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DIFFERENTIAL EFFECTS OF DARIFENACIN AND TOLTERODINE ON HEART RATE (HR) AND HEART RATE VARIABILITY (HRV): A THREE-WAY CROSSOVER, RANDOMISED STUDY IN HEALTHY SUBJECTS

Hypothesis / aims of study
Use of antimuscarinic agents in the treatment of overactive bladder (OAB) may increase HR via blockade of M_2 muscarinic receptors. Higher HR is associated with an increase in all-cause mortality and cardiovascular disease (1). In addition, decreased HRV is associated with an increased risk of cardiac events (2). In contrast to darifenacin (DAR), which is a highly selective M_3 blocker, tolterodine (TOL) is a relatively non-selective M_2/M_3 receptor blocker with greater relative affinity for M_2. The aim of this study was to evaluate HR changes and HRV following treatment with DAR compared with TOL.

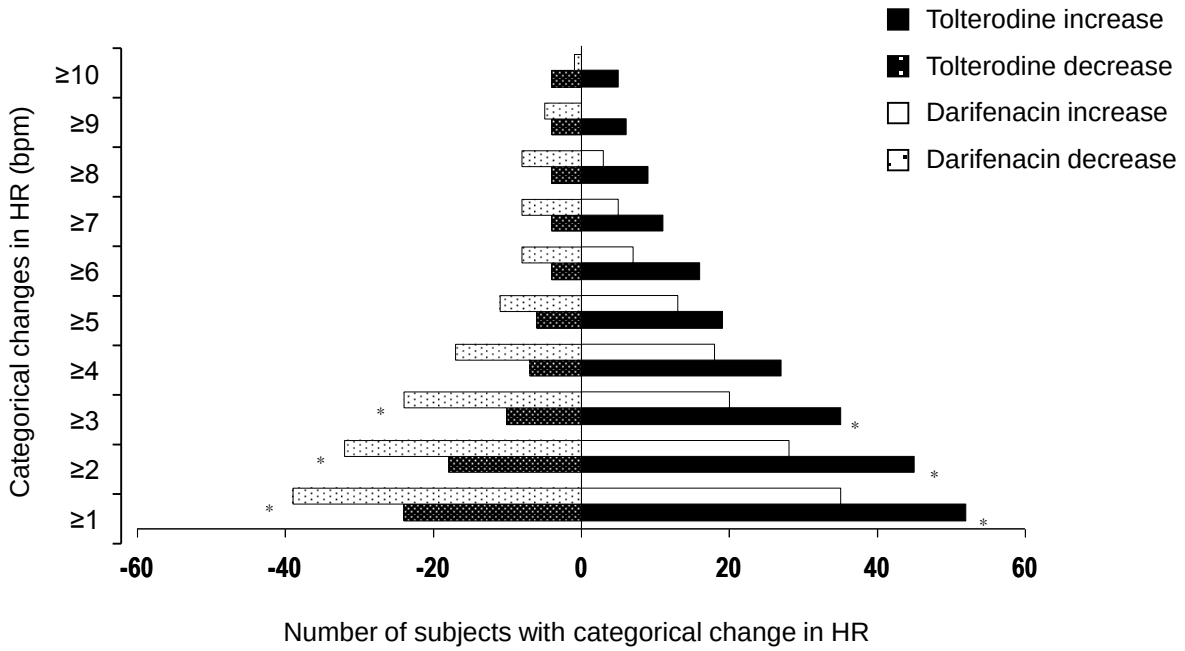
Study design, materials and methods
In this prospective, 3-way crossover, placebo-controlled, double-blind, double-dummy, multicenter study, healthy subjects ≥ 50 years of age were randomized in equal proportions to one of six treatment sequences. Each sequence consisted of 7-day treatment with DAR 15 mg o.d., TOL 4 mg o.d. and placebo (PBO), separated by 14-day washout periods. The primary endpoint was change from baseline in mean HR, assessed using 24-hour (h) ambulatory electrocardiogram (Holter monitoring) at steady-state exposure (Day 7 of each treatment period). Hourly HR, HRV and adverse events were also recorded.

Results
117 subjects were randomized, of which 108 completed all 3 treatment periods. Mean age was 58 years and 63% of subjects were female. Mean change from baseline in 24-h HR was higher with TOL vs DAR (difference: 2.24 beats per minute [bpm]; p=0.0004) and TOL vs PBO (difference=1.84 bpm; p=0.0037), but similar between DAR vs PBO (p=0.5219). Further post-hoc categorical analyses of the number of subjects with increases of a single bpm from ≥1 bpm to ≥10 bpm confirmed that more subjects had an increase in HR on TOL compared with DAR and PBO across each increment (Figure 1). There were no statistically significant differences between DAR and PBO with regard to the number of subjects with increases in HR for any of the categorical HR increase groups. Conversely, a statistically significantly greater proportion of subjects receiving DAR had a decrease in HR of ≥1–≥3 bpm compared with those receiving TOL (p<0.02; Figure 1). However, there was no statistically significant difference between DAR and PBO in the number of subjects with decreases in HR within each 1 bpm increment group. Mean hourly HR values were statistically significantly higher with TOL than with DAR at most hourly intervals from 5–17 hours post-dose or with PBO at most hourly intervals from 5–12 hours post-dose. HRV over 24 h was reduced with TOL vs PBO, but was similar between DAR and PBO. Adverse events (AEs) were reported by 20.5% subjects with TOL, 31.0% with DAR and 18.4% with PBO. The most commonly reported AEs were dry mouth and constipation. One SAE was reported during the study (hypersensitivity reaction to DAR).

Interpretation of results
This study demonstrates that DAR and TOL differ in their effects on HR in healthy volunteers. The changes in HR and HRV seen with TOL vs PBO compared with DAR vs PBO may be the result of differences in M_2 receptor selectivity between these drugs.

Concluding message
As increased HR and decreased HRV are associated with increased CV risk, careful selection of OAB antimuscarinic treatment may be warranted.

Figure 1.
Pairwise comparison of categories of HR increase by single bpm increments (from ≥1 bpm to ≥10) during individual treatment



*p<0.05

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Clinicaltrials.gov, NCT 00703703**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**This was a multicentre trial. The protocol and amendments were reviewed by the Institutional review board for each center**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**