Direct Oral Anticoagulant Management in Patients Undergoing Cardiac Implantable Electronic Device Procedures

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Disclosures

- Marci Farquhar-Snow
  - Nothing to disclose
  - No conflict of interest
- Michelle Alland
  - Nothing to disclose
  - No conflict of interest

Abbreviations

AF	Atrial fibrillation
ASA	Aspirin
CIED	Cardiac Implantable Electronic Devices -permanent pacemaker and/or implantable cardiodefibrillator
DAPT	Dual antiplatelet therapy -aspirin plus clopidogrel, ticagrelor, or prasugrel
DOAC	Direct Oral Anticoagulant -rivaroxaban, apixaban, dabigatran
OAC	Oral Anticoagulants

Background

- Annually, 10-15% patients on OAC undergo procedures that require periprocedural management
- No US consensus guidelines for DOACs in periprocedural setting until recently (2017)
- 70% institutions do not have standardized protocols for periprocedural management of DOACs
- Overall OAC use rate increased from 52.4% to 60.7% among eligible AF patients

Douketis et al., 2012; Flake et al., 2015; Oktay, 2015; Marzec et al, 2017

Aims of Research

- Evaluate trends in periprocedural management of DOACs surrounding CIED procedures
- Evaluate longitudinal change in DOAC management practices
- Analyze factors contributing to decision-making process for DOAC management surrounding CIED procedures.
- Identify DOAC management strategies that are safe for patients undergoing CIED procedures.

Part 1:
Trends in DOAC Management in Patients Undergoing CIED Procedures

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Objectives

1. Describe research/recommendations for periprocedural management of DOACs surrounding CIED procedures
2. Evaluate practice trends in periprocedural management of DOACs surrounding CIED procedures

DOAC Profiles

Dabigatran
Direct thrombin inhibitor

- Onset: 1 hr
- Peak: 2-4 hr
- Half-life: 12-17 hr

Apixaban
Factor Xa Inhibitor

- Onset: 3-4 hr
- Peak: 3-4 hr
- Half-life: 12 hr

Rivaroxaban
Factor Xa Inhibitor

- Onset:
- Peak: 2-4 hr
- Half-life:
  5-9 hr age 20-45
  11-13hr age >45

Package Recommended Hold Times

Dabigatran
Direct thrombin inhibitor

- 1 to 2 days (CrCl >50mL/min) or 3-5 days (CrCl < 50 mL/min)
- “Consider longer times in major surgery, spinal puncture, or placement of a spinal or epidural catheter”

Apixaban
Factor Xa Inhibitor

- At least 48 hours prior to procedures with a moderate to high risk of clinically significant bleeding
- At least 24 hours prior procedures with low risk of bleeding or where bleeding “non-critical and easily controlled”

Rivaroxaban
Factor Xa Inhibitor

- At least 24 hours before surgical procedure to reduce the risk of bleeding
- “Increased risk of bleeding should be weighed against urgency of intervention”

Methods

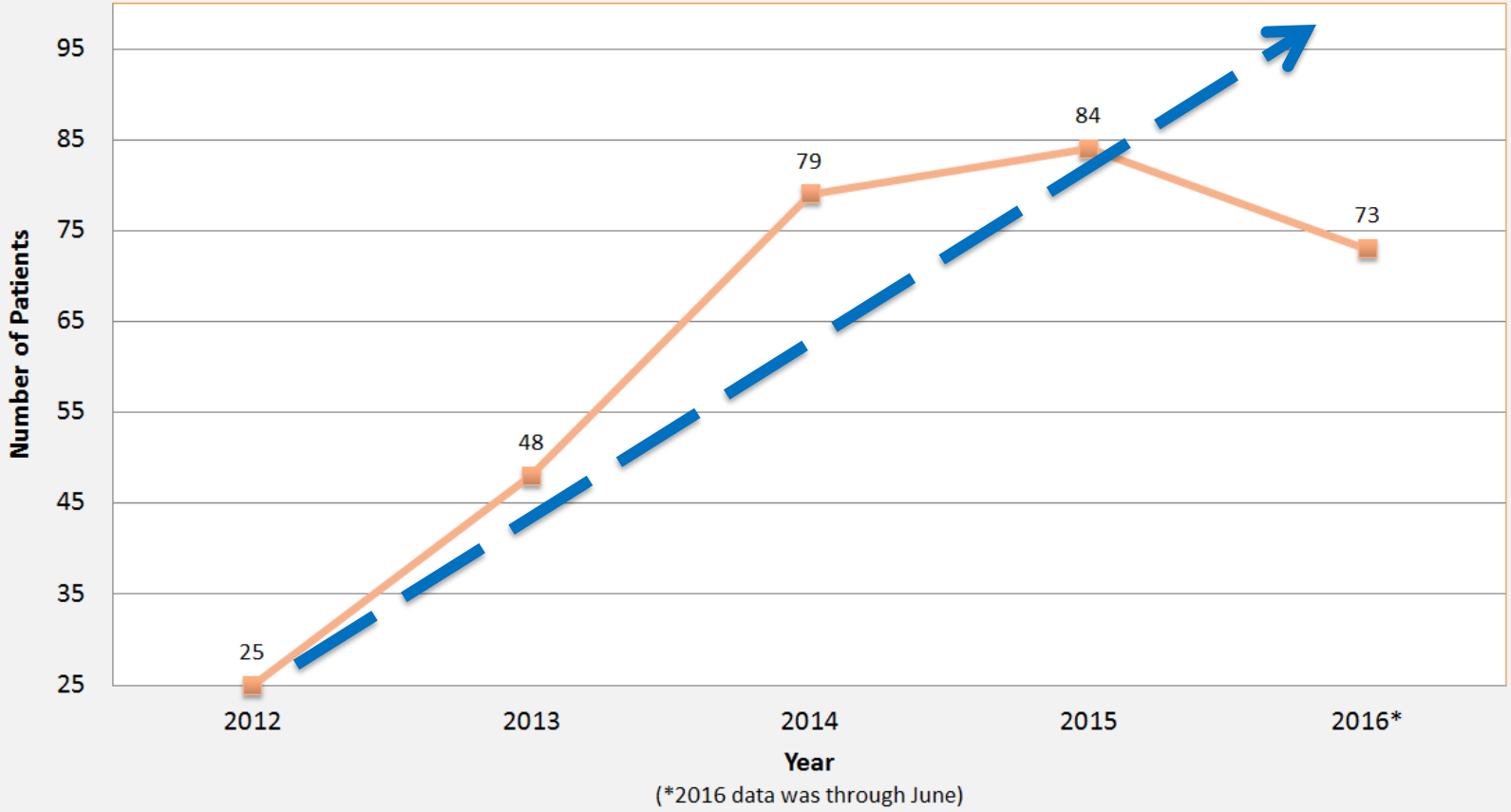
- Retrospective chart review
- All adult patients on DOACs at time of CIED procedure
- Mayo Clinic (Arizona, Jacksonville, Rochester) from January 2012 - June 2016
- N=309

Data Collected

- Number of days DOAC held before and after procedure
- Frequency of bridging with heparin
- Comorbidities
- Concurrent medications
- CHA2DS2-VASc and HASBLED scores
- Age
- Procedure type
- Facility location
- Year
- Bleeding and thrombotic complication rates

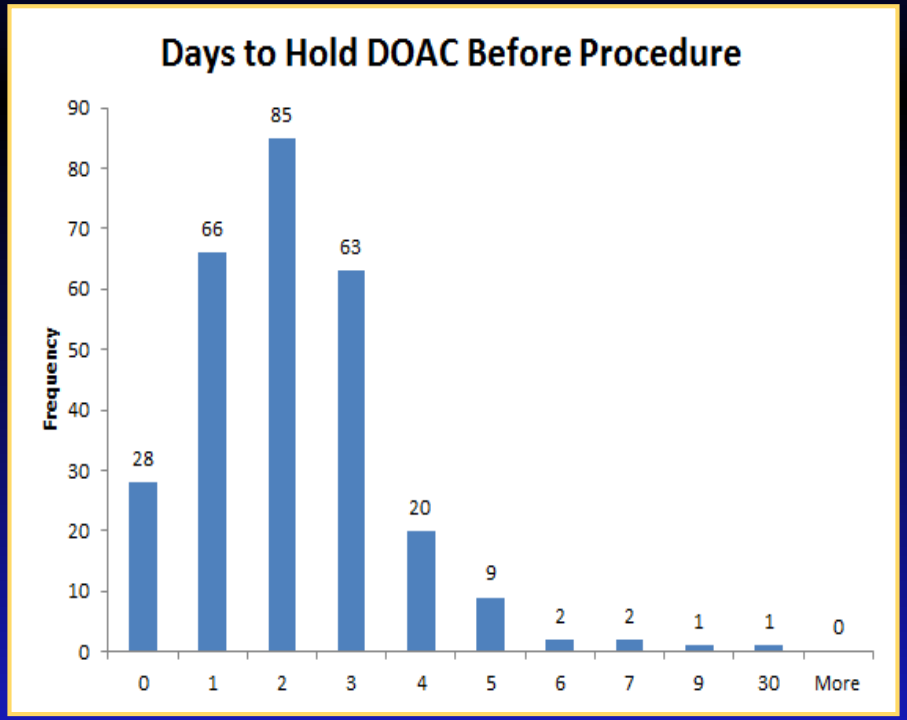
DOAC Use: Trend 2012-2016

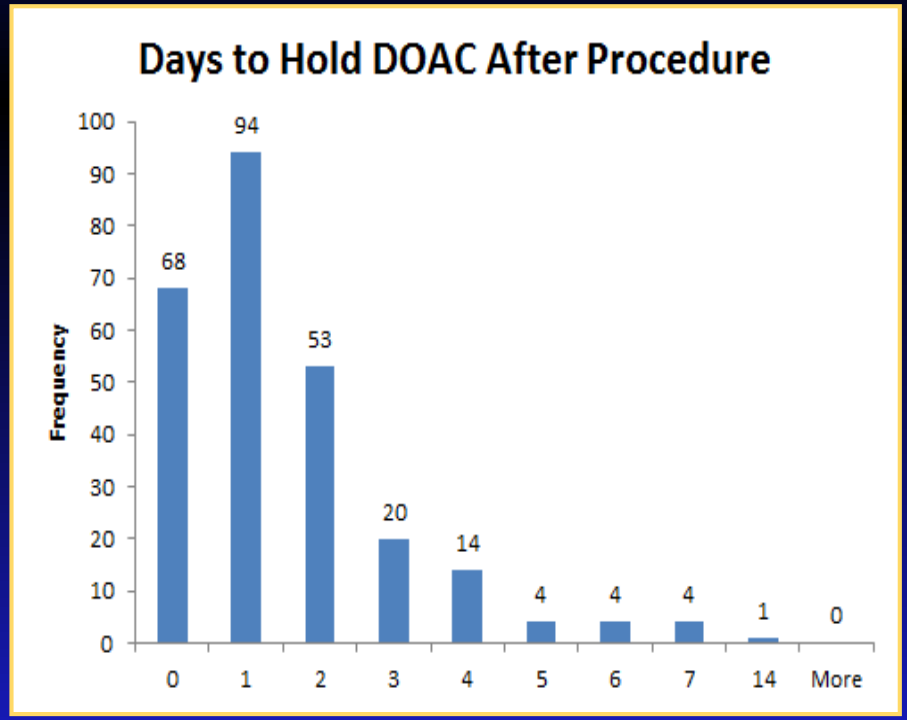
(Based on patients meeting study inclusion criteria)



(*2016 data was through June)

Results: Periprocedural Management





Summary of Trends

- Average # of days held prior to procedure: 2.2
- Average # of days held after procedure: 1.5
- Bridging rate with unfractionated heparin 8.3%

- No significant practice differences across three hospital sites between 2008-2014

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Guidance Statement for interruption of a DOAC periprocedurally:

1. **Interrupt therapy for low bleed-risk procedures in:**
   - **Patients treated with any of the approved DOACs for a duration based on the estimated CrCl (Table 2).**
2. **Interrupt therapy for intermediate, high, or uncertain bleed-risk procedures in:**
   - **Patients treated with any of the approved DOACs for a duration based on the estimated CrCl (Table 2).**

Part 2:

Factors Influencing Management of DOACs in Patients Undergoing CIED Procedures

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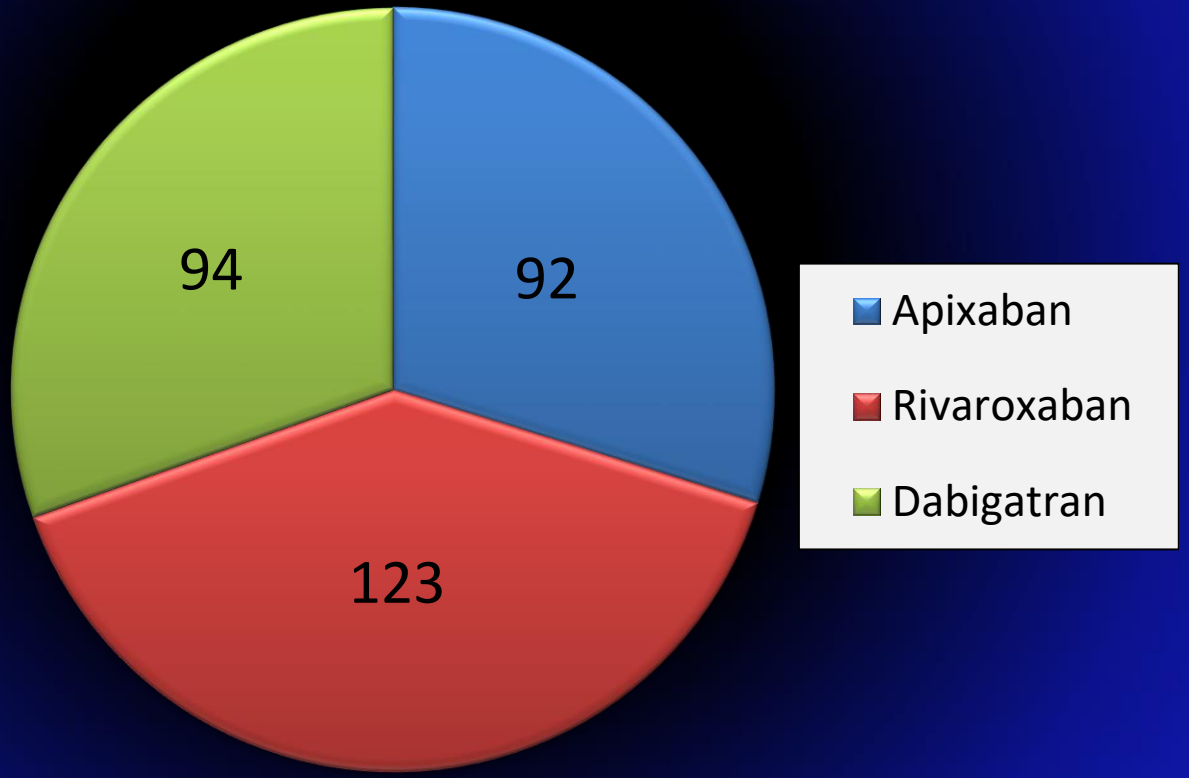
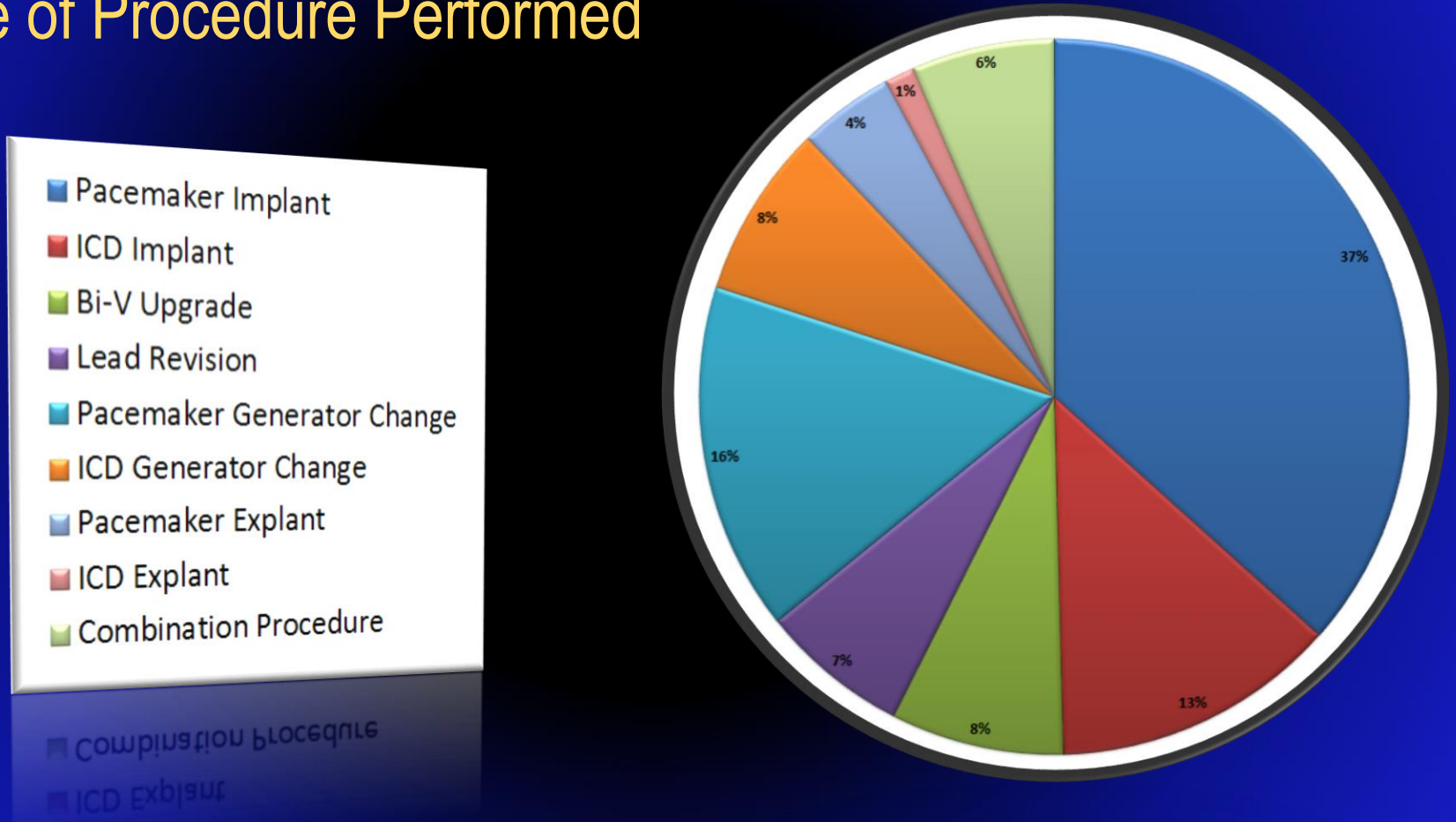
Objectives

1. Describe factors that impact bleeding and thrombotic risks for patients on OAC in the periprocedural setting
2. Analyze factors contributing to decision-making process regarding periprocedural management of DOACs

Type of DOAC Used



Type of Procedure Performed



Estimation of Risk

CHA_2DS_2 VASc Score

C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age >75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thrombo-embolism	2
V	Vascular disease	1
A	Age 65-74	1
Sc	Sex category (female)	1

HASBLED Score

H	Hypertension	1
A	Abnormal renal and/or liver function	1 or 2
S	Stroke	2
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients on warfarin)	2
E	Elderly (patients >65 years old)	1
D	Drugs (cocomittant ASA or NSAIDs) and/or alcohol abuse	1 or 2

Estimation of Risk

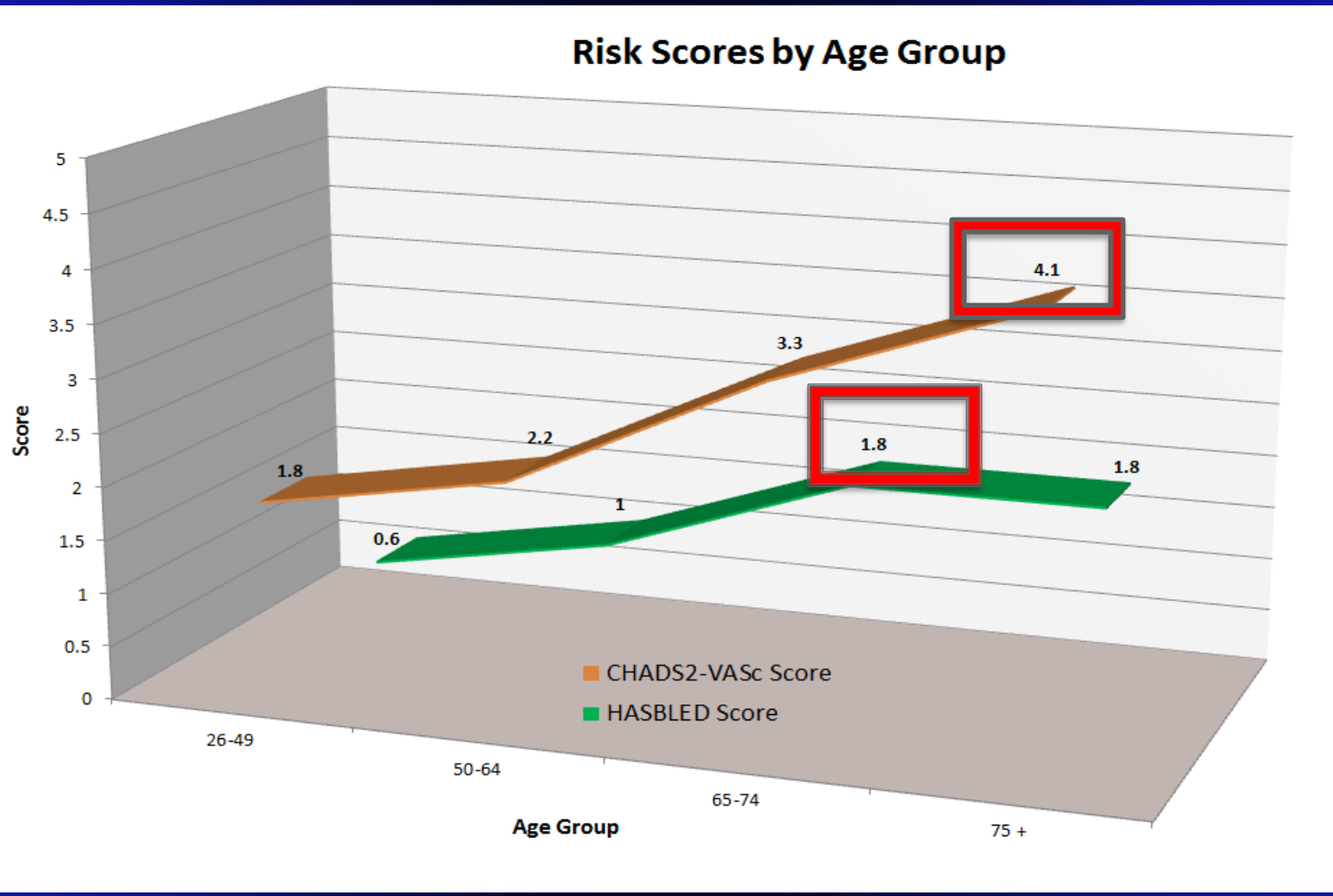
CHA_2DS_2 VASc Score

Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (percent/year)*
0	1	0 percent
1	422	1.3 percent
2	1230	2.2 percent
3	1730	3.2 percent
4	1718	4.0 percent
5	1159	6.7 percent
6	679	9.8 percent
7	294	9.6 percent
8	82	6.7 percent
9	14	15.2 percent

HASBLED Score

HAS-BLED score (total points)	Bleeds per 100 patient-years*
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5 to 9	Insufficient data


Risk Scores by Age Group
Score
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1.8
2.2
3.3
4.1
0.6
1
1.8
1.8
CHADS2-VASc Score
HASBLED Score
26-49
50-64
65-74
75 +
Age Group

Statistical Analysis

There was NO significant difference in **holding** DOAC prior based upon:

- Gender
- Comorbidities
- Concurrent ASA use
- Renal function
- CHADS2 VASc or HASBLED score
- Age
- Sex

Dependent Variable = Days to Hold Prior to Procedure

		N	Pct (%)	Mean (SD)	Range	p-value [1]
Gender						0.379
	Female	86	31.00%	2.4 (3.3)	0.0 - 30.0	
	Male	191	69.00%	2.1 (1.4)	0.0 - 9.0	
CAD / PAD						0.115
	No	168	60.60%	2.4 (2.5)	0.0 - 30.0	
	Yes	109	39.40%	2.0 (1.4)	0.0 - 9.0	
PE / DVT						0.987
	No	264	95.30%	2.2 (2.2)	0.0 - 30.0	
	Yes	13	4.70%	2.2 (1.5)	0.0 - 5.0	
Hypertension						0.309
	No	99	35.70%	2.1 (1.3)	0.0 - 5.0	
	Yes	178	64.30%	2.3 (2.5)	0.0 - 30.0	
Afib / Aflutter						0.543
	No	19	6.90%	2.1 (1.1)	0.0 - 4.0	
	Yes	258	93.10%	2.2 (2.2)	0.0 - 30.0	
CVA / TIA						0.752
	No	239	86.30%	2.2 (2.2)	0.0 - 30.0	
	Yes	38	13.70%	2.3 (1.8)	0.0 - 9.0	
Thrombophilia						0.316
	No	276	99.60%	2.1 (1.4)	0.0 - 9.0	
	Yes	1	0.40%	30.0 (--)	30.0 - 30.0	
ASA						0.542
	No	175	63.20%	2.3 (2.5)	0.0 - 30.0	
	Yes	102	36.80%	2.1 (1.4)	0.0 - 9.0	
DAPT						0.055
	No	268	96.80%	2.3 (2.2)	0.0 - 30.0	
	Yes	9	3.20%	1.3 (1.1)	0.0 - 3.0	
CKD Stage						0.484
	not checked/UTA	67	24.20%	1.9 (1.6)	0.0 - 9.0	
	60+	128	46.20%	2.4 (2.8)	0.0 - 30.0	
	30 - 59	78	28.20%	2.2 (1.4)	0.0 - 6.0	
	15 - 29	4	1.40%	2.3 (1.0)	1.0 - 3.0	
Age		277	100.00%	73.8 (10.7)	37.0 - 93.0	0.611
Has Bled Score		277	100.00%	1.6 (0.9)	0.0 - 4.0	0.355
CHADS2 VASc Score		277	100.00%	3.6 (1.5)	0.0 - 8.0	0.566

Statistical Analysis

There was NO significant difference in **resuming** DOAC based upon:

- Gender
- Comorbidities
- Concurrent ASA use
- Renal function
- CHADS2 VASc or HASBLED score
- Age
- Sex

Dependent Variable = Days to Hold After Procedure

		N	Pct (%)	Mean (SD)	Range	p-value [1]
Gender						0.711
	Female	83	31.70%	1.6 (1.5)	0.0 - 7.0	
	Male	179	68.30%	1.5 (1.7)	0.0 - 14.0	
CAD / PAD						0.498
	No	159	60.70%	1.6 (1.5)	0.0 -7.0	
	Yes	103	39.30%	1.4 (1.9)	0.0 - 14.0	
PE / DVT						0.247
	No	247	94.30%	1.5 (1.7)	0.0 - 14.0	
	Yes	15	5.70%	1.9 (1.7)	0.0 - 6.0	
Hypertension						0.794
	No	103	39.30%	1.6 (1.5)	0.0 - 7.0	
	Yes	159	60.70%	1.5 (1.8)	0.0 - 14.0	
Afib / Aflutter						0.236
	No	19	7.30%	1.9 (1.5)	0.0 - 6.0	
	Yes	243	92.70%	1.5 (1.7)	0.0 - 14.0	
CVA / TIA						0.132
	No	229	87.40%	1.5 (1.7)	0.0 - 14.0	
	Yes	33	12.60%	2.0 (1.7)	0.0 - 7.0	
Thrombophilia						N/A
	No	261	99.60%	1.5 (1.7)	0.0 - 14.0	
	Yes	1	0.40%	0.0 (--)	0.0 - 0.0	
ASA						0.797
	No	166	63.40%	1.6 (1.5)	0.0 - 7.0	
	Yes	96	36.60%	1.5 (1.9)	0.0 - 14.0	
DAPT						0.014
	No	253	96.60%	1.6 (1.7)	0.0 - 14.0	
	Yes	9	3.40%	0.6 (0.7)	0.0 - 2.0	
CKD Stage						0.313
	not checked/UTA	247	94.30%	1.5 (1.6)	0.0 - 14.0	
	60+	3	1.10%	0.7 (1.2)	0.0 - 2.0	
	30 - 59	1	0.40%	6.0 (--)	6.0 - 6.0	
	15 - 29	8	3.10%	1.1 (0.8)	0.0 - 3.0	
Age		262	100.00%	73.9 (10.5)	37.0 - 93.0	0.783
Has Bled Score		262	100.00%	1.6 (0.8)	0.0 - 4.0	0.412
CHADS2 VASc Score		262	100.00%	3.5 (1.5)	0.0 - 7.0	0.155

Summary

- Patients on DAPT had DOAC held significantly less days *after* the procedure.
- Patients receiving cardiodefibrillator had DOAC held significantly more days *after* the procedure.
- Patients receiving either pacemaker or defibrillator generator change had DOAC held significantly less days *after* the procedure.

Part 3:

Complication Rates Associated with DOACs in Patients Undergoing CIED Procedures

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Objectives

1. Describe bleeding and thrombotic complication rates for patient on DOAC in the periprocedural period surrounding CIEDs
2. Identify DOAC management strategies at lowest risk for complications surrounding CIED procedures

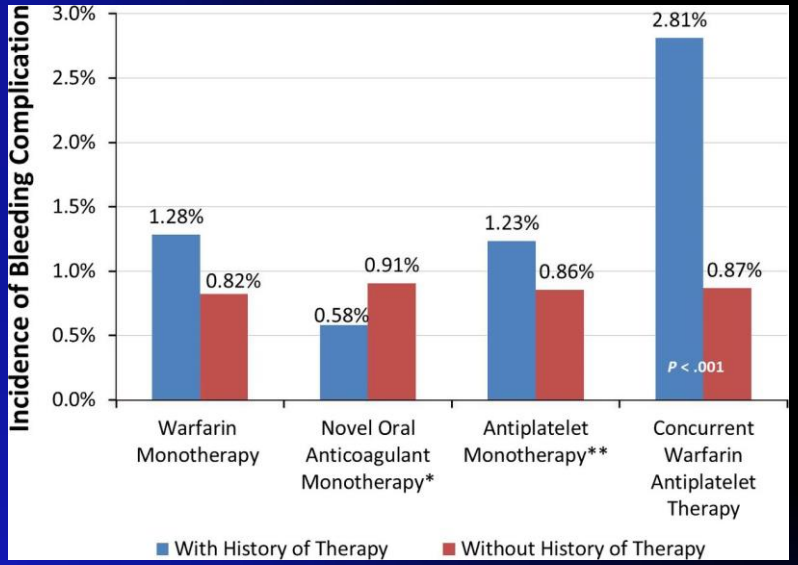
Current Literature

- To our knowledge – no studies published looking specifically at complications/outcomes of patients on DOACs at the time of CEID procedures
- Estimated bleeding complication rate after CEID implant in patients on *warfarin* ~2-4%

Current Literature

Incidence of bleeding:

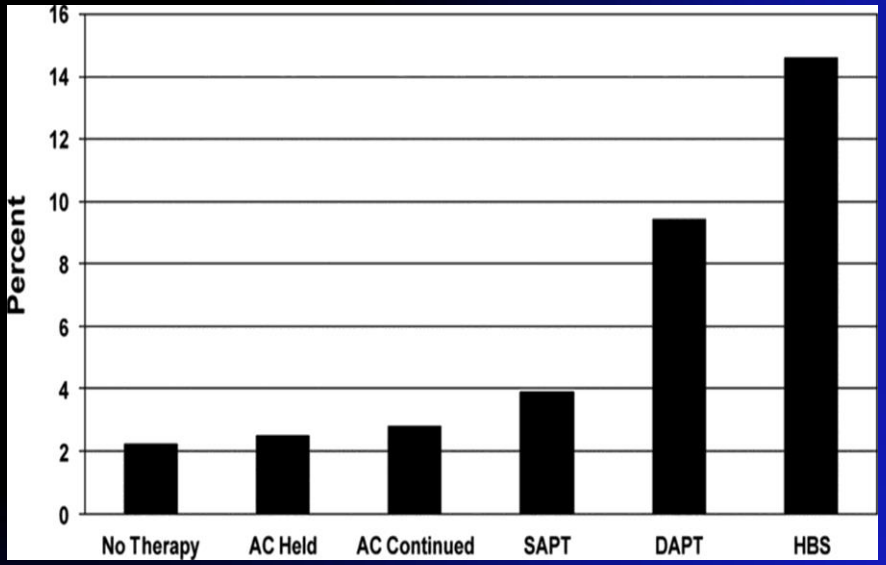
- ranged from 0.58% to 2.81% (mean 0.89%)
- ranged by type of pharmaceutical therapy



Nichols, 2017 (JAHA)

Combined incidence of bleeding complications:

- 274 of 5978 (4.6%)
- ranging from 2.2% (no therapy) to 14.6% (HBS)



Bernard et al, 2012 (Circulation EP)

Results: Complications

- No thrombotic complications
- Three bleeding complications
  - Case 1: 71yo F, pacemaker generator change with LV lead addition, rivaroxaban held 1 day before and restarted the same day as the procedure. Not on ASA.
  - Case 2: 93yo M, pacemaker generator change, rivaroxaban not stopped, also on ASA.
  - Case 3: 73yo M, pacemaker generator change, rivaroxaban held 2 days before and 2 days after, also on ASA.

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Guidance Statement for interruption of a DOAC periprocedurally:

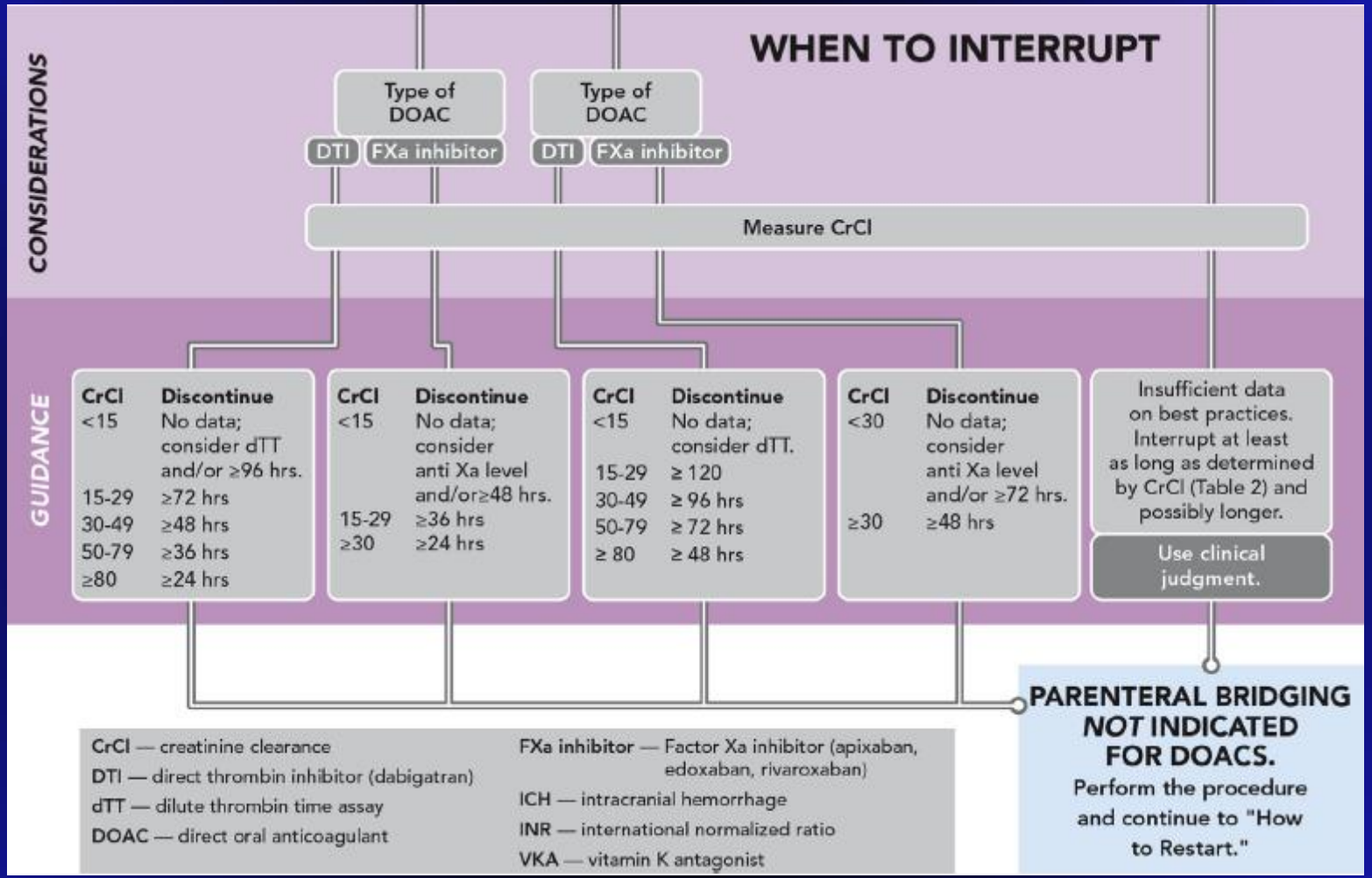
1. Interrupt therapy for low bleed-risk procedures in:
   - Patients treated with any of the approved DOACs for a duration based on the estimated CrCl (Table 2).
2. Interrupt therapy for intermediate, high, or uncertain bleed-risk procedures in:
   - Patients treated with any of the approved DOACs for a duration based on the estimated CrCl (Table 2).

Bleeding Risk Factors

TABLE 1 Patient Bleed Risk Factors

HAS-BLED parameters (52)*
Hypertension†
Abnormal renal function‡
Abnormal liver function§
Prior stroke
History of or predisposition to (anemia) major bleeding
Labile INR (VKA)‖
Elderly (>65 years)
Concomitant use of an antiplatelet agent or nonsteroidal anti-inflammatory drug
Alcohol or drug usage history (≥8 drinks/week)¶
Additional items included in the periprocedural management algorithm
Prior bleed event within 3 months (including intracranial hemorrhagic)
Quantitative or qualitative platelet abnormality
INR above the therapeutic range at the time of the procedure (VKA)
Bleed history from previous bridging
Bleed history with similar procedure

Doherty, 2017 (JACC)



Doherty, 2017 (JACC)

ACC Consensus Recommendations

TABLE 2 Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

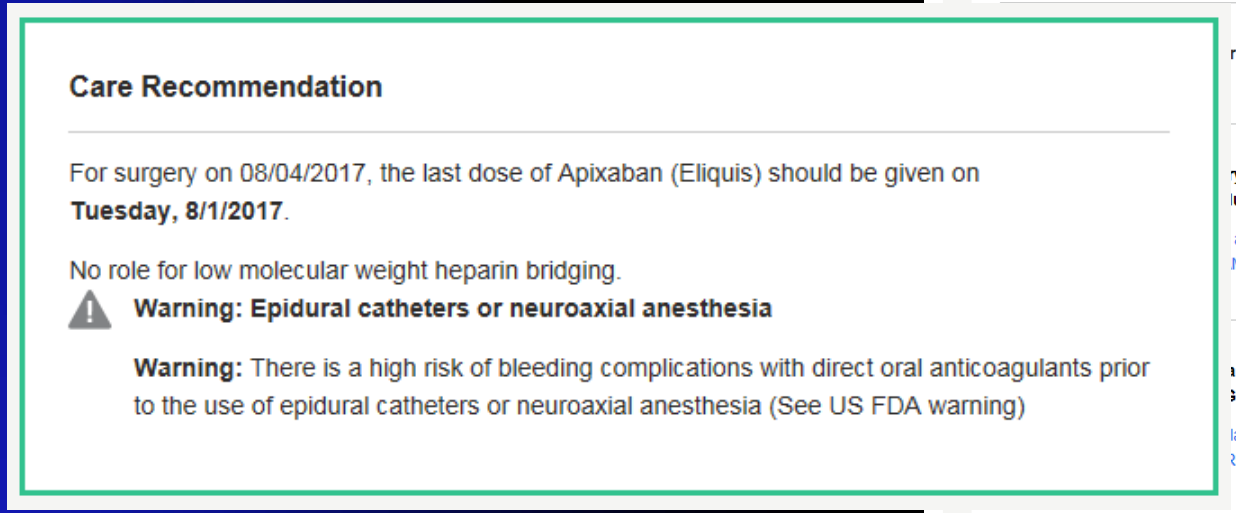
	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

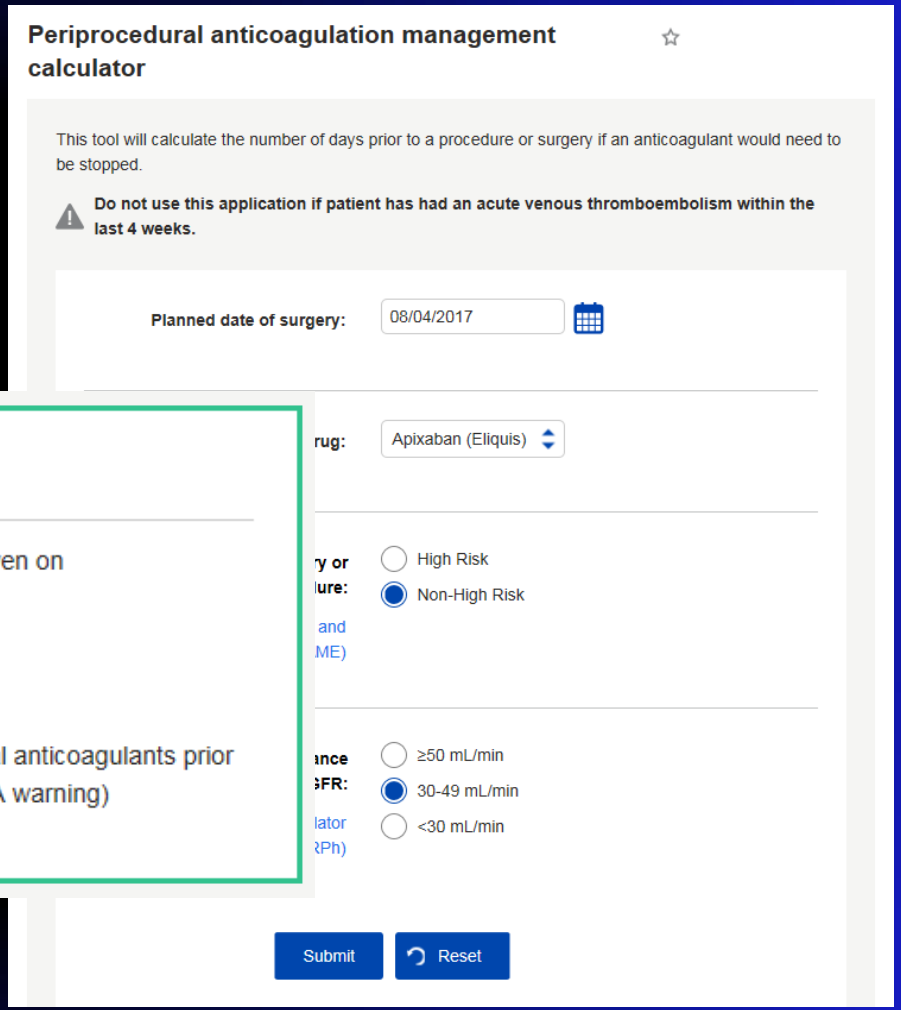
NOTE: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk (46,60-67).

CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; dTT = dilute thrombin time.

Doherty, 2017 (JACC)

Clinical Tool: AskMayoExpert





Conclusions

- Overall, CIED procedures in patients treated with DOACs appear to have a low complication rate of bleeding or thrombosis; regardless of DOAC management strategy.
- No correlation with CHADS2VASc and HASBLED scores relating to bleeding or thrombosis (though data limited)

Future Implications

- Prospective study to evaluate bleeding complication rates with uninterrupted DOAC administration
- Prospective study comparing complication rates with warfarin versus DOAC use in CIED procedures.
- Evaluate trends in management between physician providers or advanced practice providers.
- Development of standardized consensus guidelines
- Investigate difference in management strategies in various geographical areas

Next Steps

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