

The Prudent Prescriber

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Pharm Reps \neq Rational Prescribing

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A Quick Update of Atrial Fib: CHADs & DOACs:

Whom to treat and with which drug

The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society atrial fibrillation (AF) guideline and the 2012 European Society of Cardiology AF guidelines prefer the CHA2DS2-VASc score for risk estimation.

What do CHA2DS2-Vasc Scores Mean?

- Patients with a CHA2DS2-VASc score of 2 or greater are at higher risk.
- Patients with a CHA2DS2-VASc score of 0, who are uncommon, are at low risk.
- The rate of ischemic stroke in patients with a CHA2DS2-VASc score of 1 ranges from 0.6% to 2.75%. *This broad range, which spans the 1 to 2% per year threshold for initiation of anticoagulation, results from populations with different risks.*
- Some studies have shown hypertension and vascular disease are at the lower end of the risk range while age between 65 and 74 was at the higher end.

When the CHADs2 is replaced with CHA2DS2-VASc Score

In a study of 10,132 new onset atrial fib patients,
CHADs2: 71.8% would be treated
CHA2DS2-VASc: 90.8% would be treated

O'Brien JAMA Int Med 175(5): 848; May 2015

Antibiotics do
NOT

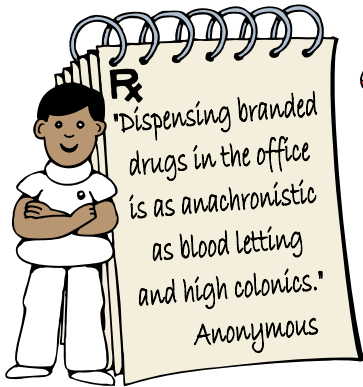


help
acute bronchitis

**β -blockers in
post-MI
save
lives**



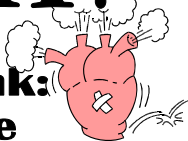
Pill splitters save
BIG



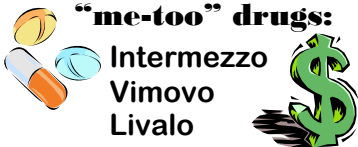
CHE?

Think:

Ace
Aldactone
B-blocker
Dig
Diuretic

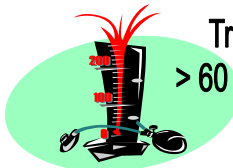


Avoid these expensive
"me-too" drugs:



Intermezzo
Vimovo
Livalo
Pristiq
Viibyrd
Edarbi
Daliresp

Treat patients
> 60 years to 150/90



NOW AVAILABLE
ON THE
GENERIC MARQUEE

Frova \rightarrow frovatriptan
Voltaren gel \rightarrow diclofenac Na 1% gel
Crestor \rightarrow rosuvastatin
Nuvigil \rightarrow armodafinil
Jalyn \rightarrow dutasteride/tamsulosin
Ortho Tri-Cyclen Lo \rightarrow Tri-Lo-Marzia,
Tri-Lo-Sprintec, & others

Definition and scores for CHADS ₂ and CHA ₂ DS ₂ -VASC	
CHADS ₂ acronym	Score
Congestive HF	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6
CHA ₂ DS ₂ -VASC acronym	Score
Congestive HF	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65 to 74 years	1
Sex category (ie, female sex)	1
Maximum score	9

Stroke risk stratification with the CHADS ₂ and CHA ₂ DS ₂ -VASC scores	
CHADS ₂ acronym	Unadjusted ischemic stroke rate (% per year)*
0	0.6%
1	3.0%
2	4.2%
3	7.1%
4	11.1%
5	12.5%
6	13.0%
CHA ₂ DS ₂ -VASC acronym	Unadjusted ischemic stroke rate (% per year)*
0	0.2%
1	0.6%
2	2.2%
3	3.2%
4	4.8%
5	7.2%
6	9.7%
7	11.2%
8	10.8%
9	12.2%

Which Drug?

Drug	Usual Dose	Comments	Cost/month
Direct Factor Xa inhibitors			
Apixaban (Eliquis)	5 mg BID	Interacts with CYP3A4 substrates: list is a mile long. Apixaban is approved for patients with ESRD.	\$334
Edoxaban (Savaysa)	60mg once a day	Not in patients with CrCl>95	\$291
Rivaroxaban (Xarelto)	20 mg once a day	Evening meal; interacts with CYP3A4 substrates	\$334
Direct thrombin Inhibitor			
Dabigatran (Pradaxa)	150 mg BID	Store in original container; dyspepsia is common; reversal agent available (pricey)	\$334
Vitamin K Antagonist			
Warfarin	2-10 mg once a day	Lots & lots of drug interactions; dietary restrictions; monitoring required; reversal agent cheap	\$8.50 plus INRs

Adapted From
Medical Letter
 April 11, 2016

RCTs DOACs vs Warfarin

	Stroke or Systemic Embolism	Hemorrhagic Stroke	Ischemic Stroke	Intracranial Bleeding	Major Bleeding	INR in Therapeutic Range
Dabigatran	RR 0.66	RR 0.26	RR 0.76	RR 0.40	RR 0.93	64%
Rivaroxaban	HR 0.88	HR 0.59	HR 0.94	HR 0.67	HR 1.04	55%
Apixaban	HR 0.79	HR 0.51	HR 0.92	HR 0.42	HR 0.69	62%
Edoxaban	HR 0.79	HR 0.54	HR 1.00	HR 0.47	HR 0.80	65%

Dabigatran: Connolly et al [NEJM](#) 2009;361:1139.

Rivaroxaban: Patel et al [NEJM](#) 2011;365:883.

Apixaban: Granger et al [NEJM](#) 2011; 365: 981.

Edoxaban: Giugliano et al [NEJM](#) 2013; 369: 2093.

“Real World” look at Safety and Efficacy of Direct Oral Anticoagulants (DOACs) and Warfarin (Coumadin)

Observational study of 62,000 oral anticoagulant naïve patients with non-valvular atrial fib (Larsen, BMJ 2016, June 16)

At the end of one year:

- * Risk for ischemic stroke or systemic embolism lower for rivaroxaban (but not dabigatran or apixaban) than with warfarin (hazard ratio, 0.83). Risk for ischemic stroke alone did not differ between DOACs and warfarin.
- * Risks for all cause death, any bleeding or major bleeding were significantly lower with apixaban and dabigatran (but not rivaroxaban) compared with warfarin (HR = 0.63).
- * Risk for intracranial bleeding was significantly lower with dabigatran and rivaroxaban (but not apixaban) compared with warfarin. (HRs 0.40 and 0.56, respectively).
- * No outcome was **WORSE** with any DOAC than with warfarin.

This study is a little reassuring...

Although observational in design and open to other biases, this study paints a picture of how well these new short acting, very expensive, can't test for their presence in the patient in front of you, DRUGS work... in a very Non-Adherent world.

Good Candidates for Warfarin (Coumadin)

- Patients already on warfarin who are comfortable with periodic INR measurement and whose INR has been relatively easy to control with a time in the therapeutic range of at least 65 percent.
- Patients who are not likely to comply with the twice daily dosing of dabigatran or apixaban and who are unable to take rivaroxaban or edoxaban.
- Patients for whom the DOAC agents will lead to an unacceptable increase in costs.

- Patients with chronic severe kidney disease whose estimated glomerular filtration rate is less than 30 mL/min. Apixaban is approved for patients with ESRD.
- Patients for whom the DOAC agents are contraindicated, including those on enzyme-inducing antiepileptic drugs (eg, phenytoin) and patients with HIV on protease inhibitors.

How large is the size effect of DOACs vs warfarin?

- Meta-analysis of 4 RCT (71,683 patients with atrial fib)
- Median age 72 years
- DOACs associated with better outcomes than warfarin
 - reduction in vascular related mortality, NNT = 189
 - reduction in bleeding related mortality, NNT = 313
 - reduction in intracranial bleeding, NNT = 118

Liew, *J Throm Haemost* 12(9):1149; Sept 2014

My Take:

- The newer CHAD scoring system will increase the number of atrial fibrillation patients being treated. Is this over-treatment?
- In both large observational and randomized controlled trials, DOACs outperform warfarin on almost all parameters of safety and efficacy.
- The effect size of these advantages is clinically pretty small. NNTs advantage over warfarin in low 100s and up.
- There are no head to head studies comparing the various DOACs. They do differ in dosing frequency, renal dosing and drug interaction profiles, but not cost.
- Talk to patients regarding the economics and the vagaries of the different treatments.

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