Grapefruit juice prolongs the QT interval of healthy volunteers and patients with long QT syndrome

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BACKGROUND The list of medications linked to drug-induced long QT syndrome (LQTS) is diverse. It is possible that foods products too have QT-prolonging potential.

OBJECTIVE We tested the effects of grapefruit juice on the QT interval with the methodology used by the pharmaceutical industry to test new drugs.

METHODS This was an open-label, randomized, crossover study with blinded outcome evaluation, a thorough QT study of grapefruit juice performed according to the Guidelines for the Clinical Evaluation of QT/QTc for Non-antiarrhythmic Drugs. Thirty healthy volunteers and 10 patients with congenital LQTS were studied. Healthy volunteers drank 2 L of grapefruit juice (in divided doses), or received 400 mg oral moxifloxacin, in a randomized crossover study. Patients with LQTS were tested with only grapefruit. Repeated baseline, off-drug, and on-drug (grapefruit or moxifloxacin) electrocardiograms were scanned and coded. QT measurements were done with electronic calipers.

RESULTS In comparison to off-drug electrocardiograms, grapefruit juice led to significant rate-corrected QT (QTc) prolongation. The absolute net QTc prolongation from grapefruit was 14.0 ms (95% confidence interval 6.2–21.7 ms; \( P < .001 \)). The QT-prolonging effects of grapefruit in healthy volunteers were comparable with those of moxifloxacin. The QT-prolonging effects of grapefruit juice were greater in female patients and particularly marked in patients with LQTS (net QTc prolongation 21.8 ms; 95% confidence interval 3.4–35.3 ms; \( P = .034 \)).

CONCLUSION Grapefruit juice, at doses tested, prolongs the QT interval. The effect is significant in healthy volunteers, greater in female patients, and more so in patients with LQTS.

KEYWORDS Adverse events; Drug-induced long QT syndrome; Proarrhythmia

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Introduction

The list of medications that prolong the QT interval and can provoke potentially torsades de pointes (TdP) continuously expands.1,2 This list includes not only antiarrhythmic drugs but also medications with no cardiac indications (eg, some antibiotics, antihistamines, or antipsychotic drugs). These medications prolong the QT interval mainly by blocking a specific “IKr” potassium channel on the myocardial cell membrane, thus prolonging ventricular repolarization.1,2 The risk of developing TdP in patients taking drugs with IKr blockade capabilities varies from 4% for antiarrhythmic drugs to <0.01% for noncardiac medications.1,3 The risk depends on the strength of IKr blockade but also on patient characteristics4; most patients who develop TdP from medications have identifiable risk factors, such as heart disease, slow heart rate, and female sex.4 In this regard, QT-prolonging medications pose a high risk for patients with congenital long QT syndrome (LQTS).5 This is because such patients have reduced “repolarization reserve” owing to their genetically defective ion channels.6 Therefore, it is common practice to advise patients with LQTS to avoid medications with IKr channel blocker capabilities.1

Zitron et al7 reported that flavonoids contained in pink grapefruit block IKr in vitro. They also reported that drinking 1 L of grapefruit juice caused QT prolongation in a small group of healthy volunteers.7 The QT prolongation provoked by grapefruit was small (≈12 ms). A subsequent small study recording only 2 electrocardiograms (ECGs), before and after the consumption of grapefruit, also reported small QT prolongation.7 This is important because drugs causing minor QT prolongation in healthy volunteers may provoke significant QT prolongation when administered to large unselected

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patient populations with comorbidities and may rarely provoke TdP in susceptible individuals.\textsuperscript{2}

Thorough QT/QTc studies are routinely performed by pharmaceutical companies for newly developed drugs to get a better appreciation of their QT-prolonging potential.\textsuperscript{9} The goal of thorough QT studies is not to establish the extent to which a drug is proarrhythmic but to identify drugs that need further assessment of this hazard.\textsuperscript{7} Such studies are performed in 30–50 volunteers using strict criteria\textsuperscript{10}: To ascertain that the population studied is large enough and the system used is sensitive enough to detect a small QT-prolonging potential of the tested medication—when such risk actually exists—studies include, as positive control, a medication with confirmed, albeit small, QT-prolonging properties.\textsuperscript{10} The positive control most commonly used is a single oral dose of 400 mg moxifloxacin, an antibiotic that blocks $I_{Ks}$ and reproducibly leads to detectable QT prolongation.\textsuperscript{10} To get a better appreciation of the QT-prolonging potential of grapefruit, we performed a thorough QT study of grapefruit juice using the criteria of the pharmaceutical industry.

**Methods**

**Study design**

This was an open-label, randomized, crossover study with blinded outcome evaluation performed according to Guidelines for the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs.\textsuperscript{10} We studied 40 subjects: a control group of 30 healthy volunteers and a long QT group (10 patients with LQTS). All participants provided informed consent for participation in the study, which was approved by our ethics committee.

**Healthy group**

Volunteers were eligible for inclusion if they were healthy adults of normal weight, not taking medications, and with a normal ECG. Subjects were excluded from the control group if they had even slight QT prolongation (rate-corrected QT [QTc] interval $>$450 ms for both sexes).\textsuperscript{11} To simplify estimations of the QTc intervals, we excluded candidates with sinus arrhythmia. The long QT group consisted of 10 adults with LQTS type 1 (3 patients), type 2 (5 patients), and type 3 (2 patients). They continued their medication regimen ($\beta$-blockers for 6 patients and no therapy for 4). In patients with implanted defibrillators, the devices were programmed to pace the atrium at 80 beats/min, while $\beta$-blockers were continued, to reduce heart rate variation to a minimum. Nearly half of the participants were of female sex (Supplemental Table 1).

**Interventions**

Subjects who passed the screening phase and provided informed consent were hospitalized on 2 occasions, 7 days apart, each time for 2 days (Figure 1). Thus, the study period consisted of 4 days. To maintain heart rate fluctuations to a minimum, all the ECGs were recorded after 15 minutes of bed rest and only minimal activity was allowed between recordings. All study participants received the same diet throughout the study days.

![Figure 1](image-url)

**Figure 1** Design of the thorough QT study. Consented patients were hospitalized twice, 1 week apart, each time for 2 days (period 1 [day 1–2] and period 2 [day 3–4]). Every day started with 3 electrocardiograms (ECGs), recorded 30 minutes apart, defined as baseline ECG of the day. The first day of each hospitalization period (day 1 and day 3) were dedicated to record repeated ECGs (at hourly intervals) without any drug intervention, defined as off-drug ECGs. Patients were randomized to moxifloxacin or grapefruit on day 2. The alternative drug was tested on day 4. The doses used were (1) a single dose of moxifloxacin 400 mg and (2) grapefruit juice (1 L after the baseline ECGs and 2 doses of 0.5 L 4 and 6 hours later. Patients with long QT syndrome underwent baseline and off-drugs ECG recordings on day 1 and then baseline followed by grapefruit on day 2.
Every day, starting at 8 AM, we recorded 3 resting ECGs 30 minutes apart, defined as baseline ECG for that day. On day 1, we then recorded ECGs every 60 minutes, defined as off-drug ECGs, which were compared with the baseline recordings of that day to evaluate the circadian variation of the QT/QTc interval. On day 2, we repeated the 3 baseline ECGs and then randomly assigned the participants to an interventional drug: moxifloxacin (400 mg single oral dose) or fresh pink grapefruit juice. In the original protocol, the first grapefruit juice dose consisted of 1 L after the baseline ECG recordings and was followed by 2.5 L doses 4 and 6 hours later. ECGs were recorded every hour for the next 3 hours and every 30 minutes during hours 3–12.

Subjects were discharged after 48 hours and were readmitted 7 days later for 2 additional days (days 3 and 4, Figure 1). During day 3, repeated off-drug ECGs were recorded as on day 1. On day 4, controls received the interventional drug (moxifloxacin or grapefruit) not given during day 2 of the first hospitalization. For ethical reasons, the LQTS group did not receive moxifloxacin. Furthermore, since the first patient with LQTS developed excessive QT prolongation after drinking grapefruit juice (Figure 2), we amended the protocol so that only the first 2 doses of grapefruit were given to subsequent patients with LQTS.

Electrocardiographic measurements
Six experienced physicians performed all measurements manually. Every ECG was scanned, coded, and presented in arbitrary sequence to the measuring physicians to keep them unaware of the intervention (off-drug, moxifloxacin, or grapefruit) and timing (onset, drug effect, or end of the study). Scanning was performed at a 300% magnification and 300 dpi resolution (3.39 ms/pixel). All measurements were done using electronic calipers (EP-calipers v1.9 from EP-Studios, 2017, Louisville, Kentucky). Three complexes (QT and its preceding R-R interval) were measured for each ECG and the results averaged, yielding a theoretical accuracy of \( \pm 1.1 \) ms. For quality assurance, the first author repeated the measurements for each patient at arbitrary times, corroborating \( \pm 7\% \) (456 of 6330) of all QT/R-R measurements \([P < .001 \text{ for both}]\); mean difference of only 0.1 ms [95% confidence interval (CI) -0.10 to 0.31 ms; \( P = .292 \)] for R-R intervals and 0.15 ms [95% CI -0.01 to 0.32 ms; \( P = .065 \)] for QT intervals). A Bland-Altman plot demonstrated high accuracy of measurements at long and short R-R intervals (Supplemental Figure 1). QTc intervals were calculated using the Bazett, Fridericia, and Framingham formulas.

Statistical methods
The baseline QTc interval was defined each day, for each patient, as the mean QTc interval of his/her first 3 ECGs of the day before any intervention. Thus, each patient had 4 baseline QTc values, 1 for each study day. The delta QTc is the difference between the QTc interval measured at each of the predefined time intervals after an intervention and the

![Figure 2](https://example.com/figure2.png)

**Figure 2** QT prolongation after drinking grapefruit juice in a patient with long QT syndrome. Electrocardiogram (ECG) during maximal QT prolongation after the ingestion of grapefruit juice (bottom trace) and off-drug at the same time 1 day previously (top trace). Both traces are from a 61-year-old male patient with long QT syndrome type 1 treated with \( \beta \)-blockers. Note that despite a similar heart rate (46 beats/min vs 48 beats/min), the QT interval is longer after grapefruit administration. This rate-corrected QT (QTc) prolongation >500 ms by grapefruit led to a change in the study protocol: Subsequent patients with long QT syndrome received only 2 doses of grapefruit juice instead of the 3 doses given to healthy controls.
baseline QTc interval. The maximal QTc interval is the maximal QTc value measured for each patient at any time between 2 and 6 hours from the administration of the study drug (moxifloxacin or grapefruit) and parallel times for the off-drug measurements. Maximal QTc prolongation for each patient is the difference between his/her maximal QTc interval and his/her baseline QTc interval. Finally, the drug-related net QTc increment is the baseline-adjusted delta QTc after drug administration (moxifloxacin or grapefruit) minus the delta QTc off-drug. This net QTc increment, ascribed to a drug, subtracts the diurnal variation of the QTc interval from the QT prolongation after drug administration and is the main outcome in thorough QT studies.\textsuperscript{15}

Differences in R-R and QT measurements for the corresponding measurement were compared using a pairwise Student \( t \) test; correlation between measurements was assessed using a Pearson correlation test, and overall accuracy throughout the measurement range was tested using a Bland-Altman plot (Supplemental Figure 1). Differences in baseline characteristics, QTc measurement, and delta QTc values between different groups were assessed using a paired or unpaired Wilcoxon test, as appropriate. CIs were calculated using \( t \) score values. Differences in proportions were assessed using a Fisher exact test. To assess the overall effect of the different interventions between groups, a repeated-measures linear mixed-effect model was built using the trial group, the trial phase, and their interaction as fixed factors and subject number as random factor. Interaction terms that were nonsignificant were excluded from the model. The 95\% CIs for the model parameters were calculated using a profile likelihood method. The results are presented as mean \( \pm \) SD or mean with 95\% CI. Differences were considered statistically significant when \( P < .05 \). Calculations were done using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Effects of grapefruit and moxifloxacin on the heart rate**

All study subjects adhered to the study protocol. Neither moxifloxacin nor grapefruit juice had significant effects on the heart rate of participants. Thus, variations in heart rate remained within \( \leq 7.5 \) beats/min for all participants at all times (Supplemental Figure 2). No adverse events occurred.

**Effects of grapefruit and moxifloxacin on the QT interval of healthy volunteers**

The circadian variation of the QTc interval in the absence of drugs was small, with all mean QTc values remaining between \(-5\) and \(+5\) ms from the baseline QTc interval of the respective day throughout the entire off-drug recordings. Moreover, the 2 off-drug QTc graphs (day 1 and day 3) were similar (\( P > .3 \) for all comparisons) (Figure 3A). In contrast, the mean QTc interval increased significantly after exposure to moxifloxacin (Figure 3B). The moxifloxacin-induced QT prolongation peaked 3 hours, with a maximal QTc prolongation of 20.4 ms (95\% CI 15.8–25.00 ms). The net QT increment from moxifloxacin was 17.5 ms (95\% CI 11.2–23.8 ms; \( P < .001 \)). The difference from the corresponding off-drug measurements was statistically significant throughout hours 2–7 after moxifloxacin ingestion (Figure 3B).

Grapefruit juice led to QTc prolongation that first became statistically significant 3 hours after the consumption of the first 1 L of grapefruit (Figure 3C). This grapefruit-induced QT prolongation peaked at 4.5 hours, with a maximal mean QTc prolongation of 13.8 ms (95\% CI 7.6–20.0 ms). The net QTc prolongation from grapefruit was 14.0 ms (95\% CI 6.2–21.7 ms; \( P < .001 \)). The grapefruit-induced QT prolongation lasted up to the end of the measurement period, with QTc values significantly longer than the corresponding off-drug measurements throughout hours 3–7 after the first dose. A direct comparison between the peak effect of moxifloxacin and grapefruit juice showed that moxifloxacin had a stronger, yet nonstatistically significant different, effect on QTc prolongation, with a difference of 6.9 ms (\( P = .102 \)) compared with grapefruit juice. QTc-prolonging effects by moxifloxacin and by grapefruit remained statistically significant when using other QT correction formulas (Supplemental Figures 3 and 4 and Supplemental Table 2).

**Effects of grapefruit on the QT interval of patients with LQTS**

Patients with LQTS did not receive moxifloxacin. Also, since the first patient with LQTS developed QT prolongation considered excessive with 3 doses of grapefruit (Figure 2), we amended the protocol so that all remaining patients with LQTS received only the first 2 doses of grapefruit juice (total 1.5 L). Even with this reduced dose, patients with LQTS developed marked QT prolongation from grapefruit juice (Figure 3D). The QT prolongation reached statistical significance already 2 hours after the consumption of 1 L of grapefruit, peaked once at 5.5 hours, with a maximal mean QTc prolongation of 26.5 ms (95\% CI 14.9–38.2 ms), and peaked once again 4 hours after the second dose, with a maximal QTc prolongation of 29.7 (95\% CI 11.0–48.5 ms). The net QTc prolongation from grapefruit in patients with LQTS was 21.8 ms (95\% CI 13.4–35.3 ms; \( P = .034 \)). The QT prolongation persisted by the end of the measurement period, and the difference from the respective off-drug values was statistically significant between 2 and 8 hours after the first grapefruit juice ingestion. Significant QTc-prolonging effects of grapefruit were observed with all QT correction formulas (Supplemental Figures 3 and 4).

**Individual maximal QTc prolongation**

In healthy volunteers, the individual maximal QTc prolongation at any time within 2–6 hours of drug administration was 28.6 ± 12.1 ms (range 6.1–66.5 ms) for moxifloxacin and 22.8 ± 11.0 ms (range 7.1–58.7 ms) for grapefruit juice but only 8.8 ± 9.6 ms (range –8.0 to 35.3 ms) during
repeated off-drug measurements \( (P < .001 \) for moxifloxacin or grapefruit vs off-drug measurements) (Figure 4A).

For patients with LQTS, the individual maximal QTc prolongation was 31.3 ± 17.8 ms (range 8.3–57.7 ms) at any time after grapefruit administration but was only 10.1 ± 7.9 ms (range 2.5–19.8 ms) during multiple off-drug measurements \( (P = .004 \) for grapefruit vs off-drug values). Marked QTc (≥40 ms) prolongation from grapefruit occurred more commonly in patients with LQTS than in healthy volunteers even though all but one of the patients with LQTS drank smaller quantities of grapefruit juice (Figure 4B). In fact, this degree of QT prolongation was more common when patients with LQTS drank grapefruit juice than when healthy volunteers received moxifloxacin (Figure 4B).

Regression model

The mixed-effects regression model (Table 1) showed, as expected, that the characteristics female sex and LQTS were independently associated with longer QT intervals. The model demonstrated independent QTc prolongation in healthy subjects by moxifloxacin (by 8.5 ms; 95% CI 6.1–10.9 ms) and independent QT prolongation by grapefruit (by 4.1 ms; 95% CI 1.9–6.3 ms). Female patients had a stronger response to moxifloxacin and grapefruit \( (P < .05 \) in comparison with male patients), and patients with LQTS had a stronger response to grapefruit \( (P < .001 \) in comparison to healthy volunteers).

Discussion

There are >200 medications with reported QT-prolonging risk,\textsuperscript{16} including 57 drugs with “confirmed risk” and 241 medications with “conditional risk” of TdP.\textsuperscript{16} Medications in the last category increase the risk of TdP only in susceptible individuals with additional risk factors. The majority of these medications do not even have cardiac indications, yet cause unintended QT prolongation because they block IKr potassium channels in myocardial cells.\textsuperscript{1,2} With so many drugs, of such varied composition, blocking the IKr channel, it is reasonable to assume that food compounds also have IKr channel blocker properties, raising the possibility that proarrhythmic food exists. After the in vitro demonstration of IKr blockade by flavonoids contained in grapefruit,\textsuperscript{7} we tested the effects of grapefruit juice on the QT interval using the rigorous criteria required from the pharmaceutical industry: a randomized crossover design, accurate and blinded QT analysis, and a study population sufficiently large to detect the small QT prolongation expected for moxifloxacin.\textsuperscript{9} The
net QTc prolongation observed in our study with use of moxifloxacin is similar to that reported in numerous thorough QT studies.\textsuperscript{15} We are therefore confident that our results accurately represent the effects of pink grapefruit, at the doses used, on the QT interval.

**Main findings**

Our study shows that grapefruit juice prolongs the QT interval, more in female patients and more so in patients with LQTS. The net increase in QT interval caused by grapefruit in healthy volunteers was of only 14 ms, a small increase in absolute terms. However, when it comes to tested medications, QT increments in this range generally lead the Food and Drug Administration to call for precautionary statements, because compounds with a net QTc prolongation of 5–20 ms during thorough QT studies are often associated with increased proarrhythmic risk when used in large populations.\textsuperscript{17} Thus, if grapefruit juice was a new drug in development, the results of the present study would call for additional studies with stringent QT interval monitoring before issuing a final recommendation based on its expected benefits and risks.\textsuperscript{18} The summary of product characteristics (a legal document approved as part of the marketing authorization of medicines) packed with the tablets of moxifloxacin, mentions potential QT prolongation–related clinical conditions in its list of warnings.\textsuperscript{19} and the patient information leaflet includes a “do not take this drug” warning for patients with abnormal heart rhythm.\textsuperscript{20} This is relevant because, in our study, the net

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**Table 1**  
Linear model table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative QTc prolongation (95% CI) (ms)</th>
<th>(P)</th>
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<td>&lt;.001</td>
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<tr>
<td>Moxifloxacin treatment</td>
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<td>Patients with LQTS</td>
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<tr>
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<td>.044</td>
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<tr>
<td>Grapefruit treatment in patients with LQTS</td>
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<td>&lt;.001</td>
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<tr>
<td>Grapefruit treatment in female patients</td>
<td>2.9 (0.2–5.5)</td>
<td>.033</td>
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<tr>
<td>Moxifloxacin treatment in female patients</td>
<td>4.3 (1.3–7.2)</td>
<td>.005</td>
</tr>
</tbody>
</table>

CI = confidence interval; LQTS = long QT syndrome; QTc = rate-corrected QT.
QT prolongation from grapefruit was similar to that caused by moxifloxacin.

The greater QT-prolonging effects of grapefruit in female patients are consistent with the fact that I<sub>Kr</sub> blockers are more proarrhythmic in women. 2,21 Finally, the 21-ms QTc prolongation provoked by grapefruit in patients with LQTS is expected and worrisome. It is expected because patients with LQTS have impaired repolarization reserve. It raises concerns for this patient population because compounds causing QT prolongation in this range in healthy volunteers during thorough QT studies are more likely to be proarrhythmic in susceptible patients. 17

The issue of proarrhythmic food
Alcoholic torsade de pointes 22 may well represent the first example of “proarrhythmic food,” rarely becoming clinically significant when consumed in toxic amounts. Also, a patient with LQTS who developed TdP after drinking large amounts of grapefruit juice and tonic water highlights the potential risks of proarrhythmic food in susceptible patients. 22 Tonic water contains small amounts of quinine, an isomer of quinidine, a classic I<sub>Kr</sub> blocker. In this example of “drug-induced TdP,” both “drugs” are actually food products.

The degree of QT prolongation observed in thorough QT studies provides only a rough estimate of the risk of TdP by a given drug in clinical practice. With this limitation in mind, one may extrapolate the available long-term data on moxifloxacin to estimate the risk of arrhythmias related to grapefruit because the net QTc prolongation caused by grapefruit or moxifloxacin was similar. TdP has been documented during clinical use of moxifloxacin, 16 but estimating the risk in population studies has been difficult. Voluntary reporting of drug-related adverse events (prone to underreporting bias) leads to an estimated risk of <3 per million treated patients. 24 In controlled studies, the risk of arrhythmic complications was not higher for patients receiving moxifloxacin than for “comparators” (patients receiving other antibiotics). 25 However, many of the comparators were QT-prolonging antibiotics (macrolides). 26 Thus, the risk of TdP from moxifloxacin in the general population, although difficult to quantitate, appears to be small, and the same probably holds true for grapefruit.

Limitations
(1) The doses of grapefruit tested were large. No inference of the effects of the daily consumption of smaller quantities of grapefruit can be made from our study. It should be noted, however, that the QT prolongation induced by grapefruit became statistically significant already after the ingestion of 1 L of grapefruit. (2) The amount of moxifloxacin contained in a single pill is meticulously controlled. In contrast, the quantity of I<sub>Kr</sub>-blocking flavonoids per liter of grapefruit juice may differ between fruits. (3) In the absence of a placebo arm, it is difficult to define the influence of drinking a liter of fluid on the QT interval. (4) Formulas used to correct the QT interval for heart rate variations are imperfect. However, the heart rate of study participants varied by <7.5 beats/min during the study and the effects of grapefruit were observed with all QT correction formulas.

Clinical implications
Grapefruit juice is already listed among the substances to be avoided when taking QT-prolonging medications. 1 This is because grapefruit increases the proarrhythmic potential of such medications by inhibiting their metabolism and increasing their bioavailability. 26 The confirmed QT-prolonging effect of grapefruit is likely to further increase the risk of proarrhythmia, and grapefruit should definitively be avoided when taking QT-prolonging drugs.

Conclusions
Grapefruit juice per se is not regarded as a proarrhythmic drug. Our study shows that in large doses, grapefruit juice prolongs the QT interval to a similar degree as moxifloxacin, an antibiotic with confirmed but low risk of TdP. Our study does not imply that the daily consumption of grapefruit juice involves any measurable risk for the general population. A possible exception could be the consumption of “health drinks” containing highly concentrated grapefruit products.

Patients with LQTS should be informed that drinking grapefruit juice in large quantities may impose risk. Also, when patients with LQTS present with TdP, it is common practice to inquire about recently consumed drugs. We suggest that the medical history intake in such cases should also include questions about recently consumed food products. We have known proarrhythmic drugs for >44 years; we may soon be discussing “proarrhythmic food.”

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.04.039.

References


