UMC Utrecht

Personalised medicine in cardiology

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University Medical Center Utrecht

Personalised medicine in cardiology

Large RCT's
Large cohorts

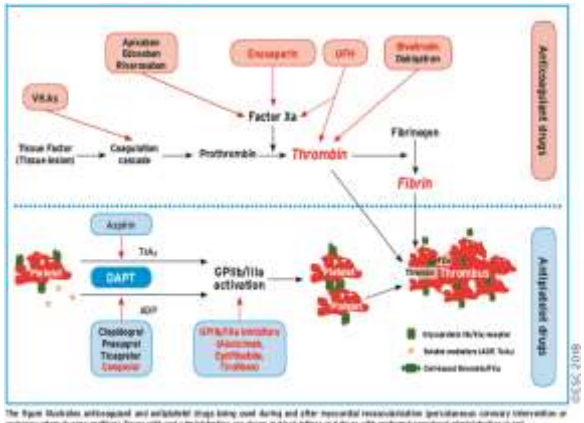
Risk scores
PGx

Tools
personalised medicine

Clinical Pharmacists

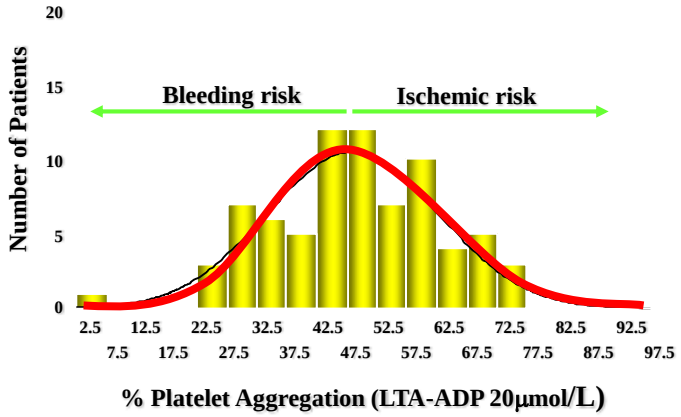
ACS
AF
CVRM

Antiplatelet drugs and pharmacological targets



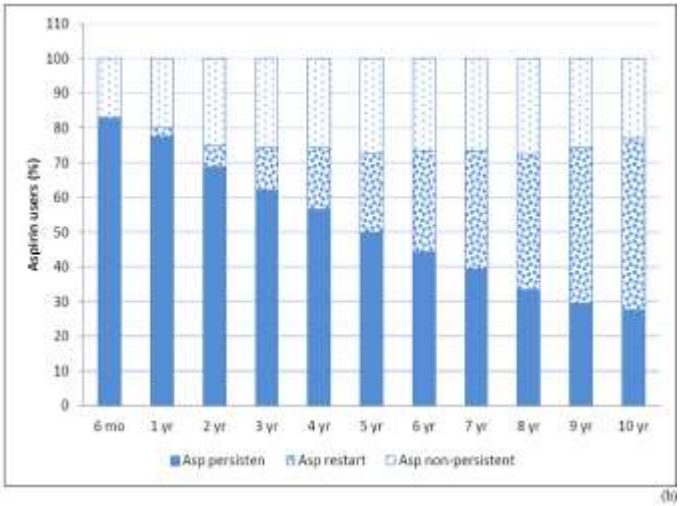
From: 2018 ESC/EACTS Guidelines on myocardial revascularization
Eur Heart J. Published online August 25, 2018. doi:10.1093/eurheartj/ehy394

Interindividual variability of effect clopidogrel



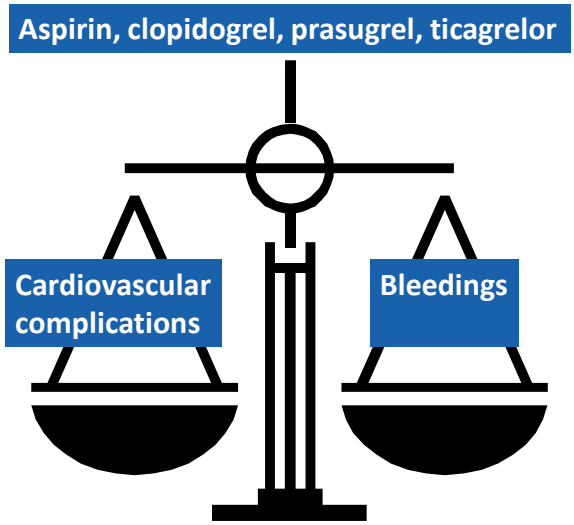
Angiolillo et al, Am J Cardiol 2006; 97: 38

Patterns of use after first myocardial infarction



Yasmina, Thesis, 2017, University Utrecht

Antiplatelet drugs



Risk Score acute coronary syndrome

GRACE: in hospital death

Risk factor
Age
Heart rate
Systolic blood pressure
CHF
Creatinine
ST –segment deviation
Cardiac arrest
Elevated troponin

CRUSADE: in hospital major bleeding

Risk factor
Hematocrit
GFR: Cockcroft-Gault
Heart rate
Systolic blood pressure
Prior vascular disease
CHF
Sex

Aspirin: studies with > 500 subjects

Table 1. Summary of the results of studies (n > 500 patients) investigating the influence of several polymorphisms on antiplatelet drugs and surrogate*/clinical endpoints

Drug	Gene	Variant	Outcome	Type of study	Interaction		Conclusion
					Yes**	No**	
Aspirin	GPIIIa	$P1^{A2}$	Clinical endpoints (MACE) Clinical endpoints (ST) Surrogate endpoints	Cohort Cohort Meta-analysis	1	1 1	Uncertain association
	GPIa	C807T	Clinical endpoints (MACE) Surrogate endpoints	Cohort Meta-analysis		1 1	No association
	GPIb	rs2243093	Clinical endpoints (MACE)	Cohort		1	No association
	GPIX	rs1613662	Clinical endpoints (MACE)	Cohort		1	No association
	$P2Y_{12}$	Haplotype H1/H2	Surrogate endpoints	Meta-analysis		1	No association
	$P2Y_1$	A1622G	Surrogate endpoints	Meta-analysis		1	No association
	COX-1	rs3842787 A842G C50T	Clinical endpoints (MACE) Surrogate endpoints Surrogate endpoints	Cohort Meta-analysis Meta-analysis		1 1 1	No association
	COX-2	G-765C	Clinical endpoints (MACE)	Cohort	1		Probable
	PEAR1	rs2768759 rs12041331	Clinical endpoints (MACE) Surrogate endpoints Clinical endpoints (MACE)	Cohort Cohort Case-control	1	1 1	Uncertain association
	Aprv(s)	rs3798220	Clinical endpoints (MACE)	RCT	1		Probable

Yasmina, Pharmacogenomics 2014; 15: 509-28

Clopidogrel and platelet fuction tests

Light transmittance aggregometry (LTA)

VerifyNow® P2Y12 assay

Plateletworks®

IMPACT-R

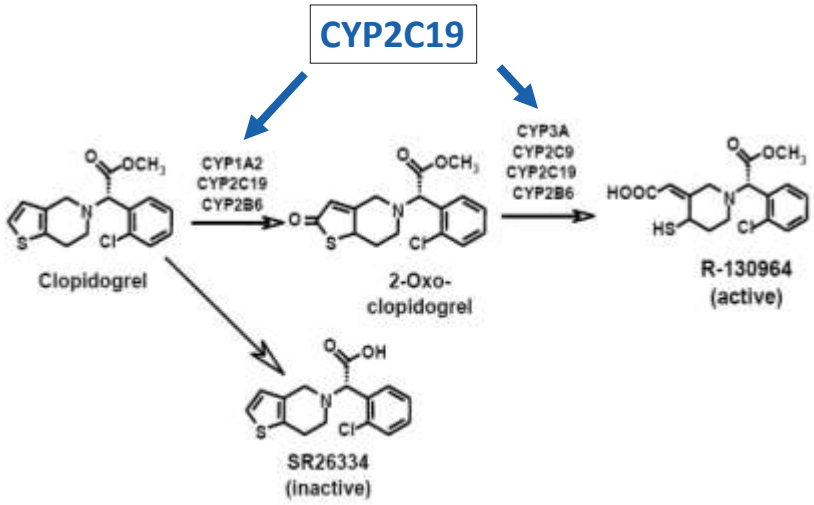
PFA-100® system

Prospective RCT's, Tailoring on tests are negative i.e. GRAVITAS, TRIGGER-PCI, ARCTIC, ANTARCTIC

No personalised medicine based on platelet function tests

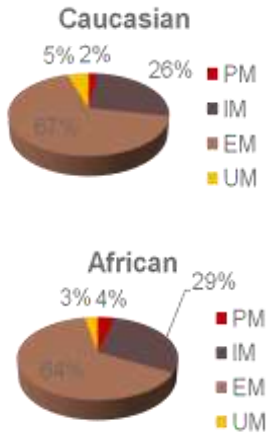
Breet et al, AHA november 2009

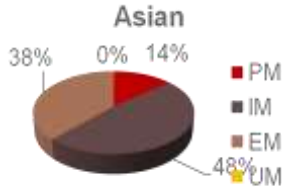
Metabolism clopidogrel



Mega et al, NEJM 2008; 4: 354

CYP2C19 genotype and phenotype



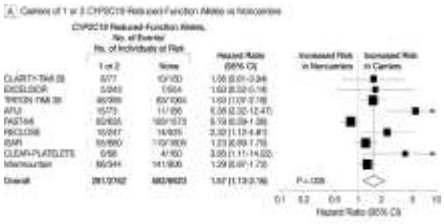


PM: poor metabolizer; *2/*2, *2/*3, *3/*3
IM: intermediate metabolizer; *1/*3, *1/*2
EM: extensive metabolizer
UM: ultrarapid metabolizer, *17/*17

IM en PM: lower concentration active metabolite
IM en PM: higher platelet reactivity

Xie, Annu Rev Pharmacol Toxicol 2001; 41: 815

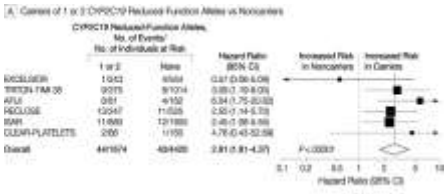
Clinical endpoints clopidogrel: meta-analysis



Carriers of 1 or 2 non functional CYP2C19 alleles

MACE:

HR 1.57 (1.13 – 2.16)



Stent thrombosis:

HR 2.81 (1.81 – 4.37)

Mega, JAMA 2010; 304: 1821

EMA SPC Plavix

4.4. Special warnings and precautions for use

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Sectie 5.2.

Summary results CURE, CHARISMA, CLARITY-TIMI, TRITON-TIMI, ACTIVE

Popular Risk Score study

Elective PCI - unstable angina, NSTEMI

while on clopidogrel

1 punt	**CYP 2C19 IM**
1 punt	**ACS (<14 days no platelet function)**
2 pt	**CYP 2C19 PM**
2 pt	**High platelet reactivity**
½ pt	**Diabetes mellitus**
½ pt	**Stent length > 30 mm**
½ pt	**LV Ejection Fraction <30%**
< 2 pt	**Clopidogrel**
≥ 2 pt	**Prasugrel**

Popular cohort

<2 pts: TE 6.6%

≥2 pts: TE 12.0%

Testing 3 times a day

Janssen et al, unpublished

POPular Risk Score *versus* POPular Cohort

Results

- Risk Score Cohort: n = 1119 patients
- POPular Cohort: n = 893 patients

- **Thrombotic Events: 3.7% *versus* 8.4%**
- **TIMI Major bleeding: 0.7% *versus* 2.5%**

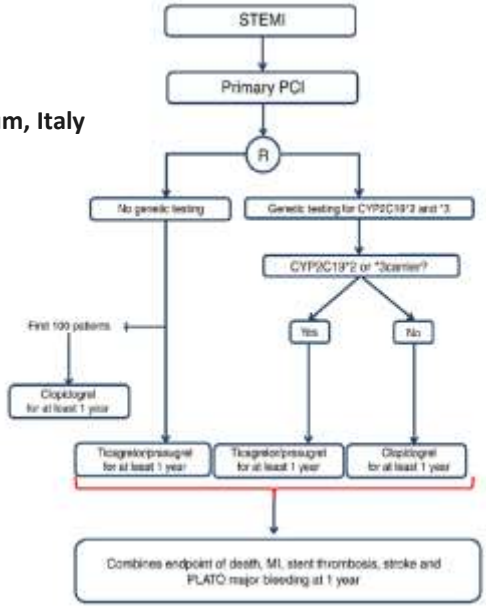
Janssen et al, unpublished

POPular Genetics

2700 patients

Centers in The Netherlands, Belgium, Italy

Inclusion completed April 2018



ZonMw

POPular Genetics: primary objectives

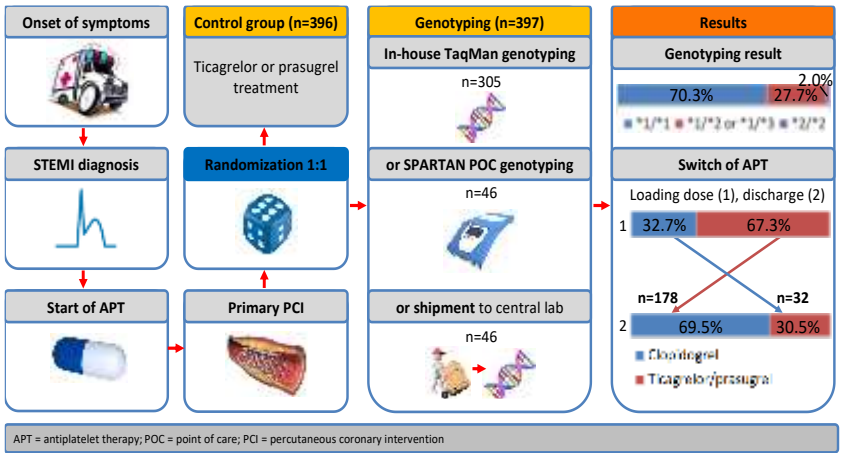
- **Net clinical benefit** (combined endpoint efficacy and safety):
- To assess whether PGx is noninferieur compared to ticagrelor or prasugrel

- **Safety** (PLATO major and minor bleedings):
- To assess whether PGx is superior compared to ticagrelor or prasugrel

- **Costeffectiveness and QoL:**
- Caluculation QALY's, net costs per life-year gained, net costs per QALY

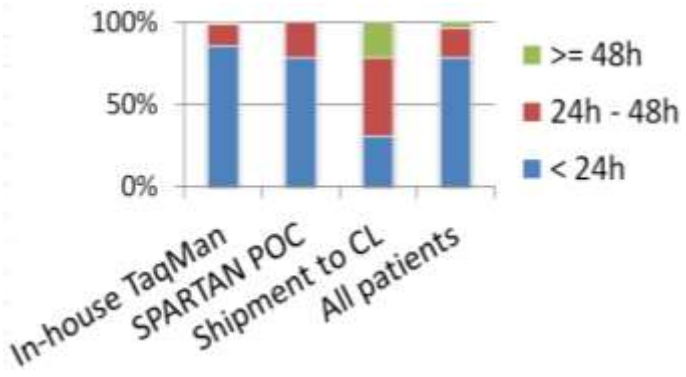
ZonMw

POPular Genetics: feasibility



ZonMw

POPular Genetics: feasibility



Even in the setting of STEMI testing within 48 hours is feasible

ZonMw

Atrial fibrillation

Atrial fibrillation is the arrhythmia with the highest prevalence

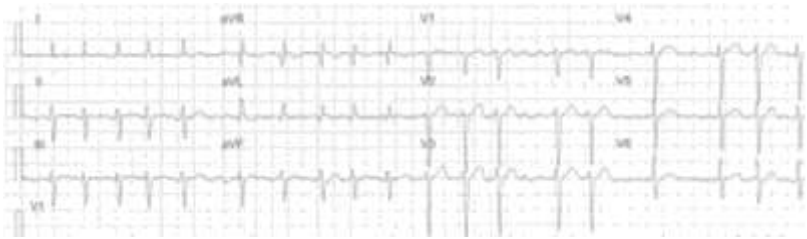
- General population 0.4 -1.0%
- Patients with cardiovascular disease 4%
- Patients with age > 70 – 80 years 8%
- Patients with severe heart failure >40%

20 – 30% of all strokes are due to atrial fibrillation

Symptoms atrial fibillation

- **Quality of life is impaired independent of other cardiovascular conditions**

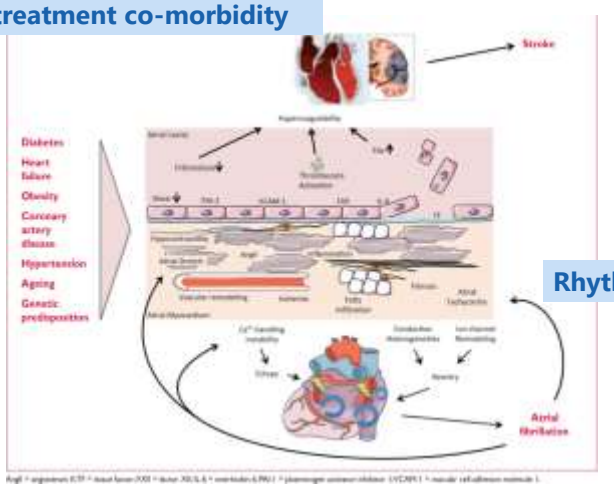
- Symptoms: palpitations, dyspnoea, chest tightness, lethargy, sleeping difficulties, psychosocial distress



Drug treatment co-morbidity

Oral anticoagulants

Rhythm or rate control



From: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

Long-term treatment atrial fibrillation

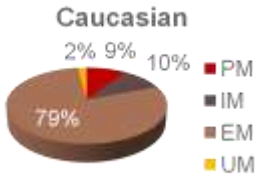
Improves AF related symptoms, may preserve cardiac function

- Rhythm control
  - Restoring and maintaining sinus rhythm
  - **Flecainide, propafenone**, sotalol, amiodarone
  - Flecainide, propafenone patients with no or minimal signs for structural heart disease, ischaemic heart disease, reduced left ventricular ejection fraction, pro-arrhythmic effects.

- Rate control
  - Lowering ventricular rate
  - **Beta-blocker**, digoxin, diltiazem, verapamil
  - Diltiazem, verapamil only if LVEF > 40%

CYP2D6 alleles and predicted phenotypes

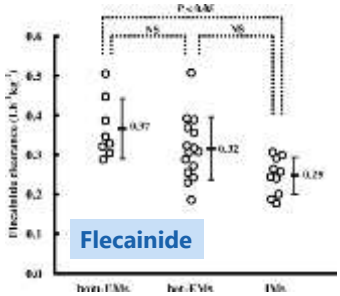
Allele	Enzyme activity	SGD
*1	normal	1
*2	normal	1
*3	none	0
*4	none	0
*5	none	0
*6	none	0
*9	reduced	0.5
*10	reduced	0.5
*17	reduced	0.5
*41	reduced	0.5
*1XN/*2XN	increased	NX1

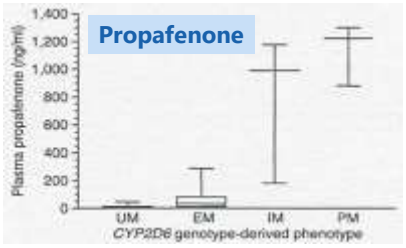


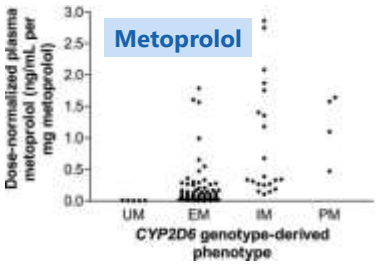
Predicted phenotype:
PM: 0 – 0
IM: 1 – 0 0.5 – 0.5
EM: 1 – 1 2X1 – 0
UM: 3X1 – 0 2X1 – 1

www.amplichip.us

Pharmacokinetics and CYP2D6 genotypes







Genetic variants CYP2D6 influence pharmacokinetics

Doki, Eur J Clin Pharmacol 2006; 62: 919-26
Morike, Clin Pharmacol Ther 2008; 84: 104-10
Fux, Clin Pharmacol Ther 2005; 78: 378-87

DPGW guidelines CYP2D6

Drug	PGx	Recommendation
Flecainide	PM	50% of starting dose, ECG, measuring blood levels
	IM	75% of starting dose, ECG, measuring blood levels
	UM	measuring blood levels
Propafenone	PM	30% of starting dose, ECG, measuring blood levels
	IM	measuring blood levels, ECG, monitor side effects
	UM	measuring blood levels, ECG
Metoprolol	PM	25% of starting dose
	IM	50% of starting dose
	UM	250% of starting dose
Carvediolol	PM	no adjustment or additional monitoring
	IM	no adjustment or additional monitoring
	UM	no adjustment or additional monitoring

Risk Score atrial fibrillation

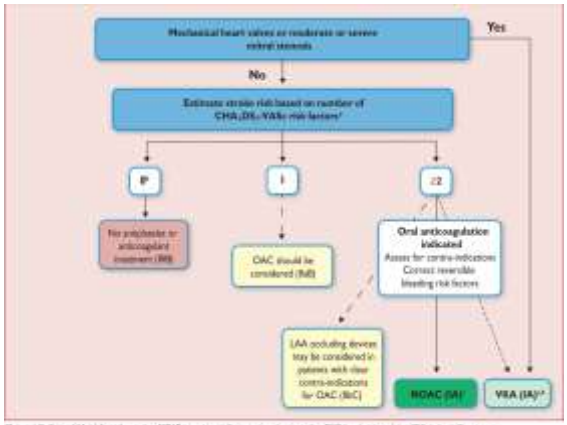
CHA_2DS_2VASc

Risk factor	Score
Congestive heart	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease	1
Age 65–74	1
Sex category (i.e. female sex)	1

HAS-BLED

Risk factor	Score
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	2
Bleeding	1
Labile INRs	2
Elderly (e.g. age >65 years)	1
Drugs or alcohol (1 point each)	1 or 2

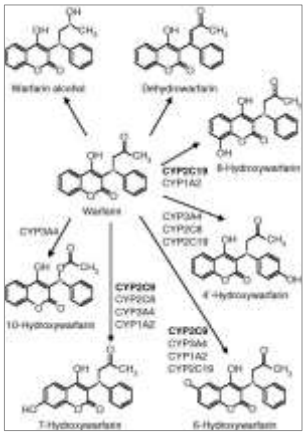
Oral anticoagulants



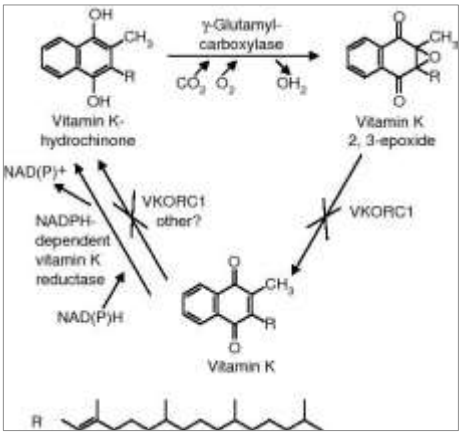
From: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS
Eur Heart J. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

Vitamin K antagonists

CYP2C9

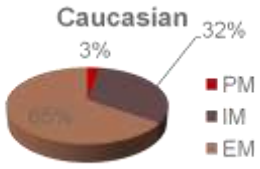


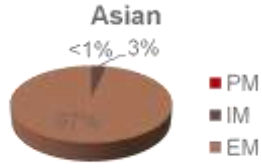
VKORC1

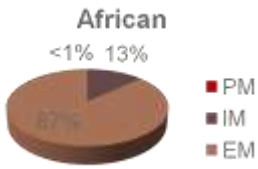


Stehle, Clin Pharmacokinet 2008; 47: 553

CYP2C9 genotype and phenotype frequency





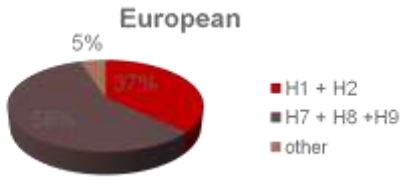


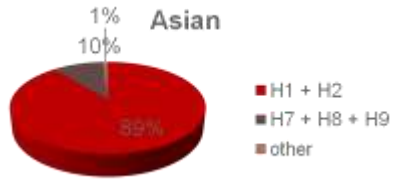
Less functional alleles: *2, *3

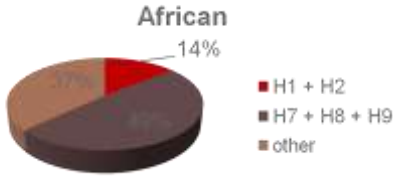
Predicted phenotype:
PM: *2/*2, *2/*3, *3/*3
IM: *1/*2, *1/*3
EM: *1/*1

Xie, Adv Drug Deliv Rev 2002; 54: 1257

VKORC1 haplotypes in populations



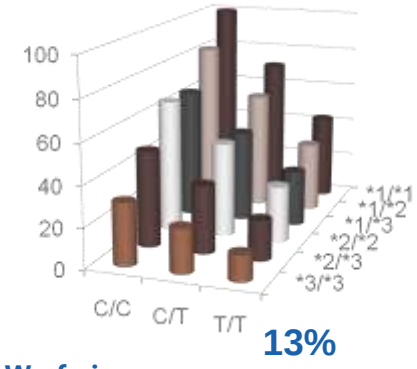




H1 + H2: *1137T*
H7 + H8 + H9: *1137C*

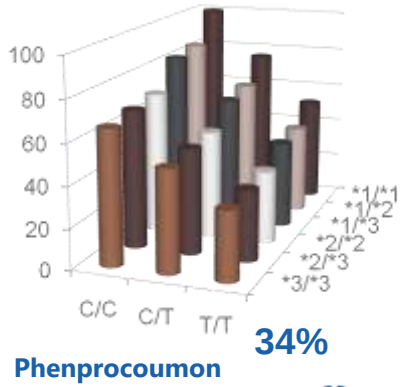
Rieder, NEJM 2005; 352: 2285

Coumarins and CYP2C9 – VKORC1 genotypes



13%

Warfarin

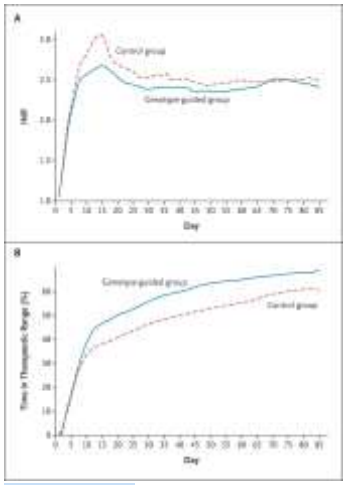


34%

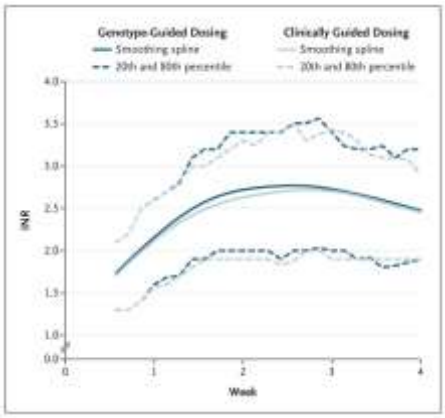
Phenprocoumon

Stehle, Clin Pharmacokinet 2008; 47: 553

RCT's genotype guided VKA



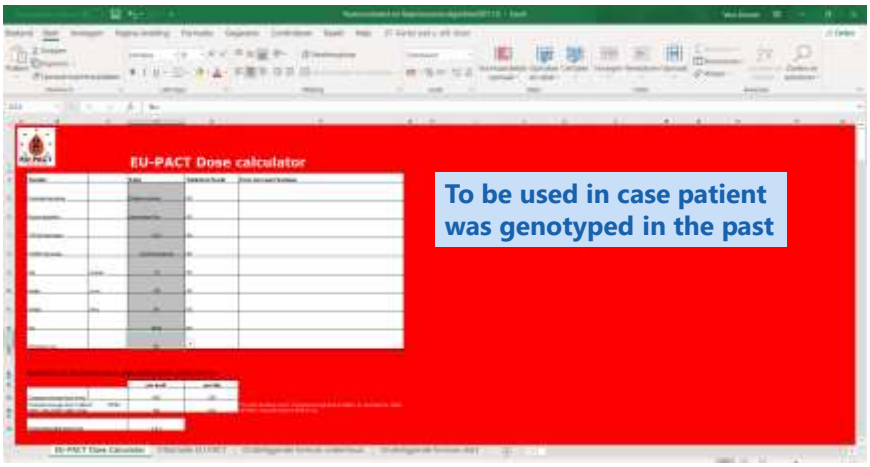
EU-PACT



COAG

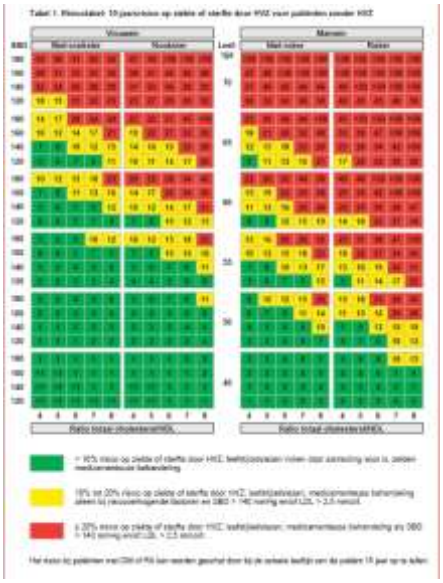
Pirmohamed, NEJM 2013; 369: 2294-303
Kimmel, NEJM 2013; 369: 2283-93

Many genotype based dosing algorithms



www.knmp.nl

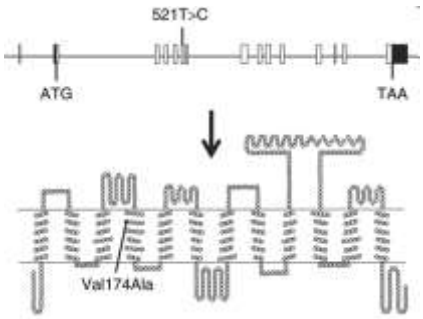
Cardiovascular risk management

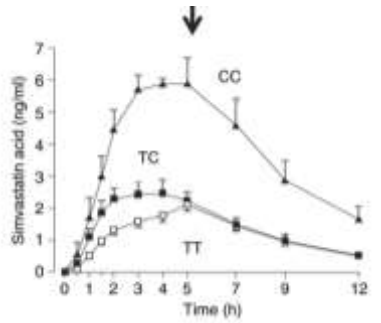


- Patient:
  - Gender
  - Smoker/non-smoker
  - SBP
  - Ratio TC/HDL
- Risk of (fatal) CVD
- Statins, antihypertensive drugs, aspirin, ACE inhibitors

SLCO1B1 genotype and simvastatin

- SLCO1B1 transporter plays a role in transport of statins into liver
- Carriers of the C allele have a reduced transporter capacity



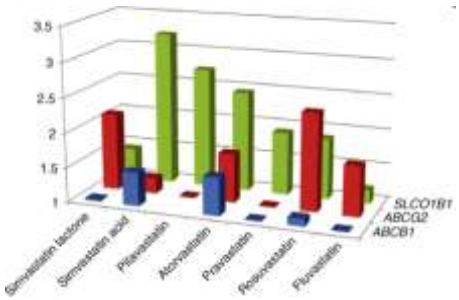


SLCO1B1 and statin induced myopathy

- GWAS cohort
  - 85 cases en 90 controles of SEARCH trial, n=12,000, 80 mg simvastatin
- Replication
  - Heart Protection Study, n=20,000, 40 mg simvastatin
- **Risk myopathy**
  - **OR 4.5 (2.6 – 7.7) per C copy**
  - **OR 16.9 (4.7 – 61.6) CC vs TT**

SEARCH collatorative group, NEJM 2008; 359: 789-99

AUC statins per SLCO1B1 genotype



SLCO1B1 CC *versus* TT

Pravastatin, rosuvastatin less influenced by SLCO1B1 genotype

DPGW guidelines SLCO1B1

Drug	PGx	Recommendation
Simvastatin	521 TC	select other statin or max dose of 40 mg
	521 CC	select other statin
Atorvastatin	521 TC or 521 CC	if additional risk factors: select other statin or monitor side effects if no additional risk factors: monitor side effects

Take home messages

- Risk scores are tools for personalised medicine.
- Opportunities for personalised medicine in antiplatelet therapy i.e. selection of antiplatelet drug by CYP2C19 genotyping of PCI patients with stenting.
- Several cardiovascular drugs require an intervention in combination with certain genotypes.