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ABU DHABI, UAE

16TH WORLD STROKE CONGRESS

VITAMIN K ANTAGONISTS IN PATIENTS WITH BREAKTHROUGH STROKES ON DOACS

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Disclosures

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X	I have a relationship with a for-profit and/or a not-for-profit organization to disclose:

Company Name	Direct financial payments/honoraria	Membership on advisory boards or speakers' bureaus	Funded grants or clinical trials	Patents on a drug, product or device	All other investments or relationships
Bristol-Myers Squibb	x (lecture fees)				
AstraZeneca	x (lecture fees)				
Boston Scientific					x (participation in an educational program)

X	I am a cardiologist (i.e., not a stroke neurologist).

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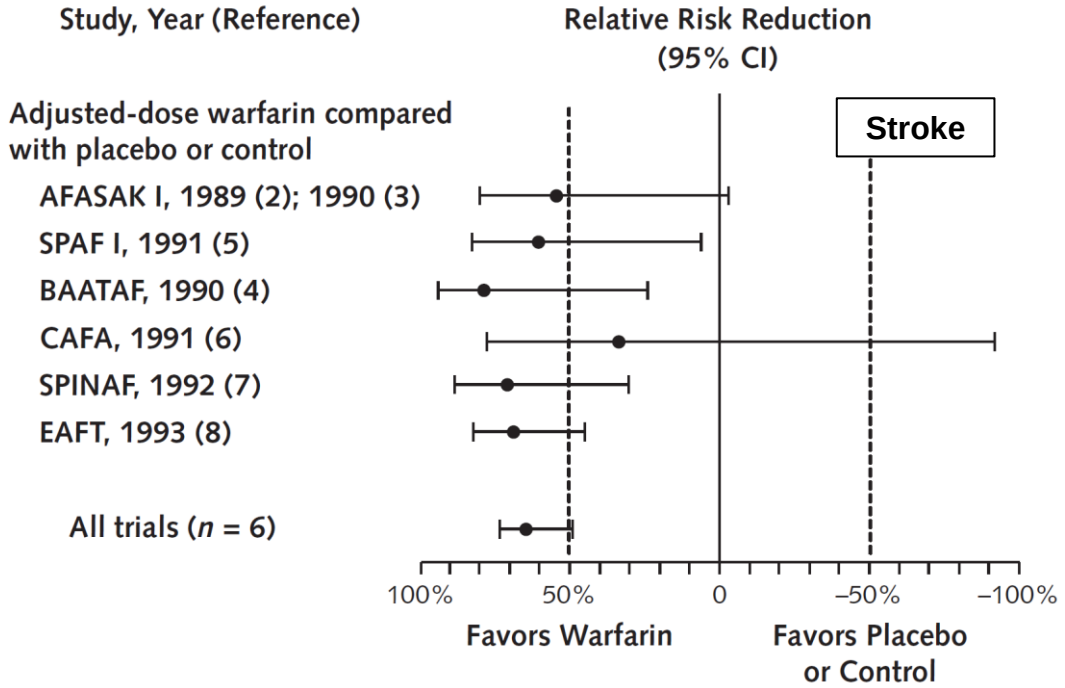
Warfarin for stroke prevention

Meta-analysis of RCTs: warfarin vs. placebo/control in atrial fibrillation (AF)



Stroke:
Risk ratio (RR) 0.36 (95% CI 0.26-0.51)

Ischemic stroke:
RR 0.33 (95% CI 0.23-0.46)

Intracranial hemorrhage:
~2-fold increase (RR not calculable)

Major extracranial hemorrhage:
RR 1.66 (95% CI 0.82-3.35)

All-cause mortality:
RR 0.74 (95% CI 0.57-0.97)

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Hart RG, et al. Ann Intern Med. 2007 Jun 19;146(12):857-67.

DOACs vs. warfarin in patients with AF

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Individual patient data meta-analysis (IPDMA) of RCTs (COMBINE-AF)

Efficacy (DOAC vs. warfarin)

Outcome	Hazard ratio (95% CI)
Ischemic stroke	0.81 (0.74-0.89)
Systemic embolism	0.71 (0.51-0.99)
All-cause mortality	0.92 (0.87-0.97)

Safety (DOAC vs. warfarin)

Outcome	Hazard ratio (95% CI)
Any bleeding	0.86 (0.74-1.00)
Major bleeding	0.86 (0.74-1.01)
Intracranial bleeding	0.45 (0.37-0.56)

Compared to warfarin, direct oral anticoagulants (DOACs)

- reduce ischemic stroke, systemic embolism and death
- provide a modest (and statistically non-significant) reduction in any and major bleeding
- markedly reduce intracranial bleeding

Carnicelli AP, et al. Circulation. 2022 Jan 25;145(4):242-255.

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DOACs vs. warfarin in patients with AF

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Subgroup analyses in patients with prior stroke

Subgroup analysis (year)	DOAC	Outcome	Event rate (%/year) on DOAC	Event rate (%/year) on warfarin	Hazard ratio (95% CI)
RE-LY[1] (2010)	Dabigatran 150 mg BID	Ischemic/ unknown stroke	1.75	1.75	1.00 (0.65-1.54)
ROCKET AF[2] (2012)	Rivaroxaban 20 mg QD	Ischemic/ unknown stroke	2.34	2.27	1.03 (0.82-1.30)
ARISTOTLE[3] (2012)	Apixaban 5 mg BID	Ischemic/ unknown stroke	1.92	2.23	0.86 (0.60-1.22)
ENGAGE-AF TIMI 48[4] (2016)	Edoxaban 60 mg QD	Ischemic stroke	2.04	2.13	0.96 (0.73-1.25)

[1] Diener HC, et al. Lancet Neurol.2010 Dez;9(12):1157-1163.
[2] Hankey GJ, et al. Lancet Neurol. 2012 Apr;11(4):315-22
[3].Easton JD, et al. Lancet Neurol. 2012 Jun;11(6):503-11.
[4] Rost NS, et al. Stroke. 2016 Aug;47(8):2075-82.

„Breakthrough stroke“: stroke while on oral anticoagulation

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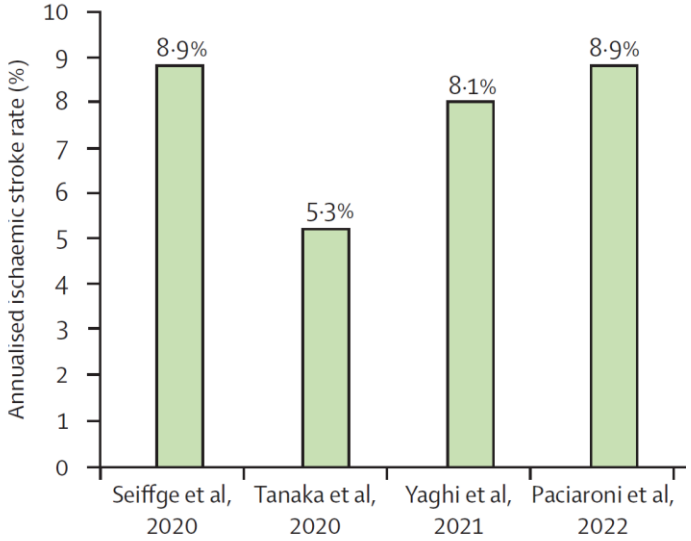
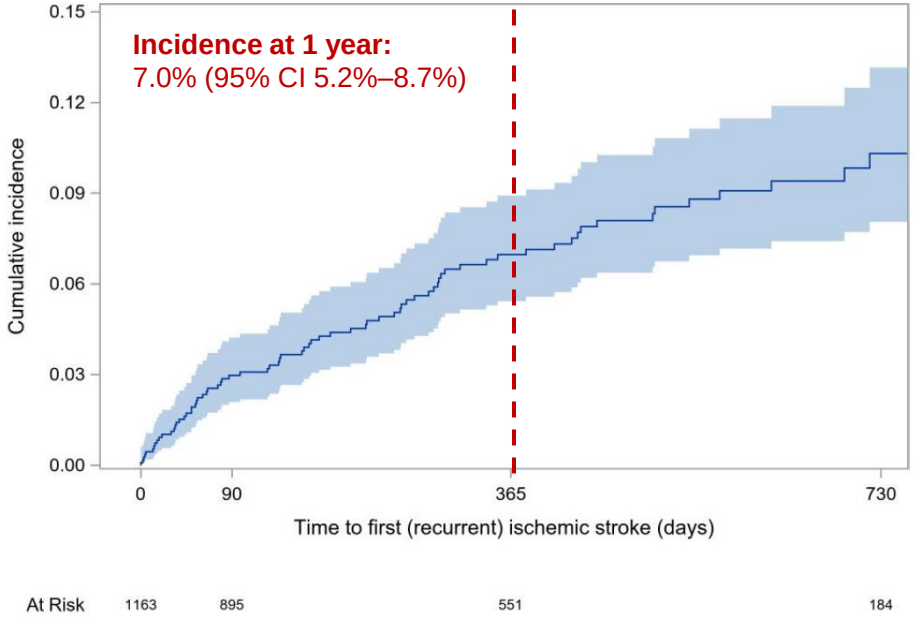
Recent breakthrough stroke – very high risk of recurrent stroke

Observational studies



IPDMA of DOAC/warfarin RCTs (COMBINE AF)



Seiffge DJ, et al. Lancet Neurol. 2024 Apr;23(4):404-417.

Benz AP, et al. Eur Heart J. 2023 May 21;44(20):1807-1814.

„Breakthrough stroke“: current practice patterns

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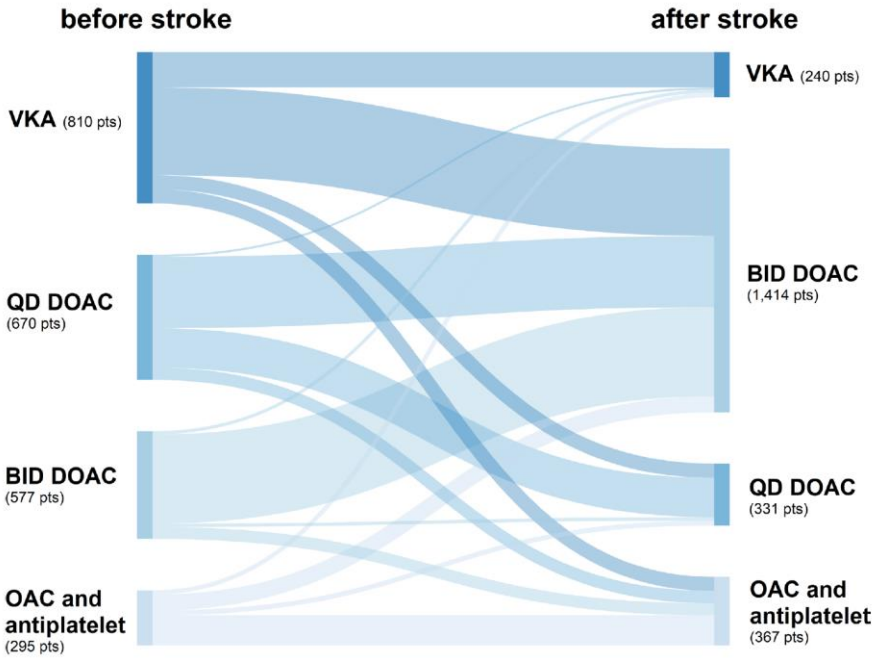
Antithrombotic treatment



Mechanical treatment

- Left atrial appendage occlusion: (currently) unproven
- Carotid filters: not available

Polymeris AA, et al. J Neurol Neurosurg Psychiatry. 2022 Jun;93(6):588-598.

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„Breakthrough stroke“ on a DOAC: DOAC (continuation) or switch to VKA?

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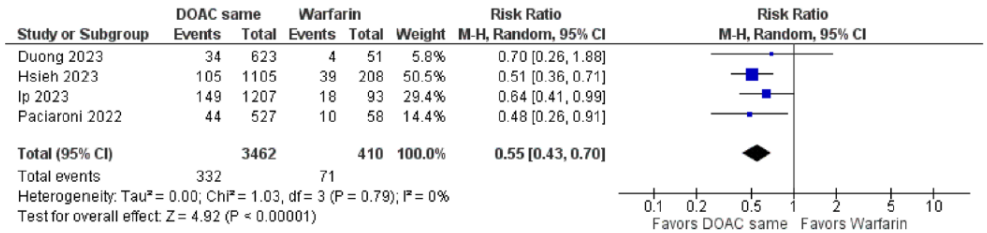
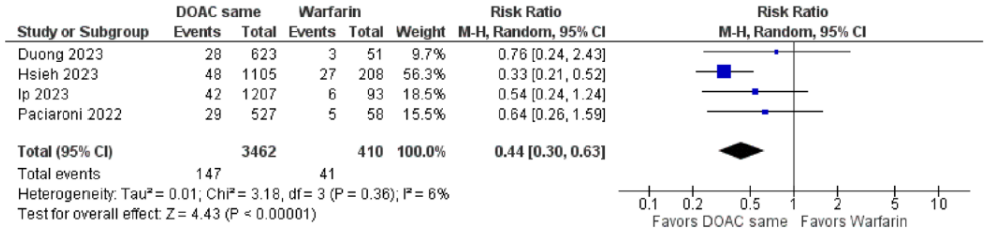
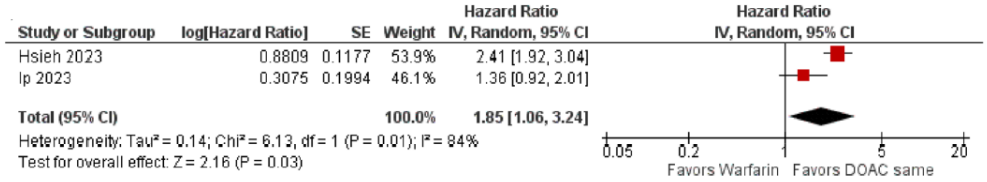
Meta-analysis: observational studies (no RCTs available)







Recurrent ischemic stroke:
45% reduction with DOAC vs. VKA

„Hemorrhagic events“:
56% reduction with DOAC vs. VKA

All-cause mortality:
46% reduction with DOAC vs. VKA

Mota Telles JP, et al. Int J Stroke. 2024 Aug 9:17474930241270443.

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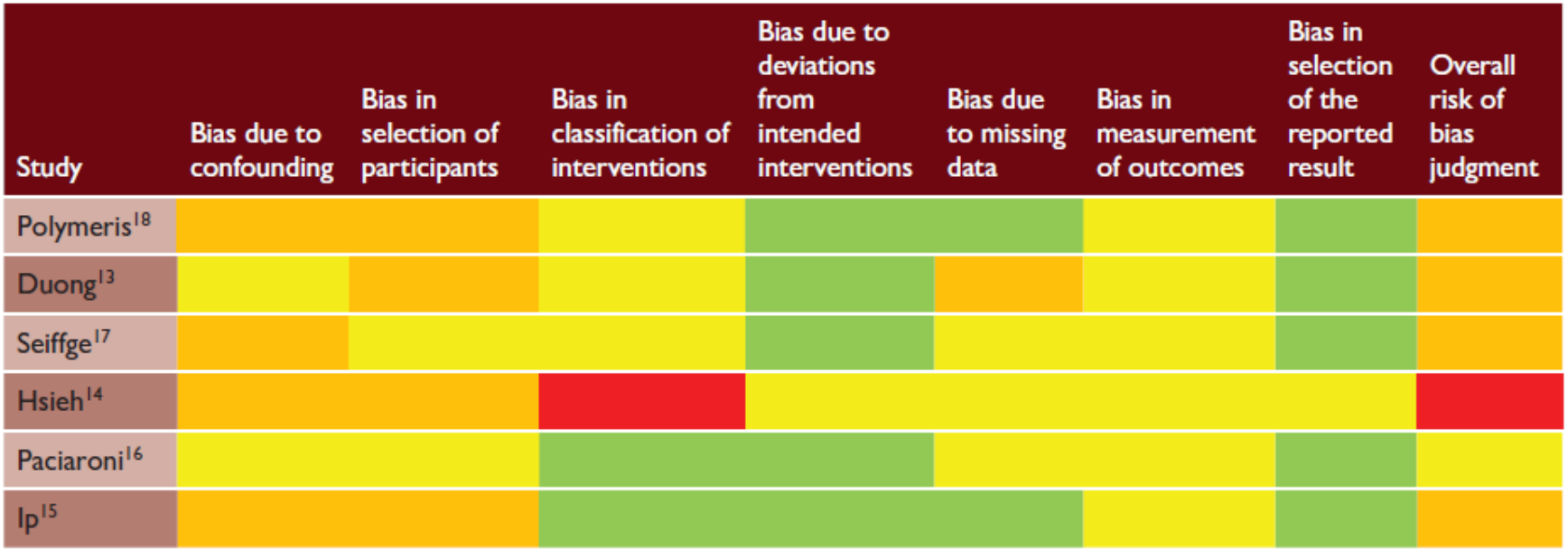
Limitations of available evidence: risk of bias

Meta-analysis: observational studies



Risk of bias summary for non-randomized studies (ROBINS-I):
Low; Moderate; Serious; Critical.

Mota Telles JP, et al. Int J Stroke. 2024 Aug 9:17474930241270443.

DOACs are inferior to VKA in select populations

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Randomized clinical trials

Clinical scenario	Trial (year)	Outcome	Patients with event on DOAC	Patients with event on VKA	Hazard ratio (95% CI)
Mechanical heart valve	RE-ALIGN[1] (2013)	Stroke	5.4%	0	Not estimable
	PROACT-Xa[2] (2023)	Stroke	3.3%	0	Not estimable
Antiphospholipid syndrome	TRAPS[3] (2018)	Stroke	6.8%	0	Not estimable
	Ordi-Ros et al.[4] (2019)	Stroke	9.5%	0	Not estimable
Rheumatic heart disease-associated AF	INVICTUS[5] (2022)	Stroke	3.7%	2.6%	1.54 (1.10-2.16)

[1] Eikelboom JW, et al. N Engl J Med. 2013 Sep 26;369(13):1206-14.
[2] Wang TY, et al. NEJM Evid. 2023; 2(7)
[3] Pengo V, et al. Blood. 2018 Sep 27;132(13):1365-1371.
[4] Ordi-Ros J, et al. Ann Intern Med. 2019 Nov 19;171(10):685-694.
[5] Connolly SJ, et al. N Engl J Med. 2022 Sep 15;387(11):978-988.

„Breakthrough stroke“ on a DOAC – another chance for VKA?

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Limitations of DOAC therapy

DOAC	VKA
• Fixed dosing for all patients – "one size fits all" • Absence of monitoring of adherence and anticoagulation effect • Single-factor inhibition • Short drug elimination half-lives combined with relatively long dosing intervals • Pharmacogenetic differences in DOAC metabolism	• Dose titration – optimal effect • Monitoring of adherence and anticoagulation effect • Multi-factor inhibition • Long half-lives

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SWITCH-AF –
VKA vs. DOAC after „breakthrough stroke“

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A randomized clinical trial

Multicenter, phase IV, prospective, randomized, open-label, two-arm study with blinded-endpoint evaluation

Hypothesis:

In patients with AF and breakthrough stroke on DOAC therapy, switching to a VKA, compared to DOAC of choice, reduces the risk of stroke or systemic embolism.

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SWITCH-AF –
VKA vs. DOAC after „breakthrough stroke“

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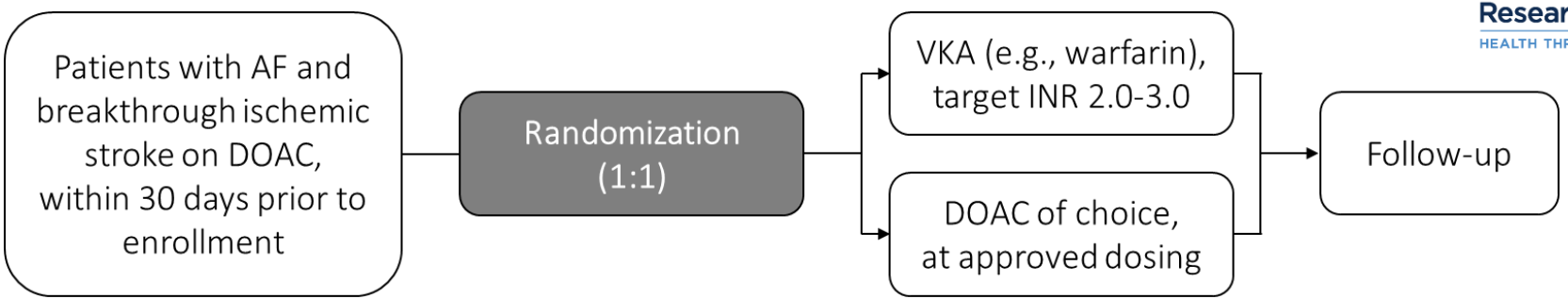
Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Design



N = approx. 3,500

Primary efficacy outcome:
Stroke or systemic embolism

Primary safety outcome:
ISTH major bleeding

Coordination: Population Health Research Institute, McMaster University, Hamilton, Canada

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SWITCH-AF –
VKA vs. DOAC after „breakthrough stroke“

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Eligibility criteria

Inclusion criteria:

1. Written informed consent provided.
2. Age >18 years.
3. Documented history of AF or atrial flutter.
4. Ischemic stroke while on a DOAC within 30 days prior to enrollment identified on imaging.
5. In the opinion of the investigator, it is safe to initiate oral anticoagulation with either a VKA or a DOAC within 48 hours of randomization.

Exclusion criteria:

1. There is strong evidence for the qualifying stroke event to be associated with permanent discontinuation of DOAC therapy (for any reason)
2. Patient is unable or unwilling to take oral anticoagulation
3. History of intracranial bleeding.
4. Patient is on chronic hemodialysis or likely to need renal replacement therapy during the course of the trial.

Summary

1. DOACs offer clear advantages over VKA therapy for most patients with AF.
2. Some patients suffer a „breakthrough stroke“ while on a DOAC
   → (very) high risk of recurrent stroke
3. The optimal treatment strategy after „breakthrough stroke“ on DOAC is uncertain.
4. Observational studies associating VKA use following „breakthrough stroke“ with large increases in adverse outcomes are at (serious) risk of bias.
5. A randomized trial of VKA vs. DOAC in this population is warranted and in preparation (SWITCH-AF).

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