Association of Electronic Cigarette Use With Myocardial Infarction: Persistent Uncertainty

We read with interest the cross-sectional analysis of the National Health Interview Surveys by Alzahrani et al.,[1] specifically the finding of the association of electronic cigarette (EC) use with prior myocardial infarction (MI). Of concern, however, is the fact that 95% of EC users were also former or current tobacco cigarette (TC) smokers, and the timing of the MI relative to onset of EC use is unknown. For example, did the MI occur while the participant was a TC smoker, and EC use initiated later as a smoking-cessation strategy?[2] The authors considered this possibility and did attempt to control for TC smoking as a confounding factor in their regression model. Further, they argue that a misclassification error would bias the findings toward the null, thereby underestimating the true risks of EC use. However, we would like to point out that this assumption is only true if the misclassification error is random. A systematic misclassification of participants who only became EC users after an MI (true non-EC users at the time of the MI) as EC users with MI would bias the results away from the null. There is reason to believe that misclassifying an individual with an MI as an EC user when he or she is a non-EC user, rather than vice versa, is more likely. Although not approved as a cessation device, ECs are often used by TC smokers to stop smoking[2]—and many people are motivated to quit smoking after an MI.[3] Thus, TC smokers who switched to ECs after an MI are as vulnerable to misclassification as EC users with MI in this survey. Even a small misclassification of only 10% of MI sufferers as EC users who were not EC users at the time of the MI could explain the association of MI with EC use reported in this study.[1]

This point is illustrated in this hypothetical example: Assuming the true absolute risk of an MI in a population is 10%, and that, in our hypothetical example, ECs do not increase the odds of an MI, then the true OR of MI in EC users is 1.0 (same odds of an MI in an EC user versus non-EC user). In our hypothetical example, using similar ratios as presented in Alzahrani's report, the true N of non-EC users=10,000 people, and true N of EC users=1,750 people, (thus, 14.9% of 11,750 people are EC users), and the "true" 2 × 2 table is shown as Table 1.

Accordingly, the OR is 0.111/0.111=1.0. However, if only 10% of the 1,000 who were actually non-EC users at

the time of the MI are nonrandomly misclassified as EC users, the table changes as below. The 100 are incorrectly added to the 175 and removed from the 1,000 (Table 2).

Now the OR=0.1746/0.100=1.746, the same OR reported by Alzahrani et al.[1] In summary, the apparent OR is not conservative; it would actually overestimate the risk of an MI associated with EC use, because this misclassification is nonrandom. Note that only the non-EC users with an MI are misclassified, a nonrandom misclassification. The possibility of this systematic misclassification is not accounted for in the statistical analysis provided in this report.

How to help circumvent this problem? The authors could, and should, present a subanalysis of the association of MI with EC use in the group of participants who have never used TCs. There are more than 40,000 people in this never-TC smoker group, of which 2,500 were EC users. A graded EC use effect (lowest in former EC users, intermediate in some day EC users, and highest in daily EC users) would further strengthen the argument. This analysis was not presented.

Finally, the authors fail to put their conclusion that daily EC use is associated with increased risk for MI in the proper perspective. Their stated rationale[1] for performing this study is the observation that ECs "are often promoted as a safer alternative to conventional cigarettes." In fact, if their results are correct (and this is arguable as explained above), one could conclude that their findings support this observation. According to their results, MI risk is lower in daily EC users (OR=1.79) compared with daily TC smokers (OR=2.72), although both are worse than nonsmokers. Perhaps this is another message of the study, and TC smokers, if unable or

Table 1. Hypothetical Association of Electronic Cigarette (EC) Use With Prior Myocardial Infarction (MI)

Use	No MI	MI	Total	Odds MI
EC use	1,575	175	1,750	0.111
No EC use	9,000	1,000	10,000	0.111

Table 2. Hypothetical Association of Electronic Cigarette (EC) Use With Prior Myocardial Infarction (MI), With 10% Misclassification of EC Users

Use	No MI	MI	Total	Odds MI
EC use	1,575	275	1,850	0.1746
No EC use	9,000	900	9,900	0.1000

unwilling to quit entirely, should be encouraged to switch to ECs, potentially saving thousands of lives.[4] This harm reduction strategy has been embraced successfully in England,[5] and we would argue, should be considered more widely.

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E-cigarettes: Stick to the Evidence

Middlekauff and Gornbein[1] argued that "there is reason to believe" people who have had a myocardial infarction (MI) would be more likely to use e-cigarettes than those who did not, which would result in a systematic misclassification error that could explain the association we[2] found between e-cigarette use and having had an MI.

This assertion is surprising because Gaalema et al.[3] (reference 3 in their letter) concluded, based on longitudinal analysis of the first two waves of the Population Assessment of Tobacco and Health dataset, that having an MI was not a significant predictor of initiating non-combusted tobacco (mostly e-cigarettes) use ($p=0.20$). Furthermore, they found, "cardiac status was significantly negatively associated with switching completely from combusted to non-combusted products. While 9.2% of those with no change in health status switched [from combusted tobacco, mostly cigarettes] to non-combusted use, none of those experiencing a new MI switched ($p=0.0015$)." Thus, any differential misclassification is in the opposite direction from what Middlekauff and Gornbeing speculate, which strengthens our conclusion that e-cigarette use is associated with the risk of having had an MI.

Our analysis of the National Health Interview Survey shows comparable results (Table 1). Without correcting for covariates, having had an MI was negatively associated with using e-cigarettes. This association became nonsignificant when controlling for covariates. These findings are also evidence against reverse causality.

Middlekauff and Gornbein misinterpret the ORs we present. With respect to never smokers who never used e-cigarettes, the ORs for MI associated with daily smoking controlling for e-cigarette use is 2.72 (95% CI=2.29, 3.24) and daily e-cigarette use controlling for smoking is 1.79 (95% CI=1.20, 2.65). (Although the point estimates of the risk are different, this difference is not statistically significant, $p=0.08$.) As we point out in our paper, the odds of having had an MI for someone switching completely from daily cigarette to daily e-cigarette use can be calculated as the odds associated with being a former smoker times the odds associated with being a daily e-cigarette user divided by the odds of being a daily smoker, 1.09, which is not harm reduction.

Limiting the analysis to e-cigarette-only users is not a good idea because most e-cigarette users are dual users with cigarettes so it is important to study the effects of e-cigarette use simultaneously with cigarettes. Limiting the analysis to sole e-cigarette users would not only be less clinically relevant, but would substantially reduce the sample size and the power of the analysis.

Although Middlekauff and Gornbein are correct that using e-cigarettes for harm reduction has been embraced in England, they do not mention that, as elsewhere,[4] smokers who use e-cigarettes are less, not more, likely to quit smoking[5] and that e-cigarettes are attracting low-risk youth to nicotine use, who are then at high risk of progressing to cigarettes.[6] Rather than a public health