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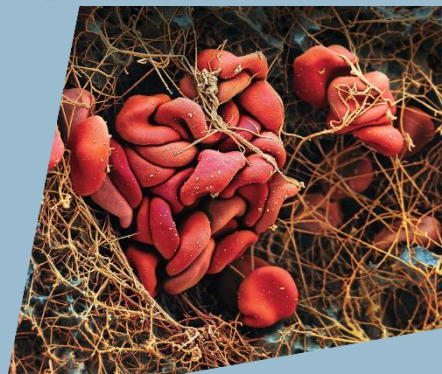
Antikoagulační terapie: Současný stav a budoucí vývoj

Miloš Táborský, Marián Fedorco

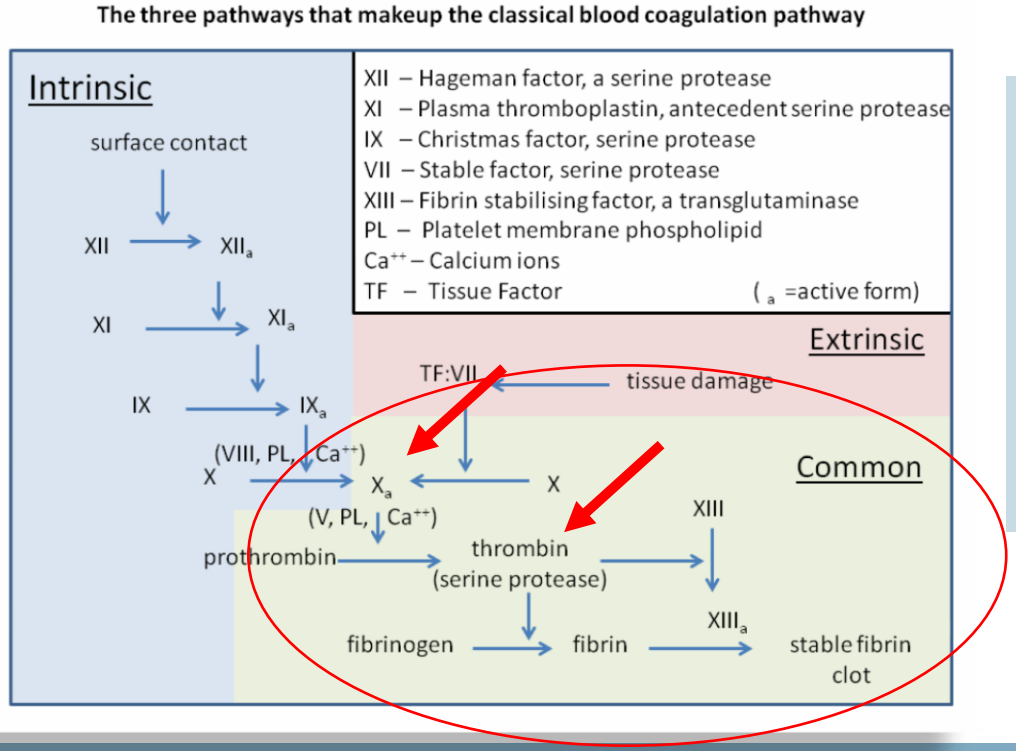
15.5.2023



Obecné principy

- Hemostáza – velmi sofistikovaný reparační mechanismus primárně sloužící k zástavě krvácení při poškození cévní stěny
- Hemostáza má vztah k ostatním reparačně-zánětlivým pochodům
- **Tři základní složky:** 1. Primární destičková hemostáza
  2. Hemokoagulace – koagul. kaskáda
  3. Vasokonstrikce

Koagulační kaskáda



Vnitřní cesta spouštěna: zánětlivé reparační pochody (TEN, sepse), stagnací krve (FS), kontaktem s cizím povrchem (mimotělní cirkulace, spojky aj.)

Vnější cesta spouštěna: poškozením tkání (úraz, operace, **ruptura plátu** a zánětlivě reparačními pochody (aktivace makrofágů, trombocytů apod.)

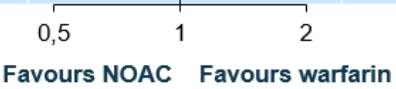
Proč hledat nové cesty antikoagulace

- U všech zavedených antikoagulačních terapií dominuje inhibice společné cesty koagulace
- Prakticky to znamená, že potlačujeme hemostázu aktivovanou jak vnitřní, tak vnější cestou
- Tlumit vnější cestu nemusí být vždy výhodné – vyšší riziko krvácení
- **Cíl – selektivní blokáda vnitřní cesty** – předpoklad snížení hemoragických komplikací

Co se potvrdilo za 10 let klinické praxe

Stroke/systemic embolism*

	NOAC events (%)#	Warfarin events (%)	RR (95% CI)	*p*-value
RE-LY (dabigatran)	134/6076 (2.2)	199/6022 (3.3)	0.66 (0.53–0.82)	0.0001
ROCKET AF (rivaroxaban)	269/7081 (3.8)	306/7090 (4.3)	0.88 (0.75–1.03)	0.12
ARISTOTLE (apixaban)	212/9120 (2.3)	265/9081 (2.9)	0.80 (0.67–0.95)	0.012
ENGAGE AF-TIMI 48 (edoxaban)	296/7035 (4.2)	337/7036 (4.8)	0.88 (0.75–1.02)	0.10
Combined (random)	**911/29,312 (3.1)**	**1107/29,229 (3.8)**	0.81 (0.73–0.91)	<0.0001



Major bleeding‡

?

	NOAC events (%)#	Warfarin events (%)	RR (95% CI)	*p*-value
RE-LY (dabigatran)	375/6076 (6.2)	397/6022 (6.6)	0.94 (0.82–1.07)	0.34
ROCKET AF (rivaroxaban)	395/7111(5.6)	386/7125 (5.4)	1.03 (0.90–1.18)	0.72
ARISTOTLE (apixaban)	327/9088 (3.6)	462/9052 (5.1)	0.71 (0.61–0.81)	<0.0001
ENGAGE AF-TIMI 48 (edoxaban)	444/7012 (6.3)	557/7012 (7.9)	0.80 (0.71–0.90)	0.0002
Combined (random)	**1541/29,287 (5.3)**	**1802/29,211 (6.2)**	0.86 (0.73–1.00)	0.06

Metaanalýza 4 studií

Jasná potřeba alternativní AK terapie

- **23%** of patients did not receive the correct label-recommended dose of NOAC according to a study of AF in the United Kingdom[2]
- Underdosing of NOACs is common due to concerns about bleeding[3]

- **~40%** of patients with AF in the GLORIA-AF antithrombotic treatment registry did not receive NOACs[4]

There remains a **medical need** for **alternative treatment options for AF** with an **improved safety profile** and **equivalent or superior efficacy** to current treatment options[1]

1. Weitz JL, Fredenburgh. Front Med (Lausanne) 2017;4:19; 2. García Rodríguez LA et al. BMJ Open 2019;9:e031341; 3. Suarez Fernandez C et al. J Comp Eff Res 2020;9:509–523; 4. Bayer V et al. J Am Heart Assoc 2022;11:e023907.

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I: Nová cesta: Inhibitory faktoru XI

Charakteristika základních představitelů inhibitorů faktoru XI

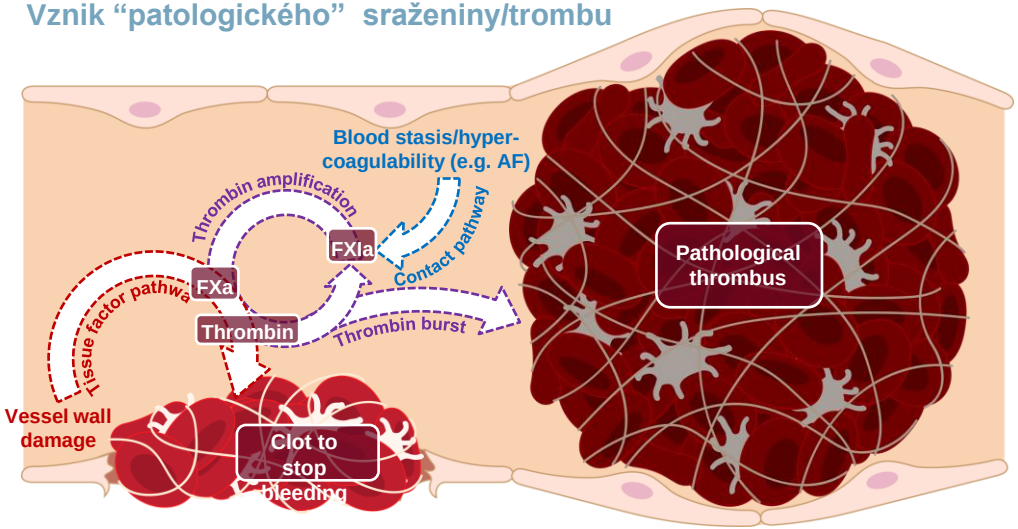
Inhibitory faktoru XI	Charakteristika
Monoklonální protilátky	
Abelacimab	Obě molekuly na bazi plně humánních monoklonálních protilátek
Osocimab	Nástup účinku do 1 hod, doba trvání účinku 4 týdny, aplikace s.c. 1x měsíčně, studie fáze III
Malomolekulární inhibitory (xiany)	
Asundexian	Malomolekulární selektivní inhibitor faktoru XIa
Milvexian	Nástup účinku do 1 hodiny, délka trvání účinku 24 hod, aplikace 1-2x denně p.o., studie fáze III
Inhibující oligonukleotidy typu ASO	
ISIS 416858	Inhibující ologonukleotid typu ASO snižující syntézu faktoru XI, délka trvání účinku 36 měsíců !

Asundexian inhibuje FXIa s očekávanou prevenci vzniku “patologického” trombu a zachováním normalní hemostázy [1–4]

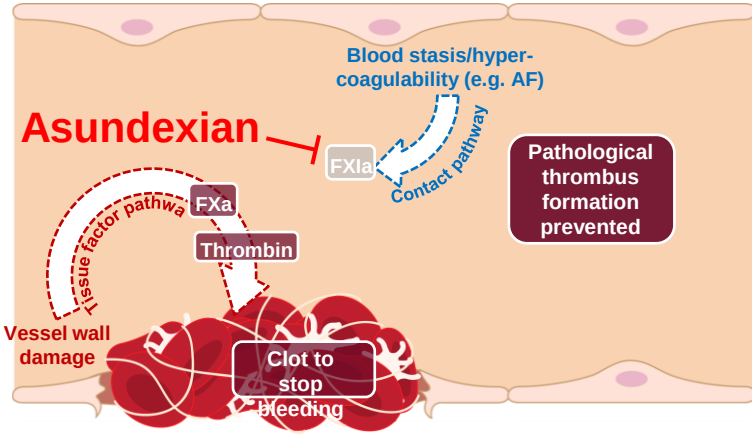
Mechanizmus účinku asundexianu

Pacienti s vysokým rizikem trombotické příhody

Vznik “patologického” sraženiny/trombu



Inhibice FXIa asundexianem



AF, atrial fibrillation; F, factor.

1. Piccini JP et al. Lancet 2022 (accepted); 2. Gailani D et al. J Thromb Haemost 2015;13:1383–1395; 3. Fredenburgh JC, Weitz JI. Hämostaseologie 2021;41:104–110; 4. Sohara H et al. J Am Coll Cardiol 1997;29:106–112.

PACIFIC AF Study

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators*

Summary

Background Direct-acting oral anticoagulant use for stroke prevention in atrial fibrillation is limited by bleeding concerns. Asundexian, a novel, oral small molecule activated coagulation factor XIa (FXIa) inhibitor, might reduce thrombosis with minimal effect on haemostasis. We aimed to determine the optimal dose of asundexian and to compare the incidence of bleeding with that of apixaban in patients with atrial fibrillation.

Methods In this randomised, double-blind, phase 2 dose-finding study, we compared asundexian 20 mg or 50 mg once daily with apixaban 5 mg twice daily in patients aged 45 years or older with atrial fibrillation, a CHA_2DS_2-VASc score of at least 2 if male or at least 3 if female, and increased bleeding risk. The study was conducted at 93 sites in 14 countries, including 12 European countries, Canada, and Japan. Participants were randomly assigned (1:1:1) to a treatment group using an interactive web response system, with randomisation stratified by whether patients were receiving a direct-acting oral anticoagulant before the study start. Masking was achieved using a double-dummy design, with participants receiving both the assigned treatment and a placebo that resembled the non-assigned treatment. The primary endpoint was the composite of major or clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis criteria, assessed in all patients who took at least one dose of study medication. This trial is registered with ClinicalTrials.gov, NCT04218266, and EudraCT, 2019-002365-35.

Findings Between Jan 30, 2020, and June 21, 2021, 862 patients were enrolled. 755 patients were randomly assigned to treatment. Two patients (assigned to asundexian 20 mg) never took any study medication, resulting in 753 patients being included in the analysis (249 received asundexian 20 mg, 254 received asundexian 50 g, and 250 received apixaban). The mean age of participants was 73·7 years (SD 8·3), 309 (41%) were women, 216 (29%) had chronic kidney disease, and mean CHA_2DS_2-VASc score was 3·9 (1·3). Asundexian 20 mg resulted in 81% inhibition of FXIa activity at trough concentrations and 90% inhibition at peak concentrations; asundexian 50 mg resulted in 92% inhibition at trough concentrations and 94% inhibition at peak concentrations. Ratios of incidence proportions for the primary endpoint were 0·50 (90% CI 0·14–1·68) for asundexian 20 mg (three events), 0·16 (0·01–0·99) for asundexian 50 mg (one event), and 0·33 (0·09–0·97) for pooled asundexian (four events) versus apixaban (six events). The rate of any adverse event occurring was similar in the three treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban.

Interpretation The FXIa inhibitor asundexian at doses of 20 mg and 50 mg once daily resulted in lower rates of bleeding compared with standard dosing of apixaban, with near-complete in-vivo FXIa inhibition, in patients with atrial fibrillation.

Published Online
April 3, 2022
https://doi.org/10.1016/S0140-6736(22)00456-1

See Online/Comment
https://doi.org/10.1016/S0140-6736(22)00563-3

*The PACIFIC-AF Investigators are listed in full in the appendix (pp 3–10)

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I. INTERNÍ KLINIKA KARDIOLOGICKÁ
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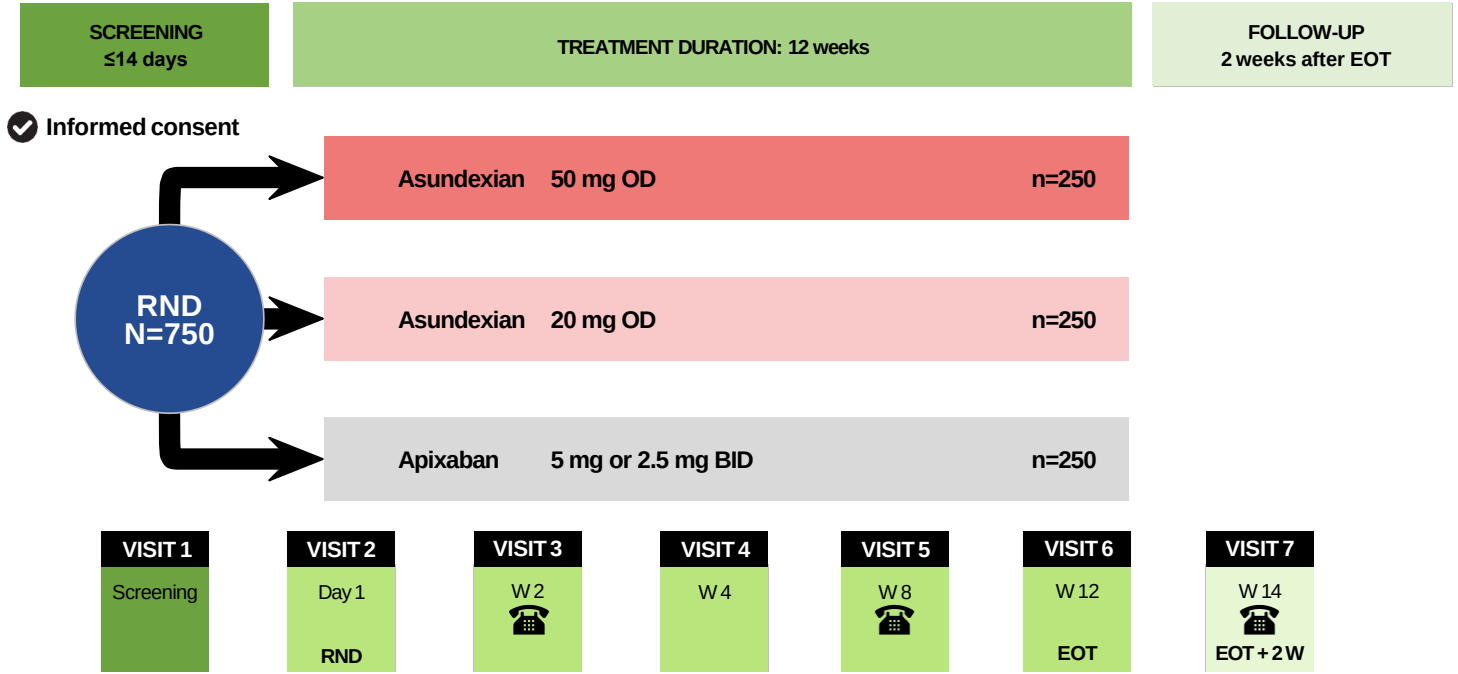
PACIFIC-AF testovala bezpečnostní profil a dávku Asundexianu Vs Apixaban u pacientů s FS

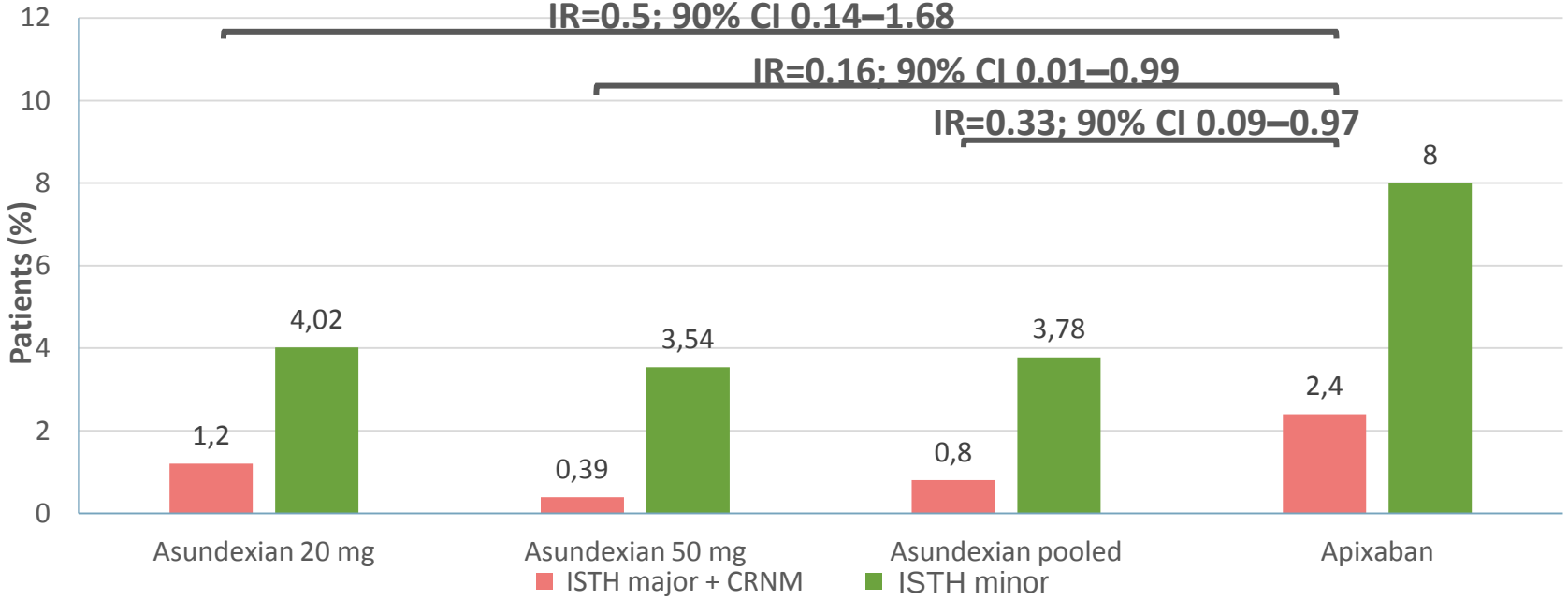


Randomization was stratified based on whether participants received a NOAC before study start or were not treated with any oral anticoagulant

AF, atrial fibrillation; BID, twice daily; EOT, end of treatment; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily; RND, randomization; W, week.
Piccini JP et al. Lancet 2022 (accepted).

Asundexian snížil počet krvácivých příhod Vs Apixaban při téměř úplné inhibici FXIa*

Primary safety outcome: Composite of ISTH major or CRNM bleeding



No ISTH major bleeding occurred in any treatment arm.
**Asundexian reduced FXI levels by ≥90% at peak concentration. CRNM, clinically relevant non-major; IR, ratio of incidence proportions; ISTH, International Society on Thrombosis and Haemostasis. Piccini JP et al. Lancet 2022*

PACIFIC – Stroke Study

Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke (PACIFIC-Stroke): an international, randomised, double-blind, placebo-controlled, phase 2b trial

Ashkan Shoamanesh, Hardi Mundl, Eric E Smith, Jaime Masjuan, Ivan Milanov, Teruyuki Hirano, Alina Agafina, Bruce Campbell, Valeria Caso, Jean-Louis Mas, Qiang Dong, Peter Turcani, Hanne Christensen, Jose M Ferro, Roland Veltkamp, Robert Mikulik, Gian Marco De Marchis, Thompson Robinson, Robin Lemmens, Adam Stepien, Stefan Greisenegger, Risto Roine, Laszlo Csiba, Pooja Khatri, Jonathan Coutinho, Arne G Lindgren, Andrew M Demchuk, Pablo Colorado, Bodo Kirsch, Christoph Neumann, Laura Heenan, Lizhen Xu, Stuart J Connolly, Robert G Hart, for the PACIFIC-Stroke Investigators

Summary

Background Asundexian (Bayer AG, Leverkusen, Germany), an oral small molecule factor XIa (FXIa) inhibitor, might prevent thrombosis without increasing bleeding. Asundexian's effect for secondary prevention of recurrent stroke is unknown.

Methods In this randomised, double-blind, placebo-controlled, phase 2b dose-finding trial (PACIFIC-Stroke), patients with acute (within 48 h) non-cardioembolic ischaemic stroke were recruited from 196 hospitals in 23 countries. Patients were eligible if they were aged 45 years or older, to be treated with antiplatelet therapy, and able to have a baseline MRI (either before or within 72 h of randomisation). Eligible participants were randomly assigned (1:1:1:1), using an interactive web-based response system and stratified according to anticipated antiplatelet therapy (single *vs* dual), to once daily oral asundexian (BAY 2433334) 10 mg, 20 mg, or 50 mg, or placebo in addition to usual antiplatelet therapy, and were followed up during treatment for 26–52 weeks. Brain MRIs were obtained at study entry and at 26 weeks or as soon as possible after treatment discontinuation. The primary efficacy outcome was the dose–response effect on the composite of incident MRI-detected covert brain infarcts and recurrent symptomatic ischaemic stroke at or before 26 weeks after randomisation. The primary safety outcome was major or clinically relevant non-major bleeding as defined by International Society on Thrombosis and Haemostasis criteria. The efficacy outcome was assessed in all participants assigned to treatment, and the safety outcome was assessed in all participants who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT04304508, and is now complete.

Findings Between June 15, 2020, and July 22, 2021, 1880 patients were screened and 1808 participants were randomly assigned to asundexian 10 mg (n=455), 20 mg (n=450), or 50 mg (n=447), or placebo (n=456). Mean age was 67 years (SD 10) and 615 (34%) participants were women, 1193 (66%) were men, 1505 (83%) were White, and 268 (15%) were Asian. The mean time from index stroke to randomisation was 36 h (SD 10) and median baseline National Institutes of Health Stroke Scale score was 2·0 (IQR 1·0–4·0). 783 (43%) participants received dual antiplatelet treatment for a mean duration of 70·1 days (SD 113·4) after randomisation. At 26 weeks, the primary efficacy outcome was observed in 87 (19%) of 456 participants in the placebo group versus 86 (19%) of 455 in the asundexian 10 mg group (crude incidence ratio 0·99 [90% CI 0·79–1·24]), 99 (22%) of 450 in the asundexian 20 mg group (1·15 [0·93–1·43]), and 90 (20%) of 447 in the asundexian 50 mg group (1·06 [0·85–1·32]; t statistic −0·68; p=0·80). The primary safety outcome was observed in 11 (2%) of 452 participants in the placebo group versus 19 (4%) of 445 in the asundexian 10 mg group, 14 (3%) of 446 in the asundexian 20 mg group, and 19 (4%) of 443 in the asundexian 50 mg group (all asundexian doses pooled *vs* placebo hazard ratio 1·57 [90% CI 0·91–2·71]).

Interpretation In this phase 2b trial, FXIa inhibition with asundexian did not reduce the composite of covert brain infarction or ischaemic stroke and did not increase the composite of major or clinically relevant non-major bleeding compared with placebo in patients with acute, non-cardioembolic ischaemic stroke.

Published Online September 2, 2022 https://doi.org/10.1016/S0140-6736(22)01588-4

See Online/Comment https://doi.org/10.1016/S0140-6736(22)01703-2

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www.thelancet.com Published online September 2, 2022
https://doi.org/10.1016/S0140-6736(22)01588-4

Klinické efekty u pacientů s CMP

	Placebo (n=456)	Asundexian 10 mg group (n=455)	Asundexian 10 mg *vs* placebo	Asundexian 20 mg group (n=450)	Asundexian 20 mg *vs* placebo	Asundexian 50 mg group (n=447)	Asundexian 50 mg *vs* placebo
Primary outcome							
Ischaemic stroke or covert infarcts*	87 (19%)	86 (19%)	0·99 (0·79–1·24)	99 (22%)	1·15 (0·93–1·43)	90 (20%)	1·06 (0·85–1·32)
Secondary outcomes							
Components of the primary outcome*							
Incident covert brain infarcts on MRI†	64 (14%)	63 (14%)	0·99 (0·75–1·30)	74 (16%)	1·17 (0·90–1·51)	74 (17%)	1·17 (0·91–1·52)
Recurrent symptomatic ischaemic stroke*	23 (5%)	24 (5%)	1·05 (0·66–1·67)	25 (6%)	1·10 (0·69–1·75)	17 (4%)	0·75 (0·45–1·26)
Efficacy outcomes‡							
Recurrent symptomatic ischaemic stroke§	28 (6%)	26 (6%)	0·93 (0·59–1·45)	26 (6%)	0·94 (0·60–1·47)	22 (5%)	0·80 (0·50–1·27)
Any recurrent stroke§	30 (7%)	26 (6%)	0·86 (0·56–1·34)	26 (6%)	0·88 (0·56–1·36)	25 (6%)	0·85 (0·54–1·32)
Disabling stroke (mRS score of ≥4)§	3 (1%)	5 (1%)	1·67 (0·50–5·55)	5 (1%)	1·69 (0·51–5·62)	1 (<1%)	0·34 (0·05–2·27)
Recurrent symptomatic ischaemic stroke, vascular death, or myocardial infarction§	35 (8%)	33 (7%)	0·94 (0·63–1·40)	30 (7%)	0·87 (0·58–1·30)	33 (7%)	0·96 (0·64–1·43)
Recurrent symptomatic ischaemic stroke, incident covert brain infarct on MRI, cardiovascular death, myocardial infarction and systemic embolism*	79 (17%)	80 (18%)	0·95 (0·76–1·20)	87 (19%)	1·06 (0·85–1·33)	81 (18%)	1·03 (0·82–1·30)
All-cause mortality§	10 (2%)	10 (2%)	1·00 (0·48–2·09)	6 (1%)	0·60 (0·26–1·41)	17 (4%)	1·72 (0·89–3·32)
Post-hoc exploratory outcomes‡							
Transient ischaemic attack	11 (2%)	10 (2%)	0·91 (0·44–1·87)	2 (<1%)	0·18 (0·05–0·64)	2 (<1%)	0·18 (0·05–0·65)
Recurrent symptomatic ischaemic stroke or transient ischaemic attack	38 (8%)	35 (8%)	0·92 (0·63–1·35)	28 (6%)	0·74 (0·49–1·12)	24 (5%)	0·64 (0·41–0·98)

Data are n (%) or hazard ratio with 90% CI in parentheses, or crude incidence ratio with 90% CI in parentheses. The cause-specific Cox proportional hazard model is modelled on the basis of the time to first occurrence of the event. The independent variable is treatment. Hazard ratios are calculated separately for all comparisons. mRS=modified Rankin Scale. *Proportion of outcomes at 26 weeks and accompanying crude incidence ratios for these binary event outcomes are presented. †Incident covert brain infarct data missing in 352 patients and imputed in patients who did not otherwise meet the primary efficacy outcome based on having a symptomatic recurrent ischemic stroke. ‡Hazard ratios calculated using Cox proportional hazard model are presented. §Proportion of outcomes at end study.

www.thelancet.com Published online September 2, 2022
https://doi.org/10.1016/S0140-6736(22)01588-4

PACIFIC-AMI Study

Circulation
Volume 146, Issue 16, 18 October 2022; Pages 1196-1206
https://doi.org/10.1161/CIRCULATIONAHA.122.061612

ORIGINAL RESEARCH ARTICLE

A Multicenter, Phase 2, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Finding Trial of the Oral Factor XIa Inhibitor Asundexian to Prevent Adverse Cardiovascular Outcomes After Acute Myocardial Infarction

Editorial, see p 1207

Sunil V. Rao, MD, Bodo Kirsch, MSc, Deepak L. Bhatt, MD, MPH, Andrzej Budaj, MD, PhD, Rosa Coppolecchia, DO, MPH, John Eikelboom, MBBS, MSc, Stefan K. James, MD, PhD, W. Schuyler Jones, MD, Bela Merkely, MD, PhD, MSc, DSc, Lars Keller, MD, Renicus S. Hermanides, MD, PhD, Gianluca Campo, MD, José Luis Ferreiro, MD, PhD, Taro Shibasaki, MD, Hardi Mundl, MD, and John H. Alexander, MD, MHS

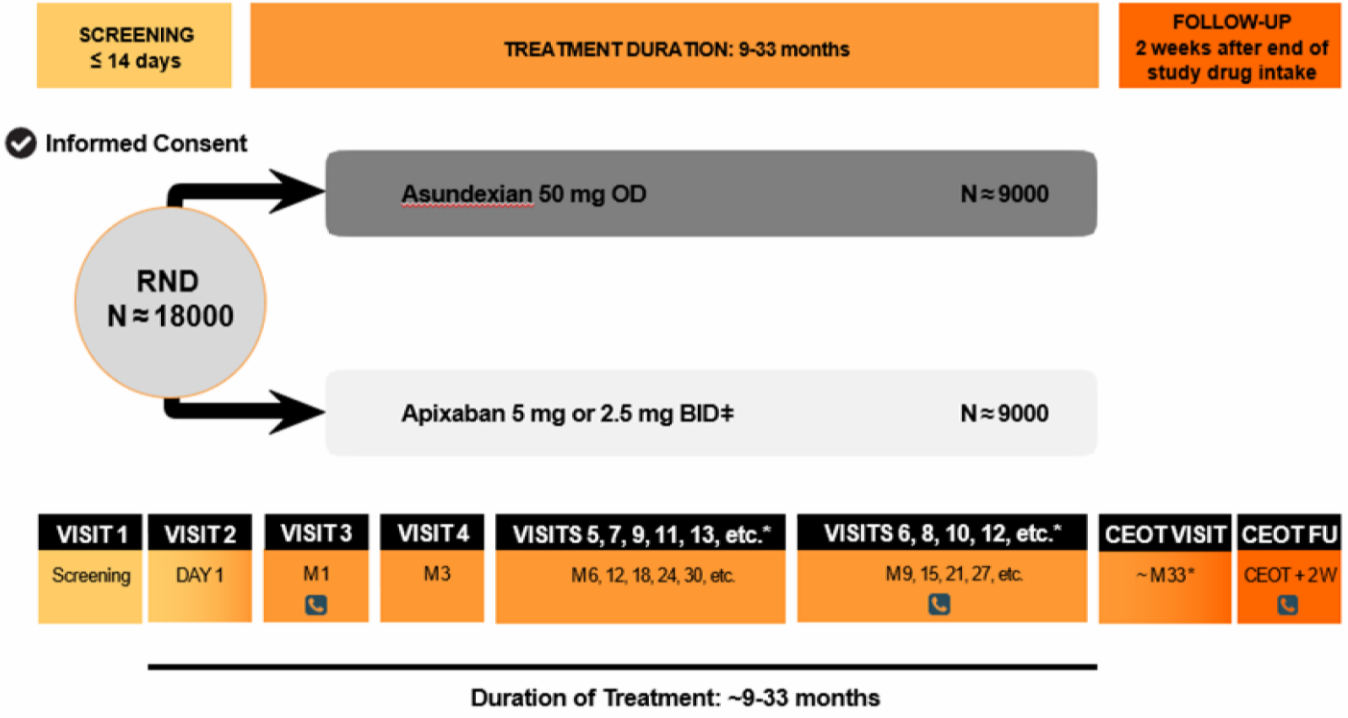
Rao SV.10.1161/CirculationAHA.122.061612.

Efektivita a bezpečnost asundexianu u pacientů s AMI

	Asundexian 10 mg (N=395)	Asundexian 20 mg (N=397)	Asundexian 50 mg (N=402)	Asundexian Total (N=1194)	Placebo (N=399)	Total (N=1593)
Safety outcomes						
BARC bleeding type 2, 3, or 5	30 (7.59%)	32 (8.06%)	42 (10.45%)	104 (8.71%)	36 (9.02%)	140 (8.79%)
Type 2	27 (6.84%)	29 (7.30%)	39 (9.70%)	95 (7.96%)	31 (7.77%)	126 (7.91%)
Type 3	5 (1.27%)	3 (0.76%)	3 (0.75%)	11 (0.92%)	5 (1.25%)	16 (1.00%)
Type 5	0	0	0	0	0	0
All bleeding	70 (17.72%)	75 (18.89%)	82 (20.40%)	227 (19.01%)	85 (21.30%)	312 (19.59%)
	Asundexian 10 mg (N=397)	**Asundexian 20 mg (N=401)**	**Asundexian 50 mg (N=402)**	**Asundexian 20 mg + 50 mg (N=803)**	**Placebo (N=401)**	**Total (N=1601)**
Efficacy outcomes*						
CV death, MI, stroke, or stent thrombosis	27 (6.80%)	24 (5.99%)	22 (5.47%)	46 (5.73%)	22 (5.49%)	95 (5.93%)
CV death	7 (1.76%)	4 (1.00%)	5 (1.24%)	9 (1.12%)	2 (0.50%)	18 (1.12%)
MI	18 (4.53%)	20 (4.99%)	18 (4.48%)	38 (4.73%)	17 (4.24%)	73 (4.56%)
Stroke	4 (1.01%)	3 (0.75%)	0	3 (0.37%)	2 (0.50%)	9 (0.56%)
Ischemic stroke	4 (1.01%)	2 (0.50%)	0	2 (0.25%)	2 (0.50%)	8 (0.50%)
Hemorrhagic stroke	0	1 (0.25%)	0	1 (0.12%)	0	1 (0.06%)
Stent thrombosis	4 (1.01%)	5 (1.25%)	4 (1.00%)	9 (1.12%)	4 (1.00%)	17 (1.06%)
All-cause mortality	10 (2.52%)	7 (1.75%)	10 (2.49%)	17 (2.12%)	7 (1.75%)	34 (2.12%)

Rao SV.10.1161/CirculationAHA.122.061612.

OCEANIC-AF Study



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II: Další novinky v oblasti antikoagulační terapie

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1. Antikoagulační léčba po TAVI

Tři základní studie s TAVI a AK terapií

	Patient Ages at Baseline	
ENVISAGE-TAVI AF*	Edoxaban 82.1 ± 5.4 years	VKA 82.1 ± 5.5 years
ATLANTIS†	Apixaban 81.6 ± 6.1 years	Standard-of care 82.3 ± 6.4 years
GALILEO‡	Rivaroxaban 80.4 ± 7.1 years	Antiplatelet 80.8 ± 6.0 years

Současná doporučení ESC

Recommendations	Class*	Level†
OAC is recommended lifelong for TAVI patients who have other indications for OAC.	I	B
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.	I	A
Routine use of OAC is not recommended after TAVI in patients with no baseline indication for OAC.	III	B

Vahanian A. Eur Heart J 2022, 43:561-563.

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2. Je NOAC (rivaroxaban) indikován v léčbě FS u pacientů revmatickým postižením srdce?

ORIGINAL ARTICLE

Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

S.J. Connolly, G. Karthikeyan, M. Ntsekhe, A. Haileamlak, A. El Sayed, A. El Ghamrawy, A. Damasceno, A. Avezum, A.M.L. Dans, B. Gitura, D. Hu, E.R. Kamanzi, F. Maklady, G. Fana, J.A. Gonzalez-Hermosillo, J. Musuku, K. Kazmi, L. Zühlke, L. Gondwe, C. Ma, M. Paniagua, O.S. Ogah, O.J. Molefe-Baikai, P. Lwabi, P. Chillo, S.K. Sharma, T.T.J. Cabral, W.M. Tarhuni, A. Benz, M. van Eikels, A. Krol, D. Pattath, K. Balasubramanian, S. Rangarajan, C. Ramasundarahettige, B. Mayosi,* and S. Yusuf, for the INVICTUS Investigators†

ABSTRACT

BACKGROUND

Testing of factor Xa inhibitors for the prevention of cardiovascular events in patients with rheumatic heart disease–associated atrial fibrillation has been limited.

METHODS

We enrolled patients with atrial fibrillation and echocardiographically documented rheumatic heart disease who had any of the following: a CHA_2DS_2VASc score of at least 2 (on a scale from 0 to 9, with higher scores indicating a higher risk of stroke), a mitral-valve area of no more than 2 cm^2, left atrial spontaneous echo contrast, or left atrial thrombus. Patients were randomly assigned to receive standard doses of rivaroxaban or dose-adjusted vitamin K antagonist. The primary efficacy outcome was a composite of stroke, systemic embolism, myocardial infarction, or death from vascular (cardiac or noncardiac) or unknown causes. We hypothesized that rivaroxaban therapy would be noninferior to vitamin K antagonist therapy. The primary safety outcome was major bleeding according to the International Society of Thrombosis and Hemostasis.

RESULTS

Of 4565 enrolled patients, 4531 were included in the final analysis. The mean age of the patients was 50.5 years, and 72.3% were women. Permanent discontinuation of trial medication was more common with rivaroxaban than with vitamin K antagonist therapy at all visits. In the intention-to-treat analysis, 560 patients in the rivaroxaban group and 446 in the vitamin K antagonist group had a primary-outcome event. Survival curves were nonproportional. The restricted mean survival time was 1599 days in the rivaroxaban group and 1675 days in the vitamin K antagonist group (difference, –76 days; 95% confidence interval [CI], –121 to –31; P<0.001). A higher incidence of death occurred in the rivaroxaban group than in the vitamin K antagonist group (restricted mean survival time, 1608 days vs. 1680 days; difference, –72 days; 95% CI, –117 to –28). No significant between-group difference in the rate of major bleeding was noted.

CONCLUSIONS

Among patients with rheumatic heart disease–associated atrial fibrillation, vitamin K antagonist therapy led to a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding. (Funded by Bayer; INVICTUS ClinicalTrials.gov number, NCT02832544.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Connolly can be contacted at connostu@phri.ca or at the Population Health Research Institute, 30 Birge St., Hamilton, ON L8L 0A6, Canada.

*Deceased.

†A complete list of the INVICTUS investigators is provided in the Supplementary Appendix, available at NEJM.org.

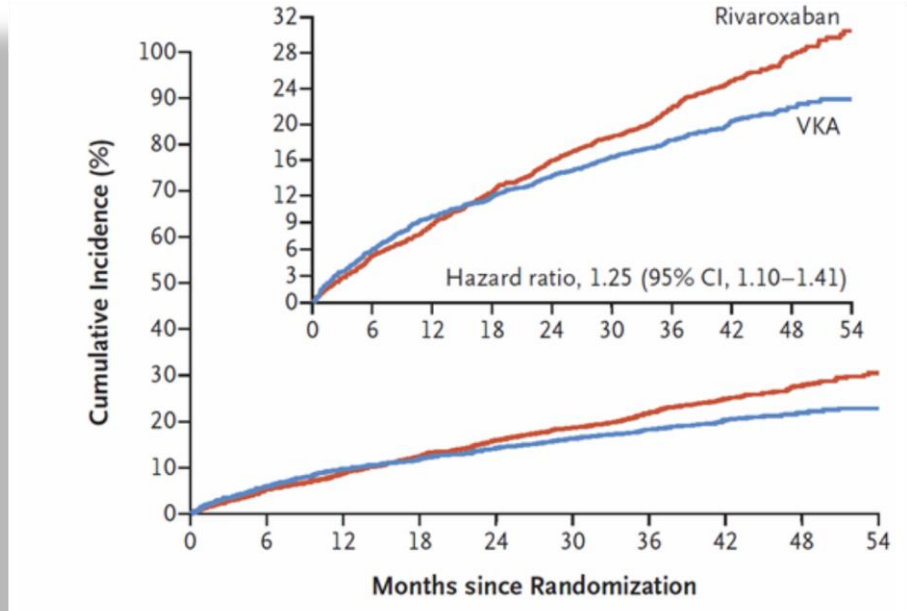
This article was published on August 28, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2209051

Conolly S J. New Engl J Med 2022:387: 978-88.

Cumulative Incidence of the Composite of Stroke, Systemic Embolism, Myocardial Infarction, or Death from Vascular or Unknown Causes (Primary Outcome)

Rivaroxaban vs. warfarin



Conolly S J. New Engl J Med 2022:387: 978-88.

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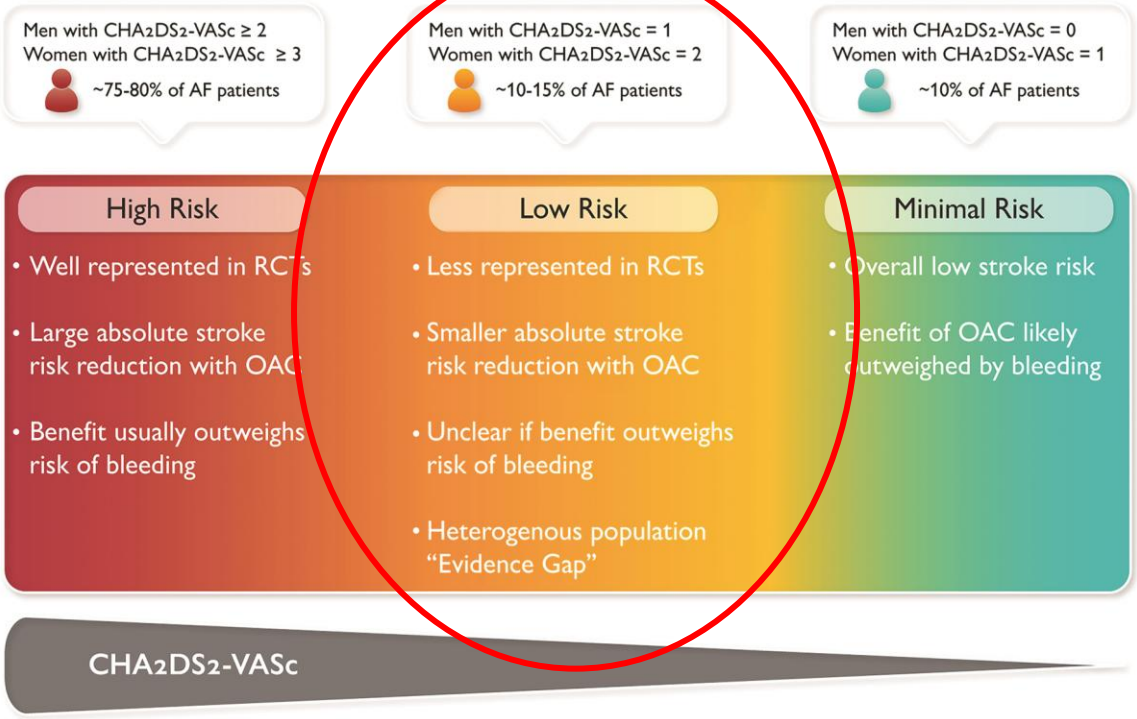
3. Manažment antikoagulační léčby u pacientů s nízko rizikovou FS

Riziko CMP a potencionální benefit orální AK terapie u pacientů s FS a nízkým TE rizikem v závislosti na CHA2DS2VASc skore



Eur Heart J, Volume 43, Issue 37, 1 October 2022, Pages 3539–3541, https://doi.org/10.1093/eurheartj/ehac099

Oral anticoagulants in patients with atrial fibrillation at low stroke risk: a multicentre observational study

Joris J. Komen [1,2], Anton Pottegård [3], Aukje K. Mantel-Teeuwisse [1], Tomas Forslund [2,4], Paul Hjemdahl [4], Björn Wettermark[5], Jesper Hallas [3], Morten Olesen [3], Marion Bennie [6,7], Tanja Mueller [6], Raymond Carragher [6], Øystein Karlstad [8], Lars J. Kjerpeseth [8], and Olaf H. Klungel [1,3]*

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Received 8 February 2021; revised 30 January 2022; accepted 15 February 2022; online publish-ahead-of-print 10 March 2022

See the editorial comment for this article 'Atrial fibrillation and stroke: who is low risk and what are we going to do about it?', by W.F. McIntyre and D. Linz, https://doi.org/10.1093/eurheartj/ehac099.

Abstract

Aims There is currently no consensus on whether atrial fibrillation (AF) patients at low risk for stroke (one non-sex-related CHA_2DS_2-VASc point) should be treated with an oral anticoagulant.

Methods and results We conducted a multi-country cohort study in Sweden, Denmark, Norway, and Scotland. In total, 59 076 patients diagnosed with AF at low stroke risk were included. We assessed the rates of stroke or major bleeding during treatment with a non-vitamin K antagonist oral anticoagulant (NOAC), a vitamin K antagonist (VKA), or no treatment, using inverse probability of treatment weighted (IPTW) Cox regression. In untreated patients, the rate for ischaemic stroke was 0.70 per 100 person-years and the rate for a bleed was also 0.70 per 100 person-years. Comparing NOAC with no treatment, the stroke rate was lower [hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.56–0.94], and the rate for intracranial haemorrhage (ICH) was not increased (HR 0.84; 95% CI 0.54–1.30). Comparing VKA with no treatment, the rate for stroke tended to be lower (HR 0.81; 95% CI 0.59–1.09), and the rate for ICH tended to be higher during VKA treatment (HR 1.37; 95% CI 0.88–2.14). Comparing NOAC with VKA treatment, the rate for stroke was similar (HR 0.92; 95% CI 0.70–1.22), but the rate for ICH was lower during NOAC treatment (HR 0.63; 95% CI 0.42–0.94).

Conclusion These observational data suggest that NOAC treatment may be associated with a positive net clinical benefit compared with no treatment or VKA treatment in patients at low stroke risk, a question that can be tested through a randomized controlled trial.

Stratifikované závěry studie

	NOAC vs. no treatment	*P* for interaction	VKA vs. no treatment	*P* for interaction	NOAC vs. VKA	*P* for interaction
Stroke		0.591		0.140		0.071
Female	0.65 (0.43–0.98)		1.06 (0.67–1.68)		0.68 (0.44–1.06)	
Male	0.57 (0.29–1.13)		0.68 (0.46–1.00)		1.15 (0.80–1.66)	
Bleed		0.179		0.877		0.337
Female	1.54 (1.07–2.22)		1.37 (0.89–2.11)		0.98 (0.67–1.42)	
Male	1.12 (0.84–1.49)		1.43 (1.06–1.93)		0.78 (0.6–1.02)	
Stroke		0.984		0.979		0.404
<65 years	0.58 (0.26–1.30)		0.81 (0.49–1.36)		1.15 (0.67–1.95)	
≥65	0.73 (0.54–1.00)		0.81 (0.56–1.16)		0.88 (0.63–1.22)	
Stroke		0.784		0.570		0.398
Has low	0.73 (0.53–1.01)		0.87 (0.60–1.26)		0.84 (0.60–1.19)	
Has high	0.50 (0.22–1.13)		0.73 (0.44–1.20)		1.08 (0.68–1.73)	
Bleed		0.815		0.172		0.270
Has low	1.25 (0.92–1.70)		1.62 (1.17–2.24)		0.77 (0.58–1.01)	
Has high	1.19 (0.85–1.65)		1.08 (0.54–2.14)		0.98 (0.70–1.38)	

Observační data ukazují, že léčba NOAK může mít u pacientů s FS a nízkým rizikem TE komplikací pozitivní klinický benefit ve srovnání v terapii warafarinem.

Komen J J. European Heart Journal (2022) 43, 3528–3538

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4. Trojitá léčba pacientů s FS podstupující PCI – jak dlouho ?

Pouze týden nebo delší dobu ???

Default duration of triple antithrombotic therapy should be one week

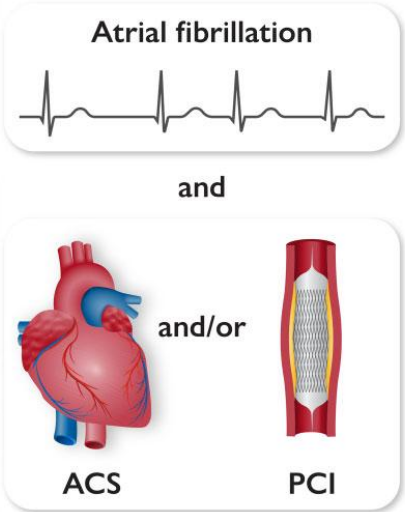
Pro

Five major trials in this field including almost 12,000 patients showed that 1-week TT followed by OAC plus SAPT reduced bleeding with a similar rate of ischaemic events compared with 6-12 months TT

The number of patients enrolled in these 5 trials and the trials' cumulative results exclude an absolute risk increase of ischaemic events > 1.4% for 1-week vs long-term TT and show an absolute risk reduction > 8% for bleeding

No subgroup has been shown to benefit from long-term TT

Reducing bleeding has important benefits for patients' quality of life and ability to avoid hospitalizations



Contra

The abrupt shortening of TT duration by guidelines from 6 months to one week stems from the evidence of RCTs which, however, have important limitations

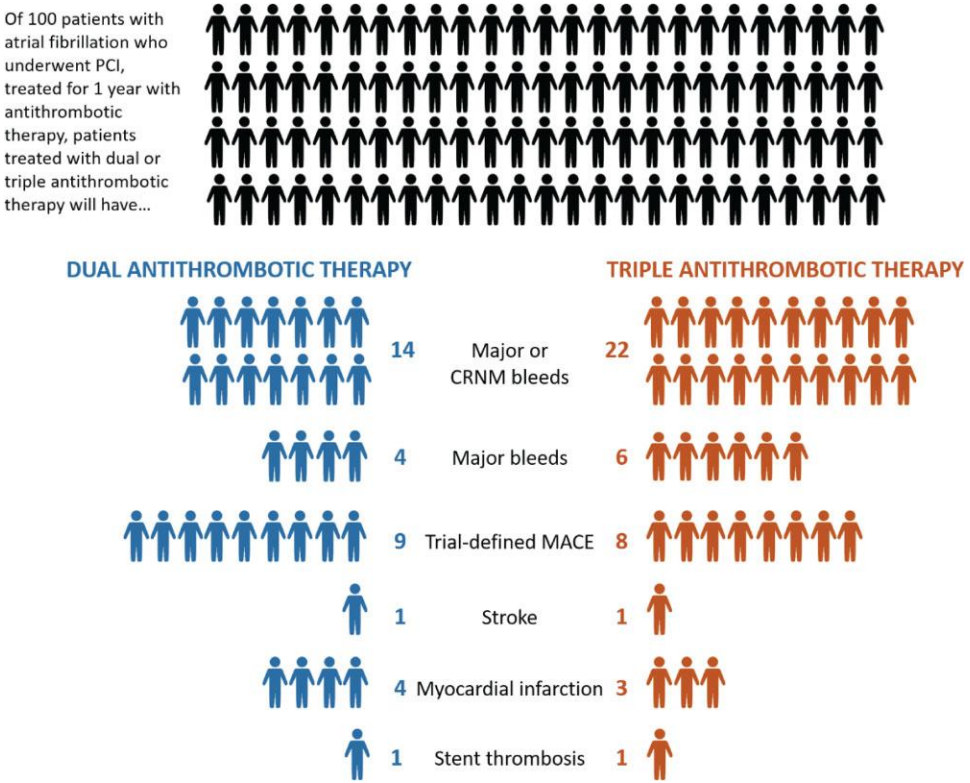
1-week TT is associated with increased risk of ischaemic events, which may be of concern particularly among high-ischaemic risk subgroups of patients such as those with ACS or complex PCI

The increased risk of bleeding conferred by TT is counterbalanced by a reduction of ischaemic events up to 30 days after PCI/ACS

The need for more personalized antithrombotic regimens prevents from recommending a 1-week TT for the majority of patients

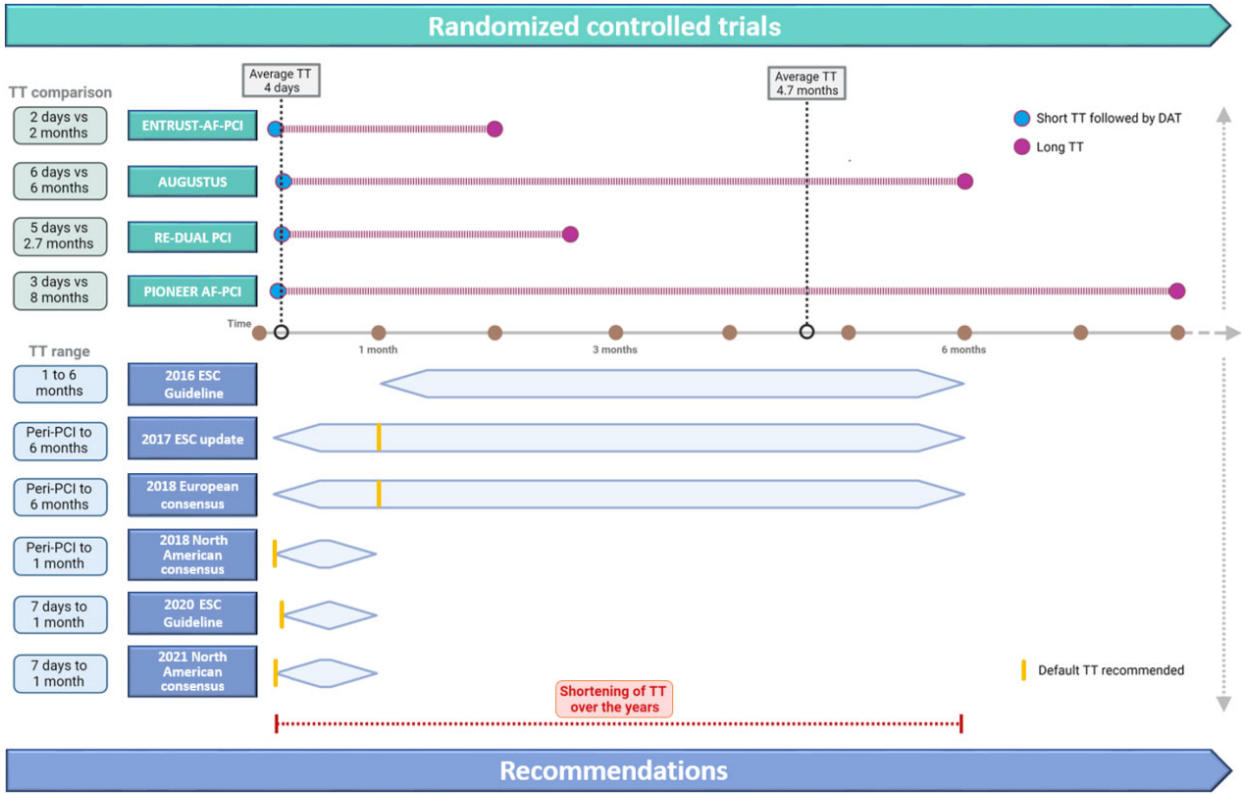
De Caterina R. European Heart Journal (2022) 43, 3512–3527

Pro zkrácení doby TT



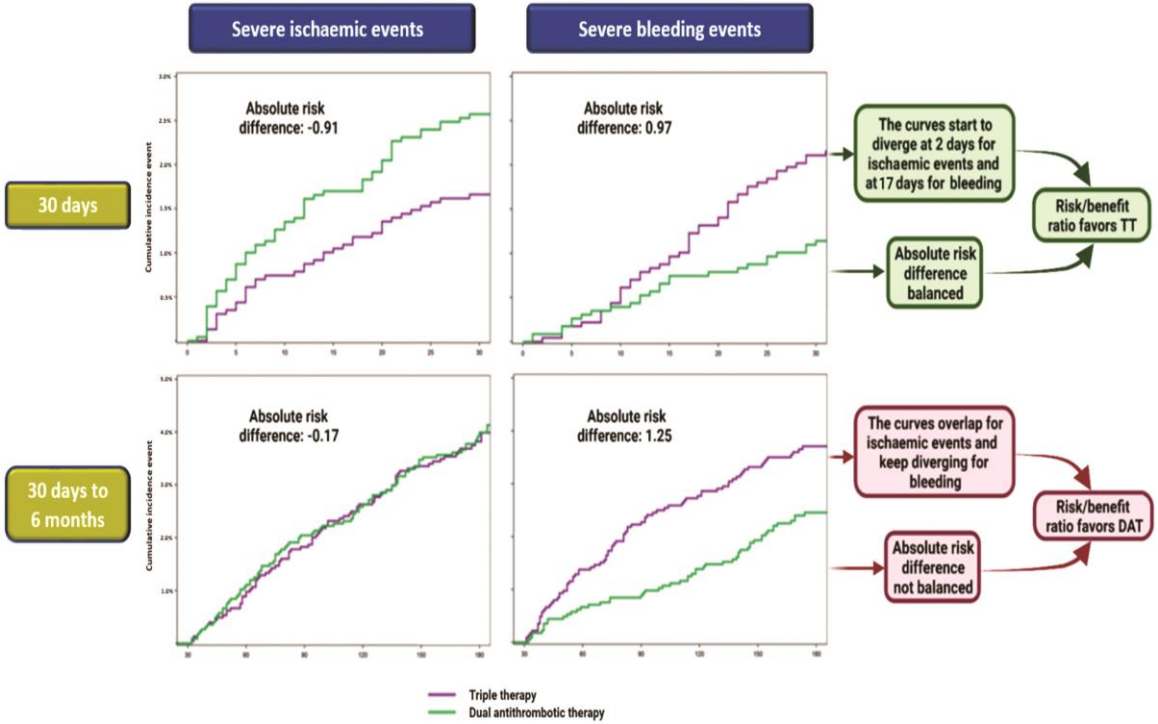
De Caterina R. European Heart Journal (2022) 43, 3512–3527

Proti zkrácení doby TT



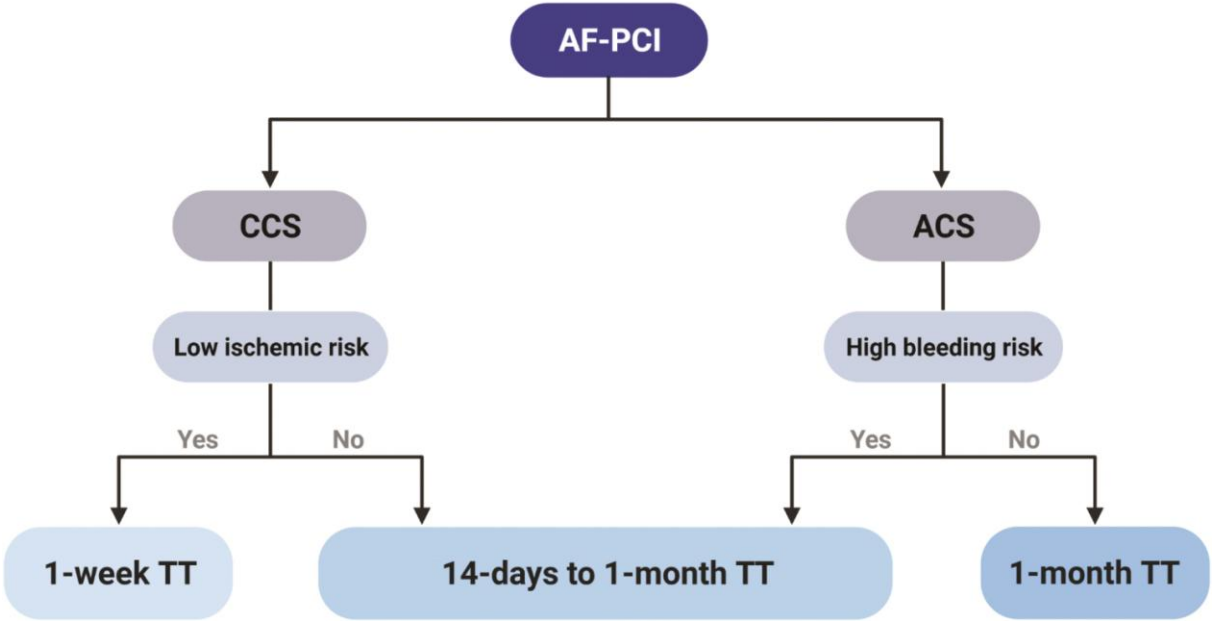
De Caterina R. European Heart Journal (2022) 43, 3512–3527

Kompromis mezi těžkým krvácením a ischemickými příhodami od randomizace do 30 dnů a od 30 dnů do 6 měsíců



Eur Heart J, Volume 43, Issue 37, 1 October 2022, Pages 3512–3527, https://doi.org/10.1093/eurheartj/ehac394

Navrhovaný algoritmus pro přizpůsobení délky trvání triple antitrombotické terapie u pacientů s FS a PCI



Eur Heart J, Volume 43, Issue 37, 1 October 2022, Pages 3512–3527, https://doi.org/10.1093/eurheartj/ehac29

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III: Budoucnost ?

Inhibitory FXI ???
RCT III. fáze s asundexianem

- **OCEANIC – AF**
- Asundexian x Apixaban
- Kompozitní endpoint: Úmrtí/krvácivé komplikace/ TE komplikace

- **OCEANIC- STROKE**
- **OCEANIC - AMI**

Take home message

- Jasný posun k bezpečnější a cílené AK terapii
- NOACs se stávají v roce 2023 generickými molekulami
- Inhibitory faktoru XI představují velký potenciál
- Současné indikace VKA v oblasti chlopenních vad zůstávají a pravděpodobně se měnit nebudou
- Předpoklad zavedení asundexianu do běžné klinické praxe – cca 5-6 let

Děkuji za pozornost

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