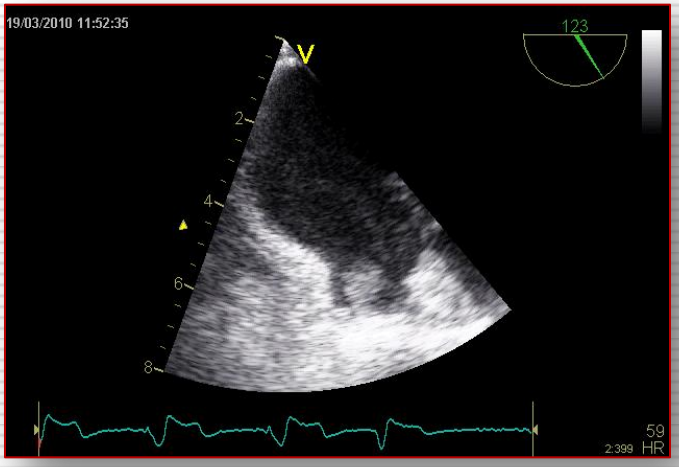
Antikoagulační terapie u FS: Novinky 2012

České kardiologické dny 2012



Miloš Táborský
Praha
29. listopadu 2012

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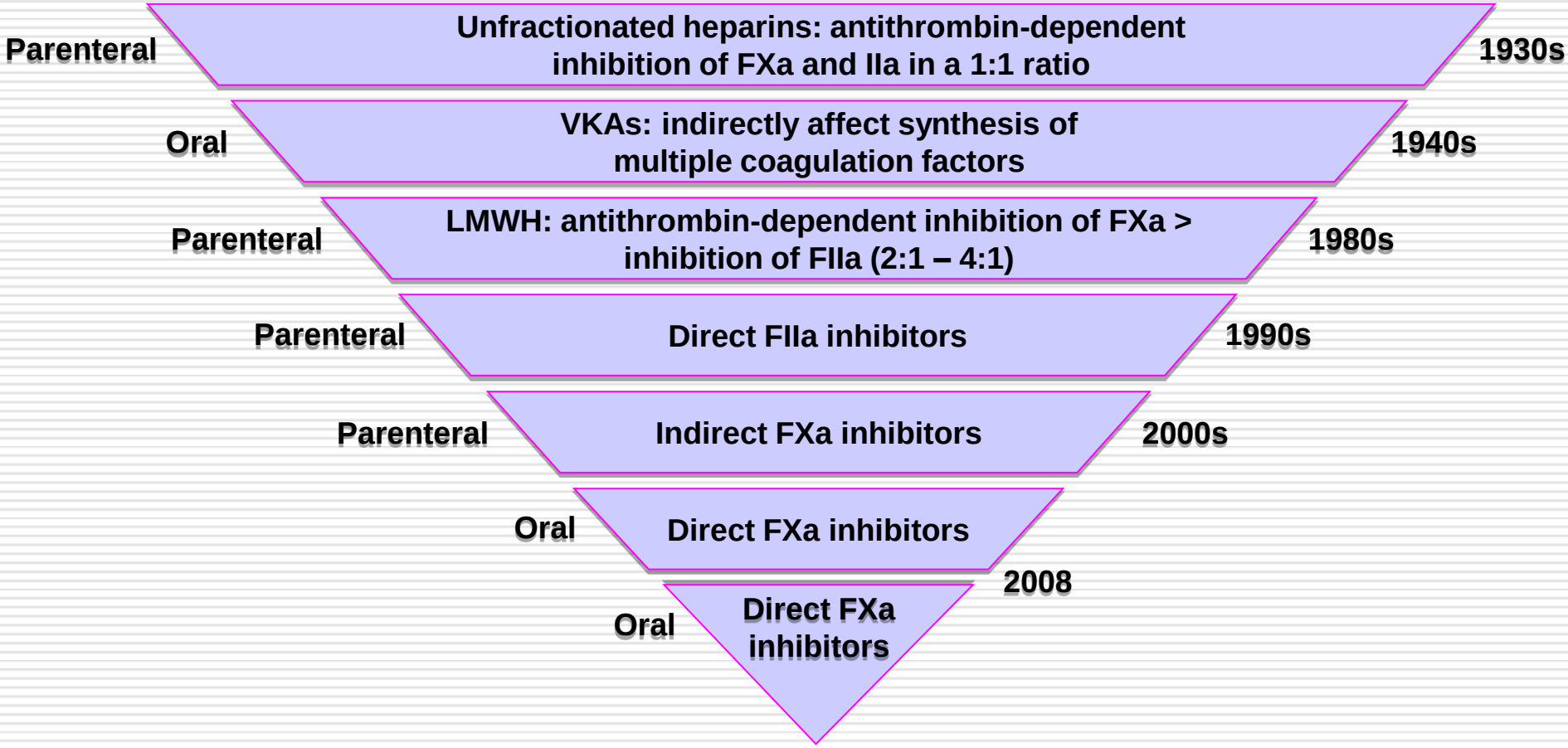
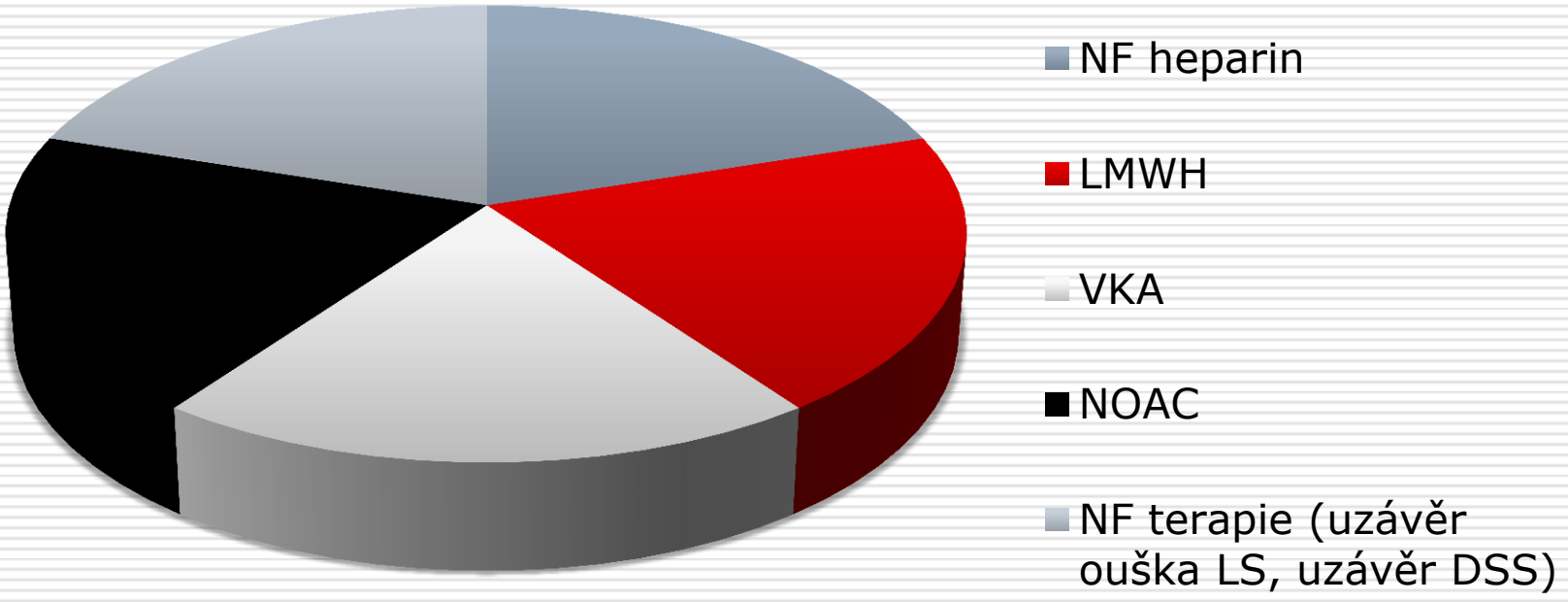
Historický vývoj antikoagulační léčby



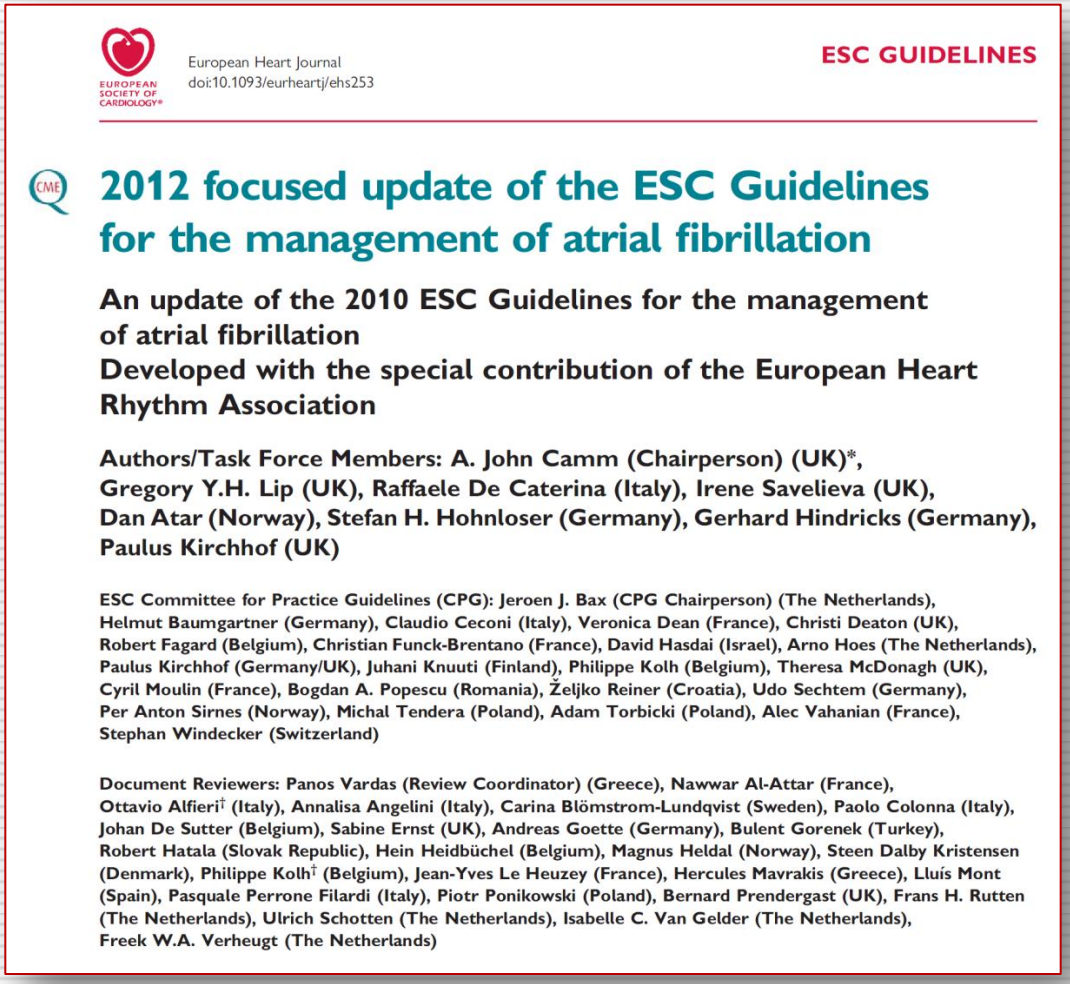
Perzborn E. Nature Rev Drug Dis. 2011;10:61-75.

Spektrum AK terapie



I. Standardy léčby FS 2012

ESC Update 2012



European Heart Journal
doi:10.1093/eurheartj/ehs253

ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

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European Heart Journal
doi:10.1093/eurheartj/ehs253.

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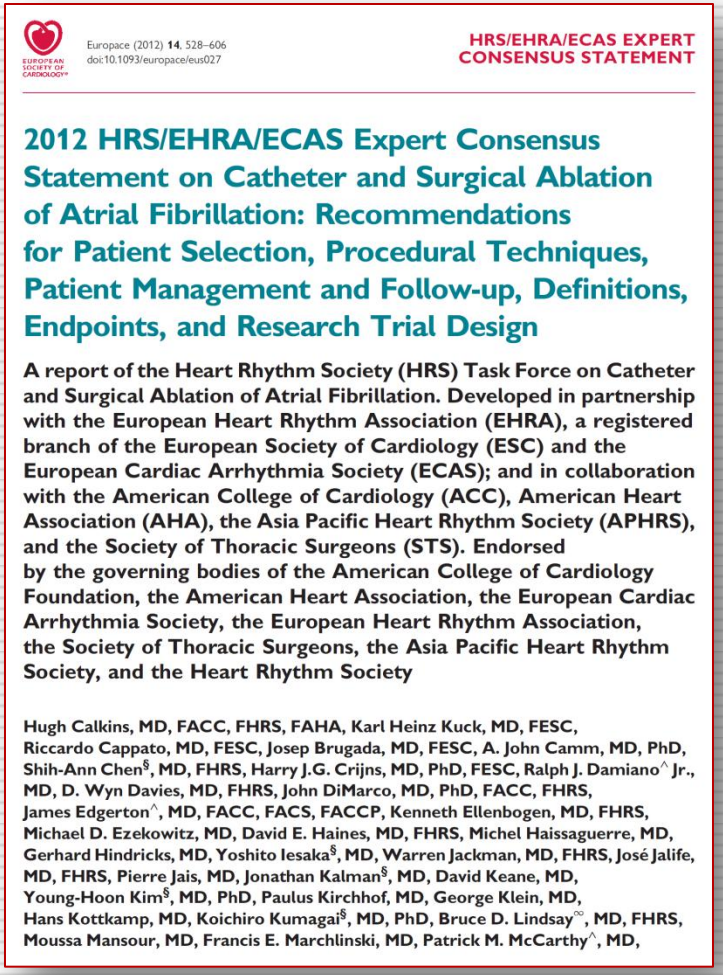
Expert Consensus Statement on Catheter and Surgical AF ablation



Europace (2012) 14, 528–606
doi:10.1093/europace/eus027

HRS/EHRA/ECAS EXPERT CONSENSUS STATEMENT

2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design

A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society

Hugh Calkins, MD, FACC, FHRS, FAHA, Karl Heinz Kuck, MD, FESC, Riccardo Cappato, MD, FESC, Josep Brugada, MD, FESC, A. John Camm, MD, PhD, Shih-Ann Chen[§], MD, FHRS, Harry J.G. Crijns, MD, PhD, FESC, Ralph J. Damiano[^] Jr., MD, D. Wyn Davies, MD, FHRS, John DiMarco, MD, PhD, FACC, FHRS, James Edgerton[^], MD, FACC, FACS, FACCP, Kenneth Ellenbogen, MD, FHRS, Michael D. Ezekowitz, MD, David E. Haines, MD, FHRS, Michel Haissaguerre, MD, Gerhard Hindricks, MD, Yoshito Iesaka[§], MD, Warren Jackman, MD, FHRS, José Jalife, MD, FHRS, Pierre Jais, MD, Jonathan Kalman[§], MD, David Keane, MD, Young-Hoon Kim[§], MD, PhD, Paulus Kirchhof, MD, George Klein, MD, Hans Kottkamp, MD, Koichiro Kumagai[§], MD, PhD, Bruce D. Lindsay[∞], MD, FHRS, Moussa Mansour, MD, Francis E. Marchlinski, MD, Patrick M. McCarthy[^], MD,

European Heart Journal (2012) 14, 528-606.

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AF Monitoring Standards

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2012) **14**, 591–592
doi:10.1093/europace/eus073

EP WIRE

Monitoring in the management of atrial fibrillation

Thorsten Lewalter[1]*, John Morgan[2], Franck Halimi[3], Gregory Lip[4], Nikolaos Dagres[5], and Carina Blomström-Lundqvist[6], conducted by the Scientific Initiative Committee, European Heart Rhythm Association

[1]Department of Cardiology and Intensive Care, University of Bonn, Isar Heart Center Munich, Sonnenstr. 24-26, 80331 Munich, Germany; [2]BUPA Southampton, England, UK; [3]Centre Médico-Chirurgical Parly 2, 21 rue Moxouris, 78150 Le Chesnay, France; [4]University of Birmingham, Centre for Cardiovascular Sciences, City Hospital Birmingham, England, UK; [5]Second Cardiology Department, Attikon University Hospital, University of Athens, Athens, Greece; and [6]Department of Cardiology, Institution of Medical Science, Uppsala University, Uppsala, Sweden

We performed a survey on current practice of atrial fibrillation (AF) detection and monitoring and its relevance in patient management among the European Heart Rhythm Association Research Network. The focus of this questionnaire is on the use and relevance of remote AF detection in device patients and its clinical consequences like starting oral anticoagulation or improving device programming to avoid inappropriate shock therapy. Remote device data are already used by 76.8% of the centres in their implantable cardioverter defibrillator/cardiac resynchronization therapy device patients to detect AF and trigger relevant clinical decision making! The majority of these centres are also asking for the option of remote device programming.

Keywords Atrial fibrillation • Rhythm monitoring • Implantable cardioverter defibrillator • Remote monitoring

European Heart Journal (2012) 14, 591-592.

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Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines 2012

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for Atrial Fibrillation

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

John J. You, MD; Daniel E. Singer, MD; Patricia A. Howard, PharmD; Deirdre A. Lane, PhD; Mark H. Eckman, MD; Margaret C. Fang, MD, MPH; Elaine M. Hylek, MD, MPH; Sam Schulman, MD, PhD; Alan S. Go, MD; Michael Hughes, PhD; Frederick A. Spencer, MD; Warren J. Manning, MD; Jonathan L. Halperin, MD; and Gregory Y. H. Lip, MD

You JJ, et al. Chest. 2012.141;e531S–e575S.
http://chestjournal.chestpubs.org/content/141/2_suppl/e531S.full.html

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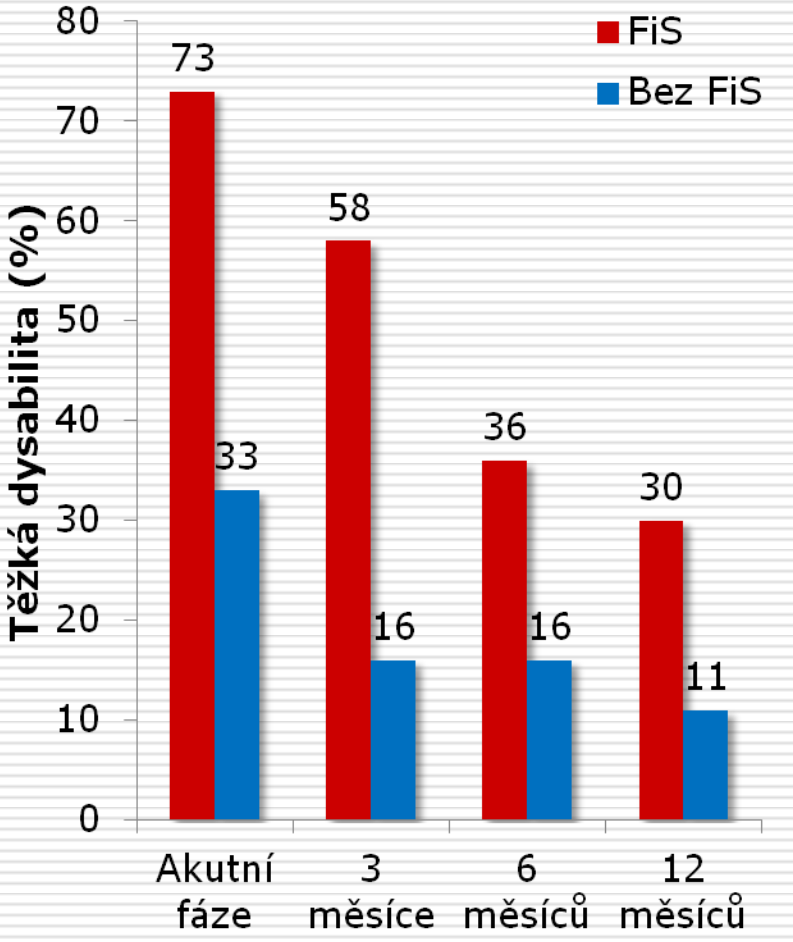
II: Fibrilace síní a CMP

CMP při fibrilaci síní má horší průběh

- Fibrilace síní způsobuje min. 15% iktů[1–3]

CMP při fibrilaci síní je spojená s…

- Vysokým rizikem rekurence
  - 12% na rok[4]
- Větší dysabilitou[5]
- Vyšší mortalitou[5]



1. Go et al, 2001; 2. Wolf et al, 1991; 3. Singer et al, 2008; 4. Hart et al, 1998; 5. Lin et al, 1996

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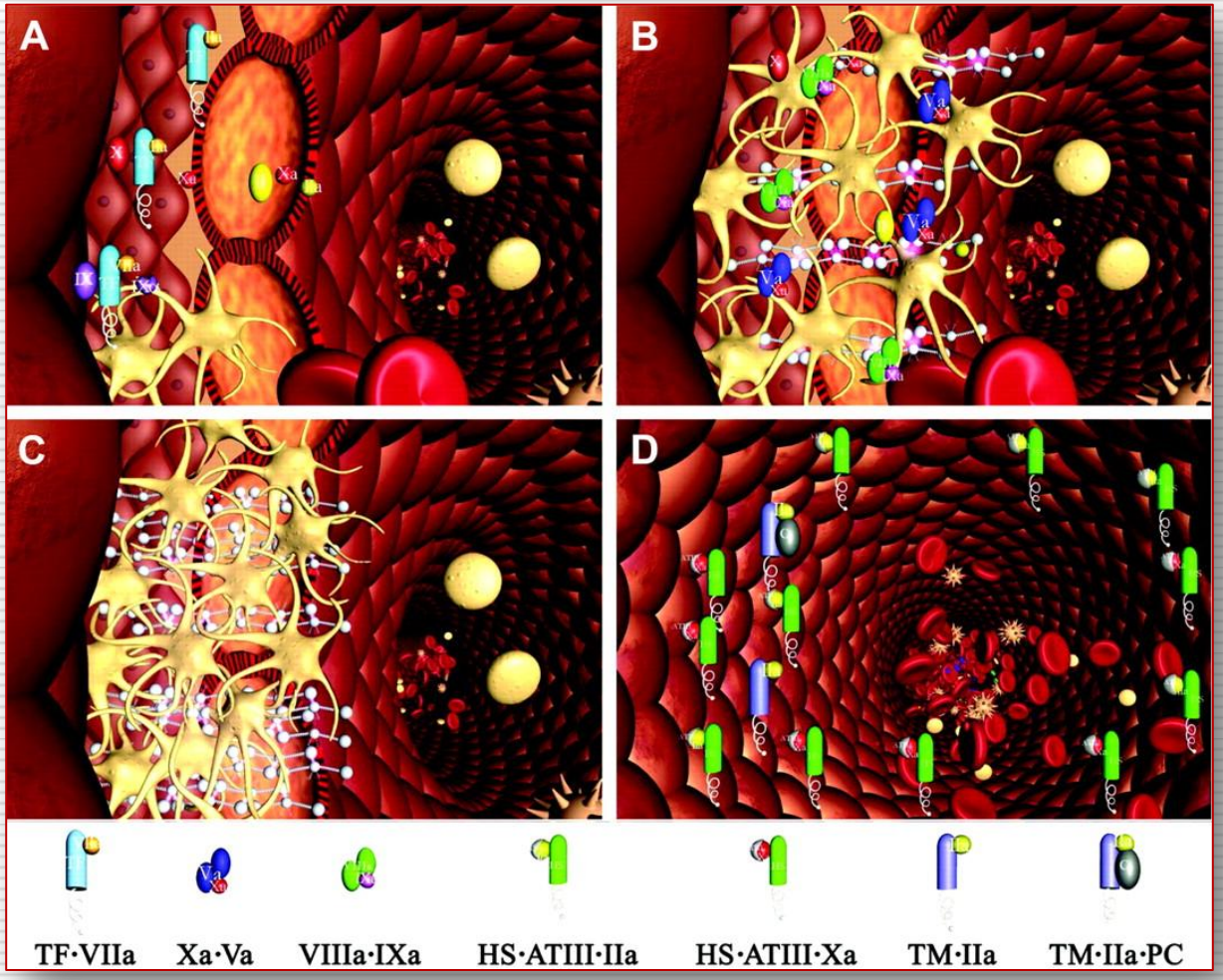
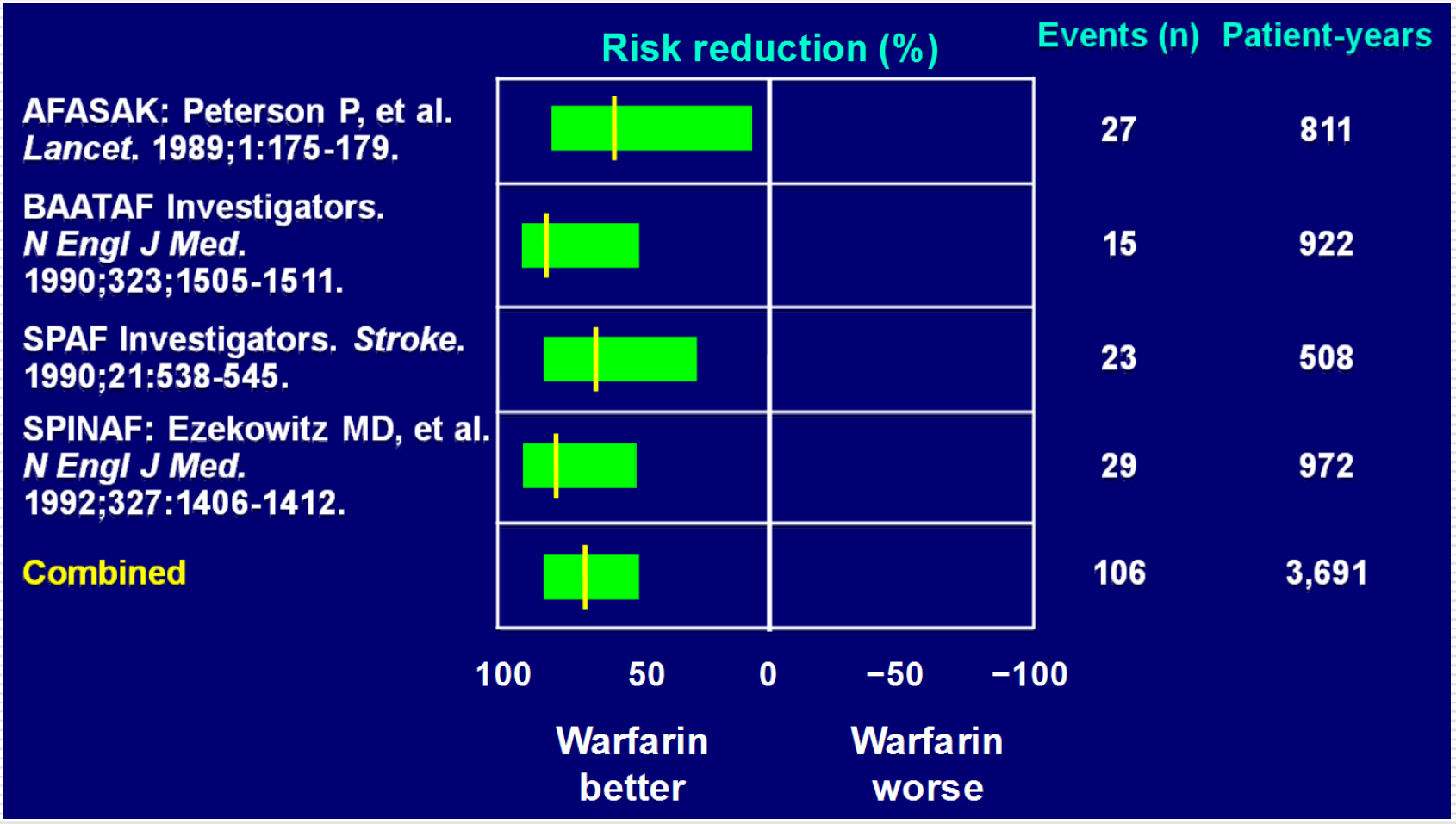
Antikoagulancia: Redukce prokoagulačních substrátů – prevence vzniku trombu



Mann KG. Circulation. 2011;124:225-235.

Redukce vzniku CMP: Srovnání warfarinu a placeba



Warfarin: Major bleeding rate

125 195 pacientů s AK terapií warfarinem
věk: > 65 let
FU: 13 let
průměrný výskyt velkého krvácení: 3,8 % /pacientorok

CHADS2 score	Major bleeding rate (%per person-year)
0	1.8
1	2.5
2-3	4.3
4-6	6.7

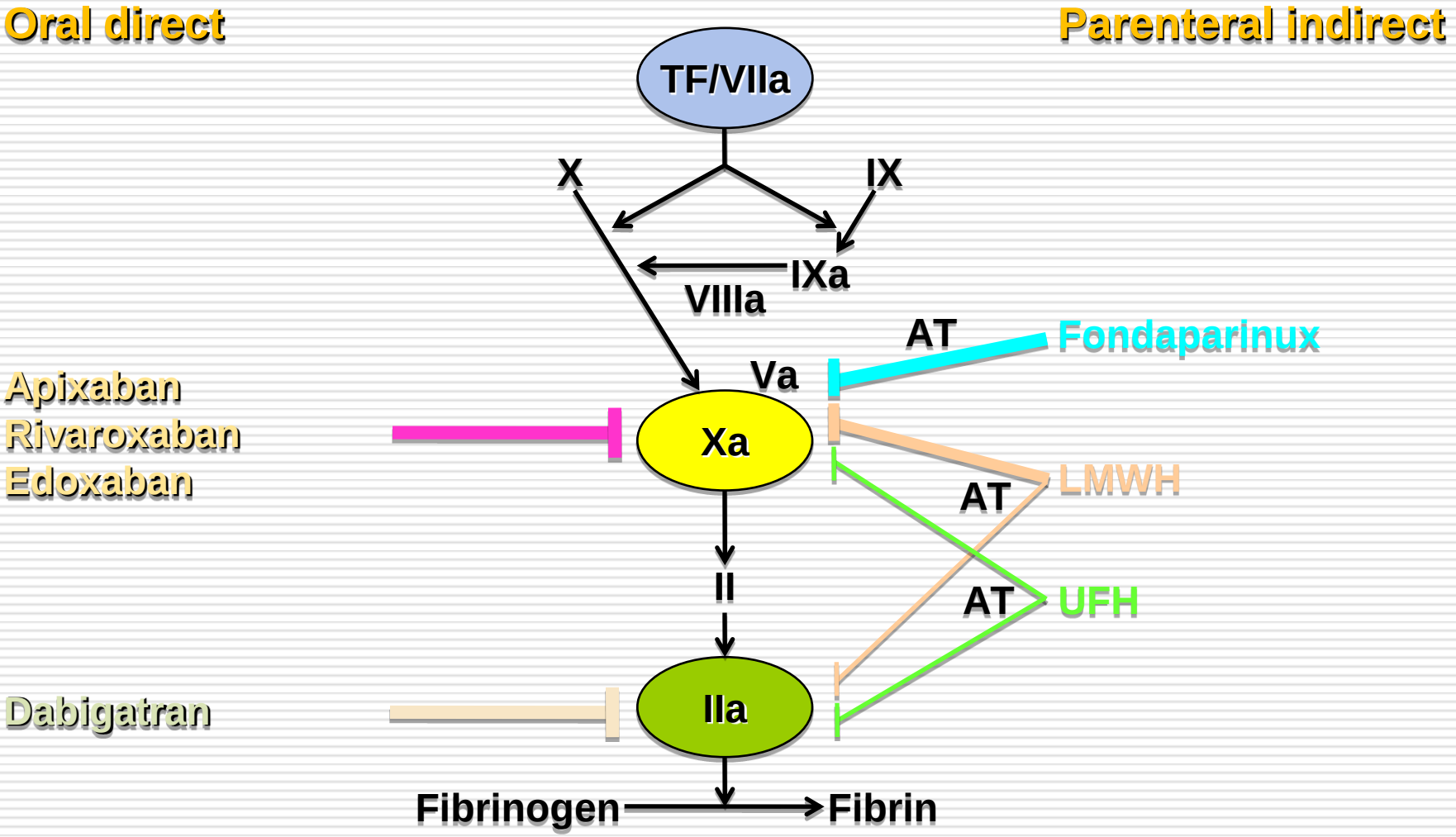
Gomes T, CMAJ 2012;12:heart.org. 26.11.2012

Warfarin: Vliv věku na krvácivé komplikace

Age (y)	Major bleeding rate (% per person-year)
≤75 or under	2.9
> 75	4.6

Gomes T, CMAJ 2012;12:heart.org. 26.11.2012

NOAC: Postavení v antikoagulační kaskádě



Weitz JI, Bates SM. J Thromb Haemost. 2005;3:1843-1853.

III: Současný pohled ESC na postavení nových antikoagulancií v prevenci TE komplikací FS

Characteristics of New Oral Anticoagulants

Drug	Dabigatran	Rivaroxaban	Apixaban	Betrixaban	Edoxaban
Inhibits	Thrombin	Factor Xa	Factor Xa	Factor Xa	Factor Xa
$T_{1/2}$ (h)	14 – 17	5 – 9	12	19 – 24	6 – 12
Regimen	Twice daily	Once or twice daily	Twice daily	Once daily	Once daily
Peak:trough	2:1	12:1 (once daily)	3 – 5:1	≈ 3:1	≈ 3:1
Renal excretion of absorbed drug (%)	≈ 80	35 – 45	25 – 30	≈ 15	35
Potential for drug–drug interactions	P-gp inhibitor	CYP3A4 substrate and P-gp inhibitor	CYP3A4 substrate and P-gp inhibitor	Not substrate for major CYPs	CYP3A4 substrate and P-gp inhibitor

Usman MH, Ezekowitz MD. Curr Treat Cardiovasc Med. 2008;10:388-397.
Piccini JP, et al. Curr Opin Cardiol. 2010;25:312-320.

The Big Three: Comparing Study Design

Trial	Inclusion	Design	Duration (median)	Enrollment (N)	No. sites	TTR (mean)
RE–LY	$CHADS_2 \geq 1$ (50% VKA naïve)	Open-label	2 y (≈ 730 d)	18,113	951	64% 67% warfarin-experienced 61% warfarin-naïve
ROCKET AF	$CHADS_2 \geq 2$ (87% $CHADS_2 \geq 3$)	Sham INR	589 d exposure, 707 d including period off drug during follow-up	14,264	1,178	55%
ARISTOTLE	$CHADS_2 \geq 1$ (30% VKA naïve)	Sham INR	1.8 y	18,201	1,034	62%

Connolly SJ, Ezekowitz MD, et al. N Engl J Med. 2009;361:1139-1151; Patel MR, et al. N Engl J Med. 2011;365:883-891; Granger CB, et al. N Engl J Med. 2011;365:981-992.

The Big Three: Comparing Patient Risk

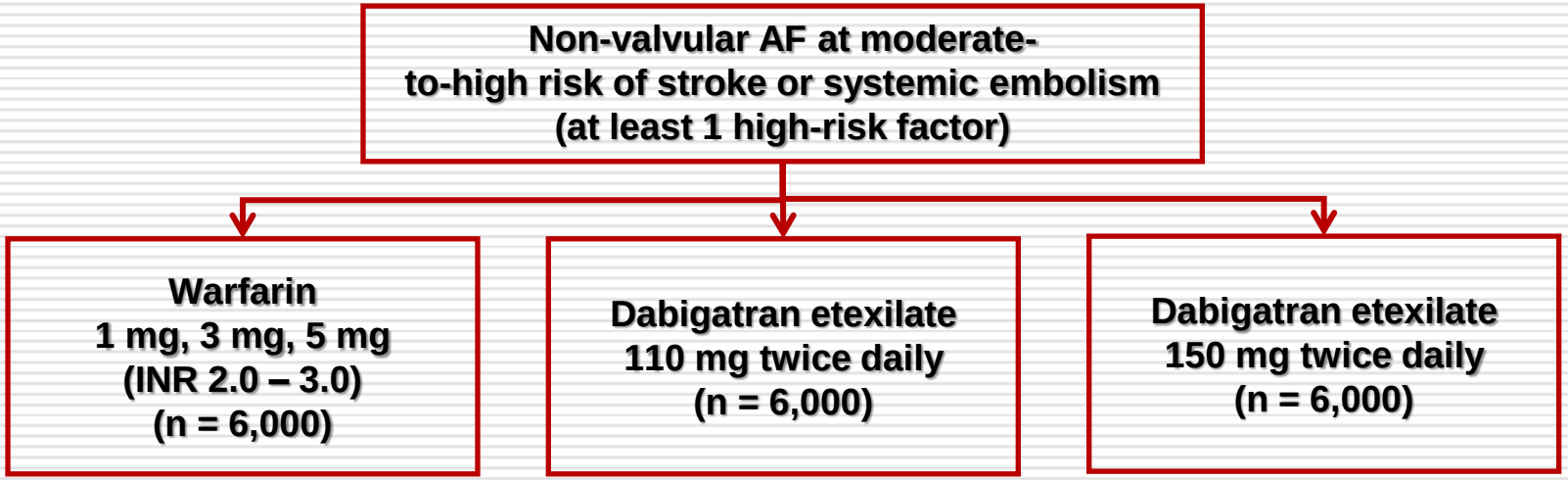
Trial	Mean or Median (IQR) patient age (y)	Mean $CHADS_2$ score	$CHADS_2$ ≤ 1*	$CHADS_2$ = 2	$CHADS_2$ ≥ 3	Prior stroke / TIA (%)	Warfarin naïve (%)
RE–LY	71.5	2.1	≈ 32	≈ 35	≈ 33	≈ 20	≈ 50
ROCKET AF	73 (65 – 78)	3.5	0	13	87	≈ 55	≈ 38
ARISTOTLE	70 (63 – 76)	2.1	34	36	30	≈ 20†	≈ 33

***RE–LY included patients with $CHAD_2$ = 0 while ARISTOTLE did not**
†Includes systemic embolism

Connolly SJ, Ezekowitz MD, et al. N Engl J Med. 2009;361:1139-1151; Patel MR, et al. N Engl J Med. 2011;365:883-891; Granger CB, et al. N Engl J Med. 2011;365:981-992.

RE–LY

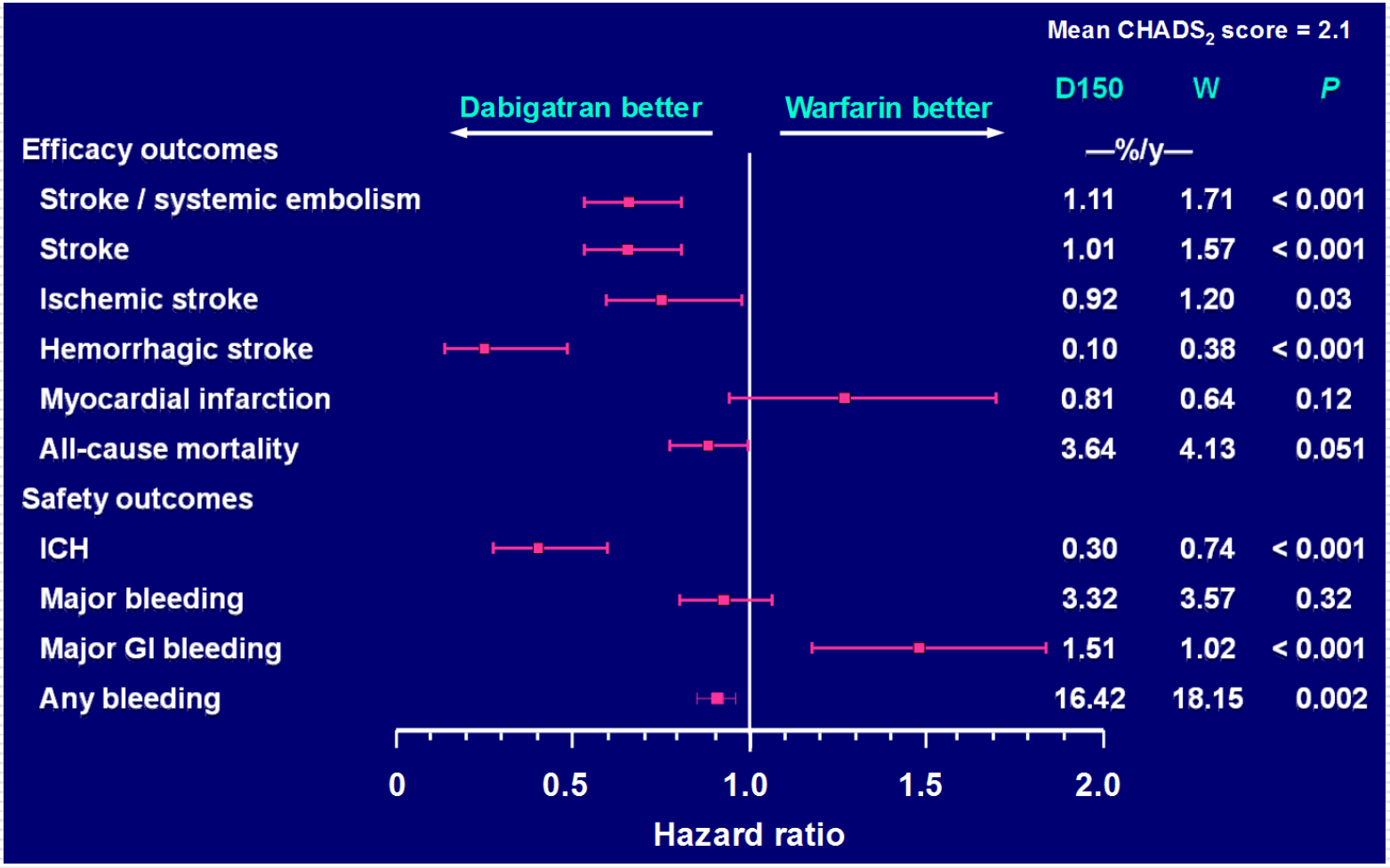
Dabigatran for Stroke Prevention in Atrial Fibrillation



- 1° objective: noninferiority to warfarin
- Minimum 1-year, maximum of 3 years, and mean of 2 years of follow-up
- 1° endpoint: stroke + systemic embolism

Ezekowitz MD, et al. Am Heart J. 2009;157:805-810.

RE–LY: Dabigatran 150 mg Twice Daily



Connolly SJ, Ezekowitz MD, et al. N Engl J Med. 2009;361:1139-1151.
Connolly SJ, Ezekowitz MD, et al. N Engl J Med. 2010;363:1875-1876.

Study Design

Risk factors
- CHF
- Hypertension
- Age ≥ 75 y
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or systemic embolus

Atrial fibrillation

Rivaroxaban

20 mg /d
(15 mg for CrCl 30 – 49 mL/min)

Randomize
Double-blind / double-dummy
(N ≈ 14,000)

Warfarin

INR target: 2.5
(2.0 – 3.0 inclusive)

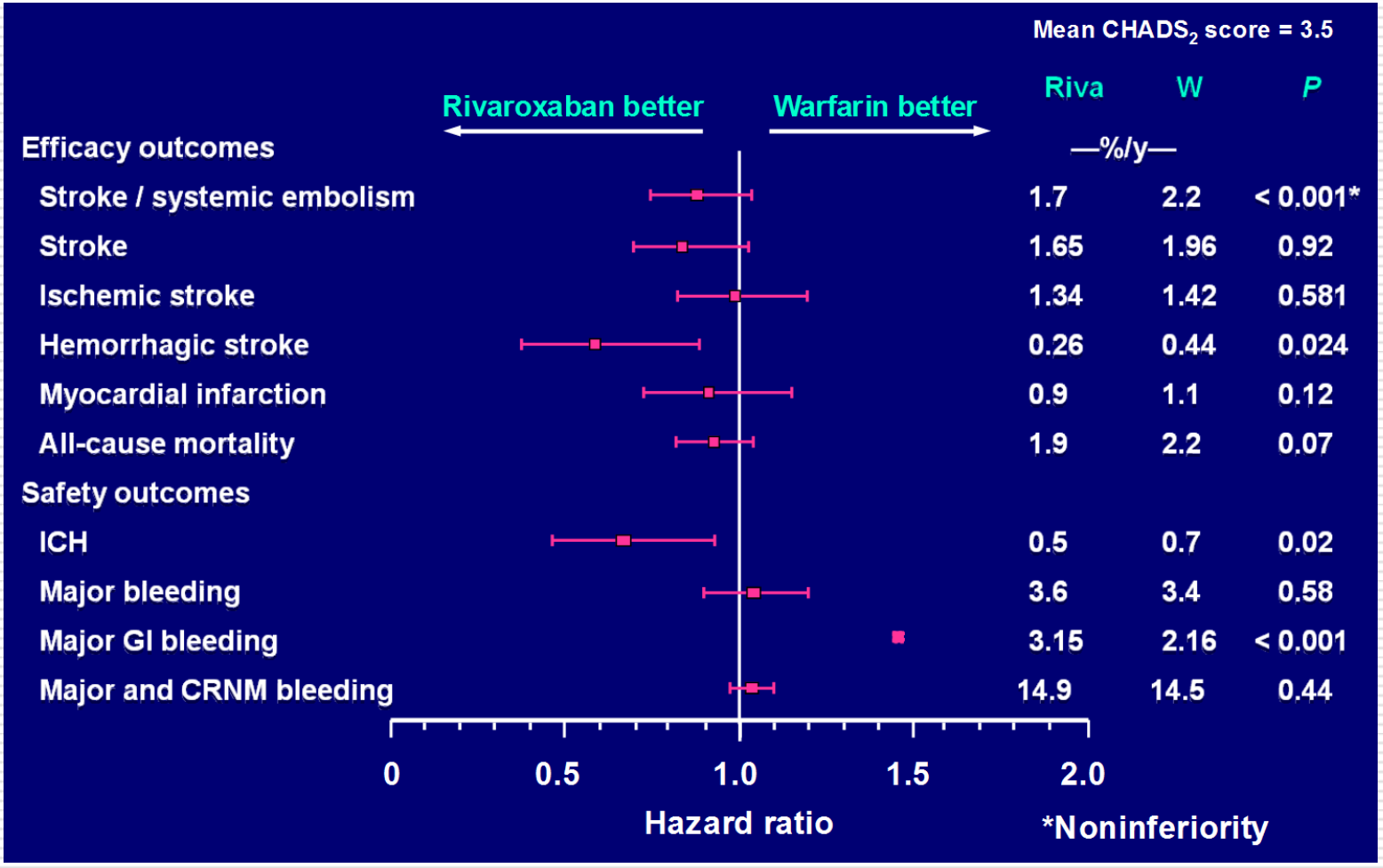
Monthly monitoring
Adherence to standard-of-care guidelines

Primary endpoint: Stroke or non-CNS systemic embolism

* Enrollment of patients without prior stroke, TIA or systemic embolism and only 2 factors capped at 10%

ROCKET AF Study Investigators. Am Heart J. 2010;159:340-347.e1.

ROCKET AF: Rivaroxaban



Patel MR, et al. N Engl J Med. 2011;365:883-891.

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ARISTOTLE: Apixaban

Inclusion risk factors
- **Age ≥ 75 y**
- **Prior stroke, TIA, or SE**
- **HF or LVEF ≤ 40%**
- **Diabetes mellitus**
- **Hypertension**

Randomize
double blind,
double dummy
(N = 18,201)

Major exclusion criteria
- **Mechanical prosthetic valve**
- **Severe renal insufficiency**
- **Need for aspirin plus thienopyridine**

Apixaban 5 mg PO twice daily
(2.5 mg twice daily in selected pts*)

Warfarin
(target INR, 2 – 3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

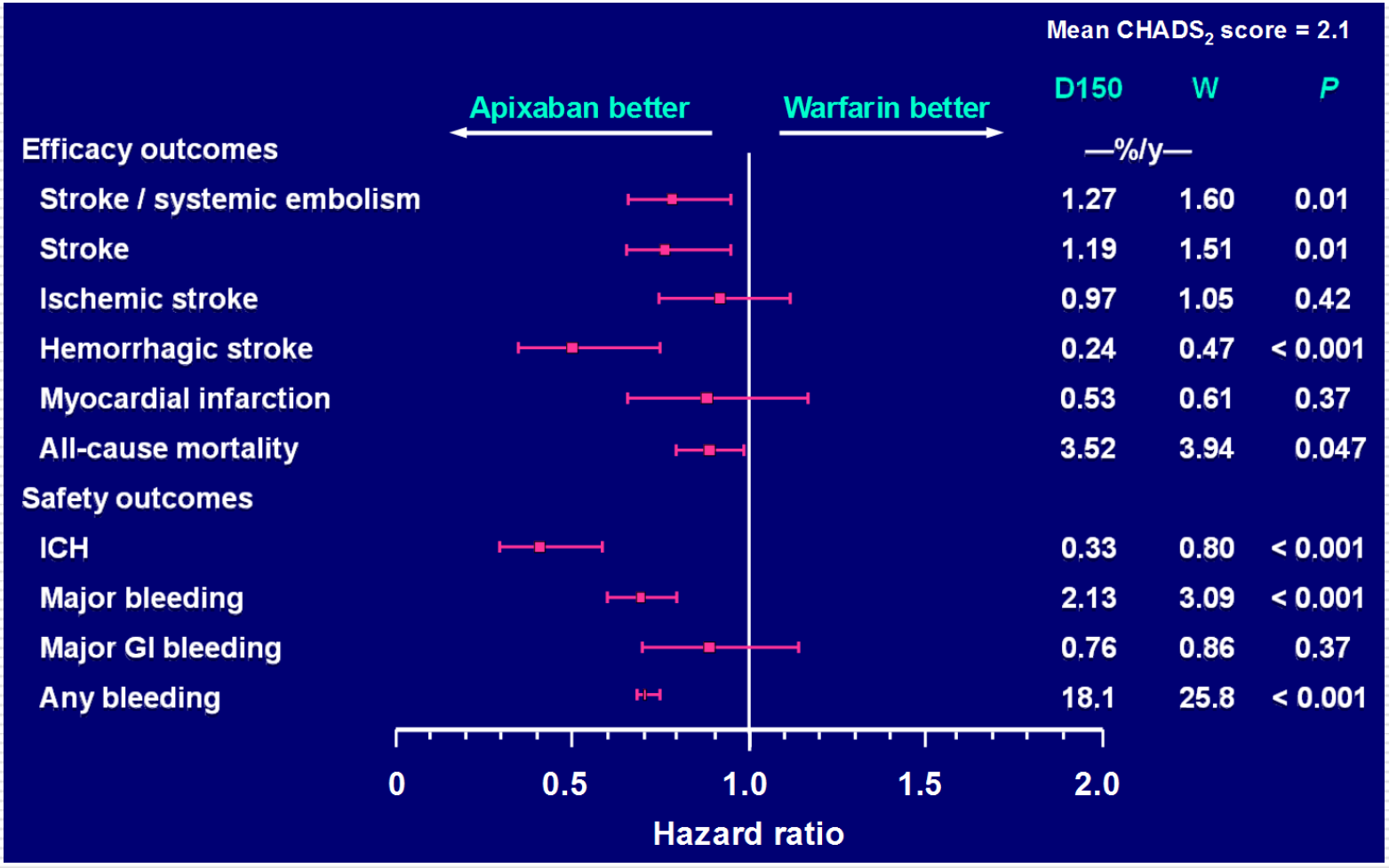
Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

*2.5 mg was used in patients meeting two or more of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine level ≥ 1.5 mg /dL.

Lopes RD, et al. Am Heart J. 2010;159:331-339.

ARISTOTLE: Apixaban



Granger CB, et al. N Engl J Med. 2011;365:981-992.

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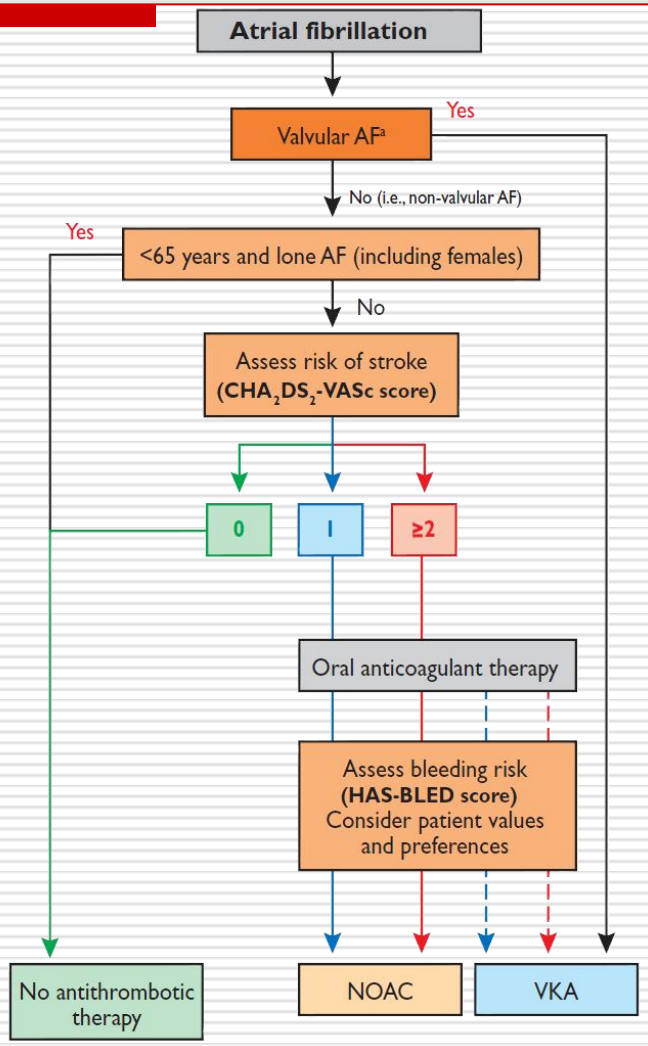
Indikace AK terapie a volba AK



Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.
Colour: CHA_2DS_2-VASc; green = 0, blue = 1, red ≥2.
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED = see text; NOAC = novel oral anticoagulant; OAC = oral anticoagulant; VKA = vitamin K antagonist.
[a]Includes rheumatic valvular disease and prosthetic valves.

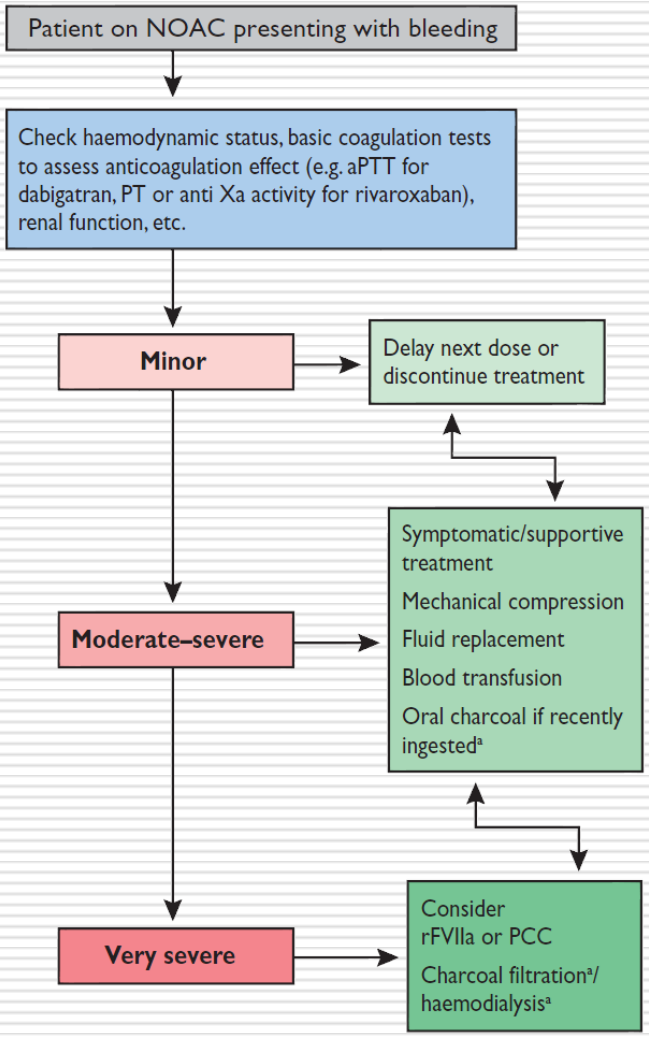
European Heart Journal
doi:10.1093/eurheartj/ehs253.

IV: NOAC: Specifické situace

Populace s vysokým rizikem krvácení

- Renální insuficience
- Jaterní nedostatečnost
- Komedikace (ovlivnění P4503A4 a PGP)
- Další poruchy krvácení
  - Poruchy srážení krve
  - Dekomp. hypertenze
  - Akutní nebo subakutní vředová choroba GIT
  - Retinopatie
  - Nedávné mozkové krvácení
  - Cévní abmormity CNS
  - St.p. operace mozku
  - Bronchiektazie nebo anamn. hemoptýzy

Management krvácení u nemocných s novými antikoagulancii



aPTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = activated recombinant factor VII.
[a]With dabigatran.

European Heart Journal
doi:10.1093/eurheartj/ehs253.

2012 ACCP Guidelines for Antithrombotic Therapy For Patients Undergoing Cardioversion for AF

Patient features	Recommended antithrombotic therapy
AF of > 48 h or unknown duration with elective cardioversion	Therapeutic anticoagulation (dose-adjusted VKA,* LMWH, or dabigatran) for ≥ 3 weeks before cardioversion *OR* TEE-guided approach with abbreviated anticoagulation ✓ Therapeutic anticoagulation ≥ 4 weeks after successful cardioversion
AF of known duration ≤ 48 h with elective cardioversion	Immediate anticoagulation with IV UFH or LMWH, then therapeutic anticoagulation (dose-adjusted VKA,* LMWH, or dabigatran) ✓ ≥ 4 weeks after successful cardioversion
Urgent cardioversion for hemodynamically unstable AF	Parenteral anticoagulation as soon as possible, then therapeutic anticoagulation (dose-adjusted VKA,* LMWH, or dabigatran) ✓ ≥ 4 weeks after successful cardioversion
Cardioversion of atrial flutter	As for patients undergoing cardioversion for AF

- Long-term antithrombotic therapy should follow the risk-based recommendations for AF

*Target INR, 2.0 – 3.0

You JJ, et al. Chest. 2012.141;e531S–e575S. http://chestjournal.chestpubs.org/content/141/2_suppl/e531S.full.html

ACCP 9 (2012) Recommendations for Patients With AF and Concomitant ACS or CAD

Condition	Guideline recommendations
AF + stable CAD (no ACS or revascularization within the previous year)	▪ VKA alone (if patient chooses oral anticoagulation) rather than combination of VKA + ASA (Grade 2C)
$CHADS_2 \geq 2$ + BMS or DES	▪ Triple therapy rather than dual-antiplatelet therapy during the first month after BMS or first 3 – 6 months after DES (Grade 2C) ▪ After initial period of triple therapy, VKA + single-antiplatelet therapy rather than VKA alone (Grade 2C) ▪ At 12 months, antithrombotic therapy is suggested as for patients with AF + stable CAD
$CHADS_2 = 0 / 1$ + BMS or DES	▪ Dual-antiplatelet therapy rather than triple therapy during first 12 months after stent placement (Grade 2C) ▪ At 12 months, antithrombotic therapy is suggested as for patients with AF + stable CAD

- For recommendations in favor of oral anticoagulation, guidelines suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA.
- Triple therapy = VKA + ASA + clopidogrel; dual-antiplatelet therapy = ASA + clopidogrel

You JJ, et al. Chest. 2012.141;e531S–e575S. http://chestjournal.chestpubs.org/content/141/2_suppl/e531S.full.html

Prevence CMP u pacientů s FS a CHRI

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2012 Focused Update

Guidance for antithrombotic therapy of patients with chronic kidney disease is provided in relation to estimated GFR as follows:

a) eGFR 30 > mL/min: We recommend that such patients receive antithrombotic therapy according to their $CHADS_2$ score as detailed in recommendations for patients for patients with normal renal function	**Strong recommendation; high-quality evidence**

Skanes AC, et al. Can J Cardiol. 2012;28:125-136.

Prevence CMP u pacientů s FS a CHRI

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2012 Focused Update

b) eGFR 15 – 30 mL/min and not on dialysis: We suggest that such patients receive antithrombotic therapy according to their $CHADS_2$ score as for patients with normal renal function. The preferred agent for these patients is warfarin.	**Weak recommendation; low-quality evidence**
c) eGFR < 15 mL/min (on dialysis): We suggest that such patients not routinely receive either OAC or ASA for stroke prevention in atrial fibrillation.	**Weak recommendation; OAC: moderate-quality evidence; ASA: low-quality evidence**

Skanes AC, et al. Can J Cardiol. 2012;28:125-136.

V: Guidelines ESC FS a metaanalýza NOAC

Souhrn update guidelines ESC 2012 I

- Při absenci jakéhokoli přímého porovnání nových antitrombotik je nevhodné definitivně rozhodnout, které z nových antitrombotik je nejlepší, vezmeme-li v úvahu heterogenitu jednotlivých studií.
- Nepřímo srovnávající analýzy nenaznačují hluboké rozdíly v účinnostních endpointech mezi novými antitrombotiky, ale major krvácení se jeví menší u dabigatranu 110 2x denně a u apixabanu.
- U pacientů s CHA_2DS_2-VASc score ≥2 jsou všechna nová antitrombotika superiorní vůči warfarinu s pozitivním net clinical benefitem, nezávisle na riziku krvácení.

Souhrn update guidelines ESC 2012 II

- Nová perorální antitrombotika nabízejí lepší účinnost, bezpečnost a pohodlí ve srovnání s orálními antikoagulancii s antagonisty vitaminu K. Takže pokud jsou doporučena perorální antikoagulancia, jedno z nových antitrombotik by měly být zváženy namísto inhibitorů vitaminu K (VKA)
- Není dostatečná evidence doporučit jedno nové perorální antitrombotikum nad jiným, protože některé klinické charakteristiky pacientů, **compliance léčby a tolerabilita** a cena mohou být důležitými faktory pro volbu antikoagulancia.

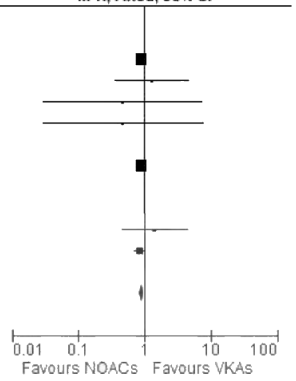
Camm JA, Lip GYH, Caterina R, 2012 focused update of the ESC Guidelines for the management of atrial fibrillation, doi:10.1093/eurheartj/ehs253

Metaanalýza nových antikoagulancií I

a) Total mortality

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	0	104	0	62		Not estimable
PETRO	0	166	0	70		Not estimable
RE-LY	884	12091	487	6022	41.1%	0.90 [0.81, 1.01]
WEITZ	11	713	3	250	0.3%	1.29 [0.36, 4.57]
CHUNG	1	159	1	75	0.1%	0.47 [0.03, 7.44]
YAMASHITA	1	260	1	125	0.1%	0.48 [0.03, 7.62]
ARISTOTLE-J	0	148	0	74		Not estimable
ARISTOTLE	603	9120	669	9081	42.4%	0.90 [0.81, 1.00]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	7	637	5	637	0.3%	1.40 [0.45, 4.39]
ROCKET-AF	208	7061	250	7082	15.8%	0.83 [0.70, 1.00]
Total (95% CI)		**30584**		**23531**	**100.0%**	**0.89 [0.83, 0.96]**
Total events	1715		1416			

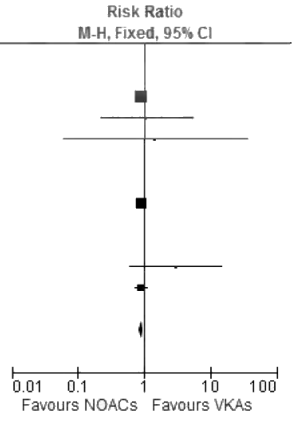
Heterogeneity: Chi² = 1.91, df = 6 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.24 (P = 0.001)



b) Cardiovascular mortality

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	0	104	0	62		Not estimable
PETRO	0	166	0	70		Not estimable
RE-LY	563	12091	317	6022	43.8%	0.88 [0.77, 1.01]
WEITZ	6	713	2	250	0.3%	1.05 [0.21, 5.18]
CHUNG	1	159	0	75	0.1%	1.43 [0.06, 34.57]
YAMASHITA	0	260	0	125		Not estimable
ARISTOTLE-J	0	148	0	74		Not estimable
ARISTOTLE	308	9120	344	9081	35.7%	0.89 [0.77, 1.04]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	6	637	2	637	0.2%	3.00 [0.61, 14.81]
ROCKET-AF	170	7061	193	7082	19.9%	0.88 [0.72, 1.08]
Total (95% CI)		**30584**		**23531**	**100.0%**	**0.89 [0.82, 0.98]**
Total events	1054		858			

Heterogeneity: Chi² = 2.36, df = 5 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)



Dentali F: Circulation 2012: DOI: 10.1161/CIRCULATIONAHA.112.115410.

Komplexní kardiovaskulární centrum

Lékařská fakulta Univerzity Palackého v Olomouci

I. INTERNÍ KLINIKA KARDIOLOGICKÁ
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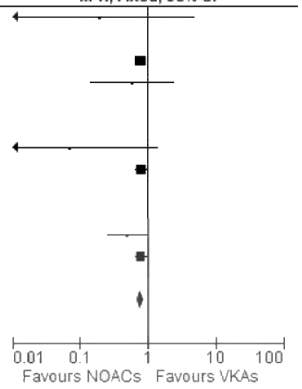
Metaanalýza nových antikoagulancií II

a) Stroke or Systemic Embolism

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	0	104	1	62	0.2%	0.20 [0.01, 4.84]
PETRO	0	166	0	70		Not estimable
RE-LY	317	12091	202	6022	33.4%	0.78 [0.66, 0.93]
WEITZ	5	713	3	250	0.5%	0.58 [0.14, 2.43]
CHUNG	0	159	0	75		Not estimable
YAMASHITA	0	260	0	125		Not estimable
ARISTOTLE-J	0	148	3	74	0.6%	0.07 [0.00, 1.37]
ARISTOTLE	212	9120	265	9081	32.9%	0.80 [0.67, 0.95]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	11	637	22	637	2.7%	0.50 [0.24, 1.02]
ROCKET-AF	188	7081	240	7090	29.7%	0.78 [0.65, 0.95]
Total (95% CI)		**30604**		**23539**	**100.0%**	**0.77 [0.70, 0.86]**
Total events	733		736			

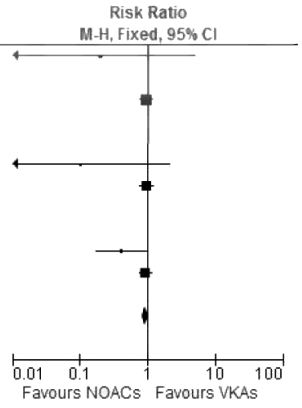
Heterogeneity: Chi² = 4.90, df = 6 (P = 0.56); I² = 0%
Test for overall effect: Z = 4.94 (P < 0.00001)



b) Ischemic stroke

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	0	104	1	62	0.4%	0.20 [0.01, 4.84]
PETRO	0	166	0	70		Not estimable
RE-LY	255	12091	134	6022	34.6%	0.95 [0.77, 1.17]
CHUNG	0	159	0	75		Not estimable
YAMASHITA	0	260	0	125		Not estimable
ARISTOTLE-J	0	148	2	74	0.6%	0.10 [0.00, 2.07]
ARISTOTLE	149	9120	155	9081	30.0%	0.96 [0.77, 1.20]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	7	637	17	637	3.3%	0.41 [0.17, 0.99]
ROCKET-AF	149	7061	161	7082	31.1%	0.93 [0.74, 1.16]
Total (95% CI)		**29871**		**23281**	**100.0%**	**0.92 [0.81, 1.04]**
Total events	560		470			

Heterogeneity: Chi² = 6.40, df = 5 (P = 0.27); I² = 22%
Test for overall effect: Z = 1.35 (P = 0.18)



Dentali F: Circulation 2012: DOI: 10.1161/CIRCULATIONAHA.112.115410.

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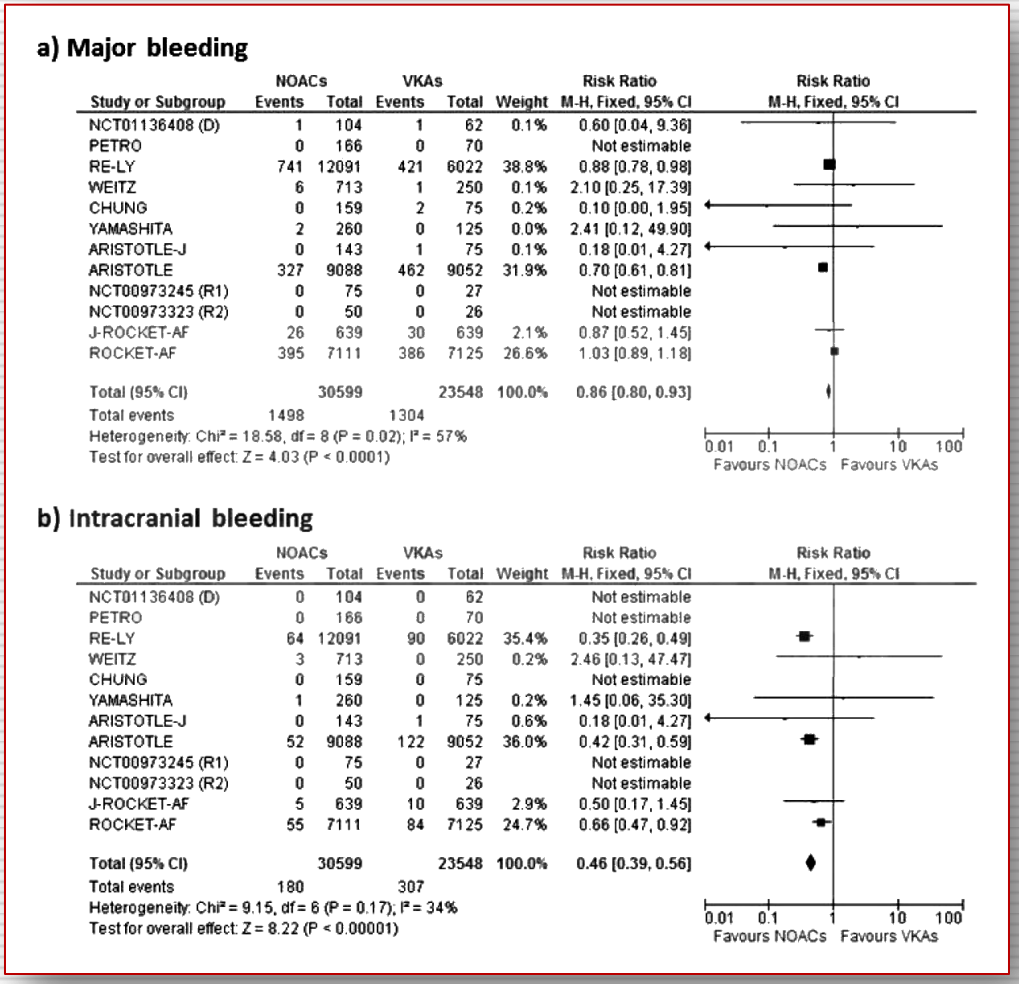
Metaanalýza nových antikoagulancií III



a) Major bleeding

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	1	104	1	62	0.1%	0.60 [0.04, 9.36]
PETRO	0	166	0	70		Not estimable
RE-LY	741	12091	421	6022	38.8%	0.88 [0.78, 0.98]
WEITZ	6	713	1	250	0.1%	2.10 [0.25, 17.39]
CHUNG	0	159	2	75	0.2%	0.10 [0.00, 1.95]
YAMASHITA	2	260	0	125	0.0%	2.41 [0.12, 49.90]
ARISTOTLE-J	0	143	1	75	0.1%	0.18 [0.01, 4.27]
ARISTOTLE	327	9088	462	9052	31.9%	0.70 [0.61, 0.81]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	26	639	30	639	2.1%	0.87 [0.52, 1.45]
ROCKET-AF	395	7111	386	7125	26.6%	1.03 [0.89, 1.18]
Total (95% CI)		30599		23548	100.0%	0.86 [0.80, 0.93]
Total events	1498		1304			

Heterogeneity: Chi² = 18.58, df = 8 (P = 0.02); I² = 57%
Test for overall effect: Z = 4.03 (P < 0.0001)

Risk Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours NOACs Favours VKAs

b) Intracranial bleeding

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	0	104	0	62		Not estimable
PETRO	0	166	0	70		Not estimable
RE-LY	64	12091	90	6022	35.4%	0.35 [0.26, 0.49]
WEITZ	3	713	0	250	0.2%	2.46 [0.13, 47.47]
CHUNG	0	159	0	75		Not estimable
YAMASHITA	1	260	0	125	0.2%	1.45 [0.06, 35.30]
ARISTOTLE-J	0	143	1	75	0.6%	0.18 [0.01, 4.27]
ARISTOTLE	52	9088	122	9052	36.0%	0.42 [0.31, 0.59]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	5	639	10	639	2.9%	0.50 [0.17, 1.45]
ROCKET-AF	55	7111	84	7125	24.7%	0.66 [0.47, 0.92]
Total (95% CI)		30599		23548	100.0%	0.46 [0.39, 0.56]
Total events	180		307			

Heterogeneity: Chi² = 9.15, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 8.22 (P < 0.00001)

Risk Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours NOACs Favours VKAs

Dentali F: Circulation 2012: DOI: 10.1161/CIRCULATIONAHA.112.115410.

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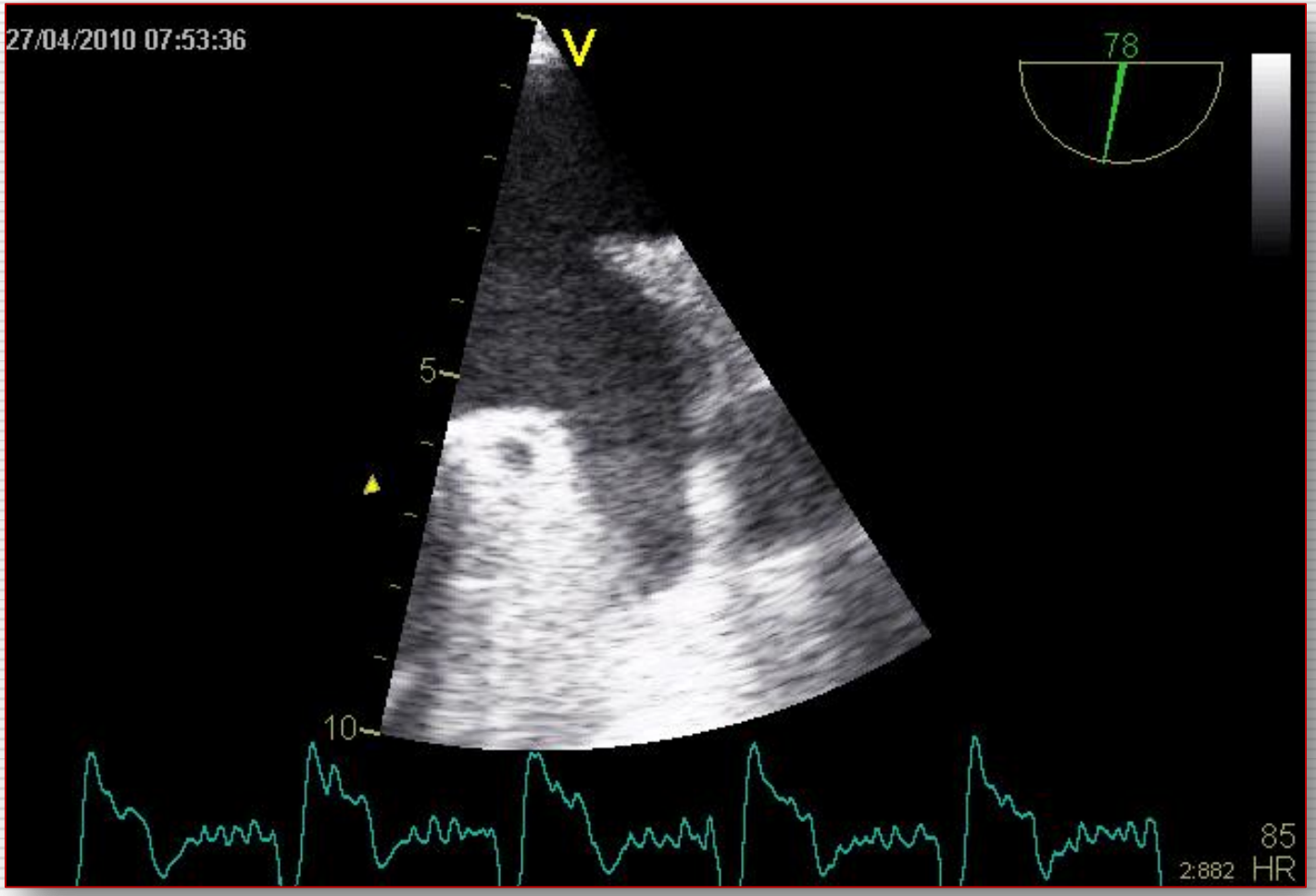
Doporučení do klinické praxe

- Výběr antitrombotika → vždy individuální (riziko TE, compliance, benefit pro pacienta, ekonomické aspekty …)
- Nepoužívejte NOAC v jiných než schválených indikacích (např. mechanické chlopenní náhrady aj.)
- Věnujte pozornost renálním funkcím a jejich vývoji
- Žádné z NOAC nemá specifické antidotum !
- Dodržujte SPC a limitace plátců zdravotní péče pro úhradu NOAC

Cíl antikoagulační léčby



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