Online-only Appendices to Perlstein et al. “The Creating an Optimal Warfarin Nomogram (CROWN) Study” (Thromb Haemost 2012; 107.1)

Appendix 1. Algorithm A.

Initiation dosing

VKORC1 Haplotype

CYP2C9 Genotype	A/A	A/B	B/B
*1*1	4	6	8
*1*2	3	5	7
*1*3	3	5	7
*2*2	2	4	6
*2*3	3	5	7
*3*3	2	4	6

Dose adjustment:

(-) 1 mg if age > 65 years

(+) 1 mg if height > 175 cm

(-) 1 mg if height < 155 cm

(-) 1 mg if weight < 50 kg

(+) 1 mg if weight > 100 kg

(-) 2 mg if medication use*

(+) 2 mg if medication use**

(-) 2 mg if ALT > 110 IU/L

(+) 1 mg if $\geq$ 3 vegetable servings per day or enteral tube

feeding

Minimum allowable dose 1 mg, maximum allowable dose 10

mg

*Any of acetaminophen (> 1 g m/day), daily alcohol Intake, aspirin (> 325mg/d), non-steroidal anti-inflammatory drug (more than 4 tablets per day), amiodarone, cephalosporins, ciprofloxacin, clofibrate, clopidogrel, levofloxacin, erythromycin, azithromycin, clarithromycin, fluconazole, metronidazole, isoniazid, cimetidine, omeprazole, pantoprazole, sufamethoxazole/trimethoprim, tamoxifen, thyroid hormone, or fluoxetine. ** Any of rifampin, dicloxacillin, nafcillin, griseofulvin, carbamazepine, oral contraceptives, barbiturates, haloperidol, sucralfate, antithyroid drugs, or cholestyramine.

Maintenance dosing

Coumadin dose for next 4 days* = (goal INR / current INR) $^{1/3}$ X current 4-day dose

*With continued dose adjustments for medications and dietary intake as listed above for initial dosing.

Appendix 2. Algorithm B.

Initiation dosing

VKORC1 Haplotype

CYP2C9 Genotype	A/A	A/B	B/B
*1*1	3	4	5
*1*2	3	4	5
*1*3	2.5	2.5	4
*2*2	2	2	2.5
*2*3	2	2	2.5
*3*3	0.5	1	1

Dose adjustment:

(-) 1 mg if age > 65 years

(+) 1 mg if height > 175 cm

(-) 1 mg if height < 155 cm

Maintenance Dosing

Achieved INR	Dose adjustment relative to previous dose
< 2	20% increase (10% increase for CYP2C9 *3*3)
2 < INR < 3	No adjustment
3 < INR < 4	20% decrease
4 < INR < 5	25% decrease
5 < INR < 6	30% decrease
INR > 6	50% decrease

Appendix 3. Algorithm C.

Initiation dosing

CYP2C9 Genotype	VKORC1 Haplotype		
	A/A	A/B	B/B
*1*1	3.5	5	7
*1*2	3	4	4.5
*1*3	2.5	3	4
*2*2	1	1.5	2.5
*2*3	1	1.5	2.5
*3*3	1	1	1

Maintenance Dosing

Achieved INR	Dose adjustment relative to previous dose
< 1.8	20% increase (10% increase for CYP2C9 *3*3)
1.8 < INR < 3.2	No adjustment
3.2 < INR < 4	20% decrease
4 < INR < 5	25% decrease
5 < INR < 6	30% decrease
INR > 6	50% decrease

Appendix 4.

Warfarin PK/PD model

A population model that describes the PK of S-warfarin and the PK/PD relationship between exposure and INR was applied. The model for pharmacokinetics of warfarin was derived from Hamberg and colleagues[16], and the relationship between warfarin concentration and prothrombin complex activity was adapted from Chan and colleagues and modified to describe the relationship between warfarin concentration and INR.[21, 36]

Pharmacokinetic (PK) Modelling

Warfarin is a racemic mixture of two enantiomers: S-warfarin and R-warfarin. S-warfarin is known to be 3-5 times more potent as a vitamin K antagonist than R-warfarin and it is metabolised by CYP2C9. In this analysis, only S-warfarin was considered to describe the mechanism of action. A two-compartment model with first-order input and first-order elimination was applied (see below). Since the free concentrations of the drug are responsible for the anticoagulant effect of the drug, protein binding of warfarin was taken into account for expressing unbound plasma levels. The concentration was imputed given established PK parameters because the study did not measure warfarin levels.(21) CYP2C9 genotype status as well as clinical factors such as age and concomitant medications that induce or inhibit CYP2C9 were adjusted as covariates.

Absorption:

$$\frac{dX_a}{dt} = -k_a \bullet X_a$$

Plasma:

$$\frac{dX_{Cp}}{dt} = (k_a \bullet X_a) + X_{Ct} \bullet \left(\frac{CL_2}{V_2}\right) - X_{Cp} \bullet \left(\frac{CL_2}{V_1}\right) - X_{Cp} \bullet \left(\frac{CL_1}{V_1}\right)$$

Tissue:

$$\frac{dX_{Ct}}{dt} = X_{Cp} \bullet \left(\frac{CL_2}{V_1}\right) - X_{Ct} \bullet \left(\frac{CL_2}{V_2}\right)$$

where

k_a First order rate constant for the absorption of S-Warfarin from the gut into the blood stream

CL Clearance of S-Warfarin

CL_2 Inter-compartmental clearance of S-Warfarin

V_1 Volume of distribution of S-Warfarin in the plasma compartment

V_2 Volume of distribution of S-Warfarin in the peripheral tissue compartment

Since the free concentrations of the drug are responsible for the anticoagulant effect of the drug, protein-binding of warfarin was taken into account for expressing unbound plasma levels. Free plasma warfarin concentrations were determined as:

$$C_{p,free} = C_p \bullet f_{unbound}$$

Pharmacodynamic (PD) Modelling:

The clotting activity after warfarin exposure was defined as prothrombin complex activity (PCA) and described by an indirect response model with S-warfarin unbound concentration as an exposure.

$$\frac{dPCA}{dt} = kout \bullet \left[\frac{100}{1 + \left(\frac{C_{p,free}}{IC_{50}} \right)^{\gamma}} - PCA \right]$$

Since the anticoagulant response generally obtained is INR, the response data can be transformed to PCA with the use of functional relationship between INR and prothrombin time (PT) and PCA(36, 37) described in the equations below:

$$PCA = \frac{a}{PT(\text{sec}) - b}$$

where a=426; b=7.75

$$INR = \frac{PT(\text{sec}) + 0.242}{9.5981}$$

The CROWN trial measured INR rather than PCA; thus, the equations above were not well-suited to the observed study data. Hence, the original PD model was modified to describe the relationship between concentration and INR directly as follows:

$$\frac{dINR}{dt} = kin - kout \bullet INR \bullet \left[1 - \frac{C_{p,free}}{\left(C_{p,free} + IC_{50} \right)} \right]$$