THE WARFGEN service

Genotype-guided Warfarin Dosing in Local Patients Initiating Oral Anticoagulation

A Clinical Outcomes Study

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2015 JCR Joint meeting of Coronary Revascularization

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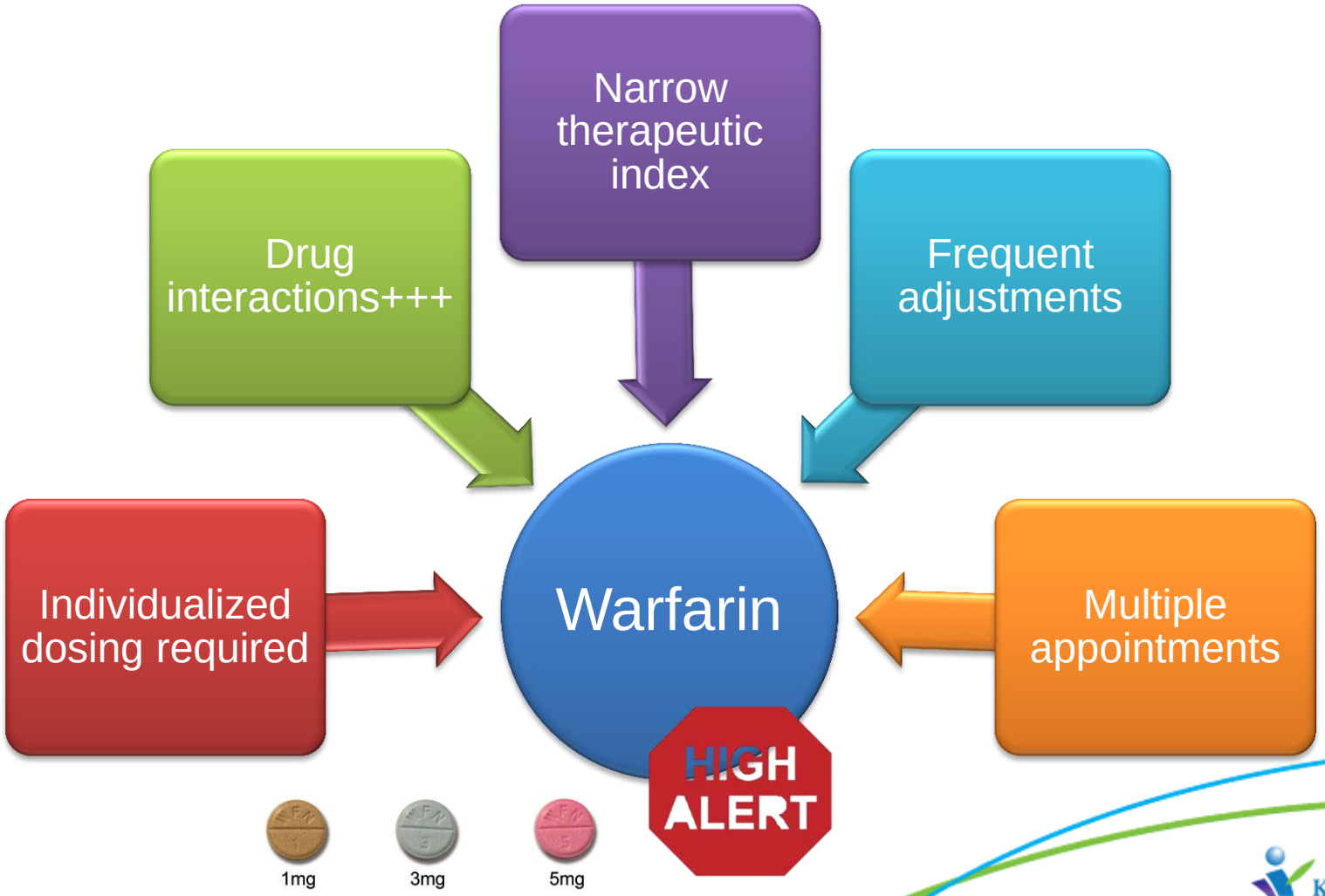
Challenges to Warfarin Management



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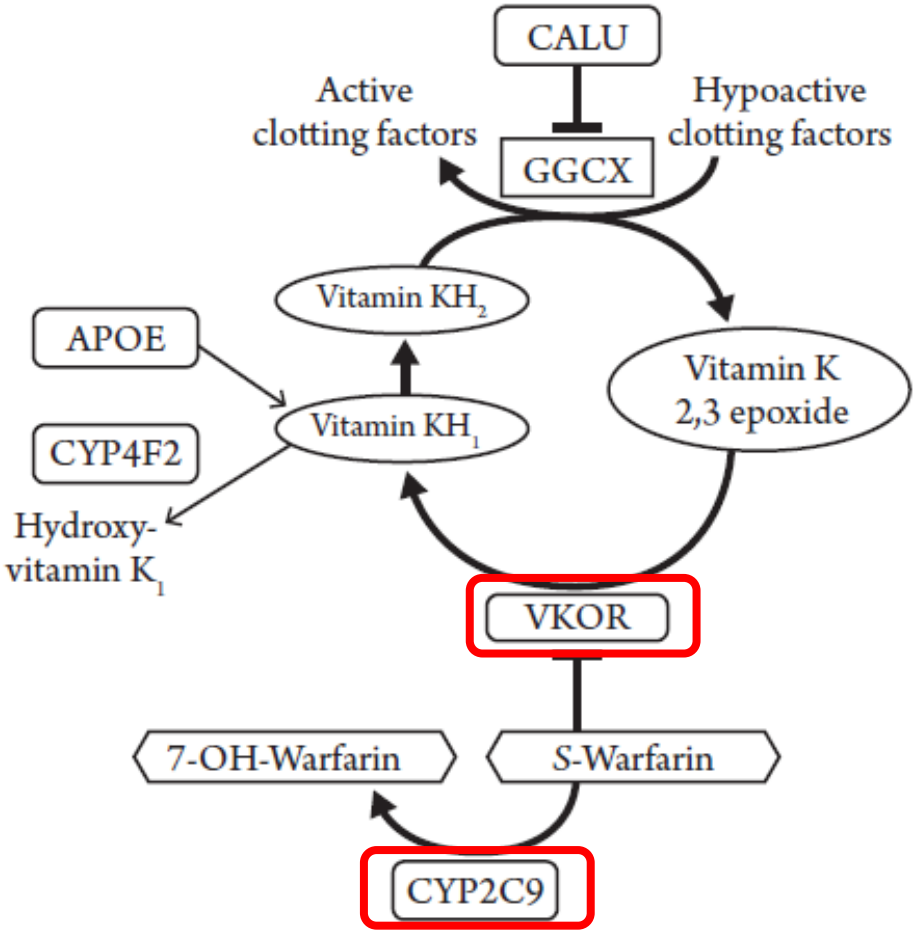
Warfarin Genotyping

Where polymorphisms occur



Vitamin K Epoxide Reductase VKOR		
GG (Wild Type)	GA (Hetero-zygous)	AA (Homo-zygous)

Cytochrome P450 2C9		
*1 (Wild Type)	*2	*3

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Warfarin Genotyping

Prevalence of common variants

Table 3. Prevalence, by Race, of common allelic variants associated with Warfarin metabolism

		Prevalence		
Gene	**Allele**	**Caucasians (%)**	**Asians (%)**	**African Americans (%)**
VKORC1	-1639A	60	99	25
CYP2C9	CYP2C9*2	20	<1	4
	CYP2C9*3	12	6-8	2
	CYP2C9*5	<1	<1	1-2
	CYP2C9*6	<1	<1	4
	CYP2C9*8	<1	<1	12
	CYP2C9*11	<1	<1	4
CYP4F2	Rs2108622: G>A	40	50	0-10

Jaekyu S, Larisa C**.** Warfarin Pharmacogenetics. Pharmacotherapy Self-Assessment Program VII Chronic Illnesses. 2009:51-65.

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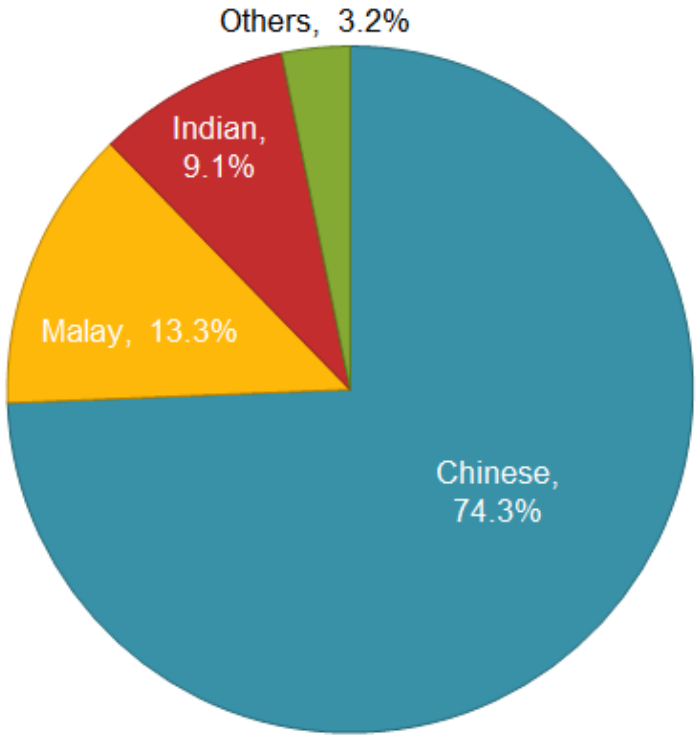
Distribution of Ethnicities
Singapore



Dept of Statistics, Singapore
http://www.singstats.gov.sg

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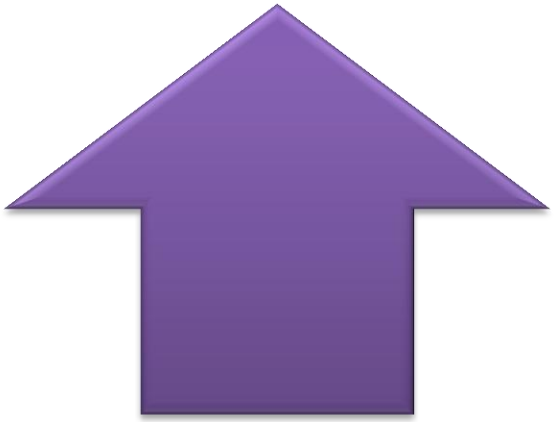
Warfarin Genotyping
What we know



Benefits[1-3]

- ↑ time within therapeutic range
- ↓ out-of-range INRs
- ↓ adverse events

Challenges

- Availability of technology in hospital setting
- Ease of day-to-day use

1. Anderson JL et al. Circulation. 2012;125(16):1997-2005.
2. Pirmohamed M et al. N Engl J Med. 2013;369(24):2294-303.
3. Epstein RL et al. Journal of the American College of Cardiology. 2010;55(25):2804-12.

The WARFGEN Project

Hypothesis

Using genotype information to guide dosing can further improve anticoagulation management in patients newly initiated on warfarin

Physician starts warfarin → Dr orders genotyping as lab test → DNA taken from existing blood sample e.g. FBC → TAT 1-day - 80% 2-day - 90% → IP Anticoag p'cist calculates predicted dose + clinical factors → Recommends to team

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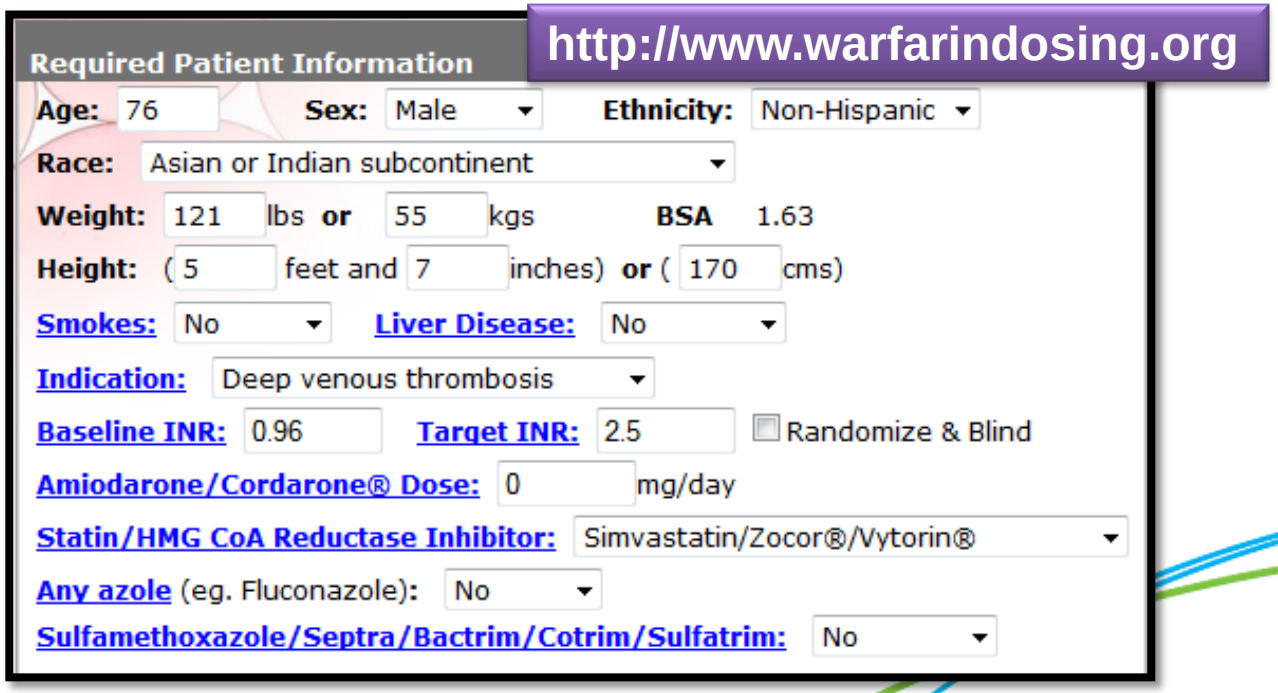
Dose Calculation

Using Dosing Algorithm

- Algorithm by Gage et al

$$\exp[0.9751 - 0.3238 \times \text{VKOR3673G>A} + 0.4317 \times \text{BSA} - 0.4008 \times \text{CYP2C9*3} - 0.00745 \times \text{age} - 0.2066 \times \text{CYP2C9*2} + 0.2029 \times \text{target INR} - 0.2538 \times \text{amiodarone} + 0.0922 \times \text{smokes} - 0.0901 \times \text{African-American race} + 0.0664 \times \text{DVT/PE}]$$

where the SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous, and race is coded as 1 if African American and 0 otherwise.



Gage BF et al. Clin Pharmacol Ther. 2008;84(3):326-31.

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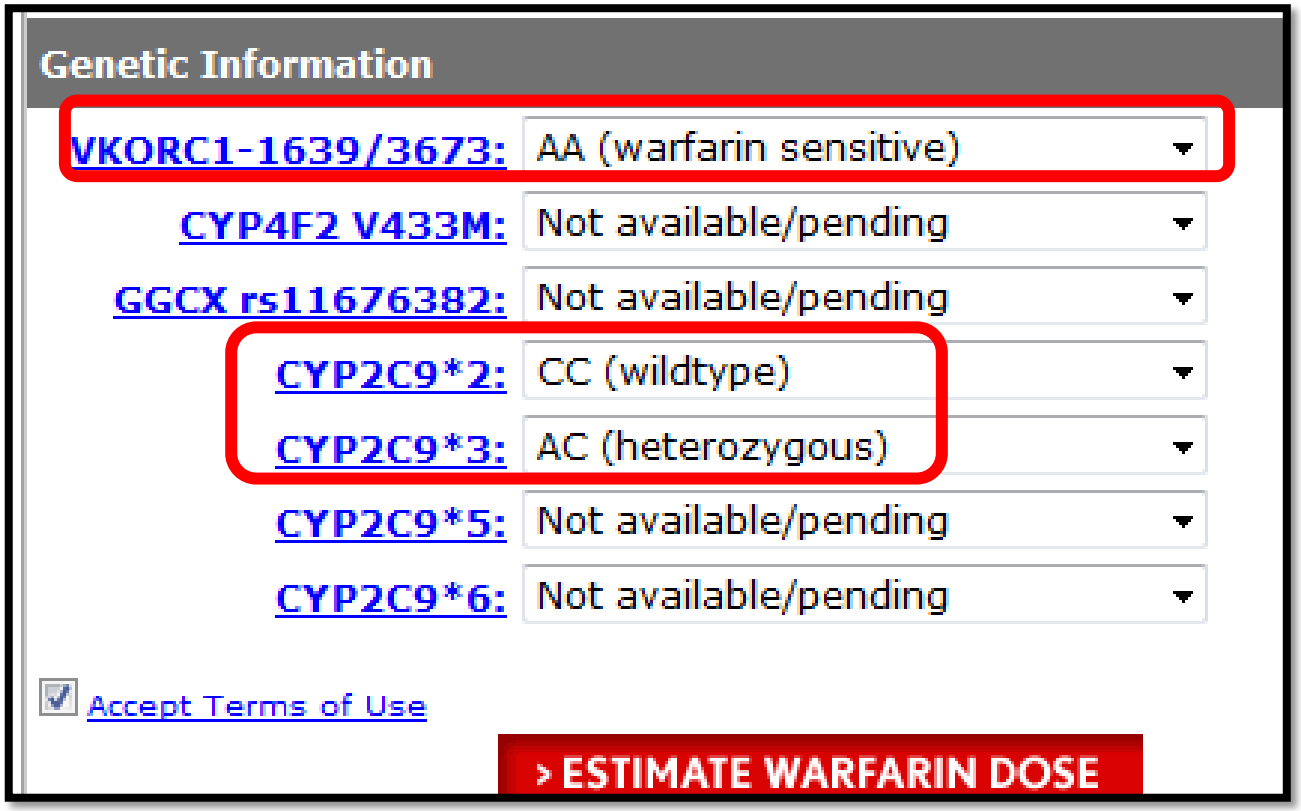

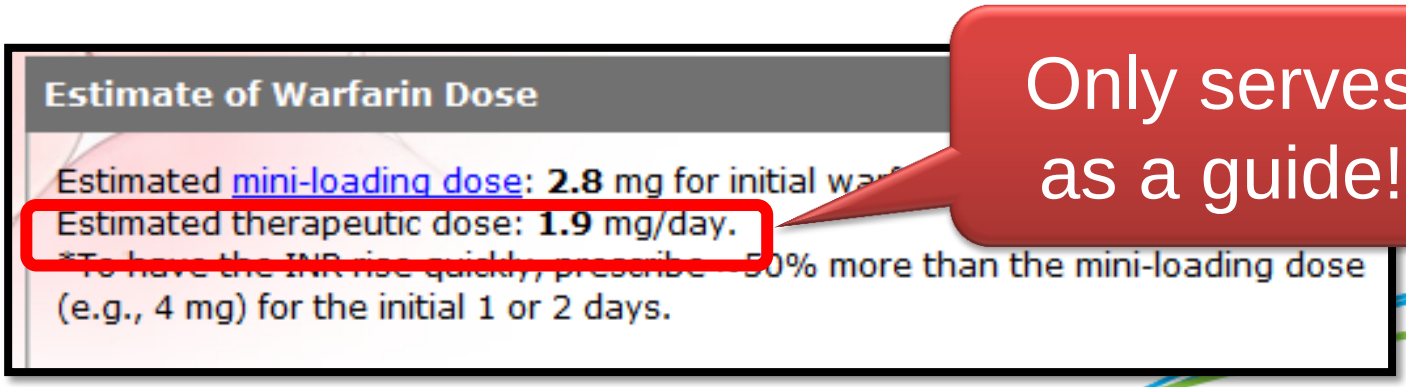

Only serves as a guide!

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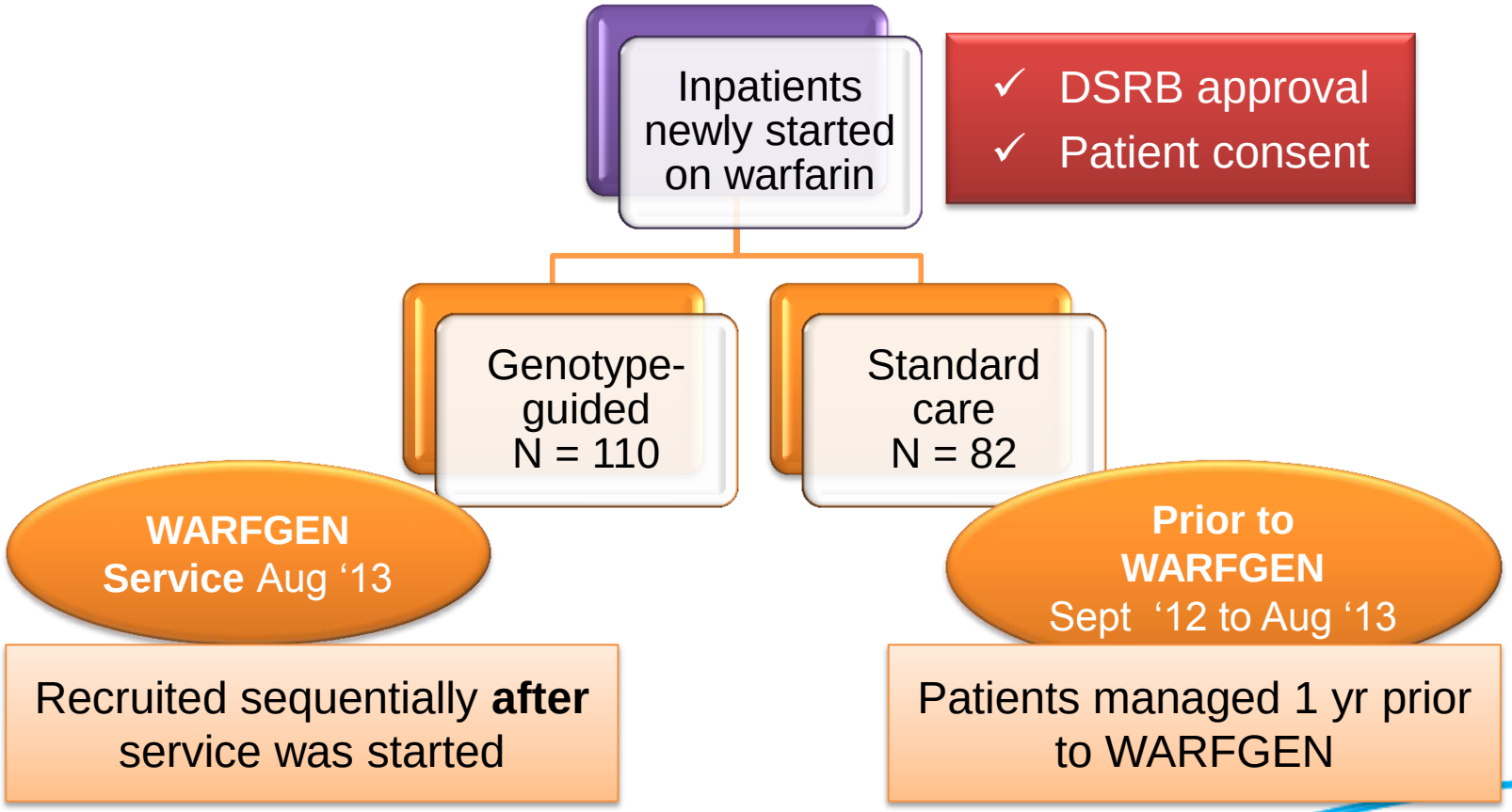
Study Design



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Clinical Outcomes Study Outcomes

1.Time-in-Therapeutic Range (%) of 1.8 – 3.2

- ‘Gold standard’ for anticoagulation management

2.Time (days) required to achieve stable dose

- Can it reduce the number of titration steps / appointments ?

3. Time (days) to reach therapeutic INR range

- Can we hit a safe range sooner?

4. Incidence of bleeding / thromboembolic events

- INR > 5

Results

Baseline Demographics

Characteristic	Standard Care Group (N=82)	Genotype-Guided Group (N=110)	P value
Age in years - mean (SD)	60.4 ± 12.5	62.4 ± 13.0	0.29
Male sex - no. (%)	33 (40.2)	47 (42.7)	0.37
Ethnic group - no. (%)			
Chinese	48 (58.5)	59 (53.6)	0.06
Malay	19 (23.2)	41 (37.3)	
Indian	11 (13.4)	9 (8.2)	
Caucasian / Others	4 (4.9)	1 (0.9)	
Weight in kg - mean (SD)	72.1 ± 17.1	66.3 ± 13.7	0.01*
CrCl ml/min Mean (SD)	100 ± 51.7	135.3 ± 62.4	<0.01*

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Characteristic	Standard Care Group (N=82)	Genotype-Guided Group (N=110)	P value
Primary indication for warfarin - no. (%)			0.058
Atrial fibrillation	25 (30.5)	45 (40.9)	
DVT / PE	37 (45.1)	33 (30.0)	
Stroke / TIA	4 (4.9)	7 (6.4)	
Valve replacement	0 (0.0)	1 (0.9)	
Intracardiac thrombus	8 (9.8)	22 (20.0)	
Acute limb ischemia	2 (2.4)	1 (0.9)	
Others	6 (7.3)	1 (0.9)	
Comorbidities that may affect INR - no. (%)			0.02*
None	67 (81.7)	67 (60.9)	
Risk of fluid overload (CHF / ESRF)	11 (13.4)	33 (30.0)	
Thyroid disorders	3 (3.7)	5 (4.5)	
Psychiatric disorders	1 (1.2)	2 (1.8)	
Malignancy / cancer	0 (0.0)	0 (0.0)	
Current use of			
Statins (any)	42 (51.2)	81 (73.6)	<0.01*
Amiodarone	0 (0.0)	7 (6.4)	0.02*
Antiplatelets	27 (32.9)	28 (23.5)	0.38
Azole antifungals	1 (1.2)	0 (0.0)	0.25

Genotype-guided group had
- More AF & IC thrombus
- Fewer VTE
- More had risk of fluid overload (↑INR)
- More on statins & amiodarone

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Distribution of Genetic Variants
N = 110

	Chinese (%) (N=59)	Malays (%) (N=41)	Indians (%) (N=9)
VKORC1 (1639G>A)			
No variants/WT	3 (5.1)	4 (9.8)	5 (55.5)
Heterozygous	14 (23.7)	19 (46.3)	3 (33.3)
Homozygous	**42 (71.2)**	18 (43.9)	1 (11.1)
CYP2C9*2			
No variants/WT			8 (88.9)
Heterozygous			1 (11.1)
Homozygous			0
CYP2C9*3			
No variants/WT			7 (77.8)
Heterozygous			1 (11.1)
Homozygous	0	0	1 (11.1)

Many warfarin sensitive: VKOR mutants

CYP2C9 mutants very rare: <1%

- ✓ Published literature
- ✓ Clinical observations
- ✓Differences between ethnicities – unique to Singapore!

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Proposal of pharmacogenetics-based warfarin dosing algorithm in Korean patients

Jung Ran Choi[1,10,11], Jeong-Oh Kim[1,11], Dae Ryong Kang[2], Seong-Ae Yoon[1], Jung-Young Shin[1], XiangHua Zhang[1], Mee Ork Roh[3], Hyung Joo Hong[3], Young-Pil Wang[4], Keon-Hyon Jo[4], Kwang-Soo Lee[5], Ho-Jung Yun[6], Yong-Seog Oh[6], Ki-Dong Yoo[7], Hee-Gyeong Jeon[8], Yoon Sook Lee[9], Tae Sun Kang[9], Hyun-Joo Park[9], Myeon Woo Chung[9] and Jin-Hyoung Kang[1,3]

Warfarin is a commonly prescribed anticoagulant drug for the prevention of thromboembolic disorders. We investigated the contribution of genetic variations of four genes and clinical factors to warfarin dose requirement and provided a warfarin-dosing

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TT (homozyg)	87.4
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Choi JR et al. J Hum Genet. 2011;56(4):290-5.

Pharmacogenetic distribution of warfarin and its clinical significance in Korean patients during initial anticoagulation therapy

Aerin Kwon · Sang-Ho Jo · Hyoung-June Im · Yun-A Jo · Ji-Young Park · Hee Jung Kang · Han-Sung Kim · Hyoun Chan Cho · Young Kyung Lee

VKORC1 1639	N (%)
AA (homozyg)	89.0
GA (heterozyg)	11.0
GG (wild)	0.0
CYP2C9	**N (%)**
*1 / *1 (wild)	87.0
*1 / *3 (het var)	11.0
*3 / *3 (homo var)	2.0

Kwon A et al. J Thromb Thrombolysis. 2011;32(4):467-73.

Similar to S'poreans of Chinese ethnicity

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Clinical Outcomes Study
Primary Outcomes

Outcomes	Standard Care (N = 82)	Genotype-guided (N = 110)	P value
Mean 90-day Time In Therapeutic Range (%)	**72.3** (± 25.5) (N=81)	**70.9** (± 23.3) (N=104)	*0.46*
Time (days) to achieve stable dose	**11.0** ± 27.2	**10.0** ± 18.8	*0.70*
Time (days) to achieve therapeutic INR	**6.0** ± 12.6	**5.2** ± 17.4	*0.67*
Adverse events (no.) **Incidence of INR ≥ 5** **Bleeding / TE**	 **2** 0	 10 0	 -

No significant difference in outcomes

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Clinical Outcomes Study
Primary Outcomes

Outcomes	Standard Care (N = 81)	Genotype-guided (N = 104)	P value
Mean 90-day Time In Therapeutic Range (%)	**72.3** (± 25.5)	**70.9** (± 23.3)	*0.46*

Landmark Trial	Mean TTR	Singapore's TTR
RE-LY (dabigatran)	64%	68%
ROCKET-AF (rivaroxaban)	55%	
ARISTOTLE (apixaban)	62%	68%
AVERRROES (apixaban)	64%	

Study TTR > than published literature

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Algorithm Performance Prediction Accuracy - Gage et al

- Mean overestimation of

  0.4 ± 1.3 mg/day

  - i.e., actual doses are lower
  - Possibly:
    - Clinical factors
      - » e.g. fever, sepsis, fluid overload
    - Factors unaccounted for

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Algorithm Performance
Comparison of Predictive Accuracy

$$10\left[\exp\left(0.838 - 0.005 \times \text{Age} + 0.003 \times \text{Weight} - 0.189 \times \textit{CYP2C9}*3 - 0.283 \times \textit{VKOR}\ 381\ \text{CC} - 0.119 \times \textit{VKOR}\ 381\ \text{TC}\right)\right]$$

Warfarindosing.org

Gage et al-based prediction

$R^2 = 0.95$

Tham et al prediction[1]

$R^2 = 0.69$

$R^2 = 0.68$

Actual stable dose

Better algorithm needed!

Tham LS et al. Clin Pharmacol Ther. 2006;80(4):346-55.

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Discussion
Achievements

- Fully operational PGx dosing service in KTPH
- Relevance of genotyping established
  - Large % do have high warfarin sensitivity
  - Springboard for Warfarin Genotype Registry
    - Collaboration with International Groups
- Evaluated performance of published algorithms in our population
  - Gage vs Tham et al.


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Further Research

Moving forward

- Benefit for special populations
  - CKD ± dialysis
  - Multiple comorbidities
  - Drug interactions
    - Rifampicin (pTB)
- Impact of other genes
  - CYP 4F2, yet-to-be-discovered

THE WARFGEN service

Genotype-guided Warfarin Dosing in Local Patients Initiating Oral Anticoagulation

A Clinical Outcomes Study

Thank you

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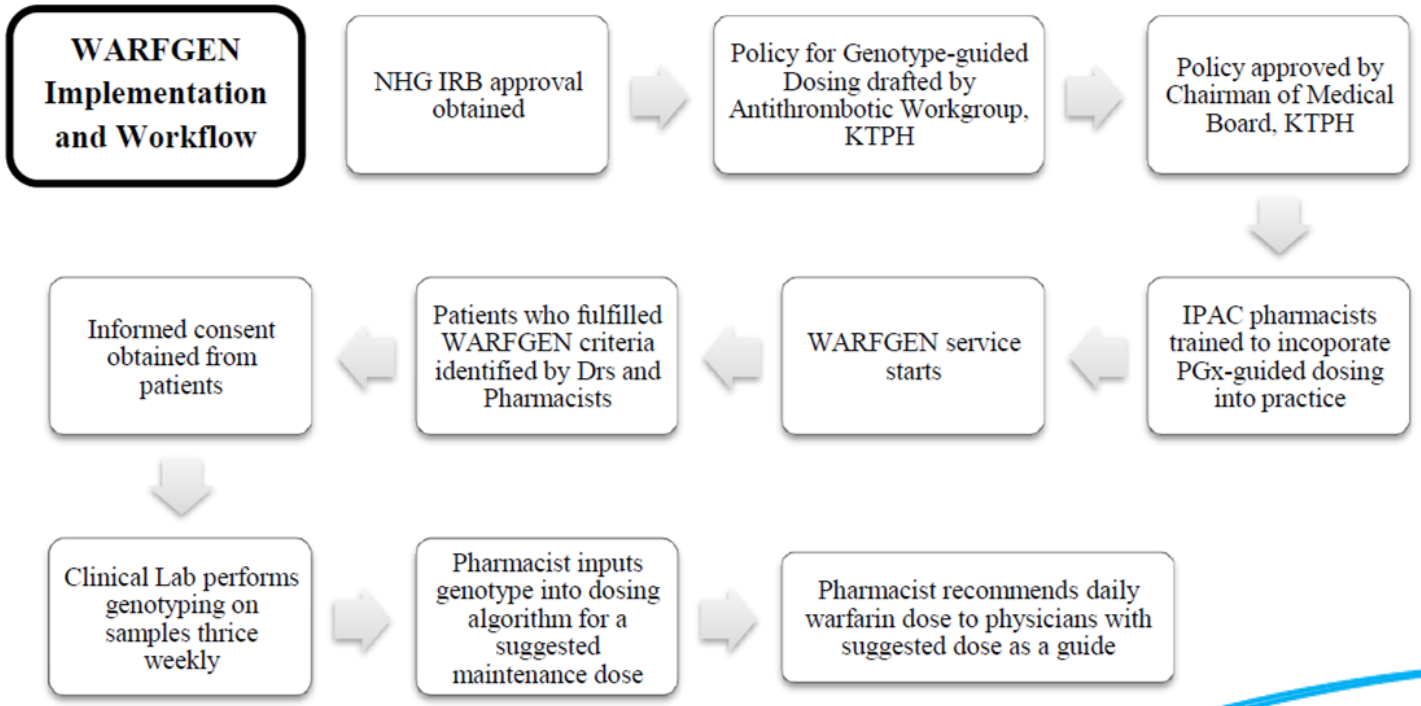
Backup Slides

WARFGEN – 3 phases

PHASE 2: Implementation of the KTPH Genotype-guided Dosing Service



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New Oral Anticoagulants vs. Warfarin Treatment: No Need for Pharmacogenomics?

WL Baker[1,2] and KW Chamberlin[1,2]

For patients requiring long-term anticoagulation, oral vitamin K antagonists (VKAs) such as warfarin have overwhelming efficacy data and present significant challenges. In addition to the potential exposure to numerous drug–drug and drug–food interactions, patients receiving warfarin require frequent monitoring. It had been hoped that the integration of pharmacogenomic with clinical information would improve anticoagulation control with warfarin, but trials have not supported this aim. Novel oral anticoagulants (NOACs) offer both advantages and disadvantages and deserve consideration in appropriate patients

of events, VKA therapy can be expected to prevent 15 deaths and 15 nonfatal strokes per 1,000 patients while resulting in 8 additional nonfatal major extracranial bleeds.[1] These benefits become more dramatic in individuals at higher risk.

Despite the benefits of VKAs, fewer than half of eligible patients are receiving such therapy, and many are not having it optimized. A meta-analysis of trials published in the United States showed that only 55% (95% confidence interval (CI) 51–58%) of patient treatment time is within the therapeutic international normalized ratio (INR) range (TTR).[2] Those seen in dedicated anticoagulation

ship between TTR and event rates.[3] Apart from excessively elevated or depressed values, a single INR outside the therapeutic range poses little risk. However, when patients have lower TTR than desired, significant increases in major adverse events have been seen.[3] Therefore, identifying strategies to optimize control of VKA therapy and potentially improve clinical outcomes is paramount.

Role of pharmacogenomics in warfarin dosing

Warfarin is a racemic mixture of its *R*- and *S*-enantiomers, with *S*-warfarin having the higher potency (two- to

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Baker WL, Chamberlin KW. Clinical Pharmacology & Therapeutics. 2014;96(1):17-9.

Warfarin Genotyping

Dollar$ and cents (sense)

$70 - $130

(depending on kit)

Approx cost of ONE repeat SUBS ACC Pharmacist SOC visit	
Consultation	$15
PT / INR	$16
Transport (Taxi, 2-way)	$20 x 2 = $40
Salary forgone	$20/hr x 3 = $60
Total	$131

	HEALTHASSIST	pioneer generation
Warfarin ~$3 - 6 per month	✓	✓
Rivaroxaban 20mg ~$180 per month	✗	✗

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Warfarin Genotyping

Dollars and ene

USD $60
70,000 KRW

Approx cost of ONE repeat SUBS ACC Pharmacist SOC visit (USD)	
Consultation	$15
PT / INR	$12
Transport (Taxi, 2-way)	$15 x 2 = $30
Salary forgone	$20/hr x 3 = $60
Total	**~USD $120 140,000 KRW**

	HEALTHASSIST	pioneer generation
Warfarin ~USD$2-4/mth	✓	✓
Rivaroxaban 20mg ~USD$130/mth	✗	✗

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Warfarin Genotyping

Era of NOACs

	HEALTHASSIST	pioneer generation
Warfarin ~$3 - 6 per month	✓	✓
Rivaroxaban 20mg ~$180 per month	✗	✗

Limitations on NOAC use

- Renal impairment
  - CrCl <30 ml/min or ESRD dialysis
  - No reliable form of dose adj
- Valvular AF
  - Prosthetic heart valves, sigf rheumatic heart dz
- Strong CYP3A4 and P-gp inhibitors / inducers
  - Rifampicin, azole antifungals, protease inhibitors (HIV)
- When monitoring or reversal is desired
  - E.g. bleeding, bridging, poor compliance

Superiority of NOACs in reducing bleeding was diminished when center-based TTR was ≥ 66%

How would you re-design your study?

- Time-to-event Endpoints
  - Protocolize INR taking
    - IP – every day or other day once stable
    - OP – ACC appts at weekly intervals, then longer once stable

Do we still need genotyping?

- No
  - Specialized pharmacist anticoag (IPAC / ACC) appeared to perform as well
  - NOACs (and their antidotes) are on the horizon
- Yes
  - Warfarin still the most widely used anticoagulant at present
  - Special populations need warfarin

Recent Warfarin Genotyping RCTs

Summary

Characteristics	COAG (US)[1] N = 1,015	EU-PACT (Europe)[2] N = 455
Genotyping	Genetic dosing algorithm with clinical & genotype data	
Comparator (Standard Care)	Clinical maintenance dose algorithm (age, black race, smoker, BSA, amio, target INR, DVT/PE)	Standard loading dose strategy ≤75yrs: 10, 5, 5mg >75yrs: 5, 5, 5mg f/b "local clinical practice"
Median Time to Therapeutic INR	Not reported	21 vs 29 days (p<0.001)
Median Time to Stable Dose	Not reported	44 vs 59 days (p=0.003)
Time-In-Therapeutic Range	45.2% vs 45.4% (p=0.91)	67.4% vs 60.3% (p<0.001)
Incidence of INR≥4	19.5% vs 18.4% (p=0.59)	27.0% vs 36.6% (p=0.03)

1. Kimmel SE et al. NEJM 2013;369(24):2283-93.
2. Pirmohamed M et al. NEJM 2013;369(24):2294-303.

TTR Performance (RE-LY)
By Geographical Region

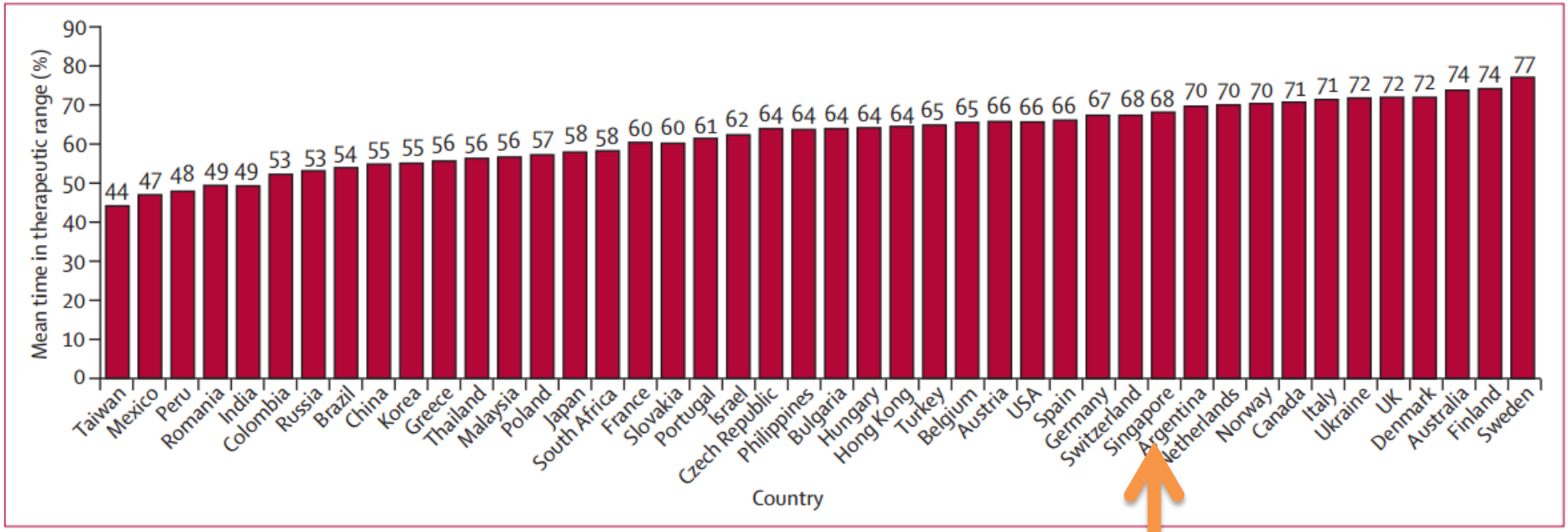
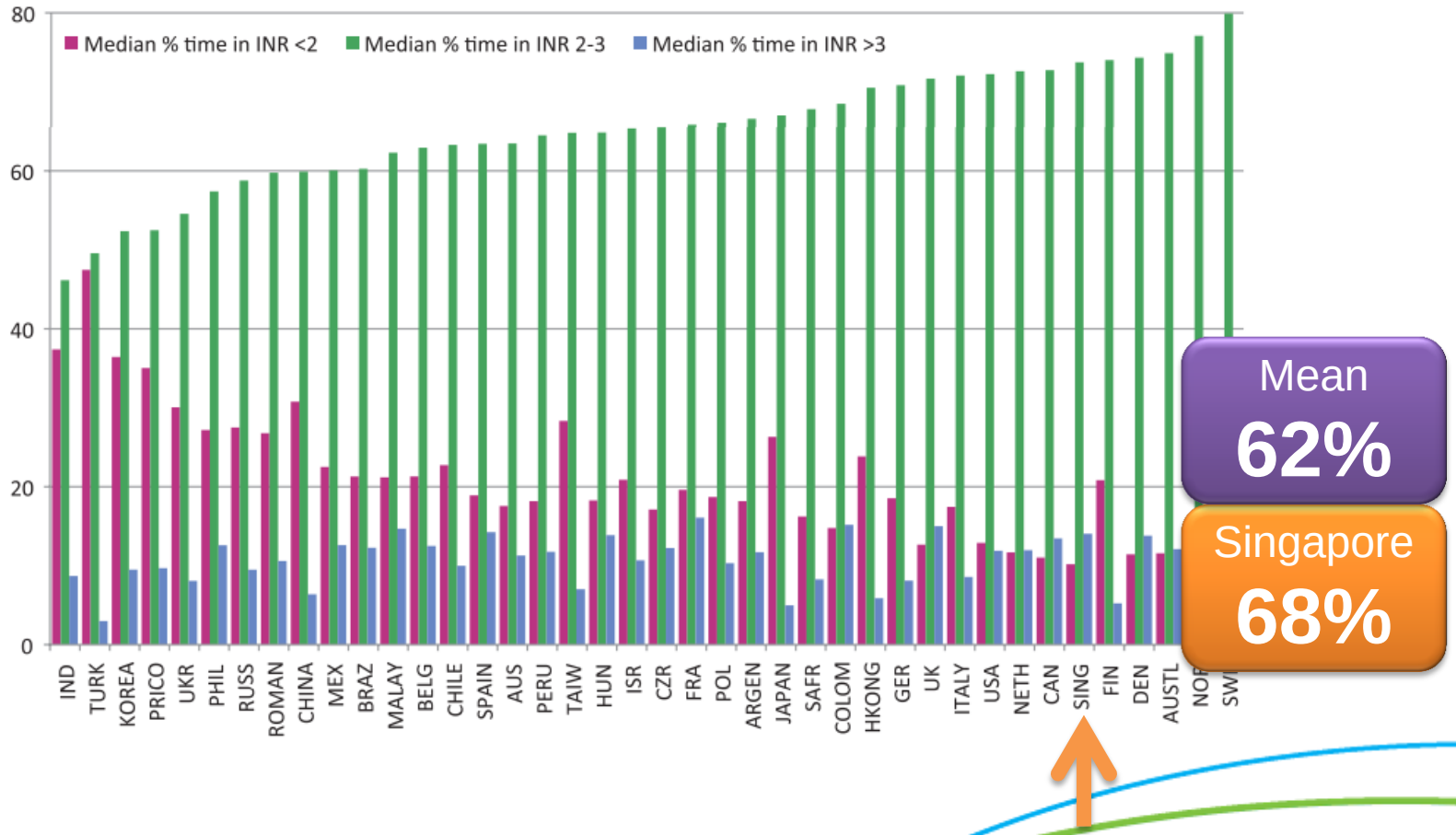


Figure 1: **Country distribution of mean time in therapeutic range in the RE-LY trial**

Mean	Singapore
64%	68%

Wallentin L, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of INR control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. The Lancet; 376(9745):975-83.

TTR Performance (ARISTOTLE)
By Geographical Region



Wallentin L et al. Efficacy and Safety of Apixaban Compared With Warfarin at Different Levels of Predicted International Normalized Ratio Control for Stroke Prevention in Atrial Fibrillation. Circulation. 2013;127(22):2166-76.

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Genetic Variants

Singapore vs Korea – Similarities

	Singapore Chinese
VKORC1 (1639G>A)	
No variants/WT	3 (5.1)
Heterozygous	14 (23.7)
Homozygous	**42 (71.2)**
CYP2C9*2	
No variants/WT	59 (100)
Heterozygous	0
Homozygous	0
CYP2C9*3	
No variants/WT	53 (89.8)
Heterozygous	6 (10.2)
Homozygous	0

70% homozygous variant
90% at least 1 variant

100% wild type
Variants are absent

90% wild type
10% heterozyg variants

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