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CYP2D6 Genotype-guided Metoprolol Therapy in Cardiac Surgery Patients: Rationale and Design of the Pharmacogenetic-guided Metoprolol Management for Postoperative Atrial Fibrillation in Cardiac Surgery (PREEMPTIVE) Pilot Study

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Abstract

Objectives: The Preemptive Pharmacogenetic-guided Metoprolol Management for Atrial Fibrillation in Cardiac Surgery (PREEMPTIVE) pilot trial aims to use existing institutional resources to develop a process for integrating CYP2D6 pharmacogenetic test results into the patient electronic health record, to develop an evidence-based clinical decision support tool to facilitate *CYP2D6* genotype-guided metoprolol administration in the cardiac surgery setting, and

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Conflict of Interest

The authors have no conflicts of interest to disclose.

Supplementary materials

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to determine the impact of implementing this *CYP2D6* genotype-guided integrated approach on the incidence of postoperative atrial fibrillation (AF), provider, and cost outcomes.

Design: One-arm Bayesian adaptive design clinical trial.

Setting: Single center, university hospital.

Participants: The authors will screen (including *CYP2D6* genotype) up to 600 (264 ± 144 expected under the adaptive design) cardiac surgery patients, and enroll up to 200 (88 ± 48 expected) poor, intermediate, and ultrarapid *CYP2D6* metabolizers over a period of 2 years at a tertiary academic center.

Interventions: All consented and enrolled patients will receive the intervention of *CYP2D6* genotype-guided metoprolol management based on *CYP2D6* phenotype classified as a poor, intermediate, extensive (normal), or ultrarapid metabolizer.

Measurements and Main Results: The primary outcome will be the incidence of postoperative AF. Secondary outcomes relating to rates of *CYP2D6* genotype-guided prescription changes, costs, lengths of stay, and implementation metrics also will be investigated.

Conclusions: The PREEMPTIVE pilot study is the first perioperative pilot trial to provide essential information for the design of a future, large-scale trial comparing *CYP2D6* genotype-guided metoprolol management with a nontailored strategy in terms of managing AF. In addition, secondary outcomes regarding implementation, clinical benefit, safety, and cost-effectiveness in patients undergoing cardiac surgery will be examined.

Keywords

atrial fibrillation; cardiac surgery; clinical decision support tool; *CYP2D6* polymorphisms; metoprolol; outcomes

ALTHOUGH USUALLY self-limited, postoperative atrial fibrillation (AF) has a profound impact on postoperative adverse outcomes, increasing both intensive care unit (ICU) and total hospital lengths of stay, and consequently total hospital costs.^{1–3} Based on combined outcomes reported in the control groups of 40 randomized clinical trials of prophylactic therapy for postoperative AF and in 3 large observational trials in the absence of prophylactic therapy, the average incidence of postoperative AF was 30% after coronary artery bypass grafting (CABG) surgery, 40% after valve surgery, and 50% after combined CABG/valve surgery.^{2,4} Indeed, the impact of postoperative AF on hospital resources is significant, with a 2008 study estimating additional healthcare costs exceeding \$10,000 per patient, translating to more than \$2 billion each year in the United States alone.⁵ Therefore, postoperative AF after cardiac surgery is common, associated with adverse postoperative outcomes, and when prevented can lead to reductions in postoperative adverse events, hospital length of stay, and costs.

Sympathetic activation or an exaggerated response to adrenergic stimulation has been identified as an important trigger for postoperative AF.⁶ As a result, pharmacologic attenuation of that response using β -blockers has been considered a mainstay in the prevention and treatment of postoperative AF.⁷ Owing to the widespread availability of

inexpensive generic formulations, insurance coverage, and numerous indications for use, metoprolol is frequently prescribed for older patients with cardiovascular disease in the United States (<https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartD.html>). Metoprolol is metabolized by a well-characterized enzyme, cytochrome P-450 2D6 (CYP2D6), with pharmacogenetic biomarkers included in its Food and Drug Administration drug label.⁸ Compared with other β -blockers, metoprolol is the most dependent on this enzyme, with 70% to 80% of its metabolism directed through this pathway,⁹ thus affecting the drug's elimination half-life, plasma concentrations, heart rate response,^{10,11} and risk for bradycardia, hypotension, and other adverse effects.^{12–14} To the authors' knowledge, there are no studies examining the contribution of *CYP2D6* genetic variation on efficacy and safety of β -blockers in the perioperative setting. However, a recent meta-analysis¹⁵ of existing trials and a retrospective cohort study¹⁶ of perioperative β -blocker use in the setting of noncardiac surgery found that increased mortality was confined to trials that used β -blockers dependent on CYP2D6 metabolism. These observations indicate that genetic variation in *CYP2D6* may affect metoprolol pharmacokinetics, efficacy, and safety. Thus, a *CYP2D6* genotype-guided metoprolol management strategy could reduce the risk of postoperative AF, bradycardia, and hypotension in patients undergoing cardiac surgery, thereby contributing to a reduction in postoperative adverse outcomes, lengths of stay, and costs.

The widespread implementation of pharmacogenetic testing for genetic variants involved in drug metabolism remains limited by several barriers, including the perceived costs versus benefits of implementation, the logistics of pharmacogenetic sample collection, analysis, and interpretation, and the usability, safety, and accessibility of associated clinical decision support (CDS) tools.¹⁷ The potential benefits of reducing the incidence of postoperative AF are expected to increase efficacy and safety of metoprolol, and potentially other β -blockers, and promote a more cost-effective use of hospital resources through a reduction in length of stay. The cardiac surgery acute care setting also provides a unique test-bed to demonstrate that implementation of pharmacogenetic testing across a wider panel of medications (eg, opioids, antiemetics, and anticoagulation with vitamin K antagonists) can improve relevant health outcomes. Thus, the implementation of *CYP2D6* genotype-guided metoprolol management in the cardiac surgery setting can be used as a template to guide the implementation for pharmaco-genetic-guided management for pain, postoperative nausea and vomiting, and anticoagulation. Furthermore, this template can be used in other inpatient care settings across a hospital system.

The Preemptive Pharmacogenetic-guided Metoprolol Management for Atrial Fibrillation in Cardiac Surgery (PREEMPTIVE) pilot study is the first perioperative pilot trial to test the hypothesis that, compared with current metoprolol prescribing practices (one dose fits all, and/or using a trial-and-error dosing approach), implementation of *CYP2D6* genotype-guided perioperative metoprolol administration in cardiac surgery care will reduce the risk of postoperative AF and subsequently improve postoperative outcomes, patient satisfaction, resource utilization, and cost. The findings of this pilot study will provide essential information on the design of a future, large-scale trial comparing *CYP2D6* genotype-guided

metoprolol management with a nontailored strategy in terms of implementation, clinical benefit, safety, and cost-effectiveness in patients undergoing cardiac surgery.

Study Objectives

The PREEMPTIVE Pilot trial aims to use existing institutional resources to develop a process for integrating CYP2D6 pharmacogenetic test results into the patient electronic health record (EHR), to develop an evidence-based CDS tool to facilitate *CYP2D6* genotype-guided metoprolol administration in the cardiac surgery setting, and to determine the impact of implementing this *CYP2D6* genotype-guided integrated approach on patient, provider, and cost outcomes. The authors will test the hypothesis that integrating pharmacogenetic data relevant to the *CYP2D6* genotype into EHR-based dosing recommendations for metoprolol will significantly reduce the incidence of postoperative AF in cardiac surgery (primary outcome). In addition, the authors will rigorously explore several secondary outcomes, including ICU and hospital lengths of stay (in hours), rates of genome-tailored prescription changes, and provider-reported effectiveness outcomes, as well as hospital costs. The definitions of primary and secondary outcomes of the study objectives are provided in Table 1.

Study Design and Population

The PREEMPTIVE Pilot trial will screen up to 600 (264 ± 144 expected under the adaptive design) cardiac surgery patients, and enroll up to 200 (88 ± 48 expected) altered (poor, intermediate, and ultrarapid) CYP2D6 metabolizers undergoing cardiac surgery over 2 years at a tertiary academic center. The study population consists of patients who will be scheduled to undergo elective CABG surgery, heart valve repair/replacement, or combined CABG and heart valve repair/replacement (Table 2). Patients undergoing emergent surgery will be excluded. Patients will be identified through current institutional referral pathways well in advance of their scheduled cardiac surgery. The authors will generate an algorithm to facilitate patients' identification and selection based on the study's inclusion and exclusion criteria. The authors will use flyers to encourage patient enrollment and participation. These flyers will convey information about enrollment criteria, intervention protocol, and possible risks of participation in language that is understandable to all patients. The flyer (Appendix Supplementary Fig 1) will be posted in waiting rooms, hallways, and other patient encounter and treatment areas, and distributed by healthcare providers. Thus, in addition to the study team reaching out to patients, patients may initiate their own participation.

The study was approved on April 25, 2019 by the Institutional Review Board (IRB #190578) and will be conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. The study is registered on (NCT03943927). The trial is supported by a so-called Innovation Grant of a tertiary academic center. The authors are solely responsible for the design, conduct, and analyses of this study, and for the drafting and editing of this manuscript and its final contents.

CYP2D6 Genotyping

After obtaining written informed consent, the study team will collect a blood sample (4 mL) from all patients upon their first preoperative visit to the outpatient cardiac surgery clinic. Whole blood will undergo genotyping at the tertiary academic center's Molecular Diagnostic Laboratory at the Vanderbilt University Medical Center (VUMC). Genotyping will be performed using a laboratory developed test for *CYP2D6* variants selected by the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment Clinical Content Team.¹⁷ The updated 2019 multigene assay includes the analysis of 45 variants representing 10 genes and is performed using the Taqman Array Card format and a QuantStudio 7 instrument (Thermo Fisher Scientific, Waltham, MA) (Table 3). The tertiary academic center's Molecular Diagnostics Laboratory will interpret the results and report each patient's genotype and corresponding phenotype for the *CYP2D6* gene. The phenotype will classify a patient as a poor, intermediate, extensive (normal), or ultrarapid metabolizer based on the CYP2D6 copy number and identified variants in accordance with the consensus agreement listed in the Clinical Pharmacogenetics Implementation Consortium guidelines (<https://cpicpgx.org>). This laboratory test is currently part of the EHR order sets for pharmacogenetics testing at VUMC with an approximate turnaround time of 3 to 4 days. Once testing has been completed, a patient's genotype and corresponding phenotype is available in the EHR. A short turnaround time makes this assay a realistic choice for those scheduled for elective cardiac surgery.

Implementation of an Evidence-based Clinical Decision Support Tool

As the first step of this process, the authors will modify the current version of the "Adult Open-Heart Surgery (Preoperative/ Postoperative)" order set in their current Epic eStar (Verona, WI) EHR system by building a metoprolol best practice advisory (BPA) alert. The modified order set will be activated automatically only for patients consented for and enrolled in the study. The Adult Open-Heart Surgery Order Set (Fig 1) is routinely completed by members of the cardiac surgery care team before and/or on the day of surgery for all cardiac surgery patients as part of their care. The BPA will trigger when the metoprolol suborder set is opened and the medication is ordered. The authors will design a decision algorithm for *CYP2D6* genotype-guided metoprolol prescription and dosing based on recent guidelines (Royal Dutch Association for the Advancement of Pharmacy, Pharmacogenetics Working Group¹⁸ and Clinical Pharmacogenetic Implementation Consortium [<https://cpicpgx.org>]) and institutional preferences guided by the current literature. Based on a 12.5 mg q12h standard dose for cardiac surgery patients, the CDS tool will recommend a dose reduction to 6.25 mg q12h for poor and intermediate metabolizers, a dose increase to 25.0 mg q12h for ultrarapid metabolizers, and no dose change for extensive (normal) metabolizers (Fig 2). A working group consisting of relevant surgical, anesthesia, and pharmacy stakeholders will vet and improve the authors' CDS algorithm.

The CDS, implemented as a BPA in Epic eStar, will be designed and developed by a team led by the study's coinvestigators. The authors will use a User-Centered Design^{19,20} approach that starts with the results of the interviews and observations, moves to design requirements, and then uses iterative design and testing to achieve an optimal user interface

within the constraints of Epic eStar. Implementation of this protocol requires context-sensitive and timely rules-based processing within the EHR. At present, the authors anticipate that the CDS will be designed to (1) trigger an order for metoprolol if genomic data are available; (2) execute the metoprolol algorithm to produce an ordering recommendation; (3) notify the provider if the patient has an abnormal phenotype and guide them to order as indicated; (4) provide information to enhance compliance with the recommendations; (5) capture provider actions and reasons (if any) for not following the recommendation; (6) report process metrics at regular intervals; and (7) allow for updates of content or presentation to be implemented easily. Once the authors have developed the BPA, usability testing will be conducted with each type of targeted user (eg, anesthesia providers, cardiac surgeons, physician advanced practice providers, trainees, and pharmacists) to ensure usefulness, ease of use, satisfaction, and optimal placement in their regular workflow. After sufficient testing and refinement, the CDS will be introduced as new subjects are enrolled into the study. To identify potential barriers to implementation after rollout, the authors will continuously collect the following process-related outcomes: (1) number of enrolled patients where the CDS failed to report the genetic test results at the appropriate time in the patient's perioperative care; (2) proportion of CDS recommendations that were acknowledged and accepted by a provider; (3) proportion of CDS recommendations that were acknowledged but ignored by the provider; and (4) reasons for nonadherence to recommendations (using prepopulated choices such as "clinically inappropriate recommendation" and "provider preference," as well as a free text option). The authors also will conduct post-implementation interviews to assess both provider and patient usage to guide further refinements.

Treatment Regimen

This is a prospective, one-arm Bayesian adaptive design clinical trial, and enrolled patients will not be randomized (Fig 3). The Bayesian adaptive design of the authors' clinical trial will provide a framework in which information about the study endpoints will be used, as it is accrued during their study, to make efficient adaptations to the study design by stopping early if there is strong evidence of efficacy or futility. This adaptive study design reduces the expected sample size needed to make statistical inferences about the study intervention, thus shortening the trial length and reducing the overall cost of the authors' pilot study. Although adaptive trials can be designed using non-Bayesian methods, the Bayesian approach significantly simplifies the design, implementation, and interpretation of adaptive trials.^{21,22} All consented and enrolled patients will receive the intervention of *CYP2D6* genotype-guided metoprolol management based on *CYP2D6* phenotype classified as a poor, intermediate, extensive (normal), or ultrarapid metabolizer.

Data Collection and Follow-Up

All relevant clinical data and postoperative outcomes including AF occurring within 30 days after surgery will be collected. Clinical data and postoperative outcomes will be those that are routinely captured by the authors' cardiac surgery service for the Society of Thoracic Surgeons' Adult Cardiac Surgery Database (<https://www.sts.org/registries-research-center/sts-national-database>).²³ Additional relevant clinical data routinely captured in Epic eStar

(eg, CYP2D6 phenotype-associated adverse drug events) will be extracted through the assistance of the tertiary center's Anesthesiology & Perioperative Informatics Research Division.

Study Endpoints and Planned Data Analysis

The primary outcome will be new onset postoperative AF during the first 7 days after surgery and ascertained by presence of a documented rhythm; AF-specific cardioversions; AF-specific amiodarone, diltiazem, or magnesium administration; or hospital diagnoses/billing diagnoses. The secondary outcomes will be (1) rates of genome-tailored prescription changes; (2) ICU and hospital length of stay (in hours); (3) cost outcomes (medical, implementation, and healthcare-related costs); and (4) process-related outcomes related to CDS recommendation adoption (Table 1).

A Bayesian procedure will be used to compare the incidence of the primary outcome in study participants (who will all receive *CYP2D6* genotype-guided metoprolol management) versus a reference incidence (denoted p_{ref}) based on historical data in this patient population at the authors' institution.²⁴ The beta-binomial model with uniform prior probability will be used to model the primary outcome probability. Interim analyses will be performed after enrolling 40, 80, 120, and 160 *CYP2D6* altered metabolizers to consider early stopping for efficacy or futility, and final analysis at a maximum sample size of 200 enrolled patients. Both efficacy and futility will be evaluated at multiple interim and final analysis. If either efficacy or futility is concluded in the interim analysis, the study will be terminated. Efficacy of the intervention will be concluded if the estimated incidence of the primary outcome under the study intervention (denoted p_{int}) is significantly smaller than the reference incidence, with respect to posterior probability. In notation, after n subjects have been observed, efficacy is concluded if the following is satisfied:

$$Pr(p_{\text{int}} < p_{\text{ref}} | x_{(n)}) > \gamma_{\text{eff}}$$

where $x_{(n)}$ is the collection of primary outcome data observed on the first n subjects, and γ_{eff} is the efficacy threshold. Likewise, futility will be concluded if there is little chance that the efficacy threshold will be met by the end of the study. In notation, futility will be concluded if the following is satisfied:

$$Pr(p_{\text{int}} < p_{\text{ref}} | x_{(\text{max})}) < \gamma_{\text{fut}}$$

where $x_{(n)}$ is the collection of primary outcome data observed at the maximum sample size, and γ_{fut} is the futility threshold. The efficacy and futility thresholds, γ_{eff} and γ_{fut} , were selected to ensure a type-I error probability of 5%. The values of the reference incidence p_{ref} and efficacy and futility thresholds γ_{eff} and γ_{fut} were determined to be 0.270, 0.975, and 0.200, respectively (see following section for justification of reference incidence). The incidence of the primary outcome under the study intervention will be estimated using the posterior mode with 95% credible interval using the maximum *a posteriori* method.

Secondary outcomes will be analyzed by estimating the typical values (eg, mean, incidence, as appropriate) under the study intervention using the appropriate Bayesian techniques. Uninformative prior probabilities will be used throughout. Furthermore, the authors will conduct exploratory outcome analyses in patient subgroups by (1) age (≥ 70 v <70 years); (2) sex; (3) race (white, black, other); (4) procedure type (CABG, valve repair/replacement, and combined CABG and valve repair/replacement); and (5) receiving versus not receiving perioperative statins, amiodarone, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory drugs according to *CYP2D6* genotype-guided CDS implementation status. Of note, measuring and using ICU and hospital length of stay as secondary outcomes is always subject to potential bias owing to the considerable impact of hospital-related processes such as delay in transfer, lack of supporting facilities to discharge to, and staffing. To overcome these potential barriers of objective assessment of ICU and hospital length of stay, the authors will collect historical data about these delays, summarize, and present them alongside the corresponding summaries collected in the proposed study. Furthermore, at the authors' institution, there is a feature in Epic eStar platform for capturing and reporting barriers to discharge from the ICU, step-down, and hospital. In this study, the authors will use information captured through that feature to help account for reasons of delayed discharge.

Reference AF Incidence, Power, and Sample Size

To estimate the power and sample size of the proposed study, the authors collected institutional historical data for the incidence of postoperative AF after CABG (25.4%), valve repair/replacement (28.1%), and combined CABG and valve repair/replacement (38.7%) surgeries. The overall incidence of AF was 27.0% (95% CI: 25.6, 28.4; N = 3,880) of patients who underwent cardiac surgery between July 1, 2011 and November 2, 2017 at VUMC. For the purposes of assessing intervention efficacy and futility, the reference incidence was selected to be 27%, a representative average across the subgroups.

Using BioVU®, the VUMC's independent DNA biobank, the authors estimated the prevalence of patients with poor (21.3%), intermediate (9.5%), and ultrarapid metabolizer (2%) status from recorded *CYP2D6* genotypes for approximately 40,000 patients. Based on these data, statistical simulation was used to evaluate the properties of a one-arm Bayesian adaptive design (Fig 3), allowing for early stopping for efficacy or futility as described above. The authors specified a relative reduction in postoperative AF incidence of 35% (ie, from a reference incidence of 27%) as a minimum detectable effect, on average across poor, intermediate, and ultrarapid *CYP2D6* metabolizers. The results of this simulation revealed that the authors' proposed one-arm study will have about 82% power with regard to the minimum-detectable effect, and an average ($\pm$ standard deviation) sample size of 88 ± 46 . Based on the authors' institutional data, 67% of the patients undergoing cardiac surgery are extensive (normal) metabolizers, and 33% are poor, intermediate, or ultrarapid metabolizers. Therefore, to meet the target enrollment sample size of altered metabolizers, the authors will need to screen approximately 3 times as many (264 ± 144) potential study participants. Patients who are classified as extensive (normal) metabolizers based on their respective *CYP2D6* genotype will receive routine care but will be observed similarly to patients with other *CYP2D6* genotypes.

Risk and Benefit for Study Participants

The authors will use the Thermo Fisher Taqman Array Card on the QuantStudio 7 instrument as a validated clinical laboratory developed test genotyping platform for targeted *CYP2D6* genotyping. Using this clinically approved genotyping platform assures care providers participating in the study that indications for use, methods, and result interpretation, quality control and assay limitations, clinical validity and interpretation, benefits and risks, and safety and efficacy have been evaluated in accordance with guidelines established for a high complexity Clinical Laboratory Improvement Amendments certified laboratory.

The potential risks to study participants include loss of confidential genetic information, and the risk that the genetic information could expose the patient to increased risk regarding employment discrimination or denial, limitation, or higher premiums for life, health, disability, and long-term care insurance coverage. The Genetic Information Nondiscrimination Act (<https://www.eeoc.gov/laws/statutes/gina.cfm>)²⁵ makes it illegal for health insurance companies, group health plans, and most employers to discriminate based on genetic information. Regardless, the pharmacogenes evaluated on the Illumina VeraCode ADME Core Panel Assay (Illumina, Inc, San Diego, CA) to be used in this study are only known to be associated with altered drug responses, and thus, the result of genetic testing would be unlikely to lead to insurance discrimination (were it legal), as alternative therapies are available for patient management. It is the authors' expectation that pharmacogenetic information derived in this study will lead to safer and more effective metoprolol therapy, and because the ultimate prescribing decisions will be left to the physicians, there will be minimal risks with basing metoprolol therapy on *CYP2D6* metabolizer status.

Participation may directly benefit study participants. *CYP2D6* genotype may help to guide metoprolol dosing decisions that could result in metoprolol dose adjustments that could increase efficacy and safety, and/or reduce risk for metoprolol-related adverse events. Furthermore, *CYP2D6* genotyping may help identify patients at risk for adverse effects for other drugs metabolized by *CYP2D6*; for example, atypical metabolism of codeine, tramadol, or hydrocodone could cause toxicity, and it may lead participating providers to prescribe opioids that are not dependent on *CYP2D6* biotransformation, to use lower potency opioids, or to select nonopioid-based analgesic regimens. Further, *CYP2D6* genotype also may help to identify a small subset of patients in whom the antiemetic ondansetron will have a reduced efficacy for the prevention of postoperative nausea and vomiting, potentially prompting participating providers to prescribe alternative, non-*CYP2D6* dependent antiemetics. Similarly, genotype information for the 9 other pharmacogenes contained within this assay and listed in the patient's EHR will be accessible to all healthcare providers, enabling adjustments to other medications as appropriate.¹⁷

Discussion

In the PREEMPTIVE Pilot study, the authors will investigate and collect data necessary to conduct a feasibility assessment and design of a future large-scale clinical trial on implementation, clinical benefit, safety, and cost-effectiveness of a *CYP2D6* genotype-

guided metoprolol management protocol. There are considerable potential benefits of *CYP2D6* genotype-guided metoprolol management in the clinical care of cardiac surgery patients who are at high risk for postoperative AF and its related outcomes. Evidence in the literature is sufficient to suggest that *CYP2D6* polymorphisms impact metoprolol pharmacokinetics.^{13,14,26,27} There remains debate on whether differences in metoprolol pharmacokinetics significantly alter its cardioselectivity,²⁸ or how resulting differences in the heart rate response after metoprolol administration are translated into a differential risk for postoperative AF. The authors do not yet understand how *CYP2D6* genotype-driven differences in metoprolol pharmacokinetics influence its clinical efficacy and safety in acute-care settings.

In this study, the authors also will seek to identify barriers to the perioperative implementation of a pharmacogenetic study through a pilot implementation of a *CYP2D6* genotype-guided metoprolol management protocol in the cardiac surgery setting. In the past, several human-and organizational-level barriers have been identified and described,²⁹ but it can be challenging to determine which of these barriers present the most significant challenges to the successful implementation and conduct of a pharmacogenetic study. One particular approach would be to follow a previously described specific pharmacogenetic implementation development pathway.³⁰ Specifically, the authors will employ a User-Centered Design approach^{19,20} that uses a mixed-methods approach to understand the context of use and intended users' goals, determines design requirements, and then uses iterative design and testing to achieve an optimal user interface, including triggering mechanisms and timing, within the framework of the Epic eStar platform. This approach also will ensure that, before implementation, the authors' protocol, including the CDS algorithm, will be validated and receive the necessary support of the participating providers. Key elements of a successful implementation of CDS are present, including the comprehensive engagement and training of end users, optimization of the user experience with the software, adequate and persistent technical support, and commitment from departmental and hospital stakeholders and leadership.^{31,32}

Several different study designs were considered for this pilot study. Given the allele frequencies of the different *CYP2D6* genotypes, and the feasibility and cost of conducting a pharmacogenetic pilot study, the authors have opted to use a one-arm Bayesian adaptive design trial. This approach will allow them to make planned and well-defined changes in key design parameters of the trial based on ongoing data collected during the study. It also will ensure that this pilot trial will satisfy goals of validity, efficiency, and safety. Moreover, this study design will allow the authors (1) to reassess the allele frequencies of the *CYP2D6* genotype and subsequently their target sample size; (2) to observe and collect information on responses to metoprolol administration, and, thus, to reduce any uncertainty regarding the *CYP2D6* genotype-guided metoprolol management; and (3) to frequently assess the results and modify the trial as needed, including early stopping for efficacy or futility. Nevertheless, this trial design approach requires a different analytical methodology in which the authors will combine data collected from different stages of the pilot trial, potentially affecting the statistical distribution of the estimated treatment effect.³³

CYP2D6 allele frequencies could vary significantly across major ethnic groups.³⁴ Furthermore, certain CYP2D6 allele frequencies could be under- or overrepresented in patients seeking medical care.³⁵ Therefore, for this pilot trial, the authors opted to use a one-arm study design. This was a pragmatic and cost-sensitive decision. Because a *CYP2D6* genotype-based guidance for metoprolol management for patients who are extensive metabolizers (normal metabolizers) will not be provided, these patients will be used as the reference group to which the authors will compare the impact of their *CYP2D6* genotype-guided metoprolol management protocol for patients with poor, intermediate, and ultrarapid metabolizer phenotypes. Accordingly, this design will improve efficiency, reduce cost, and minimize risk for study participants while maximizing the quality of information needed to determine the safety and efficacy of the *CYP2D6* genotype-guided metoprolol management protocol.

In conclusion, the PREEMPTIVE Pilot trial will be the first one-arm Bayesian adaptive design study in the setting of cardiac surgery to evaluate the effect and implementation of a *CYP2D6* genotype-guided metoprolol management protocol intended to decrease the incidence of postoperative AF. Secondary endpoints of the study will include rates of genome-tailored prescription changes, ICU, and hospital lengths of stay, and cost- and process-related outcomes. This pilot trial is expected to inform the design, conduct, and safety of a future, large-scale randomized multicenter trial comparing *CYP2D6* genotype-guided metoprolol management with a nontailored strategy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Current Epic eStar (Verona, WI) “Adult Open-Heart Surgery Order Set” for metoprolol use.

Fig 2.

A starting point for the clinical decision support tool for *CYP2D6* genotype-guided metoprolol management.

- “Adult Open Heart Surgery Order Set” will be modified by linking and displaying information of the *CYP2D6* genotyping result.
- The Clinical Decision Support tool imbedded in the order set will provide the following recommendation based on the result of the *CYP2D6* genotyping:
 - “Poor Metabolizer” and “Intermediate Metabolizer”: This patient is predicted to be a *CYP2D6* poor metabolizer and may be at an increased risk of a poor response due to increased plasma concentrations of metoprolol. Consider selecting a dose of metoprolol decreased by 50%. Please consult a clinical pharmacist for more information.
 - “Extensive (Normal) Metabolizer”: no change in dosing
 - “Ultrarapid Metabolizer”: This patient is predicted to be a *CYP2D6* ultrarapid metabolizer and may be at an increased risk of a poor response due to increased plasma concentrations of metoprolol. Consider selecting a dose of metoprolol increased to 200%. Please consult a clinical pharmacist for more information.
- Example for Clinical Decision Support tool dosing is described in Figure 3.

Fig 3.
One-arm Bayesian adaptive design of the study.

Table 1

Definition of Primary and Secondary Outcomes

Outcome Variable Name	Outcome Variable Definition
Primary outcome	
Postoperative AF	<ul style="list-style-type: none"> New onset postoperative AF during the first 7 days after surgery and ascertained by postoperative EKG or rhythm strip, and/or documented in progress notes, nursing notes, and/or change in medication
Secondary outcomes	
A) Rates of genome-tailored prescription changes	<ul style="list-style-type: none"> Rate of change in metoprolol prescription dose from default dose to the lower or higher recommendation based on CYP2D6 metabolizer status during the course of the study
B) Length of stay (in hours)	<ul style="list-style-type: none"> Number of hours between date of surgery and (1) time and date of intensive care unit/step-down unit discharge; and (2) time and date of hospital discharge
C) Cost outcomes	<ul style="list-style-type: none"> Medical cost: the sum of genetic testing, inpatient hospital care, and inpatient physician care costs using hospital and physician billing data Implementation cost: the number of hours required to implement and to maintain the CDS tool in Epic eStar (Verona, WI) using the average hourly rate of a health IT programmer Healthcare-related costs: patient-specific index hospitalization billing information from the tertiary academic center's patient data repository
D) Process-related outcomes	<ul style="list-style-type: none"> Number of enrolled patients where the CDS failed to report back on genetic test results at the appropriate time in the patient's postoperative care Proportion of CDS recommendations that were acknowledged and accepted by provider responsible for "Adult Open-Heart Surgery" order set Proportion of CDS recommendations that were acknowledged but ignored by provider responsible for "Adult Open-Heart Surgery" order set Reasons for nonadherence to recommendations (prepopulated choices such as "clinically inappropriate recommendation" and "provider preference," as well as free text options)

Abbreviations: AF, atrial fibrillation; CDS, clinical decision support.

Table 2

Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none">• Age 18 years old• Scheduled for elective (non-emergency) cardiac surgery, defined as coronary artery bypass grafting, valve repair, or valve replacement	<ul style="list-style-type: none">• Contraindications for metoprolol• History of allergic reactions to metoprolol• History of persistent atrial fibrillation

Table 3

List of Genes Included in the Pharmacogenomics Test Panel as of June 2019

Gene	Enzyme	Sample Medications
<i>DPYD</i>	Dihydropyrimidine dehydrogenase	fluoropyrimidines (5-fluorouracil)
<i>CYP2C19</i>	Cytochrome P450 2C19	diazepam, clopidogrel, mephenytoin, omeprazole, proguanil, prasugrel, ticagrelor
<i>CYP2C9</i>	Cytochrome P450 2C9	warfarin, fluvoxamine
<i>CYP2D6</i>	Cytochrome P450 2D6	atomoxetine, carvedilol, fluoxetine, quinidine, metoprolol , propafenone, propranolol, risperidone, tiotropium, tamoxifen
<i>CYP3A5</i>	Cytochrome P450 3A5	tacrolimus
<i>CYP4F2</i>	Cytochrome P450 4F2	warfarin
<i>NUDT15</i>	Nudix hydrolase 15	thiopurine
<i>SLCO1B1</i>	Solute carrier organic anion transporter family member 1B1	simvastatin
<i>TPMT</i>	Thiopurine methyltransferase	azathioprine
<i>VKORC1</i>	Vitamin K epoxide reductase complex subunit 1	warfarin