Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing PCI, Real World Clinical Practice in Japan

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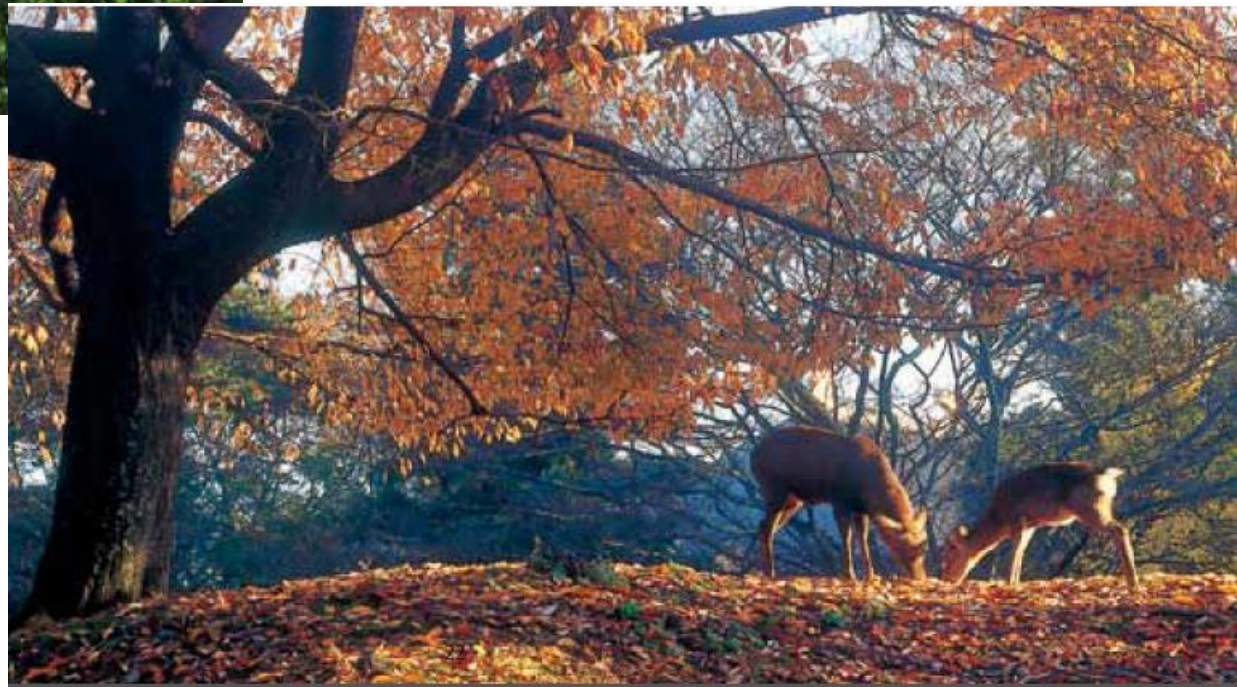
on behalf of the CREDO-KYOTO cohort-2 registry investigators

Tenri Hospital in Nara

Tenri Hospital 1001 Beds

Welcome to Nara, the birthplace of Japanese history.



Background

- Approximately 10% of patients undergoing PCI have concomitant atrial fibrillation (AF).

- Most of those AF patients undergoing PCI have an indication for oral anticoagulation (OAC) to prevent stroke or systemic thromboembolism as well as antiplatelet therapy (APT) to prevent stent thrombosis.

- In patients receiving drug-eluting stents (DES), long-term dual APT (DAPT) with aspirin plus thienopyridine is recommended.

- Although a great concern about bleeding complications has been raised for such a “triple” antithrombotic therapy, the prevalence and intensity as well as the safety and efficacy of OAC in combination with DAPT in “a real world” AF patients undergoing PCI is unknown.

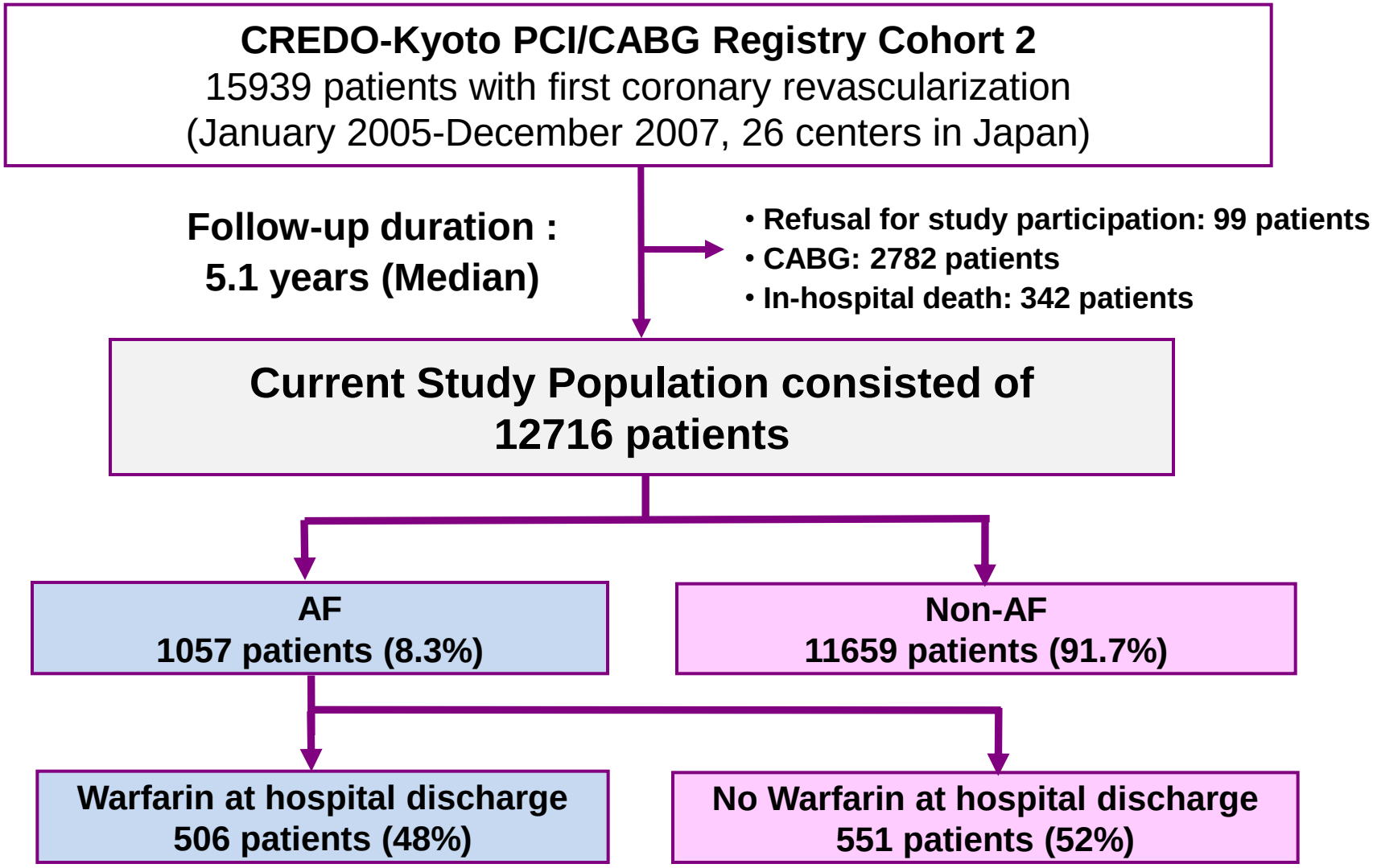
Purpose

The purpose of this study was to evaluate

- *Clinical impact of AF*
- *Prevalence and intensity as well as safety and efficacy of OAC for AF*

in “a real world” patients undergoing PCI mostly treated with DAPT in the Era of Warfarin (2005-2007).

Study Flow Chart



Endpoint Measures

- *Primary Endpoint Measure*
  - *Stroke*
    - *Ischemic stroke*
    - *Hemorrhagic stroke*
- *Secondary Endpoint Measures*
  - *Death*
  - *MI*
  - Major bleeding

Definitions

- ***Stroke***

  Ischemic or hemorrhagic stroke requiring hospitalization
  with symptoms lasting >24 hours.

  - ***Ischemic stroke***

    The sudden onset of a focal neurologic deficit in a location
    consistent with the territory of a major cerebral artery.
    Hemorrhagic and ischemic stroke were distinguished by the imaging studies.

  - ***Hemorrhagic stroke***

    Cerebral, subdural, epidural, or subarachnoid hemorrhage

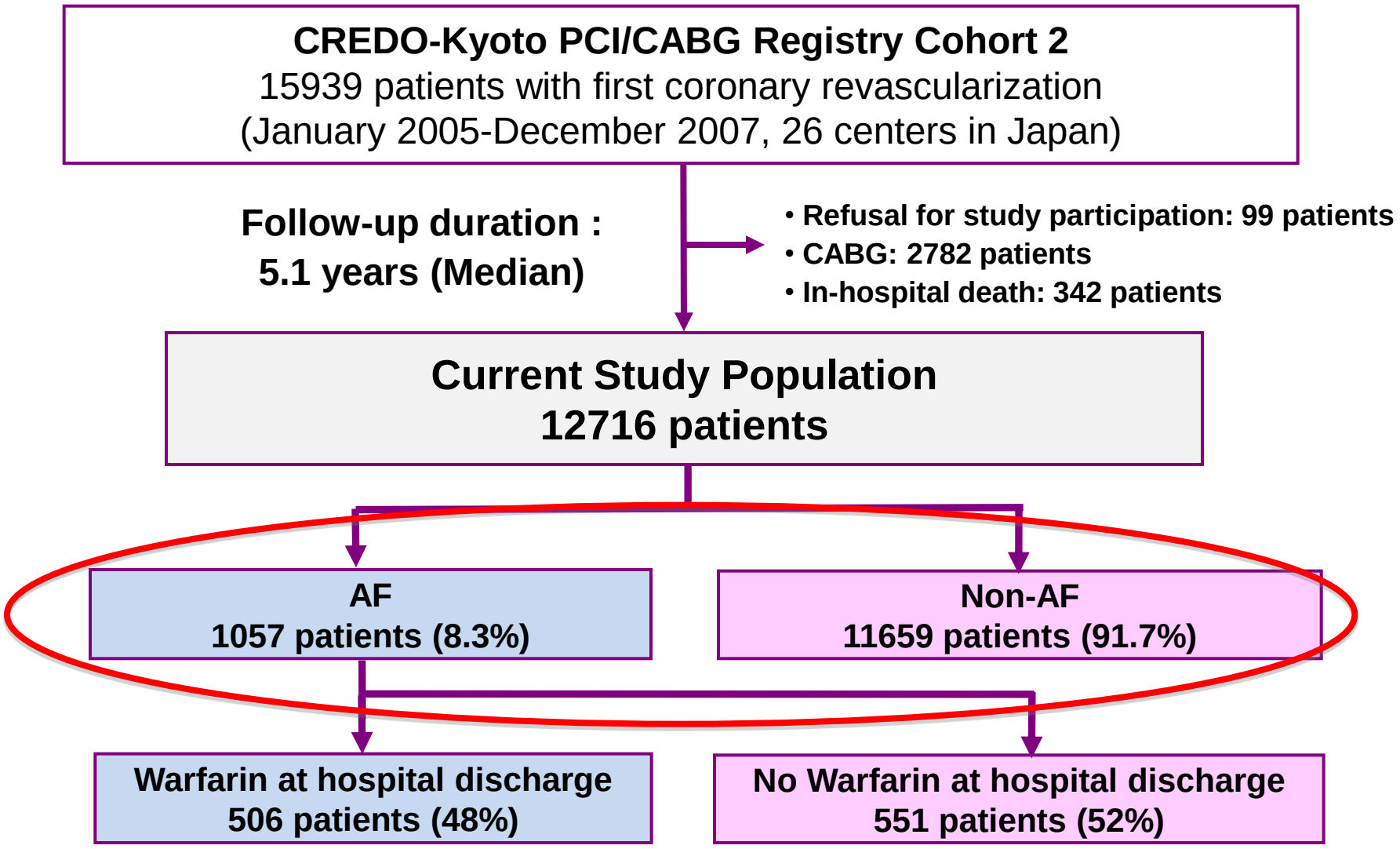
- ***Major bleeding***

  Moderate or severe bleeding by the GUSTO classification

  - *Moderate* : Bleeding that requires blood transfusion
    but dose not result in hemodynamic compromise

  - *Severe* : Either intracranial hemorrhage or bleeding that causes
    hemodynamic compromise and requires intervention

Study Flow Chart

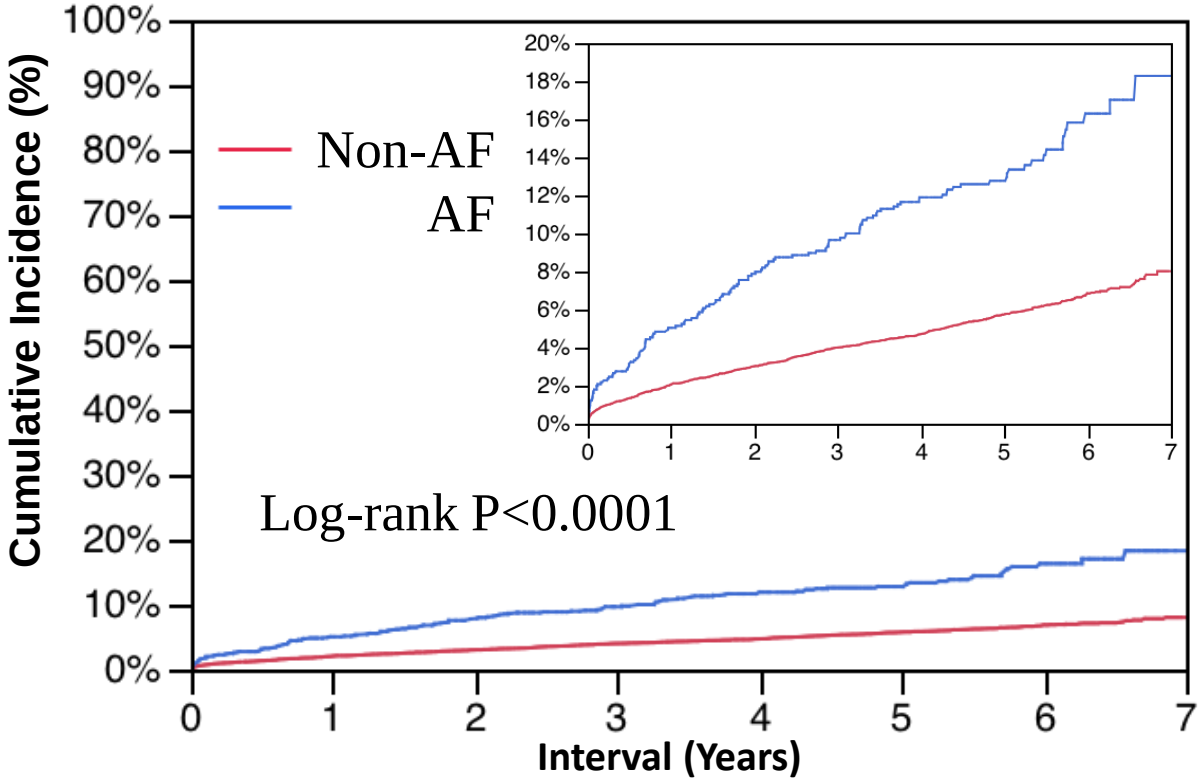


Clinical Characteristics

	AF	Non-AF	P value
	n=1057	n=11659	
Age (years)	72.5±9.3	67.6±11.1	<0.0001
Male	71%	72%	0.43
Acute myocardial infarction	37%	35%	0.11
Hypertension	85%	82%	0.007
Diabetes mellitus	34%	38%	0.02
Prior stroke	19%	10%	<0.0001
Prior intracranial bleeding	3%	2%	0.008
Heart failure	39%	16%	<0.0001
Multivessel disease	50%	55%	0.001
eGFR<30	10%	7%	0.0002
DES use	48%	53%	0.0009
DAPT(Aspirin+Thienopyridine)	94%	97%	<0.0001

Primary Endpoint Measure

Stroke



Adjusted HR = 2.04

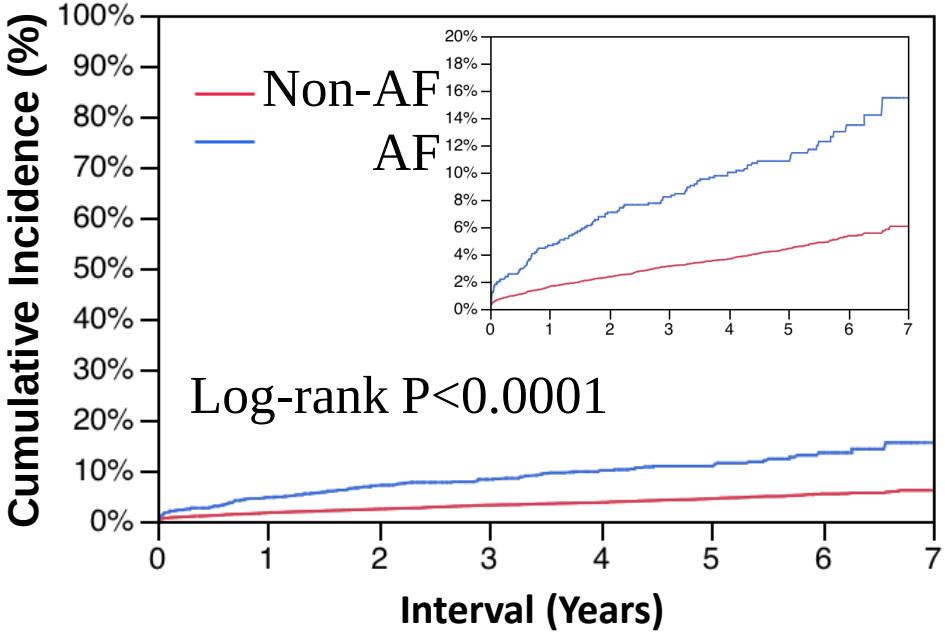
(95%CI :1.67-2.50)

p<0.0001

Interval	0 day	1year	3 years	5 years	7 years
Non-AF group					
N of patients with events		237	445	603	666
N of patients at risk	11659	10929	9975	6126	244
Cumulative incidence		2.1%	4.0%	**5.8%**	8.0%
AF group					
N of patients with events		52	95	120	134
N of patients at risk	1057	935	785	455	18
Cumulative incidence		5.0%	9.7%	**12.8%**	18.3%

Ischemic Stroke

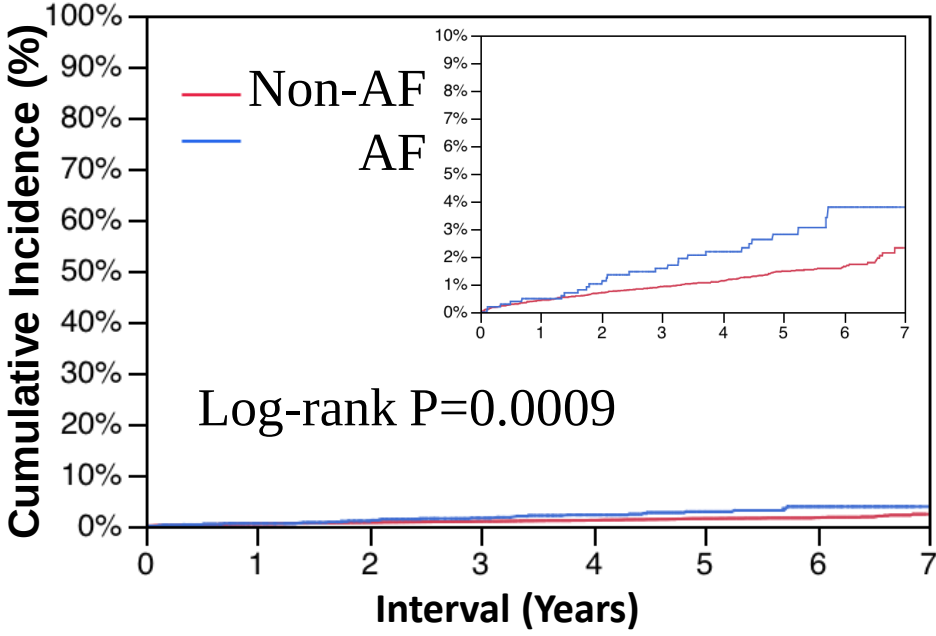
Adjusted HR = 2.17
(95%CI :1.74-2.72)
p<0.0001



Interval	0 day	1year	3 years	5 years	7 years
Non-AF group					
N of patients with events		189	348	464	515
N of patients at risk	11659	10958	10027	6178	245
Cumulative incidence		1.7%	3.1%	**4.4%**	6.1%
AF group					
N of patients with events		48	81	102	113
N of patients at risk	1057	936	787	458	18
Cumulative incidence		4.7%	8.2%	**10.8%**	15.5%

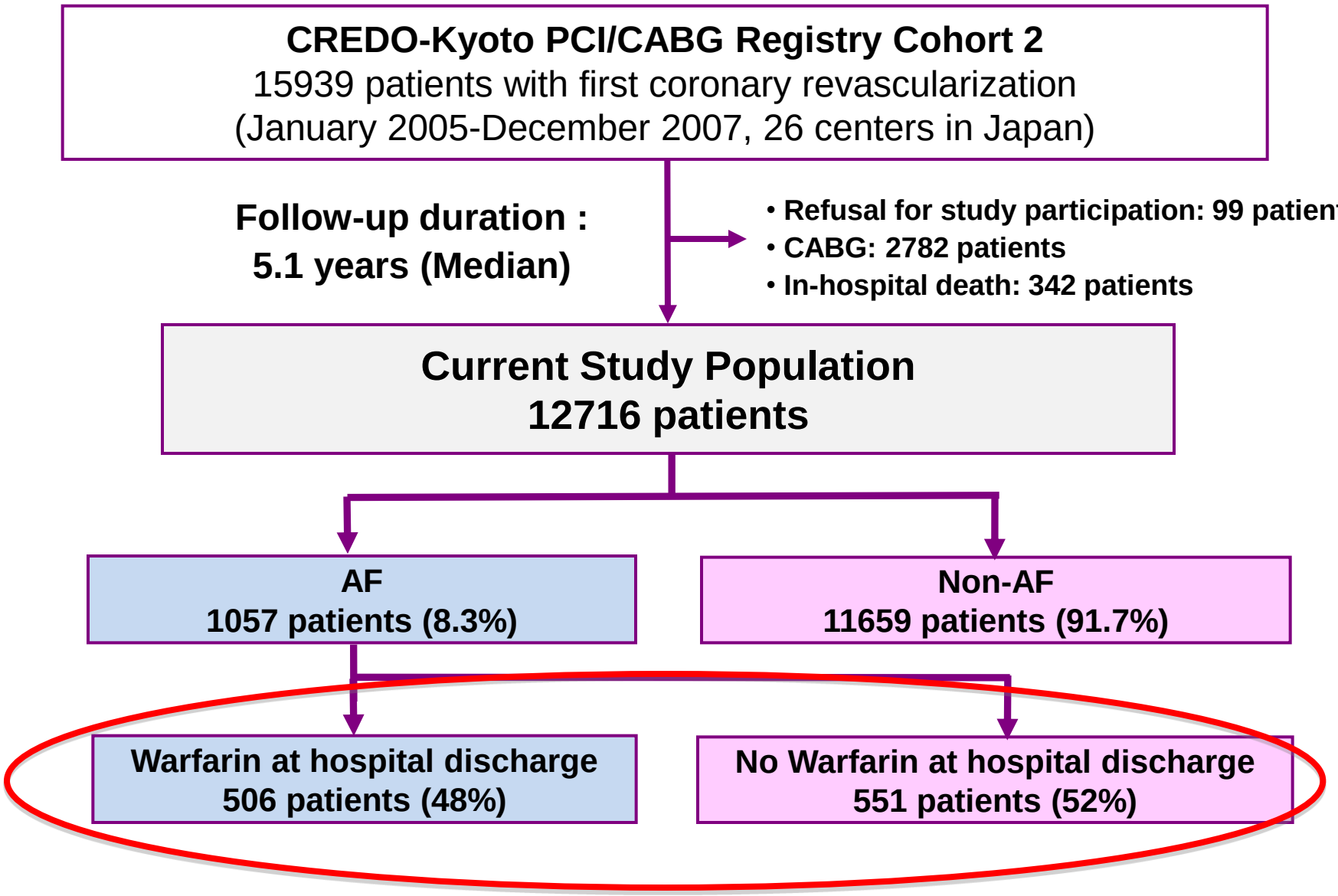
Hemorrhagic Stroke

Adjusted HR = 1.82
(95%CI :1.18-2.79)
p=0.006



Interval	0 day	1year	3 years	5 years	7 years
Non-AF group					
N of patients with events		49	102	151	166
N of patients at risk	11659	11079	10228	6343	255
Cumulative incidence		0.4%	0.9%	**1.5%**	2.3%
AF group					
N of patients with events		5	15	24	27
N of patients at risk	1057	972	832	485	21
Cumulative incidence		0.5%	1.6%	**2.8%**	3.8%

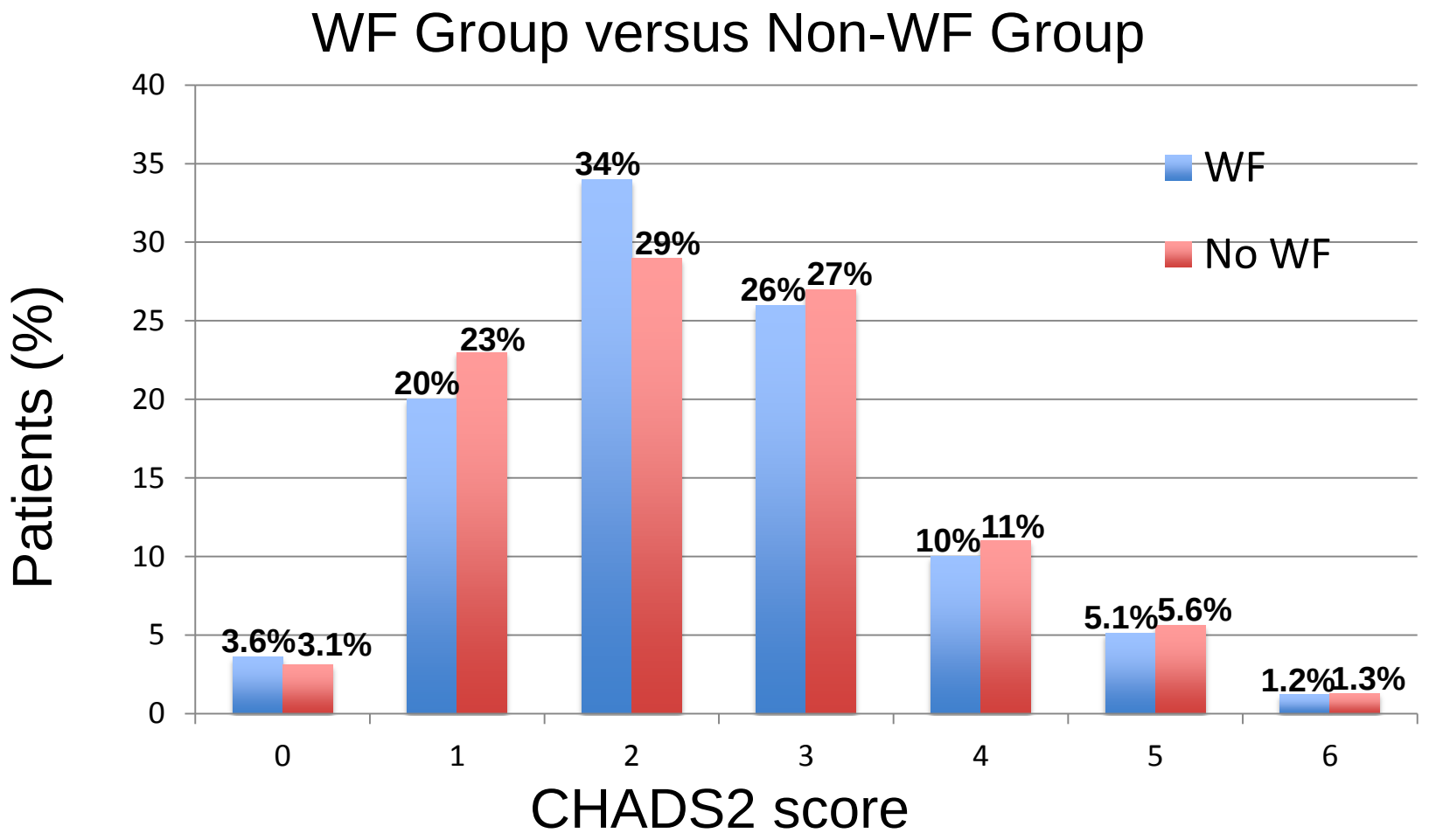
Study Flow Chart



Clinical Characteristics

	Warfarin	No Warfarin	P value
	n=506	n=551	
Age (years)	72.0±8.8	73.0±9.7	0.08
≧75 years	42%	48%	0.04
Male	76%	67%	0.002
Acute myocardial infarction	33%	41%	0.01
Hypertension	86%	85%	0.58
Diabetes mellitus	35%	34%	0.63
Current smoking	23%	22%	0.5
Heart failure	40%	39%	0.82
Multivessel disease	47%	53%	0.06

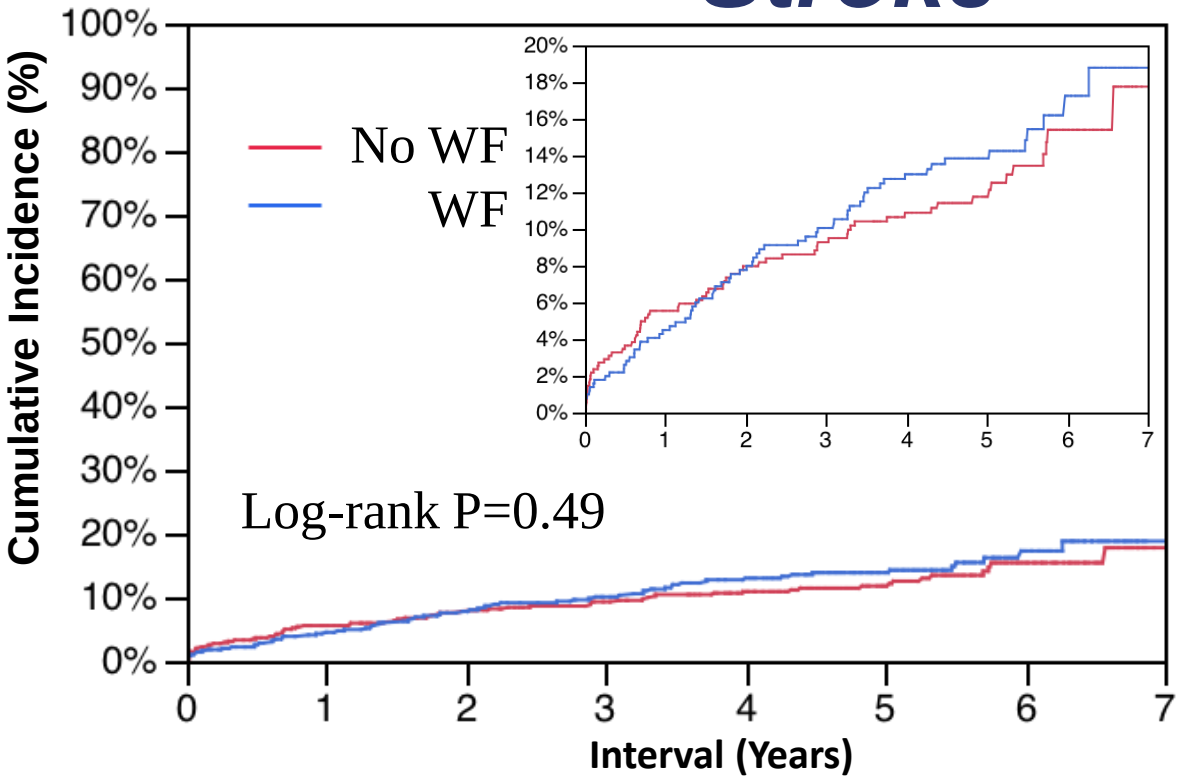
Distribution of CHADS2 Score



CHADS2 score	0	1	2	3	4	5	6	Total
No WF group (N)	17	128	158	149	61	31	7	551
WF group (N)	18	99	172	132	53	26	6	506

Primary Endpoint Measure

Stroke



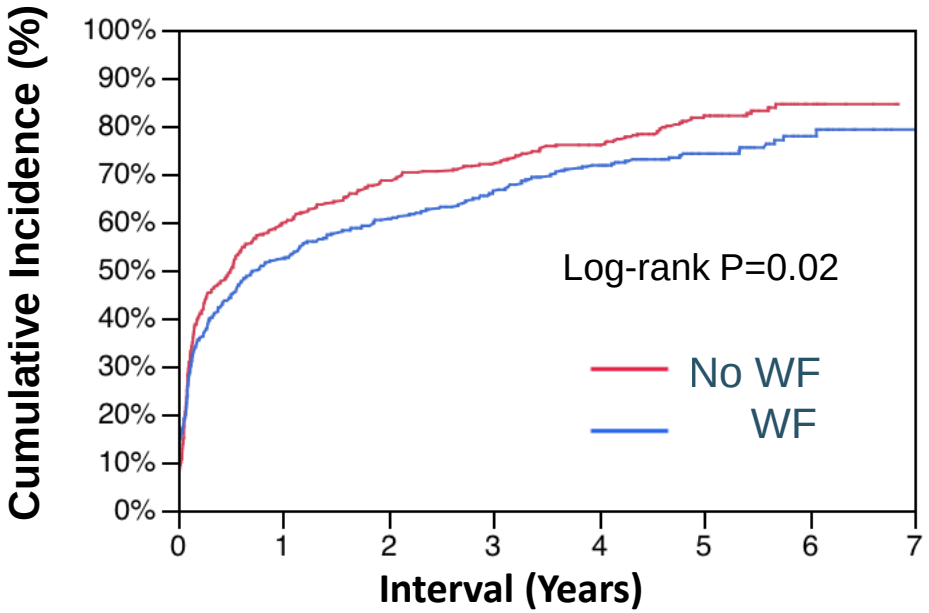
Adjusted HR = 1.15

(95%CI :0.78-1.69)

p=0.49

Interval	0 day	1year	3 years	5 years	7 years
No WF group					
N of patients with events		30	48	58	66
N of patients at risk	551	487	407	240	10
Cumulative incidence		5.5%	9.3%	**11.8%**	17.8%
WF group					
N of patients with events		22	47	62	68
N of patients at risk	506	449	379	217	9
Cumulative incidence		4.5%	10.1%	**13.8%**	18.8%

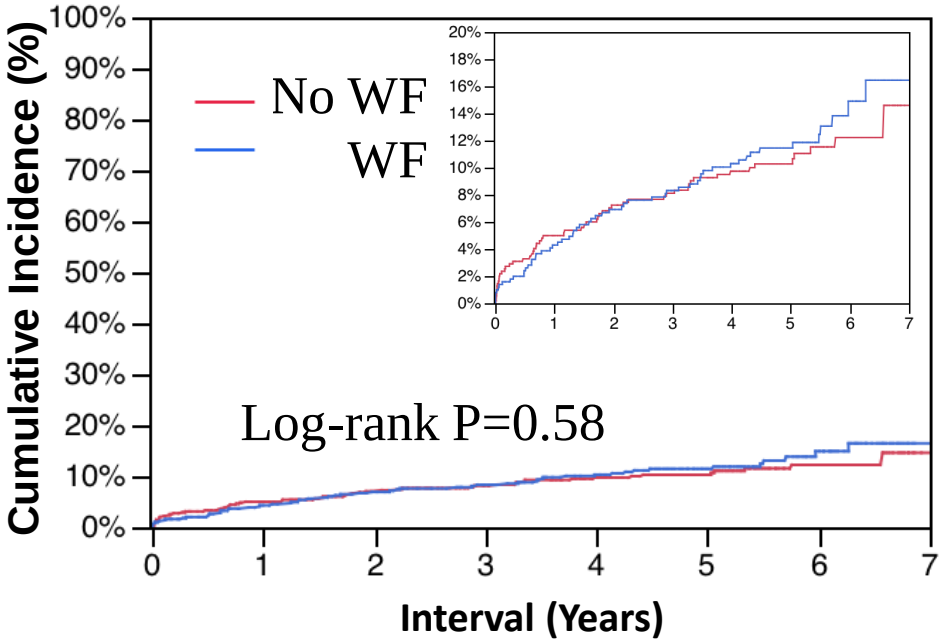
Persistent Discontinuation of DAPT(Aspirin and Thienopyridine)



Interval	0 day	1years	3 years	5 years	7 years
No WF group					
N of patients with discontinuation		319	378	416	
N of patients at risk	551	198	128	47	
Cumulative incidence		60.0%	72.2%	**82.1%**	
WF group					
N of patients with discontinuation		259	319	345	351
N of patients at risk	506	217	130	54	2
Cumulative incidence		52.4%	66.7%	**74.2%**	79.2%

Ischemic Stroke

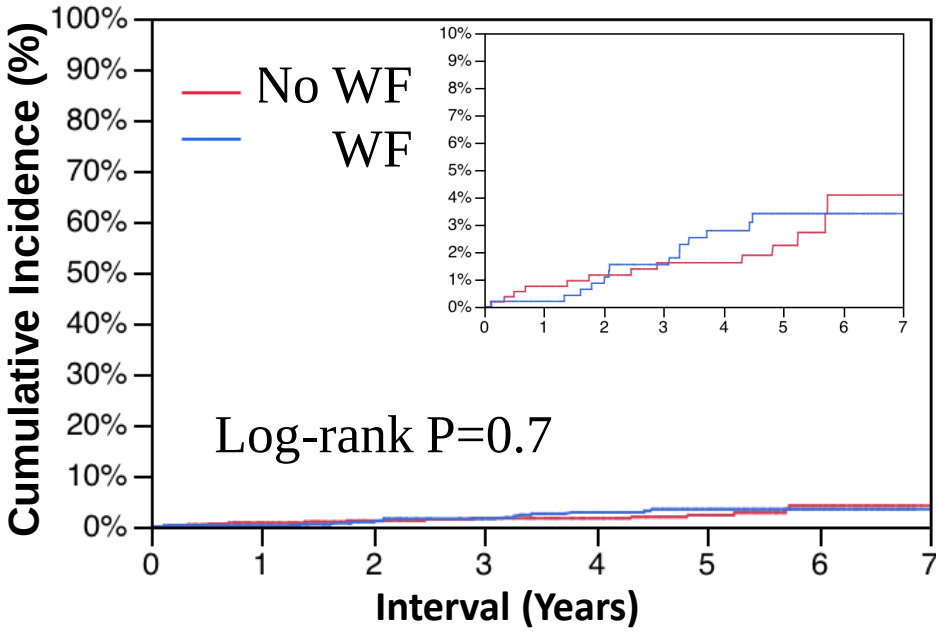
Adjusted HR = 1.17
(95%CI :0.76-1.80)
p=0.47



Interval	0 day	1year	3 years	5 years	7 years
No WF group					
N of patients with events		27	42	51	56
N of patients at risk	551	487	407	241	10
Cumulative incidence		5.0%	8.1%	**10.3%**	14.6%
WF group					
N of patients with events		21	39	51	57
N of patients at risk	506	450	381	219	9
Cumulative incidence		4.3%	8.3%	**11.5%**	16.5%

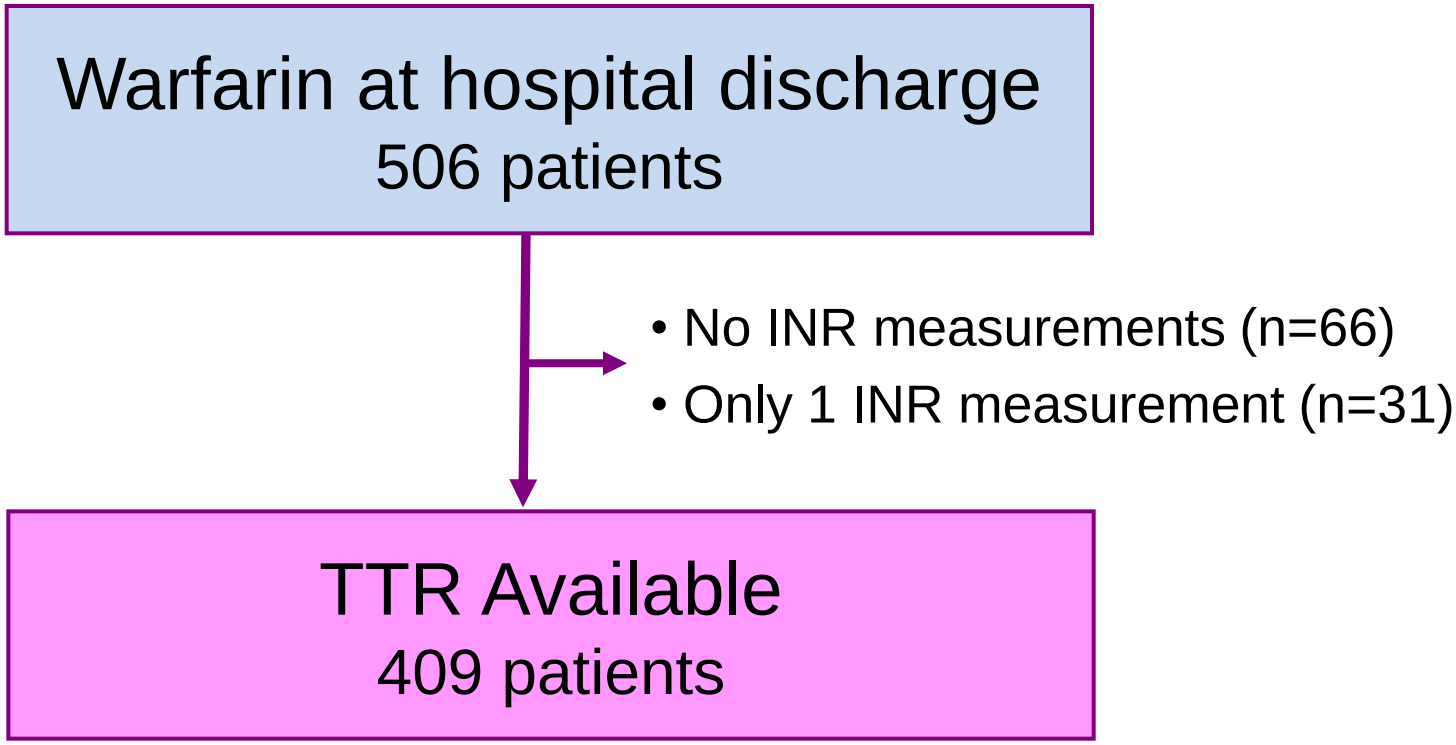
Hemorrhagic Stroke

Adjusted HR = 1.54
(95%CI :0.59-4.03)
p=0.38



Interval	0 day	1year	3 years	5 years	7 years
No WF group					
N of patients with events		4	8	10	13
N of patients at risk	551	505	426	252	12
Cumulative incidence		0.8%	1.6%	**2.2%**	4.1%
WF group					
N of patients with events		1	7	14	14
N of patients at risk	506	468	407	235	10
Cumulative incidence		0.2%	1.5%	**3.4%**	3.4%

PT-INR Measurements and TTR



Intensity of OAC in the WF group

(N=409)

Therapeutic INR Range	Time Below Therapeutic INR Range (%)	TTR(%)	Time Above Therapeutic INR Range (%)
2.0 - 3.0	72.4	24.2	3.4
1.6 - 2.6	40.2	52.6	7.2

- *The Therapeutic INR range of 1.6-2.6 was used to calculate TTR in the current analysis.*
- *Comparisons were made between the 2 groups :*
  Patients with a TTR ≥65% and those with a TTR <65%.

TTR≧65%

154 patients (38%)

VS

TTR<65%

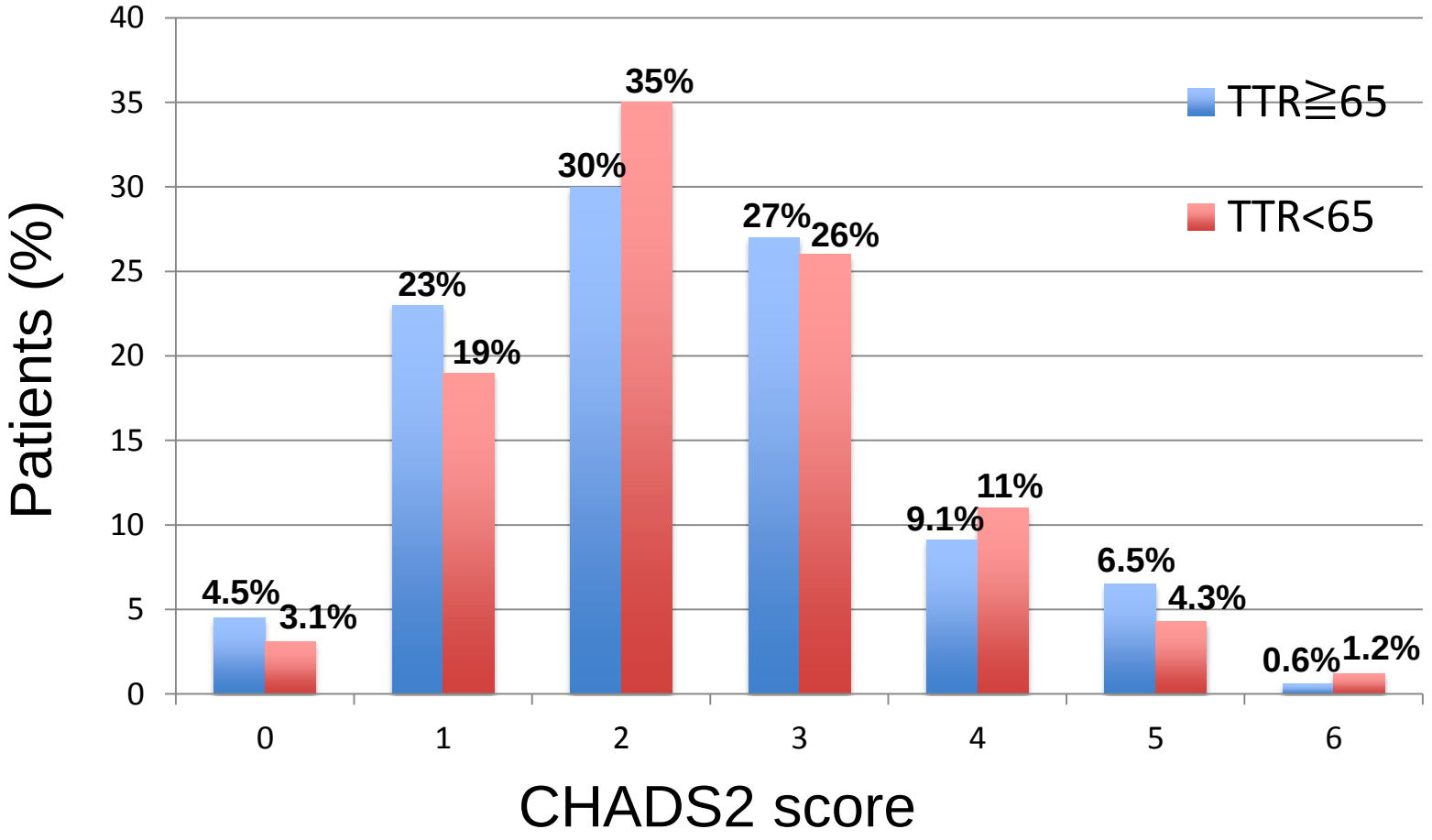
255 patients (62%)

Clinical characteristics

	TTR≧65%	TTR<65%	P value
	n=154	n=255	
Age (years)	69.8±8.4	72.3±8.8	0.002
≧75 years	30%	45%	0.002
Male	82%	76%	0.1
Hypertension	87%	87%	0.92
Diabetes mellitus	36%	36%	0.88
Heart failure	37%	39%	0.71
Multivessel disease	46%	49%	0.62
Prior stroke	23%	17%	0.15
Prior intracranial bleeding	1%	2%	0.72
Aspirin	96%	98%	0.19
Thienopyridine	95%	95%	0.97
DAPT(Aspirin+Thienopyridine)	92%	93%	0.67

Distribution of CHADS2 Score

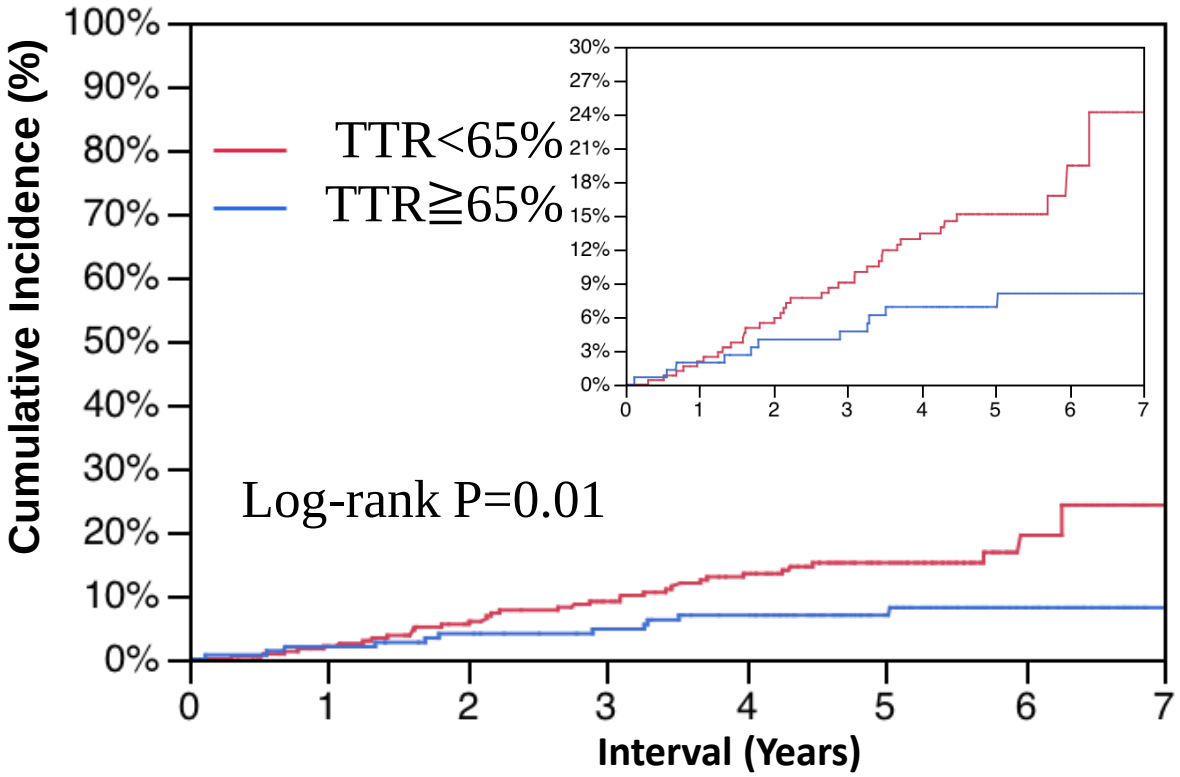
TTR ≥65% versus TTR <65%



CHADS2 score	0	1	2	3	4	5	6	Total
TTR<65% group (N)	8	48	90	67	28	11	3	255
TTR≧65% group (N)	7	35	46	41	14	10	1	154

Primary Endpoint Measure

Stroke



Adjusted HR = 0.30

(95%CI :0.12-0.79)

p=0.01

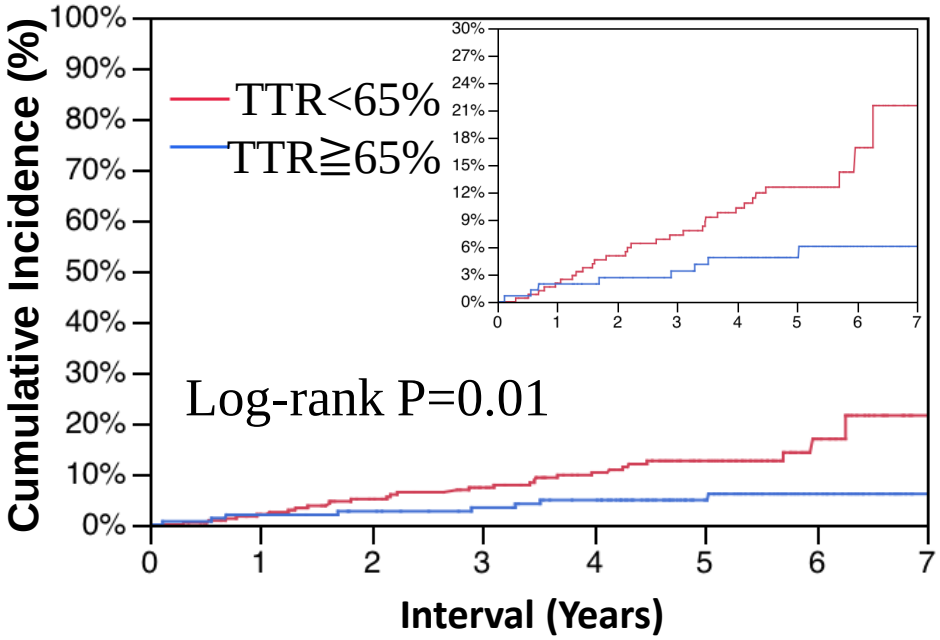
Interval	0 day	1year	3 years	5 years	7 years
TTR<65% group					
N of patients with events		5	21	33	36
N of patients at risk	255	236	194	104	3
Cumulative incidence		2.0%	9.1%	**15.1%**	24.2%
TTR≧65% group					
N of patients with events		3	7	10	11
N of patients at risk	154	149	134	81	3
Cumulative incidence		2.0%	4.7%	**6.9%**	8.1%

Ischemic Stroke

Adjusted HR = 0.21

(95%CI :0.06-0.71)

p=0.01



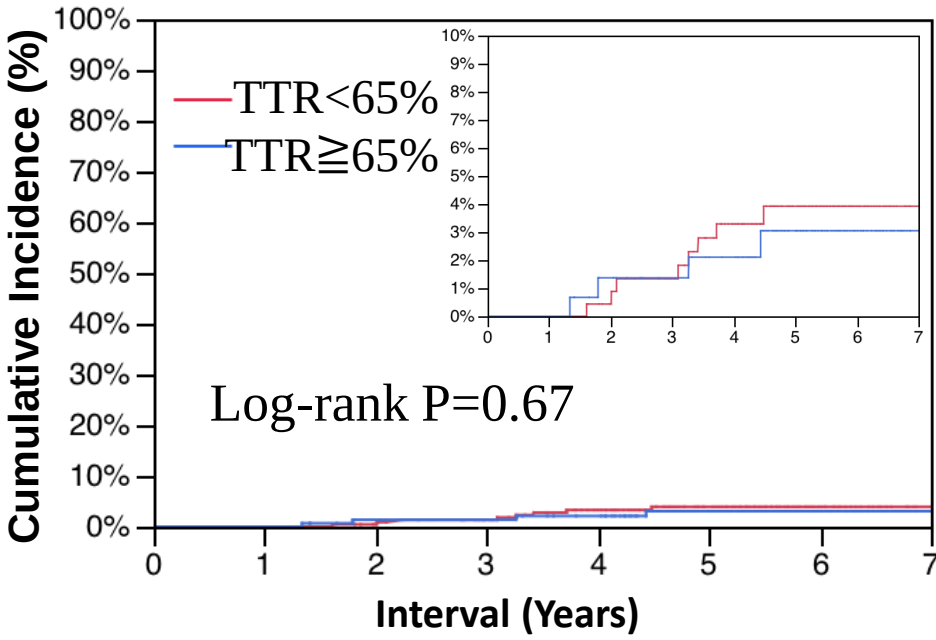
Interval	0 day	1year	3 years	5 years	7 years
TTR<65% group					
N of patients with events		5	17	27	30
N of patients at risk	255	236	195	105	3
Cumulative incidence		2.0%	7.3%	**12.6%**	21.5%
TTR≧65% group					
N of patients with events		3	5	7	8
N of patients at risk	154	149	134	81	3
Cumulative incidence		2.0%	3.4%	**4.9%**	6.1%

Hemorrhagic Stroke

Unadjusted HR = 0.77

(95%CI :0.23-2.57)

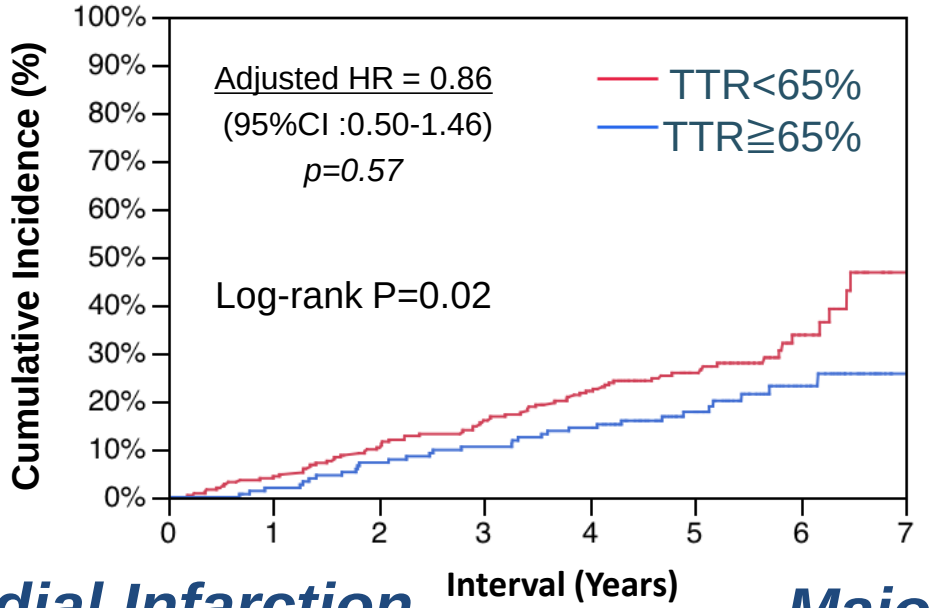
p=0.68



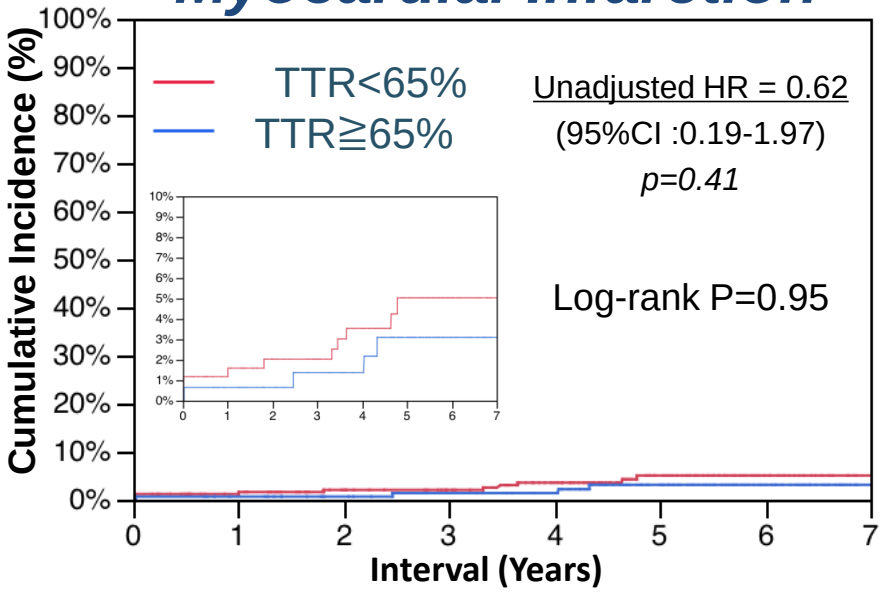
Interval	0 day	1year	3 years	5 years	7 years
TTR<65% group					
N of patients with events		0	3	8	8
N of patients at risk	255	241	208	113	4
Cumulative incidence		0%	1.3%	**3.9%**	3.9%
TTR≧65% group					
N of patients with events		0	2	4	4
N of patients at risk	154	151	136	82	3
Cumulative incidence		0%	1.4%	**3.1%**	3.1%

Secondary Endpoit Measures

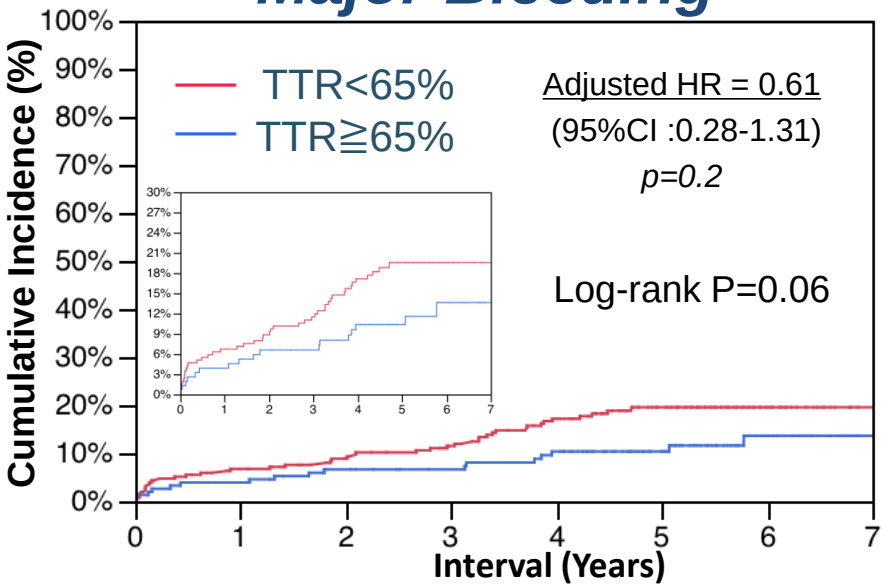
All-cause Death



Myocardial Infarction



Major Bleeding



Summary 1

- AF co-existed in 1,057 (8.3%) out of 12,716 patients undergoing PCI.

- AF was independently associated with significantly higher risk for stroke.

AF vs. Non-AF

- The 5-year stroke rate : 12.8% vs. 5.2%
- Adjusted HR for stroke : 2.04

- Obviously warfarin was underused (only 48%) in AF patients at hospital discharge.

- Warfarin use was not associated with improved long-term stroke outcome.

Summary 2

- Intensity of OAC by warfarin in AF patients was mostly suboptimal.

- Using the INR range of 1.6-2.6, 38% of patients had a TTR ≥65%.

- Patients with a TTR ≥65% were associated with markedly reduced risk for stroke as compared with those with a TTR <65%

TTR ≥65% vs. TTR <65%

- The 5-year stroke rate : 6.9% vs. 15.1%
- Adjusted HR for stroke : 0.30

Limitations

- Regarding the effect of warfarin therapy on stroke outcome, we could not deny the influence of selection bias and unmeasured confounders due to observational study design, although the patient background was not so much different regardless of warfarin use.

- Stroke events were not necessarily adjudicated by neurologists

- Because of retrospective data collection on PT-INR data, we did not have PT-INR data in all patients with warfarin therapy, and the number and interval of PT-INR measurements varied widely.

- TTR cut-off level of 65% with INR range of 1.6-2.6 was not pre-specified. However, the results were consistent even when TTR cut-off level was set at 60% or 70%, respectively.

Conclusions

- Although AF was independently associated with higher risk for stroke, OAC with warfarin was underused and its intensity was mostly suboptimal in “a real world” AF patients undergoing PCI in Japan.

- When AF patients with warfarin therapy were stratified according to the intensity of warfarin control, those with a TTR ≥65% (INR range:1.6-2.6) were associated with markedly reduced risk for ischemic stroke as compared with those with a TTR <65%.

- Optimal OAC is mandatory for prevention of stroke in AF patients undergoing PCI, even though most of these patients are managed with concomitant DAPT.

- Further investigation should be warranted to define the optimal antithrombotic regimen using APT on top of “optimal” OAC.

Thank you for your attention