Interactions of circulating, digoxin-like, steroids with rate control therapy for atrial fibrillation in the RATE-AF randomised clinical trial

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Background: Numerous endogenous cardiotonic steroids (CTS) similar to digoxin are thought to exist in humans, but this remains unproven and their clinical impact is unknown.

Purpose: To identify and quantify CTS in patients with atrial fibrillation (AF) and heart failure (HF), and assess their interaction with the clinical efficacy of digoxin treatment within a randomised controlled trial.

Methods: Patients with permanent AF and symptoms of HF were randomised to low-dose digoxin or beta-blockers for rate control (Rate control Therapy Evaluation in permanent Atrial Fibrillation trial, RATE-AF). EDTA plasma was collected at baseline and 6 months, with a range of CTS measured using a novel ultra-high-performance liquid chromatography tandem-mass spectrometry assay. Outcomes at 6-months were the mEHRA class score, New York Heart Association (NYHA) class, NT-pro B-type natriuretic peptide (BNP), and a composite of all adverse events. Multiple regression models were used to assess treatment efficacy (intention-to-treat analysis) adjusted for age, sex and ejection fraction, with interaction terms for baseline CTS.

Results: 160 patients were randomised and contributed to this study. Mean age was 76 years (SD 8), 46% women and median NT-proBNP 1057 pg/mL (interquartile range [IQR] 778), with demographics comparable between group. 80 patients were randomised to digoxin and 80 patients were randomised to beta-blockers, principally bisoprolol. Patients randomised to digoxin had significantly better functional outcomes compared to beta-blockers, with two-class improvement in mEHRA score odds ratio 5.95 (95% CI 2.78 to 24.06; p<0.001) and mean adjusted difference in NYHA class -0.60 (95% CI -0.86 to -0.34; p<0.001). There were fewer patients with adverse events in those allocated to digoxin (137/6; 17.1%) versus beta-blockers (44/74; 59.5%), with odds ratio 0.29 (95% CI 0.12 to 0.52; p<0.001). The CTS bufalin, cinobufagin, cinobufotalin, digoxigenin, digitoxigenin, dihydroouabain, marinobufagenin, ouabain, ouabagenin and telinobufagenin were all identified in patient samples, but most were at low concentrations or below the lower quantification limits; Figure 1. Digoxigenin and digitoxigenin were the most abundant CTS, with median quantifications of 0.079 nM (IQR 0.152) and 0.024 nM (IQR 0.051). Baseline CTS concentrations did not interact with digoxin treatment efficacy for any outcome; Figure 2. No significant change was seen in CTS concentrations from baseline to 6-months in those treated with digoxin. Digoxin quantification using mass spectrometry was strongly correlated with the clinical immunoassay at 6-months (r=0.88; p<0.001).

Conclusions: Low-dose digoxin improves symptoms and functional class compared to beta-blockers in patients with permanent AF and HF, independently from a range of CTS with similar chemical structure. The role of CTS in humans remains uncertain, however they do not appear to interact with the therapeutic effect of digoxin.

Figure 1