HMC RESEARCH PROTOCOL

Study Title:	**Clinical Implementation of Pharmacogenetic- Guided Dosing of Warfarin in Patients with Heart Valve Replacement in Qatar**
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Content

1. Synopsis

Warfarin is an oral anticoagulant, widely prescribed in clinical practice for the prophylaxis of thromboembolic complications after valve replacement surgery. Warfarin treatment is limited by its narrow therapeutic index, high sensitivity to drug interaction, and the large interindividual variation that affects the dose required for a target anticoagulant effect. In Qatar, warfarin therapy is initiated using empiric doses after valve replacement surgery and coagulation status is regularly monitored by keeping the international normalized ratio (INR) value in the target range which makes the precision of the anticoagulant therapy of warfarin is challenging. Various reports showed a clear association between genetic variability and warfarin dosing that may provide a more precise prediction of warfarin dosing and allow accurate and safe anticoagulant therapy. Therefore, the availability of rapid genetic testing may help in considering the right dosing of warfarin for patients following heart valve surgery. This study aims to evaluate the anticoagulation management using point-of-care (POC) genotype-guided dosing based on the validated genotype-based warfarin dosing model which will help pave the way for the use of pharmacogenetic (PGx) testing for warfarin individualized therapy in routine clinical practice in Qatar.

2. Abbreviations

PGx: pharmacogenetics
INR: International normalized ratio
POC: Point of care
TTR: Time in therapeutic range
VKORC: vitamin K epoxide reductase gene
IWPC: International Warfarin Pharmacogenetics Consortium

3. Introduction

Heart valve replacement is one of the main surgical treatments for heart valve disease (1). Postoperative valve-related thromboembolism is considered one of the serious complications of valve replacement surgery leading to ischemic stroke, heart failure, and even sudden death (2, 3). Therefore, initiation of long-term anticoagulant therapy is inevitable to reduce thromboembolic complications after valve replacement surgery (1). Regardless of its limitations, warfarin is the only oral anticoagulant recommended by the clinical guidelines as antithrombotic therapy following valve replacement surgery as the use of other new direct oral anticoagulants is contraindicated for this purpose (4, 5). Warfarin treatment is complicated by the great variability in the individual response besides its narrow therapeutic and higher drug interaction liability (6, 7) which can lead to unpredicted (up to 20-fold) dose requirements (8). Additionally, the increased sensitivity

to warfarin response is well documented early after valve replacement surgery and warfarin dosing initiation protocols in this regard are empirical (9, 10).

The precision of the early anticoagulant treatment of warfarin in patients after heart replacement surgery is challenging. The antithrombotic effect of warfarin may take days to be manifested, thus increasing the dose to achieve target international normalized ratio (INR) may increase the risk of bleeding events during the initial phase of therapy (11, 12). Current warfarin treatment guidelines have set clinical algorithms to predict the required warfarin dosing based on an assessment of the INR and clinical factors (10). Dosing algorithms considering only clinical factors were able to predict only 15–25% of the variability in warfarin dosage (8, 10, 11). Therefore, the adoption of guidelines that include not only clinical factors but also genetic polymorphism, could give a better prediction tool for appropriated warfarin dosing.

Candidate-gene association studies have identified common genetic variations in, CYP2C9 *2 and *3 alleles that have been reported to decrease warfarin metabolic capacity and increase its half-life (13). The other variant in the vitamin K epoxide reductase gene (VKORC) also influences the warfarin dosing as it affects the extrinsic clotting pathway, which warfarin antagonizes(8, 13). Therefore, variations in these genes significantly influence warfarin dose requirements, time to achieve therapeutic anticoagulation, rate of INR increase, and risk of major bleeding (11, 14).

It has been shown that warfarin dosage estimation using pharmacogenetic algorithms has been shown to improve anticoagulation control. Multivariable highly performing validated algorithms of the International Warfarin Pharmacogenetics Consortium (IWPC) (8), and the Gage (15) are available for clinical use based on both clinical and genetic factors and these can explain about 50% of the variability in the warfarin doses. Therefore, it is important to implement precise individual dosing of warfarin to ensure its safety and effectiveness

Based on accumulating data, FDA has updated the drug label for warfarin and recommended considering CYP2C9 and VKORC1 genotype information in the selection of warfarin dosing further, warfarin CPIC guidelines, published in 2011, strongly recommend warfarin dosing based on genotype (13). However, routine clinical use of genotyping for CYP2C9 and VKORC1 in warfarin-treated patients is not largely adopted in the clinical settings in Qatar.

Hypothesis: Warfarin treatment is mandatory after cardiac surgery; the study is designed to evaluate whether pharmacogenetic testing could affect the 30 days outcome.

Study novelty

Relevance/Significance of the study

It is important to validate this warfarin pharmacogenetic technique in cardiac surgery settings and to assess whether it may affect clinical outcome within 30 days.

4. Objectives of the study

This study is designed to determine whether warfarin pharmacogenetic testing can enhance patient outcomes within 30 days after heart valve replacement. In this regard, we are going to adopt a point of care (POC) genotyping platform for determining patient phenotype at the time of initial dosing decision so we can avoid the treatment delay due to the turnaround time of genotyping testing and get the ultimate benefit of precise estimation of the initial and maintenance doses of warfarin for patient followed valve replacement. Additionally, the current study aims to improve anticoagulation efficacy and reduce the risk of thrombosis and bleeding

1. The purpose of the study is to implement reactive PGx-testing in personalizing therapy of warfarin in patients with heart valve replacement via adopting POC PGx reactive testing
2. To investigate the clinical efficacy of genotype-guided dosing of warfarin administration compared to clinically fixed warfarin dosing in terms of coagulation control
3. To evaluate the feasibility of the clinical implementation of the warfarin PGx-based dosing to predict warfarin maintenance dose in patients undergoing mechanical valve replacement.
4. To compare warfarin PGx-based versus conventional warfarin treatment in terms of time to reach therapeutic anticoagulation, association with warfarin related complications (bleeding, pericardial effusion).

Indicate if this is a retrospective data review

- * **Retrospective Chart/data Review** (required)

Provide the date range of the chart review

Data collected retrospectively of 300 patients during 4-year period from 01-01-2019 to 01-10-2022.

Data Collection sheet is attached (supplement 1)

5. Study design and methodology

5.1. Designing and setting

This study is designed as a two-arm comparative study (prospective cohort study vs. retrospective study). The study includes heart patients undergoing heart valve replacement and eligible for warfarin treatment post-surgery. The study is designed to demonstrate whether genotype-guided dose prediction improves the safety and efficacy of warfarin treatment compared to non-tailored strategy.

The prospective cohort genotype-guided strategy (intervention group) of 150 patients, will be compared against a traditional retrospective clinical dosing strategy (control group) which will be 300 patients from 01-01-2019 to 01-10-2022.

The patients of the intervention group will be recruited prospectively in the heart hospital, HMC. Before being assigned to the surgery, eligible patients will be recruited in the study after signing written informed consent. The genetic test will be performed as soon as possible, and the result will be reported 2 days before the surgery

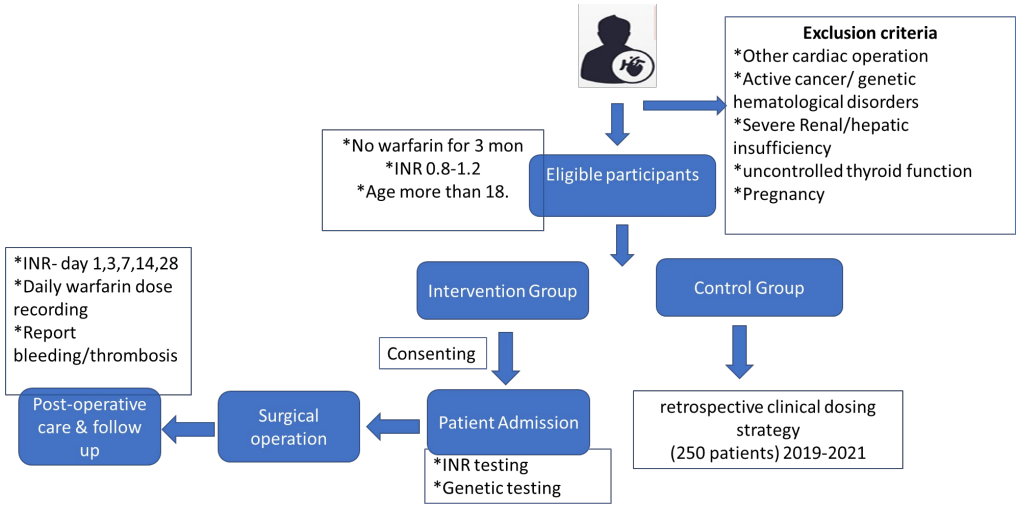

Figure (1): schematic representation of the proposed study design

5.2 Study intervention and research method

Initial warfarin dosing is calculated for the intervention group before the scheduled surgery. The calculated warfarin dose (predicted dose) is estimated according to IWPC and Gage algorithms (8, 15)

The Gage algorithms to estimate the optimal clinical warfarin dose (mg/day) is:

$$\exp\ [0.613 + (0.425\ \times\ \text{BSA}) - (0.0075\ \times\ \text{age}) + (0.156 \times \text{African-American race}) + (0.216\ \times\ \text{target INR}) - (0.257 \times \text{amiodarone}) + (0.108\ \times\ \text{smokes}) + 0.0784^{*}\ \text{DVT / PE}],$$

where exp is the exponential function; BSA is in m2; race is 1 if African American (0 otherwise); target INR is the desired INR (e.g., 2.5); amiodarone is 1 if the patient is taking that drug (and 0 otherwise); and DVT/PE is 1 if the indication for warfarin is deep venous thrombosis (DVT) or pulmonary embolism (PE). The accuracy of the derived pharmacogenetics model depended on race: R2 was 57% in 838 Caucasian participants and 31% in 153 African-American patients.

For IWPC algorithim has two-tailed algorithms for both warfarin pharmacogenetic dosing and warfarin clinical dosing. The output of these algorithms must be squared to compute weekly dose in mg.

Warfarin pharmacogenetic dosing algorithm			
		5.6044	
-		0.2614 x	Age in decades
+		0.0087 x	Height in cm
+		0.0128 x	Weight in kg
-		0.8677 x	*VKORC1*^ A/G
-		1.6974 x	*VKORC1* A/A
-		0.4854 x	*VKORC1* genotype unknown
-		0.5211 x	*CYP2C9* *1/*2
-		0.9357 x	*CYP2C9* *1/*3
-		1.0616 x	*CYP2C9* *2/*2
-		1.9206 x	*CYP2C9* *2/*3
-		2.3312 x	*CYP2C9* *3/*3
-		0.2188 x	*CYP2C9* genotype unknown
-		0.1092 x	Asian race
-		0.2760 x	Black or African American
-		0.1032 x	Missing or Mixed race
+		1.1816 x	Enzyme inducer status
-		0.5503 x	Amiodarone status
=	**Square root of weekly warfarin dose****		

Warfarin clinical dosing algorithm		
	4.0376	
-	0.2546 x	Age in decades
+	0.0118 x	Height in cm
+	0.0134 x	Weight in kg
-	0.6752 x	Asian race
+	0.4060 x	Black or African American
+	0.0443 x	Missing or Mixed race
+	1.2799 x	Enzyme inducer status
-	0.5695 x	Amiodarone status
=	**Square root of weekly warfarin dose****	

Legend for use of algorithms:

• Age in decades = 1 for 10-19, 2 for 20-29, etc…

• VKORC1 G/A = 1 if heterozygous for rs9923231, otherwise zero

• VKORC1 A/A = 1 if homozygous for A at rs9923231, otherwise zero

• VKORC1 genotype unknown = 1 if rs9923231 genotype missing or unknown, otherwise zero

• CYP2C9 *1/*2 = 1 if CYP2C9 genotype is *1/*2, otherwise zero

• CYP2C9 *1/*3 = 1 if CYP2C9 genotype is *1/*3, otherwise zero

• CYP2C9 *2/*2 = 1 if homozygous for CYP2C9 *2 allele, otherwise zero • CYP2C9 *2/*3 = 1 if CYP2C9 genotype is *2/*3, otherwise zero

• CYP2C9 *3/*3 = 1 if homozygous for CYP2C9 *3 allele, otherwise zero

• CYP2C9 genotype unknown = 1 if CYP2C9 genotype unknown, otherwise zero

• Asian Race = 1 if self-reported race is Asian, otherwise zero

• Black/African American = 1 if self-reported race is Black or African American, otherwise zero

• Missing or Mixed race = 1 if self-reported race is unspecified or mixed, otherwise zero
• Enzyme inducer status = 1 if patient taking carbamazepine, phenytoin, rifampin, or rifampicin, otherwise zero

• Amiodarone status = 1 if patient taking amiodarone, otherwise zero

Both IWPC and Gage algorithms are integrated into a web-based model to make dose calculation more integrative which is available at http://www.warfarindosing.org,

For The control group, patients received an initiation dosage of warfarin according to the regular clinical routine.

Patients are administered oral warfarin at the predicted dose starting on the 3rd day following surgery. After 3 days of anticoagulant therapy, warfarin doses are adjusted depending on the measured INR values.

All patients were followed up for 30 days unless an adverse event occurred. INR should be reviewed on days 1, 3, 7, 14, 21 and 28 days

5.3. Study population inclusion/exclusion criteria

Patients of at least 18 years old, scheduled for single or double mechanical

prosthetic valve replacement are recruited over a period of two year. We aim to recruit 150 patients all of whom will be followed up for 30 days post-surgery. Patients included in the study will undergo a clinical examination, and routine laboratory tests the genotyping data analysis and interpretations will be performed by the bioinformatics team in the Qatar Genome program (QGP)

- Inclusion criteria
- Patients of (18-75) years old
- Not to use warfarin in the past 3 months
- Has normal INR value of 0.8-1.2
- Signing informed consent
- Exclusion criteria
- History of any other cardiac operation
- Having a diagnosis of active cancer/ hematological disorders
- having severe renal/hepatic insufficiency
- Having abnormal thyroid function
- Detection of pregnancy
- Inability to provide written consent.

5.4. Assessment variables

- Patients' characteristics: Including age, weight, gender, smoking status, nationality, BMI.

- Clinical characteristics: Recording of medical history, concomitant medication, and INR measurements.

- Outcome measures

A. The primary outcomes:

1- The percentage of time in the therapeutic range (TTR) during a 30-day timeframe. The TTR was defined as the percentage of the time the patient INR within the target range during 30 days of therapy according to the method of Rosendaal and colleagues (16).

2- The time to achieve the therapeutic INR during a 30-day timeframe. The time to achieve the first INR in the therapeutic range is defined as the time from the initiation of warfarin therapy until the first INR reached the

treatment anticoagulation range.

B. The secondary outcomes

1- The time to reach a stable dose from day 5 to day 30. The time to reach a stable dose is defined as INR within a target range for a specified dose for a period of at least 10 days.

2- Incidence of INR>4 during 4 weeks, which indicates over-anticoagulation.

3- Incidence of INR < 2.0, which indicates under-anticoagulation.

4- The frequency of dosage changes over a 4-week period

5- Minor and major bleeding events in addition to hemorrhagic complications.

6- Thromboembolic events and recurrent thrombosis, stroke incidence in patients with AF (markers of lack of efficacy).

7- Incidence of warfarin sensitivity that is defined as a dose of 1.5 mg or less per day on 3 successive clinic visits (stable dose)

5.5. Genotyping strategy

Eligible patients are recruited in the study after signed written informed consent. Genetic testing for CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910), and VKORC1 -1639G→A (rs9923231) are carried out using point-of-care genotyping technology (ParaDNA, LCG,). Genotype results along with clinical information are used to calculate warfarin loading dose based on a validated published PGx algorithm. On day 4 another dosing algorithm is calculated based on clinical and genetic data as well as INR measurement (17). Afterward, the dosing follows the standard procedures utilized by the clinics.

5.6. International normalization ratio (INR) measurement

Using 3-4 ml blood sample, patients' anticoagulation status is routinely monitored (by measurement of INR) on Day 1, 3, 7 (during patient admission). Then INR will be measured using an automatic POC analyzer during the follow up visits in days 14, 21 and 28 in anticoagulation clinic.

5.7. Study duration and timeline

a. Patients selection and recruiting – (36 months)

- Ensure alignment of the selected patients with the pre-identified inclusion/exclusion criteria.

- Follow-up patient recruitment and data collection.

b. Ensure consenting process and report patient withdrawal (36 months)

c. Assessment of clinical variables, clinical outcome, and lab test

d. Ensure reporting of all patients' variables as identified previously and collect patient's data information and results

e. Monitoring and follow up patients – (1, 3, 7, 14, 21 and 28 days post-surgery)

- Ensure adherence to visiting dates and prescribed medication
- Report any observed side effects.

f. Quality assurance – (Throughout the study- 36 months)

- Ensure the quality of research and technology results.

h. Statistics and data interpretation – (6 months)

6. Informed consent

a. Before entering the studies, each patient will be given oral and written information and written informed consent (Arabic/English), patients who are unable or refuse to give informed consent will be excluded

b. The patients will be recruited from heart hospital, cardiothoracic department where the consent form will be introduced to the participant by one of our team member

c. The subject will be identified according to a pre-identified inclusion/exclusion criteria by a physician during their referral to cardiothoracic department for heart valve replacement. Once our physician team identify an eligible participant he will be introduced to the study during his clinical visit.

d. 1-2 days before scheduled the surgery, the participant will be invited to read the consent form carefully before deciding whether you want to take part. The information will also be discussed with the participant by the research team. If there is anything the participant does not understand about this study, he can ask the doctor and/or the research team any questions before he makes his decision.

7- Data collection

- Special study forms will be prepared to collect data regarding patient characteristics (age, weight, gender, past medication history, …..etc)

- Clinical outcome data will be collected face-to-face during clinical visits 30 days post-surgery. we will schedule a clinical follow up plan, and phone interviews will be scheduled every week with patients to ensure medication adherence (phone script is attached)
- Patients who are going to withdraw or who will be lost to follow-up will be treated as censored at the date of the last contact.
- Patients who agreed to participate in the study will be asked to provide a buccal swab for genotyping analysis and a 3-4 ml blood sample for INR measurement.
- Subjects who experience adverse effect will not be excluded from the final study analysis

8- Data Management and Analysis plan

- Data will be collected de-identified, codes will be used to cover patient identifiers such as Name, HC no., DOB. The link between the code and the identifier will be destroyed once the study finishes and the de-identified data will be stored for at least five years
- Clinical outcome data will be collected using the Cerner system in HMC
- Genomic data will be provided by the POC analyzer and stored in the electronic health record (HER) (if applicable) of the patient to be used in the future.
- Data and blood samples will have a specific code by independent investigators this code will be further used through the data collection procedure.
- The principal investigator is the one who has full access to the study data.
- Deviation from Hardy–Weinberg equilibrium (HWE) for polymorphisms will be checked using the chi-squared test with one degree of freedom. Continuous data will be expressed as mean ± standard deviation (SD). While categorical data will be expressed as a percentage. All statistical analyses will be performed using the SPSS program for Windows and Golden Helix SNP & Variation Suite for genetic analysis

A univariate analysis followed by a multivariate logistic regression will be performed to investigate the influence of baseline risk factors.

- A 2-sided likelihood ratio test was used to calculate the P-value. Hazard ratios are reported with 95% CIs. The proportional hazards assumption will be investigated by testing the interaction between treatment groups and the logarithm of follow-up time. When the assumption was violated, a post hoc analysis was undertaken to estimate the treatment effect over different segments of the follow-up period. The time segments are chosen based on the clinical importance of these periods.
- Analysis for comparisons between both treatment groups (intervention and control) will be performed to assess the effect of the CYP2C9*2/*3 and VKORC1 -1639G→A (rs9923231) on a different component of the primary endpoint and other outcomes
- Sample size calculation using (https://clincalc.com/stats/samplesize.aspx) assuming that the anticipated incidence for control group 61 ±15%with anticipated increase of 8% by keeping class error 0.5, power of 80% and enrollment ratio 1:2 (intervention vs control). The anticipated incidence in both control and cases are proposed according to previous investigations done by team and according to the international data (18,19)
- be developed prior to any data analysis and missing data will be handled and minimized as possible

9- Bio-specimen and sample collection

- Patients who agreed to participate in the study will be asked to provide a buccal swab for genetic testing and a 2 ml blood sample for INR assessment. The blood will be drawn using a sterile disposable syringe and then collected in an EDTA tube
- The subject will be given written oral information regarding the study before the initiation of the study. If the subject decides to withdraw from the study his/her bio-specimen will be destroyed. However, proceeded data will be kept in records

10- Adverse event reporting

- Research team members will provide a strategy to identify, report any adverse reaction or undesirable medical condition throughout the clinical

study by providing extensive and close follow-up.

- Participants would be provided with a point-of-contact in case they have any complication or adverse effect that they could report
- Any patient experiencing an undesirable adverse reaction will be subject to extensive medical assessment and he will be excluded from the study.
- any unanticipated problems will be reported to IRB within timelines will be reported within timelines i.e. 7 days for serious adverse events and 14 days to any other unanticipated problems.
- Subjects who experience adverse effect will not be excluded from the final study analysis

11- Ethical consideration

The study will be conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP), and within the laws and regulations of MoPH in Qatar.

12- Anticipated results and evaluation criteria

The project aims to implement PGx testing in the clinical setting in Qatar which helps in personalizing anticoagulant therapy for more efficient treatment and fewer side effects.

13- Plans for disseminating research results

The main dissemination task that the partners of the project will participate in is the transfer of the findings and knowledge to the scientific community through the publication of scientific research papers in highly impacted journals.

We are going to present our data at different regional and global conferences this can be crucial for diffusing results particularly early results. Participation in scientific conferences allow us to receive feedback and spread awareness of the project in the community

14- Future plans

By assessing the clinical utility and validity of clopidogrel PGx testing, we are planning to provide preemptive PGx testing for CYP2C9 and VKORC1for the Qatari population and connect the genomic data into EHR.

15. "Sponsor, Funding and Collaborator Information

HMC will collaborate with Qatar Genome Program (QGP) as a member in Qatar Foundation (QF) in terms of sponsorship and funding

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