Cardiac Toxicity of Anti-Tuberculosis Drugs, Proper Monitoring and Management of Cardiac Toxicity

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Key Questions

- Cardiac toxicity of anti-tuberculosis drugs
- Approaches to monitoring and risk management
- Groups at risk of developing serious cardiac complications
- Cases of management of patients with serious concomitant pathology of the cardiovascular system

New Drugs' Safety Profile

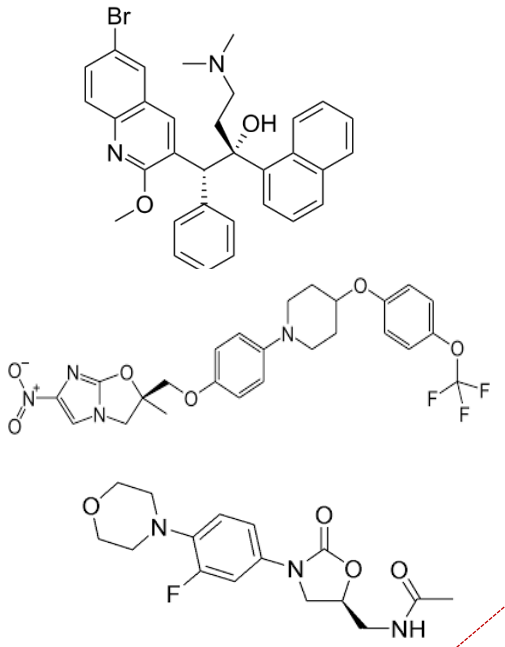
Bdq, Dlm, Cfz, Mfx

Cardiotoxic effects:

- **QT interval prolongation** *(QT interval prolongation, dysrhythmia/ conduction disorder)*

Bdq

- **Direct cardiomyotoxic effect**
- *(localized/ disseminated changes in the myocardium, hypertrophy, overload of the heart, AHF, progression of HF, etc.)*



Bdq

Hepatotoxicity:

- **AT elevated activity**
- **Hepatitis**

Lzd

Mitochondrial toxicity:

- **Neurotoxicity** *(damage to the peripheral nervous system, the optic nerve)*
- **Hematoxicity** *(anaemia, thrombocytopenia, leukopenia)*
- **Lactic acidosis**

Potentially disabling

Dlm

Albumin-dependent biotransformation

Account for the majority of serious treatment-related outcomes

Potentially life-threatening

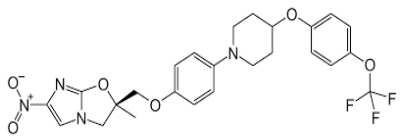
Drug interactions:

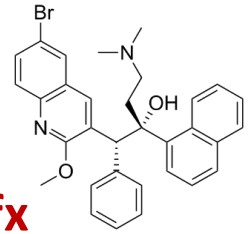
- **With QT interval-prolonging drugs**
- **With drugs that change the pharmacokinetics of Bdq, Dlm**

Risk factors:

- the presence of ischemic/ dysmetabolic disorders,
- history of rhythm disorders, heart failure
- age of patients
- alcohol consumption
- electrolyte disorders

Mechanisms of Proarrhythmogenic and Cardiotoxic Effects of Anti-Tuberculosis Drugs





Bdq, Dlm, Cfz, Mfx

QT-interval prolongation *(ether-à-go-go-related potassium channel HERG)*

QT-interval prolongation, **dysrhythmia**/ conductivity disorder

Account for the majority of serious treatment-related outcomes

Bdq

Direct cardiac myotoxic effect

Ischemic and dysmetabolic disorders, coronary artery diseases, rhythm disorders

Localized/ disseminated **changes in the myocardium**, hypertrophy, overload of the heart, **ACD, AHF**, **progression** of HF, and others

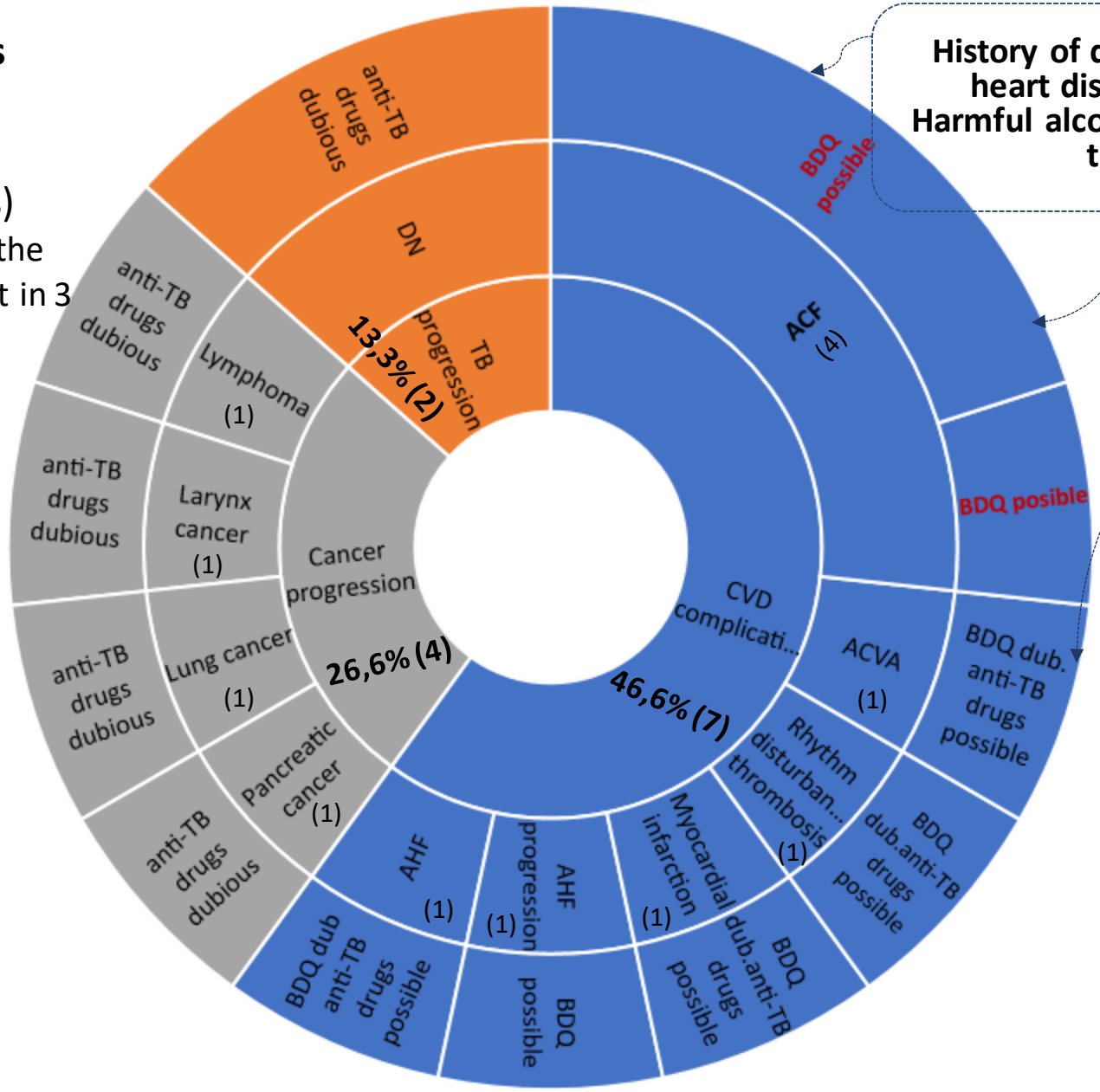
Potentially life-threatening

Risk factors

- the presence of ischemic/ dysmetabolic disorders,
- history of rhythm disorders, heart failure
- age of patients
- alcohol consumption
- electrolyte disorders
- drug interaction

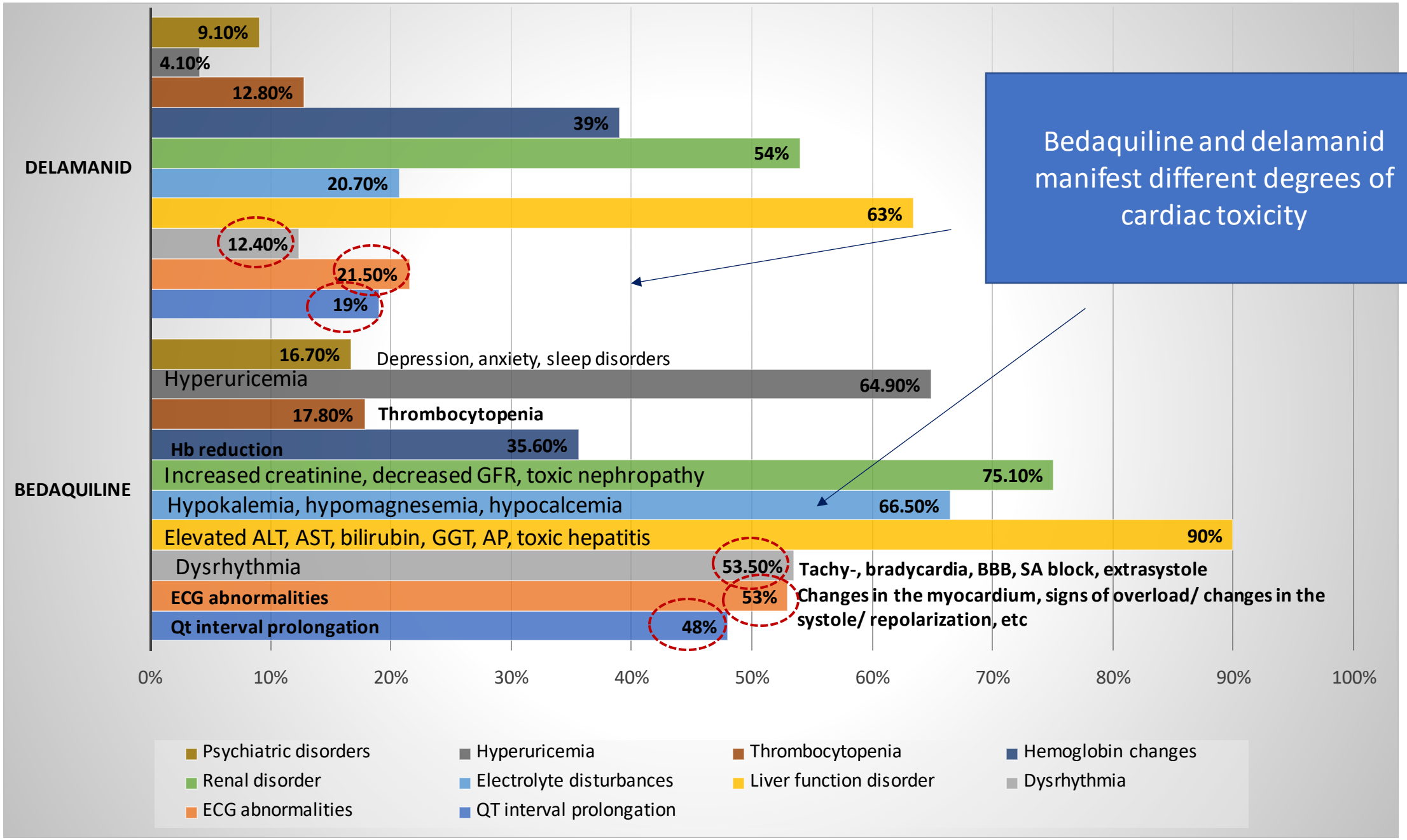
New Treatment Regimens' Safety Profile: Deaths

Bdq + anti-TB drugs
2.1 % (16)
deaths
(out of 763 patients)
Association of Bdq with the outcome was not ruled out in 3 (0.4%) SAEs



History of dysmetabolic/ ischemic heart disorders, heart failure
Harmful alcohol consumption during treatment (2)

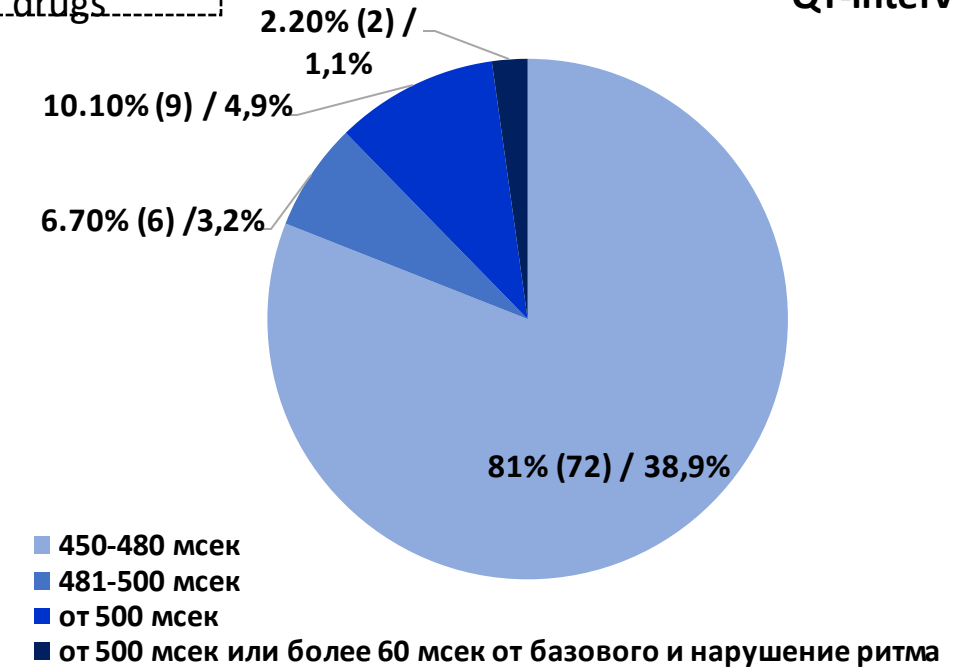
New Treatment Regimens' Safety Profile: Very Common AEs



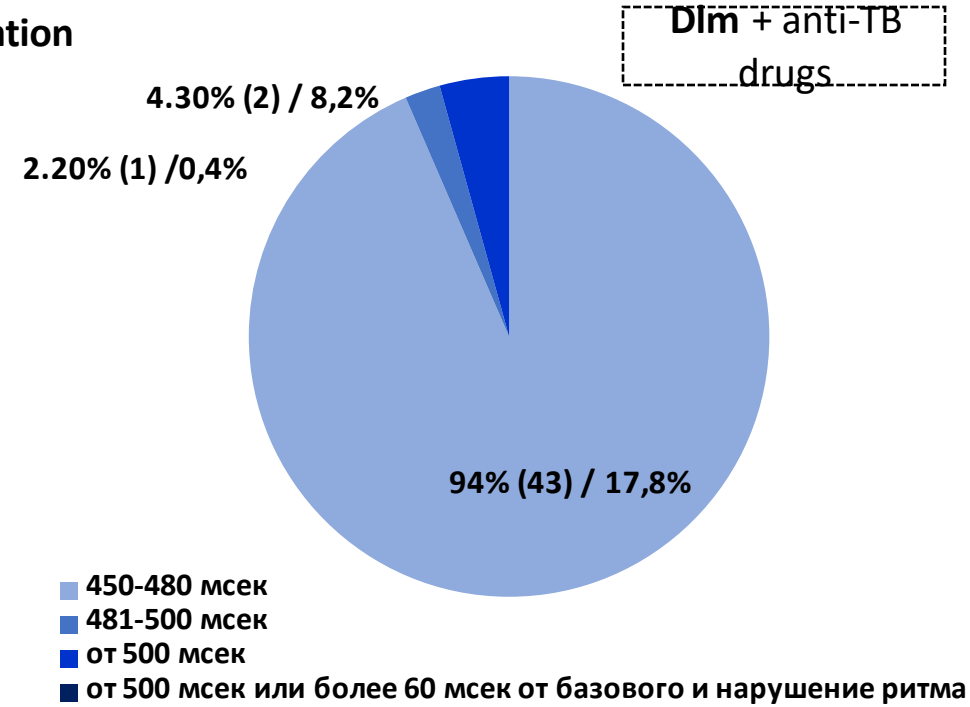
New Treatment Regimens' Safety Profile: Cardiac Toxicity

Bdq + anti-TB drugs

QT-interval prolongation



Dlm + anti-TB drugs



Proarrhythmogenic properties
(prolongation of the QT interval, rhythm/ conduction disorders)

Dysmetabolic / ischemic disorders
(localized/ disseminated myocardial changes, hypertrophy, overload of the heart, ACF, AHF, progression of HF, etc.)

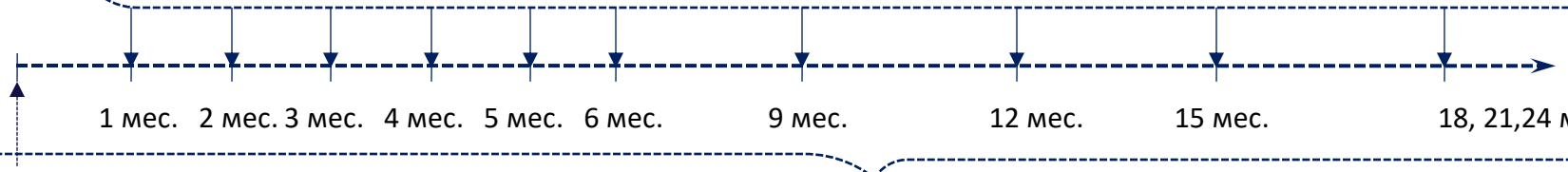
Risk factors
- the history of (ischemic / dysmetabolic and rhythm disorders)
- age
- alcohol consumption
- electrolyte disorders
- drug interaction

RMM:
- regular monitoring (considering individual risk factors)
- minimization of modifiable risk factors
taking immediate measures in case of AE
accounting for the drug interaction
non-inclusion/ exclusion of patients for whom the risk overweighs the benefit

Bdq: Baseline Treatment Safety Criteria, Safety Monitoring and Risk Mitigation

Monitoring over the entire treatment:

- *Regular **ECG** monitoring, and **QTcF assessment***
- *For patients with risk factors – **MORE FREQUENT MONITORING AND HOSPITALIZATION IN CASE OF DETERIORATION***
- *Regular laboratory monitoring of **AST, ALT**, Alkaline phosphatase, **bilirubin**, GGT, lipase, **creatinine, GFR**, TSH, **K+, Mg2+, Ca2+ blood parameters**, glucose*
- *Regular clinical monitoring, control of peripheral neuropathy, vision, examination by an ophthalmologist, examination by a neurologist and a psychiatrist (if indicated)*



During enrollment:

- *Duration of the **QTcF interval ≤ 450 msec (PI)***
- ***Absence of severe liver function disorders***
- ***No history of rhythm disorders** (torsade de pointes, ventricular arrhythmias), coronary artery diseases, heart failure*
- *Absence of hypothyroidism, including in the past*
- *Absence of bradyarrhythmia, including in the past – absence of hypokalemia*
- *Simultaneous administration of fluoroquinolones, with a significant potential for prolongation of the QT interval (Mfx, Gfx)*
- *Absence of pregnancy*

Discontinuation of treatment if:

- ***QTcF interval is > 500 msec***
- ***Elevation of AST, ALT > more than 5 times** of the upper threshold, or **AST, ALT, bilirubin > more than 2 times the upper threshold***

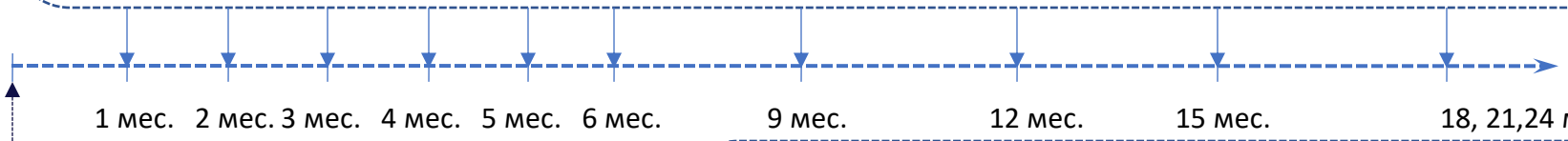
Drug interaction control:

- *With drugs that prolong the QT interval (fluoroquinolones, clofazimine)*
- *With hepatotoxic drugs*
- *Inhibitors (such as, ART, ketoconazole, itraconazole, clarithromycin) and inducers of CYP3A4 (such as, carbamazepine, phenobarbital, phenytoin)*

Dlm: Baseline Treatment Safety Criteria, Safety Monitoring and Risk Mitigation

During the entire treatment:

- *Regular **ECG** monitoring, **QTsF assessment***
- *Regular laboratory monitoring of AST, ALT, ALP, bilirubin, GGT, creatinine, GFR, TSH, **K+, Mg2+, Ca2+** blood parameters, **albumin**, glucose*
- *Regular clinical monitoring, examination by an ophthalmologist, examination by a neurologist (if indicated)*



During enrollment:

- *Patients with an albumin level < **2.8 g/dl** should not be included*
- *QTcF interval > 500 msec*
- *On strong CYP3A4 inhibitors (for example, carbomazepine)*
- *A history of rhythm disorders (torsade de pointes, ventricular arrhythmias), coronary artery diseases, HF, electrolyte disorders and other **risk factors** for rhythm disorders- if the benefit exceeds the risk and **with very frequent monitoring***
- *It is not recommended for patients with moderate to severe hepatic impairment*
- *Mandatory informed consent*

Treatment discontinuation/ more stringent monitoring if:

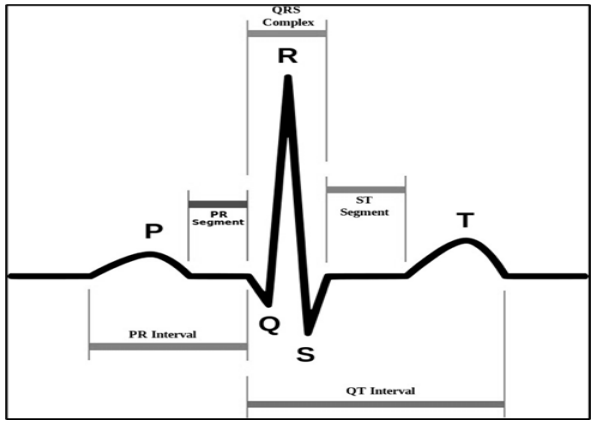
- *QTcF interval > **500** msec*
- *With QTcF >**450/470 m**/f – more frequent monitoring of ECG and electrolytes, correction*
- *Albumin level < **3.4 g/dl** more frequent ECG monitoring*

Drug interaction monitoring:

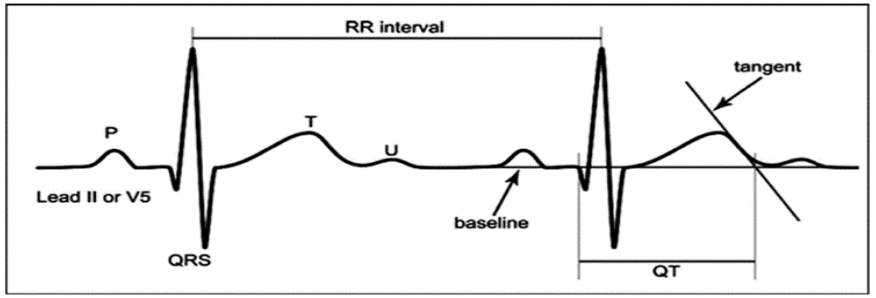
- *With drugs that prolong the QT interval (fluoroquinolones, clofazimine); with FQs*
- *QT increased by 60 msec – more frequent monitoring*
- *With hepatotoxic drugs*
- *CYP3A4 inhibitors – (such as, lopinavir/ritonavir) - increased plasma concentrations of the metabolite and the risk of prolongation of the QT interval*

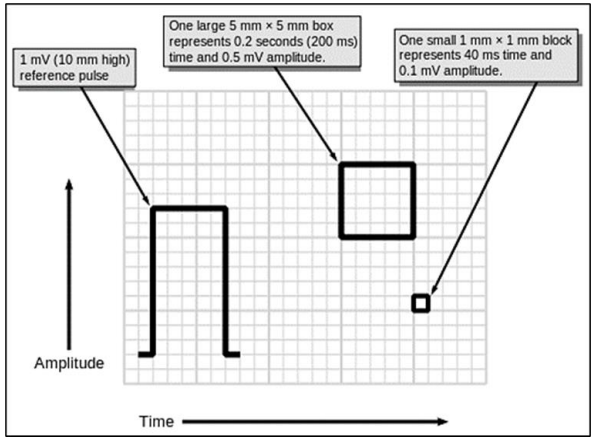
Routine Minimal Monitoring of Cardiac Toxicity and Rhythm Disturbances

Monitoring and evaluation	Recommended frequency
ECG	**Before the onset of treatment with Bdq or Dlm, then at least 2, 4, 8, 12, and 24 weeks after the start of treatment. ECG monitoring should be performed monthly if other QT interval-prolonging drugs (Mfx, Cfz) are taken.**
Serum potassium, magnesium, calcium	**Before the start of treatment and monthly in patients receiving Bdq, Dlm**. It is repeated when ECG abnormalities are detected (prolongation of the QT interval). Every 1-3 weeks in patients with HIV infection, diabetes and risk factors.
Albumin	**Before the start of treatment, then regularly in patients receiving Dlm** (risk of prolongation of the QTcF interval)



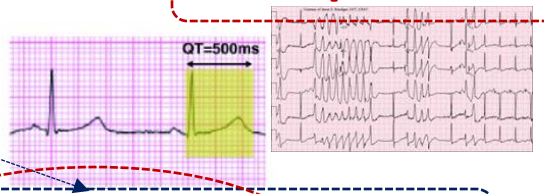
$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$





Management of AE: QT Interval Prolongation

Bdq, Dlm, FQs, Cfz



QTcF INTERVAL PROLONGATION

450 m (470 f) msec or 60 msec of the baseline > QTcF ≤ 500 msec

- Confirmed by re-measurement
- Serum electrolyte measurement (K^+, Ca^{2+}, Mg^{2+})

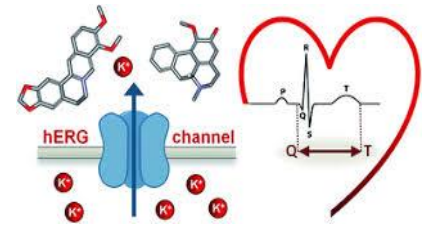
  - K^+, Ca^{2+}, Mg^{2+} within normal range
    Patient is stable
    - Continue taking the drug; weekly (minimum) QTcF monitoring
  - K^+, Ca^{2+}, Mg^{2+} abnormal
    - Discontinuation of Bdq and injectable agents
      Restoring the level of electrolytes to normal
      Weekly (minimum) QTcF monitoring

QTcF > 500 msec

- Confirmed by re-measurement
- Discontinuation of Bdq, Dlm and other QT prolonging drugs
- Assessing and keeping the level of serum electrolytes within the normal range (K^+, Ca^{2+}, Mg^{2+})
- Weekly (minimum) QTcF monitoring
- Monitoring of kidney and liver function

QT Interval Prolongation: Risk Factors and Risk Management

Non-modifiable risk factors	Potentially modifiable risk factors
Female (in 70% of cases)	**Hypokalemia** or **severe hypomagnesemia**
Age (increases with age)	**Bradycardia**
Genetic predisposition • Congenital QT interval prolongation • Family history of sudden death • History of drug-induced QT prolongation	**Drug interaction** • Prescription of >1 QT interval prolonging drugs • Prescription of drugs that inhibit the metabolism of drugs that prolong the QT interval • Drugs that cause disorders of serum electrolytes or kidney / liver function
Organic heart damage/LV Dysfunction Low LV ejection fraction, LV hypertrophy, myocardial ischemia	**Fasting or obesity** *(visceral)*
Elimination disturbance due to kidney or liver diseases	**High plasma concentrations** due to overdose or high rate of intravenous administration



Regular risk factors monitoring and control *(drugs, nutrition, abnormalities)*

Drug interaction control
Individualized monitoring of **QTcF**

Risk factor control *(nutrition)*

Adjust the dose

In all cases:
Measuring QTcF before starting treatment
A risk-based approach to determine a more frequent individual QTcF monitoring plan (1 or more risk factors**)**

QT Interval Prolongation: Risk Factors

QT interval-prolonging drugs

Anti-infective	Antiarrhythmic	Antipsychotic drugs	Opioid analgesics	Antiemetics	Antidepressants	Proton pump Inhibitors
Clarithromycin **Erythromycin** **Chloroquine** **Hydroxycloroquine** **Pentamidine** Azithromycin Roxithromycin Telithromycin **Moxifloxacin** Amantadine Gatifloxacin	**Amiodarone** **Disopyramide** **Dofetilide** **Ibutilide** **Procainamide** **Quinidine** **Sotalol**	**Chlorpromazine** **Haloperidol** **Risperidone** **Quetiapine** Sertindole Ziprasidone Lithium Clozapine Olanzapine **Thioridazine**	Methadone	Ondansetron Dolasetron Granisetron	Escitalopram **Venlafaxine** **Amitriptyline** **Desipramine** **Imipramine** **Sertraline**	Omeprazole Esomeprazole Pantoprazole

Risk factors of hypokalemia, hypomagnesemia

Loop and thiazide-type diuretics	Furosemide, hydrochlorothiazide, indapamide
Nephrotoxic drugs	Aminoglycosides, amphotericin B, cisplatin and others
Disruption of the transport function of the renal tubules Alcoholism Diarrhea, vomiting	

Additional Measures to Minimize the Risk in Patients with Cardiovascular Diseases

Hypertension

Coronary arteries diseases (MI)

Cardiomyopathy

Dysrhythmia

Start of treatment

- **Additional individual assessment of the benefit-risk ratio**, taking into account alternatives
- **Expanded cardiological examination**
- **Consultation with a cardiologist** for evaluation **at the stage of enrolment, monitoring and detection of abnormalities**
- **Increased frequency of ECG and electrolyte monitoring** (up to several times a week), focus on the indicators of CVD progression
- **Assessment and minimization of other risk factors** (alcohol, revision of concomitant therapy, etc.)
- **Taking immediate measures when detecting abnormalities in the parameters**
- **Informing the patient about the high risk of cardiac disorders** (during treatment and for several months after its completion) and the **symptoms of deterioration** (tachycardia, palpitations, syncope, dizziness, weakness

End of treatment

Management of Patients with Concomitant Cardiovascular Disease

A patient (female, 1964 year of birth). Diagnosis: **Disseminated pulmonary tuberculosis, MBT+, XDR, complicated by bilateral pleurisy.**

RD1-2. **IHD: ACS, aortic atherosclerosis. 1st stage AV insufficiency with regurgitation, 1st stage MV with regurgitation, 1st stage TV with regurgitation. H2A NYHA3. Erdheim-Chester disease** (04.2017). Autoimmune thyroiditis. Nodular goiter. The manifestation of CVD on the background of cerebral atherosclerosis.

Ultrasound of the heart: The aorta is not dilated, indurated, aortic valve fibrosis, 1st degree aortic regurgitation, MV fibrosis, 1st degree mitral regurgitation, 1st degree regurgitation at TV , 2nd degree at PAV. LV myocardial hypertrophy, IVS, RV dilatation, LV systolic function is preserved, EF 57%, dilatation of the trunk of the left branch of the PA, PAT 35.7 mmHg

ECG: Sinus rhythm, the heart rate is 68/min, the horizontal position of the EAH. Disseminated changes in the left ventricular myocardium. At the beginning of treatment - QTcF 440 msec.

Additional cardiology consultation

Dlm, Lzd, Cfz, Cs, Imp Amx/Clv (6 months of treatment)
Mfx, Imp/Cst, Amx/Clv, Cfz, Cs (3 months)
Mfx, PAS, Cfz, Cs (2 months)

Practical Examples of Management of Patients with Concomitant Cardiovascular Disease

ECG monitoring at the initial stage – 2 times a week, then weekly; the monitoring rate was adapted based on the obtained results

1. Further ECG abnormalities: there was an increase in the spread of diffuse changes in the LV myocardium, an episode of sinus tachycardia was recorded, a prolongation of the ventricular electrical systole was repeatedly recorded.

2. Prolongation of the QTcF interval – for 3 months from 450 to 480 msec

The patient was discharged in a satisfactory condition for further treatment with positive clinical and laboratory dynamics. She completed the treatment, was de-registered. To date, there has been no data on a relapse.

Conclusion

- New anti-tuberculosis drugs are characterized by a set of safety profile features, including effects of cardiac toxicity.
- Prescription of treatment regimens containing new anti-TB drugs should take into account the risk of cardiac toxicity with an individual assessment of the risk-benefit ratio in the presence of risk factors.
- Recommendations on the management of patients provide for a mandatory set of treatment monitoring measures to ensure the detection of dangerous cardiovascular disorders. Monitoring should be adapted to the individual risk factors of the patient.
- Risk management measures ensure the prevention of adverse treatment outcomes and the achievement of therapeutic effect, including in patients with risk factors for cardiovascular complications.

Thank you for attention!

Questions?