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Cardiovascular Safety of Roflumilast

To the Editor:

In this issue of CHEST (see page 758), White et al report significantly lower major adverse cardiovascular events (MACEs) for roflumilast compared with placebo (hazard ratio, 0.65; 95% CI, 0.45-0.93; P = .019) from data in 12,054 patients with COPD. In addition to the studies analyzed not being designed or powered to examine cardiovascular outcomes, we would like to point out other limitations of the study.

First, the incidence of nonfatal stroke was the only component of MACEs that showed a statistically significant difference. It may not be appropriate to use a composite outcome if the magnitude of treatment effects is not comparable across the outcome components. It may be fair to say that roflumilast could decrease cerebrovascular events but not cardiovascular events or mortality because roflumilast was not associated with a lower incidence of such MACE components compared with placebo.

Second, the incidence of atrial fibrillation was not included in the study. Our recent meta-analysis showed that atrial fibrillation was significantly more frequent with roflumilast than with placebo (0.4% vs 0.2%; P = .02). The COPD safety pool White et al included this information, and they should have incorporated it into the study.

Third, the discontinuation rate because of adverse effects was significantly more frequent with roflumilast than with placebo (15% vs 9.2%; P < .0001). The incidence of dropout rates between the two groups may have affected the study results. The results may have been quite different if all patients recruited for roflumilast continued to take the drug during the entire study period.

Outcomes could have been adjusted, using person-years of exposure as a denominator.

In conclusion, the study by White et al does not provide enough evidence to support the cardiovascular safety of roflumilast. More studies are needed to further investigate the cardiovascular safety of the drug.

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Response

To the Editor:

The intention of our study, reported in this issue of CHEST, was to evaluate the cardiovascular (CV) safety of roflumilast in > 12,000 patients with COPD using adjudicated major adverse CV events (MACEs) of CV death, nonfatal myocardial infarction, and nonfatal stroke. The results of our study showed that the hazard ratios for roflumilast relative to placebo were similar and in the same direction (<1) for all three components of this MACE composite. Oba and Lone stated incorrectly that stroke was the only MACE component that was significantly different for roflumilast relative to placebo. In fact, none of the components met statistical significance for a reduction in CV events. We concluded that our large analysis demonstrated the lack of a CV safety concern for roflumilast in patients with moderate to severe COPD, and the results generated the hypothesis of potential benefit, particularly in those patients lacking CV comorbidities at baseline. The absolute and relative CV effects of roflumilast are currently being evaluated in purposefully designed, prospective randomized trials.

William B. White, MD
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on behalf of the coauthors

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