# POPular Genetics

**Vera Deneer, ziekenhuisapotheker – klinisch farmacoloog**

**St. Antonius Ziekenhuis, Nieuwegein / Utrecht**

**GGG symposium, Amsterdam, 16 april 2015**

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**Disclosure belangen spreker**

| (potentiële) belangenverstrengeling | Zie hieronder |
|---|---|
| Voor bijeenkomst mogelijk relevante relaties met bedrijven | Bedrijfsnamen |
| •Sponsoring of onderzoeksgeld<br>•Honorarium of andere (financiële) vergoeding<br>•Aandeelhouder<br>•Andere relatie, namelijk … | •AstraZeneca<br>•n.v.t.<br>•n.v.t.<br>•n.v.t. |

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# Duale antiplaatjestherapie

**STEMI, primaire PCI**

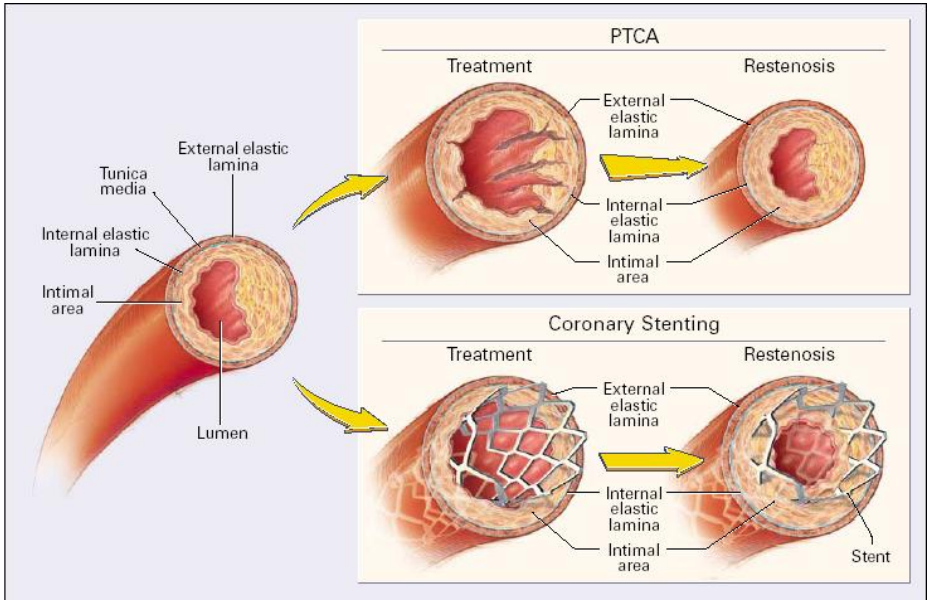
**Acute stenttrombose:**

- **hoge mortaliteit**

**ACS en PCI:**

- **acetylsalicylzuur in combinatie met clopidogrel, prasugrel of ticagrelor**

- **voorkoming stenttrombose, myocardinfarct, beroerte**

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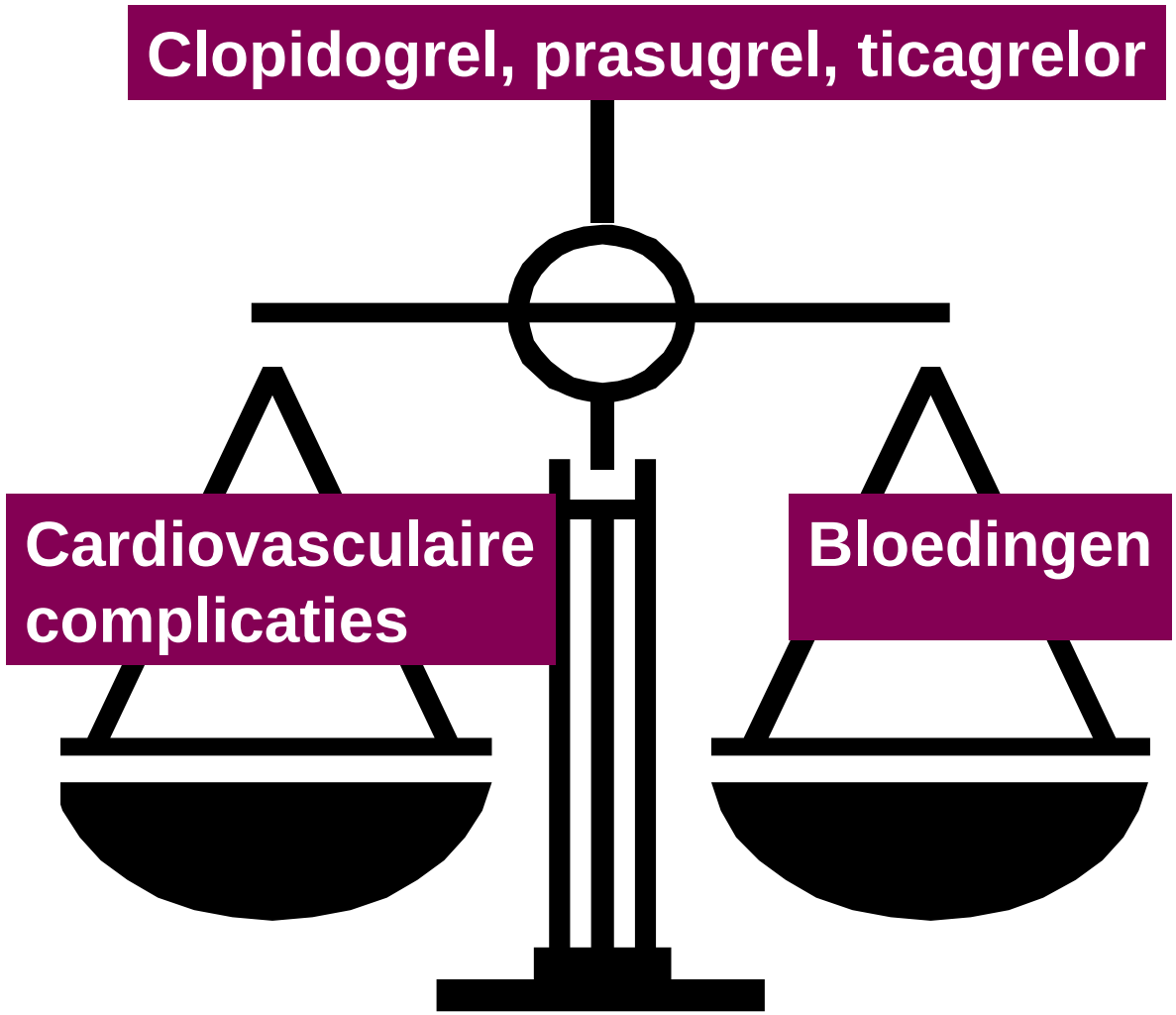
# Duale antiplaatjestherapie PCI met stent

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# Risicoscores atriumfibrilleren

## $CHA_2DS_2VASc$

| Risicofactor | Score |
|---|---|
| **C**ongestive heart | **1** |
| **H**ypertension | **1** |
| **A**ge >75 | **2** |
| **D**iabetes mellitus | **1** |
| **S**troke/TIA/thrombo-embolism | **2** |
| **V**ascular disease | **1** |
| **A**ge 65–74 | **1** |
| **S**ex category (i.e. female sex) | **1** |

## HAS-BLED

| Risicofactor | Score |
|---|---|
| **H**ypertension | **1** |
| **A**bnormal renal and liver function (1 point each) | **1 or 2** |
| **S**troke | **2** |
| **B**leeding | **1** |
| **L**abile INRs | **2** |
| **E**lderly (e.g. age >65 years) | **1** |
| **D**rugs or alcohol (1 point each) | **1 or 2** |

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# Risicoscores acuut coronair syndroom

## GRACE: in hospital death

| Risicofactor |
| --- |
| Age |
| Heart rate |
| Systolic blood pressure |
| CHF |
| Creatinine |
| ST –segment deviation |
| Cardiac arrest |
| Elevated troponin |

## CRUSADE: in hospital major bleeding

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

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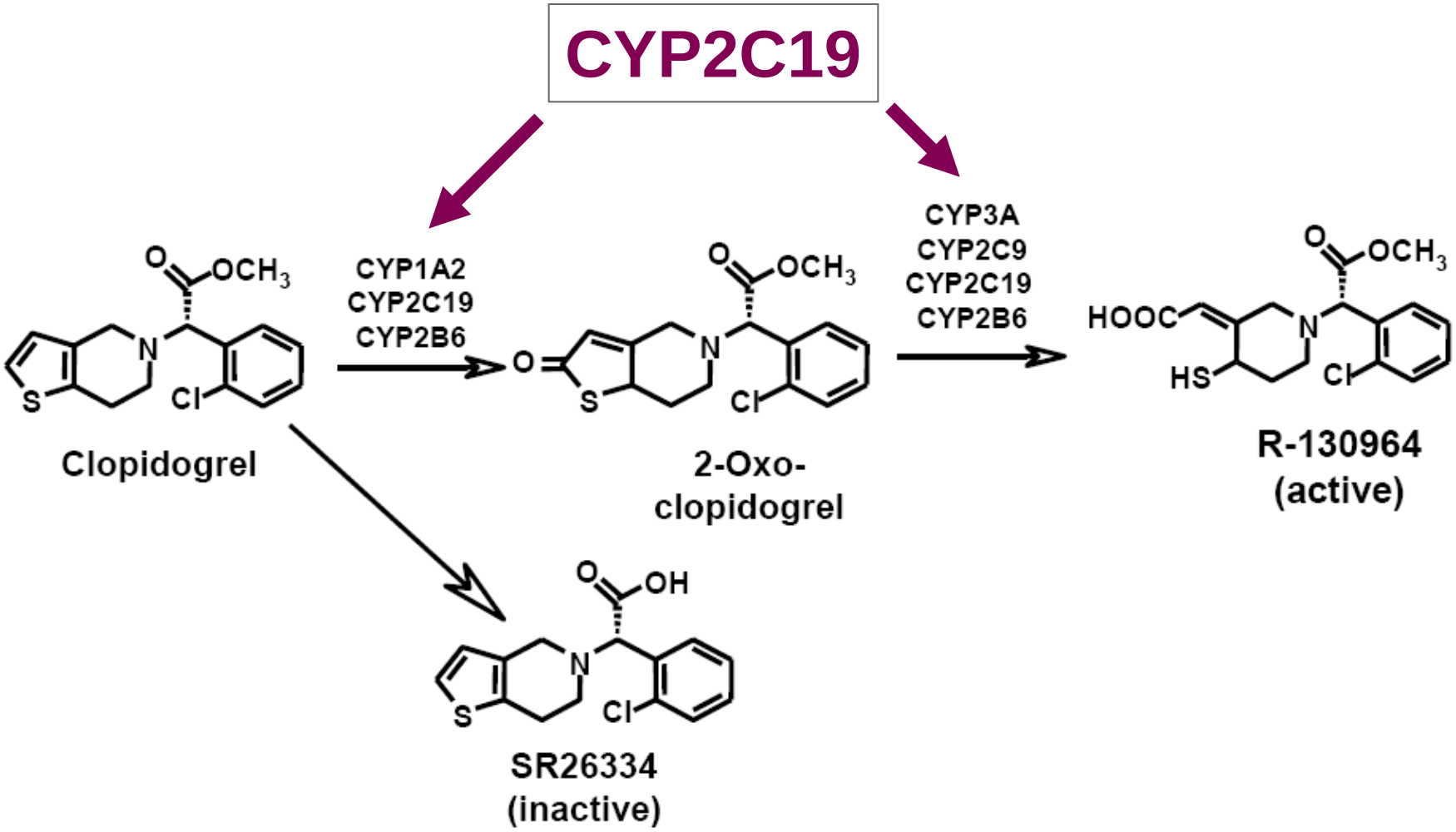
**De afgelopen 10 jaar veel farmacogenetische studies:**
**Initieel geregistreerde geneesmiddelen, investigator initiated onderzoek**

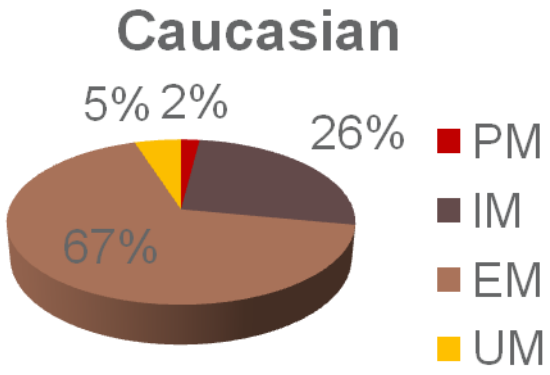
**Meer informatie m.b.t. farmacogenetische biomarkers in SPCs**

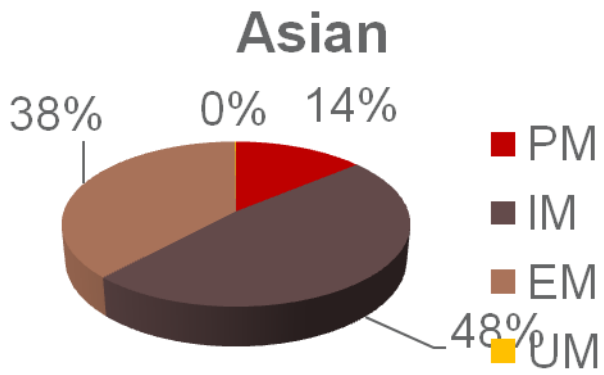
# Metabolisme clopidogrel

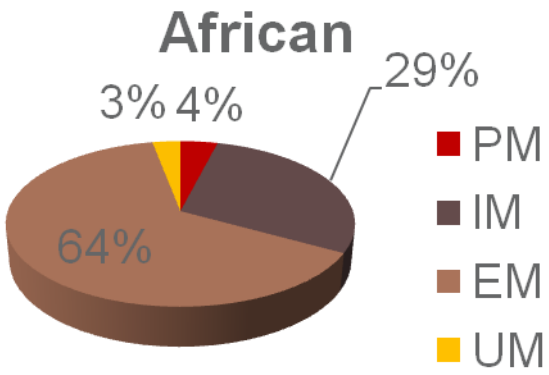



Mega et al, NEJM 2008; 4: 354

# CYP2C19 genotype en fenotype




**PM: poor metabolizer**
**IM: intermediate metabolizer**
**EM: extensive metabolizer**
**UM: ultrarapid metabolizer**

**IM en PM: lagere concentratie actieve metaboliet clopidogrel**
**IM en PM: hogere plaatjesreactiviteit**

Xie et al, Annu Rev Pharmacol Toxicol 2001; 41: 815

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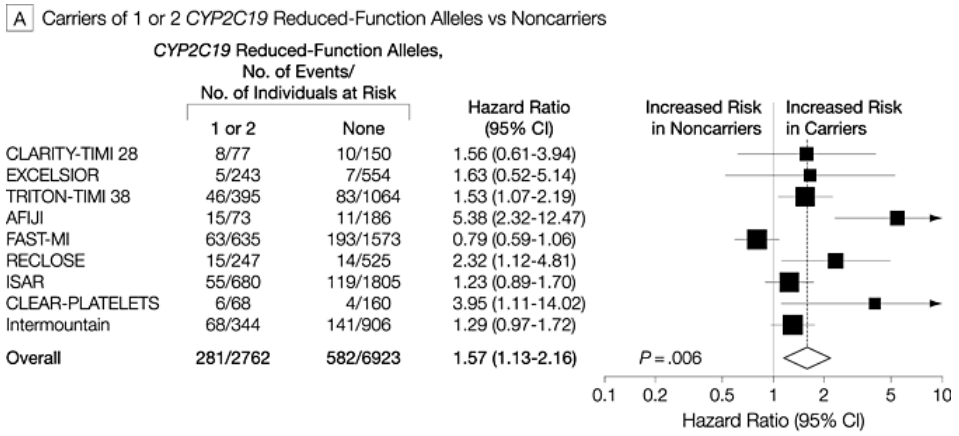
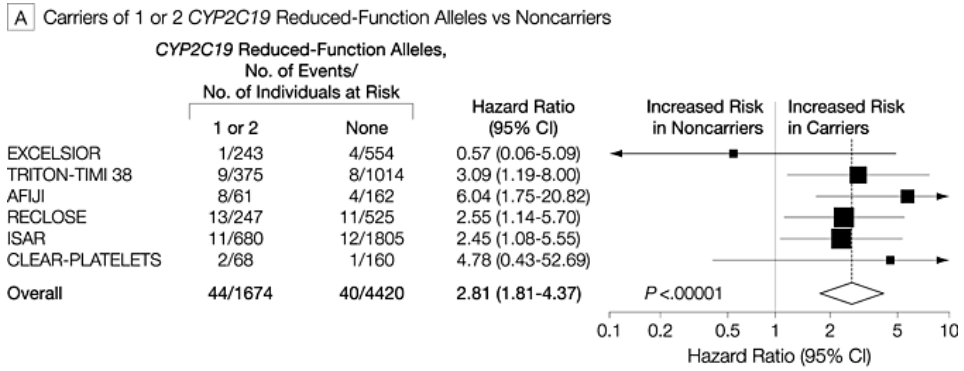
# Klinische eindpunten clopidogrel: meta-analyse




**Dragers van 1 of 2 niet functionele CYP allelen**

**MACE:**

**HR 1.57 (1.13 – 2.16)**




**Stenttrombose**

**HR 2.81 (1.81 – 4.37)**

Mega et al, JAMA 2010; 304: 1821

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# 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.

# FDA Label Plavix augustus 2010

**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

*See full prescribing information for complete boxed warning.*

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

**Gevolgd door expert opinion:**
**Geen gegevens effectiviteit op PGx gebaseerde farmacotherapie**

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# POPular Genetics

**Cost-effectiveness of CYP2C19 genotype guided treatment with antiplatelet drugs in patients with ST-segment-elevation myocardial infarction undergoing immediate percutaneous coronary intervention with stent implantation: optimization of treatment**

**Doelmatigheidsonderzoek: DO 171102022**

**Rationale and design, Am Heart J 2014: 168: 16-22.**

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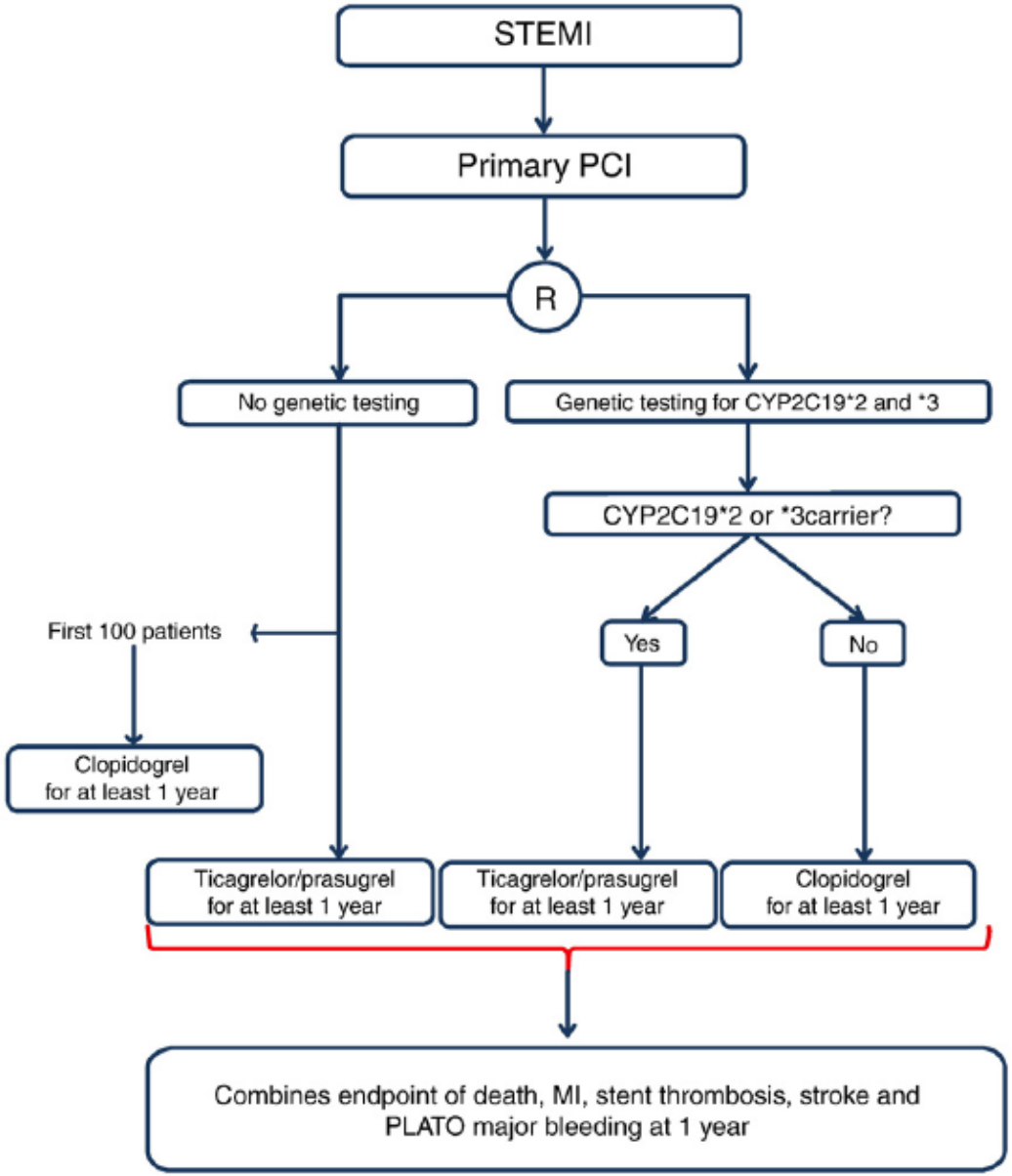
STEMI
Primary PCI
R
No genetic testing
Genetic testing for CYP2C19*2 and *3
CYP2C19*2 or *3carrier?
First 100 patients
Yes
No
Clopidogrel
for at least 1 year
Ticagrelor/prasugrel
for at least 1 year
Ticagrelor/prasugrel
for at least 1 year
Clopidogrel
for at least 1 year
Combines endpoint of death, MI, stent thrombosis, stroke and
PLATO major bleeding at 1 year

# POPular Genetics: primaire doelen

**Net clinical benefit** (gecombineerd eindpunt effectiviteit en veiligheid):

Vaststellen of PGx noninferieur is in vergelijking met ticagrelor of prasugrel

**Veiligheid** (PLATO major en minor bleedings):

Vaststellen of PGx superieur is in vergelijking met ticagrelor of prasugrel

**Kosten-effectiviteit en QoL**:

Berekening QALY's, net costs per life-year gained, net costs per QALY

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# Inclusies op 15 april 2015: 1161

| Centrum | Onderzoeker | Perc. |
|---|---|---|
| St. Antonius Ziekenhuis, Nieuwegein | Jur ten Berg | 69.9% |
| Isala Klinieken, Zwolle | Arnoud van ‘t Hof | 16.1% |
| UMC Utrecht | Folkert Asselbergs | 6.5% |
| OLV Aalst | Vincent Flore | 2.9% |
| OLVG, Amsterdam | Jean-Paul Herrman | 2.4% |
| Meander Medisch Centrum, Amersfoort | Fabrizio Spano | 1.1% |
| Amphia Ziekenhuis, Breda | Willem Dewilde | 1.0% |
| Twee centra gaan starten | | |

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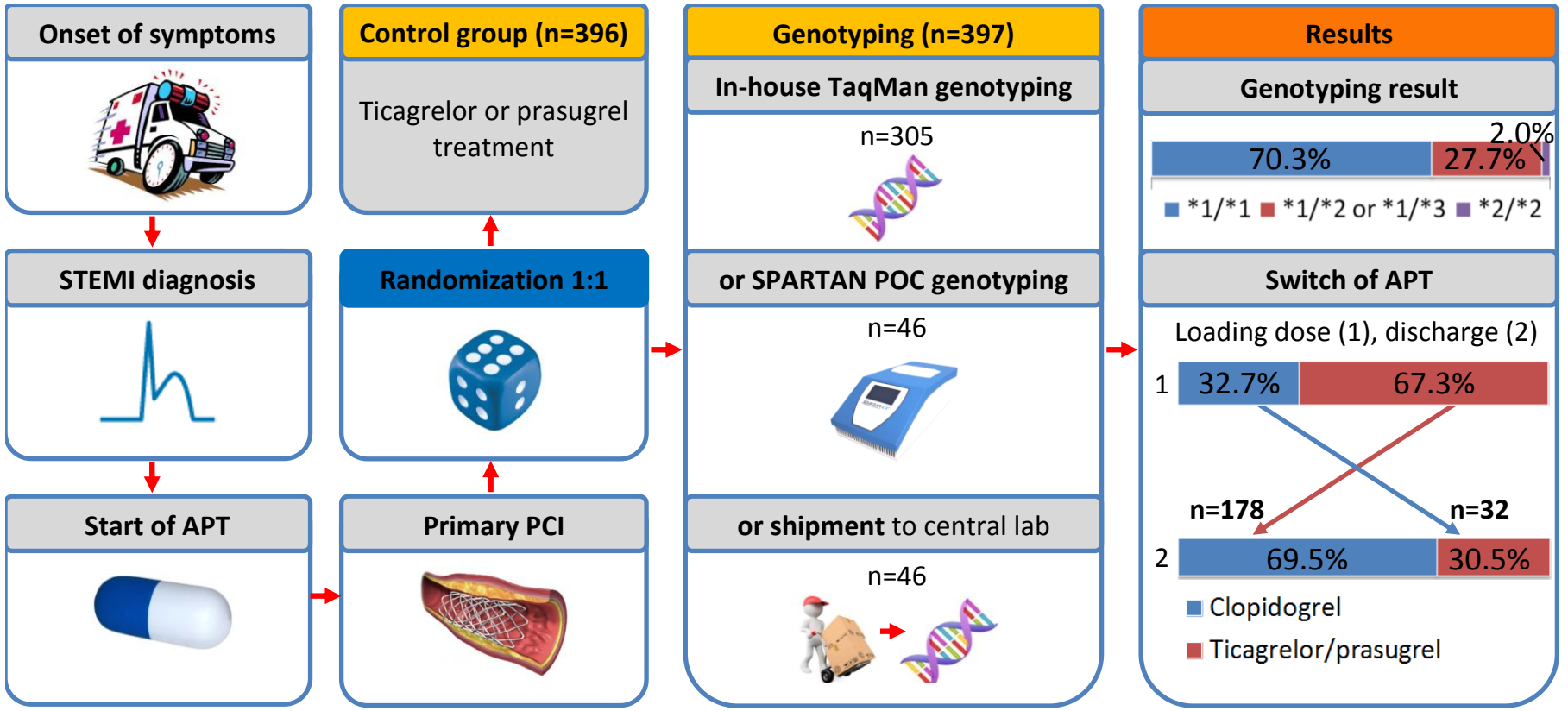
# POPular Genetics: feasibility




APT = antiplatelet therapy; POC = point of care; PCI = percutaneous coronary intervention

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# POPular Genetics: feasibility


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# Beloop

**Wijziging beleid ambulances**

- **Van opladen met clopidogrel naar veelal ticagrelor**

**In 2012 nieuwe ECG richtlijn**

- **Eerste keus ticagrelor of prasugrel**

**Wijzigen controle groep (usual care), hypothese, vraagstelling**

**Commitment, concurrerende studies**

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# Eindresultaat

**Randomized clinical trial met klinisch relevante eindpunten**

**Indien hypothese wordt bevestigd; PGx plaatjestherapie:**

- **Netto klinisch voordeel gelijkwaardig**
- **Veiliger**
- **In ieder geval grote besparing op geneesmiddelkosten**

**Niet mogelijk zonder subsidie van ZonMw en gedreven clinici en onderzoekers**

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# POPular Genetics

**St. Antonius Ziekenhuis Nieuwegein, afdeling Cardiologie**

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Maarten Postma

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