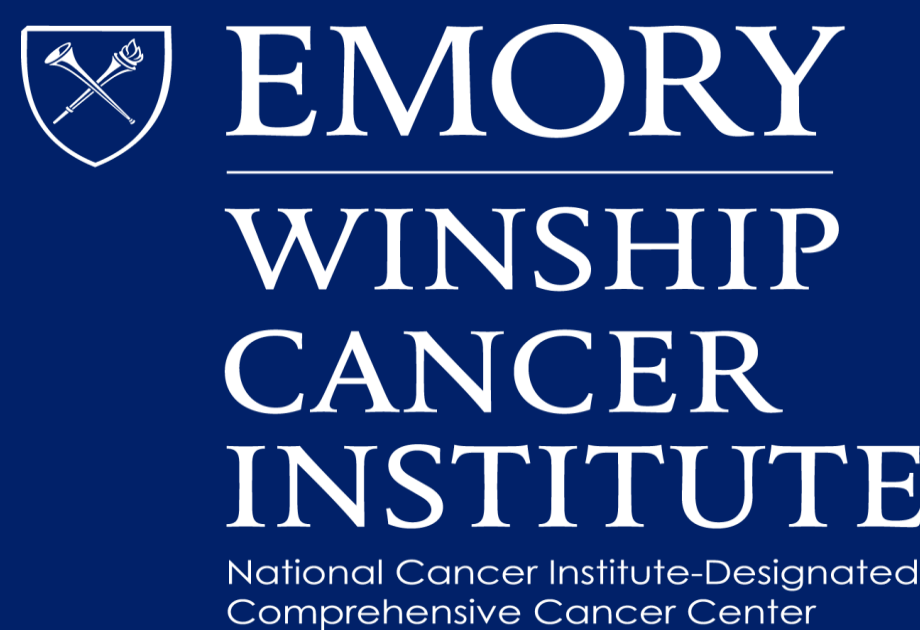
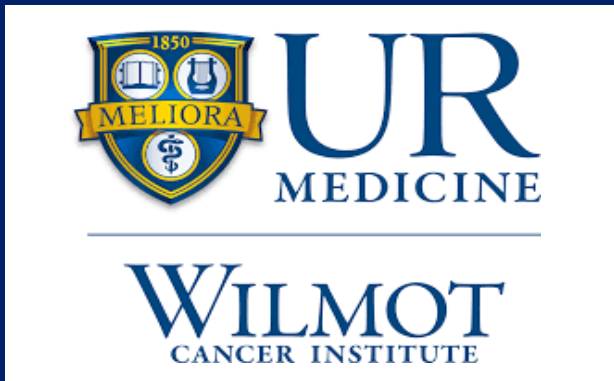


CLINICAL TRIAL IN DEVELOPMENT: ATORVASTATIN TO REDUCE CISPLATIN-INDUCED HEARING LOSS

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Background

Data from multiple studies have established cisplatin, often at high doses of 100 mg/m², as the standard radiosensitizing agent for the treatment of locally advanced head and neck squamous cell carcinoma (HNSCC). There is a major need for therapies that reduce cisplatin-induced hearing loss, which can be dose-limiting and is burdensome for cancer survivors. Statins are FDA-approved drugs used to treat hyperlipidemia. Statin use is associated with improved hearing function in older adults, improved auditory sensitivity in subjects with noise-induced hearing loss, and reduced tinnitus. **We conducted an observational study in patients receiving cisplatin for HNSCC.** Approximately 40% of subjects were taking a statin at the time of cisplatin treatment. **Odds ratio (OR) analysis showed that an atorvastatin user (44% of statin users) is 53% less likely to acquire a cisplatin-induced hearing loss than a non-statin user (Figure 1).** Importantly, 3-year survival was not different between atorvastatin users and non-statin users.

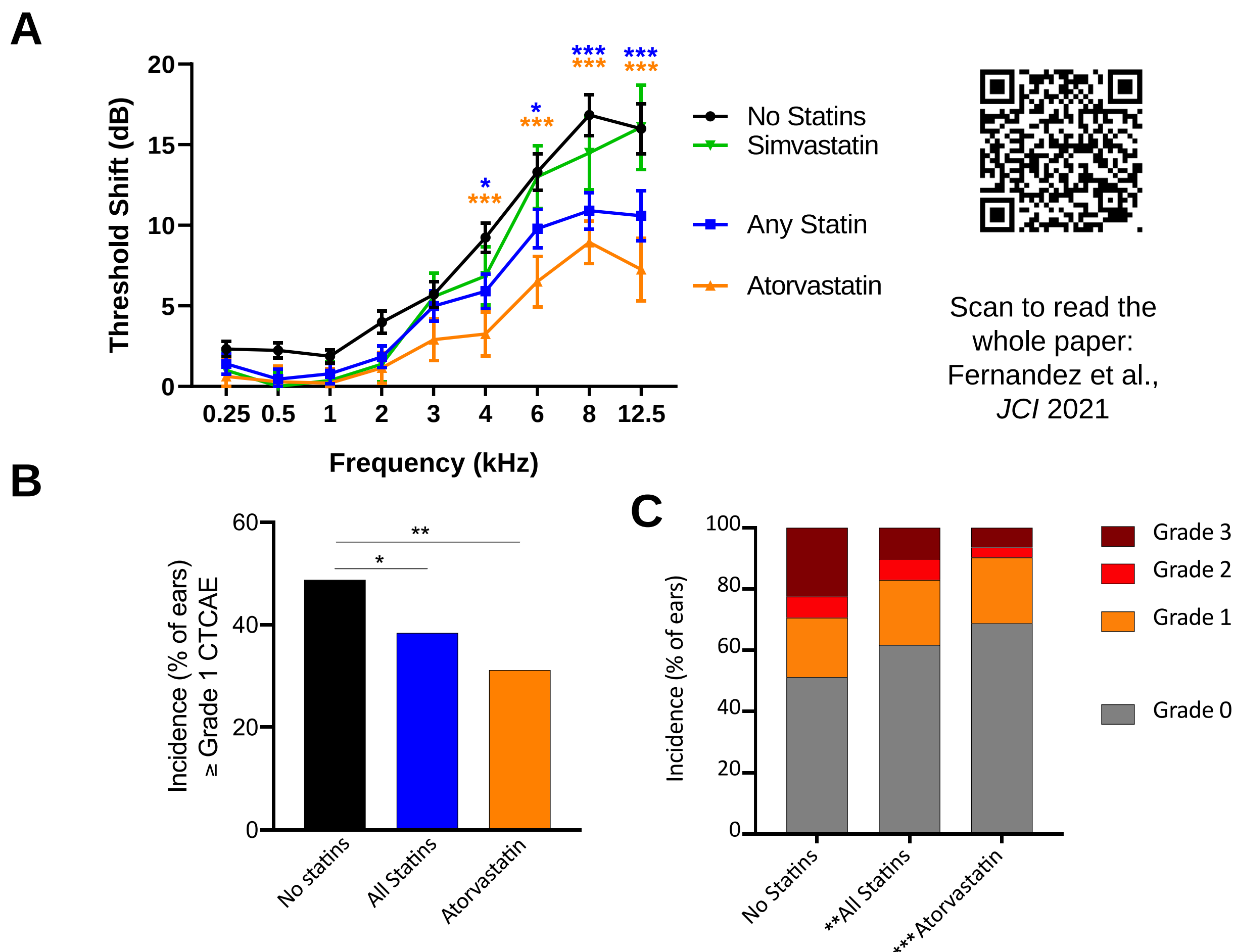
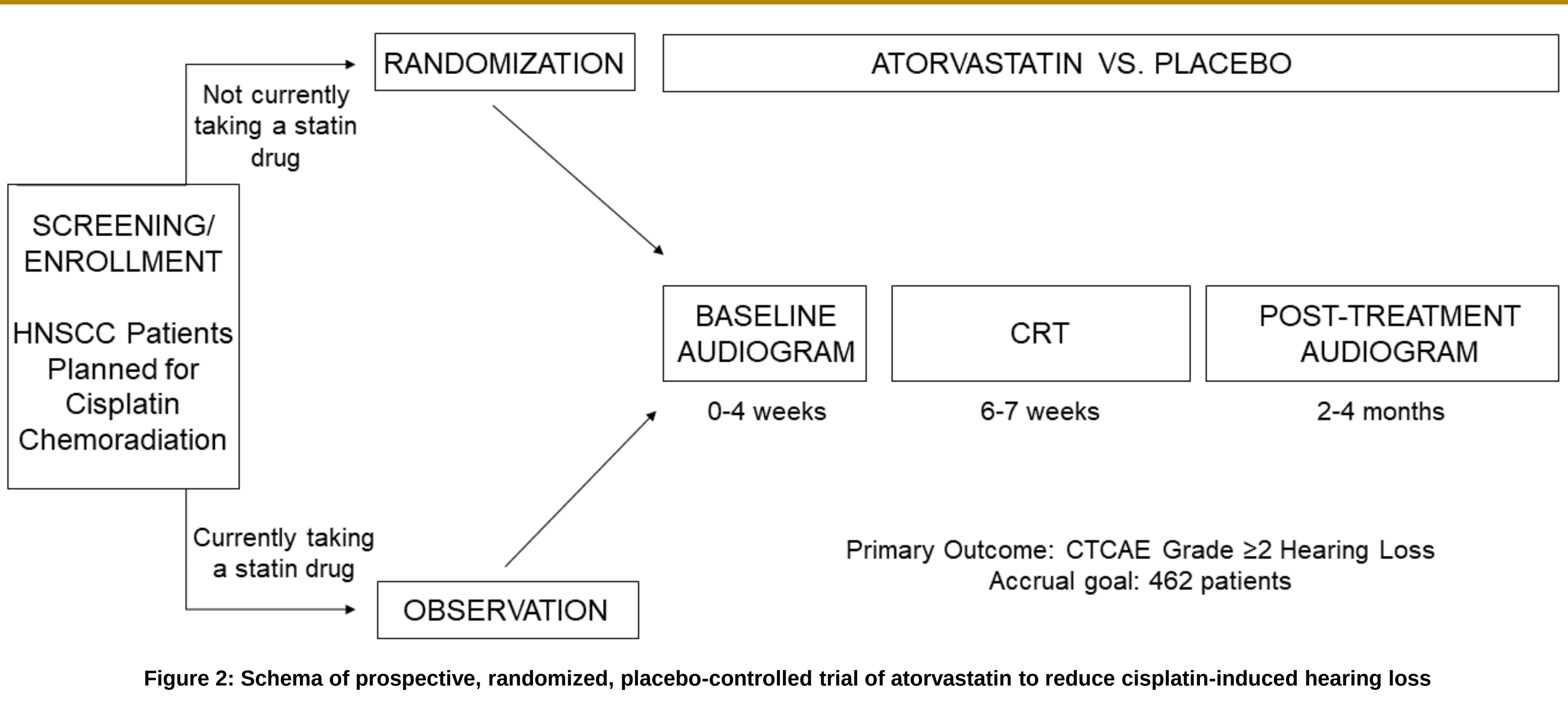


Figure 1: Atorvastatin use is associated with reduced cisplatin-induced hearing loss. Baseline audiometric thresholds were compared to thresholds obtained following cisplatin treatment to determine cisplatin-induced threshold shift. **A:** In subjects not taking a statin, cisplatin treatment resulted in threshold shift that was more severe at higher frequencies. Subjects taking statins had less cisplatin-induced hearing loss than subjects who were not taking statins. Atorvastatin users had significantly less cisplatin-induced hearing loss than non-statin users. **B:** The incidence of cisplatin-induced hearing loss amongst non-statin users is 48% per CTCAE criteria. Subjects taking any statin, particularly atorvastatin, had significantly lower incidence of cisplatin-induced hearing loss than non-statin users. **C:** Use of statins, particularly atorvastatin, is associated with reduced severity of hearing loss. *p<0.05, **p<0.01, ***p<0.001.

Based on these data, we designed a phase 3, randomized, double-blind, placebo-controlled interventional study to determine the extent to which atorvastatin reduces cisplatin-induced hearing loss in adults with HNSCC (**Figure 2**). This will be a multisite study including NIH/NIDCD (coordinating site), Emory University, University of Rochester, and University of Maryland.

Schema



Impact

Atorvastatin is an inexpensive drug with a good safety profile. If atorvastatin significantly reduces cisplatin-induced hearing loss, it could change current treatment paradigms and lead to enhanced quality of life for thousands of cancer survivors each year.

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Study Outcomes

Primary Outcome (Interventional Arm): Determine the extent to which atorvastatin reduces the incidence of cisplatin-induced hearing loss in patients with HNSCC. **We hypothesize that atorvastatin will significantly reduce the incidence of hearing loss in HNSCC patients treated with cisplatin chemoradiation therapy (CRT), consistent with our observational study.** Subjects with previously untreated HNSCC who are scheduled for cisplatin-based CRT and are not already taking a statin (n = 188) will be randomized to receive either oral atorvastatin (20 mg) or placebo daily throughout CRT and for 3 months afterward (total 7 months). Baseline audiometric thresholds will be measured prior to onset of cisplatin therapy and again 2-4 months after completion of all cycles of cisplatin. **The primary outcome is the incidence of a CTCAEv5.0 Grade 2 or higher hearing loss** (threshold shift >25 dB averaged at 2 contiguous frequencies in one ear) following cisplatin-based CRT comparing subjects taking atorvastatin vs. those taking a placebo.

Secondary Outcome (Observational Arm): Examine whether statins other than atorvastatin reduce cisplatin-induced hearing loss in patients with HNSCC. Our pilot data indicate that approximately 40% of eligible subjects with HNSCC will be already taking a statin at enrollment. These subjects will be enrolled into an observational arm to examine whether other statins (and other doses of atorvastatin) may be protective as a secondary outcome. We hypothesize that other statins will also be associated with reduced cisplatin-induced hearing loss, as suggested by our pilot data (**Figure 3**).

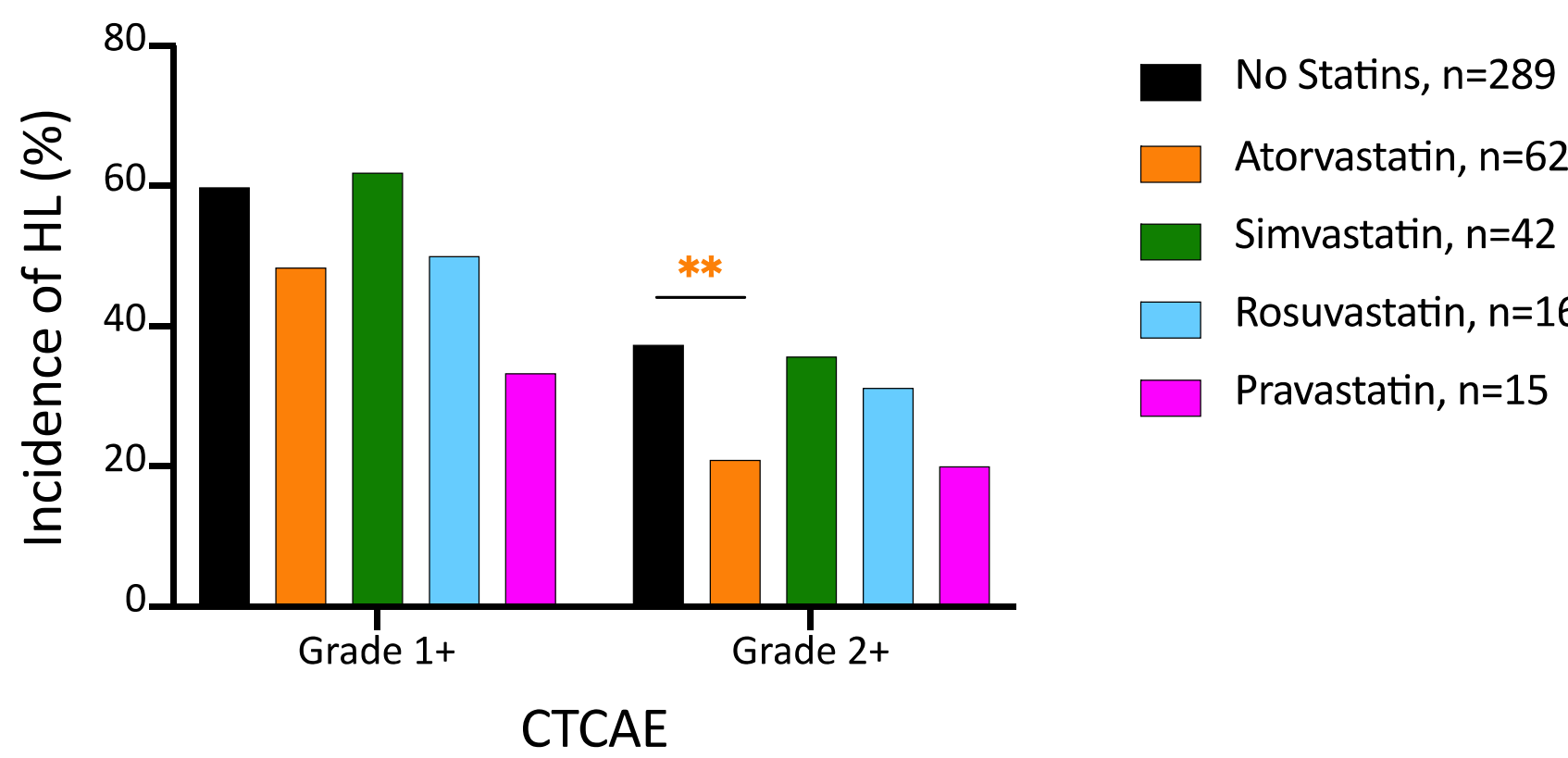


Figure 3: Other statins may be associated with reduced cisplatin-induced hearing loss. Baseline audiometric thresholds were compared to thresholds obtained following cisplatin treatment to determine cisplatin-induced threshold shift. In addition to atorvastatin, pravastatin also appeared to be protective while simvastatin did not; however, our pilot study was not sufficiently powered to draw conclusions on statins other than atorvastatin. **p<0.01

Tertiary Outcome: Estimate whether statins affect survival in patients with HNSCC. Subjects will be followed for two years after CRT to estimate 2-year overall and disease-free survival. Based on our pilot study, **we hypothesize that subjects taking atorvastatin or other statins will have similar survival outcomes to subjects not taking statins.** Our study will not be powered to detect minor survival differences; however, we will follow subjects to rule out any major survival differences.