Published in final edited form as:

Clin Lung Cancer. 2020 January ; 21(1): 21–27.e5. doi:10.1016/j.clcc.2019.07.008.

QTc interval-prolonging medications among patients with lung cancer: implications for clinical trial eligibility and clinical care

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Abstract

Background—Concomitant medication use, including agents that prolong the QTc interval, may exclude cancer patients from clinical trials. To estimate potential impact on accrual, we determined the prevalence of QTc-prolonging medication prescriptions in a national patient cohort.

Methods—We identified adult patients in the Veterans Affairs system diagnosed with lung cancer 2003–2016. QTc-interval prolonging medications and risk category were obtained from CredibleMeds®. We calculated prevalence of prescriptions for QTc-prolonging medications with known or possible risk of torsades de pointes in the 3 months up to and including date of cancer diagnosis. Rates across patient groups were compared using Chi-square test.

Results—280,068 patients were included in the study. Mean age was 70 years, 98% were male, and 72% were white. Overall, 28.4% were prescribed a QTc-prolonging medication, and 7.3% were prescribed two or more in the three months leading up to cancer diagnosis. The most commonly prescribed QTc-prolonging medications were antimicrobials (14.0%), psychiatric agents (10.2%), antiemetics (2.6%), and cardiac medications (1.7%). Excluding antimicrobials, 18.4% of patients were prescribed a QTc-prolonging medication.

Conclusions—A substantial proportion of individuals with lung cancer are prescribed QTc-prolonging medications. These prescriptions may limit eligibility for clinical trials and complicate

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Conflicts of Interest:

The authors have no conflicts of interest to report.

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the administration of standard cancer therapies. Further research into the actual clinical risks and optimal management of QTc-prolonging medications in cancer populations is warranted.

MicroAbstract

Use of QTc-interval prolonging medications is a common exclusion criterion in clinical trials. To explore its potential effect, a cohort of lung cancer patients in the Veterans Affairs system was studied to determine the prevalence of such drugs. Among 280,068 patients, 28.4% were prescribed at least one QTc-interval prolonging medication, and 7.3% were prescribed two or more, warranting further research into the actual clinical risks and optimal management of QTc-prolonging medications in cancer populations.

Keywords

clinical research; exclusion criteria; onco-cardiology; targeted therapy; thoracic oncology

Fewer than two percent of adult patients with cancer participate in clinical trials in the United States.^{1,2} Multiple factors contribute to low accrual rates, including patient and physician preferences, trial availability, and stringent eligibility criteria.^{34–11} In recent years, increasing scrutiny has been placed on common yet rarely justified exclusion factors, including history of prior cancer, HIV diagnosis, history of brain metastases, and reduced renal function.^{12–16} However, relatively little attention has been devoted to concomitant medication usage, such as those agents that convey a hypothetical risk of QTc interval prolongation. Similar to pharmaceuticals with potential for drug-drug interactions, use of these medications may be prohibited in cancer clinical trials, particularly studies of tyrosine kinase inhibitors.¹⁷ Clinicians and investigators are likely to have little difficulty recalling trial enrollment challenges due to medications associated with QTc interval prolongation or drug-drug interactions. Indeed, tyrosine kinase inhibitors targeting all of the recognized druggable genomic alterations in lung cancer (EGFR, ALK, ROS1, BRAF, MET, HER2, RET) are associated with QTc prolongation.^{18–2122,23}

QTc prolongation may increase the likelihood of fatal ventricular tachyarrhythmias, most commonly torsade de pointes (TdP). While often transient, TdP can degenerate into ventricular fibrillation when sustained.¹⁸ Accordingly, regulatory agencies such as the United States Food and Drug Administration (FDA) scrutinize the effect on cardiac repolarization of novel therapeutics to anticipate possible cardiac toxicity. However, the relationship between QTc abnormalities and cardiac events is complex. Not all, particularly mild, QTc prolongation is dangerous. In addition, QTc prolongation is relatively common among individuals with cancer, and there have been calls for a re-evaluation of an approach some experts consider overly conservative.^{14,24,25} To assess the potential impact of the current strategy on clinical trials and patient care, we determined the prevalence of QTc-prolonging medication prescriptions in a national cohort of patients with lung cancer.

Methods

Study Design and Data Sources

This was a retrospective, observational, cross-sectional study evaluating the prevalence of QTc interval-prolonging medications in adult patients with incident lung cancer. We included adult (age ≥ 18 years) patients with lung cancer from January 1, 2003, to December 31, 2016, from the Veterans Affairs (VA) Corporate Data Warehouse (CDW), a well-established source of data for lung cancer and other malignancies in which the incident cancers approximately mirror those observed among U.S. men.^{26–28} We used the VA Informatics and Computing Infrastructure (VINCI) to host and analyze the data. The CDW includes all data from Veterans Health Information Systems and Technology Architecture (VistA), inpatient and outpatient administrative data sets (Medical SAS Datasets, MedSAS), cost information (from the Decision Support System, DSS), and other non-VistA data through Text Integration Utilities. Data in the CDW includes inpatient and outpatient diagnosis/procedure codes, pharmacy, and laboratory data.

Patient Selection

Patient data were selected from the CDW if they had an International Classification of Diseases (ICD) 9 or 10 code for lung cancer (ICD-9 codes 162.0–162.9 and ICD-10 code C34.00–34.90), which includes both non-small cell and small cell histologic subtypes. The index date was the date of lung cancer diagnosis. Patients were included in the study if they had one or more primary care visit at a VA facility in the one year prior to the index date.

QTc interval-prolonging medication and exposure definitions

We obtained a list of QTc-prolonging medications from CredibleMeds®, an on-line resource developed and maintained by the Arizona Center for Education and Research on Therapeutics that is frequently cited for its database of QT prolonging drugs, stratified by risk of causing torsade de pointes (see Supplementary Table 1).^{22,29–31} Our principal analyses included those medications with known risk of causing Torsades de Pointes (TdP). As defined by CredibleMeds®, these include (1) medications that prolong the QTc interval and are clearly associated with a known risk of TdP, even when taken as recommended; and (2) medications with possible risk of TdP, defined as medications that prolong the QTc interval but currently lack evidence for a risk of TdP when taken as recommended. These risk categories of TdP were selected due to their common use as exclusion criteria in cancer clinical trial protocols. Frequency and duration of drug use was extracted using VA CDW administrative claims data identifying QTc-interval prolonging drug dispensation. We focused our primary analysis on the time period starting 3 months before and including the lung cancer diagnosis because these prescriptions were likely to be active at the time of treatment initiation or clinical trial enrollment. Recognizing potential confounding effects of other anti-cancer therapies or related supportive care agents, we performed an additional analysis on the 12-month time period starting from lung cancer diagnosis to explore the potential impact of QTc prolonging medication use on eligibility for clinical trials beyond first-line therapy.

Statistical analysis

For our primary analyses, we defined QTc-prolonging medication use as receipt of a prescription for an agent with known or possible risk of TdP during the 3 months leading up to and including the index lung cancer diagnosis because these prescriptions were likely to be active at the time of treatment initiation or clinical trial enrollment. Additional analyses were conducted a priori using broader time intervals (up to 6 months and up to 12 months prior to lung cancer diagnosis, and up to 12 months following the lung cancer diagnosis) and using broader definition of QTc-prolonging medications (including those with conditional risk of TdP and undetermined risk of TdP). We calculated prevalence of use across patient populations and time periods using Chi-square tests. Cox proportional hazard regression analyses were used to evaluate association of QTc-prolonging medication prescriptions and overall survival. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Results

From January 2003 to December 2016, 280,068 patients were diagnosed with lung cancer. Mean age was 70 years, 98% were male, and 72% were white. Additional demographic characteristics are listed in Table 1. Overall, 79,655 patients (28.4%) were prescribed QTc-prolonging medications. Compared to patients not prescribed QTc-prolonging agents, patients receiving QTc-prolonging medications were marginally younger (mean age 68.9 years versus 70.9 years; $P<0.001$) and more likely to be black (14.1% versus 11%; $P<0.001$).

Table 2 lists the top 20 most commonly prescribed QTc-prolonging agents in the study cohort. Among these medications, 35% were antimicrobials, 25% were psychiatric therapies, 10% were cardiovascular agents, and 10% were antiemetics. Because the time period analyzed in this study preceded the index lung cancer diagnosis, none of the identified QTc-prolonging medications were lung cancer treatments. Indeed, only 12 patients (<0.001%) in the cohort were prescribed a QTc-prolonging therapy for any cancer type as follows: lapatinib (breast cancer; $n=6$), nilotinib (chronic myeloid leukemia; $n=5$), bosutinib (chronic myeloid leukemia; $n=1$). The proportion of patients prescribed QTc-prolonging mutations across TdP risk classifications (known, possible, conditional, undetermined) and over varying time intervals is shown in Table 3. For most risk classifications, extension of the analyzed time period from 3 months up to 12 months prior to cancer diagnosis did not substantially increase the prevalence of QTc interval-prolonging medication prescription rates. Excluding antimicrobials—which are often prescribed for only limited periods—from the analysis, 18.4% of patients were prescribed QTc-prolonging medications (Supplemental Table 2).

Table 4 shows the proportion of patients who were prescribed multiple QTc-prolonging medications (with known or possible risk of TdP). In the 3 months leading up to a lung cancer diagnosis, 7.3% of patients were prescribed two or more QTc-prolonging agents; in the 12-month time period, 13.5% of patients were prescribed two or more QTc-prolonging medications. Including agents from all risk categories, 34% of patients were prescribed multiple QTc-prolonging medications during the 3-month pre-diagnosis time period. Figure

1 shows the proportion of patients prescribed QTc-prolonging medications over the study period.

We also analyzed prevalence of QTc-prolonging medication prescriptions during the 12 months following lung cancer diagnosis. Demographic characteristics of individuals receiving such prescriptions was comparable to the cohort leading up to lung cancer diagnosis. Notably, the overall prescription rate was greater during the post-diagnosis time period, with 37.3% prescribed one and 11.6% prescribed two or more QTc-prolonging medications. This difference likely reflected supportive care directly related to cancer therapy, as more than half of these prescriptions were for the antiemetics ondasetron and promethazine (see Supplemental Table 3).

In terms of clinical outcomes, receipt of QTc-prolonging medication prescriptions in the 3 months leading up to lung cancer diagnosis was associated with inferior overall survival [hazard ratio (HR) 1.21; 95% confidence interval (CI) 1.21–1.23, $P<0.001$] (Supplemental Figure 1). However, receipt of QTc-prolonging medication prescriptions in the 12 months following lung cancer diagnosis was associated with slightly better overall survival [HR 0.97; 95% CI, 0.96–0.98, $P<0.001$] (Supplemental Figure 2).

Discussion

While several clinical trial exclusion criteria have come under scrutiny, those related to concomitant medication use have not received such attention. Given increasing rates in polypharmacy across populations, as well a growing number of cancer therapies—particularly molecularly targeted therapies such as tyrosine kinase inhibitors—that convey potential risk of QTc prolongation, these pharmacologic considerations are may have considerable impact on patient selection. Indeed, tyrosine kinase inhibitors targeting all of the common genomic alterations in lung cancer (EGFR, ALK, ROS1, BRAF, MET, HER2, RET) are associated with potential QTc prolongation.^{19–21}

Our present study confirms these suspicions. In our national cohort of almost 300,000 patients with lung cancer, almost 30% were prescribed at least one QTc-prolonging medication in the months prior to lung cancer diagnosis. Medication category and prescription timeline patterns suggest that most of these medications represented chronic or recurrent treatments. Almost 10% of patients were taking more than one QTc-prolonging agent. Because clinical trial enrollment often occurs beyond the first-line setting, we also analyzed of QTc-prolonging drug prescriptions in the 12 months following lung cancer diagnosis. As we suspected, rates of such prescriptions were higher than pre-diagnosis, with the increase largely reflecting oncology-specific supportive care therapies. Together, these findings suggest that QTc-prolonging medication use may present not only a potential obstacle to clinical trial enrollment, but also one that is challenging to address simply through prescription substitution or discontinuation.

The association of QTc-prolonging medication prescriptions with survival likely reflects medical comorbidities (which we were unable to capture in the present analysis) rather than increased rates of cardiac events. This hypothesis is supported by differences in the pre- and

post-diagnosis cohorts. Cardiovascular, psychiatric, and antimicrobial medications accounted for the majority of prescribed QTc-prolonging therapies leading up to diagnosis, during which time receipt of QTc-prolonging prescriptions was associated with inferior survival. Following diagnosis, more than half of QTc-prolonging medication prescriptions were oncology supportive care therapies, a surrogate marker of sufficient fitness to receive standard systemic cytotoxic therapies. Accordingly, during this time, receipt of QTc-prolonging medications was associated with superior survival.

Two possible paths forward would allow increased participation in clinical trials. The first is to discontinue the QTc-prolonging agent, and substitute with an agent without QTc-prolonging properties. This approach may have most relevance for antimicrobials, but may be less feasible for psychiatric, cardiovascular, and antiemetic agents, as clinicians might have difficulty finding substitutes. Approximately one-third of the most frequently prescribed QTc-prolonging medications in this study were antimicrobial agents. It could be argued that these medications are typically short-term regimens that only temporarily interfere with study enrollment or treatment. However, given the extensive smoking history of many of these patients, the prevalence of chronic obstructive pulmonary disease as a comorbid condition, and the immunosuppressive effects of many cancer therapies, in reality patients with lung cancer are likely to return to these medications repeatedly over time. That the antibiotic classes impacted by QTc considerations—fluoroquinolones and macrolides—are otherwise among the most convenient and tolerated, may further complicate medical management. Even after removing antimicrobials from our analysis, almost 20% of patients were still prescribed QTc-prolonging medications, a prevalence exceeding that of medical comorbidities cited as hindering trial accrual, such as HIV, prior cancer diagnosis, and hepatic dysfunction^{32,33}. Of particular relevance to cancer populations is the prohibition of antiemetics such as ondansetron due to QTc-related concerns. 5-HT₃ agonists revolutionized the treatment of cancer by mitigating unremitting nausea. Altering prescribing patterns of these medications may threaten patients' quality of life during treatment.

The other path to increased participation is to relax eligibility requirements for clinical trials, which might be considered in the setting of the ill-defined risk and association of arrhythmia with QT-prolongation. Current recommendations for assessment of QTc prolongation and arrhythmia potential were developed by the Expert Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and culminated in the E14 guidelines.³⁴ These guidelines suggest that all medications undergo rigorous assessment via the Thorough QT Study (TQTS). In the TQTS, a new medication's repolarization effects on the QT interval over its dose range are explored in a randomized, placebo-controlled trial with healthy adults. However, the TQTS is not well suited for oncologic therapies because the use of cancer treatments at therapeutic levels in healthy adults and the administration of placebo in patients with cancer may not be ethically acceptable.³⁵ As a result, TdP risk assessment for cancer therapeutics remains challenging.

There is also ongoing debate about the reliability of QT-interval measurement and standardization of techniques to correct the QT interval for heart rate (i.e., calculation of the corrected QT-interval, the QTc) as well as the applicability of what is considered the upper

limit of normal for QTc among cancer patients. The ICH's E14 guidelines do not specify which correction formula (e.g., Bazett or Friedericia) to use, with each formula yielding a different QTc value. Resulting inconsistencies limit the ability to generalize QTc reference ranges.^{24,34,35}

Additionally, the relationship between QTc prolongation and arrhythmia risk is non-linear and complex, with differences reported across patient populations, etiology (medication versus congenital), and medication types.³⁶ Key studies of QTc-associated arrhythmia risk often report 40-year event rates,³⁷ a parameter of questionable relevance to individuals with advanced cancer. Even after prolonged periods, the true risk of drug-induced TdP appears remarkably low. In studies of patients receiving proarrhythmic medications and undergoing continuous monitoring, the incidence of TdP ranges 1–4/100,000 patients.^{21,38–40}

The exclusion of patients taking QTc-prolonging medications could disproportionately affect elderly patients, who although representing approximately two-thirds of patients with cancer, account for only 25–30% of clinical trial participants.^{41–45} Elderly individuals have more co-morbidities and polypharmacy than younger patients.⁴¹ Barriers to their enrollment have particular implications for a disease such as lung cancer, for which the average age at diagnosis exceeds 70 years.^{46,47} Whether the recent increase in QTc-prolonging medication prescriptions will continue is not clear. Nor do we know what factors underlie it, such as new medication approvals, new safety characterizations of existing medications, or database characteristics.

How can clinical investigators, study sponsors, and regulatory authorities reconsider the ubiquitous practice of excluding QTc-prolonging agents from clinical trials? Given the acuity of both cardiac arrhythmias and suboptimally treated cancer, a revised approach is urgently needed. Because QTc prolongation poses risk of arrhythmia over decades, it may be feasible to monitor closely those patients whose concomitant medications are associated with QTc prolongation, rather than broadly excluding them from enrollment in trials. Such an approach would benefit not only the individual patient newly handed the opportunity to participate in a study, but information gained from that real-world experience could then be used to guide eligibility considerations for future trials and regulatory indications.

Our study has a number of limitations. Due to its setting in the VA system, the study population is overwhelmingly male and white, a demographic that may have different prescription patterns than other groups. Similarly, restrictions in VA pharmacy formularies may not reflect wider prescribing patterns, although the most commonly prescribed QT-prolonging medications in this study appear to represent widely used therapies. Our data captures only medications prescribed within the VA system, thereby potentially underestimating use rates when patients receive prescriptions elsewhere. Lack of data on over-the-counter medications is unlikely to have a meaningful effect on our findings, however, as few of these agents are associated with QTc prolongation. Importantly, our cohort lacks comorbidity data and cause-specific mortality, which substantially limits the interpretation of clinical outcomes. Our pharmacy dataset also lacks disease stage, potentially limiting assessment of impact our reported QTc-prolonging medication exposure rate on specific clinical trial enrollment. Because demographic characteristics of other

national VA dataset studies match that of our cohort,²⁶ we anticipate that stage distribution (approximately two-thirds locally advanced or advanced) may as well. Furthermore, the use of QTc-prolonging medications as clinical trial exclusion criteria may be relevant to all lung cancer stages, as small molecule inhibitors associated with QTc-related restrictions such as osimertinib are now under study in early-stage lung cancer (,). We also recognize that in some cases QTc-prolonging medications may not be the sole reason for patient exclusion from a clinical trial. For instance, patients receiving anti-arrhythmic cardiac medications might be excluded due to the underlying dysrhythmia, independent of any concomitant medications. Nevertheless, among the top 20 QTc-prolonging medications in our cohort, only one was an anti-arrhythmic and the indications for the other top medications (eg, depression, arthritis, pain, nausea) are unlikely to be considered exclusionary in most clinical trials. Similarly, we recognize that reasons for non-participation in cancer clinical trials are highly complex, and that it is not known to what extent revisiting a single eligibility criterion would impact accrual.⁴⁸ Key strengths of the study include a large national patient sample, a contemporary time period, and detailed pharmacy data.

Conclusion

Concomitant prescriptions for QTc-prolonging medications occur among approximately one-third of patients with lung cancer, a rate that has increased by 20% over the past 15 years. Some of these patients use multiple such agents, on a chronic basis, rendering prescription modification or discontinuation difficult. Use of these medications may prohibit enrollment in clinical trials and complicate routine clinical care. The actual clinical risk of these medications remains unclear. Cancer clinical trial eligibility criteria are broadly recognized as overly stringent and hindering scientific progress. To balance patient safety and access to oncology trials, a greater understanding of the true impact and optimal management of QTc-prolonging medications among individuals with cancer is urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Ms. Dru Gray for providing assistance with manuscript preparation, and Helen Mayo, MLS, for providing assistance with literature searches.

Funding

Supported in part by a National Cancer Institute (NCI) Midcareer Investigator Award in Patient-Oriented Research (K24 CA201543–01, to D.E.G.), the NCI Small Grants Program for Cancer Research (1R03CA191875, to D.E.G.), an NCI National Clinical Trials Network Lead Academic Performance Site (LAPS) Award (5U10CA180870, to D.E.G.), National Institute of Diabetes and Digestive and Kidney Diseases Career Development Award (K08 DK101602, to C.A.A.), the UT Southwestern Center for Translational Medicine (UL1 TR001105 to C.A.A.), and the Cancer Prevention and Research Institute of Texas (CPRIT 50C1324901, to V.G.Z.).

References

1. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291(22):2720–2726. [PubMed: 15187053]
2. Friedman MA, Cain DF. National Cancer Institute sponsored cooperative clinical trials. *Cancer*. 1990;65(10 Suppl):2376–2382. [PubMed: 2334876]
3. Tournoux C, Katsahian S, Chevret S, Levy V. Factors influencing inclusion of patients with malignancies in clinical trials. *Cancer*. 2006;106(2):258–270. [PubMed: 16397866]
4. Howerton MW, Gibbons MC, Baffi CR, et al. Provider roles in the recruitment of underrepresented populations to cancer clinical trials. *Cancer*. 2007;109(3):465–476. [PubMed: 17200964]
5. Avis NE, Smith KW, Link CL, Hortobagyi GN, Rivera E. Factors associated with participation in breast cancer treatment clinical trials. *J Clin Oncol*. 2006;24(12):1860–1867. [PubMed: 16622260]
6. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol*. 1999;52(12):1143–1156. [PubMed: 10580777]
7. Gerber DE, Rasco DW, Skinner CS, et al. Consent timing and experience: modifiable factors that may influence interest in clinical research. *J Oncol Pract*. 2012;8(2):91–96. [PubMed: 23077435]
8. Lara PN Jr., Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. *J Clin Oncol*. 2001;19(6):1728–1733. [PubMed: 11251003]
9. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *New England Journal of Medicine*. 2015;373(17):1627–1639. [PubMed: 26412456]
10. Viability of cancer clinical research: patient accrual, coverage, and reimbursement. American Medical Association Council on Scientific Affairs. *J Natl Cancer Inst*. 1991;83(4):254–259. [PubMed: 1994054]
11. Saterén WB, Trimble EL, Abrams J, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J Clin Oncol*. 2002;20(8):2109–2117. [PubMed: 11956272]
12. Bradley J, Kelly K, Stinchcombe TE. The Ever-Increasing Number of Trial Eligibility Criteria: Time to Bend the Curve. *J Thorac Oncol*. 2017;12(10):1459–1460. [PubMed: 28939144]
13. Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. *J Natl Cancer Inst*. 2015;107(4).
14. Beaver JA, Ison G, Pazdur R. Reevaluating Eligibility Criteria - Balancing Patient Protection and Participation in Oncology Trials. *N Engl J Med*. 2017;376(16):1504–1505. [PubMed: 28423289]
15. Gore L, Ivy SP, Balis FM, et al. Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Minimum Age Working Group. *J Clin Oncol*. 2017;35(33):3781–3787. [PubMed: 28968169]
16. Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. Impact of prior cancer on eligibility for lung cancer clinical trials. *J Natl Cancer Inst*. 2014;106(11).
17. Coppola C, Rienzo A, Piscopo G, Barbieri A, Arra C, Maurea N. Management of QT prolongation induced by anti-cancer drugs: Target therapy and old agents. Different algorithms for different drugs. *Cancer Treat Rev*. 2018;63:135–143. [PubMed: 29304463]
18. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). *Drug Saf*. 2013;36(5):295–316. [PubMed: 23620167]
19. Schiefer M, Hendriks LEL, Dinh T, Lalji U, Dingemans AC. Current perspective: Osimertinib-induced QT prolongation: new drugs with new side-effects need careful patient monitoring. *Eur J Cancer*. 2018;91:92–98. [PubMed: 29413968]
20. Menna P, Salvatorelli E, Minotti G. Cancer drugs and QT prolongation: weighing risk against benefit. *Expert Opin Drug Saf*. 2017;16(10):1099–1102. [PubMed: 28699784]

21. Brell JM. Prolonged QTc interval in cancer therapeutic drug development: defining arrhythmic risk in malignancy. *Prog Cardiovasc Dis.* 2010;53(2):164–172. [PubMed: 20728704]
22. Woosley R, Heise CW, and Romero KA. QTdrugs List. www.CredibleMeds.org. Accessed October 9, 2017.
23. <https://www.micromedexsolutions.com/micromedex2/librarian/>. Accessed 04/12/2019.
24. Varterasian M, Meyer M, Fingert H, et al. Baseline heart rate-corrected QT and eligibility for clinical trials in oncology. *J Clin Oncol.* 2003;21(17):3378–3379. [PubMed: 12947082]
25. Naing A, Veasey-Rodrigues H, Hong DS, et al. Electrocardiograms (ECGs) in phase I anticancer drug development: the MD Anderson Cancer Center experience with 8518 ECGs. *Ann Oncol.* 2012;23(11):2960–2963. [PubMed: 22745218]
26. Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. *J Clin Oncol.* 2012;30(13):1447–1455. [PubMed: 22454424]
27. Landrum MB, Keating NL, Lamont EB, Bozeman SR, McNeil BJ. Reasons for underuse of recommended therapies for colorectal and lung cancer in the Veterans Health Administration. *Cancer.* 2012;118(13):3345–3355. [PubMed: 22072536]
28. Zullig LL, Jackson GL, Dorn RA, et al. Cancer incidence among patients of the U.S. Veterans Affairs Health Care System. *Mil Med.* 2012;177(6):693–701. [PubMed: 22730846]
29. Weeke PE, Kelleman JS, Jespersen CB, et al. Long-term proarrhythmic pharmacotherapy among patients with congenital long QT syndrome and risk of arrhythmia and mortality. *Eur Heart J.* 2019.
30. Wang M, Szepletowska B, Polonsky B, et al. Risk of Cardiac Events Associated With Antidepressant Therapy in Patients With Long QT Syndrome. *Am J Cardiol.* 2018;121(2):182–187. [PubMed: 29174490]
31. Woosley RL, Black K, Heise CW, Romero K. [CredibleMeds.org](http://www.CredibleMeds.org): What does it offer? *Trends Cardiovasc Med.* 2018;28(2):94–99. [PubMed: 28801207]
32. Ahn DH, Mehta N, Yorjo JT, Xie Y, Yan J, Gerber DE. Influence of medical comorbidities on the presentation and outcomes of stage I–III non-small-cell lung cancer. *Clin Lung Cancer.* 2013;14(6):644–650. [PubMed: 23886797]
33. Kim ES, Bruinooge SS, Roberts S, et al. Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. *J Clin Oncol.* 2017;35(33):3737–3744. [PubMed: 28968170]
34. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Steering Committee: ICH Harmonized Tripartite Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs, E14.; 2005; Geneva, Switzerland.
35. Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. *Journal of Clinical Oncology.* 25(22):3362–3371.
36. Darbar D, Kimbrough J, Jawaaid A, McCray R, Ritchie MD, Roden DM. Persistent atrial fibrillation is associated with reduced risk of torsades de pointes in patients with drug-induced long QT syndrome. *J Am Coll Cardiol.* 2008;51(8):836–842. [PubMed: 18294569]
37. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med.* 2003;348(19):1866–1874. [PubMed: 12736279]
38. Darpo B Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. *European Heart Journal Supplements.* 2001;3(suppl_K):K70–K80.
39. Whellan DJ, Green CL, Piccini JP, Krucoff MW. QT as a safety biomarker in drug development. *Clin Pharmacol Ther.* 2009;86(1):101–104. [PubMed: 19474784]
40. Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and proarrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. *Cardiovasc Res.* 2000;47(2):219–233. [PubMed: 10947683]
41. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol.* 2003;21(7):1383–1389. [PubMed: 12663731]

42. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med.* 1999;341(27):2061–2067. [PubMed: 10615079]
43. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol.* 2004;22(22):4626–4631. [PubMed: 15542812]
44. Hurria A, Dale W, Mooney M, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. *J Clin Oncol.* 2014;32(24):2587–2594. [PubMed: 25071116]
45. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol.* 2005;23(13):3112–3124. [PubMed: 15860871]
46. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7–30. [PubMed: 29313949]
47. Rasco DW, Yan J, Xie Y, Dowell JE, Gerber DE. Looking beyond surveillance, epidemiology, and end results: patterns of chemotherapy administration for advanced non-small cell lung cancer in a contemporary, diverse population. *J Thorac Oncol.* 2010;5(10):1529–1535. [PubMed: 20631635]
48. Unger JM, Cook E, Tai E, Bleyer A. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. *Am Soc Clin Oncol Educ Book.* 2016;35:185–198. [PubMed: 27249699]

Clinical Practice Points

- Concomitant use of QTc-interval prolonging drugs is a frequent exclusion criterion in clinical trials, particularly in those involving tyrosine-kinase inhibitors. However, the actual risk of clinically significant dysrhythmias in oncologic patients is poorly understood.
- Almost 30% of adult patients in a national cohort of patients in the Veterans Affairs health system are prescribed at least one QTc-interval prolonging drug, and almost 10% are two or more, most of which are used chronically.
- Increased scrutiny of the rationale for routine exclusion of patients from clinical trials based on use of QTc-interval prolonging drugs is needed to optimize trial accrual and avoid potentially unnecessary and cumbersome medication adjustments.

Figure 1.
Prevalence of prescriptions for QTc-prolonging medications over time

Table 1.

Baseline characteristics in patients with and without QTc-prolonging medication exposure

Characteristic n (%)	QTc (Known or Possible Risks) Prescription (N=79,655)	No QTc (Known or Possible Risks) Prescription (N=200,413)	Total population (N=280,068)
Age (Years), Mean +/- SD	68.9 +/- 10.0	70.9 +/- 9.9	70.3 +/- 10.0
Male	77539 (97.3)	196752 (98.2)	274291 (97.9)
Race			
White	58993 (74.1)	143516 (71.6)	202509 (72.3)
Black	11259 (14.1)	22106 (11.0)	33365 (11.9)
Other	2516 (3.2)	5658 (2.8)	8174 (2.9)
Unknown	6887 (8.7)	29133 (14.5)	36020 (12.9)

Table 2.

Top 20 most commonly prescribed QTc-prolonging medications in the study cohort from 3- months prior to diagnosis up to and including date of diagnosis

QT-prolonging medication	Medication category	TdP risk Classification	Rate of Usage [*] (%)
Azithromycin	Antimicrobial	Known	4.5
Citalopram	Psychiatric	Known	4.3
Moxifloxacin	Antimicrobial	Known	3.4
Vardenafil	Erectile dysfunction	Possible	2.7
Ciprofloxacin	Antimicrobial	Known	2.6
Levofloxacin	Antimicrobial	Known	2.4
Mirtazapine	Psychiatric	Possible	2.3
Ondansetron	Antiemetic	Known	2.1
Gatifloxacin	Antimicrobial	Known	1.4
Venlafaxine	Psychiatric	Possible	1.3
Promethazine	Antiemetic	Possible	1.3
Donepezil	Psychiatric	Known	1.1
Amiodarone	Cardiovascular	Known	1
Risperidone	Psychiatric	Possible	0.9
Methadone	Analgesic	Known	0.7
Cilostazol	Cardiovascular	Known	0.7
Nortriptyline	Psychiatric	Possible	0.6
Fluconazole	Antimicrobial	Known	0.5
Clarithromycin	Antimicrobial	Known	0.4
Chloroquine	Antirheumatict [†]	Known	0.4

^{*} 3 months prior to or at Cohort Entry Date

[†] Less commonly prescribed as an antimicrobial for prevention or treatment of malaria

Table 3.

QTc-prolonging medication prescriptions by risk classification and time period

TdP Risk Classification	Prevalence of prescriptions (%)		
	Up to 3 months prior to or at Cohort Entry Date	Up to 6 months prior to or at Cohort Entry Date	Up to 12 months prior to or at Cohort Entry Date
Known Risk	22.1	26	30.6
Possible Risk	9.9	11.3	13.3
Conditional Risk	38.1	40.9	44.1
Undetermined	30.3	32.8	35.3
Known or Possible	28.4	32.6	37.3
Any	59.9	63	66

Table 4.

Number of QTc-prolonging medications taken by patients according to time interval

Total number of QTc- prolonging medications (known or possible risk of TdP)	Proportion of patients (%) by time-frame prior to or at diagnosis		
	3 months	6 months	12 months
1	21.2	22.8	23.9
2	5.7	7.3	9.2
3	1.3	1.9	3.0
4	0.3	0.6	1.3

TdP, torsades de pointes