폐혈관 SCHOOL 2022

Perioperative Management for Patients with VTE

황 헌 규

순천향대학교 구미병원 호흡기내과

일시: 2022.11.26(토) 14:00~

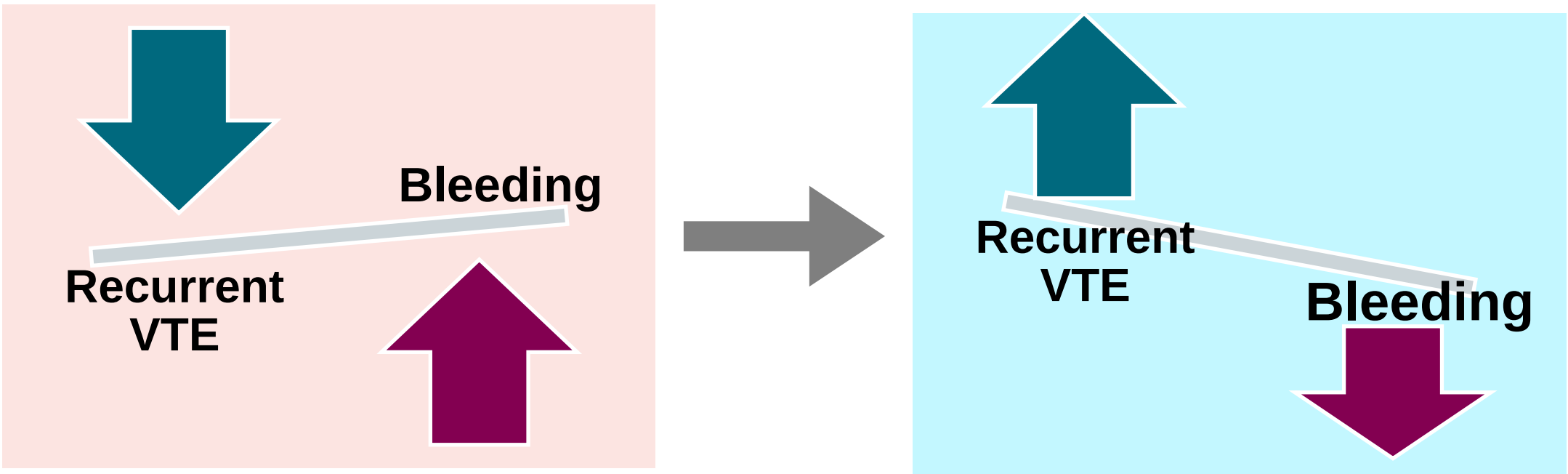
장소: 서울 과학기술회관 (SC Convention Center)

Contents

- Introduction: Paradigm shift in DOACs era
- Stomach cancer in patient with VTE
- Bronchoscopic exam
- Gastric polyp
- Cataract
- Warfarin management in procedure

Introduction

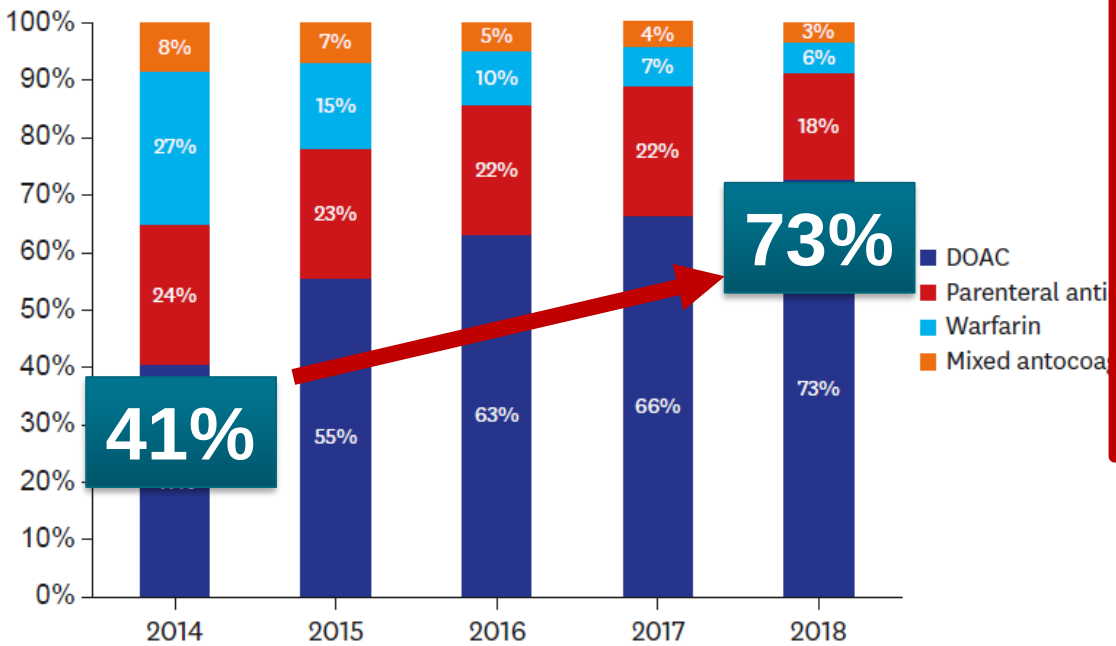
- Main points
  1. **Recurrent VTE** vs **Bleeding** during procedure
  2. **Warfarin** → **DOACs**

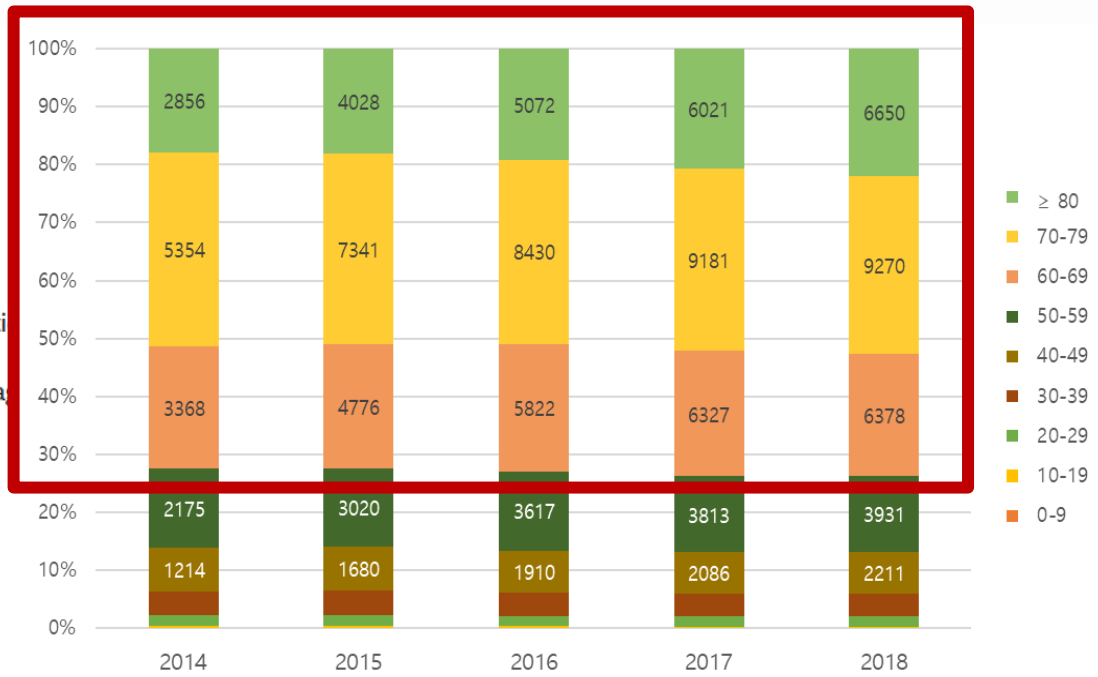


Douketis Chest 2022
Hwang JKMS 2017

DOACs Era for patients with VTE in South Korea

- Proportion of **DOACs** in VTE: 41% (2014)→ 73% (2018) → ? (2022)





60세이상이 VTE의 73%
고령의 질환

Hwang JKMS 2022

DOACs in patients with VTE in South Korea

- Approximately **15% to 20%** of patients with VTE will require a surgery/procedure **annually**.[1]

- Things to consider
  - Aging & fracture
  - Cancer & survival → more procedure
  - Recurrent VTE (5-year: 21.5% 95%CI 17.7-25.4, Single center, Korea)[2]
  - Recurrence rate 1 year after stopping anticoagulation[3,4]
    - Persistent minor-10.7% (IBD, lower limb paralysis, thrombophilia, BMI>30, CrCl <50ml/min)
    - Transient minor -7.1% (Immobilization, travel >8hr, pregnancy, lower limb trauma)

1. Douketis Chest 2022
2. Hwnag Tuberc Respir Dis 2019
3. Prins et al Blood 2018:2(7):788
4. Kearon et al J Thromb Haemost 2016;14:1480-1483

- Main points
  - Recurrent VTE vs Bleeding during procedure
  - Warfarin → DOACs

- Paradigm shift from "**Bridging**" to "**Perioperative management**"
  - Based on **rapid onset and offset** of action of DOACs
  - **Bleeding** outcome in BRIDGING study: What happened?

Douketis Chest 2022
Hwang JKMS 2017

Warfarin → DOACs

- Most evidence from perioperative management in patients with Afib (BRIDGE, PAUSE study)
- Few study from in patients with VTE (Retrospective study, Ottawa ON, Canada)

Journal of Thrombosis and Haemostasis, **15**: 925–930 DOI: 10.1111/jth.13670

ORIGINAL ARTICLE

Thrombotic and bleeding outcomes following perioperative interruption of direct oral anticoagulants in patients with venous thromboembolic disease

J. SHAW,*†‡ C. DE WIT,† G. LE GAL*†‡ and M. CARRIER*†‡
Department of Medicine, Division of Hematology, The Ottawa Hospital; †Ottawa Hospital Research Institute; and ‡Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

Douketis Chest 2022
Shaw J Thromb Haemost 2017;15(5):925-930

Case 1.
Stomach cancer in patient with VTE

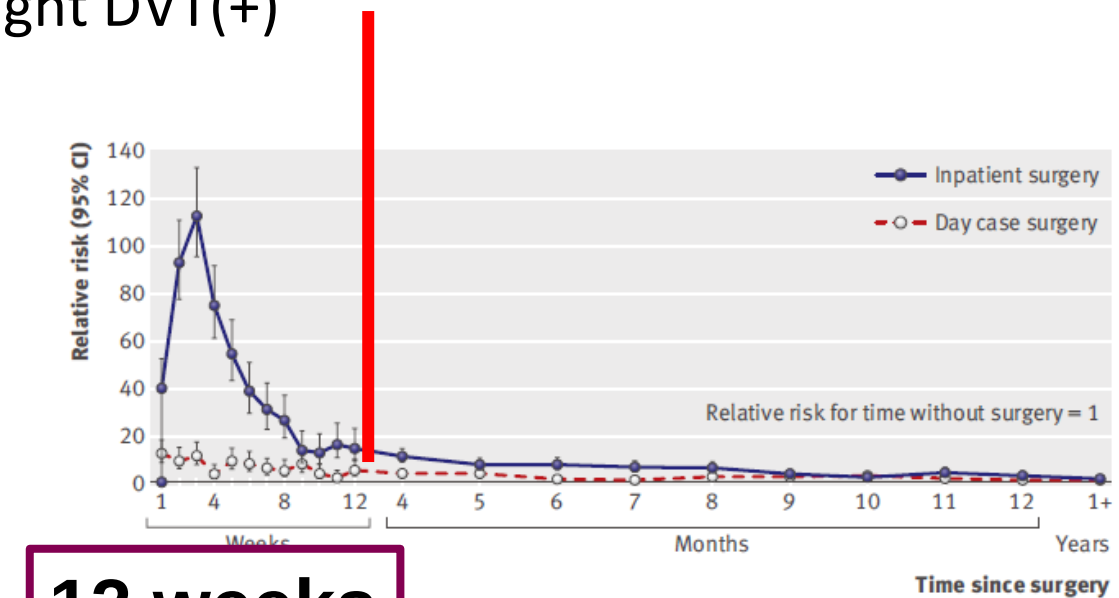
Case 1. Stomach ca in patient with VTE

- Deep vein thrombosis (2020.10월)진단.
- 교통사고(TA)로 2020년7월 입원중 협진된 환자

- 과거력 2016 우측편마비(+)- 당시 Right DVT(+)
- 사고전 ambulation가능(+)

- Assessment

Risk factor: previous VTE
Trauma (TA): 3 month earlier
Duration: indefinite treatment



12 weeks

Sweetland et al BMJ 2009;339:b4583

Case 1. Stomach ca in patient with VTE

Problem

1. Indefinite treatment with DOAC (apixaban)
2. APS: all negative
3. 응급수술 필요할 시 항응고제 사용 고지하도록 교육

4. 소화가 잘 안되고, 흑색변으로 시행한 검사에서 Stomach ca with liver metastasis (2021.8월)
5. 수술전 혈전응고제 관리는? (수술예정일 2021.10월)

- **BRIDGE vs PAUSE: Warfarin vs DOAC**
- **When to stop prior to operation/procedure**
- **Bleeding risk vs VTE recurrence**

	VTE
High >10%/m risk of VTE	Recent (< 3 mo and especially 1 mo) VTE
	Severe thrombophilia (deficiency of protein C, protein S or antithrombin; homozygous factor V Leiden or prothrombin gene mutation or double heterozygous for each mutation, multiple thrombophilias)
	Antiphospholipid antibodies
	Associated with vena cava filter
	Active cancer associated with high VTE risk[a]
Moderate 4-10%/m risk of VTE	VTE within past 3-12 mo
	Recurrent VTE
	Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene mutation)
	Active cancer or recent history of cancer[c]
	VTE > 12 mos ago

Douketis Chest 2022

Case 1. Stomach ca in patient with VTE: Procedural bleed risk

High-bleed-risk (30-day riks of major bleed ≥ 2%)

- Major surgery with extensive tissue injury
- Cancer surgery, especially solid tumor resection (lung, esophagus, gastric, colon, hepatobiliary, pancreatic)
- Major orthopedic surgery, including shoulder replacement surgery
- Reconstructive plastic surgery
- Major thoracic surgery
- Urologic or GI surgery, especially anastomosis surgery
- Transurethral prostate resection, bladder resection, or tumor ablation
- Nephrectomy, kidney biopsy
- Colonic polyp resection
- Bowel resection
- Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography
- Surgery in highly vascular organs (kidneys, liver, spleen)
- Cardiac, intracranial, or spinal surgery
- Any major operation (procedure duration > 45 minutes)
- Neuraxial anesthesia[b]
- Epidural injections

Douketis Chest 2022

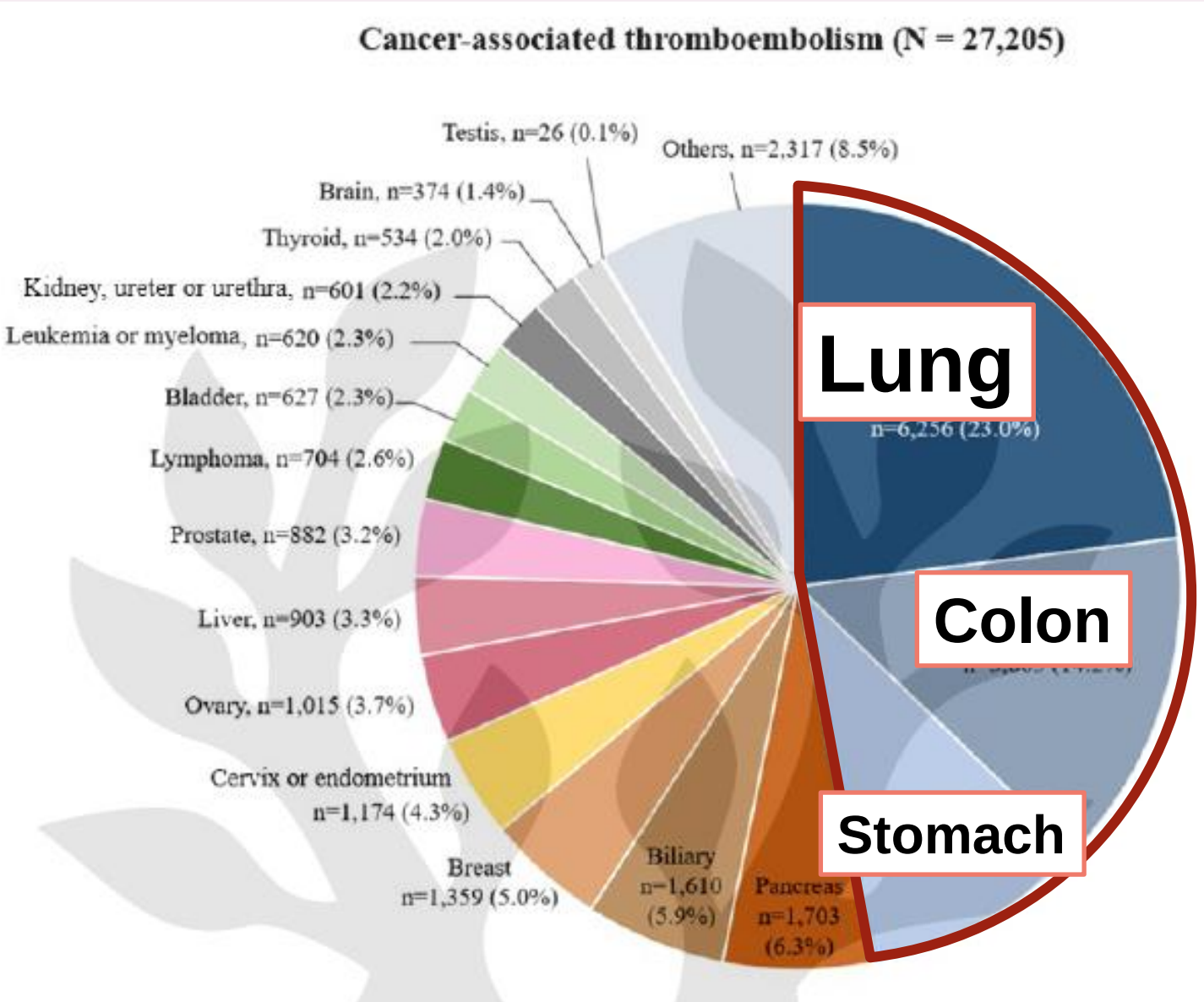
Case 1. Stomach ca in patient with VTE: HIRA data (2014—2018)

CAT in HIRA (Korea)

1. Lung ca: 23%
2. Colorectal ca: 14.2%
3. Stomach ca: 9.7%

Cumulative incidence of major GI bleeding

- **DOAC** vs PAC
- 4.9% vs 3.0% p<0.01



Kim Thromb Haemost 2022

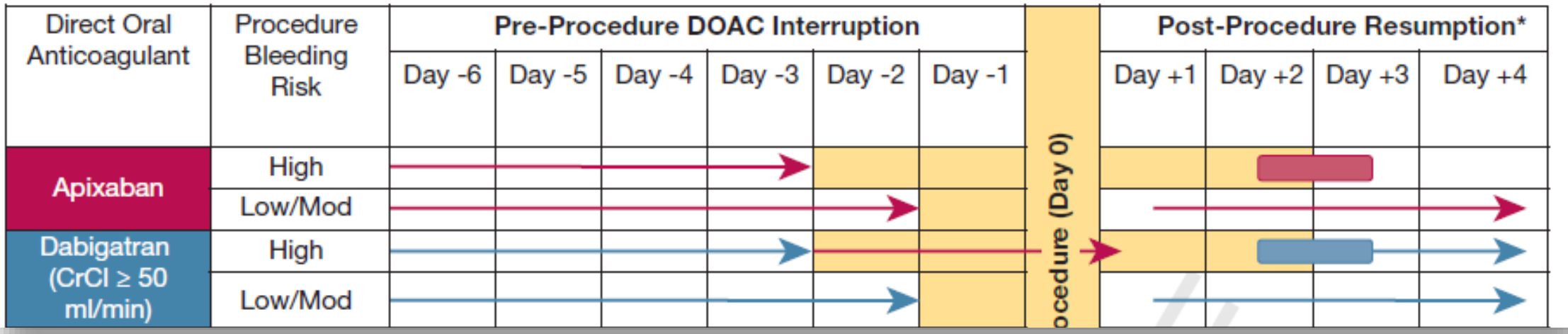
Table 3 Recommended timing for pre-procedure discontinuation of NOAC

NOAC agent	Mechanism of action	Renal function (GFR in mL/min)	Recommended time to hold the medication (days)	
			Standard risk for bleeding	High risk for bleeding
Dabigatran (Pradaxa)	Direct thrombin inhibitor	<30	2–4 (46); 4 (47)	>5 (46); 6 (47)
		30–50	>2 (46); 2 (47)	4 (46,47)
		≥50	1 (46,47)	2–3 (46); 2 (47)
Rivaroxaban (Xarelto)	Direct Factor Xa inhibitor	15 to <30	4 (48)	Consider withholding for longer period before high-risk bleeding procedures
		30–59	3 (48)	
		60–90	2 (48)	
		>90	≥1 (48)	
Apixaban (Eliquis)	Direct Factor Xa inhibitor	<50	5 (48)	
		50–59	3 (48)	
		>60	1–2 (48)	
Edoxaban (Savaysa)	Direct Factor Xa inhibitor	15 to <50	2–3 (49)	
		50–80	1–2 (49)	
		>80	1 (49)	

2017년 bleeding risk와 GFR에 따른 시술전 약제중단시기 권고하였으나, 2022년에는 bleeding risk로 권고로 변경됨(Dabigatran만 예외).

1. Youness et al J Thorac Dis 2017;9:S1022-1033

Case 1. Stomach ca in patient with VTE

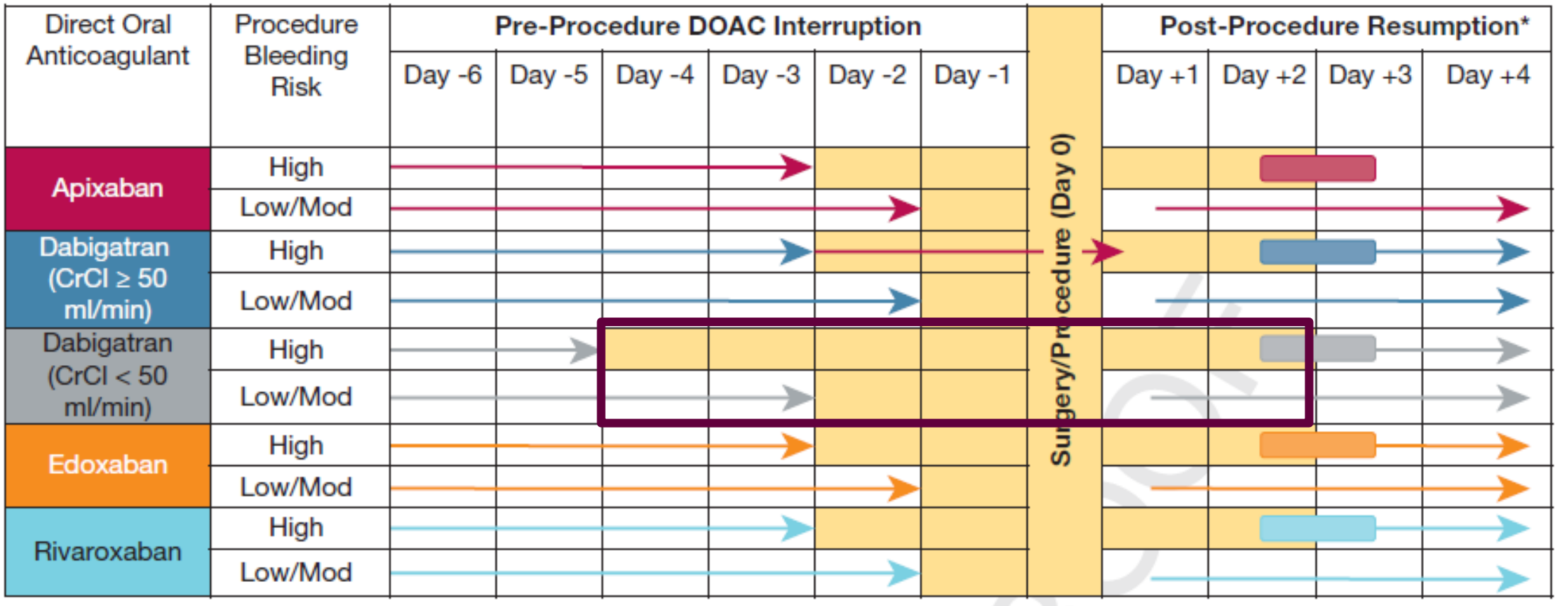


Perioperative management in patient with Stomach ca on Apixaban

- High >10%/m **risk of VTE**
- High-bleed-risk (30-day riks of **major bleed** ≥ 2%)
- **Renal function**?

Douketis Chest 2022

Case 1. Stomach ca in patient with VTE



Douketis Chest 2022

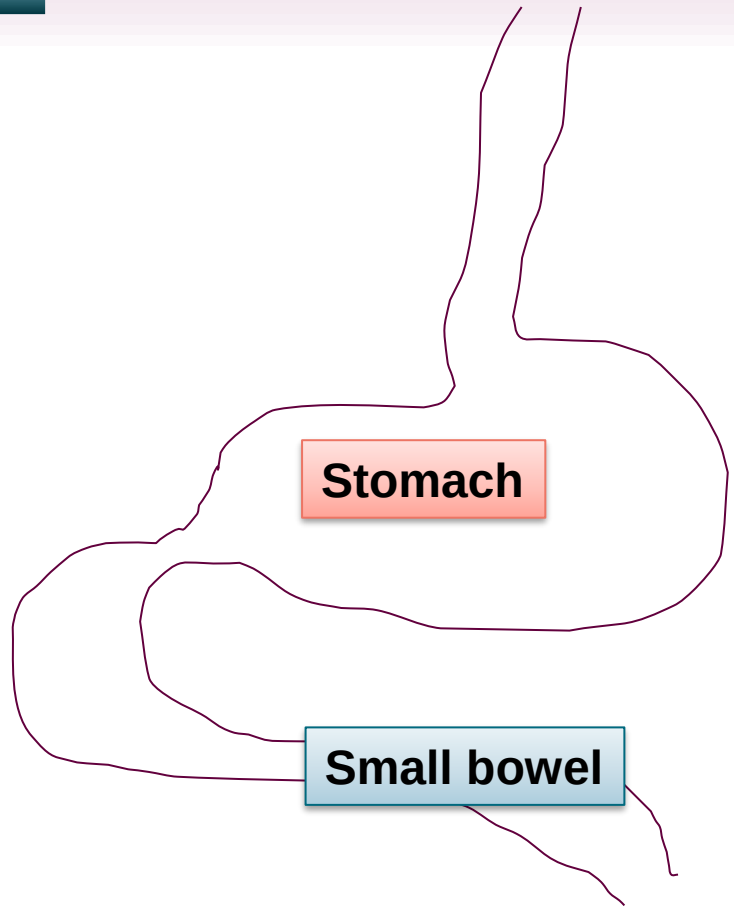
Case 1. Stomach ca in patient with VTE

이 환자에서 수술(Gastrectomy) 후 적절한 항응고제는

1. Warfarin
2. LMWH
3. Rivaroxaban
4. Apixaban
5. Dabigatran
6. 출혈위험이 크므로 끊고 관찰한다.

Douketis Chest 2022

Case 1. Stomach ca in patient with VTE: DOACs after gastrectomy



산성환경필요

- Rivaroxaban
- Edoxaban
- Dabigatran (lower part of stomach and duodenum)

Proximal small intestine

- Warfarin: Proximal small intestine
- Edoxaban
- Dabigatran

산성환경 불필요

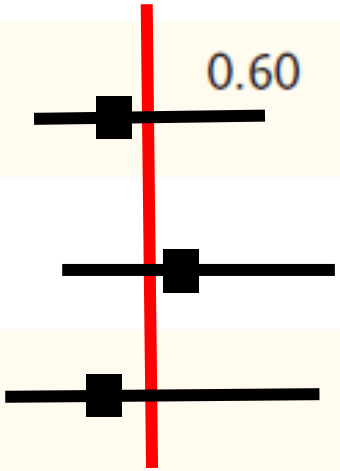
- Apixaban
  - **55% in distal small intestine & ascending colon**
  - **Stomach and proximal intestine**

Hwang 2022 JKMA

Caravaggio 연구에서 major bleedin(safety outcome)은 두군(Apixaban vs Dalteparin)간에 차이를 보이지 않았다.

Caravaggio study

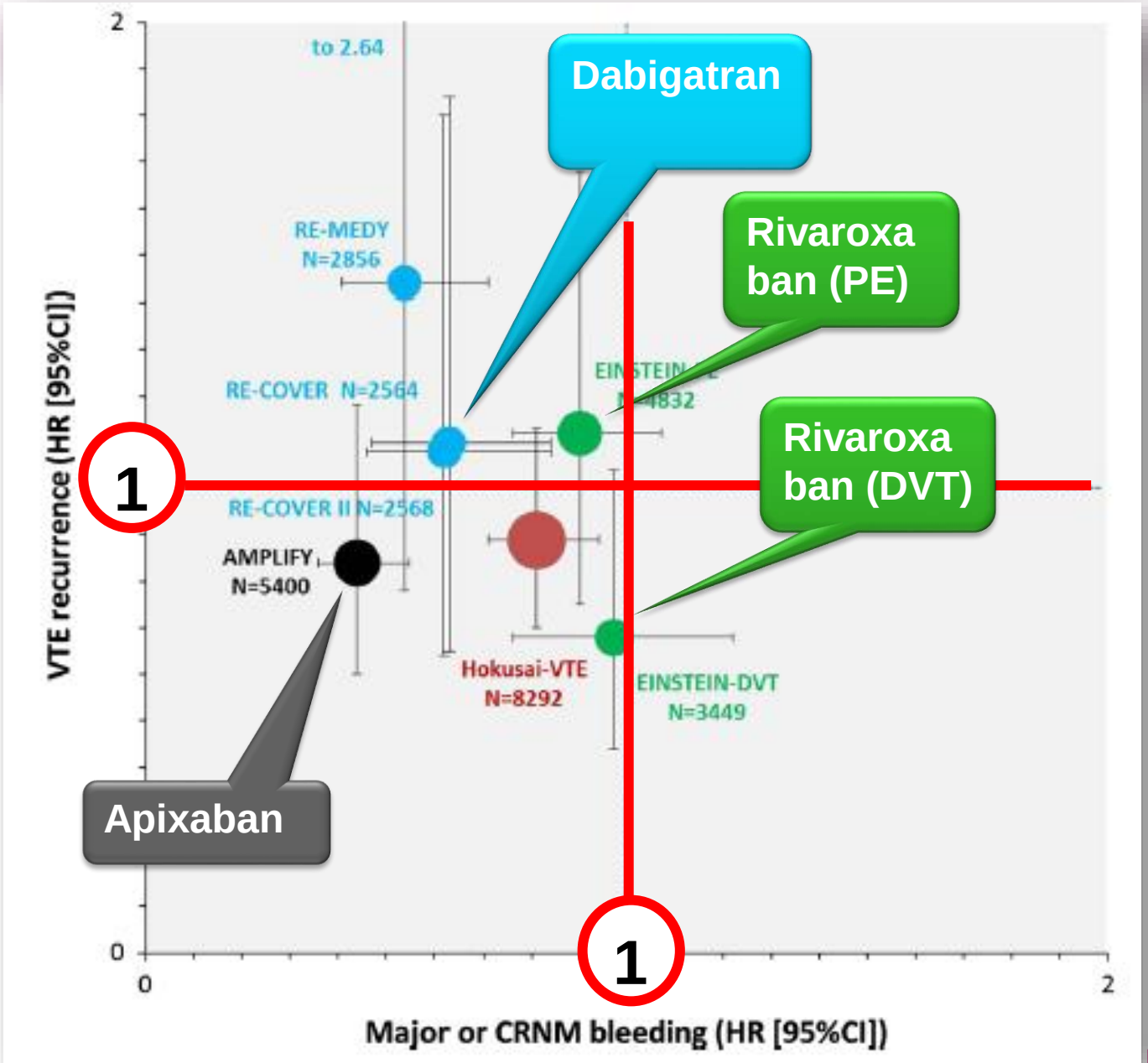
	Apixaban	Dalteparin	Hazard Ratio
Primary safety outcome — no. (%)			
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)
Major nongastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)



1. Agnelli N Engl J Med 2020

Selection among anticoagulants

- Bleeding complication
- Once daily versus bid
- Body weight
- Renal function
- Patient's preference



1. Cohen et al. Adv Ther 2014; (31): 473-493

Case

- Bronchoscopic biopsy (Case 2.)
- Gastric polypectomy

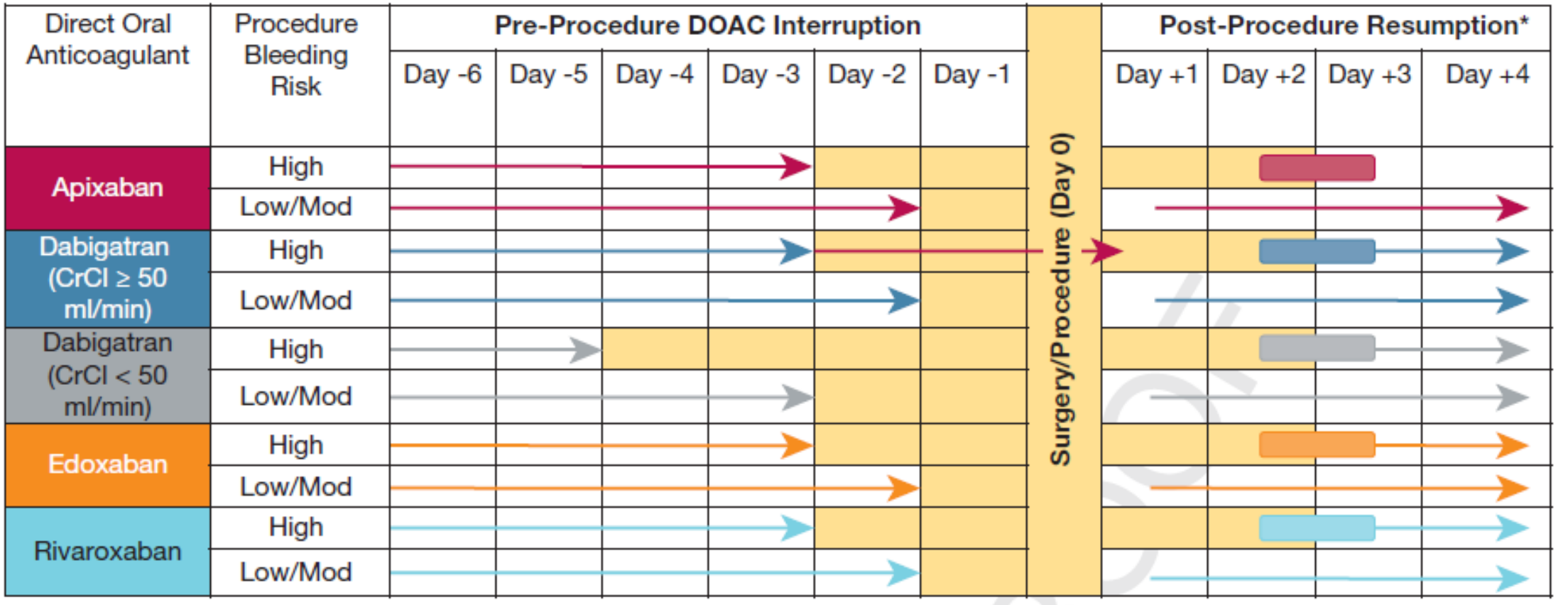
Case 3. Procedural bleed risk

Low/moderate-bleed-risk procedure (30-day risk of major bleed 0%--2%)

- Arthroscopy
- Cutaneous/lymph node biopsies
- Foot/hand surgery
- Coronary angiography[d]
- GI endoscopy ± biopsy
- Colonoscopy ± biopsy
- Abdominal hysterectomy
- Laparoscopic cholecystectomy
- Abdominal hernia repair
- Hemorrhoidal surgery
- Bronchoscopy ± biopsy

Douketis Chest 2022

Case 2. Low/moderate-bleed-risk surgery/procedure: ACCP 2022 guideline



VTE recurrence risk는?

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Bleeding rate in various bronchoscopic interventions: Review

Procedure	Risk of bleeding	Overall bleeding rate (%)
Airway inspection/BAL	Low	< 0.12/5
EBUS	Low	0.2%
Endobronchial forceps biopsy	Intermediate	0.45~17.2%
Transbronchial biopsy	Intermediate	19~5%
Endobronchial cryobiopsy	High	18.2%
Therapeutic bronchoscopy, mean bleeding volume (mL) [min-mix]	High	6.7 mL [0-30]
Trans-bronchial cryobiopsy	High	9-53%

1. Youness et al J Thorac Dis 2017;9:S1022-1033

Case 3.

- Gastric polypectomy

ORIGINAL ARTICLE: Clinical Endoscopy

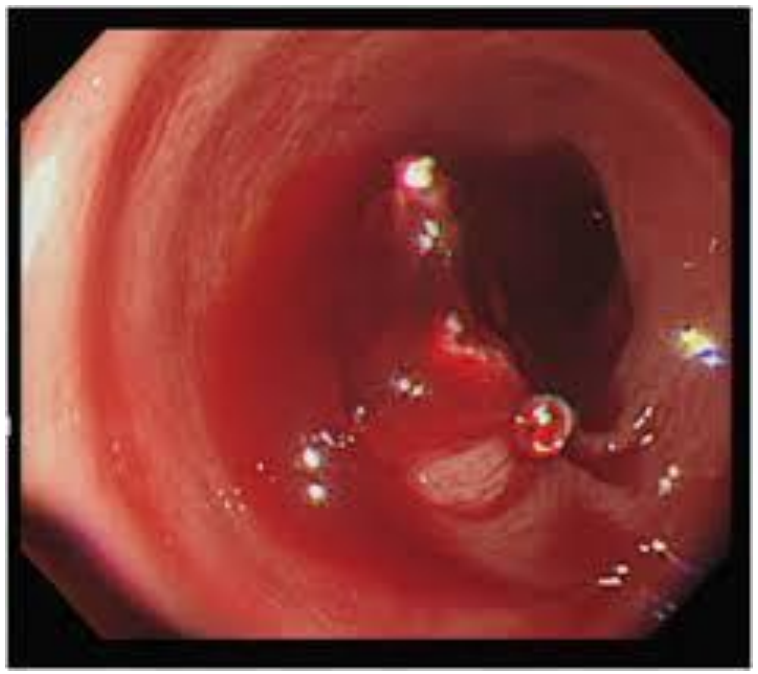
Risk factors for postpolypectomy bleeding in patients receiving anticoagulation or antiplatelet medications (CME)

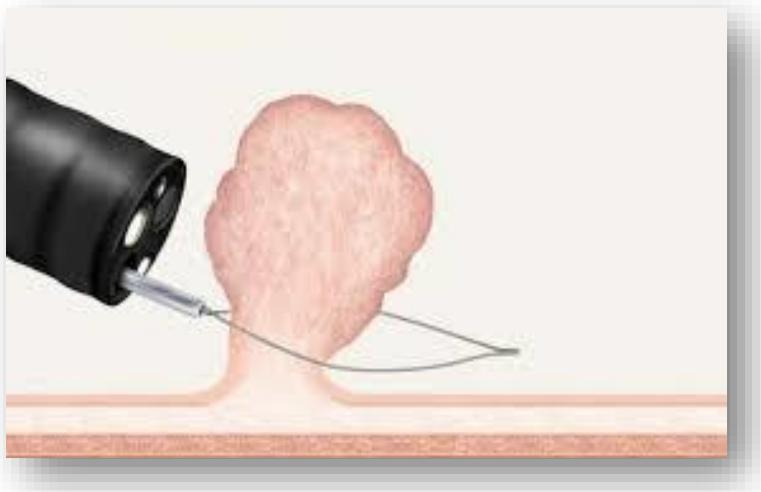
David Lin, MD,[1,2] Roy M. Soetikno, MD,[2] Kenneth McQuaid, MD,[3] Chi Pham, BS,[4] Gilbert Doan, BS,[4] Shanshan Mou, MD,[2] Amandeep K. Shergill, MD,[3] Ma Somsouk, MD,[5] Robert V. Rouse, MD,[6] Tonya Kaltenbach, MD[2,3]

Palo Alto, San Francisco, California, USA

Risk factors for postpolypectomy bleeding in patients receiving anticoagulation

- Retrospective cohort and case control
- 2 tertiary-care medical centers from 2004 to 2012.
- 59 Case: male patients with hematochezia after polypectomy
- 174 Nonbleeding control: matched to cases 3 to 1





1. Lin 2018 Gastrointest Endosc 2018;87:1106-13

TABLE 4. Risk factors of postpolypectomy bleeding in patients on antithrombotics*

Postpolypectomy bleeding n=59

Matched control n=174

Risk factor			Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*P* value
Restart within 1 week	44	60	4.50 (2.21-9.44)	–	< .001
Polyp size, mm					
≤5	8	39	Reference	–	Reference
6-9	8	58	0.67 (0.23-1.97)		.46
10-19	19	54	1.72 (0.70-4.53)		.25
≥20	24	23	5.09 (2.03-13.85)		< .001
Multiple large polyps	12	14	2.92 (1.14-7.29)	–	.001
Cautery use in right side of colon	45	96	2.61 (1.29-5.52)	–	.004
Prophylactic clip placement	26	64	1.35 (0.71-2.57)	–	.32
Warfarin, n = 66	17	49			
Heparin bridge	13	9	14.4 (3.28-71.8)	10.27 (2.51-42.1)	.0001
Polyp size ≥2 cm	7	2	16.45 (2.48-174)	8.8 (1.28-60.7)	.027

1. Lin 2018 Gastrointest Endosc 2018;87:1106-13

TABLE 4. Risk factors of postpolypectomy bleeding in patients on ant

Postpolypectomy bleeding n=59

Matched control n=174

Risk factor		OR, p-value
Restarting antithrombotics	within 1 week postpolypectomy	OR 4.50; p < 0.001
Polyp size	>=20mm	OR 5.09; p<0.001
Multiple large polyp		OR 2.92; p=0.001
Cautery use	Cautery use in right colon	OR 2.61; p=0.004
Bridging in patients on warfarin	Bridging anticoagulation	OR 12.27; p=0.0001

			Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*P* value
Polyp size ≥2 cm	7	2	16.45 (2.48-174)	8.8 (1.28-60.7)	.027

Case 4.

- Cataract operation
- Dental care

Case 3. Procedural bleed risk

Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi)

Ophthalmologic (cataract) procedures

Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings

Pacemaker or cardioverter-defibrillator device implantation

Minimal-bleed-risk procedure
(30-day risk of major bleed 0%)

Douketis Chest 2022

Case 4. Cataract operation

- Phacoemulsification of cataract in patients taking DOACs
- Prospective study (Dabigatran, Rivaroxaban or Apixaban)

- 35 eyes of 25 patients (age: from 63 to 92 years, mean 77.6 years)
- All surgery videotaped
- Examined at 1 and 7 days after operation

- Outcome: intra-operative in 5 eyes, no intra-ocular bleeding **without discontinuing DOAC treatment**

1. Douketis Chest 2022
2. Barequet Graefes Arch Clin Exp Ophthalmol 2019;257(12):2671-2676
3. Sheich Thromb Res 2021;203:27-32

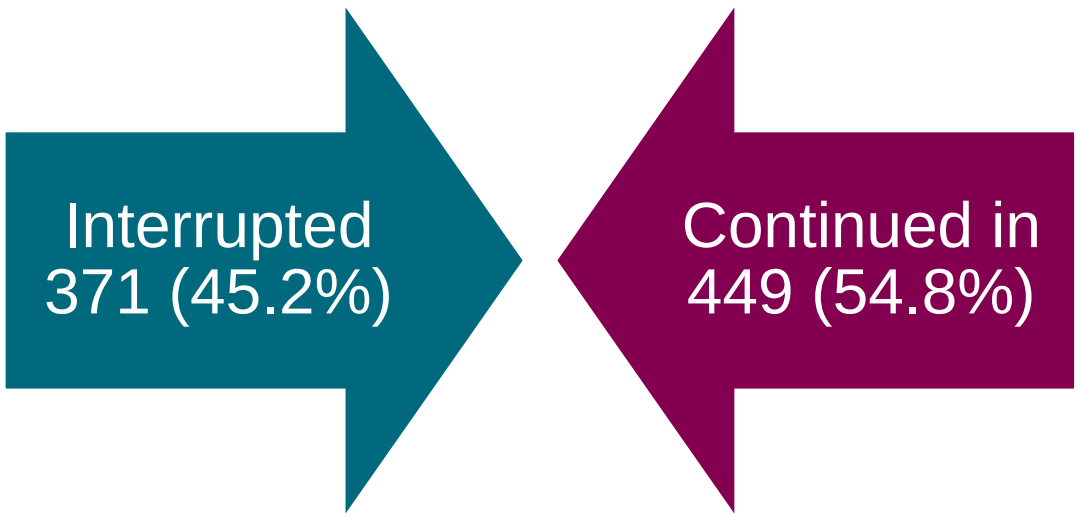
Case 4. low risk operation

- Low risk procedure
- 820 patients
- 1412 procedures

DOAC interruption was common for gastrointestinal endoscopy, electrophysiology device implantation, and cardiac catheterization while it was less common for cardioversion, dermatologic procedures, and subcutaneous injection.

Published in final edited form as:
Thromb Res. 2021 July ; 203: 27–32. doi:10.1016/j.thromres.2021.04.006.

Comparison of temporary interruption with continuation of direct oral anticoagulants for low bleeding risk procedures



1. Douketis Chest 2022
2. Sheich Thromb Res 2021;203:27-32

Case 4. low risk operation

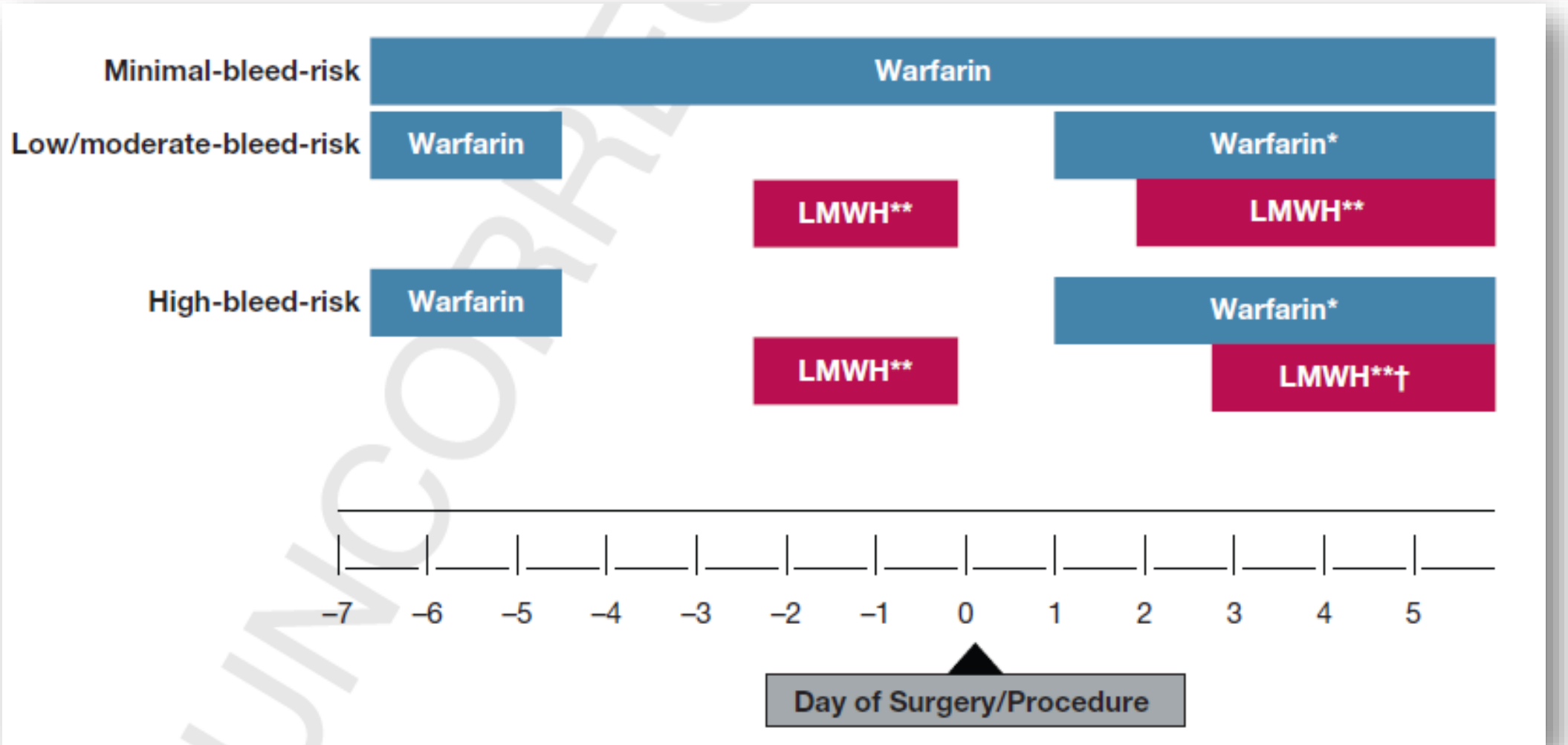
- Bleeding risk was lower in **DOACs temporary interruption group**
- **OR 0.62, 95% CI 0.41-0.95**

- Conclusion: Prospective study on low bleeding risk procedure are needed to secure the safety.

1. Douketis Chest 2022
2. Sheich Thromb Res 2021;203:27-32

Patients on Warfarin

BRIDGE trial



Douketis et al NEJM 2015; 373(9): 823-833
Horlocker Reg Anesth Pain Med 2018; 43(3): 263-309
Douketis Chest 2022

Perioperative management in Korea

Retrospective study
Single center
Aug 2009 ~ July 2011

Number	49
Male, n (%)	25 (51)
Age, mean (range)	63 (19-84)
Indication of anticoagulation, n (%)	
Venous thromboembolism	34 (69)
Atrial fibrillation	9 (18)
Replacement of cardiac valve (mechanical)	3 (6)
Others	3 (6)
Reasons of bridging anticoagulation, n (%)	
Major surgery/procedure	29 (59)
Minor surgery/procedure	20 (41)
Experience on warfarin, n (%)	
Warfarin naïve (≤90days)	20 (41)
Warfarin experienced (>90 days)	21 (59)
Duration on warfarin, days, median (range)	122 (6-6016)
Comorbid condition, n (%)	
Active malignancy (within 6 months)	16 (33)
CHF	3 (6)
CVA or TIA	3 (6)
Ischemic heart disease	4 (8)
Renal insufficiency (GFR <30 mL/min)	10 (20)

1. Hwang J Korean Med Sci 2017; 32: 942-947

BRIDGE trial

BRIDGE trial

- In patients with **atrial fibrillation** who need an interruption in **warfarin** treatment for an elective operation or other elective invasive procedure
- Randomized, double-blind, placebo-controlled trial
- LMWH (100IU of dalteparin/kg) vs placebo
- Follow-up of patients continued for 30 days after the procedure.
- 1884
- Primary outcome
  - ATE
    - stroke,
    - TIA,
    - systemic embolism
  - Major bleeding

Douketis et al NEJM 2015; 373(9): 823-833
Douketis Chest 2022

BRIDGE trial

Total 1884	No bridging (n=950)	Bridging (n=934)	
Arterial thromboembolism	0.4%	0.3%	95%CI -0.6 to 0.8 P=0.01 for noninferiority
Major bleeding	1.3%	3.2%	RR=0.41 95%CI 0.2 to 0.78 P=0.005 for superiority

Conclusion

"No bridging" is noninferior to bridging with LMWH and decreased the risk of major bleeding.

1. Douketis et al NEJM 2015; 373(9): 823-833
2. Steffel Europace 2018; 20(8): 1231-1242

Impact of "BRIDGE study" on care delivery

- **Analysis between 2010 and 2017**
- **Before and after the BRIDGE trial publication (July 2015)**
- **The use of bridging anticoagulation declined**

2010	BRIDGE trial (2015)	2017
27.8% 95% CI 20.5%-35.1%	→	**13.6%** 95% CI, 9.0%-18.2%

1. Barnes Am J Med 2019

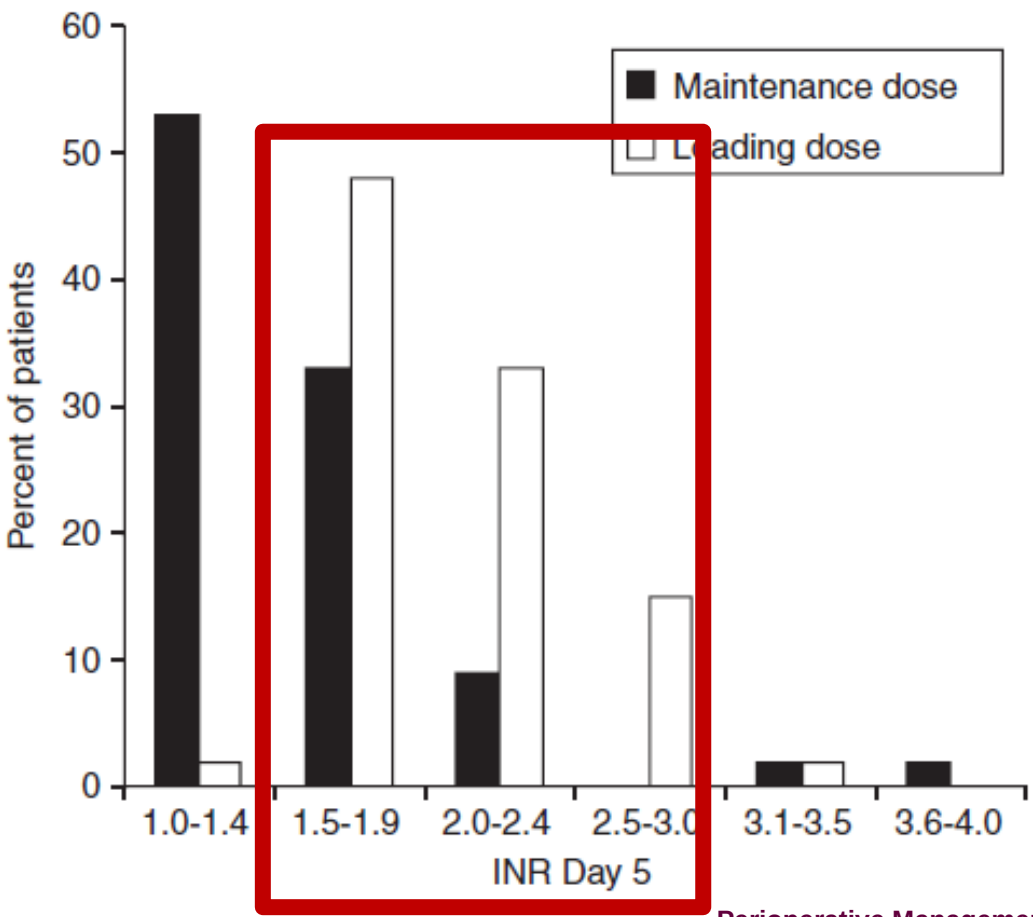
Loading dose vs maintenance dose of warfarin for reinitiation after invasive procedure

ORIGINAL ARTICLE

Loading dose vs. maintenance dose of warfarin for reinitiation after invasive procedures: a randomized trial

S. SCHULMAN,*†‡ H.-G. HWANG,†§ J. W. EIKELBOOM,*†¶ (
J. DELANEY†
*Thrombosis and Atherosclerosis Research Institute; †Department of Medicine, Throm
Institutet, Stockholm, Sweden; §Department of Medicine, Soonchunhyang University (
¶Population Health Research Institute, McMaster University, Hamilton, ON, Canada

- Proportion of INR >=2.0 on day 5
- RR 0.27 (0.10-0.60)
- 4x



1. Schulman J Thromb Haemost 2014

Take home message

Take-Home message

- **Recurrent VTE** vs **Bleeding** during procedure
- Warfarin → **DOACs**
- Based on **rapid onset and offset** of action of DOACs
- Paradigm shift from "**Bridging**" to "**Perioperative management**"
- Focused **on Bleeding outcome**

경청해 주셔서 감사합니다.