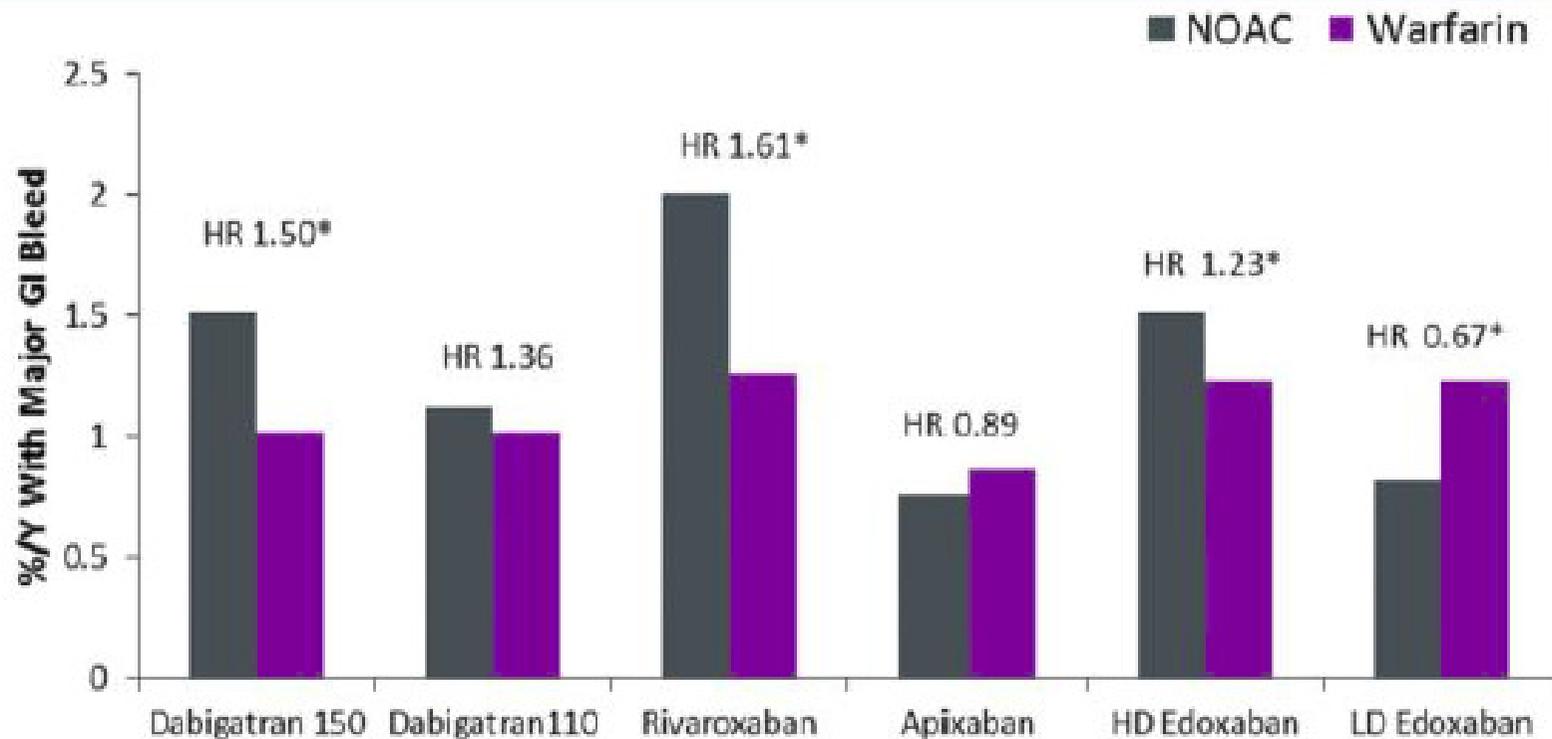


# Restarting anticoagulation after bleeding

## How?

# GI bleeding

# GI blødning: NOAC vs. VKA



\*Statistically significant



## Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study

Cite this as: *BMJ* 2015;351:h5876

### Within two years

39.9% (95% confidence interval 38.4% to 41.3%, n=1745) of the patients had died

12.0% (11.0% to 13.0%, n=526) had experienced thromboembolism

17.7% (16.5% to 18.8%, n=788) major bleeding

12.1% (11.1% to 13.1%, n=546) recurrent gastrointestinal bleeding.

27.1% (n=924) of patients did not resume antithrombotic treatment.

- All patients with atrial fibrillation discharged from hospital after gastrointestinal bleeding while receiving antithrombotic treatment.
- Follow-up started 90 days after discharge
- 4602 patients (mean age 78 years) were included.
- Reduced risk of all cause mortality with restart of oral anticoagulation (hazard ratio 0.39, 95% confidence interval 0.34 to 0.46)
- Reduced risk of thromboembolism with restart of oral anticoagulation (0.41, 0.31 to 0.54),
- Restarting oral anticoagulation alone was the only regimen with an increased risk of major bleeding (1.37, 1.06 to 1.77);
- Difference in risk of recurrent gastrointestinal bleeding was not significant between patients who restarted an antithrombotic treatment regimen and those who did not resume treatment.
- Better outcomes for all cause mortality and thromboembolism compared with patients who did not resume treatment, despite an increased longitudinal associated risk of bleeding.



*Am J Gastroenterol* 2015; 110:328–335;

In-hospital transfusion requirements, need for intensive care unit care, and etiology of GIB were similar between the two groups.

Restarting anticoagulation at discharge after GIB was associated with fewer thromboembolic events without a significantly increased risk of recurrent GIB at 90 days.

## The Risks of Thromboembolism Vs. Recurrent Gastrointestinal Bleeding after Interruption of Systemic Anticoagulation in Hospitalized Inpatients With Gastrointestinal Bleeding: A Prospective Study

- **Prospective observational cohort study on consecutive patients admitted to the hospital who had GIB while on systemic anticoagulation.**
- **Patients contacted by phone 90 days after discharge**
- **197 patients developed GIB while on systemic anticoagulation.**
- **Following index GIB, anticoagulation was discontinued in 76 patients (39%) at discharge.**
- **7 (4%) patients suffered a thrombotic event and 27 (14%) patients were readmitted for GIB.**
- **Anticoagulation continuation was independently associated on multivariate regression with a lower risk of major thrombotic episodes within 90 days (hazard ratio (HR)=0.121, 95% confidence interval (CI)=0.006–0.812,  $P=0.03$ ).**
- **Patients with any malignancy at time of GIB had an increased risk of thromboembolism.(HR=6.1, 95% CI=1.18–28.3,  $P=0.03$ ).**
- **Anticoagulation continuation at discharge was not significantly associated with an increased risk of recurrent GIB or death within 90 days.**



**Am J Cardiol 2014;113:662–668**

Decision to restart warfarin after an episode of major GIB is associated with improved survival and decreased thromboembolism without increased risk of GIB after 7 days of interruption.

### **Restarting Anticoagulation and Outcomes After Major Gastrointestinal Bleeding in Atrial Fibrillation**

- Retrospective cohort study that enrolled subjects who developed GIB while on anticoagulation from 2005 to 2010.
- 1,329 patients developed major GIB.
- Warfarin was restarted in 653 cases (49.1%).
- Restarting warfarin was associated with
  - decreased thromboembolism (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.54 to 0.93,  $p < 0.01$ )
  - reduced mortality (HR 0.67, 95% CI 0.56 to 0.81,  $p < 0.0001$ )
  - but not recurrent GIB (HR 1.18, 95% CI 0.94 to 1.10,  $p = 0.47$ ).
- When the outcomes were stratified by duration of warfarin interruption, restarting warfarin after 7 days was not associated with increased risk of GIB but was associated with decreased risk of mortality and thromboembolism compared with resuming after 30 days of interruption.



[Br J Haematol.](#) 2017  
Apr;177(2):185-197.

## Reintroduction of anti-thrombotic therapy after a gastrointestinal haemorrhage: if and when?

- Practice is variable and not necessarily evidenced-based.
- Overall, for patients that are either anticoagulated or using antiplatelet drugs for secondary prophylaxis, there is a clear benefit to restarting these agents.
- However, there is limited data to guide when this should occur.
  - For individuals at low risk of re-bleeding, current guidelines suggest single agent aspirin can be continued without interruption, assuming haemostatic control has been confirmed endoscopically.
  - For those at higher bleeding risk, aspirin should be withheld, but reintroduced early (within 3 days of index endoscopy).
- However, randomised evidence is lacking, as are studies including more modern agents or combined anticoagulant/ antiplatelet regimens.
- Guidance statements are limited and management suggestions must be extrapolated from clinical trials, retrospective studies and data relating specifically to warfarin and aspirin.

## Conclusion

- No randomised study
- Limited evidence suggest restarting AC after stabilisation.



# INTRACRANIAL HEMORRHAGE

## The problem

### Controversies in Stroke

Section Editors: Carlos A. Molina, MD, PhD, and Magdy H. Selim, MD, PhD

#### The Case:

This is a 62-year-old man who presents with an intracerebral hemorrhage (ICH) while taking warfarin for atrial fibrillation. His INR is 2.5. His CHADS score is 3.

#### The Questions:

- (1) Should warfarin be restarted to decrease the risk of future thromboembolism?
- (2) Does the location of the ICH or the indication for anticoagulation influence the decision?
- (3) If warfarin is to be restarted, when?

#### The Controversy:

RESUMPTION OF ORAL ANTICOAGULATION FOLLOWING WARFARIN-ASSOCIATED ICH.

*Stroke*. 2011;42:3661-3662.

*Stroke. 2011;42:3661-3662.*

## Discussion

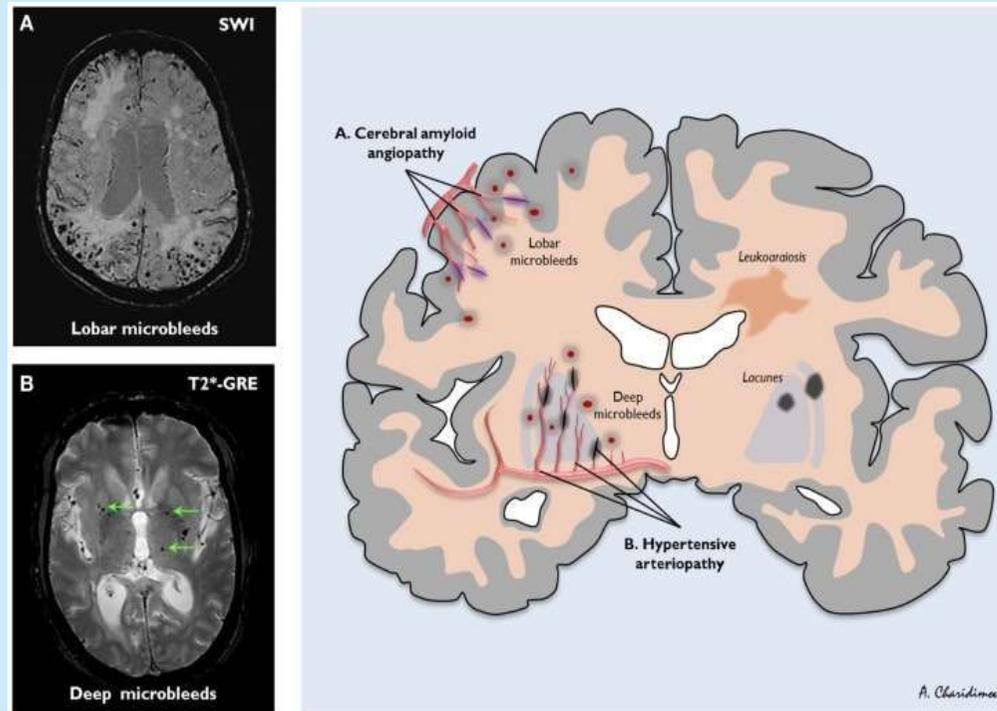
- No prospective data are available that particularly looked at patients with atrial fibrillation, need for anticoagulation), and an intracranial bleeding that occurred in association with warfarin treatment.
- Smaller retrospective studies report low risk of ischemic events during the first 3 weeks before warfarin was restarted.
- The largest retrospective analysis reported re-bleedings both inpatients who resumed warfarin and those who did not; however, arterial thromboembolic events occurred more frequently. *Stroke.2010;41:2860 – 2866.*
- HAS-BLED does not include prior ICH in the basis of risk estimation.

*Stroke. 2011;42:3661-3662.*

## Discussion

- It is assumed that patients with lobar location of ICH have a higher probability of rebleeding, compared with deep hemispheric bleeding, and only patients with deep hemispheric location should receive warfarin again.
  - Deep ICH: 2 % recurrence
  - Lobar ICH: 15 % recurrence
- If warfarin is to be restarted, when?
- Currently available data are contradictory.
- A review of 6 observational studies on oral anticoagulation in patients with mechanical valves concluded that restarting oral anticoagulation after 7 to 14 days appeared safe. *Tromb Haemost. 2009;101:290 –297.*
- However, a delay of reintroduction of warfarin until between 10 and 30 weeks has also been suggested. *Stroke.2010;41:2860 –2866.*
- Probability of ICH recurrence is highest during the early phase after the index bleeding and decreases over time, whereas risk of ischemic events increases over time and will cross at some point in time.

# Cerebral amyloid angiopathy Microbleeds

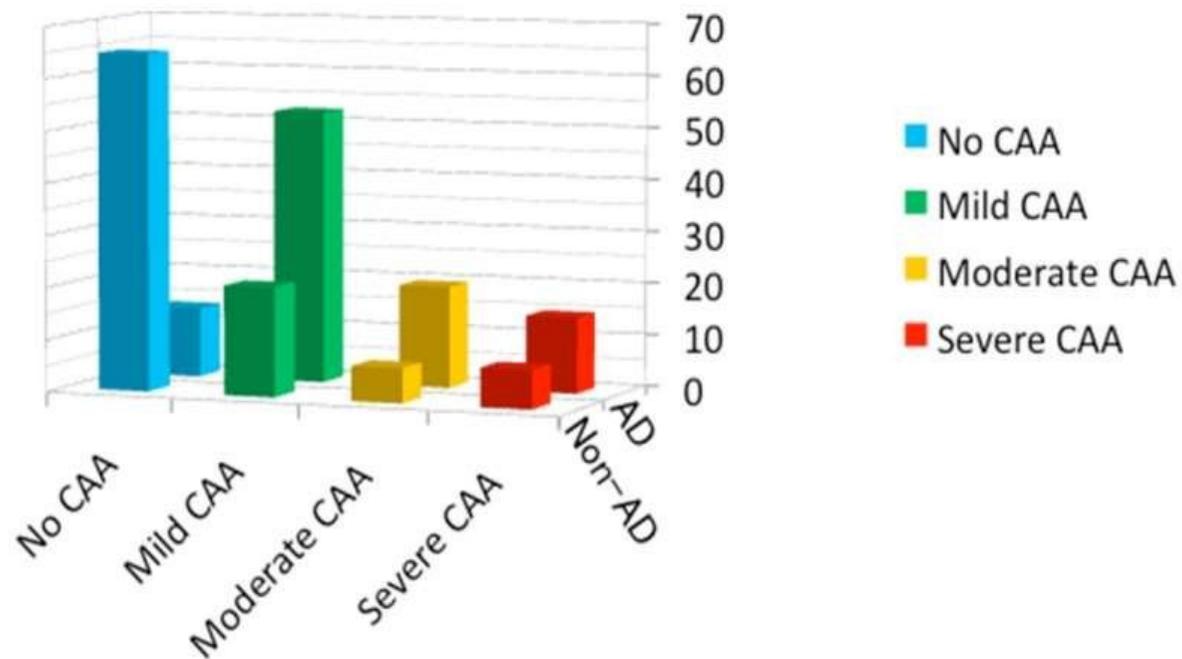


# Prevalence of cerebral microbleeds

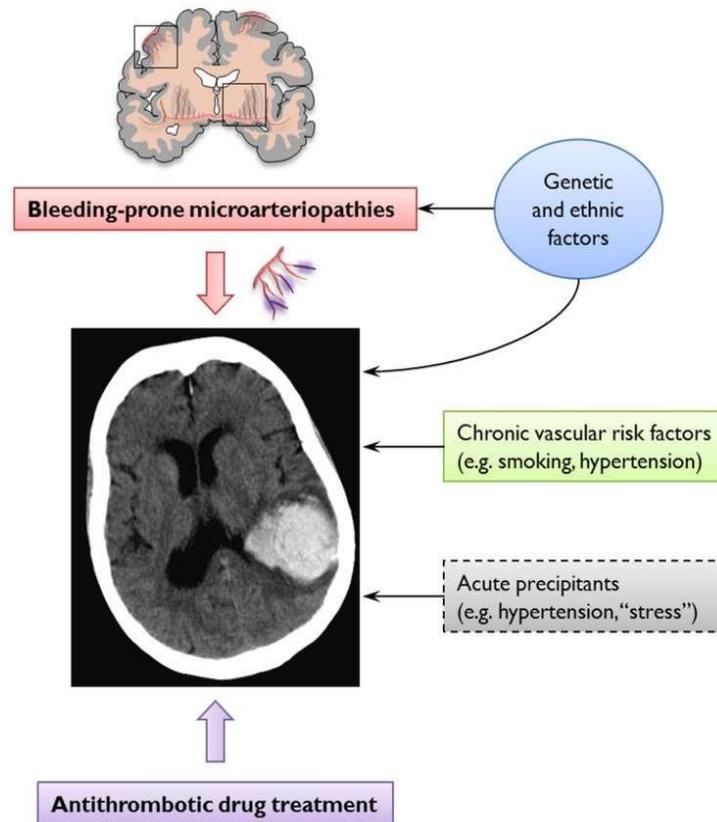
| Age range | Cerebral microbleeds | Mutiple microbleeds |
|-----------|----------------------|---------------------|
| 45-49     | 6.5 %                | 0.7 %               |
| 50-59     | 11.5 %               | 3.4 %               |
| 60-69     | 16.8 %               | 4.9 %               |
| 70-79     | 28.9 %               | 14.9 %              |
| ≥ 80      | 37.7 %               | 22.4 %              |

Poels et al. Stroke 2010;41:S103-6  
Rotterdam studiet

Prevalence in subjects with spontaneous ICH: 68 %  
(Fisher M. Frontiers in neurology. 2013;4:137)



The distribution of the severity of CAA in elderly individuals (n = 201; age, 85.9 ± 8.0 years) with and without Alzheimer's disease (AD), based on an autopsy series including AD (n = 82; age, 86.1 ± 7.9 years) and non-AD cases (n = 119; age, 85.7 ± 8.0 years).



Charidimou et al. Front Neurol  
2012;3:133

# Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding

## A Nationwide Cohort Study

Peter Brønnum Nielsen, MSc, PhD; Torben Bjerregaard Larsen, MD, PhD;  
Flemming Skjøth, MSc, PhD; Anders Gorst-Rasmussen, MSc, PhD;  
Lars Hvilsted Rasmussen, MD, PhD; Gregory Y.H. Lip, MD

Circulation  
2015

6138 patienter med atrieflimren og ICH

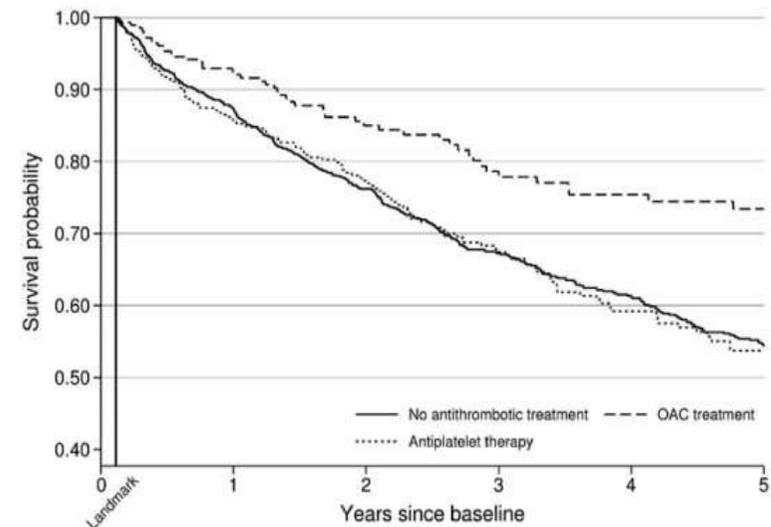
1752 patienter som har været i AK-behandling indenfor det sidste halve år før ICH (1997-2013)

Opfølgning fra 6 uger efter udskrivelse

35 % genoptog AK-behandling (10 % af alle)

43 % kom i pladehæmmerbeh

22 % ingen behandling



**Figure 3.** Five-year Kaplan–Meier survival curve for restarting OAC treatment, for receiving antiplatelet therapy, and for not receiving antithrombotic treatment with the use of a landmark at 6 weeks (relative to discharge from hospital) for treatment regimens stratification. OAC indicates oral anticoagulation.

# Restarting Anticoagulant Therapy After Intracranial Hemorrhage

## A Systematic Review and Meta-Analysis

Murthy et al., Stroke 2017

- Systematic review and meta-analysis to summarize the associations of anticoagulation resumption with the subsequent risk of ICH recurrence and thromboembolism
- Predictor variable was resumption of anticoagulation.
- Outcome measures were thromboembolic events (stroke and myocardial infarction) and recurrence of ICH.
- Eight studies were eligible for inclusion in the meta-analysis, with 5306 ICH patients. Almost all studies evaluated anticoagulation with vitamin K antagonists.
- Reinitiation of anticoagulation was associated with a significantly lower risk of thromboembolic complications (pooled relative risk, 0.34; 95% confidence interval, 0.25–0.45;  $Q=5.12$ ,  $P$  for heterogeneity=0.28).
- There was no evidence of increased risk of recurrent ICH after reinstatement of anticoagulation therapy,
- Significant heterogeneity among included studies (pooled relative risk, 1.01; 95% confidence interval, 0.58–1.77;  $Q=24.68$ ,  $P$  for heterogeneity <0.001).
- No significant publication bias was detected in our analyses.

# Prevention of recurrent ICH

## 1. Stratifying risk:

1. lobar location
2. older age
3. presence and number of microbleeds on MRI
4. ongoing anticoagulation
5. Presence of apolipoprotein E  $\epsilon$ 2 or  $\epsilon$ 4 alleles (*Class IIa; Level of Evidence B*).

## 2. BP should be controlled in all ICH patients (*Class I; Level of Evidence A*).

1. Measures to control BP should begin immediately after ICH onset (*Class I; Level of Evidence A*).
  - Long-term goal BP <130/80 (*Class IIa; Level of Evidence B*).

## 3. Lifestyle modifications

Alcohol, drugs, obstructive sleep apnea, tobacco

## 4. No long-term AC following warfarin-associated spontaneous lobar ICH (*Class IIa; Level of Evidence B*).

# Prevention of recurrent ICH

5. Anticoagulation after non-lobar ICH and antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents (*Class IIb; Level of Evidence B*).

6. Optimal timing to resume oral anticoagulation after anticoagulant-related ICH is uncertain.

- Avoidance of oral anticoagulation for at least 4 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence (*Class IIb; Level of Evidence B*).
- If indicated, aspirin monotherapy can probably be restarted in the days after ICH, although the optimal timing is uncertain (*Class IIa; Level of Evidence B*).

7. The usefulness of NOACs in patients with atrial fibrillation and past ICH to decrease the risk of recurrence is uncertain (*Class IIb; Level of Evidence C*).

8. There are insufficient data to recommend restrictions on the use of statins in ICH patients (*Class IIb; Level of Evidence C*).

## RESUMING ANTICOAGULATION AFTER ICH

Ekspertene: Joshua Goldstein og Steven Greenberg; november 2010

TABLE 3

### Factors arguing for and against resuming anticoagulation after intracerebral hemorrhage

| FACTOR*   | FOR | AGAINST |
|---|-----|---------|
| <b>Etiologic factor</b>   |     |         |
| Hypertension-related hemorrhage, hypertension adequately controlled   | X   |         |
| Cerebral amyloid angiopathy   |     | X       |
| <b>Microvascular risk</b>   |     |         |
| Microbleeds on gradient-echo magnetic resonance imaging               |     | X       |
| <b>Indication for anticoagulation</b>                                 |     |         |
| Secondary prevention  | X   |         |
| Primary prevention  |     | X       |
| Atrial fibrillation, high CHADS <sub>2</sub> score                    | X   |         |
| Atrial fibrillation, low CHADS <sub>2</sub> score                     |     | X       |
| Mechanical heart valve  | X   |         |
| Hypercoagulable state   | X   |         |
| Anticipated difficulty controlling the international normalized ratio |     | X       |

Faktorer der skal overvejes før genoptagelse af antikoagulationsbeh.

# EHRA practical guide

Europace Advance Access published August 31, 2015



Europace  
doi:10.1093/europace/euv309

**EHRA PRACTICAL GUIDE**

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## **Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation**

# Intracranial bleeds

- According to the labelling of VKAs and also of the NOACs, a history of a spontaneous intracranial bleed constitutes a contraindication against anticoagulation, unless the cause of the bleeding has been reversed.
  - Uncontrolled hypertension, triple therapy, and INR  $<4-5$  in patients on VKAs.
- Arguments for not resuming or initiating anticoagulation after ICH
  - Older age, persistent uncontrolled hypertension, lobar bleeds, severe white matter lesions, multiple microbleeds on magnetic resonance angiography ( $>30$ ), chronic alcoholism and need for DAPT after PCI.
- Patients with cortical bleeds or CAA have a much higher risk of recurrent bleeding and should not be anticoagulated.
  - CAA be assumed when there is a family history of ICH  $<60$  years and/or early dementia.
  - Severe small vessel disease and a high number of microbleeds are also suggestive of amyloid angiopathy.

# Epidural and subdural hematomas

- Epidural haematomas are always traumatic
  - Start or reinitiate anticoagulation after 4 weeks although there are no specific data.
- Traumatic subdural haematoma
  - Start or reinitiate anticoagulation after 4 weeks, except for at least one-third of these patients who are chronic alcoholics.
- Spontaneous subdural haematomas

INR>3: anticoagulation can reasonably be restarted after 4 weeks.

INR normal or the patient was not anticoagulated: AC contraindicated

Left atrial appendage should be considered as potential substitutes for the contra-indicated resumption of long-term anticoagulation.

## 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)



## LAA for stroke prevention

- The most common justification for LAA occlusion devices in clinical practice is a perceived high bleeding risk and, less often, contraindications for OAC.
- Unfortunately, LAA occluders have not been tested in such populations.
- Furthermore, LAA occluders have not been compared with NOAC therapy in patients at risk for bleeding, or with thoracoscopic LAA clipping.
- Stroke on treatment
- At least 2% of anticoagulated patients with AF will experience a serious bleeding event per year.
- Observational data suggest that OAC can be reinitiated even after an intracerebral bleeding event.
- APACHE-AF [Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage

# Konklusion

- Of great importance
  - Type of ICH
  - Potential reversible risk factors
  - How to reduce risk of new ICH
  - Risk stratification
- Many patients with lobar hemorrhage or cerebral amyloid angiopathy may remain at higher risk of anticoagulant-related ICH recurrence than thromboembolic events and would therefore be best managed without anticoagulants.
- Those with deep hemispheric ICH, hypertension that can be well controlled, and a high risk of disabling thromboembolism may receive net benefit from restarting anticoagulation.