Genetic-Guided Pharmacotherapy for Cardiovascular Disease: A Systematic and Critical Review of Economic Evaluations

EE131

Ka Keat Lim[1], Rositsa Koleva-Kolarova[2], Hanin Farhana Kamaruzaman[3,4], Yoko Laurence[1], Ahmad Amir Kamil[1], Phil Chowienczyk[5], Charles Wolfe[1,6], Julia Fox-Rushby[1]

(1) School of Life Course & Population Sciences, King's College London, UK, (2) Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, UK, (3) Health Economics and Health Technology Assessment (HEHTA), School of Health and Wellbeing, University of Glasgow, UK (4) Malaysian Health Technology Assessment Section (MaHTAS), Medical Development Division, Ministry of Health Malaysia, Malaysia (5) King's College London British Heart Foundation Centre, St. Thomas' Hospital, London, UK (6) National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London, UK

BACKGROUND

- Genetic-guided pharmacotherapy (PGx) is not recommended in clinical guidelines for patients at risk of or diagnosed with cardiovascular diseases (CVD).
- However, the role of genes in predisposing to CVD or modifying response to CVD pharmacotherapy has been extensively studied in economic evaluations.
- Decreasing cost and wider availability of genetic testing suggests that PGx may be useful in the management of CVD.

STUDY OBJECTIVES

- To examine the extent and quality of evidence from economic evaluations (EEs) of PGx in CVD.

METHODS

SEARCH STRATEGIES

- Systematic search of three general (Medline, Embase, Web of Science Core Collection) and three subject-specific bibliographic databases (Econlit, NHS Economic Evaluation Database (NHSEED), Health Technology Assessment (HTA)) from inception until 27 June 2022, supplemented by searches on websites of four HTA agencies (UK NICE, French HAS, Canadian CADTH, Dutch ZonMw).
- Three concepts: economic evaluation (EE), genetic-guided pharmacotherapy (PGx), CVD.

STUDY SELECTION

- Two researchers (KKL and RKK independently screened the articles for eligibility.
- Any disagreements were resolved via consensus / discussions.

Inclusion criteria	Exclusion criteria
• Full EE providing both costs and outcomes • Genetic testing followed by pharmacotherapy for individuals with or at risk of CVD	• Hypothetical genetic tests • Study protocols, editorials, opinion articles, conference abstracts, letters.

DATA EXTRACTION

- Using a bespoke data extraction form, we extracted the study design, study and patient characteristics, details of interventions and comparators, analyses and findings of base-case conclusions (whether PGx was cost-saving, cost-effective, not cost effective or dominated by comparator).

METHODOLOGICAL QUALITY ASSESSMENT

- Two researchers (KKL, RKK, HFK, AAK worked in pairs) independently assessed methodological quality using CHEC-Extended [1,2]. CHEC-Extended comprises 20 items. Each item was rated "Yes / Rather Yes", "No / Rather No" or "Unclear".
- Any disagreement was resolved via consensus / discussions.

DATA ANALYSES & PRESENTATIONS

- Study design, study characteristics & patient characteristics – We analysed the number and percentage of EEs in each category.
- Interventions – We categorised PGx based on the purpose of testing, the pharmacotherapy (Px) affected, and how the Px was expected to change based on genetic test findings.
- Comparators – We categorised comparators into three – no testing no Px, no testing universal Px or non-genetic test guide Px.
- We determined whether a PGx was cost-effective based on reported or calculated incremental net monetary benefit (INMB) in the base-case.
- We identified variables that changed the base-case conclusions based on the willingness-to-pay threshold declared in each EE.

RESULTS

STUDY SELECTION FLOW CHART

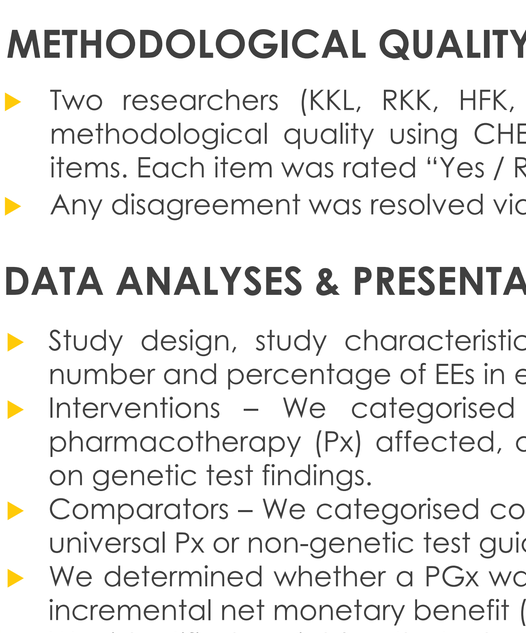

Figure 1 Study selection flow chart.

Study Characteristics (N = 92):

- 88% used cohort models - models accounted for the effect of PGx using relative risk reduction (n=41), lower probabilities of adverse events (n=23), time within treatment biomarker's therapeutic range (n=15) or test accuracy (n=13).
- 85% performed cost-utility analyses
- 78% published 2010 or after
- 70% adopted healthcare perspective only
- 57% funded by public or non-profit
- 47% from North America, 36% from Europe
- 22% examined ≥65 years old

Types of CVD

- 38% coronary artery disease (CAD)
- 20% atrial fibrillation (AF)
- 20% familial hypercholesterolemia (FH)
- 11% venous thromboembolism (VTE)
- 11% others (e.g., hypertension, heart failure), or non-specific.

RESULTS

TYPES OF PGX AND COMPARATORS

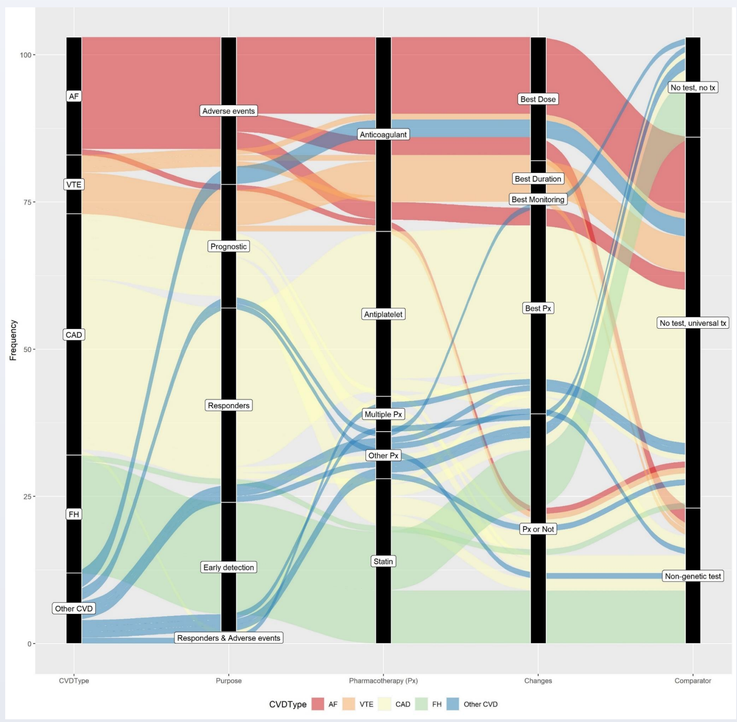

Table 2 Summaries of genetic-guided pharmacotherapy for CVD examined in the included EEs and their comparators.

- 103 unique comparisons of a PGx vs a comparator
- PGx defined as the purpose of testing, pharmacotherapy (Px), and changes in Px after testing

Purpose of Testing	Px	Px Changes after testing	Comparators
To identify responders to Px (32%)	Anticoagulant (32%)	Px or no Px (38%)	No testing, universal Px (61%)
To prevent adverse events from Px (24%)	Antiplatelet (27%)	Choose the best Px (35%)	Non genetic test to guide Px (22%)
To detect CVD earlier (21%)	Statins (27%)	Choose the best dose (20%)	No testing, no Px (17%)
To prognosticate CVD (20%)	Other Px (8%)	Choose the best duration (6%)	
To prevent adverse events & to identify responders (2%)	Multiple Px (6%)	Choose the best monitoring intensity (1%)	

BASE-CASE FINDINGS

Of 362 comparisons reporting quality-adjusted life years, 256 found a positive INMB (199 cost-effective, 60 dominant) and 98 negative INMB (76 not cost-effective, 22 dominated) for PGx.

FINDINGS FROM ONE-WAY SENSITIVITY ANALYSES

Of 783 variables tested in one-way sensitivity analyses, 154 changed conclusions; these were epidemiological variables (n=74), cost/unit price/resource use (n=29), effectiveness/relative effectiveness (n=35), or utility (n=13).

METHODOLOGICAL QUALITY RATINGS

Included EEs received between 6 to 19 "Yes / Rather Yes" ratings. None of the 92 included EE discussed reporting of ethics & distributional issues of PGx, 72 did not report structural assumptions and validation methods, 60 did not discuss generalisability of the findings, 36 did not report conflict of interest, 28 did not clear describe competing alternatives.

DISCUSSION

LIMITATIONS

- Findings may only be generalisable to North America and European countries.
- Findings reflect "average risk" individuals, because most EEs did not differentiate individuals at different risk levels.
- Conclusions on cost-effectiveness are based on base-case findings.
- List of variables in one-way sensitivity analyses may not be exhaustive due to incomplete reporting.

CONCLUSION

- Economic evaluation of genetic-guided pharmacotherapy for CVD have included a range of CVDs, settings, purposes of PGx and study designs.
- We plan to perform linear mixed models, regressing incremental net monetary benefit (INMB) on PGx characteristics (e.g., gene types, changes in pharmacotherapy based on test findings), controlling for other factors.
- We will discuss our findings with respect to data collection and model structures, PGx characteristics associated with value for money, challenges to data and methods of analysis.

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***Contact** : KK Lim, Research Fellow, ka_keat@kcl.ac.uk*