Stroke Prevention and Atrial Fibrillation (AF) Management: Navigating the Waters of Direct Oral Anticoagulants (DOACS)

Regional Education Rounds
Thunder Bay Regional Health Sciences Centre
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St Michael's Hospital

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Mitigating Potential Bias

The Regional Education Rounds Planning Committee mitigated bias by ensuring there was no Industry involvement in planning or education content.

To comply with accreditation requirements of the College of Family Physicians of Canada and The Royal College of Physicians and Surgeons of Canada, the speaker was provided with Declaration of Conflict of Interest forms, which were submitted to the NOSM CEPD Office.

On behalf of the Planning Committee, a Committee member reviewed the initial presentation supplied by the speaker to ensure no evidence of bias.

Faculty/Presenter Disclosure

- **Presenter:** Paul Dorian MD
- **Relationships with commercial interests:**
  - **Grants/Research Support: Bayer, BI. BMS, Pfizer, Servier**
  - **Honoraria: Bayer, BI. BMS, Pfizer, Servier**
  - **Consulting Fees: Bayer, BI. BMS, Pfizer, Servier .**

Disclosure of Commercial Support

- **This program has received no financial support This program has.**
- **Potential for conflict(s) of interest:**
  - Paul Dorian has received funding from BMS/Pfizer , BI, and Bayer, organizations whose products will be mentioned in this program
  - BMS/Pfizer , Bayer, and BI distribute/benefit from the sale of products that will be discussed in this program: Apixaban , Dabigatran, and Rivaroxaban

Mitigating Potential Bias

- The speaker will refer in all cases to guideline recommended and evidence based management and interventions
- When there is discussion regarding items that are not directly supported by randomized clinical trials, the speaker will indicate this

Objectives

- Identify stroke and bleeding risk factors and risk scores in atrial fibrillation
- Develop a strategy for managing therapy complications, interruptions, and dose changes
- Discuss best strategies for shared decision making with patients

"Alice came to a fork in the road. 'Which road do I take?' she asked.
'Where do you want to go?' responded the Cheshire Cat.
'I don't know,' Alice answered.
'Then,' said the Cat, 'it doesn't matter."
— Lewis Carroll, *Alice in Wonderland*

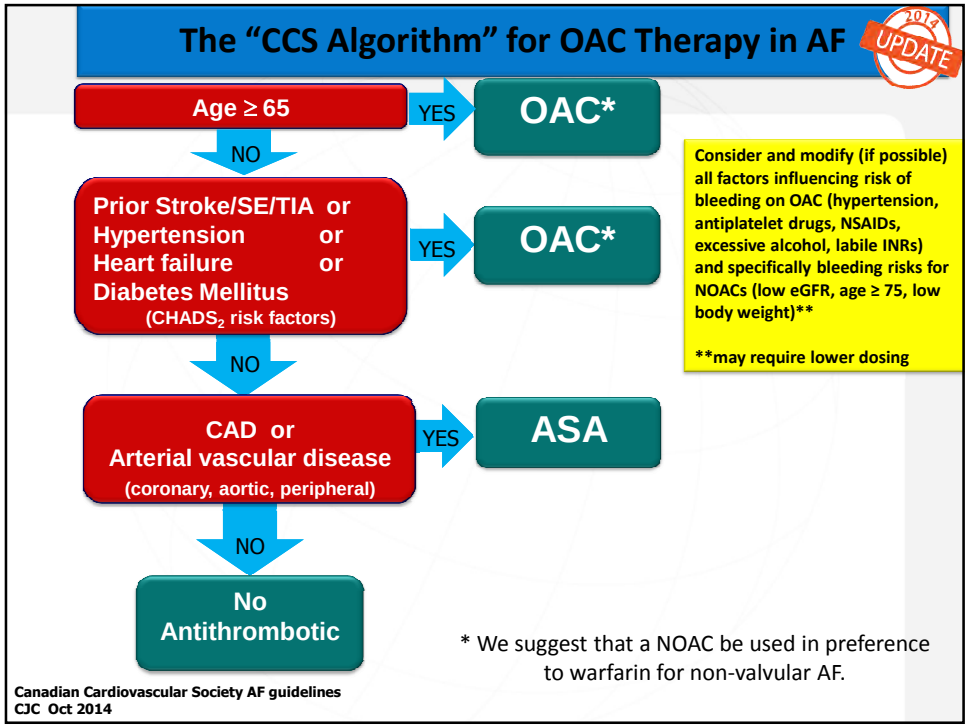
"We are our choices."
— Jean-Paul Sartre

If you are starting a 75 yr old hypertensive patient on warfarin, what is the annualized risk of a major bleed in the subsequent 30 days?

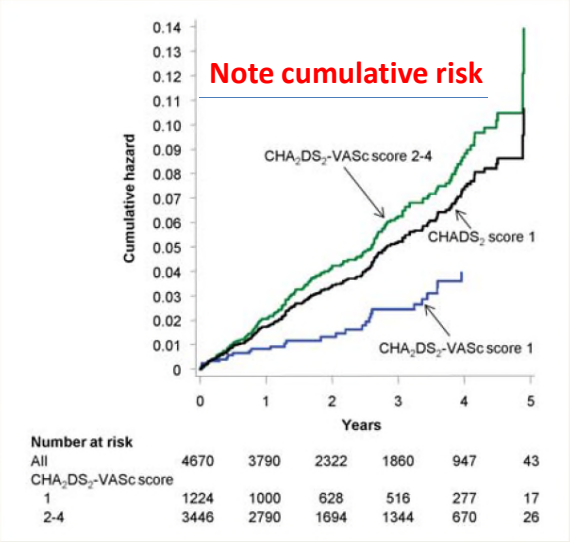
- 2%-5%
- 5% - 10%
- 10% - 15%
- 20%- 25%
- 30%-35%
- ≥ 50%

If you are starting a patient on warfarin, what is the average 1 yr. risk of a bleed followed by death (in the subsequent 30 days?)

- 0.01 % (1/10, 000)
- 0.1 % (1/1000)
- 0.5% (1/200)
- 1% (1/100)
- 2% (1/50)



Risk of stroke in the average 70 yr old AF patient on ASA is 10% over 5 years



Most CHADSVaSC = 2-4 were age > 65 + HT ± female

Most CHADSVASc = 1 were hypertension , age<65

From ACTIVE –A, W, and AVERROES ; all pts on ASA ± clopidogrel

Coppens et al Eur Ht J 2013; 34:170

Performance and Validation of a Novel Biomarker-Based Stroke Risk Score for Atrial Fibrillation

Circulation. 2016 Aug 28. pii: CIRCULATION

Conclusions—The biomarker-based ABC-stroke score was well calibrated and consistently performed better than both the CHA2DS2VASc and ATRIA stroke scores. The ABC score should be considered an improved decision support tool in the care of patients with AF ***With respect, I disagree***

The ABC-stroke score (Age/Biomarkers/clinical Hx stroke)was well calibrated with
0.76 stroke/SE events per 100 person years in the predefined low (<1%/year) risk group,
1.48 in the medium (1-2%/year) risk group, and
2.60 in the high (>2%/year) risk group for the ABC-stroke score

The one-year risk of stroke/systemic embolism (SE) is calculated using the following equations:
LP = -3.2864 + 0.8331 * Prior stroke/TIA + 0.0075 * Age + 0.2139 * ln(hs-cTnT) + 0.2879 * ln(NT-proBNP)
One-year risk of stroke/SE = 1 – 0.9863^exp{LP}

RISK and Decision aids and rationality

- Decisions depend on actual risks , and perception of risk
- Perception is as important as the actual risk, especially for low frequency events overestimation of risk at low frequencies (Kahneman)
- Requires articulation of beliefs and beliefs about beliefs
- Assessing decision aids requires measuring decisional conflict and decision satisfaction/regret
- With stroke and bleeding this is impossible to do objectively / rationally
- Requires reconciling lived experience with remembered/ predicted experience –this cannot be done rationally

Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary
Hein Heidbuchel, et al *Europace* 2015;**17**:1467–1507

Table 3
Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–Edoxaban–Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl <15 mL/min	No official indication for use			
	There is no need for pre-operative bridging with LMWH/UFH			

Peri-Procedural Management

- Very minor procedures (e.g. dental/cataract)
  - May be performed at trough concentration (not peak concentration), i.e. just before the next scheduled dose
  - Or skip one dose of dabigatran/apixaban
- Minor surgery/low bleeding risk
  - Stop NOAC 1 day before; longer if renal dysfunction
- Major surgery/high bleeding risk/spinal anesthesia
  - Stop NOAC 2 days before (2-3 days for dabigatran); longer if renal dysfunction
- Restart NOAC
  - 24h post-op for minor surgery; 48h post-op for major surgery
- **This is a very general guide; See tables at www.ThrombosisCanada.ca for more detailed info.*

D – Drug Interactions

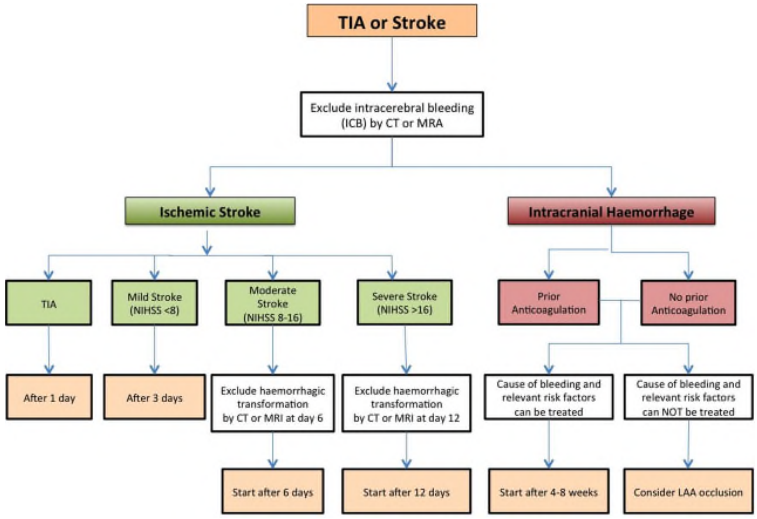
D	DRUG INTERACTIONS (review all concomitant medications)	
	ASA / other antiplatelets?	Y / N
	NSAID?	Y / N
	Other drug interactions? (Review med list / OTCs; see back)	Y / N

- Review medications, OTCs
- Concomitant aspirin use is a common reversible risk factor for bleeding in anticoagulated patients
  - In warfarin-treated patients, it doubles bleeding risks without added benefit for stroke/MI prevention (with some exceptions…)
  - In DOAC-treated patients, it nearly doubles bleeding risks

Table 3: Suggested Use of NOACs According to Patient Renal Function for Stroke Prevention in AF†

NOAC	CrCl(mL/min)	Drug Dose	Comment
Dabigatran	≥ 50	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding or in the elderly (e.g. age ≥ 80 years) Measure CrCl every 12 months
	30-49	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding (e.g. age ≥ 80 years) Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid dabigatran	Consider warfarin as alternative anticoagulant
Rivaroxaban	≥ 50	20 mg daily	Measure CrCl every 12 months
	30-49	15 mg daily	Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid rivaroxaban	Consider warfarin as alternative anticoagulant
Apixaban	≥ 50	5 mg twice daily	Measure CrCl every 12 months
	25-49	5 mg twice daily	2.5 mg twice daily in patients with 2 of following: (1) creatinine ≥ 133 µmol/L; (2) age ≥ 80 years; (3) body weight ≤ 60 kg Measure CrCl every 6 months *and* with acute illness
	15-24	No dose recommendations can be made	Very limited clinical data with apixaban Consider warfarin as alternative anticoagulant
	< 15	Avoid apixaban	Consider warfarin as alternative anticoagulant

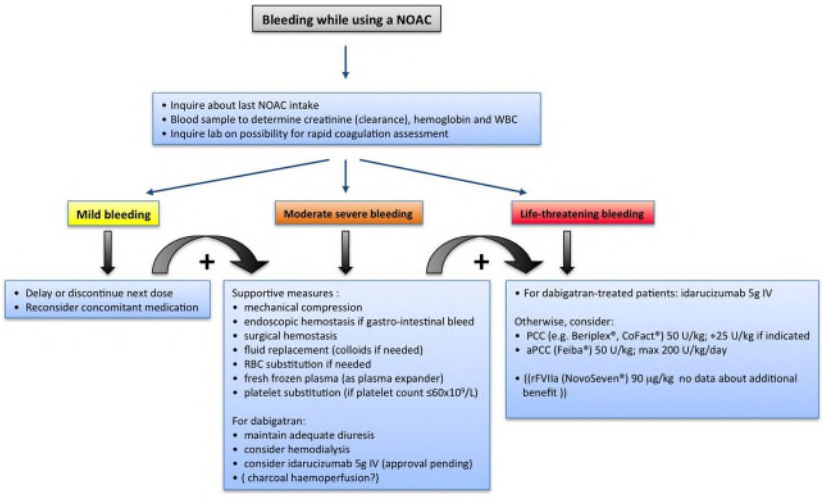
Flowchart for the initiation or re-initiation of anticoagulation after transient ischaemic attack (TIA)/stroke or intracerebral haemorrhage.



Hein Heidbuchel et al. Eur Heart J 2016;eurheartj.ehw058

European Heart Journal

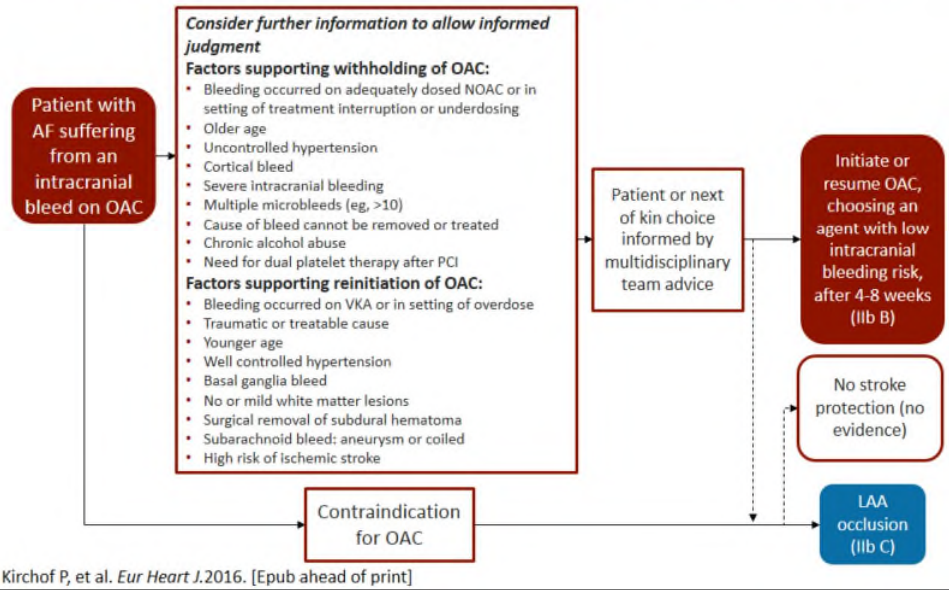
Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy.



Hein Heidbuchel et al. Eur Heart J 2016;eurheartj.ehw058

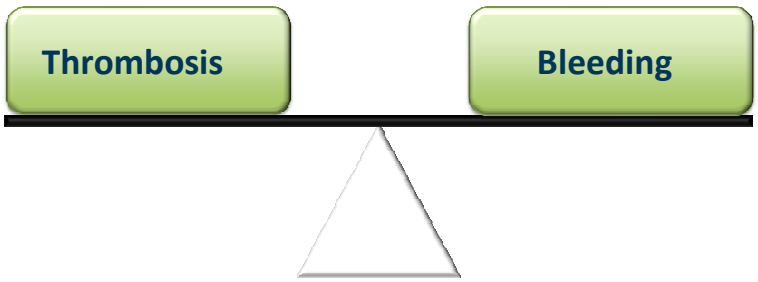
European Heart Journal

2016 ESC Guidelines for AF: Initiation or Resumption of Anticoagulation in AF Patients After an Intracranial Bleed



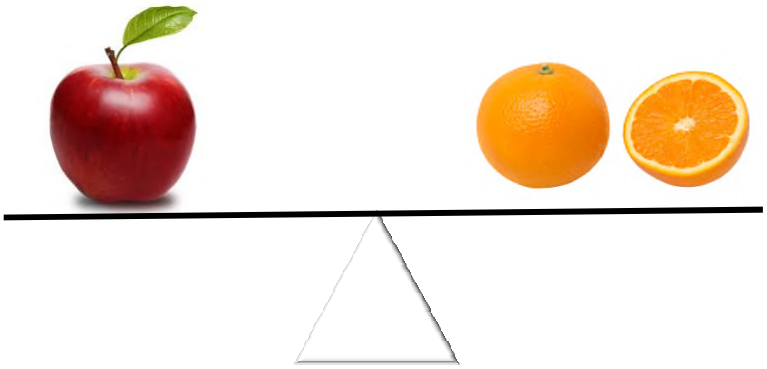
Kirchof P, et al. *Eur Heart J.*2016. [Epub ahead of print]

The efficacy and safety dilemma of oral anticoagulants for stroke prevention



Is this the correct metaphor ?

The efficacy and safety dilemma of oral anticoagulants for stroke prevention



Thrombosis Bleeding

Rates of hemorrhage during warfarin therapy for atrial fibrillation

Gomes et al CMAJ, February 5, 2013, 185(2) E121

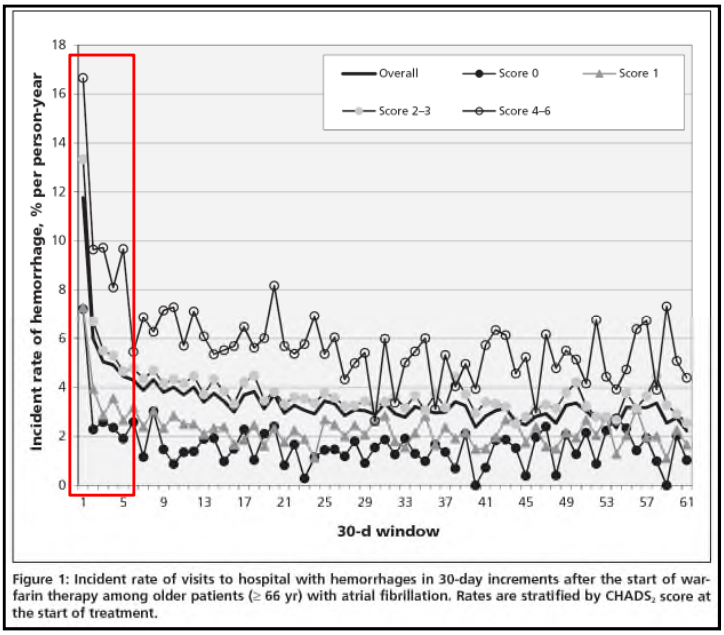


Figure 1: Incident rate of visits to hospital with hemorrhages in 30-day increments after the start of warfarin therapy among older patients (≥ 66 yr) with atrial fibrillation. Rates are stratified by $CHADS_2$ score at the start of treatment.

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin	
							Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*		
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10

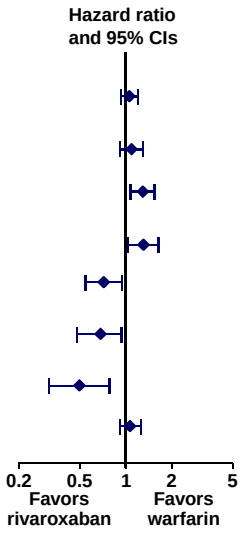
Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery

Connolly et al. 2009 N Engl J Med; 361:1139-51

Patel *et al.* N Engl J Med. 2011 Sep 8;365(10):883-91

ROCKET AF – Bleeding Analysis

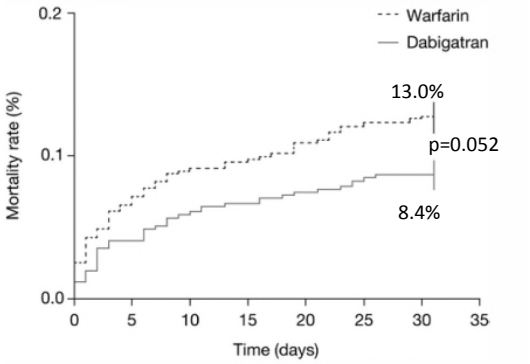
Parameter	Rivaroxaban (N=7111) n (% per year)	Warfarin (N=7125) n (% per year)	Hazard ratio (95% CI)
Principal safety endpoint	**1475 (14.9)**	1449 (14.5)	1.03 (0.96,1.11)
Major bleeding	**395 (3.6)**	386 (3.4)	1.04 (0.90,1.20)
Hemoglobin drop (≥2 g/dl)	**305 (2.8)**	254 (2.3)	1.22 (1.03,1.44)*
Transfusion	**183 (1.6)**	149 (1.3)	1.25 (1.01,1.55)*
Critical organ bleeding	**91 (0.8)**	133 (1.2)	0.69 (0.53,0.91)*
Intracranial hemorrhage	**55 (0.5)**	84 (0.7)	0.67 (0.47,0.93)*
Fatal bleeding	**27 (0.2)**	55 (0.5)	0.50 (0.31,0.79)*
Non-major clinically relevant bleeding	**1185 (11.8)**	1151 (11.4)	1.04 (0.96,1.13)



Major bleeding from gastrointestinal site (upper, lower and rectal): rivaroxaban = 224 events (3.2%); warfarin = 154 events (2.2%); *p*<0.001*

Safety population – as-treated analysis; *statistically significant

Outcomes after Major Bleeding: Dabigatran vs. Warfarin

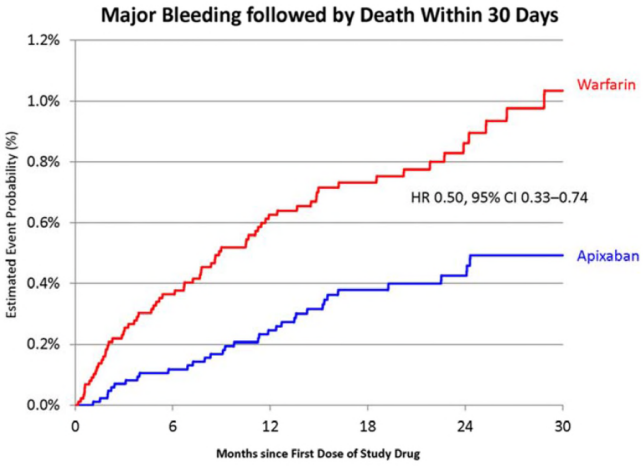


Thirty-day mortality rate after a major bleeding event.

- N=1034 with 1121 major bleeds in 5 phase III trials comparing dabigatran with warfarin in 27419 patients
- Major bleeds with dabigatran treated more frequently with blood transfusions (61% vs. 42%), less frequently with plasma (20% vs. 31%)
- Patients who experienced a bleed had a shorter ICU stay if previously treated with dabigatran vs. warfarin (mean 1.6 vs. 2.7 nights, p=0.01)

Majeed et al. Circulation. 2013; 128: 2325-2332

Major Bleeding in Patients with Atrial Fibrillation Receiving Apixaban or Warfarin in the ARISTOTLE Trial: Predictors, Characteristics, and Clinical Outcomes

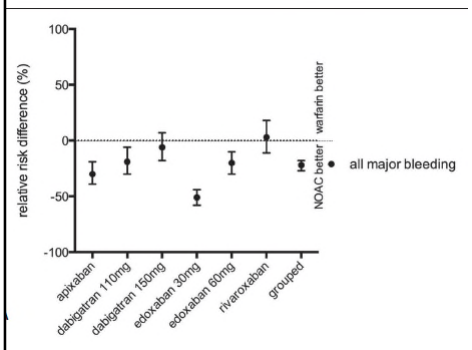


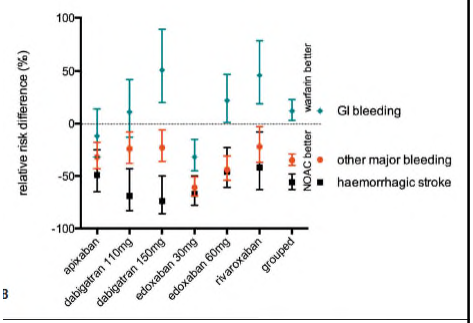
Risk of bleeding then dying on Apixaban = 1/500 in the first year
Risk of bleeding then dying on Warfarin = 1/166 (3 X the risk)

Hylek EM et al J Am Coll Cardiol. 2014 May 27;63(20):2141-7.

Organ-specific bleeding patterns of anticoagulant therapy: lessons from clinical trials

Thomas Vanassche; Jack Hirsh; John W. Eikelboom; Jeffrey S. Ginsberg
Population Health Research Institute, Thrombosis and Atherosclerosis Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada





Thromb Haemost 2014;112:918-923

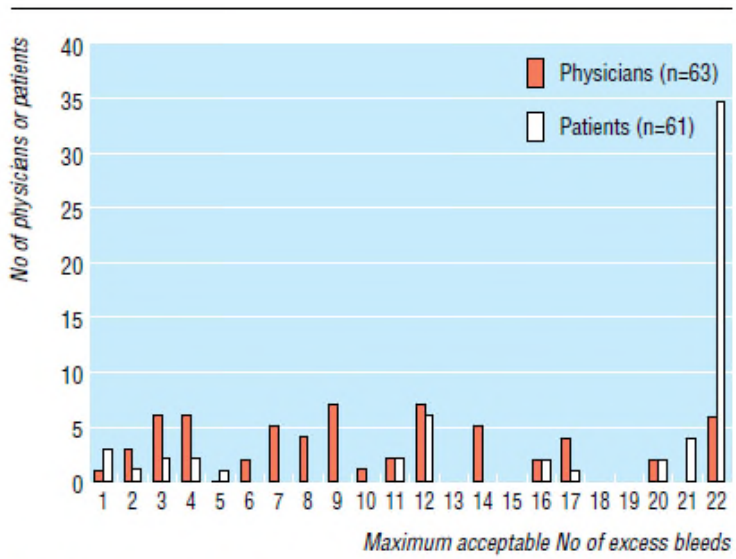


Fig 5 Bleeding thresholds for warfarin

Thirty five patients (57%) were willing to accept 22 extra episodes of bleeding in 100 patients over a two year period. Physicians' thresholds varied widely (P<0.001 for difference between groups).

Devereaux et al. BMJ 2001;323:1218

Risk aversion (psychology)

https://en.wikipedia.org/wiki/Risk_aversion_(psychology)

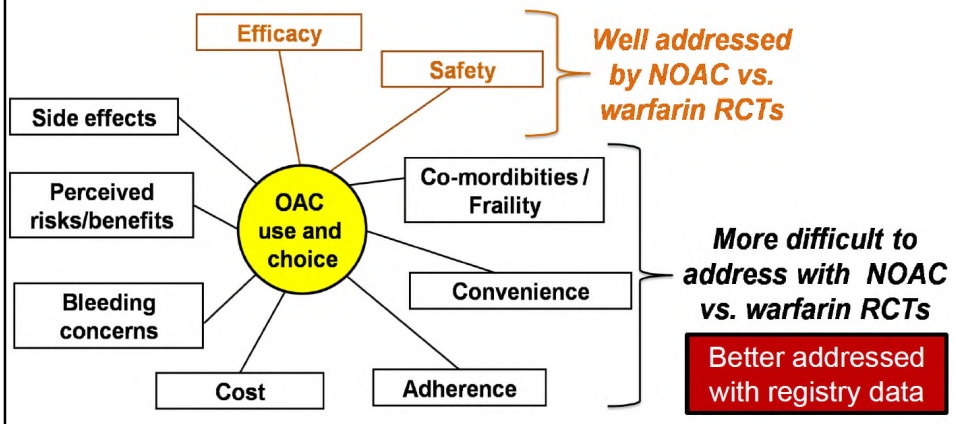
From Wikipedia, the free encyclopedia

- The negativity bias is noticeable in a plethora of situations related to the formation of risk-averse behaviour. ***Notably, any stimulus that evokes the expression of fear encourages risk-aversion***. The human brain has adapted to easily parse out these stimuli from a sea of benign stimuli .

Low probabilities, however, are overweighted, … Consequently, …people are often … risk-averse in dealing with unlikely losses

Kahneman, D., & Tverksy, A. (1984). "Choices, values, and frames". *American Psychologist* **39**: 341–350. doi:10.1037/0003-066X.39.4.341.

Factors which may determine OAC use over time in the "real world"



Evidence-Based Risk Communication: A Systematic Review

Daniella A. Zipkin, MD

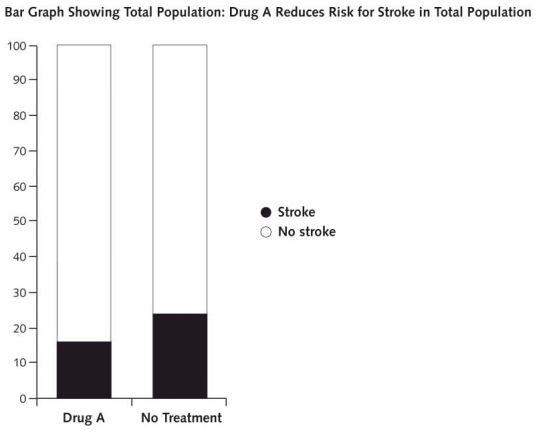
- **Conclusion:**Visual aids and absolute risk formats can improve patients' understanding of probabilistic information, whereas numbers needed to treat can lessen their understanding. Due to study heterogeneity, the superiority of any single method for conveying probabilistic information is not established, but there are several good options to help clinicians communicate with patients.

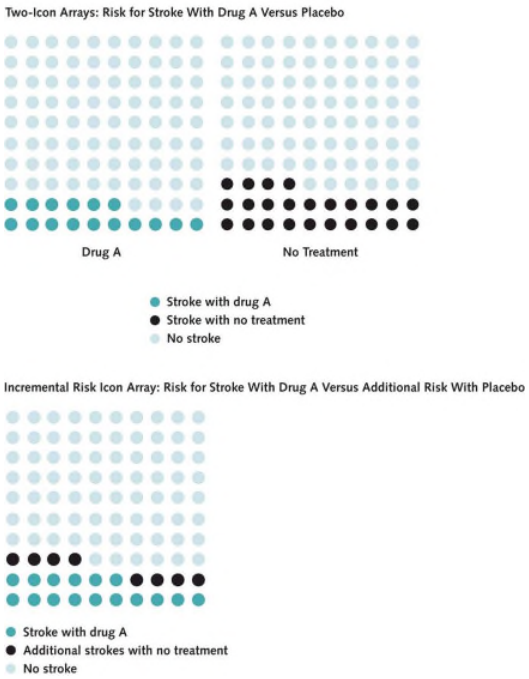
Ann Intern Med. 2014 Aug 19;161(4):270-80

Table 3. **Examples of Common Numerical Methods of Risk Communication to Show Risk for Stroke With Drug A Versus Placebo**

Method	Placebo	Drug A
Event rate	24%	16%
Natural frequency	24 out of 100	16 out of 100
ARR (can be stated as natural frequency or event rate)	–	8% or 8 out of 100
RRR	–	33%
NNT	–	13

ARR = absolute risk reduction; NNT = number needed to treat; RRR = relative risk reduction.





Ann Intern Med. 2014 Aug 19;161(4):270-80

Table 4. Recommended Approaches to Risk Communication

To improve understanding:

- Express probabilities as event rates (percentages) or natural frequencies (numerator/denominator as whole numbers)
- When using natural frequencies, use a denominator of 1000 participants
- Express benefits and risks in absolute terms, such as ARRs
- Avoid expressing benefits as NNTs
- Add bar graphs or icon arrays to natural frequencies or event rates
- Consider the use of icon arrays with smaller numerators and bar graphs with larger numerators
- Place a patient's risk in context by using comparative risks of other events
- Avoid the use of qualitative risk descriptors alone (such as "high risk")

Ann Intern Med. 2014 Aug 19;161(4):270-80

Table 4. **Recommended Approaches to Risk Communication**

To improve satisfaction:

- Supplement numerical risks with icon arrays or bar graphs
- Use an incremental risk format with icon arrays (risk with and without intervention displayed in the same array)
- Avoid the use of NNTs
- Avoid the use of qualitative risk descriptors alone

To influence acceptance of interventions:

- Realize that expressing numerical benefits as RRRs has the greatest effect on decision making
- Add baseline risks to both ARRs and RRRs to equalize their effects on decision making
- Realize that positive framing (stating benefits rather than harms) increases acceptance of therapies

ARR = absolute risk reduction; NNT = number needed to treat; RRR = relative risk reduction.

Ann Intern Med. 2014 Aug 19;161(4):270-80