ATRIAL FIBRILLATION MANAGEMENT IN OLDER ADULTS

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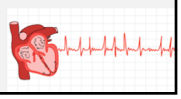
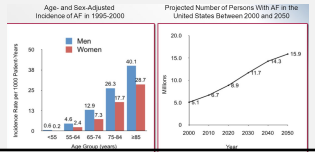
OVERVIEW

- Oral anticoagulation for stroke prevention in atrial fibrillation
  - Evidence for warfarin and novel oral anticoagulants
  - Barriers to use
  - Weighing risks/benefits
- Left atrial appendage occlusion in atrial fibrillation
- Other catheter-based interventions in atrial fibrillation
  - Pulmonary vein isolation
  - AV nodal ablation



ATRIAL FIBRILLATION (AF)

- AF is the most common arrhythmia worldwide
- Increasing prevalence with aging population
  - Nearly half of pts with AF in the US are over 75 years of age



Go AS et al. JAMA 2001;285(18):2370–5.
*Miyasaka Y et al. Circulation. 2006;114:119-125

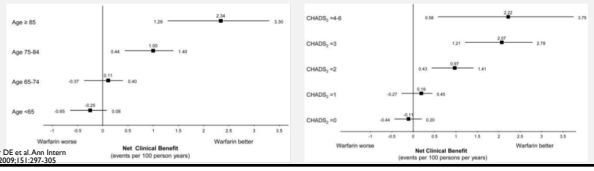
ATRIAL FIBRILLATION (AF)

- Risk of stroke with AF 5-fold higher than those without AF
- Number of strokes attributable to AF increases with age
  - 23.5% of strokes in those 80 to 89 years
  - Registry data suggests increased complications after AF-related stroke
- Oral anticoagulants (OAC) decrease risk of stroke by over 60%, however only 40-60% of eligible older adults actually receive it

Wolf PA et al. Stroke. 1991;22:983-988
Steger C et al. Eur Heart J. 2004;25:1734-40
Hagerty T & Rich MW. Cleve Clin J Med. 2017;84:35-40
Marc J et al. Lancet. 2007;370:493-503

OAC - WARFARIN

- Net clinical benefit of warfarin in thromboembolism prevention in AF is significant, with the greatest benefit in those with the highest stroke risk – those ≥85 yrs and with higher CHADS2 risk scores



Singer DE et al. Ann Intern Med. 2009;151:297-305

OAC - NOACS

- Novel oral anticoagulants (NOACs) have been tested against warfarin in 4 major randomized controlled trials, including over 70,000 patients
  - Pooled data indicate NOACs significantly reduce stroke and systemic embolism (SE), major bleeding, intracranial hemorrhage and all-cause mortality

Mean age and percentage of participants ≥ 75 years old in pivotal studies of NOACs.

	RE-LY[18] Dabigatran			ROCKET-AF[19] Rivaroxaban		ARISTOTLE[20] Apixaban		ENGAGE AF-TIMI 48[21] Edoxaban		
	D150 mg (n = 6076)	D110 mg (n = 6015)	W (n = 6022)	R (n = 7131)	W (n = 7133)	A (n = 9120)	W (n = 9081)	E60 mg (n = 7035)	E30 mg (n = 7034)	W (n = 7036)
Age (years)	71.5 ± 8.8	71.4 ± 8.6	71.6 ± 8.6	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)
≥75 yrs	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%

A: apixaban; D: dabigatran; E: edoxaban; NOACs: new oral anticoagulants; R: rivaroxaban; W: warfarin.

Karamichalakis N et al. J Geriatr Cardiol. 2016;13:718-23

OAC - NOACS

- Many studies published on use of NOACs in older adults
  - All suggest NOACs to be at least as effective as warfarin in thromboembolism prevention, with less risk of intracranial hemorrhage (ICH) and variable rates of major and minor bleeding
- 2014 prospective study on NOAC use in older adults ≥75yrs
  - Mean age 82 yrs, median CHA2DS2-VASc 5, HAS-BLED 4, high clinical complexity (79.3% cumulative illness rating scale >3)
  - Rate of major bleeding 4.4% and clinically-relevant non-major bleeding 5.7%
  - Stroke occurred in 0.88%

Lip GYH et al. Stroke. 2014;46:143-150

NOT ALL NOACS CREATED EQUAL

- Retrospective cohort study of Medicare pts with AF, comparing OAC efficacy and safety
  - All NOACS associated with lower risk of stroke/SE, ICH and all-cause mortality vs warfarin
  - Dabigatran had similar risk of stroke/SE and lower risk of major bleeding than rivaroxaban
  - Apixaban had lower risk of stroke/SE, major bleeding and all-cause mortality than dabigatran or rivaroxaban
- Ray et al studied Medicare pts with AF on OAC, finding rivaroxaban to have the highest incidence of hospitalization for GIB, lowest for apixaban
- ARISTOTLE subgroup analysis → 55 years of age, divided by number of comorbidities
  - Safety and efficacy of apixaban preserved in the highest multimorbidity group

Deitelzweig S et al. J Am Geriatr Soc. 2019;67:1662-71
Ray WA et al. JAMA. 2018;320:2221-30
Alexander KP et al. Am Heart J. 2019;208:123-131

BARRIERS TO OAC PRESCRIPTION

- Pugh et al performed a review on physicians' attitudes toward OAC prescription in older adults
  - Most cited barriers – bleeding risk, fall risk, age and patients' adherence
- Another study found the need for individualized decision making and feelings of responsibility were key deterrents

Pugh D et al Age Ageing. 2011;40:675-83
*Paz Dalmau G et al. BMC Fam Pract. 2017;18:3

OAC & FALL RISK

- Falls are common in older adults, and risk of bleeding with a fall is higher on OAC, but absolute risk increase is small
- Study of older adults with AF, deemed high fall risk, falling associated with an increased risk of ICH (1.9x higher) BUT this risk did not differ in those treated with warfarin, ASA or no antithrombotic
  - Net clinical benefit existed for those with CHADS2 ≥2
- Man-Son Hing using Markov decision model, showed fall risk was not an important factor in decision to prescribe OAC (295 falls/yr needed)

Hagerty T & Rich MW. Cleve Clin J Med. 2017;84:35-40
Gage BF et al. Am J Med.2005;118:612-17
Man-Son-Hing M et al. JAMA. 1999;12:677-85

OAC IN PTS WITH PRIOR ICH

- A recent study investigated OAC initiation in older adults with AF after ICH (mean age 83 yrs)
  - 38% prescribed OAC; 82% of those prescribed warfarin
  - OAC reduced ischemic stroke/SE/all-cause mortality
  - No difference in future spontaneous or traumatic ICH
  - Trend toward increased rate of major extracranial hemorrhage with OAC
  - Net clinical benefit favored OAC, even after ICH

Perreault S et al. J Stroke. 2019;21:195-206

NET CLINICAL BENEFIT OF OAC IN OLDER ADULTS

- OAC is not without risk in older adults
- Study of net clinical benefit (NCB) of warfarin and apixaban in >14,000 older adults ≥75 years with AF
  - NCB of warfarin decreased below 0.10 lifetime QALYs after age 87 and apixaban after age 92
  - Removing competing risks of death increased NCB for both warfarin and apixaban
- NCB of OAC may decrease above a certain age and is impacted by competing mortality risks
- Individualized shared decision making (SDM) paramount

Shah SJ et al. Circ Cardiovasc Qual Outcomes. 2019; in press

CONSIDERATIONS IN PRESCRIBING OAC

- No "one drug fits all approach" in older adults
  - Use risk tools to estimate patients stroke and bleed risk
  - Comorbidities and competing mortality risks
  - Once vs twice daily dosing
  - Adherence – NOACs have shorter half life
  - Renal function, liver function – dose adjust ONLY if established criteria met
  - Polypharmacy and drug-drug interactions
  - Bleeding history/contraindications to OAC

SHARED DECISION MAKING

- Clinician and patient (+/- caregivers) work together to make a decision based on current evidence, balancing individual risks and benefits and patient values/preferences
  - Multiple decision aids exist online to assist with SDM, using validated risk scores to create pictographs to display risks/benefits in a way the patient understands

https://anticoagulationdecisionaid.mayoclinic.org/

DECISION AIDS AVAILABLE

- https://anticoagulationdecisionaid.mayoclinic.org/
  - Has patient-specific pictographs and includes issues such as cost into decision making process
- http://mybloodclots.org/
  - Uses CHADS2VASc and HASBLEED score components, as well as patient preferences including time OAC has been on market, monitoring requirements, dosing requirements, cost of medication
  - Pictograph provided
- https://www.cardiosmart.org/SDM/Decision-Aids/Find-Decision-Aids/Atrial-Fibrillation
  - PDF for patients at very high risk, high risk, moderate risk and low risk of stroke
  - Provides generalized pictographs based on stroke risk but not specific to patient-entered factors
- https://www.anticoagulation-dst.co.uk/
  - Takes into account CHADS2VASc and HASBLED score
  - Does offer additional information like modifiable bleeding risk factors and gives patient print out with pictographs

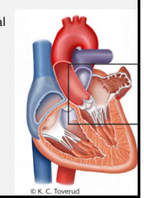
EVIDENCE FOR SHARED DECISION MAKING

- Shared decision making has been shown to:
  - Improves patient knowledge of AF and results in a more realistic understanding of stroke and hemorrhage risk
  - Improved appropriateness of OAC prescription – 12% absolute improvement
  - Reduce decisional conflict
  - Increased value congruence between clinician and patient

Man-Son-Hing M et al. JAMA. 1999;282:737-743
McAlister FA et al. CMAJ. 2005;173:496-501
Stephan LS et al. Arg Bras Cardiol. 2018;110:7-15

DECISION MADE NOT TO PRESCRIBE OAC

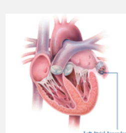
- Annual stroke risk with AF increases with age and oral anticoagulants remain first-line therapy
- In non-valvular AF, 90% of thrombi (with stroke potential) are located in left atrial appendage
- Left atrial appendage occlusion (LAAO) has emerged as promising alternative to OAC



Lunde K et al. Tidsskr Nor Legeforen. 2018.
https://tidsskriftet.no/en/2018/04/originalartikkel/catheter-based-left-atrial-appendage-closure

LEFT ATRIAL APPENDAGE OCCLUSION

- Surgical LAAO (various techniques) has been performed and evaluated for close to 2 decades
- More recently, percutaneous LAAO devices developed - WATCHMAN device
- Safety and efficacy of WATCHMAN evaluated in 2 RCTs – PROTECT AF and PREVAIL
- 2015 - US FDA approved WATCHMAN for pts with AF and whom long-term OAC is indicated, but rational reason for not adhering, and are able to tolerate warfarin for short duration



Tsai et al. Eur J Cardiothorac Surg. 2015; 47:847-54
Norton Healthcare. February 2019. https://nortonhealthcareprovider.com/left-atrial-appendage-closure-a-life-changing-procedure-for-patients-with-nonvalvular-a-fib/

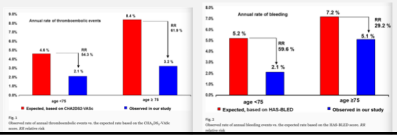
EFFICACY OF LAAO

- PROTECT AF – average age 72 years, 41% over age 75 years
  - Success rate 90.9%, complication rate 8.7%
- PREVAIL – average age 74 years, 52% over age 75 years
  - Success rate 95.1%, complication rate 4.5%
- Overall – LAAO non-inferior to warfarin for stroke/SE with significantly lower rates of hemorrhagic stroke, major bleeding and mortality

Holmes DR et al. Lancet. 2009;374:534-42
Holmes DR et al. JACC. 2014;64:1-12

LAAO IN OLDER ADULTS

- Yu et al compared LAAO in those <75 years to those ≥75 years of age
  - No difference in procedural success or short-term complications
  - Despite higher CHA2DS2-VASc score in those ≥ 75, no difference in all-cause death, CV death, stroke/TIA/SE, device thrombus at 2 years
  - Greatest risk reduction in thromboembolism in those ≥75 yrs, greatest risk reduction in bleeding in those <75 yrs



Yu J et al. Heart vessels. 2019;34:1858-65

LAAO IN HIGH BLEED RISK PTS

- ASAP trial (2013) – non-randomized study of WATCHMAN in 150 pts with AF and **contraindication to warfarin**
  - Mean age 72.5 years, 42.7% ≥75 years, mean CHA2DS2-VASc score 4.4, 93% prior hemorrhage
  - Post-procedure – Clopidogrel x 6 mo + lifelong ASA
  - Ischemic stroke rate 1.7%/yr → 77% risk reduction compared to expected stroke rate determined by CHA2DS2-VASc score
- ASAP-too trial enrolling now, data forthcoming
  - Randomized controlled trial of WATCHMAN vs SAPT/no APT in those with AF and contraindication to OAC

Reddy VY et al. J Am Coll Cardiol. 2013;61:2551-6
Boersma LV et al. Circ Arrhyth Electrophysiol. 2019;e006841

COST-EFFECTIVENESS OF WATCHMAN

- Cost-effectiveness of WATCHMAN compared to warfarin or NOAC in those with AF and previous embolic event
- WATCHMAN cost-effective relative to Dabigatran at year 5 and warfarin and apixaban at year 6
- At 10 years, LAAO had more quality adjusted life years AND lower costs than warfarin, dabigatran, apixaban and rivaroxaban

Reddy VY et al. Stroke. 2018;49:1464-70

WATCHMAN FOR ALL?!

- Procedure is not without risks, not appropriate for everyone
  - Device embolization
  - Device thrombus
  - Stroke
  - Cerebral air embolism
  - Pericardial effusion +/- tamponade
  - Major bleeding – need heparin intra-procedurally
  - Vascular complications
- Literature suggests predictors of adverse events and mortality are older age, and comorbidities (lower EF, CKD) → highest risk population
  - Comprehensive patient assessment needed to identify those with competing risks, limiting overall prognosis
  - Shared decision making **KEY;** prior to referral to cardiology

Fauchier et al. JACC. 2018;71:1528-36
Regueiro A et al. J Interv Card Electrophysiol. 2018;52:53-9

SHIFT GEARS… CATHETER-BASED INTERVENTIONS FOR AF

RATE VS RHYTHM CONTROL

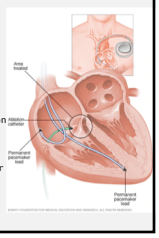
- Rate control focuses on control of ventricular rate, typically using AV-nodal blocking medications
- Rhythm control aims to maintain sinus rhythm; includes cardioversion, anti-arrhythmic medications, ablation or a combination
- Multiple randomized controlled trials have compared rate vs rhythm control in AF, with neither being shown conclusively to improve survival over the other

AF SYMPTOM MANAGEMENT

- Long-term management of symptomatic AF is often unsatisfactory, despite the numerous medications available for rate and rhythm control
- Catheter-based interventions are reserved for SYMPTOMATIC AF
  - Incomplete resolution with, did not tolerate, or have contraindications to medications

CATHETER-BASED AF INTERVENTIONS

- Pulmonary vein isolation (PVI)
  - Primary trigger for AF in most cases is electrical discharge in pulmonary veins
  - Catheter-based procedure to electrically isolate the pulmonary veins, so discharges do not activate the atria
- AV node ablation
  - Atrial fibrillation starts in left atrium and ventricular rate is controlled by conduction through AV node
  - Ablation of AV node electrically isolates the atria from the ventricle, so ventricle does not respond to AF → 3rd degree AV block, necessitating permanent pacemaker



PULMONARY VEIN ISOLATION (PVI) EFFICACY

- PVI success (free of AF recurrence) is about 70-75% at 1-year
- Long-term success 50-70% with single procedure and up to ~70-85% with multiple procedures
- Predictors of recurrence:
  - Cardiovascular disease
  - Hypertension
  - Older age
  - Untreated obstructive sleep apnea
  - Larger left atrial size

Cosedis Nielsen J et al. NEJM 2012;367:1587
Morillo CA et al. JAMA 2014;311:692-700
Jais P et al. Circ 2008;118:2498-505
Ganesan AN et al. J Am Heart Assoc. 2013;2:e004549

PULMONARY VEIN ISOLATION (PVI) EFFICACY

- PVI beneficial in those who are symptomatic despite anti-arrhythmic drug therapy – reduces AF recurrence, improves symptoms, exercise capacity and quality of life
- Without previous anti-arrhythmic use, freedom from AF at 1-yr comparable with PVI vs anti-arrhythmic drug
  - CABANA trial – Pts with AF randomized to PVI vs anti-arrhythmic drug therapy –no difference in death, disabling stroke, serious bleeding or cardiac arrest
  - However, CABANA sub-study and CAPTAF trial both report PVI associated with significant improvement in quality of life vs anti-arrhythmic drug therapy

Packer DL et al. JAMA. 2019;321:1261-74
Mark DB et al. JAMA. 2019; 321:1275-85
Blomstrom-Lundqvist C et al. JAMA. 2019;321:1059-68

FUTURE OF PVI LOOKS PROMISING

- CAMTAF, CASTLE-AF + 2 recent meta-analyses, suggest PVI beneficial in HFrEF
  - Improved mortality, hospitalizations and HF symptoms
- Retrospective study of pts with HFpEF and HFrEF undergoing PVI, found both groups benefited similarly
  - Improved function, symptoms, AF recurrence
- Recent propensity matched study showed significantly lower incidence of dementia in those ≥65 with PVI, during 9 year follow-up (aHR 0.46, p<0.04)
  - Dementia risk similar to those without AF
- Second propensity matched study found PVI significantly improved eGFR over 5 years (p<0.001)
  - Freedom from AF recurrence after PVI independently associated with improved eGFR

Marrouche NF et al. NEJM 2018;378:417-27
Hunter RJ et al. Circ Arrhythm Electrophysiol. 2014;7:31-8
Turagam MK et al. Ann Intern Med 2019;170:41-50
Black-Maier E et al. Heart Rhyth 2018;15:651-57
Hsieh YC et al. Int J Cardiol. 2019; in press
Park JW et al. J Am Heart Assoc. 2019;8:e013204

PVI IN OLDER ADULTS

- Multiple studies have investigated PVI in older adults, limited by small sample sizes, non-randomized design and most pts <80 years of age
  - Overall success rate with repeat procedures and/or addition of anti-arrhythmic drugs around 80% (similar to younger cohorts)
  - Maintenance of sinus rhythm shown to be independent predictor of survival
  - Discrepant data on complication rates in older adults, however, recently Romero et al reported on 3482 octogenarians undergoing PVI, followed for 9 yrs
    - Increased overall complication rate and rate of minor complications in octogenarians
    - No difference in major complications or mortality vs younger cohort

Shared decision making of utmost importance

Fraub D et al. Cardiol J. 2009;16:113-20
Lioni L et al. J Geriatr Cardiol. 2014;11:291-95
Nademanee K et al. Heart Rhythm 2015;12:44-51
Gautzner J et al. J Geriatr Cardiol. 2017;14:563-68

AV NODAL ABLATION

- AV nodal ablation used in highly symptomatic, drug-refractory AF patients
- Large prospective catheter ablation registry reported:
  - AV nodal ablation successful in 97.4%, serious complication rate 0.15%
  - No significant difference in success or complications in those <60 vs ≥60 years of age
- Literature shows AV nodal ablation associated with significant improvement in quality of life and ease of ADLs, with reduction in health care utilization and hospital admissions

Scheinman MM & Huang S. Pacing Clin Electrophysiol. 2000;23:1020-8
Fitzpatrick et al. Am Heart J. 1996;131:499
Wood MA et al. Circulation. 2000;101:1138-44

OAC WITH PVI & AVN ABLATION

- After successful PVI, continue OAC for at least 2 months
  - Those with CHA2DS2-VASc of 0 can stop OAC → Not our patients
  - Some experts stop OAC in CHA2DS2-VASc of 1; not based on high quality evidence → Not often our patients
  - All patients with CHA2DS-VASc >1 should **continue** OAC, irrespective of known AF recurrence → Our patients
- AV nodal ablation results in rate control, but does not stop the atria from fibrillating - thus no change in thromboembolic risk
  - Need for long-term OAC **unchanged**

TAKE HOME POINTS

- OAC is 1st line for stroke prevention in AF
- OAC benefits outweigh risks in most older adults – yet is under-prescribed
- No "one drug fits all" approach to OAC → requires shared decision making
- If patient can tolerate short-term OAC but not a good candidate for long-term, consider WATCHMAN procedure
  - High procedural success and no difference in complication rates vs younger adults
  - Not without risk (4-8%) → consider competing risks, life expectancy and engage in shared decision making

TAKE HOME POINTS

- No conclusive evidence of superiority between rate and rhythm control
- If patient still symptomatic despite medical therapy and cannot tolerate medical therapy, consider referral for catheter-based interventions
  - PVI efficacy similar to younger cohorts, with increased minor complications
  - AVN ablation safe and efficacious BUT results in pacemaker dependence
  - Neither PVI or ANV ablation change need for OAC in our patient population