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

Aroon Hingorani
Centre for Clinical Pharmacology, UCL Division of Medicine
and
Genetic Epidemiology Group,
UCL Department of Epidemiology and Public Health

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 1or 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

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PLoS one

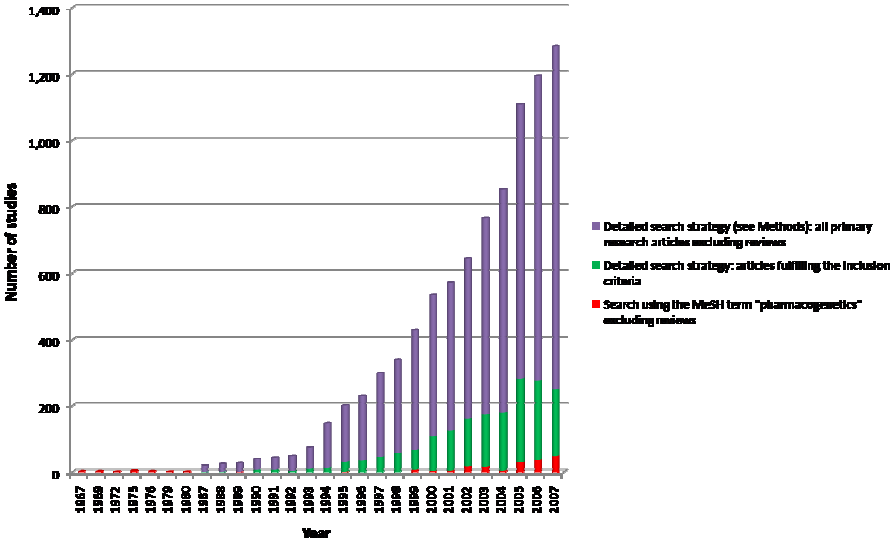
Fulfilling the Promise of Personalized Medicine? Systematic Review and Field Synopsis of Pharmacogenetic Studies

Michael V. Holmes[1], Tina Shah[1], Christine Vickery[1], Liam Smeeth[2], Aroon D. Hingorani[1,3]*, Juan P. Casas[2]*

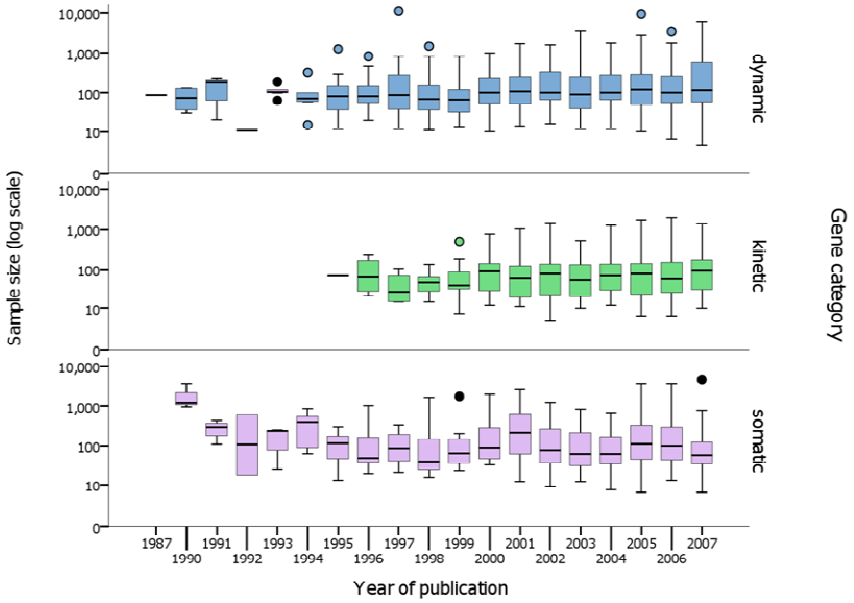
1 Centre for Clinical Pharmacology, University College London, London, United Kingdom, **2** Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom, **3** Department of Epidemiology, University College London, London, United Kingdom

Current Problems revealed

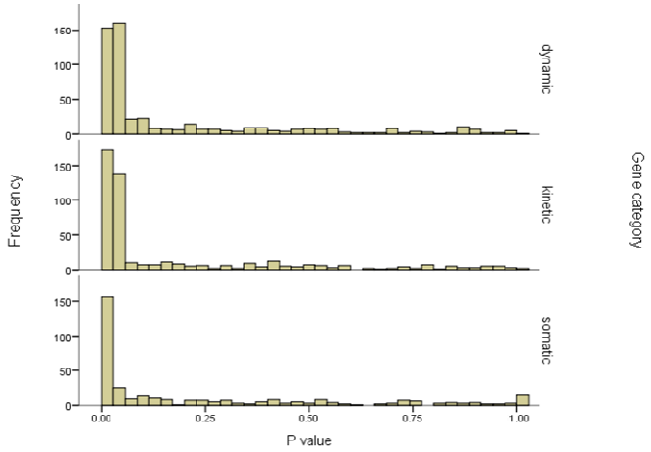
Predominance of reviews



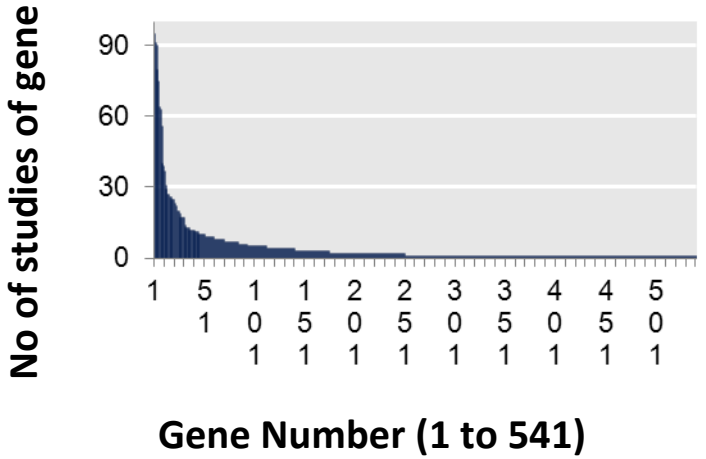
Small sample size



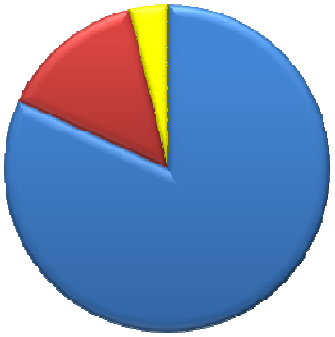
Higher prior odds or significance chasing bias?



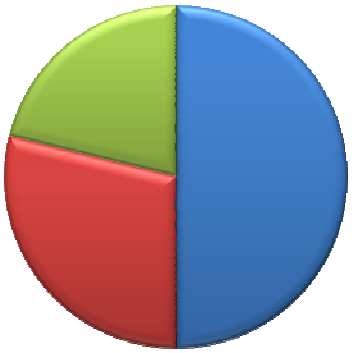
Mile wide inch deep



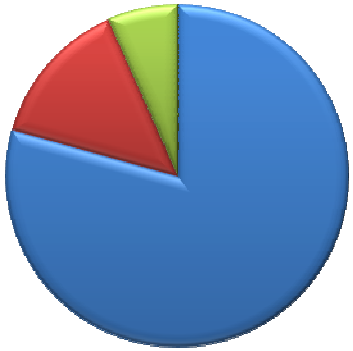
Characteristics of pharmacogenetic studies



Mainly of Europeans



Mainly of drug targets not metabolising enzymes

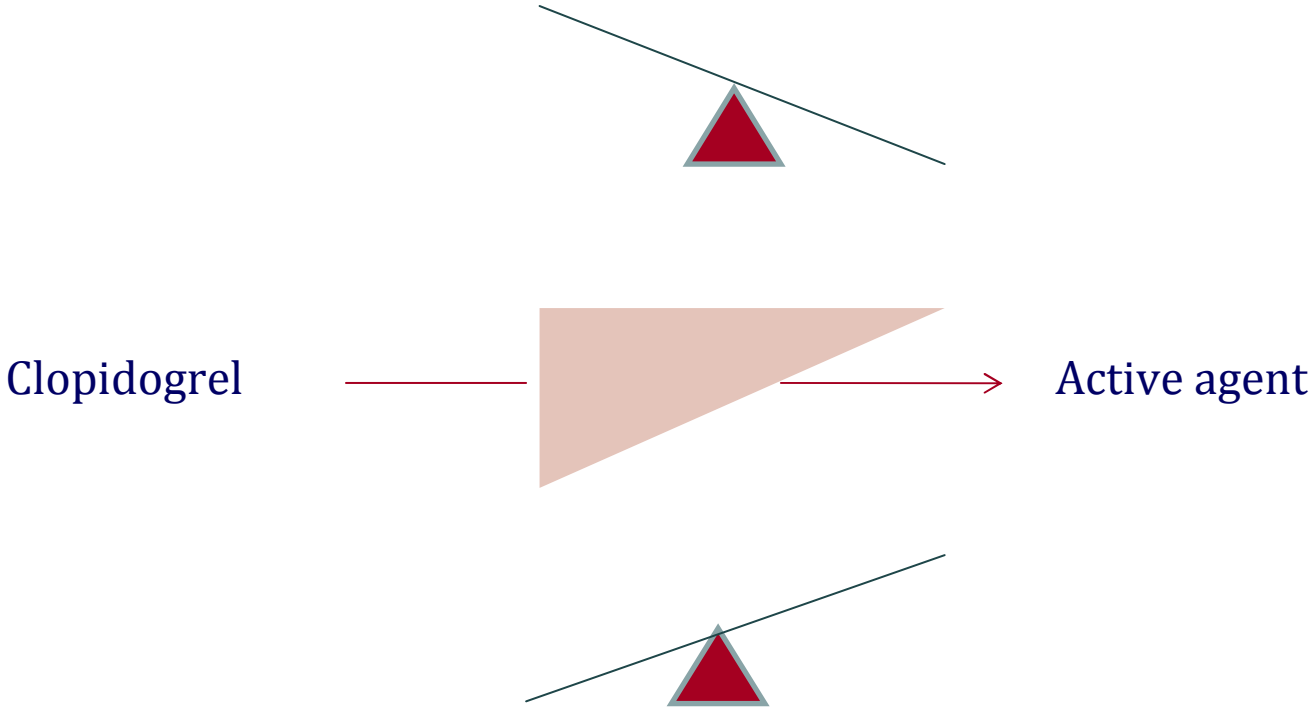


Mainly of intended rather than adverse effects

Effect of CYP2C19 genotype on clopidogrel response

Clopidogrel response

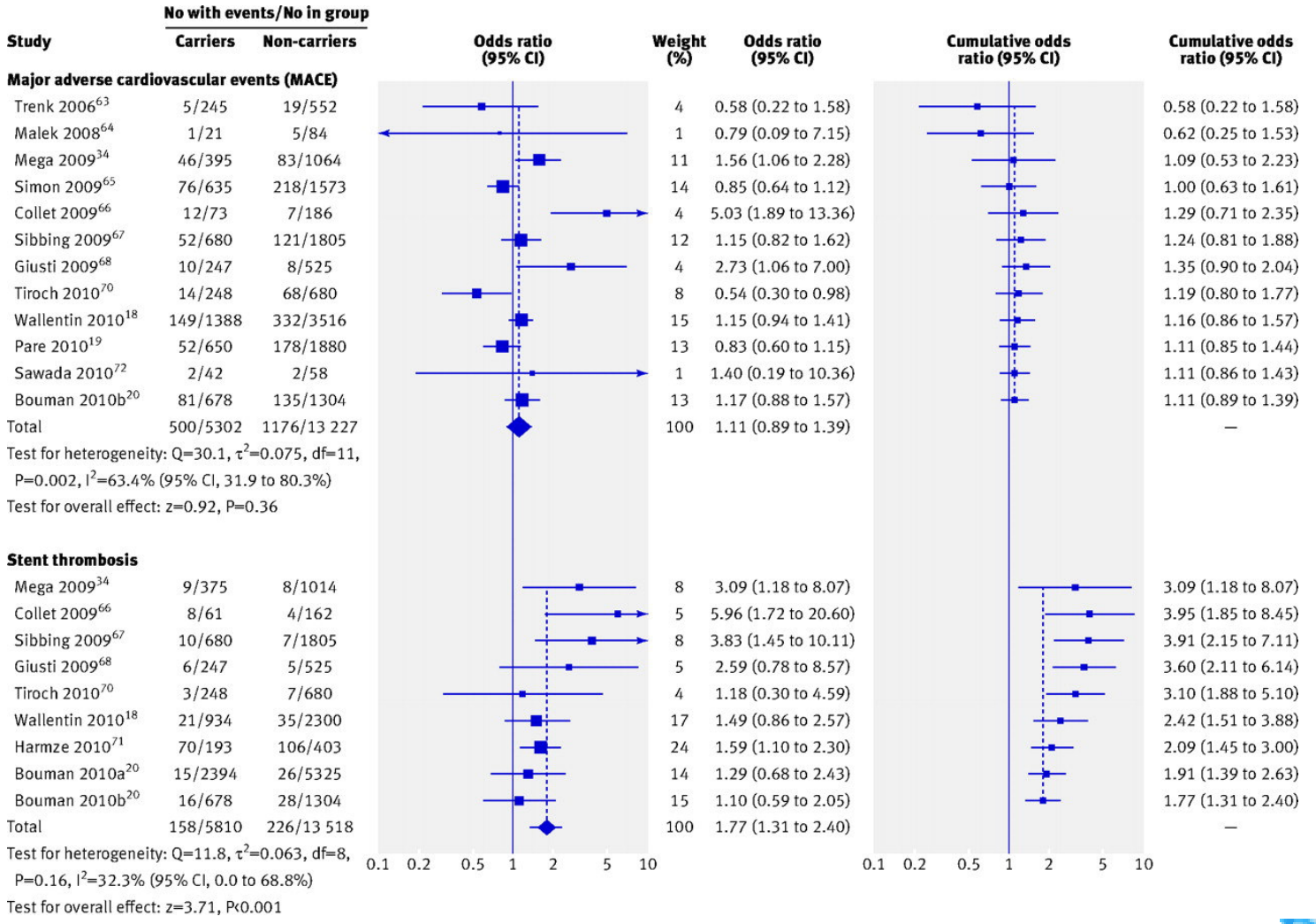
CYP 2C19
*1/*17 – fast metabolisers



CYP 2C19
*2/3/4/5/6/7/8 – poor metabolisers

FDA guidance

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.