Quando temere l'allungamento del QT indotto da farmaci oncologici?

Dott. V. Malavasi

U.O.C. Cardiologia

Azienda Ospedaliero-Universitaria di Modena

Dir.: prof G Boriani

I Congresso Nazionale di Cardio-Oncologia
Presidenti: Enrico Barbieri, Stefania Gori
25-26 gennaio 2019
IRCCS Ospedale Sacro Cuore Don Calabria, Negrar

A common challenge in this field is the impact of cancer drugs on cardiac repolarization (ie, QT prolongation) and the potential risk for the life-threatening arrhythmia torsades de pointes.

Although QT prolongation is not a perfect marker of arrhythmia risk, this has become a primary safety metric among oncologists.

Cardiologists caring for patients receiving cancer treatment should become familiar with the drugs associated with QT prolongation, its incidence, and appropriate management strategies to provide meaningful consultation in this complex clinical scenario

J Am Heart Assoc. 2017;6:e007724.

How to measure the QT interval: do it correctly

Inaccurate electrocardiographic interpretation of long QT: The majority of physicians cannot recognize a long QT when they see one

Sami Viskin, MD,* Uri Rosovski, MD,* Andrew J. Sands, MPhil, MB, BCh,† Edmond Chen, MD,§ Peter M. Kistler, MD,‡ Jonathan M. Kalman, MD,‡ Laura Rodriguez Chavez, MD,‖ Pedro Iturralde Torres, MD,‖ Fernando E. S. Cruz F, MD,¶ Osmar A. Centurión, MD,** Akira Fujiki, MD,†† Philippe Maury, MD,‡‡ Xiaomin Chen, MD,§§ Andrew D. Krahn, MD,‡ Franz Roithinger, MD,¶¶ Li Zhang, MD,[m] G. Michael Vincent, MD,[m] and David Zeltser, MD*

BACKGROUND Physicians in all fields of medicine may encounter patients with long QT syndrome (LQTS). It is important to define the percentage of physicians capable of distinguishing QT intervals that are long from those that are normal because LQTS can be lethal when left untreated.

OBJECTIVES The purpose of this study was to define the percentage of physicians in the different disciplines of medicine who can recognize a long QT when they see one.

METHODS We presented the ECGs of two patients with LQTS and two healthy females to 902 physicians (25 world-renowned QT experts, 106 arrhythmia specialists, 329 cardiologists, and 442 noncardiologists) from 12 countries. They were asked to measure the QT, calculate the QTc (the QT interval corrected for the heart rate), and determine whether the QT is normal or prolonged.

RESULTS For patients with LQTS, >80% of arrhythmia experts but <50% of cardiologists and <40% of noncardiologists calculated the QTc correctly. Underestimation of the QTc of patients with LQTS and overestimation of the QTc of healthy patients were common. Interobserver agreement was excellent among QT experts, moderate among arrhythmia experts, and low among cardiologists and noncardiologists (kappa coefficient = 0.82, 0.44, and < 0.3, respectively). Correct classification of all QT intervals as either "long" or "normal" was achieved by 96% of QT experts and 62% of arrhythmia experts, but by only <25% of cardiologists and noncardiologists.

CONCLUSIONS Most physicians, including many cardiologists, cannot accurately calculate a QTc and cannot correctly identify a long QT.

KEYWORDS QT interval; long QT; electrocardiogram

(Heart Rhythm 2005;2:569–574)

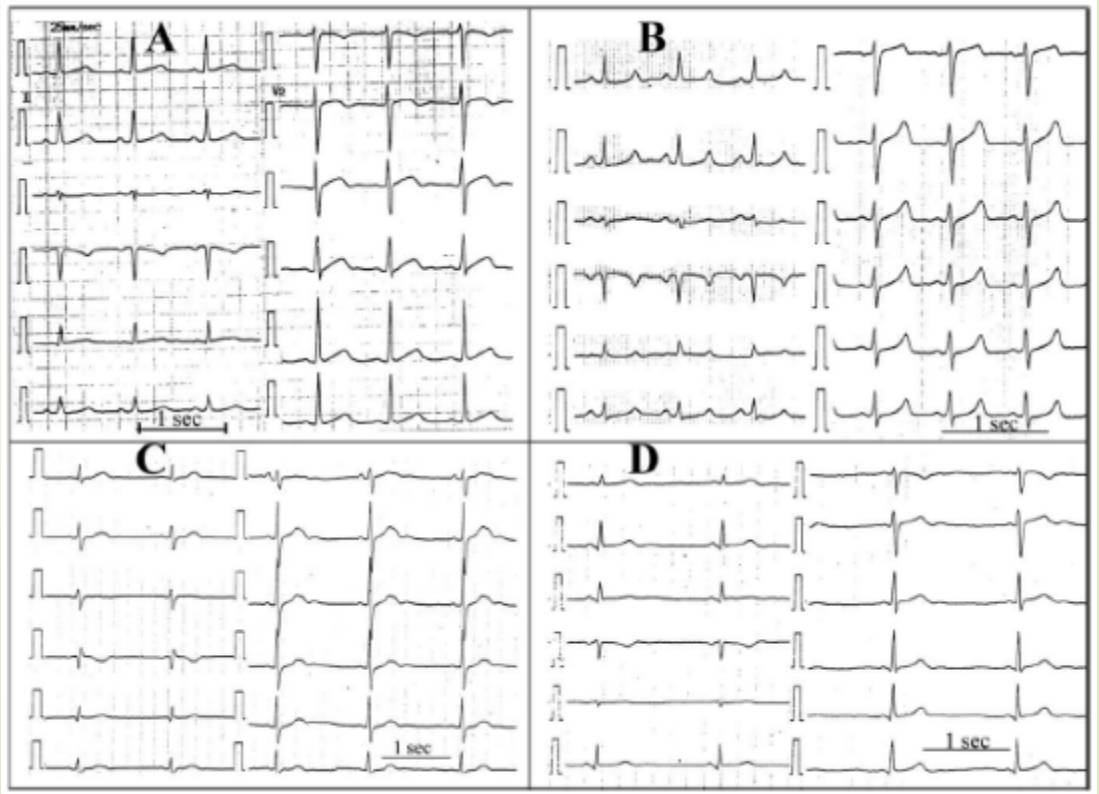
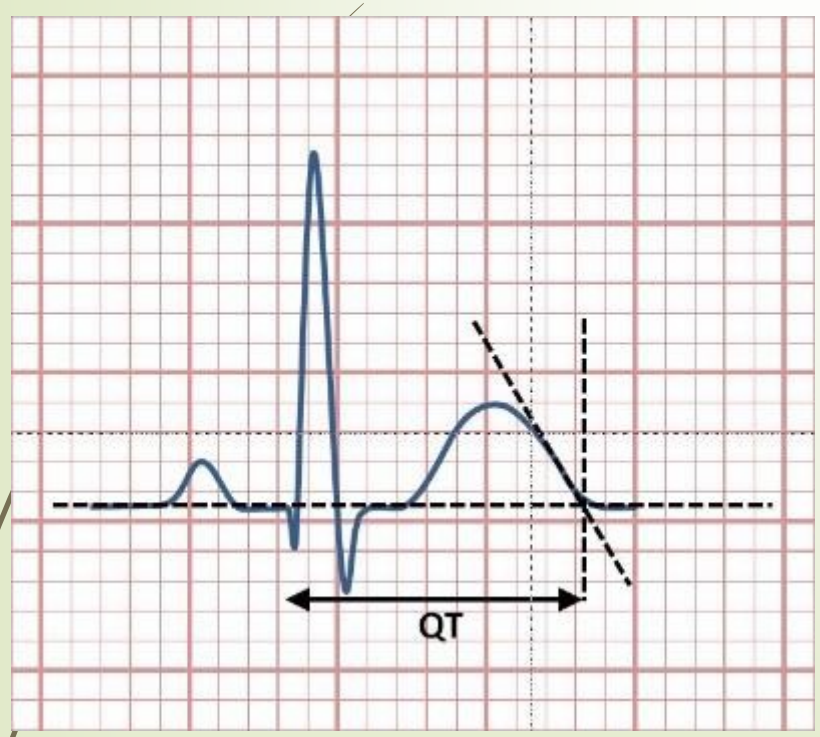


Figure 1 ECGs studied by all the participating physicians. Traces A and B are from a male and a female with congenital LQTS. Traces C and D are from healthy females. All traces were recorded at 25 mm/sec and 10 mm/mV.

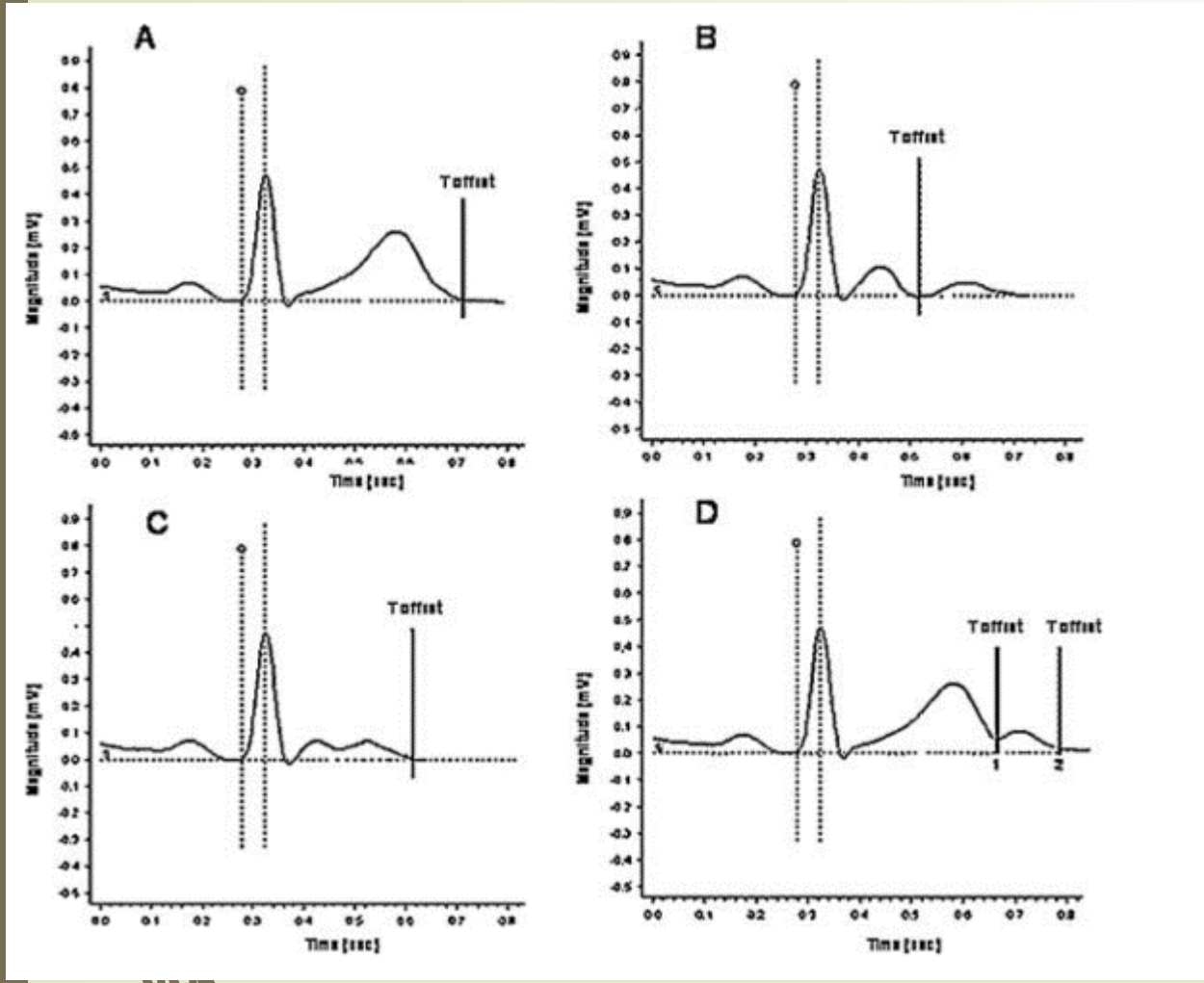
Appropriate measurement of QT/QTc



- Measurement of the QT interval should be based on leads that show the earliest QRS onset and the latest T wave offset (DII, V5), with the longest value being used.
- The QT interval should be determined as a mean value derived from at least 3–5 cardiac cycles.
- Because the QT interval is inversely proportional to heart rate, it results necessary to correct the QT interval for the heart rate.

Automatic measurement often overstimates QT interval because most machine calculate the time between the earliest QRS onset of all leads and the latest offset of the T wave. Also, automated measurements have not been validated in conduction abnormalities.

Identify the end of the T wave: not always simple



A) When the T-wave morphology is normal, the T-wave offset is identified when the descending limb returns to the TP baseline;

B) When the T wave is followed by a distinct U wave, the T-wave offset is identified when the descending limb of the T wave returns to the TP baseline before the onset of the U wave;

C) When the T wave is biphasic with T1 and T2 waves of similar amplitude, the T-wave offset is identified at the time when T2 returns to baseline;

D) When a second low-amplitude repolarization wave interrupts the terminal portion of the larger T wave, the T-wave offset should be measured both at the nadir of the two waves (1) and at the final return to baseline (2).

Goldenberg I et al. QT interval: how to measure it and what is «normal». J Cardiovasc Electophysiol, 2006.

Adjustment for heart rate

$$QT_c = \frac{QT}{\sqrt{RR}}$$

Bazett's formula

$$QTfc = \frac{QT^3}{\sqrt{RR(\text{sec})}}$$

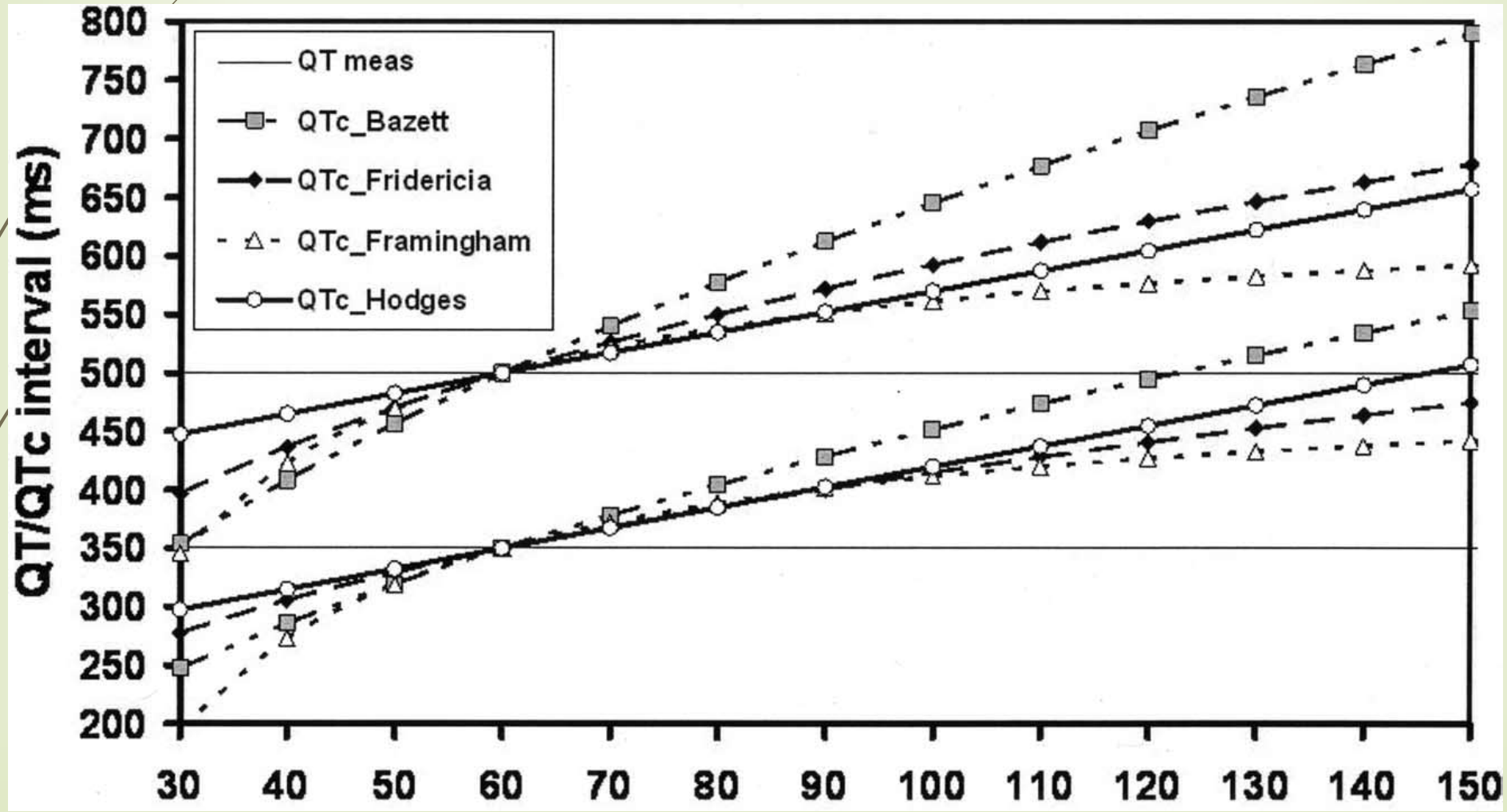
Fridericia's formula

There is no general consensus on the best formula to be utilized in clinical practice.

In resting conditions, with heart rates in the 60–90 beats/min range, most formulae provide almost equivalent results for the diagnosis of QT prolongation. However, the rate dependence of the QT interval is best described by an exponential relation.

Bazett's formula is the most commonly used. When heart rate is particularly fast or slow, the Bazett's formula may overcorrect or undercorrect, respectively, but it remains the standard for clinical use. The cube root Fridericia formula has the same limitations at slow heart rates, but is considered to reflect a more accurate correction factor in subjects with tachycardia.

A Comparison of Commonly Used QT Correction Formulae: The Effect of Heart Rate on the QTc of Normal ECGs



What is the best formula to measure QT interval?

Percentile categorization of QT interval as an approach for identifying adult patients at risk for cardiovascular death

Reza Mohebi MD[1,2], Ayesha Jehan MBBS[1], Aaron Grober MD[1], Victor Froelicher MD[1]

16531 veterans < 56 y.o.

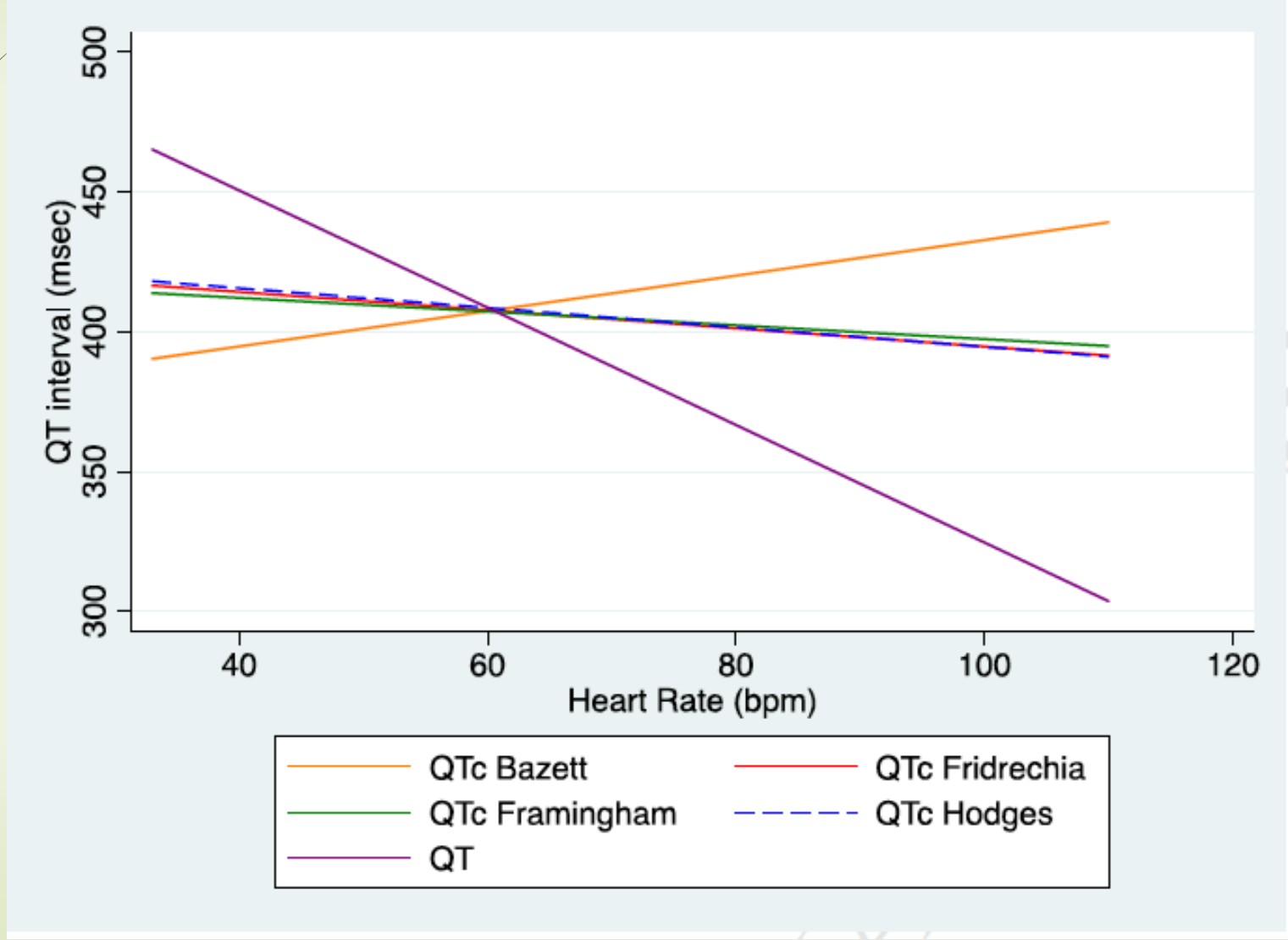
Obs 1987-1999 followed-up 17.8 years

Exclusion of WPW, PM, LBBB, QRS duration >= 124 msec, lateral T wave inversion, diagnostic Q-waves, AMI, AF/AFl, HR >110 bpm, ST depression in V5

455 CVD

Heart Rhythm. 2017 Aug;14(8):1210-1216

What is the best formula to measure QT interval?



Heart Rhythm. 2017 Aug;14(8):1210-1216

What is the best formula to measure QT interval?

Table4. Cox Hazard results using Cardiovascular death as the endpoint for the QT correction methods studied

	# prolong QT	Hazard Ratio	95%CI	p-value
QTc Fridericia*	70(.4%)	1.39	0.44-4.34	0.568
QTc Bazett's*	241(1.4%)	2.05	1.27-3.33	0.003
QTc Hodges*	87(.5%)	1.05	0.26-4.24	0.936
QTc Framingham*	61(.3%)	1.12	0.28-4.52	0.865
QT uncorrected 98th	325(1.9%)	2.08	1.28-3.39	0.003

Heart Rhythm. 2017 Aug;14(8):1210-1216

What is the best formula to measure QT interval?

6609 patients >18 years, SR, normal QRS duration and rate <90 beats bpm

A healthy subset showed 99% upper limits of normal for Bazett above current clinical standards: men 472 ms (95% CI, 464–478 ms) and women 482 ms (95% CI 474–490 ms)

In a point-prevalence study with haloperidol, the number of patients classified to be at risk for possibly harmful QT prolongation could be reduced by 50% using optimal QT rate correction.

J Am Heart Assoc. 2016

What is the best formula to measure QT interval?

Table 8. Results for QTc>ULN in Multivariate Cox Regression Analysis

	30-Day All-Cause Mortality				1-Year All-Cause Mortality			

Table 7. Patients With QTc>ULN and All-Cause Mortality Risk Stratification

		30-Day				1-Year			
	QTc>ULN	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
QTcB	3.2%	19.7%	97.0%	5.7%	99.2%	12.1%	97.2%	15.2%	96.4%
QTcFri	5.2%	27.9%	95.0%	4.9%	99.3%	16.3%	95.3%	12.5%	96.5%
QTcFra	4.6%	27.9%	95.6%	5.5%	99.3%	14.1%	95.7%	12.1%	96.4%
QTcH	5.7%	26.2%	94.5%	4.3%	99.3%	14.8%	94.7%	10.4%	96.4%
QTcR	3.5%	23.0%	96.7%	6.0%	99.3%	12.5%	96.9%	14.2%	96.4%

differences between QTc formulae. −2 LLR Δ QTcB indicates difference of −2 log likelihood ratio compared to the model including QTcB; HR, hazard ratio; QTcB, QT correction with Bazett formula; QTcFra, QT correction with Framingham formula; QTcFri, QT correction with Fridericia formula; QTcH, QT correction with Hodges formula; QTcR, QT correction with Rautaharju formula.

*P<0.050; †P<0.010; ‡P<0.005; §P<0.001.

J Am Heart Assoc. 2016

Measurement of the QT interval in presence of an intraventricular conduction delay

Three options:

- Calculate a modified QT interval by subtracting 48,5% of the duration of the QRS from the measured QT [mQT: QT-0,485x(QRS)] and then correcting it for HR with conventional formulas (1).

- Take a QTc of >550 msec as abnormal without any subtraction (1).

- Subtracte the QRS duration from the QT measurement (JT interval), using a cut off of >360 msec (2).

(1) *Bogossian H, Frommeyer G et al. New formula for evaluation of the QT interval in patients with left bundle branch block. Heart Rhytm. 2014;11:2273-2277.*

(2) *Chiladakis J, Kalogeropoulos A et al. Predicting torsade de pointes in aquired long QT syndrome: optimal identification of critical QT interval prolongation. Cardiology. 2012;122:3-11.*

QT measurement in clinical practice (oncology populations)

- QTcB most used in daily practice
- QTcFri suggested in oncology pts due to higher HR variability
- QTcH suggested for HR > 90 bpm

Normal values of the QT interval

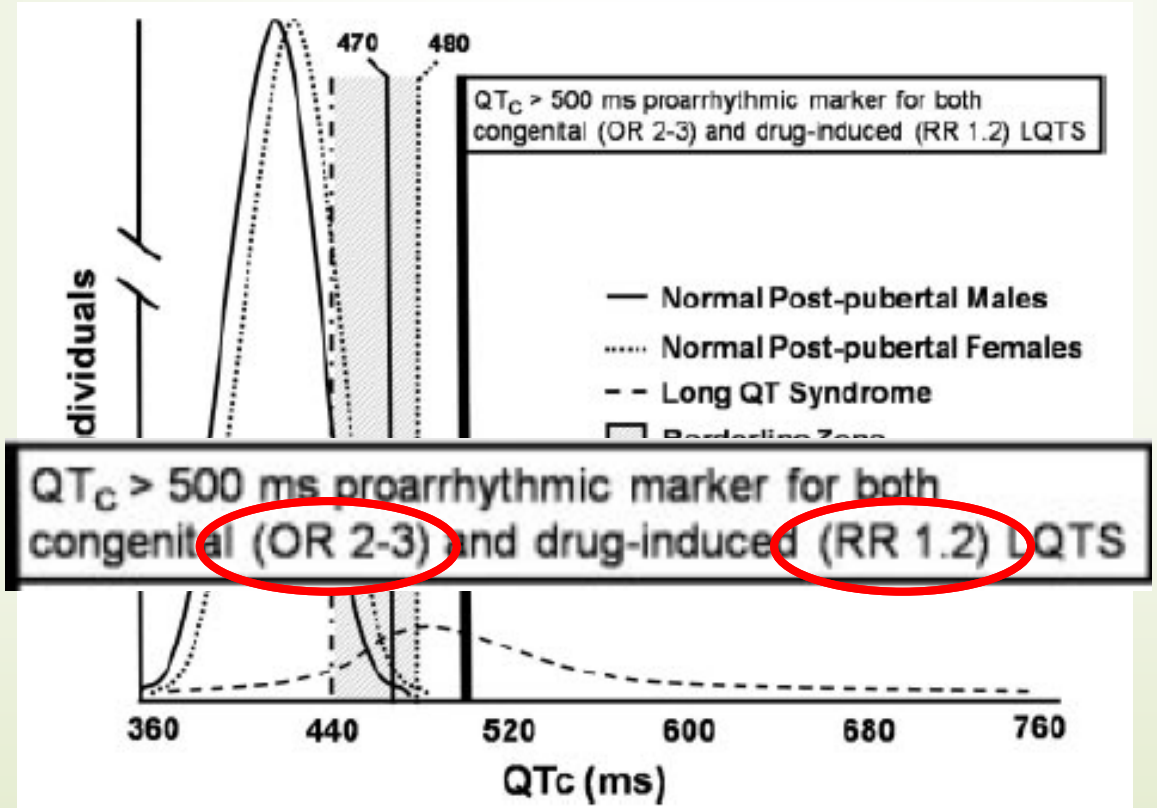


Figure 3. QT_c distribution curves in normal males and females and in a cohort of patients with congenital LQTS. Upper limits of normal (99th percentile) for QT_c are 470 ms in males and 480 ms in females. For both males and females, a QT_c >500 ms is considered dangerous. OR indicates odds ratio; RR, relative risk.

Prolonged QT = TdP?

Circulation 2010; 121: 1047–1060

QT interval and proarrhythmic effect

- Excessive prolongation of QT interval in the right setting is a major precursor of TdP, a potentially fatal form of polymorphic ventricular tachycardia (VT).
- Prolongation of the QT interval reflects prolongation of ventricular repolarization. When drug-induced, it almost always results from inhibition of the rapid component of the delayed rectifier potassium current $I_{Kr;}$ less frequently, inhibition of the slow component I_{Ks} or augmentation of inward currents can prolong the QT interval.
- **QTc intervals exceeding 500 ms are considered torsadogenic, and the risk of TdP rises progressively with further prolongations thereafter. Therefore, QT interval has come to be recognized as a surrogate marker for risk of TdP.**
- The potential of a drug to prolong the QT interval (so-called *QT-liability)* has been responsible for termination of development and withdrawal from the market of many drugs, rejection of new drugs, and prescribing restrictions on the use of new and old drugs.

Shah RR et al. Refining detection of drug-induced proarrhytmia: QT interval and TRIaD. Heart Rhythm 2005; 2:773-776.

Table 10 Risk factors for QT prolongation in cancer patients

Risk factors for QT prolongation	
Correctable	**Non-correctable**
Electrolyte imbalance • Nausea and emesis • Diarrhoea • Treatment with loop diuretics • Hypokalaemia (≤3.5 mEq/L) • Hypomagnesaemia (≤1.6 mg/dL) • Hypocalcaemia (≤8.5 mg/dL) **Hypothyroidism** **Concurrent use of QT-prolonging drugs** • Antiarrhythmic • Anti-infective • Antibiotic • Antifungal • Psychotropic • Antidepressant • Antipsychotic • Antiemetic • Antihistamine	• Family history of sudden death (occult congenital LQTS or genetic polymorphisms) • Personal history of syncope • Baseline QTc interval prolongation • Female gender • Advanced age • Heart disease • Myocardial infarction • Impaired renal function • Impaired hepatic drug metabolism

The QT interval and associated risk factors for QT prolongation should be assessed before and during treatment. QTc intervals>450 ms in men and>460 ms in women are suggested as a guideline for the upper limit of normal on baseline ECG evaluation.

QTc prolongation>500 ms and a ΔQT (i.e. change from baseline) of >60 ms are considered to be of particular concern because torsade de pointes rarely occurs when QTc is <500 ms.

European Heart Journal (2016) 37, 2768–2801

Risk score for long QT

Table 5. Calculation of Risk Score for QT_c Interval Prolongation

Risk Factors	Points
Age ≥68 y	1
Female sex	1
Loop diuretic	1
Serum K^+ ≤3.5 mEq/L	2
Admission QT_c ≥450 ms	2
Acute MI	2
≥2 QT_c-prolonging drugs	3
sepsis	3
Heart failure	3
One QT_c-prolonging drug	3
Maximum Risk Score	21

Table 6. QT_c Interval Risk Score Stratification*

Risk Score Category	Risk Score	QT_c Interval Prolongation Derivation Group, n (%)	QT_c Interval Prolongation Validation Group, n (%)
Low	<7	456 (51)	159 (53)
Moderate	7–10	319 (35)	101 (34)
High	≥11	125 (14)	40 (13)

A high-risk score ≥11 was associated with sensitivity=0.74, specificity=0.77, PPV=0.79, and NPV=0.76. In the validation group, the incidences of QTc prolongation were 15%(low risk); 37% (moderate risk); and 73% (high risk).

Circ Cardiovasc Qual Outcomes 2013

Prolonged QT = TdP?

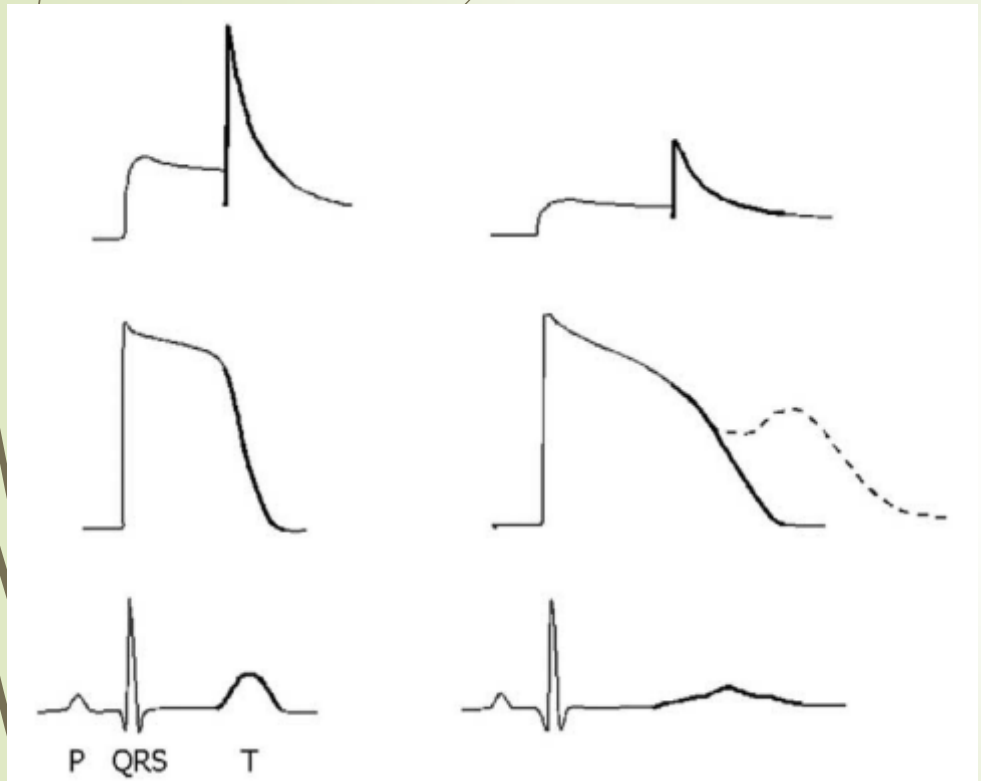


Figure 1 Block of hERG channels. **Top trace:** I_{Kr}. **Middle trace:** Action potential. **Bottom trace:** ECG. Repolarization is shown in *bold*. Block of hERG channels **(right traces)** leads to reduction in I*Kr*, triangulation, and flattening/broadening of the T wave.

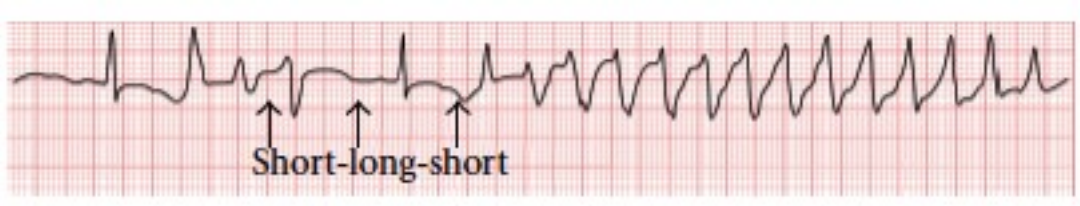
…NO!

Agents that prolong QT interval in the absence of disturbances and dispersion of repolarization have been shown not to induce TdP (e.g. ranolazine).

Disturbances and dispersion of repolarization induced by a drug are related to **triangulation** of the action potential, **reverse use dependence**, i**nstability**, and **dispersion** of APD. This set of four features (that constitute *TRIaD)* appears strongly interrelated via the blocking of hERG channels.

Shah RR et al. Refining detection of drug-induced proarrhytmia: QT interval and TRIaD. Heart Rhythm 2005; 2:773-776.

Electrical instability



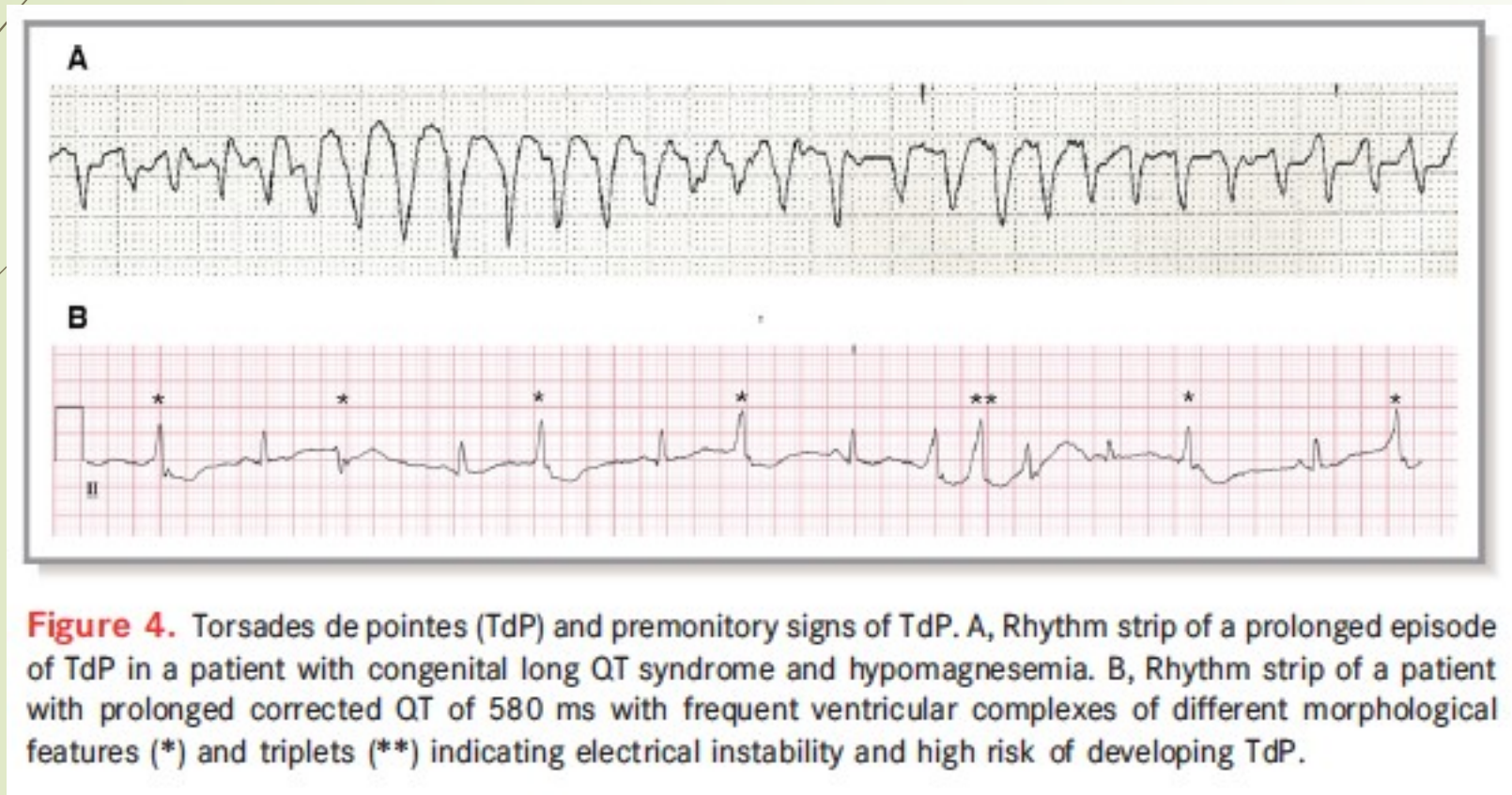
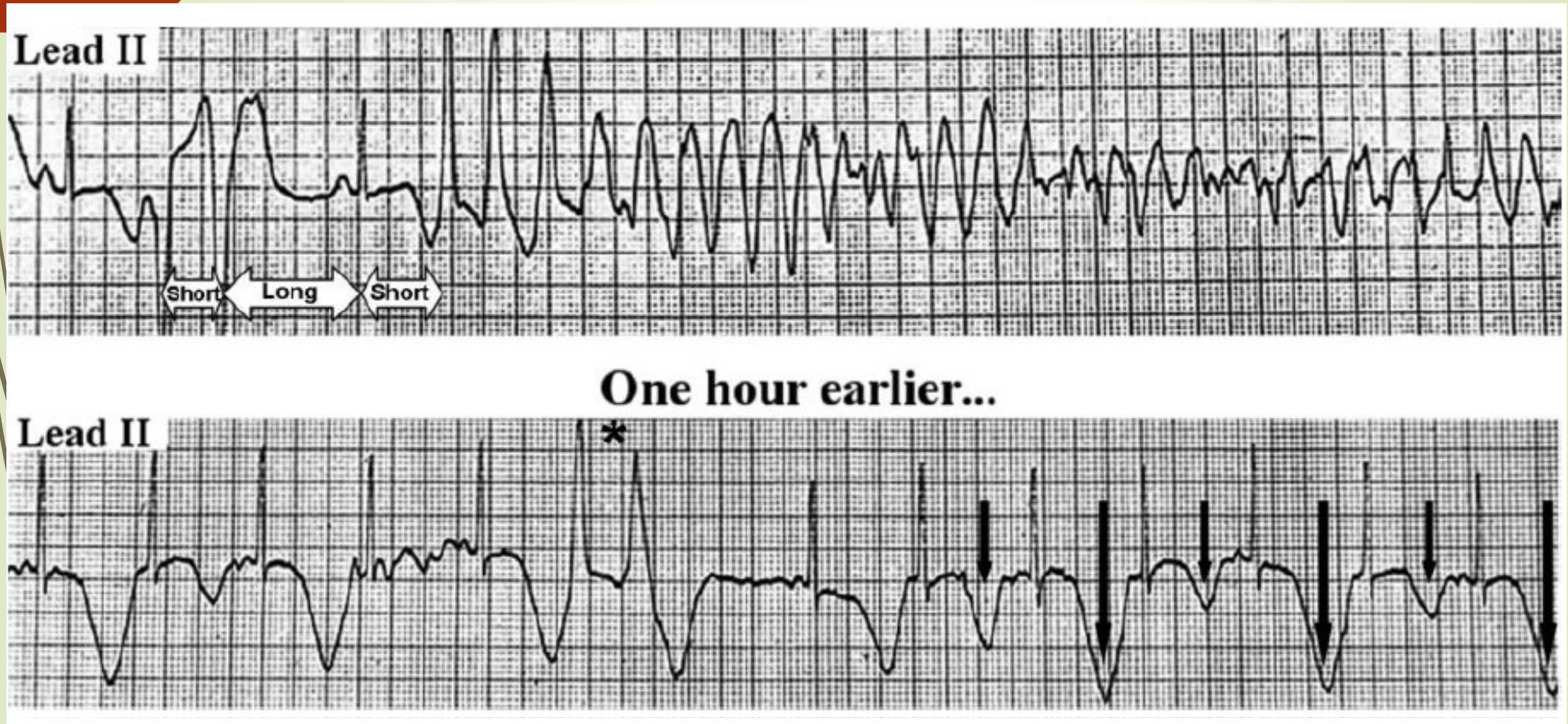


Figure 4. Torsades de pointes (TdP) and premonitory signs of TdP. A, Rhythm strip of a prolonged episode of TdP in a patient with congenital long QT syndrome and hypomagnesemia. B, Rhythm strip of a patient with prolonged corrected QT of 580 ms with frequent ventricular complexes of different morphological features (*) and triplets (**) indicating electrical instability and high risk of developing TdP.

J Am Heart Assoc. 2017
The ScientificWorld Journal Volume 2012

Risk factors for TdP in acquired long QT



Circulation 2010; 121: 1047–1060

Electrical instability

QT prolongation is often recognized as a marker of arrhythmic risk: TdP can occur even in the absence of a prolonged QT. A significant number of patients with polymorphic VT/TdP exhibit hardly any prolongation of QT interval

Other markers of arrhythmic risk are difficult to recognize bedside.

So QT interval is an easy available, even if a surrogate, parameter to identify patients at risk in clinical practice; but don't forget other ecg features (bradycardia, flattening of the T waves, T waves alternans, VPB, polimorphic VPB etc…)

The capacity for the maintenance of myocardial repolarization in the face of some degree of inhibition of repolarization has been termed repolarization reserve. Repolarization reserve is increasingly relevant to understanding the differences between patients in their response to a QT-prolonging drug and the incidence of TdP

Shah RR Heart Rhythm 2005; 2:773-776.
Ahmad K Europace 2007; suppl 4;16-22

Drug-related pro-arrhythmia

- Many non-cardiac medications inhibit potassium channels and are associated with a risk for TdP in susceptible patients (i.e. antibiotics).
- Sodium channel-blocking drugs, such as tricyclic antidepressants, may produce QRS prolongation and the typical Brugada syndrome ECG.
- New oncology drugs involved in QT prolongation
- Anthracycline cardiotoxicity is dose dependent, with higher cumulative doses increasing the risk of cardiomyopathy and lethal arrhythmias. 5-fluorouracil may cause VF due to coronary spasm.

ESC Guidelines 2015

Drug–drug interactions

- **A pharmacodynamic interaction of concomitantly used drugs can lead to a prolonged QTc interval if the individual QTc prolonging drugs have an additive or potentiating effect**
- **A pharmacokinetic effect may occur if a drug reduces the clearance of a concomitantly used QTc prolonging drug, leading to increased plasma and tissue concentrations.**
- **Pharmacokinetic interactions often involve drugs which are both metabolized by specific CYP iso-enzymes.**
- **Patients using two or more drugs concomitantly metabolized by CYP3A4 or CYP2D6, can develop QTc prolongation due to increased plasma concentrations. For example, QTc prolonging drugs such as cisapride and terfenadine are metabolized by CYP3A4 and haloperidol and thioridazine are metabolized by CYP2D6.**

Br J Clin Pharmacol 2010

Gene–drug interactions

- **Previously unrecognized LQTS can be identified in 5–20% of patients with drug-induced torsade de pointes:**
- **rare ion-channel mutations that increase the risk of QT prolongation by drug use**
- **common genetic variants that potentiate the QT prolonging effect of drugs**
- **variation within drug metabolizing and transporting proteins that influence drug pharmacokinetics**
- **Subjects with two non-functional *CYP2D6* alleles are classified as 'poor metabolizers'. Approximately 5–10% of the Caucasian population are 'poor metabolizers'. 'Poor metabolizers' using QT prolonging drugs metabolized by CYP2D6 have an increased risk of developing QTc prolongation or torsade de pointes.**

Br J Clin Pharmacol 2010

Table 9 Cancer drug agents associated with QT prolongation and Torsade de Pointes[151,153,154]

Cancer drug agents	Average QT prolongation (ms)	Increase in QTc >60 ms (%)	QTc >500 ms (%)	Torsade de pointes (%)
Anthracyclines				
Doxorubicin	14	11–14	NA	NA
Histone deacetylase inhibitors				
Depsipeptide	14	20–23.8	NA	NA
Vorinostat	<10	2.7–6	<1	NA
Tyrosine kinase inhibitors				
Axitinib	<10	NA	NA	NA
Bosutinib	NA	0.34	0.2	NA
Cabozantinib	10–15	NA	NA	NA
Crizotinib	9–13	3.5	1.3	NA
Dasatinib	3–13	0.6–3	<1.4	NA
Lapatinib	6–13	11	6.1	NA
Nilotinib	5–15	1.9–4.7	<1.2	NA
Pazopanib	NA	NA	2	<0.3
Ponatinib	<10	NA	NA	NA
Sorafenib	8–13	NA	NA	NA
Sunitinib	9.6–15.4	1–4	0.5	<0.1
Vandetanib	36	12–15	4.3–8	Described, % NA
Vemurafenib	13–15	1.6	1.6	Described, % NA
Others				
Arsenic trioxide	35.4	35	25–60	2.5

NA = not available.

European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

QT prolongation induced by cancer therapies

- QT prolongation can be caused by cancer therapies and is facilitated by electrolyte disturbances, predisposing individual factors and concomitant medications (e.g. anti-emetics, antiarrhythmics, antibiotics, psychotropes).

- The risk of QT prolongation varies with different drugs, with **arsenic trioxide** being the most relevant. This drug prolongs the QT interval in 26–93% of patients, and lifethreatening ventricular tachyarrhythmias have been reported. Prolongation of the QTc interval was observed 1–5 weeks after arsenic trioxide infusion and then returned towards baseline by the end of 8 weeks, i.e. before the second course of chemotherapy.

- Other cancer therapies that frequently induce QT prolongation are **TKI drug class**, which has the second highest incidence of QT prolongation.

Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review

Andreu Porta-Sánchez, MD MSc; Cameron Gilbert, MD; Danna Spears, MD; Eitan Amir, MD, PhD; Joy[illegible] Chan, Phar
Kumaraswamy Nanthakumar, MD; Paaladinesh Thavendiranathan, MD, SM

Table 2. Classification of the QTc Prolongation Potential Cancer Drugs Based on Our Systematic Review

Classification	Drug
High risk (>10% incidence)	Arsenic trioxide Bosutinib Capecitabine Cediranib Combretastatin (CA4P) Enzastaurin Vadimezan Vorinostat
Moderate risk (5%–10% incidence)	Belinostat Dasatinib Dovitinib Lenvatinib Sorafenib Sunitinib Vandetanib
Low risk (1%–5% incidence)	Aflibercept Imatinib Lapatinib Nilotinib Nintedanib Paclitaxel Panobinostat Ponatinib Romidepsin Vemurafenib
Very low risk (<1% incidence)	Anthracyclines Fluorouracil Afatinib Ceritinib Crizotinib Fludarabine Pazopanib Pertuzumab Trastuzumab

J Am Heart Assoc. 2017;6:e007724.

Drug Type	Drug	No. of Studies	Total No.	Range of Patients With QTc Increase, %*	Weighted Average of Patients With QTc Increase, %*	Weighted Average of Patients With QTc >500 ms, %	Arrhythmia/ SCD, No.
Antimetabolites[4,5]	Fluorouracil	1	102	0	0	0	0/0
	Capecitabine	1	52	19	19	0	0/0
Purine analogs[6]	Fludarabine	1	56	0	0	0	0/0
Antimicrotubule agents[7,8]	Paclitaxel	3	290	1–4	2.4	0	0/0
Tyrosine kinase inhibitors[9–81]	Afatinib	1	60	0	0	0	0/0
	Aflibercept	1	43	4.6	4.6	0	0/0
	Bosutinib	2	87	0–37	11.5	0	0/0
	Ceritinib	1	130	0.7	0.7	0.7	0/0
	Crizotinib	2	101	0	0.9	0.9	0/0
	Dasatinib	10 (1 with paclitaxel, 1 with ixabepilone, 1 with cetuximab)	611	1.6–73	8.0	1.0	1/0
	Dovitinib	2	49	3–15	8.1	4.1	0/0
	Imatinib	5	897	<0.5–6.9	3.1	0.02	0/0
	Lapatinib	2 (with trastuzumab+paclitaxel)	117	1.7	1.7	1.7	0/0
	Lenvatinib	2	319	0–8.1	6.5	1.2	0/0
	Nilotinib	13	3076	0–24	2.7	0.2	0/5
	Nintedanib	2	94	0–3.3	1.1	1.1	0/0
	Pazopanib	3	99	0–5.9	1.0	0	0/1
	Ponatinib	2	120	0–3.7	2.5	1.7	1/0
	Sorafenib/ sunitinib	6	280	0–17.8	8.5	1.9	0/0
	Vandetanib	32	2567	0–66.7	8.5	2.7	1/0
Histone deacetylase inhibitors[82–98]	Belinostat	3	195	0–36.0	8.7	4.1	1/0
	Panobinostat	10 (2 with bevacizumab, 1 with everolimus)	654	0–31.4	4.4	0.7	0/0
	Romidepsin	2	112	0–2.1	1.8	0	0/0
	Vorinostat	6	189	0–35.7	12.2	3.2	0/0
Proteasome inhibitor[99,100]	Bortezomib	2	22	0–10	4.5	4.5	0/0
Vascular endothelial growth factor inhibitors[101–104]	Cediranib	4 (1 with FOLFOX)	127	7.7–20.5	14.2	2.4	0/0
Antiangiogenic[105–109]	Combretastatin (CA4P)	3	110	6.5–72	22.7	0.9	0/0
	Vadimezan (ASA404)	4	77	0–100	20.8	5.2	0/0
Protein kinase C inhibitor[110–114]	Enzastaurin	5	135	6–24	11.8	2	0/0
Monoclonal antibodies[115–118]	Trastuzumab and Pertuzumab	4	167	0	0	0	0/0
B-Raf inhibitor[119,120]	Vemurafenib	2	3597	0–6.5	2.2	1.8	2/0
Other[121–136]	Arsenic trioxide	15	533	0–38	22.0	5.8	24/1

In patients treated with conventional cancer drugs, the incidence of any QTc prolongation varied between 0% and 22%, although QTc >500 ms, arrhythmias, or SCD was extremely rare.

The risk of QTc prolongation with targeted therapies was also variable (0%– 22.7%), with severe prolongation (QTc >500 ms) reported in 0% to 5.2% of the patients. Arrhythmias and SCD were rare.

Table 1. Cancer Drugs and Their Effects on QTc Prolongation Identified From the Systematic Review

J Am Heart Assoc. 2017;6:e007724.

Repolarization effects of multiple-cycle chemotherapy and predictors of QTc prolongation: a prospective female cohort study on >2000 ECGs

- 100 females (to avoid gender confounders) in CHT as outpatients
- ECG recorded preTx, after 1-3 hrs after i.v. CHT, 7-10 dd after CHT
- 992 CHT cycles (median 7)
- 2438 ECG recorded
- QTc with Bazett
- 98% on non-CHT prolonging QT drugs

Eur J Clin Pharmacol. 2015;71:1001-9

Repolarization effects of multiple-cycle chemotherapy and predictors of QTc prolongation: a prospective female cohort study on >2000 ECGs

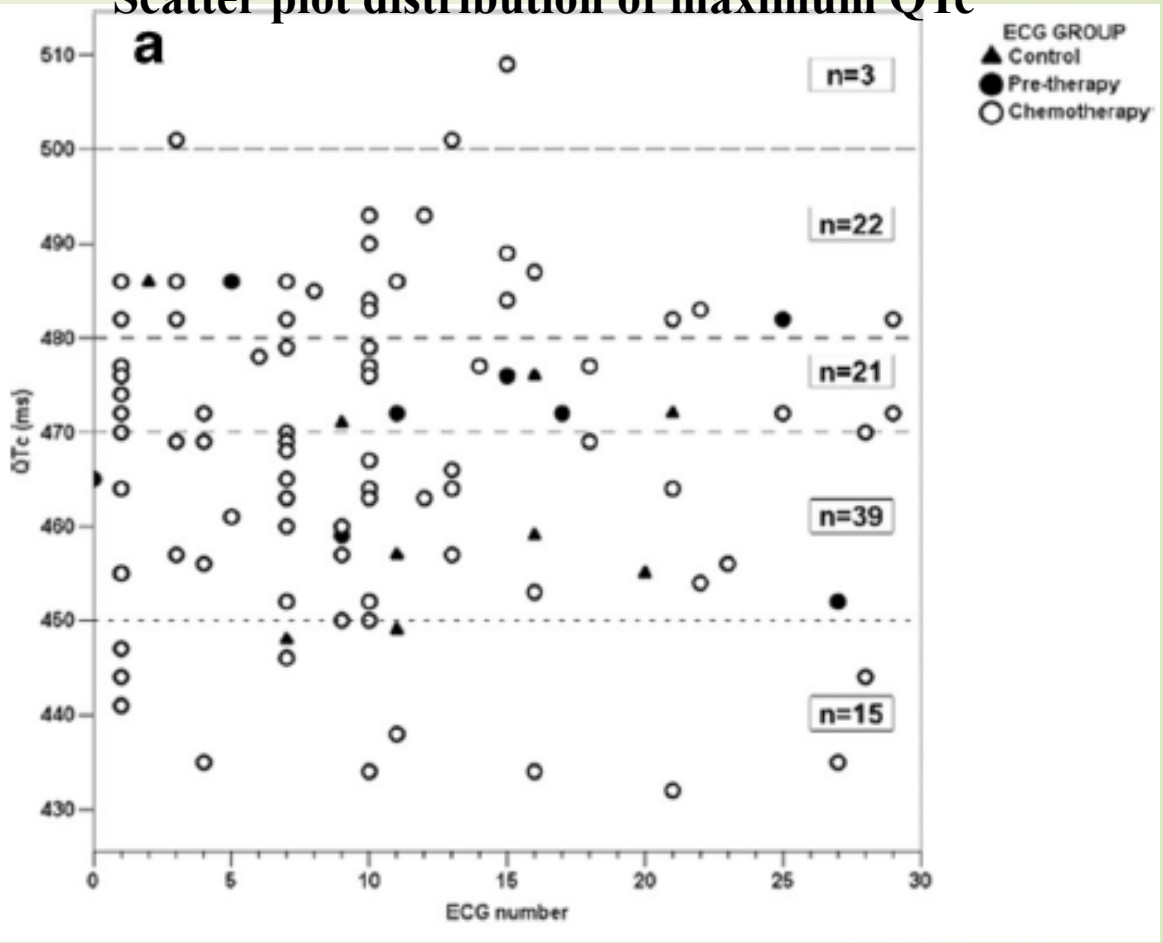
Table 2 ECG-related parameters recorded at baseline and after the first chemotherapy cycle

	Baseline ECG	First chemotherapy ECG	*p* value
HR (/min)	73±12	74±11	0.238
PR (ms)	147±20	145±20	0.184
QRS (ms)	85±12	85±13	0.783
QT (ms)	395±27	405±31	<0.001
QTc (ms)	430±22	445±22	<0.001
QTc >470 ms (pts)	2 %	13 %	0.006
ΔQTc (ms)	15±21		n.a.
ΔQTc ≥60 ms	1 %		n.a.

Values represent mean±standard deviation or number (percentage)

HR heart rate, *n.a.* not applicable

Scatter plot distribution of maximum QTc

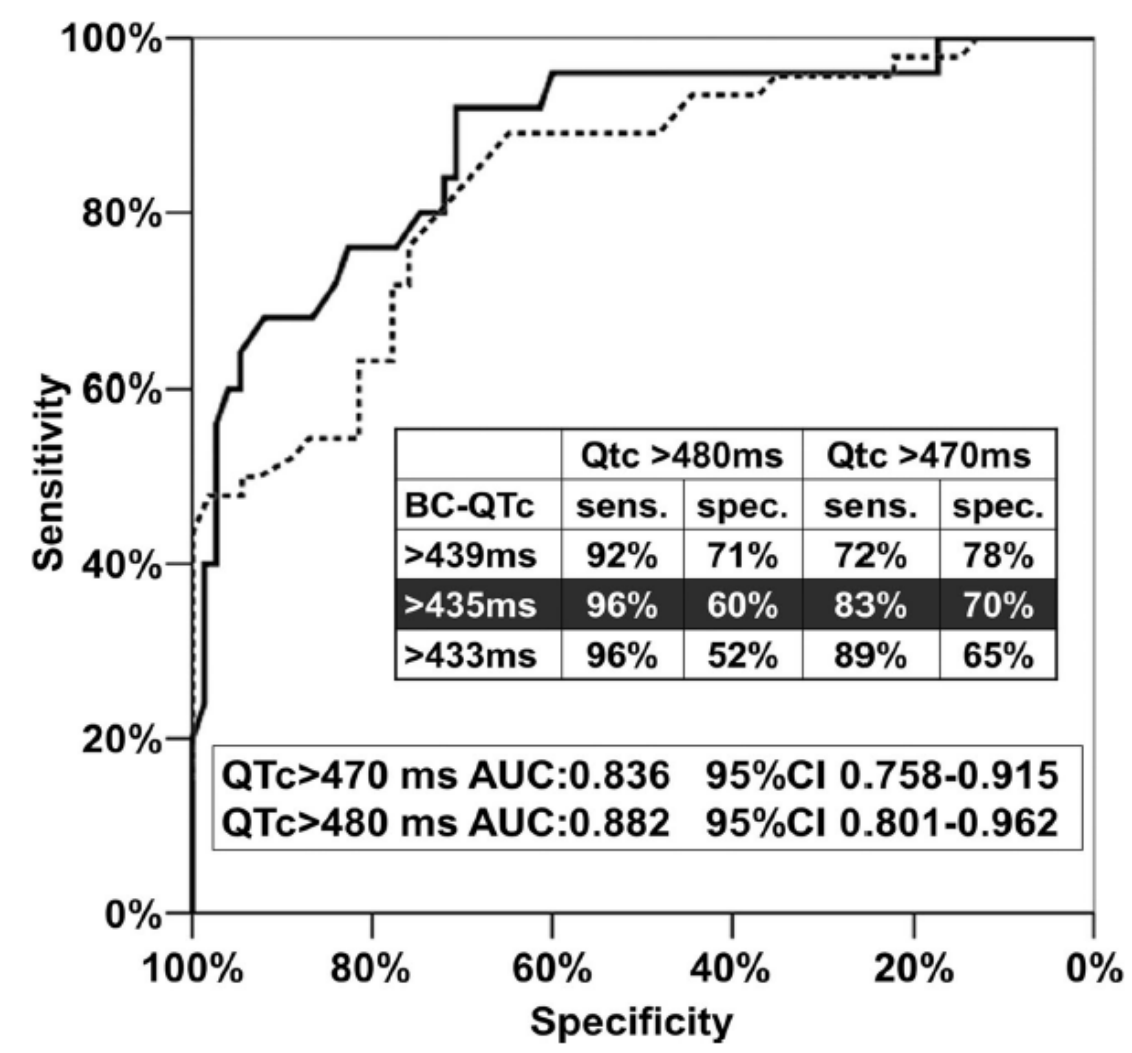


no cumulative effect was evident

max QTc after the 4th cycle in > 50% of pts

Eur J Clin Pharmacol. 2015;71:1001-9

Repolarization effects of multiple-cycle chemotherapy and predictors of QTc prolongation: a prospective female cohort study on >2000 ECGs



	Qtc >480ms		Qtc >470ms	
BC-QTc	sens.	spec.	sens.	spec.
>439ms	92%	71%	72%	78%
>435ms	96%	60%	83%	70%
>433ms	96%	52%	89%	65%

BC-QTc= the average between baseline and 1st cycle QTc

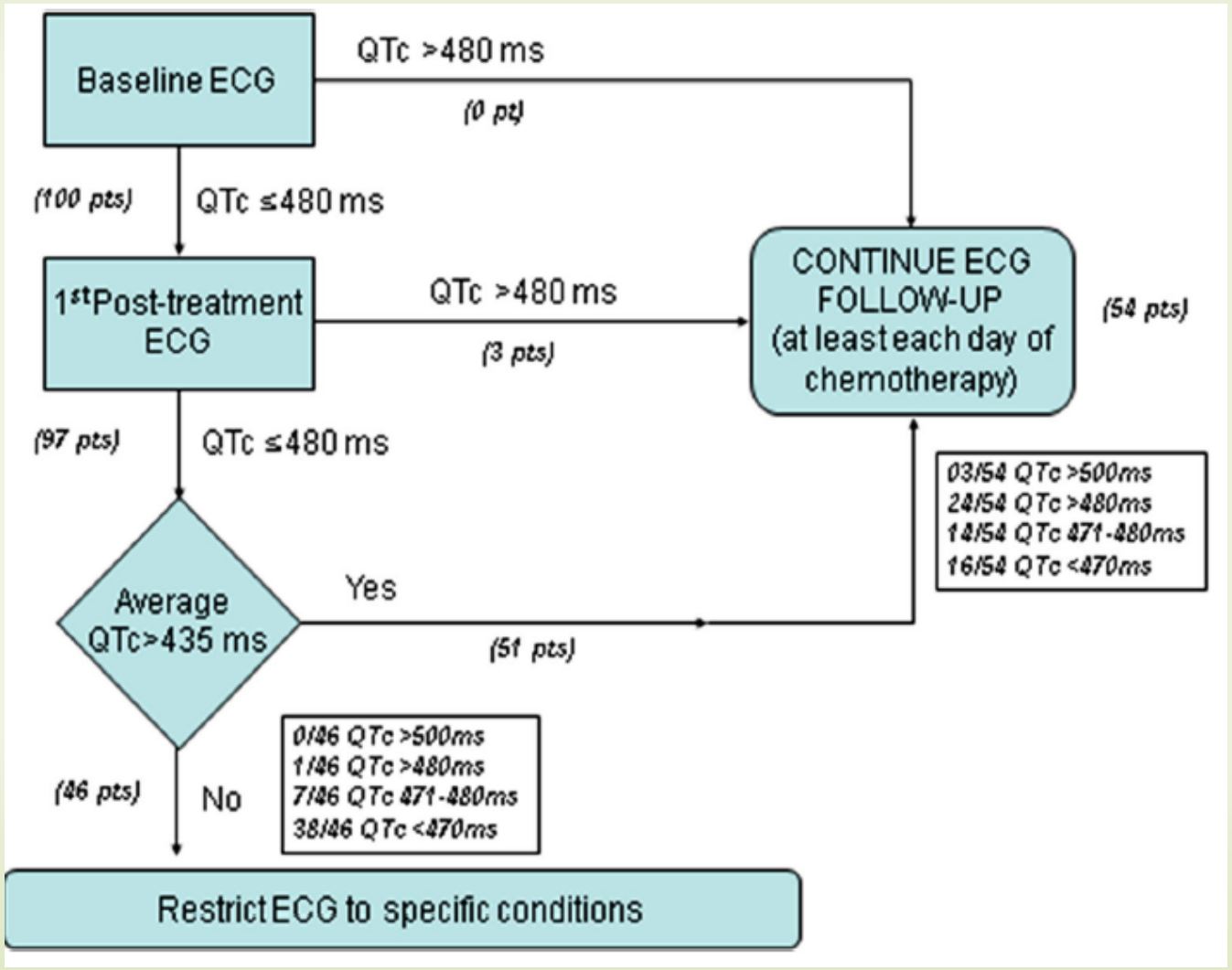
BC-QTc >435 ms identified:
100%with Max-QTc >500 ms,
96 % with Max-QTc 481–500 ms,
66 % with Max-QTc 471–480 ms.

Only 29 % of patients with Max-QTc ≤470 ms presented a BC-QTc >435 ms

Only parameter with the age able to predict QTc > 480 msec (OR 1.119 95 % CI 1.067–1.174) at multivariable analysis

Eur J Clin Pharmacol. 2015;71:1001-9

Repolarization effects of multiple-cycle chemotherapy and predictors of QTc prolongation: a prospective female cohort study on >2000 ECGs



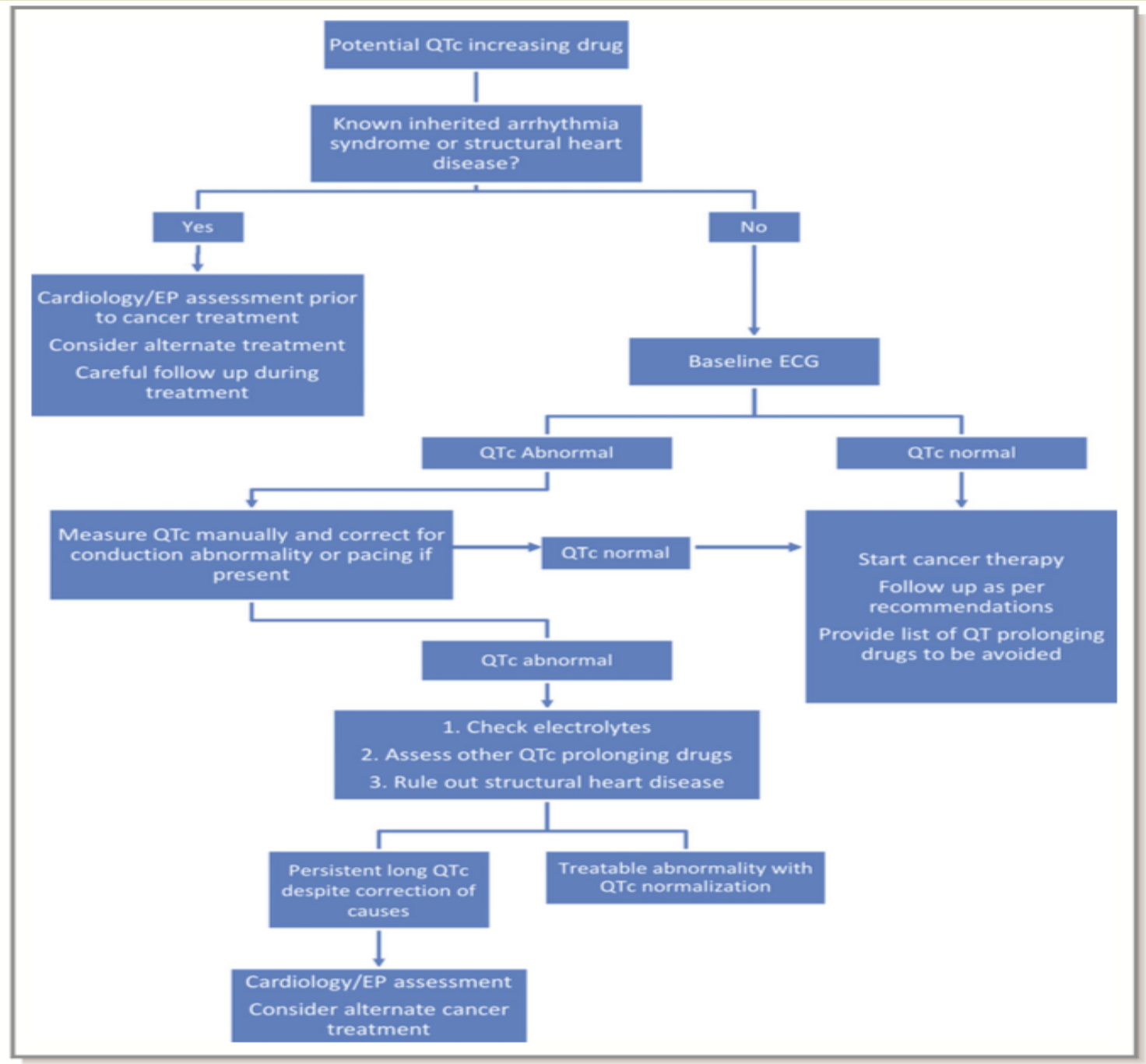
Eur J Clin Pharmacol. 2015;71:1001-9

Risk factors for TdP in acquired long QT

Table 2. Patient factors that increase the risk for torsades de pointes.

Types of risk factors	Examples
ECG abnormalities	■ QTc >500 ms or an increase of >60 ms from baseline[2,3] ■ bradycardia,[3] heart block,[3] incomplete heart block with pauses[2] ■ Concurrent drugs which affect the above[2]
Metabolic abnormalities[2]	■ Hypokalemia (e.g. vomiting, diarrhea), hypomagnesemia, hypocalcemia ■ Impaired hepatic and/or renal function ■ Concurrent drugs which affect the above (e.g. diuretics)
Others	■ Heart failure, myocardiac infarction[2] ■ Female gender[2] ■ Older age (greater than 60–65 years)[2,3,7,8]

J Oncol Pharm Practice 2018



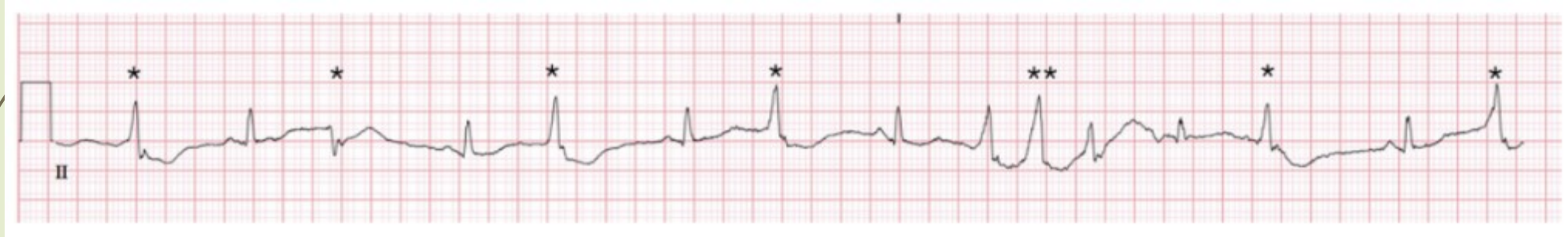
J Am Heart Assoc. 2017;6:e007724.

- A 12-lead ECG should be recorded and the QT interval, corrected for heart rate with Bazett's or Fridericia's formula, should be obtained in all patients at baseline.
- ECG and electrolyte monitoring during treatment should be considered 7–15 days after initiation or changes in dose, monthly during the first 3 months and then periodically during treatment depending on the chemotherapy drug and patient status. Patients receiving treatment with arsenic trioxide should be monitored weekly with ECG.
- Consider treatment discontinuation or alternative regimens if the QTc is >500 ms, QTc prolongation is >60 ms or arrhythmias are encountered.
- If no alternative therapy exists, treatment can be resumed at a reduced dose once the QTc normalizes and the frequency of ECG monitoring of the QT interval should be increased.
- Conditions known to provoke torsade de pointes, especially hypokalaemia and extreme bradycardia, should be avoided in patients with drug-induced QT prolongation.
- Exposure to other QT-prolonging drugs should be minimized in patients treated with potentially QT-prolonging chemotherapy.

European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

Treatment

- Recognize premonitory signs for TdP: prolonged QTc (>500 ms), severe aberration of the T-U segment, beat-to-beat instability (more marked aberration of the T wave after a long R-R interval), and/or frequent ventricular premature beats.



- The first-line treatment for TdP is magnesium sulfate, given intravenously with repeated doses if signs of electric instability persist. Next is the initiation of a b-adrenergic drug, such as isoproterenol, titrated to obtain an HR of >90 bpm. The role of antiarrhythmic therapies is less well established, but in case of refractory TdP, lidocaine infusion can be considered.
- Temporary ventricular or atrial pacing at 100 to 120 bpm should be considered if the patient is refractory to the previous measures. If the patient has a preexisting pacemaker or implantable cardioverter defibrillator system, changes in the lower rates can have the same protective effects.
- No recommendations on the role of cardiac implantable device insertion exist to date.

THM

- QT/QTc measurement should be accurate
- Prolongation of the QT interval has been assumed as a risk factor for TdP and SCD, however at present our knowledge about the relation between the QT interval and TdP is still incomplete.
- A high number of cancer drugs can prolong the QT interval, but not all of them are torsadogenic. In fact, although QTc prolongation in patient treated with these drugs is frequent, the clinical consequence, as defined by arrhythmias or SCD, remains rare.
- During treatment with cancer drugs known for prolonging QTc, an ECG should be recorded periodically (depending on the chemotherapy drug, dose and patient status).
- Risk factors known for prolonging QTc should be corrected before starting the treatment, and other QTc-prolonging drugs should be avoided.
- Discontinuation of the treatment or alternative regimens should be considered only if the QTc is >500 ms, QTc prolongation is >60 ms or significant arrhythmias are developed. If no alternatives, discuss in heart team and with the patient