*KHRS meeting*
*June 23, 2023*

# Unmet Need For AF Stroke Management Neurologist's Perspectives

**Chi Kyung Kim, MD, PhD**

**Neurology**

**Korea University Guro Hospital, Seoul Korea**

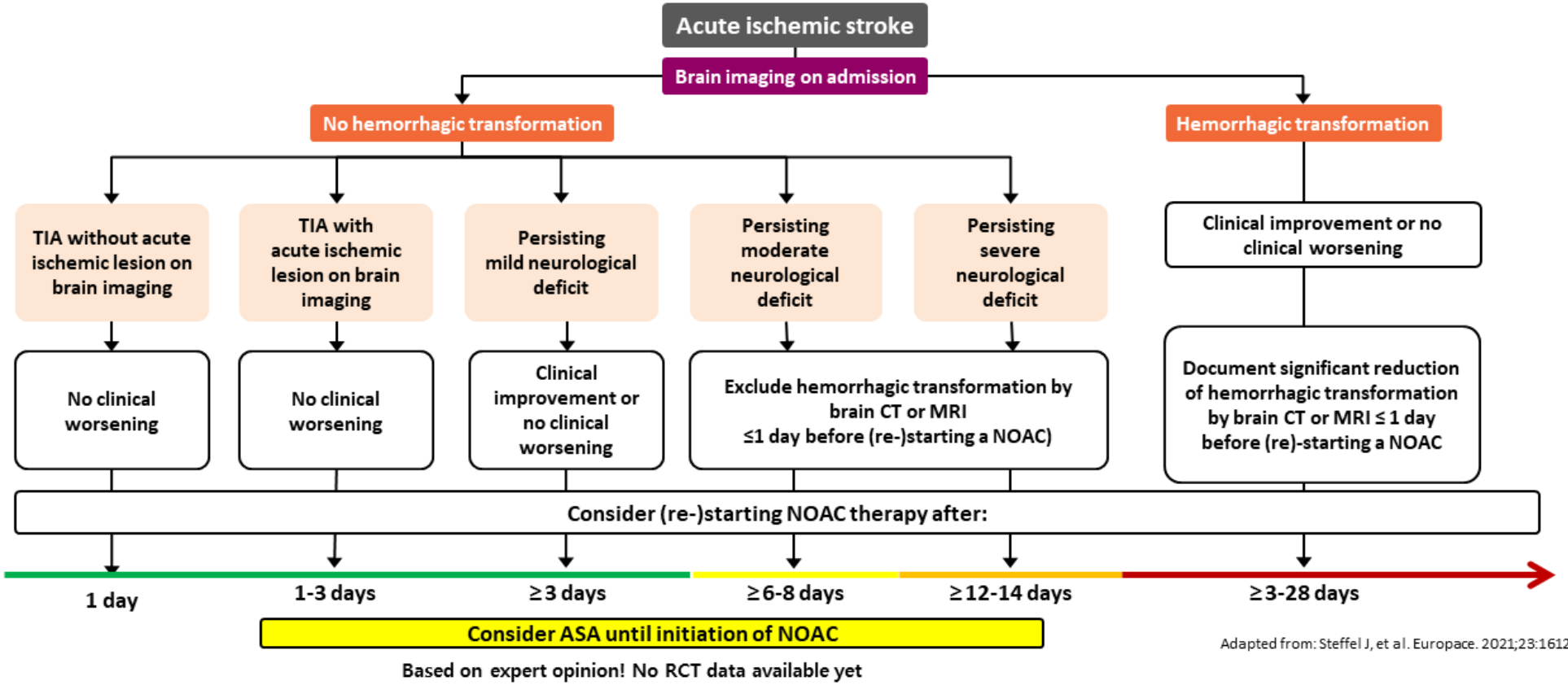
# Contents

- When do we start anticoagulation after stroke?
- How do we treat afib-related stroke patients with intracranial stenosis or cerebral small vessel diseases?
- Precision medicine for predicting future thromboembolism and bleeding after stroke with a-fib

# When do we start anticoagulation after stroke?

# After ischemic stroke

# EHRA 2021 Guidelines: (Re-) Initiation of Anticoagulation after TIA/Stroke.




Adapted from: Steffel J, et al. Europace. 2021;23:1612–1676

EHRA: European Heart Rhythm Association; CT: computed tomography; LA: left atrium; LAA: left atrial appendage; MRI: magnetic resonance imaging; NOAC: non-vitamin K antagonist oral anticoagulant; RCT: randomized clinicaltrial; TIA: transient ischaemic attack.

KOREA UNIVERSITY

KOREA UNIVERSITY GLOBAL PRIDE

# Time to re-initiation depends on infarct size: 1 – 3 – 6 – 12 day rule (Diener's Law)

| | TIA | Mild stroke | Moderate stroke | Severe stroke |
|---|---|---|---|---|
| | As soon as imaging has excluded a cerebral haemorrhage | 3–5 days after symptom onset | 5–7 days after stroke onset | 2 weeks after stroke onset |
| Day | 1 | 3 | 6 | 12 |
| NIHSS | 0 | <8 | 8-16 | >16 |

JAMA Neurology | Original Investigation

# Rivaroxaban vs Warfarin Sodium in the Ultra-Early Period After Atrial Fibrillation–Related Mild Ischemic Stroke
## A Randomized Clinical Trial

Keun-Sik Hong, MD; Sun U. Kwon, MD; Sang Hun Lee, MD; Ji Sung Lee, PhD; Yong-Jae Kim, MD; Tae-Jin Song, MD; Young Dae Kim, MD; Man-Seok Park, MD; Eung-Gyu Kim, MD; Jae-Kwan Cha, MD; Sang Min Sung, MD; Byung-Woo Yoon, MD; Oh Young Bang, MD; Woo-Keun Seo, MD; Yang-Ha Hwang, MD; Seong Hwan Ahn, MD; Dong-Wha Kang, MD; Hyun Goo Kang, MD; Kyung-Ho Yu, MD; for the Phase 2 Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients With Non-valvular Atrial Fibrillation (Triple AXEL) Study Group

Editorial page 1174
Supplemental content

**IMPORTANCE** In atrial fibrillation (AF)–related acute ischemic stroke, the optimal oral anticoagulation strategy remains unclear.

**OBJECTIVE** To test whether rivaroxaban or warfarin sodium is safer and more effective for preventing early recurrent stroke in patients with AF-related acute ischemic stroke.

**DESIGN, SETTING, AND PARTICIPANTS** A randomized, multicenter, open-label, blinded end point evaluation, comparative phase 2 trial was conducted from April 28, 2014, to December 7, 2015, at 14 academic medical centers in South Korea among patients with mild AF-related stroke within the previous 5 days who were deemed suitable for early anticoagulation. Analysis was performed on a modified intent-to-treat basis.

**INTERVENTIONS** Participants were randomized 1:1 to receive rivaroxaban, 10 mg/d for 5 days followed by 15 or 20 mg/d, or warfarin with a target international normalized ratio of 2.0-3.0, for 4 weeks.

**MAIN OUTCOMES AND MEASURES** The primary end point was the composite of new ischemic lesion or new intracranial hemorrhage seen on results of magnetic resonance imaging at 4 weeks. Primary analysis was performed in patients who received at least 1 dose of study medications and completed follow-up magnetic resonance imaging. Key secondary end points were individual components of the primary end point and hospitalization length.

**RESULTS** Of 195 patients randomized, 183 individuals (76 women and 107 men; mean [SD] age, 70.4 [10.4] years) completed magnetic resonance imaging follow-up and were included in the primary end point analysis. The rivaroxaban group (n = 95) and warfarin group (n = 88) showed no differences in the primary end point (47 [49.5%] vs 48 [54.5%]; relative risk, 0.91; 95% CI, 0.69-1.20; $P = .49$) or its individual components (new ischemic lesion: 28 [29.5%] vs 31 of 87 [35.6%]; relative risk, 0.83; 95% CI, 0.54-1.26; $P = .38$; new intracranial hemorrhage: 30 [31.6%] vs 25 of 87 [28.7%]; relative risk, 1.10; 95% CI, 0.70-1.71; $P = .68$). Each group had 1 clinical ischemic stroke, and all new intracranial hemorrhages were asymptomatic hemorrhagic transformations. Hospitalization length was reduced with rivaroxaban compared with warfarin (median, 4.0 days [interquartile range, 2.0-6.0 days] vs 6.0 days [interquartile range, 4.0-8.0]; $P < .001$).

**CONCLUSIONS AND RELEVANCE** In mild AF-related acute ischemic stroke, rivaroxaban and warfarin had comparable safety and efficacy.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT02042534

*JAMA Neurol*. 2017;74(10):1206-1215. doi:10.1001/jamaneurol.2017.2161
Published online September 11, 2017.

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** Members of the Phase 2 Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients With Non-valvular Atrial Fibrillation (Triple AXEL) Study Group are listed at the end of this article.

**Corresponding Author:** Sun U. Kwon, MD, Department of Neurology, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro, Songpa-gu, Seoul 138-736, South Korea (sukwon@amc.seoul.kr).

**Table 3. Adverse Events in the Safety Population**

| Characteristic | No. (%) | | Risk Difference, % (95% CI) | *P* Value |
|---|---|---|---|---|
| | Rivaroxaban Group (n = 98) | Warfarin Sodium Group (n = 90) | | |
| ≥1 Adverse events | 46 (46.9) | 51 (56.7) | −9.73 (−23.84 to 4.66) | .18 |
| ≥1 Adverse drug reactions | 9 (9.2) | 13 (14.4) | −5.26 (−19.41 to 9.11) | .26 |
| ≥1 Serious adverse events | 5 (5.1) | 5 (5.6) | −0.45 (−14.76 to 13.82) | >.99 |
| Withdrawal owing to adverse events | 1 (1.0) | 0 | 1.02 (−13.32 to 15.32) | >.99 |
| Death | 0 | 0 | NA | >.99 |

KOREA UNIVERSITY

JAMA Neurology 2017

KOREA UNIVERSITY GLOBAL PRIDE

Table 2. End Points in the Modified Intent-to-Treat Population

| End Point | Rivaroxaban Group, No. (%) (n = 95) | Warfarin Sodium Group, No. (%) (n = 88) | Risk Difference (95% CI) | Relative Risk (95% CI) | *P* Value | Adjusted Relative Risk (95% CI)[a] | *P* Value |
|---|---|---|---|---|---|---|---|
| Intracranial hemorrhage or recurrent ischemic lesion on results of 4-wk MRI (primary end point) | 47 (49.5) | 48 (54.5) | -5.07 (-19.52 to 9.49) | 0.91 (0.69 to 1.20) | .49 | 0.97 (0.79 to 1.18) | .73 |
| Recurrent ischemic lesion on results of 4-wk MRI[b] | 28 (29.5) | 31 (35.6) | -6.16 (-20.48 to 8.45) | 0.83 (0.54 to 1.26) | .38 | 0.85 (0.56 to 1.30) | .45 |
| Intracranial hemorrhage on results of 4-wk MRI[b] | 30 (31.6) | 25 (28.7) | 2.84 (-11.68 to 17.29) | 1.10 (0.70 to 1.71) | .68 | 1.17 (0.74 to 1.85) | .50 |
| Clinical recurrent ischemic stroke | 1 (1.1) | 1 (1.1) | -0.08 (-14.54 to 14.42) | 0.93 (0.06 to 14.59) | >.99 | NA | NA |
| Symptomatic hemorrhagic conversion or hemorrhagic stroke | 0 | 0 | NA | NA | >.99 | NA | NA |
| Major bleeding | 1 (1.1) | 0 | 1.05 (-13.44 to 15.53) | NA | >.99 | NA | NA |
| Systemic embolism | 0 | 0 | NA | NA | >.99 | NA | NA |
| Acute coronary syndrome | 0 | 0 | NA | NA | >.99 | NA | NA |
| Composite of stroke, MI, or vascular death | 1 (1.1) | 1 (1.1) | -0.08 (-14.54 to 14.42) | 0.93 (0.06 to 14.59) | >.99 | NA | NA |
| Composite of stroke, MI, vascular death, or major bleeding | 2 (2.1) | 1 (1.1) | 0.97 (-13.50 to 15.46) | 1.85 (0.17 to 20.08) | >.99 | NA | NA |
| Composite of clinical ischemic events | 1 (1.1) | 1 (1.1) | -0.08 (-14.54 to 14.42) | 0.93 (0.06 to 14.59) | >.99 | NA | NA |
| Duration of hospitalization, median (IQR), d | 4.0 (2.0-6.0) | 6.0 (4.0-8.0) | NA | NA | <.001 | NA | .002 |
| mRS score 0-1 at 4 wk[c] | 79 (84.0) | 64 (74.4) | 9.62 (-5.06 to 23.95) | 1.13 (0.97 to 1.31) | .11 | 1.04 (0.83 to 1.29) | .73 |

# Early versus Later Anticoagulation for Stroke with AF

**Early Anticoagulation?**

**Vs.**

**Later Anticoagulation?**

ORIGINAL ARTICLE

## Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

U. Fischer, M. Koga, D. Strbian, M. Branca, S. Abend, S. Trelle, M. Paciaroni, G. Thomalla, P. Michel, K. Nedeltchev, L.H. Bonati, G. Ntaios, T. Gattringer, E.-C. Sandset, P. Kelly, R. Lemmens, P.N. Sylaja, D. Aguiar de Sousa, N.M. Bornstein, Z. Gdovinova, T. Yoshimoto, M. Tiainen, H. Thomas, M. Krishnan, G.C. Shim, C. Gumbinger, J. Vehoff, L. Zhang, K. Matsuzono, E. Kristoffersen, P. Desfontaines, P. Vanacker, A. Alonso, Y. Yakushiji, C. Kulyk, D. Hemelsoet, S. Poli, A. Paiva Nunes, N. Caracciolo, P. Slade, J. Demeestere, A. Salerno, M. Kneihsl, T. Kahles, D. Giudici, K. Tanaka, S. Räty, R. Hidalgo, D.J. Werring, M. Göldlin, M. Arnold, C. Ferrari, S. Beyeler, C. Fung, B.J. Weder, T. Tatlisumak, S. Fenzl, B. Rezny-Kasprzak, A. Hakim, G. Salanti, C. Bassetti, J. Gralla, D.J. Seiffge, T. Horvath, and J. Dawson, for the ELAN Investigators*

ABSTRACT

BACKGROUND

The effect of early as compared with later initiation of direct oral anticoagulants (DOACs) in persons with atrial fibrillation who have had an acute ischemic stroke is unclear.

METHODS

We performed an investigator-initiated, open-label trial at 103 sites in 15 countries. Participants were randomly assigned in a 1:1 ratio to early anticoagulation (within 48 hours after a minor or moderate stroke or on day 6 or 7 after a major stroke) or later anticoagulation (day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke). Assessors were unaware of the trial-group assignments. The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. Secondary outcomes included the components of the composite primary outcome at 30 and 90 days.

RESULTS

Of 2013 participants (37% with minor stroke, 40% with moderate stroke, and 23% with major stroke), 1006 were assigned to early anticoagulation and 1007 to later anticoagulation. A primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group (risk difference, −1.18 percentage points; 95% confidence interval [CI], −2.84 to 0.47) by 30 days. Recurrent ischemic stroke occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group (odds ratio, 0.57; 95% CI, 0.29 to 1.07) by 30 days and in 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days (odds ratio, 0.60; 95% CI, 0.33 to 1.06). Symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups by 30 days.

CONCLUSIONS

In this trial, the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days was estimated to range from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early than with later use of DOACs. (Funded by the Swiss National Science Foundation and others; ELAN ClinicalTrials.gov number, NCT03148457.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Fischer can be contacted at urs.fischer@usb.ch or at the Department of Neurology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland.

*A list of the ELAN Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 24, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2303048





Ref) U. Fischer, et al. May 24, 2023. NEJM

# Early versus Later Anticoagulation for Stroke with AF

## Result

- Of 2013 participants (37% with minor stroke, 40% with moderate stroke, and 23% with major stroke), 1006 were assigned to early anticoagulation and 1007 to later anticoagulation.
- A primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group (risk difference, −1.18 percentage points; 95% confidence interval [CI], −2.84 to 0.47) by 30 days.
- Recurrent ischemic stroke occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group (odds ratio, 0.57; 95% CI, 0.29 to 1.07) by 30 days and in 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days (odds ratio, 0.60; 95% CI, 0.33 to 1.06).
- Symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups by 30 days.

## Conclusion

- In this trial, the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days was estimated to range from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early than with later use of DOACs.

Ref) U. Fischer.,et al. May 24, 2023. NEJM

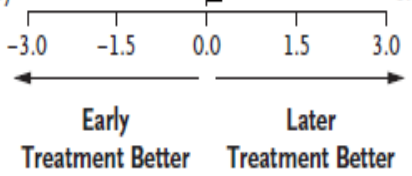
# Early versus Later Anticoagulation for Stroke with AF : Primary outcome

## Primary outcome

- Primary-outcome event occurred in 29 participants (2.9%) in the early treatment group and in 41 participants (4.1%) in the later-treatment group.
- The estimated odds ratio for a primary-outcome event in the early-treatment group as compared with the later-treatment group was 0.70 (95% confidence interval [CI], 0.44 to 1.14), and the derived risk difference was −1.18 percentage points (95% CI, −2.84 to 0.47)

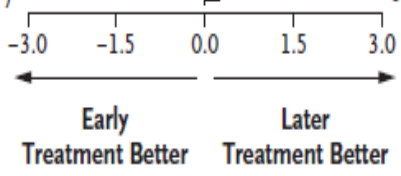
A

| Outcome within 30 Days | Early-Treatment Group (N=984) | Later-Treatment Group (N=991) | Adjusted Risk Difference (95% CI) |
|---|---|---|---|
| | *no. of events (%)* | | *percentage points* |
| Primary-outcome event | 29 (2.9) | 41 (4.1) | −1.18 (−2.84 to 0.47) |
| Major extracranial bleeding | 3 (0.3) | 5 (0.5) | −0.25 (−0.90 to 0.41) |
| Symptomatic intracranial hemorrhage | 2 (0.2) | 2 (0.2) | 0.01 (−0.52 to 0.53) |
| Recurrent ischemic stroke | 14 (1.4) | 25 (2.5) | −1.14 (−2.41 to 0.13) |
| Systemic embolism | 4 (0.4) | 9 (0.9) | −0.55 (−1.34 to 0.23) |
| Death from vascular cause | 11 (1.1) | 10 (1.0) | 0.13 (−0.84 to 1.09) |




B

| Outcome within 90 Days | Early-Treatment Group (N=968) | Later-Treatment Group (N=965) | Adjusted Risk Difference (95% CI) |
|---|---|---|---|
| | *no. of events (%)* | | *percentage points* |
| Primary-outcome event | 36 (3.7) | 54 (5.6) | −1.92 (−3.82 to −0.02) |
| Major extracranial bleeding | 3 (0.3) | 8 (0.8) | −0.61 (−1.37 to 0.14) |
| Symptomatic intracranial hemorrhage | 2 (0.2) | 2 (0.2) | 0.00 (−0.54 to 0.53) |
| Recurrent ischemic stroke | 18 (1.9) | 30 (3.1) | −1.29 (−2.72 to 0.13) |
| Systemic embolism | 4 (0.4) | 10 (1.0) | −0.70 (−1.53 to 0.13) |
| Death from vascular cause | 17 (1.8) | 16 (1.7) | 0.07 (−1.13 to 1.27) |




Ref) U. Fischer.,et al. May 24, 2023. NEJM

# Early versus Later Anticoagulation for Stroke with AF : Secondary outcome

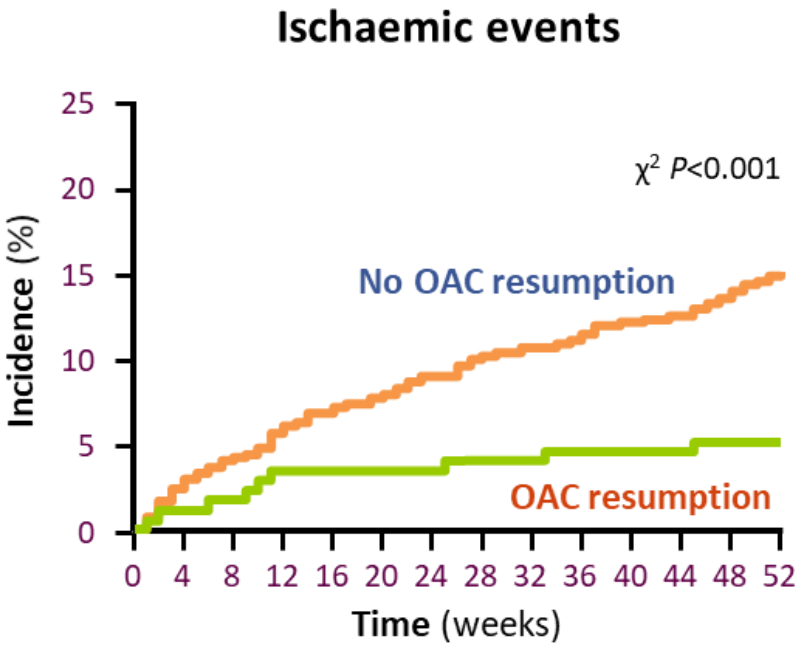
**Table 2. Primary and Secondary Efficacy Outcomes.**

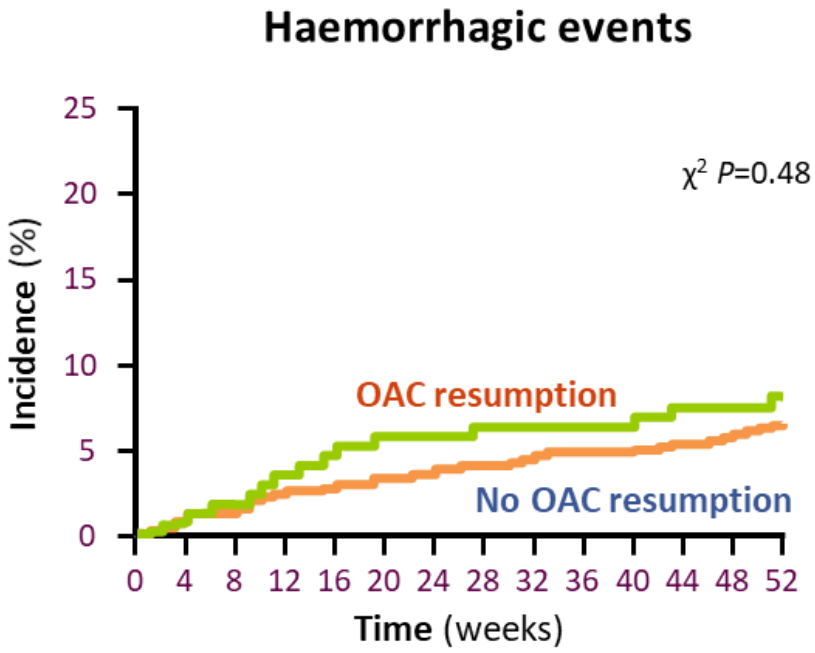
| Outcome | Early-Treatment Group (N=1006) | Later-Treatment Group (N=1007) | Adjusted Odds Ratio (95% CI)* |
|---|---|---|---|
| | *no./total no. (%)* | | |
| **Primary outcome: composite outcome at 30 days** | 29/1006 (2.9)† | 41/1007 (4.1)† | 0.70 (0.44 to 1.14)‡ |
| **Secondary outcomes at 30 days** | | | |
| Major extracranial bleeding | 3/984 (0.3) | 5/991 (0.5) | 0.63 (0.15 to 2.38) |
| Symptomatic intracranial hemorrhage | 2/984 (0.2) | 2/991 (0.2) | 1.02 (0.16 to 6.59) |
| Recurrent ischemic stroke | 14/984 (1.4) | 25/991 (2.5) | 0.57 (0.29 to 1.07) |
| Systemic embolism | 4/984 (0.4) | 9/991 (0.9) | 0.48 (0.14 to 1.42) |
| Vascular death | 11/984 (1.1) | 10/991 (1.0) | 1.12 (0.47 to 2.65) |
| Nonmajor bleeding | 30/984 (3.0) | 27/991 (2.7) | 1.13 (0.67 to 1.93) |
| Modified Rankin scale score ≤2§ | 624/997 (62.6) | 626/1000 (62.6) | 0.93 (0.79 to 1.09) |
| **Secondary outcomes at 90 days** | | | |
| Major extracranial bleeding | 3/968 (0.3) | 8/965 (0.8) | 0.40 (0.10 to 1.31) |
| Symptomatic intracranial hemorrhage | 2/968 (0.2) | 2/965 (0.2) | 1.00 (0.15 to 6.45) |
| Recurrent ischemic stroke | 18/968 (1.9) | 30/965 (3.1) | 0.60 (0.33 to 1.06) |
| Systemic embolism | 4/968 (0.4) | 10/965 (1.0) | 0.42 (0.12 to 1.21) |
| Vascular death | 17/968 (1.8) | 16/965 (1.7) | 1.04 (0.52 to 2.08) |
| Death from any cause¶ | 45/994 (4.5) | 48/995 (4.8) | 0.93 (0.61 to 1.43) |
| Nonmajor bleeding | 39/968 (4.0) | 41/965 (4.2) | 0.94 (0.59 to 1.47) |
| Modified Rankin scale score ≤2§ | 659/989 (66.6) | 654/994 (65.8) | 0.93 (0.79 to 1.09) |
| Any serious adverse event | 132/947 (13.9) | 157/993 (15.8) | |

Ref) U. Fischer.,et al. May 24, 2023. NEJM

# After hemorrhagic stroke

# OAC resumption after ICH




**Benefit of OAC for the prevention of ischaemic stroke was higher than the bleeding risk**

Study design: A retrospective cohort study at 19 German tertiary care centers (2006-2012) including 1,176 individuals for analysis of long-term functional outcome, 853 for analysis of hematoma enlargement, and 719 for analysis of OAC resumption

ICH: intracerebral hemorrhage; OAC: oral anticoagulant

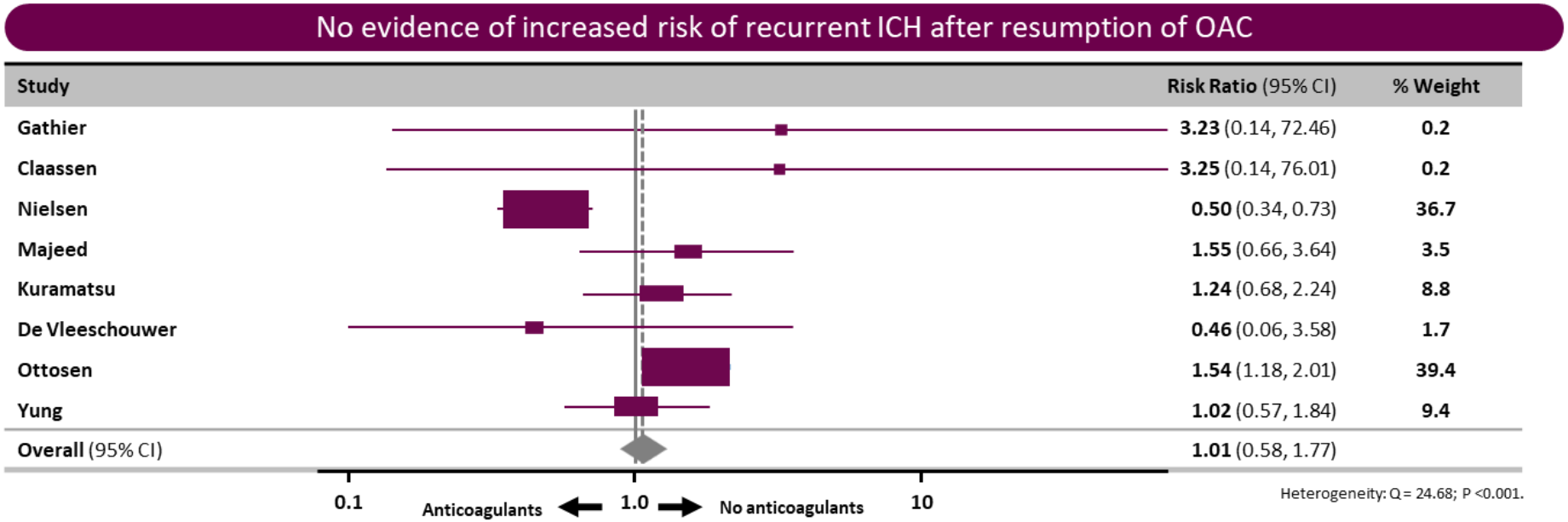
Adapted from: Kuramatsu JB, et al. JAMA. 2015;24;313(8):824-836.

KOREA UNIVERSITY

KOREA UNIVERSITY GLOBAL PRIDE

# Use of OAC Therapy after ICH

- In a meta-analysis of 8 cohort studies, reinstitution of anticoagulation after ICH was associated with a lower risk of thromboembolic complications and a similar risk of ICH recurrence.




Study design: In a meta-analysis of 8 cohort with 5,306 ICH patients, the predictor variable was resumption of AC and outcome measures were thromboembolic events (stroke and/or myocardial infarction) and recurrence of ICH. After assessing study heterogeneity and publication bias, a meta-analysis was performed using random-effects models to assess the strength of association between AC resumption and our outcomes.

ICH: intracerebral hemorrhage; OAC: oral anticoagulant; AF: atrial fibrillation; CI: confidence interval.

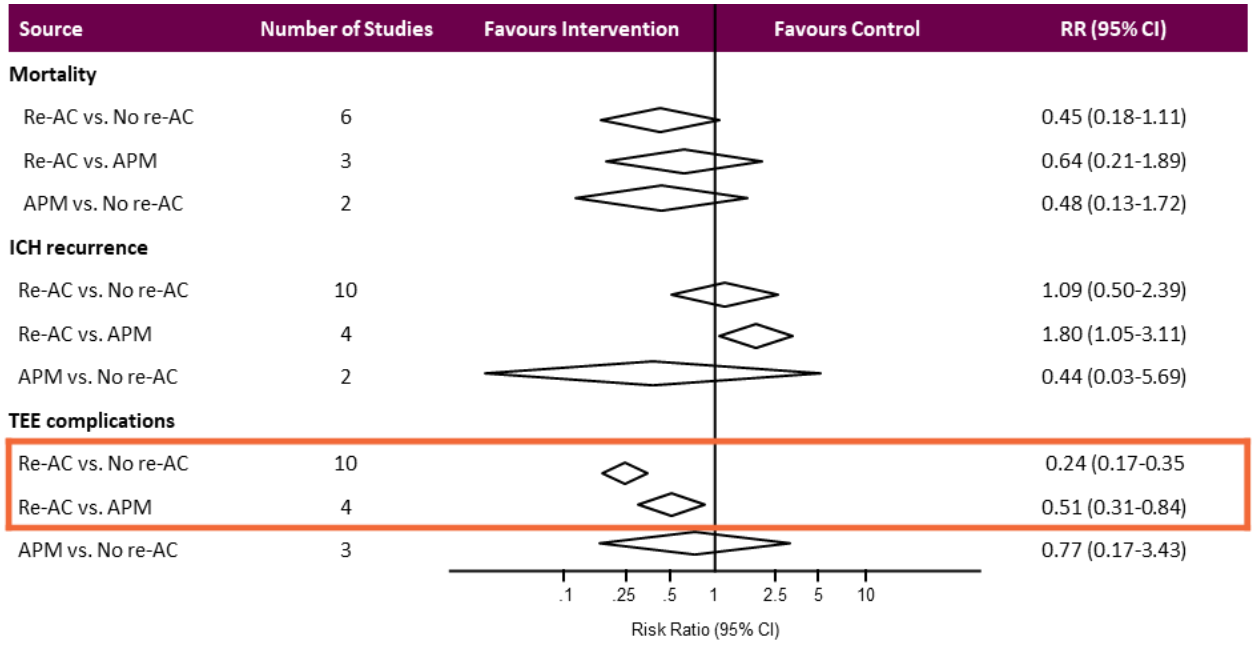
Adapted from: Murthy SB, et al. Stroke. 2017;48(6):1594-1600.

KOREA UNIVERSITY

KOREA UNIVERSITY GLOBAL PRIDE

# Resuming OAC after ICH

- Resuming anticoagulant therapy after anticoagulation-associated ICH has beneficial effects on long-term complications.




Study design: A systematic review and meta analysis in 3431 ICH participants to determine the adverse outcomes following resumption of anticoagulation in patients with anticoagulation-associated intracranial haemorrhage (ICH). The Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement was followed, and two authors independently assessed eligibility of all retrieved studies and extracted data. Primary outcomes, including long-term mortality, recurrent ICH and thromboembolic events. Secondary outcomes were the frequency of resuming anticoagulant therapy and related factors.

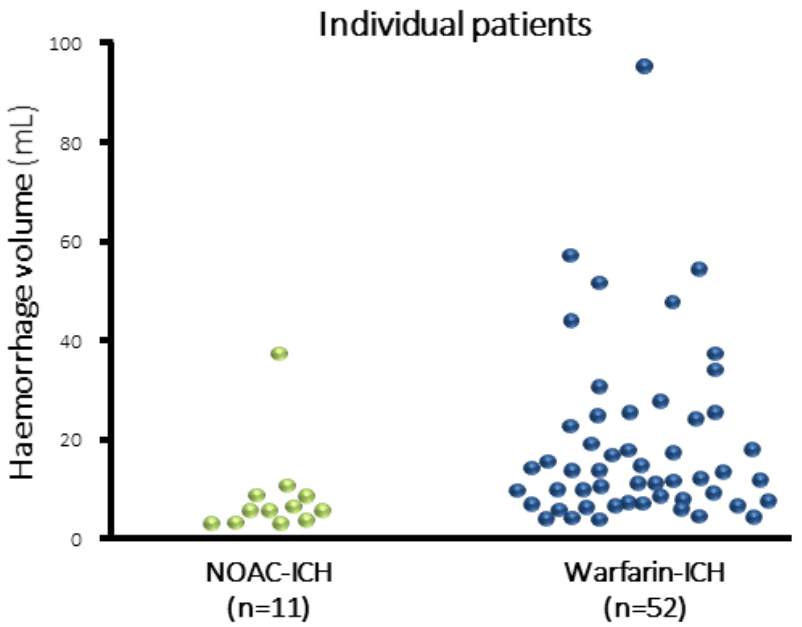
Adapted from: Zhou Z, et al. BMJ Open. 2018;8(5):e019672.

APM: antiplatelet medication; ICH: intracranial haemorrhage; Re-AC: resumption of anticoagulant therapy; TEE: thromboembolic events; CI: confidence interval.

# ICH Volume was Smaller on NOAC Treatment versus Warfarin

- ICH volumes and clinical outcomes may be better for patients receiving NOAC vs warfarin

**Volume of ICH according to oral anticoagulant type[1]**




Adapted from: Wilson D, et al. Neurology. 2016;86:1-7.

KOREA UNIVERSITY

KOREA UNIVERSITY GLOBAL PRIDE

# ESC 2020 Guidelines: (Re-)Initiation or Anticoagulation Post-intracranial Bleeding

**Risk factors for ICH**

**Modifiable**
- (uncontrolled) hypertension
- Low LDL/triglycerides
- Escessive alcohol consumption
- Current smoking
- Concomitant antiplatelet drugs
- Anticoagulant therapy
- Sympathomimetic drugs (cocaine, heroin, amphetamine, ephedrine, etc.)

**Non- modifiable**
- Older age
- Male sex
- Asian ethnicity
- Chronic kidney disease
- Cerebral disease
  -cerebral amyloid angiopathy
  -small vessel disease

**(Re)institution of OAC:**
**Decision-making post ICH in patients with AF**

**Consider risk factors for recurrent ICH**

**Address modifiable bleeding risk factors**

**Weight the risks and benefits of OAC (re)institution**
in consultation with neurologist/stroke specialist

**OAC use (with/without cerebral disease):**
(observational data, RCTs are ongoing)
- Significant decrease in stroke and mortality
- Comparable risk for recurrent ICH vs. OAC non-use

**OAC**
Class IIa, LoE C
2-4 weeks after ICH

Irreversible cause of ICH, non-modifiable risk factors, etc.

**LAA Occlusion**
Class IIb, LoE B

No stroke prevention therapy

**Additional considerations:**
- No reversible/ treatable cause of ICH
- ICH during OAC interruption
- ICH on adequate or underdosed OAC
- The need for concomitant antiplatelet therapy (e.g., ACS/PCI)

**CMB on cerebral imaging:**
- The risk of ICH increases with the presence and increasing CMB burden, but
- Regardless of CMB presence, burden and distribution, the obsolute risk of ischaemic stroke is consistently substantially higher than that of ICH in post-stroke/TIA patients

≥10 CMBs:
64 IS vs. 27 ICH events/1000 person-years
>20 CMBs:
73 IS vs. 39 ICH events/1000 person-years

Adapted from: Hindricks G, et al. Eur Heart J. 2021.

IS: ischaemic stroke; ACS: acute coronary syndrome; CMB: cerebral microbleeds; ICH: intracranial haemorrhage; LAA: left atrial appendage; LDL: low-density lipoprotein; LoE: level of evidence; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; TIA: transient ischaemic attack.

# How do we treat afib-related stroke patients with intracranial stenosis or cerebral small vessel diseases?

# With intracranial stenosis

**ORIGINAL ARTICLE**
J Clin Neurol 2012;8:251-258

Print ISSN 1738-6586 / On-line ISSN 2005-5013
http://dx.doi.org/10.3988/jcn.2012.8.4.251

**Open Access**

# Impact of $CHADS_2$ Score on Neurological Severity and Long-Term Outcome in Atrial Fibrillation-Related Ischemic Stroke

Dohoung Kim,[a] Jong-Won Chung,[a] Chi Kyung Kim,[a] Wi-Sun Ryu,[a]
Eun-Sun Park,[a] Seung-Hoon Lee,[a,b] Byung-Woo Yoon[a,b]

[a]Department of Neurology and [b]Clinical Research Center for Stroke, Clinical Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

**Received** January 22, 2012
**Revised** March 12, 2012
**Accepted** March 12, 2012

**Correspondence**
Seung-Hoon Lee, MD, PhD
Department of Neurology,
Seoul National University Hospital,
Seoul National University
College of Medicine,
101 Daehak-ro, Jongno-gu,
Seoul 110-744, Korea
**Tel** +82-2-2072-1014
**Fax** +82-2-3672-7553
**E-mail** sb0516@snu.ac.kr

**Correspondence**
Byung-Woo Yoon, MD, PhD
Department of Neurology,
Seoul National University Hospital,
Seoul National University
College of Medicine,
101 Daehak-ro, Jongno-gu,
Seoul 110-744, Korea
**Tel** +82-2-2072-2875
**Fax** +82-2-3673-1990
**E-mail** bwyoon@snu.ac.kr

**Background and Purpose** The $CHADS_2$ (an acronym for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism) score is a widely used system for estimating the risk of stroke in patients with atrial fibrillation. However, how the $CHADS_2$ score is related to stroke severity and outcome in patients with strokes due to atrial fibrillation has not yet been elucidated.

**Methods** We enrolled patients with atrial fibrillation who visited our stroke center within 7 days after the onset of acute ischemic stroke between October 2002 and September 2008. $CHADS_2$ scores were categorized into three groups: 0 points, low risk; 1 or 2 points, intermediate risk; and 3-6 points, high risk. Poor neurological state was defined as follows: a National Institutes of Health Stroke Scale (NIHSS) score of ≥2, and a modified Rankin Scale (mRS) score of ≥3 at discharge. Mortality information was ascertained as at December 2008.

**Results** A cohort of 298 patients with atrial-fibrillation-related stroke was included in this study. A high-risk $CHADS_2$ score at admission was a powerful predictor of poor neurological outcome [for NIHSS: odds ratio (OR), 4.17; 95% confidence interval (CI), 1.76-9.87; for mRS: OR, 2.97; 95% CI, 1.23-7.16] after controlling for all possible confounders. In addition, a high-risk $CHADS_2$ score was an independent predictor of all causes of death during the follow-up [hazard ratio (HR), 3.01; 95% CI, 1.18-7.65] and vascular death (HR, 12.25; 95% CI, 1.50-99.90).

**Conclusions** Although the $CHADS_2$ score was originally designed to distinguish patients with a future risk of stroke, our study shows that it may also be used to predict poor neurological outcome after atrial-fibrillation-related stroke. **J Clin Neurol 2012;8:251-258**

**Key Words** atrial fibrillation, ischemic stroke, $CHADS_2$ score, neurological severity, outcome.

**Table 3.** Adjusted odd ratios of NIHSS and mRS

| | NIHSS | | mRS | |
|---|---|---|---|---|
| | Adjusted OR (95% CI) | *p* value | Adjusted OR (95% CI) | *p* value |
| Model 1* | | | | |
| Low risk | Reference | | Reference | |
| Intermediate risk | 1.76 (0.91-3.39) | 0.09 | 1.31 (0.66-2.60) | 0.44 |
| High risk | 3.61 (1.73-7.56) | 0.001 | 2.64 (1.27-5.49) | 0.01 |
| Model 2† | | | | |
| Low risk | Reference | | Reference | |
| Intermediate risk | 2.19 (1.01-4.73) | 0.05 | 1.59 (0.70-3.63) | 0.27 |
| High risk | 4.17 (1.76-9.87) | 0.001 | 2.97 (1.23-7.16) | 0.02 |

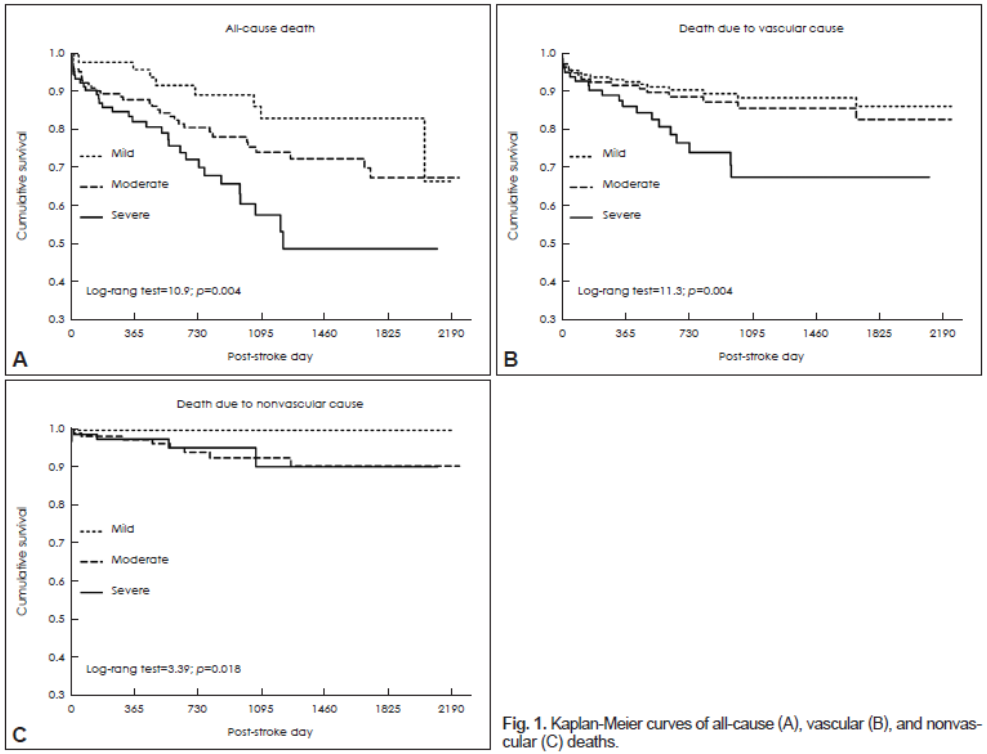



**Fig. 1.** Kaplan-Meier curves of all-cause (A), vascular (B), and nonvascular (C) deaths.

Cerebrovascular Diseases

Clinical Research in Stroke

Cerebrovasc Dis
DOI: 10.1159/000513396

Received: August 28, 2020
Accepted: November 19, 20
Published online: February

# Pre-Admission $CHADS_2$ and $CHA_2DS_2$-VASc Scores on Early Neurological Worsening

Ki-Woong Nam[a] Chi Kyung Kim[b] Sungwook Yu[c] Jong-Won Chung[d] Oh Young Bang[d] Gyeong-Moon Kim[d] Jin-Man Jung[e] Tae-Jin Song[f] Yong-Jae Kim[g] Bum Joon Kim[h] Sung Hyuk Heo[h] Kwang-Yeol Park[i] Jeong-Min Kim[i] Jong-Ho Park[j] Jay Chol Choi[k] Man-Seok Park[l] Joon-Tae Kim[l] Kang-Ho Choi[m] Yang Ha Hwang[n] Kyungmi Oh[c] Woo-Keun Seo[d, o]

[a]Department of Neurology, Seoul National University College of Medicine, Seoul, South Korea; [b]Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea; [c]Department of Neurology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea; [d]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [e]Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, South Korea; [f]Department of Neurology, Ewha Womans University, School of Medicine, Seoul, South Korea; [g]Department of Neurology, The Catholic University of Korea, Seoul, South Korea; [h]Department of Neurology, Kyung Hee University College of Medicine, Seoul, South Korea; [i]Department of Neurology, Chung-Ang University College of Medicine, Chung-Ang University Hospital, Seoul, South Korea; [j]Department of Neurology, Myongji Hospital, Hanyang University College of Medicine, Seoul, South Korea; [k]Department of Neurology, Jeju National University, Jeju, South Korea; [l]Department of Neurology, Chonnam National University Hospital, Chonnam, Chonnam, South Korea; [m]Department of Neurology, Chonnam National University Hwasun Hospital, Hwasun, South Korea; [n]Department of Neurology, Kyungpook National University Hospital, Dae-gu, Dae-gu, South Korea; [o]Department of Digital Health, SHAIST, Sungkyunkwan University, Seoul, South Korea

**Keywords**
Ischemic stroke · Atrial fibrillation · Risk scores · Prognosis · Cerebral atherosclerosis

**Abstract**

***Background:*** Stroke risk scores ($CHADS_2$ and $CHA_2DS_2$-VASc) not only predict the risk of stroke in atrial fibrillation (AF) patients, but have also been associated with prognosis after stroke. ***Objective:*** The aim of this study was to evaluate the relationship between stroke risk scores and early neurological deterioration (END) in ischemic stroke patients with AF. ***Methods:*** We included consecutive ischemic stroke patients with AF admitted between January 2013 and December 2015. $CHADS_2$ and $CHA_2DS_2$-VASc scores were calculated using the established scoring system. END was defined as an increase ≥2 on the total National Institutes of Health Stroke

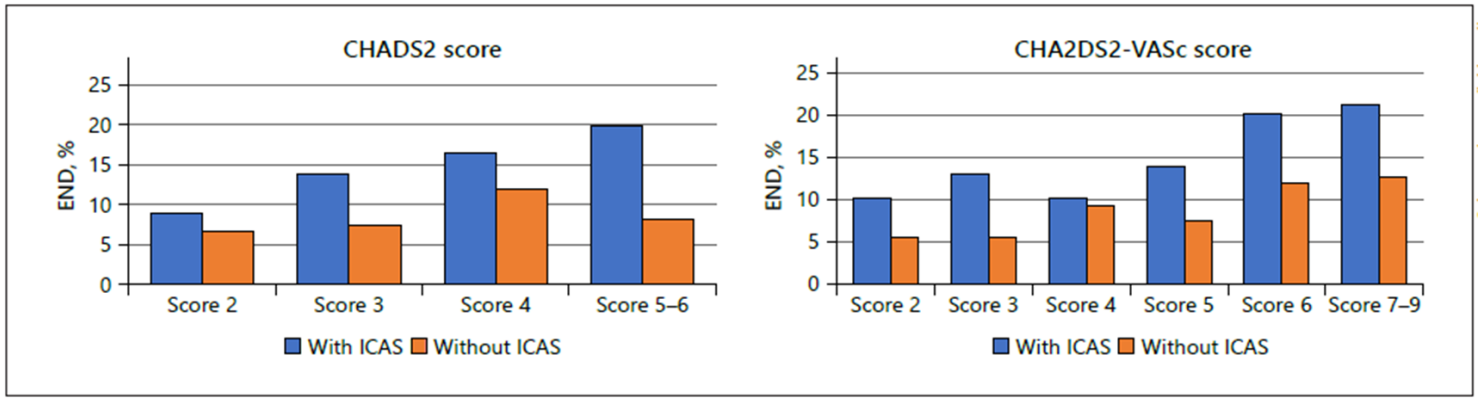


Woo-KeunSeo
Department of Neurology and Stroke Center
Samsung Medical Center, 81, Irwon-Ro, Gang-nam Gu
Seoul 06351 (South Korea)
mcastenosis@gmail.com

Chi Kyung Kim
Department of Neurology, Korea University Guro Hospital and
Korea University College of Medicine
148 Gurodong-ro, Guro-gu, Seoul 08308 (Republic of Korea)
ckkim7@korea.ac.kr

**Table 3.** Multivariable logistic regression analysis of the possible predictors for END in patients with and without ICAS

| | $CHADS_2$ score | | $CHA_2DS_2$-VASc score | |
|---|---|---|---|---|
| | adjusted OR (95% CI) | *p* value | adjusted OR (95% CI) | *p* value |
| *With ICAS* | | | | |
| Risk score | 1.24 [1.01 to 1.52] | 0.042 | 1.20 [1.04 to 1.38] | 0.011 |
| Female sex | 1.28 [0.88 to 1.87] | 0.195 | – | – |
| Initial NIHSS score | 1.02 [1.00 to 1.05] | 0.094 | 1.02 [1.00 to 1.05] | 0.093 |
| Anti-coagulant | 0.28 [0.19 to 0.42] | <0.001 | 0.28 [0.19 to 0.41] | <0.001 |
| Multiple territory multiple DWI lesions | 0.98 [0.63 to 1.53] | 0.935 | 0.98 [0.63 to 1.53] | 0.935 |
| Hemorrhagic transformation | 1.09 [0.71 to 1.66] | 0.705 | 1.09 [0.71 to 1.66] | 0.699 |
| *Without ICAS* | | | | |
| Risk score | 1.03 [0.77 to 1.38] | 0.855 | 1.11 [0.91 to 1.35] | 0.324 |
| Female sex | 1.30 [0.77 to 2.18] | 0.330 | – | – |
| Initial NIHSS score | 1.07 [1.03 to 1.10] | <0.001 | 1.07 [1.03 to 1.11] | <0.001 |
| Anti-coagulant | 0.39 [0.23 to 0.66] | <0.001 | 0.40 [0.24 to 0.67] | 0.001 |
| Multiple territory multiple DWI lesions | 2.07 [1.19 to 3.63] | 0.011 | 2.05 [1.17 to 3.59] | 0.012 |
| Hemorrhagic transformation | 1.20 [0.66 to 2.16] | 0.554 | 1.19 [0.66 to 2.15] | 0.562 |



# Anticoagulant therapy and antiplatelet

- Oral anticoagulants are more effective than antiplatelet agents in preventing stroke / SEE in patients with AF.

- But antiplatelet may be more protective in reducing vascular events in patients with CAD or at high risk of acute coronary events.

- Combination therapy of anticoagulant and antiplatelet agents is associated with increased risk of bleeding and its efficacy is not clear.

Ref) Ruff CT et al. J Am Heart Assoc. 2016;5:e002587

# Efficacy and safety of concomitant use of SAPT with Edoxaban

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

## Concomitant Use of Single Antiplatelet Therapy With Edoxaban or Warfarin in Patients With Atrial Fibrillation: Analysis From the ENGAGE AF-TIMI48 Trial

Haiyan Xu, MD; Christian T. Ruff, MD, MPH; Robert P. Giugliano, MD, SM; Sabina A. Murphy, MPH; Francesco Nordio, PhD; Indravadan Patel, MD; Minggao Shi, PhD; Michele Mercuri, MD, PhD; Elliott M. Antman, MD; Eugene Braunwald, MD

*Conclusions*—Patients with AF who were selected by their physicians to receive SAPT in addition to an anticoagulant had a similar risk of stroke/SEE and higher rates of bleeding than those not receiving SAPT. Edoxaban exhibited similar relative efficacy and reduced bleeding compared to warfarin, with or without concomitant SAPT.

Ref) Ruff CT et al. J Am Heart Assoc. 2016;5:e002587

# Study methods with and without SAPT

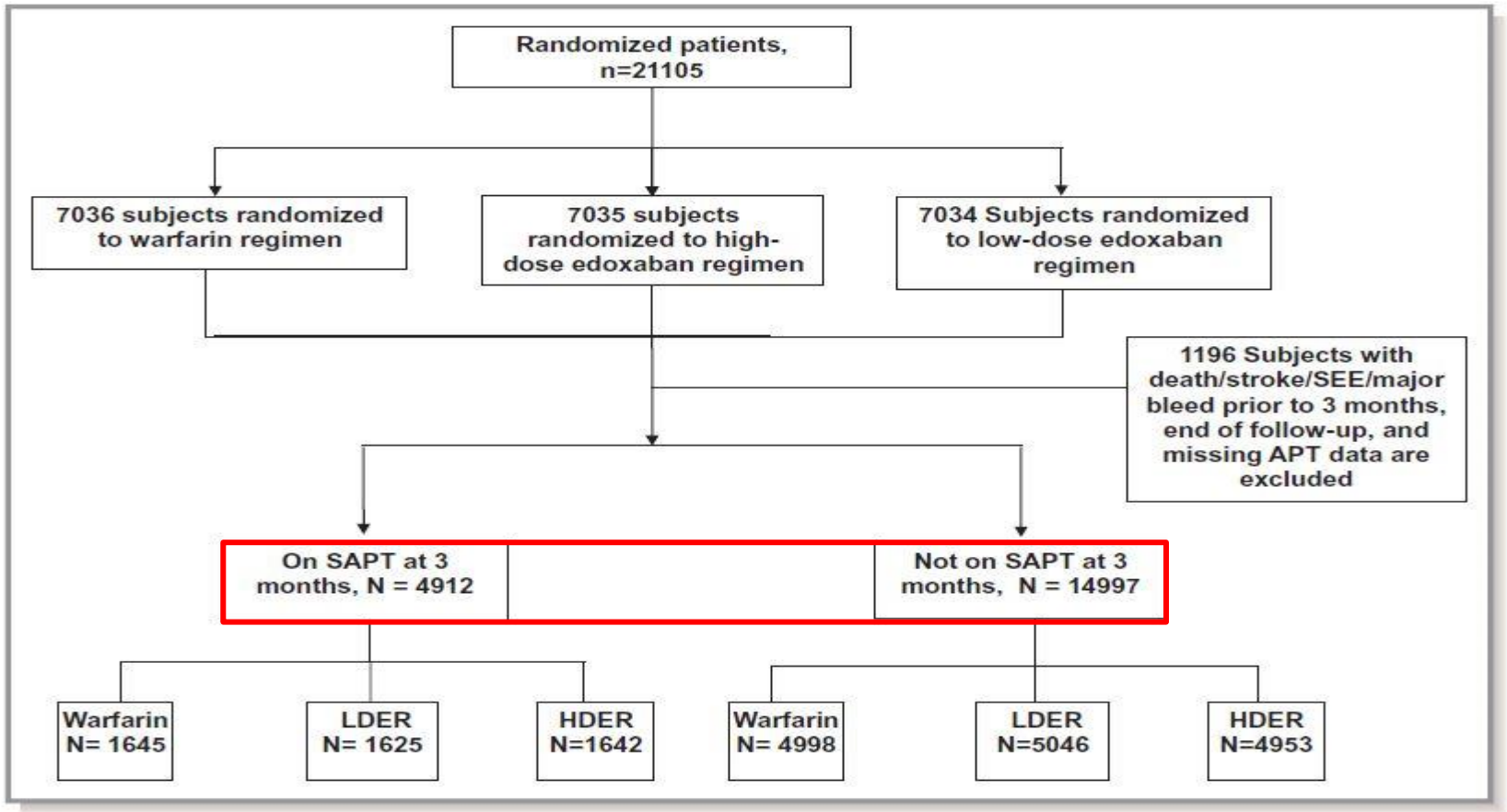



**Figure 1.** Study consort diagram. APT indicates antiplatelet therapy; HDER, high-dose edoxaban registry; LDER, low dose edoxaban regimen; SEE, systemic embolic event.

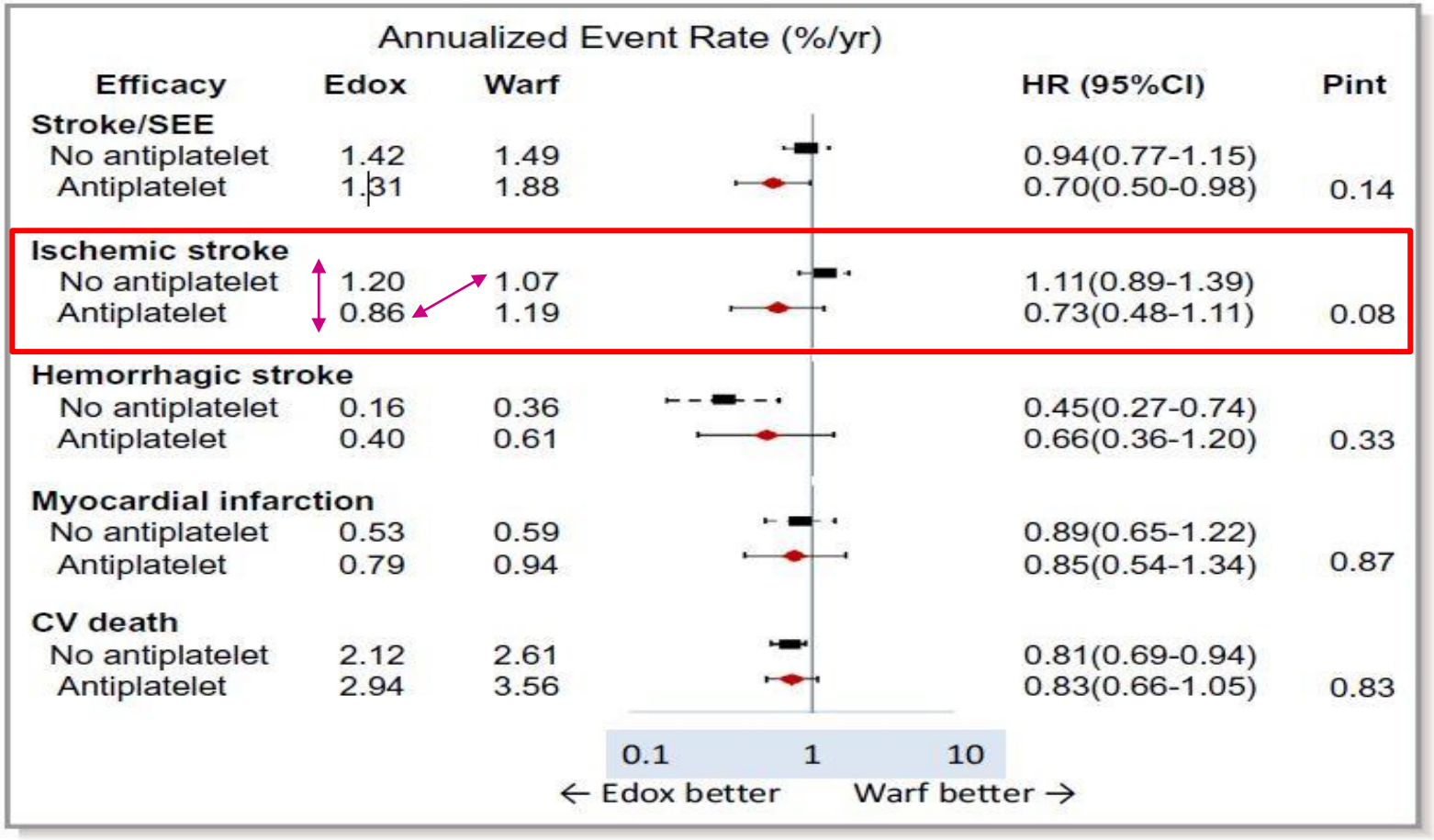
Ref) Ruff CT et al. J Am Heart Assoc. 2016;5:e002587

# Study methods with and without SAPT

| Variables | Not on SAPT (N=14 997) | On SAPT (N=4912) | *P* Value |
|---|---|---|---|
| Demographic | | | |
| Age, y, median (IQR) | 72.0 (64.0–77.0) | 72.0 (64.0–78.0) | 0.515 |
| Age ≥75 y, n (%) | 5907 (39.4) | 1973 (40.2) | 0.333 |
| Male, n (%) | 9039 (60.3) | 3346 (68.1) | 0.000 |
| Previous CAD, n (%) | 4172 (27.8) | 2403 (48.9) | 0.000 |
| Previous MI, n (%) | 1395 (9.3) | 869 (17.7) | 0.000 |
| Previous coronary revascularization, n (%) | 1177 (7.8) | 1274 (25.9) | 0.000 |
| Hypertension, n (%) | 14 040 (93.6) | 4606 (93.8) | 0.705 |
| Dyslipidemia, n (%) | 7520 (50.1) | 2979 (60.6) | 0.000 |
| Diabetes, n (%) | 5190 (34.6) | 1993 (40.6) | 0.000 |
| History of congestive heart failure, n (%) | 8669 (57.8) | 2762 (56.2) | 0.053 |
| Peripheral arterial disease, n (%) | 511 (3.4) | 278 (5.7) | 0.000 |
| Carotid arterial disease, n (%) | 744 (5.0) | 454 (9.2) | 0.000 |
| Previous stroke or TIA, n (%) | 4216 (28.1) | 1387 (28.2) | 0.866 |
| $CHADS_2$ score ≥4, n (%) | 3243 (21.6) | 1190 (24.2) | 0.000 |
| $CHA_2DS_2$-Vasc score ≥4, n (%) | 10 301 (68.7) | 3694 (75.2) | 0.000 |
| HAS-BLED score ≥3, n (%) | 5253 (35.0) | 3895 (79.3) | 0.000 |

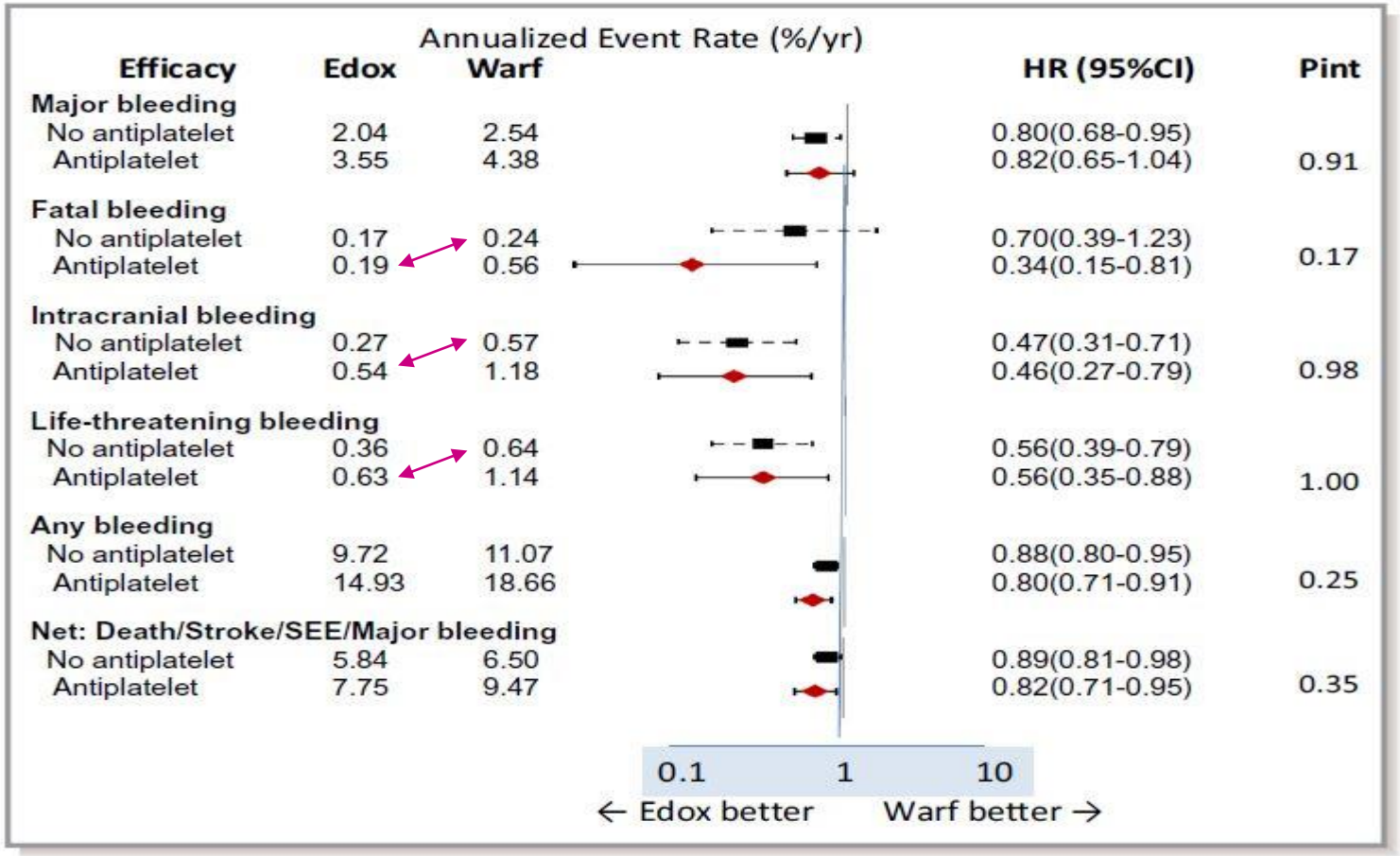
Ref) Ruff CT et al. J Am Heart Assoc. 2016;5:e002587

# Efficacy of Edoxaban vs warfarin with and without antiplatelet therapy



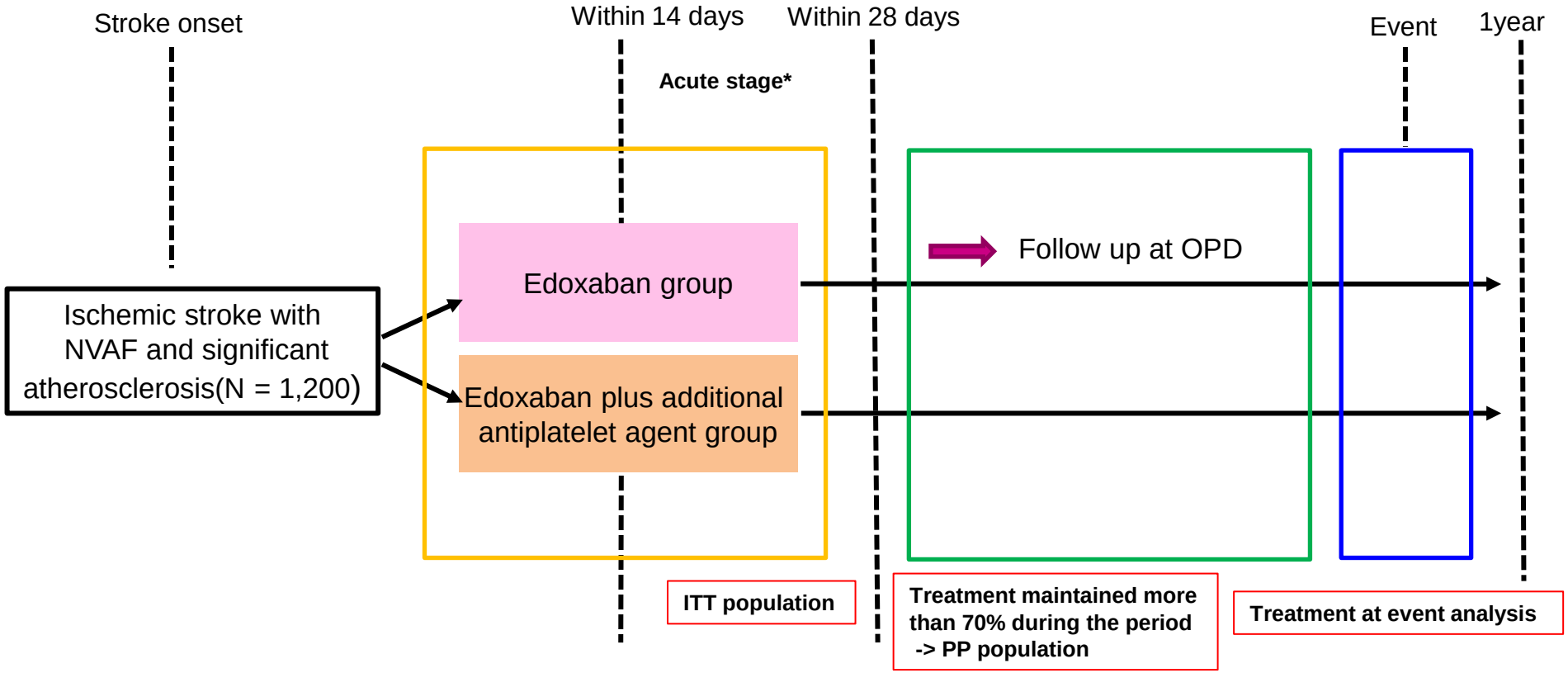

Ref) Ruff CT et al. J Am Heart Assoc. 2016;5:e002587

# Bleeding and net clinical outcome of Edoxaban vs warfarin with and without antiplatelet therapy




Ref) Ruff CT et al. J Am Heart Assoc. 2016;5:e002587

# ADDON – Ongoing study in Korea




- Primary endpoint : Time to event of major adverse cardiovascular events

  (Ischemic stroke, hemorrhagic stroke, myocardial infarction, vascular death)

Ref) https://clinicaltrials.gov/ct2/show/NCT04010955

# With cerebral small vessel disease

ARTICLE

# Serum homocysteine level is related to cerebral small vessel disease in a healthy population

Ki-Woong Nam, MD, MSc, Hyung-Min Kwon, MD, PhD, Han-Yeong Jeong, MD, Jin-Ho Park, MD, MPH, PhD, Hyuktae Kwon, MD, PhD, and Su-Min Jeong, MD

*Neurology*® 2019;92:e317-e325. doi:10.1212/WNL.0000000000006816

**Correspondence**
Dr. H.-M. Kwon
hmkwon@snu.ac.kr
or Dr. Park
kkolzzi0@gmail.com

## Abstract

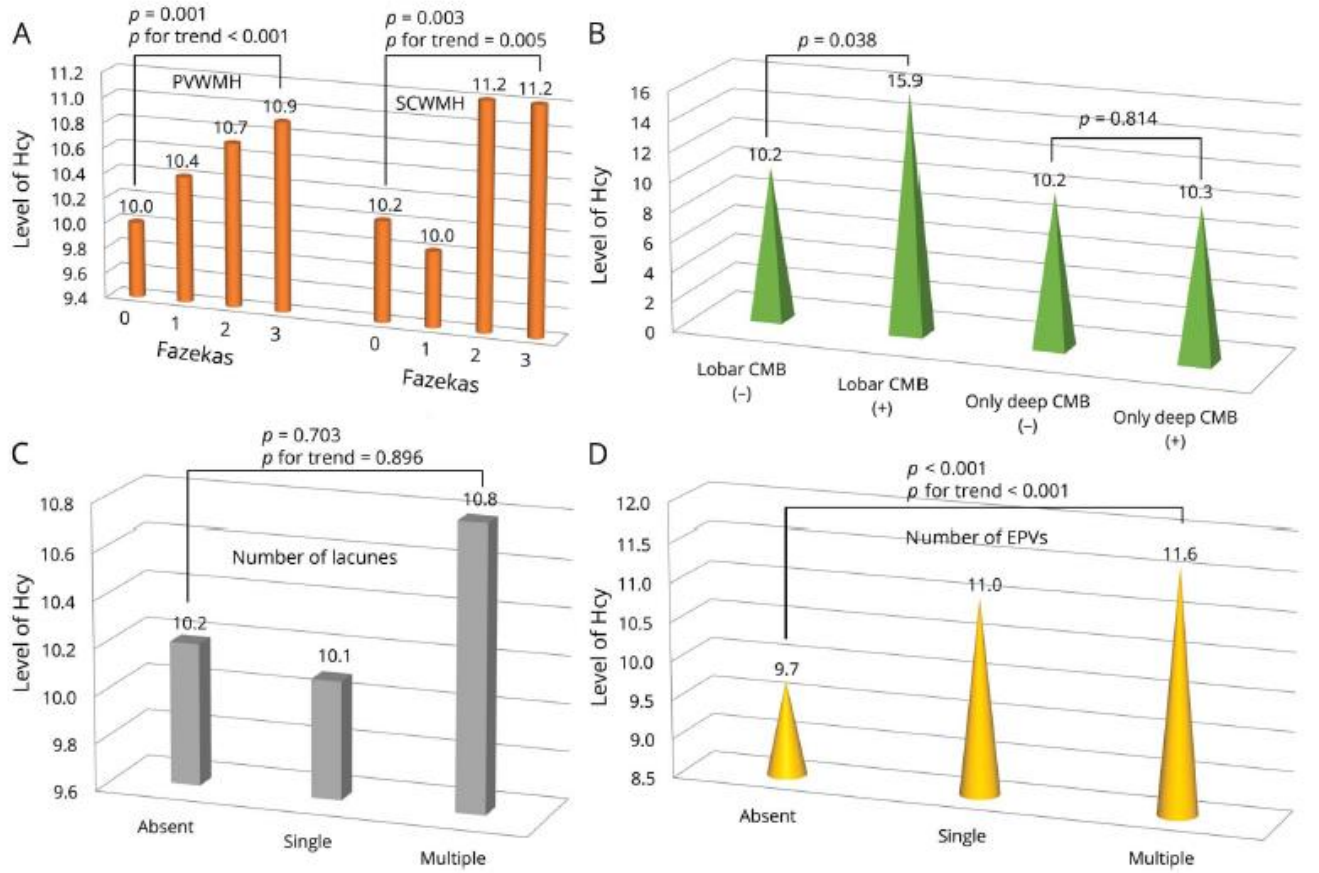
### Objective

To evaluate the relationship between serum total homocysteine (tHcy) levels and cerebral small vessel disease (cSVD) in a healthy population.

### Methods

We included consecutive participants who visited our department for health checkups between 2006 and 2013. We rated white matter hyperintensity volumes using both the Fazekas score and semiautomated quantitative methods. We also evaluated lacunes, cerebral microbleeds, and enlarged perivascular spaces (EPVS), which are involved in cSVD. To assess the dose-dependent relationship between tHcy and cSVD parameters, we scored the burdens of each radiologic marker of cSVD.

**Figure** Distribution of mean values according to the burdens of white matter hyperintensity volume, CMBs, lacunes, and EPVS



Journal of the American Heart Association

ORIGINAL RESEARCH

# Plasma Total Homocysteine Level Is Related to Unfavorable Outcomes in Ischemic Stroke With Atrial Fibrillation

Ki-Woong Nam, MSc; Chi Kyung Kim, PhD*; Sungwook Yu, PhD*; Kyungmi Oh, PhD; Jong-Won Chung, PhD; Oh Young Bang, PhD; Gyeong-Moon Kim, PhD; Jin-Man Jung, PhD; Tae-Jin Song, PhD; Yong-Jae Kim, PhD; Bum Joon Kim, PhD; Sung Hyuk Heo, PhD; Kwang-Yeol Park, PhD; Jeong-Min Kim, PhD; Jong-Ho Park, PhD; Jay Chol Choi, PhD; Man-Seok Park, PhD; Joon-Tae Kim, PhD; Kang-Ho Choi, PhD; Yang Ha Hwang, PhD; Woo-Keun Seo, PhD

**BACKGROUND:** Unlike patients with stroke caused by other mechanisms, the effect of elevated plasma total h on the prognosis of patients with both ischemic stroke and atrial fibrillation (AF) is unknown. This study ai association between tHcy level and the functional outcome of patients with AF-related stroke.

**METHODS AND RESULTS:** We included consecutive patients with AF-related stroke between 2013 and 2015 a real-world prospective cohort from 11 large centers in South Korea. A 3-month modified Rankin Scale sidered an unfavorable outcome. Since tHcy is strongly affected by renal function, we performed a subgro ing to the presence of renal dysfunction. A total of 910 patients with AF-related stroke were evaluated (m male sex, 56.0%). The mean tHcy level was 11.98±8.81 μmol/L. In multivariable analysis, the tHcy level (e 1.04; 95% CI, 1.01–1.07, per 1 μmol/L) remained significantly associated with unfavorable outcomes. In the based on renal function, tHcy values above the cutoff point (≥14.60 μmol/L) showed a close association w outcome only in the normal renal function group (adjusted odds ratio, 3.10; 95% CI, 1.60–6.01). In patients tion, tHcy was not significantly associated with the prognosis of AF-related stroke.

**CONCLUSIONS:** A higher plasma tHcy level was associated with unfavorable outcomes in patients with AF- positive association may vary according to renal function but needs to be verified in further studies.

**Key Words:** atrial fibrillation ■ homocysteine ■ ischemic stroke ■ prognosis ■ vitamin

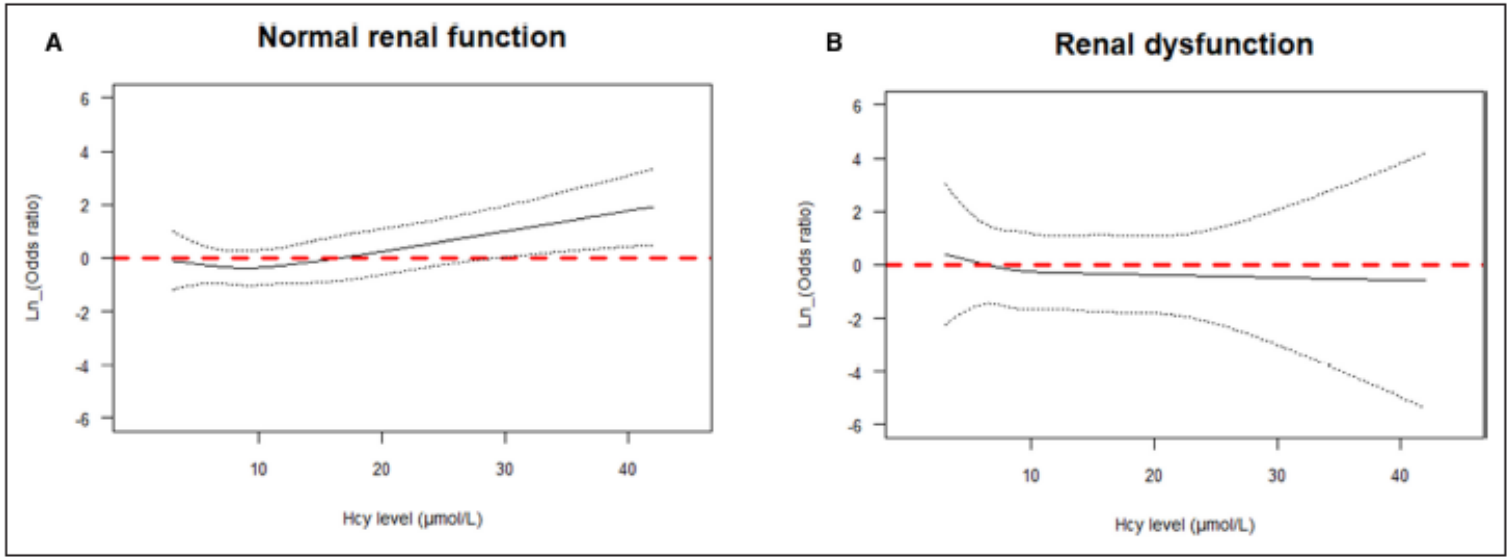



**Figure. Association between plasma total homocysteine levels and unfavorable outcomes in patients with AF-related stroke.**
In patients with normal renal function, plasma total homocysteine levels showed a clear positive correlation with unfavorable outcomes (**A**). However, this positive correlation between these two was not evident in patients with renal dysfunction (**B**). Hcy indicates homocysteine.

# Precision medicine for predicting future thromboembolism and bleeding after stroke with a-fib

KOREA UNIVERSITY

KOREA UNIVERSITY GLOBAL PRIDE

# 2020 ESC guideline: Stroke and bleeding risk assessment in patients with AF

| $CHA_2DS_2$-VASc score | Points awarded |
|---|---|
| Congestive heart failure/LV dysfunction | 1 |
| Hypertension | 1 |
| Age ≥75 years | 2 |
| Diabetes mellitus | 1 |
| Stroke (previous stroke, TIA, TE) | 2 |
| VD (CAD, previous MI, PAD or aortic plaque) | 1 |
| Age 65–74 years | 1 |
| Sex category (female) | 1 |
| **Maximum** | **9** |

**Low stroke risk**
$CHA_2DS_2$-VASc = 0 (males) or 1 (females)

| HAS-BLED score | Points awarded |
|---|---|
| Uncontrolled hypertension i.e. uncontrolled SBP | 1 |
| Abnormal renal and/or hepatic function | 1 point each |
| Stroke | 1 |
| Bleeding history or predisposition | 1 |
| Labile INR | 1 |
| Elderly | 1 |
| Drugs or excessive alcohol drinking | 1 point each |
| **Maximum** | **9** |

**High bleeding risk**
HAS-BLED ≥3

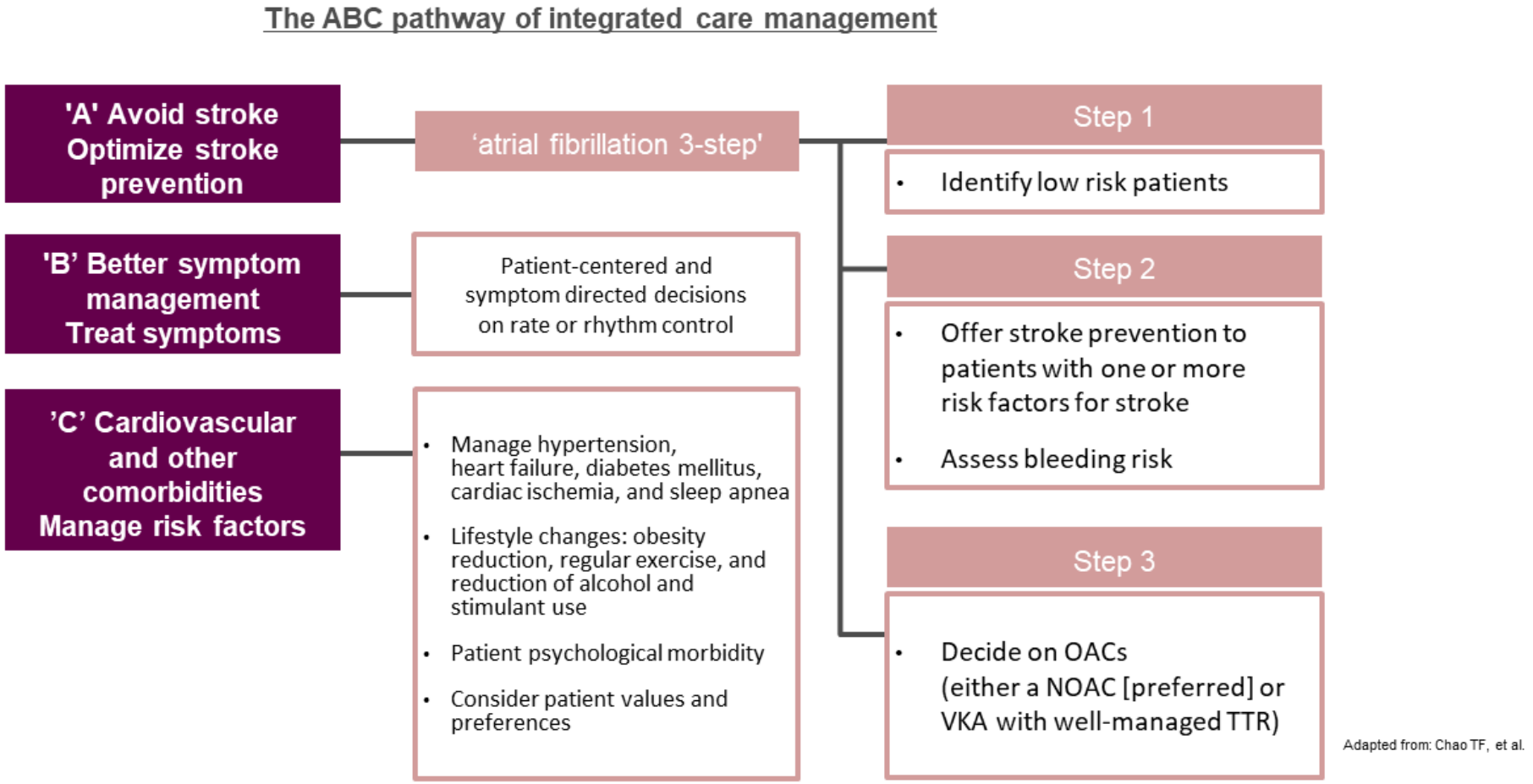
## A formal structured clinical risk factor-based assessment of stroke and bleeding risk

| Recommendations | Class | Level |
|---|---|---|
| For stroke risk assessment, a risk-factor-based approach is recommended, using the $CHA_2DS_2$-VASc clinical stroke risk score to initially identify patients at 'low stroke risk' ($CHA_2DS_2$-VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy. | I | A |
| For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify nonmodifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up. | I | B |
| For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥3) for early and more frequent clinical review and follow-up. | IIa | B |

Adapted from Hindricks G & Potpara T, et al. 2021.

AF, atrial fibrillation; CAD, coronary artery disease; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65–74, and sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; INR, international normalised ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs: non-steroidal anti-inflammatory drugs; PAD: peripheral artery disease; SBP, systolic BP; TIA/TE: transient ischaemic attack/thromboembolic event; VD, vascular disease.

# The ABC Pathway of Integrated Care Management




Adapted from: Chao TF, et al.

| HAS-BLED[33] | | ATRIA[34] | | ORBIT[35] | |
|---|---|---|---|---|---|
| Hypertension – uncontrolled (>160 mmHg systolic) | 1 | Anemia[a] | 3 | Older age (≥75 years old) | 1 |
| Abnormal renal function (SCr ≥200 µmol/L or dialysis or transplantation) or abnormal hepatic function[b] | 1 or 2 | Severe renal disease (eGFR <30 mL/min or dialysis) | 3 | Reduced hemoglobin[a], reduced hematocrit[c], or anemia | 2 |
| Stroke history | 1 | ≥75 years old | 2 | Bleeding history | 2 |
| Bleeding history or predisposition to bleeding (eg, anemia and bleeding diathesis) | 1 | Any prior hemorrhage | 1 | Insufficient kidney function (eGFR <60 mg/dL/1.73 $m^2$) | 1 |
| Labile INRs | 1 | Diagnosed hypertension | 1 | Treatment with antiplatelets | 1 |
| Elderly (>65 years old) | 1 | – | – | – | – |
| Drugs or alcohol (antiplatelet agents or NSAIDs; alcohol ≥8 units per week) | 1 or 2 | – | – | – | – |
| Maximum score | 9 | Maximum score | 10 | Maximum score | 7 |

ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2022) **8**, 778–786 **ORIGINAL ARTICLE**
https://doi.org/10.1093/ehjqcco/qcab069

# Comparison of HAS-BLED and ORBIT bleeding risk scores in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulants: a report from the ESC-EHRA EORP-AF General Long-Term Registry

**Marco Proietti[1,2,3,*,†], Giulio Francesco Romiti[4,†], Marco Vitolo[1,5,6], Tatjana S. Potpara[7,8], Giuseppe Boriani[5,‡], Gregory Y.H. Lip[1,9,‡] and on behalf of ESC-EHRA EORP-AF Long-Term General Registry Investigators[§]**

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [2]IRCCS Istituti Clinici Scientifici Maugeri, Via della Commenda 19 - 20122 Milan, Italy; [3]Department of Clinical Sciences and Community Health, University of Milan, Via della Commenda 19 - 20122 Milan, Italy; [4]Department of Translational and Precision Medicine, Sapienza—University of Rome, Rome, Italy; [5]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy; [6]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy; [7]School of Medicine, University of Belgrade, Belgrade, Serbia; [8]Intensive Arrhythmia Care, Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia; and [9]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

*Received 15 September 2021; revised 16 September 2021; accepted 20 September 2021; online publish-ahead-of-print 23 September 2021*

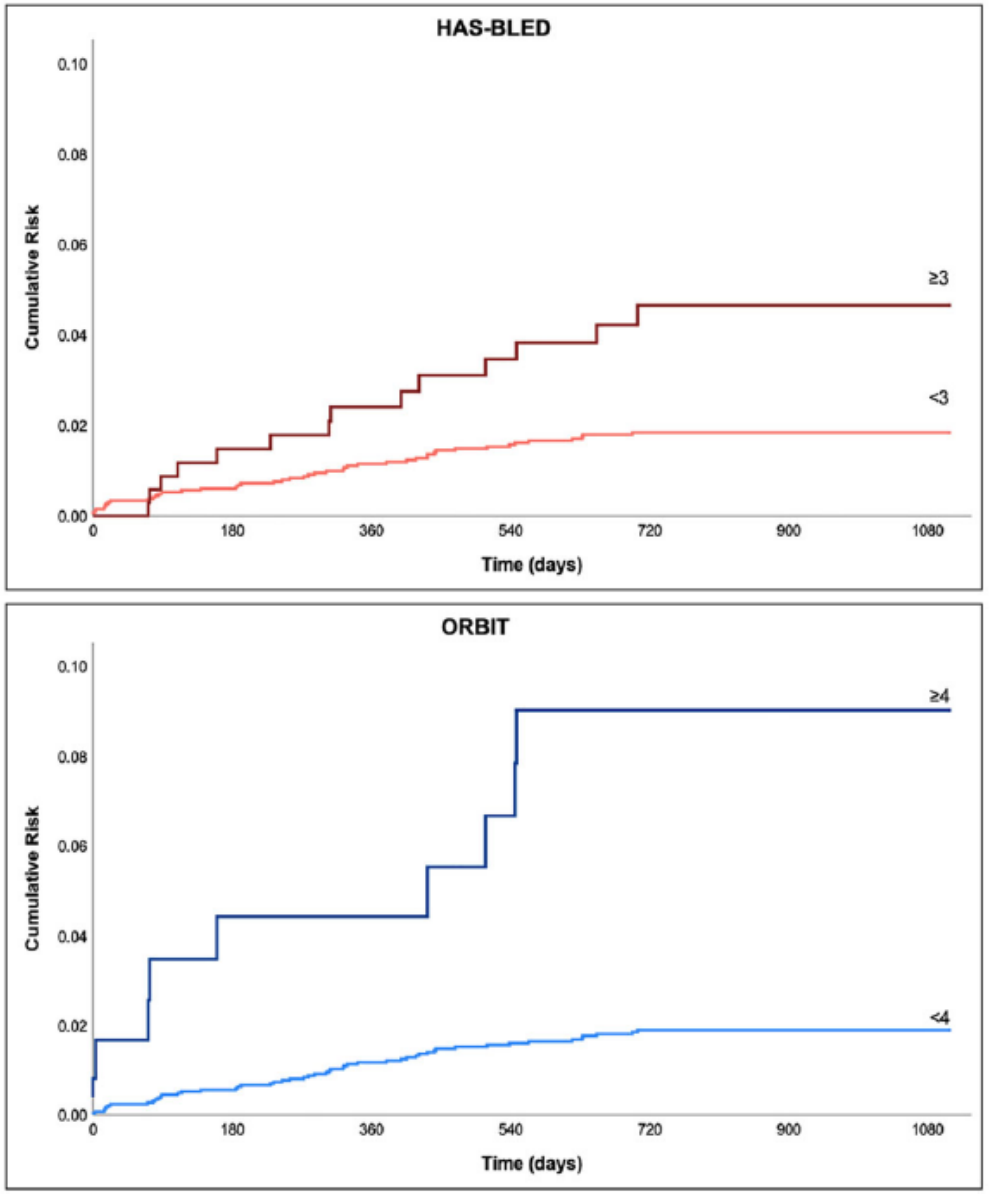



**Figure 1.** Kaplan–Meier curves for bleeding risk scores. HAS-BLED: log-rank = 9.044, $P = 0.003$; ORBIT: log-rank = 22.932, $P < 0.001$.

**Table 4** Reclassification analysis for bleeding risk scores about major bleeding occurrence

| ORBIT vs. HAS-BLED | IDI (95% CI) | *P* | NRI (95% CI) | *P* | MI (95% CI) | *P* |
|---|---|---|---|---|---|---|
| 1-year FU | −0.001 (−0.009/0.009) | 0.757 | −0.069 (−0.193/0.138) | 0.465 | −0.002 (−0.004/0.002) | 0.120 |
| 2-year FU | −0.002 (−0.018/0.015) | 0.691 | −0.117 (−0.301/0.018) | 0.093 | −0.002 (−0.013/0.001) | 0.093 |

CI, confidence interval; FU, follow-up; IDI, integrated discrimination improvement; MI, median improvement; NRI, net reclassification index.

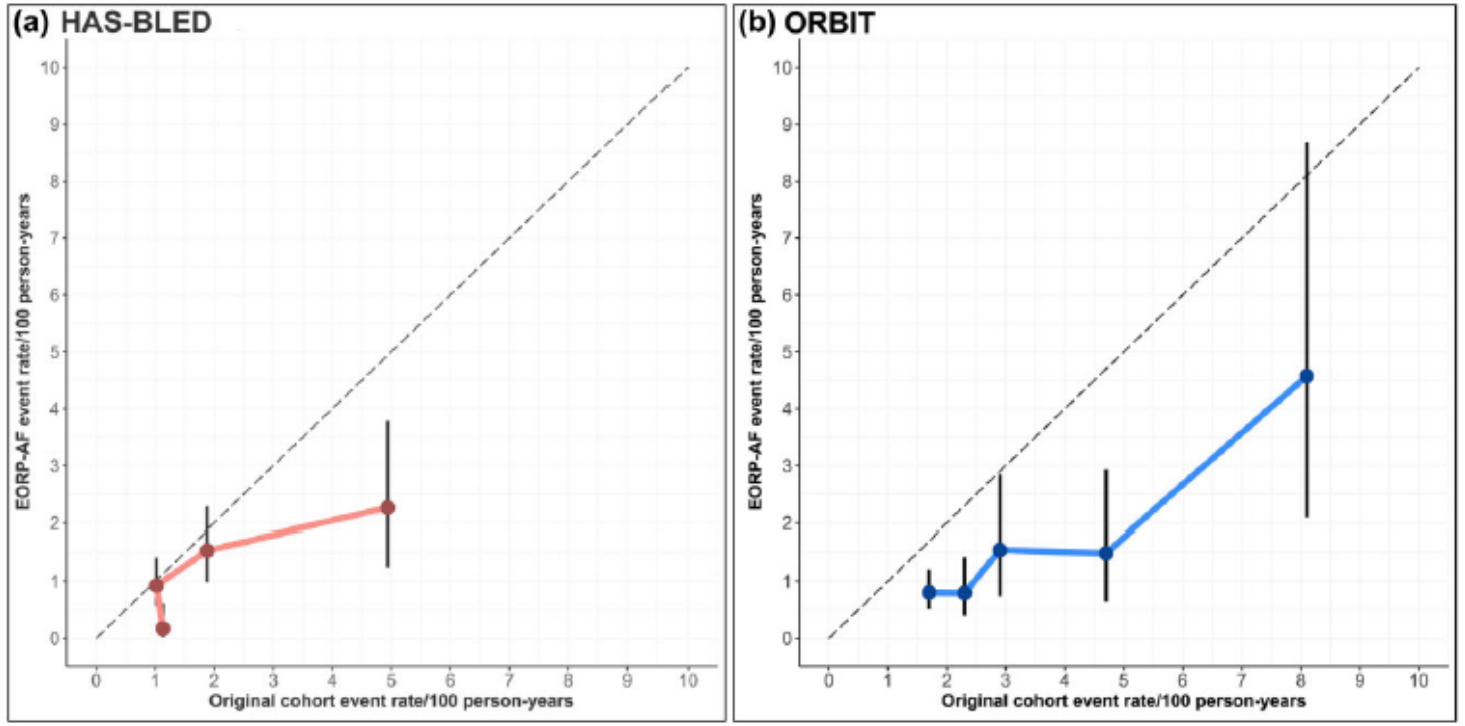



**Figure 2.** Calibration curves for bleeding risk scores in EORP-AF cohort. EORP-AF, EURObservational Research Programme in Atrial Fibrillation.

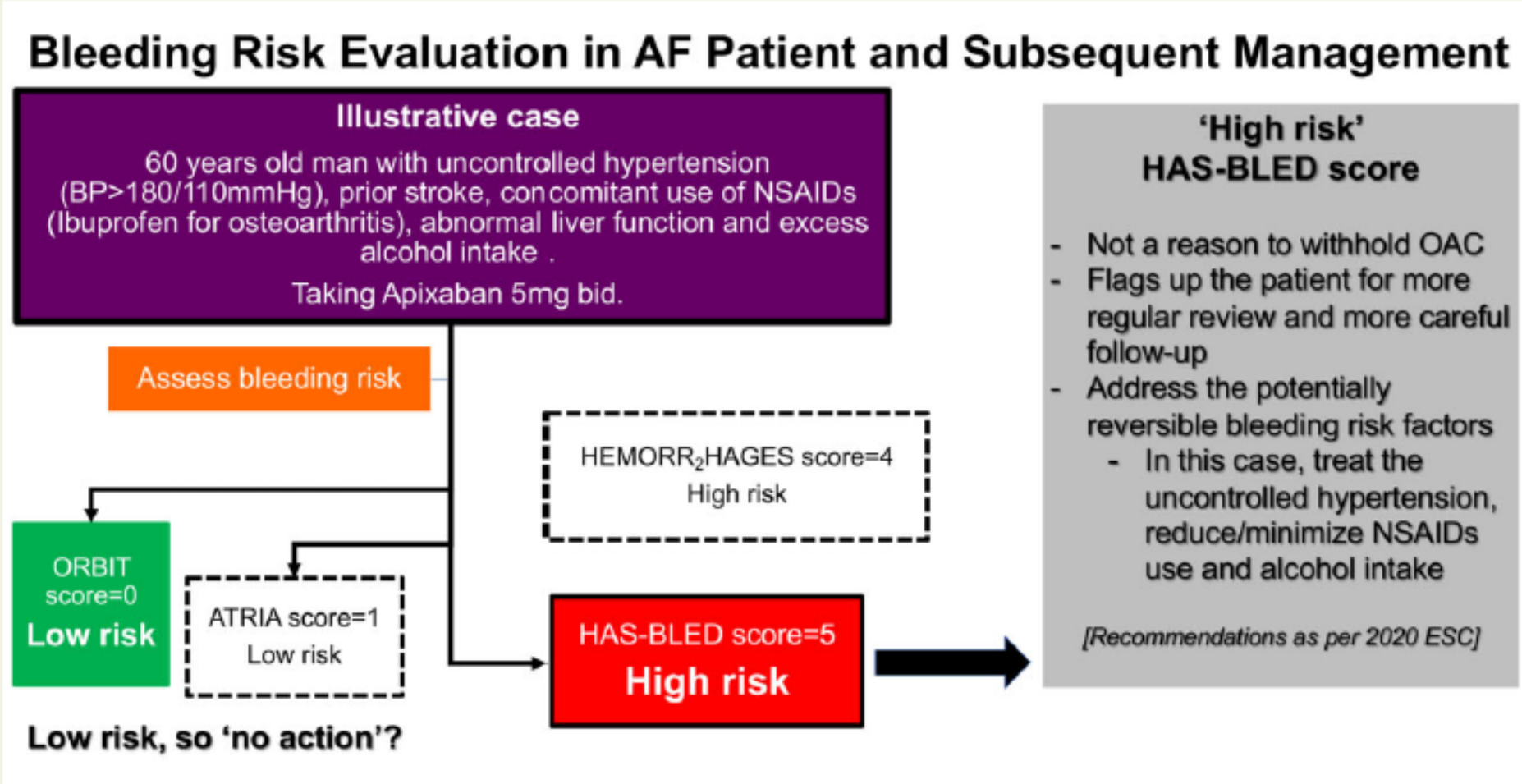


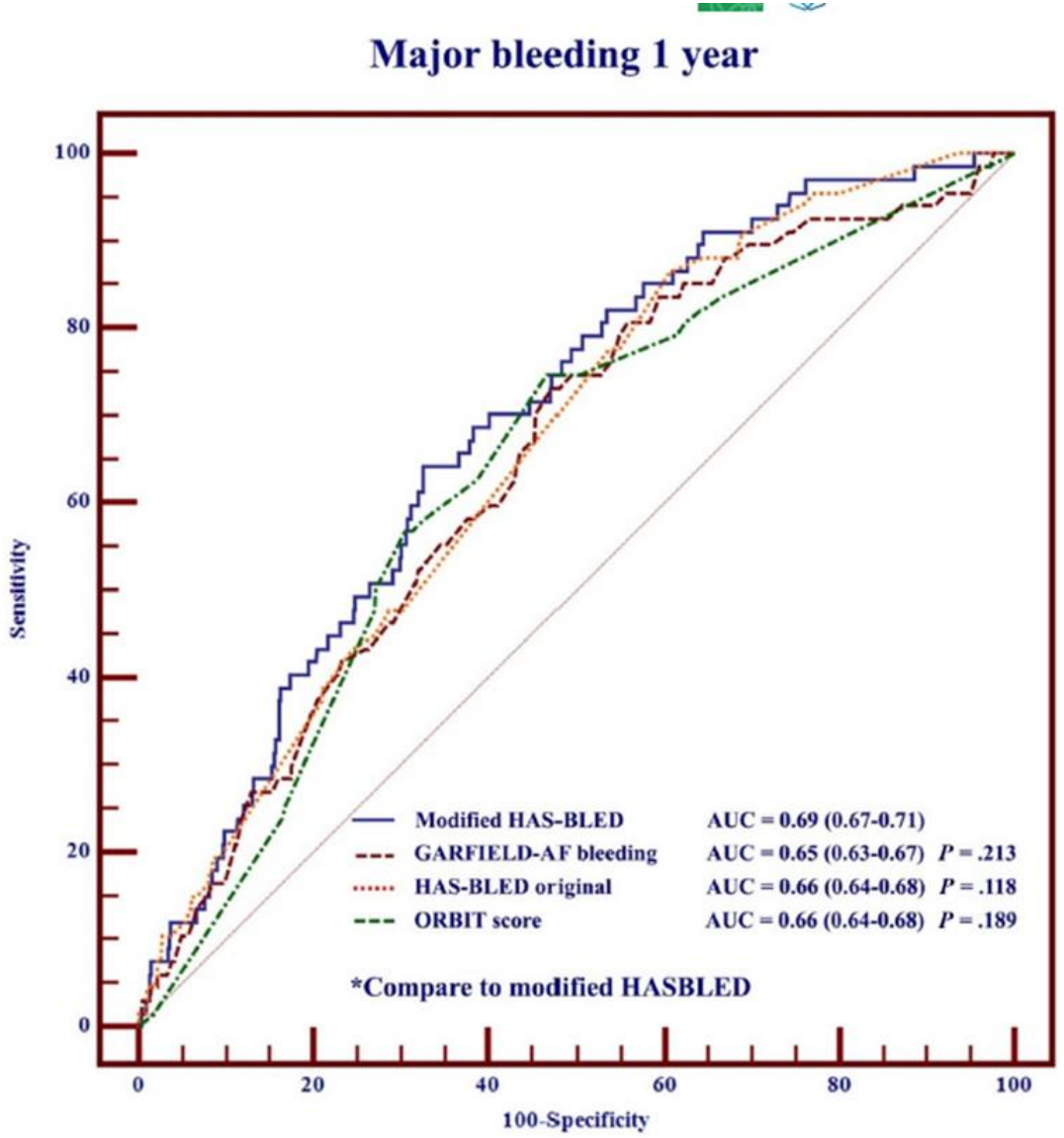

**Figure 3.** Illustrative case for baseline bleeding risk evaluation in atrial fibrillation patients. AF, atrial fibrillation; BP, blood pressure; ESC, European Society of Cardiology; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulant.

Received: 8 July 2022 | Revised: 1 March 2023 | Accepted: 6 March 2023
DOI: 10.1111/bcp.15716

ORIGINAL ARTICLE

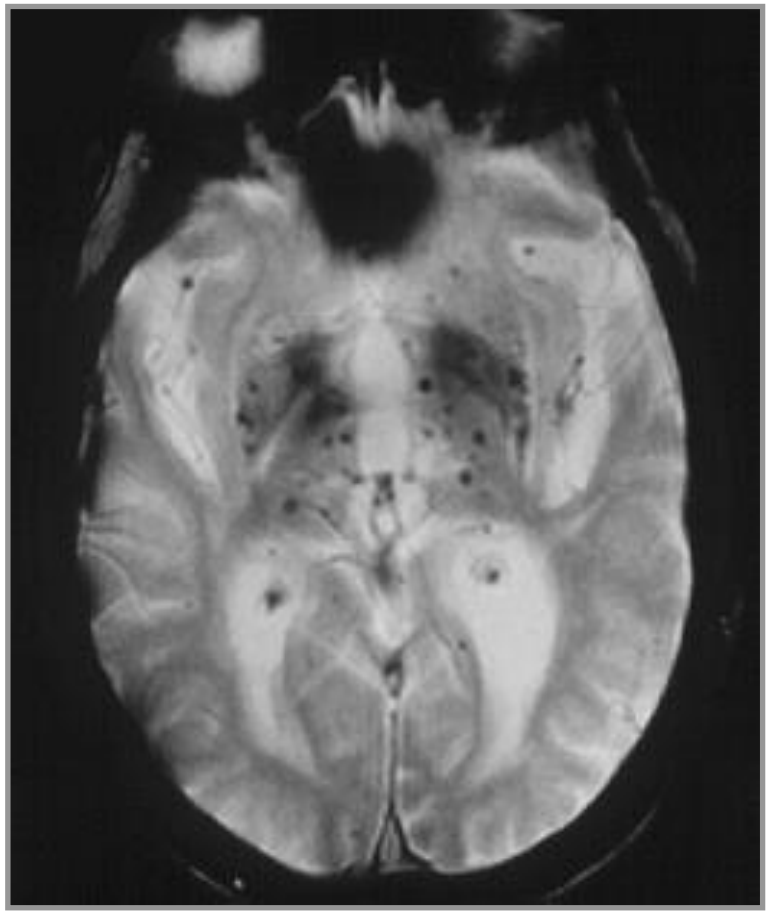
# Comparative validation of HAS-BLED, GARFIELD-AF and ORBIT bleeding risk scores in Asian people with atrial fibrillation treated with oral anticoagulant: A report from the COOL-AF registry

Ply Chichareon[1] | Arjbordin Winijkul[2] | Gregory Y. H. Lip[3,4] | Rungroj Krittayaphong[2]



# Cerebral microbleeds (CMBs)

- Visualized typically by GRE sequence
- **Small round signal loss lesion (< 5 mm)**
- Throughout the whole brain area
- Confused with calcification, small angioma or vessel signal



# Clinical Implication of CMBs

- **Risk for hemorrhagic stroke**
- In patients with lobar hemorrhage
  - 94 patients
  - The 3-year follow-up

| Number of CMBs | 1 | 2 | 3-5 | ≥6 |
|---|---|---|---|---|
| Cumulative risk of ICH, % | 14 | 17 | 38 | 51 |

Greenberg SM, et al. ***Stroke*** 2004

- In patients with ischemic stroke
  - 908 patients
  - 26 months follow-up

| Number of CMBs | 0 | 1 | 2-4 | ≥5 |
|---|---|---|---|---|
| Cumulative risk of ICH, % | 0.6 | 1.9 | 4.6 | 7.6 |

Soo YO, et al. ***J Neurology*** 2004

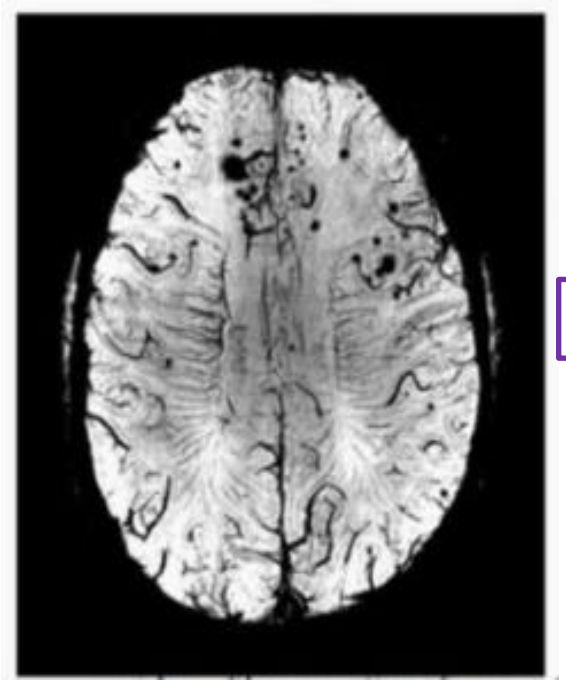


**Table 2. Incidence Rates and Hazard Ratios for the Occurrence of ICH and Death in Both Groups During Follow-Up**

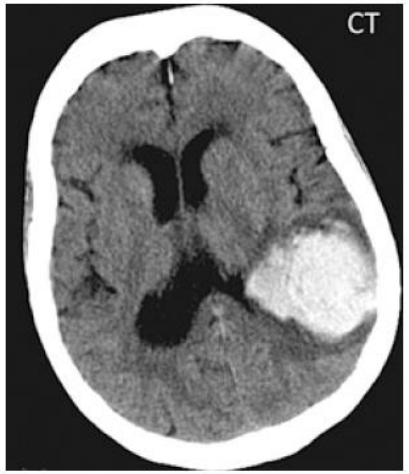
| Event Rate | No. of Patients Presenting With: Lobar Microbleed-Only (n=60) | Lobar ICH (n=240) | *P* Value |
|---|---|---|---|
| Event: occurrence of lobar ICH | | | |
| Observed person-years | 241 | 968 | … |
| No. of occurrence (%) | 12 (20) | 86 (36) | … |
| Incidence of ICH per 100 person-years (95% CI) | 5 (2.6–8.7) | 8.9 (7.1–11) | … |
| Crude hazard ratio (95% CI) | 0.57 (0.3–1.04) | Ref | 0.07 |
| Adjusted hazard ratio* (95% CI) | 0.58 (0.31–1.06) | Ref | 0.08 |
| Event: occurrence of death | | | |
| Observed person-years | 261 | 1316 | … |
| No. of occurrence (%) | 31 (52) | 105 (44) | … |
| Incidence of death per 100 person-years (95% CI) | 11.9 (8–16.8) | 8 (6.5–9.7) | … |
| Crude hazard ratio (95% CI) | 1.8 (1.2–2.8) | Ref | 0.005 |
| Adjusted hazard ratio* (95% CI) | 1.67 (1.1–2.6) | Ref | 0.02 |

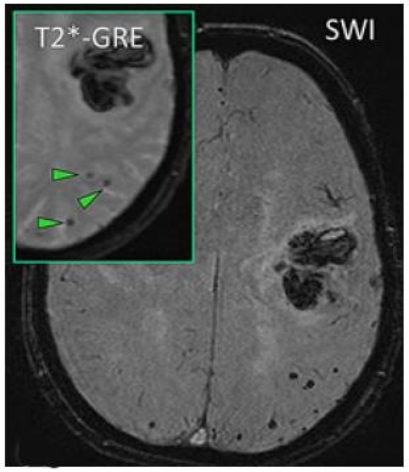
CI indicates confidence interval; ICH, intracerebral hemorrhage; and ref, reference for hazard ratios.

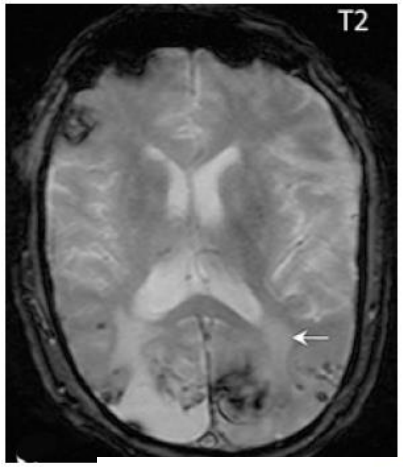
*Adjusted for age, sex, hypertension, microbleed count, and white matter hyperintensity volume.

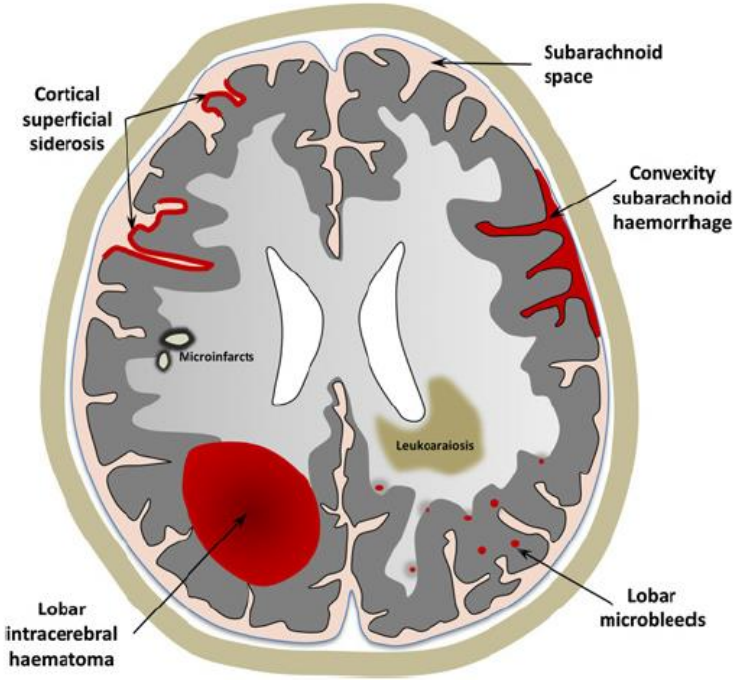
Warfarin use and older age were independent predictors of future IPH in lobar MB-only patients after correction for other covariates

# Cerebral amyloid angiopathy



# Summary

- When do we start anticoagulation after stroke?

- How do we treat afib-related stroke patients with intracranial stenosis or cerebral small vessel diseases?

- Precision medicine for predicting future thromboembolism and bleeding after stroke with a-fib

→ **Not yet!!**