

Design, analysis and reporting of pharmacogenetic studies:
insights from systematic reviews

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With acknowledgement to Dr Juan Pablo Casas, Dr Michael Holmes
Dr Pablo Perel and Professor Harry Hemingway

Stratified medicines

Broadly,

- tailoring of therapeutic decisions for specific groups of individuals
- identification of predictors of treatment response

What are the factors motivating stratified medicines research?

- **Wider range of medical interventions and new interventions are expensive**
 - The UK drugs spend is £11 billion - *Office of Fair Trading 2007*
- **More people exposed to interventions**
 - Ageing population (more chronic disease, more people with several chronic diseases)
 - Emphasis on prevention

Ensure limited healthcare resources used optimally
- **Medicines have substantial potential to do harm**
 - 5% of all hospital admissions
 - steady state bed occupancy equivalent to seven 800 bed hospitals

projected annual cost £466m

 - 5700 deaths per annum

Pirmohamed et al BMJ 2004

Maximise benefit – Minimise harm (patient safety and patient choice)
- **Concept of personalised/stratified medicines (tailored treatments) has captured the zeitgeist**

Clinicians treat individuals not groups

How might stratification modify management?

- Treatment or no treatment
- Treatment option 1 or treatment option 2
- Early treatment or delayed treatment
- More intensive or less intensive treatment

Choice, timing or intensity of treatment

When might stratification be most important?

- The intervention is expensive
- The intervention is associated with a substantial risk of harm
- The intervention requires a particular skill or expertise (cannot be offered in every case)
- Evidence for “responders” and “non-responders”

A rational means of targeting interventions

“Non-responders”

“If patients vary randomly in their response to a drug rather than some patients never responding, searches for a genetic basis for non-response are futile”

- Senn BMJ 2004; 329: 966-8

Based on a single drug challenge, a 70% observed response rate could be explained by:

30% of individuals always being non-responders

100% of people being responders but only 70% of the time

Measurement of the stratifier (response biomarker)

- Genetic variant
- Blood marker
- Tissue expression marker
- Clinical score

Measurement error and misclassification

Biological variability

Dichotomisation of a continuous predictor variable

Measuring the outcome

- Pre-specified
- Clinically relevant
- Examined with adequate power (treatment x predictor interaction)

Systematic Review and Field Synopsis

OPEN ACCESS Freely available online

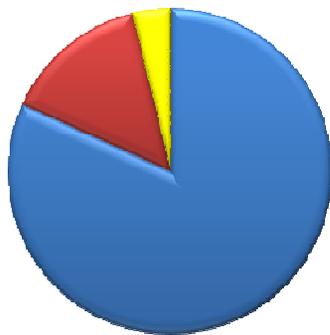


Fulfilling the Promise of Personalized Medicine? Systematic Review and Field Synopsis of Pharmacogenetic Studies

**Michael V. Holmes¹, Tina Shah¹, Christine Vickery¹, Liam Smeeth², Aroon D. Hingorani^{1,3}^{*},
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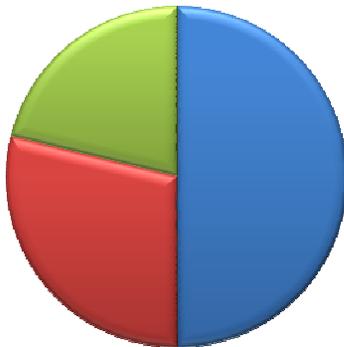
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Characteristics of pharmacogenetic studies



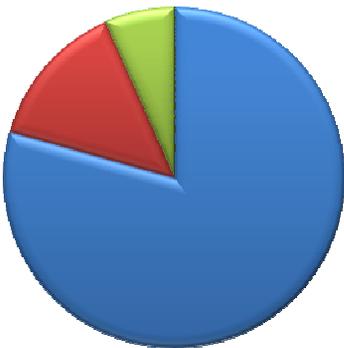
- Europe/ N. America/ Australasia
- Asia
- Elsewhere

Mainly of Europeans



- Drug target genes
- Drug handling genes
- Somatic

Mainly of drug targets not metabolising enzymes



- Intended effect
- Adverse effect
- Both

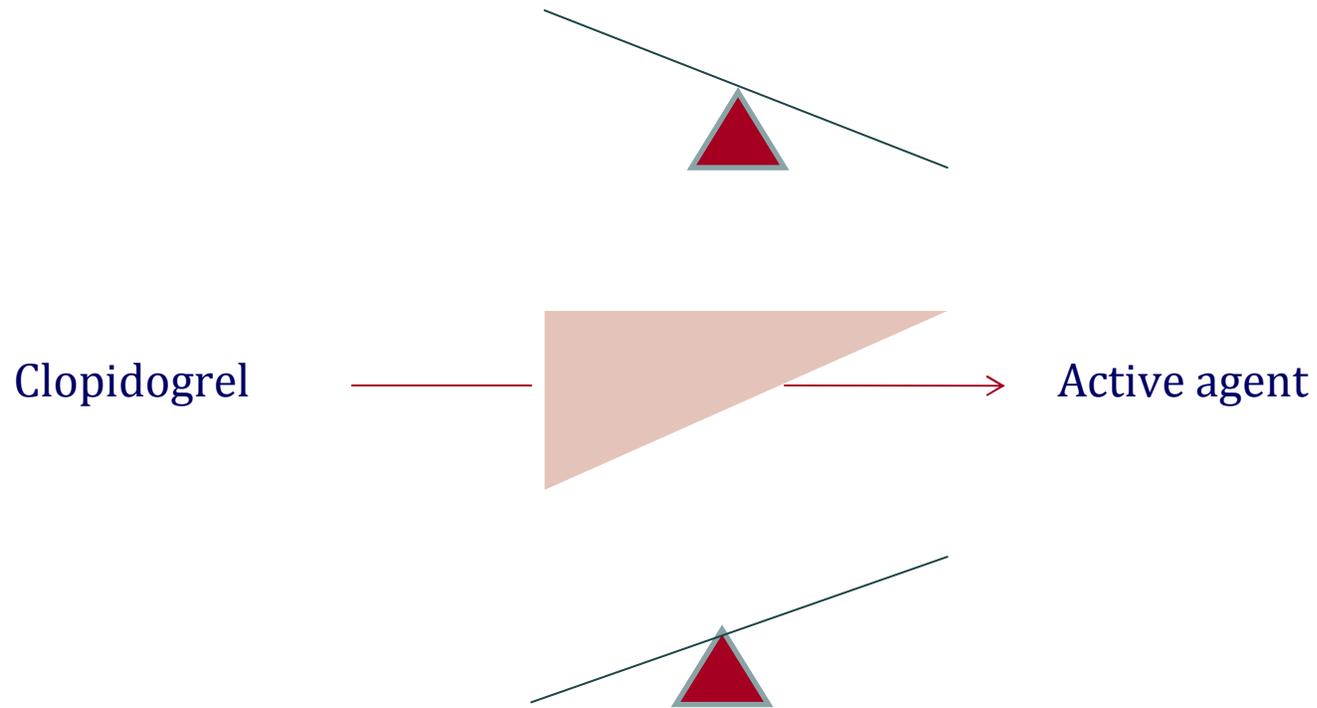
Mainly of intended rather than adverse effects

Effect of CYP2C19 genotype on clopidogrel response

Clopidogrel response

CYP 2C19

*1/*17 – fast metabolisers



CYP 2C19

*2/*3/*4/*5/*6/*7/*8 – poor metabolisers

FDA guidance

www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm

 U.S. Department of Health & Human Services

 www.hhs.gov

 U.S. Food and Drug Administration

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FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

Safety Announcement

Additional Information for Patients

Additional Information for Healthcare Professionals

Data Summary

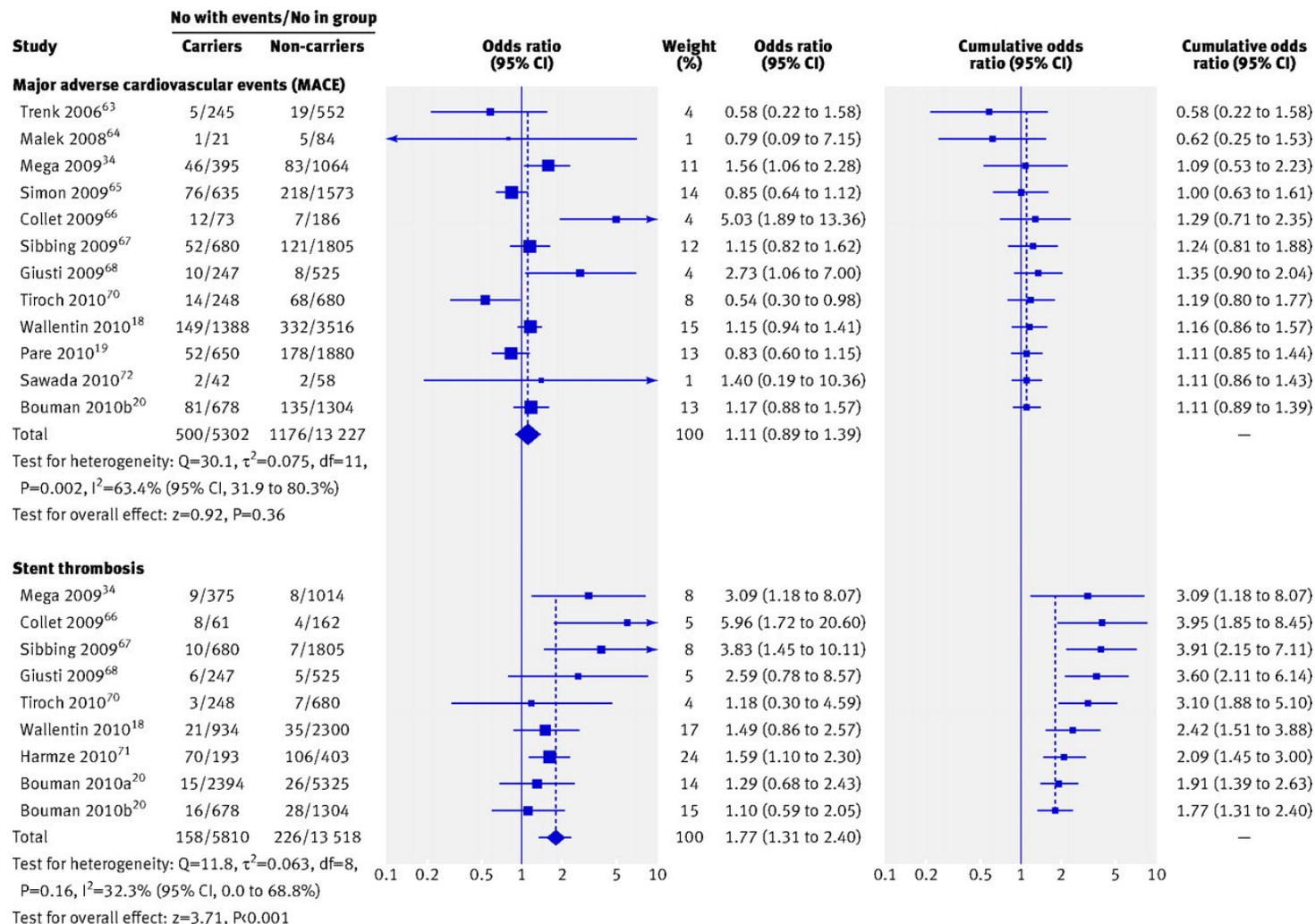
Safety Announcement

[03-12-2010] The U.S. Food and Drug Administration (FDA) has added a *Boxed Warning* to the label for Plavix, the anti-blood clotting medication. The *Boxed Warning* is about patients who do not effectively metabolize the drug (i.e. "poor metabolizers") and therefore may not receive the full benefits of the drug.

The *Boxed Warning* in the drug label will include information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

Association between loss of function polymorphisms of CYP2C19 and major adverse cardiovascular events (MACE) or stent thrombosis in patients with coronary artery disease taking clopidogrel treatment.



Bauer T et al. *BMJ* 2011;**343**:bmj.d4588



Conclusions

- Biomarkers of treatment response offer potential for more cost-effective and safe use of medical interventions
- The design, analysis and reporting of outcomes of studies of treatment response require careful consideration
- The failure to carefully consider these issues may lead to delay the clinical development of valuable biomarkers of treatment response or to premature adoption of poorly validated tests.