Factors that Contribute to the QTc Interval Prolongation in DR-TB Patients on STR Regimen

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Abstract

Introduction: QTc interval prolongation is one of the adverse drug reaction of several drugs used in DR-TB patients treated with STR regimen. Drug-induced QTc prolongation can predispose patient to develop life-threatening arrhythmia, increasing hospital length of stay and mortality. This study aims to determine factors that contribute to QTc prolongation in DR-TB patients on STR regimen.

Methods. This was an observational retrospective study using medical records of DR-TB patients who received STR regimen from August 2017 to March 2019 in tertiary hospital DR Soetomo, Surabaya, Indonesia. QTc interval was calculated by Fredericia formula. The influence of risk factors (age, body weight (BW), Body Mass Index (BMI), gender, comorbid, potassium, sodium and QTc baseline) with ΔQTc prolongation was analyzed using multiple regression. The relationship between Moxifloxacin dosage and Δ QTc was analyzed using Chi-Square test.

Results Out of the 113 DR-TB patients who received the STR therapy regimen, 98 patients were eligible for this study. They consist of 62 (%) male; 36 (%) female. Thirty-five (35,7%) of them had Diabetes Mellitus as a comorbid disease. The mean age of the patients was 44±11 years, with the mean of BMI was 20.20± 3.73. Potassium and Sodium levels at the baseline were 4.192 ± 0.58 and 138.05 ± 4.562 respectively. The QTc baseline before receiving STR regimen was 431.9±30,617ms. Patients received a dose of moxifloxacin 400 mg (5.1%) , 600 mg (59,2%), and 800 mg (35,7%) according to body weight. There were no correlation between age, BW, gender, comorbid, and sodium baseline with ΔQTc. There were correlation between potassium (p=0,001), BMI (p=0,006) and QTc baseline (p <0,001) with ΔQTc.

Conclusion QTc baseline and potassium level are factors that contribute to the prolongation of the QTc interval.

Keywords: *QTc interval prolongation, STR regimen, Drug Resistance Tuberculosis (DR-TB)*

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Introduction

Multidrug-resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB) are global concerns,

with stagnant treatment success rates of roughly 54% and 30%, respectively. Despite adverse events associated with several DR-TB drugs, newly developed drugs and shorter regimens are bringing hope [1]. However, it leads to a possibility that some factors may contribute to QTc prolongation in DR-TB patients on Shorter-Term Regimen (STR) treatment. A QTc >500 ms is considered a risk factor for ventricular arrhythmias, such as torsades de pointes (TdP), increasing hospital length of stay and mortality [2, 3]. Overall, 10-20% of patients with drug-induced QTc prolongation have genetic predisposition, and >70% have at least two other risk factors [4]. This assumes clinical importance in the presence of QT prolongation risk factors.

Drug-induced QTc prolongation is characterized by acquired QT interval prolongation and may be followed by potentially fatal proarrhythmias known as torsade de pointes, which can result in sudden cardiac death [5, 6]. Drug-induced QTc prolongation is often dose-related [7]. Depending on their dosages, certain drugs may prolong the duration of ventricular action potential and the QT interval by means of different ionic mechanisms. Most drugs that prolong the QTc interval act by blocking *hERG*-encoded potassium channels, although some drugs modify sodium channels [8]. Hypokalemia might be one of the most important risk factors for QT prolongation since some studies revealed that hypokalemia were associated with lengthening of the QT interval [9-11]. As a result of Hypokalemia, high level of sodium (Hypernatremia) may cause the same effect [12]. In the previous study, baseline of QTc was an important predictive marker of QTc prolongation in patients with Diabetes Mellitus during Severe Hypoglycemia [13]. Age is other factor that may cause QTc prolongation in DR-TB patients on STR regimen. In a healthy subjects, age significantly correlated with QT and QTc interval [14]. Prolonged QTc is more prevalent in older age [15]. QT Interval prolongation is common in obesity and shortens with weight loss [16, 17]. In line with body weight, those with higher BMI have a significantly longer QTc [18, 19]. In many studies, patients with Diabetes Mellitus comorbid had QTc prolongation as compared to those without it [20, 21]. Last but not least, gender is a factor that can also be one of QT prolongation risk factors. The relationship between gender and QT interval using administration of cardiovascular drugs showed that women are more prone than men to develop TdP [22].

Better knowledge of the QTc prolonging in relation to risk factors is needed to improve decision-making. Even though there are data on some factors that may contribute to QTc prolongation, but very little information about the risk factors in Drug-Resistant Tuberculosis (DR-TB) patients, especially during Short-Term Regimen (STR). In this study, we analyzed the effect of the risk factors on the length of the QTc interval in a hospital population. This study aims to determine factors that contribute to QTc interval prolongation in DR-TB patients on STR regimen. Besides the use of TB drug that are known to prolong the QTc interval, we analyzed the effect of the additional risk factors on the QTc interval, such as age, gender, electrolyte disturbances, comorbid (Diabetes Mellitus), body weight (BW), Body Mass Index (BMI), drug dosage, and the baseline of QTc.

Methods

Study population and design

We performed a retrospective observational study. The study population was recruited and analyzed from the medical records of Drug-Resistant Tuberculosis (DR-TB) patients who received Short-Term Regimen treatment, diagnosed from August 2017 to March 2019, was undertaken at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The diagnosis of pulmonary TB in hospitals and TB clinics is made on the basis of clinical examination, chest radiography, rapid test molecular, and sputum smear microscopy and/or sputum culture [23].

Data collection

Medical records of Drug-Resistant Tuberculosis (DR-TB) patients who received Short-Term Regimen treatment, diagnosed from August 2017 to March 2019 at tertiary hospital DR Soetomo, Surabaya, Indonesia were used as the data source. We collected and divided data of following risk factors on the length of QTc interval into groups: gender (female and male), age, comorbid, Body Mass Index (BMI), potassium, natrium, baseline QTc. Patient with missing serial ECG, incomplete medical record are excluded from this study

QTc interval measurement and interpretation

ECGs were recorded at baseline or pre-treatment, two weeks post-treatment. increase of 10mm/mV and

paper speed of 25 mm/s. Standard supine 10 s, 12-lead resting ECG was recorded with a digital ECG Biolight E30 channel with interpretation. The ECG parameters/ intervals that were assessed at each visit were heart rate (beats/minute), PR, QRS, QT, and QTc intervals (ms). All QT values were double checked by visual examination.

QT interval was measured from the beginning of the QRS complex to the end of the T-wave in the derivation where the QT interval was the most visible. QTc interval (baseline and follow up QTc) was calculated by Frederica formula ($QTcFri = QT/RR^{1/3}$) used to count QT correction [24]. QTc prolongation classified according to the Common Terminology Criteria for Adverse Events (CTCAE) guidelines version 4.03 (grade 0, QTc <450; grade 1, QTc 450-479 ms; grade 2, QTc 480-499 ms; grade 3, QTc > 500 ms; grade 4, QTc >500 ms with life-threatening signs or symptoms [25].

Single delta QTc interval denoted as ΔQTc. It estimates the differences in QTc of two ECG signal. In this study we measured QTc pre dose or baseline QTc and QTc Postdose. The formula of ΔQTc is QTc_{day0} minus QTc_{day14}. Based on ICH E14 Guideline divided ΔQTc as QTc interval increases from baseline >30 msc and >60 msc [26].

Study Drug

STR is 9-month regimen consists of kanamycin, ethionamide, moxifloxacin, clofazimine, ethambutol, and high dose isoniazid [27]. Moxifloxacin of 400 mg/ tablet (Avelox®, Bayer HealthCare) was used. Dosing moxifloxacin based of body weight. The dosing material were stored at 25° in a dry location.

Data Analysis

The statistical package SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used to analyze data. The influence of risk factors (age, body weight (BW), Body Mass Index (BMI), gender, comorbid, potassium, sodium and QTc baseline) with ΔQTc prolongation was analyzed using multiple regression. The relationship between Moxifloxacin dosage and ΔQTc was analyzed using Chi-Square test. Slope test between ΔQTc and baseline QTc using scattered plot.

Results

Study Demographics and Disposition

The study population was composed of 62 males and 36 females. The mean age of subject was 44±11 years old (males 44±12; females 44±10), and their body mass index was 20.2±3.7 kg/m^2 (males 20±3.2; female 20±4.4). Several factors could modify the risk of ΔQTc prolongation such as gender, comorbid, BMI, potassium, sodium, and baseline QTc. Based on multiple regression model, there is no significant correlation between age, gender, comorbid, and sodium level (p>0.05). Interestingly subject with underweight BMI statistically significant with ΔQTc prolongation (p=0.006; CI 95% -0.07 – -0.13) rather than overweight patients. It probably due to distribution of drug in fat tissue.

Subject with low potassium level 3.8±0.7 will increase ΔQTc prolongation (p=0.001; CI 95% -0.53 – -0.15). Low baseline QTc also (p<0.001; CI 95% -0.015 – -0.008) statistically significant with ΔQTc prolongation (table 1).

Categorical analysis of QTcF

The result of categorical analysis of the QTcF and ΔQTcF are summarized in table 2. QTcF of >500 ms observed in two subject with 800 mg of moxifloxacin. QtcF of >480 and <500 observed in three subject with 600 mg of moxifloxacin. ΔQTcF of > 60 ms observed in one patient with 400 mg moxifloxacin and nine with 600 mg. ΔQTcF was >30 and ≤60 ms in 21 subject receiving moxifloxacin with one patient in 400 mg, 12 subject with 600 mg and eight subject in 800 mg dosage.

There is no substantial variation prolong ΔQTc between moxifloxacin 600 mg and 800 mg, but the incidence of prolong ΔQTc is higher in 600 mg moxifloxacin (nine patients ΔQTc >60 msc). Based on statistical analysis, there are no significance between baseline QTcF with moxifloxacin dosage (p=0.283) and ΔQTcF (p=0.176).

The linear relationship between baseline QTc prolongation and ΔQTcF with 95% CI are shown in figure 1 which demonstrating negative slope for total subjects. Data showed low baseline QTc would increased ΔQTcF.

Table 1. Correlation between risk factor with ΔQTcF

	ΔQTcF			p	CI 95%
	≤30 (n=67)	>30 (n=21)	>60 (n=10)		
Gender Man Woman	 42 25	 14 7	 6 4	0.736	-1.890 - 0.266
Age	44 ±11	44 ±10	42±16	0.252	-0.004 - 0.150
Comorbid Yes No	 26 41	 8 13	 1 9	0.427	-1.490 - 0.350
BMI	20.8±4	19.3±3	17.7±1.5	0.006	-0,070 - -0.130
Potassium	4.3±0.5	3.9±0.5	3.8±0.7	0.001	-0.530 - -0.150
Natrium	138±4	137±5	138±5	0.869	-0.260 - 0.022
Baseline QTc	442±23	418±22	392±45	0.000	-0.015 - -0.008
QTc week 1 after drug	437±22	463±20	492±53	0.000	0.009 - 0.016

Table 2. Correlation between moxifloxacin dosage with categorical baseline QTc and ΔQTcF

	Moxifloxacin dosage			p
	400 (n=5)	600 (n=58)	800 (n=35)	
Baseline QTcF				
≤450	5	47	26	0.283
>450	0	8	7	
>480	0	3	0	
>500	0	0	2	
ΔQTcF				
≤30	3	37	27	0.176
>30	1	12	8	
>60	1	9	0	

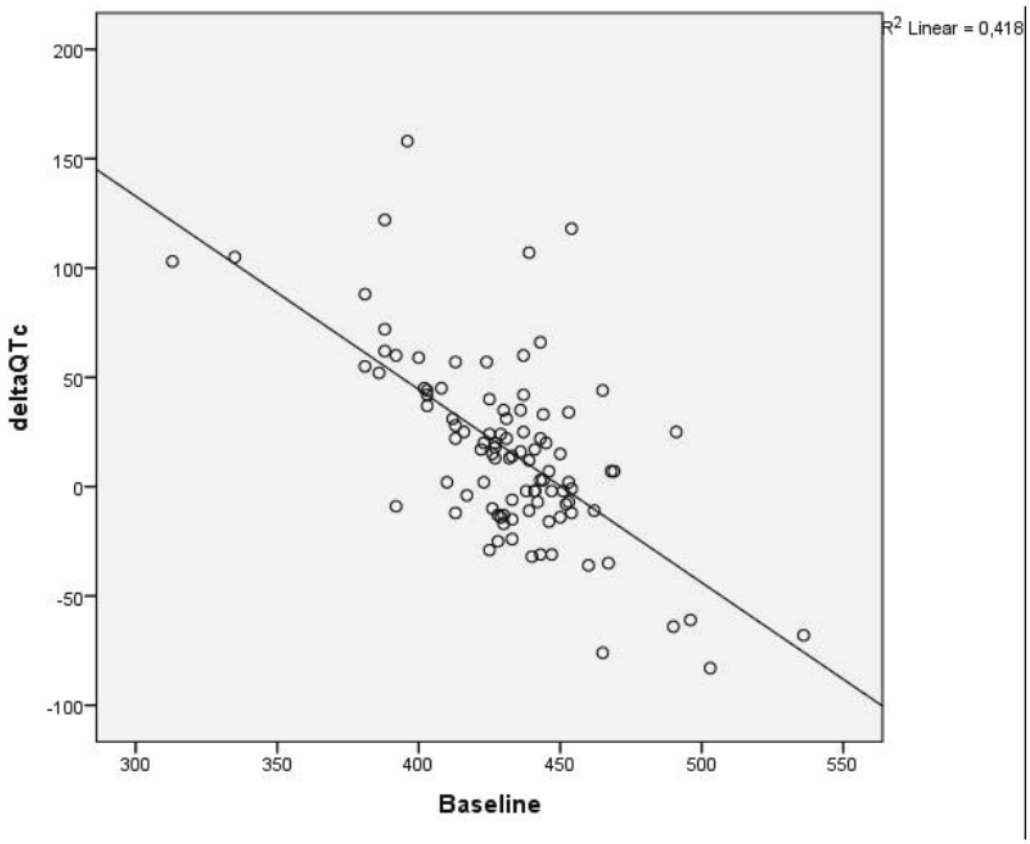

Figure 1. scatter plots of baseline QTc versus individual ΔQTc

Discussions

QT interval on the electrocardiogram (ECG) represents the action potentials in ventricular myocytes. Mechanism of QT interval prolongation is result from an increase in inward current (e.g., through sodium or calcium channels) or a decrease in outward current (e.g., through potassium channels) into action potential prolongation [28]. From this study, we found several risk factor might contribute ΔQTc prolongation. Low BMI, hypokalemia, and baseline QTc can cause ΔQTc prolongation.

Low body mass index affected QTc prolongation possibly by decreased left ventricular mass and cardiac chamber dimension [29]. Abnormal ion transport may also occur in malnourished cells independent of absolute serum electrolyte concentrations [30]. Mischisita et.al was finding that the QTc interval was significantly longer in the low BMI groups compared to the moderate BMI group in both genders [31]. It has been well known that a prolonged QTc interval is reflected in the dysfunction of the cardiac autonomic nervous system, while the cardiac autonomic nervous system is influenced by eating disorders.

Hypokalemia induced changes in ECG are probably qualitatively similar with action potential duration (APD) [32]. Low extracellular potassium enhanced inactivation and reduces IKr or increase competitive block by sodium. As a result, hypokalemia prolongs the QT interval [28].

Prolongation of QT interval may be noted when there is a delay in myocardial repolarization secondary to ionic currents from electrolyte abnormalities. Phase 3 of myocardial repolarization is predominantly mediated through delayed outward rectifier potassium currents (I_{Kr} and I_{Ks}) which are in turn dependent on extracellular potassium concentration. In case of hypokalemia, there

is decreased expression of these channels resulting in prolongation of repolarization [33].

The QTc interval may confirm the hypothesis that a low potassium leads to the occurrence of future cardiac sudden death and the incidence of CVD. Based on our results, we consider that it is necessary to perform dietary counseling, especially focusing potassium intake, depending on the body mass.

This study didn't had significance relationship between dosage of moxifloxacin with ΔQTc. We suggest that every dosage moxifloxacin can occur QTc prolongation. Previous reports have suggested that patients developing drug-induced long QT syndrome with one drug are more likely to develop drug-induced long QT syndrome with exposure to other drugs [34]. Other drug might contribute to QTc prolongation in shorter regimen is clofazimin [35].

Conclusions

Based on the results of this study, low body weight, hypokalemia, QTc baseline and QTc after 1-week after drug admission had significance effect for ΔQTc prolongation. We suggest frequent ECG monitoring to individual on STR therapy escpecially patient with risk factor that contribute ΔQTc prolongation.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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References

1. Monedero-Recuero I, Hernando-Marrupe L, Sánchez-Montalvá A, Cox V, Tommasi M, Furin J, et al. QTc and anti-tuberculosis drugs: a perfect storm or a tempest in a teacup? Review of evidence and a risk assessment. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2018.
2. Li M, Ramos LG. Drug-Induced QT Prolongation And Torsades de Pointes. P & T : a peer-reviewed journal for formulary management. 2017;42(7):473-7.
3. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: Role of the pharmacist in risk assessment, prevention and management. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC. 2016;149(3):139-52.
4. Trinkley KE, Page RL, 2nd, Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. Current medical research and opinion. 2013;29(12):1719-26.
5. Shah RR. The significance of QT interval in drug development. Br J Clin Pharmacol. 2002;54(2):188-202.
6. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. American heart journal. 2007;153(6):891-9.
7. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of Torsade de Pointes in Hospital Settings. 2010;121(8):1047-60.
8. van Noord C, Eijgelsheim M, Stricker BH. Drug- and non-drug-associated QT interval prolongation. Br J Clin Pharmacol. 2010;70(1):16-23.
9. Chen Y, Guo X, Sun G, Li Z, Zheng L, Sun Y. Effect of serum electrolytes within normal ranges on QTc prolongation: a cross-sectional study in a Chinese rural general population. BMC Cardiovascular Disorders. 2018;18(1):175.
10. Olliaro PL, Merle C, Mthiyane T, Bah B, Kassa F, Amukoye E, et al. Effects on the QT Interval of a Gatifloxacin-Containing Regimen versus Standard Treatment of Pulmonary Tuberculosis. Antimicrobial agents and chemotherapy. 2017;61(7).
11. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-

prolongation: systematic review of the evidence. International journal of clinical pharmacy. 2017;39(1):16-25.

12. Arambewela MH, Somasundaram NP, Garusinghe C. Extreme hypernatremia as a probable cause of fatal arrhythmia: a case report. Journal of medical case reports. 2016;10(1):272.
13. Cha SA, Yun JS, Lim TS, Kang YG, Lee KM, Song KH, et al. Baseline-Corrected QT (QTc) Interval Is Associated with Prolongation of QTc during Severe Hypoglycemia in Patients with Type 2 Diabetes Mellitus. Diabetes & metabolism journal. 2016;40(6):463-72.
14. Satpathy S, Satpathy S, Nayak PK. Effect of age and gender on QT interval. National Journal of Physiology, Pharmacy and Pharmacology. 2018;8(2):224-7.
15. Rabkin SW. Impact of Age and Sex on QT Prolongation in Patients Receiving Psychotropics. Can J Psychiatry. 2015;60(5):206-14.
16. Carella MJ, Mantz SL, Rovner DR, Willis PW, 3rd, Gossain VV, Bouknight RR, et al. Obesity, adiposity, and lengthening of the QT interval: improvement after weight loss. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 1996;20(10):938-42.
17. Milovancev A, Stokic E, Popovic D, Naglic D, Rankov O, Ilincic B. Body Weight Reduction and QTc Interval in Obesity. Advences in Weight Loss Management and Medical Device. 2016;1(102):2.
18. Strack C, Fessmann D, Fenk S, Waldmann K, Kempinger S, Loew T, et al. QT prolongation is frequently observed in obesity with and without the metabolic syndrome and can be reversed by long term weight reduction. European Heart Journal. 2013;34(suppl_1).
19. Waheed S, Dawn B, Gupta K. Association of corrected QT interval with body mass index, and the impact of this association on mortality: Results from the Third National Health and Nutrition Examination Survey. Obesity Research & Clinical Practice. 2017;11(4):426-34.
20. Mathur C, Gupta D. QTc prolongation in diabetes mellitus-an indicator of cardiac autonomic neuropathy. J Indian Acad Clin Med. 2006;17:34-00.
21. Bonakdar HR, Aslanpour M, Moladoust H, Sadeghipour P, Mohamadi F, Rad MA, et al. Comparison between QT Interval Parameters in Type 2 Diabetic and Nondiabetic Patients with Non-ST Elevation Myocardial Infarction. The journal of Tehran Heart Center. 2014;9(4):166-73.
22. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. Jama. 1993;270(21):2590-7.
23. WHO. Guidelines for surveillance of drug resistance in tuberculosis. 5 th Edition ed: World Health Organization; 2015.
24. Vandenberk B, Vandael E, Robyns T, Vandenberghe J, Garweg C, Foulon V, et al. Which QT Correction Formulae to Use for QT Monitoring? Journal of the American Heart Association. 2016;5(6).
25. Kloth JS, Pagani A, Verboom MC, Malovini A, Napolitano C, Kruit WH, et al. Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors. British journal of cancer. 2015;112(6):1011-6.
26. FDA. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. US Department of Health and Human Services, Food Drug Administration …; 2005.
27. Peraturan menteri kesehatan republik Indonesia nomor 67 tahun 2016 tentang penanggulangan tuberkulosis, (2016).
28. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, risk factors, and management of acquired long QT syndrome: a comprehensive review. TheScientificWorldJournal. 2012;2012:212178.
29. Spaulding-Barclay MA, Stern J, Mehler PS. Cardiac changes in anorexia nervosa. Cardiology in the young. 2016;26(4):623-8.
30. Padfield GJ, Escudero CA, DeSouza AM, Steinberg C, Gibbs K, Puyat JH, et al. Characterization of Myocardial Repolarization Reserve in Adolescent Females With Anorexia Nervosa. Circulation. 2016;133(6):557-65.
31. Michishita R, Ishikawa-Takata K, Yoshimura E, Mihara R, Ikenaga M, Morimura K, et al. Influence of Dietary Sodium and Potassium Intake on the Heart Rate Corrected-QT Interval in Elderly Subjects. Journal of nutritional science and

vitaminology. 2015;61(2):138-46.

32. Karmakar S, Ali MA, Bera R, Mazumdar H, Sen T. QT prolongation by ranitidine in hypokalemia and arrhythmogen provoked rat heart. Vascular Diseases and Therapeutics. 2017;2(4):1-5.
33. Kumar V, Khosla S, Stancu M. Torsade de Pointes Induced by Hypokalemia from Imipenem and Piperacillin. Case reports in cardiology. 2017;2017:4565182.
34. Strauss DG, Vicente J, Johannesen L, Blinova K, Mason JW, Weeke P, et al. Common Genetic Variant Risk Score Is Associated With Drug-Induced QT Prolongation and Torsade de Pointes Risk: A Pilot Study. Circulation. 2017;135(14):1300-10.
35. Ahmad Khan F, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. The European respiratory journal. 2017;50(1).

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---

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8