Metformin Reduced Recurrent Atrial Arrhythmia After Afib Ablation

— Single-center study supports use of drug in patients with overweight or obesity

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NEW ORLEANS -- The diabetes drug metformin reduced recurrent arrhythmias after a first catheter ablation procedure for atrial fibrillation (Afib) in patients with overweight or obesity but without diabetes, according to a randomized open-label study.

Over the 3 to 12 months following catheter ablation, patients who received metformin had greater freedom from recurrent atrial arrhythmia lasting more than 30 seconds, the study's primary endpoint, with 78% having no recurrence versus 58% in the ablation-alone arm (HR 0.50, 95% CI 0.20-0.90, P=0.04).

"Metformin was well tolerated by a majority of patients and we did not see large weight or glycemia changes to explain the effect we saw," said Amrish Deshmukh, MD, from the University of Michigan in Ann Arbor, who presented the results at the American Heart Association (AHA) annual meeting.

Twelve patients did not tolerate metformin, and there were a number who stopped having Afib after their ablation and did not want to take another medication, he noted. "So, I think patients who are best suited for that kind of therapy are those who are willing to take an additional medication first off, and then we titrated the drug quite slowly over 6 weeks, and that seemed to limit the side effects that would stop patients from continuing on."

The single-center META-AF study had an open-label design and a small sample size, limiting the power, Deshmukh noted.

Discussant for the trial, Gregory Schwartz, MD, PhD, of the University of Colorado in Aurora, reviewed the potential mechanisms for the use of metformin in this setting, and concluded that the hypothesis tested in META-AF "has legs."

However, he said the assumptions underlying statistical power calculations for the trial were "undoubtedly optimistic," projecting a 20% absolute risk reduction with treatment, and that 5% would be intolerant to metformin, for an estimated sample size of 150 patients. Instead, the trial was terminated prematurely after randomizing only about two-thirds of that projected sample size, and 25% of patients were intolerant of the study drug, he noted.

Despite the positive primary endpoint result, Schwartz called the results "hypothesis generating" due to those limitations. "These findings, in my opinion, support further study of metformin as a potential antiarrhythmic in a larger randomized prospective trial," he said.

Metformin is being studied at the moment in a number of trials with cancer, neurocognitive, and cardiovascular outcomes, including one that Schwartz is an investigator on, VA-IMPACT, which is looking at cardiovascular outcomes in over 7,000 patients with prediabetes and established atherosclerotic cardiovascular disease.

Unique Aspects

Paul Wang, MD, editor-in-chief of the AHA journal *Circulation: Arrhythmia and Electrophysiology*, and professor of cardiovascular medicine at Stanford University School of Medicine in California, said META-AF had "unique aspects" in that it studied patients after Afib ablation and used metformin, which is readily available and inexpensive.

He also pointed to limitations of the study, including the small sample size, lack of data on longer-term treatment effects, and applicability to technologies other than radiofrequency ablation, including pulsed field ablation.

"The implication for patient care therefore is that this study demonstrates that metformin may be used in conjunction with [Afib] ablation, but adoption may be limited by the generalizability and drug tolerance," Wang concluded. "As more data emerge for GLP-1 agonists, such agents might be used instead."

Study Details

META-AF was a randomized, parallel group, open-label trial comparing metformin after ablation to ablation alone in patients with paroxysmal or persistent Afib and a body mass index of 25 or above. Patients were excluded if they had known diabetes or were currently taking or planned to take antidiabetic medications for weight loss.

A total of 117 patients were randomized. Of these, 18 were excluded from the primary analysis either because they withdrew consent before ablation, underwent surgical rather than catheter ablation, or did not undergo ablation at all, leaving 49 patients in the metformin arm and 50 in the ablation-alone arm.

Treatment with metformin was begun 0 to 6 weeks prior to ablation and titrated to a maximum tolerated dose up to 1,000 mg twice daily. Counselling on lifestyle and risk factor modification was offered to all patients. Twelve patients did not tolerate or take metformin within 3 months of the ablation procedure; the remaining participants achieved the highest titrated dose.

The ablation strategy was antral pulmonary vein isolation, with additional ablation or antiarrhythmic medications allowed at the discretion of the treating electrophysiologist.

All patients received a hand-held ECG device, the AliveCor KardiaMobile, and were asked to record whenever they had Afib symptoms, weekly if they had no symptoms, or daily on the days they were notified of Afib by automated diagnosis, Deshmukh said.

For the primary endpoint analysis, the researchers had included a 3-month blanking period to exclude arrhythmias related to the ablation procedure, but more recent data showed that recurrence related to the procedure can likely be excluded by 1 month, Deshmukh noted. "In a post-hoc analysis, we shortened the blanking period to 1 month, and found a similar result," he said (HR 0.45, 95% CI 0.20-0.90, P=0.02).

A secondary outcome was atrial arrhythmia burden calculated using the patients' self-monitoring and other devices, including pacemakers or loop recorders.

They found Afib burden was lower in the metformin group, with an average burden of 8% versus 16% in the ablation-alone arm (P=0.02). He cautioned that "this finding should be interpreted in the context of antiarrhythmic medication use and repeat cardioversions or ablation," both of which were more common in the ablation-alone arm although the difference did not reach statistical significance.

An average weight loss of 6 kg was seen in the metformin group versus 2 kg in the ablation-alone arm, but "we did not see a statistically significant difference to indicate a treatment effect," he said. HbA1c was similar between groups both at baseline and at follow-up.

All patients had significant improvement in symptoms after catheter ablation on the Atrial Fibrillation Severity Scale, but they were not able to detect a difference in symptom severity related to intervention with metformin. "The longer-term effect of treatment with metformin was not studied; however, we're looking into the legacy effect after 1 year," Deshmukh concluded.

Disclosures

The study was funded by the Fischer Arrhythmia Fund.

Deshmukh reported no relevant disclosures.

Schwartz disclosed relationships with AstraZeneca, Sanofi, and Silence Therapeutics.

Wang reported individual stocks/stock options with Soneira, and ownership interest with HrtEx and EpiEndoAF.

Primary Source

American Heart Association

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1 Comment