Advancing age (especially older than 75 years)
- Hypertension (especially systolic blood pressure  $>160$  mm Hg)
- History of cerebrovascular disease
- Intensity of anticoagulation

Possible

- Concomitant use of aspirin<sup>30</sup>
- Cerebral amyloid angiopathy<sup>31</sup>
- Asian or Mexican-American ethnicity
- Tobacco smoking
- Heavy alcohol consumption

Imaging and genetic markers

- Leukoariosis detected by brain CT/MRI<sup>29,32</sup>
- Microbleeds by T2\*-weighted MRI
- APOE  $\epsilon$  II or IV genotype<sup>31</sup>

CT indicates computed tomography, MRI, magnetic resonance imaging.

*Stroke* 2005;36:1588-1593.

## Good control of hypertension reduces warfarin-associated intracerebral hemorrhage

as CNS bleeding, in atrial fibrillation patients. Good control of hypertension in recent clinical trials probably explains the unexpectedly low stroke rates observed during antiplatelet therapies [3]. Anticoagulation of elderly atrial fibrillation patients should come with a commitment to control blood pressure.

J Thromb Thrombolysis (2008) 25:26–32  
DOI 10.1007/s11239-007-0101-1

### Views & Reviews

#### **CME** Cerebral microbleeds on MRI Prevalence, associations, and potential clinical implications

Hans-Christian Koenneke, MD

Anticoagulation is associated with a substantial risk of ICH, with an estimated 9 to 14% of all ICH attributable to antithrombotic therapy.<sup>65</sup> In this context, several findings suggest a specific cerebrovascular predisposition for ICH, especially among anticoagulated subjects: first, despite a strong association of ICH with INR values greater than 3, most hemorrhages in patients with cerebrovascular disease occur when the INR is within the therapeutic range (2–3)<sup>66–68</sup>; second, the risk of anticoagulation-associated ICH is higher in patients with previous cerebrovascular disease compared with other cohorts,<sup>69</sup> despite higher target INR values, e.g., in patients anticoagulated for cardiac disease<sup>69–71</sup>; third, among patients anticoagulated after ischemic stroke, CT findings suggesting microangiopathy (leukoaraiosis) markedly increase the risk of ICH.<sup>72,73</sup> Thus, given the high prevalence of CMB in patients with leukoaraiosis, CMB might be a histopathologic correlate of this cerebrovascular predisposition for ICH in anticoagulation. Prospective data on this topic are urgently needed and might improve the assessment of ICH risk for patients requiring anticoagulation.

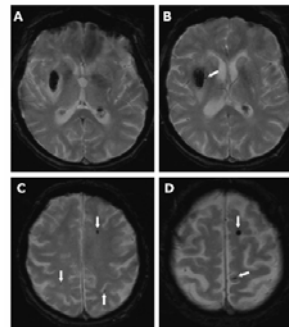


Figure. Gradient-echo MRI of a 77-year-old, hypertensive, non-demented woman 4 days after she had a right putamen intracerebral hemorrhages (ICH). There are no microbleeds in the basal ganglia or thalami (A, B). The small hypointense dot adjacent to the medial margin of the ICH (arrow in B), however, could either be part of the ICH or represent a cerebral microbleed (CMB). Several cortico-subcortical CMB of different size are visible in both hemispheres (arrows in C, D). None of these was identified on conventional T1/T2-weighted MRI. The patient was not on any antithrombotic treatment.

NEUROLOGY 2006;66:165–171

**Discussion.** With a prevalence of approximately 6%, CMB are common among healthy elderly individuals (see table 1).<sup>15,16,21,22</sup> In general, CMB prevalence increases with age, possibly due to the strong association of advanced age with CMB risk factors like leukoaraiosis, CAA, and hypertension. With re-

CMB = cerebral microbleed

CAA = cerebral amyloid  
angiopathy

NEUROLOGY 2006;66:165-171

Miten aivoverenvuodon riskiä voi pienentää?

Olisiko jonkinlaisesta vuotoennustus-  
pisteytyksestä apua?

## Review Article

# The risk of bleeding with warfarin: A systematic review and performance analysis of clinical prediction rules

Karen Dahri, Peter Loewen

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### Summary

It was the objective of this article to qualitatively review and evaluate the clinical prediction rules (CPRs) available for estimating bleeding risk in patients commencing warfarin therapy. A systematic review of PubMed (1949 to December 2006), MEDLINE (1966 to December 2006); EMBASE (1980 to December 2006), Cochrane Database of Systematic Reviews (to December 2006), and International Pharmaceutical Abstracts (1970 to December 2006) was conducted. Seven studies were found that detailed CPRs used to assess risk of bleeding prior to commencing warfarin therapy. Four studies described distinct CPRs. The remaining three studies were further validations of one of the CPRs, the Outpatient Bleeding Risk Index. The Outpatient Bleeding Risk Index was classified as being of Level 2 evidence

while the remaining three indices were classified as being of Level 4 evidence. In no case did the CPRs exhibit performance characteristics that would indicate "strong" ability to predict the presence of absence of major bleeding among warfarin recipients. The modified Outpatient Bleeding Risk Index exhibited moderate predictive ability for major bleeding in two studies, although pooling of all studies of this CPR did not reveal moderate or better performance. None of the CPRs identified "any bleeding" with moderate or strong predictive ability. None of the available CPRs exhibit sufficient predictive accuracy or have trials evaluating the impact of their use on patient outcomes. Hence, no existing CPR can be recommended for widespread use in practice at present.

### Keywords

Bleeding risk, warfarin, clinical prediction rules

Thromb Haemost 2007; 98: 980-987

## Conclusion

Bleeding risk CPRs could provide clinicians with valuable individualized patient information to aid in decision-making prior to initiation of oral anticoagulation therapy. Unfortunately, none of the available CPRs exhibit sufficient predictive accuracy or have trials evaluating the impact of their use on patient outcomes. Hence, no existing CPR can be recommended for widespread use in practice at present.

While at present the true risk may not be reliably estimated, risk factors that are known to increase an individual patient's risk of bleeding should be evaluated and minimized if possible. Further prospective trials are required to develop a CPR that can be reliably employed in clinical practice.

Thromb Haemost 2007; 98: 980-987

Yhteenveto: Miten aivoverenvuodon riskiä voi pienentää?

**TABLE 7. Avoiding CNS Bleeding During Antithrombotic Therapy**

Elderly patients and those with cerebrovascular disease are at special risk

Keep INRs  $\leq 3.0$

Warfarin combined with aspirin should be used with special caution in elderly patients and those with cerebrovascular disease

Combination of clopidogrel with aspirin may accentuate ICH risk in stroke patients

Modest blood pressure-lowering profoundly reduces CNS bleeding

ICH indicates intracerebral hemorrhage.

*Stroke 2005;36:1588-1593.*

Thrombosis Research (2007) 121, 347–352



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REGULAR ARTICLE

**Risk of bleeding in very old atrial fibrillation patients on warfarin: Relationship with ageing and CHADS<sub>2</sub> score**

Daniela Poli<sup>a,\*</sup>, Emilia Antonucci<sup>a</sup>, Rossella Marcucci<sup>a</sup>, Cinzia Fatini<sup>a</sup>, Brunetto Alterini<sup>b</sup>, Lucia Mannini<sup>a</sup>, Michela Falciani<sup>a</sup>, Rosanna Abbate<sup>a</sup>, Gian Franco Gensini<sup>a</sup>, Domenico Prisco<sup>a</sup>

**Table 2** Rate of major bleeding events in relation to age

Age	Pt/years	Total			Cerebral			Fatal	
		Rate(n)	RR (95%CI)	p	Rate(n)	RR (95%CI)	p	Rate(n)	RR (95%CI)
75–79	433	1.4 (6)	1	0.4	0.7 (3)	1	0.3	0	
80–84	271	2.6 (7)	1.8 (0.3–6.7)	0.3	2.2 (6)	3.1 (0.6–20)	0.6	1.8 (5)	NA
85–96	110	3.6 (4)	2.6 (0.5–11)	0.3	1.8 (2)	2.6 (0.2–23)	0.4	0.9 (1)	NA

Pt/years = patient/years.  
NA = not applicable.

**Table 4** Rate of major bleeding events in relation to CHADS<sub>2</sub> score

CHADS <sub>2</sub>	75–79 years			80–84 years			85–96 years		
	n/pt/years	Rate × 100 pt/years	NNH	n/pt/years	Rate × 100 pt/years	NNH	n/pt/years	Rate × 100 pt/years	NNH
1–3	5/308	1.6	62	3/195	1.5	65	1/80	1.2	80
4–6	1/126	0.8	126	4/177	2.2	44	3/30	10.0	10
All	6/433	1.4	72	7/271	2.6	39	4/110	3.6	27

Hyvin iäkkäillä potilailla (> 85 v), joilla on suuri tromboosiriski on myös hyvin suuri vuotoriski yksilölliset hoitoratkaisut

CHADS<sub>2</sub> stroke score was calculated by adding 1 point for each of the following conditions: congestive heart failure, hypertension, age > 75 years, or diabetes and 2 points for a prior stroke or transient ischemic attack.

Thrombosis Research (2007) 121, 347–352

## Kaatuilutaipumus



The American Journal of Medicine (2005) 118, 612–617



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### CLINICAL RESEARCH STUDY

## Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall

Brian F. Gage, MD, MSc,<sup>a</sup> Elena Birman-Deych, MS,<sup>a</sup> Roger Kerzner, MD,<sup>b</sup>  
Martha J. Radford, MD,<sup>c</sup> David S. Nilasena, MD, MSPH, MS,<sup>d</sup> Michael W. Rich, MD<sup>b</sup>

Potilaiden keski-ikä 80 v, 1245 suuren kaatumisriskin potilasta (33 %:lla varfariini), 18261 tavanomaisen kaatumisriskin potilasta (48 % käytti varfariinia)

**Table 3** Multivariate Cox regression showing hazard ratios (HR) of independent predictors of intracranial hemorrhage

Factor	HR (95% CI)	P Value
High-risk for falls	1.9 (1.3–2.9)	0.002
Prior stroke	2.2 (1.7–2.8)	<0.0001
Prior bleed	1.8 (1.4–2.4)	<0.0001
Neuropsychiatric impairment	1.4 (1.0–1.9)	0.055



**Table 2** Rates of intracranial hemorrhage, stratified by cohort

Intracranial hemorrhage rate (95% CI) per 100 patient-years		
Intracranial hemorrhage type	High-fall-risk patients (n = 1245)	Other patients (n = 18 261)
Traumatic	2.0 (1.3–3.1)*	0.34 (0.27–0.45)
Nontraumatic	0.7 (0.4–1.5)	0.8 (0.7–0.9)
Total*	2.8 (1.9–4.1)†	1.1 (1.0–1.3)

\*P < 0.0001 High-fall vs other patients.  
 †P = 0.0005 High-fall vs other patients.

**Table 4** Hazard ratio of warfarin for composite outcome—out-of-hospital death or hospitalization for stroke, myocardial infarction, or hemorrhage—in 1245 patients at high risk for falls

CHADS <sub>2</sub> score	Hazard ratio (95% CI)	P value	Recommended antithrombotic therapy
0–1	0.98 (0.56,1.72)	0.94	Aspirin or nil
2–6	0.75 (0.61,0.91)	0.004	Anticoagulant

CHADS<sub>2</sub> stroke score was calculated by adding 1 point for each of the following conditions: congestive heart failure, hypertension, age > 75 years, or diabetes and 2 points for a prior stroke or transient ischemic attack. CI indicates confidence interval.

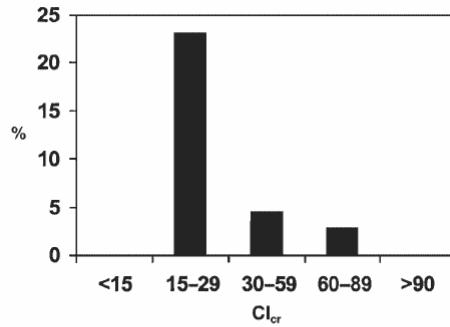
The American Journal of Medicine (2005) 118, 612–617

Despite the significant association between intracranial hemorrhage and fall risk, the findings support the use of anticoagulants in patients at high risk for falls who are at moderate to high risk of stroke. Prescribing warfarin in patients at high risk for falls with 2 or more CHADS<sub>2</sub> points was associated with a 25% relative risk reduction (HR 0.75) in the composite outcome (Table 4). When prescribing warfarin to these patients, providers could instruct them to take precautions to limit their risk of falling: wear stable shoes,<sup>21</sup> exercise regularly,<sup>22</sup> take vitamin D,<sup>23</sup> use walking aids,<sup>24</sup> and discontinue unnecessary medications.<sup>24–26</sup>

**CONCLUSION:** Patients at high risk for falls with atrial fibrillation are at substantially increased risk of intracranial hemorrhage, especially traumatic intracranial hemorrhage. However, because of their high stroke rate, they appear to benefit from anticoagulant therapy if they have multiple stroke risk factors.

The American Journal of Medicine (2005) 118, 612–617

## Munuaisten vajaatoiminta lisää vuotoriskiä erityisesti LMWH-hoidon aikana



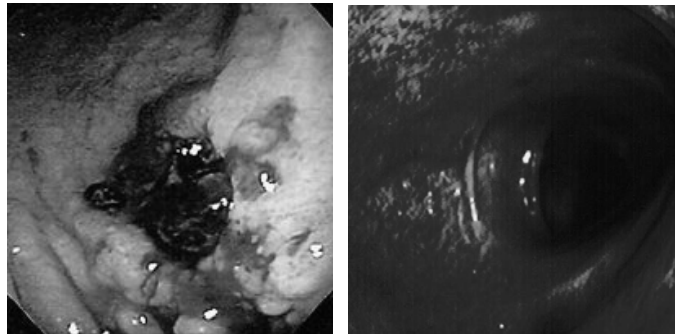
### Percutaneous Coronary Intervention-Related Bleeding Risk Factors in Current Practice

A Scott Matheis and James J O'Guerri

Figure 1. Major bleeding according to baseline chronic kidney disease stages. Patients were divided according to the degree of renal dysfunction prior to undergoing PCI. The percent incidence of major bleeding, according to REPLACE-2 criteria, was CrCl <15 mL/min, 0% (n = 6); 15-29 mL/min, 23.1% (n = 13); 30-59 mL/min, 4.5% (n = 89); 60-89 mL/min, 2.88% (n = 139); and  $\geq 90$  mL/min, 0% (n = 65). Overall  $\chi^2$  for major bleeding, p = 0.001. CrCl = creatinine clearance; PCI = percutaneous coronary intervention; Replace-2 = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Outcomes.

*Ann Pharmacother* 2005;39:1627-33.

## GI-VUOTO



## ANTITROMBOOTTINEN HOITO JA VAKAVAN GI-VUODON RISKI

Crude and adjusted odds ratios for association between use of antithrombotic drug and serious upper gastrointestinal bleeding

	Cases (exposed/unexposed)	Controls (exposed/unexposed)	Crude odds ratios (95% CI)	Adjusted odds ratios (95% CI)*
<b>Single drug regimens, current use</b>				
Aspirin alone	196/1063	4123/50 498	2.4 (2.0 to 2.8)	1.8 (1.5 to 2.1)
Clopidogrel alone	12/1063	203/50 498	3.1 (1.7 to 5.6)	1.1 (0.6 to 2.1)
VKA alone	56/1063	1227/50 498	2.2 (1.7 to 3.0)	1.8 (1.3 to 2.4)
Dipyridamole alone	36/1063	738/50 498	2.4 (1.7 to 3.4)	1.9 (1.3 to 2.8)
<b>Two drug regimens, current use</b>				
Aspirin and clopidogrel	13/1063	49/50 498	12.6 (6.6 to 24)	7.4 (3.5 to 15)
Aspirin and VKA	16/1063	114/50 498	6.4 (3.7 to 11)	5.3 (2.9 to 9.5)
Dipyridamole and aspirin	44/1063	737/50 498	3.1 (2.2 to 4.2)	2.3 (1.7 to 3.3)
<b>Past use</b>				
Aspirin	108/886	3990/44 968	1.5 (1.2 to 1.8)	0.9 (0.7 to 1.2)
Clopidogrel	4/990	111/48 847	1.8 (0.7 to 5.1)	0.8 (0.3 to 2.2)
Dipyridamole	2/992	152/48 806	0.8 (0.2 to 2.9)	0.4 (0.1 to 1.6)
VKA	48/946	1028/47 930	2.4 (1.8 to 3.3)	1.8 (1.3 to 2.4)

VKA=vitamin K antagonist.

\*Adjusted for previous discharge diagnosis of peptic ulcer, peptic ulcer bleeding, chronic obstructive lung disease, ischaemic heart disease, alcohol related diagnosis or drug use, or liver cirrhosis or renal failure; for past *Helicobacter pylori* eradication; and for concurrent use of non-steroidal anti-inflammatory drugs, antiulcer drugs, nitrate vasodilators, selective serotonin reuptake inhibitors, or systemic corticosteroids.

Melaena, hemoglobiinin merkittävä lasku tai verensiirto

BMJ  
2006;333:726

### THERAPY IN PRACTICE

Drugs Aging 2007; 24 (10): 615-628  
1170-229X/07/0010-0615/\$44.95/0

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## Bleeding Peptic Ulcer in the Elderly Risk Factors and Prevention Strategies

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Peptic ulcer bleeding is a frequent and dramatic event with both a high mortality rate and a substantial cost for healthcare systems worldwide. It has been found that age is an independent predisposing factor for gastrointestinal bleeding, with the risk increasing significantly in individuals aged >65 years and increasing further in those aged >75 years. Indeed, bleeding incidence and mortality are distinctly higher in elderly patients, especially in those with co-morbidities. NSAID therapy and *Helicobacter pylori* infection are the most prevalent aetiopathogenic factors involved in peptic ulcer bleeding.

1.65/100 000 < 65 v

5.7/ 100 000 > 65 v

12.7 / 100 000 > 75 v

**Table II.** Suggested gastroduodenal protective strategies before commencing NSAID therapy in high-risk patients

Drug	Duration (months)	PUD history	Strategy
NSAID or aspirin (acetylsalicylic acid)	<3	No	PPI co-therapy
NSAID or aspirin	>3-6	No	Test and treat for <i>Helicobacter pylori</i>
Aspirin	>3-6	Yes	Test and treat for <i>H. pylori</i>
NSAID	>3-6	Yes	Test and treat for <i>H. pylori</i> plus PPI maintenance therapy

PPI = proton pump inhibitor; PUD = peptic ulcer disease.

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Drugs Aging 2007; 24 (10)

- > 65-vuotiaista vähintään 10-25 % käyttää länsimaissa NSAID –valmisteita
- gi-leesiot syntyvät etenkin hoidon alussa < 1 kk (mucosan adaptaatioprosessi)
- adaptaatioprosessi heikompi iäkkäillä
- vanhuksilla *H. pylori* tavallinen
  
- high risk patient = ikä > 75 v tai ikä < 75 v + kortikosteroidi tai ak-hoito tai aikaisempi *H. pylori* –eradikaatioresistenssi ulcus

Lääkärin hyvät taidot ja huolellisuus  
– mutta myös järjestelmiin  
puuttuminen - pienentävät  
vuotoriskiä



ELSEVIER

CLINICAL RESEARCH STUDY

## The Safety of Warfarin Therapy in the Nursing Home Setting

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<sup>e</sup>Qualidigm, Inc, Middletown, Conn.

25 vanhainkotiä, n. 3000 asukasta,  
joista 490 käytti varfariinia, 12 kk:n  
seuranta

The American Journal of Medicine (2007) 120, 539-544

**Table 3** Types of Bleeding\*

Type	No. (%)
Ecchymoses	461 (64)
Gross hematuria	72 (10)
Gastrointestinal (occult)	47 (7)
Epistaxis	44 (6)
Gastrointestinal (overt)	38 (5)
Microhematuria	23 (3)
Vaginal	13 (2)
Hemoptysis	12 (2)
Gingival	9 (1)
Subconjunctival	4 (1)
Ear	3 (<1)
Ocular	2 (<1)
Gluteal	1 (<1)
Intracranial	1 (<1)

\*Adverse warfarin-related events could manifest as more than 1 type of bleeding.

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**Table 2** Severity and Effects of Adverse Warfarin-Related Events

	No. (%)	
	Total (n = 720)	Preventable (n = 207)
Category of severity		
Fatal	5 (1)	3 (1)
Life threatening	8 (1)	8 (4)
Serious	82 (11)	43 (21)
Minor	625 (87)	153 (74)

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Among the 207 preventable adverse warfarin-related events and the 253 potential adverse warfarin-related events, errors occurred most commonly at the prescribing (n = 321, 70%) and monitoring (n = 424, 92%) stages of warfarin management. Errors accounting for preventable events were rarely identified at the dispensing (n = 2) or administration (n = 2) stages. A total of 285 (62%) of the preventable events were associated with an error at both the prescribing and monitoring stages of warfarin management. Monitoring errors generally referred to inadequate laboratory monitoring of warfarin therapy or to a delayed response, or a failure to respond to laboratory results (ie, INR values). Among the prescribing errors, the most common were wrong dose (n = 259, 81%) and known drug interaction (n = 80, 25%).

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of warfarin therapy in the nursing home setting. If our findings are generalized to residents on warfarin in all US nursing homes, there may be approximately 34,000 fatal, life-threatening, or serious adverse warfarin-related events per year, of which the majority may be preventable. Furthermore, “near misses” are common. Many residents of

The American Journal of Medicine (2007) 120, 539-544

## Lopuksi

- vuotovaarasta huolimatta iäkkäiden suuren tromboosiriskin potilaiden antitromboottinen lääkehoito on hyödyllistä
- ylihoito on haitallista → hoitosuosituksissa kannattaa pitäytyä
- hyvin iäkkäiden (> 90 v) osalta tutkittua tietoa vähemmän
- vuotoriskiä pienentävät toimenpiteet (verenpaineen hoito, gi-limakalvon suojaus tarvittaessa, hyvä INR-kontrolli, kaatuilutaipumuksen minimointi) ovat hyödyllisiä