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Clinical Pharmacology-Driven Translational Research to Optimize Bedside Therapeutics of Sotalol Therapy

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Oral sotalol, used in adults for sinus rhythm control, is initiated at 80 mg b.i.d. and titrated to a maximum safe dose. The US Food and Drug Administration recommends monitoring the corrected QT interval (QT_c) for at least 3 days, until steady-state exposure of the drug is reached, before patient discharge, which can significantly impact the total cost of treatment. The objectives of this research were to design an accelerated intravenous sotalol loading and maintenance therapy that will reduce the hospital length of stay and to also evaluate the pharmacoeconomic impact in a hospital setting. Pharmacokinetic simulations of sotalol plasma concentrations vs. times profiles were performed to determine the optimal intravenous/oral transition regimen. A cost minimization analysis from the health sector perspective was conducted to assess the cost savings for these proposed accelerated regimens. For a chosen target dose of 120 mg b.i.d., two infusions of 40 mg over 1 hour and 20 mg over 0.5 hour, each followed up by an evaluation of QT_c, can be administered followed immediately by the target oral maintenance dose of 120 mg at the end of the second infusion. Consequently, steady-state exposure and, therefore, steady-state QT_c are obtained on the first day of therapy, facilitating an earlier hospital discharge. Two and 1-day mean total cost of −$3,123 (95% confidence interval (CI), −$3,640, −$2,607) −$4,820 (95% CI, −$5,352, −$4,288) were observed for this strategy, respectively. We are proposing an intravenous to oral transition strategy for sotalol that has the potential to significantly reduce cost and increase patient convenience.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Sotalol initiation for rhythm control requires a minimum 3-day hospital admission for continuous telemetry monitoring to reduce the risk of corrected QT interval prolongation and life-threatening arrhythmias, such as bradycardia and torsade de pointes. However, these admissions significantly contribute to the costs of atrial fibrillation management, and even an elective admission is associated with costs exceeding $3,200 per patient.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study provides a clinical pharmacology driven solution to shorten the length of hospital stay to half a day by recommending an intravenous to oral switch strategy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Our current work proposes alternative dosing strategies for initiation of sotalol therapy. The principal tenet of the approach is to leverage all clinical or clinical pharmacology information regarding sotalol to improve the bedside therapeutics. We have also demonstrated significant costs-savings by shortening the stay with no additional risk to the patient.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Clinical pharmacology combined with pharmacoeconomic outcomes analysis can provide solutions for cost-savings in therapeutic settings.

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, affecting an estimated 2.7–6.1 million people in the United States[1] and leading to more hospitalizations than all other arrhythmias.[2] The increasing prevalence of AF has resulted in substantial economic burden (costs approaching $26 billion in the United States annually), driven largely by the costs of hospital readmissions; other contributors

include the costs of initial hospitalization, outpatient care and testing, and outpatient prescription medications.[1,2]

Atrial fibrillation can be managed using a rate or rhythm control strategy. Although rate control is generally the initial treatment approach, rhythm control is used for those who remain symptomatic despite maximally tolerated rate control therapy. Of the available options for rhythm control,

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sotalol and dofetilide have fewer long-term adverse effects (AEs) but require a minimum 3-day hospital admission for continuous telemetry monitoring to reduce the risk of corrected QT (QT_c) interval prolongation and life-threatening arrhythmias, such as bradycardia and Torsade de pointes. However, these admissions significantly contribute to the costs of AF management, and even an elective admission is associated with costs exceeding \$3,200 per patient.[3]

Sotalol is a class III anti-arrhythmic drug indicated for the treatment of AF and atrial flutter. In AF treatment, sotalol is initiated at a dose of 80 mg b.i.d., with gradual titration to 240–320 mg/day as needed to maintain normal sinus rhythm. To reduce the risk of life-threatening arrhythmias, QT_c monitoring must be performed at 2–4 hours after each dose until the drug has achieved steady-state concentrations (~ 3 days given an elimination half-life of 12 hours). Previously, sotalol was only available as an oral formulation, but, recently, an intravenous formulation was developed as an alternative in patients who are unable to take oral medications.[4] However, the approved intravenous product must be administered as a 5-hour infusion and it still requires that patients be hospitalized for a minimum of 3 days for initiation of therapy. Additionally, the cost of intravenous sotalol is significantly higher than the oral product at ~ \$1,413.00 per dose.[5]

Wagner[6] states that translational medicine is bolstered by quantitative, model-based, and mechanistic approaches. We propose to use the state-of-the-art knowledge to optimize bedside therapeutics of sotalol. Sotalol-induced QT_c interval prolongation is directly related to increases in the plasma concentration of sotalol, with maximum QT_c prolongation occurring at steady-state maximum concentrations ($C_{max,ss}$). Based on the current dosing strategy, $C_{max,ss}$ can only be achieved after ~3 days of therapy, necessitating the use of QT_c monitoring during the intervening period. Accelerating the time to reach $C_{max,ss}$ by administering a front-loading dose of intravenous sotalol would allow faster dose-titration based on efficacy and changes in QT_c, and faster stabilization under optimal oral sotalol therapy.

In the present study, we propose a dosing strategy that involves the infusion of an intravenous loading dose of sotalol followed immediately by the oral maintenance dose (MD), thereby achieving target steady-state exposure on the first day of therapy. Such a dosing strategy has the potential to reduce the hospital length of stay for patients being initiated or reinitiated on sotalol therapy. Given the higher acquisition cost of intravenous sotalol, we also performed a pharmacoeconomic analysis to determine if the cost minimization associated with a shortened length of stay would impart overall cost-savings for an individual institution.

METHODS
Evaluation of the accelerated intravenous to oral dosing strategies for sotalol
Sotalol pharmacokinetic model. A two-compartment pharmacokinetic (PK) model with first-order oral absorption (with lag time) and first-order elimination, for oral and intravenous sotalol, was previously published in the US Food and Drug Administration (FDA) clinical pharmacology and biopharmaceutics review of sotalol hydrochloride's new drug application.[7,8] This well-established and validated PK model was used to perform PK simulations, predict sotalol concentrations vs. time profiles for different intravenous loading/maintenance oral dosing schemes, and select the optimal and clinically practical dosing strategies for early achievement of steady-state exposure. **Supplemental Table S1** shows the parameter estimates from the population PK model used. The predicted concentration-time profiles for the different intravenous loading/oral dosing strategies were further linked to a population pharmacodynamic (PD) model in order to assess the effect of sotalol doses and concentrations on QT_c interval prolongation.

Sotalol concentration-QT_c relationship. The primary measure used to evaluate safety after sotalol administration was QT_c prolongation, as this can potentially be life threatening and lead to sudden cardiac death. The extent of sotalol-induced QT_c prolongation was evaluated based on the mean linear relationship provided in the FDA clinical pharmacology review,[7] where

$$QT_c = \text{Baseline } QT_c + \text{Slope} \times C_p. \qquad (1)$$

baseline QT_c refers to QT_c interval recorded just before treatment initiation, C_p refers to the observed sotalol concentrations after treatment initiation, and the slope parameter describes the increase in QT_c interval, from baseline QT_c, per unit increase in sotalol concentrations (C_p). The median baseline QT_c reported in the studied patient population was 405 ms and the slope of the concentration-QT_c relationship was 0.0158 ms/ng/mL.

Dose optimization. The overall goal of sotalol dose optimization was to accelerate the achievement of $C_{max,ss}$ (preferably to the first day of treatment) without compromising safety and, hence, reducing the length of hospitalization. Optimizations were performed to determine the appropriate intravenous loading dose and titration strategy to attain stable oral maintenance therapy on the first day of treatment for sotalol-naive patients. The following intravenous loading to oral dose transitions where considered:

1. Intravenous bolus dose or intravenous short-term or long-term infusion dose to reach $C_{max,ss}$ followed by administration of the targeted MD of oral sotalol (80 mg, 120 mg, or 160 mg b.i.d.) at the next dosing interval
2. Intravenous bolus or intravenous short-term infusion dose followed immediately by an oral sotalol targeted MD to reach $C_{max,ss}$ on day 1 of treatment

Simulations of sotalol concentrations vs. time profiles for the different intravenous loading to oral dose transitions were performed using the described sotalol PK model above (**Supplemental Table S1**).

Dose titration for naive patients. Dose titration was based on the monitoring of QT_c prolongation after the administration of each intravenous loading dose targeting either an 80 mg b.i.d., 120 mg b.i.d., or 160 mg b.i.d. oral MD, respectively.

For instance, the extent of QT_c prolongation after the first intravenous loading dose (targeting an MD of 80 mg b.i.d.) would determine the feasibility and safety of pursuing the intravenous loading procedure to target a higher MD of 120 mg b.i.d.

Safety monitoring. The relationship in Eq. (1) was used to calculate the change in QT_c over time that is directly related to the change in sotalol concentrations. The optimization and titration strategy was conducted such that sotalol plasma concentrations never exceeds the $C_{max,ss}$ and, hence, $QT_{c,ss}$ for each dose level, either after the intravenous loading dose or after the oral maintenance switch. Change in QT_c was also calculated across the range of doses after assuming variability between subjects in terms of PK parameters and concentration-QT_c relationship.

Dosing in renal impairment. Sotalol is predominantly eliminated by glomerular filtration with an estimated renal clearance of 12 L/hour. Sotalol is contraindicated in patients with creatinine clearance (CRCL) < 40 mL/minutes, and the product label recommends a once daily dosing in patients with CRCL between 40 and 60 mL/minutes (i.e., about half of normal CRCL). Therefore, the intravenous loading to early oral conversion strategies in patients with mild to moderate renal impairment were evaluated by assuming that sotalol clearance is 50% (6 L/hour) of the value seen in patients with normal renal function.

Reference dose comparison. To evaluate the performance of the optimized dosing strategies, the explored dosing scenarios were compared with the reference dosing currently used in practice (80, 120, or 160 mg b.i.d. oral).

Average and Monte Carlo simulations were conducted with 1,000 patients with a mean (SD) body weight of 70 (6) kg. Variability in body weight and random variability between subjects allowed the calculation of QT_c prolongation at a range of sotalol concentrations.

Quantitative metrics and graphs of sotalol plasma concentrations or the change in QT_c over time were used to compare the dosing scenarios with reference dosing, where the goal was to ensure that $C_{max,ss}$ was never exceeded and QT_c prolongation was minimal (i.e., ≤15% of ΔQT_c).

Simulations were performed using Pumas,[9] a PK/pharmacodynamic simulation package in Julia.[10]

Pharmacoeconomic analysis
Base-case patient population. A single-center, retrospective chart review was conducted to identify eligible patients and their characteristics to include in subsequent pharmacoeconomic analysis. Sotalol is the agent of choice at our facility, a 750-bed urban medical center, for rhythm control in patients with AF or flutter who have failed a rate control strategy. Sotalol loading is performed both electively (i.e., patients are admitted specifically for therapy initiation) and in those who are deemed eligible candidates after an initial evaluation. We included all adult patients in whom sotalol was initiated for AF or flutter during an admission to our facility between October 1, 2013, and September 30,

2016. To better capture patients in whom sotalol would be the major driver of length of stay, we excluded alternative indications for sotalol, use of sotalol prior to admission, use of other anti-arrhythmics during hospitalization, death, and therapy failure, which we defined as any patient who was not discharged on sotalol.

Economic model design. A cost minimization analysis from the health sector perspective was conducted. For patients included who received oral sotalol, the length of stay and direct medical costs were collected from hospital finance. Costs represent the cost accounting by hospital administration in 2017 US dollars, not charges or payments from third-party payers. All direct costs were identified and categorized into different variable cost accounting groups (i.e., room/board, diagnostic, laboratory, therapy, supplies, pharmacy, blood, operating room, and other). Indirect costs were excluded from the analysis, as these represent fixed overhead costs incurred regardless of length of stay.

Direct medical costs for the base case (oral sotalol) were compared with the accelerated intravenous sotalol dosing strategy described previously. Two models of intravenous sotalol dosing were developed to simulate the costs associated with either a 1-day or 2-day length of stay.

Probabilistic sensitivity analysis was conducted to account for parameter uncertainty in each model. Point estimates in the base case were assigned distributions based on observed data from the retrospective sample. Average lengths of stay in the simulated intravenous sotalol scenarios were assigned normal distributions. The probabilistic sensitivity analysis used a Monte Carlo simulation of 1,000 iterations using random number generation.

Statistical analysis. Descriptive statistics for the oral sotalol cohort were used to determine the parameters and distributions for the economic model. The pharmacoeconomic analysis focused on the mean differences between cost groups in the oral and intravenous sotalol regimens resulting from 1,000 Monte Carlo simulations. A prespecified level of significance ($\alpha = 0.05$) was used to generate 95% confidence intervals (CIs).

Results of PK analysis
Supplemental Table S1 shows the parameters of the PK model used to simulate the intravenous to oral conversion strategies. Based on these parameters, **Figure 1** demonstrates that it takes about 5–6 doses to reach $C_{max,ss}$ after twice-daily 80 mg oral doses in a 70-kg subject with normal renal function.

Sotalol concentration-QT_c relationship
The relationship between sotalol concentration and QT_c prolongation was assessed based on Eq. (1) for the reference doses (80, 120, and 160 mg oral b.i.d.) in a 70-kg individual with normal renal function and a baseline QT_c of 405 ms. The concentrations established from the PK model above were used to derive the change in QT_c and is depicted in **Figure 1** where the maximum change from baseline QT_c is about 13 ms at the 80 mg dose.
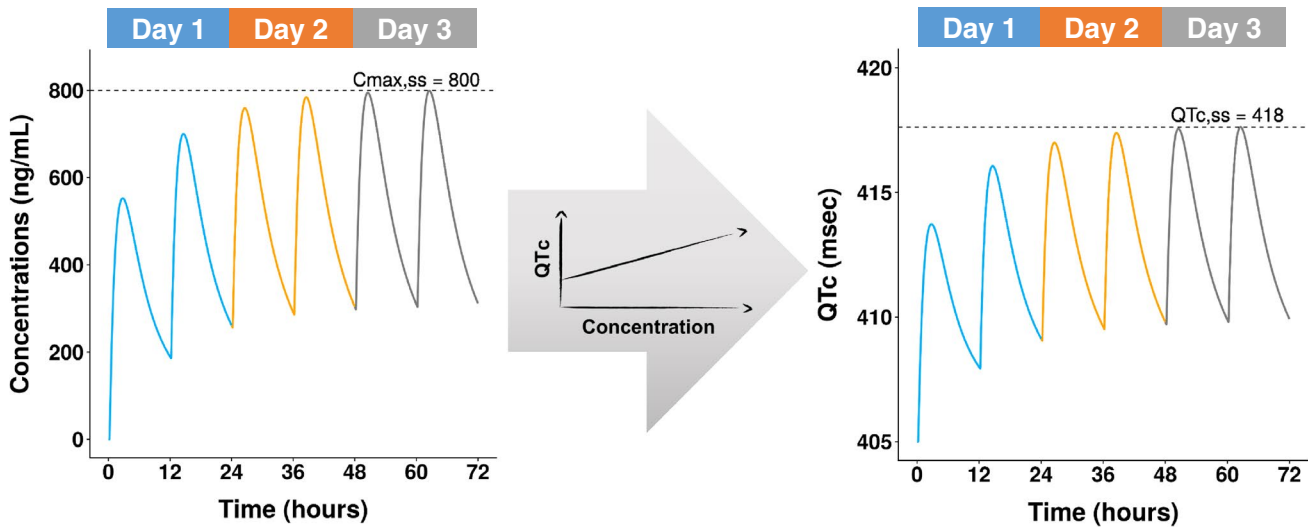
Figure 1 Sotalol plasma concentration-time profile (left panel) and the corresponding QT_c-time profile after 80 mg b.i.d. dosing for 3 days in a 700 kg healthy adult. $C_{max,ss}$, sotalol concentration at steady-state on day 3; QT_c, correct QT; $QT_{c,ss}$, corrected QT at steady-state sotalol plasma concentrations.
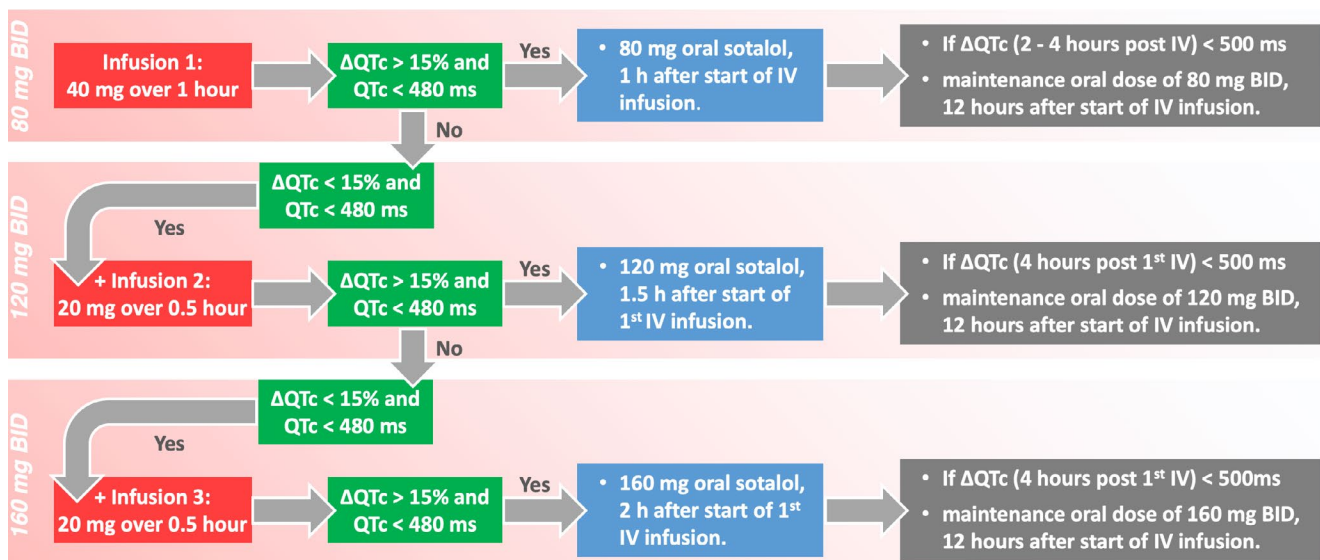

Figure 2 Recommended flowchart for accelerated intravenous (IV) sotalol loading followed by oral sotalol maintenance therapy in patients with normal renal function. QT_c, corrected QT; ΔQT_c, change from baseline QT_c. Horizontal red ribbons represent the different targeted oral maintenance dose of sotalol (80 mg b.i.d., 120 mg b.i.d. and 160 mg b.i.d.).

Dose optimization. *Dose titration for naive patients*. The flowchart in **Figure 2** describes a strategy for initiating naïve patients on sotalol via dose titration. In all cases, the common strategy followed was:

1. Record baseline QT_c
2. Administer the sotalol intravenous loading dose(s) needed to attain a targeted oral maintenance regimen
3. Measure QT_c at the end of infusion
4. If the change from baseline QT_c (ΔQT_c) at the end of infusion is acceptable, based on set safety criteria (e.g., ≤ 15% change from baseline), then either proceed to the next intravenous loading, otherwise stabilize the

patient on the current targeted oral dose and stop the intravenous escalation routine

In this titration design, a 40 mg intravenous loading dose is infused over 1 hour to target an initial oral MD of 80 mg. At the end of the 1 hour, the change from baseline QT_c is monitored and, if deemed clinically acceptable, a second intravenous loading dose of 20 mg can be infused over 0.5 hour to target an oral MD of 120 mg. A second QT_c assessment is made at this point and, if deemed clinically acceptable, a third intravenous loading dose of 20 mg can be infused over 0.5 hour to target an oral MD of 160 mg. During each titration, the intravenous infusion may be discontinued at
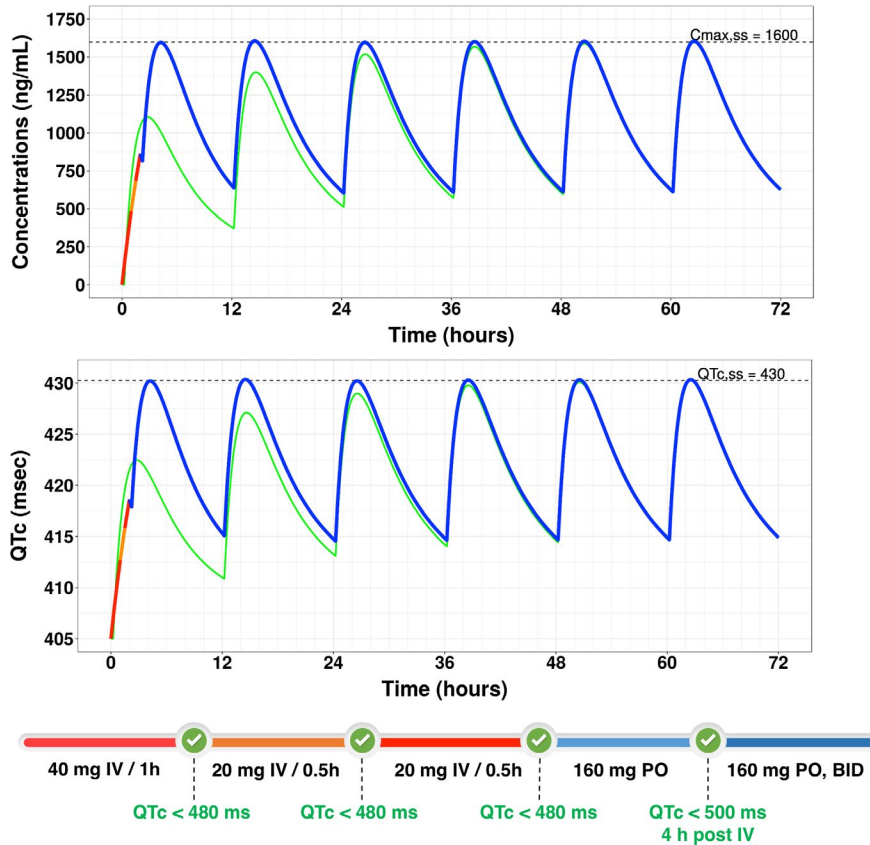
Figure 3 Predicted mean sotalol plasma concentration-time profile (upper panel) and mean QT_c-time profile (lower panel) in a 70-kg patient with normal renal function. Red and orange lines reprensent the sotalol concentration and QTc profiles from the intravenous (IV) dose administrations. The blue line represent the sotalol concentration and QTc profiles from the oral maintenance dose administration after IV loading. The green lines are the concentration and QTc profiles observed after regular administration of oral sotalol 160 mg b.i.d. without IV loading. $C_{max,ss}$, sotalol concentration at steady state on day 3; $QT_{c,ss}$, QT_c at steady state sotalol plasma concentrations.
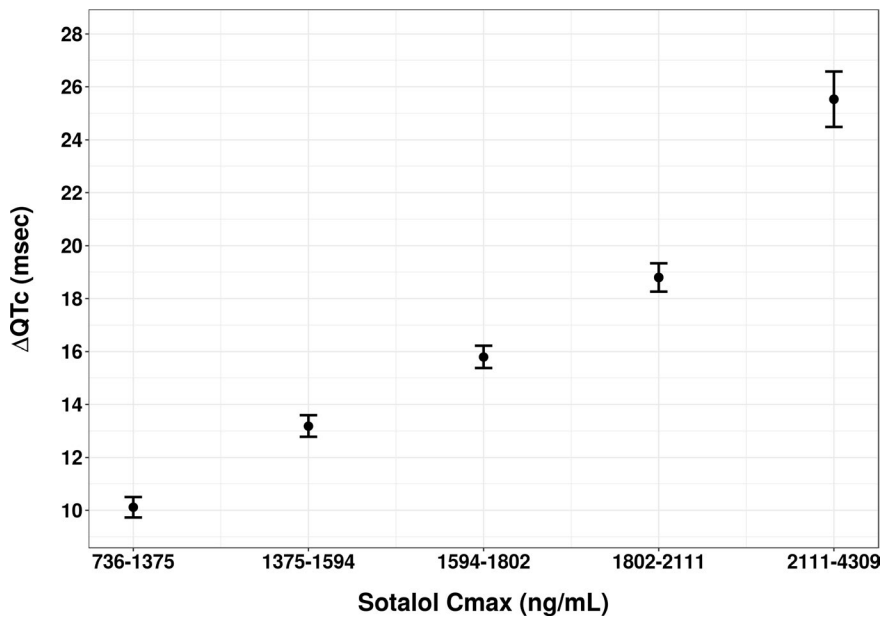

Figure 4 Predicted mean (± 95% CI of mean) changes from baseline QT_c (ΔQT_c) values across sotalol plasma concentrations covering 80, 120, and 160 mg b.i.d. doses at steady state. CI, confidence interval; C_{max}, peak plasma concentration; QT_c, correct QT.

any point for safety concerns. **Figure 3** shows the titration scheme and the corresponding predicted QT_c change for a target oral MD of 160 mg.

QT_c monitoring. In addition to ensuring that intravenous sotalol concentrations do not exceed exposures with adequate safety experience, QT_c prolongation was also evaluated using Monte Carlo simulations. **Figure 4** shows the change in QT_c from baseline across a range of concentrations observed during the intravenous/oral switch across all 3 doses, 80, 120, and 160 mg. The maximum change in QT_c from baseline at the highest concentration observed is around 30 ms, which is consistent with the FDA clinical pharmacology reviews.

Dosing in renal impairment. The optimized dosing regimens in renally impaired patients are similar to the flowchart in **Figure 2** except for two differences. First, the maintenance oral doses are given once daily as opposed to twice daily. Second, for patients with mild to moderate renal impairement (GFR of 40–60 mL/min), the second loading dose infusion is 10 mg infused over 0.5 hours rather than 20 mg. This allows the $C_{max,ss}$ to match the concentrations achieved at steady state after oral dosing. **Table 1** provides a summary of recommendations in patients with normal and impaired renal function.

Pharmacoeconomic analysis
Base-case analysis. Of the 200 patients screened who received oral sotalol during an inpatient admission between October 1, 2013, and September 30, 2016, 35 were eligible for pharmacoeconomic analyses. Of the 165 patients who were excluded, 143 were receiving sotalol prior to admission, 13 were receiving sotalol for an indication other than AF or atrial flutter, and 9 were deemed therapy failures. At baseline, the average age was 59 years old and 62.9% were men **Table 2**. The average length of stay was 4.3 days, with 51.4% of patients falling in the 4–6-day length of stay category.

Intravenous sotalol simulation. For a 2-day length of stay, a loading strategy using intravenous sotalol compared with oral sotalol resulted in a mean total cost of −$3,123

(95% CI, −$3,640, −$2,607). For a 1-day length of stay, the intravenous loading strategy resulted in a mean total cost of −$4,820 (95% CI, −$5,352, −$4,288; **Table 3**).

With the exception of pharmacy costs, all other simulated medical costs were reduced with intravenous sotalol loading when compared with the base-case of oral sotalol, regardless of an estimated 1-day or 2-day length of stay. All simulated costs were less in the 1-day length of stay model compared with the 2-day model.

DISCUSSION

Wagner[6] stated "Clinical and translational science holds the promise to put the patient at the top, the beginning, middle, and end of research. Translational medicine is evolving to become a paradigm of bedside-to-bench-to-bedside research, which will in turn drive a new era of medicine and therapeutics." In the same spirit, our current work proposes alternative dosing strategies for initiation of sotalol therapy. The principal tenet of the approach is to leverage all clinical or clinical pharmacology information regarding sotalol to improve the bedside therapeutics. The proposed strategy in sotalol-naïve patients is efficient, cost-effective, and provides checkpoints to ensure safety. Here, intravenous loading doses are given in succession, with intermittent QT_c monitoring such that target concentrations for any oral MD can be achieved on day 1 of treatment. Such a strategy would significantly shorten the length of stay for in-hospital initiation of sotalol and perhaps even permit outpatient initiation in an adequately equipped and staffed clinic.

In-hospital initiation of sotalol treatment allows patients to be monitored for potential AEs, mainly clinical QT_c prolongation. Patients are monitored until day 3 when steady-state sotalol concentrations are reached, and simultaneously, a new stable QT_c. The linear relationship between sotalol concentrations and QT_c enables us to reliably predict potential QT_c prolongation from baseline. Because the stable QT_c on day 3 correlates with $C_{max,ss}$, it is conceivable that achieving $C_{max,ss}$ earlier will produce a similar QT_c as in day 3 but much earlier without increasing the risk of QT_c prolongation. Furthermore, this strategy permits the earlier identification

Table 1 Dosing recommendation table for accelerated intravenous sotalol loading and maintenance therapy in normal patients and those with renal impairment

GFR	Target oral dose	IV loading dose	Maintenance PO dose
>60 mL/minutes	80 mg b.i.d.	40 mg/1 hour	80 mg b.i.d.
	120 mg b.i.d.	40 mg/1 hour + 20 mg/0.5 hour	120 mg b.i.d.
	160 mg b.i.d.	40 mg/1 hour + 20 mg/0.5 hour + 20 mg/0.5 hour	160 mg b.i.d.
60–40 mL/minutes	80 mg q.d.	40 mg/1 hour	80 mg q.d.
	120 mg q.d.	40 mg/1 hour + 10 mg/0.5 hour	120 mg q.d.
	160 mg q.d.	40 mg/1 hour + 10 mg/0.5 hour + 20 mg/0.5 hour	160 mg q.d.

GFR, glomerular filtration rate. IV, intravenous. PO, oral. b.i.d., twice daily. q.d., once daily.

Table 2 Baseline characteristics of patients included in the cost minimization analysis, reported as mean (standard deviation) or number (percentage)

Characteristic	Oral sotalol (n = 35)
Age (years)	59 (11)
Male sex	22 (62.9)
Race	
White	30 (85.7)
African American	5 (14.3)
Medical history	
Hypertension	21 (60.0)
Coronary artery disease	8 (22.9)
Heart failure	10 (28.6)
Chronic kidney disease	1 (2.9)
Length of hospitalization	
≤3 days	9 (25.7)
4–6 days	18 (51.4)
>6 days	8 (22.9)
Discharge dose	
80 mg twice daily	2 (5.7)
120 mg twice daily	30 (85.7)
160 mg twice daily	3 (8.6)

Table 3 Mean cost differences between intravenous and oral sotalol loading, based on 2-day and 1-day lengths of stay

	Mean difference	SD	[95% CI]
Sotalol intravenous scenario with 2-day length of stay			
Total cost difference	−$3,123	$8,334	[−$3,640 to −$2,607]
Routine	−$1,962	$4,567	[−$2,246 to −$1,679]
Diagnostics	−$28	$81	[−$33 to −$23]
Laboratory	−$478	$2,812	[−$652 to −$304]
Therapy	−$51	$196	[−$63 to −$39]
Supplies	−$906	$2,555	[−$1,064 to −$747]
Pharmacy	$1,110	$839	[$1,058 to $1,162]
Blood	−$34	$241	[−$49 to −$19]
Operating room	−$142	$1,095	[−$209 to −$74]
Other	−$633	$1,303	[−$714 to $552]
Sotalol i.v. scenario with 1-day length of stay			
Total cost difference	−$4,820	$8,586	[−$5,352 to −$4,288]
Routine	−$2,671	$4,925	[−$2,976 to −$2,366]
Diagnostics	−$38	$90	[−$44 to −$32]
Laboratory	−$624	$3,109	[−$817 to −$432]
Therapy	−$70	$215	[−$84 to −$57]
Supplies	−$1,294	$2,769	[−$1,466 to −$1,122]
Pharmacy	$1,006	$915	[$949 to $1,063]
Blood	−$44	$250	[−$59 to −$29]
Operating room	−$194	$1,146	[−$265 to −$123]
Other	−$890	$1,445	[−$979 to $800]

CI, confidence interval; SD, standard deviation.

of individuals in whom sotalol therapy must be discontinued due to excess QT_c prolongation and/or bradycardia. Therefore, our alternative intravenous/oral conversion dosing regimens harness this concept and may allow for substantial cost-savings and increased convenience.

The existing strategy for initiating intravenous or sotalol requires that steady-state concentrations be achieved (i.e., 3 days of therapy) before an MD can be selected. However, the titration schemes depicted in **Figure 2** provide the flexibility for a clinician to choose the target dose *a priori*, either based on knowledge of a prior stable dose before an interruption in therapy or based on standard of practice at the site. For example, if the chosen target dose is 120 mg b.i.d., then 2 infusions of 40 mg over 1 hour and 20 mg over 0.5 hour, each followed up by an evaluation of QT_c, can be administered followed immediately by the target oral MD of 120 mg at the end of the second infusion. Consequently, steady-state exposure and, therefore, steady-state QT_c are obtained on the first day of therapy, facilitating an earlier hospital discharge.

Reaching $C_{max,ss}$ at earlier times is not associated with significant risk, as evidenced by the abundant literature on intravenous sotalol in which infusions as rapid as 5 minutes were safely administered.[11] Sotalol 1.5 mg/kg intravenous over 5 minutes is recommended by the Advanced Cardiac Life Support (ACLS) guidelines in treatment of stable wide complex tachycardias in adult ventricular tachycardia.[11] This recommendation was developed on the basis of various studies that evaluated the safety and efficacy of rapid infusions, reporting only mild to moderate AEs, such as hypotension and dyspnea associated with the beta-blocking capabilities of sotalol,[12,13] and QT_c prolongation.[12,14] Furthermore, a large meta-analysis of the risk of Torsades de pointes in patients treated with rapid intravenous sotalol infusions showed minimal risk for patients treated with a

single intravenous infusion of sotalol as compared with oral therapy.[15] **Figure 4** shows that the QT_c prolongation across all doses in the proposed regimens is no more than 30 msec.

A slight modification in the intravenous/oral switch strategy in patients with impaired renal function is shown in **Table 1**. Another advantage of these proposed dosing regimens is that they allow clinicians to terminate an infusion at any given point if QT_c prolongs. Such flexibility is not available for an ingested tablet. Moreover, traditional loading strategies do not permit the identification of QT_c prolongation or bradycardia that would warrant discontinuation of therapy until 2–3 days into a hospital admission, thereby increasing the costs associated with treatment.

The recommendations provided here are based on sotalol exposure–QT_c relationship published by the FDA[7] derived from a randomized controlled clinical trial. Deviations may occur in routine practice, but the relationship between sotalol exposure and QT_c prolongation is well-established. Importantly, some individuals are predisposed to idiosyncratic prolongation of the QT_c interval that may contribute to AEs or otherwise warrant sotalol discontinuation. Prospective collection of observational data will help reinforce the relationship between drug exposure and risk of QT_c prolongation (and thus the recommendations derived), as well as identify features that predispose patients to an unexpected risk of QT_c prolongation. The combined use of

electrocardiographic and pharmacogenomic data may be particularly useful in this latter regard and should serve as the basis for future research.

There are two schools of thought with respect to providing evidence for a clinical recommendation. One approach is to conduct clinical trials for every hypothesis assuming no prior knowledge exists (frequentist). Another approach, with translational research underpinning, is to leverage all knowledge and modern tools to substantiate the recommendations. We elected the second approach, as the methodology followed by us has strong clinical pharmacology underpinnings. In fact, this type of approach was the primary basis for the approval of intravenous sotalol. Originally, the pharmaceutical company collected PK data in healthy subjects administered intravenous sotalol. However, intravenous sotalol was approved as a 5-hour infusion based on modeling and simulation. No additional studies were required for this approval. That is because not all hypotheses require confirmation, especially those grounded in strong clinical pharmacology principles.

Our pharmacoeconomic analysis demonstrated that an intravenous loading strategy minimized overall direct medical costs. Although this approach may shorten hospitalization to as little as 1 day, a 2-day simulation was also performed as a conservative estimate of cost savings. Assuming equal efficacy of oral and intravenous sotalol, Monte Carlo simulations demonstrated overall cost-savings with either length of stay. Further overall savings would be expected if the dosing strategies proposed in this study were adapted to an outpatient clinic, which would obviate many of the costs associated with hospitalization.

Overall pharmacy costs were increased in both intravenous scenarios, which were largely attributed to increased intravenous sotalol acquisition costs. Although the intravenous sotalol acquisition cost is estimated to be the same between the 1-day and 2-day length of stay scenarios, overall pharmacy costs are higher in the 2-day length of stay scenario given the increased non–sotalol-associated pharmacy costs for a longer length of stay.

The cost of intravenous sotalol was derived from Redbook, and an entire vial was assumed to be used per dose.[5] In practice, institutions are likely to obtain intravenous sotalol at a lower cost than what is reported in Redbook, thus our use of it in this study is a conservative estimate of drug cost. Although intravenous lines and related supplies were not separately estimated and included, that cost is likely negligible compared with other medical costs accounted for in the simulation.

Results of our cost minimization analysis should be interpreted with caution given several important limitations. First, although a small sample size served as the base case for our pharmacoeconomic analysis, the Monte Carlo simulation decreased variability of the predicted costs for the intravenous sotalol models. Additionally, medical costs were assumed to be evenly distributed throughout the hospitalization, whereas in practice, costs are generally more concentrated at the beginning of the stay. However, the total costs are accurately accounted for and do not affect the model predictions. These costs are likely to be representative of similar organizations but could vary in facilities that are not large, public, tertiary care centers. Additionally, our cost data represent hospital costs and not necessarily payer costs, which could vary across health plan and location of facility. Although we estimate cost savings in patients where intravenous sotalol would have likely been the primary driver of the length of stay, further prospective evaluation of real-world use of the intravenous formulation on length of stay would be warranted to confirm effectiveness of this intervention on that specified outcome. As with the PK analysis, future research will help validate these claims.

CONCLUSIONS

We are proposing an intravenous to oral transition strategy that may be used for the initiation of sotalol in treatment-naïve patients, as well as to restabilize patients in whom therapy was previously interrupted. This switching strategy allows maximum steady-state concentrations to be achieved as early as 4 hours after sotalol initiation, thereby shortening the required length of stay to 1 day. Given the burden that the traditional strategy places on patients and medical facilities, such a strategy has the potential to significantly reduce cost and increase patient convenience. The potential cost-savings associated with this strategy were confirmed in our pharmacoeconomic analysis, as costs were minimized due primarily to decreased length of stay despite increased drug acquisition costs.

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