



2013

Norte

25 DE OUTUBRO – 6ª FEIRA

QUEM SÃO OS DOENTES EM FIBRILHAÇÃO AURICULAR COM INDICAÇÃO PARA ANTICOAGULAÇÃO ORAL

**ANTÓNIO PEDRO MACHADO
CARLOS RABAÇAL**



Guidelines for the management of atrial fibrillation

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)[†]

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

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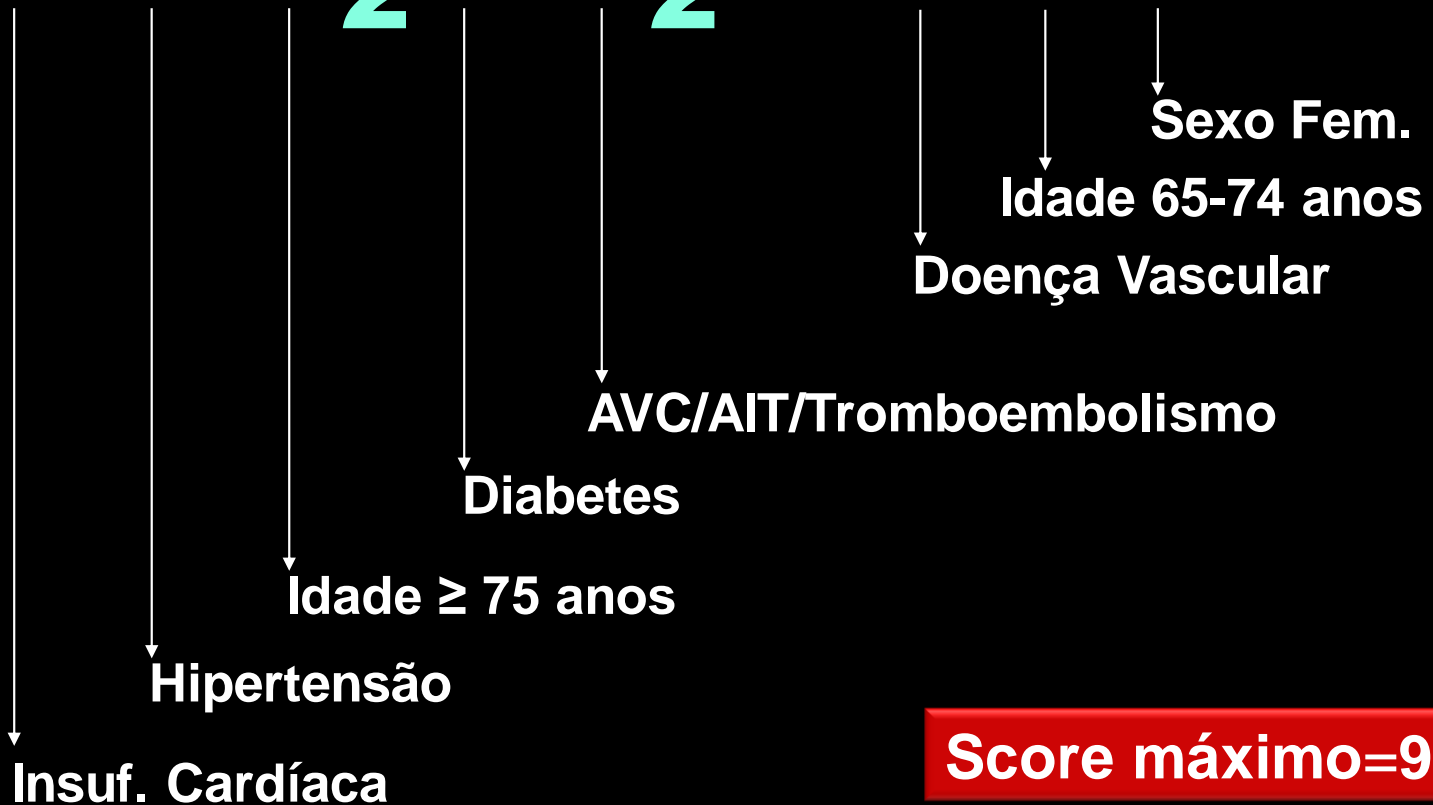
Councils: Cardiovascular Imaging, Cardiology Practice, Cardiovascular Primary Care.

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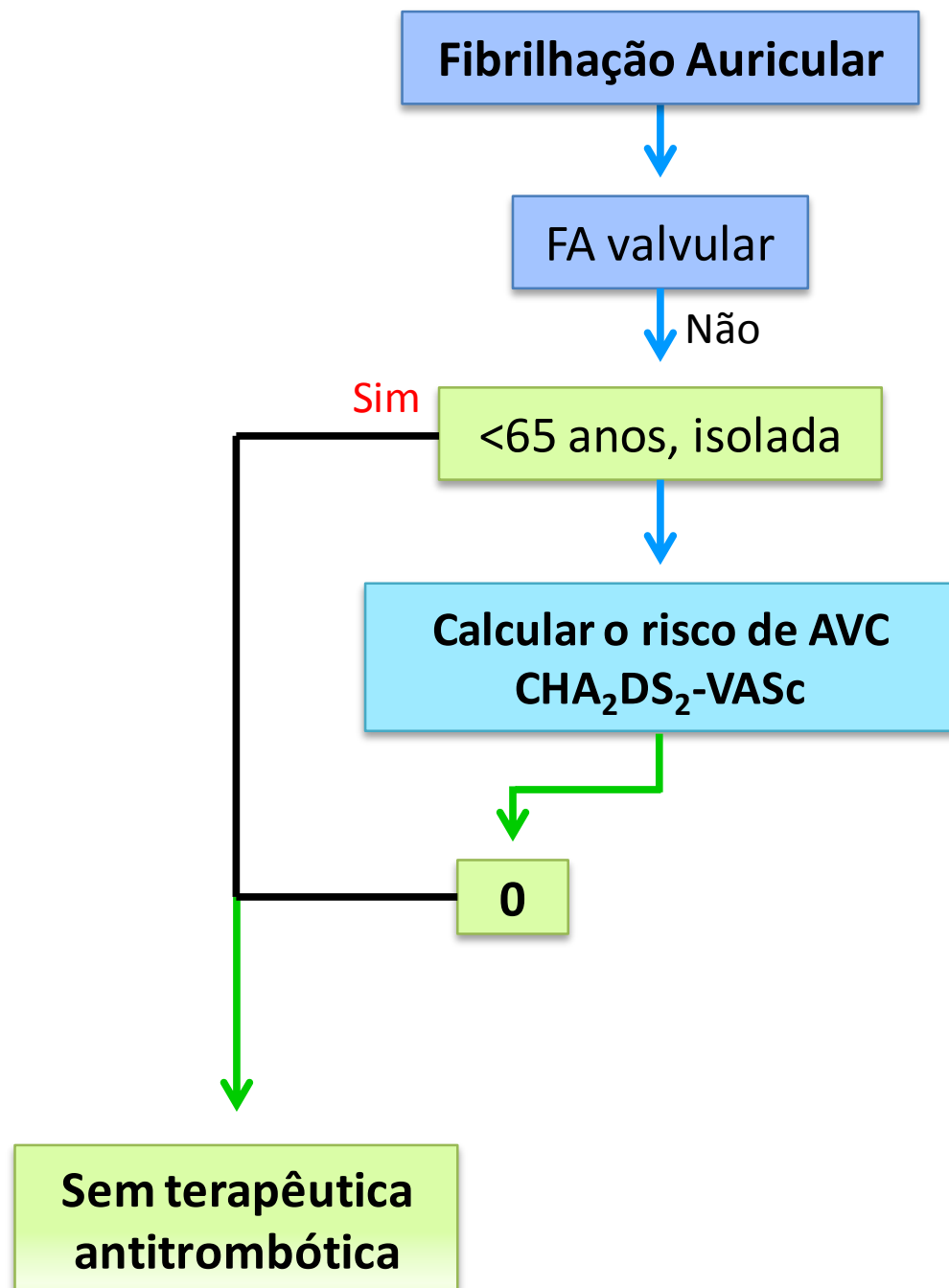
Score de risco isquêmico

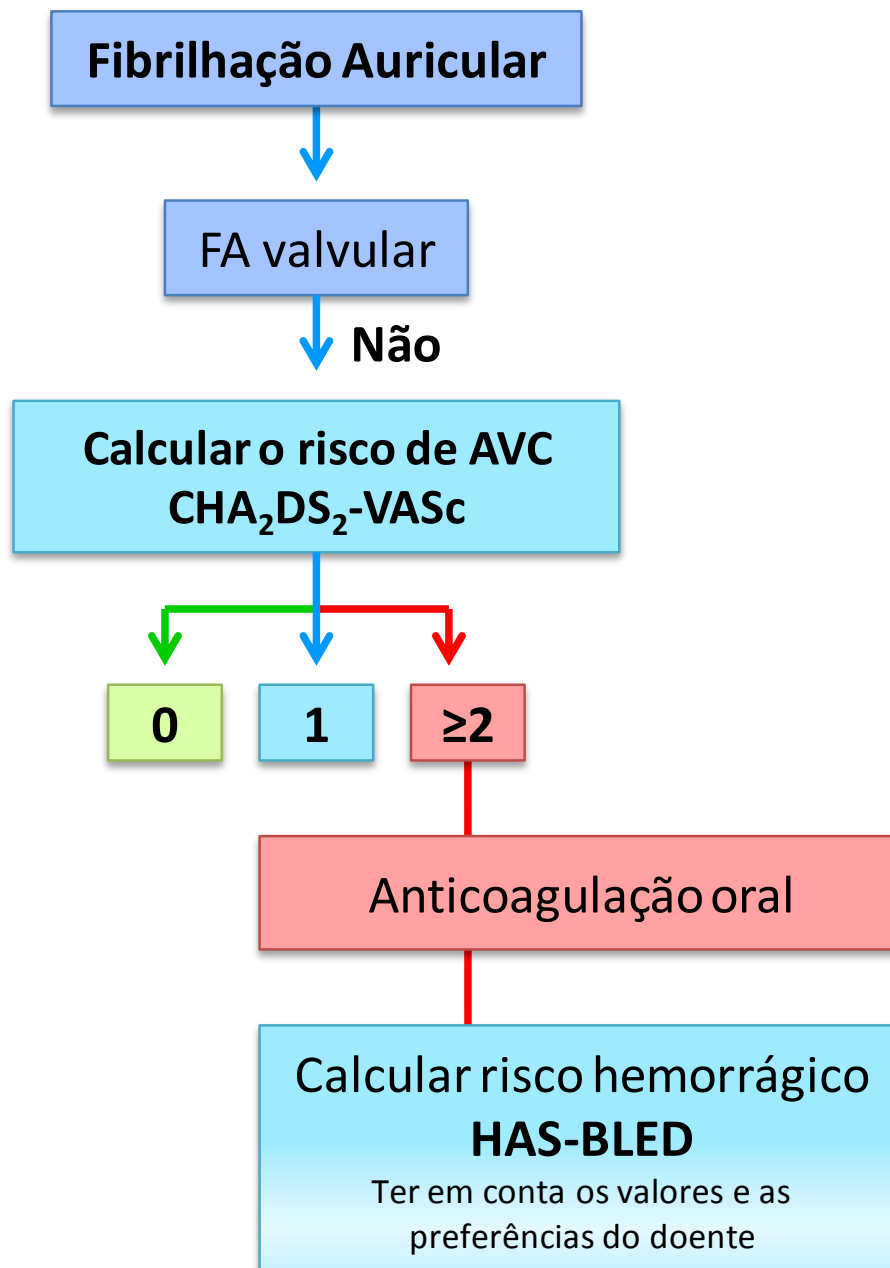
CHA₂DS₂ - VASc



Score = 1 → Considerar anticoagulação

Score ≥ 2 → Recomendada anticoagulação





Avaliar o risco hemorrágico nos doentes com indicação para anticoagulação

Risco isquémico

Risco hemorrágico

CHA₂DS₂-VASc

HAS-BLED

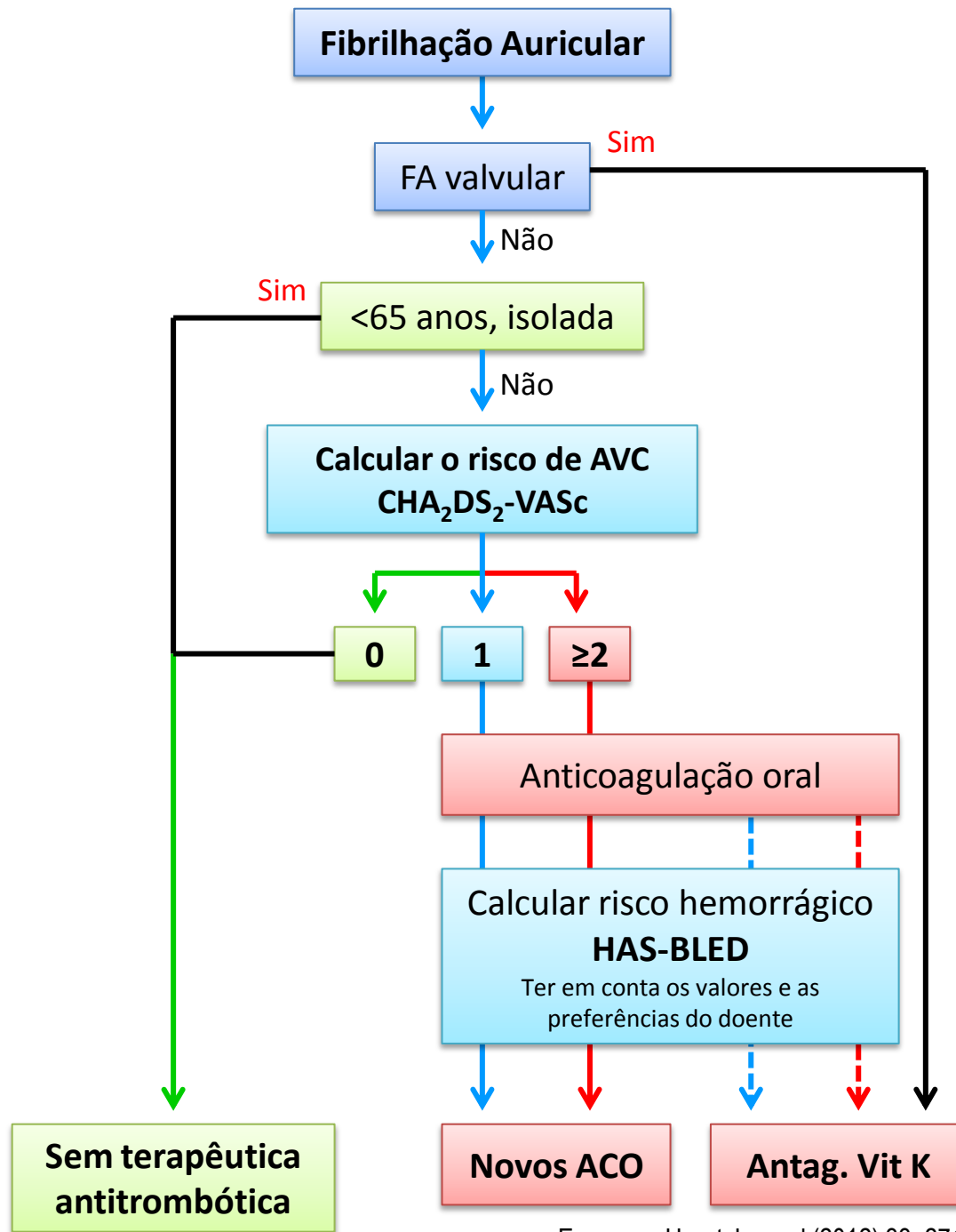
Avaliação do risco hemorrágico

Score **HAS-BLED**

HAS-BLED	Característica clínica	Pontuação
H Hypertension	Hipertensão	1
A Analysis	Função renal e hepática anormal (1 ponto cada)	1 ou 2
S Stroke	AVC	1
B Bleeding	Hemorragia	1
L Labil INR	INR lábil	1
E Elderly	Idoso (idade > 65 anos)	1
D Drugs	Fármacos ou álcool (1 ponto cada)	1 ou 2

Característica clínica	Definição
Hipertensão	PAS > 160 mmHg
Função renal anormal	Diálise crónica, transplante renal ou creatinina sérica \geq 2.25 mg/dl
Função hepática anormal	Doença hepática crónica (ex: cirrose) ou alterações bioquímicas: <ul style="list-style-type: none"> • Bilirrubina > 2x limite superior normal associada • AST/ALT/Fosfatase alcalina > 3x limite superior do normal
Hemorragia	Antecedentes hemorrágicos e/ou predisposição para hemorragia (ex: diátese hemorrágica, anemia, etc.)
INR lábil	Dificuldade em manter o INR dentro do intervalo terapêutico
Fármacos ou álcool	Consumo de anti-agregantes plaquetários, AINE ou abuso de bebidas alcoólicas

Característica clínica	Definição
Hipertensão	PAS > 160 mmHg
Função renal anormal	Diálise crónica, transplante renal ou creatinina sérica ≥ 2.25 mg/dl
Função hepática anormal	Doença hepática crónica (ex: cirrose) ou alterações bioquímicas: <ul style="list-style-type: none"> • Bilirrubina > 2x limite superior normal associada • AST/ALT/Fosfatase alcalina > 3x limite superior do normal
Hemorragia	Antecedentes hemorrágicos e/ou predisposição para hemorragia (ex: diátese hemorrágica, anemia, etc.)
INR lábil	Dificuldade em manter o INR dentro do intervalo terapêutico
Fármacos ou álcool	Consumo de anti-agregantes plaquetários, AINE ou abuso de bebidas alcoólicas



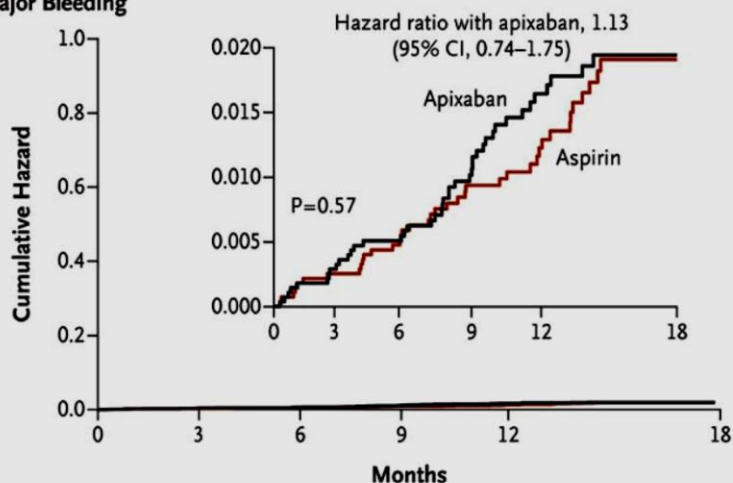
Score = 2

Score = 2/1

Averroes – Apixaban versus AAS

Hemorragias Major

B Major Bleeding

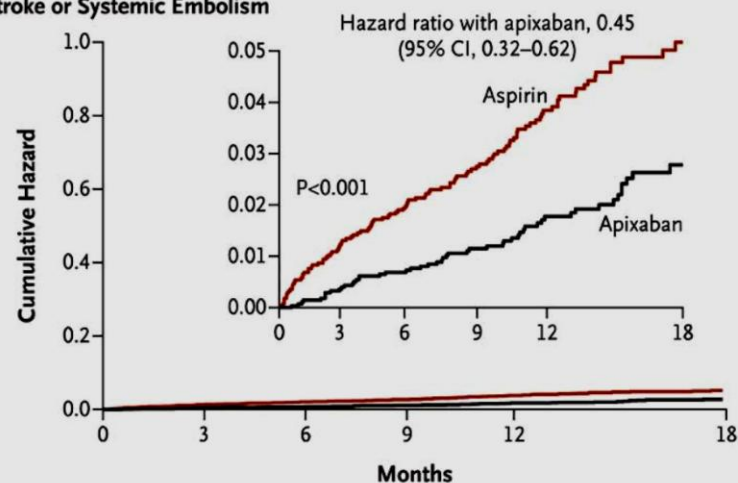


No. at Risk

Aspirin	2791	2738	2557	2140	1571	642
Apixaban	2808	2759	2566	2120	1521	622

AVC e Embolismo Sistémico

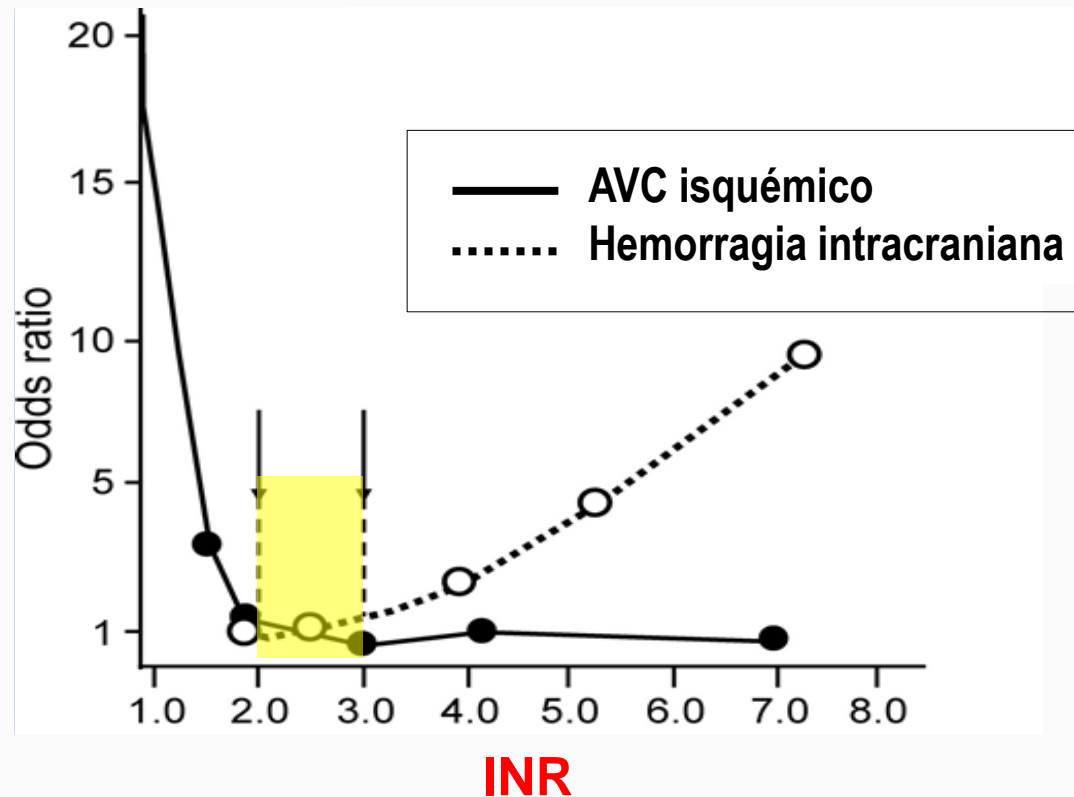
A Stroke or Systemic Embolism



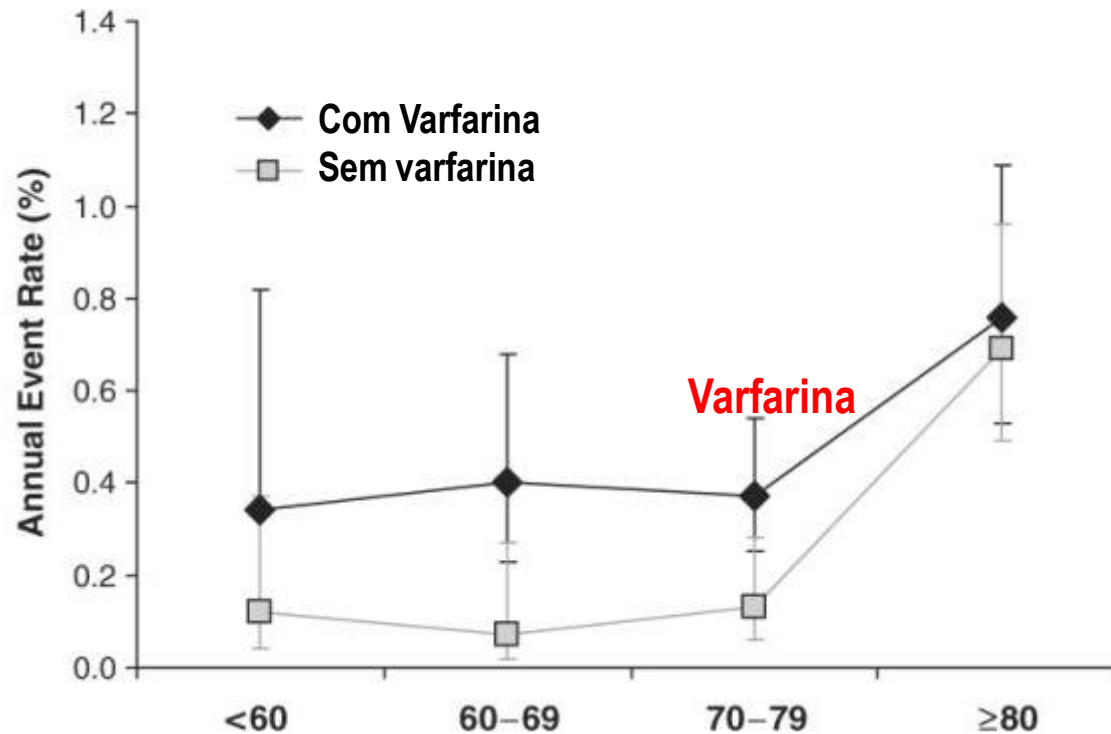
No. at Risk

Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615

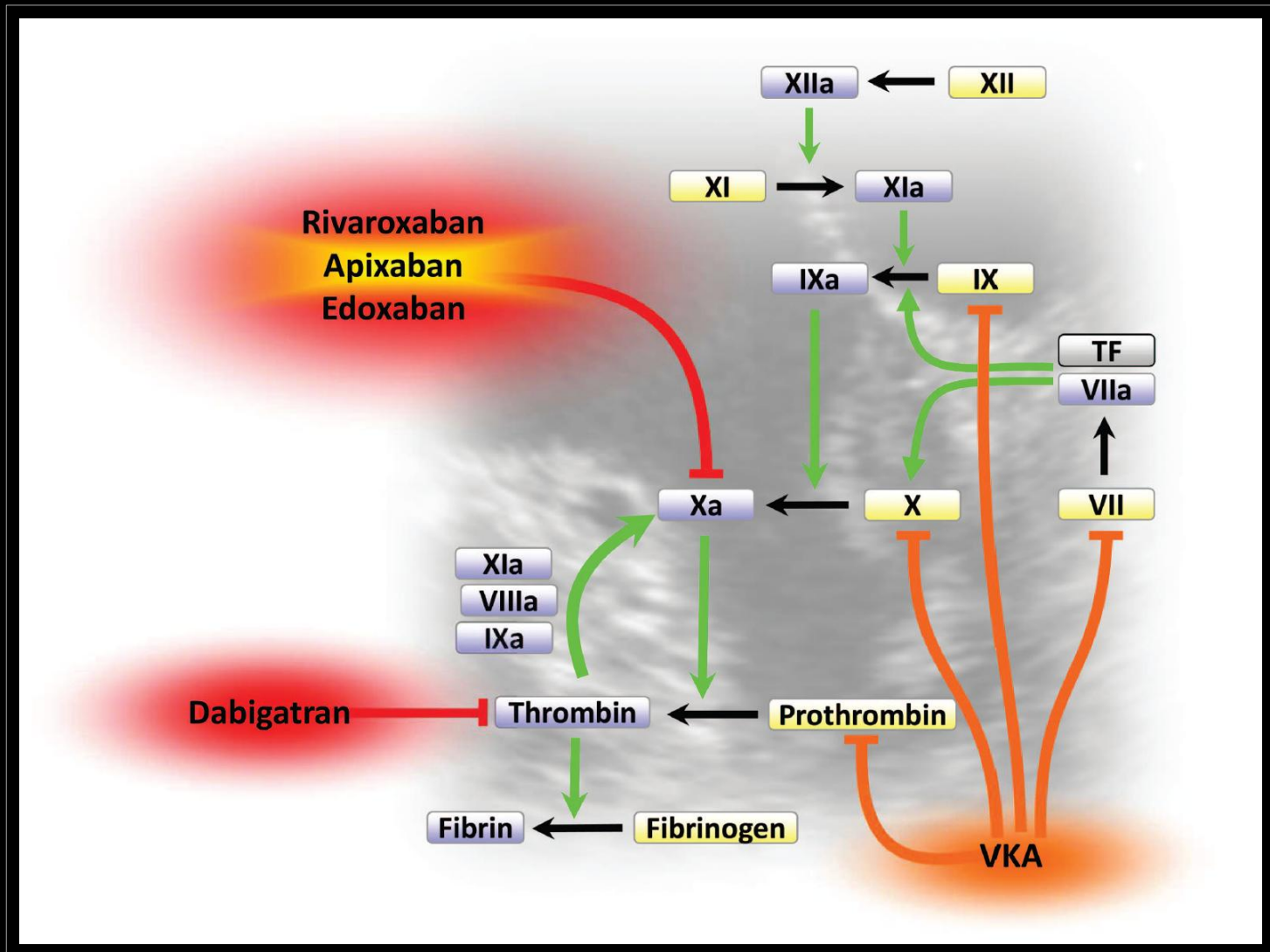
Varfarina - Intervalo terapêutico estreito



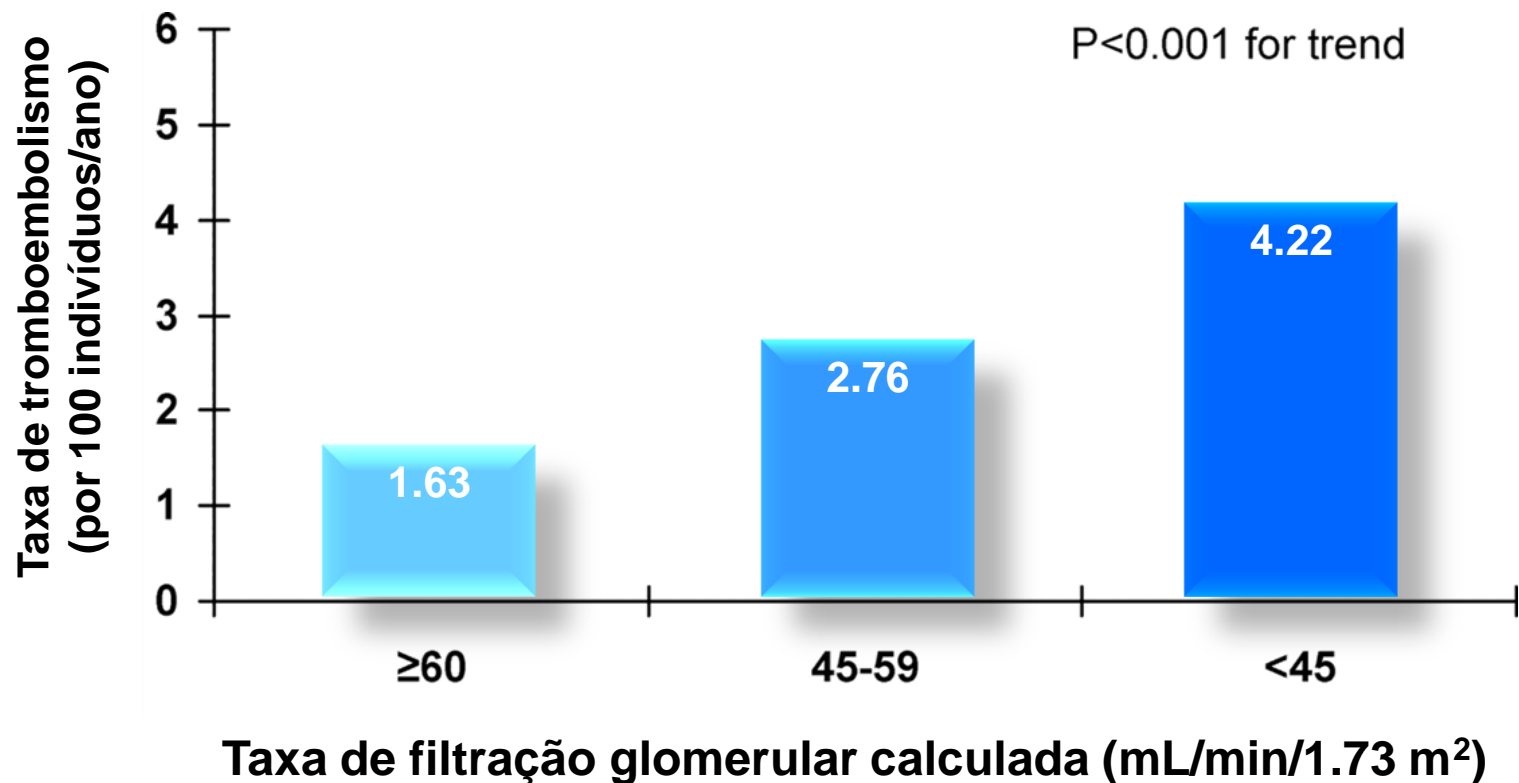
Influência da idade no aumento do risco de hemorragia intracraniana com a Varfarina



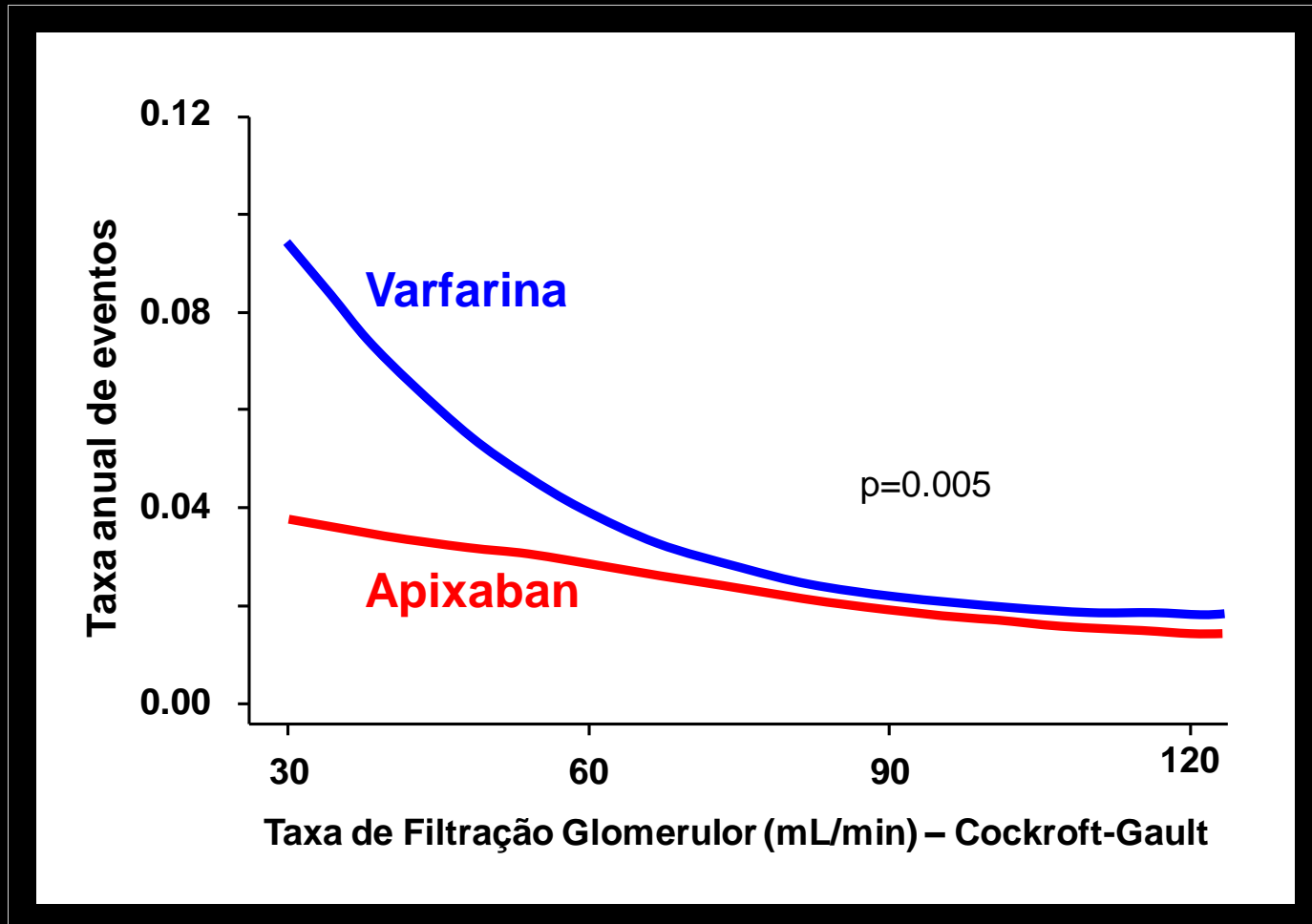
Local de acção dos novos anticoagulantes orais



A diminuição da taxa de filtração glomerular está associada ao aumento do risco de tromboembolismo na FA



Hemorragias major com varfarina ou apixaban em função da Taxa de Filtração Glomerular



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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; $P < 0.001$ for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; $P < 0.001$ for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran ($P = 0.003$) and 3.11% per year in the group receiving 150 mg of dabigatran ($P = 0.31$). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran ($P < 0.001$) and 0.10% per year with 150 mg of dabigatran ($P < 0.001$). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran ($P = 0.13$) and 3.64% per year with 150 mg of dabigatran ($P = 0.051$).

CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

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*Members of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Study Group are listed in the Appendix and the Supplementary Appendix, available with the full text of this article at NEJM.org.

Drs. Connolly, Ezekowitz, Yusuf, and Wallentin contributed equally to this article.

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Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND

The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin.

METHODS

In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.

RESULTS

In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; $P < 0.001$ for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; $P < 0.001$ for noninferiority; $P = 0.12$ for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; $P = 0.44$), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, $P = 0.02$) and fatal bleeding (0.2% vs. 0.5%, $P = 0.003$) in the rivaroxaban group.

CONCLUSIONS

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)

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*A complete listing of the steering committee members and trial investigators in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) is provided in the Supplementary Appendix, available at NEJM.org.

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Apixaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

RESULTS

The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; $P < 0.001$), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; $P = 0.047$). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; $P < 0.001$), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; $P = 0.42$).

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Granger at the Duke Clinical Research Institute, Duke University Medical Center, DUMC Box 3850, Durham, NC 27715, or at christopher.granger@duke.edu.

*The members of the steering committee, as well as other committee members and investigators in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, are listed in the Supplementary Appendix, available at NEJM.org.

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Novos anticoagulantes orais

AVC isquémico



= ↓ D₁₅₀

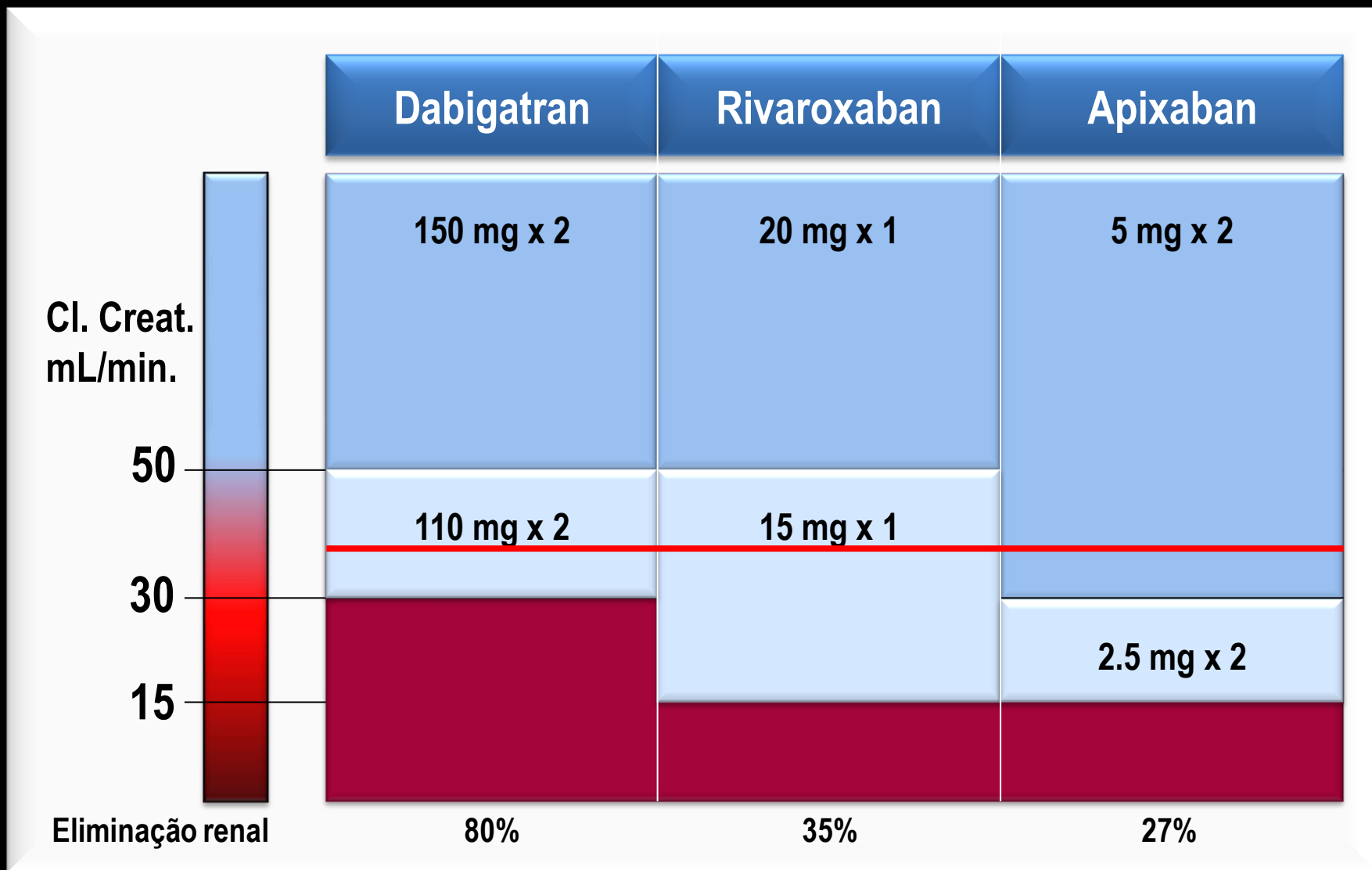
AVC hemorrágico



↓ ↓

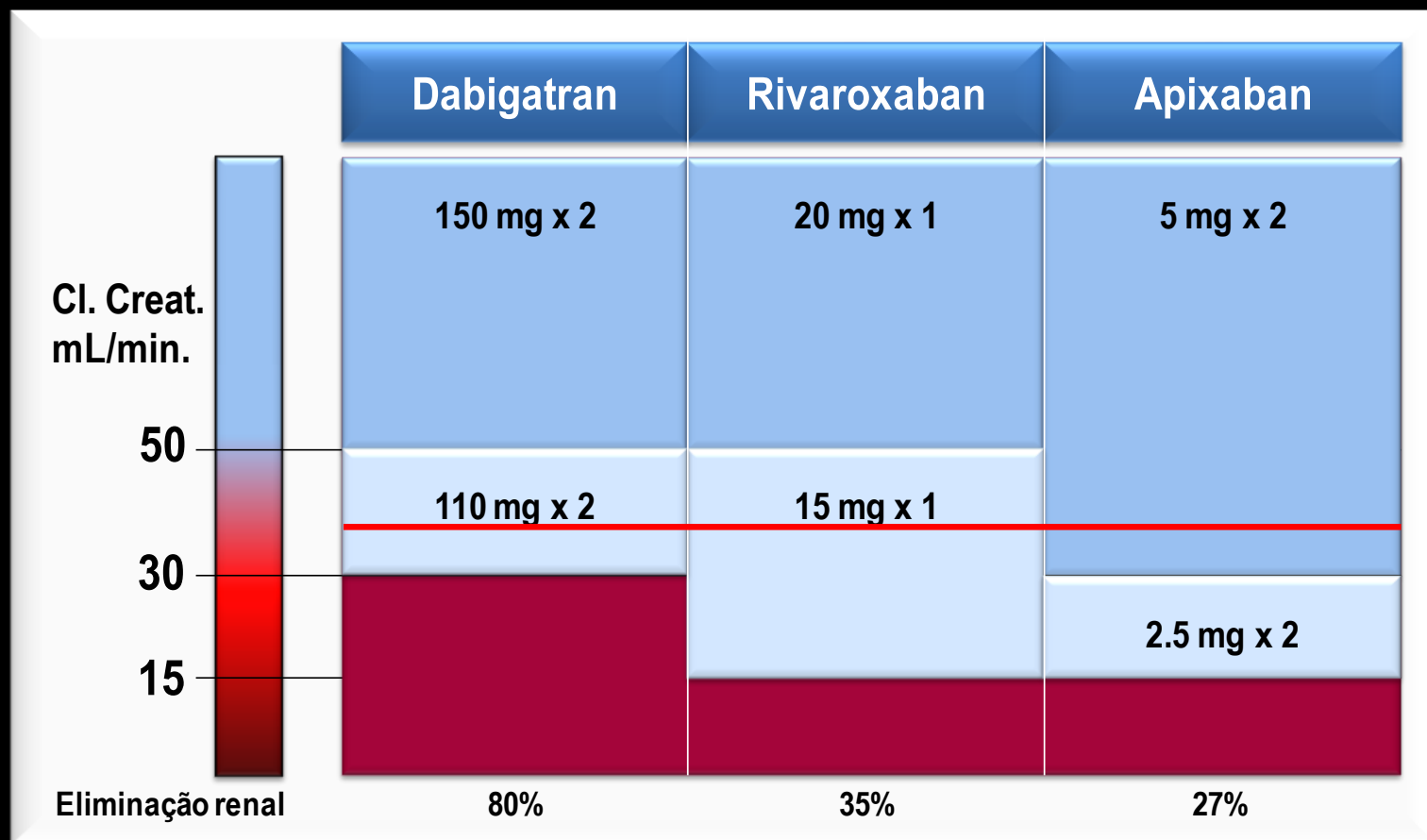
Os Novos Anticoagulantes Orais na disfunção renal

Dosagens aprovadas pela EMA na doença renal crónica



Os Novos Anticoagulantes Orais na disfunção renal

Dosagens aprovadas pela EMA na doença renal crónica



- Interação com a idade
- D110 ↓ - Hemor. major
- D150 - ↓ AVC isquémico
↑ Hem GI
- Dispepsia

- ↑ Hemorragias GI
- ↑ Necessidade transfusões
- ↓ Hemorragias fatais

- **2.5 mg** se Cr ≥ 1.5 e Idade ≥ 80 anos ou peso ≤ 65 kg
- ↓ Hemorragias major
- ↓ Mortalidade global

Novos anticoagulantes orais

AVC isquémico



= ↓ D₁₅₀

AVC hemorrágico



↓ ↓

Table 5 Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors, and recommendations towards NOAC dosing

	Via	Dabigatran	Apixaban	Edoxaban ^a	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18% ²⁹	No data yet	No effect ³⁰	No effect ^{27,31}
Digoxin	P-gp competition	No effect ³²	No data yet	No effect ³⁰	No effect ^{27,33}
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180% ²⁴ (reduce dose and take simultaneously)	No data yet	+53% (SR) ³⁰ (reduce dose by 50%) ^a	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect ²⁴	+40% ^{SmPC}	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80% ³⁰ (reduce dose by 50%) ^b	+50%
Amiodarone	P-gp competition	+12–60% ²⁴	No data yet	No effect ³⁰	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%) ^b	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100% ^{SmPC}	No data yet	Up to +160% ²⁷
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered) ²⁷
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54% ^{26,27}
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase ^{SmPC}	No data yet	Up to +153% ²⁷
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	–66% ³⁴	–54% ^{SmPC}	–35%	Up to –50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	–12–30% ^{22–24}	No data yet	No effect	No effect ^{21,25}
Other factors					
Age ≥ 80 years	Increased plasma level			No data yet	
Age ≥ 75 years	Increased plasma level			No data yet	
Weight ≤ 60 kg	Increased plasma level				
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥ 3			

- Contraindicado
- Reduzir dose
- Reduzir dose se outro amarelo associado
- Sem dados
- Recomendações baseadas em considerações farmacocinéticas