Current Real-World Status of Off-label Under- and Over-dose of Direct Oral Anticoagulants after Atrial Fibrillation Ablation: RYOUMA Registry Sub-analysis

Tabito Kino[1], Akihiko Nogami[1], Yuki Komatsu[1], Kyoko Soejima[2], Kikuya Uno[3], Koichiro Kumagai[4], Takashi Kurita[5], Masahiko Gosho[1], Kazutaka Aonuma[1], and Tomoko Ishizu[1]
for the RYOUMA Investigators

[1] University of Tsukuba, [2] Kyorin University School of Medicine,
[3] Tokyo Heart Rhythm Hospital, [4] Fukuoka Sanno Hospital, and [5] Kindai University School of Medicine.

This study supported by Daiichi Sankyo Co., Ltd

The Japanese Circulation Society
COI Disclosure

Name of Authors : Tabito Kino

The authors have no financial conflicts of interest to disclose concerning the presentation.

Real-world ablation therapY with anti-cOagUlants in Management of Atrial fibrillation (RYOUMA)

- A large, multicenter prospective observational study (UMIN000026092).
  - ✓ A total of 3,072 Japanese patients were enrolled between 2017 and 2018.
  - ✓ Patients with **atrial fibrillation (AF) who underwent catheter ablation** were analyzed.
- Clinical outcomes 1 year after AF ablation in DOAC taking group.
  - ✓ Thromboembolism 0.26%
  - ✓ Major bleeding 1.14%
- "Off-label" dose of DOACs were included
  - ✓ Underdose 13.1%
  - ✓ Overdose 4.7%

DOAC; direct oral anticoagulants. Nogami A, et al. *Circ J.* 2022.

The definition of “off-label” and “dose”

- “Off-label” describes the proper use of prescription medicines, but the dose has not been appropriate according to the approved dose reduction criteria.

e.g.) Dose reduction criteria of Edoxaban;

If any of following are criteria met, the reduced dose should be used.

a. Body weight (BW) ≤ 60kg

b. Creatinine clearance (CrCl) 15-50 ml/min

c. Concomitant use of an oral P-glycoprotein (P-gp) inhibitor

Pat. 1; BW 70, CrCl 60, P-gp(-) ➡ Edoxaban 60 mg = **On-label standard dose**

Pat. 2; BW 70, CrCl 60, P-gp(-) ➡ Edoxaban 30 mg = **Off-label underdose**

Pat. 3; BW 50, CrCl 60, P-gp(-) ➡ Edoxaban 30 mg = **On-label reduced dose**

Pat. 4; BW 50, CrCl 60, P-gp(-) ➡ Edoxaban 60 mg = **Off-label overdose**

The efficacy and safety of “off-label underdose” and “off-label overdose” according to previous reports

- Off-label underdose is controversial results for thromboembolism, major bleeding, and all cause mortality.

  Caso V, et al. *Heart.* 2023; van den Dries CJ, et al. *Br J Clin Pharmacol.* 2023; Joosten LPT, et al. *Open Heart.* 2023; Shen NN, et al. *Clin Appl Thromb Hemost.* 2023; Carnicelli AP, et al. *Circulation*. 2022; Wu X, et al. Front. *Cardiovasc. Med.* 2021; Zhang XL, et al. *Circ Cardiovasc Qual Outcomes*. 2021.

- Off-label overdose is just only harmful for clinical outcomes.

  Caso V, et al. *Heart.* 2023; Shen NN, et al. *Clin Appl Thromb Hemost.* 2023; Wu X, et al. Front. *Cardiovasc. Med.* 2021; Zhang XL, et al. *Circ Cardiovasc Qual Outcomes*. 2021.

- <u>These previous reports do not investigate after AF ablation.</u>

Objectives

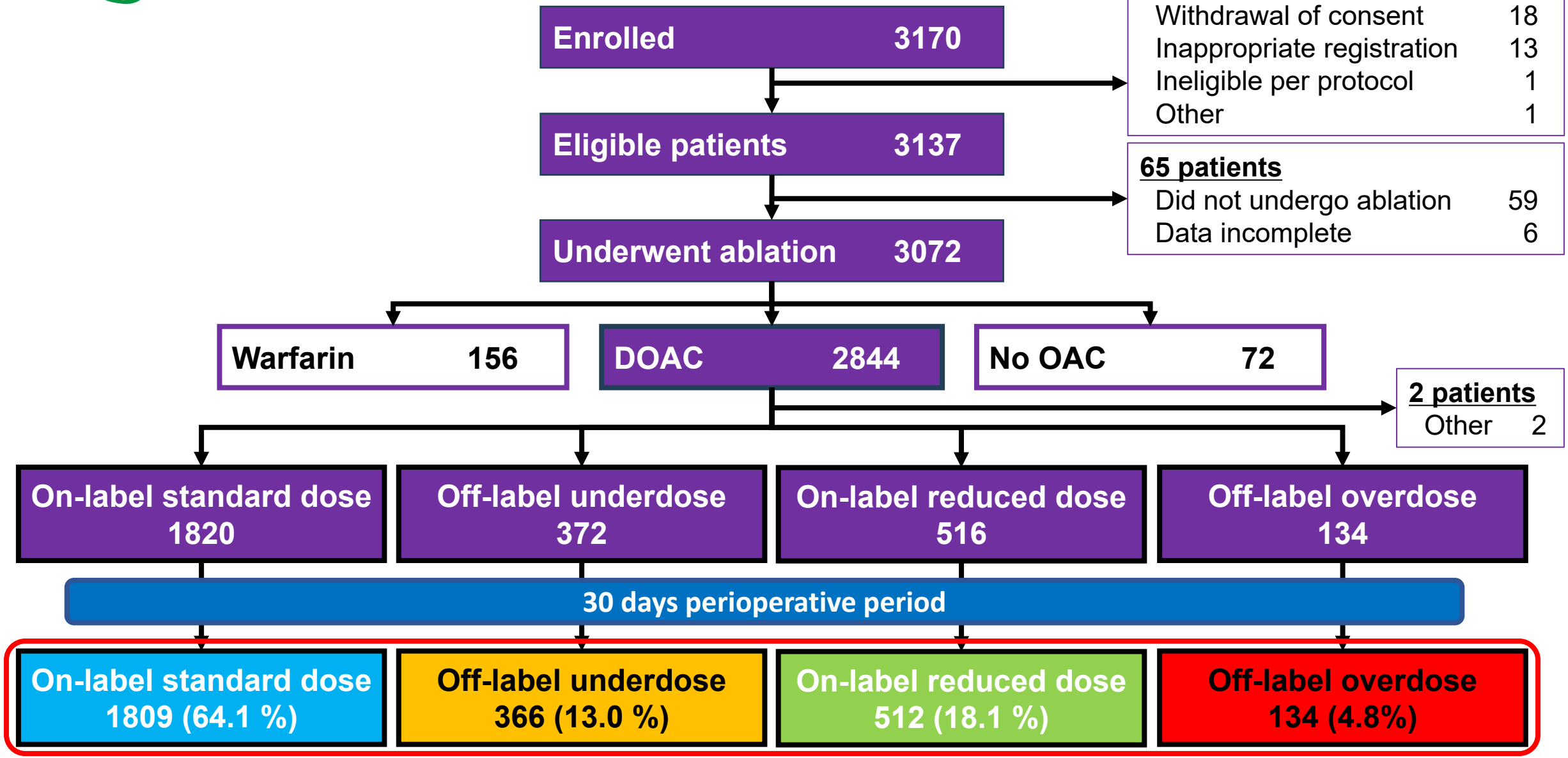
- To identify the efficacy and safety properties during the long-term follow-up periods in patients undergoing AF ablation focusing on;

1. On-label standard dose
vs.
2. Off-label underdose

3. On-label reduced dose
vs.
4. Off-label overdose

- To identify the reason off-label overdose occurred according to the approved dose reduction criteria.

Flow diagram of the enrolled patients



30 days after perioperative period = Remote period ➡ Analyzed

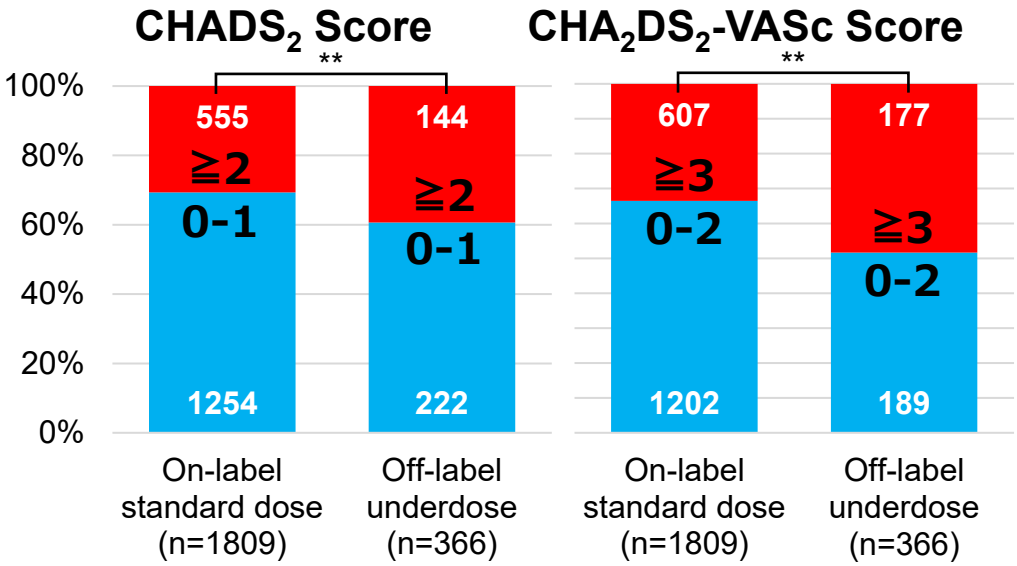
Baseline characteristics in remote period

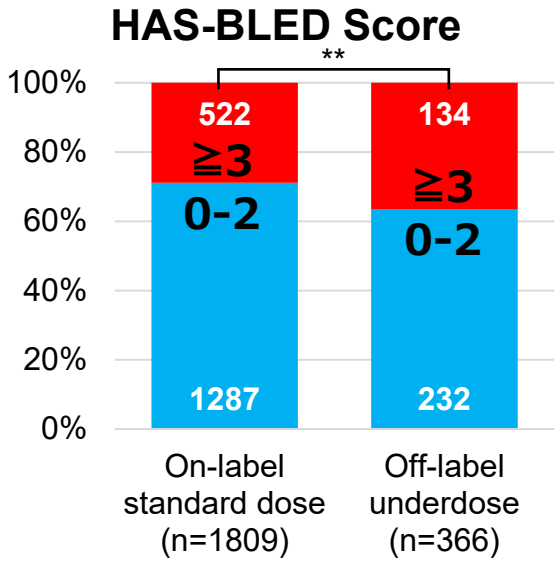
	On-Label Standard Dose (N = 1809)	Off-Label Underdose (N = 366)	P value	On-Label Reduced Dose (N = 512)	Off-Label Overdose (N = 134)	P value
Age, years	65.0 [58.0, 70.0]	**69.0 [61.0, 75.0]**	**< 0.001**	74.0 [69.0, 78.5]	**71.0 [63.0, 75.0]**	**< 0.001**
Male, n (%)	1432 (79.2)	**248 (67.8)**	**< 0.001**	228 (44.5)	**93 (69.4)**	**< 0.001**
BW, kg	68.4 [61.5, 76.4]	**64.3 [59.1, 72.5]**	**< 0.001**	54.0 [49.5, 58.8]	**60.0 [56.0, 70.0]**	**< 0.001**
Paroxysmal AF, n (%)	1127 (62.3)	245 (66.9)	0.093	354 (69.1)	**79 (59.0)**	**0.026**
$CHADS_2$ score	1.0 [0.0, 2.0]	**1.0 [0.0, 2.0]**	**0.004**	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.127
CHA_2DS_2-VASc score	2.0 [1.0, 3.0]	**2.0 [1.0, 4.0]**	**< 0.001**	3.0 [2.0, 4.0]	**2.0 [1.0, 4.0]**	**< 0.001**
HAS-BLED score	2.0 [1.0, 3.0]	**2.0 [1.0, 3.0]**	**< 0.001**	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.150
Anti-Platelet Drug , n (%)	127 (7.0)	**52 (14.2)**	**< 0.001**	57 (11.1)	9 (6.7)	0.133
Comorbidity, n (%)						
Hypertension	1096 (60.6)	236 (64.5)	0.163	306 (59.8)	71 (53.0)	0.156
Diabetes	301 (16.6)	71 (19.4)	0.201	80 (15.6)	25 (18.7)	0.397
Heart Disease	418 (23.1)	**114 (31.1)**	**0.001**	170 (33.2)	45 (33.6)	0.934
Kidney Disease	115 (6.4)	**42 (11.5)**	**< 0.001**	63 (12.3)	**8 (6.0)**	**0.037**
Laboratory Data						
Hb (g/dL)	14.4 [13.4, 15.4]	**13.9 [12.9, 14.9]**	**< 0.001**	13.3 [12.2, 14.2]	**14.1 [12.9, 14.8]**	**< 0.001**
CrCl (mL/min)	84.1 [69.9, 104.2]	**70.7 [57.4, 90.4]**	**< 0.001**	57.1 [46.2, 71.2]	**71.7 [48.5, 85.9]**	**< 0.001**

BW; body weight, CrCl; creatinine clearance. Data are shown as median [IQR, Q1, Q3] or n (%)

Baseline characteristics in remote period

	On-Label Standard Dose (N = 1809)	Off-Label Underdose (N = 366)	P value
Age, years	65.0 [58.0, 70.0]	**69.0 [61.0, 75.0]**	**< 0.001**
Male, n (%)	1432 (79.2)	**248 (67.8)**	**< 0.001**
BW, kg	68.4 [61.5, 76.4]	**64.3 [59.1, 72.5]**	**< 0.001**
Paroxysmal AF, n (%)	1127 (62.3)	245 (66.9)	0.093
$CHADS_2$ score	1.0 [0.0, 2.0]	**1.0 [0.0, 2.0]**	**0.004**
CHA_2DS_2-VASc score	2.0 [1.0, 3.0]	**2.0 [1.0, 4.0]**	**< 0.001**
HAS-BLED score	2.0 [1.0, 3.0]	**2.0 [1.0, 3.0]**	**< 0.001**
Anti-Platelet Drug , n (%)	127 (7.0)	**52 (14.2)**	**< 0.001**
Comorbidity, n (%)			
Hypertension	1096 (60.6)	236 (64.5)	0.163
Diabetes	301 (16.6)	71 (19.4)	0.201
Heart Disease	418 (23.1)	**114 (31.1)**	**0.001**
Kidney Disease	115 (6.4)	**42 (11.5)**	**< 0.001**
Laboratory Data			
Hb (g/dL)	14.4 [13.4, 15.4]	**13.9 [12.9, 14.9]**	**< 0.001**
CrCl (mL/min)	84.1 [69.9, 104.2]	**70.7 [57.4, 90.4]**	**< 0.001**





BW; body weight, CrCl; creatinine clearance. Data are shown as median [IQR, Q1, Q3] or n (%)

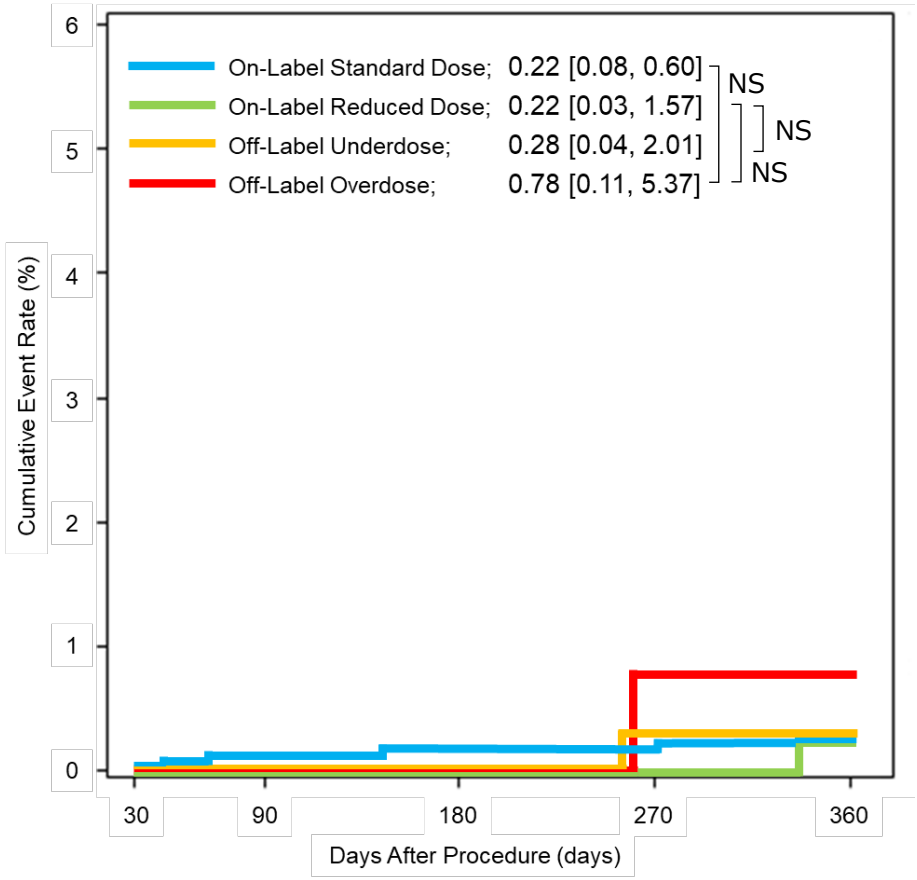
Baseline characteristics in remote period

	On-Label Standard Dose (N = 1809)	Off-Label Underdose (N = 366)	P value	On-Label Reduced Dose (N = 512)	Off-Label Overdose (N = 134)	P value
Age, years	65.0 [58.0, 70.0]	**69.0 [61.0, 75.0]**	**< 0.001**	74.0 [69.0, 78.5]	**71.0 [63.0, 75.0]**	**< 0.001**
Male, n (%)	1432 (79.2)	**248 (67.8)**	**< 0.001**	228 (44.5)	**93 (69.4)**	**< 0.001**
BW, kg	68.4 [61.5, 76.4]	**64.3 [59.1, 72.5]**	**< 0.001**	54.0 [49.5, 58.8]	**60.0 [56.0, 70.0]**	**< 0.001**
Paroxysmal AF, n (%)	1127 (62.3)	245 (66.9)	0.093	354 (69.1)	**79 (59.0)**	**0.026**
$CHADS_2$ score	1.0 [0.0, 2.0]	**1.0 [0.0, 2.0]**	**0.004**	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.127
CHA_2DS_2-VASc score	2.0 [1.0, 3.0]	**2.0 [1.0, 4.0]**	**< 0.001**	3.0 [2.0, 4.0]	**2.0 [1.0, 4.0]**	**< 0.001**
HAS-BLED score	2.0 [1.0, 3.0]	**2.0 [1.0, 3.0]**	**< 0.001**	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.150
Anti-Platelet Drug , n (%)	127 (7.0)	**52 (14.2)**	**< 0.001**	57 (11.1)	9 (6.7)	0.133
Comorbidity, n (%)						
Hypertension	1096 (60.6)	236 (64.5)	0.163	306 (59.8)	71 (53.0)	0.156
Diabetes	301 (16.6)	71 (19.4)	0.201	80 (15.6)	25 (18.7)	0.397
Heart Disease	418 (23.1)	**114 (31.1)**	**0.001**	170 (33.2)	45 (33.6)	0.934
Kidney Disease	115 (6.4)	**42 (11.5)**	**< 0.001**	63 (12.3)	**8 (6.0)**	**0.037**
Laboratory Data						
Hb (g/dL)	14.4 [13.4, 15.4]	**13.9 [12.9, 14.9]**	**< 0.001**	13.3 [12.2, 14.2]	**14.1 [12.9, 14.8]**	**< 0.001**
CrCl (mL/min)	84.1 [69.9, 104.2]	**70.7 [57.4, 90.4]**	**< 0.001**	57.1 [46.2, 71.2]	**71.7 [48.5, 85.9]**	**< 0.001**

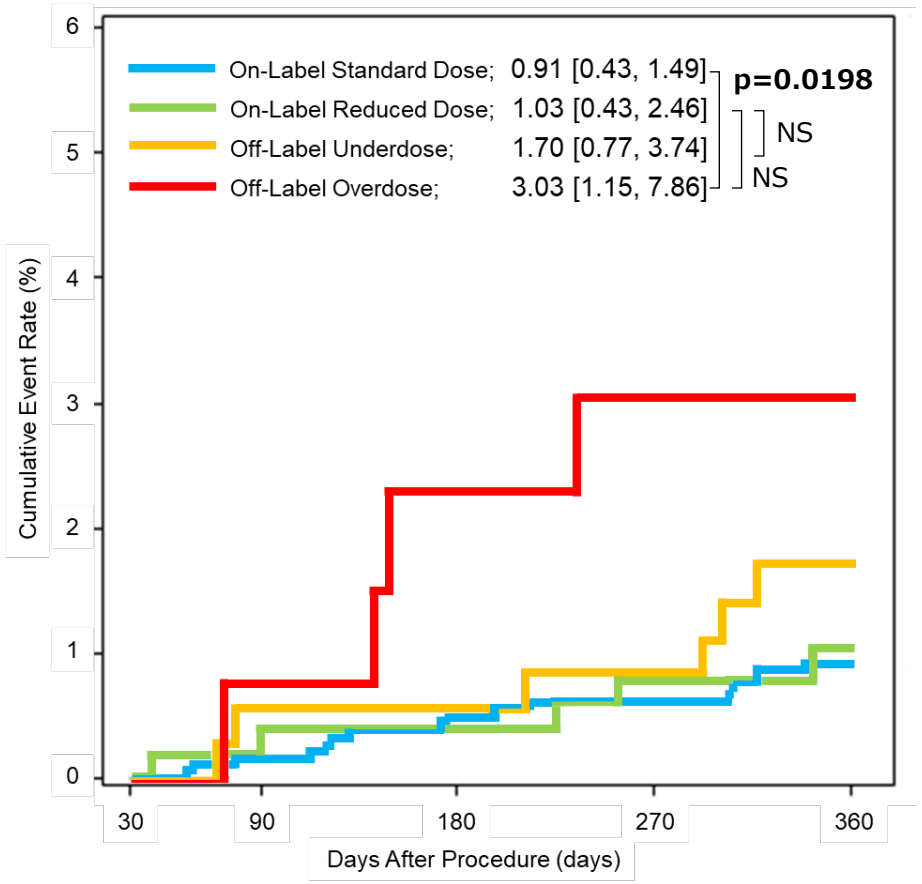
BW; body weight, CrCl; creatinine clearance. Data are shown as median [IQR, Q1, Q3] or n (%)

Efficacy and safety outcomes in remote period

Ischemic stroke/Systemic embolic events



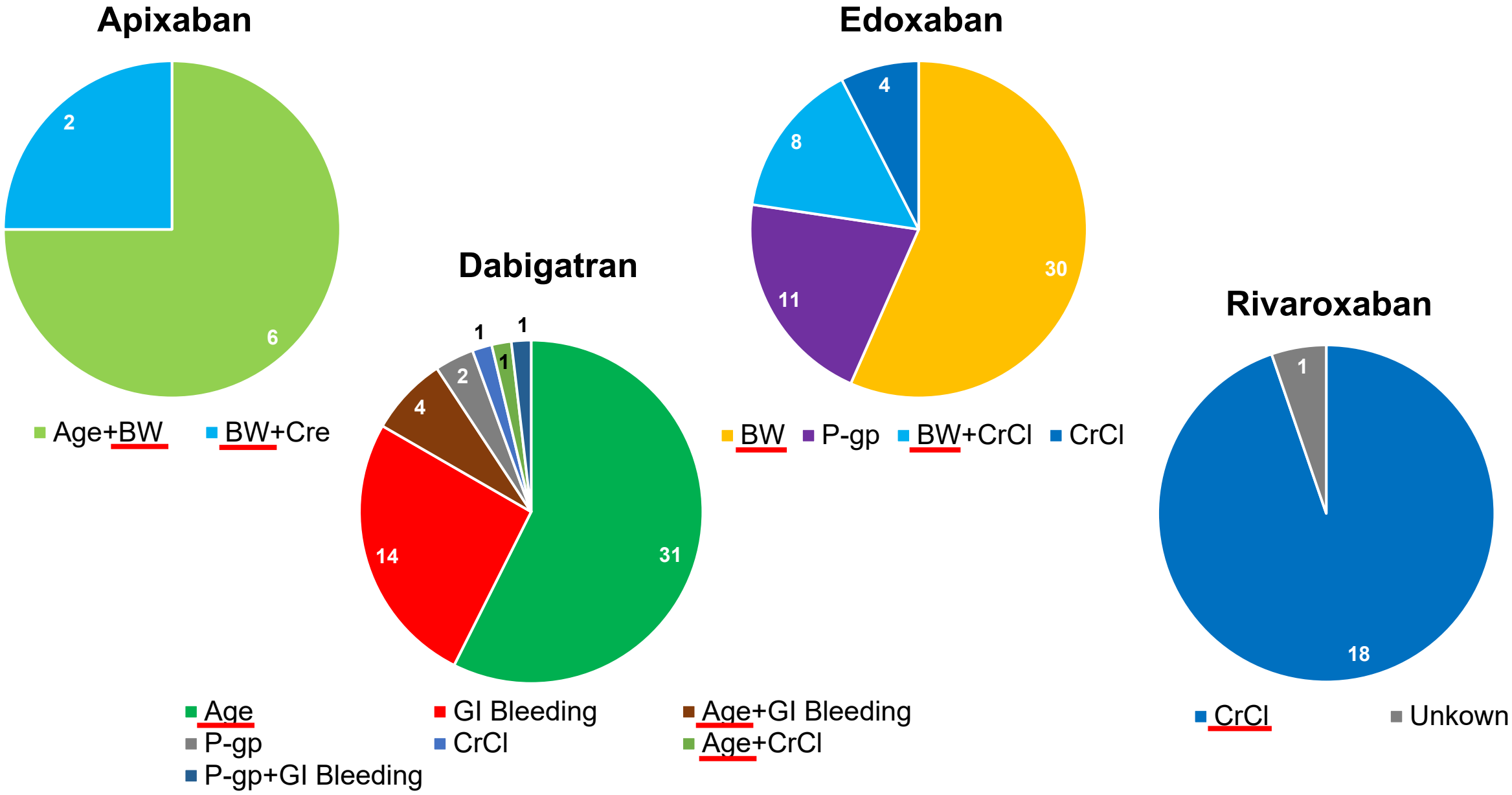
Major bleeding



- Ischemic stroke/systemic embolic events were quite low **after AF ablation**.
- Major bleeding events were significantly higher in off-label overdose.
- Off-label underdose **did not increase the risk of thromboembolism**, but **did not decrease major bleeding**.

NS; not significant

Missing criteria of dose reduction in off-label overdose group



Summary

- Thromboembolism was quite low after AF ablation.
- Off-label underdose did not increase thromboembolism and did not decrease major bleeding.
- Major bleeding events were significantly higher in off-label overdose.
- Clinicians refrained from prescribing standard dose due to several drivers in off-label underdose.
- Clinicians may overlook the dose reduction criteria in off-label overdose.

Discussions

- Drivers of off-label underdose

Based on previous literatures

Hypertension	History of minor bleeding	Surgical specialty
Congestive heart failure		
Older age	Low CrCl	
Higher CHA_2DS_2-VASc score	Concomitant use of antiplatelet drugs	
Female	Heart disease	Low BW
Higher $CHADS_2$ score	Higher HAS-BLED score	Low hemoglobin

Based on our study

Some drivers may have a potential to increase the bleeding risk, however, further studies are needed to conclude.

Caso V, et al. Heart. 2023; Gozzo L, et al. *Sci Rep.* 2021; Rymer JA, et al. *JAMA Network Open.* 2023.

Discussions

- Drivers of off-label overdose were insufficient evidence.

Caso V, et al. *Heart*. 2023.

According to our results, drivers were not associated with the risk of major bleeding events.

↓

Clinicians may overlook the dose reduction criteria including; **Age**, **BW**, and **CrCl**

↓

Clinicians should pay attention to patients' characteristics more frequently.

Conclusions

- While the proportion of major bleeding events in patients receiving off-label underdose of DOAC after AF ablation remained high, the ischemic stroke and systemic embolic events were notably low.

- Adhering to dose reduction criteria is important, as off-label overdose was significantly associated with an elevated incidence of major bleeding.