Novel Drug Might Prevent New-Onset Diabetes

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NEW ORLEANS — Succinobucol, a novel antioxidant with anti-inflammatory properties, achieved a 64% reduction in new-onset diabetes in patients with a recent acute coronary syndrome in the phase III Aggressive Reduction of Inflammation Stops Events (ARISE) trial.

Use of the investigational agent also was linked to significant reductions in cardiovascular death, MI, and stroke, compared with optimal current therapy in the 6,144-patient double-blind randomized trial, Dr. Jean-Claude Tardif reported at the annual meeting of the American College of Cardiology.

But these were prespecified secondary outcome measures. Succinobucol failed to achieve a significant impact on the primary end point, a composite of "hard" atherosclerotic outcomes and the "soft" end points of coronary revascularization and hospitalization for unstable angina, said Dr. Tardif, professor of medicine at the University of Montreal and director of research at the Montreal Heart Institute.

Succinobucol significantly reduced the incidence of cardiovascular death, MI, and stroke.

DR. TARDIF

That failure was severely punished by a single-day 60% nosedive in the stock price of AtheroGenics Inc., the trial sponsor, as some observers dismissed ARISE as a negative study. That's not how the ARISE investigators see it, though.

"I'm pretty bullish," added Dr. Marc A. Pfeffer, ARISE coprincipal investigator. "We're all looking for the next step [in cardiovascular risk reduction], and I think this is as promising as anything I've seen in terms of developments."

"We didn't hit our primary end point, but we're the ones who established that primary," he continued. "If we can come back here with another study aiming specifically at those end points and we can show positive results, then that would be the highest compliment for a clinical trial—it would change the practice of medicine," said Dr. Pfeffer, professor of medicine at Harvard Medical School, Boston.

The 6,144 ARISE participants were randomized to 300 mg/day of succinobucol or placebo for an average of 2 years starting shortly after hospitalization for an acute MI or unstable angina. All were deemed at high risk for further atherosclerotic events. Rates of utilization of secondary preventive therapies were extremely high: 90% of patients were on a statin at baseline, 80% on a β-blocker, 92% on aspirin, and 74% on an ACE inhibitor or angiotensin receptor blocker.

A total of 37% of subjects had diabetes at baseline, with a mean HbA_{1c} of 7.2%. Among the other nearly 4,000 participants, the incidence of new-onset diabetes was 4.2% with placebo and 1.6% with succinobucol, a 64% relative risk reduction. Consistent with this benefit, succinobucol resulted in a mean 0.5% lower HbA_{1c} than placebo did at 12 months in patients with diabetes at entry, and an improvement in fasting blood glucose as well.

The combined "hard" secondary atherosclerotic end point of cardiovascular death, cardiac arrest, MI, or stroke occurred in 8.2% of the placebo group and 6.7% with succinobucol, for a significant 19% relative risk reduction.

The chief side effect of succinobucol was diarrhea, reported by 23% of patients, although only one in seven of those affected discontinued the study.

Discussant Dr. Robert A. Harrington, director of cardiovascular clinical trials at the Duke Clinical Research Institute, Durham, N.C., said ARISE sends mixed signals, including unwelcome trends toward increased heart failure hospitalizations, lower HDL, and increased LDL.

Succinobucol, a potent lipophilic antioxidant, is the monosuccinic acid ester of probucol. The drug's appeal, Dr. Pfeffer said, lies in the fact that it operates by mechanisms beyond modification of the conventional risk factors such as blood pressure and lipids.

Officials at AtheroGenics indicated they plan to back a large confirmatory trial.

Dr. Tardif and Dr. Pfeffer disclosed that their financial relationship with AtheroGenics is limited to research grants. ■