Quantitative benefit-risk analysis based on linked PKPD and health outcome modelling

Professor Dyfrig Hughes

Centre for Health Economics & Medicines Evaluation

PRIFYSGOL BANGOR UNIVERSITY

MRC Hubs for Trials Methodology Research

North West Hub

Health outcome modelling

- Explicit framework for considering:
  - Long-term outcomes (length of life, quality of life)
  - Patient preferences
  - Value of additional information
- Preferred approach to Health Technology Assessment (e.g. NICE)
- Compatible with economic outcomes
  - Cost per Quality-Adjusted Life-Years (QALYs)

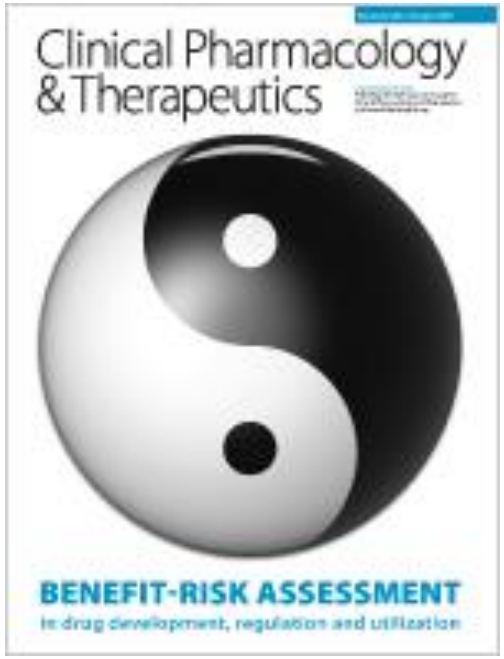
nature publishing group

PERSPECTIVES

POINT/COUNTERPOINT

Current Assessment of Risk–Benefit by Regulators: Is It Time to Introduce Decision Analyses?

DA Hughes[1], AM Bayoumi[2] and M Pirmohamed[3]



CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 82 NUMBER 2 | AUGUST 2007

Assessing A Structured, Quantitative Health Outcomes Approach To Drug Risk-Benefit Analysis

Using a health outcomes model to assess drug safety and benefits together could promote consistency and comparability across products and diseases.

by Louis P. Garrison Jr., Adrian Towse, and Brian W. Bresnahan

ABSTRACT: Regulatory authorities make difficult risk-benefit decisions when approving new drugs. Food and Drug Administration (FDA) advisory committees and reviewers must consider a complex body of evidence, including efficacy and safety results of trials, disease epidemiology, potential side effects, and patients' needs. However, this menu of information is not usually presented in a consistent and integrated framework. The members of an FDA review panel vote with some unobserved, implicit weighting of the evidence. This paper argues that outcomes research tools for modeling long-term health outcomes, measuring health preferences, and establishing the value of additional information could provide a more structured, transparent, and quantitative process of assessing risk-benefit balance. [*Health Affairs* 26, no. 3 (2007): 684–695; 10.1377/hlthaff.26.3.684]

Case study 1: Clopidogrel

nature publishing group

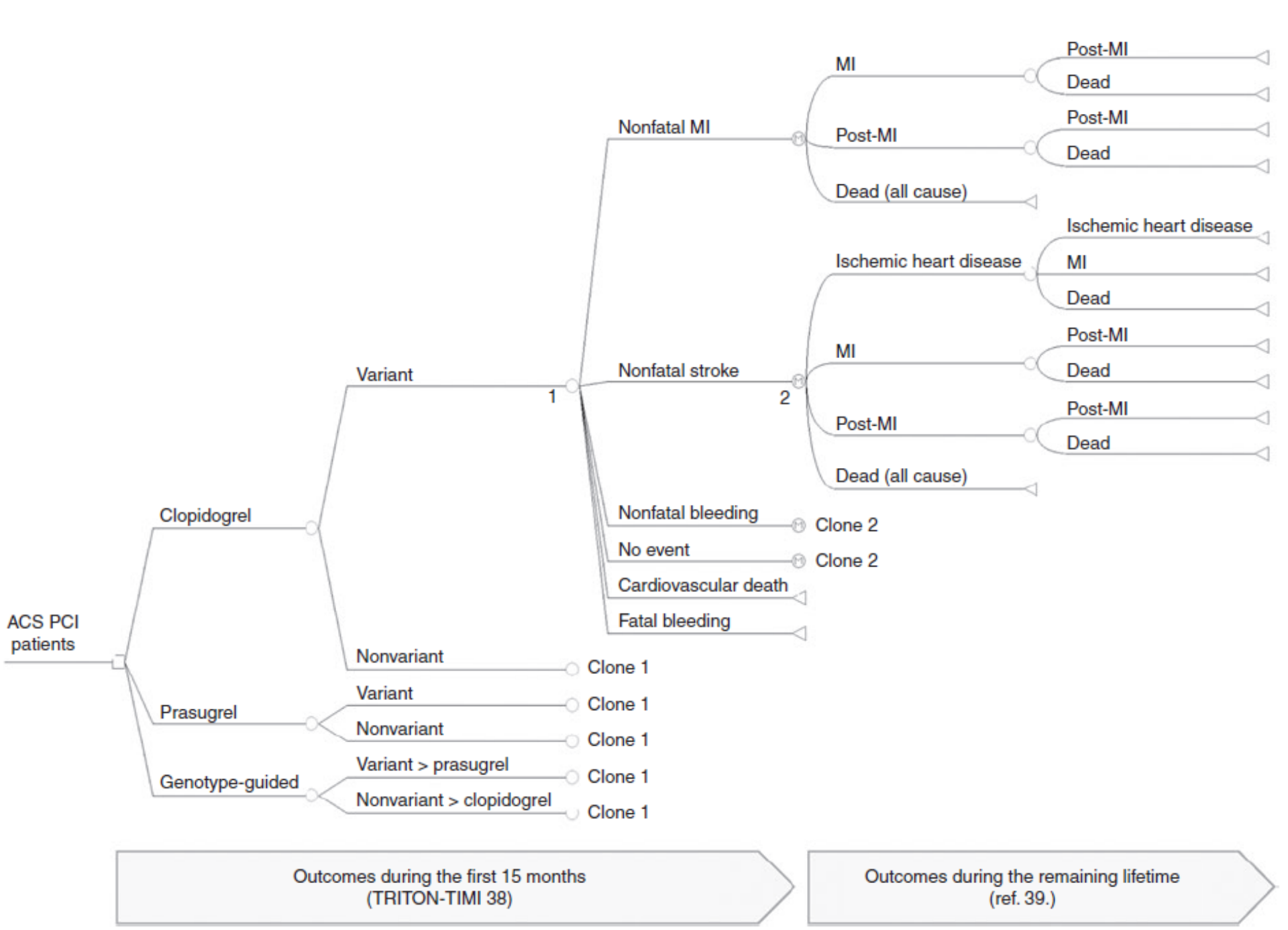
ARTICLES

See COMMENTARY page 769

A Risk–Benefit Assessment of Prasugrel, Clopidogrel, and Genotype-Guided Therapy in Patients Undergoing Percutaneous Coronary Intervention

GF Guzauskas[1,2], DA Hughes[3], SM Bradley[4] and DL Veenstra[1,2,5]

- Clopidogrel with aspirin is the standard of care to reduce the risk of thrombotic events after percutaneous coronary intervention (PCI)
- Prasugrel - associated with significantly lower rates of thrombotic events as compared with clopidogrel; but has a higher risk of major bleeding
- Clopidogrel-treated patients with reduced-function *CYP2C19* genetic variants have higher risk of thrombotic events vs patients without these variants


ACS PCI patients
Clopidogrel
Prasugrel
Genotype-guided
Variant
Nonvariant
Variant
Nonvariant
Variant > prasugrel
Nonvariant > clopidogrel
Clone 1
Clone 1
Clone 1
Clone 1
Clone 1
1
Nonfatal MI
Nonfatal stroke
Nonfatal bleeding
No event
Cardiovascular death
Fatal bleeding
Clone 2
Clone 2
2
MI
Post-MI
Dead (all cause)
Ischemic heart disease
MI
Post-MI
Dead (all cause)
Post-MI
Dead
Post-MI
Dead
Ischemic heart disease
MI
Dead
Post-MI
Dead
Post-MI
Dead
Outcomes during the first 15 months
(TRITON-TIMI 38)
Outcomes during the remaining lifetime
(ref. 39.)

Results

- Prasugrel demonstrated little difference in net benefit as compared with clopidogrel

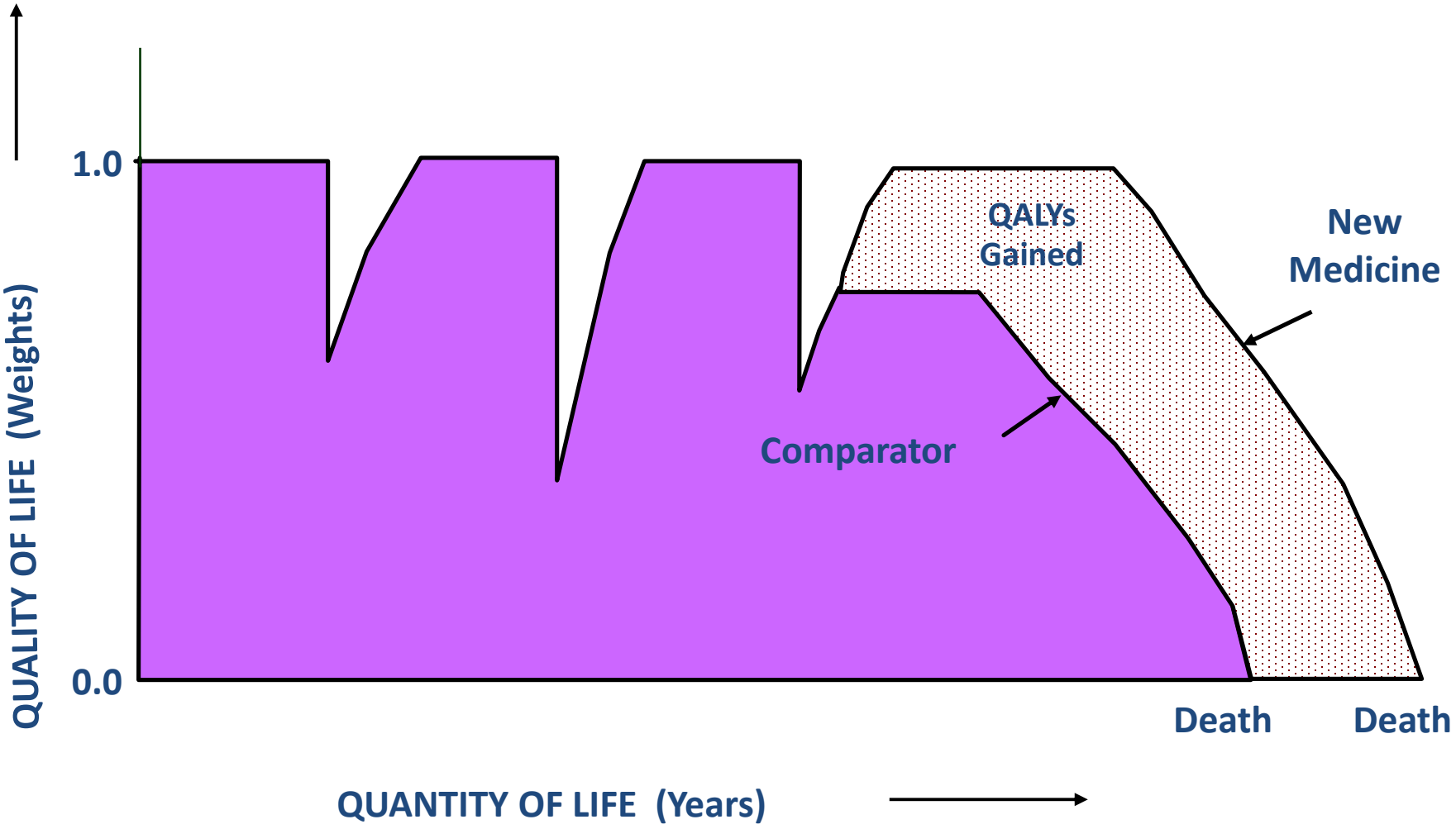
  +0.02 QALYs; (95% CR, −0.23 to 0.21)

- The genotype-guided strategy had
  - 93% probability of greater net benefit as compared with clopidogrel (+0.05 QALYs; 95% CR, −0.02 to 0.11)
  - 66% probability of greater net benefit as compared with prasugrel (+0.03 QALYs; 95% CR, −0.13 to 0.24)

QALY paradigm

- Years of life weighted by quality of life
- QoL based on utilities, which are preference-based outcomes
  - Respondents select length of time (t) in full health that they regard as equivalent to 10 years in health state X
  - Utility for health state X = t/10

Quality-Adjusted Life-Years (QALYs)



Case study 2: NOACs

nature publishing group ARTICLES

Comparative Effectiveness of Dabigatran, Rivaroxaban, Apixaban, and Warfarin in the Management of Patients With Nonvalvular Atrial Fibrillation

J Pink[1], M Pirmohamed[2] and DA Hughes[1]

Received 21 September 2012; accepted 1 April 2013; advance online publication 5 June 2013. doi:10.1038/clpt.2013.83

CLINICAL PHARMACOLOGY & THERAPEUTICS

- Dabigatran, rivaroxaban and apixaban
  - Three new oral anticoagulants
  - Evidence on comparative efficacy to warfarin demonstrated in the RE-LY, ROCKET-AF and ARISTOTLE trials
- Primary outcome of stroke or systemic embolism
  - superiority of dabigatran (1.11% v 1.71% /year; $p<0.001$) and
  - apixaban (1.27% v 1.60% /year; $p=0.01$) and
  - non-inferiority of rivaroxaban (2.1% v 2.4% /year; $p=0.12$)

Adverse events

- Rates of major bleeding were not significantly different between dabigatran 150mg and warfarin or between rivaroxaban and warfarin, but apixaban was associated with a lower risk of major bleeding (2.13% v 3.09% per year; $p<0.001$)

Quantitative indirect BRA

- Adjusted, indirect comparison
  - to assess relative benefits and harms, and help guide treatment selection
- Discrete event simulation
  - models risks of occurrence of clinical events and outcomes from patients' characteristics which are updated according to time and event history

Methods

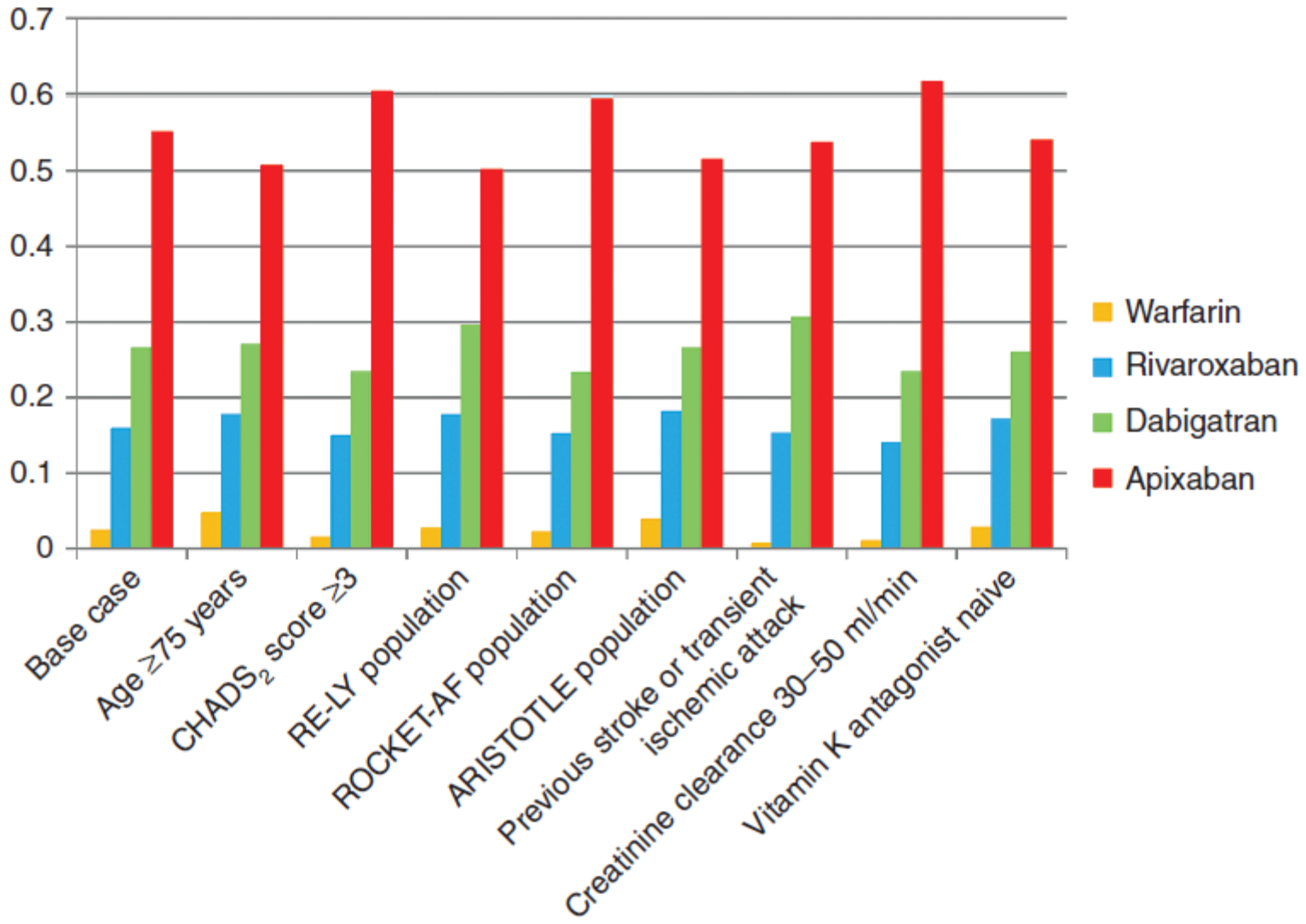
- Stroke risk profile of the US atrial fibrillation population, in terms of $CHADS_2$ scores
- Bucher method of adjustment for indirect comparisons among trials
- Probabilities of treatment discontinuation
- Utility scores from the US Medical Expenditure Panel Survey of several thousand patients

Table 1 Lifetime estimates of event rates, net health benefits, and incremental differences vs. comparator, derived from probabilistic sensitivity analysis

Referent	Mean estimate (95% central range)	Mean difference (95% central range)	Comparator
Quality-adjusted life-years			
Warfarin	5.636 (5.546, 5.733)	−0.095 (−0.242, 0.052)	Rivaroxaban
Rivaroxaban	5.731 (5.631, 5.834)	−0.011 (−0.164, 0.144)	Dabigatran
Dabigatran	5.742 (5.652, 5.854)	−0.024 (−0.174, 0.130)	Apixaban
Apixaban	5.766 (5.652, 5.881)	0.130 (−0.029, 0.265)	Warfarin
Life-years			
Warfarin	9.638 (9.498, 9.737)	−0.092 (−0.286, 0.120)	Rivaroxaban
Rivaroxaban	9.729 (9.579, 9.865)	−0.034 (−0.241, 0.172)	Dabigatran
Dabigatran	9.763 (9.604, 9.893)	−0.045 (−0.254, 0.147)	Apixaban
Apixaban	9.808 (9.655, 9.946)	0.171 (−0.031, 0.362)	Warfarin
Stroke or systemic embolism			
Warfarin	0.303 (0.264, 0.339)	0.020 (−0.033, 0.074)	Rivaroxaban
Rivaroxaban	0.283 (0.238, 0.319)	0.031 (−0.029, 0.083)	Dabigatran
Dabigatran	0.251 (0.213, 0.301)	0.050 (−0.001, 0.099)	Apixaban
Apixaban	0.201 (0.169, 0.254)	−0.102 (−0.154, −0.050)	Warfarin

Referent	Mean estimate (95% central range)	Mean difference (95% central range)	Comparator
Transient ischemic attack			
Warfarin	0.123 (0.091, 0.158)	0.031 (–0.019, 0.084)	Rivaroxaban
Rivaroxaban	0.092 (0.070, 0.123)	–0.006 (–0.057, 0.046)	Dabigatran
Dabigatran	0.097 (0.069, 0.128)	0.020 (–0.034, 0.069)	Apixaban
Apixaban	0.077 (0.055, 0.104)	–0.046 (–0.093, 0.008)	Warfarin
Intracranial hemorrhage			
Warfarin	0.073 (0.064, 0.081)	0.014 (–0.002, 0.026)	Rivaroxaban
Rivaroxaban	0.059 (0.052, 0.066)	0.018 (0.000, 0.025)	Dabigatran
Dabigatran	0.040 (0.035, 0.047)	–0.002 (–0.015, 0.014)	Apixaban
Apixaban	0.042 (0.033, 0.047)	–0.031 (–0.046, -0.013)	Warfarin
Major bleed (including intracranial hemorrhage)			
Warfarin	0.307 (0.262, 0.347)	–0.021 (–0.076, 0.036)	Rivaroxaban
Rivaroxaban	0.328 (0.283, 0.374)	0.017 (–0.037, 0.069)	Dabigatran
Dabigatran	0.311 (0.274, 0.363)	0.069 (0.014, 0.115)	Apixaban
Apixaban	0.242 (0.205, 0.278)	–0.065 (–0.116, –0.010)	Warfarin

Probabilities of treatment with highest net benefit by patient subgroup



Main findings

- Apixaban achieved highest net benefit, followed by dabigatran, rivaroxaban then warfarin
- No subgroup in which the probability of apixaban being the most effective is below 50%, and none where the probability of warfarin being the most effective is above 5%

Case study 3: PGx warfarin

- Variability in response to warfarin can be partly explained by genetic polymorphisms in
  - *CYP2C9 , VKORC1*
- People with variant alleles are at an increased risk of over-anticoagulation and bleeding
- Dosing algorithms based on PGx may result in better INR control, and hence better clinical outcomes

- No RCTs comparing PGx-warfarin with NOACs
- Multiple dosing algorithms possible

Simulation structure

- Population PKPD model of warfarin used to predict time below, in and above INR range based on a range of algorithms (NONMEM)
- Data from a systematic review used to link time in range to clinical endpoints
- Health outcome model used to extrapolate to a lifetime horizon and compare different treatments in terms of QALYs accrued
  - Based on discrete event simulation described earlier

Population PKPD model

- From Hamberg et al, CPT 2010;87:727-34 which predicts INR measurements based on dose, age and genetic information
- Patient characteristics based on those of the UK atrial fibrillation population
- Model allows for explicit incorporation of non-adherence

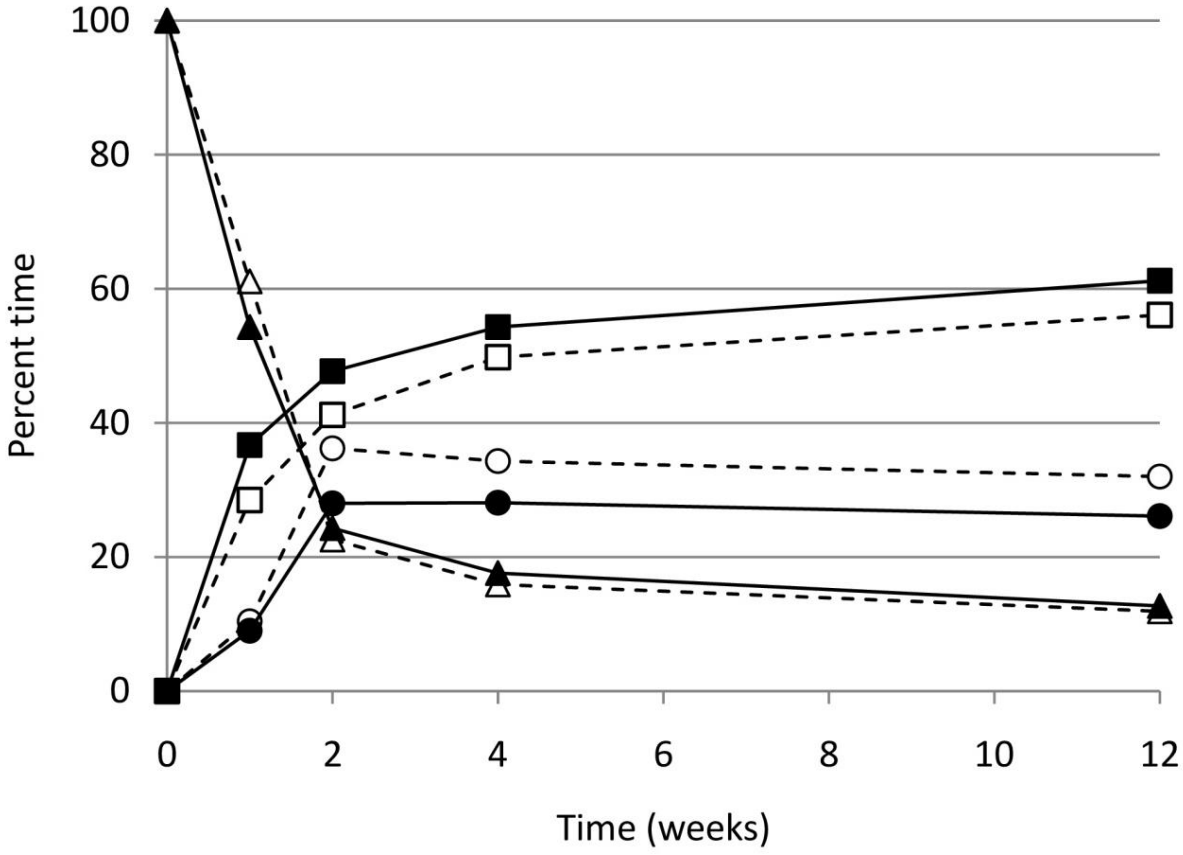
Dosing algorithms

- Loading phase
  - To achieve correct INR range as quickly as possible without over anticoagulating
- Predicted maintenance dose
  - To predict the most likely dose to maintain a patient in range in the long term
- Maintenance phase
  - Further dose adjustments are made based on INR at clinic visits
- Genetic information can be used in each stage

Algorithm selection - Example

- Loading dose: 10, 10, 5mg (days 1,2,3)
- Predicted maintenance dose: IWPC algorithms
  - A clinical algorithm based on age, height, weight, ethnicity, use of amiodarone and enzyme inducers
  - A pharmacogenetic algorithm which uses all these variables and genetic information
- Doses adjusted with the Fennerty algorithm

Population PKPD results – INR



time in range (INR 2-3)

time above range (INR >2)

time below range (INR <2)

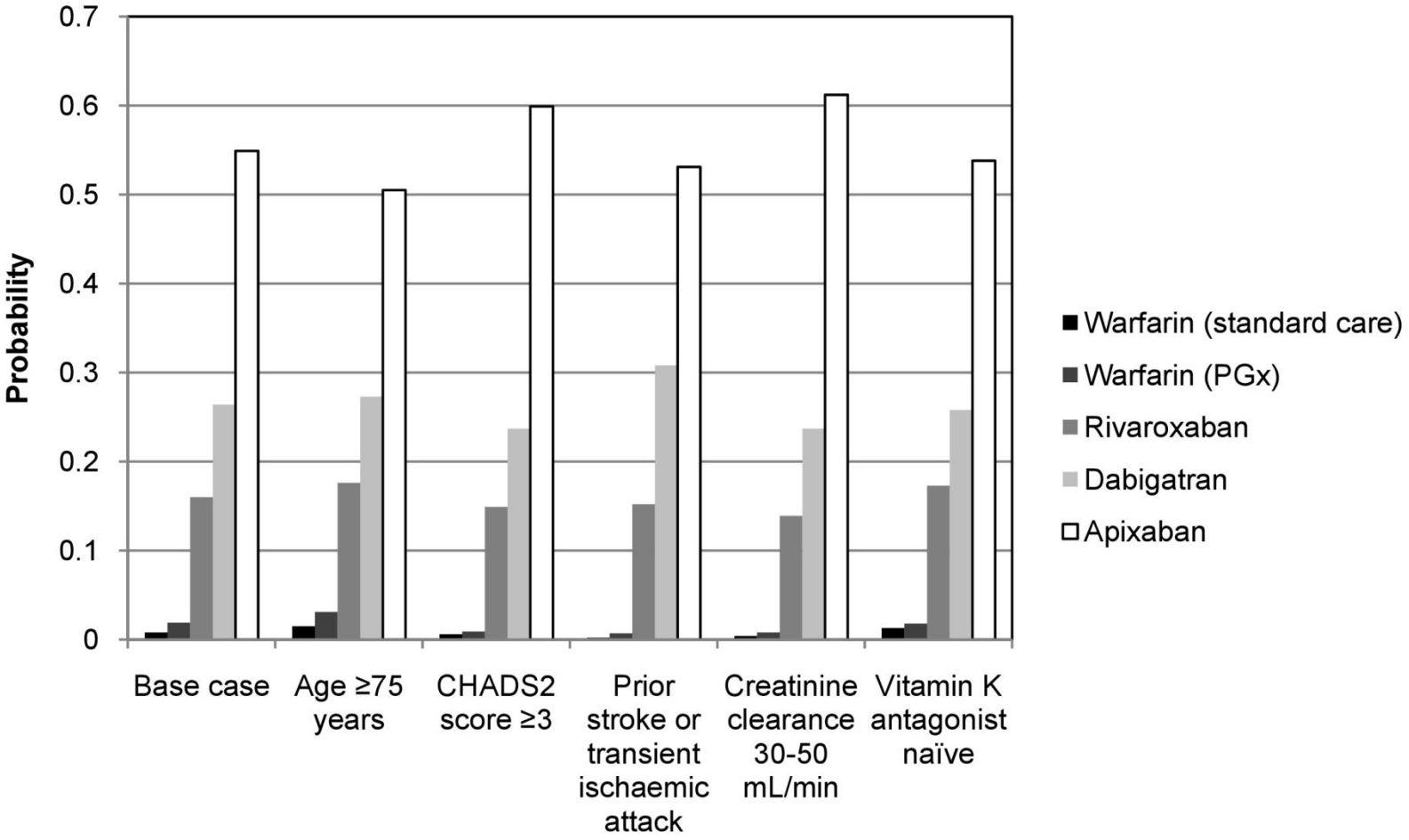
Open symbols (dashed lines) clinical algorithms
Filled symbols (solid lines) pharmacogenetic algorithm

Results

	Life extension (months)	QALYs (95% CR)
PGx warfarin	0.003	0.0031 (0.1649, 0.1327)
Rivaroxaban	1.11	0.0957 (-0.0510, 0.2431)
Apixaban	2.06	0.1298 (-0.0290, 0.2638)
Dabigatran	1.47	0.1065 (-0.0493, 0.2489)

All compared with warfarin dosed according to clinical algorithm

Sub-group analysis



Probability of each treatment accruing the largest number of QALYs

Discussion (1)

- QALYs may be considered as a measure of net health benefit
  - Derived from ***patient*** valuation of benefits and harms
- Health outcome modelling allows explicit consideration of treatment consequences
- PKPD model outputs serving as HOM inputs has utility in:
  - Early estimation of balance of benefits & harms
  - Identification of sub-populations with favourable benefit-risk profile
  - Assessing inter-patient variability and protocol deviations
- Natural extension to model-based drug development

Discussion (2)

- Linking with pharmacoeconomic models (PKPDPE)
- PKPDPE-based clinical trial simulation to inform protocol design
  - Value of information analysis to quantify the value of future research in reducing parameter uncertainty
- Early estimates of cost-effectiveness
  - Inform stop/go decisions
  - Price determination (value-based pricing)

Economic Evaluations During Early (Phase II) Drug Development

A Role for Clinical Trial Simulations?

Dyfrig A Hughes and *Tom Walley*

Prescribing Research Group, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

Mechanism-Based Approach to the Economic Evaluation of Pharmaceuticals

Pharmacokinetic/Pharmacodynamic/Pharmacoeconomic Analysis of Rituximab for Follicular Lymphoma

Joshua Pink,[1] *Steven Lane*[2] and *Dyfrig A. Hughes*[1]

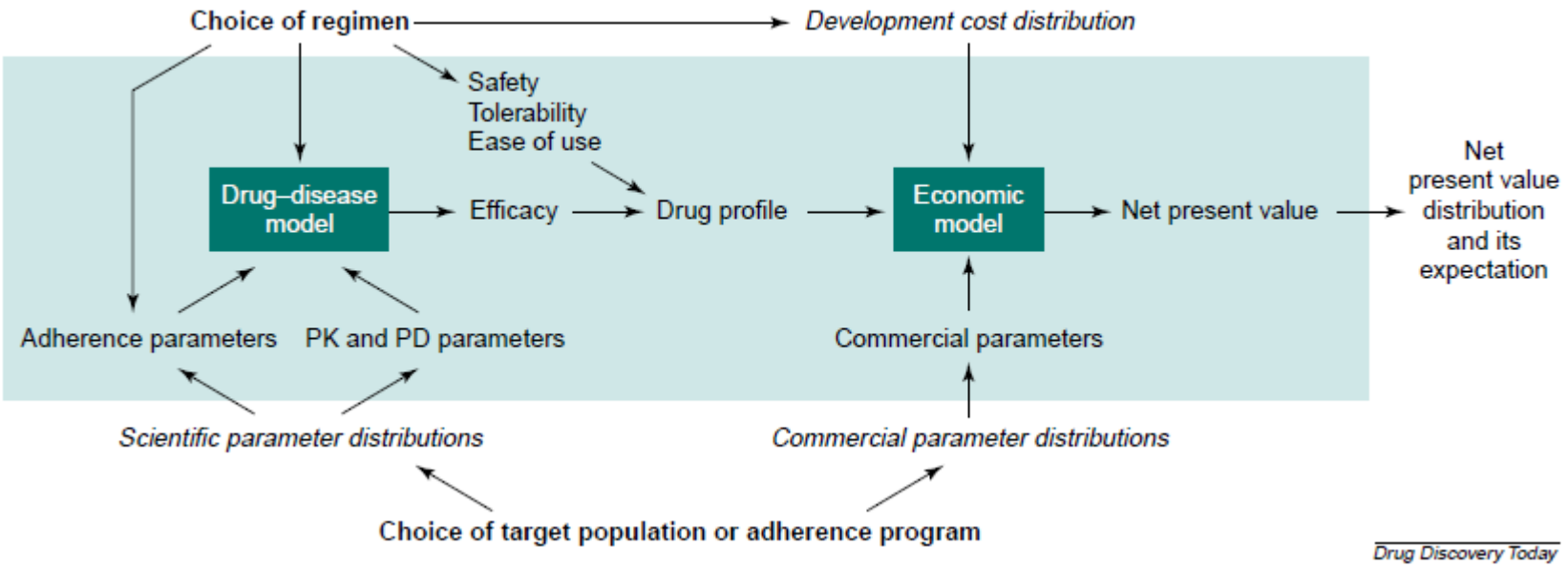
1 Centre for Health Economics and Medicines Evaluation, Institute of Medical and Social Care Research, Bangor University, Bangor, Wales

2 Department of Biostatistics, University of Liverpool, Liverpool, England

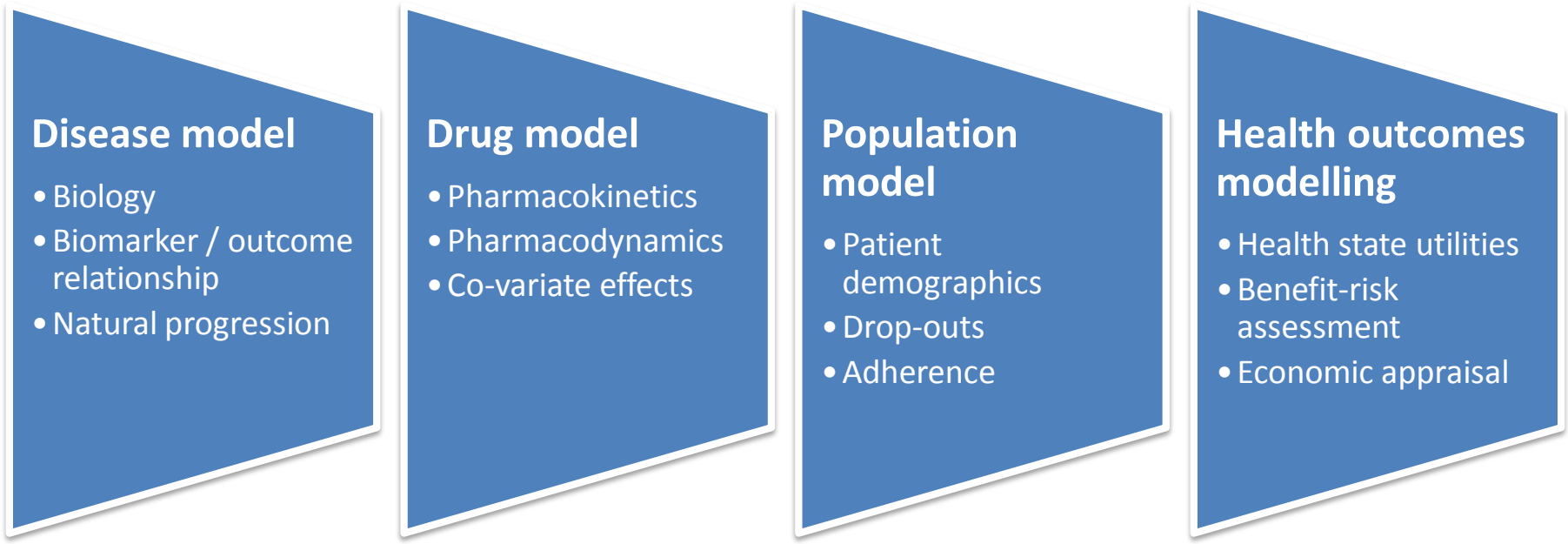
Lewis Sheiner Prize, PAGE 2011, Athens

Combining drug–disease and economic modelling to inform drug development decisions

Bill Poland and Russell Wada



A natural extension to MBDD



Milligan et al, CPT 2013 doi:10.1038/clpt.2013.54

Acknowledgements

- MRC funding
- Munir Pirmohamed, Steven Lane (University of Liverpool)
- Greg Guzauskas, Steve Bradley, Dave Veenstra (University of Washington, Seattle)
- Joshua Pink (formerly Bangor University)

Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

Mobility
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-care
- I have no problems with self-care
- I have some problems washing and dressing myself
- I am unable to wash and dress myself

Usual activities (eg. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/discomfort
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

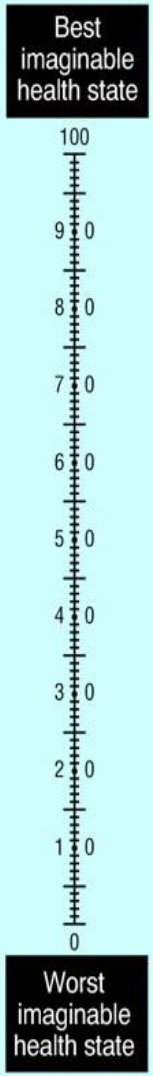
Anxiety/depression
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Your own health state today

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Your own health state today



EQ-5D preference weights

- Health state:
  - Mobility 1
  - Self-care 1
  - Usual activities 2
  - Pain/ Discomfort 2
  - Anxiety /Depression 3

  - **Health utility 0.255**