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TSOACs, DOACs, and NOACs… OH MY! Drug Safety Considerations for Using Non-VKA Oral Anticoagulants

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Conflict of Interest

The presenter has no actual or potential conflicts of interest to disclose.

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Objectives

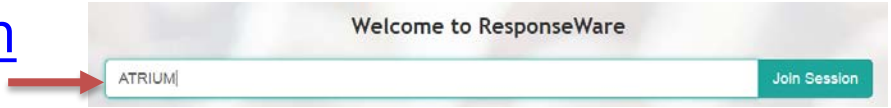
- Describe the prevalence of adverse drug events in patients taking non-vitamin K antagonist oral anticoagulants
- When given a patient case, identify common drug errors that occur with non-vitamin K antagonist oral anticoagulants
- Identify important drug interactions with non-vitamin K antagonist oral anticoagulants and, when given a patient case, appropriately select an alternative anticoagulant

Abbreviations

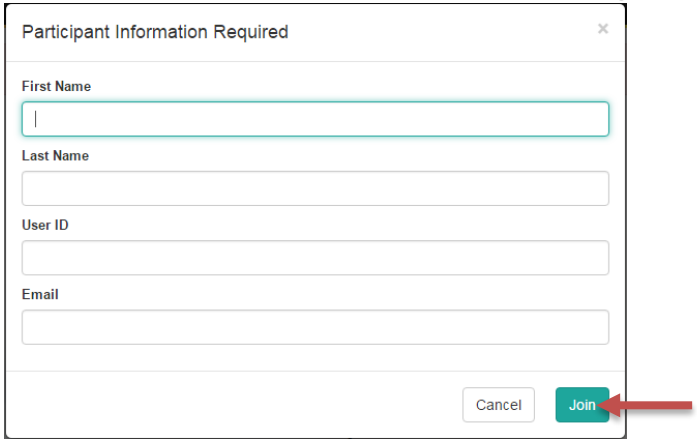
- DVT = deep vein thrombosis
- Non-Vitamin K Antagonist Oral Anticoagulants
  - NOAC = novel oral anticoagulant OR non-VKA oral anticoagulant
  - TSOAC = target-specific oral anticoagulant
  - DOAC = direct-acting oral anticoagulant
- NVAF = non-valvular atrial fibrillation
- PE = pulmonary embolism
- VTE = venous thromboembolism

Polling Response

1. Type in the following URL using your phone or mobile device: http://rwpoll.com



2. Enter the session name "ATRIUM", the click "join session"
3. Click "Join". *You do NOT have to enter your personal information*



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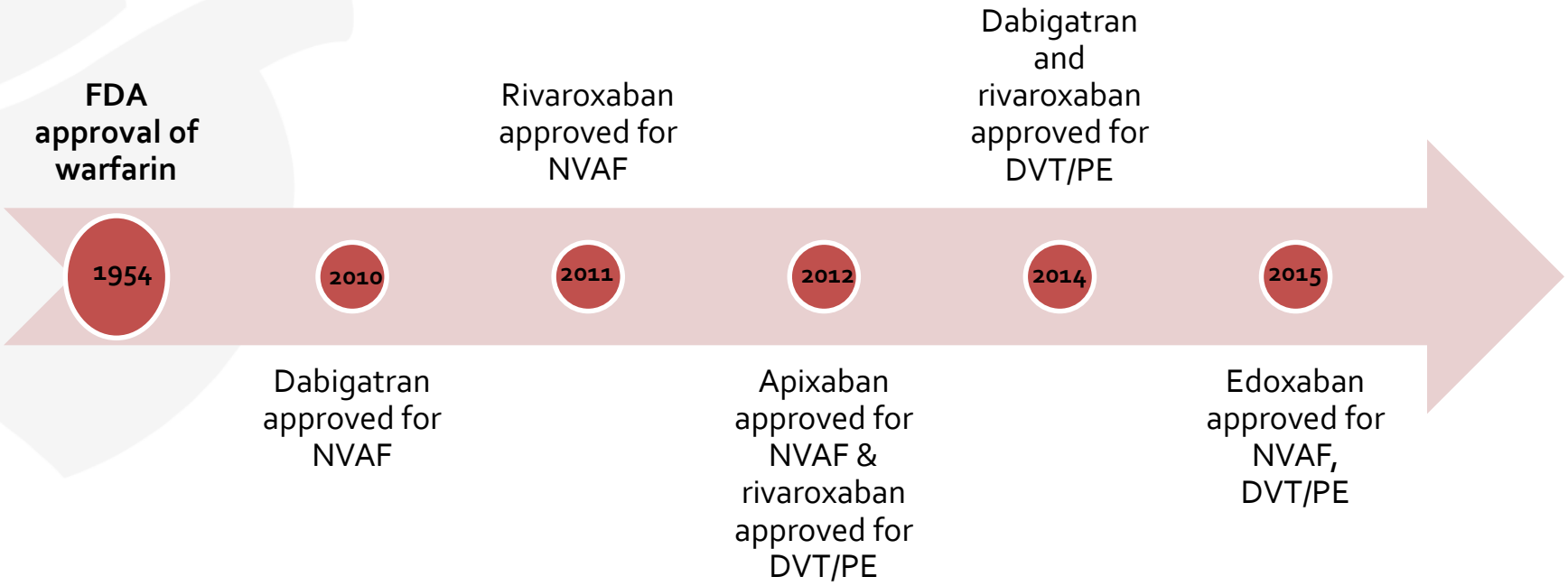
Timeline of Oral Anticoagulant Development



Silva, R. NOACs in NVAF. Cardiovascular and Hematological Agents in Medicinal Chemistry. 2014
www.fda.gov. Accessed March 1, 2017

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Trends in Oral Anticoagulant Use

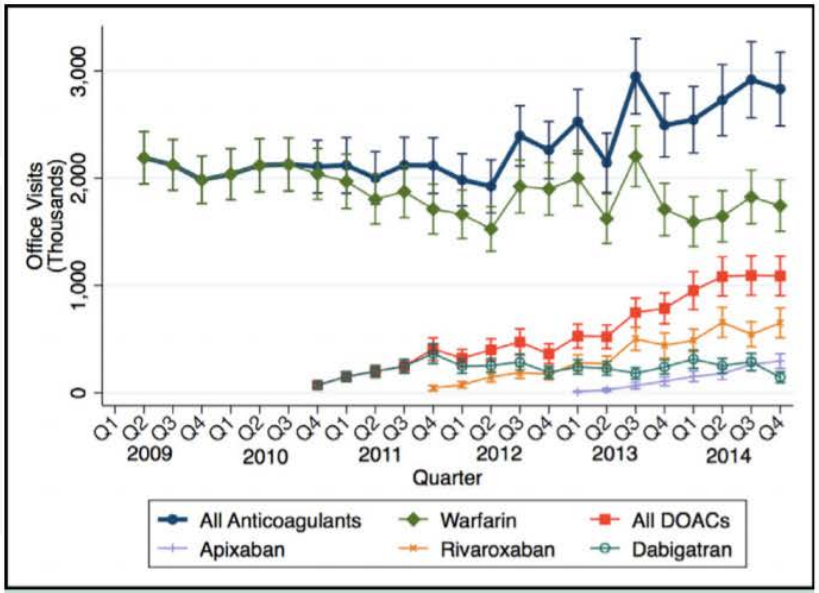

Figure 1 Quarterly use of oral anticoagulant during office visits. DOAC = direct oral anticoagulant. Source: IMS Health National Disease and Therapeutic Index, 2009-2014.

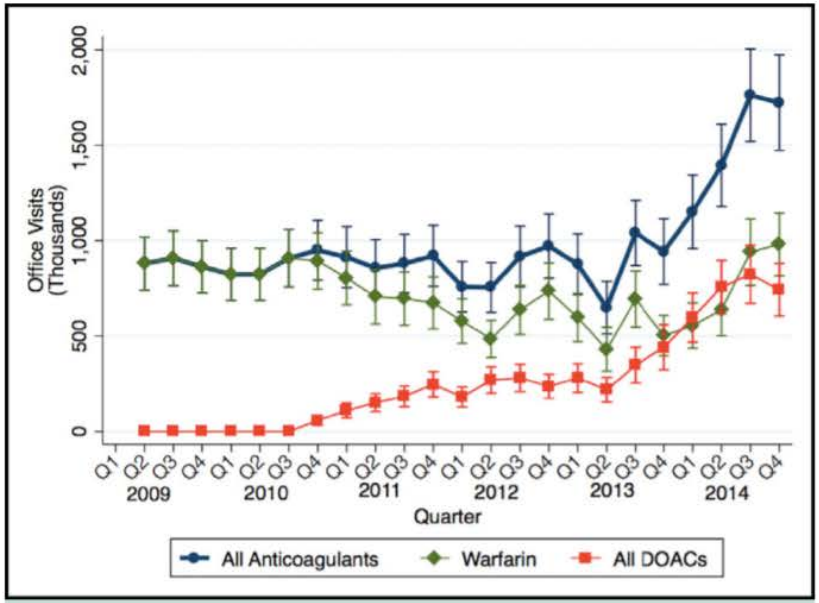

Figure 2 Quarterly visits for atrial fibrillation by anticoagulant type. DOAC = direct oral anticoagulant. Source: IMS Health National Disease and Therapeutic Index, 2009-2014.

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Barnes, et al. National Trends in Ambulatory Oral Anticoagulant Use. *Am J Med*. 2015:128, 1300-1305

Guidelines Support Using DOACs

Guideline	Recommendations
American College of Chest Physicians Guideline and Expert Panel Report: Antithrombotic Therapy for VTE Disease	In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).
2016 European Society of Cardiology Guidelines for the management of atrial fibrillation	When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist (Class IA).

Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report. *CHEST*. 2016; 149(2):315-352
2016 ESC Guidelines for the Management of Atrial Fibrillation. *Eur Heart J*. 2016.

Adverse Drug Events with Anticoagulants

- Institute for Safe Medication Practices (ISMP) high-alert medication drug class in acute care and long-term care settings
- 48% of hospital medication errors involve anticoagulants

Piazza G, Nguyen TN, Cios D, et al. Anticoagulation-associated adverse drug events. Am J Med 2011 Dec;124(12):1136-42.

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Adverse Drug Events with Anticoagulants

- In patients over 65 years old, anticoagulants are the most commonly implicated medication in emergency department visits due to an adverse drug event (ADE)
  - 17.6% of all ADE requiring ED visit attributable to oral anticoagulant
  - ~50% require hospital admission

US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA*. 2016;316(20):2115-2125.
Image courtesy of ismp.org

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Common DOAC-Related Medication Errors

- Incorrect dose or frequency for indication
- Incorrect dose for renal function and/or drug-drug interactions
- Dose adjustment based on clinical gestalt
- Dose omissions and extra doses
- Improper monitoring
- Wrong time of administration

Approved DOAC Dosing for VTE Treatment

Medication	Dose	Dose Adjustment for Renal Function
Dabigatran*	150 mg twice daily AFTER 5 days of parenteral anticoagulation	Avoid use if CrCl < 30 ml/min
Rivaroxaban**	15 mg twice daily x 21 days followed by 20 mg daily	Avoid use if CrCl < 30 ml/min
Apixaban**	10 mg twice daily x 7 days followed by 5 mg twice daily	No dosage adjustment required
Edoxaban*	60 mg daily AFTER 5 days of parenteral anticoagulation	15-50 ml/min: 30 mg once daily

*Dosing may be different with concomitant p-glycoprotein inhibitors or inducers
**Dosing may be different with concomitant p-glycoprotein and strong CYP3A4 inducers or inhibitors

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Lexicomp Online® , Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; March 1, 2017.

Approved DOAC Dosing for NVAF Treatment

Medication	Dose	Dose Adjustment for Renal Function
Dabigatran*	150 mg twice daily	CrCl 15-30 ml/min: 75 mg twice daily CrCl < 15 ml/min: Avoid use
Rivaroxaban**	20 mg once daily	CrCl 15-50 ml/min: 15 mg once daily CrCl < 15 ml/min: Avoid Use
Apixaban**	5 mg twice daily	If 2 of 3 criteria met (SCr >1.5 mg/dl; weight < 60 kg; age ≥ 80 years old): 2.5 mg twice daily
Edoxaban*‡	60 mg twice daily	CrCl 15-50 ml/min: 30 mg once daily CrCl < 15 ml/min: Avoid use

*Dosing may be different with concomitant p-glycoprotein inhibitors or inducers
**Dosing may be different with concomitant p-glycoprotein and strong CYP3A4 inducers or inhibitors
‡Contraindicated if CrCl > 95 ml/min

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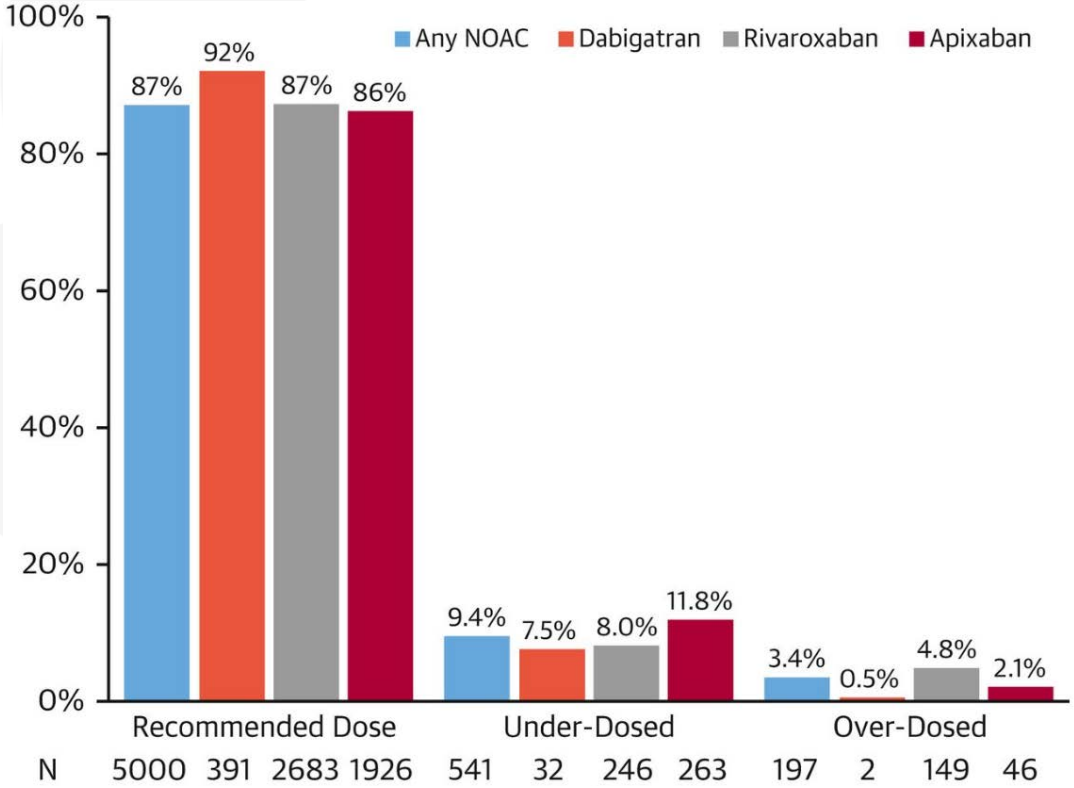
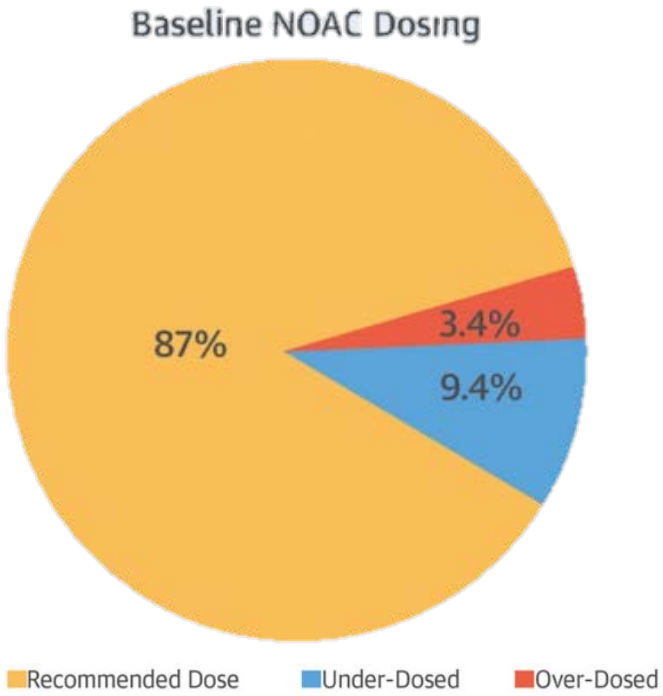
Real World Use of DOACs





Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. JACC. 2016;68:2597–604

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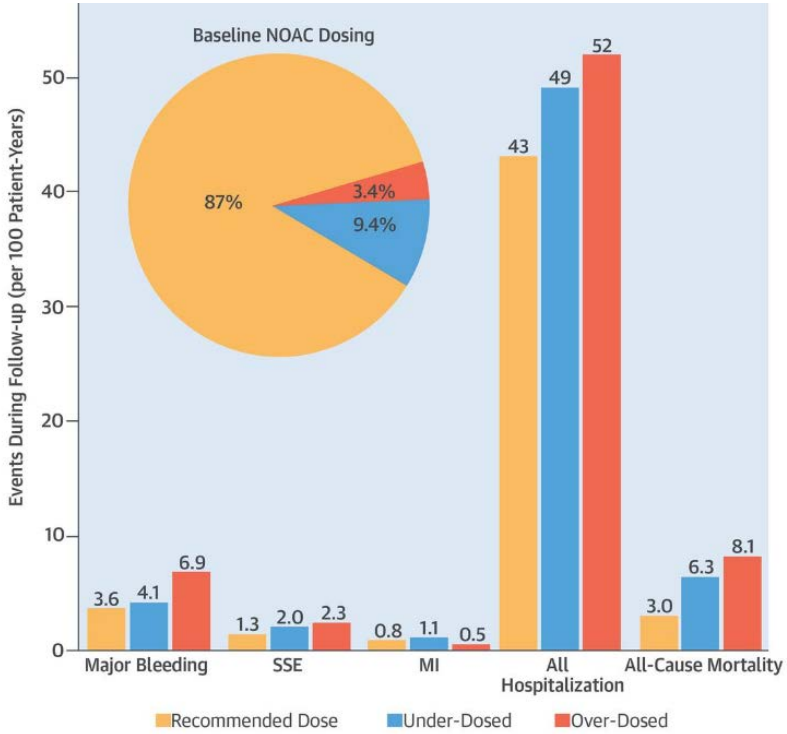
Real World Use of DOACs (*cont.*)



SSE = stroke or systemic embolism; MI = myocardial infarction

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. JACC. 2016;68:2597–604

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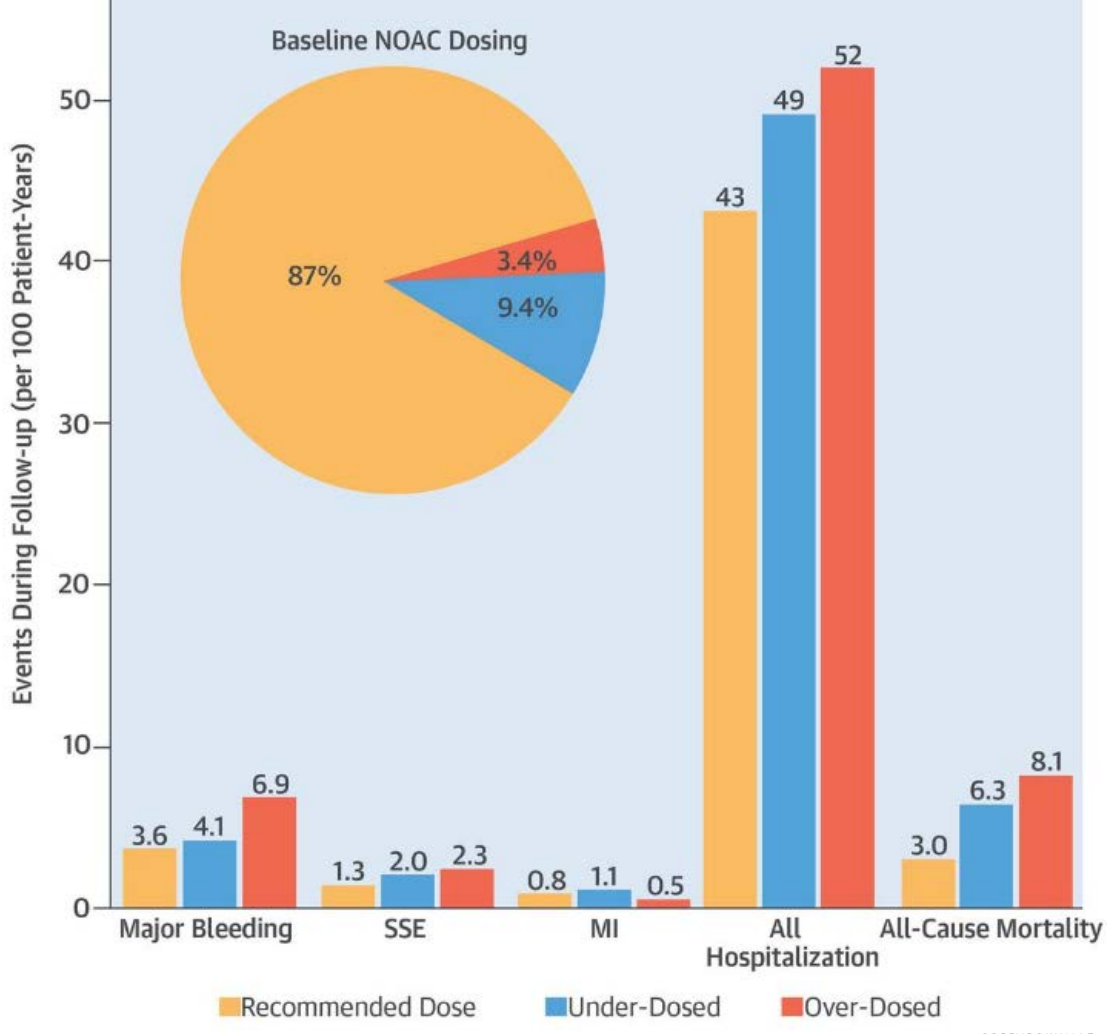

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. JACC. 2016;68:2597–604

Real World Use of DOACs (cont.)

- Characteristics of those under- or overdosed
  - Older patients
  - Females
  - Worse renal function
  - Higher CHADS-VASc
  - Higher bleeding risk

Real World Use of DOACs (cont.)

- Characteristics of those under- or overdosed
  - **Older patients**
  - Females
  - **Worse renal function**
  - Higher CHADS-VASc
  - Higher bleeding risk

Vulnerable Populations: Older Patients

- 10% of patients over 80 years old have NVAF
- Risk of renal impairment and bleeding events increases with advancing age
- Risk of stroke also increases with advancing age

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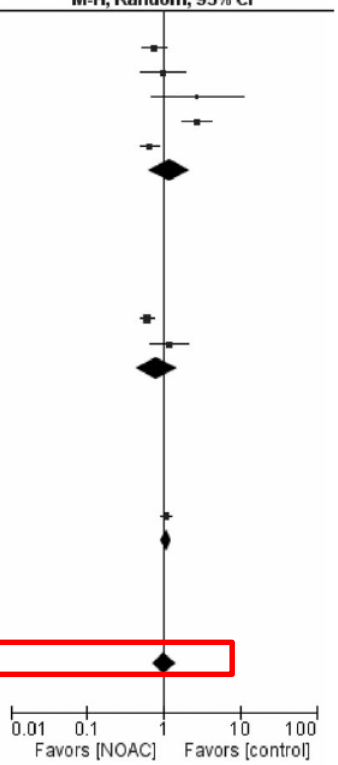
Morrill, A. Dosing of Target-Specific Oral Anticoagulants in Special Populations. *Ann Pharmacotherapy.* 2014

Vulnerable Populations: Older Patients

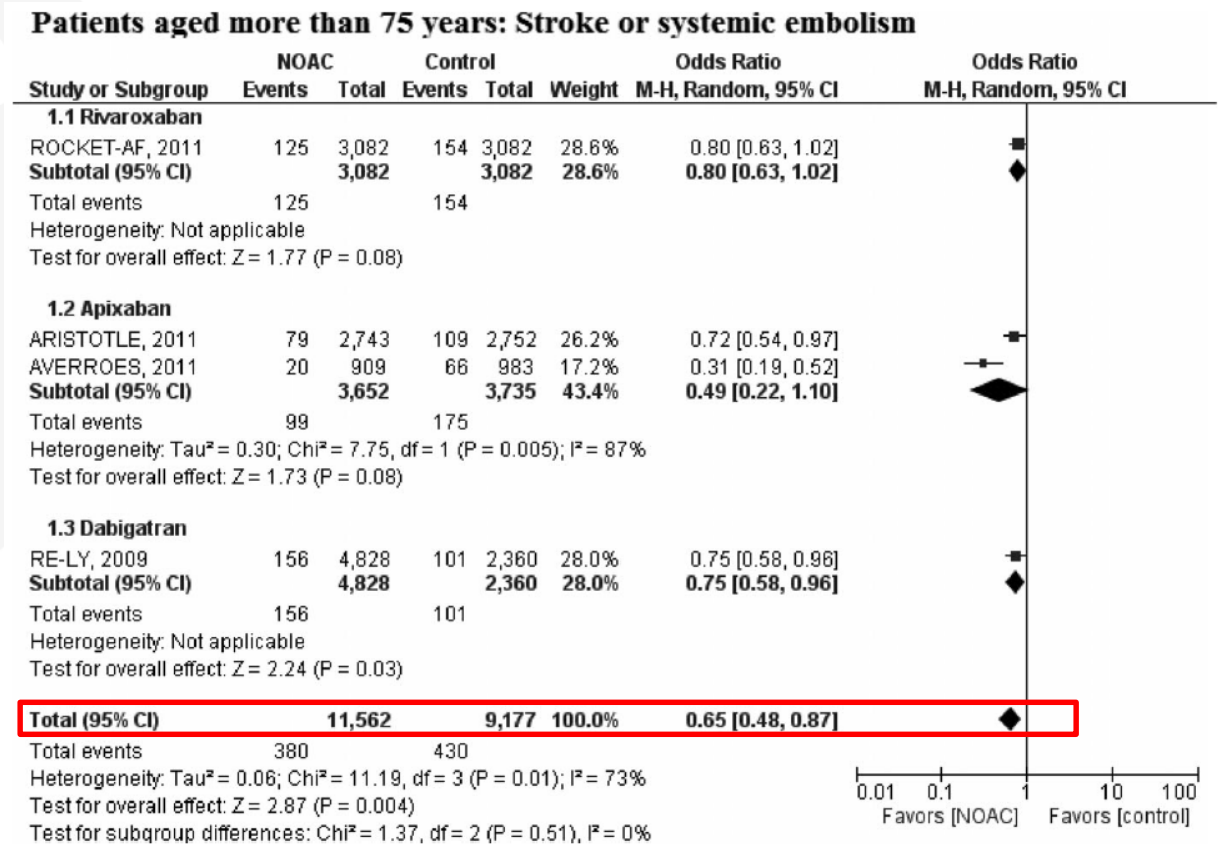
Patients aged more than 75 years: Major or clinically relevant bleeding

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1 Rivaroxaban						
EINSTEIN PE, 2012	58	440	67	401	13.9%	0.76 [0.52, 1.11]
EINSTEIN, 2010	19	215	20	223	10.2%	0.98 [0.51, 1.90]
EINSTEIN-Extension, 2010	7	88	3	98	4.4%	2.74 [0.69, 10.93]
MAGELLAN, 2013	75	1,530	29	1,548	13.1%	2.70 [1.75, 4.17]
ROCKET-AF, 2011	82	3,073	124	3,077	15.0%	0.65 [0.49, 0.87]
Subtotal (95% CI)		**5,346**		**5,347**	**5,6.7%**	**1.18 [0.64, 2.19]**
Total events	241		243			
Heterogeneity: Tau² = 0.39; Chi² = 32.62, df = 4 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 0.52 (P = 0.60)						
1.2 Apixaban						
ARISTOTLE, 2011	151	2,542	224	2,393	15.8%	0.61 [0.49, 0.76]
AVERROES, 2011	26	909	24	983	11.5%	1.18 [0.67, 2.06]
Subtotal (95% CI)		**3,451**		**3,376**	**27.2%**	**0.80 [0.43, 1.51]**
Total events	177		248			
Heterogeneity: Tau² = 0.17; Chi² = 4.54, df = 1 (P = 0.03); I² = 78%						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.3 Dabigatran						
RE-LY, 2009	450	4,828	206	2,360	16.1%	1.07 [0.90, 1.28]
Subtotal (95% CI)		**4,828**		**2,360**	**16.1%**	**1.07 [0.90, 1.28]**
Total events	450		206			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**13,625**		**11,083**	**100.0%**	**1.02 [0.73, 1.43]**
Total events	868		697			
Heterogeneity: Tau² = 0.17; Chi² = 50.25, df = 7 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi² = 0.87, df = 2 (P = 0.65), I² = 0%						



Sardar, P. New Oral Anticoagulants in Elderly Adults. J American Ger Soc. 2014

Vulnerable Populations: Older Patients



Sardar, P. New Oral Anticoagulants in Elderly Adults. J American Ger Soc. 2014

Vulnerable Populations: Older Patients

- Beer's Criteria for Potentially Inappropriate Medications to be Used with Caution in Older Adults
  - CAUTION with dabigatran in patients ≥ 75 years old and in patients with CrCl < 30 ml/min
  - Greatest incidence of gastrointestinal bleeding
- All DOACs included on list of medications to avoid or dose reduce in older adults with renal dysfunction

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American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Amer Geriat Society*. 2015

Vulnerable Population: Chronic Kidney Disease

- Dose adjustment for mild renal impairment (CrCl 50-79 ml/min) and moderate renal impairment (CrCl 30-49 ml/min) appears safe and effective
- Apixaban least impacted by renal impairment and approved for patients receiving intermittent hemodialysis (IHD)
  - Data limited in patients on IHD

Sardar, P. DOACs in Renal Insufficiency. *Canadian Journal of Cardiology.* 2014
Lexicomp Online® , Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; March 1, 2017.

Metabolism and Elimination of DOACs

Medication	Bioavailability	P-gp Substrate	CYP3A4 Substrate	Renal Elimination (%)
Dabigatran	~5%	✓	No	80%
Rivaroxaban	66%*	✓	Yes (~33%)	33%
Apixaban	50%	✓	Yes (~25%)	25%
Edoxaban	62%	✓	No	50%

P-gp =p-glycoprotein; CYP3A4 = cytochrome P450 3A4
*With food bioavailability >90%

Burnett AE, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016. 41:206–232
Guide on Practical Use of NOACs in NVAF. *Europace*. 2013.

Drug Interactions with Dabigatran

Mechanism of Interaction	Drug-Drug Interaction		Therapeutic Effect	Suggested Management
P-gp Inducers	• Barbiturates • Phenytoin	• Carbamazepine • Rifampin • St. John's wort	↓↓ dabigatran concentrations	Avoid concomitant use
P-gp Inhibitors	• Amiodarone • **Dronedarone** • Clarithromycin • Grapefruit • Tacrolimus	• Itraconazole • Ritonavir • Diltiazem • Verapamil • Cyclosporin	↑↑ dabigatran concentrations	Avoid concomitant use if CrCl < 30-50 ml/min*

P-gp =p-glycoprotein; CrCl = creatinine clearance
*Depending on indication

Burnett AE, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016. 41:206–232

Drug Interactions with Rivaroxaban and Apixaban

Mechanism of Interaction	Drug-Drug Interaction	Therapeutic Effect	Suggested Management
P-gp and *strong* CYP3A4 *inducers*	• Barbiturates • Phenytoin • Carbamazepine • Rifampin • St. John's Wort	↓↓ rivaroxaban and apixaban concentrations	Avoid concomitant use with rivaroxaban and apixaban
P-gp and *strong* CYP3a4 *inhibitors*	• Clarithromycin • Grapefruit • Itraconazole • Ritonavir	↑↑ rivaroxaban and apixaban concentrations	Avoid concomitant administration with rivaroxaban Dose reduce apixaban by 50%; if taking 2.5mg bid avoid concomitant use
P-gp and *moderate* CYP3A4 *inhibitors*	• Dronedarone • Diltiazem • Cyclosporin • Verapamil	↑ rivaroxaban and apixaban concentrations	Caution in combining with rivaroxaban if CrCl < 80 ml/min No dose adjustment with apixaban

Burnett AE, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016. 41:206–232

General Recommendations for Managing Interactions with DOACs

- Avoid agents with strong drug-drug interactions, which are more likely to cause significant changes in DOAC drug concentrations
- Attempt to switch to a DOAC that does not have an interaction or consider warfarin
- "Moderate" interactions should be taken on a case-by-case basis, with added precaution taken in patients with renal impairment

Guidance for Practical Management of DOACs. *J Thromb Thrombolysis*. 2016. 41:206–232
Managing Interactions with Direct Oral Anticoaulants. Pharmacist's Letter. May 2016.
Guide on Practical Use of NOACs in NVAF. Europace. 2013.

Other Considerations

Other Medications to Consider

- NSAIDS
- Antiplatelet drugs
- Over-the-counter medications

Real-World Example

Those who take Pradaxa (dabigatran) capsules may not know they should be swallowed whole. The capsules should never be broken, chewed, or opened to take the medicine. Studies have shown that the medicine absorbs too fast if the capsules are opened, chewed, or broken. This can cause serious bleeding.

A patient at a nursing home came to the hospital. He was vomiting blood and needed to be admitted. It is believed that some nurses at the care facility may have been opening the Pradaxa capsules and sprinkling the contents on the patient's food because he had a hard time swallowing the medicine.

ISMP. Do Not Crush List. http://www.ismp.org/tools/donotcrush.pdf
ISMP. http://www.consumermedsafety.org/medication-safety-articles/item/775-don-t-open-pradaxa-capsules

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Considerations for Administration

Medication	Crushable	Administration Considerations
Dabigatran	Do NOT crush or alter capsule integrity	Take without regard to meals
Rivaroxaban	May be crushed	Take with evening meal*
Apixaban	May be crushed	Take without regard to meals

*Doses >10 mg should be taken with meals. Doses ≤ 10 mg may be taken irrespective of meals.

ISMP. Do Not Crush List. http://www.ismp.org/tools/donotcrush.pdf. 2016

Real World Examples

- Duplications
  - Admission orders for patient includes dabigatran (home medication) *and* subcutaneous heparin for DVT prophylaxis.
  - Warfarin and rivaroxaban continued outpatient for treatment of VTE. Pharmacist at warfarin clinic identified duplication after the patient had been on both anticoagulants for several days.
  - Therapeutic once daily enoxaparin discontinued and then apixaban immediately ordered. Timing of last enoxaparin dose was not accounted for, resulting in the patient receiving apixaban 10mg within 2 hours of enoxaparin being administered.

Quarterly Watch. www.ismp.org. Accessed March 21 , 2017.
Andreica, I. Oral Anticoagulants: A review of common errors. Pennsylvania Safety Advisory. 2015

Real World Examples (cont.)

- Dosing Errors
  - Dose of DOAC missed and upon next scheduled administration time double the dose is administered by the nurse.
  - Rivaroxaban 150mg twice daily administered instead of dabigatran 150mg twice daily.
- Miscellaneous
  - Epidural catheter placement/removal while patient is on a DOAC.
  - Rivaroxaban prescribed for treatment of VTE in a patient on carbamazepine for seizures. The patient experiences recurrent VTE.

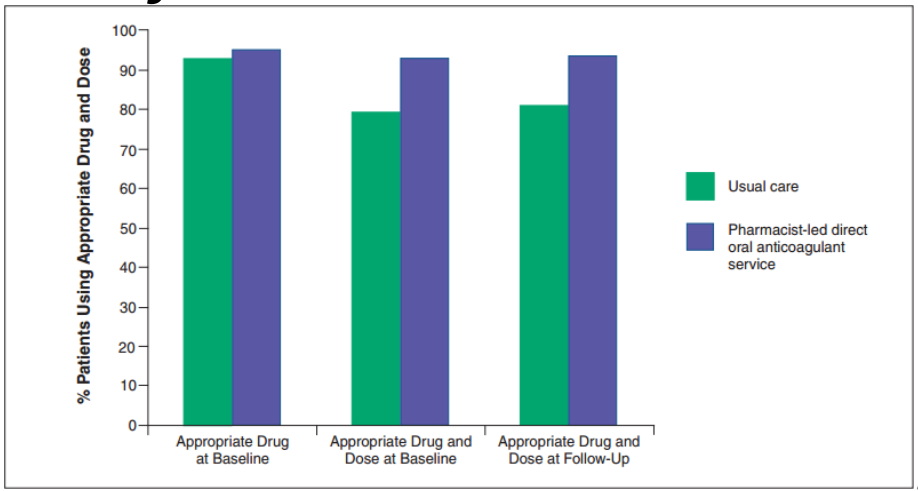
Quarterly Watch. www.ismp.org. Accessed March 21 , 2017.
Andreica, I. Oral Anticoagulants: A review of common errors. Pennsylvania Safety Advisory. 2015
Stoolberger C, et al. Recurrent VTE with Rivaroxaban and Carbamazepine. Neurol Neurochir Pol. Marcr 2017

Management Strategies

- Education
- Ordering constraints
- Alerts
- ISMP Medication Safety Self Assessment
- Pharmacist driven “anticoagulation stewardship”

Pharmacist Managed DOAC Service

"Patients referred to a pharmacist-led DOAC service were more commonly initiated and continued on the correct dosage of a DOAC appropriate for their indication compared with patients managed outside of the DOAC service."



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Ashjian E, et al. Evaluation of Pharmacist-Led Oupatient DOAC Service. *Am J Health-Syst Pharm.* 2017; 74:483-9

Resources

- http://www.doacresources.org/
- Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* (2015) 17, 1467–150
- Guidance for the Practical Management of the Direct Oral Anticoagulants in VTE Treatment. Journal of Thrombosis and Thrombolysis. (2016) 41: 206.

Don’t forget to Do a D-O-A-C Double-Check!

- **Drug-drug** interactions (including pharmacokinetic and pharmacodynamics interactions)
- **Organ** function (liver/renal function)
- **Adjustments** (for any of the above as well as age and weight)
- **Counsel!**

Conclusions

- DOACs are one of the most commonly implicated drugs associated with medication errors
- Adverse drug effects are more common with inaccurate dosing of DOACs
- DOACs require a thorough medication evaluation to monitor for any drug interactions and, depending on the interaction, may require dose adjustment or an alternative anticoagulant
- Pharmacists play an integral role in ensuring safe and appropriate use of DOACs

References

Silva, R. NOACs in NVAF. Cardiovascular and Hematological Agents in Medicinal Chemistry. 2014

www.fda.gov.

Barnes, et al. National Trends in Ambulatory Oral Anticoagulant Use. *Am J Med*. 2015:128, 1300-1305.

Shebab N, et al. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA*. 2016;316(20):2115-2125.

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Guidance for Practical Management of DOACs. *J Thromb Thrombolysis*. 2016. 41:206–232

Managing Interactions with Direct Oral Anticoaulants. Pharmacist's Letter. May 2016.

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace (2015) 17, 1467–150

ISMP. http://www.consumermedsafety.org/medication-safety-articles/item/775-don-t-open-pradaxa-capsules

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