Intracranial haemorrhage and anticoagulation

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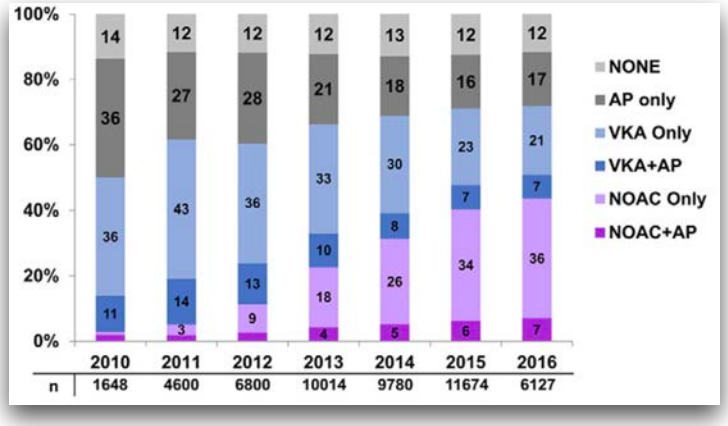
Intracranial haemorrhage and anticoagulation

Content

1. Relevance
2. Principles
3. Manangement

Thorsten Steiner 08.40-09:00 Centre Hospitalier Universitaire Vaudois, Lausanne 04.10.2018

New AF - baseline therapy in the Garfield registry



1. NOACs prescription increasing, currently at 35%
2. VKA prescription decreasing, currently at 20%
3. Combination of OAC with AP similar (7%)

AP - anti-platelets; VKA - Vitamin-K antagonist;
NOAC - non-Vitamin-K antagonist oral anticoagulant

Steinberg BA et al. *Am Heart J.* 2017;194:132-140

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Reversal of Coagulopathy

Why → Intracerebral hemorrhage
Goal: prevention of hematoma expansion

Who → **VKA** | **Dabigatran** | **Factor Xa-Inhibitor**

Relevant drug concentrations assumed ?

When → Check on:
- time last taken: half-life time, dose
- liver function, renal function
- drug-drug interaction

INR > 1.2 | Drug levels > 30ng/mL

Relevant drug concentrations assumed: Yes

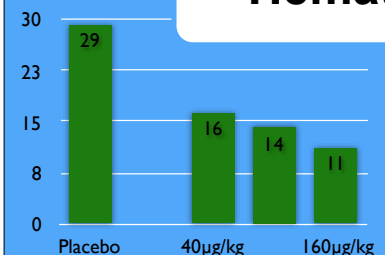
What → ? | ? | ?

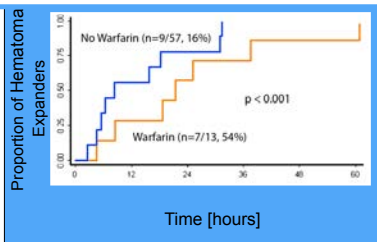
Steiner T, Weitz I J, Veltkamp R Stroke 2017 48:1432-1437

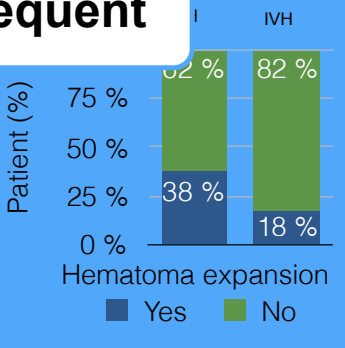
Why: The problem is hematoma expansion in different clinical settings

Spontaneous ICH	VKA-ICH	NOAC-ICH
≤ 30%*	≤ 54%*	≤ 38%*

Hematoma expansion is frequent







Hematoma expansion determines prognosis

ICH: Intracerebral hemorrhage; VKA: Vitamin K antagonist; * 33% of baseline volume

Peak and trough levels of OACs

	VKA	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Peak values (hrs)	—	2–3	1–4	2–4	1–2
Half-life (hrs)	Acenocumarol: 9 hours Warfarin: 2 days Phenprocoumon: 7 days	12–17	9 - 14	5 - 13	10 - 14

Drouet L et al. Int J Stroke. 2016;11:748-758; Kirchhof P, et al. EHRA guidelines Eur Heart J. 2016

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NOACs have a beneficial pharmacological profile compared with warfarin

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Renal excretion (%)	<1	85	~33	27	~50
Interactions	Multiple	P-gp	CYP3A4 P-gp	CYP3A4 P-gp	P-gp

Adapted from: Pradaxa®: EU SPC, 2015; Xarelto: EU SPC, 2015; Eliquis: EU SPC, 2015; Warfarin sodium: SPC, 2015; Savaysa US PI 2015

PT and aPTT sensitivities and costs

	PT Sensitivity	APTT
Rivaroxaban	74% (95% CI, 70%-78%)	n.a.
Apixaban	56% (95% CI, 47%-64%)	n.a.
Dabigatran	n.a.	98% [95% CI,89%-100%]
Cost (Medicare fee schedule)	7.29 US$	11.23 US$

Recommendation:
Factor Xa-inhibitors: If available use anti-Xa assay using a drug-specific calibrator
Dabigatran: If available use dilute thrombin time

Plasma drug levels < 30 ng/mL: absence of a significant anticoagulant effect

Scholzberg, Xu JAMA Diagnostic Test Interpretation, Sept 2018

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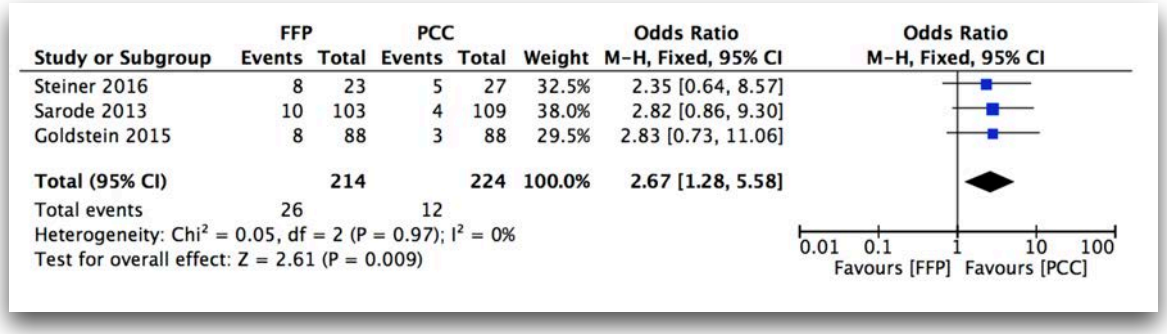
Meta-Analysis of PCC-FFP trials

Outcome: Mortality at day 90



Study or Subgroup	FFP Events	FFP Total	PCC Events	PCC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Steiner 2016	8	23	5	27	32.5%	2.35 [0.64, 8.57]
Sarode 2013	10	103	4	109	38.0%	2.82 [0.86, 9.30]
Goldstein 2015	8	88	3	88	29.5%	2.83 [0.73, 11.06]
Total (95% CI)		**214**		**224**	**100.0%**	**2.67 [1.28, 5.58]**
Total events	26		12			

Heterogeneity: Chi² = 0.05, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.61 (P = 0.009)

Steiner T, unpublished data 2017

Management of ICH related to VKA Prothrombin complex concentrate (**PCC**)

Indication threshold	Reversal agent
1.2 ≤ INR < 2	PCC: 10 U/kg i.v.
2 ≤ INR	PCC: 50 U/kg i.v.
	Vitamin-K: 10mg i.v.

Ahmed N et al.: Recommendations from the ESO-Karolinska Stroke Update. *Eur Stroke J.* 2017

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Gordon Royle, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., Peter Verhamme, M.D., Bushi Wang, Ph.D., Laura Young, M.D., and Jeffrey I. Weitz, M.D.

Pollack et a. N Engl J Med. 2017;377:431-441

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

Connolly S et al. N Engl J Med. 2016;375:1131-1141

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EHRA Practical Guide 2018 on the management of bleeding recommends idarucizumab use in patients on dabigatran

Bleeding while using a NOAC

- Inquire about last NOAC intake
- Blood sample to determine CrCl, haemoglobin etc.
- Rapid coagulation assessment, incl. plasma drug levels (if available)

Mild bleeding

- Delay or discontinue next dose
- Reconsider concomitant medication
- Reconsider choice of NOAC and dosing

Non life-threatening major bleeding

Supportive measures
- Mechanical compression
- Endoscopic haemostasis if GI bleed
- Surgical haemostasis
- Fluid replacement
- RBC substitution if needed
- Platelet substitution (if platelet count ≤60×10⁹/L)
- Consider adjuvant tranexamic acid
- Maintain adequate diuresis
- Consider idarucizumab*/ haemodialysis (if idarucizumab is not available) for dabigatran

Life-threatening bleeding

- For **dabigatran**-treated patients, **idarucizumab** 5 g IV
- For **FXa inhibitor-treated** patients: **andexanet alfa***

Otherwise, consider:
- PCC: 50 U/kg + 25 U/kg if indicated
- aPCC: 50 U/kg; max 200 U/kg/day

*Andexanet alfa is only approved in the USA
Adapted from Steffel et al. Eur Heart J 2018

Reversal of Coagulopathy

Why → Intracerebral hemorrhage
Goal: prevention of hematoma expansion

Who → **VKA** | **Dabigatran** | **Factor Xa-Inhibitor**

When →
- Relevant drug concentrations assumed ?
- Time point of last dose administered (consider peak level and half-life time of OACs), check on dose, liver function, renal function drug-drug interaction.
- Consider specific coagulation tests
  - INR > 1.2
  - Drug levels > 30ng/mL
- Relevant drug concentrations assumed: Yes

What →
- PCC 25-50 U/kg iv +Vitamin-K 10 mg iv
- Idarucizumab 5g iv
- PCC 25-50 U/kg iv* (Andexanet Alpha)

Steiner T, Weitz I J, Veltkamp R Stroke 2017 48:1432-1437

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<u>Restart</u>?

RESEARCH ARTICLE

Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage

Alessandro Biffi, MD,[1,2,3]* Joji B. Kuramatsu, MD,[4]* Audrey Leasure, BS,[5] Hooman Kamel, MD,[6] Christina Kourkoulis, BS,[1,2,3] Kristin Schwab, BA,[1,3] Alison M. Ayres, BA,[1,3] Jordan Elm, PhD,[7] M. Edip Gurol, MD, MSc,[1,3] Steven M. Greenberg, MD, PhD,[1,3] Anand Viswanathan, MD, PhD,[1,3] Christopher D. Anderson, MD, MMSc,[1,2,3] Stefan Schwab, MD,[4] Jonathan Rosand, MD, MSc,[1,2,3] Fernando D. Testai, MD, PhD,[8] Daniel Woo, MD, MS,[9] Hagen B. Huttner, MD,[4]* and Kevin N Sheth, MD[5]*

Biffi A et al. . Ann Neurol. 2017;82:755-765

Oral anticoagulation resumption and outcomes following intracerebral hemorrhage at **1 year**

	All ICH			Nonlobar ICH			Lobar ICH		
Outcome[a]	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.27	0.19–0.40	<0.0001[b]	0.25	0.14–0.44	<0.0001[b]	0.29	0.17–0.45	<0.0001[b]
Favorable outcome, mRS = 0–3	4.15	2.92–5.90	<0.0001[b]	4.22	2.57–6.94	<0.0001[b]	4.08	2.48–6.72	<0.0001[b]
All-cause stroke	0.47	0.36–0.64	<0.0001[b]	0.41	0.25–0.67	0.0004[b]	0.51	0.37–0.76	0.0006[b]
Recurrent ICH	1.20	0.95–1.58	0.21	1.17	0.89–1.54	0.27	1.26	0.88–1.71	0.22
Ischemic stroke	0.44	0.29–0.66	<0.0001[b]	0.39	0.21–0.74	0.004[b]	0.48	0.25–0.75	0.003[b]

OAT resumption is - in both non lobar and lobar ICH - associated with
- decreased mortality
- increased likelihood of favourable outcome
- Decreased likelihood of ischemic stroke
- but not of recurrent ICH

[a]All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA2DS2-VASc score, and HAS-BLED score.
[b]Statistically significant.
CI = confidence interval; HR 5 hazard ratio; ICH 5 intracerebral hemorrhage; mRS 5 modified Rankin Scale.

Biffi A et al. . Ann Neurol. 2017;82:755-765

Oral anticoagulation resumption and long-term outcomes (**beyond 1 year** (49 months)) following intracerebral hemorrhage

Outcome[a]	All ICH			Nonlobar ICH			Lobar ICH		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.32	0.15–0.66	0.002[b]	0.30	0.10–0.91	0.035[b]	0.33	0.12–0.87	0.026[b]
Favorable outcome, mRS = 0–3	3.99	1.76–9.05	0.001[b]	4.10	1.24–13.57	0.022[b]	3.89	1.26–11.98	0.019[b]
All-cause stroke	0.50	0.32–0.79	0.003[b]	0.49	0.26–0.93	0.031[b]	0.51	0.26–0.99	0.047[b]
Recurrent ICH	1.10	0.96–1.26	0.20	1.10	0.94–1.28	0.23	1.21	0.86–1.70	0.27
Ischemic stroke	0.46	0.28–0.75	0.002[b]	0.44	0.22–0.90	0.025[b]	0.48	0.25–0.94	0.032[b]

OAT resumption is - in both non lobar and lobar ICH - associated with
- decreased **mortality**
- increased likelihood of **favourable outcome**
- **decreased** likelihood of **ischemic stroke**
- but **not** of **recurrent ICH**

➡ **Similar to 1 year-results**

[a]All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA2DS2-VASc score, and HAS-BLED score.
[b]Statistically significant.
CI = confidence interval; HR 5 hazard ratio; ICH 5 intracerebral hemorrhage; mRS 5 modified Rankin Scale. Biffi A et al. . Ann Neurol. 2017;82:755-765

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Oral anticoagulation resumption and outcomes following lobar ICH related to **possible** **versus** **probable** **CAA**

Outcome[a]	Possible CAA			Probable CAA		
	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.27	0.08–0.86	0.028[b]	0.30	0.10–0.92	0.037[b]
Favorable outcome, mRS 0–3	3.40	1.22–9.46	0.020[b]	3.11	1.08–8.97	0.038[b]

OAT resumption is - in **both** possible and probable CAA - associated with
- **decreased mortality**
- **favourable outcome**

[a]All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA2DS2-VASc score, and HAS-BLED score.
[b]Statistically significant.
CI = confidence interval; HR 5 hazard ratio; ICH 5 intracerebral hemorrhage; mRS 5 modified Rankin Scale. Biffi A et al. . Ann Neurol. 2017;82:755-765

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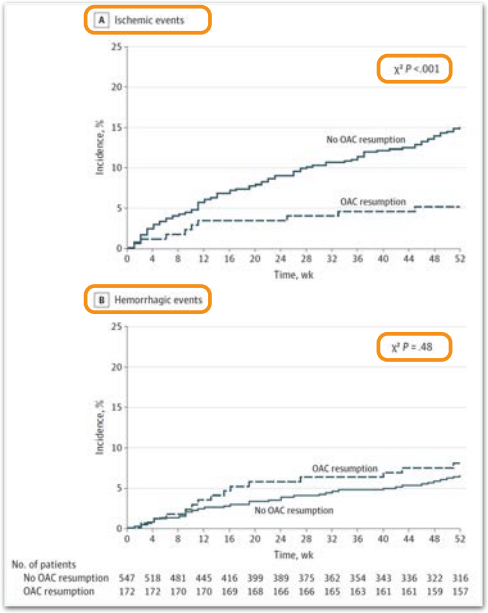
   Restart?

How high is the risk of new ischemic and hemorrhagic events after restart of OAC?

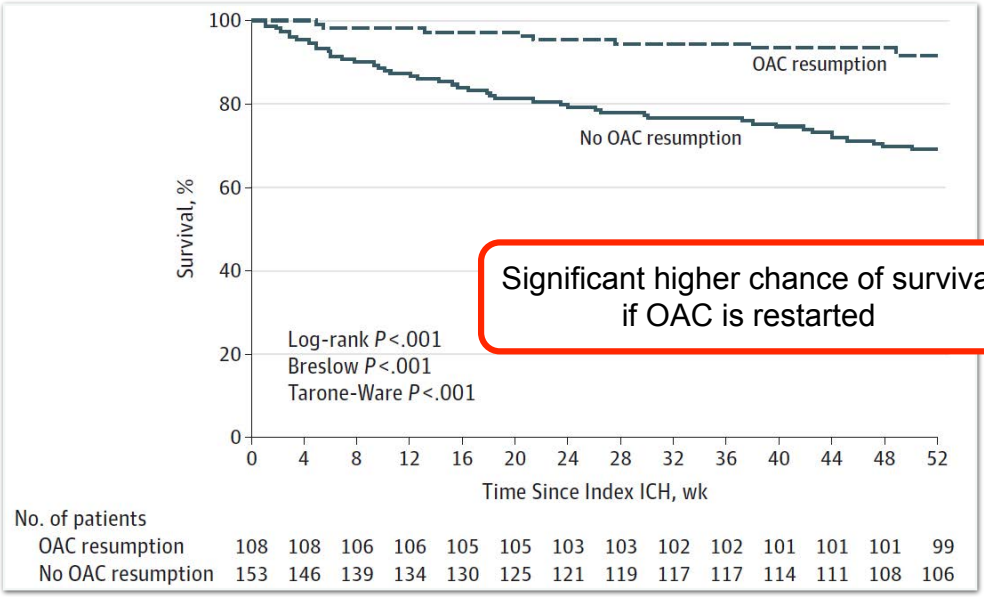


Significantly increased rate of ischemic events if OAC not restarted

No clear increase of ICH recurrence if OAC restarted

Kuramatsu JB, et al. *JAMA*. 2015;313:824-836

Survival Rates of patients with atrial fibrillation with and without OAC resumption



Significant higher chance of survival if OAC is restarted

Kuramatsu JB, et al. *JAMA*. 2015;313:824-836

Intracranial haemorrhage and anticoagulation

Restart OAC after ICH - Opinion:

1. Restarting of OAC after and OAC-associated ICH is probably indicated when there is a clear indication OAC (AFib) and blood pressure control is sufficient and after CT or MRI-control demonstrated no abnormal degradation of ICH, and no massive CMBs / Siderosis, because retrospective data demonstrated a significant increased survival and fewer ischemic events when OAC was restarted but increased rated of recurrent ICH

2. Restarting should be considered between 14 days and 10 weeks after CT or MRI demonstrated no abnormal degradation of ICH

3. Alternatively: LAA-occlusion can considered in case of clear contraindication for OAC