

Surgeon General's Workshop on Deep Vein Thrombosis
"Approaches to Treating Deep Vein Thrombosis"

Oral Anticoagulant Therapy and Its Limitations
The Importance of Expert Management

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Warfarin, 20th Most Prescribed Drug in the US

Hydrocodone w/APAP	92,720	Zoloft	29,878
Lipitor	69,766	Zocor	27,234
Lisinopril	46,207	Metformin HCL	25,473
Atenolol	44,162	Ibuprofen	25,188
Synthroid	44,056	Triamterene w/HCTZ	24,616
Amoxicillin	41,394	Ambien	24,494
Hydrochlorothiazide	41,346	Warfarin	24,290
Zithromax	37,172	Cephalexin	23,665
Furosemide	36,508	Nexium	23,642
Norvasc	34,729	Prevacid	23,629
Toprol XL	32,795	Lexapro	22,597
Alprazolam	32,405	Prednisone	22,507
Albuterol	31,220		

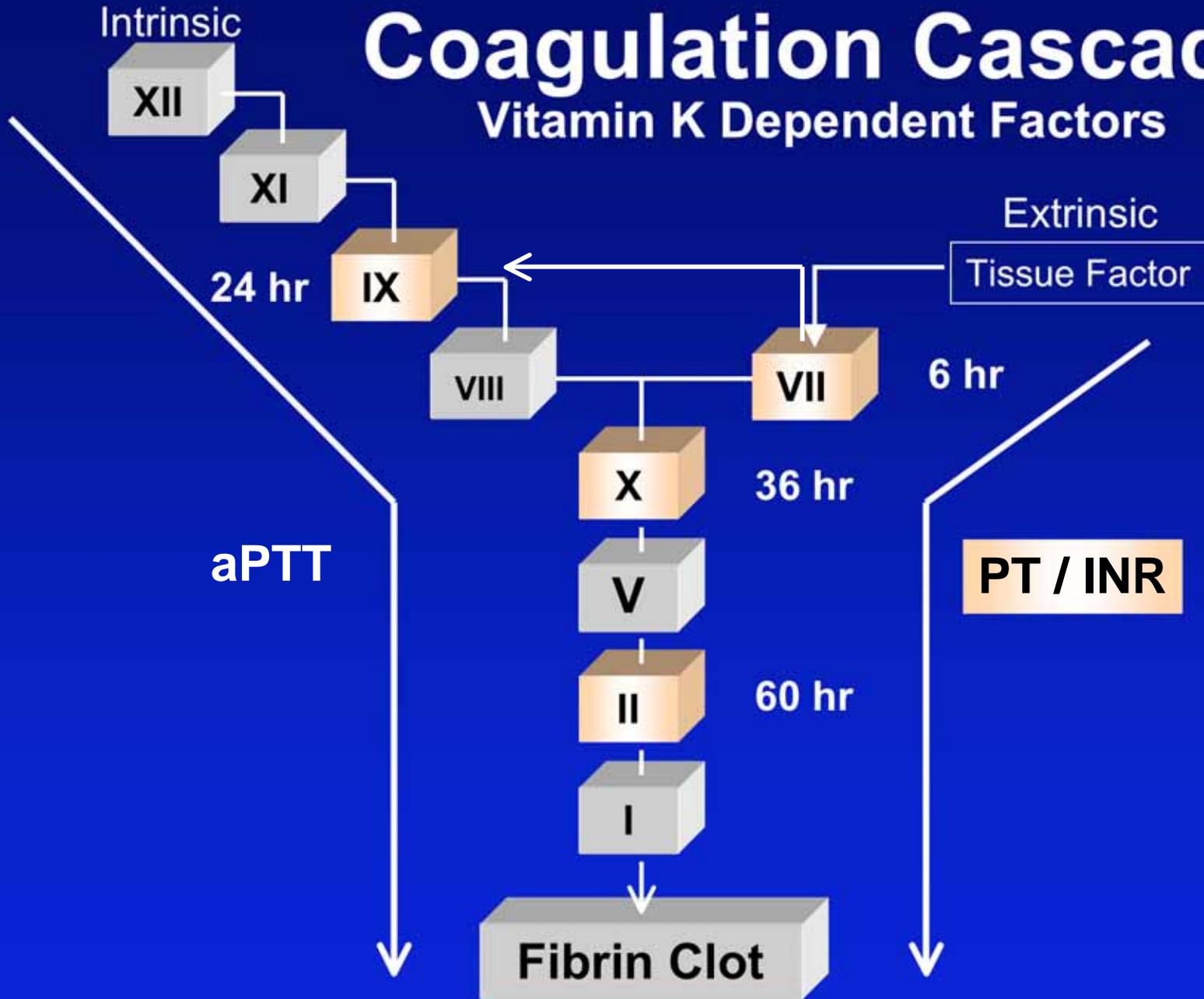
23.5 million scripts in 2000
2004 data from www.rxlist.com/top200.htm

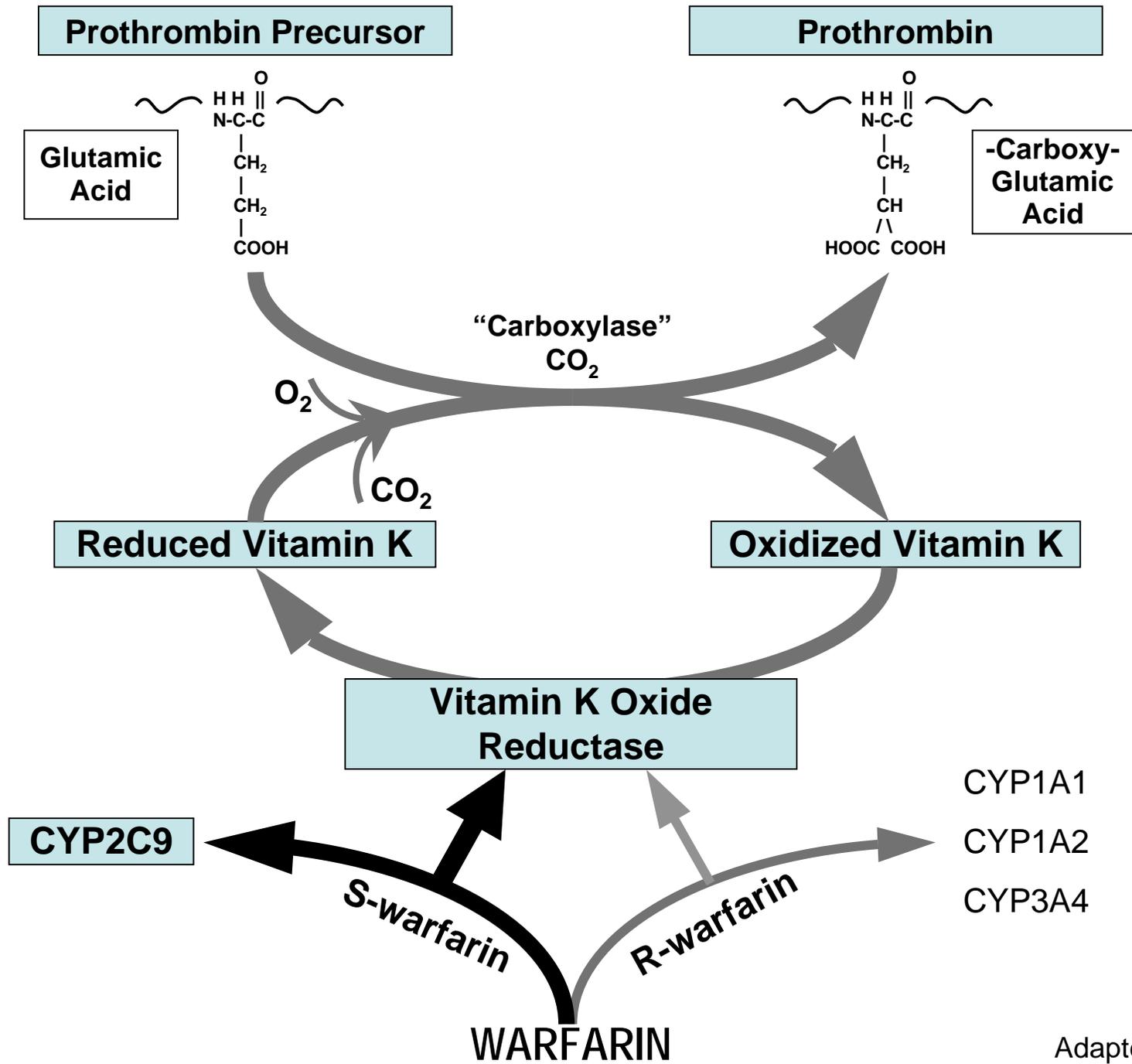
Indications for Warfarin Therapy

1. Prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.
2. Prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.
3. To reduced the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

Coagulation Cascade

Vitamin K Dependent Factors

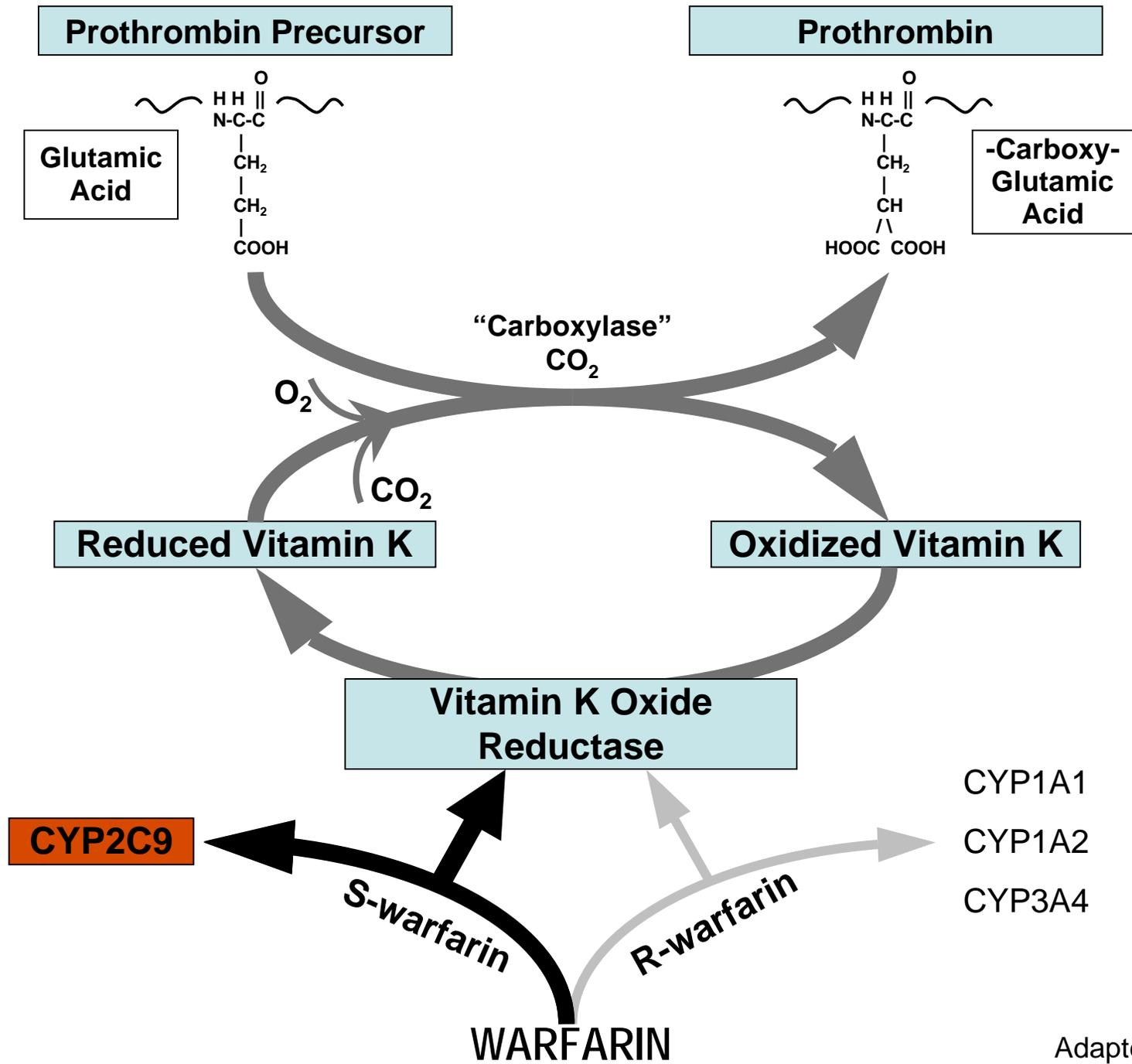




Adapted, B. Gage

Drawbacks to Warfarin Therapy

- Delayed onset and offset of action.
- Frequent blood test monitoring required:
 - the dose response is unpredictable,
 - has a narrow therapeutic range above which or below which bleeding or thromboembolism can occur, and
 - multiple factors (illness, drugs, diet, etc.) influence dose response.
- Monitoring assay has serious limitations.
- Reversibility of anticoagulant affect is slow.
- Requires labor-intensive follow up, expert dose management, and frequent patient communication.



Adapted, B. Gage

Mutations in the CYP2C9 Gene Leading to Impaired Metabolism

Two common CYP2C9 SNPs are associated with impaired metabolism of S-warfarin:

A SNP in exon 3 (C → T) is denoted CYP2C9*2

A SNP in exon 7 (A → C) is denoted CYP2C9*3

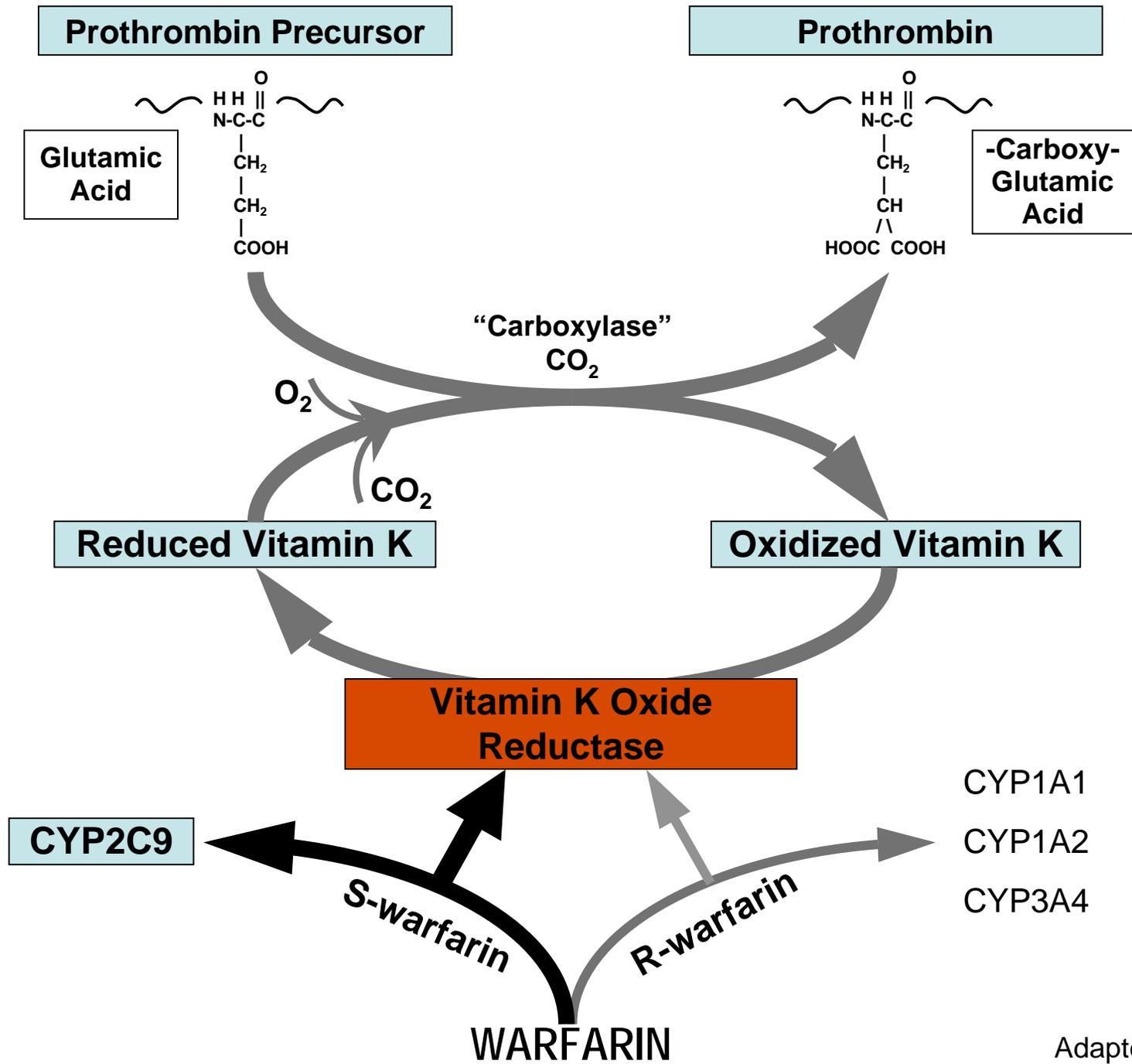
(The wild type enzyme is denoted CYP2C9*1)

Both of these point mutations are associated with reduced warfarin requirements needed to achieve and maintain a therapeutic INR

CYP2C9 Gene Variants & AC Outcomes

<u>Genotype</u>	<u>Exp / Actual Prevalence</u>	<u>Mean Dose</u>	<u>Maj / Fatal Bleeds</u>
1/1 (127)	65.7 / 68.6	5.6 MG	<small>% per pt yr</small> 5.6 %
1/*2 (28)	17.1 / 15.1	4.9	9.4 %
1/*3 (18)	13.6 / 9.7	3.3	12.5 %
*2/*2 (4)	1.1 / 2.2	4.0	22.2 %
*2/*3 (3)	1.8 / 1.6	2.3	100 %
*3/*3 (5)	0.7 / 2.7	1.6	13.3 %

Gene variant group also required more time to achieve stable dose and had increased risk of high INR



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VKORC1 Haplotype Frequency & Effect on Warfarin Dose Maintenance

<u>Haplotype</u>	<u># Patients (Freq)</u>	<u>Ave Maintenance Dose (Homozygous)</u>
H1	43 (12%)	2.9 (2.2-3.7)
H2	88 (24%)	3.0 (2.5-3.6)

H7	132 (35%)	6.0 (5.2-6.9)
H8	28 (8%)	4.8 (3.4-6.7)
H9	77 (21%)	5.5 (4.5-6.7)

Genetic Polymorphisms and Warfarin Therapy

CYP2C9 Polymorphisms¹

	<u>CYP2C9*1</u>	<u>CYP2C9*2</u>	<u>CYP2C9*3</u>
Caucasians	79% - 89%	8% - 19%	6% - 10%
Native Canadians	91%	3%	6%
African Americans	98%	1.5% - 3.6%	0.5% - 1.5%
Asians	95% - 98%	0%	1.7% - 5%

VKORC1 Haplotypes²

	<u>H1H2</u>	<u>H8H9</u>
Euro Americans	37%	58%
African Americans	14%	49%
Asian Americans	89%	10%

¹Takahashi, et al. Clinical Pharmacokinetics 2001;40:587-603. © Lippincott Williams & Wilkins

²Rieder. NEJM 2005;352:2285

High Quality Dose Management

(ie, staying within therapeutic range)

The best outcomes with warfarin therapy are achieved by knowing . . .

- When to use (**proper indications**)
- What intensity to use (**proper therapeutic range**)
- How to use (**proper dose management**)

Proper dose management requires . . .

- Dosing decisions and management of nontherapeutic INRs
- Peri-procedural dose management
- Follow-up & communication
- Education

Models of Anticoagulation Management

- η Routine Medical Care (Usual Care)
- η Anticoagulation Clinic (ACC)
- η Patient Self-Testing (PST)
- η Patient Self-Management (PSM)

Frequency of Hemorrhage & TE with Usual Care vs ACC

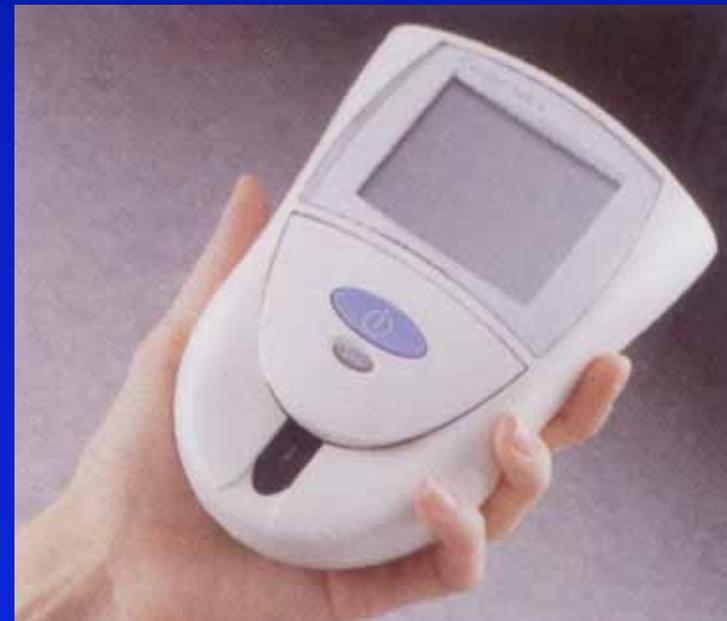
<u>Study</u>	<u>Pat Yrs</u>	<u>Major Hem</u>	<u>Rec TE</u>
7 UC Studies	3,062	5.5%	2.7%
8 ACC Studies	17,644	2.5%	1.6%

Usual Care Studies:

Landefeld 1989, Gitter 1995, Steffensen 1997, Beyth 1998,
Cortelazzo 1995, Chiquette 1998, Matchar 2002

Anticoagulation Clinic Studies:

Seabrook 1990, Fihn 1993, van der Meer 1993,
Cortelazzo 1993, Cannegieter 1995, Palareti 1996,
Chiquette 1998, Matchar 2002



PST & PSM vs UC or ACC

<u>Study</u>	<u>Comparators</u>	<u>TTR</u>	<u>Hem & TE</u>
1 Study	PST_{ACC} vs UC	56% vs 32%	14% vs 25%
3 Studies	PST_{ACC} vs ACC	73% vs 67%	no AEs
5 Studies	PSM vs UC	75% vs 54%	3.2% vs 6.1%
5 Studies	PSM vs ACC	72% vs 64%	1.4% vs 1.0%

PST Studies

Beyth2000 (RCT), White 1989 (RCT), Kaatz, Gadisseur2001 (RCT)

PSM vs UC Studies

Horstkotte1996(RCT), Hasenkam1997(RCT), Sawicki1999(RCT), Koertke2001(RCT), Preiss2001(cohort).

PSM vs ACC Studies

Ansell1995(case control), Watzke2000(RCT), Cromheecke2000(cross-over), Gadisseur2003(RCT), Menendez2005(RCT).

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