**The Role of Pharmacogenomics in Contemporary Cardiovascular Therapy:**

**A position statement from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy**

EF Magavern^1,2, JC Kaski^3, RM Turner4,5, H Drexel6,7, A Janmohamed8, A Scourfield9, D Burrage10, CN Floyd11,12, E Adeyeye2, J Tamargo13, BS Lewis14, Keld Per Kjeldsen15,16, A Niessner17, S Wassmann18, P Sulzgruber19, P Borry20,21, S Agewall22, AG Semb23, G Savarese24, M Pirmohamed4,5,25\*, MJ Caulfield\*1

1- William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

2- Department of Clinical Pharmacology, Cardiovascular Medicine, Barts Health NHS Trust, London, UK.

3- Molecular and Clinical Sciences Research Institute, St George's, University of London, United Kingdom

4-The Wolfson Centre for Personalised Medicine, Institute of Systems, Molecular and Integrative Biology (ISMIB), University of Liverpool, UK

5- Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

6- Vorarlberg Institute for Vascular Investigation & Treatment (VIVIT), Feldkirch, A Private University of the Principality of Liechtenstein, Triesen, FL

7-Drexel University College of Medicine, Philadelphia, USA

8- Department of Clinical Pharmacology, St George's, University of London, United Kingdom

9- Department of Clinical Pharmacology, University College London Hospital Foundation Trust, UK​

10-Whittington Health NHS Trust, London, UK

11- King’s College London British Heart Foundation Centre, School of Cardiovascular Medicine and Sciences, London, UK.

12- Department of Clinical Pharmacology, Guy’s and St Thomas’ NHS Foundation Trust, London, UK

13- Department of Pharmacology and Toxicology, School of Medicine, Universidad Complutense, Madrid, Spain

14- Cardiovascular Clinical Research Institute, Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

15- Department of Cardiology, Copenhagen University Hospital (Amager-Hvidovre), Copenhagen, Denmark.

16- Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark.

17-Department of Internal Medicine II, Division of Cardiology

Medical University of Vienna

18-Cardiology Pasing, Munich, Germany and University of the Saarland, Homburg/Saar, Germany

19-Medical University of Vienna, Department of Medicine II, Division of Cardiology

20-Center for Biomedical Ethics and Law, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium.

21- Leuven Institute for Human Genetics and Society, Leuven, Belgium.

22- Oslo University Hospital Ullevål and Institute of Clinical Sciences, University of Oslo, Oslo, Norway

23- Preventive Cardio-Rheuma clinic, department of rheumatology, innovation and research, Diakonhjemmet hospital, Oslo, Norway.

24-Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden

25-Liverpool Health Partners, Liverpool, UK.

^ joint first authorship

\*joint last authorship

Address for correspondence

Prof. JC Kaski

Molecular and Clinical Sciences Research Institute

St George’s, University of London

Cranmer Terrace

London SW17 0RE

UK

Abstract

There is a strong and ever-growing body of evidence regarding the use of pharmacogenomics to inform cardiovascular pharmacology. However, there is no common position taken by international cardiovascular societies to unite diverse availability, interpretation and application of such data, nor is there recognition of the challenges of variation in clinical practice between countries within Europe. Aside from the considerable barriers to implementing pharmacogenomic testing and the complexities of clinically actioning results, there are differences in the availability of resources and expertise internationally within Europe. Diverse legal and ethical approaches to genomic testing and clinical therapeutic application also require serious thought. As direct-to-consumer genomic testing becomes more common, it can be anticipated that data may be brought in by patients themselves, which will require critical assessment by the clinical cardiovascular prescriber. In a modern, pluralistic and multi-ethnic Europe, self-identified race/ethnicity may not be concordant with genetically detected ancestry and thus may not accurately convey polymorphism prevalence. Given the broad relevance of pharmacogenomics to areas such as thrombosis and coagulation, interventional cardiology, heart failure, arrhythmias, clinical trials, and policy/regulatory activity within cardiovascular medicine, as well as to genomic and pharmacology subspecialists, this position statement attempts to address these issues at a wide-ranging level.

**Introduction**

The completion of the human genome project in 2003 heralded an age of genomic promise1,2. Advances in genomic knowledge and sequencing technology have provided vital tools for the implementation of personalised medicine; i.e., the ability to use genetic information to select the right pharmacological agent, to be used at the right dose, for the right person, and at the right time, thereby maximising the efficacy of the intervention and minimising adverse drug reactions (ADR)2.

Pharmacogenomics (PGx) describes the role of genomic variation in drug response, which can relate to both pharmacokinetic and pharmacodynamic properties. Pharmacokinetics constitute the effect of the body on the drug, categorized into effects on absorption, distribution, metabolism, and excretion of the drug. Pharmacodynamics reflect the effect of the drug on the body. Both pharmacokinetics and pharmacodynamics influence efficacy, effectiveness, and toxicity. Many drugs are metabolized in the liver by cytochrome P450 (CYP) enzymes. These enzymes are encoded by various genes named according to their family (e.g., ‘2’) and subfamily (e.g., ‘C’), based on the amino acid structure. A full code indicates a specific gene, (e.g., *CYP2C9*). Other drug metabolizing enzymes, receptors, and transporters also play an important role in drug response. Indeed, whole genome approaches, including sequencing, are likely to identify new pharmacogenes, including in therapeutic target genes, which determine drug efficacy and/or safety. It is inevitable that the number of pharmacogenes with evidence of clinical utility will continue to increase, which makes pharmacogenomics a dynamic area.

The cost of genome sequencing has decreased exponentially with the emergence of next generation and 3rd generation sequencing technology, from 2.7 billion USD in 2003 to sequence the first human genome (which took 13 years) to less than 1,000 USD to sequence a whole genome in 20193–5. In order to implement personalised medicine, three main tools to target discovery in PGx studies are used: genome-wide association studies (GWASs), candidate gene analyses, and next generation sequencing (high throughput parallel sequencing)6. The first is an agnostic approach that locates a genome wide signal to a locus, while the candidate gene approach starts from a gene hypothesised to be significant. This will often be a gene that encodes protein targets of the drug, or proteins that are involved in drug pharmacokinetics. When genetic loci or single nucleotide polymorphisms (SNPs) of interest are identified, this should be replicated and may be followed by functional validation studies, although this is not always necessary, depending on the predictive accuracy of the variant. Evidence of clinical utility needs to be gathered which depends on the clinical phenotype and the gene-drug pair. The present rate of big data-based discovery, and the scale and complexity of genomic information interpretation and translation into useful therapeutic interventions present considerable challenges. The expectations of gold standard evidence from randomised controlled trials (RCTs) for PGx may not be realistic (or indeed necessary) in PGx, as each trial would look at one or a few gene variant-drug pairs7,8.

Though PGx guided therapy has been endorsed by both regulators and international consortia, there is discordance in recommendations, and PGx has remained an area of specialist interest9.

Given the rapid advances which are occurring, there is a need for professional bodies and health systems to support prescribers in understanding, interpreting and implementing evidence-based PGx in cardiovascular medicine. This is particularly timely as many prescribers begin to find themselves increasingly confronted with patients able to access PGx information through direct-to-consumer genetic testing10. Moreover, prescribers may not have access to confirmatory testing within their place of work. Given the broad relevance of PGx to areas such as thrombosis and coagulation, interventional cardiology, heart failure, arrhythmias, clinical trials, and policy/regulatory activity within cardiovascular medicine, as well as to genomic and pharmacology subspecialists, this position statement attempts to address these issues at a wide-ranging level. The following sections address evidence for specific drug-gene pairs, as well as broad genomic approaches in cardiovascular medicine, and the potential role of genomics in clinical trials. The focus is on translational aspects most likely to be encountered by non-genomically trained practitioners in day-to-day practice.

**Anticoagulants**

**Warfarin and other vitamin K antagonists**

The coumarin derivatives, warfarin, acenocoumarol and phenprocoumon, are used to prevent or treat thromboembolism. There are differences across the World and between European countries regarding which coumarin oral anticoagulant is preferred, but collectively they remain commonly prescribed, despite the rapidly increasing use of direct oral anticoagulants (DOACs)11,12. Coumarins inhibit vitamin K epoxide reductase complex subunit 1 (VKORC1), leading to hypofunctional clotting factors II, VII, IX and X13. Coumarin derivatives are all administered as a racemate. For warfarin, the S-warfarin enantiomer is preferentially metabolised by CYP2C9 and is ~3-5x more potent than R-warfarin14–16. Both acenocoumarol enantiomers are principally metabolised by CYP2C9 and, while S-acenocoumarol is more active, its short elimination half-life (1.8hr) means the majority of anticoagulant effect is through R-acenocoumarol13. For phenprocoumon, both CYP2C9 and CYP3A4 are involved in its metabolism17. Coumarin dose requirements to maintain an international normalised ratio (INR) between 2.0 and 3.0 are highly variable between individuals. For example, warfarin stable dose (WSD) ranges at least 25-fold (0.6 to 15.5 mg/day), and real world registry data of patients anticoagulated for atrial fibrillation demonstrated a mean time in the therapeutic INR range (TTR) of 65% ( ± 20%)18. This high inter-individual variation and narrow therapeutic index increase susceptibility to adverse events. Notably, 6-7% of patients prescribed warfarin were hospitalised due to bleeding over a mean follow up of 425 days, with supra-therapeutic INRs increasing bleeding risk19–21. Decreased TTR is also a predictor for increased ischaemic stroke, other thromboembolic events, major bleeding and mortality22,23.

For warfarin, approximately ~55-60% of variation in WSD can be principally explained by genetic variation in *VKORC1* (⁓25%) and *CYP2C9* (⁓15%), supplemented by *CYP4F2\*3* (⁓1-7%) and clinical factors (e.g. age, body mass index, smoking, interacting drugs, collectively <20%)24–26 (Table1).

At least 14 clinical trials testing genotype-guided warfarin dosing have been conducted, employing various algorithms that incorporate genetic (*VKORC1*, *CYP2C9* +/- *CYP4F2*) and clinical covariates25,27,28. The largest European RCT of warfarin PGx was conducted by the EU-PACT collaboration and recruited patients starting warfarin for atrial fibrillation or venous thromboembolism (VTE)29. EU-PACT compared genotype-guided warfarin dosing on days 1-5 in 227 patients to standard warfarin loading in 228 patients, with all subsequent dosing in both arms according to routine practice, and found that the primary endpoint of 12-week TTR was significantly higher in the genotype guided arm (67.4% vs 60.3%, p<0.001)29. There was no significant difference in bleeding or thromboembolic events. In EU-PACT, 99% of participants were Caucasian, and point-of-care (POC) genotyping was utilised29. A subsequent UK-based real-world implementation study with POC genotyping similarly found genotype-guided dosing increased warfarin TTR by 7%30. A recent meta-analysis incorporating EU-PACT data shows that genotype-guided warfarin dosing compares favourably to DOACs in cluster rank plots considering both thromboembolism and bleeding31.

In contrast, the US COAG trial did not find any significant difference between genotype-guided and clinically guided dosing algorithms (4-week TTR 45.2% vs 45.4%, p=0.91)32. An important distinction between the two trials is that 27% of patients recruited to COAG were African-American, but only the *CYP2C9* alleles common in Caucasians, *\*2* and *\**3, were assessed. Genotype-guided African-American patients in COAG fared less well than those clinically dosed (4-week TTR 35.2% vs 43.5%, p=0.01), highlighting the importance of patient ethnicity in considering *CYP2C9* variants32. Another difference between the trials is that the US COAG trial comparator arm used a clinical dosing algorithm whereas EU-PACT used standard care. However, clinical dosing algorithms have not been validated themselves versus usual care and the comparator arm TTR was lower in COAG than in EU-PACT.

GIFT was the largest and most recent RCT; it recruited patients undergoing elective hip or knee arthroplasty treated with perioperative warfarin and randomised them to genotype- (n=808) or clinically-guided (n=789) dosing on days 1-11. Patients were genotyped for *VKORC1* -1639G>A, *CYP2C9\*2*, *CYP2C9\*3*, and *CYP4F2* V433M. The primary composite endpoint of INR≥4, major bleeding, death (all within 30 days) plus VTE within 60 days, occurred in 10.8% and 14.7 % of patients in the genotype and clinically-guided groups, respectively (p=0.02). This result was driven mainly by a decrease in INR≥4 (p=0.04) and borderline reduction in major bleeding (p=0.06)27. Given the continued high real-world use of warfarin, these results are considered clinically relevant.

To aid implementation, there is supportive evidence for the cost-effectiveness of genotype-guided warfarin dosing, and multigene-drug testing will likely be even more advantageous33,34. Clinical guidelines for genotype-guided warfarin dosing have been developed by both the Dutch Pharmacogenetics Working Group (DPWG) and Clinical Pharmacogenetics Implementation Consortium (CPIC)35,36.

The EU-PACT collaboration also conducted RCTs of acenocoumarol and phenprocoumon PGx37. Due to low enrolment, they were combined for analysis. Though the primary outcome of 12-week TTR in the 484 eligible participants did not differ between the genotype-guided and clinically guided dosing arms (61.6% vs 60.2%, p=0.52), follow up analysis demonstrated that the acenocoumarol dosing algorithm, designed for a Dutch population, overestimated dose in Greek ancestry patients37–39.

On balance, we advocate genotype-guided dosing when commencing warfarin. To optimise the effectiveness of a genotype-informed strategy, genetic results should be available on the first day of warfarin dosing. This may require the use of point-of-care testing, or pre-emptive genotyping.

Although patient ethnicity is important in warfarin PGx, self-reported ethnicity may not always adequately represent genetic ancestry, for instance in admixed individuals. Genetic characterisation to facilitate appropriate use of ethnicity-specific warfarin algorithms may be preferable, but arguably difficult to achieve in clinical practice40. Therefore, rather than genotype for specific alleles in patients from different ethnic backgrounds, a better approach would be to genotype for all the relevant *CYP2C9*, *VKORC1* and *CYP4F2* alleles, irrespective of ethnicity/ancestry, and determine dose requirements using a “universal” algorithm, which will require development.

**Table 1**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene**  | **Variant(s)** | **Functional Effect** | **Clinical Effect** |
| *VKORC1* | -1639G>A (rs9923231) | Reduced VKORC1 transcription | Reduced warfarin requirments41 |
| *CYP2C9* | *\*2, \*3, \*5*, *\*6*, *\*8, \*11*  | Decreased CYP2C9 metabolic activity | Reduced warfarin requirements42,43 |
| *CYP4F2* | *\*3* (V433M) | Decreased hepatic CYP4F2 levels and reduced vitamin K hydroxylation | Higher warfarin requirments44 |

**Key clinical positions:**

* Prospective genotyping prior to warfarin initiation is advised where possible.
* If genotypic information is already available, it should be used to guide warfarin initiation dosing.
* *y clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Antiplatelets**

Antiplatelet therapy is the backbone of treatment for atherothrombotic diseases such as coronary artery disease and stroke. In acute coronary syndromes and patients undergoing percutaneous coronary intervention, dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist is usually recommended45,46. P2Y12 receptor antagonists include clopidogrel, prasugrel and ticagrelor. The more potent P2Y12receptor antagonists, prasugrel and ticagrelor, are usually preferred over clopidogrel in high risk cases on the basis of improved cardiovascular outcomes, albeit with an increased bleeding risk47. In stroke, single antiplatelet therapy with clopidogrel alone is usually preferred for long term secondary prevention48. However, the effectiveness of antiplatelet therapy is limited by variability in patient response; particularly to clopidogrel, partly attributed to genetic variation.

Clopidogrel is a prodrug, transformed to its active metabolite in two sequential CYP2C19 dependent steps. Up to a third of patients have reduced enzymatic activity secondary to a loss of function variant in *CYP2C19* (e.g. *\*2* or *\*3*)49. This is associated with high on-treatment platelet reactivity and an increased risk of ischaemic events50,51.

Knowledge of an individual’s genetic profile can allow personalised antiplatelet strategies in order to optimise the balance of beneficial to adverse outcomes. However, genotypic variation does not always translate into adverse clinical outcomes as, unlike platelet function testing, genotyping does not provide a direct measure of response to therapy or an assessment of non-genetic factors on platelet function. Yet platelet function testing is limited by the need to perform testing while already on treatment and lacks standard reference values and thresholds. Given the large number of patients prescribed antiplatelet agents, use of PGx to personalise treatment could have a significant effect at a population level. A PGx polygenic risk score has also been proposed as an effective risk stratification tool, and merits further investigation in a prospective clinical setting52.

Clinical trials have used both phenotype-guided (platelet function testing while on treatment) and genotype-guided (CYP2C19 status assessed before/during treatment) approaches. Meta-analysis has shown phenotype-guided approaches in patients presenting with acute coronary syndrome or with coronary artery disease undergoing percutaneous coronary intervention are not superior to standard care53. This is unsurprising given the limitations discussed. In contrast, meta-analysis of 6 randomised controlled trials using genotypic-based treatment, with 3,764 patients undergoing percutaneous coronary intervention or with acute coronary syndromes, has shown a significant reduction in net adverse clinical events (HR 0.65; 95% CI 0.45 to 0.95; p=0.03), including reduced major adverse cardiovascular events (HR 0.59; 95% CI 0.43 to 0.82; p<0.01) and reduced bleeding events (HR 0.75; 95% CI 0.61-0.93; p<0.01)54. This meta-analysis pooled studies that use different strategies and different patient populations, including those with stable and acute coronary syndromes.

Notably, the large POPular Genetics RCT found that genotype-guided therapy in patients undergoing primary PCI was non-inferior to standard treatment with prasugrel or ticagrelor in terms of a combined primary outcome of thrombotic and bleeding events, and risk of bleeding was reduced 55. The recent TAILOR-PCI trial randomised 5302 PCI patients, 1849 of whom carried loss of function *CYP2C19* alleles, to genotype guided antiplatelet therapy versus conventional therapy with clopidogrel56. The composite cardiovascular primary endpoint was 4.0% in the genotype guided and 5.9% in the non-genotype guided cohort at 1 year follow-up (hazard ratio 0.66 [95% CI, 0.43-1.02]; *P* = 0.06)56.  Unfortunately, the study was underpowered due to lower event rates than expected. However, a post hoc analysis found that the primary outcome was significantly reduced during the first 3 months after PCI (hazard ratio 0.21 [95% CI, 0.08-0.54]; *P* =  0.001), suggesting higher modifiable risk in the months immediately following stenting56. This includes the highest risk period for early in-stent thrombosis, which is the first 30 days 57.

This evidence base suggests that the genotype-guided approach could be superior to standard care in terms of both cardiovascular outcomes and reduced bleeding events, particularly in the months immediately following PCI. The availability of rapid diagnostic genetic tests means such strategies are a viable option in routine clinical practice. In other settings, such as stroke, there is still a lack of prospective large scale RCT data. However similar benefits might be anticipated, a hypothesis supported by systematic review and meta-analysis data58,59.

Clopidogrel PGx profiling for CYP2C19 remains only recommended in specific high-risk situations, such as patients with acute coronary syndrome undergoing percutaneous coronary intervention, or presenting with recurrent adverse events, and only if results are likely to change the treatment strategy. If patients are considered intermediate or poor metabolisers of clopidogrel, alternative antiplatelet agents are recommended60. More large-scale trials in patients with coronary artery disease (e.g. [GUARANTEE](https://clinicaltrials.gov/ct2/show/NCT03783351) study) are ongoing and will inform this recommendation further. Additional prospective data from large scale trials for other indications, such as stroke, are awaited before clear recommendations can be made (e.g. [PLATELET](https://clinicaltrials.gov/ct2/show/NCT04072705) study). Given the disease prevalence, even a small improvement with PGx use may translate to meaningful population level health gains.

**Key clinical positions:**

* Clopidogrel should be avoided in patients who are known to be intermediate or poor metabolisers from existing genotypic information.
* Genotyping high-risk cardiovascular patients (either high risk of thrombosis or bleed) prior to prescribing clopidogrel should be considered where possible, particularly to prevent post-stent thrombosis.
* *y clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Statins**

Statins are the most commonly prescribed lipid-lowering medication for the treatment and prevention of cardiovascular disease (CVD)61,62. Meta-analyses show a consistent relationship between the extent of low density lipoprotein cholesterol (LDL-C) reduction and CVD risk reduction, irrespective of statin choice, dose or baseline risk63–65. Statins are well-tolerated in most individuals but can rarely cause severe hepatotoxicity, and are associated with the development of diabetes mellitus66. Statin-associated muscle symptoms (SAMS) are the most commonly reported side-effect and are a common reason for treatment discontinuation67,68. SAMS range from mild myalgia without an elevation in creatine kinase to life-threatening rhabdomyolysis or autoimmune-necrotizing myositis69,70. The underlying mechanism of muscle injury is increased systemic statin exposure with intracellular skeletal myocyte entry and disruption of muscle function71.

Statin disposition is dependent on multiple enzymes and transporters, with their relative importance varying between drugs. Solute carrier anion transporter family 1B1 (*SLCO1B1)* encodes organic anion transporting polypeptide 1B1 (OATP1B1) which is central to the hepatic uptake and consequent elimination of statins. A GWAS in patients with simvastatin-induced myopathy identified an increased risk of myopathy in heterozygous and particularly homozygous carriers of the reduced function *SLCO1B1\*5* variant, which significantly increases plasma concentrations of all statins, except fluvastatin (Table 2)72. In addition to this gene dose trend, a simvastatin dose trend was observed with the risk of myopathy increasing by 2.6 and 4.3 per copy of *SLCO1B1\*5* in patients on simvastatin 40mg and 80mg daily, respectively72.

The clinical association between simvastatin-induced myopathy and *SLCO1B1\*5* has been confirmed in a recent meta-analysis, which failed to identify any other genetic loci73. There is ongoing uncertainty over the effect of *SLCO1B1\*5* on other statins as, in the example of atorvastatin, alternative anion transporters are partially responsible for hepatic uptake and its intrinsic myotoxicity may be less than compared to simvastatin74,75. Interestingly, recent work has associated *SLCO1B1\*5* with rosuvastatin-induced myotoxicity in Han Chinese patients, despite it not previously being associated with myalgia in patients of European descent76–78. This may be secondary to increased rosuvastatin exposure in individuals of Asian ancestry, which is partially explained by polymorphisms in *ABCG2*, an efflux transporter encoding breast cancer resistance protein (BCRP)79.

Other factors, such as drug-drug interactions, exercise, neuromuscular disorders, mitochondrial impairment, mevalonate pathway perturbation, immune-mediated toxicity, muscle transcriptomics and vitamin D deficiency can all contribute to myotoxicity71. It is likely that SAMS often result from a combination of these and genetic factors.

There is little prospective data available to inform clinical decision making. Peyser *et al.* randomized 159 patients with prior statin myalgia to receive *SLCO1B1* genotype informed statin therapy (GIST) versus usual care80. Rosuvastatin, pravastatin, or fluvastatin were recommended for *SLCO1B1\*5* carriers, whereas non-carriers were recommended to try any statin that they had not tried in the past. Over an 8-month follow-up, those who were randomized to GIST showed increased statin re-initiation and reduced LDL-C, but without an increase in self-reported medication adherence80. Vassy *et al.* recently completed a RCT of 408 patients treated in primary care settings, to assess potential unintended harms of PGx testing81. The findings were reassuring, showing that knowledge of *SLCO1B1* genotype did not deter from appropriate initiation of statins in accordance with guidance, and did not result in inferior LDL-C at the 1 year end point81.

The minor allele frequency of rs4149056 (*SLCO1B1\*5*) is approximately 1%, 8% and 16% in African, Asian and European populations, respectively82, and so a substantial proportion of the population may be at risk. Both CPIC and DPWG, as well as the European summary of product characteristics, recommend that individuals carrying *SLCO1B1\*5* avoid high-dose simvastatin, but the suggested clinical approach differs83,84. The CPIC guidelines recommend a lower simvastatin starting dose or an alternative statin in heterozygous carriers, alongside consideration of routine creatine kinase surveillance in those who are homozygous85. In contrast, the DPWG recommends that homozygotes avoid simvastatin entirely86. The DPWG guideline also recommends avoiding atorvastatin for individuals with other clinical risk factors for SAMS86. The EU summary of product characteristic for simvastatin states “Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype.”

As the current evidence base is limited to specific drug-gene pairs and largely retrospective, PGx testing to assess the risk of SAMS has not yet transitioned into routine clinical care, and PGx testing while on statin therapy is not usually recommended.

**Table 2**

|  |  |
| --- | --- |
| **Statin** | **Increase in Area Under the Curve** **in SLCO1B1\*5 (loss-of-function)** **homozygotes**87–91 |
| Simvastatin | 221% |
| Lovastatin  | 186% |
| Pitavastatin | 208% |
| Atorvastatin | 145% |
| Pravastatin | 91% |
| Rosuvastatin | 65% |
| Fluvastatin | 19%, non-significant  |

**Key clinical positions:**

* Avoid high-dose simvastatin (80mg) and consider an alternative statin of equivalent LDL lowering efficacy in patients known to be homozygous for the *SLCO1B1\*5* reduced function variant. *recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Beta-blockers**

Several beta-blockers, including metoprolol, carvedilol and propranolol are metabolised by CYP2D6, a phase I drug-metabolising enzyme implicated in the metabolism of 20-25% of clinically prescribed drugs92–94, and encoded by the highly polymorphic gene, *CYP2D6*. Of these, metoprolol is most highly dependent on CYP2D6 for its elimination, with 70-80% of an oral dose undergoing CYP2D6-mediated biotransformation92(Table 3). Other beta-blockers, such as atenolol and bisoprolol, undergo either no or negligible CYP2D6 metabolism92,95.

Several studies have investigated the clinical effects of *CYP2D6* in patients taking metoprolol, mostly for heart failure (HF) or hypertension (HTN). The tolerated maintenance metoprolol dose in *CYP2D6* poor metabolisers (PMs)relative to extensive (normal) metabolisers (EMs) is lower in some, but not all studies96–101. A decreased heart rate (HR) has been frequently reported in intermediate metabolisers (IMs) and particularly PMs relative to EMs, and an increased incidence of (mostly asymptomatic) bradycardia (HR<60bpm) has been reported in *CYP2D6* PMs and occasionally IMs in some but not all studies96,98,99,101–104. No association between *CYP2D6* and systolic blood pressure in metoprolol users has been identified96,98,101,103. However, at least three studies, including the two largest to date have linked *CYP2D6* PM status to a ~5 mmHg reduction in diastolic blood pressure relative to EMs, although this has not been replicated in all studies96,98,99,101–103,105. Bar an early small case-control study, clinically apparent adverse events have not been associated with *CYP2D6* PMs or IMs98,99,101,102,105–107. One limitation of some of these studies is a reliance on a single, albeit common, loss-of-function variant, *CYP2D6\*4* (rs3892097) for assigning *CYP2D6* predicted function96,97,101.

Due to the lower prevalence of *CYP2D6* ultra-rapid metabolisers (UMs) compared to IM/PMs, less research has specifically focused on this group, although HR and blood pressure do not appear to be notably different from EMs with metoprolol102,103. One study of 187 patients post myocardial infarction related *CYP2D6* duplications to ventricular rhythm disturbances, although this group also had a higher proportion of ST-elevation myocardial infarction104.

The US Food & Drug Administration (FDA)-approved metoprolol product label states that *CYP2D6* (genotype)-dependent metabolism seems to have little influence on the safety or tolerability of metoprolol108. Nonetheless, the label also notes that strong CYP2D6 drug inhibitors are expected to mimic *CYP2D6* PMs and recommends caution with co-administration of potent CYP2D6 inhibitors108. This is one example of a trend in drug labelling that urges more (appropriate) caution for drug-drug interactions than for genetic polymorphisms with the same effect. The DPWG guidance for metoprolol-*CYP2D6* recommends slower dose titration and reduced maximal doses in IMs and PMs in the event of symptomatic bradycardia or when a gradual reduction in heart rate is indicated, and suggests increasing metoprolol dose beyond the usual maximum or an alternative beta-blocker in UMs if effectiveness remains insufficient35.

On balance, if patients known to be a *CYP2D6* PM or UM are started on a beta-blocker, avoiding metoprolol seems prudent. Similarly, *CYP2D6* genotyping in patients that experience an ADR on metoprolol appears justifiable to minimise risk of future ADRs from other CYP2D6-metabolised drugs that the patient might subsequently be prescribed, and to refine the metoprolol-*CYP2D6* evidence base.

**Table 3**

|  |  |
| --- | --- |
| ***CYP2D6*****Metaboliser phenotype** | **Fold difference in metoprolol exposure (compared with normal metaboliser)**109 |
| Ultra-rapid | ~0.4 |
| Intermediate | ~2.5 |
| Poor | ~4.9 |

**Key clinical positions:**

* If genotype is known metoprolol should be avoided in CYP2D6 poor and ultrarapid metabolisers, and an appropriate substitute made (e.g., bisoprolol)
* Prescribers should be aware that co-administration of potent CYP2D6 inhibiting drugs can lead to variable phenoconversion, the extent of which will be influenced by the underlying *CYP2D6* genotype.
* underlying *CYP2D6* genotype*y clinical actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Hypertension:**

Primary Hypertension (HTN) is highly prevalent in Europe and a leading cause of morbidity and mortality despite the existence of many pharmacologic therapies and lifestyle modification recommendations110,111. There are now >1,000 genetic loci linked with blood pressure regulation through large GWASs and meta-analyses, which supports a complex polygenic mechanism of partial heritability, with most common risk alleles exerting a small effect on blood pressure112,113.

Interestingly, one of the largest multi-ethnic meta-analysis of blood pressure traits to-date included a phenome-wide association study which demonstrated uniform distribution of clinical risk based on identified genetic loci across ethnic groups, including Caucasians, Hispanics and persons of African descent113. Though PGx trials have not provided an evidence base to support genotype-guided HTN pharmacotherapy, therapeutic recommendations remain stratified by self-reported ethnicity, with ‘black’ Europeans recommended a different treatment regime (extrapolated from African American population data from the USA)110.

There is some evidence from the GenHAT study (a sub-study of ALLHAT), the largest RCT to explore gene panel risk prediction in stratified anti-hypertensive (anti-HTN) therapies, that genetic panels can predict response to different anti-HTN therapies. However, this adequately powered study (N >39,000) did not demonstrate clinically significant benefit to genetically stratified therapeutic choice114. It also failed to demonstrate different clinical outcomes for use of the studied anti-HTN therapeutics in Caucasians or participants of African descent. This trial did not include beta-blockers, which are less routinely used to treat HTN.

Thus, current evidence doesn’t support the routine use of any genomic targeted treatment or change to therapy for any variant reported for essential HTN (beta-blockers discussed separately above). There remains a need for further prospective clinical studies to either validate or discard the current practice of using self-reported ethnicity (black or white) to guide initial therapeutic choice. Prior assessment of evidence has concluded that this may be dubious115.

**Key clinical positions:**

* No clinical action advised based on current evidence
* *y clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Arrhythmias**

The main arrhythmia-predisposing condition related to pharmacotherapy and amenable to genetically guided intervention is long QT 116.

A prolonged QT interval is a well-known risk factor for ventricular arrhythmias (including torsade de pointes (TdP), a rare and unstable polymorphic ventricular tachycardia) and sudden cardiac death (SCD), and can be congenital or acquired117–121. Acquired QT prolongation can be caused by cardiac disease such as coronary heart disease and HF, but it is commonly caused by certain drugs (drug induced long QT syndrome (diLQTS))120,122. QT interval prolongation is one of the leading causes of therapeutic relabelling or withdrawal from the market. To date, >200 drugs are listed on [CredibleMeds.org](https://crediblemeds.org/) (a curated database maintained by AZCERT) as associated with QT prolongation and/or TdP123.

Susceptibility to acquired QT interval prolongation can be influenced by genetic variation; the heritability of QT interval duration in the general population (excluding congenital long QT syndrome (LQTS) patients) is estimated to be around 35%, and first-degree relatives of patients with congenital LQTS have a higher risk of drug-induced QT prolongation than non-related individuals124–127. A large number of genes associated with QT interval duration have been identified by GWAS128–130. The gene with the strongest signal related to QT interval duration is the nitric oxide synthase 1 adaptor protein gene (NOS1AP), located on chromosome 1128–134. This gene also influences impulse propagation135. Other key findings from GWAS included polymorphisms within genes known to be mutated in congenital LQTS, genes associated with intracellular calcium handling, as well as genes previously not known to influence cardiac repolarization124,129,130. A polygenic risk score comprised of 61 variants previously associated with baseline QT interval at genome-wide level was also associated with drug-induced QT prolongation, and was a significant predictor of drug-induced TdP136,137.

Several other exploratory studies have sought to identify the underlying genetic architecture predisposing to diLQTS136,138–140. One candidate gene study evaluated the genetic predisposition to diLQTS among 176 cases and 1044 controls and identified a nonsynonymous variant in *KCNE1* (rs1805128, D85N) that conferred risk of diLQTS (OR=9.0, 95% confidence interval: 3.5–22.9)138. In an exome sequencing study of 65 diLQTS cases and 148 controls, a significant excess of rare variants in *KCNE1* and *ACN9* were identified. Moreover, 37% of diLQTS cases were also carriers of a rare variant in potassium channel genes compared with 21% of controls140. These studies highlight the importance of individualized treatment and risk stratification in the setting of ADRs, but also the need for further work to translate this data to the clinical realm with thorough validation studies.

The most common mechanism by which drugs lead to acquired LQTS is blockade of the rapid component of the delayed rectifier potassium current, *I*kr, encoded by *KCNH2*, also referred to as human ether-a-go-go-related gene141*.* The risk of TdP seems to increase with higher concentrations of *I*kr blocking drugs. Thus, genetic variants that alter drug metabolism and result in higher drug concentrations can predispose to diLQTS.The reduced repolarisation reserve hypothesis proposesthat patients remain asymptomatic until multiple hits (e.g., hypokalaemia, bradycardia, and/or exposure to a drug) unmask an extreme drug response phenotype (i.e. QT prolongation) that can lead to the development of fatal arrhythmias117.

**Future prospects:**

Potentially dangerous effects of drugs may be masked when administered to a large number of patients. The risk may become evident only when genetic and environmental risk factors combine; for example, when an *I*kr blocking drug is given to an individual with a silent mutation in one of the congenital LQTS genes in the setting of hypokalaemia.

Therefore, therapeutics that are both safe and efficacious for the majority of the population may be withdrawn due to unacceptable risk in a small minority of patients. With the current emphasis on avoiding QT prolongation in drug development, it is likely that drugs that would never result in TdP in a selected population are being abandoned due to perceived risk. The challenge lies in identifying which patients, in which settings, and with which drugs or combination of drugs (and at what doses) will develop diLQTS and avoiding the combination of factors that promote TdP.

**Key clinical positions:**

* Medications known to prolong the QT interval should be avoided in those known to harbour long-QT associated genetic variants.
* Prospective genotyping in absence of phenotype or family history is not advised.

*y*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Chemotherapy induced Cardiomyopathy:**

Cardiomyopathy and HF resultant from chemotherapeutic myocyte toxicity (chemotherapy induced cardiomyopathy (CCM)) is a feared side effect of several common chemotherapeutic agents, most prominently: doxorubicin, trastuzumab, paclitaxel, and 5-fluorouracil142. The most studied amongst these is doxorubicin, with anthracycline-induced cardiotoxicity the subject of the sole existing PGx recommendation: The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) recommends genetic testing for 3 SNPs (RARG rs2229774, SLC28A3 rs7853758, UGT1A6\*4 rs17863783) prior to initiating doxorubicin or daunorubicin in children, endorsed by a moderate level B evidence based support143. Though these variants were each replicated in separate cohorts within a single published study, they have not yet been validated by further independent research. This recommendation was met with some consternation, as these SNPs lack functional validation as well as mechanistic plausibility (two are not expressed in cardiac tissue and don’t alter protein coding), and has not been incorporated into other guidelines or mainstream practice144. A recent study from the USA found that a polymorphism present in both African and European ancestry populations was associated with higher risk of cardiomyopathy in childhood cancer survivors, with disproportionately higher risk to those of African ancestry (5.43-fold vs 1.31-fold); however this population included exposure to radiotherapy as well as anthracyclines145.

While PGx studies have not yet evolved to clinical utility in risk prediction within mainstream care, recent advances have localised additional risk to those cancer patients with *TTN* truncating variants (TTNtvs).The massive titin protein, coded for by *TTN*, is integral to sarcomere function, and implicated in familial forms of DCM146,147. These genetic changes are hypothesised to create a stress cardiomyopathy phenotype that may also be expected in states such as pregnancy or alcohol excess146.

Nevertheless, the study that linked TTNtvs to CCM identified TTNtvs in only 7.5% of those with CCM, and not all the at-risk participants developed cardiomyopathy146. However, this study sets the stage for the possibility of improved risk stratification which could prospectively investigate risk modification strategies for a genetically at-risk population. Work is urgently needed in this area to advance scientific gains to clinical care.

**Key clinical positions:**

* No clinical action advised based on current evidence
* *y clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Clinical Trials**

Despite the growing worldwide burden of CVD, drug development in the field has been on a downward trend due to the numerous challenges associated with successfully bringing a new drug to the market. Compared to other therapeutic areas, developing new cardiovascular medicines is more expensive for many reasons including the requirement for trials with large sample sizes, new therapies usually add only incremental benefit to individuals on very effective polypharmacy, and increased late-phase failures. Therefore, to ensure the future of cardiovascular drug development, clinical trials need to evolve and embrace new advances to overcome these challenges148.

PGx could help address these difficulties by facilitating mechanism-based approaches for drug development in defined populations. This approach can be utilised at various stages in the drug development pathway.

Challenges for conducting PGx RCTs for drugs that are already licensed include each trial only being able to assess one or a few gene-drug pairs, and large numbers of participants needing to be recruited to include sufficient with the variant allele(s) of interest in the absence of accessible genomic data prior to recruitment56. Moreover, there are specific concerns over the generalisability of PGx RCT evidence to ethnicities inadequately represented in such trials, as they may carry different gene variants relevant to the studied drug. Furthermore, there is a lack of consensus over the evidential threshold required for PGx biomarkers whose role is to guide dose/drug selection akin to prescribing adjustments based on renal/liver function tests149.

*Phase II and III trials*

RCTs tend to require large patient numbers to show a clinical effect. However, there has been interest in improving patient selection to identify those who are most likely to benefit from the proposed treatment, which may potentially reduce the sample size requirements.

Post-hoc subgroup analyses attempt to identify PGx markers from already completed RCTs. This has clear cost saving benefits, but studies risk being under-powered and results inconclusive.

Prospective study design takes adequate powering into consideration to produce more robust evidence. Examples of this design include the following150:

* Enrichment design, where only patients who have the feature predicted to have clinical benefit are recruited or analysed. An example of this is the TAILOR-PCI trial discussed above, where the analysis was limited to those with CYP2C19 loss of function (\*2, \*3) variants 56.
* Adaptive trial design is categorised by adjusting trial features based on data amassed during the trial itself. An example of this is the GENETIC-AF trial151.
* Biomarker based all-comers design which aims to investigate the interaction between treatment effect and biomarker status, more commonly employed in oncology.
* Hybrid or combination biomarker trials, which are typically an enrichment study extending to include another technique such as adaptive design.

*Successes, failures, and opportunities – lipid modulation trials*

The discovery that mutations in *PCSK9* were a rare cause of familial hypercholesterolaemia paved the way for the development of PCSK9 inhibitors for lipid management. Yet, cholesteryl ester transfer protein (CETP) inhibitors have proven that identification of a PGx marker does not guarantee successful drug development, and multiple CETP inhibitors have failed phase III trials152.However, persistence with this therapeutic target is proving fruitful. The REVEAL trial, with the CETP inhibitor Anacetrapib showed a reduction in cardiovascular events153. Additionally, the dal-GenE trial suggests improved cardiovascular outcomes when the CETP inhibitor dalcetrapib is used with a statin in the subset of patients with the AA genotype at rs1967309 in the *ADCY9* gene154.This further demonstrates the complexities of PGx application in trials as well as the need for robust research to ensure that potentially useful therapies are not wasted.

PGx has the potential to enrich the development of new therapies in cardiovascular medicine, resulting in a more efficient and cost saving drug development route. Significant challenges exist and well-designed trials are required to ensure we have robust evidence.

*Real world evidence to evaluate PGx utility*

Due to limitations in feasibility for RCT trials for each drug-gene pair, real world evidence which uses the power of big data contained within electronic health records may prove useful. This approach would also be more likely to include more diverse populations, limiting concerns about external validity of data and health equality. An example of such an approach is the IGNITE study, which assessed outcomes for use of PGx guided antiplatelet therapy following PCI (and found increased risk of cardiovascular events in those with a CYP2C19 loss-of-function allele who were prescribed clopidogrel)155.

**Key position:**

* Pharmacogenomics offers tools that can revolutionize drug design and clinical trials and make both more economically efficient. However, prospective designs should be optimized and post-hoc subgroup analysis limitations recognized. Real world evidence may fill important gaps.

*:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

 Key clinically

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*mmendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosingotyping p Key clinically actionable Key clinically actionable recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*recommendations:*

*-Prospective genotyping prior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

*rior to warfarin initiation is recommended where possible*

*-If genotypic information is already available it should be used to guide warfarin initiation dosing*

**Key Paper Positions**

* Thrombosis, Ischemic Heart Disease and Stroke:

Evidence is strongest for pre-emptive genotyping prior to warfarin use. There is also enough evidence to advise genotype guided antiplatelet therapy in selected high-risk CV patients.

* Hypertension:

Further research is needed to translate scientific gains to the bedside. Self-identified black/white racial stratification in HTN therapeutic algorithms is not supported by genetic evidence to-date.

* Arrhythmias:

Further research is needed to advance our understanding of genetic risk loci for drug-induced long QT and to trial a PGx approach in clinical practice. Known carriers of pathogenic LQT variants should not be given medication known to prolong the QTC.

* Chemotherapy induced cardiomyopathy:

Further research is needed to translate scientific gains to the bedside.

* Clinical Trials:

PGx has the potential to improve the success, efficacy, and cost profile of drug development and clinical trials but is in early stages of development.

**Conflicts of interest**

MJC is seconded to Genomics England as Chief Scientist and part of his salary is funded by Genomics England Ltd, a wholly owned Department of Health and Social Care Company.

MP receives research funding from various organisations including the MRC, NIHR, EU Commission, HDR UK and Health Education England. He has also received partnership funding for the following: MRC Clinical Pharmacology Training Scheme (co-funded by MRC and Roche, UCB, Eli Lilly and Novartis); a PhD studentship jointly funded by EPSRC and Astra Zeneca; and grant funding from Vistagen Therapeutics. He has also unrestricted educational grant support for the UK Pharmacogenetics and Stratified Medicine Network from Bristol-Myers Squibb and UCB.  He has developed an HLA genotyping panel with MC Diagnostics, but does not benefit financially from this.  MP is also a member of the IMI Consortium ARDAT ([www.ardat.org](http://www.ardat.org)). None of the funding declared above has been directly used for the current review paper.

SA receives Speaker fees and advisory board fees from: Boehringer-Ingelheim, Daiichi Sankyo, Bayer, Thermofisher

AGS has received speaker honoraria and/or consulting fees from Sanofi, AbbVie, Novartis, Bayer and Lilly

GS reports grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, personal fees from Societa´ Prodotti Antibiotici, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, personal fees from GENESIS, personal fees from Cytokinetics, personal fees from Medtronic, grants from Boston Scientific,  outside the submitted work.

PS reports grants from Daiichi Sankyo, grants and personal fees from Boehringer-Ingelheim outside the submitted work.

**Acknowledgements**

MJC is an NIHR Senior Investigator and this work forms part of the research portfolio of the NIHR Biomedical Research Centre at Barts.

MP is an Emeritus NIHR Senior Investigator, and wishes to thank the MRC Centre for Drug Safety Science and Wolfson Centre for Personalised Medicine for infrastructure support.

References

1. Initial sequencing and analysis of the human genome. *Nature* 2001;**409**:860–921.

2. Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. *Nature* 2011;**470**:204–213.

3. National Human Genome Research Institute. DNA Sequencing Costs: Data. 2019. https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data (10 August 2020)

4. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med* 2018;**20**:1122–1130.

5. NIH National Human Genome Research Institute; Human Genome Project. https://www.genome.gov/human-genome-project/Completion-FAQ (20 October 2020)

6. Relling M V., Evans WE. Pharmacogenomics in the clinic. *Nature* 2015;**526**:343–350.

7. Pirmohamed M, Hughes DA. Pharmacogenetic tests: the need for a level playing field. *Nat Rev Drug Discov* 2013;**12**:3–4.

8. Wouden CH van der, Swen JJ, Samwald M, Mitropoulou C, Schwab M, Guchelaar H-J. A brighter future for the implementation of pharmacogenomic testing. *Eur J Hum Genet* 2016;**24**:1658–1660.

9. Shekhani R, Steinacher L, Swen JJ, Ingelman‐Sundberg M. Evaluation of Current Regulation and Guidelines of Pharmacogenomic Drug Labels: Opportunities for Improvements. *Clin Pharmacol Ther* 2020;**107**:1240–1255.

10. Howard HC, Borry P. Direct-to-consumer pharmacogenomic testing. *Pharmacogenomics* 2011;**12**:1367–1370.

11. Pengo V, Pegoraro C, Cucchini U, Iliceto S. Worldwide management of oral anticoagulant therapy: The ISAM study. *J Thromb Thrombolysis* J Thromb Thrombolysis; 2006;**21**:73–77.

12. Lutsey PL, Walker RF, MacLehose RF, Alonso A, Adam TJ, Zakai NA. Direct oral anticoagulants and warfarin for venous thromboembolism treatment: Trends from 2012 to 2017. *Res Pract Thromb Haemost* Wiley; 2019;**3**:668–673.

13. Verhoef TI, Redekop WK, Daly AK, Schie RMF Van, Boer A De, Maitland-Van Der Zee A-H, Anke D, Maitland-Van Der Zee H. Pharmacogenetic-guided dosing of coumarin anticoagulants: algorithms for warfarin, acenocoumarol and phenprocoumon. 2013;

14. O’Reilly RA. Studies on the optical enantiomorphs of warfarin in man. *Clin Pharmacol Ther* John Wiley & Sons, Ltd; 1974;**16**:348–354.

15. Wadelius M, Sörlin K, Wallerman O, Karlsson J, Yue QY, Magnusson PKE, Wadelius C, Melhus H. Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1) and other factors. *Pharmacogenomics J* Nature Publishing Group; 2004;**4**:40–48.

16. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. Pharmacol. Ther. Pergamon; 1997. p. 67–74.

17. Ufer M, Svensson JO, Krausz KW, Gelboin H V., Rane A, Tybring G. Identification of cytochromes P450 2C9 and 3A4 as the major catalysts of phenprocoumon hydroxylation in vitro. *Eur J Clin Pharmacol* Eur J Clin Pharmacol; 2004;**60**:173–182.

18. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, Singer DE, Ansell J, Blanco RG, Gersh B, Mahaffey KW, Hylek EM, Go AS, Piccini JP, Peterson ED. Patients’ time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. *Am Heart J* 2015;**170**:141-148.e1.

19. Lau WCY, Li X, Wong ICK, Man KKC, Lip GYH, Leung WK, Siu CW, Chan EW. Bleeding-related hospital admissions and 30-day readmissions in patients with non-valvular atrial fibrillation treated with dabigatran versus warfarin. *J Thromb Haemost* Blackwell Publishing Ltd; 2017;**15**:1923–1933.

20. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* Circulation; 2007;**115**:2689–2696.

21. Palareti G, Cosmi B. Bleeding with anticoagulation therapy - Who is at risk, and how best to identify such patients. Thromb. Haemost. Thromb Haemost; 2009. p. 268–278.

22. Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: A record linkage study in a large British population. *Heart* BMJ Publishing Group; 2005;**91**:472–477.

23. Cancino RS, Hylek EM, Reisman JI, Rose AJ. Comparing patient-level and site-level anticoagulation control as predictors of adverse events. *Thromb Res* Elsevier Ltd; 2014;**133**:652–656.

24. Bourgeois S, Jorgensen A, Zhang EJ, Hanson A, Gillman MS, Bumpstead S, Toh CH, Williamson P, Daly AK, Kamali F, Deloukas P, Pirmohamed M. A multi-factorial analysis of response to warfarin in a UK prospective cohort. *Genome Med* BioMed Central Ltd.; 2016;**8**:2.

25. Pirmohamed M, Kamali F, Daly AK, Wadelius M. Oral anticoagulation: A critique of recent advances and controversies. Trends Pharmacol. Sci. Elsevier Ltd; 2015. p. 153–163.

26. Borgiani P, Ciccacci C, Forte V, Siríanni E, Novelli L, Bramanti P, Novelli G. CYP4F2 genetic variant (rs2108622) significantly contributes to warfarin dosing variability in the Italian population. *Pharmacogenomics* Pharmacogenomics; 2009;**10**:261–266.

27. Gage BF, Bass AR, Lin H, Woller SC, Stevens SM, Al-Hammadi N, Li J, Rodríguez T, Miller JP, McMillin GA, Pendleton RC, Jaffer AK, King CR, Whipple BDV, Porche-Sorbet R, Napoli L, Merritt K, Thompson AM, Hyun G, Anderson JL, Hollomon W, Barrack RL, Nunley RM, Moskowitz G, Dávila-Román V, Eby CS. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: The GIFT randomized clinical trial. *JAMA - J Am Med Assoc* American Medical Association; 2017;**318**:1115–1124.

28. Xu Z, Zhang S yu, Huang M, Hu R, Li J li, Cen H jin, Wang Z ping, Ou J song, Yin S li, Xu Y qi, Wu Z kai, Zhang X. Genotype-Guided Warfarin Dosing in Patients With Mechanical Valves: A Randomized Controlled Trial. *Ann Thorac Surg* Elsevier USA; 2018;**106**:1774–1781.

29. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, Kesteven P, Christersson C, Wahlström B, Stafberg C, Zhang JE, Leathart JB, Kohnke H, Maitland-van der Zee AH, Williamson PR, Daly AK, Avery P, Kamali F, Wadelius M. A Randomized Trial of Genotype-Guided Dosing of Warfarin. *N Engl J Med* Massachussetts Medical Society; 2013;**369**:2294–2303.

30. Jorgensen AL, Prince C, Fitzgerald G, Hanson A, Downing J, Reynolds J, Zhang JE, Alfirevic A, Pirmohamed M. Implementation of genotype-guided dosing of warfarin with point-of-care genetic testing in three UK clinics: A matched cohort study. *BMC Med* BioMed Central Ltd.; 2019;**17**:76.

31. Ng SS, Lai NM, Nathisuwan S, Jahan NK, Dilokthornsakul P, Kongpakwattana K, Hollingworth W, Chaiyakunapruk N. Comparative efficacy and safety of warfarin care bundles and novel oral anticoagulants in patients with atrial fibrillation: a systematic review and network meta-analysis. *Sci Rep* Nature Research; 2020;**10**:1–11.

32. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, Rosenberg YD, Eby CS, Madigan RA, McBane RB, Abdel-Rahman SZ, Stevens SM, Yale S, Mohler ER, Fang MC, Shah V, Horenstein RB, Limdi NA, Muldowney JAS, Gujral J, Delafontaine P, Desnick RJ, Ortel TL, Billett HH, Pendleton RC, Geller NL, Halperin JL, Goldhaber SZ, Caldwell MD, Califf RM, et al. A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing. *N Engl J Med* Massachussetts Medical Society; 2013;**369**:2283–2293.

33. Zhu Y, Swanson KM, Rojas RL, Wang Z, Sauver JL St., Visscher SL, Prokop LJ, Bielinski SJ, Wang L, Weinshilboum R, Borah BJ. Systematic review of the evidence on the cost-effectiveness of pharmacogenomics-guided treatment for cardiovascular diseases. *Genet Med* 2020;**22**:475–486.

34. Dong OM, Wheeler SB, Cruden G, Lee CR, Voora D, Dusetzina SB, Wiltshire T. Cost-Effectiveness of Multigene Pharmacogenetic Testing in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention. *Value Heal* Elsevier Ltd; 2020;**23**:61–73.

35. Dutch Pharmacogenetics Working Group (DPWG). Pharmacogenetics recommendations. 2020.

36. Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, Lee MT, Gage BF, Kimmel SE, Perera MA, Anderson JL, Pirmohamed M, Klein TE, Limdi NA, Cavallari LH, Wadelius M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clin Pharmacol Ther* Nature Publishing Group; 2017;**102**:397–404.

37. Verhoef TI, Ragia G, Boer A de, Barallon R, Kolovou G, Kolovou V, Konstantinides S, Cessie S Le, Maltezos E, Meer FJM van der, Redekop WK, Remkes M, Rosendaal FR, Schie RMF van, Tavridou A, Tziakas D, Wadelius M, Manolopoulos VG, Maitland-van der Zee AH. A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon. *N Engl J Med* Massachussetts Medical Society; 2013;**369**:2304–2312.

38. Ragia G, Kolovou V, Kolovou G, Konstantinides S, Maltezos E, Tavridou A, Tziakas Di, Maitland-Van Der Zee AH, Manolopoulos VG. A novel acenocoumarol pharmacogenomic dosing algorithm for the Greek population of EU-PACT trial. *Pharmacogenomics* Future Medicine Ltd.; 2017;**18**:23–34.

39. Ragia G, Manolopoulos VG. Pharmacogenomics of anticoagulation therapy: The last 10 years. Pharmacogenomics. Future Medicine Ltd.; 2019. p. 1113–1117.

40. Hernandez W, Danahey K, Pei X, Yeo KTJ, Leung E, Volchenboum SL, Ratain MJ, Meltzer DO, Stranger BE, Perera MA, O’Donnell PH. Pharmacogenomic genotypes define genetic ancestry in patients and enable population-specific genomic implementation. *Pharmacogenomics J* Springer Nature; 2020;**20**:126–135.

41. Yuan HY, Chen JJ, Lee MTM, Wung JC, Chen YF, Charng MJ, Lu MJ, Hung CR, Wei CY, Chen CH, Wu JY, Chen YT. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Hum Mol Genet* Hum Mol Genet; 2005;**14**:1745–1751.

42. Asiimwe IG, Zhang EJ, Osanlou R, Krause A, Dillon C, Suarez‐Kurtz G, Zhang H, Perini JA, Renta JY, Duconge J, Cavallari LH, Marcatto LR, Beasly MT, Perera MA, Limdi NA, Santos PCJL, Kimmel SE, Lubitz SA, Scott SA, Kawai VK, Jorgensen AL, Pirmohamed M. Genetic Factors Influencing Warfarin Dose in Black‐African Patients: A Systematic Review and Meta‐Analysis. *Clin Pharmacol Ther* Nature Publishing Group; 2020;**107**:1420–1433.

43. Cavallari LH, Langaee TY, Momary KM, Shapiro NL, Nutescu EA, Coty WA, Viana MAG, Patel SR, Johnson JA. Genetic and Clinical Predictors of Warfarin Dose Requirements in African Americans. *Clin Pharmacol Ther* 2010;**87**:459–464.

44. McDonald MG, Rieder MJ, Nakano M, Hsia CK, Rettie AE. CYP4F2 is a vitamin K1 oxidase: An explanation for altered warfarin dose in carriers of the V433M variant. *Mol Pharmacol* Mol Pharmacol; 2009;**75**:1337–1346.

45. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, Collet J-P, Kristensen SD, Aboyans V, Baumbach A, Bugiardini R, Coman IM, Delgado V, Fitzsimons D, Gaemperli O, Gershlick AH, Gielen S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018;**39**:119–177.

46. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2016;**37**:267–315.

47. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2009;**361**:1045–1057.

48. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers D V., Tirschwell DL. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018;**49**.

49. Scott SA, Sangkuhl K, Gardner EE, Stein CM, Hulot J-S, Johnson JA, Roden DM, Klein TE, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy. *Clin Pharmacol Ther* 2011;**90**:328–332.

50. Shuldiner AR. Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy. *JAMA* 2009;**302**:849.

51. Sofi F, Giusti B, Marcucci R, Gori AM, Abbate R, Gensini GF. Cytochrome P450 2C19\*2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. *Pharmacogenomics J* 2011;**11**:199–206.

52. Lewis JP, Backman JD, Reny J-L, Bergmeijer TO, Mitchell BD, Ritchie MD, Déry J-P, Pakyz RE, Gong L, Ryan K, Kim E-Y, Aradi D, Fernandez-Cadenas I, Lee MTM, Whaley RM, Montaner J, Gensini GF, Cleator JH, Chang K, Holmvang L, Hochholzer W, Roden DM, Winter S, Altman RB, Alexopoulos D, Kim H-S, Gawaz M, Bliden KP, Valgimigli M, Marcucci R, et al. Pharmacogenomic polygenic response score predicts ischaemic events and cardiovascular mortality in clopidogrel-treated patients. *Eur Hear J - Cardiovasc Pharmacother* 2020;**6**:203–210.

53. Kheiri B, Osman M, Abdalla A, Haykal T, Pandrangi P V., Chahine A, Ahmed S, Osman K, Bachuwa G, Hassan M, Bhatt DL. CYP2C19 pharmacogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with coronary artery disease: A meta-analysis of randomized clinical trials. *Catheter Cardiovasc Interv* 2019;**93**:1246–1252.

54. Kheiri B, Simpson TF, Osman M, Kumar K, Przybylowicz R, Merrill M, Golwala H, Rahmouni H, Cigarroa JE, Zahr F. Genotype-Guided Strategy for P2Y12 Inhibitors in Coronary Artery Disease. *JACC Cardiovasc Interv* 2020;**13**:659–661.

55. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, ’t Hof AWJ van, Harst P van der, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, Mosterd A, Herrman J-PR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, Boer A de, Boersma C, Deneer VHM, Berg JM ten. A Genotype-Guided Strategy for Oral P2Y 12 Inhibitors in Primary PCI. *N Engl J Med* 2019;**381**:1621–1631.

56. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae J-H, Jeong MH, Chavez I, Gordon P, Abbott JD, Cagin C, Baudhuin L, Fu Y-P, Goodman SG, Hasan A, Iturriaga E, Lerman A, Sidhu M, Tanguay J-F, Wang L, Weinshilboum R, Welsh R, Rosenberg Y, Bailey K, Rihal C. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention. *JAMA* 2020;**324**:761.

57. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. *Eur Heart J* 2015;**36**:3320–3331.

58. Pan Y, Chen W, Xu Y, Yi X, Han Y, Yang Q, Li X, Huang L, Johnston SC, Zhao X, Liu L, Zhang Q, Wang G, Wang Y, Wang Y. Genetic Polymorphisms and Clopidogrel Efficacy for Acute Ischemic Stroke or Transient Ischemic Attack. *Circulation* 2017;**135**:21–33.

59. Simon T, Danchin N. Clinical Impact of Pharmacogenomics of Clopidogrel in Stroke. *Circulation* 2017;**135**:34–37.

60. Scott SA, Sangkuhl K, Stein CM, Hulot J-S, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. *Clin Pharmacol Ther* 2013;**94**:317–323.

61. Catapano AL, Graham I, Backer G De, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen M-R, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.

62. Audi S, Burrage DR, Lonsdale DO, Pontefract S, Coleman JJ, Hitchings AW, Baker EH. The ‘top 100’ drugs and classes in England: an updated ‘starter formulary’ for trainee prescribers. *Br J Clin Pharmacol* 2018;**84**:2562–2571.

63. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;**380**:581–590.

64. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;**388**:2532–2561.

65. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–1278.

66. Newman CB, Preiss D, Tobert JA, Jacobson TA, Page RL, Goldstein LB, Chin C, Tannock LR, Miller M, Raghuveer G, Duell PB, Brinton EA, Pollak A, Braun LT, Welty FK. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol* 2019;**39**.

67. Rasmussen JN, Chong A, Alter DA. Relationship Between Adherence to Evidence-Based Pharmacotherapy and Long-term Mortality After Acute Myocardial Infarction. *JAMA* 2007;**297**:177.

68. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): An internet-based survey of 10,138 current and former statin users. *J Clin Lipidol* 2012;**6**:208–215.

69. Alfirevic A, Neely D, Armitage J, Chinoy H, Cooper RG, Laaksonen R, Carr DF, Bloch KM, Fahy J, Hanson A, Yue Q-Y, Wadelius M, Maitland-van Der Zee AH, Voora D, Psaty BM, Palmer CNA, Pirmohamed M. Phenotype Standardization for Statin-Induced Myotoxicity. *Clin Pharmacol Ther* 2014;**96**:470–476.

70. Hopewell JC, Offer A, Haynes R, Bowman L, Li J, Chen F, Bulbulia R, Lathrop M, Baigent C, Landray MJ, Collins R, Armitage J, Parish S. Independent risk factors for simvastatin-related myopathy and relevance to different types of muscle symptom. *Eur Heart J* 2020;**41**:3336–3342.

71. Turner RM, Pirmohamed M. Statin-Related Myotoxicity: A Comprehensive Review of Pharmacokinetic, Pharmacogenomic and Muscle Components. *J Clin Med* 2019;**9**:22.

72. SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study. *N Engl J Med* 2008;**359**:789–799.

73. Carr DF, Francis B, Jorgensen AL, Zhang E, Chinoy H, Heckbert SR, Bis JC, Brody JA, Floyd JS, Psaty BM, Molokhia M, Lapeyre‐Mestre M, Conforti A, Alfirevic A, Staa T, Pirmohamed M. Genomewide Association Study of Statin‐Induced Myopathy in Patients Recruited Using the <scp>UK</scp> Clinical Practice Research Datalink. *Clin Pharmacol Ther* 2019;**106**:1353–1361.

74. Generaux GT, Bonomo FM, Johnson M, Mahar Doan KM. Impact of SLCO1B1 (OATP1B1) and ABCG2 (BCRP) genetic polymorphisms and inhibition on LDL-C lowering and myopathy of statins. *Xenobiotica* 2011;**41**:639–651.

75. Skottheim IB, Gedde-Dahl A, Hejazifar S, Hoel K, Åsberg A. Statin induced myotoxicity: The lactone forms are more potent than the acid forms in human skeletal muscle cells in vitro. *Eur J Pharm Sci* 2008;**33**:317–325.

76. Danik JS, Chasman DI, MacFadyen JG, Nyberg F, Barratt BJ, Ridker PM. Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. *Am Heart J* 2013;**165**:1008–1014.

77. Liu J-E, Liu X-Y, Chen S, Zhang Y, Cai L-Y, Yang M, Lai W-H, Ren B, Zhong S-L. SLCO1B1 521T &gt; C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case–control study. *Eur J Clin Pharmacol* 2017;**73**:1409–1416.

78. Bai X, Zhang B, Wang P, Wang G, Li J, Wen D, Long X, Sun H, Liu Y, Huang M, Zhong S. Effects of SLCO1B1 and GATM gene variants on rosuvastatin-induced myopathy are unrelated to high plasma exposure of rosuvastatin and its metabolites. *Acta Pharmacol Sin* 2019;**40**:492–499.

79. Birmingham BK, Bujac SR, Elsby R, Azumaya CT, Wei C, Chen Y, Mosqueda-Garcia R, Ambrose HJ. Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect? *Eur J Clin Pharmacol* 2015;**71**:341–355.

80. Peyser B, Perry EP, Singh K, Gill RD, Mehan MR, Haga SB, Musty MD, Milazzo NA, Savard D, Li Y-J, Trujilio G, Voora D. Effects of Delivering SLCO1B1 Pharmacogenetic Information in Randomized Trial and Observational Settings. *Circ Genomic Precis Med* 2018;**11**.

81. Vassy JL, Gaziano JM, Green RC, Ferguson RE, Advani S, Miller SJ, Chun S, Hage AK, Seo S-J, Majahalme N, MacMullen L, Zimolzak AJ, Brunette CA. Effect of Pharmacogenetic Testing for Statin Myopathy Risk vs Usual Care on Blood Cholesterol. *JAMA Netw Open* 2020;**3**:e2027092.

82. Yates A, Akanni W, Amode MR, Barrell D, Billis K, Carvalho-Silva D, Cummins C, Clapham P, Fitzgerald S, Gil L, Girón CG, Gordon L, Hourlier T, Hunt SE, Janacek SH, Johnson N, Juettemann T, Keenan S, Lavidas I, Martin FJ, Maurel T, McLaren W, Murphy DN, Nag R, Nuhn M, Parker A, Patricio M, Pignatelli M, Rahtz M, Riat HS, et al. Ensembl 2016. *Nucleic Acids Res* 2016;**44**:D710–D716.

83. Bank P, Caudle K, Swen J, Gammal R, Whirl‐Carrillo M, Klein T, Relling M, Guchelaar H. Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. *Clin Pharmacol Ther* 2018;**103**:599–618.

84. Summary of Product Characteristics: Simvastatin. https://mri.cts-mrp.eu/human/downloads/IT\_H\_0729\_001\_FinalPI.pdf (20 October 2020)

85. Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, Krauss RM, Roden DM, Feng Q, Cooper-DeHoff RM, Gong L, Klein TE, Wadelius M, Niemi M. The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for SLCO1B1 and Simvastatin-Induced Myopathy. *Clin Pharmacol Ther* 2012;**92**:112–117.

86. Dutch Pharmacogenetic Working Group of the Royal Dutch Pharmacists Association.

87. Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet Genomics* 2006;**16**:873–879.

88. Tornio A, Vakkilainen J, Neuvonen M, Backman JT, Neuvonen PJ, Niemi M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of lovastatin acid. *Pharmacogenet Genomics* 2015;**25**:382–387.

89. Deng JW, Song I-S, Shin HJ, Yeo C-W, Cho D-Y, Shon J-H, Shin J-G. The effect of SLCO1B1\*15 on the disposition of pravastatin and pitavastatin is substrate dependent: the contribution of transporting activity changes by SLCO1B1\*15. *Pharmacogenet Genomics* 2008;**18**:424–433.

90. Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M. Different Effects of SLCO1B1 Polymorphism on the Pharmacokinetics of Atorvastatin and Rosuvastatin. *Clin Pharmacol Ther* 2007;**82**:726–733.

91. NIEMI M, PASANEN M, NEUVONEN P. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. *Clin Pharmacol Ther* 2006;**80**:356–366.

92. Zisaki A, Miskovic L, Hatzimanikatis V. Antihypertensive drugs metabolism: an update to pharmacokinetic profiles and computational approaches. *Curr Pharm Des* Bentham Science Publishers Ltd.; 2015;**21**:806–822.

93. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol. Ther. Pergamon; 2013. p. 103–141.

94. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: Pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol. Ther. Pergamon; 2007. p. 496–526.

95. Leopold G. Balanced pharmacokinetics and metabolism of bisoprolol. *J Cardiovasc Pharmacol* J Cardiovasc Pharmacol; 1986;**8**:S16–S20.

96. Bijl MJ, Visser LE, Schaik RHN Van, Kors JA, Witteman JCM, Hofman A, Vulto AG, Gelder T Van, Stricker BHC. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in β-blocker users. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2009;**85**:45–50.

97. Luzum JA, Sweet KM, Binkley PF, Schmidlen TJ, Jarvis JP, Christman MF, Sadee W, Kitzmiller JP. CYP2D6 Genetic Variation and Beta-Blocker Maintenance Dose in Patients with Heart Failure. *Pharm Res* Springer New York LLC; 2017;**34**:1615–1625.

98. Rau T, Wuttke H, Michels LM, Werner U, Bergmann K, Kreft M, Fromm MF, Eschenhagen T. Impact of the CYP2D6 genotype on the clinical effects of metoprolol: A prospective longitudinal study. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2009;**85**:269–272.

99. Anstensrud AK, Molden E, Haug HJ, Qazi R, Muriq H, Fosshaug LE, Spigset O, Øie E. Impact of genotype-predicted CYP2D6 metabolism on clinical effects and tolerability of metoprolol in patients after myocardial infarction – a prospective observational study. *Eur J Clin Pharmacol* Springer; 2020;**76**:673–683.

100. Sharp CF, Gardiner SJ, Jensen BP, Roberts RL, Troughton RW, Lainchbury JG, Begg EJ. CYP2D6 genotype and its relationship with metoprolol dose, concentrations and effect in patients with systolic heart failure. *Pharmacogenomics J* Nature Publishing Group; 2009;**9**:175–184.

101. Batty JA, Hall AS, White HL, Wikstrand J, Boer RA De, Veldhuisen DJ Van, Harst P Van Der, Waagstein F, Hjalmarson Å, Kjekshus J, Balmforth AJ. An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: A MERIT-HF substudy. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2014;**95**:321–330.

102. Hamadeh IS, Langaee TY, Dwivedi R, Garcia S, Burkley BM, Skaar TC, Chapman AB, Gums JG, Turner ST, Gong Y, Cooper-Dehoff RM, Johnson JA. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. *Clin Pharmacol Ther* Nature Publishing Group; 2014;**96**:175–181.

103. Kirchheiner J, Heesch C, Bauer S, Meisel C, Seringer A, Goldammer M, Tzvetkov M, Meineke I, Roots I, Brockmöller J. Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2004;**76**:302–312.

104. Goryachkina K, Burbello A, Boldueva S, Babak S, Bergman U, Bertilsson L. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. *Eur J Clin Pharmacol* 2008;**64**:1163–1173.

105. Zineh I, Beitelshees AL, Gaedigk A, Walker JR, Pauly DF, Eberst K, Leeder JS, Phillips MS, Gelfand CA, Johnson JA. Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2004;**76**:536–544.

106. Wuttke H, Rau T, Heide R, Bergmann K, Böhm M, Weil J, Werner D, Eschenhagen T. Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2002;**72**:429–437.

107. Fux R, Mörike K, Pröhmer AMT, Delabar U, Schwab M, Schaeffeler E, Lorenz G, Gleiter CH, Eichelbaum M, Kivistö KT. Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: A prospective clinical study. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2005;**78**:378–387.

108. Novartis Pharmaceuticals Corporation. LOPRESSOR (metoprolol tartrate). 2008.

109. Blake CM, Kharasch ED, Schwab M, Nagele P. A meta-analysis of CYP2D6 metabolizer phenotype and metoprolol pharmacokinetics. *Clin Pharmacol Ther* NIH Public Access; 2013;**94**:394–399.

110. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, Simone G de, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertens* 2018;**36**:1953–2041.

111. Zhou B, Bentham J, Cesare M Di, Bixby H, Danaei G, Cowan MJ, Paciorek CJ, Singh G, Hajifathalian K, Bennett JE, Taddei C, Bilano V, Carrillo-Larco RM, Djalalinia S, Khatibzadeh S, Lugero C, Peykari N, Zhang WZ, Lu Y, Stevens GA, Riley LM, Bovet P, Elliott P, Gu D, Ikeda N, Jackson RT, Joffres M, Kengne AP, Laatikainen T, Lam TH, et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* 2017;**389**:37–55.

112. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G, Dimou N, Cabrera CP, Karaman I, Ng FL, Evangelou M, Witkowska K, Tzanis E, Hellwege JN, Giri A, Velez Edwards DR, Sun Y V., Cho K, Gaziano JM, Wilson PWF, Tsao PS, Kovesdy CP, Esko T, Mägi R, Milani L, Almgren P, Boutin T, Debette S, Ding J, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* 2018;**50**:1412–1425.

113. Giri A, Hellwege JN, Keaton JM, Park J, Qiu C, Warren HR, Torstenson ES, Kovesdy CP, Sun Y V., Wilson OD, Robinson-Cohen C, Roumie CL, Chung CP, Birdwell KA, Damrauer SM, DuVall SL, Klarin D, Cho K, Wang Y, Evangelou E, Cabrera CP, Wain L V., Shrestha R, Mautz BS, Akwo EA, Sargurupremraj M, Debette S, Boehnke M, Scott LJ, Luan J, et al. Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nat Genet* 2019;**51**:51–62.

114. Lynch AI, Eckfeldt JH, Davis BR, Ford CE, Boerwinkle E, Leiendecker-Foster C, Arnett DK. Gene panels to help identify subgroups at high and low risk of coronary heart disease among those randomized to antihypertensive treatment. *Pharmacogenet Genomics* 2012;1.

115. Johnson JA. Ethnic Differences in Cardiovascular Drug Response. *Circulation* 2008;**118**:1383–1393.

116. Schreieck J, Dostal S, Beckerath N von, Wacker A, Flory M, Weyerbrock S, Koch W, Schömig A, Schmitt C. C825T polymorphism of the G-protein β3 subunit gene and atrial fibrillation: Association of the TT genotype with a reduced risk for atrial fibrillation. *Am Heart J* 2004;**148**:545–550.

117. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* United States; 2004;**350**:1013–1022.

118. Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation. 1998.

119. International Conference on Harmonisation; guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; availability. Notice. *Fed Regist* United States; 2005;**70**:61134–61135.

120. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. *Pharmacol Rev* 2010;**62**:760–781.

121. Kannankeril PJ, Roden DM. Drug-induced long QT and torsade de pointes: recent advances. *Curr Opin Cardiol* United States; 2007;**22**:39–43.

122. Morita H, Wu J, Zipes DP. The QT syndromes: long and short. Lancet. 2008.

123. CredibleMeds. CredibleMeds.org (19 October 2020)

124. Mahida S, Hogarth AJ, Cowan C, Tayebjee MH, Graham LN, Pepper CB. Genetics of congenital and drug-induced long QT syndromes: Current evidence and future research perspectives. J. Interv. Card. Electrophysiol. 2013.

125. Hong Y, Rautaharju P, Hopkins P, Arnett D, Djoussé L, Pankow J, Sholinsky P, Rao D, Province M. Familial aggregation of QT-interval variability in a general population: Results from the NHLBI Family Heart Study. *Clin Genet* 2001;

126. Newton-Cheh C, Larson MG, Corey DC, Benjamin EJ, Herbert AG, Levy D, D’Agostino RB, O’Donnell CJ. QT interval is a heritable quantitative trait with evidence of linkage to chromosome 3 in a genome-wide linkage analysis: The Framingham Heart Study. *Hear Rhythm* United States; 2005;**2**:277–284.

127. Kannankeril PJ, Roden DM, Norris KJ, Whalen SP, George ALJ, Murray KT. Genetic susceptibility to acquired long QT syndrome: pharmacologic challenge in first-degree relatives. *Hear Rhythm* United States; 2005;**2**:134–140.

128. Chakravarti A, Pfeufer A, Kashuk C, Guo C-Y, Gieger C, Newton-Cheh C, O’Donnell CJ, Arking DE, Marbán E, Wichmann HE, Hirschhorn JN, West K, Akyol M, Larson MG, Ikeda M, Spooner PM, Jalilzadeh S, Perz S, Kääb S, Illig T, Meitinger T, Kao WHL, Post W. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nat Genet* 2006;

129. Pfeufer A, Sanna S, Arking DE, Müller M, Gateva V, Fuchsberger C, Ehret GB, Orrú M, Pattaro C, Köttgen A, Perz S, Usala G, Barbalic M, Li M, Pütz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WHL, Mühleisen TW, Dei M, Happle C, Möhlenkamp S, Crisponi L, Erbel R, Jöckel K-H, Naitza S, Steinbeck G, et al. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet* 2009;**41**:407–414.

130. Newton-Cheh C, Eijgelsheim M, Rice KM, Bakker PIW de, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JCM, Hofman A, Heckbert SR, O’Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BHC. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet* 2009;**41**:399–406.

131. Post W, Shen H, Damcott C, Arking DE, Kao WHL, Sack PA, Ryan KA, Chakravarti A, Mitchell BD, Shuldiner AR. Associations between genetic variants in the NOS1AP (CAPON) gene and cardiac repolarization in the Old Order Amish. *Hum Hered* 2007;

132. Aarnoudse AJLHJ, Newton-Cheh C, Bakker PIW De, Straus SMJM, Kors JA, Hofman A, Uitterlinden AG, Witteman JCM, Stricker BHC. Common NOS1AP variants are associated with a prolonged QTc interval in the rotterdam study. *Circulation* 2007;

133. Tobin MD, Kähönen M, Braund P, Nieminen T, Hajat C, Tomaszewski M, Viik J, Lehtinen R, Ng GA, Macfarlane PW, Burton PR, Lehtimäki T, Samani NJ. Gender and effects of a common genetic variant in the NOS1 regulator NOS1AP on cardiac repolarization in 3761 individuals from two independent populations. *Int J Epidemiol* 2008;

134. Lehtinen AB, Newton-Cheh C, Ziegler JT, Langefeld CD, Freedman BI, Daniel KR, Herrington DM, Bowden DW. Association of NOS1AP genetic variants with QT interval duration in families from the diabetes Heart Study. *Diabetes* 2008;

135. Kapoor A, Sekar RB, Hansen NF, Fox-Talbot K, Morley M, Pihur V, Chatterjee S, Brandimarto J, Moravec CS, Pulit SL, Pfeufer A, Mullikin J, Ross M, Green ED, Bentley D, Newton-Cheh C, Boerwinkle E, Tomaselli GF, Cappola TP, Arking DE, Halushka MK, Chakravarti A. An enhancer polymorphism at the cardiomyocyte intercalated disc protein NOS1AP locus is a major regulator of the QT interval. *Am J Hum Genet* 2014;

136. Behr ER, Ritchie MD, Tanaka T, Kääb S, Crawford DC, Nicoletti P, Floratos A, Sinner MF, Kannankeril PJ, Wilde AAM, Bezzina CR, Schulze-Bahr E, Zumhagen S, Guicheney P, Bishopric NH, Marshall V, Shakir S, Dalageorgou C, Bevan S, Jamshidi Y, Bastiaenen R, Myerburg RJ, Schott JJ, Camm AJ, Steinbeck G, Norris K, Altman RB, Tatonetti NP, Jeffery S, Kubo M, et al. Genome wide analysis of drug-induced torsades de pointes: Lack of common variants with large effect sizes. *PLoS One* 2013;

137. Strauss DG, Vicente J, Johannesen L, Blinova K, Mason JW, Weeke P, Behr ER, Roden DM, Woosley R, Kosova G, Rosenberg MA, Newton-Cheh C. Common genetic variant risk score is associated with drug-induced QT prolongation and torsade de pointes risk. *Circulation* 2017;

138. Kääb S, Crawford DC, Sinner MF, Behr ER, Kannankeril PJ, Wilde AAM, Bezzina CR, Schulze-Bahr E, Guicheney P, Bishopric NH, Myerburg RJ, Schott JJ, Pfeufer A, Beckmann BM, Martens E, Zhang T, Stallmeyer B, Zumhagen S, Denjoy I, Bardai A, Gelder IC Van, Jamshidi Y, Dalageorgou C, Marshall V, Jeffery S, Shakir S, Camm AJ, Steinbeck G, Perz S, Lichtner P, et al. A large candidate gene survey identifies the KCNE1D85N polymorphism as a possible modulator of drug-induced torsades de pointes. *Circ Cardiovasc Genet* 2012;

139. Paulussen ADC, Gilissen RAHJ, Armstrong M, Doevendans PA, Verhasselt P, Smeets HJM, Schulze-Bahr E, Haverkamp W, Breithardt G, Cohen N, Aerssens J. Genetic variations of HCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J Mol Med* 2004;

140. Weeke P, Mosley JD, Hanna D, Delaney JT, Shaffer C, Wells QS, Driest S Van, Karnes JH, Ingram C, Guo Y, Shyr Y, Norris K, Kannankeril PJ, Ramirez AH, Smith JD, Mardis ER, Nickerson D, George AL, Roden DM. Exome sequencing implicates an increased burden of rare potassium channel variants in the risk of drug-induced long QT interval syndrome. *J Am Coll Cardiol* 2014;

141. Roden DM, Viswanathan PC. Genetics of acquired long QT syndrome. J. Clin. Invest. 2005.

142. Magdy T, Burmeister BT, Burridge PW. Validating the pharmacogenomics of chemotherapy-induced cardiotoxicity: What is missing? *Pharmacol Ther* 2016;**168**:113–125.

143. Aminkeng F, Ross CJD, Rassekh SR, Hwang S, Rieder MJ, Bhavsar AP, Smith A, Sanatani S, Gelmon KA, Bernstein D, Hayden MR, Amstutz U, Carleton BC. Recommendations for genetic testing to reduce the incidence of anthracycline‐induced cardiotoxicity. *Br J Clin Pharmacol* 2016;**82**:683–695.

144. Craig LA, Ekert PG, Conyers R, Elliott DA. Genetic determinants of anthracycline cardiotoxicity – ready for the clinic? *Br J Clin Pharmacol* 2017;**83**:1141–1142.

145. Sapkota Y, Qin N, Ehrhardt MJ, Wang Z, Chen Y, Wilson CL, Estepp J, Rai P, Hankins JS, Burridge PW, Jefferies JL, Zhang J, Hudson MM, Robison LL, Armstrong GT, Mulrooney DA, Yasui Y. Genetic variants associated with therapy-related cardiomyopathy among childhood cancer survivors of African ancestry. *Cancer Res* 2020;canres.2675.2020.

146. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, Toepfer CN, Getz K, Gorham J, Patel P, Ito K, Willcox JA, Arany Z, Li J, Owens AT, Govind R, Nuñez B, Mazaika E, Bayes-Genis A, Walsh R, Finkelman B, Lupon J, Whiffin N, Serrano I, Midwinter W, Wilk A, Bardaji A, Ingold N, Buchan R, Tayal U, et al. Genetic Variants Associated With Cancer Therapy–Induced Cardiomyopathy. *Circulation* 2019;**140**:31–41.

147. Linschoten M, Teske AJ, Cramer MJ, Wall E van der, Asselbergs FW. Chemotherapy-Related Cardiac Dysfunction. *Circ Genomic Precis Med* 2018;**11**.

148. Jackson N, Atar D, Borentain M, Breithardt G, Eickels M van, Endres M, Fraass U, Friede T, Hannachi H, Janmohamed S, Kreuzer J, Landray M, Lautsch D, Floch C Le, Mol P, Naci H, Samani NJ, Svensson A, Thorstensen C, Tijssen J, Vandzhura V, Zalewski A, Kirchhof P. Improving clinical trials for cardiovascular diseases: a position paper from the Cardiovascular Round Table of the European Society of Cardiology. *Eur Heart J* 2016;**37**:747–754.

149. Turner RM, Pirmohamed M. Cardiovascular Pharmacogenomics: Expectations and Practical Benefits. *Clin Pharmacol Ther* Clin Pharmacol Ther; 2014;**95**:281–293.

150. Pereira NL, Sargent DJ, Farkouh ME, Rihal CS. Genotype-based clinical trials in cardiovascular disease. *Nat Rev Cardiol* 2015;**12**:475–487.

151. Piccini JP, Abraham WT, Dufton C, Carroll IA, Healey JS, Veldhuisen DJ van, Sauer WH, Anand IS, White M, Wilton SB, Aleong R, Rienstra M, Krueger SK, Ayala-Paredes F, Khaykin Y, Merkely B, Miloradović V, Wranicz JK, Ilkhanoff L, Ziegler PD, Davis G, Emery LL, Marshall D, Kao DP, Bristow MR, Connolly SJ. Bucindolol for the Maintenance of Sinus Rhythm in a Genotype-Defined HF Population. *JACC Hear Fail* 2019;**7**:586–598.

152. Tall AR, Rader DJ. Trials and Tribulations of CETP Inhibitors. *Circ Res* 2018;**122**:106–112.

153. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N Engl J Med* 2017;**377**:1217–1227.

154. Tardif J-C, Dubé M-P, Pfeffer MA, Waters DD, Koenig W, Maggioni AP, McMurray JJV, Mooser V, White HD, Heinonen T, Black DM, Guertin M-C. Study design of Dal-GenE, a pharmacogenetic trial targeting reduction of cardiovascular events with dalcetrapib. *Am Heart J* 2020;**222**:157–165.

155. Cavallari LH, Lee CR, Beitelshees AL, Cooper-DeHoff RM, Duarte JD, Voora D, Kimmel SE, McDonough CW, Gong Y, Dave C V., Pratt VM, Alestock TD, Anderson RD, Alsip J, Ardati AK, Brott BC, Brown L, Chumnumwat S, Clare-Salzler MJ, Coons JC, Denny JC, Dillon C, Elsey AR, Hamadeh IS, Harada S, Hillegass WB, Hines L, Horenstein RB, Howell LA, Jeng LJB, et al. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2018;**11**:181–191.

 **Figures**

Figure 1 – Summary graphic of ESC WG clinical PGx advice

Figure 2 - Areas with promise for PGx translation – key opportunities for research



**Figure 1:** “Summary graphic of ESC WG clinical PGx advice”

This flow graphic illustrates the modes in which patients may have genetic testing, either prior to clinical encounter or indicated during a clinical encounter (where genotyping may be indicated prior to warfarin initiation or to guide antiplatelet therapy in high-risk patients). This information from diverse sources may then impact on the prescribing of metoprolol, simvastatin, clopidogrel and warfarin, to increase therapeutic efficacy and decrease the probability of adverse drug reactions.

Abbreviations:

Adverse drug reactions (ADR)

Direct-to-consumer (DTC)



**Figure 2:** “Areas with promise for PGx translation”

Key opportunities for research to advance pharmacogenomics and facilitate translation to the bedside.