Ethnic Differences in Genetic Frequency and Warfarin Dose

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Background

- Warfarin is an effective oral anticoagulant for preventing and treating for the thromboembolic diseases such as atrial fibrillation(AF) , heart valve replacement, deep venous thrombosis and pulmonary embolism.

J Am Coll Cardiol; 2007;50:2156–61

Circulation; 2003;107:1692-1711

Background

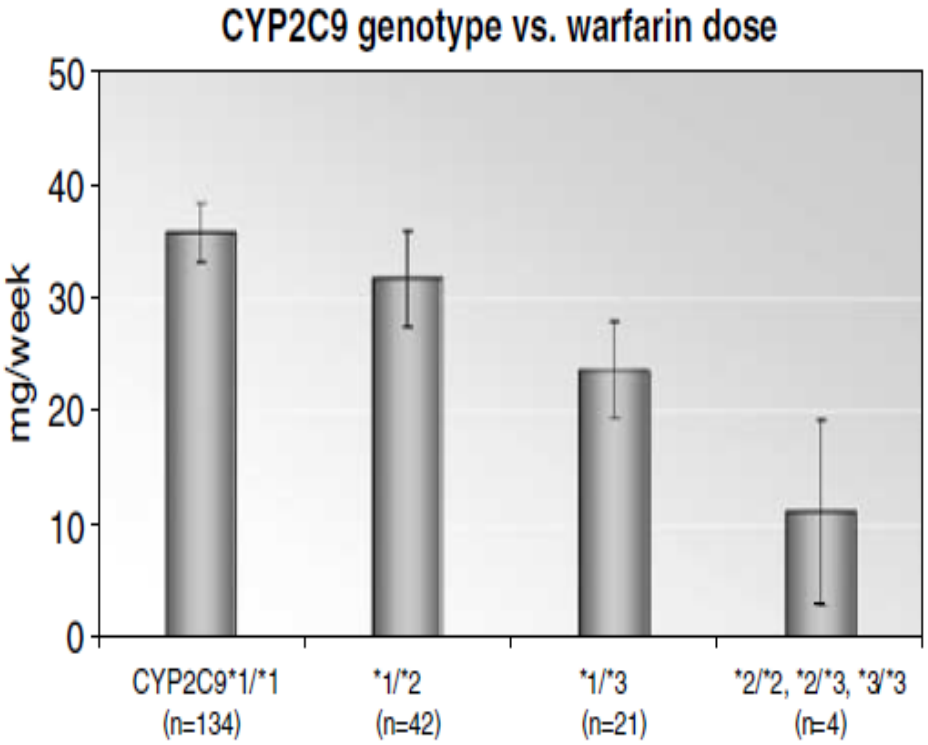
- Determining optimal warfarin dose(OWD) is challenging due to warfarin disadvantages

- Several studies exhibited that CYP2C9 , VKORC1 and CYP4F2 genetic polymorphism (GP) affect OWD, but the impact of GP on OWD in Koreans is unclear

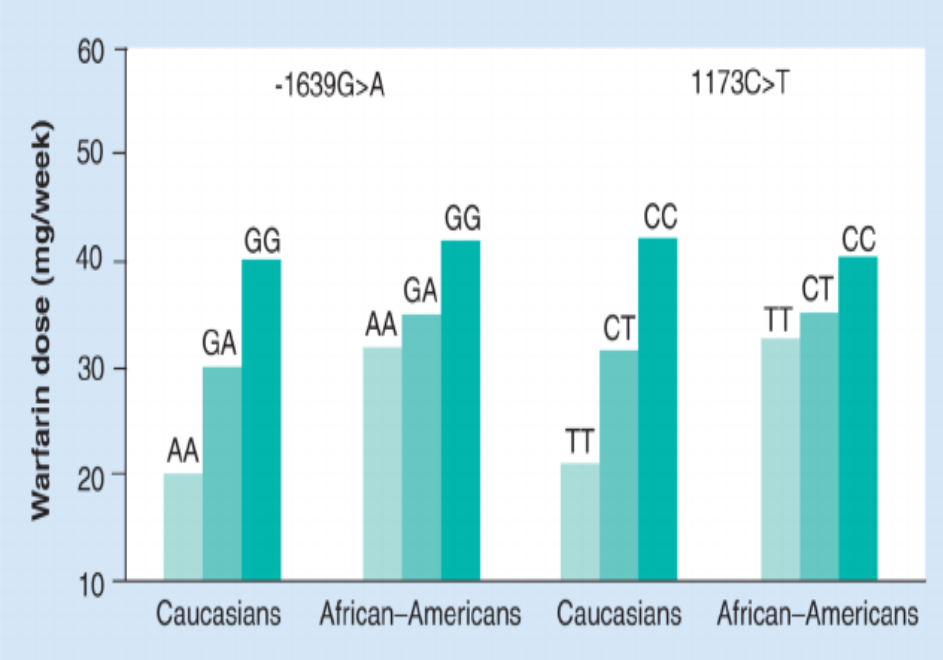
Circulation; 2012;125:1997-2005

Intern Med J Exper Clin Res; 2015;21:3577-3582

Background(Caucasian)



VKORC 1 genotype vs. warfarin dose

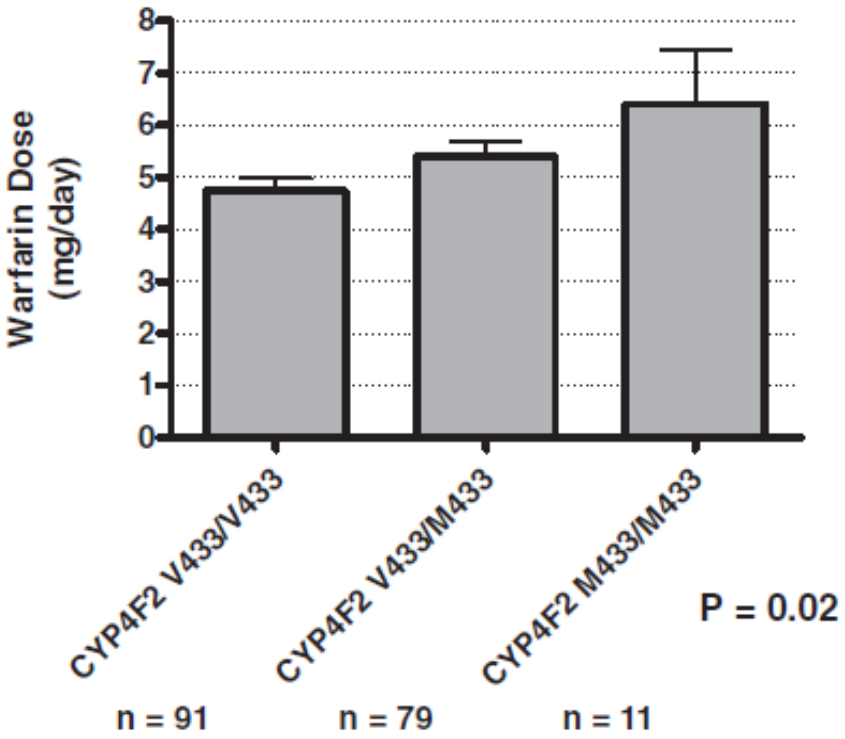


*Future Cardiol;*2012;8:563–576

Pharmacogenomics J;2004;4:40-8

Background(Caucasian)

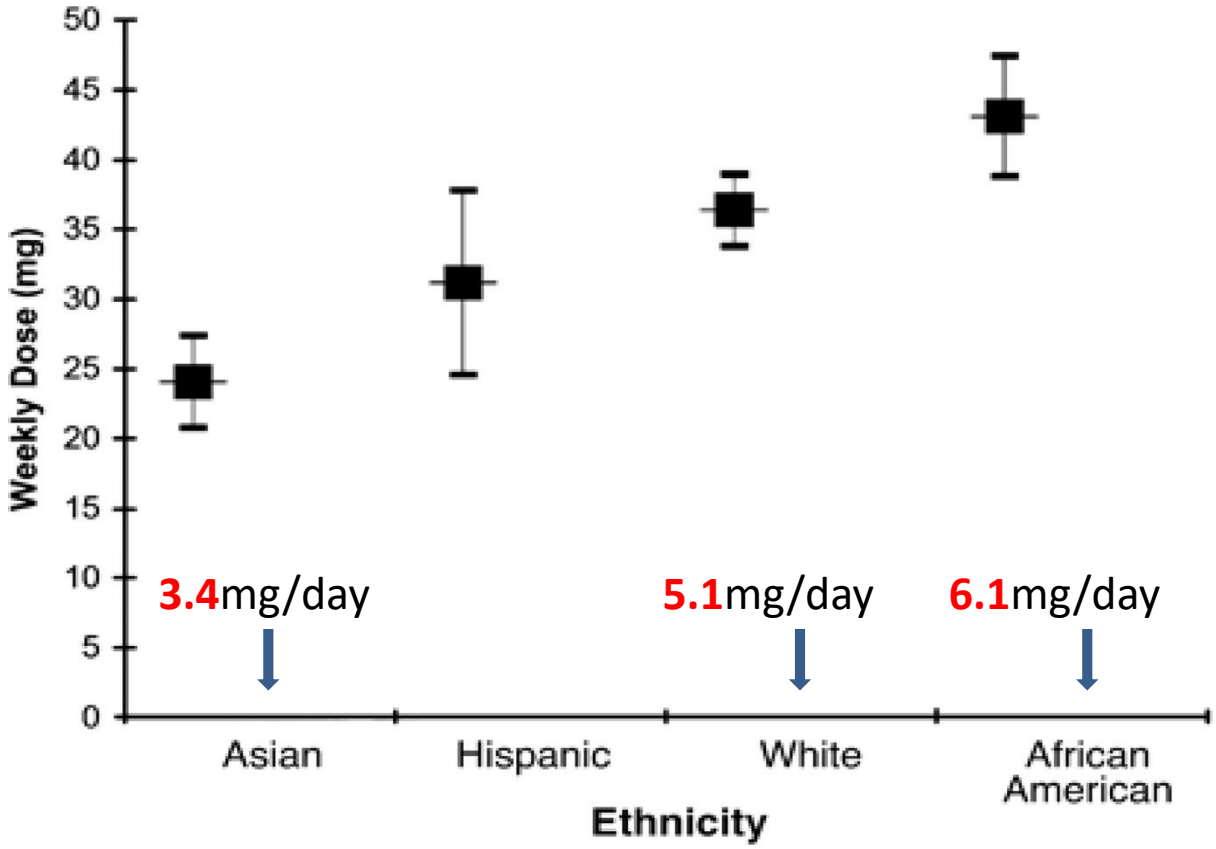
CYP4F2 genotype vs. warfarin dose



Mol Pharmacol; 2009;75:1337–1346

Background

Average warfarin dose requirements by ethnicity for a therapeutic INR of 2-3



Circulation;2008;118:1383-1393

Study Aim

- We sought to define whether genetic polymorphism is linked to optimal warfarin dose in Korean patients and compare these data with historic evidence in Chinese, Japanese, and Caucasians.

Methods

- ABI-Prism 3130 genetic analyzer (Applied Biosystems, CA, USA)

Classification	Genotypes		
VKORC1	AA	GA	
CYP2C9	*1/*1	*1/*3	
CYP4F2	GG	GA	AA

Methods

- Korean patients (n=148) visiting anticoagulation clinic were included.
- Clinical characteristics、optimal warfarin dose、INR、VKORC1 、CYP2C9 and CYP4F2 genes were assessed.
- The optimal warfarin dose was defined as the maintenance dose that a patient's INR was within target range at least 3 consecutive laboratory measurements separated by at least 1 week.
- The index dataset was compared with historic controls of other ethnicities.

Circulation; 2012;125:1997-2005

Methods

European Heart Journal (2016) **37**, 2893–2962
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B

- It recommend target INR range between **2.0 and 3.0** in patients on vitamin K antagonist(VKA).
- But Asian patients have a **lower** target INR range compared to other ethnicities.

Eur Heart J; 2016; 37:2893–2962

Methods

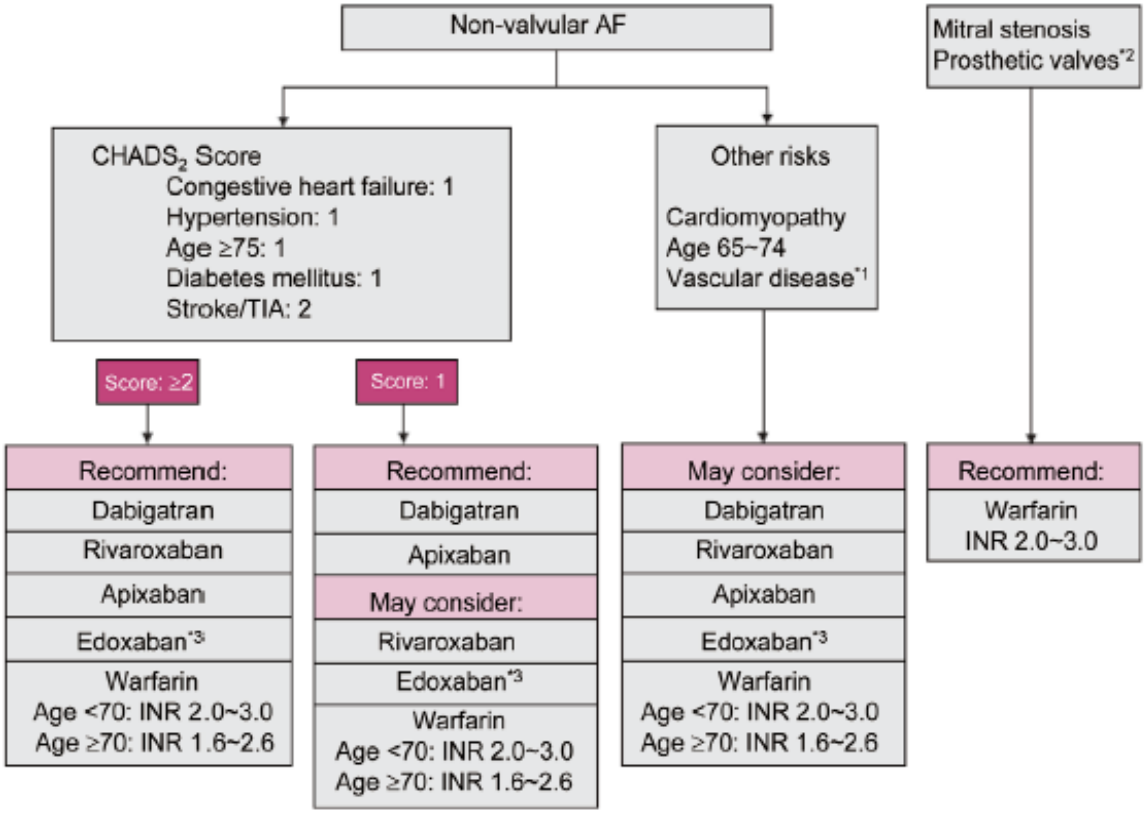
Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

JCS GUIDELINES

Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013)

– Digest Version –

JCS Joint Working Group



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

Circ J; 2014; 78**:** 1997–2021

Methods

- **Inclusion criteria**

➢ indication to be treated with warfarin.

➢ age between 20-80 years with body weight above 50kg.

- **Exclusion criteria**

➢ chronic liver failure

➢ using novel anticoagulant

➢ active malignancy

➢ renal disease (Creatinine >2.0 mg/dl or eGFR < 45 ml/min)

➢ life expectancy <1 year

Methods

- **SPSS v 20.0 (SPSS IBM, Chicago, IL, USA)**

  -Categorical variables

  Chi-square or Fisher exact test

  -Continuous variables

  Independent-samples t-test or ANOVA

  Post-hoc analysis by Bonferroni or Tamhane

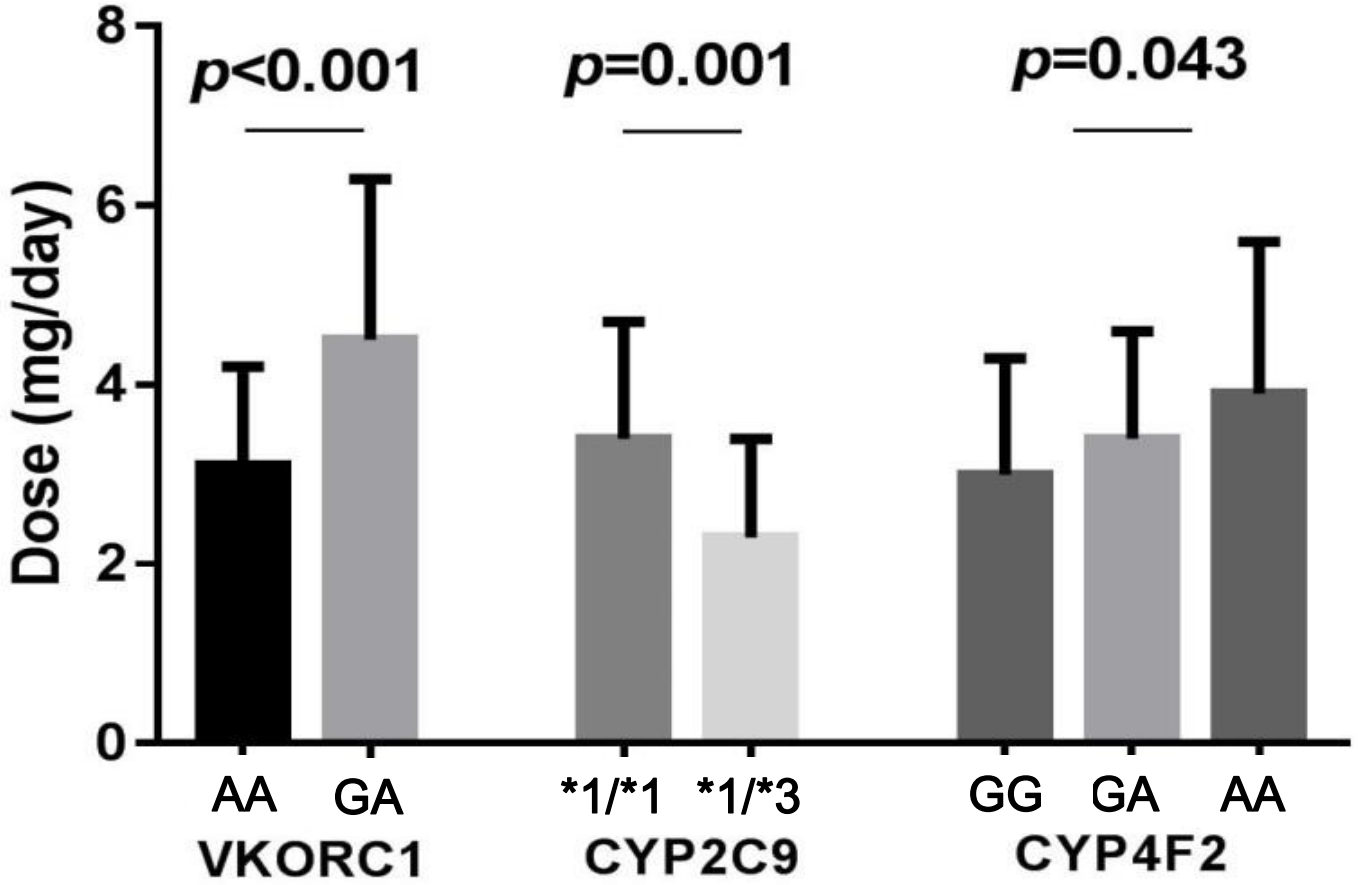
Results: Baseline Characteristic

	Numbers of patients	Warfarin dose(mg/day)	P value
Sex			
Female	75(51%)	3.3±1.5	0.859
Age≥70	50(34%)	2.9±1.0	**0.012**
<70	98(66%)	3.5±1.4	
BMI≥23	90(61%)	3.5±1.4	**0.014**
<23	58(39%)	2.9±1.1	
Smoking	19(13%)	3.2±1.1	0.751
Alcohol	16(11%)	3.8±1.3	0.132
Disease			
AF	119(80%)	3.1±1.2	**<0.001**
Thromboembolic disease	21(14%)	3.3±1.1	0.839
Heart valve disease	36(24%)	3.6±1.4	0.096
Cerebral infarction	27(18%)	3.3±1.3	0.917
CHF	47(31%)	3.1±1.2	0.417
HTN	55(37%)	3.3±1.1	0.922
DM	28(19%)	3.2±1.7	0.761
HLP	12(8%)	3.1±1.3	0.718

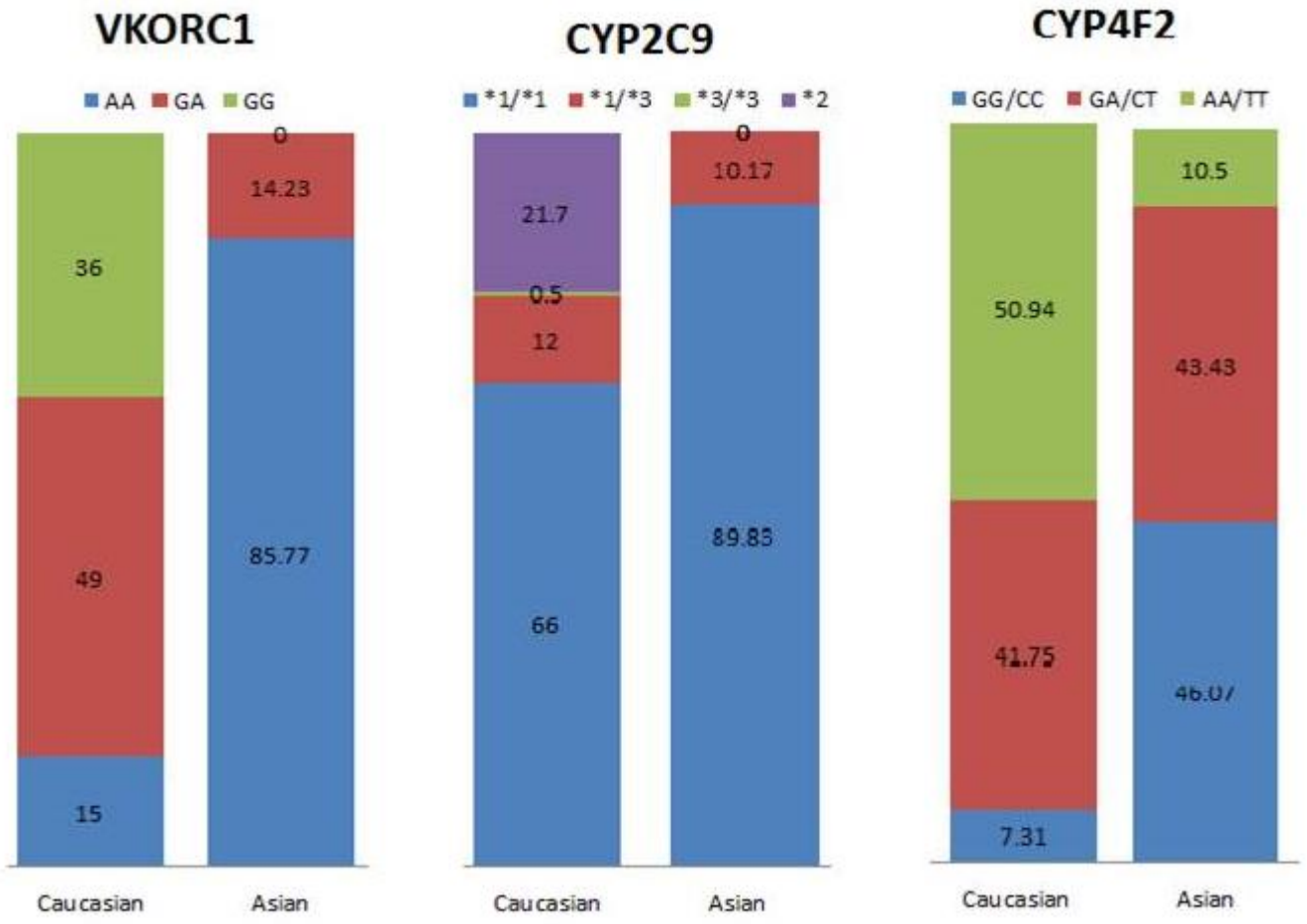
Results: Baseline Characteristic-Continued

	Numbers of patients	Warfarin dose(mg/day)	P value
Medications			
β inhibition	15(10%)	3.7±1.2	0.253
Amiodarone	42(28%)	2.7±1.1	**0.002**
ARB	26(18%)	3.4±1.1	0.699
ACEI	14(9%)	3.1±1.2	0.649
Asprin	24(16%)	3.2±1.1	0.622
Clopidogrel	24(16%)	3.2±1.1	0.777
Statins	29(20%)	3.2±1.2	0.603
CCB	33(22%)	3.0±1.2	0.208
Diuretics	98(66%)	3.1±1.3	0.029
Nitrates	13(9%)	3.4±1.1	0.642
EF≥50	106(72%)	3.4±1.4	0.093
<50	36(28%)	3.0±1.1	

Results: Genetic Influence on Warfarin Dose



Results: Different Genetic Frequencies: East Asian vs Caucasian



Thrombosis Research; 2015;135:861–866
*J Thromb Thrombolysis;*2012;34:120–125
*Blood;*2009;113:784-792

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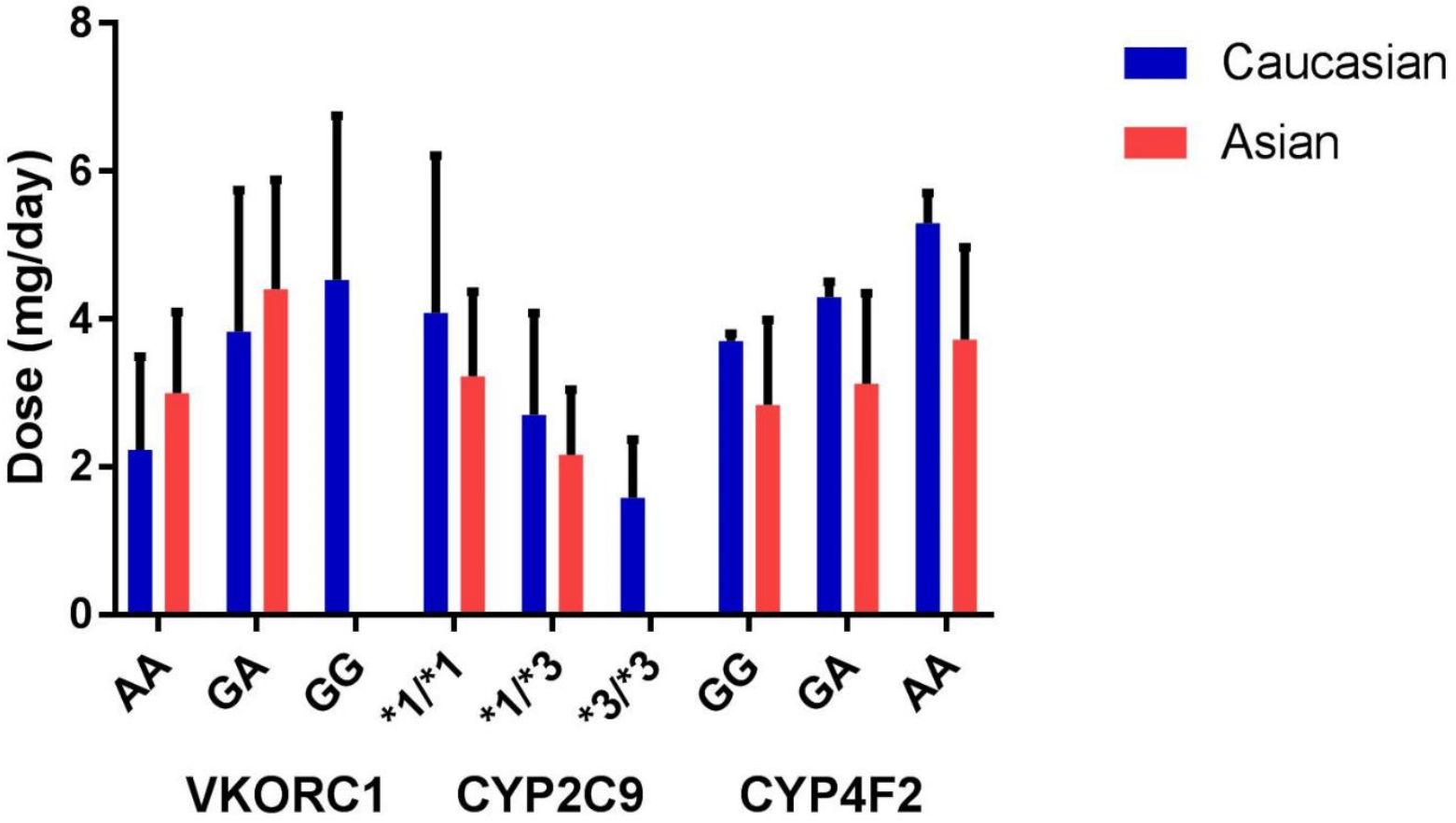

Front Pharmacol;2017;31;8:323
Thrombosis Research; 2015; 135:861–866
Blood;2005;106:2329-2333

Conclusions

- Asian and Caucasian have different optimal warfarin dose and genetic frequencies.
- Universal international optimal warfarin dose guidelines may consider patient ethnicity, however, this hypothesis requires further evidence.

Limitations

- Single center and limited number patients;

- We did not compare other ethnicities, such as blacks or/and African Americans.

Thank you for your attention!