Drug-induced QT interval prolongation and major adverse cardiac events: Meta-analysis of randomized controlled trials

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Background

- QT-prolonging medications (**QTPMeds**) have become a major source of clinical concern regarding medication-related major adverse cardiac events (**MACE**)
- **MACE** events are rare and it is not clear if all **QTPMeds** create harm, or in which circumstances.

Objectives

- **Systematically review the study data on** the association between **QTPMeds** and **MACE**
- Here we report on a subset of **randomized trials**.

Methods

- A systematic search using Medline, Embase, Cochrane Library, and Google Scholar (1996-2021)
- **Inclusion criteria:** Randomized trials with a placebo comparator group with adult patients
- **Exclusion criteria:** Pediatric population, healthy volunteers, both no adverse event or cardiac monitoring
- **Data analysis:** Random effect Mantel-Haenzel odds ratios with Treatment Arm Continuity Corrections

Provisional Results

Fig 1: No. of included RCTs, by WHO ATC drug classification

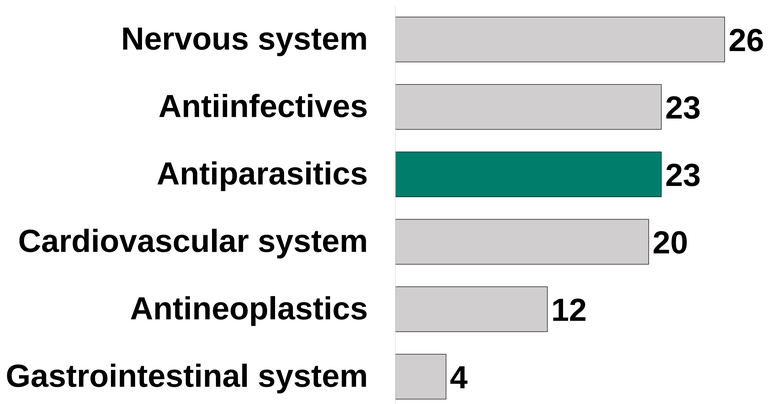
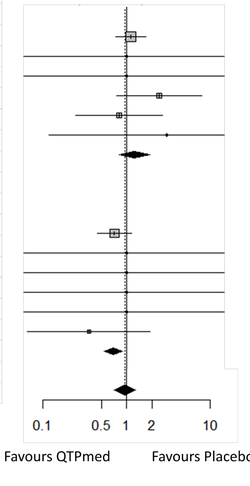


Fig 2: Forest plot – Hydroxychloroquine, Chloroquine vs Placebo, by type of MACE

Subgroup	Experimental n/N	Placebo n/N	Risk Ratio (MH, Random, 95%CI)
Hydroxychloroquine (19 trials)			
All-cause mortality	46	40	1.12 (0.74; 1.70)
Torsades de pointes	0	0	1.00 (0.02; 50.39)
Sudden cardiac death	0	0	1.00 (0.02; 50.39)
Non-fatal cardiac arrests	10	4	2.43 (0.76; 7.73)
Ventricular tachyarrhythmias	5	6	0.81 (0.25; 2.65)
Seizures	1	0	2.97 (0.12; 74.07)
Total HCQ MACE (95% CI)	**62/1998**	**50/1942**	**1.23 (0.81; 1.87)**
Chloroquine (4 trials)			
All-cause mortality	26	26	0.71 (0.45; 1.14)
Torsades de pointes	0	0	1.00 (0.02; 52.80)
Sudden cardiac death	0	0	1.00 (0.02; 52.80)
Non-fatal cardiac arrests	0	0	1.00 (0.02; 52.80)
Ventricular tachyarrhythmias	0	0	1.00 (0.02; 52.80)
Seizures	2	4	0.36 (0.07; 1.90)
Total CQ MACE (95% CI)	**28/122**	**30/87**	**0.69 (0.54; 0.88)**
Total Antiprotozoal MACE (95%CI)	**90/2120**	**80/2029**	**0.96 (0.72; 1.29)**



Discussion

- Most trials are not statistically powered to detect **MACE**
- Incoming data from **over 300 additional randomized trials** will further explore these outcomes across other drug classes and families
- **Strengths:** Innovative question**,** PRISMA methodology, inclusion of zero event trials
- **Limitations**: Exclusion of combination-arm trials, interaction effects

Conclusions

- Our completed meta-analysis of RCTs on Hydroxychloroquine-chloroquine indicates a **lack of evidence** of increased risk of **MACE**
- We still have a large number of RCTs to review on other known **QTPMeds** and their risk of **MACE**
- This work accompanies a program of research to use hospital EHR data with much larger sample sizes to address the same questions.

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