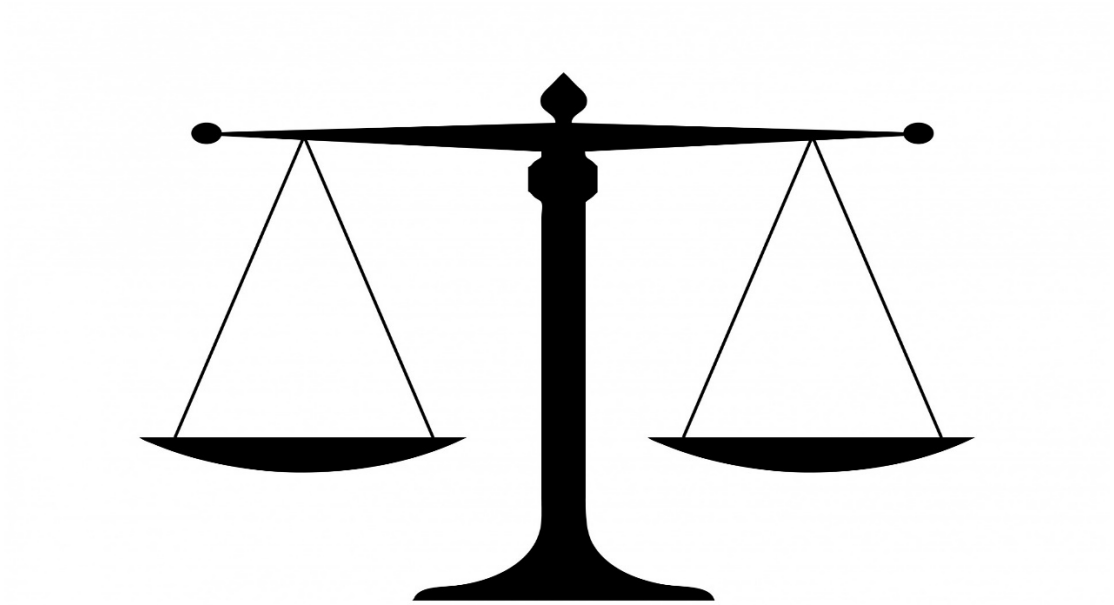
Risky Business: Judging the Use of Novel Oral Anticoagulants for Atrial Fibrillation in Patients with Renal Dysfunction



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Learning Objectives:

1. Explain the requirement of anticoagulation in patients with atrial fibrillation (AF).
2. Describe the risks of using anticoagulation in patients with renal dysfunction.
3. Summarize the evidence for the use of novel oral anticoagulants in patients with atrial fibrillation (AF) and renal dysfunction.
4. Define when and how novel oral anticoagulants should be used in patients with renal dysfunction.

Introduction to Atrial Fibrillation

- Definition[1,2]
  - Supraventricular R stemming from disorganized atrial activity

- Etiologies[2]
  - High blood pressure
  - Coronary heart disease
  - Heart failure
  - Congenital heart defects

- Prevalence and Risk[3]
  - 2.7 to 6.1 million Americans nationwide
  - 10 to 20 fold higher in patients with ESRD
  - Risk Factors
    - Age > 65 years
    - Women > men
    - European decent > African Americans
    - Cardiac disease

- Types[4]
  - Non-valvular AF (NVAF) or Valvular AF: Dependent upon the presence or absence of rheumatic mitral stenosis, mechanical or bio prosthetic heart valve or mitral valve repair

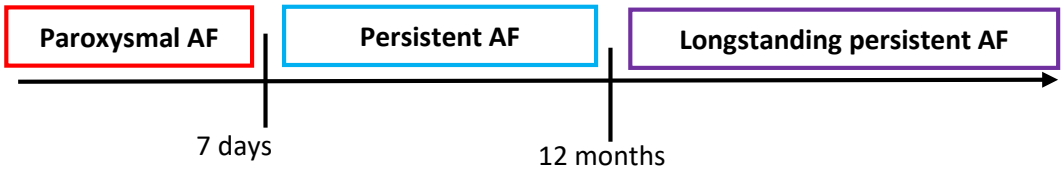


Figure 1. Time in Atrial Fibrillation

  - Permanent AF: maintenance of atrial fibrillation that results in discontinuation of further attempts to restore and maintain normal sinus rhythm

- Complications[2]
  - Heart failure: chambers beating rapidly → ventricles incompletely filled → decreased perfusion
  - Stroke: blood pooling in atria → blood clots form → blood clot breaks and enters brain

- Treatment[2]
  - Rate control: Slows the rate at which ventricles are beating
  - Rhythm control: Maintains normal sinus rhythm
  - Anticoagulation: Prevents blood clots from forming ultimately preventing stroke

Prevention of Stroke in Patients with Atrial Fibrillation

Assessing Stroke Risk

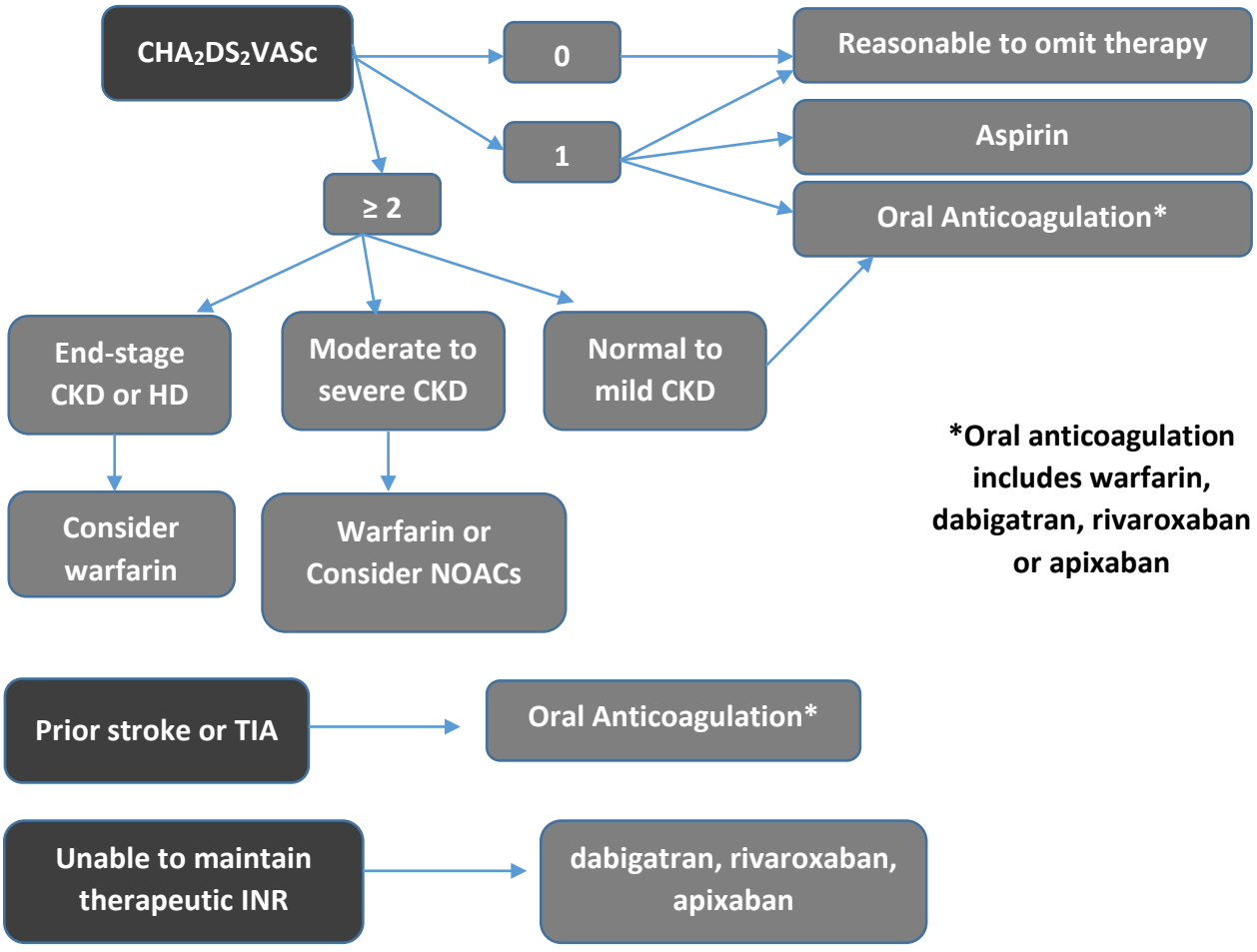
- Validated scoring tools used to stratify risk of stroke and help guide clinical decisions[5,6]

Table 1: $CHADS_2$ Score[2]	
RISK FACTOR	Score
Congestive Heart Failure	**1**
Hypertension	**1**
Age ≥ 75 years	**1**
Diabetes mellitus	**1**
Stroke/TIA/TE	**2**
Maximum score	**6**

Table 2: CHA_2DS_2VASc Score[2]	
RISK FACTOR	Score
Congestive Heart Failure	**1**
Hypertension	**1**
Age ≥ 75 years	**2**
Diabetes mellitus	**1**
Stroke/TIA/TE	**2**
Vascular disease (prior MI, PAD or aortic plaque)	**1**
Age 65-74 y	**1**
Sex category (i.e. female sex)	**1**
Maximum score	**10**

2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation

Figure 2. Non-Valvular Atrial Fibrillation



Valvular Atrial Fibrillation

- Warfarin
  - Recommended anticoagulant
  - INR target depends on location and type of valve

- NOACS: not yet studied

Assessing Bleed Risk

- The HAS-BLED score is a validated scoring tool used to assess a patients' risk for bleeding[7]

- A HAS-BLED score **≥ 3** indicates high risk for bleeding[4]

Table 3: HAS-BLED Score[4,7]	
Risk Factor	**Score**
Age > 65	**1**
Hypertension *Uncontrolled, > 160 mmHg systolic*	**1**
Stroke History	**1**
Renal disease *Dialysis, transplant, Cr > 2.26 mg/dL or > 200 µmol/L*	**1**
Liver disease *Cirrhosis or bilirubin > 2x normal with AST/ALT/AP > 3x normal*	**1**
Alcohol use *≥ 8 drinks/week*	**1**
Prior major bleeding or predisposition to bleeding	**1**
Labile INR *Unstable/high INRs, time in therapeutic range <60%*	**1**
Medication usage predisposing to bleeding *Antiplatelet agents, NSAIDs*	**1**
Interpretation	**High risk ≥ 3**

Figure 3. *History of anticoagulants*

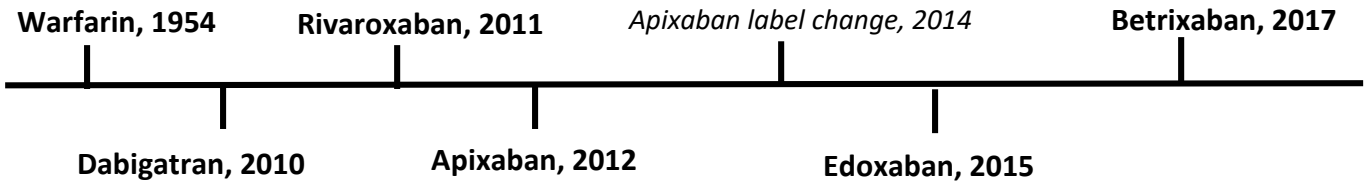


Figure 4. Warfarin Mechanism of Action

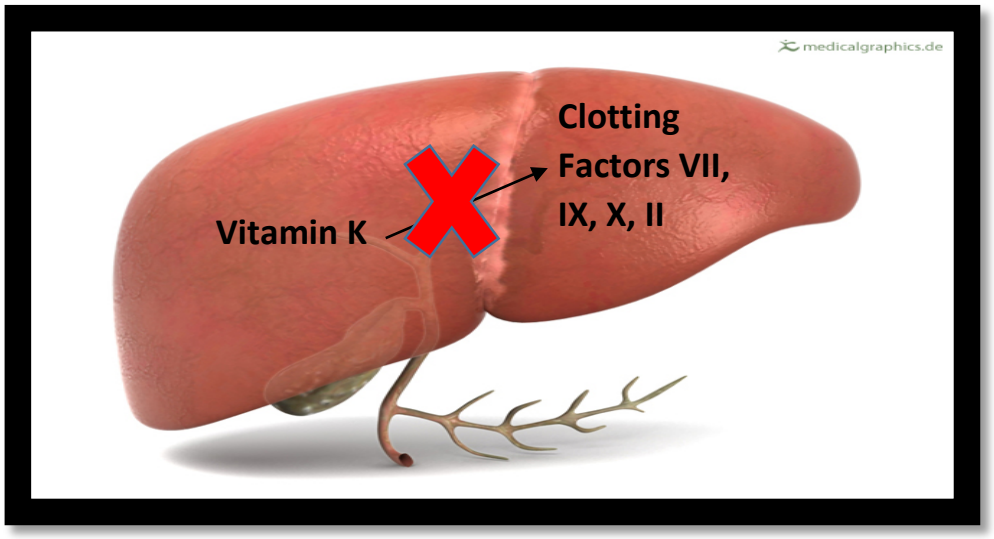
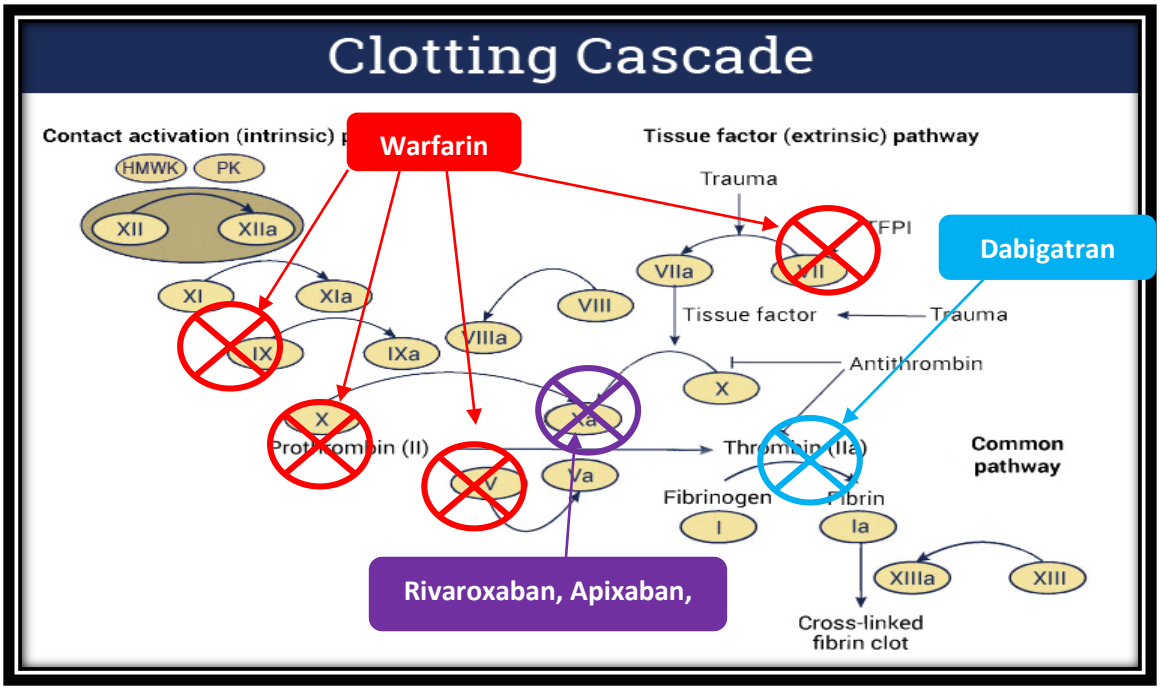


Table 4: Warfarin (Coumadin)[8,9]	
Mechanism of Action	Inhibits the vitamin K epoxide reductase complex 1; depleting functional vitamin K reserves and reduces synthesis of active clotting factors
FDA Indications	• Prophylaxis and treatment of DVT and PE • Prophylaxis and treatment of thromboembolic complications of AF • Prophylaxis and treatment of thromboembolic complications with cardiac valve replacement
Interactions	• CYP 2C9, 2C8, 2C19, 1A2 and 3A4 • Alcohol • Foods rich in Vitamin K
Monitoring	• INR
Advantages	• Individualized dosing • Well known safety and efficacy profile for different disease states
Disadvantages	• Numerous drug and food interactions • Frequent monitoring

Table 5: NOACS			
Drug	**Mechanism of Action**	**Indication**	**Interactions**
Dabigatran (Pradaxa)[10,11]	Inhibits both free and fibrin-bound thrombin	• Treatment and Prevention of DVT • NVAF • Postoperative VTE prophylaxis	P-gp inducers and inhibitors
Rivaroxaban (Xarelto)[12,13]	Reduces thrombin formation by inhibiting Factor Xa	• Treatment of DVT/PE • Reduction of risk of recurrent DVT/PE • NVAF • Postoperative VTE prophylaxis	CYP3A4 inducers and inhibitors
Apixaban (Eliquis)[14,15]	Reduces thrombin formation by inhibiting Factor Xa	• Treatment of DVT/PE • Reduction of risk of recurrence of DVT/PE • NVAF • Postoperative VTE prophylaxis	CYP3A4 inducers and inhibitors
Edoxaban (Savaysa)[16,17]	Reduces thrombin formation by inhibiting Factor Xa	• Treatment of DVT/PE • NVAF	P-gp inducers and inhibitors
Betrixaban (Bevyxxaa)[18,19]	Reduces thrombin formation by inhibiting Factor Xa	• VTE prophylaxis in acute medically ill patients	P-gp inducers and inhibitors

Figure 5: Clotting Cascade and Anticoagulant Targets



Renal Dysfunction

Chronic Kidney Disease (CKD)

- Definition: Gradual decline in renal function over time[20,21]

- Common Etiologies[20,21]
  - Hypertension
  - Diabetes
  - Malformations
  - Autoimmune disorders
    - Goodpasture's Syndrome
    - Systemic Lupus Erythematosus
  - Polycystic kidney disease

- Prevalence[20,22]
  - 30 million Americans have CKD
  - Prevalence has remained relatively stable since 2004
  - ESRD prevalence is 3.7 times greater in African Americans and 1.4 times greater in Native Americans
  - Cardiovascular Vascular Disease (CVD) and CKD
    - Approximately 70% of CKD patients ≥ 66 years old have CVD
    - Atherosclerotic heart disease is the most common CVD among CKD patients

- Complications[20,21]
  - Hypertension
  - Anemia
  - Bone and mineral disorder
  - **Uremia[23,24,25]**
    - Definition: Buildup of urea and other nitrogenous waste compounds that are usually excreted by the kidney

Table 6: Complications of Uremia

System	Complication(s)
Skin	• Pruritus • Skin necrosis
Cardiovascular	• Heart failure • Uremic pericarditis
Neurologic	• Encephalopathy • Seizures
Bone	Muscle Weakness
Endocrine	• Hyperlipidemia • Glucose intolerance due to insulin resistance
Laboratory	• ⇧ Potassium, phosphate, magnesium and uric acid • ⇩ Sodium, calcium • Metabolic acidosis
Hematologic	• Anemia • Platelet dysfunction

- Predisposition to bleeding due to defects in:
  - Platelet-vessel well interaction and adhesion
  - Platelet secretion
  - Platelet aggregation

- Treatment
  - Dialysis
  - Kidney transplant
  - Management of anemia
  - Platelet transfusion

o **Pharmacokinetic alterations**
  - Metabolism and excretion: alterations can cause drug accumulation and potentially increase adverse effects

Figure 6: METABOLISM

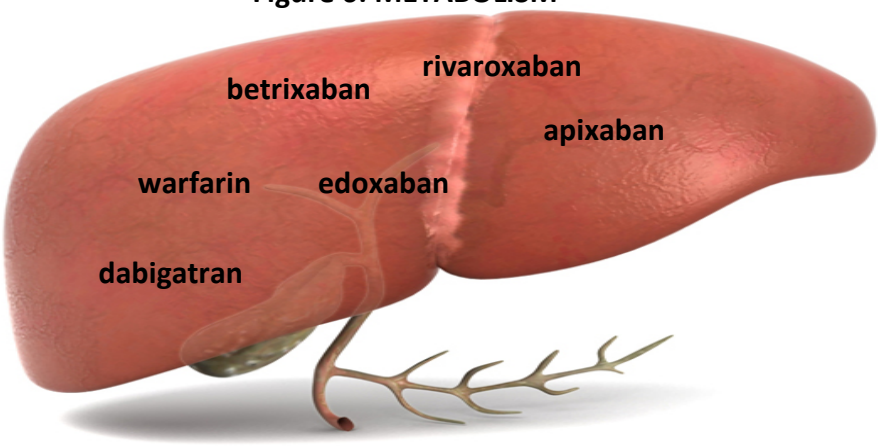
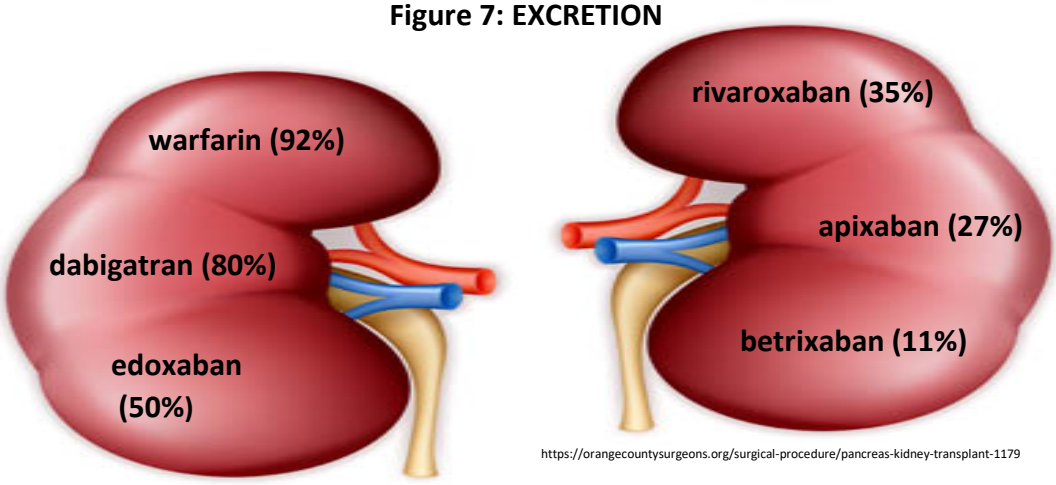


Figure 7: EXCRETION

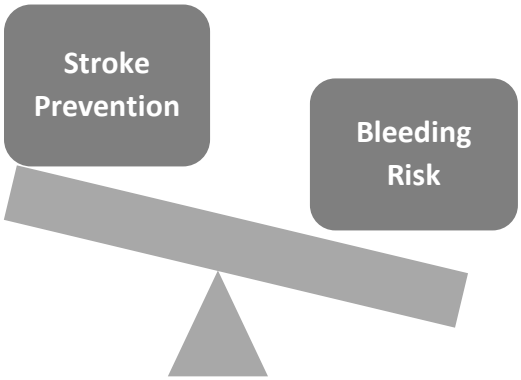


https://orangecountysurgeons.org/surgical-procedure/pancreas-kidney-transplant-1179

Table 7: Pharmacokinetic Studies of NOACS in Renal Impairment			
Study	**Study Design**	**Population**	**Results**
Dias 2015[26]	Open-label single dose rivaroxaban study	• 16 patients (8 healthy; 8 ESRD)	• 35% decrease in clearance when dosed **after** dialysis • 30% decrease in clearance when dosed **before** dialysis
De Vriese 2015[27]	Cohort rivaroxaban dose finding study	• 18 patients (12 patients received single dose administration; 6 patients multiple dose administration)	• Dialysis has little effect on elimination • AUC of 10 mg dose in ESRD patients similar to 20 mg dose in healthy patients • Multiple 10 mg doses C-trough is similar to ROCKET-AF patients with residual kidney function
Chang 2015[28]	Open-label single dose apixaban study	• 8 patients with CrCl > 80mL/min • 10 patients CrCl > 50mL/min to ≤ 80mL/min • 7 patients with CrCl ≥ 30 mL/min to ≤ 50 mL/min • 7 patients with CrCl < 30mL/min	• CrCl > 50mL/min to ≤ 80mL/min →16% apixaban AUC increase • CrCl ≥ 30 mL/min to ≤ 50 mL/min → 29% increase in apixaban AUC • CrCl < 30mL/min → 38% increase in apixaban AUC
Wang 2016[29]	Open-label parallel single dose apixaban study	• 16 patients (8 healthy; 8 ESRD)	• Apixaban AUC was 36% higher when administered after HD

How Should Patients with AF and Renal Dysfunction be Anticoagulated?

Figure 8: Atrial Fibrillation and Renal Dysfunction



Literature Review

Table 8: Warfarin and End-Stage Renal Disease		
	Study	**Results**
Harel et al.[30]	Meta-analysis of 14 studies that reported rate of stroke and or bleeding	No clear benefit or risk associated with the use of warfarin in AF patients on dialysis

Table 9: Renal Population in NOAC Drug Approval Studies		
	Study	**Exclusion**
Connolly et al.[31]	Dabigatran versus Warfarin in Patients with Atrial Fibrillation	**CrCl < 30 mL/min**
Patel et al.[32]	Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation	**CrCl < 30 mL/min**
Granger et. al[33]	Apixaban versus Warfarin in Patients with Atrial Fibrillation	**CrCl < 25 mL/min) OR SCr > 2.5 mg/dL**
Giugliano et al.[34]	Edoxaban versus Warfarin in Patients with Atrial Fibrillation	**CrCl < 30 mL/min**

Table 10:
Steuber TD, Shiltz DL, Cairns AC et al. A Multicenter Analysis of Factors Associated with Apixaban-Related Bleeding in Hospitalized Patients with End-Stage Renal Disease on Hemodialysis *Annals of Pharmacotherapy* 2017 51(11) 854-960

<table>
<tr><td>Objective</td><td colspan="2">Find variables associated with bleeding events in hospitalized ESRD patients on HD taking apixaban.</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study Design</td><td colspan="2">• Multicenter, retrospective, cohort study
• Enrollment: January 1, 2013 to March 31, 2016
• Participants who met inclusion were categorized into two cohorts: bleeding and no bleeding</td></tr>
<tr><td>Patient Selection</td><td><u>Inclusion:</u>
• ≥ 18 years of age
• Received ≥ 2 doses of apixaban in the hospital while receiving chronic, scheduled HD
• Included apixaban continuation from outpatient, newly started or conversion from another agent</td><td><u>Exclusion:</u>
• Received inconsistent HD (acute HD)
• CRRT
• Converted inappropriately from another anticoagulant
• Did not receive apixaban consecutively</td></tr>
<tr><td>Outcomes</td><td colspan="2">• <u>Primary Outcome:</u> Bleeding defined by ISTH, CRNMB, any bleeding (regardless of severity)
• Variables studied include age, gender, weight, BMI, new start or continuation of apixaban, total daily dose, concurrent aspirin use, cumulative aspirin exposure, concurrent interacting medications, number of inpatient HD sessions during apixaban use, all-cause mortality, missed HD sessions, absence or presence of prior bleeding events, presence of liver injury, length of stay (LOS)</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">• Fisher’s exact test, Student’s t-test and Pearson correlation coefficient
• Statistical correlation (weak < 0.4, moderate = 0.4 - 0.6, strong > 0.6)
• Alpha of 0.05
• Logistic Regression with odds ratio and 95% confidence interval</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">• N = 114 patients
• average age 66
• predominantly female

<table><tr><th>Characteristic</th><th>Apixaban N(%)</th></tr><tr><td>New start apixaban</td><td>52 (46%)</td></tr><tr><td>Concomitant aspirin use</td><td>66 (58%)</td></tr><tr><td>Concurrent interacting medications</td><td>66 (58%)</td></tr><tr><td>NVAF indication</td><td>75 (66%)</td></tr><tr><td>Apixaban total daily dose (mg)</td><td>5</td></tr></table></td></tr>
<tr><td>Study Outcomes</td><td colspan="2"><u>Comparison of Continuous Variables Between No Bleeding and Bleeding Events</u>

<table><tr><th></th><th>No Bleeding (n=97), Median (IQR)</th><th>Any Bleeding (n=17), Median (IQR)</th><th>P Value</th><th>All Bleeding Correlation Coefficient</th></tr><tr><td>Age (years)</td><td>64 (52-73)</td><td>66 (53-73)</td><td>0.67</td><td>----</td></tr><tr><td>Weight (kg)</td><td>76 (59-92)</td><td>76 (68-96)</td><td>0.18</td><td>----</td></tr><tr><td>BMI (kg/m^2)</td><td>27 (22-33)</td><td>28 (25-37)</td><td>0.14</td><td>----</td></tr><tr><td>Apixaban total daily dose (mg)</td><td>5 (5-10)</td><td>9.5 (5-10)</td><td>0.23</td><td>----</td></tr><tr><td>Apixaban total exposure (mg)</td><td>25 (12.5-45)</td><td>50 (15-80)</td><td>0.03</td><td>0.20</td></tr><tr><td>Aspirin total exposure (mg)</td><td>162 (0-486)</td><td>162 (0-486)</td><td>0.40</td><td>----</td></tr><tr><td>Total HD sessions</td><td>2 (1-3)</td><td>3 (2-5)</td><td><0.01</td><td>0.27</td></tr></table></td></tr>
</table>

Total hospital LOS (days)	2.5 (3.5-10.5)	13.1 (6.2-16)	**<0.01**	0.28

Logistic Regression Explaining Bleeding Events

	Odds Ratio	95 % CI	P Value
Apixaban total daily dose (mg)	1.72	1.20-2.48	**0.003**
Apixaban total exposure (mg)	0.97	0.93-1.01	0.055
Indication: VTE	0.74	0.07-7.93	0.805
Indication: NVAF	11.54	0.84-157.96	0.067
Age (years)	1.00	0.94-1.07	0.899
Gender (female)	1.43	0.32-6.33	0.640
Weight (kg)	1.02	0.99-1.06	0.203
BMI > 30kg/m^2	0.21	0.02-1.88	0.161
Total HD sessions	2.04	1.06-3.92	**0.033**
Continuation of apixaban	13.07	1.54-110.54	**0.018**
Concurrent aspirin use	1.56	0.29-8.25	0.607
Aspirin total exposure (mg)	1.00	0.99-1.01	0.387
Concurrent interacting medications	0.14	0.03-0.79	**0.026**
Total hospital LOS	1.14	0.99-1.31	0.059

Author's Conclusion

- Risk of bleeding event predicted by continuation of outpatient apixaban, increased apixaban total daily dose, and increased number of HD sessions while on apixaban
- Potential for apixaban to accumulate in ESRD patients and cause bleeding
- Until additional apixaban studies exist warfarin should be the drug of choice in ESRD patients
- Apixaban may be considered with laboratory and clinical monitoring. Lower doses should be used if a patient has a contraindication to or prefers to avoid warfarin

Critique

Strengths:

- Studied bleeding rates with multiple doses of apixaban
- Included ESRD patients
- Utilized ISTH bleeding criteria
- Included both outpatient continuation and new inpatient start of apixaban

Limitations:

- Retrospective study
- Small sample size
- No comparator
- No efficacy outcomes
- Only studied hospitalized patients
- Short duration of follow-up
- Did not specify duration of outpatient apixaban use

Take away summary

Bleeding events occurred in only 15% of hospitalized patients on chronic hemodialysis. The likelihood of bleeding was increased by the number of HD sessions. In addition, the likelihood of bleeding was also increased by the total daily dose of apixaban and continuation of apixaban from the outpatient setting. Overall, apixaban was safe in 85% of the hospitalized patients on chronic hemodialysis. It is important to note that over half of the patients were on apixaban 2.5 mg twice daily. While lower doses may be safer, we do not know if they are effective in this patient population as efficacy was not evaluated in this study.

Table 11:
Stanton BE, Barasch NS, Tellor KB, et al. Comparison of the Safety and Effectiveness of Apixaban versus Warfarin in Patients with Severe Renal Impairment. *Pharmacotherapy* 2017; 37(4):412-419

Objective	To evaluate safety and efficacy of apixaban versus warfarin in patients with severe renal impairment	
Methods		
Study Design	Single centered, retrospective cohort study	
Patient Selection	**Inclusion Criteria:** • ≥ 18 years old • Received at least one dose of apixaban or warfarin • Therapeutic INR while admitted • Enrollment: January 30, 2014 to December 31, 2015 • CrCl < 25 mL/min or SCr > 2.5 mg/dL or receiving HD or peritoneal dialysis	**Exclusion Criteria:** • Unable to obtain accurate labs before dose • Not able to calculate CrCl • CRRT patients
Outcomes	**Primary outcome:** Major bleeding defined by ISTH	**Secondary outcomes:** • Composite of major bleeding, clinically relevant non-major bleeding, minor bleeding • Stroke in NVAF or recurrent VTE in patients being treated for DVT or PE
Statistical Analysis	• Student *t* test, Chi-squared, Fisher's exact test • Alpha of 0.05 • SPSS software to analyze results	
Results		
Baseline Characteristics	• N = 146 • Average age 79, predominantly white females • Average treatment days in hospital 4.3 days for apixaban and 3.8 days for warfarin • Apixaban dosing 2.5mg BID (45 patients), 5mg BID (27 patients) and 10mg BID (1 patient)	

Characteristic	Apixaban (N=73)	Warfarin (N=73)	P Value
SCr (mg/dL)	2.9 ± 1.8	3.2 ± 2.3	0.341
Severe renal impairment			
ESRD	46 (63)	46 (63)	> 0.99
ESRD on dialysis	7 (9.6)	7 (9.6)	----
	20 (27.4)	20 (27.4)	----
NVAF indication	53 (72.6)	53 (72.6)	> 0.99
CHA_2DS_2VASc	6.1 ± 1.3	5.6 ±1.5	0.100
HAS-BLED	3.4 ± 0.9	3 ± 0.9	0.062
Concomitant Antiplatelet Agents			
Aspirin	44 (60.3)	36 (49.3)	0.183
Clopidogrel	7 (9.6)	2 (2.7)	0.166
Aspirin and/or clopidogrel	47 (64.44)	36 (49.3)	0.66

Study Outcomes

Outcome	Apixaban	Warfarin	P Value
Major Bleeding	7 (9.6%)	13 (17.8%)	0.149
Composite Bleeding	16(21.9%)	20 (27.4%)	0.442
Stroke	4 (7.5%)	4 (7.5%)	> 0.99
VTE recurrence	0(0)	0(0)	---

Conclusions and Evaluation

Author's Conclusion

Apixaban could potentially be safe in this population with close monitoring as there were no statistically significant differences in bleeding, stroke or VTE.

Critique

Strengths:

- Included patients with severe renal impairment
- ISTH criteria used to define bleeding
- Follow-up of at least 5 months
- Included both outpatient continuation and new inpatient start

Limitations:

- Retrospective
- Single center
- Small sample size
- Small portion of patients on HD
- Efficacy was not a primary outcome
- Power of 33%
- Physicians made anticoagulation decisions independently

Take away Summary

Although not statistically significant, there were fewer major overall bleeding events in the apixaban group compared to the warfarin group. This suggests that apixaban may be just as safe as warfarin in patients with CrCl 15-25 mL/min, SCr > 2.5 mg/dL or on dialysis. In addition, more than half of the patients were taking apixaban 2.5 mg twice daily, which appears to be safe in terms of bleeding; however, efficacy was not a primary outcome and we are therefore unable to conclude if apixaban 2.5 mg twice daily effective in this patient population.

Footnotes

1. Non-major bleeding defined as clinical overt bleeding that did not meet qualifications for major bleeding but led to hospitalization, medical or surgical treatment for bleeding, change in antithrombotic therapy because of bleeding.
2. Renal function
    - Severe: CrCl 15-25 mL/min or SCr > 2.5 mg/dL and not receiving dialysis
    - End-stage renal disease: CrCl < 15 mL/min and not receiving dialysis
    - End-stage renal disease and receiving dialysis: Receiving hemodialysis or peritoneal dialysis

Table 12:
Sarratt SC, Nesbit R, Moye R. Safety Outcome of Apixaban Compared with Warfarin in Patients with End-Stage Renal Disease. *Annals of Pharmacotherapy* 2017, Vol 51 (6) 445-450

Objective	Compare bleeding rates in patients on apixaban or warfarin on chronic hemodialysis	
Methods		
Study Design	• Retrospective cohort study at University of Tennessee Medical Center • Enrolled from May 31, 2011 to December 31, 2015 in 4:1 ratio in warfarin and apixaban cohorts	
Patient Selection	**Inclusion:** • ≥ 18 years of age • On chronic HD • Received apixaban or warfarin for the treatment or prevention of VTE	**Exclusion:** • Admitted for an active bleed from a trauma (i.e. fall, motor vehicle accident) • Warfarin INR goal greater than 2-3 • History of hypercoagulable state
Outcomes	**Primary:** Major bleeding	**Secondary:** Clinically relevant non-major bleeding[1] and minor bleeding events
Statistical Analysis	• 255 patients needed for 80% power • Alpha of 0.05 • Two-sided Chi-squared, Fishers exact test, T-test or Mann-Whitney U test • SPSS software to analyze results	
Results		
Baseline Characteristics	• N=160 • Mean age in apixaban arm was 70 and 66 for warfarin, predominantly Caucasian males • More than half of patients on apixaban 2.5mg BID • Most common indication was AF • Median CHA_2DS_2-VASc score was 5	

Study Outcomes

Bleeding Rates	Apixaban (N=40), n(%)	Warfarin (N=140), n(%)	P Value
Major Bleeding	0 (0)	7 (5.8)	0.338
Decrease in hemoglobin ≥ 2g/dL	0 (0)	3 (2.5)	0.574
Transfusion of ≥ 2 units of blood products	0 (0)	5 (4.2)	0.332
Bleeding from a critical site	0 (0)	0 (0)	----
Fatal bleeding	0 (0)	0 (0)	----
Clinically relevant non-major bleeding	5 (12.5)	7 (5.8)	0.166
Unexpected hematoma	0 (0)	2 (1.7)	0.561
Epistaxis	2 (5)	0 (0)	0.061
Gingival bleeding	0 (0)	0 (0)	----
Hemoptysis	1 (2.5)	1 (0.8)	0.439
Hematuria	0 (0)	0 (0)	----
Gastrointestinal bleeding	1 (2.5)	3 (2.5)	0.688
Rectal bleeding	1 (2.5)	2 (1.7)	0.581
Minor bleeding	1 (2.5)	3 (2.5)	0.737
Any bleeding	6 (15)	17 (14.2)	0.438

Study Outcomes

Other Secondary Outcomes	Apixaban, N=40	Warfarin, N=140	P Value
LOS, days, mean [range]	8.8 [1-19]	9.0 [2-16]	0.871
Lowest Hgb in g/dl, mean [range]	8.6 [6.9-10.3]	8.9 [6.1-10.4]	0.315
Highest INR, mean [range]	----	3.5 [1.3-20.0]	----
Concomitant medications (%)			
Antiplatelet	15 (37.5)	53 (44.2)	0.291
Anticoagulants	9 (22.5)	43 (35.8)	0.119
NSAIDS	4 (10)	6 (5)	0.269
ESA	10 (25)	29 (24.2)	0.915
Other	0 (0)	10 (8.3)	0.067
Major interacting medications	----	57 (47.5)	----

Conclusions and Evaluation

Author's Conclusion

No significant difference in bleeding rates between apixaban and warfarin. Apixaban should be used cautiously in patients with ESRD until there is more insight into the effect of multiple doses on drug accumulation and clinical outcomes.

Critique

Strengths:

- ISTH major bleeding definition

Limitations:

- Evaluated safety only
- No follow-up
- **Did not meet power**
- No INR at time of bleed recorded
- Paper chart documentation

Take away summary

Overall bleeding rates were not significantly different between apixaban and warfarin; however, the study did not meet power. In terms of bleeding, the apixaban group had no major bleeds; however, the rate of clinically relevant non-major bleeding was higher compared to warfarin. Similar to previous studies, more than half of the patients were on reduced dose apixaban and this appeared to be safe in terms of bleeding. However, efficacy was not evaluated in the study and therefore, we are unable to determine if reduced dose apixaban is safe and effective in this patient population.

Footnotes

1. Clinically non-major bleeding defined as any bleeding compromising hemodynamics resulting in hospitalization, unexpected hematoma or excessive wound hematoma, epistaxis, gingival bleeding, hemoptysis, hematuria, gastrointestinal bleeding, rectal bleeding and any other bleeding resulting in intervention.

Summary of Literature Reviewed

Table 13: Summary of Literature		
Author	**Objective**	**Take away**
Steuber et al .	Evaluated patients on HD receiving apixaban	• Bleeding events occurred in 15% of hospitalized patients on chronic hemodialysis • Total daily dose and number of HD sessions increases the risk of bleeding • More than half of patients were on 2.5 mg BID • Efficacy not evaluated
Stanton et al.	Compared bleeding events between apixaban and warfarin in patients with CrCl 15-25 mL/min or SCr > 2.5 mg/dL or on dialysis	• No statistically significant difference in bleeding • Fewer bleeding events with apixaban • More than half of patients were on 2.5 mg BID • Efficacy not evaluated as a primary outcome
Sarratt et al.	Compared bleeding rates between apixaban and warfarin in patients on HD	• No significant difference in overall bleeding rates • Apixaban group had no major bleeds • Apixaban had higher rate of CRNMB • More than half of patients were on 2.5 mg BID • Efficacy not evaluated

Data Limitations and Future Directions

- Longer follow-up periods
    - Current studies have short follow-up durations
    - Need to gain insight into the long term effects of apixaban

- Efficacy & safety data
    - Current studies primarily focused on safety outcomes
    - Need data that evaluates safety and efficacy together as primary outcomes
    - Need to study the efficacy of reduced dose of 2.5 mg twice daily

- Larger randomized controlled trials
    - Current studies are small retrospective cohorts
    - Larger studies that are powered to detect a difference are needed

- Role of betrixaban
    - Currently only studied and approved for VTE prophylaxis
    - Small percentage excreted through kidneys so could potential be promising in ESRD patients
    - Need to study safety and efficacy in patients with NVAF

Figure 9: Recommended Treatment Algorithm

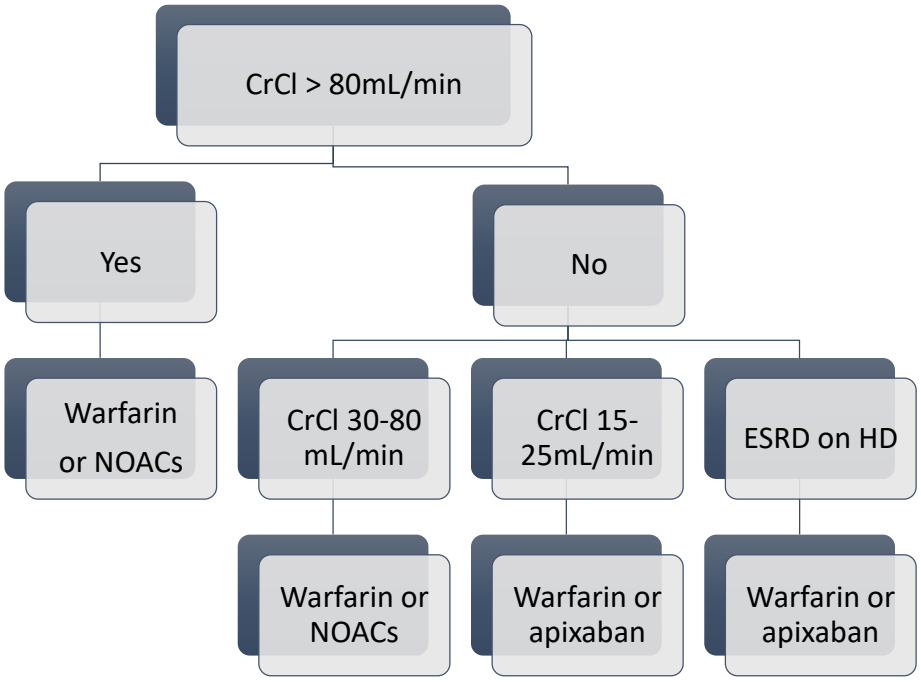
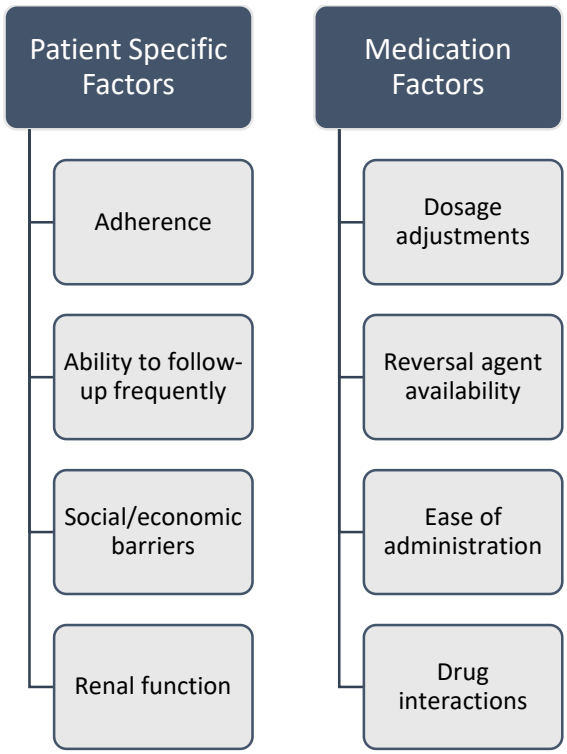


Figure 10: *Agent Selection*



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Appendices

Appendix A: Abbreviations	
Abbreviation	**Description**
A.Flutter	Atrial Flutter
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice a day
BMI	Body mass index
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
CrCl	Creatinine Clearance
CRNMB	Clinically relevant non-major bleeding
DM	Diabetes Mellitus
DVT	Deep Vein Thrombosis
ECHO	Echocardiograph
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
HD	Hemodialysis
HTN	Hypertension
INR	International normalized ratio
IQR	Inter-quartile range
ISTH	International Society on Thrombosis and Haemostasis
LOS	Length of stay
NVAF	Non-valvular Atrial Fibrillation
PE	Pulmonary Embolism
P-gp	P-glycoprotein
SCr	Serum Creatinine
TIA	Transient Ischemic Attack
ULN	Upper limit normal
VTE	Venous Thromboembolism

Appendix B: International Society on Thrombosis and Haemostasis Criteria for Major Bleeding [35,36]	
Definition	**Criteria**
ISTH	Major Bleeding in non-surgical patients: • Fatal bleeding • Symptomatic bleeding from critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome • Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) • Bleeding leading to a transfusion of two or more units of whole blood or red cells Clinically Relevant non-major bleeding: Any sign or symptom of hemorrhage that does not fit the ISTH major bleeding criteria but meets at least one of the following: • Requiring medical intervention by a healthcare provider • Leading to hospitalization or increased level of care • Prompting a face to face evaluation

Appendix C: PK Parameters of Anticoagulants [8,9,10,11,12,13,14,15,16,17,18,19]		
Drug	**Metabolism**	**Excretion**
Warfarin	Hepatic; CYP 2C9, 2C8, 2C19, 1A2 and 3A4	Urine (92 % metabolites)
Dabigatran	Hepatic	Urine (~80 %)
Rivaroxaban	Hepatic; CYP 3A4 predominantly	Urine (~66 %); feces
Apixaban	Hepatic; CYP 3A4 predominantly	Feces; urine (~27 %)
Edoxaban	Minimally through CYP3A4	Urine (primarily unchanged)
Betrixaban	Hepatic; minimally through CYP450 pathway	Primarily feces (~85 %); urine

Appendix D: CKD Staging Based on eGFR[20]		
Stage	**eGFR (mL/min/1.73 m^2)**	**Termed**
1	> 90	Normal
2	60-89	Mild decrease
3a	45-59	Mild to moderate decrease
3b	30-44	Moderate to Severe decrease
4	15-29	Severe decrease
5	< 15	Kidney Failure

Appendix E: NOAC Indication and Dosing[10,11,12,13,14,15,16,17,18,19]		
	Indication	**Dosing**
Dabigatran	Treatment and Prevention of DVT	150 mg BID
	NVAF	150 mg BID
	Postoperative VTE prophylaxis	110 mg given 1-4 hours after completion of surgery and hemostasis is achieved; 220 mg daily (hip replacement duration is 28-35 days and knee replacement 10-14 days)
Rivaroxaban	Treatment of DVT/PE	15 mg BID with food for 21 days; then 20 mg daily
	Reduction of risk of recurrent DVT/PE	20 mg daily
	NVAF	20 mg daily with evening meal
	Postoperative VTE prophylaxis	10 mg daily, initiated after surgery one hemostasis is achieved (hip replacement duration 35 days; knee replacement 12 days)
Apixaban	Treatment of DVT/PE	10 mg BID x 7 days then 5mg daily
	Reduction of risk of recurrence of DVT/PE	2.5 mg BID after at least 6 months of treatment for DVT
	NVAF	5 mg BID
		2.5 mg BID; if patient has 2 of the following: Age ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5mg/dL
	Postoperative VTE prophylaxis	2.5 mg BID beginning 12-24 hours after surgery (hip replacement duration 35 days and knee replacement 12 days)
Edoxaban	Treatment of DVT/PE	60 mg daily
	NVAF	60 mg daily
Betrixaban	VTE prophylaxis	160 mg x 1 dose; then 80 mg daily

Appendix F: Patient Population in NOAC Drug Approval Trials			
	Study	**Inclusion**	**Exclusion**
Connolly et al.[29]	Dabigatran versus Warfarin in Patients with Atrial Fibrillation	• AF documented on ECHO • ≥ 1 additional risk factor for stroke[1]	• Severe heart-valve disorder • Stroke within 14 days • Severe stroke within 6 months prior to screening • Condition that would increase risk of hemorrhage • Active liver disease • Pregnancy • CrCl < 30mL/min
Patel et al.[30]	Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation	• NVAF confirmed by ECHO • Elevated risk[2]	• CrCl < 30mL/min • Other exclusion criteria listed based on cardiac risk, hemorrhage risk and other therapies and comorbidities.
Granger et. al[31]	Apixaban versus Warfarin in Patients with Atrial Fibrillation	• A. Fibrillation or A. Flutter at enrollment or at least 2 episodes documented by ECHO at least 2 weeks apart in the 12 months before enrollment. • At least 1-risk factor for stroke[3]	• A. Fibrillation due to reversible cause • Other conditions other than A. Fibrillation that required anticoagulation • Stroke within 7 days • Need for aspirin >165mg daily or DAPT (ASA and Clopidogrel) • Severe renal insufficiency (SCr > 2.5 mg/dL or CrCl < 25 mL/min); moderate • Severe mitral stenosis
Giugliano et al.[32]	Edoxaban versus Warfarin in Patients with Atrial Fibrillation	• ≥ 21 years of age • Documented A. Fibrillation within 12 months before randomization • CHA_2DS_2VASc score ≥ 2 • Planned anticoagulation therapy for duration of trial	• AF due to reversible cause • CrCl < 30 mL/min • High risk of bleeding • Use of dual antiplatelet therapy • Moderate-severe aortic stenosis • Other conditions that required anticoagulation • ACS • Coronary revascularization • Stroke within 30 days of randomization • Inability to follow study procedures.

Foot notes:

1. Previous stroke or TIA, LVEF < 40%, NYHA Class II or higher heart failure symptoms within 6 months before screening, age at least 75 years, or 65-74 years old with DM HTN or CAD.
2. Elevated risk was defined as history of stroke, TIA or systemic embolism or at least two of the following (HF, LVEF ≤ 35%, HTN, ≥ 75 years old, or presence of diabetes)
3. Age ≥ 75 years, prior stroke, TIA or systemic embolism, symptomatic HF within 3 months or LVEF < 40%, diabetes, hypertension requiring medications

Appendix G: Example Substrates, Inducers and Inhibitors			
Protein/Enzyme	**Anticoagulant Substrates**	**Inducers**	**Inhibitors**
P-gp[37]	• Dabigatran • Apixaban • Rivaroxaban • Edoxaban • Betrixaban	• Amiodarone • Verapamil • Erythromycin • Clarithromycin	• Carbamazepine • Rifampin
CYP-3A4[38]	• Rivaroxaban (major) • Apixaban (major) • Warfarin (minor)	• Phenytoin • Phenobarbital • Oxcarbazepine	• Amiodarone • Clarithromycin • Grape Fruit • Diltiazem • Fluoxetine
CYP 2C9[39]	• Apixaban (minor) • Warfarin (major)	• Rifampin	• Gemfibrozil • Trimethoprim
CYP 2C8[40]	• Apixaban (minor) • Warfarin (minor)	• Carbamazepine • Phenytoin • Rifampin	• Amiodarone • Clopidogrel • Fluconazole • Sulfamethoxazole • Metronidazole
CYP 2C19[41]	• Apixaban (minor) • Warfarin (minor)	• Carbamazepine • Phenytoin • Rifampin	• Clopidogrel • Esomeprazole • Fluconazole • Fluoxetine • Oxcarbazepine
CYP 1A2[42]	• Apixaban (minor) • Warfarin (minor)	• Carbamazepine • Rifampin • Smoking	• Cimetidine • Ciprofloxacin