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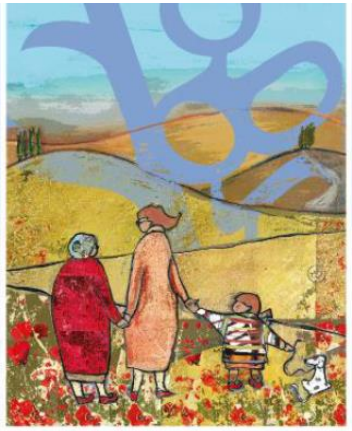

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DRUG-ASSOCIATED CORRECTED QT PROLONGATION IN ELDERLY HOSPITALIZED PATIENTS: RESULTS FROM A TWO YEARS SURVEY IN INTERNAL MEDICINE

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La sindrome del QT lungo (LQTS) predispone ad aritmie ventricolari maligne, in particolare alla torsione di punta (TdP). Un intervallo QT corretto per la frequenza cardiaca (QTc) >500 ms è associato in letteratura con un rischio da 2 a 3 volte maggiore di TdP.

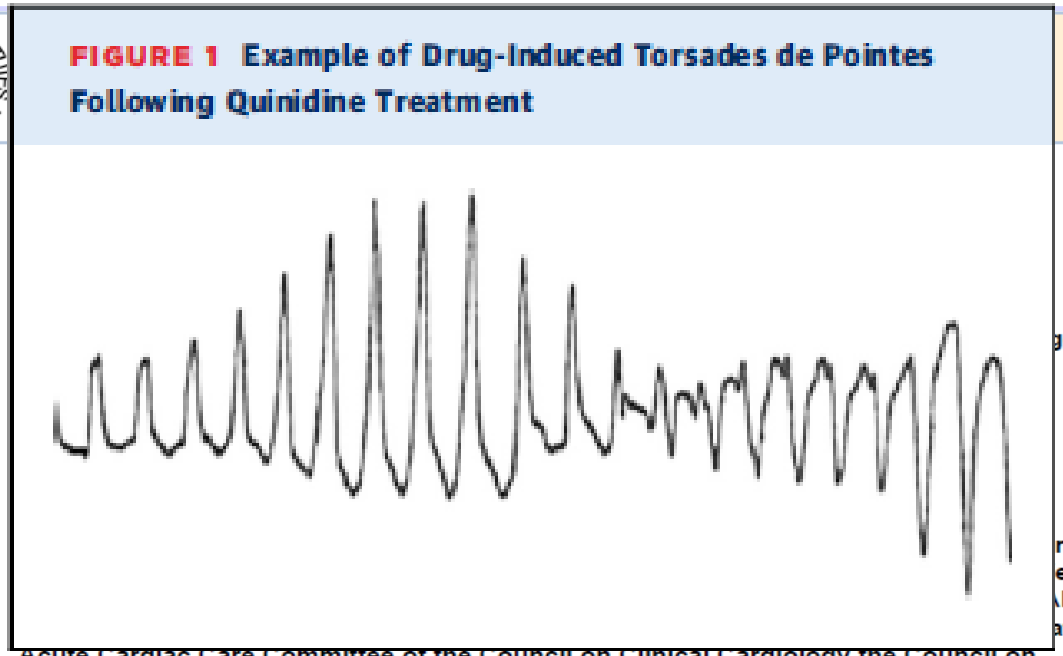

FIGURE 1 Example of Drug-Induced Torsades de Pointes Following Quinidine Treatment

Acute Cardiac Care Committee of the Council on Clinical Cardiology the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation

I pazienti geriatrici rappresentano un ampio gruppo di pazienti a particolare rischio di LQTS e TdP poiché sono largamente esposti ai farmaci che possono prolungare il QT e poiché spesso accumulano più fattori di rischio come ***bradicardia, ipokaliemia, ipocalcemia, ipomagnesemia, cardiopatie, flogosi.***

Therapeutic Advances in Drug Safety

Drug-induced QT interval prolongation: mechanisms and clinical management

Senthil Nachimuthu, Manish D. Assar and Jeffrey M. Schussler

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Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Aging with multimorbidity: A systematic review of the literature

Alessandra Marengoni[a,b,*], Sara Angleman[a], René Melis[a,c], Francesca Mangialasche[a,d], Anita Karp[a,e], Annika Garmen[a,e], Bettina Meinow[a,e], Laura Fratiglioni[a,e]

[a] Aging Research Center, NVS Department, Karolinska Institutet and Stockholm University, Sweden
[b] Geriatric Unit, Department of Medical and Surgery Sciences, University of Brescia, Italy
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[d] Institute of Gerontology and Geriatrics, Department of Clinical and Experimental Medicine, University of Perugia, Italy
[e] Stockholm Gerontology Research Center, Stockholm, Sweden

Drugs Aging
DOI 10.1007/s40266-017-0467-5

CrossMark

ORIGINAL RESEARCH ARTICLE

Prevalence and Risk Factors of Drug-Associated Corrected QT Prolongation in Elderly Hospitalized Patients: Results of a Retrospective Analysis of Data Obtained Over 6 Months

Ophélie Maison[1] · Blandine de la Gastine[2] · Laurent Dayot[2] · Sylvain Goutelle[1,3,4]

Un recente studio che utilizza i dati del REPOSI ha riportato una prevalenza d'uso di farmaci che possono prolungare il QT del 55,2% nei pazienti anziani all'ingresso in reparto. In ogni caso mancano gli studi italiani che indagano la prevalenza e i fattori determinanti della LQTS farmaco-correlata nei pazienti anziani ospedalizzati.

Drugs Aging (2016) 33:53–61
DOI 10.1007/s40266-015-0337-y

CrossMark

ORIGINAL RESEARCH ARTICLE

Prevalence and Risk Factors Associated with Use of QT-Prolonging Drugs in Hospitalized Older People

C. Franchi[1] · I. Ardoino[2] · R. Rossio[3] · A. Nobili[1] · E. M. Biganzoli[2] · A. Marengoni[4] · M. Marcucci[2,5] · L. Pasina[1] · M. Tettamanti[1] · S. Corrao[6] · P. M. Mannucci[7] · The REPOSI Investigators

Obiettivi

Arrhythmia riSk associated to iaTrogEnic QT pRolongation in hOspitalIzed elDerly patients (ASTEROID)

Agenzia Italiana del Farmaco AIFA

Rischio aritmico associato a sindrome del QT lungo iatrogeno in pazienti anziani ospedalizzati.

Obiettivo primario

- **Stima della prevalenza di LQTS in pazienti anziani ospedalizzati in trattamento con farmaci che possono prolungare l'intervallo QT.**

Obiettivi secondari

- **Stima della prevalenza d'uso di farmaci che possono prolungare l'intervallo QT in pazienti anziani.**
- **Identificazione di cofattori di rischio associati a LQTS iatrogeno in pazienti anziani ospedalizzati.**

Criteri di inclusione

- Età ≥ 65 aa
- In trattamento con almeno un farmaco all'ingresso in reparto
- Disponibili a fornire il proprio consenso libero e informato

Criteri di esclusione

- Alterazioni del ritmo e/o della conduzione intraventricolare che non rendessero possibile una corretta misurazione del QTc (fibrillazione atriale, bigeminismo, complesso QRS > 120 ms o onda T non identificabile)

Materiali e metodi

- Misurazione automatica dell'intervallo QTc

- Livelli sierici di potassio, calcio, magnesio e creatinina

- Informazioni sulle **caratteristiche** dei pazienti (età, sesso, BMI), sulla **terapia** assunta e sulle **variabili associate secondo letteratura ad un prolungamento dell'intervallo QTc**, in particolare ipotiroidismo, DM di tipo 2, ipertensione e cardiopatie (sindrome coronarica acuta, cardiomiopatia ipertrofica/scompenso cardiaco, cardiopatia ischemica cronica, ipertrofia del ventricolo sinistro).

Definizione di LQTS

- La **LQTS** è definita come un intervallo QTc ≥ 450 ms nei maschi e ≥ 470 ms nelle femmine secondo la correzione di Bazett

Curriculum in Cardiology

Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes

Akshay Gupta, MD, Andrew T. Lawrence, MD, Kousik Krishnan, MD, Clifford J. Kavinsky, MD, PhD, and Richard G. Trohman, MD *Chicago, IL*

Journal of the American College of Cardiology
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Cardiac Rhythm Disorders

Prolonged QTc Interval and Risk of Sudden Cardiac Death in a Population of Older Adults

Sabine M. J. M. Straus, MD, PhD,*†‡ Jan A. Kors, PhD,† Marie L. De Bruin, PhD,§ Cornelis S. van der Hooft, MD,†‖ Albert Hofman, MD, PhD,* Jan Heeringa, MD,* Jaap W. Deckers, MD, PhD,* J. Herre Kingma, MD, PhD,‖¶ Miriam C. J. M. Sturkenboom, PhD,*† Bruno H. Ch. Stricker, PhD,*‖ Jacqueline C. M. Witteman, PhD*

Rotterdam, the Hague, Utrecht, and Groningen, the Netherlands

Classificazione dei farmaci che possono prolungare il QT

- Farmaci con **rischio noto** di TdP
- Farmaci con **rischio possibile** di TdP
- Farmaci con **rischio condizionale** di TdP (possono causare TdP solo in certe condizioni)

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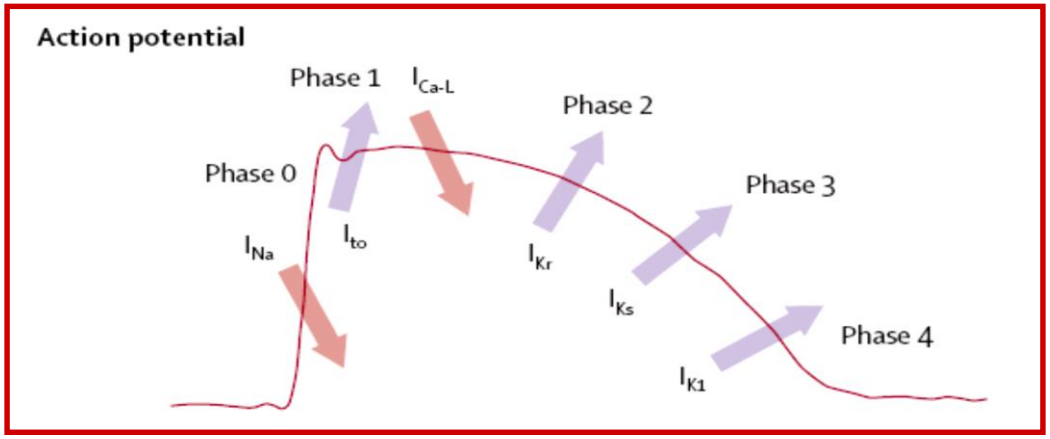
Risultati


Action potential
Phase 0
Phase 1
Phase 2
Phase 3
Phase 4
I_{Na}
I_{to}
I_{Ca-L}
I_{Kr}
I_{Ks}
I_{K1}

Caratteristiche demografiche, cliniche e laboratoristiche dei pazienti

Variable	*patients (n = 243)*
Age [a]	*79.65 (±8.27)*
Females [b]	*122 (50.2%)*
BMI [a]	*25.32 (±4.79)*
HR [a] *(bpm)*	*76.02 (±13.28)*
Uncorrected QT [a] *(ms)*	*406.92 (±49.09)*
QTc [a] *(ms)*	*453.70 (±43.77)*
LQTS [b,d]	*89 (36.6%)*
QTc > 500 [b] *(ms)*	*29 (11.9%)*
Total number of drugs [a]	*7.10 (±3.04)*
QT drugs users [b,c]	*218 (89.7%)*
Number of QT drugs [a]	*2.04 (±1.27)*
>1 QT drug users [b,c]	*156 (64.2%)*
>2 QT drugs users [b,c]	*82 (33.7%)*
>4 days QT drugs users [b,c]	*165 (67.9%)*
List 1 [b,c] *drugs users*	*74 (30.5%)*
List 2 [b,c] *drugs users*	*25 (10.3%)*
List 3 [b,c] *drugs users*	*206 (84.8%)*
Serum Potassium (mEq/L) [a†]	*4.11 (±0.58)*
Serum Calcium (mg/dL) [a†]	*8.30 (±0.81)*
Serum Magnesium (mg/dL) [a†]	*1.91 (±0.32)*
Creatinine (mg/dL) [a]	*1.21 (±0.84)*
Bradycardia [b] *(heart rate <60 bpm)*	*28 (11.5%)*
Hypokalemia [b†] *(<3.5 mEq/L)*	*23 (9.7%)*
Hypocalcemia [b†] *(<8.0 mg/dL)*	*63 (26.8%)*
Hypomagnesemia [b†] *(<1.5 mg/dL)*	*18 (7.9%)*
Hypercreatininemia [b] *(>1.2 mg/dL)*	*99 (40.7%)*
Hypertension [b]	*152 (63.0%)*
Hypothyroidism [b]	*18 (7.4%)*
Type 2 diabetes [b]	*60 (24.7%)*
Acute Coronary Syndrome [b]	*3 (1.2%)*
Dilated cardiomyopathy/heart failure [b]	*34 (14.0%)*
Chronic ischemic cardiopathy [b]	*43 (17.7%)*
Left ventricular hypertrophy [b]	*52 (21.4%)*

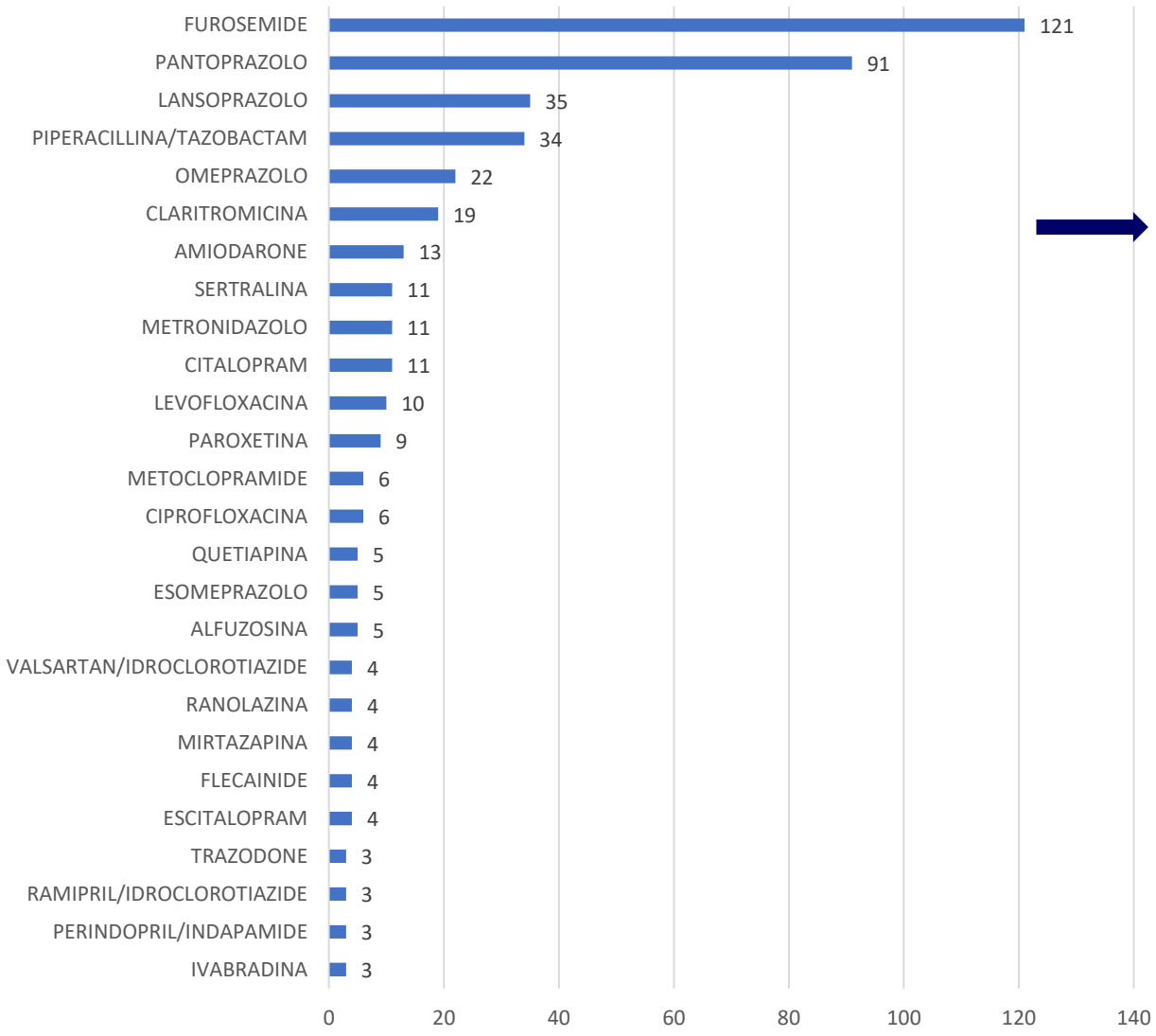
[a] mean (±SD); [b] n (%); [c] drugs on admission from https://www.crediblemeds.org; [d] defined as QTc interval QTc ≥ 450 ms in males e ≥ 470 ms in females using Bazett's correction formula; [†] potassium, calcium and magnesium meausurements available in 237, 235 and 229 patients, respectively.

Analisi delle variabili dicotomiche
Fattori di rischio farmacologici associati a LQTS

Variable	*OR*	*95%CI*	*P-value*
Univariate analysis			
QT drugs users	*2.51*	*0.91-6.93*	*0.069*
>1 QT drug users	*1.87*	*1.06-3.31*	*0.029*
>2 QT drugs users	*2.18*	*1.26-3.76*	*0.005*
>4 days QT drugs users	*2.29*	*1.25-4.18*	*0.006*
List 1 drugs users	*1.50*	*0.85-2.62*	*0.157*
List 2 drugs users	*2.02*	*0.88-4.65*	*0.092*
List 3 drugs users	*1.68*	*0.77-3.66*	*0.188*
Multivariate analysis			
>4 days QT drugs users	*2.35*	*1.11-4.95*	*0.025*

*We used the χ^2 test or the Fisher exact test (in case of n <5).

Prevalenza d'uso dei farmaci che possono prolungare l'intervallo QT



	%
Cardiovascolari	33,1
PPI	32,9
Antibiotici	18,0
Antidepressivi	11,8
Altri	4,2

Front Pharmacol. 2018; 9: 363.
Published online 2018 Apr 20. doi: [10.3389/fphar.2018.00363]
PMCID: PMC5922007
PMID: 29731714

Proton Pump Inhibitors and Serum Magnesium Levels in Patients With Torsades de Pointes

Pietro E. Lazzerini,[1,*] Iacopo Bertolozzi,[2] Francesco Finizola,[1] Maurizio Acampa,[3] Mariarita Natale,[1] Francesca Vanni,[1] Rosella Fulceri,[4] Alessandra Gamberucci,[4] Marco Rossi,[1,5] Beatrice Giabbani,[1] Michele Caselli,[1] Ilaria Lamberti,[1] Gabriele Cevenini,[6] Franco Laghi-Pasini,[1,†] and Pier L. Capecchi[1,†]

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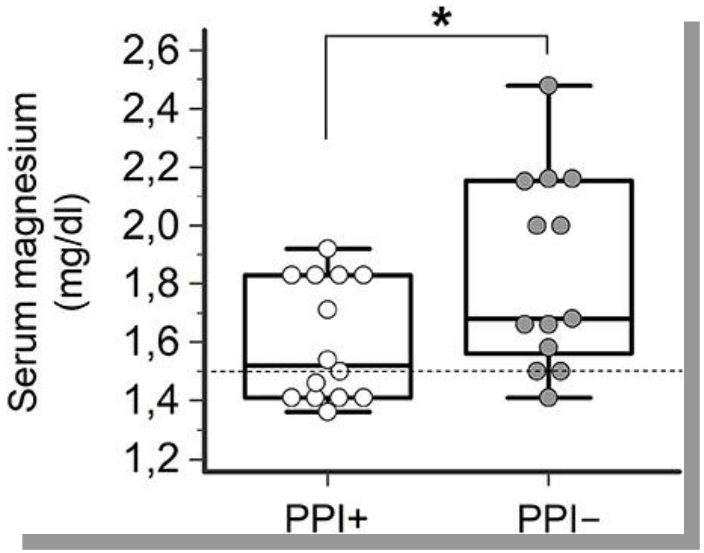

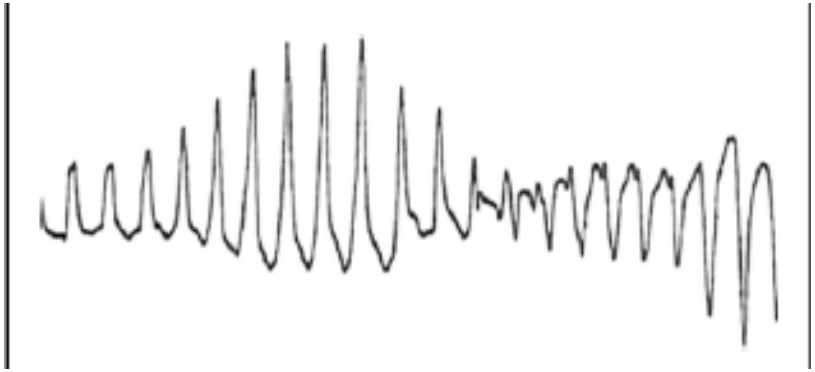

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Coupling Data Mining and Laboratory Experiments to Discover Drug Interactions Causing QT Prolongation

Tal Lorberbaum, MA,[a,b] Kevin J. Sampson, PhD,[c] Jeremy B. Chang, PhD,[b] Vivek Iyer, MD, MSE,[d] Raymond L. Woosley, MD, PhD,[e] Robert S. Kass, PhD,[c] Nicholas P. Tatonetti, PhD[b]

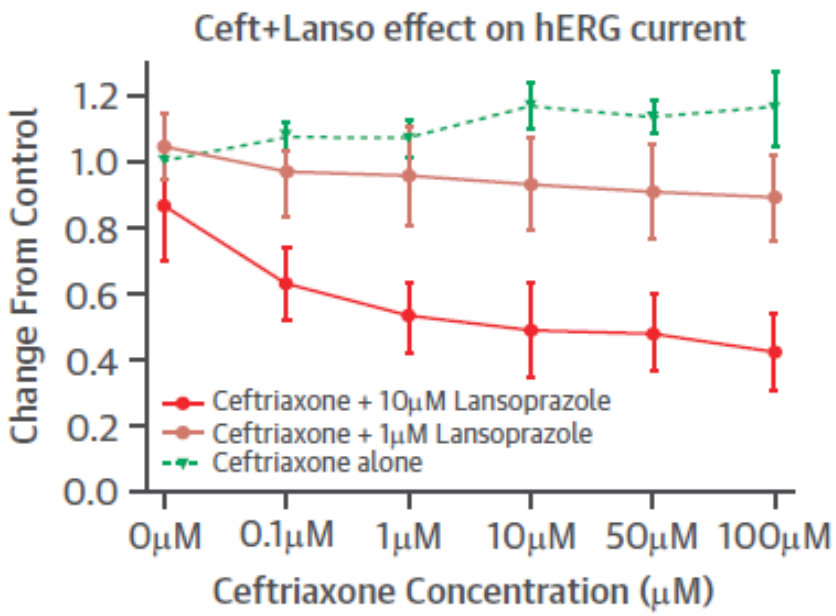
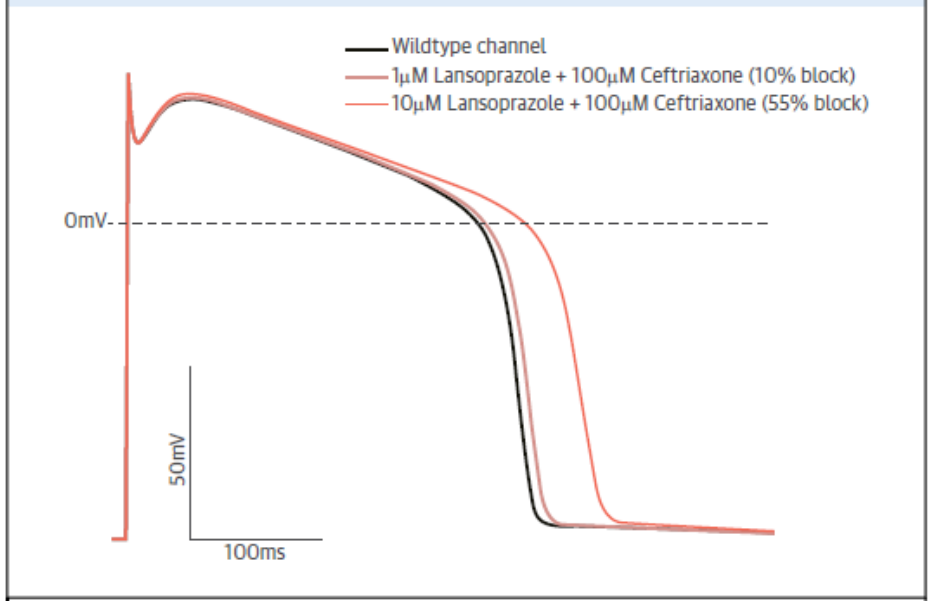


FIGURE 2 Results of the Computational Model of Ventricular Epicardial Myocytes

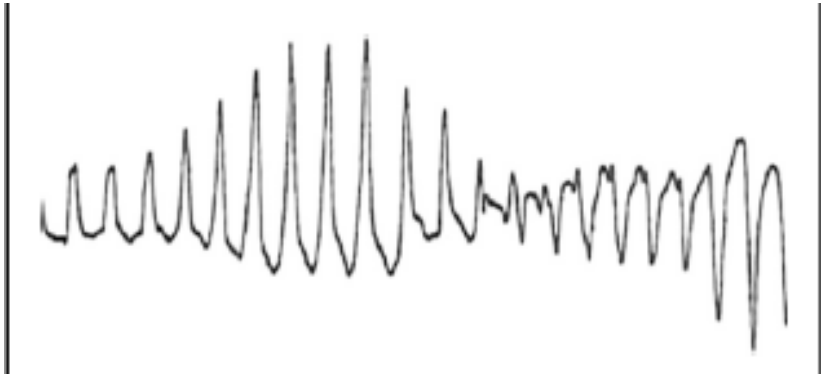


JACC VOL. 69, NO. 14, 2017
APRIL 11, 2017:1873–81

Combination Therapy With Ceftriaxone and Lansoprazole, Acquired Long QT Syndrome, and Torsades de Pointes Risk

*Pietro Enea Lazzerini, MD
Iacopo Bertolozzi, MD
Marco Rossi, PharmD
Pier Leopoldo Capecchi, MD
Franco Laghi-Pasini, MD

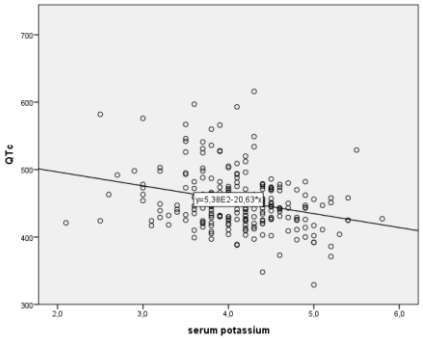
In a cohort of 40 patients presenting Tordade de Pointes, we found **that 5% patients were receiving CFX+LSZ** when TdP developed. Notably, this percentage was identical to that observed with levofloxacin, clarithromycin, or promazine (5% each) and was higher than that seen with ciprofloxacin, sotalol, or haloperidol (2%), which all represent well-recognized QT-prolonging medications. Only amiodarone (27%) and citalopram, fluconazole, or sertraline (7%) were more frequently administered.

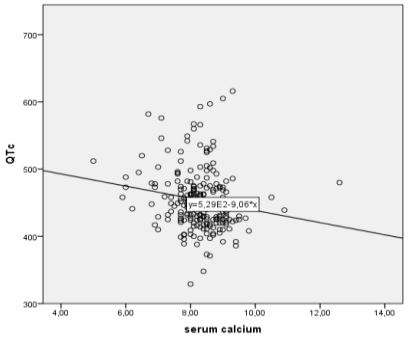


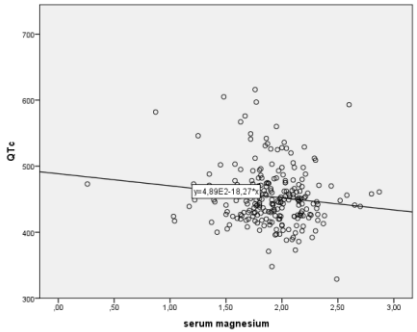
Ceftriaxone+Lansoprazolo	n = 8
di cui LQTS	n = 5
di cui QTc > 500 ms	n = 3

Analisi delle variabili continue

Variable	*Pearson r*	*P-value*
Age	*0.159*	*0.013*
BMI	*-0.091*	*0.172*
Serum Potassium (mEq/L)	*-0.280*	*<0.0001*
Serum Calcium (mg/dL)	*-0.166*	*0.011*
Serum Magnesium (mg/dL)	*-0.133*	*0.044*
Creatinine (mg/dL)	*0.066*	*0.304*
Total number of drugs	*0.119*	*0.064*
Number of QT drugs	*0.200*	*0.002*





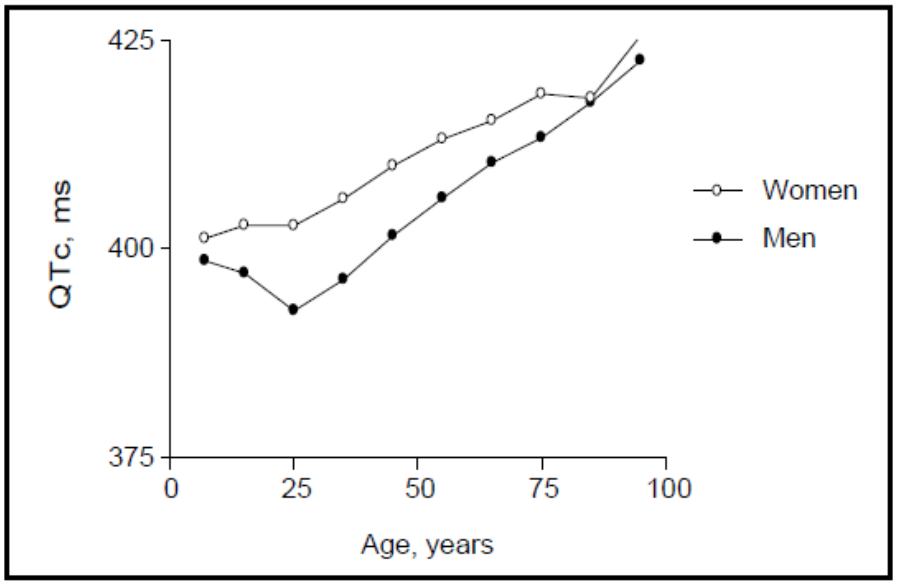


Analisi delle variabili dicotomiche
Fattori di rischio clinici associati a LQTS

Variable	*OR*	*95%CI*	*P-value**
Univariate analysis			
Male sex	*2.16*	*1.26-3.68*	*0.004*
Bradycardia	*0.96*	*0.42-2.17*	*0.915*
Hypokalemia	*1.40*	*0.59-3.34*	*0.450*
Hypocalcemia	*2.06*	*1.14-3.71*	*0.015*
Hypomagnesemia	*1.81*	*0.69-4.77*	*0.222*
Hypercreatininemia	*1.64*	*0.96-2.78*	*0.068*
Hypertension	*1.25*	*0.73-2.17*	*0.414*
Hypothyroidism	*3.84*	*1.39-10.64*	*0.006*
Type 2 diabetes	*1.21*	*0.66-2.20*	*0.532*
Acute Coronary Syndrome	*3.52*	*0.31-39.35*	*0.556*
Dilated cardiomyopathy/heart failure	*3.35*	*1.58-7.09*	*0.001*
Chronic ischemic cardiopathy	*1.65*	*0.85-3.21*	*0.138*
Left ventricular hypertrophy	*1.66*	*0.89-3.09*	*0.108*
Multivariate analysis			
Male sex	*2.83*	*1.55-5.19*	*0.001*
Hypocalcemia	*2.17*	*1.13-4.18*	*0.020*
Hypothyroidism	*3.74*	*1.25-11.22*	*0.019*
Dilated cardiomyopathy/heart failure	*3.65*	*1.58-8.46*	*0.003*

*We used the χ^2 test or the Fisher exact test (in case of n <5).

Figure 3 Corrected QT (QTc) for men and women using the mean values for figures 1 and 2



The means for each formulae were averaged and not weighted according to their sample size because the studies varied markedly in their sample size and the largest study would bias the overall result. Further, the graph is useful for illustrative purposes rather than a precise determination of values as the different formulae cannot be readily averaged.

La Revue canadienne de psychiatrie, vol 60, no 5, mai 2015

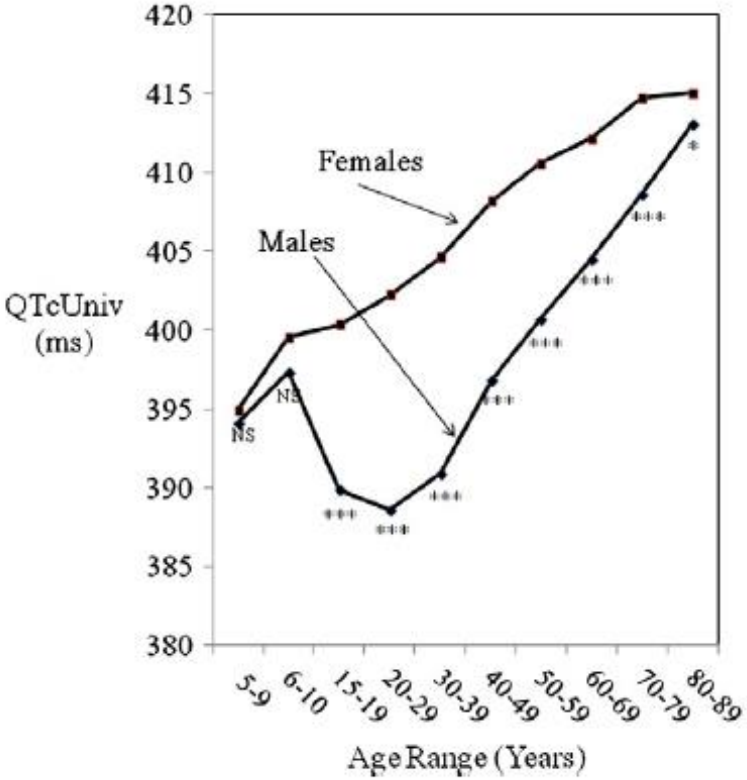


Fig. 3. Mean values with standard errors of rate-adjusted QT by the QTcMod formula in men and women by age. QTc decreases in adolescent boys with no decrease in adolescent girls, and there is a gradual nearly linear increase with age in both sex groups of adults.

P.M. Rautaharju et al. / International Journal of Cardiology 174 (2014) 535–540

OXFORD JOURNALS American Journal of Epidemiology

Am J Epidemiol. 2011 Aug 15; 174(4): 403–411.
Published online 2011 Jul 18. doi: [10.1093/aje/kwr172]

PMCID: PMC3202165
PMID: 21768401

Sex-Steroid Hormones and Electrocardiographic QT-Interval Duration: Findings From the Third National Health and Nutrition Examination Survey and the Multi-Ethnic Study of Atherosclerosis

Yiyi Zhang, Pamela Ouyang, Wendy S. Post, Darshan Dalal, Dhananjay Vaidya, Elena Blasco-Colmenares, Elsayed Z. Soliman, Gordon F. Tomaselli, and Eliseo Guallar*

Sex differences on the electrocardiographic pattern of cardiac repolarization: Possible role of testosterone

Héctor Bidoggia, MD,[a] Juan P. Maciel, MD,[a] Norberto Capalozza, MD,[a] Susana Mosca, MD,[b] Enrique J. Blaksley, BSc,[a] Esteban Valverde, EEng,[c] Guillermo Bertran, BSc,[c] Pedro Arini, EEng,[c] Marcelo O. Biagetti, BSc,[c] and Ricardo A. Quinteiro, MD,PhD[c] *Buenos Aires, Argentina*

Effects of Testosterone on Ventricular Repolarization in Hypogonadic Men

Beny Charbit, MD[a,b,d,*], Sophie Christin-Maître, MD, PhD[c,e], Jean-Louis Démolis, MD, PhD[a,b], Elsa Soustre, PharmD[a,b], Jacques Young, MD, PhD[f], and Christian Funck-Brentano, MD, PhD[a,b,d]

Conclusioni 1

- **La prevalenza di LQTS è alta (36,6%) nei pazienti anziani ospedalizzati e i farmaci che possono prolungare il QT sono ampiamente prescritti in questi pazienti all'ingresso in reparto (89,7%).**

- **In questi pazienti le diselettrolitemie, in particolare la ipopotassiema, la ipocalcemia e la ipomagnesemia, contribuiscono all'allungamento del QT.**

Conclusioni 2

- **In età geriatrica si annulla la differenza tra maschi e femmine nell'intervallo QT.**

- **Il nostro studio evidenzia quindi la necessità di una maggiore educazione sull'appropriatezza prescrittiva dei farmaci che possono prolungare il QT, soprattutto per i pazienti anziani che sono a maggior rischio cumulativo di aritmie potenzialmente fatali, tenendo altresì in considerazione le altre possibili cause di sindrome del QT lungo acquisito.**

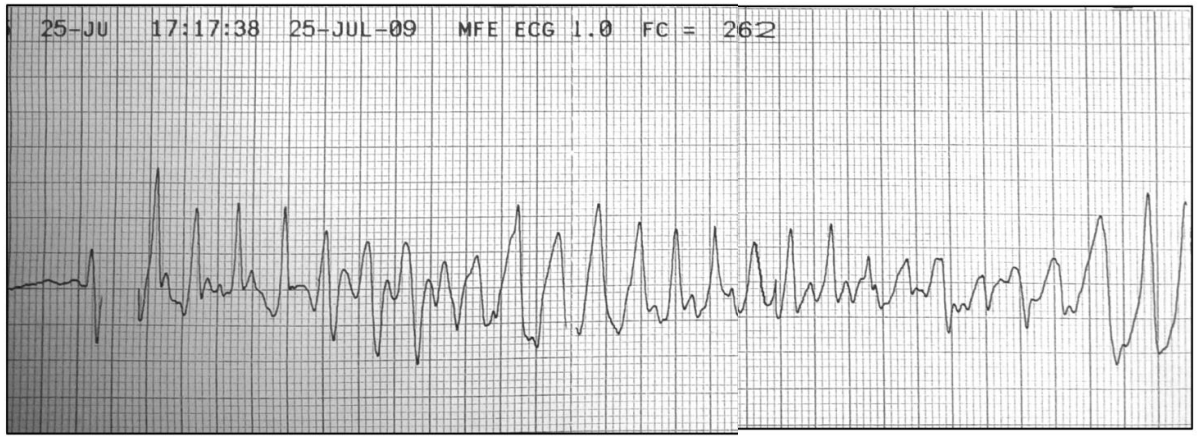
TABLE 1 | Demographic, clinical and laboratory characteristics of patients with Torsades de pointes.

Patients, n	48
Age, median years (interquartile range)	81(73–85)
Females, n	31/48(65%)
Mean QTc, ms(range)	596.0 ± 80.7(490–910)
Electrolyte imbalances, n	37/47(79%)
Hypokalemia	28/45(62%)
Hypocalcemia	22/37(59%)
Hypomagnesemia	7/27(26%)
Concomitant diseases*, n	45/48(94%)
Cardiac diseases	40/48(83%)
Left ventricular hypertrophy	19/48(40%)
Dilated cardiomyopathy/heart failure	13/48(27%)
II-III degree atrioventricular block	10/48(21%)
Acute coronary syndrome	9/48(19%)
Chronic coronary artery disease	7/48(15%)
Sinus bradycardia	6/48(13%)
Extra-cardiac diseases	20/48(42%)
Diabetes mellitus type II	13/48(27%)
Chronic kidney disease	8/48(17%)
Hypothyroidism	2/48(4%)
Subarachnoid hemorrhage	1/48(2%)
Cirrhosis	1/48(2%)
Anorexia nervosa	1/48(2%)
HIV infection	1/48(2%)
QTc prolonging-medications, n	34/48(71%)
Amiodarone	14/48(29%)
Citalopram	5/48(10%)
Sertraline	4/48(8%)
Fluconazole	3/48(6%)
Trazodone	3/48(6%)
Levofloxacin	2/48(4%)
Clarithromycin	2/48(4%)
Promazine	2/48(4%)
Quetiapine	2/48(4%)
Mean medication number per patient	1.1 ± 1.0
Anti-Ro/SSA positivity, n	18/32(56%)
Systemic inflammation, n†	38/48(79%)
C-reactive protein, mg/dl(range)	2.66(0.1–29.65)
Definite inflammatory diseases	22/48(46%)
Acute infections	15/48(31%)
Immuno-mediated diseases	5/48(10%)
Others	2/48(4%)
Mean QTc-prolonging risk factor number per patient§	5.3 ± 1.5

ORIGINAL RESEARCH ARTICLE

Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes

Pietro Enea Lazzerini,[1] Franco Laghi-Pasini,[1] Iacopo Bertolozzi,[2] Gabriella Morozzi,[1] Sauro Lorenzini,[1] Antonella Simpatico,[1] Enrico Selvi,[1] Maria Romana Bacarelli,[1] Francesco Finizola,[1] Francesca Vanni,[1] Deana Lazaro,[3] Ademuyiwa Aromolaran,[3] Nabil El Sherif,[3] Mohamed Boutjdir,[3,4] Pier Leopoldo Capecchi[1]



BMJ

Lazzerini PE, *et al*. *Heart* 2017;**103**:1821–1829. doi:10.1136/heartjnl-2016-311079

British Cardiovascular Society

Grazie per l'attenzione!

ORIGINAL ARTICLES

IMAJ • VOL 14 • APRIL 2012

QT Interval Disturbances in Elderly Residents of Long-Term Care Facilities

Emily Lubart MD, Refael Segal MD, Stella Megid MD, Alexandra Yarovoy MD and Arthur Leibovitz MD

Shmuel Harofe Geriatric Medical Center, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Prolongation of QTc was detected in 48 patients (28%) based on the mean of 12 ECG leads, and in 45 patients (25%) based on lead L2 [Table 3]. Only a small proportion of these patients (n=7, 15%) had QTc above 500 msec.

Drugs Aging (2016) 33:53–61
DOI 10.1007/s40266-015-0337-y

CrossMark

ORIGINAL RESEARCH ARTICLE

Prevalence and Risk Factors Associated with Use of QT-Prolonging Drugs in Hospitalized Older People

C. Franchi[1] · I. Ardoino[2] · R. Rossio[3] · A. Nobili[1] · E. M. Biganzoli[2] · A. Marengoni[4] · M. Marcucci[2,5] · L. Pasina[1] · M. Tettamanti[1] · S. Corrao[6] · P. M. Mannucci[7] · The REPOSI Investigators

(55.2 %) were prescribed at least one QT-prolonging drug

Furosemide[a]	1364	47.2
Pantoprazole[a]	340	11.8
Amiodarone[b]	216	7.5

Published in final edited form as:
Circ Cardiovasc Qual Outcomes. 2013 July ; 6(4): 479–487. doi:10.1161/CIRCOUTCOMES.113.000152.

Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients

James E. Tisdale, PharmD[*,†], **Heather A. Jaynes, MSN**[*], **Joanna R. Kingery, PharmD**[‡], **Noha A. Mourad, MS**[*], **Tate N. Trujillo, PharmD**[‡], **Brian R. Overholser, PharmD**[*,†], and **Richard J. Kovacs, MD**[*,§]

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PACING AND CLINICAL ELECTROPHYSIOLOGY
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Full Access

Electrocardiographic and Clinical Predictors of Torsades de Pointes Induced by Almokalant Infusion in Patients with Chronic Atrial Fibrillation or Flutter: A Prospective Study

BIRGITTA HOULTZ, BÖRJE DARPÖ, NILS EDVARDSSON, PER BLOMSTRÖM, JOHANNES BRACHMANN, HARRY J.G.M. CRIJNS, STEEN M. JENSEN, ELISABETH SVERNHAGE, HANS VALLIN, KARL SWEDBERG

First published: 30 June 2006 | https://asbproxy.unisi.it:2731/10.1111/j.1540-8159.1998.tb00150.x
| Cited by: 60

ELSEVIER

New age- and
correction forr

Pentti M. Rautahar

[a] Division of Public Health Scien
[b] Cardiology Division, Universit
[c] Cardiology Division, Universit

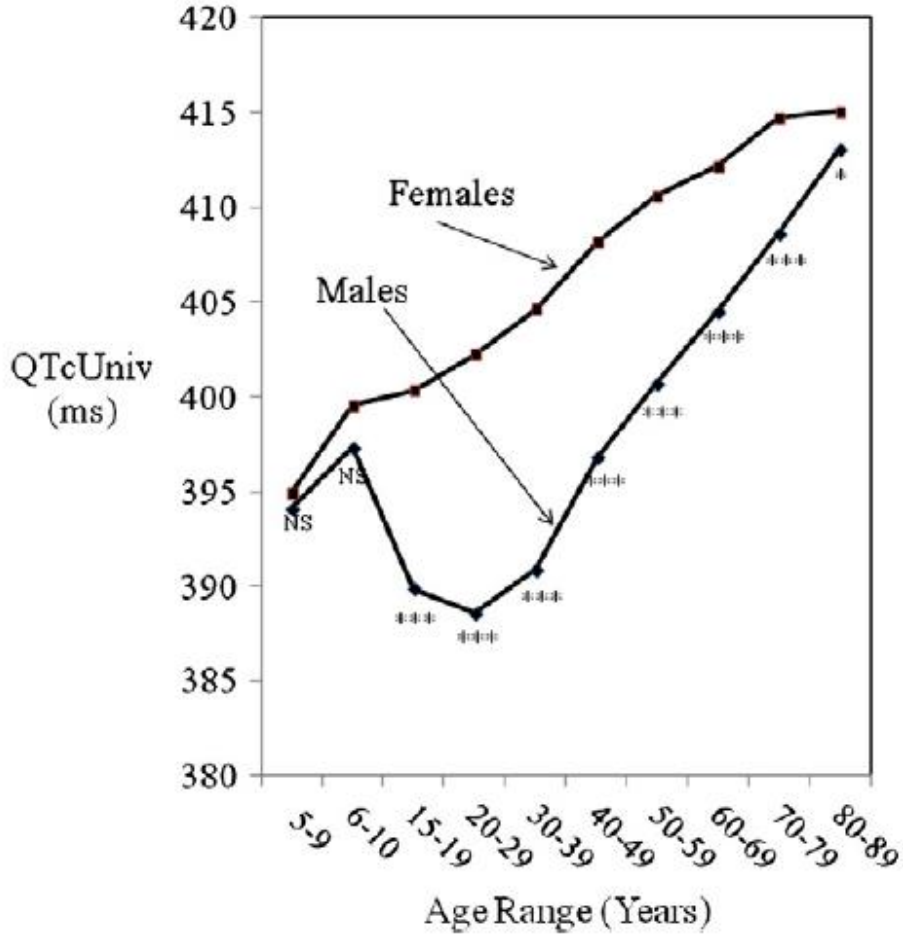

Fig. 3. Mean values with standard errors of rate-adjusted QT by the QTcMod formula in men and women by age. QTc decreases in adolescent boys with no decrease in adolescent girls, and there is a gradual nearly linear increase with age in both sex groups of adults.

CARDIOLOGY

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Grazie per l'attenzione!

Variable	*patients (n = 243)*
Age [a]	*79.65 (±8.27)*
Females [b]	*122 (50.2%)*
BMI [a]	*25.32 (±4.79)*
HR [a] *(bpm)*	*76.02 (±13.28)*
Uncorrected QT [a] *(ms)*	*406.92 (±49.09)*
QTc [a] *(ms)*	*453.70 (±43.77)*
LQTS [b,d]	*89 (36.6%)*
QTc > 500 [b] *(ms)*	*29 (11.9%)*
Total number of drugs [a]	*7.10 (±3.04)*
QT drugs users [b,c]	*218 (89.7%)*
Number of QT drugs [a]	*2.04 (±1.27)*
>1 QT drug users [b,c]	*156 (64.2%)*
>2 QT drugs users [b,c]	*82 (33.7%)*
>4 days QT drugs users [b,c]	*165 (67.9%)*
List 1 [b,c] *drugs users*	*74 (30.5%)*
List 2 [b,c] *drugs users*	*25 (10.3%)*
List 3 [b,c] *drugs users*	*206 (84.8%)*
Serum Potassium (mEq/L) [a†]	*4.11 (±0.58)*
Serum Calcium (mg/dL) [a†]	*8.30 (±0.81)*
Serum Magnesium (mg/dL) [a†]	*1.91 (±0.32)*
Creatinine (mg/dL) [a]	*1.21 (±0.84)*
Bradycardia [b] *(heart rate <60 bpm)*	*28 (11.5%)*
Hypokalemia [b†] *(<3.5 mEq/L)*	*23 (9.7%)*
Hypocalcemia [b†] *(<8.0 mg/dL)*	*63 (26.8%)*
Hypomagnesemia [b†] *(<1.5 mg/dL)*	*18 (7.9%)*
Hypercreatininemia [b] *(>1.2 mg/dL)*	*99 (40.7%)*
Hypertension [b]	*152 (63.0%)*
Hypothyroidism [b]	*18 (7.4%)*
Type 2 diabetes [b]	*60 (24.7%)*
Acute Coronary Syndrome [b]	*3 (1.2%)*
Dilated cardiomyopathy/heart failure [b]	*34 (14.0%)*
Chronic ischemic cardiopathy [b]	*43 (17.7%)*
Left ventricular hypertrophy [b]	*52 (21.4%)*

Variabile	pazienti n (201)
Età [a]	80,05 (±8,35)
Maschi [b]	101 (50,2%)
BMI [a]	25,32 (±4,96)
FC [a] (bpm)	76,18(±13,63)
QT non corretto [a] (ms)	406,45 (±46,95)
LQTS [b,d]	78 (38,8%)
QTc [a] (ms)	452,64 (±39,62)
QTc > 500 [b] (ms)	24 (11,9%)
Numero totale di farmaci [a]	7,04 (±2,98)
Pz in terapia con farmaci che possono prolungare il QT [b,c]	175 (87,1%)
N. di farmaci che possono prolungare il QT [a]	1,90 (±1,25)
Pz in terapia con >1 farmaco che può prolungare il QT [b,c]	119 (59,2%)
Pz in terapia con farmaci che possono prolungare il QT per più di 4 giorni [b,c]	129 (64,2%)
Pz in terapia con farmaci della Lista 1 [b,c]	60 (29,9%)
Pz in terapia con farmaci della Lista 2 [b,c]	20 (10,0%)
Pz in terapia con farmaci della Lista 3 [b,c]	162 (80,6%)
Potassiemia (mEq/L) [a]	4,11 (±0,58)
Calcemia (mg/dL) [a]	8,29 (±0,80)
Magnesemia (mEq/L) [a]	1,90 (±0,31)
Creatinina (mg/dL) [a]	1,21 (±0,82)
Bradicardia [b] (fc <60 bpm)	24 (11,9%)
Ipokaliemia [b] (<3,5 mEq/L)	19 (9,5%)
Ipocalcemia [b] (<8,0 mg/dL)	52 (25,9%)
Ipomagnesemia [b](<1,5 mEq/L)	14 (7,3%)
Ipercreatininemia [b] (>1,2 mg/dL)	81 (40,3%)
Ipertensione [b]	122 (60,7%)
Ipotiroidismo [b]	17 (8,5%)
Diabete mellito di tipo 2 [b]	49 (24,4%)
Sindrome Coronarica Acuta [b]	3 (1,5%)
Cardiomiopatia dilatativa/Scompenso cardiaco [b]	28 (13,9%)
Cardiomiopatia ischemica [b]	36 (17,9%)
Ipertrofia del ventricolo sinistro [b]	48 (23,9%)

Tab.1 Caratteristiche demografiche, cliniche e laboratoristiche dei pazienti

a media (±SD); b n (%); c farmaci all'ingresso in reparto da https://www.crediblemeds.org; d definito come intervallo Qtc, QTc ≥ 450 ms nei machi e ≥ 470 ms nelle femmine secondo la formula di Bazett.

Variabile	Pazienti con LQTS[d] n (78)	Pazienti senza LQTS [d] n (123)	P-value [e]
Età [a]	82,01 (±8,69)	78,81 (±7,91)	0.008
Maschi [b]	49 (62,8%)	52 (29,8%)	0.005
BMI [a]	24,33 (±3,39)	25,93 (±5,65)	0.176
Numero totale di farmaci [a]	7,69 (±2,96)	6,63 (±2,94)	0.017
Pz in terapia con farmaci che possono prolungare il QT [b,c]	74 (94,9%)	101 (82,1%)	0.009
N. di farmaci che possono prolungare il QT [a]	2,23 (±1,18)	1,69 (±1.25)	0.002
Pz in terapia con >1 farmaco che può prolungare il QT [b,c]	55 (70,5%)	64 (52,0%)	0.009
Pz in terapia con farmaci che possono prolungare il QT per più di 4 giorni [b,c]	63 (80,8%)	66 (53,7%)	<0.0001
Pz in terapia con farmaci della Lista 1 [b,c]	28 (35,9%)	32 (26,0%)	0.136
Pz in terapia con farmaci della List 2 [b,c]	12 (15,4%)	8 (6,5%)	0.040
Pz in terapia con farmaci della List 3 [b,c]	69 (88,5%)	93 (75,6%)	0.025
Potassiemia (mEq/L) [a]	3,97 (±0,55)	4,21 (±0,58)	0.004
Calcemia (mg/dL) [a]	8,11 (±0,99)	8,41 (±0,63)	0.006
Magnesemia (mEq/L) [a]	1,91 (±0,38)	1,90 (±0,26)	0.864
Creatinina (mg/dL) [a]	1,41 (±0,96)	1,09 (±0,69)	0.011
Bradicardia [b](fc <60 bpm)	7 (9,0%)	17 (13,8%)	0.302
Ipokalemia [b] (<3,5 mEq/L)	8 (10,3%)	11 (8,9%)	0.726
Ipocalcemia [b] (<8,0 mg/dL)	28 (35,9%)	24 (19,5%)	0.008
Ipomagnesemia [b](<1,5 mEq/L)	7 (9,0%)	7 (5,7%)	0.360
Ipercreatininemia [b] (>1,2 mg/dL)	37 (47,4%)	44 (35,8%)	0.100
Ipertensione [b]	50 (64,1%)	72 (58,5%)	0.431
Ipotiroidismo [b]	11(14,1%)	6 (4,9%)	0.022
Diabete mellito di tipo 2 [b]	19 (24,4%)	30 (24,4%)	0.996
Sindrome Coronarica Acuta [b]	2 (2,6%)	1 (0,8%)	0.561
Cardiomiopatia dilatativa/Scompenso cardiaco [b]	17 (21,8%)	11 (8,9%)	0.010
Cardiomiopatia ischemica [b]	18 (23,1%)	18 (14,6%)	0.128
Ipertrofia del ventricolo sinistro [b]	22 (28,2%)	28 (21,1%)	0.252

a media (±SD); b n (%); c farmaci all'ingresso in reparto da https://www.crediblemeds.org; d definito come intervallo Qtc, QTc ≥ 450 ms nei machi e ≥ 470 ms nelle femmine secondo la formula di Bazett.; e il t-test o il test di Mann–Whitney (in caso di distribuzione non-normale) sono stati usati per le variabili continue, mentre il test del $\chi 2$ o il test esatto di Fisher (in caso di n <5) sono stati usati per le variabili categoriche.

Tab.2 Confronto tra le caratteristiche dei pazienti con e senza LQTS all'ingresso in reparto.

Analisi statistica delle variabili dicotomiche

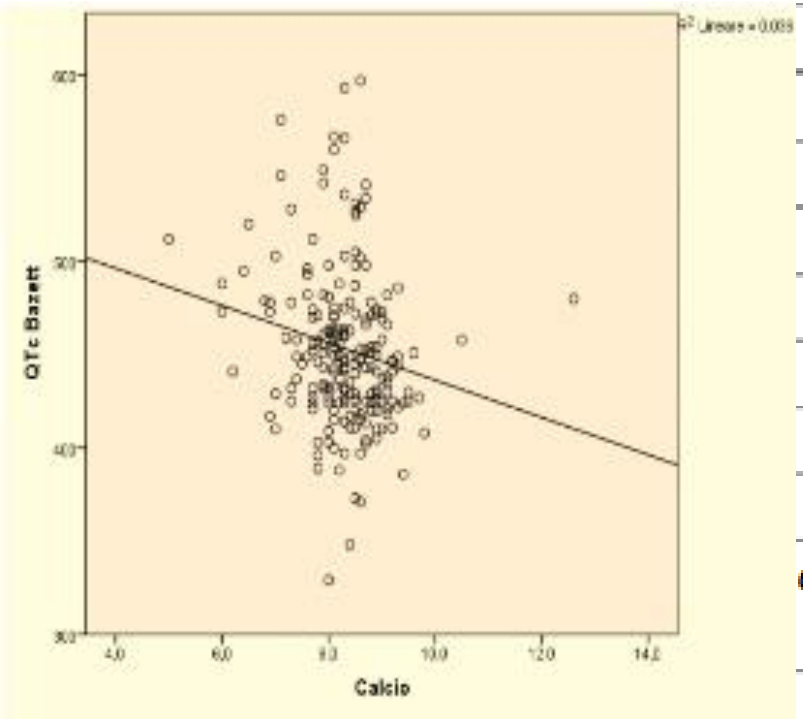
Variabile	OR	95%CI	P-value
Analisi univariata			
Pz in terapia con farmaci che possono prolungare il QT	4,03	1,33-12,19	0.009
Pz in terapia con >1 farmaco che può prolungare il QT	2,20	1,21-4,02	0.009
Pz in terapia con farmaci che possono prolungare il QT da più di 4 giorni	3,63	1,86-7,06	<0.0001
Pz in terapia con farmaci della Lista 1	1,59	0,86-2,94	0.136
Pz in terapia con farmaci della Lista 2	2,61	1,02-6,72	0.040
Pz in terapia con farmaci della Lista 3	2,47	1,10-5,54	0.025
Analisi multivariata			
Pz in terapia con farmaci che possono prolungare il QT da più di 4 giorni	3,43	1,36-8,63	0.009

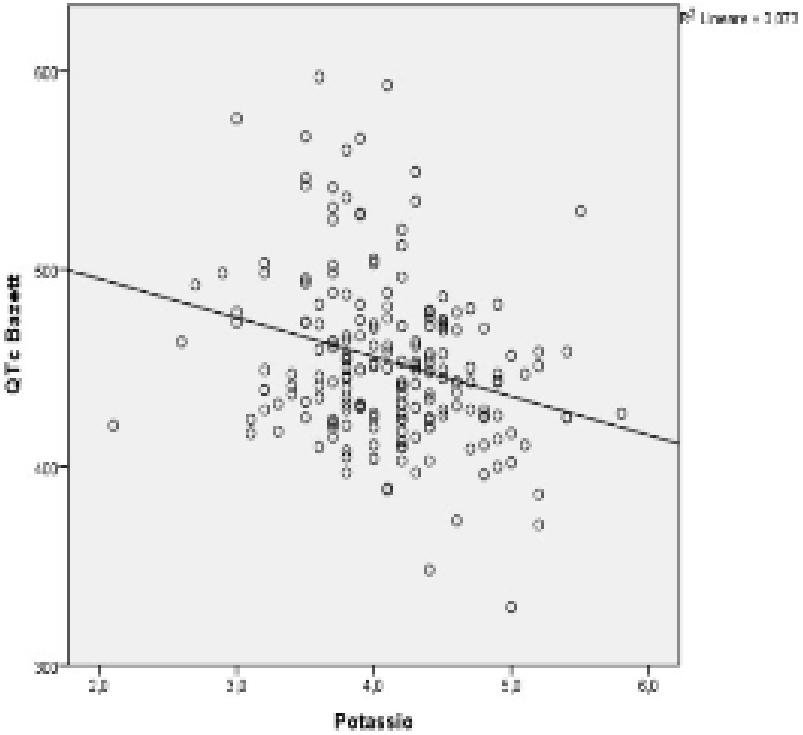
Tab. 3 Analisi dei fattori di rischio farmacologici associati al prolungamento dell'intervallo QTc

Variabile	OR	95%CI	P-value
Analisi univariata			
Sesso maschile	2,31	1,23-4,13	0.005
Bradicardia	0,61	0,24-1,56	0.302
Ipokalemia	1,19	0,45-3,10	0.726
Ipocalcemia	2,36	1,24-4,50	0.008
Ipomagnesemia	1,66	0,56-4,93	0.360
Ipercreatininemia	1,62	0,91-1,57	0.100
Ipertensione	1,26	0,70-2,27	0.431
Ipotiroidismo	3,20	1,13-9,05	0.022
Diabete mellito di tipo 2	1,00	0,52-1,93	0.996
Sindrome coronarica acuta	3,21	0,29 -36,01	0.561
Cardiomiopatia dilatativa/Scompenso cardiaco	2,84	1,25-6,44	0.010
Cardiopatia ischemica	1,75	0,85-3,62	0.128
Ipertrofia del ventricolo sinistro	1,46	0,76-2,82	0.252
Analisi multivariata			
Sesso maschile	2,84	1,46-5,56	0.002
Ipocalcemia	2,66	1,25-5,66	0.011
Cardiomiopatia dilatativa/Scompenso cardiaco	3,08	1,20-7,88	0.019

Tab. 4 Analisi dei fattori di rischio clinici associati al prolungamento dell'intervallo QTc

Analisi statistica delle variabili continue





Tab 5 Analisi statistica delle variabili continue

Farmaci che possono prolungare il QT (>2 prescrizioni)	Numero di prescrizioni (%)	Categoria di rischio per TdP [a]
Antibiotici		
Claritromicina	17 (4,5%)	Noto
Piperacillina/Tazobactam	20 (5,2%)	Condizionale
Metronidazolo	10 (2,6%)	Condizionale
Levofloxacina	9 (2,4%)	Noto
Ciprofloxacina	5 (1,3%)	Noto
Psichiatrici		
Citalopram	11 (2,9%)	Noto
Sertralina	8 (2,1%)	Condizionale
Paroxetina	7 (1,8%)	Condizionale
Quetiapina	5 (1,3%)	Condizionale
Venlafaxina	5 (1,3%)	Possibile
Escitalopram	4 (1,0%)	Noto
Mirtazapina	4 (1,0%)	Possibile
Trazodone	3 (0,8%)	Condizionale
Cardiovascolari		
Furosemide	99 (25,9%)	Condizionale
Amiodarone	6 (1,6%)	Noto
Ivabradina	3 (0,8%)	Condizionale
Ranolazina	3 (0,8%)	Possibile
Altri		
Pantoprazolo	71 (18,6%)	Condizionale
Lansoprazolo	30 (7,9%)	Condizionale
Omeprazolo	21 (5,5%)	Condizionale
Metoclopramide	6 (1,6%)	Condizionale
Alfuzosina	3 (0,8%)	Possibile

Tab 5 Farmaci prescritti che possono prolungare il QT, classificati per uso terapeutico e rischio di TdP.

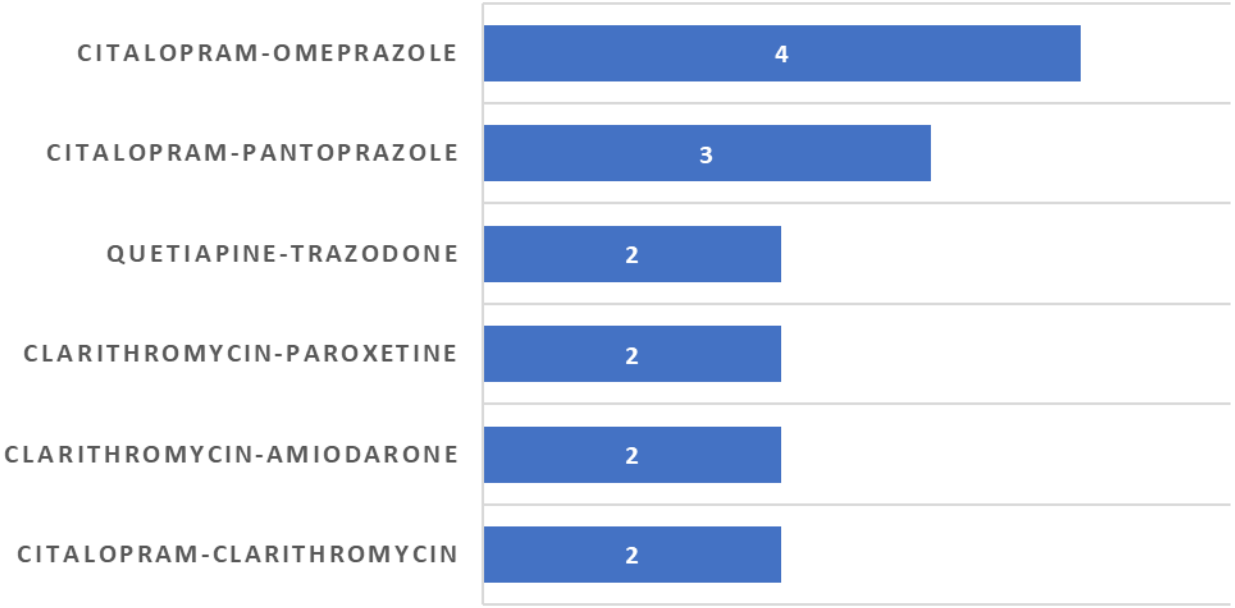
a classificazione da http**://www.Crediblemeds.org/**

Prevalenza d'uso dei farmaci che possono prolungare l'intervallo QT

QT-prolonging drugs (> 2 prescriptions)	*Number of prescriptions (n= 498)*	*QT risk category [a]*
Antimicrobials		
piperacillin/tazobactam	*34 (6.8%)*	*conditional*
clarithromycin	*19 (3.8%)*	*known*
metronidazole	*11 (2.2%)*	*conditional*
levofloxacin	*10 (2.0%)*	*known*
ciprofloxacin	*6 (1.2%)*	*known*
Antidepressants		
citalopram	*11 (2.2%)*	*known*
sertraline	*11 (2.2%)*	*conditional*
paroxetine	*9 (1.8%)*	*conditional*
venlafaxine	*7 (1.4%)*	*possible*
escitalopram	*4 (0.8%)*	*known*
mirtazapine	*4 (0.8%)*	*possible*
trazodone	*3 (0.6%)*	*conditional*
Cardiovascular		
furosemide	*121 (24.3%)*	*conditional*
amiodarone	*13 (2.6%)*	*known*
flecainide	*4 (0.8%)*	*known*
ranolazine	*4 (0.8%)*	*Possible*
valsartan/hydrochlorothiazide	*4 (0.8%)*	*conditional*
ivabradine	*3 (0.6%)*	*conditional*
ramipril/hydrochlorothiazide	*3 (0.6%)*	*conditional*
perindopril/indapamide	*3 (0.6%)*	*conditional*
Proton pump inhibitors		
pantoprazole	*91 (18.3%)*	*conditional*
lansoprazole	*35 (7.0%)*	*conditional*
omeprazole	*22 (4.4%)*	*conditional*
esomeprazole	*6 (1.2%)*	*conditional*
Others		
metoclopramide	*6 (1.2%)*	*conditional*
quetiapine	*5 (1.0%)*	*conditional*
alfuzosin	*5 (1.0%)*	*possible*

a classificazione da http**://www.Crediblemeds.org/**

Interazioni farmacologiche predisponenti per LQTS secondo il software Micromedex (n>1)



Interazioni farmacologiche predisponenti per LQTS secondo il software Micromedex

Interazioni farmaco-farmaco predisponenti per LQTS (n>1)	Classe terapeutica		n
	Farmaco 1	Farmaco 2	
citalopram - omeprazolo	antidepressivo	PPI	4
citalopram - pantoprazolo	antidepressivo	PPI	3
quetiapina - trazodone	antipsicotico	antidepressivo	2
citalopram - claritromicina	antidepressivo	antibiotico	2
claritromicina - amiodarone	antibiotico	antiaritmico	2
claritromicina - paroxetina	antibiotico	antidepressivo	2