# A pilot randomized trial of oral magnesium supplementation on supraventricular arrhythmias

**NCT 02837328**

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## Materials and Methods

The study was registered at Clinicaltrials.gov **(**# NCT02837328). The study protocol was approved by the University of Minnesota Institutional Review Board, and all participants provided written informed consent.

*Study participants*

Participants 55 years of age or older were recruited using fliers, the University of Minnesota StudyFinder website, invitations to individuals enrolled in the ResearchMatch research volunteer database, and invitations to University of Minnesota School of Public Health employees. Exclusion criteria included a prior history of heart disease (coronary heart disease, heart failure, AF), stroke, known kidney disease; use of type I or III antiarrhythmic drugs or digoxin; current use of magnesium supplements; any prior history of allergy or intolerance to magnesium; lactose intolerance; prior history of inflammatory bowel disease or any severe gastrointestinal disorder. Use of multivitamins was allowable, since these typically contain relatively low dosages of Mg (e.g. 50 mg).

Eligible participants attended a baseline visit where measurements were conducted and a Zio® XT Patch (ZioPatch; iRhythm Technologies, Inc., San Francisco, California) heart rhythm monitor was applied by trained staff. After wearing the ZioPatch for 2 weeks, participants were randomized 1:1 to either 400 mg magnesium oxide or placebo using block randomization within two strata of age (younger than 65 and 65 and older). The randomization was carried out separately for the two randomization strata, age younger than 65 and 65 and older. In each group, a randomization schedule was generated using randomly permuted blocks of random sizes.

Block sizes of 2, 4 or 6 were permitted. The randomization was implemented using the blockrand package in R.

Following randomization, participants were mailed the study intervention, which they took for a total of 12 weeks. Ten weeks after beginning the study intervention, participants took part in a follow-up clinic visit, and a second ZioPatch was applied. Participants continued the study intervention until the second ZioPatch was removed (2 weeks after the follow-up clinic visit) (Figure 1).

*Study intervention and blinding*

The University of Minnesota Institute for Therapeutics Discovery and Drug Development produced the active study intervention (400 mg magnesium oxide) and matched placebo (lactose) according to Good Manufacturing Practices. The University of Minnesota Investigational Drug Service managed bottling per the randomization scheme. Study participants and all study staff were blinded to the treatment given.

*Measurements*

At the baseline and follow-up clinic visits, participants completed questionnaires and trained study staff conducted physiological measurements (i.e., anthropometry, blood pressure), phlebotomy, and applied the ZioPatch device. Treatment compliance was assessed by a pill count at the follow-up visit. At intervention days 21, 42 and 80 participants were also emailed unique links to online questionnaires, administered via REDCap [15], which queried compliance and asked the following open-ended question about adverse effects: “Since starting the study,

have you experienced anything out of the ordinary?" Participant blinding was also assessed on intervention day 80, the last day of the study.

The ZioPatch was used to identify premature atrial contractions (PACs). PACs are supraventricular arrhythmias associated with the future risk of AF [16-18] and are considered an intermediate phenotype of the arrhythmia, reflecting the underlying cardiac substrate that facilitates the development of AF [19]. Participants were asked to wear the ZioPatches for 2 weeks after each clinic visit. Information obtained from the ZioPatch devices was processed by the ZEUS algorithm, a comprehensive system that analyzes electrocardiographic data received from the device [20]. We counted as PACs isolated supraventricular ectopic beats, supraventricular ectopic couplet total count, and supraventricular ectopic triplet total count. Total PACs were then divided by number of hours the ZioPatch recorded analyzable data, which yielded PACS per hour.

Participants were asked to fast for 8 hours prior to blood draws. Serum magnesium and glucose were measured using the Roche Cobas 6000 at the University of Minnesota Advanced Research and Diagnostic Laboratory. Blood pressure was measured with the participant sitting, after a 5 minute rest, with a random zero sphygmomanometer (Omron Digital Blood Pressure Monitor HEM-907XL). Three measurements were taken; all three measurements were averaged for use in analyses. Height and weight were measured with participants in light clothing, and shoes removed. Height was measured with a research stadiometer and weight with a scale.