Comment on *E-Cigarettes and Cardiovascular Risk: Beyond Science and Mysticism*

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We read with particular interest the short review and opinion by Lippi et al about the potential cardiovascular risk of using e-cigarettes.[1] It is our opinion that certain aspects presented in the article should be further addressed and clarified.

The potential risk for cardiovascular disease from e-cigarette use was mainly attributed by the authors to the effects of nicotine. However, several studies have shown that nicotine intake does not elevate cardiovascular risk. Long-term inhalation of nicotine was studied in animals; researchers did not observe any adverse effects on the lungs or development of atherosclerosis.[2] A recent meta-analysis of controlled smoking cessation trials found that, although nicotine replacement therapies (NRTs) had a higher rate of any cardiovascular events, this was driven only by minor events such as heart palpitations; no elevation in the incidence of major adverse cardiovascular events (MACE) was found.[3] Use of NRTs in high-risk individuals was similarly not associated with an elevated risk for MACE.[3] A population-based case-controlled study among 68 hospitals in the US found that the use of nicotine patches did not elevate the risk of first myocardial infarction.[4] A meta-analysis of 34 randomized controlled trials showed that NRTs did not pose any elevated risk for myocardial infarction, stroke, palpitations, angina, arrhythmia, or hypertension compared with placebo-treated patients.[5] Even in patients with established cardiovascular disease, use of NRTs did not confer any additional risk compared with placebo and in fact their use was associated with reduced ischemia-related perfusion defects and elevated time to exercise-induced ischemia.[6] Currently, there is consensus that nicotine has minimal effects in initiating and propagating atherosclerosis.[7] Moreover, Lippi et al seem to have exaggerated on the toxicity of liquid nicotine present in e-cigarettes. Mayer recently showed that the traditionally proposed nicotine lethal dose of 30 to 60 mg came from dubious experiments performed more than 150 years ago.[8] By evaluating postmortem examinations, he defined that the lethal dose would be 500 to 1,000 mg of acute intake, almost 20 times higher than currently assumed. In fact, this represents the total amount of nicotine that should be absorbed; knowing that voluminous vomiting is the first and main symptom of nicotine intoxication, it seems obvious that you need to ingest even higher amounts of nicotine to absorb lethal quantities. Further support for this came from a recent presentation of three cases of attempted suicide by ingesting nicotine liquid used for e-cigarettes; none of the cases were fatal, with one of them ingesting 1,500 mg of nicotine.[9]

Smokeless tobacco is an alternative form of nicotine intake which does not involve combustion. Still it contains tobacco and several contaminants present in it. Snus is considered the least harmful type of smokeless tobacco due to the manufacturing process and selection of tobacco. A meta-analysis of epidemiological studies have found that, in nonsmokers, snus use results in mild elevation in fatal cardiovascular events while it had a paradoxical protective effect in nonfatal events compared with nonusers.[10] In fact, the risk for fatal events was attributed to one study only, with four more studies showing no added risk. Another meta-analysis revealed that those who switched from cigarette to snus use reduced to half the risk for developing cardiovascular disease compared with smokers.[11]

Because of the absence of combustion and of cured tobacco, e-cigarettes are reasonably expected to significantly reduce the cardiovascular risk in smokers who switch. Obviously, there is no definite proof for that because long-term epidemiological studies cannot be performed until after several years of use by a significant part of the population. None can exclude the possibility of some residual risk, but this can only be evaluated by surveillance of use in the population level. Lack of long-term studies cannot be a valid argument to support that e-cigarettes should be banned or restricted, especially because we know that the levels of toxins emitted from e-cigarette use are minimal and

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by orders of magnitude lower compared with tobacco cigarettes.[12,13] In some cases, exposure to toxic chemicals is similar to pharmaceutical NRTs.[14] Nicotine intake is unlikely to significantly elevate harm; health organizations such as the Medicines and Healthcare Products Regulatory Agency and the National Institute for Health and Care Excellence in the United Kingdom are currently proposing the long-term use of nicotine (in the form of NRTs) as a substitute for smoking, acknowledging that a significant proportion of smokers are unable to quit with currently approved medications.[15,16] Obviously, it would be preferable for smokers to quit either by themselves or by using approved methods. E-cigarettes are an option for the majority of smokers who cannot quit and currently available evidence suggests that they are expected to be less harmful than tobacco.[16]

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