Comparing the Relationship between TTR level and 1-year Survival Outcomes in Korean Atrial Fibrillation Patients Treating with Warfarin

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Aim

- It is unknown whether <u>time in the therapeutic range</u> (TTR) level associates with the risk of adverse outcomes in atrial fibrillation (AF) patients with warfarin. We compared 1-year outcomes for in Korean AF patients with warfarin according to TTR level.

- We wanted to know TTR rate in the clinical practice between cardiology and neurology department.

Methods

- A single-center retrospective study.

- AF patients with warfarin medication
    - Total eligible 1,877 patients from cardiology (n=1,279) and neurology (n=598)

- Outcomes: 1-year combined outcomes of MACE and Bleeding
    - MACE (ischemic stroke, non-fatal myocardial infarction, all-cause death)
    - Bleeding (BARC type 3 or 5).

Baseline Characteristics of Study Patients

	TTR≥60(n=579)	TTR<60(n=1,298)	P
Male	295(51.1)	717(55.2)	0.106
Age	67.4±11.2	67.5±11.6	0.876
Age≥75	162(28.1)	401(30.8)	0.227
HTN	238(41.2)	541(41.6)	0.881
DM	103(17.9)	295(22.7)	0.018
CHF	112(19.4)	279(21.5)	0.313
Pre TIA or Stroke	172(29.8)	289(22.2)	0.000
Hypercholesterolemia	22(3.8)	61(4.7)	0.392
Hepatic impairment	16(2.8)	36(2.8)	0.996
Renal impairment	33(5.7)	82(6.3)	0.624
Smoking	24(4.2)	52(4.0)	0.872
Alcoholic	29(5.0)	63(4.8)	0.868
Pre bleeding episode	7(1.2)	16(1.2)	0.974
Concomitant malignant disease	9(1.6)	39(3.0)	0.068
CHADS2	1.4±1.3	1.3±1.2	0.205
CHADS2-VASc	2.6±1.7	2.4±1.7	0.237
HAS-BLED	1.5±1.0	1.4±1.0	0.333

Baseline Characteristics of Study Patients

	CI(n=1,279)	NU(n=598)	P
Male, n (%)	680(53.2)	332(55.5)	0.341
Age	66.4±11.7	69.7±10.7	0.000
Age>75 , n (%)	343(26.8)	220(36.8)	0.000
HTN, n (%)	473(37.0)	306(51.2)	0.000
DM, n (%)	268(21.0)	130(21.7)	0.698
CHF, n (%)	330(25.8)	61(10.2)	0.000
Pre TIA or stroke, n (%)	116(9.1)	345(57.7)	0.000
Hypercholesterolemia, n (%)	65(5.1)	18(3.0)	0.042
Hepatic impairment, n (%)	38(3.0)	14(2.3)	0.438
Renal impairment, n (%)	91(7.1)	24(4.0)	0.009
CAD, n (%)	196(15.3)	62(10.4)	0.004
Smoking, n (%)	39(3.0)	37(6.2)	0.001
Alcoholic, n (%)	45(3.5)	47(7.9)	0.000
Pre bleeding episode, n (%)	17(1.3)	6(1.0)	0.550
Concomitant malignant disease	36(2.8)	12(2.0)	0.301
CHADS2	1.0±1.1	2.0±1.3	0.000
CHADS2-VASc	2.1±1.5	3.4±1.7	0.000
HAS-BLED	1.2±1.0	2.0±1.0	0.000

Definition
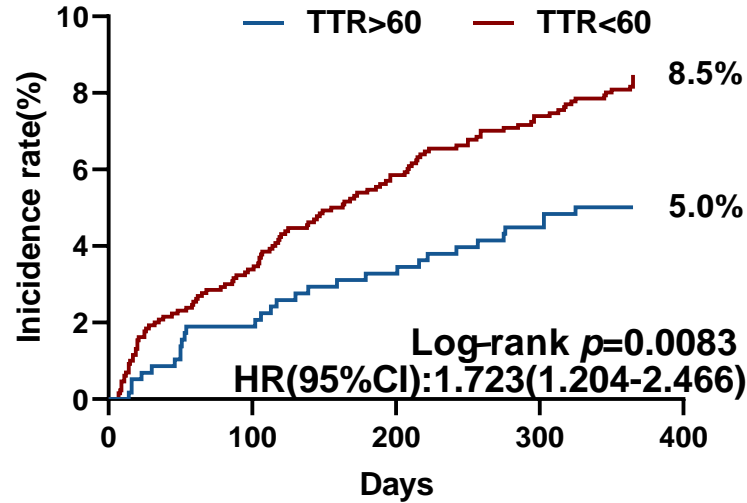
- The target INR of TTR is 2.0 to 3.0
  - ✓ Low INR>50 were defined : the percentages of low INR under 2 exceeding 50%
  - ✓ High INR>50 were defined : the percentages of high INR over 3 exceeding 50%

- The bleeding is definited by BRAC type bleeding
  - ✓ Type 3a : Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL; transfusion with overt bleeding
  - ✓ Type 3b : Overt bleeding plus hemoglobin drop < 5 g/dL ; cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents
  - ✓ Type 3c : Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
  - ✓ Type 5a : Probable fatal bleeding
  - ✓ Type 5b : Definite fatal bleeding

Results

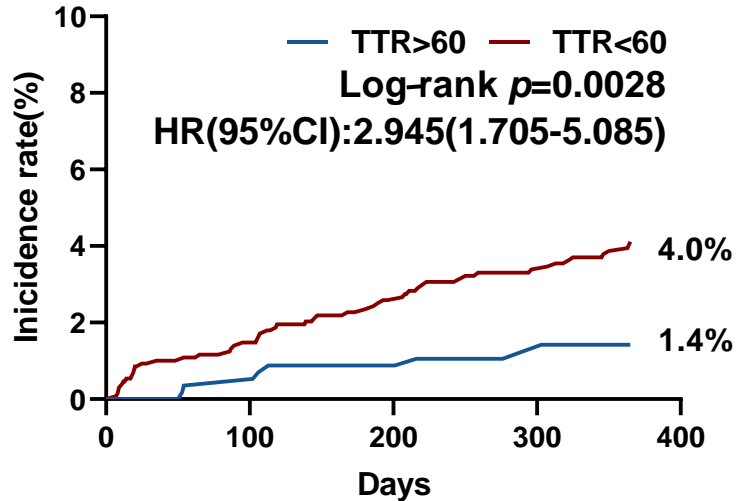|	CI(n=1,279)	NU(n=598)	P	Total(n=1877)
TTR, mean±SD	36.0±32.2	48.6±33.6	0.000	40±33.1
TTR≥60, n(%)	341(26.7)	238(39.8)	0.000	579(30.8)
Low INR>50, n(%)	769(60.1)	253(42.3)	0.000	1022(54.5)
HighINR>50, n(%)	14(1.1)	24(4.0)	0.000	38(2.0)
MACE	31(2.4)	29(4.8)	0.005	60(32)
Ischemic Stroke	15(1.2)	7(1.2)	0.997	22(1.2)
Non-fatal MI	7(0.5)	0(0.0)	0.070	7(0.4)
All cause death	8(0.6)	18(3.0)	0.000	26(1.4)
Bleeding	48(3.8)	43(7.2)	0.001	91(4.8)
BRAC type 3	46(3.6)	35(5.9)	0.025	81(4.3)
BRAC type 5	2(0.2)	8(1.3)	0.002	10(0.5)

Results: MACE + Bleeding

Results

MACE

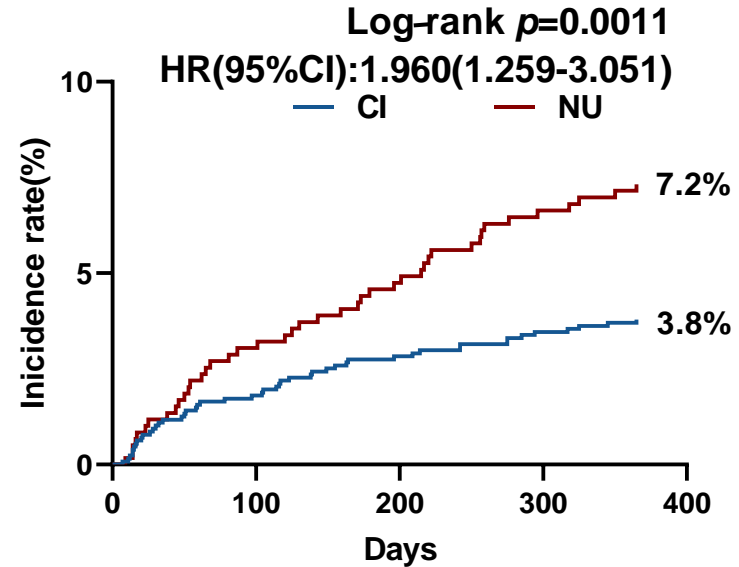TTR>60 — TTR<60
Log-rank *p*=0.0028
HR(95%CI):2.945(1.705-5.085)

4.0%

1.4%

Bleeding

TTR>60 — TTR<60
Log-rank *p*=0.1467
HR(95%CI):1.424(0.9140-2.218)

5.3%

3.8%

Results:

MACE

Log-rank *p*=0.0045
HR(95%CI):2.051(1.189-3.540)

Bleeding

Log-rank *p*=0.0011
HR(95%CI):1.960(1.259-3.051)

Results

MACE

Log-rank *p*=0.0051

Bleeding

Log-rank *p*=0.2216

Legend: TTR>60, Low INR> 50, HighINR>50
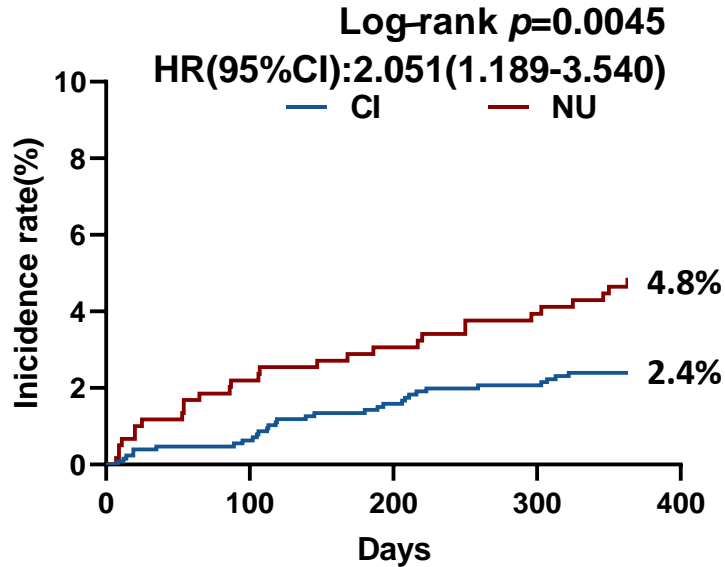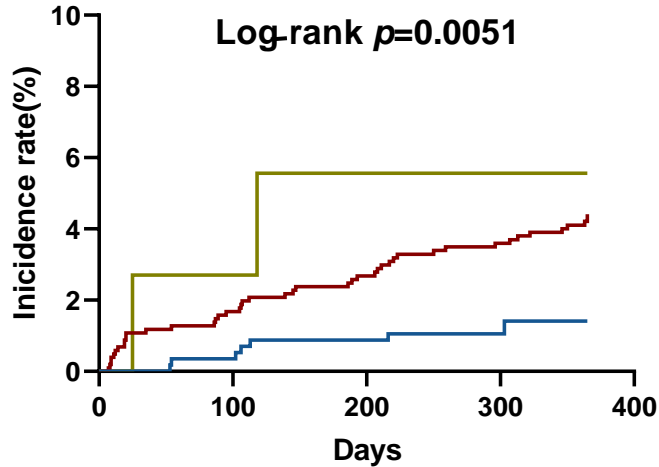
MACE	n(%)	HR(95%CI)	P
TTR>60(n=579)	8(1.4)	reference	
Low INR>50(n=1022)	44(4.3)	3.181(1.498-6.756)	0.003
High INR>50(n=38)	2(5.3)	4.088(0.868-19.25)	0.075
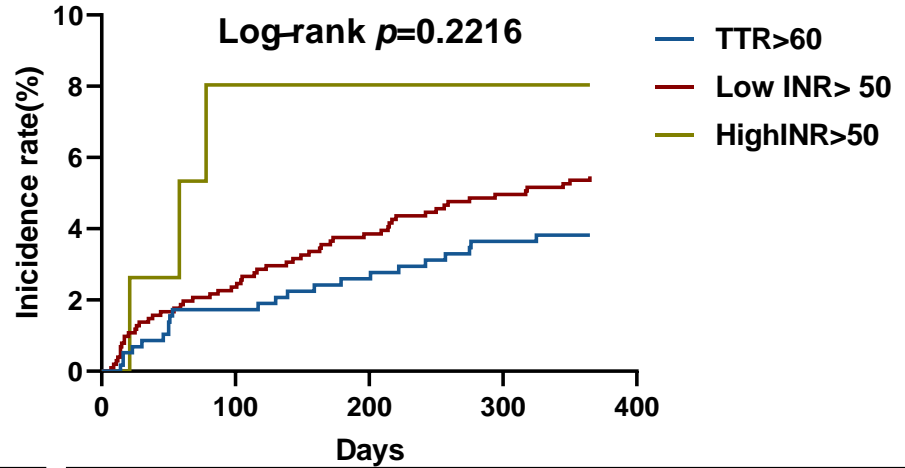
Bleeding	n(%)	HR(95%CI)	P
TTR>60(n=579)	22(3.8)	reference	
Low INR>50(n=1022)	55(5.4)	1.444(0.881-2.368)	0.145
High INR>50(n=38)	3(7.9)	2.223(0.665-7.429)	0.194

Low INR>50 and High INR>50 were defined as the percentages of low INR under 2 and high over 3 exceeding 50%.

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Results: Ischemic Stroke

Log-rank *p*=0.0096

— TTR>60
— Low INR> 50
— HighINR>50
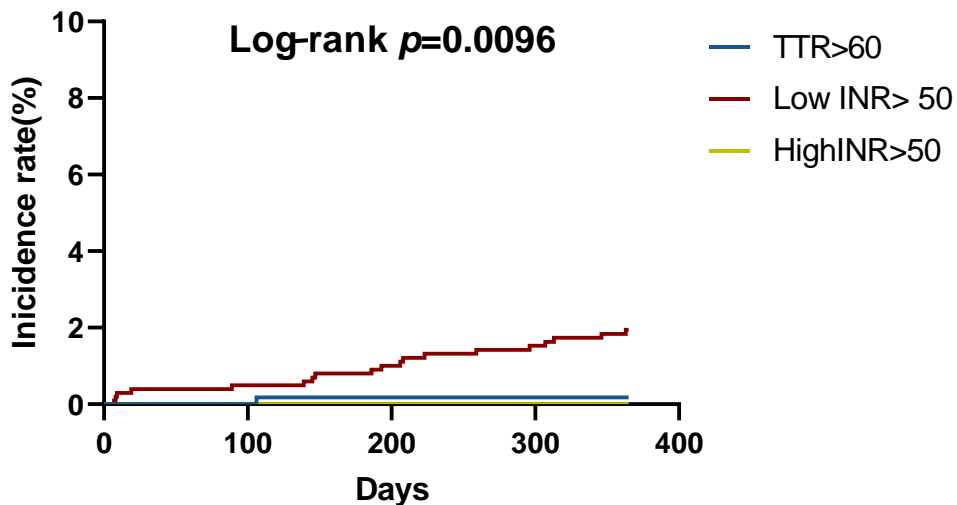
Ischemic Stroke	n(%)	HR(95%CI)	P
TTR>60(n=579)	1(0.2)	reference	
Low INR>50(n=1022)	19(1.9)	11.002(1.473-82.187)	0.019
High INR>50(n=38)	0(0.0)	0	0.982

The Low INR>50 and High INR>50 were defined as the percentages of low INR under 2 and high over 3 exceeding 50%.
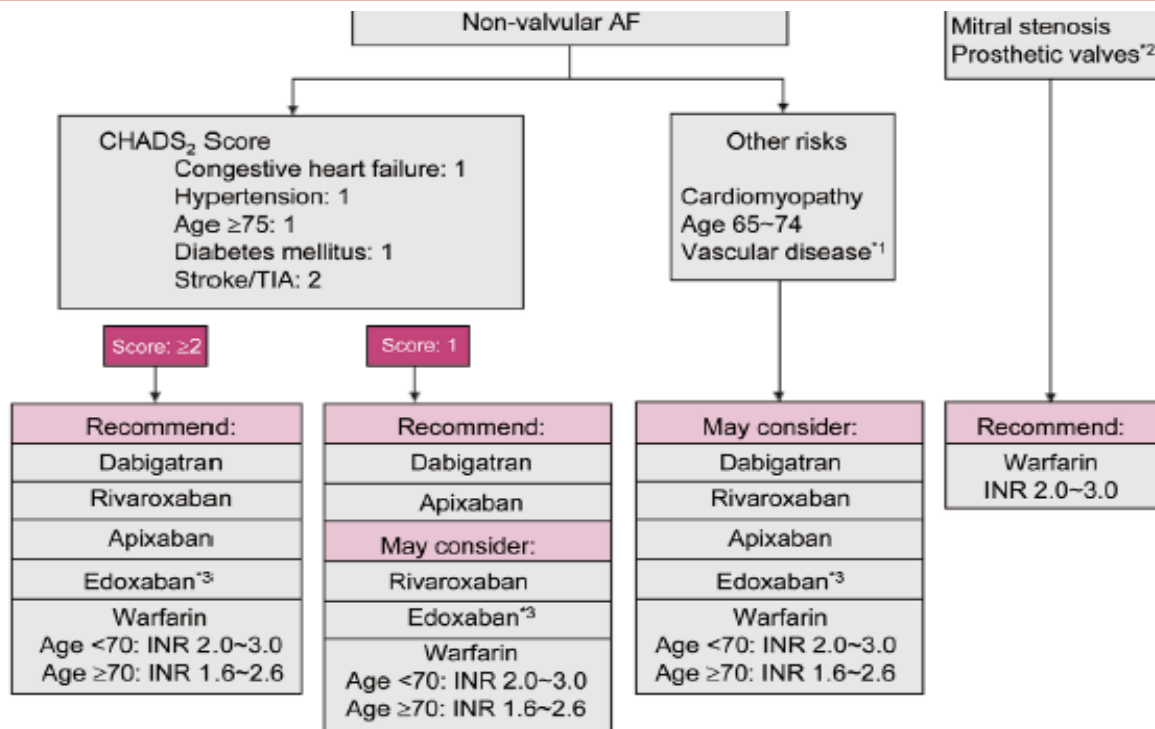
Conclusion

- Korean AF patients with higher TTR level had better 1-year outcomes than those with lower TTR level during warfarin treatment.

- Compared to cardiology, neurology patients had higher TTR range as well as MACE and bleeding.

- High INR>50 patients had higher MACE risk, Low INR>50 patients had higher ischemic stroke risk.

Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013)
– Digest Version –
JCS Joint Working Group

Non-valvular AF

CHADS$_2$ Score
Congestive heart failure: 1
Hypertension: 1
Age ≥75: 1
Diabetes mellitus: 1
Stroke/TIA: 2

Other risks

Cardiomyopathy
Age 65~74
Vascular disease[*1]

Mitral stenosis
Prosthetic valves[*2]

Score: ≥2

Recommend:
Dabigatran
Rivaroxaban
Apixaban
Edoxaban[*3]
Warfarin
Age <70: INR 2.0~3.0
Age ≥70: INR 1.6~2.6

Score: 1

Recommend:
Dabigatran
Apixaban
May consider:
Rivaroxaban
Edoxaban[*3]
Warfarin
Age <70: INR 2.0~3.0
Age ≥70: INR 1.6~2.6

May consider:
Dabigatran
Rivaroxaban
Apixaban
Edoxaban[*3]
Warfarin
Age <70: INR 2.0~3.0
Age ≥70: INR 1.6~2.6

Recommend:
Warfarin
INR 2.0~3.0

Age	Target INR range
Age≥70	1.6-2.6
Age< 70	2.0-3.0

20. Optimizing dose adjustments of vitamin-K antagonists

In spite of the preferred use of NOACs for stroke prevention in eligible patients with AF,[3] some situations still require the use of VKA, including patients with mechanical heart valves as well as those with AF in the setting of rheumatic mitral stenosis. As such, mastering VKA therapy and dosing to keep patients in the therapeutic range remains an important skillset.

Beyond the standard target INR of 2.0–3.0 much of the optimal management of VKA therapy in AF is experience - rather than evidence-based. As such, various algorithms exist for the management of different VKA[464,465] and experience in the past decades has led to different clinical routines (e.g. anticoagulation clinics, self-measurement via point-of-care devices etc.). One aspect, however, is key to success in VKA treated patients: Maintenance of a high time in therapeutic range (TTR) has been shown to reduce the risk of ischaemic and bleeding events and should be the primary goal in the treatment of these patients independent of the type management approach. Conversely, a change in the approach to these patients needs to be considered if a low TTR is consistently observed.

Table 17 Maintenance Warfarin dosing for out-of-therapeutic-range international normalized ratio

INR	Dose adjustment per week
≤1.5	↑ by 15%/week
1.6–1.9	↑ by 10%/week
2–2.9	Unchanged
3–3.9	↓ by 10%/week
4–4.9	Hold 1 dose, then restart with dose ↓ by 10%/week
≥5	Hold until INR is 2–3, then restart with dose ↓ by 15%/week

Suggested dose adjustment in case of out-of-therapeutic-range INR.[472] Importantly, dosing is optimized not using daily dose adjustments but adjustments based on the weekly intake in warfarin.

usefulness of using dosing algorithms to optimize VKA dosing and

kcj
Korean Circulation Journal

Review Article

Check for updates

2018 Korean Guideline of Atrial Fibrillation Management

Recommendations for stroke prevention in patients with AF

Recommendations	Class	Level
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B
When OAC is initiated in a patient with AF who is eligible for a NOAC, a NOAC is recommended in preference to a vitamin K antagonist.	I	A
When patients are treated with a vitamin K antagonist, TTR should be kept as high as possible (ideally aiming for TTR >65–70%) and be closely monitored.	I	A
Bleeding risk assessment should be performed for all patients with AF at every patient contact and should initially focus on potentially modifiable bleeding risk factors.	I	B
The HAS-BLED score is recommended to address modifiable bleeding risk factors in all AF patients. Those potentially at high risk (HAS-BLED score ≥3) warrant more frequent and regular reviews or follow-up.	I	A
In patients on vitamin K antagonists with consistently low time in INR therapeutic range (e.g., TTR <65%), we recommend considering interventions to improve TTR or switching to NOACs.	I	A

2019 JCR

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