RISKY BUSINESS: HOW TO MANAGE ATRIAL FIBRILLATION IN PATIENTS WHO ARE AT A HIGH BLEEDING RISK

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ELIZABETH PETROVITCH, PHARM.D., BCPS
CLINICAL PHARMACIST SPECIALIST - CARDIOLOGY

LEARNING OBJECTIVES

- Describe risk factors for bleeding for patients receiving anticoagulants or anti-platelets.
- Describe different bleeding risks among patients receiving warfarin, direct oral anticoagulants, and anti-platelets.
- Identify a management strategy for a patient with AFIB at a high risk of bleeding.

ATRIAL FIBRILLATION

- 33.5 million men and women estimated worldwide
- Average annual stroke rate is 1.5% in randomized control trials
  - Differs in real world
- Oral anticoagulation (OAC) can prevent the majority of ischemic strokes in AF

European Heart Journal 2016;37:2893-2962
Circulation. 2014;130:e199-e267

BENEFIT AND USE OF OAC

- Net clinical benefit almost universal
  - Exception – patients at very low stroke risk
- Underuse or premature termination of OAC is common
- Bleeding events, severe and nuisance can occur with OAC
  - Lead to perceived "high bleed risk"
- Stroke risk often exceeds the bleed risk on OAC

European Heart Journal 2016;37:2893–2962

ASSESSING THE RISK

STROKE RISK ASSESSMENT

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65–74 years	+1
Sex category (female)	+1

CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

	Score		Adjusted Stroke Rate (% per y)
$CHADS_2$		$CHADS_2^*$	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 y	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2

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WHAT MAKES A PATIENT HIGH RISK FOR BLEED?

Modifiable bleeding risk factors
Hypertension (especially when systolic blood pressure is >160 mmHg)[a,b,c]
Labile INR or time in therapeutic range <60%[b] in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs[c,d]
Excess alcohol (≥8 drinks/week)[a,b]
Potentially modifiable bleeding risk factors
Anaemia[a,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]

Non-modifiable bleeding risk factors
Age[a] (>65 years)[a] (≥75 years)[a,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent kidney disease or renal transplant[a,c]
Cirrhotic liver disease[a]
Malignancy[a]
Genetic factors[b]
Biomarker-based bleeding risk factors
High-sensitivity troponin[a]
Growth differentiation factor-15[a]
Serum creatinine/estimated CrCl[a]

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WHAT FACTORS ARE ASSOCIATED WITH BLEED RISK?

- Overlapping factors for bleed and stroke
  - HTN
  - Age
  - Prior stroke
- Leads to many high stroke risk patients being high bleed risk

HOW CAN I ASSESS THESE FACTORS?

- Multiple tools available to assess
  - Developed in differing populations
- Bleed risk scoring tools
  - HAS-BLED
  - HEMORR2HAGES
  - ATRIA
  - ORBIT
  - ABC

HAS-BLED

- Population
  - Euro Heart Survey on AF in 3,456 patients with atrial fibrillation followed for 12 months
- Interpretation:
  - Low (0)
  - Intermediate (1–2)
  - High (3)
- Components:
  - 1 point for each
    - Hypertension
    - Abnormal renal function
    - Abnormal liver function,
    - Stroke
    - Bleeding history or predisposition
    - Labile INR
    - Age > 65
    - Drug/alcohol use concomitantly

HEMORR2HAGES

- Population:
  - National Registry of Atrial Fibrillation (NRAF)
  - 3791 hospitalized Medicare patients with atrial fibrillation
  - Discharged on warfarin and followed for 36 months
- Interpretation:
  - Low (0–1)
  - Intermediate (2–3)
  - High (≥ 4)
- Components:
  - 1 point for each of the following
    - Hepatic disease/Renal disease
    - Alcohol abuse
    - Malignancy
    - Age >75 years
    - Reduced platelet count or function,
    - Hypertension (uncontrolled)
    - Anemia
    - Genetic factors
    - Excessive fall risk
    - Stroke
  - 2 points for
    - Previous hemorrhage

ATRIA BLEEDING RISK SCORE

- Population:
  - Developed in 9186 atrial fibrillation patients enrolled in a large integrated healthcare system
  - Followed for 6 years
- Interpretation:
  - Low (0–3)
  - Intermediate (4)
  - High (5–10)
- Components:
  - Anemia (3 points)
  - Severe renal disease (3 points)
  - Age ≥ 75 yrs (2 points)
  - Prior bleed (1 point)
  - Hypertension (1 point)

HOW GOOD ARE THESE TOOLS?

- Validation studies performed in subgroups of clinical trials, outpatients with atrial fibrillation, prospective cohorts, and administrative databases of hospitalized patient
- No single risk score consistently superior to others in predicting hemorrhage
- HAS-BLED is better at discriminating risk than the HEMORR2HAGES or ATRIA scoring systems
- All scores had C indexes <0.70 in the receiver operating curves,
  - Indicating only modest performance and poor predictive accuracy.

J Thromb Thrombolysis. 2013; 35(3): 312–319

ASSESS YOUR ASSESSMENT

- Carefully evaluate the risk factors that attribute to the high risk score
  - Are they modifiable?
    - If so, intervene!
  - Are they non-modifiable?
    - Weigh the risks of stroke vs bleed associated with the factors

MODIFIABLE RISK FACTORS

- Uncontrolled hypertension
  - Increases the risk of ICH
  - Treat according to current HTN guidelines
- Labile INR
  - If high TTR cannot be maintained (≥70%)
  - Consider use of DOACs
- Alcohol use
- Medication predisposing to bleeding
  - Triple therapy
    - Minimize time on triple therapy
    - Use lowest dose and combination with lowest bleed risk

A NOTE ON FALLS AND DEMENTIA

- Associated with increase mortality in AF patients
  - But without evidence of increased ICH
- Withhold anticoagulation in certain situations
  - Severe uncontrolled falls
    - Epilepsy or advanced multisystem atrophy with backwards falls
  - Dementia where compliance and adherence cannot be ensured

J Thromb Haemost 2015;13:495–504

ASSESSMENT KEY POINTS

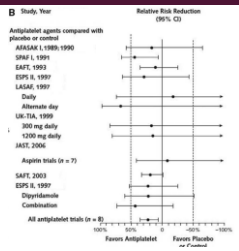
- Use a tool
  - HAS-BLED most widely utilized
- Keep in mind the accuracy of the score
- When evaluating the performance of a risk score
  - Consider if the ability to categorize a patient at high or low risk for an outcome would change the decision to anticoagulate or not

EVALUATING TREATMENT OPTIONS

AVAILABLE ANTITHROMBOTIC TREATMENTS

- No treatment
- Aspirin
- Aspirin + Clopidogrel
- Warfarin
- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban

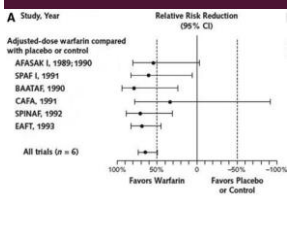
ANTIPLATELET THERAPY

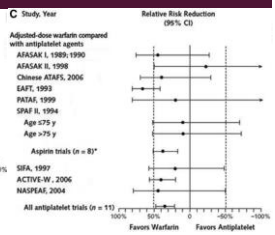


- Limited evidence
- VKA therapy is superior to ASA or ASA + clopidogrel in stroke prevention
  - Annual stroke risk 5.6% vs 3.9%
- Antiplatelet treatment increases bleeding risk
  - Similar rates bleeding rates to OAC
- Best suited for
  - Patients at low stroke risk
  - Need for stroke prevention in patients who cannot take DOAC, adequately monitor a VKA, or have significant drug-drug interactions with all other options

Circulation. 2014;130:e199–e267

WARFARIN THERAPY





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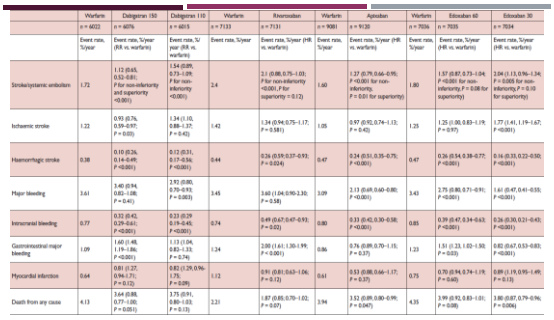
OAC PHARMACOKINETICS

	Warfarin	Edoxaban	Apixaban	Rivaraxoban	Dabigatran
Prodrug	No	No	No	No	Yes
Absolute Bioavailability	100%	62%	50%	10mg: 80% to 100% 20mg: 66% (food ↑)	3% to 7%
Tmax	4 hours	1 to 2 hours	3 to 4 hours	2 to 4 hours	1 hour
Protein binding	99%	40% to 59%	87%	92% to 95%	35%
Metabolism	Major: CYP2C9 Minor: CYP1A2, 2A4, 2C19, 2C18, 2C8	Major: Hydrolysis Minor: CYP3A4	Major: CYP3A4 Minor: CYP1A2, 2C8, 2C9, 2C19, 2J2	Oxidative degradation by CYP3A4/5 and 2J2	Esterase-catalyzed hydrolysis
Half-life	20 to 60 hours (mean 40 hours)	8 to 10 hours	~12 hours	5 to 9 hours	12 to 17 hours
Renal Clearance of parent drug	< 1% (<1% removed by HD)	50% (9% removed by HD)	27% (7% removed by HD)	36% (< 1% removed by HD)	80% (50-60% removed by HD)



	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	n = 6076		n = 7133		n = 7131		n = 9081	n = 9120	n = 7036	n = 7035	n = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/ year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.11 (0.65, 0.53–0.81; *P* for non-inferiority and superiority <0.001)	1.34 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.18 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94, 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59, 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.83–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04, 0.90–1.20; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29, 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67, 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.83–1.33; *P* = 0.74)	1.24	2.00 (1.61, 1.30–1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.96–1.71; *P* = 0.12)	0.82 (1.29, 0.96–1.75; *P* = 0.09)	1.12	0.91 (0.81, 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.31	1.87 (0.81, 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

European Heart Journal 2016;37:2893–2962

META ANALYSIS DATA: ATRIAL FIBRILLATION

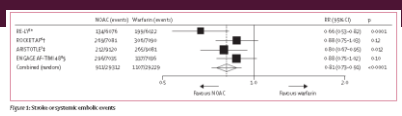


Figure 1: Stroke or systemic embolic events

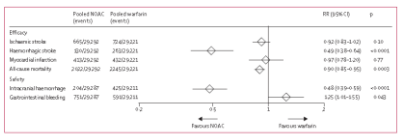


Figure 2: Secondary efficacy and safety outcomes

Lancet 2014;383:955–62

META ANALYSIS DATA: ATRIAL FIBRILLATION

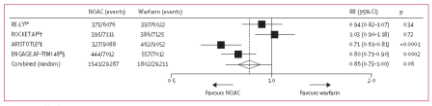


Figure 3: Major bleeding

Lancet 2014;383:955–62

WHERE IS DATA LACKING?

Indications not studied
- LV thrombus (case reports)
- Cardiomyopathy
- Acute stroke
- Secondary prevention of CV disease
- HIT

Indications with no benefit/with harm
- Post-ACS
- Mechanical heart valves

Populations not tested
- Pregnancy
- Extremes of body weight (< 45 kg or > 150 kg)

Certain subgroups
- Valvular AF
- Triple therapy
- High risk thrombophilia
- Cancer related thrombosis

Potentially interacting drugs

Non-bleeding adverse events
- Allergy
- Rash
- Dyspepsia

PUTTING TOGETHER A PLAN

1. HISTORY AND ASSESSMENT

- Stroke risk assessment
  - CHADS-VASc
- Bleed risk assessment
  - HAS-BLED

2. DECISION TO ANTICOAGULATE

- Shared decisions making
  - Patient
  - Caregiver
  - Providers
- Provide EDUCATION
  - Patients/caregivers seem to have more awareness of bleed risk than stroke risk

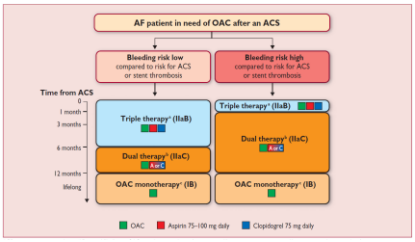
3. WHAT AGENT TO CHOOSE

- Use patient risk factors and drug specific factors to guide
  - Bleeding events
    - ICH risk lower with DOACs vs warfarin
    - GI bleed risk varies with agents
  - Ability to monitor
    - Patients with drug-drug interactions
    - Patients not well represented in clinical trials with DOACs (renal/hepatic dysfunction)
  - Affordability
  - Adherence
    - Once vs twice daily regimens
    - Longer vs shorter half life and missed doses

4. USE STRATEGIES TO MINIMIZE BLEEDING ON OAC

- Identify modifiable risk factors
- Regular follow up and monitoring (where applicable)
- Re-assess risk factors on a regular basis
- Patient education

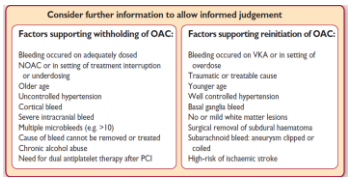
WHAT ABOUT TRIPLE THERAPY?



SO YOU DID EVERYTHING RIGHT, AND YOUR PATIENT HAD A BLEED. NOW WHAT?

- Therapy should be paused to control active bleeding
  - However, absolute contraindications to long-term OAC after a bleeding episode are rare
- Nuisance bleeds → consider a change from one anticoagulant to another
- Address causes or triggers of major bleeding events can be treated and/or eliminated
  - Uncontrolled hypertension, gastrointestinal ulcers, and intracranial aneurysms
- Reinitiating of anticoagulation after a bleeding event is often clinically justified
- Discontinuation and recommencement of OAC, should be taken by a multidisciplinary team
  - Balancing the estimated risk of recurrent stroke and bleeding
  - Considering the bleeding risk of different stroke prevention therapies.
- LAA exclusion or occlusion might be an alternative in selected patients

ANTICOAGULATION POST ICH



Consider further information to allow informed judgement

Factors supporting withholding of OAC:	Factors supporting reinitiation of OAC:
Bleeding occured on adequately dosed NOAC or in setting of treatment interruption or underdosing	Bleeding occured on VKA or in setting of overdose
Older age	Traumatic or treatable cause
Uncontrolled hypertension	Younger age
Cortical bleed	Well controlled hypertension
Severe intracranial bleed	Basal ganglia bleed
Multiple microbleeds (e.g. >10)	No or mild white matter lesions
Cause of bleed cannot be removed or treated	Surgical removal of subdural haematoma
Chronic alcohol abuse	Subarachnoid bleed: aneurysm clipped or coiled
Need for dual antiplatelet therapy after PCI	High-risk of ischaemic stroke

- If re-initiating
  - Choose agent with low ICH risk
  - Wait 4-8 weeks after bleed to resume

CONCLUSIONS

- Use of OAC in high bleed risk is challenging
- Proper assessment of stroke and bleed risk are critical
- Warfarin and DOACs are preferred over ASA + Clopiogrel, even in high bleed risk
  - DOAC may afford a reducation in bleed risk in some sitautions
- Regular monitoring and follow up are critical for success
- Patient education is CRITICAL!

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