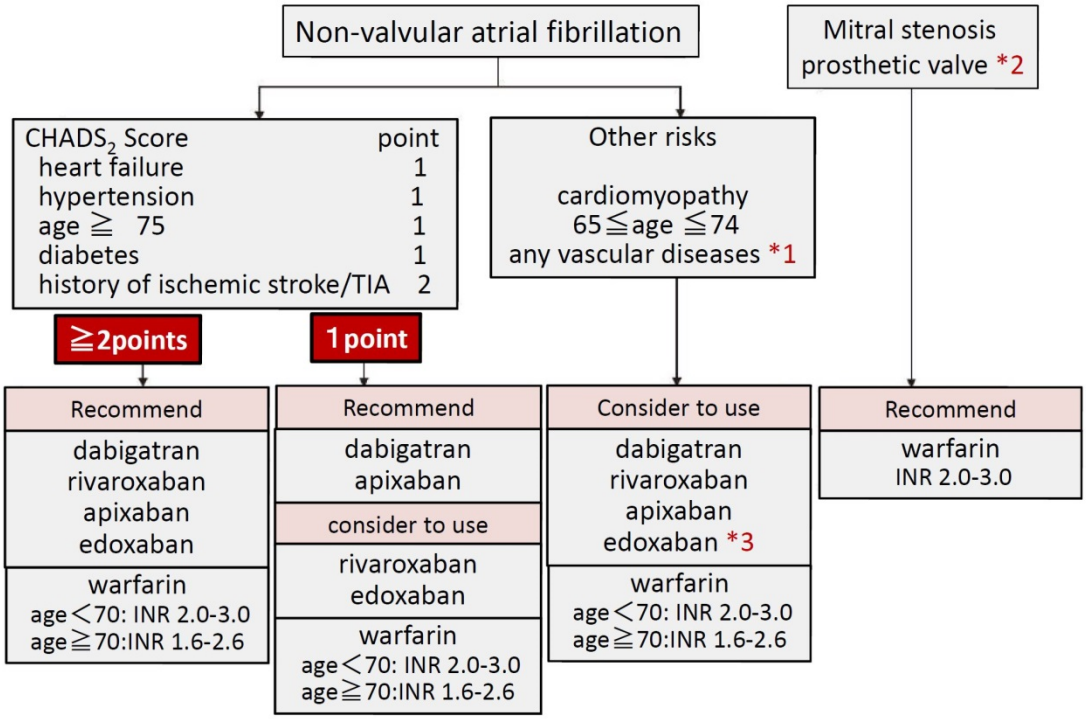
Supplementary materials

Tables and Figures in the text and supplementary Figures for the article on "dabigatran" in #2 issue of Med Check TIP, 2015 are all shown in this supplementary materials.

Supplement 1:

Recommended anticoagulant therapy by the Japanese Circulation Society



Note: New oral anticoagulants are preferable to warfarin if they have equivalent levels of recommendation.

From the reference [4] the Guidelines for Pharmacological Treatment of Atrial Fibrillation (2013 revised)

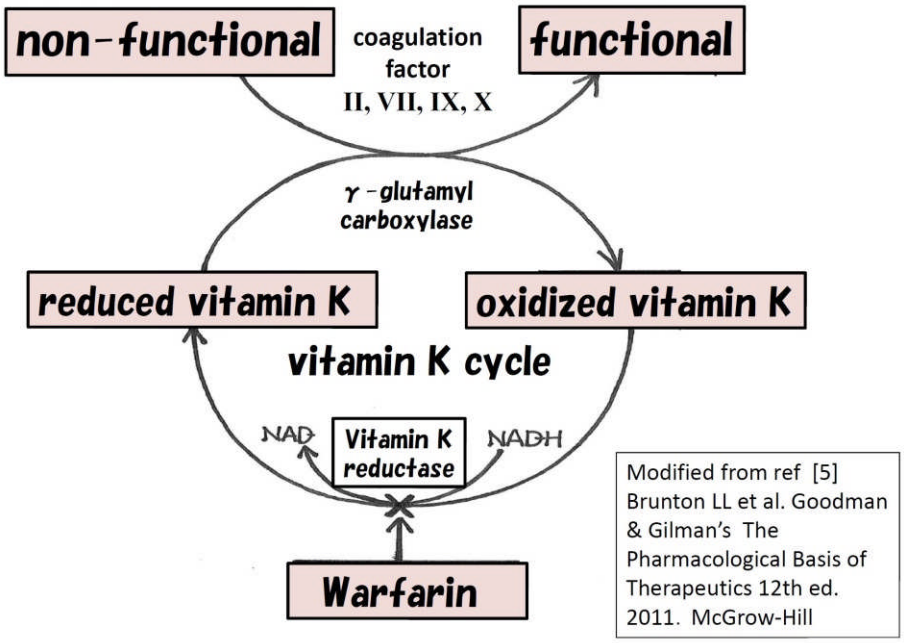
*1: Vascular diseases include past history of myocardial infarction, plaque in aorta, and peripheral vascular diseases etc.

*2: Prosthetic valves include both mechanical valves and tissue valves.

*3: This is not reimbursed by the national medical insurance as of December 2013.

An underline was added by the editorial team.

Supplement 2 : Pharmacological mechanism of action of warfarin (from ref [5] simplified)



See the text for explanation of the mechanisms

Figure 1 : Action of oral anticoagulants on coagulation factors

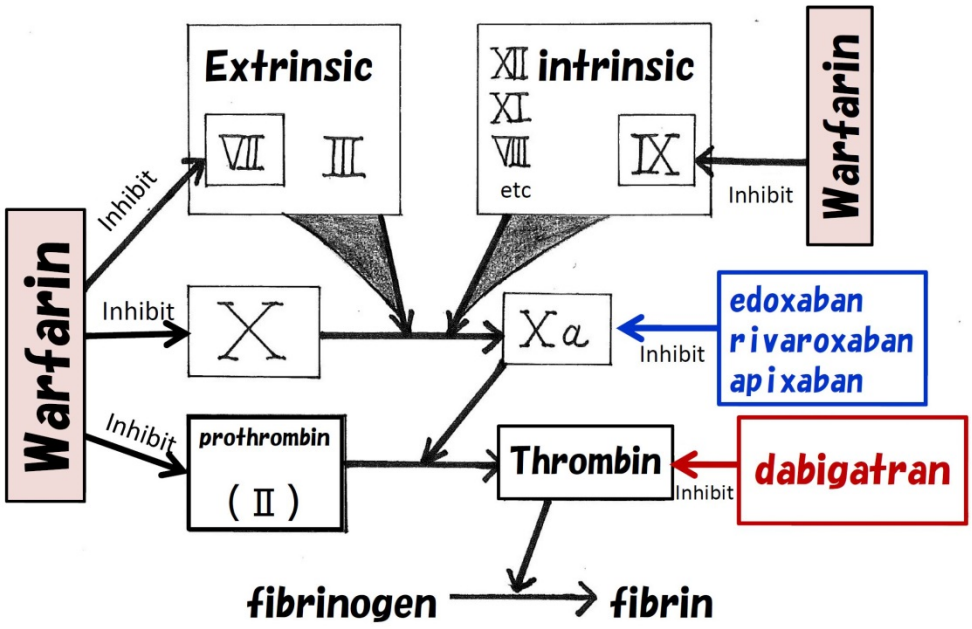
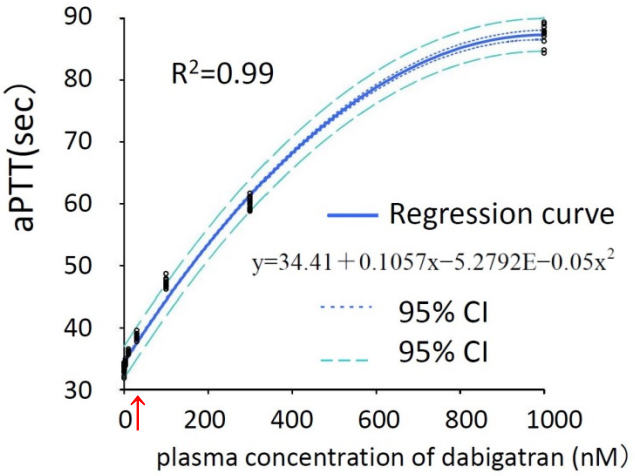


Figure 2: Correlation between concentration of dabigatran and coagulation test results: activated Partial Thromboplastin Time (aPTT）

[data from SBA[1a]

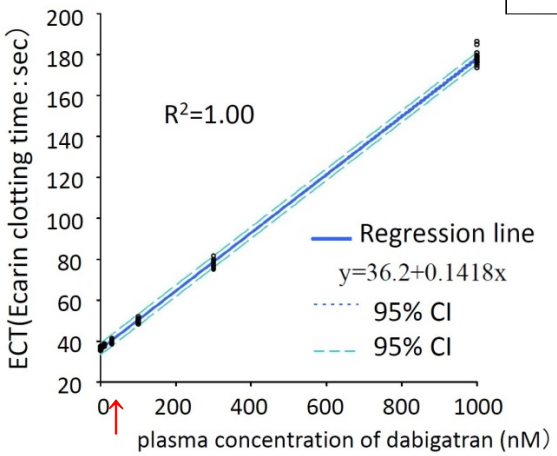


Major bleeding may increase at more than 38 nM (50 ng/mL) [ref 6]

Supplement 3: Correlation between concentration of dabigatran and coagulation test results (part 2):

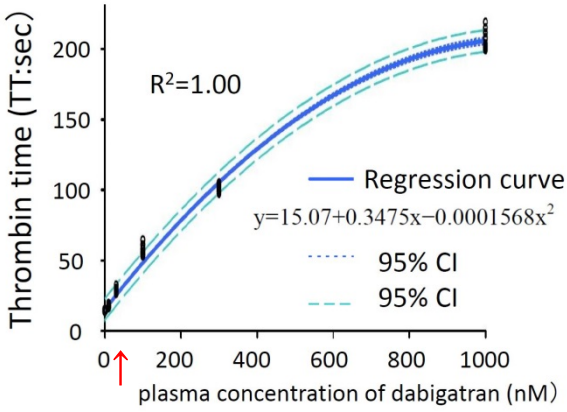
a Ecarin Clotting Time (ECT)

[data from SBA[1a]



Major bleeding may increase at more than 38 nM (50 ng/mL) [ref 6]

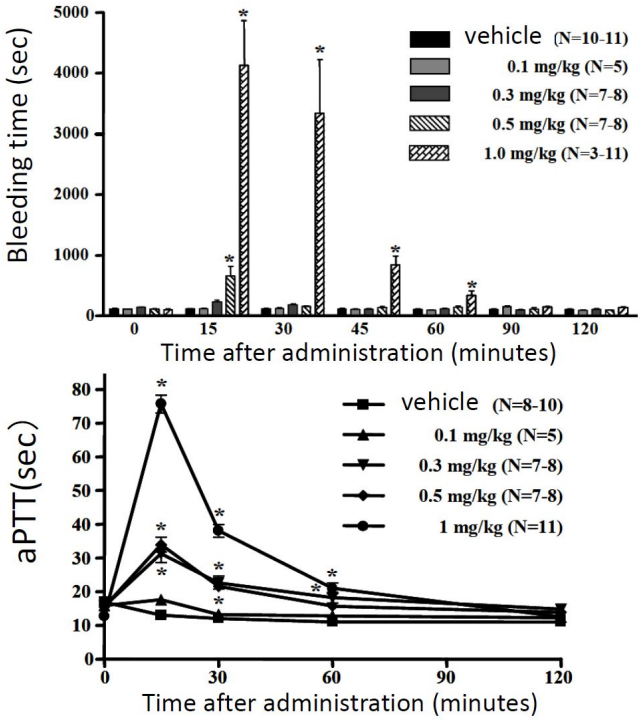
b.Thrombin time（TT）



Major bleeding may increase at more than 38 nM (50 ng/mL) [ref 6]

Figure 3：aPTT and bleeding time after dabigatran administration

[data from SBA[1a]



*: significant compared with baseline data

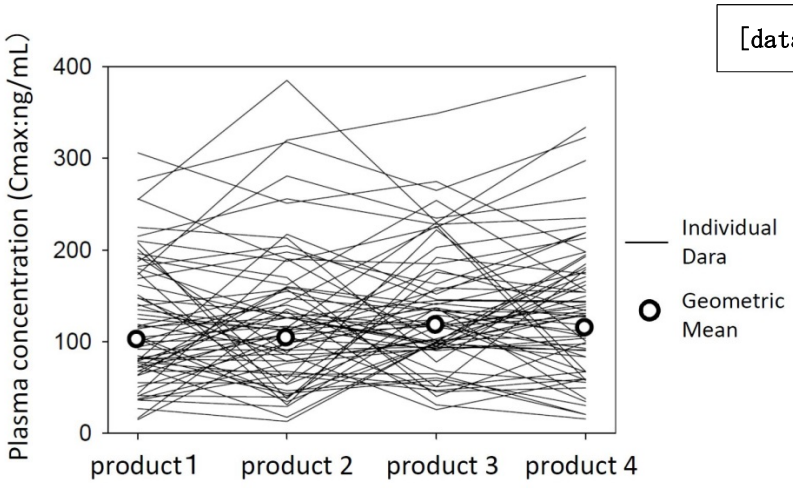
Rats were administered (i.v.) with dabigatran (D). At the time just after injection when plasma concentration may be maximum (15 min.), aPTT and the bleeding time was the most prolonged.

In the 0.3mg/kg or more groups, aPTT prolonged more than 30 sec. and bleeding time prolonged compared with control, 0.1mg/kg group and baseline data. 1mg/kg group showed more than 70 sec. of aPTT and more than 4000 sec. of bleeding time at 15 min. and showed prolonged bleeding time at 60 min. even when aPTT decreased (significantly more than the baseline data).

This may mean that bleeding time is closely related to aPTT and risk of bleeding is well predicted by aPTT.

Figure 4：Inter-individual difference of plasma concentration (Cmax) of dabigatran

[data from SBA[1a]



Inter individual difference of plasma concentration (Cmax) for older products (product 1 and 2） and newer products (product 3 and 4). According to the approximate measurement from the graph, ratio of concentration of maximum to that of minimum may be 30. Ratio up to 400 is reported **[ref. 6].**

Table 1: Summary of the RE-LY study

events	Warfarin (Wa)			dabigatran (110mg)			dabigatran (D150mg)			D110mg vs Wa		D150mg vs Wa	
	N=6022			N=6015			N=6076			OR	P	OR	P
	n	%	%/yr	n	%	%/yr	n	%	%/yr	*a	*b	*a	*b
(a) Outcome events													
Primary outcome *c	199	3.3	1.69	182	3.0	1.53	134	2.2	1.11	0.91	NS	0.66	***
Hemorrhagic stroke	45	0.7	0.38	14	0.2	0.12	12	0.2	0.10	0.31	****	0.26	****
All cause mortality	487	8.1	4.13	446	7.4	3.75	438	7.2	3.64	0.91	NS	0.88	NS
Major bleeding	397	6.6	3.36	322	5.4	2.71	375	6.2	3.11	0.80	**	0.93	NS
Net outcome *d	901	15.0	7.64	844	14.0	7.09	832	13.7	6.91	0.92	NS	0.91	*
Primary+major bleeding	596	9.9	5.1	504	8.4	4.24	509	8.4	4.22	0.83	**	0.83	**
(b) Discontinuation													
Discontinued (1 year)	608	10.2		862	14.5		935	15.5		1.49	****	1.62	****
Discontinued (2 years)	902	16.6		1161	20.7		1211	21.2		1.36	****	1.41	****
(c) Reasons of discontinuation													
patient's decision	375	6.2		440	7.3		474	7.8		1.17	*	1.25	***
outcome events	130	2.2		192	3.2		164	2.7		1.48	***	1.25	NS
serious adverse event	**105**	**1.7**		**163**	**2.7**		**166**	**2.7**		**1.55**	***	**1.57**	***
GI symptoms *e	**38**	**0.6**		**134**	**2.2**		**130**	**2.1**		**3.53**	****	**3.39**	****
GI bleeding	54	0.9		58	1.0		80	1.3		1.08	NS	1.47	*
Others	200	3.3		174	2.9		197	3.2		0.87	NS	0.98	NS

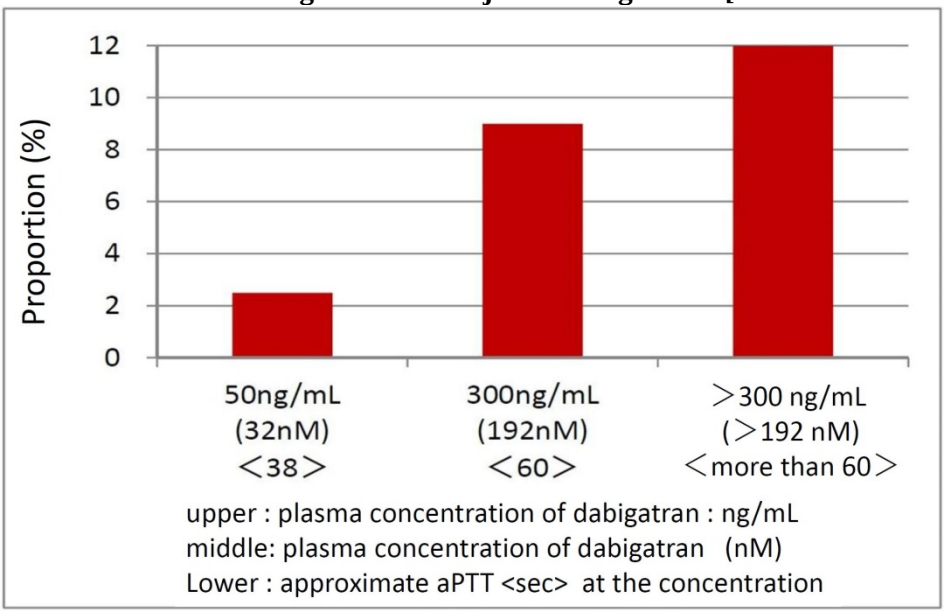
*a : OR: odds ratio *b: p value, ****:p<0.0001, ***:p<0.001, **: p<0.01, *: p<0.05, NS: p>0.05

*c: Primary outcome includes ischemic stroke or systemic embolism.

*d: Net outcome (The net clinical benefit outcome) is the composite outcome including primary outcome, pulmonary embolism, myocardial infarction, death, or major bleeding.

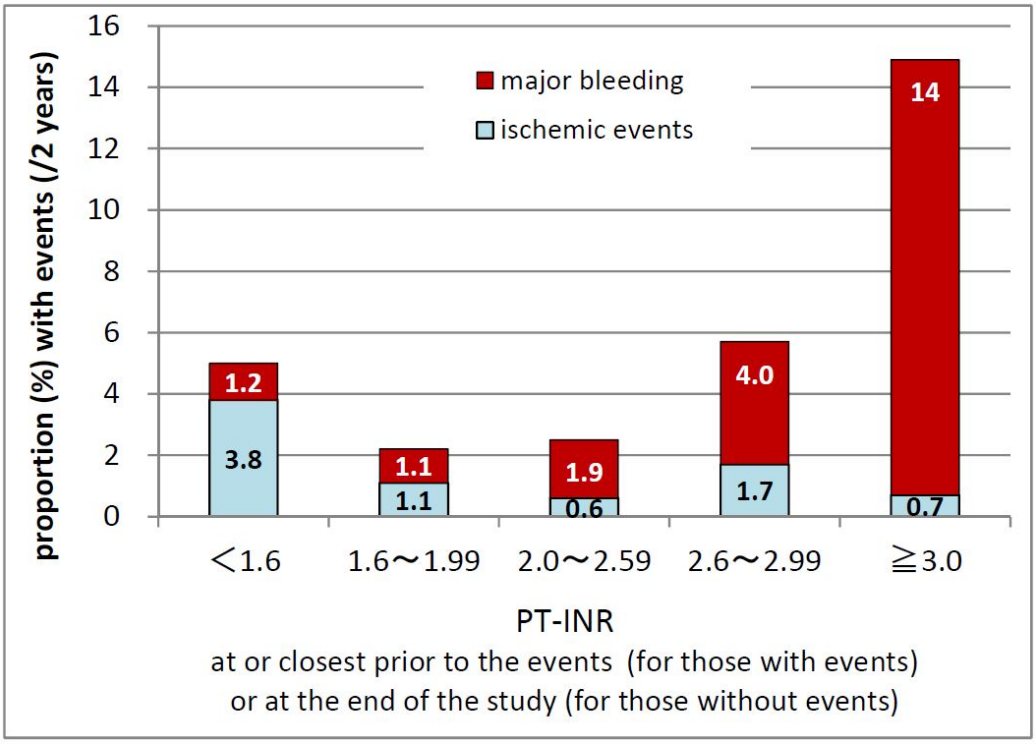
Supplement 4a:

Plasma concentration of dabigatran and major bleeding events [from data on ref. 6]



Supplement 4b:

PT-INR at or closest prior to the event and composite outcome in patients treated with warfarin*

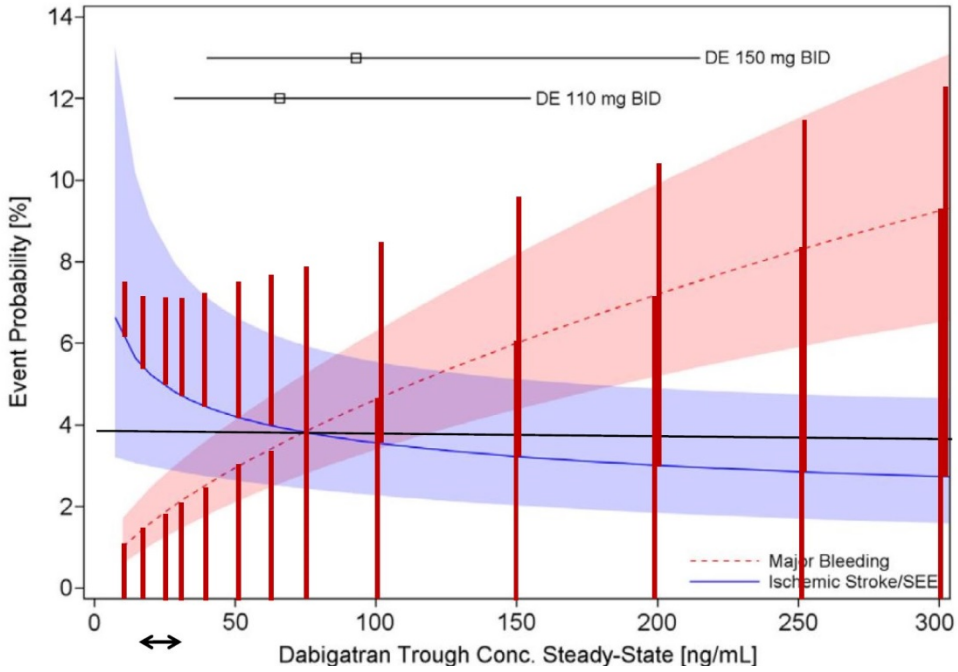


*: Reconstructed graph using the data in the ref [13b]

Optimal dose may be far lower: Subgroup analysis shows

An additional analysis using data of the RE-LY from ref [14]

Figure 5: Estimated total risk of "ischemic stroke/systemic embolism + major bleeding events" and concentration of dabigatran [ref 14] (original figure is shown as supplement 5)



Total risk of "ischemic stroke/systemic embolism + major bleeding events" is estimated by adding the risks of major bleeding on the risks of "ischemic stroke/systemic embolism + major bleeding events" as indicated by the red vertical line shown in the above (Figure 8b.
As we could consider the optimal concentration of dabigatran may be the concentration at which the **total risk of "ischemic stroke/systemic embolism + major bleeding events" is the least,** it may be about 15 ~ 30 ng/mL (11 ~ 23 nM) from the data in ref [14]. Hence not only 150mg b.i.d but also 110 mg b.i.d. may be far more compared with optimal dose.

Supplement 5: Original figure in ref [14]